Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende daratumumab i kombination med bortezomib, melphalan og prednison til nydiagnosticerede patienter med knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte

Vers. 2.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedrørende daratumumab i kombination med bortezomib, melphalan og prednison til patienter med nydiagnosticeret til knoglemarvskræft, version 2.0
2. Forhandlingsnotat fra Amgros vedr. daratumumab
3. Høringssvar fra ansøger inkl. evt. efterfølgende dialog
4. Medicinrådets vurdering vedr. daratumumab i kombination med bortezomib, melphalan og prednison til patienter med nydiagnosticeret til knoglemarvskræft, version 1.0
5. Ansøgers endelige kliniske ansøgning vedr. daratumumab
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering af daratumumab i kombination med bortezomib, melphalan og prednison til nydiagnosticerede patienter med knoglemarvskræft (myelomatose), version 2.0

Medicinrådet

Medicinrådets sundhedsøkonomiske afrapportering

Daratumumab i kombination med bortezomib, melphalan og prednison

Patienter med nydiagnosticeret knoglemarvskræft

Version 2.0

Indholdsfortegnelse

Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for daratumumab i kombination med bortezomib, melphalan og prednison (DaraBorMelPred) til patienter med nydiagnosticeret knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte (HDT/STS), samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under "*Sekretariatets vurdering*". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.

Afsnit 2.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

Opsummering

Baggrund

I den ansøgte behandlingskombination er daratumumab i kombination med bortezomib, melphalan og prednison indiceret til patienter med nydiagnosticeret knoglemarvskræft, som ikke er kandidater til HDT/STS. Omkring 250 patienter pr. år er kandidater til den ansøgte indikation i Danmark. Medicinrådets sekretariats vurdering tager udgangspunkt i dokumentation indsendt af Janssen.

Analyse

Analysen estimerer de inkrementelle omkostninger pr. patient ved behandling med Dara-BorMelPred sammenlignet med:

- bortezomib, lenalidomid og dexamethason (BorLenDex)
- bortezomib, melphalan og prednison (BorMelPred)
- lenalidomid i kombination med dexamethason, givet i 18 serier (LenDex18)

Analysen forløber over en tidshorisont på 15 år og resultatet præsenteres i sygehuspotekernes indkøbspris (SAIP).

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, Medicinrådets sekretariat mener er mest sandsynligt, er de inkrementelle omkostninger pr. patient over en tidshorisont på 15 år for DaraBorMelPred sammenlignet med:

- BorLenDex ca. [redacted] DKK
- BorMelPred ca. [redacted] DKK
- LenDex18 ca. [redacted] DKK

Hvis analysen udføres med apotekernes indkøbspris (AIP), bliver de inkrementelle omkostninger pr. patient til sammenligning ca. 1 mio. DKK sammenlignet med BorLenDex, ca. 1,05 mio. DKK sammenlignet med BorMelPred og ca. 1,06 mio. DKK sammenlignet med LenDex18.

Der er 250 patienter pr. år der er kandidater til behandlingerne. Ved nuværende fordeling er det antaget, at 150 patienter modtager BorLenDex, 50 patienter modtager Bor-MelPred, og 50 patienter modtager LenDex18.

Medicinrådets sekretariat vurderer, at såfremt regionerne anbefaler DaraBorMelPred, vil budgetkonsekvenserne i det 5. år efter en anbefaling være ca. [redacted]. DKK.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 95 mio. DKK.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. juni 2021

Konklusion

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne, og dermed har behandlingslængden stor betydning. Endvidere spiller ændringer i de efterfølgende behandlinger, som konsekvens af at daratumumab gives tidligere, en stor rolle.

Dokumentoplysninger	
Godkendelsesdato	23. juni 2021
Dokumentnummer	117926
Versionsnummer	2.0

Liste over forkortelser

AIP	Apotekernes indkøbspris
BorLenDex	Bortezomib i kombination med lenalidomid og dexamethason
BorMelPred	Bortezomib i kombination med melphalan og prednison
DarBorMelPred	Daratumumab i kombination med bortezomib, melphalan, prednison
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
I.v.	Intravenøs
KM	Kaplan-Meier
LenDex	Lenalidomid i kombination med dexamethason givet til progression
LenDex18	Lenalidomid i kombination med dexamethason givet i 18 serier
OS	Overlevelse
PD	Progression
PFS	Progressionsfri overlevelse
PH	*Proportional Hazard*
PomBorDex	Pomalidomid i kombination med bortezomib og dexamethason
PomDex	Pomalidomid i kombination med dexamethason
SAIP	Sygehusapotekernes indkøbspriser
S.c.	Subkutant
TTTD	*Time to treatment discontinuation* (behandlingsstop)

1. Baggrund for den økonomiske analyse

Janssen-Cilag A/S (herefter omtalt som ansøger) er indehaver af markedsføringstilladelsen for daratumumab og har den 2. juni 2020 indsendt en ansøgning til Medicinrådet om anbefaling af daratumumab i kombination med bortezomib, melphalan og prednison som standardbehandling på danske hospitaler til patienter med nydiagnosticeret knoglemarvskræft, som ikke er kandidater til HDT/STS (1.-linjebehandling). Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den økonomiske analyse, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er sekretariatets vurdering af den fremsendte økonomiske analyse (herefter omtalt som analysen).

1.1 Patientpopulation

Knoglemarvskræft er en uhelbredelig, livstruende og livsforkortende, men behandlingsfølsom hæmatologisk kræftsygdom. Knoglemarvskræft er den næsthyppigste hæmatologiske kræftsygdom i Danmark, hvor i alt ca. 2.300 patienter anslås at leve med sygdommen [2]. Der diagnosticeres ca. 380 behandlingskrævende patienter om året i Danmark, og medianalder ved diagnose er ca. 71 år [3].

Behandlingen af knoglemarvskræft varetages på de hæmatologiske afdelinger. Den medicinske behandling består af forskellige lægemiddelkombinationer, der har vist sig mere virksomme end enkeltstofbehandlinger [4]. Behandlingen er ikke kurativ, så ud over forlænget overlevelse er målet med behandlingen at give patientenerne længst mulige sygdomsfrie perioder med bedst mulig livskvalitet.

Nydiagnosticerede patienter inddeles overordnet i to patientgrupper, efter hvorvidt de er kandidater til højdosiskemoterapi med stamcellestøtte (HDT/STS) eller ej. Dette afgøres på baggrund af almentilstand og komorbiditet (om patienten har andre sygdomme). Patienter med knoglemarvskræft, som er yngre end 65-70 år og uden betydende komorbiditet, behandles med HDT/STS, såfremt de ønsker det.

Patienter med behandlingskrævende knoglemarvskræft, som ikke er kandidater til HDT/STS, tilbydes andre medicinske kombinationsbehandlinger [8]. Den patientpopulation udgør ca. 250 patienter årligt, svarende til ca. 2/3 af de behandlingskrævende nydiagnosticerede patienter. Blandt de nuværende behandlingsmuligheder anvendes oftest en kombination af enten bortezomib, lenalidomid og dexamethason (BorLenDex), bortezomib, melphalan og prednison (BorMelPred) eller lenalidomid og dexamethason (LenDex) [9]. Patienter, der ikke er kandidater til HDT/STS, har en medianoverlevelse på ca. 3 år og en median progressionsfri overlevelse på ca. 18 måneder [10].

1.1.1 Komparator

Medicinrådet har defineret bortezomib i kombination med lenalidomid og dexamethason (BorLenDex), bortezomib i kombination med melphalan og prednison (BorMelPred) og lenalidomid i kombination med dexamethason i 18 cyklusser (LenDex18) som komparatorer for patientpopulationen defineret i afsnit 1.1, se Tabel 1. Komparatorerne er alternative behandlingsmuligheder, baseret på en individuel vurdering af patienten. Den sundhedsøkonomiske analyse bliver udført på en sammenligning af daratumumab overfor alle komparatorer.

Tabel 1: Definerede populationer og komparatorer

Population	Komparator
Patienter med nydiagnosticeret knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte	BorLenDex
	BorMelPred
	LenDex18

1.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af DaraBorMelPred som standardbehandling på danske hospitaler af den nævnte indikation. Medicinrådet har vurderet værdien af DaraBorMelPred ud fra følgende kliniske spørgsmål:

Klinisk spørgsmål 1*:*

Hvad er værdien af daratumumab i kombination med bortezomib, melphalan og prednison samt efterfølgende som vedligeholdelsesbehandling (daratumumab monoterapi), sammenlignet med nuværende standardbehandling til voksne patienter med nydiagnosticeret knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte?

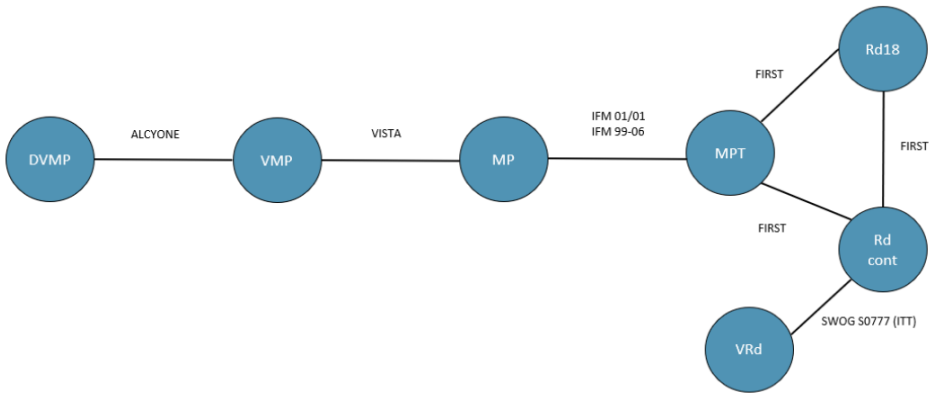
2. Vurdering af den økonomiske analyse

Ansøger har indsendt en økonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for DaraBorMelPred, sammenlignet med BorLenDex, BorMelPred, LenDex18 og LenDex. I det nedenstående vil den økonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

2.1 Antagelser og forudsætninger for model

Den økonomiske model har til formål at estimere de inkrementelle omkostninger pr. patient for DaraBorMelPred sammenlignet med BorLenDex, BorMelPred og LenDex18 ved 1. linjebehandling af knoglemarvskræft.

Sammenligningen mellem DaraBorMelPred og BorMelPred er lavet på baggrund af data fra det kliniske studie ALCYONE [11]. Ansøger anvender en netværksmetaanalyse (NMA) for sammenligningen af DaraBorMelPred med BorLenDex og LenDex. Der er tale om en ikke publiceret netværksanalyse, som ansøger har udarbejdet. Sammenligningen med BorLenDex er baseret på studiet SWOG S0777 [12], hvor populationen er yngre end patienterne i ALCYONE [11]. Sammenligningen med LenDex er baseret på studierne FIRST[13], VISTA[14], IFM 01/01 [15] og IFM99-06 [16].
Figur 1 beskriver opbygningen af netværksmetaanalysen.



Figur 1. Netværk af evidens for OS og PFS mellem studierne anvendt i analysen
D: daratumumab, V: bortezomib, M: melphalan, P: prednison, T: thalidomid, R: lenalidomid, d: dexamethason, cont.: kontinuerligt frem til progression

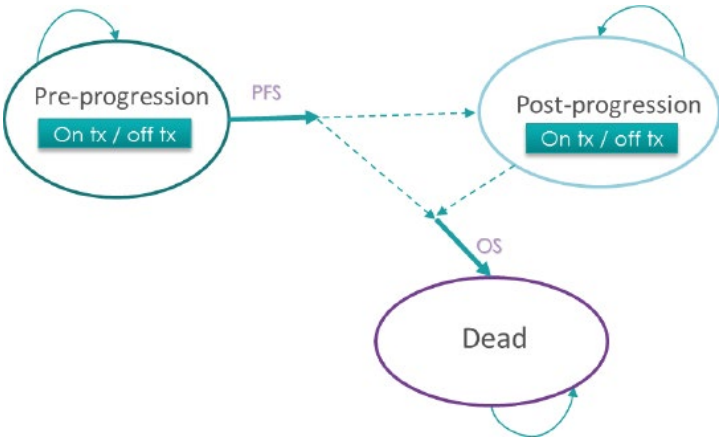
Ansøger inkluderer efterfølgende behandlingslinjer for knoglemarvskræft i modellen.

2.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival model* der inddeler patientkohorten i stadier. Tiden, patienten er progressionsfri (PFS), defineres i modellen ud fra PFS-data fra kliniske studier, som ekstrapoleres. Alle patienter starter i PFS-stadiet og bevæger sig videre til

progressionsstadie (post-progression i figur 2) eller stadiet død. Tiden frem til stadiet død estimeres ud fra overlevelsesdata (OS). Tiden, hvor patienter befinder sig i progressionsstadiet indtil død, er defineret ud fra PFS og OS. Se Figur 2 for modelstrukturen.

For at estimere behandlingslængden for DaraBorMelPred anvender ansøger tid til behandlingsstop (TTTD) data fra studiet, aflæst fra Kaplan-Meier-kurver. For at estimere behandlingslængden for komparatorerne, som ikke har fast behandlingslængde, anvender ansøger medianværdier for TTTD fra studierne med eksponentiel funktion. Dette gøres for at få et estimat for den samlede studiepopulation, dvs. også den andel, der ikke har opnået medianen.



Figur 2: Ansøgers figur af modelstrukturen i omkostningsanalysen.
Pre-progression svarer til PFS-stadiet, post-progression svarer til progressionsstadiet. I begge stadier kan man være i behandling (on tx) eller ikke i behandling (off tx).

Statistiske overvejelser for ekstrapoleringer

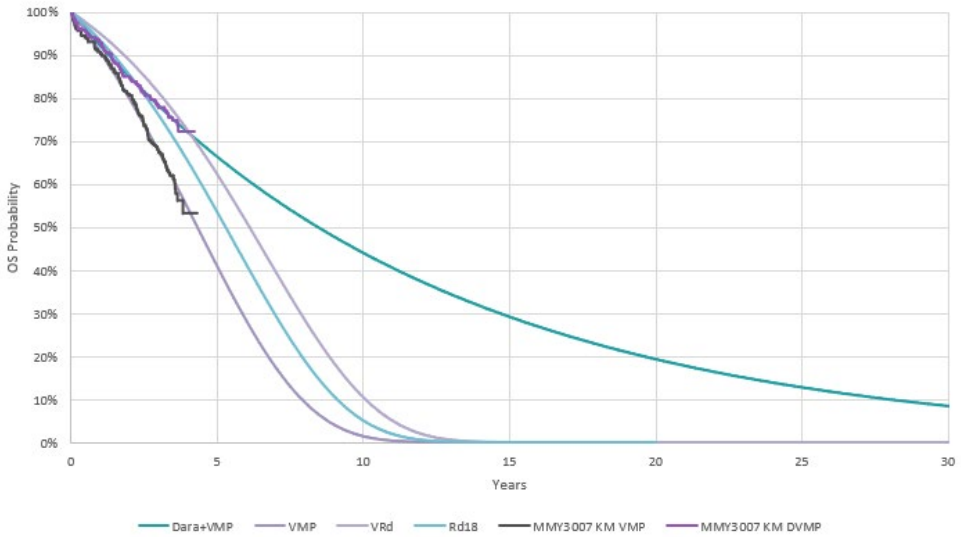
Ansøger har testet Kaplan-Meier (KM)-kurverne for PFS og OS for proportional hazard (PH) mellem DaraBorMelPred og BorMelPred. Antagelsen vurderes ikke at være opfyldt, og derfor vælges individuelle parametriske funktioner til at fremskrive effektkurverne for DaraBorMelPred og BorMelPred i modellen. Ansøger har ekstrapoleret KM-kurverne i studiet og testet alle parametriske kurvers fit på studiedata, hvorefter den parametriske funktion med bedste statistiske fit og klinisk validitet er valgt. Der er for OS valgt eksponentiel funktion for DaraBorMelPred og Gombertz-funktion for BorMelPred. Der er for PFS valgt Weibull-funktion for DaraBorMelPred og eksponentiel funktion for BorMelPred. Ansøger vælger ligeledes at anvende KM-data til og med uge 58, hvorefter ansøger har ekstrapoleret med de parametriske funktioner.

For de øvrige komparatorer anvender ansøger hazard ratios (HR) for BorMelPred baseret på netværksmetaanalysen som reference for hhv. BorLenDex og LenDex. Dette gøres for både OS og PFS. Se Tabel 2 for HR for OS og PFS mellem behandlingerne sammenlignet med BorMelPred, samt medianværdier og kilder. Se Figur 3 og 4 for ekstrapolerede kurver for PFS og OS .

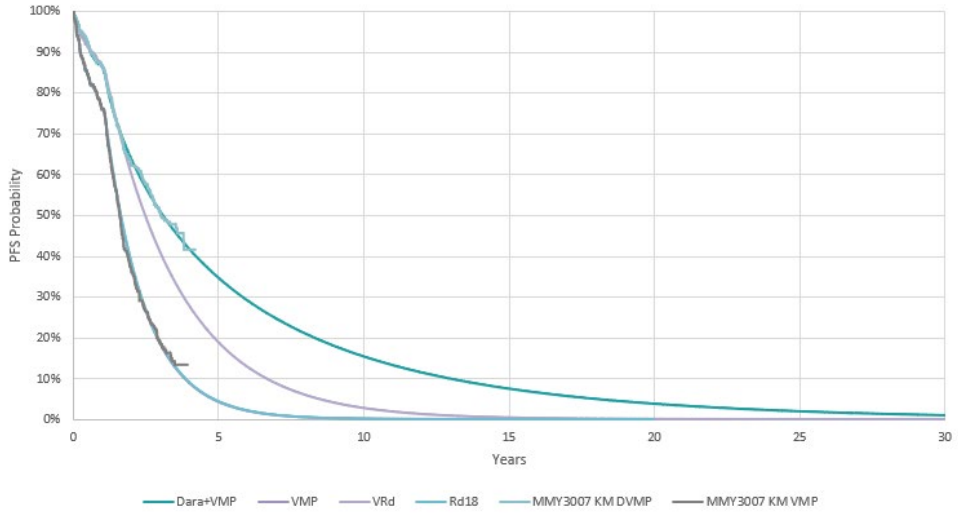
Tabel 2: 1.-linjebehandling medianer og HR-værdier for PFS og OS

Behandling	Median PFS			Median OS		
	Måne-der	HR	Kilde	Måneder	HR	Kilde
DaraBor-MelPred	35,5	0,42	NMA*	68,6	0,60	NMA*
BorLenDex	29,7	0,53	NMA*	72,9	0,53	NMA*
LenDex18	14,5	0,99	NMA*	63,4	0,70	NMA*
BorMelPred	19,6	-	ALCYONE	55,5	-	ALCYONE

**Ansøgers egen netværksmetaanalyse, 2020*

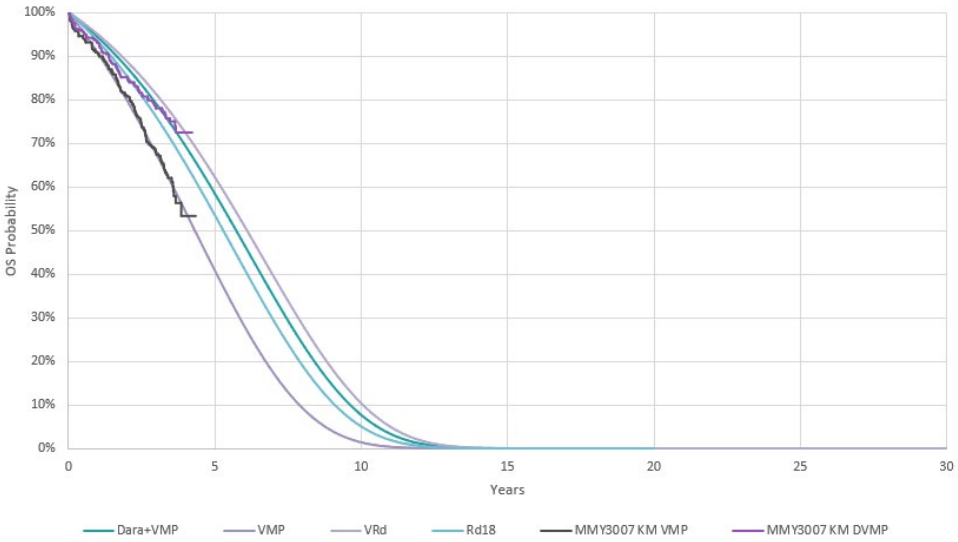


Figur 3: Ekstrapolerede OS-kurver for alle behandlingsregimer 1. linje

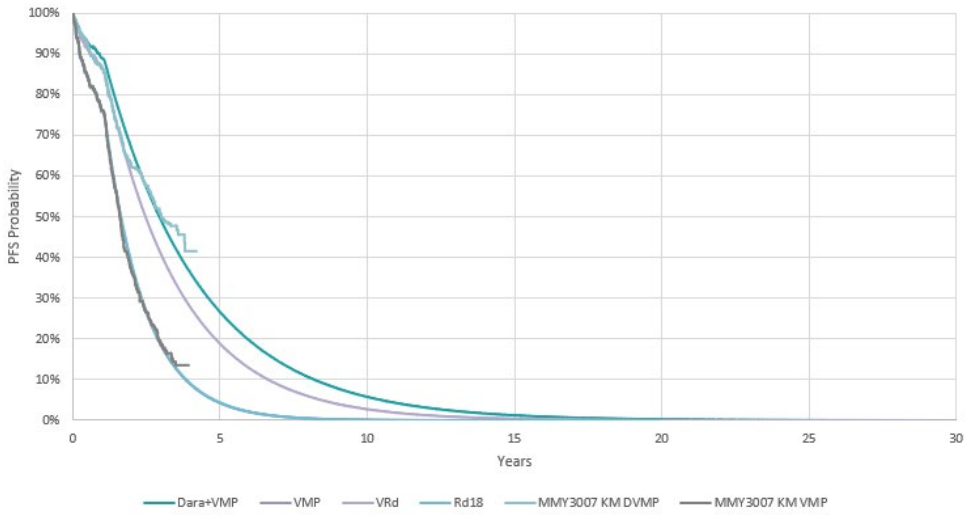


Figur 4: Ekstrapolerede PFS-kurver for alle behandlingsregimer 1. linje
**ikke muligt at se VMP, da kurven fra Rd18 dækker. V: bortezomib, M: melphalan, P: prednison*

Ansøger har tilføjet muligheden for, at HR for BorMelPred anvendes som reference for OS- og PFS-kurverne for DaraBorMelPred. Se Figur 5 og Figur 6 for ekstrapolering af OS og PFS baseret på denne metode.



Figur 5: Ekstrapolerede OS-kurver for alle behandlingsregimer 1. linje baseret på HR sammenlignet med BorMelPred

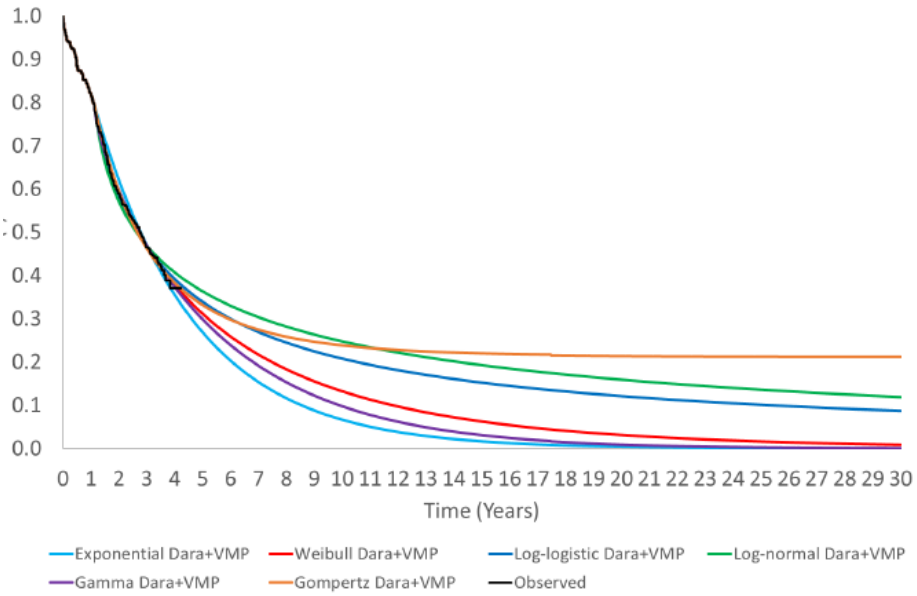


Figur 6: Ekstrapolerede PFS-kurver for alle behandlingsregimer 1. linje baseret på HR sammenligning med BorMelPred
*ikke muligt at se VMP-kurven, da kurven fra Rd18 dækker

For DaraBorMelPred er der for ekstrapolerede TTTD valgt Weibull-funktionen som bedste fit, hvor ansøger har tilføjet ekstrapolationsfunktionen til KM-data fra uge 58. Da BorMelPred gives i en afgrænset periode, antages det, at behandlingen stoppes efter det maksimale antal doser defineret i SPC'et. For de øvrige komparatorer anvender ansøger eksponentielfunktionen på medianværdier. Se Tabel 3 for mediane behandlingslænger og Figur 7 for ekstrapolerede TTTD af DaraBorMelPred.

Tabel 3: 1.-linjebehandlingslængder baseret på medianværdier for TTTD (tid til behandlingsstop) fra studierne

Behandling	Medianbehandlingslængder [Måneder]	Kilde
DaraBorMelPred	33	ALCYONE
BorMelPred	12	ALCYONE
BorLenDex	23,4	Durie et al. 2018 [12]
LenDex18	16,6	Facon et al. 2018 [13]



Figur 7: Ekstrapolerede TTTD for DaraBorMelPred 1. linje. Y-aksen angiver andel, der er stoppet i behandling.

2. linjebehandling

Da der ikke er studiedata specifikt for 2.-linjebehandling efter de forskellige 1.-linjebehandlinger, estimerer ansøger PFS for 2.-linjebehandling ved eksponentiel ekstrapolering på medianværdier baseret på ansøgers netværksmetaanalyse af data fra studierne CASTOR[17] og POLLUX[18] (DaraBorDex vs. BorDex og DaraLenDex vs. LenDex). Se Tabel 4 for medianværdier for PFS og kilder.

Tabel 4: 2.-linjebehandlingslængder baseret på medianværdier for PFS og TTTD

Behandling	Median-TTTD		Median PFS		
	Måneder	Kilde	Måneder	HR	Kilde
DaraLenDex	34	ALCYONE	37,7	0,44	POLLUX (vs. LenDex)
DaraBorDex	13,3	ALCYONE	24,1	0,32	ASPIRE (vs. BorDex)
CarDex	9,2	ENDEAVOR (9)	14,5	0,53	ASPIRE (vs. BorDex)
CarLenDex	20,2	ASPIRE(28)	24,1	0,69	POLLUX (vs. LenDex)
EloLenDex	17	ELOQUENT-2 (31)	23,4	0,71	POLLUX (vs. LenDex)

Behandling	Median-TTTD		Median PFS		
	Måneder	Kilde	Måneder	HR	Kilde
IxaLenDex	15,6	TOURMALINE (32)	22,3	0,75	NMA ASCO 2017(vs. LenDex)
PomBorDex	8,8	OPTIMISMM (33)	11,2	0,61	OPTIMISMM
PomDex	4,2	Dimopoulus et al. 2013 (34)	12,1	1,38	NMA ASCO 2017 (vs. LenDex)
LenDex	15,9	POLLUX	16,6	1,0	ASPIRE

Ansøger estimerer behandlingslængder i 2. linje ved at tilføje eksponentiel kurve på TTTD-medianværdier fra studier, se tidligere Tabel 4.

Ansøger har anvendt en konstant mortalitetsrate i PFS-stadiet i 2.-linjebehandling estimeret fra ALCYONE-studiet [11], hvor mortalitetsraten for DaraBorMelPred er anvendt for DaraBorMelPred-armen og mortalitetsraten for BorMelPred er anvendt for komparatorarmene.

3. linjebehandling

For 3.-linjebehandling har ansøger anvendt en medianbehandlingslængde på 9 måneder for alle kombinationsbehandlinger, baseret på studiet Kumar et al. [20].

Sekretariatets vurdering

Fagudvalget vurderer, at de ekstrapolerede kurver for DaraBorMelPred, baseret på studiedata, giver urealistisk høje OS- og PFS-værdier. Fagudvalget har vurderet, at metoden, hvor ekstrapolationen er estimeret med HR for BorMelPred som reference, giver et mere klinisk plausibelt billede. Sekretariatet anvender derfor denne metode.

Fagudvalget har vurderet, at PFS-værdier fra studierne er bedre estimater for behandlingslængderne end TTTD, som ansøger har anvendt. Sekretariatet anvender i hovedanalysen derfor PFS som estimat for behandlingslængde både i 1. linje og 2. linje.

Der er stor usikkerhed forbundet med efterfølgende behandlinger, da behandlingsforløbene i studierne ikke svarer til dansk klinisk praksis. Fagudvalget vurderer, at der er stor usikkerhed ved de ekstrapolerede data og efterfølgende behandlingsregimer, da disse er svære at estimere på grund af individuelt tilpassede behandlingsregimer. Betydning af ekskludering af efterfølgende behandlingslinjer vises i en følsomhedsanalyse.

Ansøger har både indleveret en sammenligning med LenDex18 (LenDex givet i 18 cyklusser) og LenDex (LenDex givet til progression). Protokollen efterspørger kun LenDex18, og kun denne sammenligning vil blive vist.

Sekretariatet ændrer metoden for ekstrapolering af OS og PFS for DaraBorMelPred til at være baseret på HR-værdier med reference til BorMelPred.

Sekretariatet anvender PFS som estimat for behandlingslængde.

2.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv i overensstemmelse med Medicinrådets anvisninger. Analysen har en tidshorisont på ti år. Ansøger argumenterer for, at tidshorisonten er passende, da patienterne oftest har gennemgået tre behandlingslinjer efter ti år. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %, jf. Medicinrådets metodehåndbog.

Sekretariatets vurdering

Baseret på de ekstrapolerede OS-data, som fagudvalget har fundet mest sandsynlige, ses at få patienter stadig er i live mellem 10 år og 15 år. Sekretariatet mener derfor, at 15 år er den nødvendige tidshorisont for analysen, for at den kan afspejle alle forskelle i omkostninger. En tidshorisont på 15 år vil være lang nok til at inkludere behandlingsomkostninger for tre behandlingsregimer, patienternes alder og forventede levetid taget i betragtning. Sekretariatet medtager ansøgers analyse med en tidshorisont på 10 år i en følsomhedsanalyse for at vise betydningen af tidshorisonten.

Sekretariatet ændrer tidshorisonten til 15 år, så alle patienter er døde i modellen.

2.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den økonomiske analyse af DaraBorMelPred sammenlignet med BorLenDex, BorMelPred og LenDex18. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger og patientomkostninger. Ansøgers estimering af lægemiddelomkostninger bygger altid på AIP, hvilket sekretariatet udskifter med SAIP i den endelige afrapportering.

2.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive produkters produktresuméer (SPC'er). Ansøger anvender en gennemsnitsvægt på 73,4 kg og et gennemsnitligt overfladeareal på 1,84 m^2 baseret på *Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft*. Se Tabel 5 for lægemiddelpriser.

Behandlingen DaraBorMel gives i serier a seks uger, som i det følgende:

- *Daratumumab* (som en af følgende)
  - 16 mg pr. kg intravensøst (i.v.) ugentlig i serie 1, hver tredje uge i serie 2-9 og herefter hver fjerde uge frem til progression
  - 1.800 mg subkutant (s.c.) ugentlig i serie 1, hver tredje i serie 2-9 og herefter hver fjerde uge frem til progression
- *Bortezomib* 1,3 mg pr. m^2 s.c. 2 gange ugentlig i uge 1, 2, 4 og 5 i serie 1 og én gang ugentlig i uge 1, 2, 4 og 5 i serie 2-9
- *Melphalan* 9 mg pr. m^2 peroralt (p.o.) på dag 1-4 i serie 1-9
- *Prednison* 60 mg pr. m^2 p.o. på dag 1-4 i serie 1-9
- *Dexamethason* 20 mg p.o. eller i.v. ugentlig i serie 1, hver tredje uge i serie 2-9 og herefter hver fjerde uge frem til progression

Behandlingen BorLenDex gives i otte serier a 21 dage, som i det følgende:

- *Lenalidomid* 25 mg p.o. på dag 1-14
- *Bortezomib* 1,3 mg pr. m^2 s.c. på dag 1, 4, 8 og 11
- Dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11 og 12

Dernæst serier a 28 dage indtil progression:

- *Lenalidomid* 25 mg p.o. på dag 1-21
- *Dexamethason* 40 mg p.o. på dag 1, 8, 15 og 22

LenDex gives i 18 serier af 28 dages varighed som i det følgende:

- Lenalidomid: 25 mg p.o. på dag 1-21
- Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22.

BorMelPred gives i 9 serier a 35 dages varighed som i det følgende:

- Bortezomib 1,3 mg pr. m^2 s.c. på dag 1, 8, 15 og 22
- Melphalan 9 mg pr. m^2 p.o. på dag 1-4
- *Prednison* 100 mg pr. m^2 p.o. på dag 1-4

Tabel 5: Anvendte lægemiddelpriser, SAIP, februar 2020

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Daratumumab	20 mg/ml	5 ml	[redacted]	Amgros
	20 mg/ml	20 ml	[redacted]	
	1.800 mg	1 stk.	[redacted]	
Bortezomib	3,5 mg	1 htgl.	[redacted]	Amgros

Melphalan	2 mg	25 stk.	[redacted]	Amgros
Prednison	5 mg	100 stk.	[redacted]	Amgros
	25 mg	100 stk.	[redacted]	
Lenalidomid	25 mg	21 stk.	[redacted]	Amgros
	20 mg	21 stk.	[redacted]	
Dexamethason	1 mg	100 stk.	[redacted]	Amgros
	4 mg	20 stk.	[redacted]	

Ansøger anvender den relative dosisintensitet fra studierne ALCYONE (DaraBorMelPred og BorMelPred), Usmani et al. (LenDex18) og SWOG S0777 (BorLenDex). Ansøger inkluderer ikke spild i analysen, da de argumenterer for, at deling af hætteglas er dansk klinisk praksis.

Ansøger anvender cyklusser på 42 dage for BorMelPred samt 8 administrationer i cyklus et for bortezomib.

Sekretariatets vurdering

Daratumumab har pr. 7. juli 2020 fået EMA-godkendelse til subkutant brug. Ansøger har kun indsendt en model, der inkluderer intravenøs behandling med daratumumab. [redacted]

Den antagede relative dosisintensitet for lenalidomid er 82,46 %. Fagudvalget har vurderet, at denne er høj. Sekretariatet ændrer denne til 70 %.

Fagudvalget vurderer ligeledes, at mange patienter med lenalidomid vil få dosis justeret. Sekretariatet udarbejder en følsomhedsanalyse, hvor dosis er 20 mg i stedet for 25 mg.

Sekretariatet accepterer ansøgers antagelser for lægemiddelomkostninger, men ændrer cykluslængden til 35 dage og til 4 administrationer i cyklus et for BorMelPred.
Sekretariatet ændrer den relative dosis intensitet til 70 % for lenalidomid.
Sekretariatet tilføjer en følsomhedsanalyse, hvor daratumumab gives subkutant til alle patienter.
Sekretariatet tilføjer en følsomhedsanalyse, hvor lenalidomid gives som 20 mg.

2.2.2 Hospitalsomkostninger

Ansøger har opdelt monitoreringsomkostninger ud fra, om patienten befinder sig i PFS-stadie eller PD-stadie, samt hvilken behandling patienten får. I PFS-stadiet er hospitalsomkostninger forbundet med administration af lægemidlerne og det antal administrationer, patienten får ved behandling med lægemidlerne inden for de forskellige behandlingsregimer. Follow-up-omkostninger ved behandling er antaget at ske på de tider, patienten får administration. Administrationsomkostningerne er opgjort ved hjælp af DRG-taksten 17MA98 MDC17 2020 for både subkutan og intravenøs behandling. Ansøger anvender samme takst til et follow-up-besøg for de lægemidler, hvor administration ikke sker på hospitalet. For DaraBorMelPred antages ikke et follow-up-besøg, da follow-up antages at ske samtidig med administration. Se Tabel 6 og
Tabel 7 for frekvensen af follow-up-besøg for PFS og PPS.

Tabel 6: Hospitalsomkostninger per monitorering og administration

Behandling	Enhedsomkostning pr. besøg [DKK]	Takst	Kilde
DaraBorMelPred BorLenDex BorMelPred LenDex18	3.235	17MA98 MC17	Ambulante DRG-takser 2020

Tabel 7: Frekvens af monitorering og administration pr. måned, i PFS-stadiet og PPS-stadiet

	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex
PFS: Hæmatologisk follow-up	0	0,69	0,69	0,69
PPS: Hæmatologisk follow-up	0,92	0,92	0,92	0,92

Ansøger inkluderer præmedicin (profylaktisk medicin) til de lægemidler, som kræver det og antager, at alle patienter modtager præmedicin ved behandling med disse lægemidler, se Tabel 8.

Tabel 8: Præmedicin for specifikke lægemidler

Behandling	Præ-medicin
Daratumumab	Sodium chlorid 9 mg/ml

Behandling	Præ-medicin
	Methylprednisolon 100 mg Paracetamol 650 mg til 1.000 mg Diphenhydramin 25 mg til 50 mg
Lenalidomid	Antitrombotisk medicin
Bortezomib	Sodium chlorid 9 mg/ml Antiviral profylaksis

Ansøger pålægger desuden en terminalomkostning på 2.685 DKK baseret på DRG-taksten 15MP02 2020 ved patienter, der dør under PFS- eller PD-stadiet. Ansøger vurderer, at dette er et lavt estimat og har udarbejdet en følsomhedsanalyse med et højere et estimat for disse omkostninger.

Sekretariatets vurdering

Der er stor usikkerhed omkring det præcise estimat for forskellen i ressourceomkostningerne mellem subkutan og intravenøs administration. Det er på baggrund af dialog med fagudvalget vurderet, at lægemidler administreret intravenøst er mere ressourcekrævende end subkutan behandling. DRG-taksten for administration er ens mellem subkutan og intravenøs behandling. Der er ikke foretaget en følsomhedsanalyse for forskellen mellem subkutan og intravenøs administration. Den præcise betydning for udskiftning af subkutan daratumumab er derfor ikke belyst. Omkostninger sammenlignet med behandlingsregimerne i 1.-linjebehandling vil formentlig være lavere for DaraBorMelPred, hvis der anvendes subkutan administration, men eftersom daratumumab benyttes i flere efterfølgende behandlingslinjer, der ligeledes er inkluderet i analysen, er betydningen for resultatet ikke belyst.

Sekretariatet accepterer ansøgers tilgang.

2.2.3 Bivirkningsomkostninger

Ansøger har inkluderet omkostninger for bivirkninger højere end grad 3, og som forekommer hos mere end 5 % af patienterne. Ansøger inkluderer kun forskel i omkostninger til bivirkninger for 1.-linjebehandling for at simplificere modellen, og fordi patientpopulationerne er forskellige i mange af studierne.

Ansøger antager, at patienterne kan behandles samme dag. Derfor anvender ansøger DRG-taksten 17MA98 MDC17 på 3.285 DKK. Se Tabel 9 for bivirkningsfrekvenserne.

Tabel 9: Kumulative sandsynligheder for bivirkninger mellem behandlingerne, %

	DaraBor-MelPred	BorMelPred	LenDex18	Bor-LenDex	LenDex
Stigning i alanin aminotransferase	0 %	0 %	0 %	5 %	0 %
Anæmi	17,3 %	19,8 %	15,7 %	12,2 %	18,2 %
Asteni	0 %	0 %	6,1 %	0 %	7,7 %
Ryg smerter	0 %	0 %	6,3 %	0 %	7,0 %
Hjertefejl	0 %	0 %	7,2 %	0 %	11,8 %
Katarakt	0 %	0 %	0 %	0 %	5,8 %
Dyb venetrombose eller lungeemboli	0 %	0 %	5,6 %	0 %	7,9 %
Dehydrering	0 %	0 %	0 %	8,4 %	0 %
Diarré	0 %	0 %	0 %	9,2 %	0 %
Dyspnæ	0 %	0 %	0 %	6,1 %	5,6 %
Embolisme	0 %	0 %	0 %	6,9 %	0 %
Træthed	0 %	0 %	8,5 %	14,5 %	7,3 %
Hyperglycæmi	0 %	0 %	0 %	7,3 %	5,3 %
Hypertension	5 %	0 %	0 %	0 %	0 %
Hypokalsemi	0 %	0 %	0 %	6,5 %	0 %
Hypokalemi	0 %	0 %	0 %	11,5 %	6,6 %
Hypoatremi	0 %	0 %	0 %	6,5 %	0 %
Hypotension	0 %	0 %	0 %	7,6 %	0 %

	DaraBor-MelPred	BorMelPred	LenDex18	Bor-LenDex	LenDex
Infektion	0 %	0 %	21,9 %	0 %	28,9 %
Leukocytopeni	8,1 %	8,5 %	5,6 %	8,8 %	0 %
Lunge infektion	0 %	0 %	0 %	7,3 %	0 %
Lymfopeni	7,8 %	6,2 %	0 %	18,7 %	5,6 %
Muskeltræthed	0 %	0 %	0 %	8,4 %	0 %
Neutropenia	40,2 %	39,0 %	26,5 %	9,9 %	27,8 %
Periferal motor neutropati	0 %	0 %	0 %	6,5 %	0 %
Periferal sensorisk neuropati	0 %	0 %	0 %	20,6 %	0 %
Lungebetændelse	13 %	4,2 %	8,3 %	0 %	8,1 %
Udslæt	0 %	0 %	5,2 %	0 %	6,2 %
Synkope	0 %	0 %	0 %	8,8 %	0 %
Trombocytopeni	34,7 %	37,9 %	8 %	17,2 %	8,3 %
Kilde	ALCYONE	ALCYONE	FIRST	SWOG S0777	FIRST

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang.

2.2.4 Omkostninger til efterfølgende behandling

Ansøger inkluderer omkostninger til efterfølgende behandlinger. Der er inkluderet læge-middelomkostninger, administrationsomkostninger og monitorering. Ansøger har lavet en følsomhedsanalyse, hvor omkostninger til efterfølgende behandlinger ekskluderes.

Ansøger antager, at 88,9 % af patienterne vil modtage 2.-linjebehandling. Derudover antager de, at yderligere 62,5 % af disse patienter vil modtage 3.-linjebehandling.

Ud fra nuværende rekommandationer antager ansøger at:

- Patienter, der modtager DaraBorMedPred i 1. linje, vil modtage en lenalidomidholdig behandling (EloLenDex og CarLenDex) i 2. linje, dog vil få modtage PomBorDex eller CarDex.

- For patienter, der behandles med BorMelPred i 1. linje, vil størstedelen behandles med DaraLenDex i 2. linje, få vil blive behandlet med regimerne DaraBorDex, CarLenDex og EloLenDex. Derudover vil nogle patienter modtage LenDex.

- For patienter behandlet med BorLenDex i 1. linje vil størstedelen i 2. linje modtage DaraLenDex, mens nogle få vil modtage DaraBorDex, CarDex eller PomBorDex.

- For patienter, der modtager LenDex18 i 1. linje, vil størstedelen modtage DaraLenDex i 2. linje. Nogle vil modtage DaraBorDex, og få vil modtage CarDex eller PomBorDex.

Ansøger antager, at patienter i 3.-linjebehandling behandles med CarDex, PomDex eller PomBorDex. For simplificering antages lige fordeling (33,3 % hver) mellem disse regimer, da det ikke kan spores, hvilke tidligere behandlingsregimer patienterne har fået.

Jf. afsnit 2.1 anvendes ekstrapolerede medianværdier for behandlingslængden i 2.-linjebehandling. For PFS anvendes HR-reference værdier fra netværksmetaanalyserne. Se Tabel 10 for anvendte medianværdier for behandlingslængde og kilderne, se Tabel 4 for PFS og HR-værdier for 2.-linjebehandling.

Tabel 10: 2.-linjebehandlingslængder baseret på medianværdier

Behandling	Medianbehandlingslængder [Måneder]	Kilde
DaraLenDex	34	POLLUX [18]
DaraBorDex	13,3	CASTOR [17]
CarDex	9,2	ENDEAVOR[21]
CarLenDex	20,2	ASPIRE [19]
EloLenDex	17,0	ELOQUENT-2[22]
IxaLenDex	15,6	TOURMALINE[23]
PomBorDex	8,8	OPTIMISMM [24]
PomDex	4,2	Dimopoulus et al.[25]

Behandling	Medianbehandlingslængder [Måneder]	Kilde
LenDex	15,9	POLLUX [18]

Se **Tabel 11** for ansøgers fordeling af 2.-linjebehandling på de forskellige lægemiddelkombinationer. I følsomhedsanalysen, hvor LenDex i 1. linje anvendes frem til progression, vil færre modtage DaraLenDex (50 %) i 2.-linjebehandling, og flere (40 %) vil modtage DaraBorDex.

Tabel 11: Fordelingen af efterfølgende behandlingsregimer

2.-linjebehandling	1.-linjebehandling			
	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex
DaraLenDex	0 %	80 %	70 %	40 %
DaraBorDex	0 %	5 %	20 %	40 %
CarDex	15 %	0 %	5 %	10 %
CarLenDex	15 %	5 %	0 %	0 %
EloLenDex	45 %	5 %	0 %	0 %
LenDex	10 %	5 %	0 %	0 %
PomBorDex	15 %	0 %	5 %	10 %

I **Tabel 12** ses dosis og lægemiddelpriser for efterfølgende behandling.

Tabel 12: Anvendte lægemiddelpriser, SAIP, februar 2020

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Elotuzumab	300 mg	1 stk.	[redacted]	Amgros
	400 mg	1 stk.	[redacted]	
Pomalidomid	1 mg	21 stk.	[redacted]	Amgros
	2 mg	21 stk.	[redacted]	

	3 mg	21 stk.	[redacted]	
	4 mg	21 stk.	[redacted]	
Carfilzomib	10 mg	1 stk.	[redacted]	Amgros
	30 mg	1 stk.	[redacted]	
	60 mg	1 stk.	[redacted]	
Ixazomib	2,3 mg	3 stk.	[redacted]	Amgros
	3 mg	3 stk.	[redacted]	
	4 mg	3 stk.	[redacted]	
Panobinostat	10 mg	6 stk.	[redacted]	Amgros
	15 mg	6 stk.	[redacted]	
	20 mg	6 stk.	[redacted]	
Thaladomid	50 mg	28 stk.	[redacted]	Amgros
Cyclophosphamid	50 mg	100 stk.	[redacted]	Amgros

Sekretariatets vurdering

Sekretariatet har efter dialog med fagudvalget vurderet, at den efterfølgende behandling, som er valgt i analysen, ikke afspejler den kliniske praksis i Danmark, hvor patienterne overvejende vil modtage behandlinger, de ikke har modtaget tidligere.

Tabel 13: Fagudvalgets vurdering af fordelingen af efterfølgende 2.-linjebehandlingsregimer

2.-linjebehandling	1.-linjebehandling			
	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex
DaraLenDex	0 %	80 %	60 %	0 %
DaraBorDex	0 %	0 %	30 %	65 %
CarDex	0 %	0 %	0 %	25 %

2.-linjebehandling	1.-linjebehandling			
	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex
CarLenDex	40 %	10 %	0 %	0 %
EloLenDex	40 %	5 %	0 %	0 %
LenDex	10 %	5 %	10 %	0 %
PomBorDex	0 %	0 %	0 %	10 %
IxaLenDex	10 %	0 %	0 %	0 %

Fagudvalget vurderer desuden en anderledes fordeling af 3.-linjebehandling.

Tabel 14: Fagudvalgets vurdering af fordelingen af efterfølgende 3.-linjebehandlingsregimer

3.-linjebehandling	1.-linjebehandling			
	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex
CarDex	30 %	50 %	60 %	40 %
PomDex	60 %	40 %	20 %	50 %
PomBorDex	10 %	10 %	20 %	10 %

Sekretariatet accepterer ansøgers antagelser om inkludering af efterfølgende behandlingslinjer, men der er stor usikkerhed omkring efterfølgende behandling. Sekretariatet ændrer i hovedanalysen estimaterne for efterfølgende behandling til fagudvalgets estimater og udarbejder en følsomhedsanalyse uden efterfølgende behandling.

2.2.5 Patientomkostninger

Patientomkostninger er omkostninger forbundet med den tid, patienterne bruger til at komme til ambulante besøg, og den tid de bruger på administration af lægemidlerne på hospitalet. Ansøger inkluderer patientomkostninger i 1.- og 2.-linjebehandling. Patientomkostninger er estimeret på baggrund af ansøgers antagelser samt EPAR'en for de forskellige lægemidler. Ansøger anvender omkostninger på 100 kr. for transport og 179 kr. for patientomkostning pr. time, baseret på Medicinrådets værdisætning af enhedsomkostninger. Ansøger antager, at hæmatologiske opfølgningsbesøg foretages samtidig med administrering af lægemidler i de tilfælde, administrationen foregår på hospitalet. Se Tabel 15 for opfølgningsbesøg, ventetid og administrationstid.

Tabel 15: Patienttid pr. besøg, relateret til opfølgning, ventetid og administration af forskellige regimer

Administrationstype	Tid		Reference
Hæmatologisk follow-up	90 min.		Ansøgers antagelse
Ventetid på hospital	30 min.		Ansøgers antagelse
DaraBorMelPred og andre bortezomib holdige regimer (BorLenDex, BorMelPred, PomBorDex)			
Administration af daratumumab	Uge 1-2: 360 min	Fra uge 3: 180 min.	EPAR + ansøgers antagelse
Administration af daratumumab + bortezomib	Uge 1-2: 375 min.	Fra uge 3: 195	EPAR + ansøgers antagelse
Administration af bortezomib s.c. (inkl. alle bortezomibholdige regimer)	15 min.		EPAR + antagelse at bortezomib administreres på 15 min.
Andre regimer			
EloLenDex (administration af elotuzumab)	60 min.		EPAR + ansøgers antagelse
CarLenDex: administration af carfilzomib	30 min.		EPAR + ansøgers antagelse
CarDex: administration af carfilzomib	60 min.		EPAR + ansøgers antagelse

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang.

2.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i hovedanalysen. Ansøger har udarbejdet en række følsomhedsanalyser, hvor betydningen af ændringer i de forskellige antagelser, som indgår i hovedanalysen, undersøges. Følgende følsomhedsanalyser er udført:

- *Udvidelse af modellens tidshorisont til 15 år*
- *Udvidelse af modellens tidshorisont til 20 år*

- *Patienternes vægt justeres med -/+ 5 %*
- *2.-linjebehandling fortsættes til progression*
- *Terminalomkostning ændres til 13.134 DKK (DRG-takst 2019) (ændret fra 2.685 DKK DRG-takst 2020)*
- *Ekskludering af præmedicinering*
- *For DaraBorMelPred anvendes for OS ekstrapolering funktionerne Gamma og Weibull*
- *For DaraBorMelPred og BorMelPred anvendes for OS ekstrapolering Gamma-funktionen*
- *Konstant ratio af død i 2. linje PFS (mellem død og PFS baseret på ALCYONE) på 19,32 % for DaraBorMelPred-armen og 13,21 % for komparatorer*
- *Spild indgår i analysen*
- *For DaraBorMelPred og BorMelPred anvendes for OS ekstrapolering Gamma-funktionen og tidshorisont på 15 år*

Sekretariatets vurdering

Sekretariatet mener, at ansøgers følsomhedsanalyser er relevante og præsenterer følgende:

- *Patienternes vægt justeres med -/+ 5 %*
- *Terminalomkostning ændres til 13.134 DKK (DRG-takst 2019)*
- *Ekskludering af præmedicinering*
- *DaraBorMelPred som referencekurve*
- *Konstant ratio af død i 2. linje PFS (mellem død og PFS baseret på ALCYONE) på 19,32 % for DaraBorMelPred-armen og 13,21 % for komparatorer*

Sekretariatet mener, at usikkerheden ved efterfølgende behandlinger bør undersøges og udfører derfor en følsomhedsanalyse, hvor efterfølgende behandlinger er ekskluderet. Sekretariatet udfører ligeledes en følsomhedsanalyse, hvor daratumumab gives subkutant til alle patienter, og en følsomhedsanalyse hvor dosis af lenalidomid er reduceret til 20 mg.

Tabel 16: Begrundelse for følsomhedsanalyser

Følsomhedsanalyse	Basisantagelse	Sekretariatet
Ekskludering af efterfølgende behandling	Inklusive efterfølgende behandling	Efterfølgende behandling er usikker, og for at vise de inkrementelle omkostninger kun er forbundet med de behandlingsregimer, der vurderes i vurderingsrapporten, vises en følsomhedsanalyse
Subkutan administration af daratumumab	I.v.-administration af daratumumab	Da daratumumab har fået EMA-godkendt subkutan behandling, og denne administrationsform forventes at blive anvendt i dansk klinisk praksis, vises en

Følsomhedsanalyse	Basisantagelse	Sekretariatet
		analyse, [redacted] Det er ikke muligt at illustrere betydningen af ressourceomkostninger.
Lenalidomid dosering 20 mg	Lenalidomid 25 mg	Der er usikkerhed omkring reducering af dosis, og fagudvalget har vurderet, at der vil blive anvendt en lavere dosis. Betydningen af dette vises i en følsomhedsanalyse.
Tidshorisont på 10 år	Tidshorisont på 15 år	Ansøger har indsendt en analyse med tidshorisont på 10 år. Sekretariatet viser betydningen af en kortere tidshorisont ved at anvende 10 år som tidshorisont i en følsomhedsanalyse.

2.4 Opsummering af basisantagelser

I Tabel 17 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 17: Basisantagelser for ansøgers og sekretariatets hovedanalyse

Basisantagelser		Ansøger	Sekretariatet
Komparator		BorMelPred BorLenDex LenDex18	BorMelPred BorLenDex LenDex18
Modeltype		Partitioned survival model	Partitioned survival model
Tidshorisont		10 år	15 år
Diskonteringsrate		4 %	4 %
Inkluderede omkostninger		Lægemiddelomkostning Hospitalsomkostning Bivirkningsomkostninger Patientomkostning Efterfølgende behandling	Lægemiddelomkostning Hospitalsomkostning Bivirkningsomkostninger Patientomkostning Efterfølgende behandling (ændring i fordeling)
OS	DaraBorMelPred	Eksponentiel funktion	HR vs. BorMelPred fra NMA
	BorMelPred	Gombertz	Gombertz
	BorLenDex	HR vs. BorMelPred fra NMA	HR vs. BorMelPred fra NMA
	LenDex18	HR vs. BorMelPred fra NMA	HR vs. BorMelPred fra NMA
PFS	DaraBorMelPred	KM fra ALCYONE og Weibull-funktion fra uge 58	HR vs. BorMelPred fra NMA
	BorMelPred	KM fra ALCYONE – Eksponentiel funktion fra uge 58	KM fra ALCYONE – Eksponentiel funktion fra uge 58
	BorLenDex	HR vs. BorMelPred fra NMA	HR vs. BorMelPred fra NMA

Basisantagelser		Ansøger	Sekretariatet
LenDex18		HR vs. BorMelPred fra NMA	HR vs. BorMelPred fra NMA
Behandlings-længde 1. linje	DaraBor-MelPred	KM fra ALCYONE og Wei-bull-funktion fra uge 58	PFS
	BorMelPred	Fast 12 måneder	Fast 12 måneder
	BorLenDex	Median 23,4 måneder	PFS
	LenDex18	Median 16,6 måneder	PFS
Behandlingslængde 2. linje		Median behandlingslængde x måneder baseret på studier, ekstrapoleret med eksponentiel funktion	Behandlingslængde baseret på PFS
Behandlingslængde 3. linje		Median 9 måneder (baseret på Kumar et al.)	Median 9 måneder (baseret på Kumar et al.)
Dosering		Som angivet i SPC	Som angivet i SPC
Effektmål		TTD	PFS
Håndtering af usikkerhed		One-way følsomhedsanalyse	One-way følsomhedsanalyse
Monitoreringsomkostninger		DRG-takst 2020	DRG-takst 2020

3. Resultater

3.1 Resultatet af sekretariatets hovedanalyse

Sekretariatets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, men med følgende justeringer:

- Tidshorisont på 15 år
- Anden metode for ekstrapolering af OS og PFS for DaraBorMelPred (HR for BorMelPred anvendes som reference)
- Behandlingslængde estimeres fra PFS
- Ændring af cykluslængde og administration af BorMelPred
- Ændring af relative dosisintensitet for lenalidomid til 70 %
- Ændring i fordeling af efterfølgende behandling

Sekretariatets hovedanalyse viser, at de inkrementelle omkostninger pr. patient bliver ca. [redacted] DKK sammenlignet med BorMelPred, ca. [redacted] DKK sammenlignet med BorLenDex, og ca. [redacted] DKK sammenlignet med LenDex, over en tidshorisont på 15 år. Udføres analysen med AIP, bliver den inkrementelle omkostning pr. patient ca. 1,05 mio. DKK, ca. 1 mio. DKK, og ca. 1,06 mio. DKK for sammenligningen mellem hhv. BorMelPred, BorLenDex og LenDex. Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 18.

Tabel 18: Resultatet af Medicinrådets sekretariats hovedanalyse, DKK, diskonterede tal

[DKK]	DaraBorMelPred	BorMelPred	BorLenDex	LenDex18
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	243.044	162.601	192.628	61.263
Patientomkostninger	46.889	13.865	16.201	6.264
Efterfølgende behandlinger	[redacted]	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

3.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse har sekretariatet udført følgende følsomhedsanalyser:

- *Ekskludering af efterfølgende behandling*

- *Tidshorisont på 10 år*
- *Justering af patienternes vægt -/+ 5 %*
- *Terminalomkostning 13.134 DKK (DRG-takst 2019)*
- *HR for DaraBorMelPred anvendes som reference til komparatorerne*
- *Konstant ratio af død i 2. linje PFS (mellem død og PFS baseret på ALCYONE) på 19,32 % for DaraBorMelPred og 13,21 % for komparatorer*
- *Ekskludering af præmedicinering*
- *Lenalidomid 20 mg*

Resultatet af følsomhedsanalysen hvor de efterfølgende behandlingslinjer udelades fra beregningen af de inkrementelle omkostninger, viser, at inddragelse af efterfølgende behandlinger har stor betydning for analysens resultat. Dette hænger sammen med, at behandlingspraksis er, at patienterne får kombinationer indeholdende daratumumab i enten 1. eller 2. linje. Rykkes daratumumab frem i første linje, vil man for disse patienter spare udgifterne til datatumumab j de efterfølgende linjer. Og omvendt vil patienter, der ikke er behandlet med datatumumab i 1. linje, typisk blive behandlet med dette i de efterfølgende linjer.

Tabel 19: Resultat af følsomhedsanalyser, inkrementelle omkostninger for DaraBorMelPred mellem BorMelPred, BorLenDex og LenDex18

Følsomhedsanalyse		BorMelPred	BorLenDex	LenDex18
Hovedanalyse		[redacted]	[redacted]	[redacted]
Ekskl. efterfølgende behandling		[redacted]	[redacted]	[redacted]
Tidshorisont 10 år		[redacted]	[redacted]	[redacted]
Vægtjustering	+5 %	[redacted]	[redacted]	[redacted]
	-5 %	[redacted]	[redacted]	[redacted]
Ændret terminalomkostning		[redacted]	[redacted]	[redacted]
DaraBorMelPred som HR-reference		[redacted]	[redacted]	[redacted]
Konstant ratio for død i PFS 2. linje		[redacted]	[redacted]	[redacted]
Ekskludering af præmedicin		[redacted]	[redacted]	[redacted]
Lenalidomid 20 mg (uden efterfølgende behandling)		[redacted]	[redacted]	[redacted]

4. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at DaraBorMelPred vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- DaraBorMelPred bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- DaraBorMelPred bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers budgetkonsekvensanalyse

4.1.1 Ansøgers estimat af patientantal og markedsandel

Ansøger estimerer et samlet patientantal på 360 patienter årligt, baseret på Medicinrådets protokol for vurdering af DaraBorMelPred til nævnte indikation. Ansøger antager, at 80 % af disse vil modtage behandling i 1. linje, og at 192 patienter starter behandling.

Ansøger antager på baggrund af nuværende behandlingsvejledning, at 60 % behandles med BorLenDex, og 20 % behandles med LenDex og BorMelPred i 1. linje.

Ansøger antager, at hvis DaraBorMelPred anbefales, vil DaraBorMelPred få en markedsandel på 20 % år 1, stigende til 35 % fra år tre. Se tabel for fordelingen af DaraBorMelPred ved anbefaling.

Tabel 20 viser ansøgers estimat for det årlige nye patientantal.

Tabel 20: Ansøgers estimat af antal nye patienter pr. år

Anbefales					
	År 1	År 2	År 3	År 4	År 5
DaraBorMelPred	38	57	67	67	67
BorMelPred	31	27	25	25	25
BorLenDex	92	81	75	75	75
LenDex18	31	27	25	25	25
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5

DaraBorMelPred	0	0	0	0	0
BorMelPred	38	38	38	38	38
BorLenDex	115	115	115	115	115
LenDex18	38	38	38	38	38

Sekretariatets vurdering

Ansøger har inkluderet samme omkostninger, som indgår i deres hovedanalyse. Sekretariatet anvender egen hovedanalyse til beregning af budgetkonsekvenserne.

Sekretariatet antager, at 250 patienter pr. år kandiderer til DaraBorMelPred, som er estimeret af fagudvalget.

I forhold til ansøgers vurdering har fagudvalget vurderet, at en højere andel vil modtage DaraBorMelPred, såfremt det anbefales, og at ca. 50 % vil modtage DaraBorMelPred år 1 og 55 % det efterfølgende år. DaraBorMelPred vil desuden ikke tage markedsandel fra LenDex, men i højere grad tage markedsandele fra BorMelPred og dels fra BorLenDex. BorMelPred vil ikke blive brugt i efterfølgende behandlingslinjer, hvis DaraBorMelPred anbefales. Derfor vil 5 % af patienterne modtage BorMelPred år 1, 30 % vil modtage BorLenDex, og 15 % vil modtage LenDex.

Sekretariatet udfører egen budgetkonsekvensanalyse, hvor omkostninger er baseret på sekretariatets hovedanalyse, og hvor markedsandelene ændres til estimaterne fra fagudvalget

4.2 Sekretariatets budgetkonsekvensanalyse

Sekretariatet har i sin budgetkonsekvensanalyse korrigeret ansøgers estimater for markedsoptag. Med udgangspunkt i fagudvalgets forventninger anvendes følgende estimater for markedsoptaget for DaraBorMelPred:

- Markedsandel 30 % af BorLenDex-populationen
- Markedsandel 15-20 % af BorMelPred-populationen
- Markedsandel 5 % af LenDex18-population

Beregningen af budgetkonsekvenser tager udgangspunkt i de omkostninger, der i dag er forbundet med behandling af det antal patienter, som jf. Tabel 20 behandles med hhv. BorLenDex, BorMelPred og LenDex18 sammenlignet med omkostningerne til behandling af samme antal patienter, hvor DaraBorMelPred har overtaget den angivne markedsandel fra de pågældende lægemidler. Medicinrådets sekretariat estimerer, at en samlet anbefaling af DaraBorMelPred vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5, se Tabel 21.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne samlet ca. 95 mio. DKK.

Tabel 21: Sekretariatets analyse af totale budgetkonsekvenser for DaraBorMelPred over for alle komparatorer, mio. DKK, ikkediskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5. Diskussion

Behandling med DaraBorMelPred er forbundet med høje inkrementelle omkostninger sammenlignet med alle komparatorer. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for de forskellige behandlinger, især behandlinger givet til progression (DaraBorMelPred og BorLenDex).

De høje inkrementelle omkostninger hænger sammen med, at daratumumab, som er et dyrt lægemiddel rykkes op i en tidligere behandlingslinje. Især bør man være opmærksom på, at ved kombinationen DaraBorMelPred gives daratumumab hver 4. uge indtil progression, som vedligeholdelsesbehandling. Da der typisk er en længere progressionsfri periode i 1. behandlingslinje, vil patienterne få daratumumab i en længere periode her, end i senere behandlingslinjer.

De høje inkrementelle omkostninger for DaraBorMelPred sammenlignet med BorLenDex på trods af inkludering af efterfølgende behandling, skyldes at behandlingsregimerne CarLenDex og EloLenDex givet efter DaraBorMelPred er dyrere behandlingsregimer end hhv. DaraBorDex og CarDex givet efter BorLenDex.

5.1 Usikkerheder

Inddragelse af efterfølgende behandling har stor betydning for analysens resultat. Dette hænger sammen med de omkostninger der er forbundet til lægemidlerne givet i hhv. 1. og 2. linje. Behandlingsregimer indeholdende dyre lægemidler (daratumumab, lenalidomid og carfilzomib) og rækkefølgen af anvendelse betyder meget især for lægemidler givet til progression, da der er længere PFS i 1. linjebehandling.

Der er store usikkerheder forbundet med de kliniske antagelser og økonomiske estimater. Dette skyldes blandt andet, at ekstrapoleringerne for de forskellige behandlinger er baseret på data fra forskellige studier, da der ikke findes studier med direkte sammenligninger for alle komparatorer. Derfor er ekstrapoleringerne baseret på ansøgers netværksmetaanalyser, hvilket indebærer en stor usikkerhed. De efterfølgende behandlinger givet i de respektive studier, som netværksmetaanalysen baseres på, er ikke i overensstemmelse med dansk klinisk praksis, og dette kan have betydning for, om den estimerede effekt er korrekt.

Der er antaget ens behandlingslængde for 3.-linjebehandling på baggrund af fagudvalgets vurdering. Dette er gjort for at simplificere modellen, men det vil næppe være gældende for alle behandlingsregimer i klinisk praksis. Det skyldes, at patienterne ikke nødvendigvis har fulgt de skitserede behandlingsregimer i modellen, og i alle linjer kan patientpopulationerne, der indgår i studierne, adskille sig fra patienterne i den danske patientpopulation. Efterfølgende behandling i dansk klinisk praksis fastlægges ud fra en individuel vurdering af patientens tidligere behandlinger, komorbiditeter, patientpræferencer og tidligere bivirkninger og er derfor meget usikker at estimere. Ekskluderes efterfølgende behandling, øges meromkostningerne væsentligt.

Ansøger har estimeret PFS og OS baseret på ekstrapoleret studiedata, hvor bedste statistiske og plausible fit er valgt. Fagudvalget har dog vurderet, at metoden, hvor HR fra BorMelPred anvendes som reference for ekstrapoleringen, giver det mest plausible billede af ekstrapolerede PFS og OS for DaraBorMelPred. Der er stor usikkerhed ved estimerede PFS og OS, og det har stor betydning for analysens resultat.

Det at skifte fra intravenøs til subkutan administration af daratumumab har lille betydning for analysens resultat. Dog er administrationsomkostninger sparet ved subkutan behandling ikke medregnet i analysen. Kun lægemiddelpris ved subkutan behandling er medregnet i analysen. Dette betyder, at patientens vægt kan have betydning for analysens resultat, da daratumumab i.v. doseres ud fra vægt.

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7. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
2.0	23. juni 2021	Anbefalingen revurderes på baggrund af en ny forhandlet pris. Den forhandlede pris er fortrolig og fremgår derfor ikke. Anbefalingen er tilpasset nyt layout for Medicinrådets dokumenter.
1.0	21. oktober 2020	Godkendt af Medicinrådet.

8. Bilag

8.1 Resultatet af ansøgers hovedanalyse

Ansøger estimerer i analysen de inkrementelle omkostninger pr. patient for DaraBor-MelPred sammenlignet med BorMelPred, BorLenDex og LenDex18.

Tabel 22: Resultatet af Medicinrådets sekretariats hovedanalyse, DKK, diskonterede tal

[DKK]	DaraBorMelPred	Bor-MelPred	BorLenDex	LenDex18
Lægemiddelomkostninger (1. linje)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger (inkl. lægemiddelomkostninger til 2.-linjebehandling og 3.-linjebe-handling)	1.297.016	2.595.913	1.829.042	2.394.264
Patientomkostninger	54.543	38.476	36.096	32.160
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

8.2 Resultatet af ansøgers budgetkonsekvensanalyse

I nedenstående tabel ses ansøgers resultat af budgetkonsekvensanalysen.

Tabel 23: Ansøgers analyse af totale budgetkonsekvenser for DaraBorMelPred, mio. DKK, ikkedis-konterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	28.04.2021 (revurdering)
Leverandør	Janssen-Cilag
Lægemiddel	Daratumumab (Darzalex)
Ansøgt indikation	Nydiagnosticerede voksne med myelomatose, som ikke er egnet til højdosis kemoterapi med stamcelleterapi

Forhandlingsresultat

Amgros har opnået følgende volumenbaseret aftale på daratumumab. Aftalen er indgået på SC formulering, som udgør 98% af salget. De sidste 2% er på IV formuleringen.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

*AIP 1800 mg= 38.118,06 (marts 2021)

[redacted]

Tilbuddet består af en volumenbaseret aftale, der indeholder 3 niveauer hvor hvert niveau svarer til 4-5 måneders salg, baseret på det nuværende forbrug.
[redacted]

I dag er der et lille forbrug på IV formuleringen (ca. 2%). Forbruget af IV formuleringen er blevet omregnet til SC og indgår i den samlede volumenbaserede aftale.

Der er en gældende aftale i dag, og som supplement kan den nye betingede aftale træde i kraft d. 29.4.2021 og vare indtil d. 31.3.2023

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi har opnået den bedste pris på daratumumab. Denne vurdering baserer vi på følgende punkter:

[redacted]

Konklusion

Amgros forventer ikke at kunne få en bedre pris før der kommer større konkurrence på området.

[redacted]

[redacted]

Relation til markedet

Den årlige behandlingspris i lægemiddelomkostninger for daratumumab, lenalidomid, carfilzomib, ixazomib og pomalidomid vises i tabellen herunder (priser pr 1.1.2021).

Lægemiddel	Dosering	1 års behandling (DKK)
Daratumumab	1800 mg s.c. ugentligt i fra uge 1-6 (6 doser) og hver tredje uge fra uge 7-52(16 doser)	[redacted]
Daratumumab	16 mg pr. kg i.v. ugentligt fra uge 1-6 (6 doser) og hver tredje uge fra 7-23. herefter hver 4 uge	[redacted]
Lenalidomid	25 mg dag 1-14 af 21 dage i 8 serier Dernæst serier af 28 dage Lenalidomid 25 mg p.o. på dag 1-21	[redacted]
Carfilzomib	Serie 1: 20 mg/m2 dag 1 og 2-56 mg/m2 dag 8, 9, 15 og 16 Serie 2 og over: 56 mg/m2 dag 1, 2, 8, 9, 15 og 16	[redacted]
Ixazomib	4 mg Dag 1, 8 og 15 ud af 28, hver 4 uge	[redacted]
Pomalidomid	4 mg. Dag 1-21 hver 4 uge	[redacted]

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø

29. September 2020

Consultation response to the Medicines Council concerning the clinical assessment of Darzalex® in combination with bortezomib, melphalan, and prednisone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation

On a general note, Janssen appreciates the possibility to provide a hearing answer, and Janssen would like to thank the Secretariat for a good dialogue during the process. Janssen would also like to thank the Secretariat and the Expert Committee for the work conducted, and acknowledge the descriptions provided by the Expert Committee with the data indicating a large added clinical benefit for the outcome measure *survival* (OS & PFS) in favor of Darzalex® in combination with bortezomib, melphalan, and prednisone (DaraBorMelPred) for the comparison versus bortezomib in combination with melphalan and prednisone (BorMelPred).

Janssen disagrees with the statements regarding data not being mature and the rather large weight put on potential bias due to censoring in the categorization of the added clinical benefit for DaraBorMelPred versus BorMelPred. The data has been delivered according to the requests in the protocol, and the analyses are based on a pre-specified interim analysis (1-3). For PFS, the median has been reached which is usually considered mature. At a median follow-up of 40.1 months less than 50% are censored in both arms making it possible to calculate the median PFS for both arms.

On page 11 in the clinical assessment report, the following is stated; *Ansøger beskriver, at populationen i SWOG-studiet i gennemsnit er yngre og med bedre funktionsniveau og vurderer, at dette har betydning for effektmålene OS og PFS, men ikke for behandlingsophør.*

Janssen has provided argumentation and supporting evidence (page 69-70 in clinical application) to show that the patient population in the SWOG S0777 trial in terms of baseline characteristics are likely better off at baseline for the outcome measure; *treatment discontinuations due to adverse events* compared to the patient population enrolled in the ALCYONE trial. In the application, a naïve comparison and an indirect comparison was conducted. In the application, it is argued that in case DaraBorMelPred can show an advantage compared to bortezomib in combination with lenalidomide and dexamethasone (BorLenDex) despite the likely bias in favor of BorLenDex, the indirect comparison should serve as solid evidence for awarding an added clinical benefit.

Best regards,
Janssen-Cilag A/S

Jacob Petersen
Health Economics, Market Access and Reimbursement Manager

References:

1. Janssen. Statistical Analysis Plan. A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (D-VMP), in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High-dose Therapy. [updated 19 July 2017. Available from: https://clinicaltrials.gov/ProvidedDocs/79/NCT02195479/SAP_001.pdf.
2. Janssen. Clinical Protocol. A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (D-VMP), in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High-dose Therapy. [updated 14 February 2018. Available from: https://clinicaltrials.gov/ProvidedDocs/79/NCT02195479/Prot_000.pdf.
3. Maria-Victoria Mateos, Michele Cavo, Joan Blade, Meletios A Dimopoulos, Kenshi Suzuki, Andrzej Jakubowiak, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2019.

Fra: Louise Klokker Madsen
Til: "Petersen, Jacob [JACDK]"
Cc: Karen Kleberg Hansen
Emne: Kvittering for høringssvar vedr. daratumumab
Dato: 1. oktober 2020 08:09:00
Vedhæftede filer: image001.png

Kære Jacob

Tak for jeres høringssvar vedrørende Medicinrådets vurdering af lægemidlets værdi for daratumumab i kombination med bortezomib, melphalan og prednison til behandling af nydiagnosticerede patienter med knoglemarvskræft.

Vi har gennemgået jeres kommentarer til vurderingsrapporten og har noteret at I er uenige i vurderingen vedr. modenhed af PFS-data samt fagudvalgets vægtning af usikkerhederne ved data. Vi finder ikke, at jeres kommentarer giver anledning til at ændre den nuværende kategorisering.

Jeres høringssvar indgår i den videre behandling af sagen og bliver offentliggjort sammen med den endelige anbefaling. Den godkendte vurdering er offentliggjort på Medicinrådets hjemmeside.

Vh Louise

Fra: Petersen, Jacob [JACDK] <jpeter68@ITS.JNJ.com>
Sendt: 29. september 2020 20:35
Til: Louise Klokker Madsen <LKM@medicinraadet.dk>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>; Louise Greve Dal <LGD@medicinraadet.dk>; Pernille Winther Johansen <pwj@medicinraadet.dk>
Emne: RE: Høring over godkendt vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for daratumumab

Kære Louise,

Vedhæftet findes høringssvaret fra Janssen.

Med venlig hilsen,
Jacob

From: Louise Klokker Madsen <LKM@medicinraadet.dk>
Sent: 23. september 2020 18:44
To: Petersen, Jacob [JACDK] <jpeter68@ITS.JNJ.com>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>; Louise Greve Dal <LGD@medicinraadet.dk>; Pernille Winther Johansen <pwj@medicinraadet.dk>
Subject: [EXTERNAL] Høring over godkendt vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for daratumumab

Kære Jacob

Sekretariatet fremsender hermed den endelige vurdering af lægemidlets værdi samt sundhedsøkonomisk afrapportering for daratumumab i kombination med bortezomib, melphalan og prednison til behandling af nydiagnosticerede patienter med knoglemarvskræft, som Medicinrådet godkendte på rådsmødet i dag (den 23. september 2020).

De vedhæftede dokumenter er derfor samme versioner, som I tidligere har haft i høring.

Vi ser frem til at modtage jeres eventuelle høringssvar inden den 30. september 2020.

Vh
Louise

Fra: Louise Klokker Madsen
Sendt: 11. september 2020 10:04
Til: Petersen, Jacob [JACDK] <jpeter68@ITS.JNJ.com>
Cc: Karen Kleberg Hansen <kkh@medicinraadet.dk>; Louise Greve Dal <LGD@medicinraadet.dk>
Emne: Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for daratumumab

Kære Jacob

Sekretariatet fremsender hermed udkast til Medicinrådets vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for daratumumab i kombination med bortezomib, melphalan og prednison til behandling af nydiagnosticerede patienter med knoglemarvskræft.

Medicinrådet drøfter vurderingen af lægemidlets værdi og modelantagelserne for den sundhedsøkonomiske afrapportering den 23. september. I får besked fra sekretariat, hvis Rådet har ændringer til vurderingen udarbejdet af fagudvalget.

I har i alt 20 dage til at sende eventuelle bemærkninger til kategoriseringen af lægemidlets værdi og den sundhedsøkonomiske afrapportering. Jeres frist for at indgive høringssvar er derfor den 30. september. I er selvfølgelig velkomne til at sende eventuelle bemærkninger inden denne dato. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen.

Vurderer sekretariatet og fagudvalget, at jeres høringssvar giver anledning til at revurdere kategoriseringen af lægemidlets værdi, skal Rådet drøfte vurderingen igen. Det vil med overvejende sandsynlighed udskyde tidspunktet for Rådets drøftelse af anbefalingen. Jeres eventuelle høringssvar indgår i det materiale, som bliver fremlagt for Medicinrådet i forbindelse med behandlingen af anbefalingen. Jeres eventuelle høringssvar bliver offentliggjort sammen med anbefalingen.

Vh Louise

Louise Klokker Madsen
Sundhedsvidenskabelig konsulent
+45 21 30 02 59
lkm@medicinraadet.dk

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø
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medicinraadet@medicinraadet.dk
www.medicinraadet.dk

Medicinrådets behandling af personoplysninger

Når du har kontakt med Medicinrådet (f.eks. når du sender en e-mail til os), indsamler og behandler vi dine personoplysninger (f.eks. kontaktoplysninger i form af navn, e-mailadresse, titel/stilling mv.) I Medicinrådets persondatapolitik finder du mere information om Medicinrådets behandling af personoplysninger, dine rettigheder og oplysninger om, hvordan du kan kontakte os.

Medicinrådet

Medicinrådets vurdering vedrørende daratumumab i kombination med bortezomib, melphalan og prednison til behandling af nydiagnosticerede patienter med knoglemarvskræft (myelomatose)

Version 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette sammenfatter vi i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Godkendt af Medicinrådet 23. september 2020
Dokumentnummer 89084
Versionsnummer 1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf

Indhold

1 Medicinrådets konklusion

Komparator BorMelPred
Medicinrådet vurderer, at daratumumab i kombination med bortezomib, melphalan og prednison giver en **merværdi af ukendt størrelse** sammenlignet med bortezomib, melphalan og prednison til nydiagnosticerede patienter med knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte. Evidensens kvalitet vurderes at være meget lav.

Komparator LenDex
Medicinrådet vurderer, at daratumumab i kombination med bortezomib, melphalan og prednison giver en **merværdi af ukendt størrelse** sammenlignet med lenalidomid og dexamethason til nydiagnosticerede patienter med knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte. Evidensens kvalitet vurderes at være meget lav.

Komparator BorLenDex
Medicinrådet vurderer, at den samlede værdi af daratumumab i kombination med bortezomib, melphalan og prednison sammenlignet med bortezomib, lenalidomid og dexamethason **ikke kan kategoriseres**. Rådet vurderer dog, at daratumumab i kombination med bortezomib, melphalan og prednison samlet set ikke har dårligere effekt eller sikkerhedsprofil end bortezomib, lenalidomid og dexamethason.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

• **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.

• **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.

• **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

• **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

Samlet værdi kan ikke kategoriseres: På grund af usikkerheder omkring effektforhold er det ikke muligt at kategorisere lægemidlets samlede værdi.

Medicinrådet vurderer kvaliteten af de data, der ligger til grund for vurderingen af lægemidlet (evidensens kvalitet) i en af følgende GRADE-kategorier:

• **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.

• **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.

• **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.

• **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2 Begreber og forkortelser

BorLenDex	Lenalidomid i kombination med bortezomib og dexamethason
CI	Konfidensinterval
DaraBorMelPred	Daratumumab i kombination med bortezomib, melphalan og prednison
EMA	*European Medicines Agency*
EORTC	*European Organization for Research and Treatment of Cancer*
EPAR	*European public assessment report*
GRADE	*Grading of Recommendations Assessment, Development and Evaluation System*
HDT/STS	Højdosiskemoterapi med stamcellestøtte
HR	*Hazard ratio*
OS	*Overall survival* (samlet overlevelse)
PFS	*Progression free survival* (progressionsfri overlevelse)
QLQ-C30	*Quality of life questionnaire*
RR	Relativ risiko

3 Introduktion

Formålet med Medicinrådets vurdering af daratumumab i kombination med bortezomib, melphalan og prednison (DaraBorMelPred) som mulig standardbehandling til nydiagnosticerede patienter med knoglemarvskræft (myelomatose), som ikke er egnede til højdosiskemoterapi med stamcellestøtte, er at vurdere den værdi, behandlingen har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Janssen-Cilag A/S. Vi modtog ansøgningen den 2. juni 2020.

Det kliniske spørgsmål er:

Hvad er værdien af daratumumab i kombination med bortezomib, melphalan og prednison samt efterfølgende som vedligeholdelsesbehandling, sammenlignet med nuværende standardbehandling til voksne patienter med nydiagnosticeret knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte?

3.1 Knoglemarvskræft

Knoglemarvskræft er en uhelbredelig, livstruende og livsforkortende, men behandlingsfølsom hæmatologisk kræftsygdom. Sygdommen skyldes, at én type af hvide blodlegemer (plasmaceller) i knoglemarven ændrer karakter og herved bliver ondartede. Patienten kan på grund af nedsat funktion af knoglemarven opleve symptomer på svækket immunforsvar som infektioner og på blodmangel, som medfører, at patienten oplever bl.a. træthed og åndenød. Ændringerne i knoglemarven fremmer aktiviteten af celler, som nedbryder knoglerne og reducerer aktiviteten af de celler, som opbygger knoglevæv. Derfor nedbrydes knoglerne, og patienten får øget risiko for knoglebrud, oplever knoglesmerter og får forhøjet kalk i blodet. Hos størstedelen af patienter med knoglemarvskræft kan der påvises et ikkefunktionelt antistof (M-komponent) eller dele heraf (frie lette kæder) i blod og urin. M-komponenten og de lette kæder dannes af de maligne plasmaceller. Hos nogle patienter vil de lette kæder give anledning til nyreskader eller egentligt nyresvigt [1]. Målinger af M-komponenten og de frie lette kæder bruges til at diagnosticere patienterne og til at følge sygdommens udvikling.

Knoglemarvskræft er den næsthyppigste hæmatologiske kræftsygdom i Danmark, hvor i alt ca. 2.300 patienter anslås at leve med sygdommen [2]. Der diagnosticeres ca. 380 behandlingskrævende patienter om året i Danmark, og medianalder ved diagnose er ca. 71 år [3].

3.2 Daratumumab til nydiagnosticerede patienter

I den ansøgte behandlingskombination er daratumumab kombineret med bortezomib, melphalan og prednisolon (DaraBorMelPred). Kombinationen er EMA-godkendt til nydiagnosticerede patienter, som ikke er kandidater til højdosiskemoterapi med stamcellestøtte (HDT/STS) og doseres som følger i serier a 6 uger:

- Daratumumab (som en af følgende)
    - 16 mg pr. kg i.v. ugentligt i serie 1, hver tredje uge i serie 2-9 og herefter hver fjerde uge frem til progression
    - 1800 mg s.c. ugentligt i serie 1, hver tredje uge i serie 2-9 og herefter hver fjerde uge frem til progression
- Bortezomib 1,3 mg pr. m^2 s.c. 2 gange ugentligt i uge 1, 2, 4 og 5 i serie 1 og én gang ugentligt i uge 1, 2, 4 og 5 i serie 2-9
- Melphalan 9 mg pr. m^2 p.o. på dag 1-4 i serie 1-9
- Prednison 60 mg pr. m^2 p.o. på dag 1-4 i serie 1-9

- Desuden dexamethason 20 mg p.o. eller i.v. i serie 1, hver tredje uge i serie 2-9 og herefter hver fjerde uge frem til progression

Daratumumab har desuden følgende EMA-godkendte indikationer [4]:

- som monoterapi (i kombination med dexamethason) til behandling af voksne patienter med recidiverende og refraktær knoglemarvskræft, som tidligere har fået behandling med en proteasomhæmmer og et immunmodulerende middel, og som har vist sygdomsprogression under den sidste behandling.
- i kombination med lenalidomid og dexamethason (DaraLenDex) eller bortezomib og dexamethason (DaraBorDex) til behandling af voksne patienter med knoglemarvskræft, som tidligere har fået mindst én behandling.
- i kombination med lenalidomid og dexamethason (DaraLenDex) til behandling af voksne patienter med nydiagnosticeret knoglemarvskræft, som ikke er kandidater til HDT/STS.

Ingen af de nævnte indikationer er behandlet i en proces for nye lægemidler i Medicinrådet (de to førstnævnte er taget i brug, inden Medicinrådet blev etableret). Daratumumab monoterapi samt DaraLenDex og DaraBorDex til tidligere behandlede patienter indgår i Medicinrådets behandlingsvejledning vedrørende knoglemarvskræft.

3.3 Nuværende behandling

Behandlingen af knoglemarvskræft varetages på de hæmatologiske afdelinger. Den medicinske behandling består af forskellige lægemiddelkombinationer, der har vist sig mere virksomme en enkeltstofbehandlinger [5]. Behandlingen er ikke kurativ, så ud over forlænget overlevelse er målet med behandlingen at give patientenerne længst mulige symptomfrie perioder med bedst mulig livskvalitet.

Nydiagnosticerede patienter inddeles overordnet i to patientgrupper, efter hvorvidt de er kandidater til HDT/STS eller ej. Dette afgøres på baggrund af almentilstand og komorbiditet. Patienter med knoglemarvskræft, som er yngre (oftest yngre end 65-70 år) og uden betydende komorbiditet, behandles med HDT/STS, såfremt de ønsker det. Denne behandling er internationalt anerkendt som det bedste valg uden ligeværdige alternativer [6–8].

Patienter med behandlingskrævende knoglemarvskræft, som ikke er kandidater til HDT/STS, tilbydes andre medicinske kombinationsbehandlinger [9]. Den patientpopulation udgør ca. 250 patienter årligt, svarende til ca. 2/3 af de behandlingskrævende nydiagnosticerede patienter. Blandt de nuværende behandlingsmuligheder anvendes oftest en kombination af enten bortezomib, lenalidomid og dexamethason (BorLenDex), bortezomib, melphalan og prednison (BorMelPred) eller lenalidomid og dexamethason (LenDex) [10]. Patienter, der ikke er kandidater til HDT/STS, har en medianoverlevelse på ca. 3 år og en median progressionsfri overlevelse på ca. 18 måneder [11]. Den gennemsnitlige levetid i baggrundsbefolkningen er for 75-årige ca. 11 år for mænd og 13 år for kvinder. For 80-årige er den gennemsnitlige levetid 8 år for mænd og 10 år for kvinder (estimater fra Danmarks Statistik, www.dst.dk).

4 Metode

Medicinrådets protokol for vurdering af daratumumab i kombination med bortezomib, melphalan og prednison til behandling af nydiagnosticerede patienter med knoglemarvskræft beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

Det kliniske spørgsmål er:

Hvad er værdien af daratumumab i kombination med bortezomib, melphalan og prednison samt efterfølgende som vedligeholdelsesbehandling, sammenlignet med nuværende standardbehandling til voksne patienter med nydiagnosticeret knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte?

Nuværende standardbehandling blev i protokollen defineret som en af følgende komparatorer:

1. Bortezomib, lenalidomid og dexamethason (BorLenDex) doseret som følger:
   I de første otte serier a 21 dage
   Lenalidomid 25 mg p.o. på dag 1-14
   Bortezomib 1,3 mg/m^2 s.c. på dag 1, 4, 8 og 11
   Dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11 og 12
   Dernæst serier a 28 dage indtil progression
   Lenalidomid 25 mg p.o. på dag 1-21
   Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22

2. Lenalidomid og dexamethason (LenDex) doseret som følger:
   18 serier a 28 dages varighed
   Lenalidomid 25 mg p.o. på dag 1-21
   Dexamethason 40 mg p.o. på dag 1, 8, 15, og 22

3. Bortezomib, melphalan og prednisolon (BorMelPred) doseret som følger:
   9 serier a 35 dages varighed
   Bortezomib s.c. 1,3 mg/m^2 på dag 1, 8, 15 og 22
   Melphalan p.o. 9 mg/m^2 på dag 1, 2, 3, 4
   Prednisolon p.o. 100 mg på dag 1, 2, 3, 4

5 Resultater

5.1.1 Litteratur

Nedenfor beskriver og vurderer vi den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen og har desuden tilføjet yderligere to kliniske studier (IFM 01/01 og IFM 99-06), som var nødvendige for at kunne lave indirekte sammenligninger baseret på en netværksmetaanalyse, hvilket ansøger ønskede. Sekretariatet accepterer denne tilgang, da studierne blev anvendt i Medicinrådets behandlingsvejledning vedr. knoglemarvskræft, godkendt den 19. maj 2019. Ansøger har i alt identificeret 10 artikler med resultater fra 6 kliniske studier til besvarelse af det kliniske spørgsmål. Artikler samt kliniske studier fremgår af tabel 1, hvor det også er angivet, hvordan data fra studierne er anvendt i sammenligningerne mellem DaraBorMelPred og komparatorer.

Tabel 1. Litteratur, som ansøger har identificeret og anvendt: 10 artikler baseret på 6 kliniske studier.

Reference	Studienavn, NCT-nummer og interventioner*	Start og forventet afslutningsdato, median opfølgningstid	Sammenligning med komparator
Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma, Mateos et al., The New England journal of medicine, 2018 [12] *Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomized, open-label, phase 3 trial, Mateos et al., The Lancet, 2020* [13]	**ALCYONE** NCT02195479 DaraBorMelPred vs. BorMelPred	9. dec. 2014- 20. okt. 2021 Median opfølgningstid: 40,1 mdr.	BorMelPred (direkte sammenligning: OS, PFS, behandlingsophør, livskvalitet) LenDex (indirekte sammenligning: OS, PFS) BorLenDex (indirekte sammenligning: behandlingsophør, naiv sammenligning: OS, PFS)
Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma, Benboubker et al., N Engl J Med., 2014 [14] *Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma., Facon T et al., Blood, 2018* [15] *Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide., Delforge M et al., Haematologica, 2015* [16]	**FIRST** NCT00689936 LenDex vs. LenDex18 MelPredThal	21. aug. 2008 – 14. juli 2016 Median opfølgningstid: 67 mdr.	LenDex (indirekte sammenligning: OS, PFS) BorLenDex (anvendt som mellemled i netværket)
Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial., Hulin et al., J Clin Oncol., 2009 [17]	**IFM 01/01** NCT00644306 MelPred vs. MelPredThal	april 2002- maj 2007 Median opfølgningstid: 47,5 mdr.	LenDex (anvendt som mellemled i netværket) BorLenDex (anvendt som mellemled i netværket)
Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomized trial., Facon et al., Lancet., 2007 [18]	**IFM 99-06** NCT00367185 MelPred vs. MelPredThal	maj 2000- okt. 2005 Median opfølgningstid: 51,5 mdr.	LenDex (anvendt som mellemled i netværket) BorLenDex (anvendt som mellemled i netværket)
Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma., San Miguel et al., N Engl J Med., 2008 (18) *Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma., San Miguel et al., J Clin Oncol., 2013* [19]	**VISTA** NCT00111319 BorMelPred vs. MelPred	dec. 2004- juli 2007^ Median opfølgningstid: 60,1 mdr.	LenDex (anvendt som mellemled i netværket) BorLenDex (anvendt som mellemled i netværket)
Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open- label, phase 3 trial., Durie B et al., Lancet., 2017 [20]	**SWOG S0777** NCT00644228 BorLenDex vs. LenDex	1. april 2008- 1. juli 2016^ Median opfølgningstid: 69 mdr.	BorLenDex (indirekte sammenligning: behandlingsophør, naiv sammenligning: OS, PFS)

**Studiedosering af lægemidlerne fremgår af bilag 1.*
^Sidste dataindsamling for primære effektmål

Studiepopulationerne
De inkluderede studier, som fremgår af tabel 1, omhandler alle primærbehandling af patienter, der ikke er kandidater til HDT/STS. Dog er der i SWOG S0777 også inkluderet patienter, som er kandidater til HDT/STS. Dermed er populationen i dette studie yngre og i bedre performance status end i de øvrige studier og i forhold til den danske patientpopulation.

Fagudvalget bemærker desuden mindre forskelle i studiepopulationerne med hensyn til alder og nyrefunktion. Der er enkelte studier, hvor medianalderen er højere (IFM 01/01), eller nyrefunktionen er bedre (ALCYONE) sammenlignet med øvrige studier. Fagudvalget vurderer, at med undtagelse af SWOG S0777, er studiepopulationerne sammenlignelige.

Med undtagelser af studiepopulationen i SWOG-studiet anser fagudvalget studiepopulationerne som tilstrækkeligt repræsentative for den danske patientpopulation, om end de generelt er lidt yngre og i bedre performance status, som det ofte gør sig gældende for patienter i kliniske studier.

Baselinekarakteristika oplyst fra ansøger fremgår af tabel 2.

Tabel 2: Baselinekarakteristika for studier inkluderet i den endelige ansøgning.

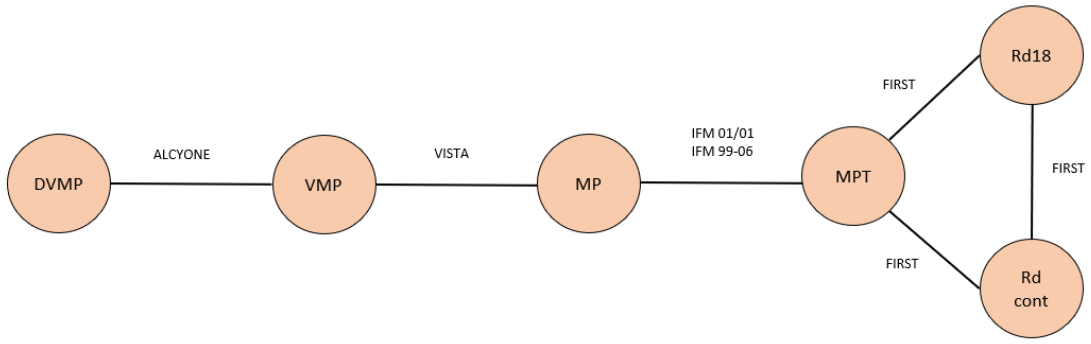
TRIAL	Location of study	Median Follow up (mont-h)	Treatment arms	N	Median Age (years)	Female (%)	Race white (%)	MM type-IgG (%)	ISS-stage III (%)	ECOG 0 (%)	ECOG 1 (%)	ECOG 2 (%)	High-risk cytogen-etic abnorm-ality (%)
ALCYONE	Asia–Pacific, Europe, Latin America, North America	40.1	DaraBorMelPred BorMelPred	350 356	71 71	54 53	85 85	40.9 39.3	40.6 36.2	22 28	52 49	26 24	16.9 14.9
FIRST	US, Canada, Asia Pacific, Europe	67.0	LenDex LenDex18 MelPredThal	535 541 547	73 73 73	45 50 48	89 89 90	62 61 64	40 40 41	29 30 29	48 49 50	22 21 20	17 20 19
IFM 01/01	Europe	47.5	MelPred MelPredThal	116 113	78.5	47 62			30 35				
IFM 99–06	Europe	51.5	MelPred MelPredThal	196 125		34 50			30 29				
VISTA	US, Canada, Europe, Latin America, Asia pacific	60.1	BorMelPred MelPred	344 338	71 71	49 51	88 87	64 62	35 34				
SWOG S0777 (EPAR)	US, Puerto Rico, Saudi Arabia	69.0	BorLenDex LenDex	263 260	63 63	38 47			33 34	40 39	49 46	11.4 13.8	

5.1.2 Databehandling og analyse

Nedenfor beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål. Databehandlingen adskiller sig for de tre komparatorer, og disse er beskrevet hver for sig.

Komparator BorMelPred
Ansøger har anvendt direkte sammenligninger for alle effektmål, baseret på data fra ITT-populationen fra ALCYONE-studiet. Bivirkninger er opgjort som *treatment emergent adverse events (TEAE)*, det vil sige de uønskede hændelser, som forekommer efter opstart af behandlingen. TEAE er dermed ikke nødvendigvis vurderet at være relateret til behandlingen. Uønskede hændelser af grad 3-4 er afgrænset til de hændelser, der forekommer hos mindst 5 % (i stedet for alle uønskede hændelser af grad 3-4). Ansøger har foretaget denne afgrænsning for at kunne lave en ensartet opgørelse på tværs af komparatorer. Sekretariatet accepterer ansøgers datagrundlag, databehandling og analyser for hvert effektmål.

Komparator LenDex
Da der ikke findes direkte sammenligninger, har ansøger valgt at lave netværksmetaanalyser, baseret på netværket vist i Figur 1. Ansøger vurderer, at de inkluderede studier er tilstrækkeligt sammenlignelige til at kunne indgå i netværket, baseret på baselinedata (tabel 2). Fagudvalget er enig i denne vurdering. For komparator LenDex er der lavet netværksmetaanalyser for effektmålene *OS*, *PFS* og *behandlingsophør*. For alle netværksmetaanalyser har ansøger valgt at anvende fixed effects models. På grund af netværkets simple endimensionelle struktur (figur 1) svarer ansøgers netværksmetaanalyse til sekventiel brug af Buchers metode til indirekte sammenligning.



Figur 1: Ansøgers netværk af studier til sammenligning af DaraBorMelPred med LenDex for effektmålene OS og PFS. DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex givet i 18 mdr., Rd cont: LenDex givet indtil progression.

Bivirkninger er opgjort som *treatment emergent adverse events (TEAE)*, det vil sige de uønskede hændelser, som forekommer efter opstart af behandlingen. TEAE er dermed ikke nødvendigvis vurderet at være relateret til behandlingen. Uønskede hændelser af grad 3-4 er afgrænset til de hændelser, der forekommer hos mindst 5 % (i stedet for alle uønskede hændelser af grad 3-4).

Sekretariatet accepterer ansøgers datagrundlag, databehandling og analyser for effektmålene *OS*, *PFS*, *behandlingsophør* og *bivirkninger*.

For effektmålet livskvalitet har ansøger valgt ikke at foretage sammenlignende analyser, fordi der ikke er baselinedata tilgængelige for gruppen af patienter, der har fået LenDex i 18 måneder. Ansøger har valgt ikke at lave en naiv sammenligning på grund af risiko for bias, fordi der kun findes data samlet for patienter, som fik LenDex henholdsvis i 18 måneder og indtil progression. Sekretariatet og fagudvalget er ikke enig i ansøgers begrundelse for at udelade en sammenligning vedr. effektmålet *livskvalitet*. Derfor har fagudvalget foretaget en naiv sammenligning for livskvalitet baseret på studiedata fra ALCYONE og FIRST.

Komparator BorLenDex
Da der ikke findes direkte sammenligninger, har ansøger valgt at lave en netværksmetaanalyse, baseret på netværket vist i Figur 1 med tillæg af et yderligere studie; SWOG S0777. Ansøger beskriver, at populationen

i SWOG-studiet i gennemsnit er yngre og med bedre funktionsniveau og vurderer, at dette har betydning for effektmålene *OS* og *PFS*, men ikke for behandlingsophør. For *behandlingsophør* vurderer ansøger således, at de inkluderede studier er tilstrækkeligt sammenlignelige til at kunne indgå i netværket, baseret på baselinedata (tabel 2). Derfor er der for komparator BorLenDex lavet en netværksmetaanalyse for effektmålet *behandlingsophør*.

For effektmålene OS og PFS har ansøger lavet en naiv sammenligning baseret på studiedata fra ALCYONE og SWOG S0777.

For effektmålet *livskvalitet* er der ikke rapporteret data i SWOG-studiet, og det har derfor ikke været muligt for ansøger at sammenligne effekten på livskvalitet ved behandling med DaraBorMelPred i forhold til BorLenDex.

Bivirkninger er opgjort som *treatment emergent adverse events (TEAE)*, det vil sige de uønskede hændelser, som forekommer efter opstart af behandlingen. TEAE er dermed ikke nødvendigvis vurderet at være relateret til behandlingen. Uønskede hændelser af grad 3-4 er afgrænset til de hændelser, der forekommer hos mindst 5 % (i stedet for alle uønskede hændelser af grad 3-4).

Sekretariatet accepterer ansøgers datagrundlag, databehandling og analyser for effektmålene *OS*, *PFS*, *bivirkninger* og *livskvalitet*. For effektmålet *behandlingsophør* er sekretariatet og fagudvalget ikke enige i ansøgers vurdering, idet det ikke er sandsynliggjort, hvorfor forskellen i studiepopulationerne ikke skulle have betydning for behandlingsophør. Derfor har fagudvalget foretaget en naiv sammenligning for behandlingsophør baseret på studiedata fra ALCYONE og SWOG S0777 og således ikke inddraget netværksmetaanalysen for behandlingsophør i vurderingen.

Vedr. overlevelsesdata
I protokollen er det defineret, at fagudvalget ønsker data for medianoverlevelsen. Såfremt data ikke er modne, ønsker fagudvalget data for overlevelsesraten efter tre år, og såfremt disse ikke er modne, ønsker fagudvalget data for PFS. Ansøger har angivet data for overlevelsesraten efter tre år samt data for PFS. Sekretariatet vurderer, at data for overlevelse i ALCYONE-studiet ikke er modne, idet data for langt størstedelen af deltagerne på opfølgningstidspunktet er censureret, hvilket giver en usikkerhed i forhold til den beregnede Hazard ratio (HR). Tilsvarende er 3-års overlevelsesraten umoden, da der er et betydeligt antal censureringer før 36 måneder – særligt i BorMelPred-armen. Data for PFS har en højere grad af modenhed, men også her er der mange censureringer, der giver usikkerhed i forhold til HR og 3-års PFS-raten.

5.1.3 Evidensens kvalitet

Studierne er vurderet ved Cochranes risk of bias tool 2.0. Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 2.

For sammenligningen med BorLenDex er der tale om en naiv sammenligning, da forskelle i studiepopulationerne er for forskellige til, at der kan foretages formelle statistiske analyser. Evidensens kvalitet kan derfor ikke vurderes.

For sammenligningen med BorMelPred og LenDex er GRADE anvendt til at foretage en systematisk og transparent vurdering af evidensens kvalitet. Nedenfor følger en beskrivelse af vurderingen af evidensens kvalitet. GRADE-profiler fremgår af bilag 2.

Inkonsistens og unøjagtighed
For sammenligningen med BorMelPred er der kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens for samtlige effektmål. For effektmålene *behandlingsophør* og *livskvalitet* er

konfidensintervallerne så brede, at der er usikkerhed om estimatet. Derfor nedgraderes ét niveau for unøjagtighed for disse effektmål.

For sammenligningen med LenDex er der for hver behandling kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens for samtlige effektmål. For effektmålene *overlevelse* og *livskvalitet* er der stor usikkerhed om estimatet. Derfor nedgraderes to niveauer for unøjagtighed for disse effektmål.

Risiko for bias
Halvdelen af de inkluderede studier har lav risiko for bias i forhold til metoden for randomisering, som er tilstrækkeligt beskrevet i studierne. Med undtagelse af ét studie (IFM 01/01) er alle studierne ublindede, og der vurderes derfor at være høj risiko for bias for effektmålene *behandlingsophør* og *livskvalitet*. Derfor er der generelt nedgraderet ét niveau for disse effektmål. For effektmålene *samlet overlevelse* og *progressionsfri overlevelse* er der ikke nedgraderet for risk of bias, selv om der for nogle studier er uklarhed om risikoen for bias i forhold til vurderingen af PFS. Flere studier vurderes at have høj eller uklar risiko for bias på grund af manglende data, mens alle studierne har lav risiko for bias ved udvælgelsen af resultater, der rapporteres. Det bemærkes, at der i flere af studierne er medforfattere med økonomiske interessekonflikter i forhold til de lægemidler, der er undersøgt i studierne.

Indirekthed
Fagudvalget vurderer, at populationen i SWOG S0777 er yngre og med bedre performance status end danske patienter med nydiagnosticeret knoglemarvskræft, som ikke er kandidater til HDT/STS. Sammenligningen med BorLenDex sker derfor på et indirekte evidensgrundlag og derfor er der nedgraderet for indirekthed.

For sammenligningen med LenDex vurderer fagudvalget, at studiepopulationerne svarer til den danske patientpopulation, hvad angår de væsentlige parametre. Der er dog tale om en indirekte sammenligning, og derfor er der nedgraderet for indirekthed.

Samlet vurdering af evidensens kvalitet
For sammenligningen med BorMelPred er evidensens kvalitet meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

For sammenligningen med LenDex er evidensens kvalitet meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

For sammenligningen med BorLenDex kan evidensens kvalitet ikke vurderes.

5.1.4 Effektestimater og kategorier – komparator BorMelPred

Af tabel 3 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1, komparator BorMelPred.

Tabel 3. Resultater for klinisk spørgsmål 1 (direkte analyse af DaraBorMelPred sammenlignet med BorMelPred, baseret på data fra ALCYONE-studiet)

Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel [95 % CI]	Foreløbig værdi	
Samlet overlevelse (OS)	Median OS *(MKRF: 6 mdr)*	Kritisk	*Median OS er ikke nået og data er ikke modne*	Kan ikke kategoriseres	HR: 0,60 [0,46; 0,80] *Data er ikke modne*	Stor merværdi	Merværdi af ukendt størrelse
	Overlevelsesrate ved tre år (såfremt data for median OS ikke er modne) *(MKRF: 5 procentpoint)*	Kritisk	10,1 procentpoint *Data er ikke modne*	Kan ikke kategoriseres			
	Median PFS (såfremt data for overlevelse ikke er modne) *(MKRF: 6 mdr)*	Vigtig	17,1 *Data er ikke modne*	Kan ikke kategoriseres	HR: 0,42 [0,34; 0,51] *Data er ikke modne*	Stor merværdi	
Behandlingsophør	Andel, der ophører med behandling pga. uønskede hændelser (adverse events) *(MKRF: 10 procentpoint)*	Kritisk	-2,3 [-6,3; 1,6] procentpoint	Ingen dokumenteret merværdi	RR 0,74 [0,44; 1,21]	Kan ikke kategoriseres	Ingen dokumenteret merværdi
Livskvalitet	Pointændring over tre år målt med EORTC QLQ-C30 *(MKRF: 10 point)*	Vigtig	4,4 [-1,8; 10,7] point	Ingen dokumenteret merværdi			Ingen dokumenteret merværdi
Bivirkninger	Kvalitativ gennemgang	Vigtig					
Samlet kategori for lægemidlets værdi		Merværdi af ukendt størrelse					
Kvalitet af den samlede evidens		Meget lav					

CI = konfidensinterval, HR = hazard ratio, RR = relativ risiko. i.a. = ikke angivet. Grå celle: kan ikke beregnes.

Samlet overlevelse

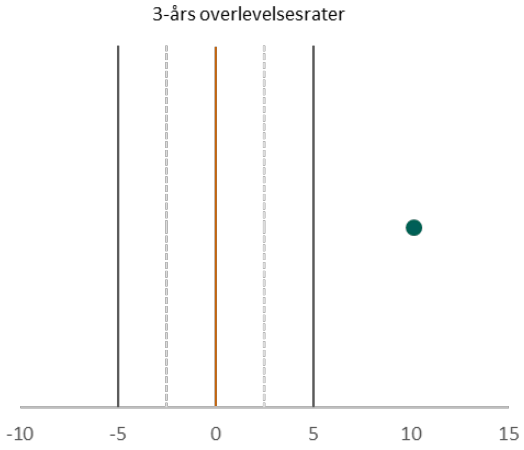
Som beskrevet i protokollen er effektmålet *overlevelse* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi behandlingsmålet ved knoglemarvskræft er at sikre længst mulig overlevelse under hensyntagen til patientens livskvalitet. Som beskrevet i afsnit 5.1.2 vurderes data ikke at være modne, hvilket betyder, at estimaterne er usikre. Fagudvalget tager højde for denne usikkerhed i kategoriseringen af værdien for effektmålet *overlevelse*.

Den mediane overlevelse er ikke nået i nogen af de to arme i ALCYONE-studiet. Den foreløbige værdi for forskellen i medianer kan derfor ikke kategoriseres.

Den absolutte forskel i overlevelsesrater efter 3 år er 10,1 procentpoint (78,0 % [73,2; 82,0] for DaraBorMelPred og 67,9 % [62,6; 72,6] for BorMelPred). Ansøger har beregnet et konfidensinterval: [5,4; 14,8] efter anmodning fra fagudvalget. Det indebærer imidlertid usikkerhed at beregne konfidensintervaller omkring forskelle i overlevelsesrater, især når konfidensintervallerne omkring overlevelsesraterne pr. arm ikke er symmetriske. Derfor anvendes konfidensintervallet ikke i vurderingen. Punktestimatet er afbildet i Figur 2. Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel. Da konfidensintervallet er for usikkert til at kunne anvendes i vurderingen, kan den foreløbige værdi ikke kategoriseres.

Den mediane PFS er 36,4 [32,1; 45,9] måneder for DaraBorMelPred og 19,3 [18; 20,4] måneder for BorMelPred. Da der ikke kan beregnes et konfidensinterval omkring forskellen, kan den foreløbige værdi ikke kategoriseres.

Baseret på den relative effektforskel, som fremgår af tabel 3, har DaraBorMelPred foreløbigt en stor merværdi vedr. både overlevelse (HR 0,60 [0,46; 0,80]) og PFS (HR: 0,42 [0,34; 0,51]).



Figur 2: Punktestimat for den absolutte forskel for 3-års-overlevelsesrater. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Fagudvalget vurderer, at DaraBorMelPred aggregeret har en merværdi af ukendt størrelse vedr. overlevelse, sammenlignet med BorMelPred.

Punktestimaterne for median overlevelse og median PFS overstiger den mindste klinisk relevante forskel, og de relative effektforskelle indikerer en stor merværdi. Selv om data umiddelbart tyder på en stor merværdi, bør det tolkes med varsomhed, idet overlevelsesdata vurderes at være umodent. Fagudvalget mener, at data

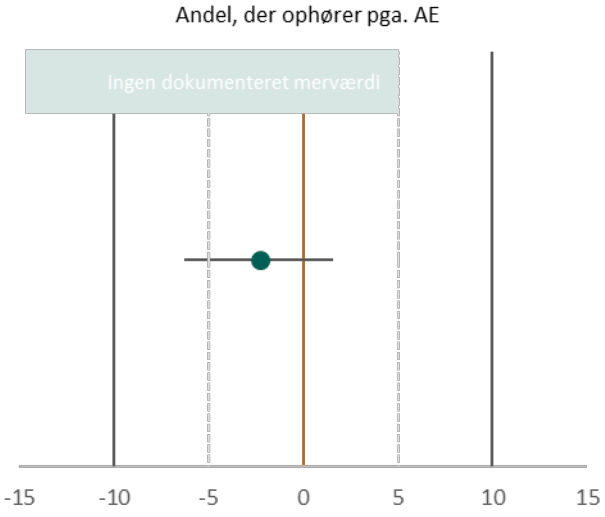
tydeligt indikerer, at DaraBorMelPred har en merværdi, men den eksakte kategori (lille, moderat eller stor) kan ikke fastsættes grundet usikkerhederne.

Fagudvalget bemærker, at kun 10 % patienterne, der i studiet fik BorMelPred, blev behandlet med daratumumab efterfølgende. I dansk praksis vil næsten alle patienter på et tidspunkt blive behandlet med daratumumab, hvilket formodes at forbedre overlevelsen. Dette bidrager til usikkerheden på overførbarheden af størrelsesordenen på effektforskellen til den danske population.

Behandlingsophør

Som beskrevet i protokollen er effektmålet *behandlingsophør grundet uønskede hændelser* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det udtrykker, hvor godt behandlingen tolereres af patienterne.

Forskellen i andelen af patienter, som oplever hændelser, der medfører behandlingsophør, er -2,3 [-6,3; 1,6] procentpoint, som vist i Figur 3. Andelen, der ophørte behandlingen på grund af uønskede hændelser, var for DaraBorMelPred 24 ud af 346 (6,9 %) og for BorMelPred 33 ud af 354 (9,3 %). Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor er den foreløbige værdi af DaraBorMelPred vedr. behandlingsophør ingen dokumenteret merværdi.



Figur 3: Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel, der ophører behandling grundet uønskede hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Baseret på den relative effektforskel (RR 0,74 [0,44; 1,21]), som fremgår af tabel 3, kan værdien af DaraBorMelPred foreløbigt ikke kategoriseres vedr. behandlingsophør.

Fagudvalget vurderer, at DaraBorMelPred aggregeret har ingen dokumenteret merværdi vedr. behandlingsophør, fordi data ikke viser, at der er forskel sammenlignet med BorMelPred.

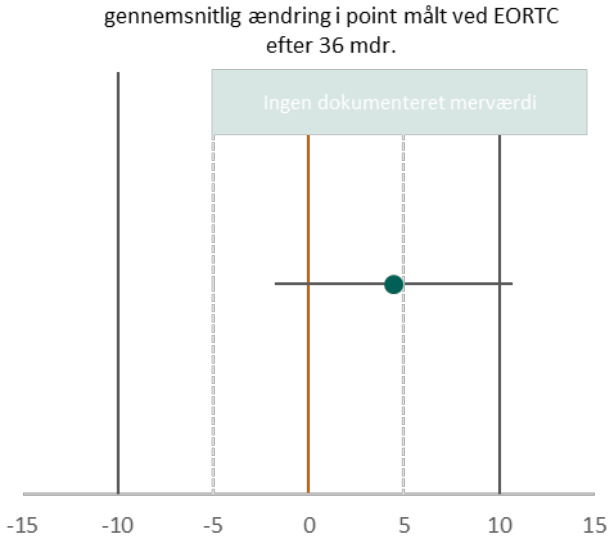
Fagudvalget bemærker, at behandlingsophør ikke forekommer oftere, selv om der tillægges endnu et lægemiddel til behandlingen. Fagudvalget tilskriver dette, at bivirkningerne ved daratumumab generelt, i overensstemmelse med fagudvalgets kliniske erfaring, er acceptable for patienterne og håndterbare i klinisk praksis.

Livskvalitet

Som beskrevet i protokollen er effektmålet *livskvalitet* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi både sygdommen i sig selv samt bivirkninger ved behandlingerne direkte påvirker patientens livskvalitet. Desuden findes endnu ingen kurative behandlingsformer, og en række af lægemidlerne gives kontinuerligt indtil progression. Patienterne lever derfor med at være i behandling i en stor del af tiden.

Efter tre år havde patienter i behandling med DaraBorMelPred en gennemsnitlig stigning i livskvalitet på 12,3 [8,8; 15,8] point, målt med spørgeskemaet EORTC QLQ-C30 på en skala fra 0-100. For patienter i behandling med BorMelPred var den gennemsnitlige stigning på 7,9 [2,5; 13,2]. Dermed er punktestimatet for den absolutte effektforskel 4,4 [-1,8; 10,7] point, som vist i Figur 4. Dette afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har DaraBorMelPred foreløbigt ingen dokumenteret merværdi vedr. livskvalitet.

Disse data er for den længste opfølgningstid; tre år. På det tidspunkt var der data tilgængeligt for 80 patienter i behandling med DaraBorMelPred og 31 patienter i behandling med BorMelPred. Til sammenligning var der efter tre måneder data for henholdsvis 262 og 245 patienter. Her var der en gennemsnitlig stigning i livskvalitet på 7,3 [5,1; 9,5] point for DaraBorMelPred og 3,9 [1,6; 6,2] for BorMelPred. Dermed var forskellen 3,4 [0,5; 6,4]; omtrent den samme uanset om livskvaliteten blev målt efter tre måneder eller tre år.



Figur 4: Punktestimat og 95 % konfidensinterval for den absolutte forskel for livskvalitet. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Da der kun er efterspurgt data for livskvalitet, der kan opgøres på den absolutte skala, er der ikke et relativt effektestimat for livskvalitet

Fagudvalget vurderer, at DaraBorMelPred aggregeret har ingen dokumenteret merværdi vedr. livskvalitet, fordi data ikke viser, at der er forskel sammenlignet med BorMelPred.

Bivirkninger

I protokollen er angivet, at fagudvalget ønskede en opgørelse af de hyppigste bivirkninger af enhver grad (forekommer hos > 10 % af patienterne) samt alle bivirkninger af grad 3-4, der er rapporteret i de kliniske studier, hvor DaraBorMelPred er undersøgt som behandling til nydiagnosticerede patienter med knoglemarvskræft.

Ansøger har angivet *treatment emergent adverse events (TEAE), det vil sige* de uønskede hændelser, som forekommer efter opstart af behandlingen, hos mindst 10 % af patienterne. Disse fremgår af bilag 3.

Ansøger har angivet de hyppigste grad 3-4 uønskede hændelser. For at kunne sammenligne på tværs af komparatorer, har ansøger valgt at angive de grad 3-4 uønskede hændelser, der forekommer hos mindst 5 % af patienterne. Disse fremgår af Tabel 4.

Fagudvalget bemærker, at der er en højere frekvens af luftvejsinfektioner og infektioner generelt, både når det drejer sig om uønskede hændelser af enhver grad og dem af grad 3/4. Herudover ser DaraBorMelPred ikke ud til at være forbundet med væsentligt flere bivirkninger end BorMelPred alene. Det er kendt, at behandling med daratumumab påvirker infektionsfrekvensen i særligt de øvre luftveje, men fagudvalget vurderer, at de hændelser vil være håndterbare i klinikken. Det stemmer også overens med et tilsyneladende sammenligneligt behandlingsophør ved de to behandlinger.

Tabel 4: Uønskede hændelser grad 3-4, som forekommer hos mindst 5 % af patienterne. Upublicerede data-on-file fra ALCYONE-studiet med en median opfølgningstid på 40,1 mdr.

	DaraBorMelPred (n = 346)	BorMelPred (n = 354)
Reference	Janssen, data-on-file	Janssen, data-on-file
Patients with Grade 3 or 4 TEAEs	277 (80,1%)	274 (77,4%)
Blood and lymphatic system disorders	**211 (61,0%)**	**219 (61,9%)**
Neutropenia	139 (40,2%)	138 (39,0%)
Anaemia	60 (17,3%)	70 (19,8%)
Thrombocytopenia	120 (34,7%)	134 (37,9%)
Lymphopenia	27 (7,8%)	22 (6,2%)
Leukopenia	28 (8,1%)	30 (8,5%)
Infections and infestations	**92 (26,6%)**	**53 (15,0%)**
Pneumonia	45 (13,0%)	15 (4,2%)
Respiratory, thoracic and mediastinal disorders	**30 (8,7%)**	**13 (3,7%)**
Hypertension	19 (5,5%)	6 (1,7%)

5.1.5 Effektestimater og kategorier – komparator LenDex

Af tabel 5 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1, komparator LenDex.

Sammenligningen er foretaget på baggrund af en netværksmetaanalyse af de relative effektestimater. Ansøger har beregnet de absolutte effektestimater for overlevelse og PFS ved en naiv sammenligning af effektestimaterne fra arme i to forskellige studier (ALCYONE og FIRST). Forskellene på de absolutte effektmål for *overlevelse* og *PFS* vil derfor ikke blive anvendt i kategoriseringen.

Den absolutte forskel på behandlingsophør mellem DaraBorMelPred og LenDex er beregnet på baggrund af det relative effektestimat og en antaget hændelsesrate i komparatorgruppen på 13,15 %. Den antagede hændelsesrate er baseret på data fra FIRST-studiet og stemmer overens med niveauet i dansk klinisk praksis.

Tabel 5. Resultater for klinisk spørgsmål 2 (indirekte analyse af DaraBorMelPred sammenlignet med LenDex, baseret på date fra studierne ALCYONE og FIRST)

Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel [95 % CI]	Foreløbig værdi	
Samlet overlevelse	Median overlevelse (MKRF: 6 mdr)	Kritisk	*Medianen er ikke nået, og data er ikke modne*	Kan ikke kategoriseres	HR: 0,86 [0,56; 1,32] *Data er ikke modne*	Kan ikke kategoriseres	Kan ikke kategoriseres
	Overlevelsesrate ved tre år (såfremt data for median overlevelse ikke er modne) (MKRF: 5 procentpoint)	Kritisk	*Beregnet ved en naiv sammenligning. Data er ikke modne*	Kan ikke kategoriseres			
	Median PFS (såfremt data for overlevelse ikke er modne) (MKRF: 6 mdr)	Vigtig	*Beregnet ved en naiv sammenligning. Data er ikke modne*	Kan ikke kategoriseres	HR: 0,43 [0,27; 0,68] *Data er ikke modne*	Stor merværdi	
Behandlingsophør	Andel, der ophører med behandling pga. uønskede hændelser (adverse events) (MKRF: 10 procentpoint)	Kritisk	-10,78 [-12,23; -6,84] procentpoint	Merværdi af ukendt størrelse	RR: 0,18 [0,08; 0,48]	Stor merværdi	Stor merværdi
Livskvalitet	Pointændring over tid målt med EORTC QLQ-C30 (MKRF: 10 point)	Vigtig	i.a.	-			Kan ikke kategoriseres
Bivirkninger	Kvalitativ gennemgang	Vigtig					
Samlet kategori for lægemidlets værdi		Merværdi af ukendt størrelse					
Kvalitet af den samlede evidens		Meget lav					

CI = konfidensinterval, HR = hazard ratio, RR = relativ risiko. i.a. = ikke angivet. Grå celle: kan ikke beregnes/vurderes.

Samlet overlevelse

Som beskrevet i protokollen er effektmålet *overlevelse* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi behandlingsmålet ved knoglemarvskræft er at sikre længst mulig overlevelse under hensyntagen til patientens livskvalitet. Som beskrevet i afsnit 5.1.2 vurderes data ikke at være modne, hvilket betyder, at estimaterne er usikre. Fagudvalget tager højde for denne usikkerhed i kategoriseringen af værdien for effektmålet *overlevelse*.

Den mediane overlevelse er ikke nået for hverken DaraBorMelPred eller LenDex. Den foreløbige værdi for forskellen i medianer kan derfor ikke kategoriseres.

Den relative effektforskel for overlevelse er baseret på den indirekte sammenligning i netværksmetaanalysen, HR 0,86 [0,56; 1,32]. Konfidensintervallet indeholder både positiv og negativ værdi og indebærer en stor usikkerhed. Derfor kan den foreløbige værdi ikke kategoriseres.

Den relative effektforskel for PFS er baseret på den indirekte sammenligning i netværksmetaanalysen. Baseret på den relative effektforskel (HR: 0,43 [0,27; 0,68]) har DaraBorMelPred foreløbigt en stor værdi vedr. PFS. Data for PFS er imidlertid ikke modne.

Ansøger bemærker, at antagelserne for at kunne beregne de absolutte forskelle baseret på HR for overlevelse og PFS ikke er opfyldte. Derfor har ansøger foretaget en naiv sammenligning af overlevelsesraten efter 3 år, baseret på data fra arme i to forskellige studier. Her er forskellen 12 procentpoint (78,0 % [73,2; 82,0] for DaraBorMelPred og 66 % for LenDex). Dette estimat er meget usikkert og kan ikke lægges til grund for vurderingen. Ud fra en naiv sammenligning er forskellen i den mediane PFS 15,4 måneder (36,4 [32,1 – 45,9] måneder for DaraBorMelPred og 21 måneder for LenDex). Dette estimat er meget usikkert og kan ikke lægges til grund for vurderingen.

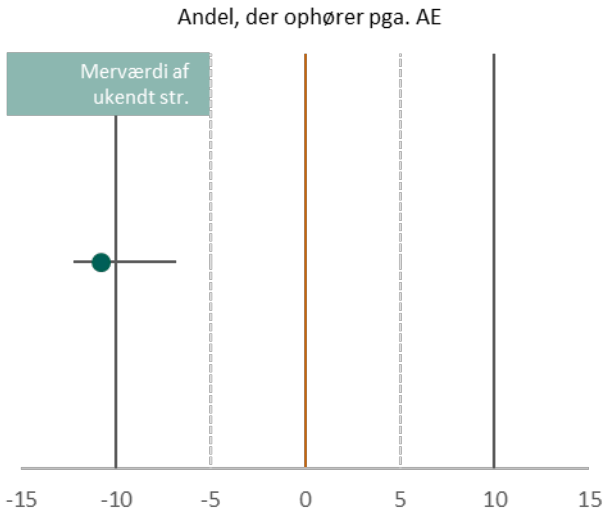
Fagudvalget vurderer, at den aggregerede værdi for DaraBorMelPred vedr. overlevelse ikke kan kategoriseres, fordi data er behæftet med stor usikkerhed, idet der er tale om en indirekte sammenligning af umodne data.

Behandlingsophør

Som beskrevet i protokollen er effektmålet *behandlingsophør grundet uønskede hændelser* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det udtrykker, hvor godt behandlingen tolereres af patienterne.

Andelen, der ophørte behandlingen på grund af uønskede hændelser, var for DaraBorMelPred 24 ud af 346 (6,8 %) og for LenDex 71 ud af 540 (12,2 %). Fagudvalget bemærker, at der er forskel på den mediane opfølgningstid i studierne, 40 måneder i ALCYONE-studiet (DaraBorMelPred) og 67 måneder i FIRST (LenDex). Omvendt er LenDex en tidsafgrænset behandling, hvorimod behandlingen med DaraBorMelPred fortsætter til progression. Dette kan medvirke til at øge usikkerheden på forskellen i behandlingsophør.

Punktestimatet for den absolutte effektforskel er beregnet ud fra den relative risiko baseret på eventraten for LenDex-armen. Den beregnede forskel er -10,78 [-12,23; -6,84] procentpoint, som vist i Figur 5. Dette afspejler en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet er tættere på den klinisk relevante forskel end på 0 (ingen effekt). Derfor er den foreløbige værdi af DaraBorMelPred en stor merværdi vedr. behandlingsophør.



Figur 5: Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel, der ophører behandling grundet uønskede hændelser. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Baseret på den relative effektforskel (RR: 0,18 [0,08; 0,48]), som fremgår af tabel 5, har DaraBorMelPred foreløbigt en stor merværdi vedr. behandlingsophør.

Fagudvalget vurderer, at DaraBorMelPred aggregeret har en stor merværdi vedr. behandlingsophør, fordi data indikerer, at behandlingen er veltolereret og forbundet med et klinisk relevant mindre behandlingsophør.

Livskvalitet

Som beskrevet i protokollen er effektmålet livskvalitet vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi både sygdommen i sig selv samt bivirkninger ved behandlingerne direkte påvirker patientens livskvalitet. Desuden findes endnu ingen kurative behandlingsformer, og en række af lægemidlerne gives kontinuerligt indtil progression. Patienterne lever derfor med at være i behandling i en stor del af tiden.

Ansøger har ikke indsendt data for livskvalitet for sammenligningen mellem DaraBorMelPred og LenDex. Derfor har fagudvalget foretaget en naiv sammenligning baseret på data fra studierne.

Efter tre år havde patienter i behandling med DaraBorMelPred en gennemsnitlig stigning i livskvalitet på 12,3 [8,8; 15,8] point, målt med spørgeskemaet EORTC QLQ-C30 på en skala fra 0-100 *(global health)*. For patienter i behandling med LenDex var den gennemsnitlige stigning målt på samme skala 5 point (standardafvigelse 27,33) ved længste opfølgningstid (ikke nærmere angivet). Med en naiv sammenligning er forskellen 7,3 point. Dette afspejler ikke en klinisk relevant effektforskel. På grund af den store usikkerhed kan værdien ikke kategoriseres vedr. livskvalitet.

Bivirkninger

I protokollen blev defineret, at fagudvalget ønskede en opgørelse af de hyppigste bivirkninger af enhver grad (forekommer hos > 10 % af patienterne) samt alle bivirkninger af grad 3-4, der er rapporteret i de kliniske studier, hvor DaraBorMelPred er undersøgt som behandling til nydiagnosticerede patienter med knoglemarvskræft. Desuden en vurdering af om sammenligningen af hændelsesfrekvenser kan foretages på

forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling og hvordan bivirkningerne er opgjort og rapporteret.

Ansøger bemærker, at dataindsamling og rapportering af uønskede hændelser er sammenlignelige mellem de to studier ALCYONE og FIRST. Uønskede hændelser blev i begge studier rapporteret i overensstemmelser med de internationalt anerkendte kriterier defineret af *the National Cancer Institute Common Terminology Criteria for Adverse Events*.

Ansøger har angivet *treatment emergent adverse events (TEAE)*, det vil sige de uønskede hændelser, som forekommer efter opstart af behandlingen hos mindst 10 % af patienterne. Disse fremgår af Bilag 3.

De hyppigste grad 3-4 uønskede hændelser er angivet i tabel 6. For at kunne sammenligne på tværs af komparatorer har ansøger valgt at angive de grad 3-4 uønskede hændelser, der forekommer hos mindst 5 % af patienterne.

Fagudvalget bemærker, at der ikke er forskel på andelen af patienter, der oplever grad 3-4 uønskede hændelser. Der er generelt en højere frekvens af hæmatologiske hændelser også af grad 3-4 ved behandling med DaraBorMelPred – særligt fremhæves trombocytopeni og neutropeni af grad 3-4, og frekvensen af øvre luftvejsinfektioner er også forhøjet. Fagudvalget vurderer, at bivirkningsprofilen for DaraBorMelPred er håndterbar, da neutropeni og infektioner ofte kan forebygges ved anvendelse af G-CSF og trombocytopeni ved dosisreduktion. Data indikerer, at det ikke er hændelser af grad 3-4, der driver det højere behandlingsophør ved behandling med LenDex, men at forskellen måske snarere skal findes i summen af mange mindre alvorlige bivirkninger, såsom træthed og gener fra mave-tarm-systemet.

Tabel 6: Uønskede hændelser grad 3-4, som er rapporteret hos mindst 5 % af patienterne. For DaraBorMelPred er angivet upublicerede data-on-file fra ALCYONE-studiet med en median opfølgningstid på 40,1 mdr. For LenDex er angivet data fra FIRST-studiet med en median opfølgningstid på 37 mdr. Bindestreg angiver, at forekomsten er under 5 % eller ikke er rapporteret.

	DaraBorMelPred (n = 346)	LenDex (n = 540)
Reference	Janssen, data-on-file	BenBoubker et al. 2014. table 3 p. 915 (12)
Analysis set: safety	346	540
Total number of subjects with toxicity grade 3 or 4 TEAE	277 (80,1%)	433 (80%)
MedDRA system organ class / preferred term		
Blood and lymphatic system disorders	**211 (61,0%)**	-
Neutropenia	139 (40,2%)	143 (26%)
Thrombocytopenia	120 (34,7%)	43 (8%)
Anaemia	60 (17,3%)	85 (16%)
Leukopenia	28 (8,1%)	30 (6%)
Lymphopenia	27 (7,8%)	18 (3%)
Infections and infestations	**92 (26,6%)**	**118 (22%)**
Pneumonia	45 (13,0%)	45 (8%)
Respiratory, thoracic and mediastinal disorders	**30 (8,7%)**	**-**
Dyspnea	-	22 (4%)
Hypertension	**19 (5,5%)**	**-**
Cardiac disorder	**-**	**39(7%)**
Fatigue	**-**	**46 (9%)**
Asthenia	**-**	**33 (6%)**
Back pain	**-**	**34 (6%)**
Hypokalemia	**-**	**20 (4%)**
Hyperglycemia	**-**	**23 (4%)**
Rash	**-**	**28 (5%)**
Cataracts	**-**	**14 (3%)**
Constipation	**-**	**10 (2%)**
Peripheral sensory neuropathy	**-**	**2 (<1%)**

ALCYONE: Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

5.1.6 Effektestimater og kategorier – komparator BorLenDex

Det er ikke muligt at foretage sammenlignende analyser mellem DaraBorMelPred og BorLenDex, fordi data stammer fra to studier (ALCYONE og SWOG S0777), hvor populationerne er for forskellige til, at en statistisk sammenlignende analyse bør foretages. Ansøger har derfor foretaget naive sammenligninger for effektmålene *OS* og *PFS*. Fagudvalget har foretaget en naiv sammenligning for effektmålet *behandlingsophør*. Resultaterne fremgår af Tabel 7.

Tabel 7: Resultater for klinisk spørgsmål 3 (naive sammenligninger af DaraBorMelPred sammenlignet med BorLenDex, baseret på data fra studierne ALCYONE og SWOG S0777). For median PFS er angivet data fra to subgrupper fra SWOG S0777-studiet, som fagudvalget vurderer, er mere sammenlignelige med populationen i ALCYONE-studiet; ikke kandidater til HDT/STS og alder ≥ 65 år.

	DaraBorMelPred	BorLenDex	Naiv sammenligning
Median OS	Medianen er ikke opnået, og data er ikke modne	Medianen er ikke opnået, og data er ikke modne	-
Overlevelsesrate ved 3 år (%)	78,0 [73,2; 82,0]	Ikke rapporteret	-
Median PFS (mdr.)	36,4 [32,1; 45,9]	41,7 [33,1; 51,1]	5,3
Ikke kandidater til HDT/STS		37,5 [22,6; 50,3]	1,1
Alder ≥ 65 år		34	2,4
Behandlingsophør	24 ud af 346 (6,9 %)	55 ud af 241 (22,8 %)	15,9 procentpoint

Samlet overlevelse

Som beskrevet i protokollen er effektmålet *overlevelse* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi behandlingsmålet ved knoglemarvskræft er at sikre længst mulig overlevelse under hensyntagen til patientens livskvalitet.

Ansøger beskriver, at data for median OS ikke er modne for DaraBorMelPred, og at der ikke er rapporteret overlevelse ved 36 måneders opfølgning for BorLenDex. Da der således ikke findes modne overlevelsesdata, har ansøger beskrevet data for PFS.

Den mediane PFS var for DaraBorMelPred 36,4 [32,1; 45,9] måneder og for BorLenDex 41,7 [33,1; 51,1] måneder. Forskellen er 5,3 måneder, hvilket er større end den mindste klinisk relevante forskel på 3 måneder som defineret i protokollen. Ansøger understreger, at en sammenligning mellem disse estimater skal tolkes med forbehold, fordi patienterne, der fik BorLenDex, i gennemsnit var yngre og med bedre funktionsniveau end patienterne, der fik DaraBorMelPred. Ansøger præsenterer eksplorative subgruppeanalyser for at belyse effekten af BorLenDex hos den del af patientpopulationen, der ligner den danske population bedst. For subgruppen af patienter, som ikke var kandidater til HDT/STS, var den mediane PFS 37,5 måneder [22,6; 50,3]. For subgruppen af patienter, som var mindst 65 år, var den mediane PFS 34 måneder (intet estimat for usikkerhed angivet). Ansøger understreger også her, at studiepopulationerne ikke er fuldt sammenlignelige. Fagudvalget vurderer dog, at disse subgruppepopulationer er tilstrækkeligt sammenlignelige med populationen i ALCYONE-studiet.

Da der ikke er foretaget en sammenlignende analyse, kan værdien vedr. effektmålet *overlevelse* ikke kategoriseres. Fagudvalget vurderer, at DaraBorMelPred på baggrund af datamaterialet ser ud til ikke at være et dårligere behandlingsalternativ end BorLenDex.

Behandlingsophør

Som beskrevet i protokollen er effektmålet *behandlingsophør grundet uønskede hændelser* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det udtrykker, hvor godt behandlingen tolereres af patienterne.

Andelen, der ophørte behandlingen på grund af uønskede hændelser, var for DaraBorMelPred 24 ud af 346 (6,9 %) og for BorLenDex 55 ud af 241 (22,8 %). I en naiv sammenligning er forskellen således 15,9 procentpoint, hvilket overstiger den mindste klinisk relevante forskel på 10 procentpoint.

Da der ikke er foretaget en sammenlignende analyse, kan værdien vedr. effektmålet *behandlingsophør* ikke kategoriseres. Fagudvalget vurderer, at DaraBorMelPred ser ud til at være forbundet med et lavere behandlingsophør end BorLenDex. Fagudvalget bemærker, at resultater for effektmålet *behandlingsophør* sandsynligvis er underestimeret i SWOG-studiet, fordi studiepopulationen er yngre og med bedre performance end den danske patientpopulation, og man derfor vil forvent,e at de tolererer behandlingen bedre.

Livskvalitet

Da der ikke er rapporteret data for livskvalitet for BorLenDex (SWOG S0777), er det ikke muligt at sammenligne effekten på livskvalitet i forhold til DaraBorMelPred. Værdien vedr. effektmålet *livskvalitet* kan derfor ikke kategoriseres.

Bivirkninger

I protokollen blev defineret, at fagudvalget ønskede en opgørelse af de hyppigste bivirkninger af enhver grad (forekommer hos > 10 % af patienterne) samt alle bivirkninger af grad 3-4, der er rapporteret i de kliniske

studier, hvor DaraBorMelPred er undersøgt som behandling til nydiagnosticerede patienter med knoglemarvskræft. Desuden en vurdering af om sammenligningen af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling og hvordan bivirkningerne er opgjort og rapporteret.

Ansøger har angivet *treatment emergent adverse events (TEAE)*, det vil sige de uønskede hændelser, som forekommer efter opstart af behandlingen, hos mindst 20 % af patienterne, fordi der ikke er data tilgængelige for uønskede hændelser hos mindst 10 % af de patienter, der bliver behandlet med BorLenDex. Data fremgår af bilag 3.

Ansøger beskriver, at dataindsamling og rapportering af uønskede hændelser er sammenlignelige mellem de to studier, ALCYONE og SWOG S0777. I EMAs EPAR for lenalidomid er rapporteret uønskede hændelser af enhver grad, som forekommer hos mindst 20 % af patienterne under initial behandling med BorLenDex (de første 24 uger). For at få den bedste sammenligning har ansøger angivet data for DaraBorMelPred, hvor uønskede hændelser af enhver grad, som forekommer hos mindst 20 % af patienterne, er rapporterede [REF].

Ansøger bemærker, at forskelle i studiepopulationerne kan føre til bias til fordel for BorLenDex. Desuden har SWOG S0777 længere opfølgningstid end ALCYONE. Dog inkluderer data rapporteret for BorLenDex kun de første 24 ugers behandling, mens data for DaraBorMelPred også inkluderer perioden med daratumumab indtil progression.

Baseret på opgørelsen er den samlede byrde af grad 3-4 hændelser sammenlignelig for de to behandlinger. Der er flere hæmatologiske hændelser ved behandling med DaraBorMelPred, mens behandling med BorLenDex er forbundet med hyppigere forekomst af perifer neuropati og andre bivirkninger, der for patienten opleves som meget generende, herunder embolier, træthed, synkope og lavt blodtryk.

Tabel 8: Uønskede hændelser grad 3-4, som forekommer hos mindst 5 % af patienterne. For DaraBorMelPred er angivet upublicerede data-on-file fra ALCYONE-studiet med en median opfølgningstid på 40,1 mdr. For BorLenDex (undersøgt i SWOG S0777-studiet) er angivet data fra EPAR'en for lenalidomid [REF] for den initiale behandlingsperiode (24 uger). Bindestreg angiver, at forekomsten er under 5 % eller ikke er rapporteret.

	DaraBorMelPred (n = 346)	**BorLenDex (n = 262)**
Reference	Janssen, data-on-file	EPAR. Cutoff 01. December 2016, table 41 p. 55 (6)
Number of patients	346	262
Total number of subjects with toxicity grade 3 or 4 TEAE	277 (80.1%)	200 (76.3%)
Blood and lymphatic system disorders	**211 (61.0%)**	**104 (39.7%)**
Neutropenia	139 (40.2%)	26 (9.9%)
Thrombocytopenia	120 (34.7%)	45 (17.2%)
Anaemia	60 (17.3%)	32 (12.2%)
Leukopenia	28 (8.1%)	23 (8.8%)
Lymphopenia	27 (7.8%)	49 (18.7%)
Infections and infestations	**92 (26.6%)**	**36 (13.7%)**
Infection	-	1 (0.4%)
Lung infection	-	19 (7.3%)
Pneumonia	45 (13.0%)	-
Respiratory, thoracic and mediastinal disorders	**30 (8.7%)**	**26 (9.9%)**
Dyspnea	-	16 (6.1%)
Vascular disorders	-	**41 (15.6%)**
Hypertension	19 (5.5%)	-
Hypotension	-	20 (7.6%)
Embolism	-	18 (6.9%)
Nervous System Disorders	**-**	**89 (34.0%)**
Syncope	-	23 (8.8%)
Peripheral sensory neuropathy	-	54 (20.6%)

General Disorders and Administration Site Conditions	-	**49 (18.7%)**
Fatigue	-	38 (14.5%)
Investigations	-	**29 (11.1%)**
Alanine aminotransferase increased	-	13 (5.0%)
Renal and Urinary Disorders	-	8 (3.1%)
Renal failure acute	-	7 (2.7%)
Musculoskeletal and Connective Tissue Disorders	-	**45 (17.2%)**
Muscular weakness	-	22 (8.4%)
Metabolism and Nutrition Disorders	-	**85 (32.4%)**
Hyperglycemia	-	19 (7.3%)
Hyponatremia	-	17 (6.5%)
Hypokalemia	-	30 (11.5%)
Hypocalcemia	-	17 (6.5%)
Dehydration	-	22 (8.4%)

6 Andre overvejelser

Administrationsform
Daratumumab er oprindeligt godkendt af EMA til intravenøs administration, men blev i juni 2020 også godkendt af EMA til subkutan administration. Et studie [21] viser, at responsrater, median PFS samt sikkerhedsprofil er sammenlignelige for de to administrationsformer, men at patienttilfredsheden generelt er højere ved subkutan administration, hvor der også er færre infusionsrelaterede reaktioner. Den gennemsnitlige opfølgningstid i studiet er 7,5 måneder, og overlevelsesdata er ikke modne. Fagudvalget vurderer, at administrationsformerne kan betragtes som ligeværdige, og begge kan anvendes.

Efterfølgende behandlinger
Af protokollen fremgår et ønske fra fagudvalget om, at ansøger så vidt muligt belyser, hvilke behandlinger patienterne, der indgik i ALCYONE-studiet, modtager efterfølgende, herunder andelen af patienter i henholdsvis interventions- og kontrolarmen, der får daratumumab i senere behandlingslinjer.

Ansøger har svaret på dette med følgende oplysninger:

I ALCYONE-studiet fik 317 patienter 2.-linjebehandling (33 % af 350 patienter i DaraBorMelPred-armen og 57 % af 356 patienter i BorMelPred-armen).

Ud af de 317 patienter fik 22 daratumumab som 2.-linjebehandling:

- 21 (10,4 %) i BorMelPred-armen
    - 12 fik daratumumab/lenalidomid/dexamethason
    - 5 fik daratumumab/bortezomib/dexamethason
    - 2 fik daratumumab/carfilzomib/dexamethason
    - 2 fik daratumumab monoterapi
- 1 (0,9 %) i DaraBorMelPred-armen.
    - 1 fik daratumumab/lenalidomid/dexamethason

Ud af de 317 patienter fik tre patienter, alle fra BorMelPred-armen, en anden CD38-behandling (carfilzomib/dexamethason/isatuximab). Dette var kun rapporteret, hvis mindst 3 patienter fik det.

Fagudvalget bemærker, at det er en forholdsvis lille andel, som får daratumumab efter behandling med BorMelPred, sammenlignet med dansk praksis. Denne forskel kan betyde, at den samlede overlevelse i BorMelPred-armen er underestimeret i forhold til dansk praksis, da daratumumab i efterfølgende linjer er forbundet med forbedret overlevelse.

Konsekvenser af introduktion af daratumumab i første linje
Af protokollen fremgår et ønske fra fagudvalget om informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlingerne i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

Ansøgers svar er opsummeret i det følgende:

Introduktionen af DaraBorMelPred i første linje forventes at påvirke både valg af førstelinjebehandling og efterfølgende behandlinger. Ansøger forventer, at størstedelen af de patienter, som får DaraBorMelPred i første linje, vil få en lenalidomidholdig behandling i anden linje. Dette kan være elotuzumab + lenalidomid + dexamethason (EloLenDex), baseret på nuværende lægemiddelrekommendation (maj 2020), hvor EloLenDex er førstevalg til patienter, der ikke kan få daratumumab i anden linje. Andenvalget til disse patienter er carfilzomib + lenalidomid + dexamethason (CarLenDex), som ansøger også forventer vil blive anvendt. Ansøger bemærker, at der muligvis vil være en præference for hjemmeadministration, og at nogle patienter forventes at blive tilbudt LenDex på trods af muligheden for mere effektive behandlinger. Fagudvalget er enig i ansøgers betragtninger, men bemærker at ixazomib + lenalidomid + dexamethason (IxaLenDex) også er en behandlingsmulighed til patienter, som har et ønske om tabletbehandling, og at denne behandling formentlig vil blive foretrukket frem for LenDex.

Ansøger forventer også, at nogle patienter ikke vil få en lenalidomidholdig behandling i anden linje, men i stedet blive tilbudt f.eks. pomalidomid + bortezomib + dexamethason (PomBorDex) eller carfilzomib + dexamethason (CarDex). Fagudvalget bemærker, at dette kun vil gælde et lille mindretal, da man i dansk praksis stort set altid vil vælge at behandle med lenalidomid efter behandling med daratumumab.

Ansøger finder det usandsynligt, at behandlingsvarighed og effekt bliver negativt påvirket ved introduktion af DaraBorMelPred som førstelinjebehandling, da virkningsmekanismen af daratumumab adskiller sig fra de øvrige behandlingsalternativer i 2. og 3. linjer.

Ansøger bemærker, at introduktion af DaraBorMelPred i første linje ikke vil udelukke senere anvendelse af proteasominhibitorer (f.eks. bortezomib), da anvendelsen af bortezomib i DaraBorMelPred-behandlingen er tidsbegrænset og ikke fortsætter til progression.

Fagudvalget har ingen bemærkninger til ansøgers svar.

7 Fagudvalgets konklusion

Komparator BorMelPred
Fagudvalget vurderer, at DaraBorMelPred giver en **merværdi af ukendt størrelse** sammenlignet med BorMelPred til nydiagnosticerede patienter med knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte.

Fagudvalget lægger vægt på, at data for overlevelse og PFS indikerer, at der er en stor merværdi, men at de umodne data sammen med den lave andel, der behandles med daratumumab i BorMelPred armen efterfølgende, bidrager med usikkerhed på effektforskellen. Samtidig ser behandling med DaraBorMelPred ikke ud til at være forbundet med væsentligt flere bivirkninger, forringet livskvalitet eller højere behandlingsophør.

Komparator LenDex
Fagudvalget vurderer, at DaraBorMelPred giver en **merværdi af ukendt størrelse** sammenlignet med LenDex til nydiagnosticerede patienter med knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte.

Fagudvalget bemærker, at effekten på overlevelse ser ud til at være ligeværdig med LenDex og lægger samtidig vægt på, at behandling med DaraBorMelPred ser ud til at være forbundet med et lavere behandlingsophør.

Komparator BorLenDex
Fagudvalget vurderer, at den samlede værdi af DaraBorMelPred **ikke kan kategoriseres,** jævnfør Medicinrådets metoder, sammenlignet med BorLenDex til nydiagnosticerede patienter med knoglemarvskræft, som ikke er egnede til højdosiskemoterapi med stamcellestøtte, fordi data er usikre og ikke kan sammenlignes i en formel statistisk analyse.

Samlet set vurderer fagudvalget, at DaraBorMelPred effektmæssigt er et ligeværdigt behandlingsalternativ sammenlignet med BorLenDex, på baggrund af tilgængelige data. Fagudvalget har i vurderingen inddraget ansøgers subgruppeanalyser, hvor data indikerer, at den mediane PFS er sammenlignelig for de to behandlinger. Fagudvalget vurderer, at DaraBorMelPred har en mere acceptabel bivirkningsprofil sammenlignet med BorLenDex.

8 Relation til behandlingsvejledning
Medicinrådet er i gang med at udarbejde en behandlingsvejledning, hvor behandlinger til patienter med knoglemarvskræft, der ikke tidligere har været behandlet, vil blive vurderet, herunder DaraBorMelPred.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende knoglemarvskræft (myelomatose)

Formand	**Indstillet af**
Ulf Christian Frølund Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Sjælland
Medlemmer	**Udpeget af**
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11 Versionslog

Version	Dato	Ændring
1.0	23. september 2020	Godkendt af Medicinrådet.

12 Bilag 1: dosering af lægemidler i studierne

Trial	Trial arm	Dosing
ALCYONE	Comparator arm (BorMelPred)	Velcade: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9 + Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9 + Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.
	Experimental arm (DaraBorMelPred)	Daratumumab: 16 mg/kg as intravenous infusion, once weekly, for 6 weeks in Cycle 1 and then once every 3 weeks, in Cycle 2 to 9 and thereafter, once every 4 weeks + Velcade: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9 + Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9 + Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.
FIRST	Comparator arm (MelPredThal)	Melphalan: 0.25 mg/kg/day on days 1 to 4 in 42-day cycles for 72 weeks- 12 cycles + Prednisone: 2 mg/kg/day on days 1 to 4 in 42-day cycles for 72 weeks-12 cycles + Thalidomide: 200 mg/day in 42-day cycles for 72 weeks-12 cycles.
	Experimental arm (LenDex)	Revlimid: 25 mg/day on days 1 to 21 of each 28-day cycles until disease progression + Dexamethasone: 40 mg/day on days 1, 8, 15, and 22 of each 28-day cycles until disease progression.
	Experimental arm (LenDex18)	Revlimid: 25 mg/day on days 1 to 21 of each 28-day cycles for 72 weeks- 18 cycles + Dexamethasone: 40 mg/day on days 1, 8, 15, and 22 of each 28-day cycles for 72 weeks-18 cycles
IFM 01/01	Comparator arm (MelPred)	12 cycles every 6 weeks: melphalan 0.2 mg/kg day 1 to 4, prednisone 2 mg/kg/d day 1 to 4 plus placebo 100mg/d continuously for 18 months
	Experimental arm (MelPredThal)	Melphalan, prednisone, thalidomide; 12 cycles every 6 weeks: melphalan 0.2 mg/kg day 1 to 4, prednisone 2 mg/kg/d day 1 to 4 plus thalidomide 100mg/d continuously for 18 months
IFM 99/06	Comparator arm (MelPred)	Melphalan: 0.25 mg/kg, Prednisone: 2 mg/kg
	Experimental arm (MelPredThal)	Melphalan: 0.25 mg/kg, Prednisone: 2 mg/kg, Thalidomide: not exceeding 400 mg (Thalidomide was stopped at day 4 of the last melphalan and prednisone cycle)
VISTA	Comparator arm (MelPred)	Melphalan: 9 mg/m² on days 1 to 4, during each of nine 6-week cycles + Prednisone: 60 mg/m² on days 1 to 4, during each of nine 6-week cycles.
	Experimental arm (BorMelPred)	Velcade: Twice weekly during cycles 1 to 4 and once weekly during cycles 5 to 9 (all 6-week cycles) + Melphalan: 9 mg/m² on days 1 to 4, during each of nine 6-week cycles + Prednisone: 60 mg/m² on days 1 to 4, during each of nine 6-week cycles.
SWOG S0777	Comparator arm (LenDex)	Dexamethasone PO QD on days 1, 8, 15, and 22 and lenalidomide PO QD on days 1-21. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.
	Experimental arm (BorLenDex)	Dexamethasone PO QD on days 1, 2, 4, 5, 8, 9, 11, and 12; lenalidomide PO QD on days 1-14; and bortezomib IV over 3-5 seconds on days 1, 4, 8, and 11. Treatment repeats every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity.

13 Bilag 2: Evidensens kvalitet

13.1 Cochrane, Risk of Bias

Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool.

Klinisk studie	Effektmål	Risiko for bias i randomiseringsprocessen	Risiko for bias grundet afvigelser fra tilsigtet intervention (effekt af tildeling til intervention)	Manglende data for effektmål	Risiko for bias ved indsamlingen af data	Risiko for bias ved udvælgelse af resultater der rapporteres	Overordnet risiko for bias
ALCYONE NCT02195479	Overlevelse, PFS	Lav risiko for bias	Lav risiko for bias	Høj risiko for bias	Lav risiko for bias	Lav risiko for bias	Forbehold for risiko for bias
	Behandlings-ophør, livskvalitet		Høj risiko for bias		Høj risiko for bias		
FIRST NCT00689936	Overlevelse, PFS	Lav risiko for bias	Lav risiko for bias	Forbehold for risiko for bias	Lav risiko for bias	Lav risiko for bias	Forbehold for risiko for bias
	Behandlings-ophør, livskvalitet		Høj risiko for bias		Høj risiko for bias		
IFM 01/01	Overlevelse, PFS	Forbehold for risiko for bias	Lav risiko for bias	Lav risiko for bias	Lav risiko for bias	Lav risiko for bias	Forbehold for risiko for bias
	Behandlings-ophør, livskvalitet		Lav risiko for bias		Lav risiko for bias		
IFM 99/06 NCT00367185	Overlevelse, PFS	Forbehold for risiko for bias	Lav risiko for bias	Lav risiko for bias	Lav risiko for bias	Lav risiko for bias	Høj risiko for bias
	Behandlings-ophør, livskvalitet		Høj risiko for bias		Høj risiko for bias		
VISTA NCT00111319	Overlevelse, PFS	Forbehold for risiko for bias	Lav risiko for bias	Lav risiko for bias	Lav risiko for bias	Lav risiko for bias	Høj risiko for bias
	Behandlings-ophør, livskvalitet		Høj risiko for bias		Høj risiko for bias		
SWOG S0777 NCT00064038	Overlevelse, PFS	Lav risiko for bias	Lav risiko for bias	Forbehold for risiko for bias	Lav risiko for bias	Lav risiko for bias	Forbehold for risiko for bias
	Behandlings-ophør, livskvalitet		Høj risiko for bias		Høj risiko for bias		

13.2 GRADE-profiler

GRADE-profil for sammenligningen mellem DaraBorMelPred og BorMelPred (ALCYONE-studiet)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	Studiedesign	Risk of bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	DaraBor MelPred	BorMelPred	Relativ [95 % CI]	Absolut		
Overlevelse, median (måneder)												
0											⨁◯◯◯ MEGET LAV	KRITISK
Overlevelse, rate ved 3 år (%)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Data er umodne[b]	350	356	HR: 0,60 [0,46; 0,80]	10,1 [5,4; 14,8] %-point	⨁⨁◯◯ LAV	KRITISK
Progressionsfri overlevelse, median (måneder)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Data er umodne[b]	350	356	HR: 0,42 [0,34; 0,51]	17,1 måned	⨁⨁◯◯ LAV	KRITISK
Behandlingsophør grundet uønskede hændelser (andel som ophører, %)												
1	Randomiseret undersøgelse	Alvorlig[c]	Alvorlig[b]	Ikke alvorlig	Alvorlig[d]	Ingen	346	354	RR: 0,74 [0,44; 1,21]	-2,3%-point [-6,3; -1,6]	⨁⨁◯◯ LAV	KRITISK
Livskvalitet, EORTC QLQ-30 (ændring fra baseline, point)												
1	Randomiseret undersøgelse	Alvorlig[e]	Alvorlig[b]	Ikke alvorlig	Alvorlig[d]	Ingen	80	31	-	4,4 point [-1,8; 10,7]	⨁◯◯◯ MEGET LAV	VIGTIG

CI: Konfidensinterval; HR: Hazard ratio; RR: Relativ risiko

a. Der er kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens.

b. Data er umodne, hvilket øger usikkerheden. Derfor nedgraderes ét niveau.

c. Studiet er ublindet, hvilket kan påvirke rapportering af bivirkninger og andelen, der ophører behandlingen på grund af bivirkninger. Derfor er der nedgraderet ét niveau på grund af risiko for bias.

d. Der er et bredt konfidensinterval, hvilket indikerer stor usikkerhed om estimatet. Derfor nedgraderes ét niveau for unøjagtighed.

e. Studiet er ublindet, hvilket kan påvirke selvrapporteret livskvalitet. Derfor er der nedgraderet et niveau på grund af risiko for bias.

GRADE-profil for sammenligningen mellem DaraBorMelPred og LenDex (FIRST-studiet)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**DaraBor MelPred**	**LenDex**	**Relativ [95 % CI]**	**Absolut**		
Overlevelse, median (måneder)												
0											⨁◯◯◯ MEGET LAV	KRITISK
Overlevelse, rate ved 3 år (%)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Meget alvorlig[c]	Data er umodne[d]	350	541	HR: 0,86 [0,56; 1,32]	12 %-point	⨁◯◯◯ MEGET LAV	KRITISK
Progressionsfri overlevelse, median (måneder)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Data er umodne[d]	350	541	HR: 0,43 [0,27; 0,68]	15,4 måned	⨁◯◯◯ MEGET LAV	KRITISK
Behandlingsophør grundet uønskede hændelser (andel som ophører, %)												
1	Randomiseret undersøgelse	Alvorlig[e]	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	346	540	RR: 0,18 [0,08; 0,48]	-10,78 %-point [-12,23; -6,84]	⨁◯◯◯ MEGET LAV	KRITISK
Livskvalitet, EORTC QLQ-30 (ændring fra baseline til længste opfølgningstid, point)												
1	Randomiseret undersøgelse	Alvorlig[e]	Alvorlig[a]	Alvorlig[b]	Meget alvorlig[f]	Ingen	80	261	-	7,3 point	⨁◯◯◯ MEGET LAV	VIGTIG

CI: Konfidensinterval; HR: Hazard ratio; RR: Relativ risiko.
a. Da effekten for hver behandling kun er undersøgt i ét studie, begge med moderate populationsstørrelser, er der risiko for inkonsistens i forhold til andre potentielle studier.
b. Da der er tale om en indirekte sammenligning, nedgraderes ét niveau for indirekthed.
c. Der er et meget bredt konfidensinterval, hvilket indikerer stor usikkerhed om estimatet. Derfor nedgraderes to niveauer for unøjagtighed.
d. Data er umodne, hvilket øger usikkerheden. Derfor nedgraderes ét niveau.
e. Studierne er ublindede, hvilket kan påvirke rapportering af bivirkninger og andelen, der ophører behandlingen på grund af bivirkninger. Derfor er der nedgraderet ét niveau på grund af risiko for bias.
d. Der er et bredt konfidensinterval, hvilket indikerer usikkerhed om estimatet. Derfor nedgraderes ét niveau for unøjagtighed.
e. Studierne er ublindede, hvilket kan påvirke selvrapporteret livskvalitet. Derfor er der nedgraderet et niveau på grund af risiko for bias.
f. Der er foretaget en naiv sammenligning, hvilket indebærer en stor usikkerhed om estimatet. Derfor er der nedgraderet ét niveau for unøjagtighed.

14 Bilag 3: Uønskede hændelser rapporteret for behandlingerne

Uønskede hændelser, som forekommer hos mindst 10 % af patienterne (for BorLenDex dog uønskede hændelser, som forekommer hos mindst 20 %). Publicerede data fra ALCYONE-studiet [12] samt upublicerede data-on-file fra ALCYONE-studiet med en median opfølgningstid på 40,1 mdr. Data cut-off var juni 2019. For LenDex (undersøgt i FIRST-studiet) er angivet data fra EPAR'en for lenalidomid [22] **med en median opfølgningstid på 37 mdr. For BorLenDex (undersøgt i SWOG S0777-studiet) er angivet data fra EPAR'en for lenalidomid** [22] **for den initiale behandlingsperiode (24 uger). Bindestreg angiver, at forekomsten er under 10 % (for BorLenDex under 20 %) eller ikke er rapporteret.**

	DaraBorMelPred (n = 346)	**BorMelPred (n = 354)**	**LenDex (n = 540)**	**BorLenDex (n = 262)**
Reference	Janssen, data-on-file, Mateos et al 2019; Supplementary appendix. Table S4 p. 13	Janssen, data-on-file	EPAR. table 24 p. 60-61 [22]	EPAR. Cutoff 1. December 2016, table 38 p. 52-53 [22]
Any TEAE	337 (97,4%)	342 (96,6%)	536	
Blood and lymphatic system disorders	**256 (74,0%)**	**269 (76,0%)**	325 (60,2%)	**208 (79.4%)**
Neutropenia	174 (50,3%)	186 (52,5%)	178 (33,0%)	77 (29.4%)
Thrombocytopenia	172 (49,7%)	190 (53,7%)	100 (18,5%)	151 (57.6%)
Anaemia	107 (30,9%)	131 (37,0%)	193 (35,7%)	179 (68.3%)
Leukopenia	47 (13,6%)	53 (15,0%)	60 (11,1%)	109 (41.6%)
Lymphopenia	39 (11,3%)	36 (10,2%)	43 (8,0%)	67 (25.6%)
Infections and infestations	**256 (74,0%)**	**171 (48,3%)**	377 (69,8%)	**92 (35.1%)**
Infection	-	-	-	3 (1.1%)
Upper respiratory tract infection	106 (30,6%)	50 (14,1%)	53 (9,8%)	-
Pneumonia	63 (18,2%)	18 (5,1%)	68 (12,6%)	-
Bronchitis	72 (20,8%)	27 (7,6%)	59 (10,9%)	-
Nasopharyngitis			54 (10,0%)	-
Viral upper respiratory tract infection	49 (14,2%)	23 (6,5%)	-	-
Urinary tract infection	39 (11,3%)	12 (3,4%)	63 (11,7%)	
General disorders and administration site conditions	**212 (61,3%)**	**184 (52,0%)**	430 (79,6%)	**221 (84.4%)**
Pyrexia	89 (25 7%)	74 (20,9%)	102 (18,9%)	37 (14.1%)
Oedema peripheral	68 (19,7%)	39 (11,0%)	169 (31,3%)	122 (46.6%)
Edema	-	-	-	0
Fatigue	60 (17,3%)	51 (14,4%)	177 (32,8%)	193 (73.7%)
Asthenia	48 (13,9%)	43 (12,1%)	123 (22,8%)	-
Gastrointestinal disorders	**195 (56,4%)**	**192 (54,2%)**	411 (76,1%)	**211 (80.5%)**
Diarrhoea	96 (27,7%)	87 (24,6%)	208 (38,5%)	104 (39.7%)
Nausea	75 (21,7%)	76 (21,5%)	128 (23,7%)	98 (37.4%)
Constipation	64 (18,5%)	65 (18,4%)	212 (39,3%)	147 (56.1%)
Vomiting	61 (17,6%)	55 (15,5%)	68 (12,6%)	-
Dyspepsia	-	-	28 (5,2%)	-
Abdominal pain	-	-	41 (7,6%)	-
Dry mouth	-	-	38 (7,0%)	-

Nervous system disorders	**178 (51,4%)**	**181 (51,1%)**	333 (61,7%)	**219 (83.6%)**
Peripheral sensory neuropathy	100 (28,9%)	122 (34,5%)	92 (17,0%)	184 (70.2%)
Peripheral neuropathy	-	-	22 (4,1%)	2 (0.8%)
Tremor	-	-	73 (13,5%)	-
Headache	-	-	52 (9,6%)	-
Dizziness	-	-	70 (13,0%)	76 (29.0%)
Paraesthesia	-	-	74 (13,7%)	3 (1.1%)
Dysgeusia	-	-	-	79 (30.2%)
Musculoskeletal and connective tissue disorders	**159 (46,0%)**	**116 (32,8%)**	-	**185 (70.6%)**
Back pain	61 (17,6%)	42 (11,9%)	-	87 (33.2%)
Arthralgia	39 (11,3%)	22 (6,2%)	-	-
Pain in extremity	38 (11,0%)	22 (6,2%)	-	-
Muscular weakness	-	-	-	64 (24.4%)
Respiratory, thoracic and mediastinal disorders	**149 (43,1%)**	**74 (20,9%)**	-	**150 (57.3%)**
Cough	68 (19,7%)	27 (7,6%)	-	77 (29.4%)
Dyspnoea	44 (12,7%)	16 (4,5%)	-	80 (30.5%)
Metabolism and nutrition disorders	**131 (37,9%)**	**125 (35,3%)**	-	**201 (76.7%)**
Decreased appetite	40 (11,6%)	46 (13,0%)	-	-
Skin and subcutaneous tissue disorders	**95 (27,5%)**	**97 (27,4%)**	-	**113 (43.1%)**
Rash	32 (9,2%)	38 (10,7%)	-	49 (18.7%)
Vascular disorders	**94 (27,2%)**	**52 (14,7%)**	-	-
Hypertension	45 (13,0%)	11 (3,1%)	-	-
Psychiatric Disorders	-	-	-	113 (43.1%)
Insomnia	-	-	-	86 (32.8%)

TRAE: Treatment emergent adverse events (uønskede hændelser, opstået efter opstart af behandling)

Medicinrådet

Application for the assessment of daratumumab in combination with bortezomib, melphalan, and prednisone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation

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1 Basic information

Contact information

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Overview of the pharmaceutical

Proprietary name	Darzalex®
Generic name	Daratumumab
Marketing authorization holder in Denmark	Janssen-Cilag A/S
ATC code	L01XC24
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies
Active substance(s)	Daratumumab
Pharmaceutical form(s)	Concentrate for solution for infusion
Mechanism of action	Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumor cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signaling and enzymatic activity.
Dosage regimen	Darzalex® dosing schedule in combination with bortezomib, melphalan and prednisone; 6-week cycle dosing regimen. **Weeks** / **Schedule** Weeks 1 to 6 — weekly (total of 6 doses) Weeks 7 to 54[a] — every three weeks (total of 16 doses) Week 55 onwards until disease progression[b] — every four weeks [a] First dose of the every-3-week dosing schedule is given at Week 7 [b] First dose of the every-4-week dosing schedule is given at Week 55 Bortezomib was administered by subcutaneous (SC) injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week

	cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Darzalex® is indicated in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
Other approved therapeutic indications	Darzalex® is indicated in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. Darzalex® is indicated in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. Darzalex® is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Darzalex® is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Darzalex® in combination with bortezomib, melphalan and prednisone
Packaging – types, sizes/number of units, and concentrations	• Darzalex®, 20 mg/ml, concentrate for solution for infusion, vial (glass), 5 ml, 1 vial • Darzalex ®, 20 mg/ml, concentrate for solution for infusion, vial (glass), 20 ml, 1 vial
Orphan drug designation	Yes

2 Abbreviations

Abbreviations (excluding abbreviations for drug combinations, see table below)

Abbreviation	Term
AE	Adverse events
ASCT	Autologous stem-cell transplantation
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
DIC	Deviance information criterion
Discon.	Discontinuation
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European public assessment report
FE	Fixed effects
GHS	Global Health Status
HAS	Haute Autorité de santé
HR	Hazard ratio
HRQoL	Health-related quality of life
IFM	Intergroupe Francais du Myélome
IRAC	Independent Response Adjudication Committee
ISS	International staging system
ITT	Intention to treat
IQR	Interquartile range
LS	Least-squares
NA	Not available
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable
NMA	Network-meta analysis
NR	Not reached
OR	Odds ratio
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
PFS	Progression-free survival
PICO	Population, intervention, comparator, outcome
RCT	Randomized controlled trial
RE	Random effects
RR	Relative risk
SCT	Stem-cell transplantation
SLR	Systematic literature review
TEAE	Treatment emergent adverse events
TIE	Transplant ineligible
Tx. discon. due to AEs	Treatment discontinuations due to adverse events

Abbreviations for drug combinations

Drug combination abbreviation(s)	Drug combination
BorLenDex / VRd / RVd	Bortezomib + lenalidomide + dexamethasone
BorMelPred / VMP	Bortezomib + melphalan + prednisone
BorMelPredThal+BorThal cont	Bortezomib + melphalan + prednisone + thalidomide & continued bortezomib + thalidomide treatment
BorThalPred	Bortezomib + thalidomide + prednisone
CycPredLen	Cyclophosphamide + prednisone + lenalidomide
DaraBorMelPred / DVMP	Daratumumab + bortezomib + melphalan + prednisone
DaraLenDex	Daratumumab + lenalidomide + dexamethasone
EloLenDex	Elotuzumab + lenalidomide + dexamethasone
LenDex / Rd	Lenalidomide + dexamethasone (to progression)
LenDex18 / Rd18	Lenalidomide + dexamethasone (18 cycles)
LenDex9	Lenalidomide + dexamethasone (9 cycles)
MelPred	Melphalan + prednisone
MelPredLen	Melphalan + prednisone + lenalidomide
MelPredThal	Melphalan + prednisone + thalidomide

Terms used throughout application

Primary term used in this application	Term considered interchangeable (for this application)
Absolute difference	Risk difference
Medicines Council	The term “Medicines Council” is used broadly throughout the application and may reflect specific tasks conducted by for example the Expert Committee and/or the Secretariat.
Outcome measure	Endpoint
Transplant ineligible (TIE)	• Ineligible for autologous stem-cell transplantation (ASCT) • Ineligible for transplant • Ineligible for high dose chemotherapy with stem-cell transplant

3 Summary

This application is concerning daratumumab in combination with bortezomib, melphalan and prednisone (DaraBorMelPred) as standard treatment for patients with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy with stem-cell transplant. The protocol was published by the Medicines Council and stated three comparators which will be highlighted below. The outcome measures of interest to the Expert Committee: overall survival (OS), progression-free survival (PFS), treatment discontinuations due to adverse events (tx. discon. due to AEs), health related quality of life (HRQoL) and a qualitative assessment of the adverse events (AEs)/side effects. The qualitative assessment of AEs will be conducted by the Expert Committee (as per request) and overview tables have been provided for each clinical question. The median OS has not been reached for DaraBorMelPred. The 36-months rate of overall survival and PFS are therefore provided as requested by the Expert Committee.

<u>DaraBorMelPred vs. bortezomib in combination with melphalan and prednisone (BorMelPred) – Direct comparison based on the ALCYONE (MMY3007) trial</u>

The median OS was not reached in either of the treatment arms. OS HR: 0.60 (95% CI: 0.46-0.80) in favor of DaraBorMelPred. The 36-months OS rate was 78.0% (95% CI: 73.2-82.0) for DaraBorMelPred and 67.9% (95% CI: 62.6-72.6) for BorMelPred. PFS HR: 0.42 (95% CI: 0.34-0.51) in favor of DaraBorMelPred. The median PFS was reached at 36.4 months (95% CI: 32.1–45.9) for DaraBorMelPred and 19.3 months (95% CI: 18.0–20.4) for BorMelPred. The HRQoL data showed a clinically meaningful change from baseline. Tx. discon. due to AEs was 6.9% for DaraBorMelPred and 9.3% for BorMelPred. The time-adjusted analysis of tx. discon. due to AEs resulted in a HR in favor of DaraBorMelPred: HR=0.48 (95% CI: 0.26-0.86). The absolute difference for tx. discon. due to AEs: -2.3% (95% CI: -6.3%, 1.6%) in favor of DaraBorMelPred.

<u>DaraBorMelPred vs. lenalidomide in combination with dexamethasone for 18 4-week cycles (LenDex18) - Network meta-analysis (NMA)</u>

OS HR: 0.86 (95% CI: 0.56-1.32) in favor of DaraBorMelPred. The 36-months overall survival rate was 78.0% (95% CI: 73.2-82.0) for DaraBorMelPred and 66% for LenDex18. PFS HR: 0.43 (95% CI: 0.27-0.68) in favor of DaraBorMelPred. The median PFS was reached at 36.4 months (95% CI: 32.1-45.9) for DaraBorMelPred and 21 months for LenDex18. It was not possible to conduct a comparison of HRQoL. Tx. discon. due to AEs was 6.9% for DaraBorMelPred and 13.1% for LenDex18. The RR was 0.18 (95% Crl: 0.08-0.48) which was consistent with the NMA conducted by the Medicines Council in the evaluation of multiple myeloma. The absolute difference for tx. discon. due to AEs: -10.8% (-12.2%, -6.8%) in favor for DaraBorMelPred.

<u>DaraBorMelPred vs. lenalidomide in combination with bortezomib and dexamethasone (BorLenDex) - Narrative comparison and network meta-analysis</u>

A narrative comparison of OS, PFS, and tx. discon. due to AEs were conducted since the SWOG S0777 trial (BorLenDex) included more fit and younger patients compared to ALCYONE (median age: 71 vs. 63; 89.7% of DaraBorMelPred patients being > 65 compared to 38% of BorLenDex patients). It was not possible to draw conclusions for OS and PFS. For tx. discon. due to AEs, an NMA was conducted and a conservative estimate was provided since the data applied for BorLenDex is based on induction only (24 weeks) as well as a younger and more fit population compared to DaraBorMelPred. For DaraBorMelPred, tx. discon. due to AEs were accounted for throughout all treatment cycles. The trial results for DaraBorMelPred was 6.9% and 22.8% for BorLenDex. The RR was 0.08 (95% Crl: 0.03-0.26) and the absolute difference was calculated to be -21.0% (95% CI: -22.1%, -16.9%) in favor DaraBorMelPred with fewer tx. discon due to AEs.

The superiority of DaraBorMelPred compared to BorMelPred and LenDex18 was clear both from an efficacy and tolerability perspective. It was not possible to properly compare the efficacy of DaraBorMelPred vs. BorLenDex, but in terms of tolerability, it was evident that DaraBorMelPred outperformed BorLenDex.

4 Literature search

The following comparators were specified in the protocol for DaraBorMelPred by the Medicines Council (1):

- Bortezomib in combination with melphalan and prednisone (BorMelPred)
- Lenalidomide in combination with dexamethasone for 18 4-week cycles (LenDex18)[1]
- Lenalidomide in combination with bortezomib and dexamethasone (BorLenDex)

4.1 Databases and search strategy

4.1.1 Data sources and search syntax

The systematic literature search (SLR) was executed in accordance to the search-syntax provided by the Medicines Council in the protocol for daratumumab in combination with bortezomib, melphalan and prednisone (DaraBorMelPred) (1). The search protocol requested a search in two different data sources, namely PubMed and Cochrane. As such, the search syntax as provided by Medicines Council were run in Medline via PubMed and Central via Cochrane library on the 4th of February 2020. See Appendix A – Primary SLR for the specific search syntaxes.

As part of the literature search, a manual search was performed on EMA (European Medicines Agency) European public assessment reports (EPAR), specifically on summary of product characteristics of daratumumab (2); bortezomib (3); lenalidomide (4); and dexamethasone (5) individually to identify potential publications that were not included in the search engines as well as the EPARs for the specified comparators (6, 7) and for DaraBorMelPred(8).

A network-meta analysis (NMA) was conducted to establish the relative efficacy of;

- DaraBorMelPred versus LenDex18
- DaraBorMelPred versus BorLenDex (only for treatment discontinuations due to adverse events)

A broader SLR was needed than the initial published search syntax in the DaraBorMelPred protocol to capture all relevant links for the network of evidence utilized in the NMA. With guidance from the Secretariat, the NMA conducted by the Medicines Council for the evaluation of the therapeutic area of multiple myeloma was utilized as a foundation for previously identified studies. The search was run in Medline via PubMed and Central via Cochrane library. The network link applied was for the newly diagnosed multiple myeloma (NDMM) patients who are ineligible for autologous stem-cell transplant, in short, transplant ineligible (TIE) patients. Based on the findings from the SLR conducted by the Medicines Council for the evaluation of multiple myeloma, the network of evidence and the search syntax were utilized as the foundation for the broader literature search. The SLR for the therapeutic area of multiple myeloma was updated by the Medicines Council in October 2018. With guidance from the Secretariat, an update was needed capturing literature from October 2018 to present to assess whether new studies were published during this period. This was done by utilizing the search syntax applied in the evaluation of multiple myeloma but narrowing the search down to TIE patients.

[1] To ensure addressing the requested dosing regimen for the comparator, lenalidomide in combination with dexamethasone (LenDex to progression or LenDex for 18 4-week cycles (LenDex18)), the Secretariat (Medicines Council) was consulted. The Secretariat stated that the Expert Committee was interested in the LenDex18 regimen.

4.1.2 Eligibility criteria and PICOS

The SLR was conducted using explicit criteria for inclusion and exclusion of studies. After removing duplicate hits, two reviewers independently screened the retrieved hits and any inconsistency between the screening results of the two reviewers was solved by mutual discussion or the involvement of a third reviewer. Exclusion of publications was first done on title and abstract level, followed by inclusion or exclusion of papers after reading full text articles and the reason of exclusion is documented. The overall selection process is reported in a PRISMA diagram. The eligibility criteria used in this SLR are provided in Table 1. The inclusion/exclusion criteria are based on the search protocol as provided by the Medicines Council. Data extraction was performed in a project-specific Microsoft Excel document where two reviewers extracted all the relevant data and again, any inconsistency was as solved by mutual discussion or the involvement of a third reviewer.

TABLE 1: STUDY ELIGIBILITY CRITERIA, PICO

	Inclusion criteria	Exclusion criteria
Population	• Adult patients with newly-diagnosed multiple myeloma who are ineligible for autologous stem-cell transplant	• Previously treated multiple myeloma patients • Multiple myeloma patients eligible for autologous stem-cell transplant • NDMM population without intent to transplant • Indications other than multiple myeloma
Intervention	• Daratumumab + Bortezomib + Melphalan + Prednisone (DaraBorMelPred)	
Comparator	• Bortezomib + Melphalan + Prednisone (BorMelPred) • Lenalidomide + Dexamethasone (LenDex) • Bortezomib + Lenalidomide + Dexamethasone (BorLenDex)	• Studies that do not contain at least one therapy of interest

Outcomes	• Median overall survival (OS)
	  ○ Survival rate at 3 years in case median OS is immature
	• Median progression-free survival (PFS)
	  ○ In case OS is immature
	• Treatment discontinuation due to adverse events
	• Change in Health-related Quality of Life (HRQoL)
		• Studies that do not contain any relevant outcomes

Study design	• Randomized Clinical Trials	• Narrative reviews, editorials, opinions, case series • Systematic literature reviews and network meta-analyses • Clinical guidelines • Animal/laboratory studies • Preclinical and biological studies • Non-randomized or single arm trials • Cohort studies

	Inclusion criteria	Exclusion criteria
Type of publication	• Peer-reviewed published full-text articles • Data from the EMAs EPARs	• Abstract only
Language	• English	• Any other language
Date	• No date restriction	
*The full texts of any systematic reviews and meta-analyses on relevant RCTs were acquired and hand-searched to find any additional relevant primary studies or additional outcomes not identified through the database searches		

4.1.3 Literature search and research question

The following research question was formulated upfront and was guiding through the SLR:

- What is the value of DaraBorMelPred compared with current standard of care for adult patients with NDMM patient who are ineligible for high dose chemotherapy with stem-cell transplant?

Additionally, as part of the current protocol search, a manual search was performed on relevant EPARs.

4.1.4 Additional search (secondary SLR)

To ensure that important studies were not missed by the search protocol as provided by the Medicines Council, specifically for the network of evidence used for the NMA, an additional SLR search was conducted. This additional search built upon a previously conducted SLR by the Medicines Council (9) for the therapeutic area of multiple myeloma and the search was run in Medline via PubMed and Central via Cochrane library. This search used a broader search syntax and broader inclusion criteria than the one provided for DaraBorMelPred since it covered the whole therapeutic area. This means that the search was not limited solely to the combination treatments DaraBorMelPred, BorMelPred, LenDex18 and BorLenDex.

The additional search was performed on the 27th of February 2020. The Medicines Council search was conducted up to 25th of October 2018. This broader search was limited from 25th of October 2018 to present (27th of February 2020). The broader search would ensure that all relevant trials for the indication of NDMM TIE patients would be captured.

In Appendix B – Secondary SLR the following can be found: the search syntax and hits (9.4), a PRISMA flow diagram, and a list of excluded studies.

4.2 Results

The primary SLR search was run in both Medline via PubMed and Central via Cochrane library on the 4th of February 2020. The search in PubMed and Cochrane resulted in a total of n=357 hits (see Appendix A – Primary SLR). Checking for overlap resulted in n=278 original hits based on a combination of PubMed and Cochrane. After the first phase of title and abstract screening, a total of 202 and 51 hits were excluded respectively as these hits did not meet the inclusion criteria. This resulted in a total of n=25 papers for full-text screening. A total of 10 publications were included for review and data extraction as these studies complied to inclusion criteria. These 10 publications included n=4 different trials, i.e.: ALCYONE (MMY3007), FIRST, VISTA, and SWOG S0777. The network of evidence will be emphasized in later sections. Table 2 in the following section will highlight all the relevant studies used for this application.

Two additional trials have been included manually since these were not captured by the search protocol for DaraBorMelPred. Inclusion of these two trials, IFM 01/01 and IFM 99-06, was relevant for the link between

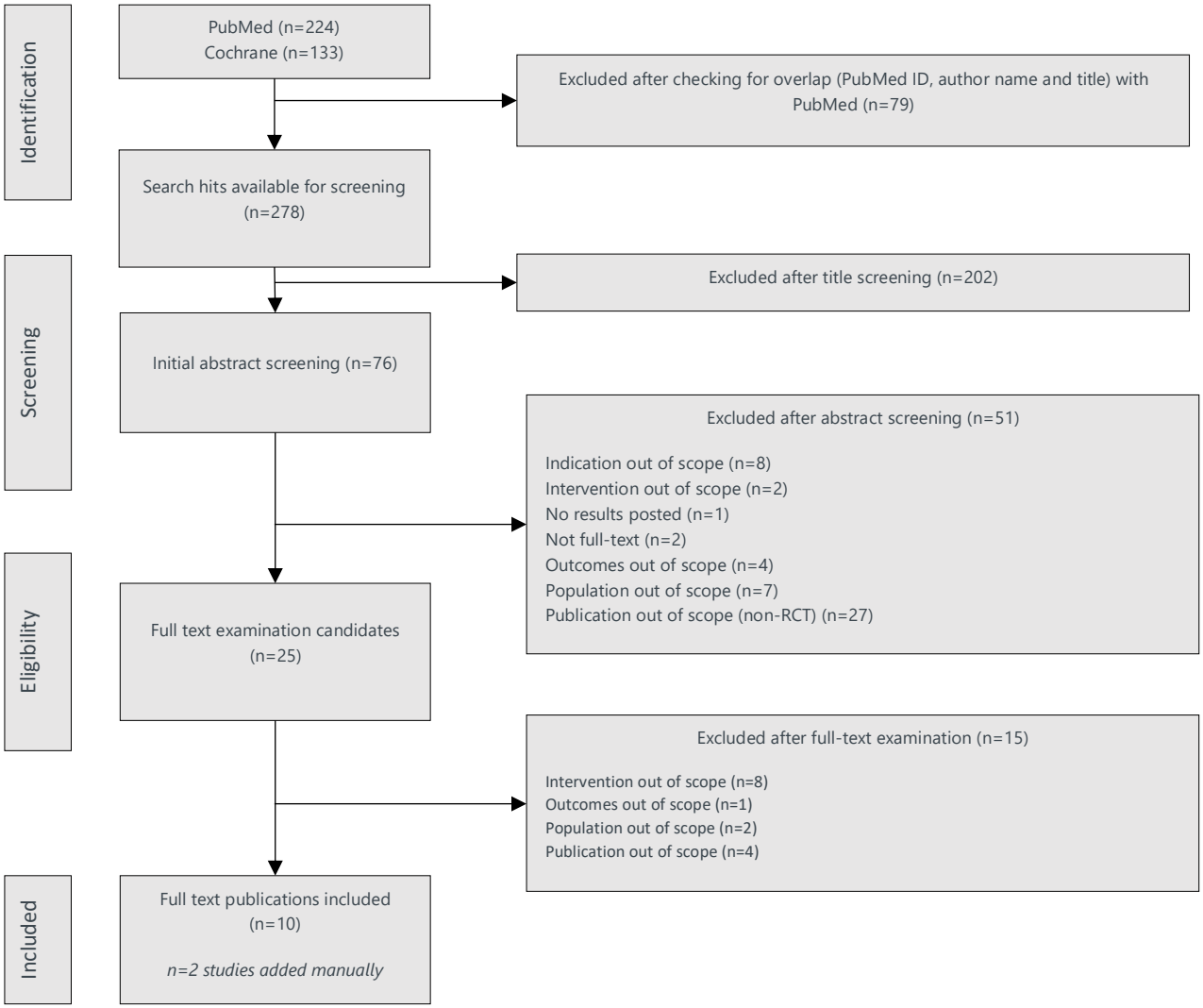
melphalan + prednisone (MelPred) vs. melphalan + prednisone + thalidomide (MelPredThal) in the NMA. This was aligned with the Secretariat and justified by referencing the captured studies and the resulting network which was conducted by the Medicines Council for the therapeutic area of multiple myeloma (9). The network identified by the Medicines Council for multiple myeloma can be found in section 5, Figure 2.

One trial, the SWOG S0777 that investigates BorLenDex versus lenalidomide in combination dexamethasone to progression (LenDex) among NDMM patients *without intent for immediate autologous stem cell transplantation* was captured by the protocol search as well. This trial was the only study that did not comply to the protocol population inclusion criteria (i.e. TIE patients), however this study has been included due to an overlapping patient population (i.e. TIE patients) and the prespecified treatment comparator, BorLenDex. Efficacy data of BorLenDex in the NDMM TIE population only is currently not available. The lack of comparative trial data hampers an indirect treatment comparison with a bias against DaraBorMelPred and additional details will be provided in later sections. Despite missing randomized controlled trial (RCT) efficacy and safety data for BorLenDex in the same population (TIE patients only), BorLenDex has been included in an NMA based on the intent-to-treat (ITT) population for the outcome measure, treatment discontinuations due to adverse events (AEs). A narrative comparison has been conducted across outcome measures.

Including the two manually added studies (IFM 01/01, IFM 99-06) resulted in a total of n=6 trials for the combined PubMed and Cochrane search.

The PRISMA flow diagram can be found below in Figure 1.

FIGURE 1: PRISMA FLOW DIAGRAM OF STUDY SELECTION



4.3 Overview of included studies

The literature search resulted in a total of n=4 different trials on NDMM TIE patients. Additionally, two trials (IFM 01/01 and IFM 99-06) were included manually as these were not captured by the search. As mentioned, this was justified by referencing the included studies and the NMA network presented by the Medicines Council (9). Therefore, a total of n=6 trials were included for review and data extraction. Table 2 provides an overview of the included trials.

In Table 2, the included RCT are stated as well as their relevance for the clinical question.

TABLE 2: RELEVANT STUDIES INCLUDED IN ASSESSMENT (LIST OF INCLUDED RCTS) – PRIMARY SLR

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma, Mateos et al., The New England journal of medicine, 2018 (10) Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomized, open-label, phase 3 trial, Mateos et al., The Lancet, 2019 (11)	ALCYONE	NCT02195479	December 9, 2014 – October 20, 2021	DaraBorMelPred vs. BorMelPred (Q1) DaraBorMelPred vs. LenDex18 (Q2) DaraBorMelPred vs. BorLenDex (Q3)
Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma, Benboubker et al., N Engl J Med., 2014 (12) Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma., Facon T et al., Blood, 2018 (13) Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide., Delforge M et al., Haematologica, 2015 (14, 15)	FIRST[a]	NCT00689936	August 21, 2008 – July 14, 2016	DaraBorMelPred vs. LenDex18 (Q2) DaraBorMelPred vs. BorLenDex (Q3)
Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial., Hulin et al., J Clin Oncol., 2009 (16)	IFM 01/01	NCT00644306	April 2002 – May 2007	DaraBorMelPred vs. LenDex18 (Q2) DaraBorMelPred vs. BorLenDex (Q3)
Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomized trial., Facon et al., Lancet., 2007 (17)	IFM 99-06	NCT00367185	May 2000 – October 2005	DaraBorMelPred vs. LenDex18 (Q2)
Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma., San Miguel et al., N Engl J Med., 2008 (18) Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma., San Miguel et al., J Clin Oncol., 2013 (19)	VISTA	NCT00111319	December 2004 – July 2007*	DaraBorMelPred vs. LenDex18 (Q2) DaraBorMelPred vs. BorLenDex (Q3)

Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial., Durie B et al., Lancet., 2017. (20)	SWOG S0777	NCT00644228	April 1, 2008 – July 1, 2016*	DaraBorMelPred vs. BorLenDex (Q3)
	*Final data collection date for primary outcome measure			

a) Please note, since FIRST investigated both LenDex and LenDex18, this trial would be the only study that would be included in the current SLR if the comparator eligibility criteria would be solely focused on LenDex18 as comparator.

4.4 Main characteristics of included studies

The main characteristics of the studies included in the assessment are presented in the following section. This section will also include *within trial difference* since these results are also used for the NMA. In addition, an overview table (Table 3) has been created summarizing the main characteristics across the studies. An overview of the main study characteristics for each study separately can be found in the Appendix A – Primary SLR, section 9.2.

The list of excluded studies can be found in Appendix A – Primary SLR, section 9.3.

TABLE 3: INCLUDED RCTS IN THE SLR

TRIAL	Location of study	Median Follow up (mont-h)	Treatment arms	N	Median Age (years)	Female (%)	Race white (%)	MM type-IgG (%)	ISS-stage III (%)	ECOG 0 (%)	ECOG 1 (%)	ECOG 2 (%)	High-risk cytogenetic abnormality (%)
ALCYONE	Asia–Pacific, Europe, Latin America, North America	40.1	DaraBorMelPred	350	71	54	85	40.9	40.6	22	52	26	16.9
			BorMelPred	356	71	53	85	39.3	36.2	28	49	24	14.9
FIRST	US, Canada, Asia Pacific, Europe	67.0	LenDex	535	73	45	89	62	40	29	48	22	17
			LenDex18	541	73	50	89	61	40	30	49	21	20
			MelPredThal	547	73	48	90	64	41	29	50	20	19
IFM 01/01	Europe	47.5	MelPred	116	78.5	47			30				
			MelPredThal	113		62			35				
IFM 99–06	Europe	51.5	MelPred	196		34			30				
			MelPredThal	125		50			29				
VISTA	US, Canada, Europe, Latin America, Asia pacific	60.1	BorMelPred	344	71	49	88	64	35				
			MelPred	338	71	51	87	62	34				
SWOG S0777* **(EPAR)**	US, Puerto Rico, Saudi Arabia	69.0	BorLenDex	263	63	38			33	40	49		11.4
			LenDex	260	63	47			34	39	46		13.8

*Despite of not complying to the population inclusion criteria, this study has been included due to an overlapping patient population (TIE patients) and since this is the only RCT evaluating BorLenDex in the NDMM patient population.

4.4.1 DaraBorMelPred studies (ALCYONE)

ALCYONE is a phase III, randomized, controlled, open-label, parallel-arm, multicenter study with 706 patients. The study was designed to compare the efficacy of daratumumab in combination with bortezomib, melphalan and prednisone (DaraBorMelPred) to that of bortezomib, melphalan and prednisone (BorMelPred) in terms of progression-free survival (PFS) in patients with NDMM who are ineligible for transplant. Patients were considered transplant ineligible if they were ≥ 65 years of age or < 65 years of age with comorbid conditions that would have a negative impact on tolerability to high dose chemotherapy used in ASCT. The median age in the study population was 71 years (10, 11, 21).

A prespecified interim analysis was done at a median follow-up of 16.5 months (data-cut June 2017) (10). The latest data cut is from another prespecified interim analysis with a median follow-up time of 40.1 months (data-cut July 2019) (11).

Within trial differences

ECOG performance status was divided the following way (DaraBorMelPred vs. BorMelPred): 0 (23% vs. 28%), 1 (52% vs. 49%) and 2 (26% vs. 24%). ISS disease staging: I (20% vs. 19 %), II (40% vs. 45 %) and III (41% vs. 36 %). Regarding high-risk cytogenetic abnormalities: the rates were 17% vs. 15%. Overall, patient baseline characteristics are assessed to be generally well balanced between treatment arms as expected. The differences observed in ISS disease staging and ECOG performance status are variances which can naturally occur in a randomized trial. All arms were also informally tested using Chi-square, Wilcoxon rank-sum, and median tests and no significant differences were found.

The EPAR for DaraBorMelPred notes that: *the baseline demographics are overall well-balanced between the two treatment arms. The majority of patient are white, with a median age of 71 years. However, there were 12 more patients below 65 years in the DaraBorMelPred arm, while there were slightly more patients above 65 in the BorMelPred arm. The medical history of patients < 65 years was analyzed, showing 53% in the DaraBorMelPred arm having an ECOG PS score of 2 vs. 33% in the BorMelPred arm. Those with PS score of 1 had medical comorbidities such as cardiac, respiratory, central nervous disorders or others rendering them transplant-ineligible (8) p. 50*. It is important to note that it is stated in the EPAR that the two treatment arms overall were well-balanced. The 12 more patients approximately accounts for 3.5 percentage points more patients below 65 years in the DaraBorMelPred arm compared to the BorMelPred arm. However, considering the additional analyses of the medical history of the respective patients, and the findings in terms of ECOG PS score, it is assumed to be balanced out across the two treatment arms.

4.4.2 LenDex18 studies (FIRST)

FIRST is a randomized, open-label, three-arm, phase III study with 1623 patients and a median follow-up of 37 months for surviving patients at original data cut off (12) and 67 months based on the final analysis among surviving patients (13). The FIRST study investigated the efficacy and safety of lenalidomide plus low-dose dexamethasone when given until progressive disease (LenDex) or for 18 four-week cycles (LenDex18) versus the combination of melphalan, prednisone, and thalidomide (MelPredThal) given for 12 six-week cycles in patients with previously untreated multiple myeloma. The study included ≥ 65-year-old patients (or, if younger than 65 years of age, not eligible for stem cell transplantation) with newly diagnosed, symptomatic and measurable multiple myeloma. The median age was 73 years in the three arms (15).

Within trial differences

The three treatment arms seemed to be well balanced in the FIRST trial with no notable differences.

4.4.3 BorLenDex studies (SWOG S0777)

SWOG S0777 is a phase III, randomized, parallel-arm, open-label, multicenter study with 525 patients (20). The SWOG S0777 study evaluated the addition of bortezomib to lenalidomide and dexamethasone (BorLenDex), as initial treatment, followed by continued lenalidomide and dexamethasone until disease progression in patients with previously untreated multiple myeloma who were not planned for immediate autologous stem-cell transplant (4). The median age in the study population was 63 years.

The SWOG S0777 trial has multiple data cuts and varying sources as well as different patients being analyzed depending on the source. Due to the importance of this regimen (BorLenDex) for the evaluation of DaraBorMelPred, the available data is summarized below focusing on the publications identified in the SLR, the EPAR, and the data with the longest follow-up.

- The original data analysis was published in 2017 by Durie et al. (20) and was based on a data cut-off of 5th of November 2015. The median overall follow up was 55 months (IQR: 48–68), 54 months (IQR: 47–66) for BorLenDex, and 56 months (50–70) for the LenDex arm.
- Data is presented in the EPAR with a data cut-off of 1st of December 2016. The median follow-up (based on Kaplan-Meier estimate) for all surviving subjects was 69 months (6). This data cut-off is used in one of the clinical questions of interest. The following efficacy data is available in the EPAR for this specific data cut-off:
    - PFS results available: PFS (SWOG censoring)
    - PFS results available: PFS (Independent Response Adjudication Committee (IRAC), EMA Censoring)
    - PFS results available: PFS by IRAC review and EMA censoring rules for ITT population, by intent to transplant at progression
    - OS results available
- Additional data is presented in the EPAR with a data cut-off of 15th of May 2018. The median follow-up (based on Kaplan-Meier estimate) for all surviving subjects was 84.2 months (6). The following efficacy data is available in the EPAR:
    - PFS results available: PFS (SWOG censoring)
    - OS results available
- For the data cut-off of 15th of May 2018 (84.2 months follow-up), an abstract has been presented at a congress (22). In addition, a conference presentation is accessible with additional subgroup analysis (23).

The SWOG S0777 is a cooperative group study and not originally designed to support regulatory application for market authorization, Celgene obtained rights to the data for this study and developed the dataset and an analysis plan appropriate to support a regulatory submission to health authorities. The analysis from Celgene of the SWOG S0777 trial was submitted in a clinical study report (CSR). The CSR analysis includes an additional 52 patients due to reassessment of ineligibility; these patients were excluded from the Durie et al. 2017 publication. The CSR analysis assessed the intention to treat (ITT) population with IRAC review with SWOG censoring rules, EMA censoring, and FDA censoring (24) p.35. The results based on EMA censoring (data cut-off of 1st of December 2016) will be reported which is in line with the submission from Celgene of BorLenDex in Denmark and the data that the Medicines Council used in the evaluation of BorLenDex (25).

Table 4 provides an overview of the data-sets available and originates from the pan-Canadian Oncology Drug Review Initial Clinical Guidance Report for BorLenDex for Multiple Myeloma (24) p.35. It provides useful overview of the populations analyzed based on the SWOG S0777 data. Among other, this report also provides suggested definitions for different terms used for the patient population: 1) transplant eligible, 2) transplant ineligible, 3) intent to transplant and 4) no intent to transplant for which is of particular relevance for the clinical question focusing on DaraBorMelPred and BorLenDex (see DaraBorMelPred compared to BorLenDex section Progression free-survival (Median PFS)).

TABLE 4: SUMMARY OF PATIENT POPULATION'S DATA SET (PAN-CANADIAN ONCOLOGY DRUG REVIEW) (24)

	Clinical Summary Report[3]		Primary Publication (Durie et al. 2017)[1]		Conference Abstract (Durie et al. 2018)[2]	
Author	Submitter		Durie et al.		Durie et al.	
Data cutoff date	November 5, 2015 (Primary Analysis)	December 1, 2016 (Follow-up)	November 5, 2015 (Primary Analysis)		May 15, 2018 (Follow-up)	
Population	Intention to Treat		Per Protocol (eligible analysable)		Per Protocol (eligible analysable	
Treatment Arm	VLd	Ld	VLd	Ld	VLd	Ld
Enrolled	264	261	264	261	264	261
-Withdrew/invalid consent*	1	1	1	1	1	1
-Deemed ineligible	-	-	21	31	21	31
-Deemed ineligible at 2018 update[&]	-	-	-	-	7	4
Total Population Analyzed	263	260	242	230	235	226[†]
Enrolled minus Total Population Analyzed	N=2[#]		N=54		N=63	

Baseline Characteristics	See section 6.3.2.1, table 8	See section 6.3.2.1, table 7	Not Reported[&]
Outcome Assessment by IRAC	Yes	No	No
Censoring Applied	NCI - SWOG, EMA and FDA	NCI - SWOG	NCI - SWOG

Abbreviations: IRAC: Independent Response Adjudication Committee
* deemed ineligible mainly due to missing, insufficient, or early or late baseline data (n=41)
[†] The CSR indicated the total population analyzed as 225, but correct number should be 226
[&] Missing, insufficient, early/late baseline laboratory data and other reasons (n=11)[2]
[#] The CSR does not give an account for the two patients that are missing from the analysis. It is unclear if these are the two patients who withdrew consent (n=1) and or had invalid consent (n=1).

Figure reprinted from: pan-Canadian Oncology Drug Review Initial Clinical Guidance Report. Lenalidomide (Revlimid) plus Bortezomib plus Dexamethasone for Multiple Myeloma. June 19, 2019
VLd: BorLenDex; Ld: LenDex

Within trial differences

In the EPAR the following is stated: *The baseline characteristics were well-balanced between the treatment groups, except for the cytogenetic risk, the frailty and the age: patients in* BorLenDex *arm seemed to be in a better condition at screening than patients in the* LenDex *arm. However, the slight numeric differences in cytogenetic risk, frailty, and age between the two treatment arms were not considered clinically meaningful (6) p. 45*

Extracted from the EPAR: Baseline clinical characteristics as of 1st of December 2016 (ITT Population-Study SWOG S0777) (6)

- 38% was age ≥ 65 in the BorLenDex arm while the number was 48% in the LenDex arm (20)

- ISS stage III was reported in 32.7% of patients in BorLenDex versus 33.5% of patients in LenDex. Revised ISS stage III was 9.9% in the BorLenDex arm compared to 8.8% in the LenDex arm.
- 11.4% were classified as high risk in the BorLenDex arm versus 13.8 % in the LenDex arm.
- In the BorLenDex arm, 21.3% were classified as frail compared to 27.7% in the LenDex arm, with 78.3% and 72.3% respectively classified as not being frail. ECOG performance status 2 was 7.2% in BorLenDex versus 12.3% LenDex.
- 37.6% were female in the BorLenDex arm and 47.3% in the LenDex arm.

The relevant differences between the SWOG S0777 trial and the ALCYONE trial will be highlighted under the respective clinical question (*Relevant differences between studies*).

Studies used for the NMA

The below studies were utilized to construct the link in the NMA for DaraBorMelPred vs. LenDex18 and DaraBorMelPred vs. BorLenDex (more details to follow in the subsequent sections).

4.4.4 VISTA

VISTA is a randomized, open-label phase III study with 682 patients and a median follow-up of 60.1 months based on the final analysis (12). The VISTA study investigated the efficacy of bortezomib plus melphalan-prednisone (BorMelPred) with melphalan-prednisone (MelPred) alone for nine 6-week cycles in patients with newly diagnosed myeloma who were ineligible for high-dose therapy. The median age in the study population was 71 years.

Within trial differences

The baseline characteristics seemed well balanced between treatment arms except the proportion of patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 where it was 9% for BorMelPred and 24% in the MelPred arm.

4.4.5 IFM 01/01

IFM 01/01 is a randomized, placebo-controlled phase III study with 282 patients and a median follow up of 47.5 months. The IFM 01/01 investigated the efficacy of melphalan and prednisone plus thalidomide for 12 cycles every 6 weeks and continuous thalidomide for 18 months in patients older than 75 years with newly diagnosed myeloma (16).

Within trial differences

Baseline demographics and disease characteristics seemed to be well balanced between the two arms except for sex (47% females in the MelPred arm vs. 62% in the MelPredThal arm).

4.4.6 IFM 99-06

The IFM 99-06 is a randomized, open-label phase III study with 500 patients and a median follow up of 51.5 months. The IFM 99-06 investigated the relative efficacy and safety of melphalan and prednisone (MelPred) versus melphalan and prednisone plus thalidomide (MelPredThal) or versus reduced-intensity stem cell transplantation using melphalan 100 mg/m² (MEL100). The regimens were evaluated in patients aged 65 to 75 years (17).

Within trial differences

Overall, the three arms seemed to be well balanced with slight differences in high risk features and ISS staging. However, sex was not well balanced (34% females in the MelPred arm vs. 50% in the MelPredThal arm).

5 Network Meta-Analysis

A network meta-analysis (NMA) is performed on the identified relevant RCTs. As such, the NMA aimed to identify the value of DaraBorMelPred among NDMM patients who are TIE versus the prespecified comparators.

The results presented in this report use the latest data-cut of ALCYONE with a median follow-up of 40.1 months. Table 5 presents the OS and PFS HRs of the data-cuts published in peer-reviewed journals / EPAR for DaraBorMelPred. PFS and OS showed improved relative efficacy for DaraBorMelPred compared to BorMelPred with the latest data-cut compared to the first data-cut.

TABLE 5: SUMMARY OF RELATIVE EFFICACY OS/PFS DATA FROM ALCYONE - DIFFERENT DATA-CUTS

	Overall survival (HR, CI 95%)	Progression-free survival (HR, CI 95%)
ALCYONE (MMY3007) June 2017 (10) **Median follow-up 16.5 months**	DaraBorMelPred versus BorMelPred NA. Kaplan-Meier available in supplementary appendix.	DaraBorMelPred versus BorMelPred HR: 0.50 (95% CI: 0.38-0.65)
ALCYONE (MMY3007) July 2019 (11) **Median follow-up 40.1 months**	DaraBorMelPred versus BorMelPred HR: 0.60 (95% CI: 0.46-0.80)	DaraBorMelPred versus BorMelPred HR: 0.42 (95% CI: 0.34-0.51)

5.1 Rationale for a Network Meta-Analysis

In the absence of head-to-head RCTs comparing DaraBorMelPred with prespecified comparators for NDMM patients who are ineligible for ASCT, a SLR and NMAs were conducted. The NMA is specifically addressing the LenDex18 comparator across outcome measures as well as the BorLenDex comparator for the outcome treatment discontinuations due to AEs despite the differences in the patient population. NMAs focusing on DaraBorMelPred vs. BorLenDex for OS and PFS were not conducted due to the none-comparable patient populations and the anticipated biased results.

An NMA is an indirect treatment comparison which can be applied when there are more than two possible interventions for a specific indication and those interventions are linked through a network anchored in a common comparator. Through an NMA, a pooled treatment effect is estimated for each intervention, making a comparison between interventions more reliable. The results of the SLR suggests that there is no clear rank in the efficacy of the available treatments; an NMA is a good option to reliably assess the efficacy of the available treatments.

The NMA was not relevant for the comparison of DaraBorMelPred vs. BorMelPred since the head-to-head RCT, ALCYONE is available. As stated in the protocol for DaraBorMelPred, the Secretariat identified the below article as relevant which can be used for the direct comparison vs. BorMelPred (1):

- Mateos MV et al. *Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial.* Lancet. 2020 Jan 11;395(10218):132-141 (10, 11)

5.1.1 NMA oriented to the Danish setting

The Medicines Council provided a protocol specifically tailored for DaraBorMelPred (1). This NMA was based on RCTs identified in the conducted SLR. Trials with relevant treatment comparators to DaraBorMelPred have been included in the NMA based on the Danish setting.

5.2 Methods

5.2.1 Network relevant for the Danish setting

The NMA only considered and included comparator treatments relevant to the Danish setting which were provided in the search syntaxes by Medicines Council (1). Treatments in orange are relevant treatment comparators for DaraBorMelPred in Denmark, whereas the treatments in blue were necessary to construct links in the network of evidence for the NMA. Different abbreviations for the treatments have been used in the NMA compared to what the Medicines Council have previously used (9) which have been translated below. Wherever possible, the abbreviations used by the Medicines Council have been applied.

- BorMelPred = VMP (Velcade®(bortezomib) + melphalan + prednisone)
- LenDex18 = Rd18 (Revlimid®(lenalidomide) 18 cycles + dexamethasone)
- BorLenDex = VRd (Velcade®(bortezomib) + (Revlimid®(lenalidomide) + dexamethasone)
    - *BorLenDex was studied in the SWOG S0777 trial which did not include solely TIE NDMM patients. However, BorLenDex is recommended for standard treatment in Denmark and is one of the comparators specified by the Expert Committee in the DaraBorMelPred protocol and is thus included.*
- MelPred = MP (melphalan + prednisone)
- MelPredThal = MPT (melphalan + prednisone + thalidomide)
- LenDex = Rd continuous (Revlimid®(lenalidomide) continuous + dexamethasone)

5.2.2 Systematic Literature Review

As mentioned, the SLR resulted in 10 publications reporting n=4 different trials on NDMM patients who are ineligible for transplant. Additionally, two trials (IFM 01/01 and IFM 99-06) were included manually as these were not captured by the protocol search as described in section 4.2. The inclusion of the missing trials was aligned with the Medicines Council Secretariat and justified by referencing the included studies and the NMA network presented by the Medicines Council from the time when the therapeutic area of multiple myeloma was evaluated (9). These two trials allowed the link between MelPred and MelPredThal in the network. This resulted in a total of n=6 trials that were included in the SLR.

As mentioned previously, the SWOG S0777 study was captured by the protocol search but did not comply to the population inclusion criteria. However, it was included since it is standard treatment in Denmark and one of the comparators requested by the Expert Committee.

RCTs that investigated relevant treatments for the Danish setting, and corresponding patient baseline characteristics are presented in Table 3: Included RCTs in the SLR in the previous section. All the included treatments were relevant in terms of constructing links in the network of evidence of the NMA. The exact information on dosing protocols per trial per treatment can be found in Appendix C – NMA section 9.11. The included trials in the NMA were considered sufficiently similar in terms of baseline characteristics except for SWOG S0777. The differences and justifications are addressed in Appendix C – NMA section 9.7 and under the clinical questions addressing the comparators (LenDex18 & BorLenDex) where the NMA has been utilized.

5.2.3 NMA assumptions & NMA conducted by the Medicines Council

See Appendix C – NMA, section 9.7 for detailed NMA assumptions for the analysis conducted by the applicant.

Note that for all NMAs, fixed effects (FE) models are presented. This was based on an assessment for each relevant clinical question (presented later) and because the included studies were assessed to be sufficiently similar in terms of baseline characteristics (except SWOG S0777). In addition to the statistical justification provided for each clinical question, the Medicines Council conducted their own NMA applying the assumption of fixed effects when the therapeutic area of multiple myeloma was evaluated, specifically for the NDMM TIE patients (9). In the evaluation conducted by the Medicines Council, the following was stated (translated from Danish to English):

Most studies that included primary treatment of patients ineligible for transplant could be included in the network meta-analysis. The Expert Committee assesses that the populations in these studies are sufficiently similar to be able to perform the network meta-analysis with an assumption of fixed effects. However, the scientific committee notes minor differences in study populations in terms of cytogenetic risk profile, age, and renal function. In terms of cytogenetic risk profile, there is variation in the proportion of patients with high-risk cytogenetics. One study has a somewhat larger proportion of patients with a poorer cytogenetic risk profile, just as there are some studies where the median age is higher or renal function is better compared to other studies. (9) p. 24

The network for the NMA conducted by the Medicines Council can be found below in Figure 2 and it should be noted that BorLenDex was not included primarily due to the more fit patient population in the SWOG S0777 trial. The findings from the NMA conducted by the Medicines Council for the TIE patients can be found in Appendix D – NMA conducted by the Medicines Council, Figure 20 (OS), Figure 21 (PFS), and Figure 22 (treatment discontinuations due to AEs) (9). Note that the findings are based on a literature search from 25th of October 2018, and it also includes treatments that are not of interest for this specific submission which is focusing on the comparators specified in the protocol for DaraBorMelPred (1). Furthermore, at the time of analysis by the Medicines Council, the data for DaraBorMelPred was considered too immature to evaluate PFS & OS (16.5 months follow up at that time). However, the treatment discontinuations due to AEs was evaluated for DaraBorMelPred.

FIGURE 2: NETWORK OF EVIDENCE IN THE DANISH NMA FOR NDMM TIE POPULATION CONDUCTED BY THE MEDICINES COUNCIL

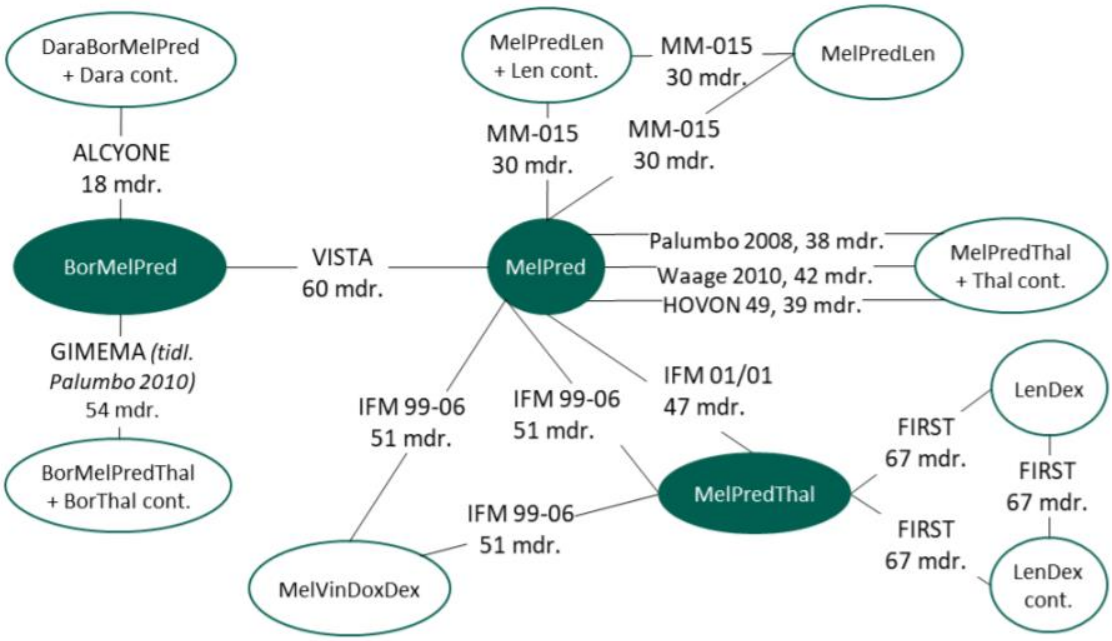


Figure reprinted from: Medicinrådet (2020). Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose). Version 1.2. Figure 3 p. 34 (9)

5.3 NMA analyses

Two analyses have been conducted and the two analyses differ in included treatment regimens. The first analysis includes the comparison between DaraBorMelPred and LenDex18 and it is conducted for OS, PFS, and treatment discontinuations due to AEs. The other analysis aimed to assess the impact of BorLenDex in the network of evidence in terms of treatment discontinuations due to AEs.

The NMA focusing on BorLenDex was conducted using data of the intent to treat (ITT) population from SWOG S0777 for the outcome measure treatment discontinuations due to AEs. One of the limitations of including BorLenDex (SWOG S0777) based on the available data are the different patient population compared DaraBorMelPred (ALCYONE). The differences between the trials and related limitations to the analysis is highlighted in detail in section 6.1.4 for the clinical question focusing on DaraBorMelPred vs. BorLenDex in the section Relevant differences between studies & Comparative analyses. This analysis is considered a conservative estimate and the results from the NMA can be applied in the categorization of the added clinical benefit. The rationale for this can be found under the clinical question in section 6.1.4 for the clinical question focusing on DaraBorMelPred vs. BorLenDex.

For each of the considered outcome measures, a different dataset was used based on the availability of the outcome measures in the trials. The individual datasets per outcome measure are presented for the relevant clinical question.

TABLE 6: INCLUDED REGIMENS IN THE NMA ANALYSES

NMA DaraBorMelPred vs. LenDex18	NMA DaraBorMelPred vs. BorLenDex (ITT)
▪ DaraBorMelPred (D-VMP) ▪ BorMelPred (VMP) ▪ MelPred (MP) ▪ MelPredThal (MPT) ▪ LenDex (Rd continuous) ▪ LenDex18 (Rd18)	▪ DaraBorMelPred (D-VMP) ▪ BorMelPred (VMP) ▪ MelPred (MP) ▪ MelPredThal (MPT) ▪ LenDex (Rd continuous) ▪ LenDex18 (Rd18) ▪ ***BorLenDex (VRd) - ITT***

5.4 Statistical Programming – see appendix

Appendix C – NMA, section 9.10

5.5 Reporting of Results

The results of the NMA are presented per outcome measure in section 6 (clinical questions). For each outcome measure the following results are presented:

- Network of evidence
- Choice of statistical model (Deviance Information Criterion (DIC) scores and total residual deviance for Random Effects (RE) model and FE model)
- Evaluation of NMA assumptions
- Summary of the empirical evidence used as input for the outcome measure specific analysis
- Matrix of relative efficacy from all treatment comparisons
- Forest plots with LenDex18 as reference treatment

5.5.1 Forest Plots

Forest plots graphically represent the relative effectiveness of each treatment against the reference treatment LenDex18 for each outcome measure. They present the point estimate and the credible intervals (CrI) of the relative pooled treatment effects.

5.6 Available results from the applicant's NMA

Table 7 presents an overview of all the evidence available per outcome measure. A total of three outcome measures have been evaluated for DaraBorMelPred vs. LenDex18 and one outcome measure for DaraBorMelPred vs. BorLenDex (ITT). Analyses were run on all the available data per outcome measure. This means that the NMAs were run on all outcome measures using all trials in the network, except for the analysis on treatment discontinuation due to AEs since IFM 99-06 has been excluded from the network because of lacking data.

TABLE 7: OVERVIEW AVAILABLE EVIDENCE PER TRIAL

Type of analysis	Trial	Outcome measures		
		Overall survival	Progression-free survival	Discontinuation due to adverse events
NMA DaraBorMelPred vs. LenDex18	ALCYONE	x	x	x
	VISTA	x	x	x
	IFM 01/01	x	x	x
	IFM 99-06	x	x	
	FIRST	x	x	x
NMA* DaraBorMelPred vs. BorLenDex (ITT)	SWOG S0777(ITT)			x

*The two NMAs represents the same network of evidence with the only difference of the inclusion of SWOG S0777 in the analysis focusing on DaraBorMelPred vs. BorLenDex.

The results from the NMA will be presented in the following sections where relevant, hence, for the comparison of DaraBorMelPred vs. LenDex18 and DaraBorMelPred vs. BorLenDex. Lastly, the results from the NMA will not be presented for the comparison vs. BorMelPred since the head-to-head study, ALCYONE is available for the direct treatment comparison as specified in the protocol for DaraBorMelPred (1).

6 Clinical questions

Clinical question specified by the Expert Committee (translated from Danish to English):

6.1 What is the value of daratumumab in combination with bortezomib, melphalan, and prednisone, plus subsequently as maintenance treatment compared with current standard of care for adults patients with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy with stem-cell support?

As previously stated, the Expert Committee has specified three comparators of interest, namely,

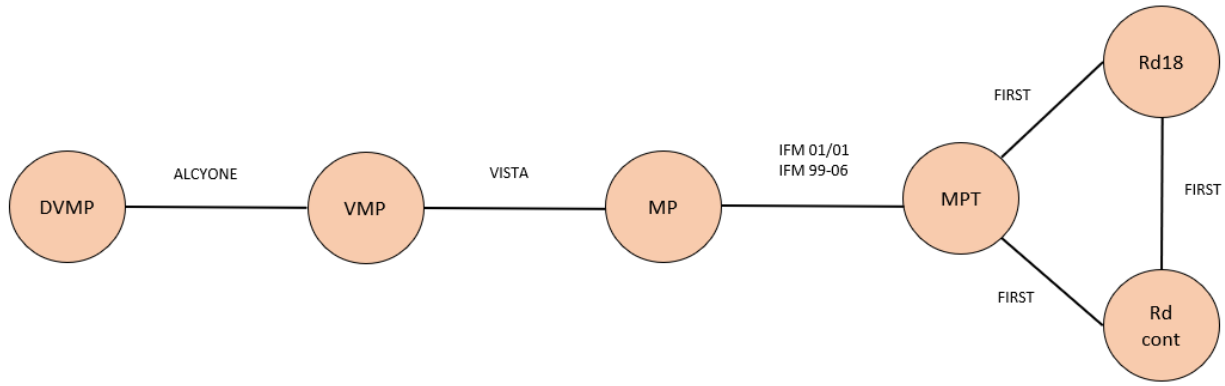
a) BorMelPred: Bortezomib + melphalan + dexamethasone
b) LenDex18: Lenalidomide + dexamethasone. 18 four-week cycles.
c) BorLenDex: Bortezomib + lenalidomide + dexamethasone

Each of the comparators will be addressed separately in the following sections.

Please note that the Main characteristics of included studies are summarized in the previous section, 4.4 and related Appendix A – Primary SLR, section 9.2 for detailed Main characteristics of included studies based on the template provided by the Medicines Council.

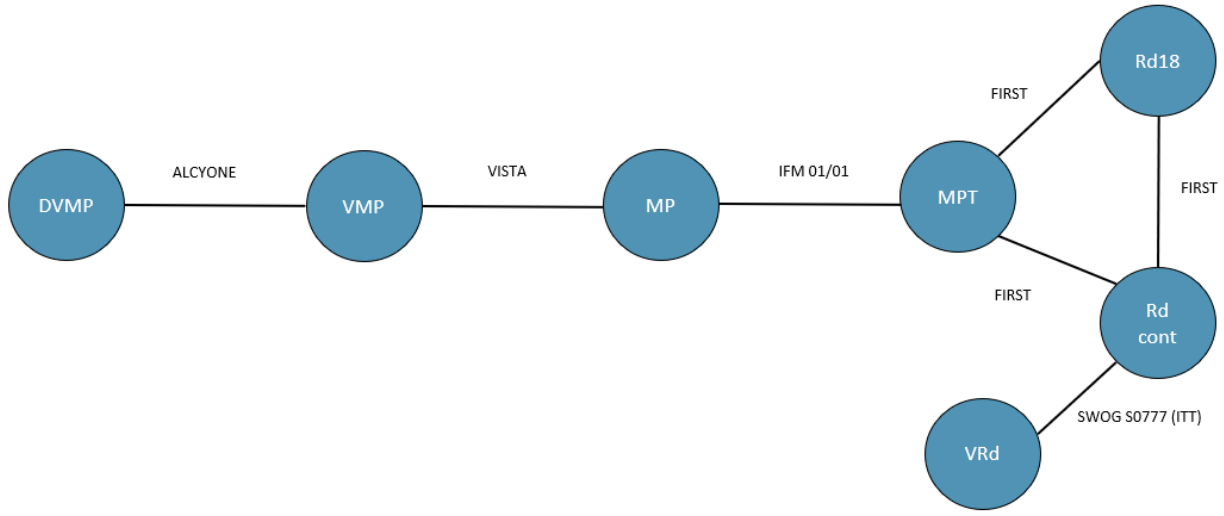
The comparison between DaraBorMelPred and LenDex18 (OS, PFS, treatment discontinuations due to AEs) as well as the comparison between DaraBorMelPred and BorLenDex (treatment discontinuations due to AEs) will utilize the same studies for the link in the network of evidence for the indirect comparison except the addition of SWOG S0777 for the comparison between DaraBorMelPred and BorLenDex.

FIGURE 3: NETWORK OF EVIDENCE FOR PFS & OS (DARABORMELPRED VS. LENDEX18)



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex

FIGURE 4: NETWORK OF EVIDENCE FOR TREATMENT DISCONTINUATIONS DUE TO AES (DARABORMELPRED VS. LENDEX18 AND DARABORMELPRED VS. BORLENDEX)



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex, VRd: BorLenDex

Since the same studies are utilized for two separate clinical questions (except SWOG S0777), the relevant results per study are summarized in the following section.

Presentation of relevant studies

See Main characteristics of included studies section 4.4 for the requested brief summary of the studies included in the assessment of the related clinical question.

In the following section, the results per study will be reported as requested. The qualitative review of adverse events will be reported separately under each clinical question based on the relevant study for the narrative comparison. The results per study can also be found in Appendix F – Results per study in the template provided by the Medicines Council.

Results per study

6.1.1.1.1 ALCYONE (DaraBorMelPred vs. BorMelPred)

The ALCYONE study compared DaraBorMelPred and BorMelPred. The median follow-up is 40.1 month (95% CI: 37.4-43.1) which is the longest follow-up currently available (11). The results reported for this data-cut is used throughout the clinical questions.

The median OS has not been reached in neither the DaraBorMelPred arm nor the BorMelPred arm. The OS HR is 0.60 (95% CI: 0.46-0.80) in favor of the DaraBorMelPred arm. The OS rate at 3-years is 78.0% (95% CI: 73.2-82.0) for DaraBorMelPred and 67.9% (95% CI: 62.6-72.6) for the BorMelPred.

The median PFS was reached at 36.4 months (95% CI: 32.1-45.9) for DaraBorMelPred and reached at 19.3 months (95% CI: 18.0-20.4) for BorMelPred. The HR for PFS is 0.42 (95% CI: 0.34-0.51) in favor of DaraBorMelPred.

Health related quality of life has not been published in a peer-reviewed journal or the EPAR, but data-on-file will be presented for the clinical question for DaraBorMelPred vs. BorMelPred.

Treatment discontinuations due to AEs is (24/346=6.94%) for DaraBorMelPred and (33/354=9.32%) for BorMelPred.

6.1.1.1.2 FIRST (LenDex vs. LenDex18 vs. MelPredThal)

The FIRST study compared LenDex and LenDex18 to MelPredThal. The median follow-up is 67.2 months (range: 0-86.8) for surviving patients in the FIRST trial (13) and these results are used throughout the relevant clinical questions. However, the comparison of LenDex18 vs. MelPredThal for OS and PFS, the latest values were obtained from a data cut-off date of 21st of January 2016; median follow-up 48.3 and 17.7 months, respectively (15). Lastly, based on median duration of follow-up among surviving patients of 37 months (12), this data cut has been used for the HRQoL data and the reporting of adverse events since this was the longest follow-up available for these outcome measures.

The median OS is 59.1 months (95% CI: 53.9-65.9) in the LenDex arm versus 62.3 months (95% CI: 53.6-68.7) for LenDex18 and 49.1 months (95% CI: 44.3-53.5) for MelPredThal. The OS HR is 1.02 (95% CI: 0.86-1.20) for LenDex vs. LenDex18; 0.78 (95% CI: 0.67-0.92) for LenDex vs. MelPredThal (13), and 0.77 (95% CI: 0.66-0.90) for LenDex18 vs. MelPredThal (15). The OS rate at 3-years is 70% for LenDex, 66% for LenDex18, and 62% for MelPredThal (12). The OS rate at 4-years is 59.0% for LenDex, 58.0% for LenDex18, and 51.7% for MelPredThal (13).

The median PFS was reached at 26.0 months for LenDex, 21.0 months for LenDex18 and 21.9 months for MelPredThal (13). The HR for PFS is 0.70 (95% CI: 0.60-0.81) for LenDex vs. LenDex18, 0.69 (95% CI: 0.59-0.79) for LenDex vs. MelPredThal (13), and 0.99 (95% CI: 0.86-1.14) for LenDex18 vs. MelPredThal (15).

Health related quality of life data has been published based on data from the FIRST trial. The main publication (14) was identified in the SLR and reports data from EORTC QLQ-C30, QLQ-MY20 and EQ-5D. Data from EORTC QLQ-C30 is requested in the DaraBorMelPred protocol and is therefore reported. The main publication reports data based on a pooled analysis (LenDex and LenDex18) vs. MelPredThal. These results may be relevant as LenDex and LenDex18 are following the same regimen up to cycle 18 where LenDex18 is discontinued. These results have been inserted in the appendix (11.1.2). Clinicaltrials.gov is reporting the data per treatment arm and this data is reported below as well as in the appendix (15). Clinicaltrials.gov does not report data on baseline values for HRQoL and the pooled baseline characteristics for LenDex and LenDex18 is therefore reported below based on the supplementary appendix of Deforge et al. 2015 (14).

The applicant has consulted with the Secretariat regarding which of the EORTC QLQ-C30 scales are of interest for the Expert Committee. The Secretariat expressed that the Expert Committee is primarily interested in the Global Health Status (GHS). The results from the GHS scale is therefore presented below based on the FIRST study and presented in section 6.1.2 for ALCYONE study.

TABLE 8: BASELINE VALUES FOR EORTC QLQ-C30 – POOLED ANALYSIS

	LenDex (LenDex and LenDex18 pooled)		MelPredThal	
Baseline values	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Global Health Status	1015	51.7 (24.36)	508	50.8 (24.16)

TABLE 9: CHANGE FROM BASELINE - EORTC QLQ-C30

	LenDex		LenDex18		MelPredThal	
	n	Change from baseline, mean (SD)	N	Change from baseline, mean (SD)	n	Change from baseline, mean (SD)
Global Health Status						
Number of subjects analyzed	508		507		508	
Month 1	438	0.4 (23.98)	441	-1.3 (23.93)	415	1.0 (23.68)
Month 3	421	4.8 (24.15)	413	4.7 (25.15)	396	4.3 (26.04)
Month 6	369	5.9 (25.93)	376	5.4 (23.88)	351	6.1 (25.98)
Month 12	302	4.8 (26.42)	299	3.2 (25.38)	252	6.5 (25.90)
Month 18	246	6.4 (28.02)	238	5.7 (24.86)	178	4.8 (27.05)
Study discon.	203	-0.1 (27.07)	261	5.0 (27.33)	257	0.3 (28.07)

Note: Constructed scale and change from baseline are calculated based on the mean scale linear transformation of raw score. Discon: discontinuation visit

Table reproduced based on results from ClinicalTrials.gov: Study to Determine Efficacy and Safety of Lenalidomide Plus Low-dose Dexamethasone Versus Melphalan, Prednisone, Thalidomide in Patients With Previously Untreated Multiple Myeloma (FIRST) (15)

Treatment discontinuation due to AEs were (64/532=12.03%) for LenDex, (71/540=13.15%) for LenDex18, and (76/541=14.05%) for MelPredThal based on the latest data-cut.

6.1.1.1.3 VISTA (BorMelPred vs. MelPred)

The VISTA study compared BorMelPred to MelPred. The median follow-up is 60.1 months (range: 0-74) which is the data for the longest follow-up reported (19). However, PFS is based on previous data-cut (median follow-up of 16.3 months) (18) since PFS could not be updated at the final analysis because they were based on central laboratory assessment and due to the highly significant initial benefit observed for this outcome measure. For treatment discontinuations due to AEs, the data is based on a previous data-cut as well (36.7 months follow-up) (26) since latest data-cut did not include adverse event data.

The median OS is 56.4 months in the BorMelPred arm versus 43.1 months for MelPred. The OS HR is 0.695 (95 % CI: 0.567-0.852) in favor of the BorMelPred arm. The OS rate at 5-years is 46.0% (95% CI: 40.3-51.8) for BorMelPred and 34.4% (95% CI: 28.9-39.9) for the MelPred arm (19).

The median PFS was reached at 21.7 months BorMelPred and at 15.2 months for MelPred. The HR for PFS is 0.56 in favor of BorMelPred (18).

Health related quality of life has not been published based on the VISTA study.

Treatment discontinuation due to AEs were based on a previous data-cut due to that the latest data cut did not include adverse event data: 15.3% for BorMelPred versus 14.2% for MelPred. Data represent discontinuation of all treatment (26).

6.1.1.1.4 IFM 01/01 (MelPredThal vs. MelPred)

The IFM 01/01 study compared MelPredThal to MelPred. The median follow-up is 47.5 months which is the longest follow-up available trial (16) and these results are used throughout the relevant clinical questions.

The median OS is 44.0 months (95% CI: 33.4-58.7) in the MelPredThal arm versus 29.1 months (95% CI: 26.4-34.9) for MelPred. The OS HR is 0.68 in favor of the MelPredThal arm. The OS rate at 3-years is not reported.

The median PFS was reached at 24.1 months (95% CI: 19.4-29.0) for MelPredThal and at 18.5 months (95% CI: 14.6-21.3) for MelPred. The HR for PFS is 0.62 in favor of MelPredThal.

Health related quality of life has not been published based on the IFM 01/01 study.

Treatment discontinuation due to adverse events were 42.5% for MelPredThal versus 12.9% for MelPred.

6.1.1.1.5 IFM 99-06 (MelPredThal vs. MelPred)

The IFM 99-06 study compared MelPredThal to MelPred. The median follow-up is 51.5 months (95% CI: 34.4-63.2) (17) which is the longest follow-up available and these results are used throughout the relevant clinical questions.

The median OS is 51.6 months (95% CI: 26.6-NR) in the MelPredThal arm versus 33.2 months (95% CI: 13.8-54.8) for MelPred. The OS HR is 0.59 (95% CI: 0.46-0.81) in favor of the MelPredThal arm. The OS rate at 3-years is not reported.

The median PFS was reached at 27.5 months for MelPredThal and at 17.8 months for MelPred. The HR for PFS is 0.51 (95% CI: 0.39-0.66) in favor of MelPredThal.

Health related quality of life has not been published based on IFM 99-06.

Treatment discontinuation due to adverse events were 45% for MelPredThal and not reported in MelPred arm.

6.1.1.1.6 SWOG S0777 (BorLenDex vs. LenDex)

The SWOG S0777 study compared BorLenDex and LenDex. As specified in 4.4.3 and shown in Table 4, different data cuts and analyzed patient populations exist as the patient population in the EPAR is not identical to the patient population reported in Durie et al. 2017 (13). The main ITT data reported for OS and PFS in this application are based on the data from the EPAR using the data cut-off of 1st of December 2016 (6). The median follow-up (based on Kaplan-Meier estimate) for all surviving subjects was 69 months (6). The median follow-up for all patients in the BorLenDex arm was 61.6 months (min, max: 0.2, 99.4) and 59.4 months (min, max: 0.4-99.1) for LenDex (4). This was the data cut-off date used for the assessment of BorLenDex by the Medicines Council (25) *p. 51, 94, 159 (page number in the merged PDF)* and thus reported in this application as well. The data for treatment discontinuation due to AEs is based on shorter follow-up (median follow up of 55 months for BorLenDex in the SWOG S0777 study, applying the data from the original manuscript by Durie et al. 2017 (20) and as utilized in the assessment of BorLenDex by the Medicines Council (25). The qualitative assessment of AEs is based on data from the EPAR, initial treatment (24 weeks) (6).

The median OS was reported to be 89.1 months (95% CI: 76.1-NR) for BorLenDex and 67.2 (95% CI: 58.4-90.8) for LenDex using the cut-off of 1st of December 2016 with a hazard ratio of 0.75 (95% CI: 0.58-0.97), p=0.002786) in favor of BorLenDex (4, 6, 25). With a shorter follow-up (55 months) for BorLenDex in the SWOG S0777 study, the original manuscript (Durie et al. 2017) reports a median overall survival for the BorLenDex arm of 75 months (13).

The median PFS was reached at 41.7 months (95% CI: 33.1-51.5) for BorLenDex and 29.7 months (95% CI: 24.2-37.8) for LenDex. The HR for PFS is 0.76 (95% CI: 0.62-0.94) in favor of BorLenDex. These results are using the cut-off of 1st of December 2016 and EMA censoring reported in the EPAR (6).

Health related quality of life has not been published for BorLenDex based on the SWOG S0777 trial.

Treatment discontinuations due to adverse events is (55/241=22.82%) for BorLenDex and (22/226=9.73%) for LenDex (initial 24 weeks treatment only). This is the data applied in the analysis to obtain a conservative estimate, and it was used by Celgene/Medicines Council in the evaluation of BorLenDex (25) and originates from Durie et al. 2017 (13). The reason for minor differences in safety population for LenDex is due to this application utilized the *patients evaluable for toxic effects* (20) p. 522, Durie et al. 2017. The BorLenDex evaluation utilized 229 in the denominator for the LenDex arm. As highlighted in subsequent section Treatment discontinuation due to adverse events, data is reported in the EPAR accounting for both initial treatment + continued LenDex, which resulted in 37% and 25% treatment discontinuations due to treatment emergent adverse events (TEAE) for BorLenDex and LenDex, respectively (6). Additional subgroup analyses are also highlighted in the EPAR (initial treatment only) including intent to transplant at progression as well impact of age which will be reported in the subsequent section.

6.1.2 DaraBorMelPred compared to BorMelPred

The comparison of DaraBorMelPred vs. BorMelPred is based on the results from the ALCYONE trial.

Presentation of relevant studies

As stated in the protocol for DaraBorMelPred, the Secretariat identified the following manuscript based on the ALCYONE trial as relevant and which can be used for the direct comparison vs. BorMelPred (1):

- Mateos MV et al. *Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial.* Lancet. 2020 Jan 11;395(10218):132-141 (11)

See section 4.4.1 for a presentation of ALCYONE and Appendix A – Primary SLR section 9.2.1 for a detailed presentation according to the template provided.

Relevant differences between studies

The study is a direct comparison of the treatments DaraBorMelPred and BorMelPred and therefore no difference exists regarding study characteristics. See section 4.4.1 for *within trial differences* for the ALCYONE trial.

Results per study

The results per study are outlined in detail in Appendix F – Results per study, section 11.1.1 (results per study) and 11.2.1 (results per PICO) based on the template provided by the Medicines Council.

For the comparison of DaraBorMelPred vs. BorMelPred, this section will cover the *comparative* analysis. The results for each outcome measure relevant for the clinical question is presented.

Comparative analyses

Overall survival (Median OS and OS-rate at 36 months)

As described in the protocol for DaraBorMelPred:

> *Den mediane overlevelse hos patienter, der ikke behandles med højdosis kemoterapi med stamcellestøtte, er ca. 3 år. Ved fastsættelsen af den mindste klinisk relevante forskel skelner fagudvalget mellem, om komparator er tidsbegrænset eller til progression. Da interventionen løber til progression, bør der være en større effektforskel, hvis der sammenlignes med en tidsbegrænset behandling. Fagudvalget har vurderet, at den mindste klinisk relevante forskel i medianoverlevelse mellem intervention og komparator er 6 måneder, når komparator er en tidsbegrænset behandling. 6 måneder er valgt på grund af den relativt lange nuværende mediane overlevelse, og at interventionen gives i 1. linje indtil progression. Hvis komparator også løber til progression, er den mindste klinisk relevante forskel 3 måneder.*
> *Såfremt data for medianoverlevelsen ikke er modne ønsker fagudvalget data for overlevelsesraten efter tre år. Den nuværende 3-årsoverlevelse i den danske population er ca. 58 % baseret på tal fra 2014-2017. Fagudvalget vurderer, at den mindste klinisk relevante forskel for overlevelsesraten er 5 procentpoint, svarende til at ca. 12 patienter flere vil være i live efter 3 år.*

At a median follow-up of 40.1 months from the ALCYONE trial, the median OS was not reached in neither of the treatment arms (Table 10). Since the median OS has not been reached, the 36-months OS rate is provided below as requested by the Expert Committee.

At a median follow-up of 40.1 months, a total of 209 (DaraBorMelPred: 83; BorMelPred: 126) OS events were observed. There was a statistically significant improvement in OS for patients in the DaraBorMelPred arm compared with the BorMelPred arm (HR: 0.60; 95% CI: 0.46-0.80; p=0.0003; Figure 5); the risk of death

was reduced by 40% (11). The 36-months overall survival rate was 78.0% (95% CI: 73.2-82.0) for DaraBorMelPred and 67.9% (95% CI: 62.6-72.6) for BorMelPred.

TABLE 10: OVERALL SURVIVAL RESULTS – BORMELPRED VS. DARABORMELPRED

Overall survival[d]	BorMelPred(n=356)	DaraBorMelPred (n=350)
Number of events, n (%)	126 (35.4)	83 (23.7)
Median (95% CI)	NE (43.9, NE)	NE (NE, NE)
Hazard ratio (95% CI)[a] **p-value[b]**		0.60 (0.46, 0.80) 0.0003
36-month OS rate, % (95% CI)	67.9 (62.6, 72.6)	78.0 (73.2, 82.0)
Estimated difference, 36-month OS rate, % (95% CI)[c]		10.1 (5.4, 14.8)

CI = confidence interval; NE = not evaluable; OS = overall survival
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio < 1 indicates an advantage for DaraBorMelPred. [b] p-value is based on unstratified log-rank test. [c] 95% CI is approximated using the WALD type confidence intervals. [d] Unstratified analysis

The absolute difference for the 36-months rate of overall survival is 10.1 percentage points comparing the two rates naively by simple subtraction (78.0 - 67.9=10.1) in favor for DaraBorMelPred. The absolute difference including the confidence interval is 10.1% (95% CI: 5.4, 14.8) where the confidence interval is approximated using the WALD type confidence intervals.

FIGURE 5: KAPLAN-MEIER ESTIMATES OF OVERALL SURVIVAL (ITT) - DARABORMELPRED

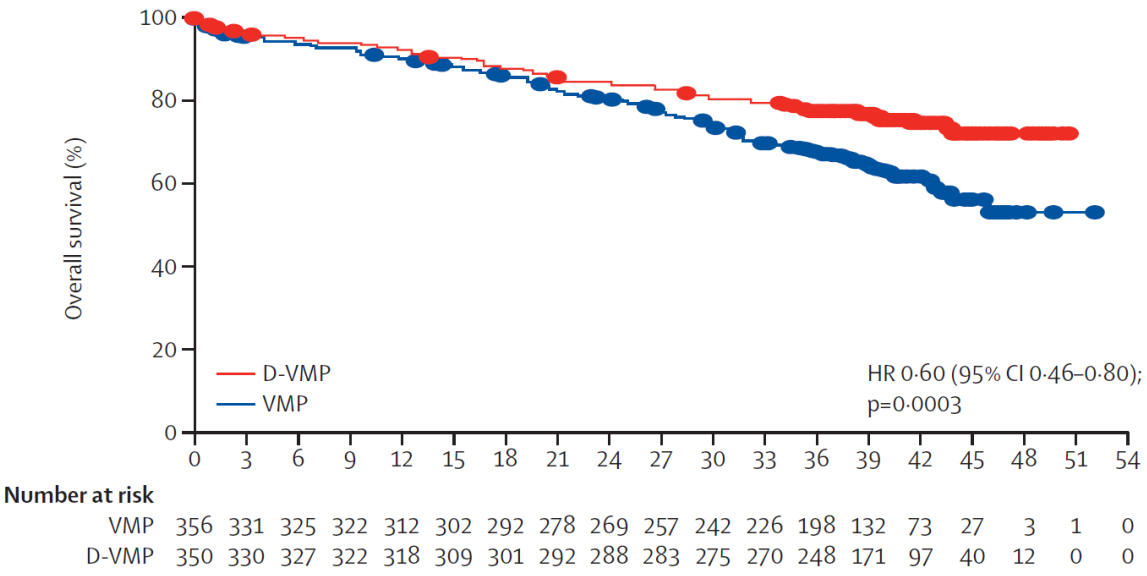


Figure reprinted from: Mateos, M. V., Cavo, M., Blade, J., Dimopoulos, M. A., Suzuki, K., Jakubowiak, A., ... & Pour, L. (2020). Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. The Lancet, 395(10218), 132-141.
D-VMP: DaraBorMelPred; VMP: BorMelPred.

Progression-free survival (Median PFS)

Since the median OS has not been reached, PFS data is provided as requested by the Expert Committee.

Based on a median follow-up time of 40.1 months, a total of 441 (DaraBorMelPred: 176; BorMelPred: 265) PFS events were observed. There was a statically significant improvement in PFS for patients in the DaraBorMelPred arm compared with the BorMelPred arm (HR: 0.42; 95% CI: 0.34-0.51; p<0.0001;Figure 6);

the risk of disease progression or death was reduced by 58%. The median PFS in the DaraBorMelPred arm was reached at 36.4 months (95% CI: 32.1–45.9) compared with 19.3 months (18.0–20.4) in the BorMelPred arm (Table 11) (11).

TABLE 11: PROGRESSION-FREE SURVIVAL RESULTS – BORMELPRED VS. DARABORMELPRED

Progression-free survival[c]	BorMelPred(n=356)	DaraBorMelPred (n=350)
Number of events, n (%)	265 (74.4)	176 (50.3)
Median, months (95% CI)	19.3 (18.0, 20.4)	36.4 (32.1, 45.9)
Hazard ratio (95% CI)[a]		0.42 (0.34, 0.51)
p-value[b]		<0.0001

CI = confidence interval; NE = not evaluable

[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS (I, II, or III), region (Europe vs Other) and age (<75 years vs ≥75 years) as randomised. A hazard ratio <1 indicates an advantage for DaraBorMelPred. [b] p-value is based on the log-rank test stratified with ISS (I, II, or III), region (Europe vs Other) and age (<75 years vs ≥75 years) as randomised. [c] Based on computerized algorithm.

For the comparison of the two medians naively, the absolute difference between the two treatments is 17.1 months (36.4 vs. 19.3) in favor of DaraBorMelPred.

FIGURE 6: KAPLAN-MEIER ESTIMATES OF PROGRESSION-FREE SURVIVAL (ITT) - DARABORMELPRED

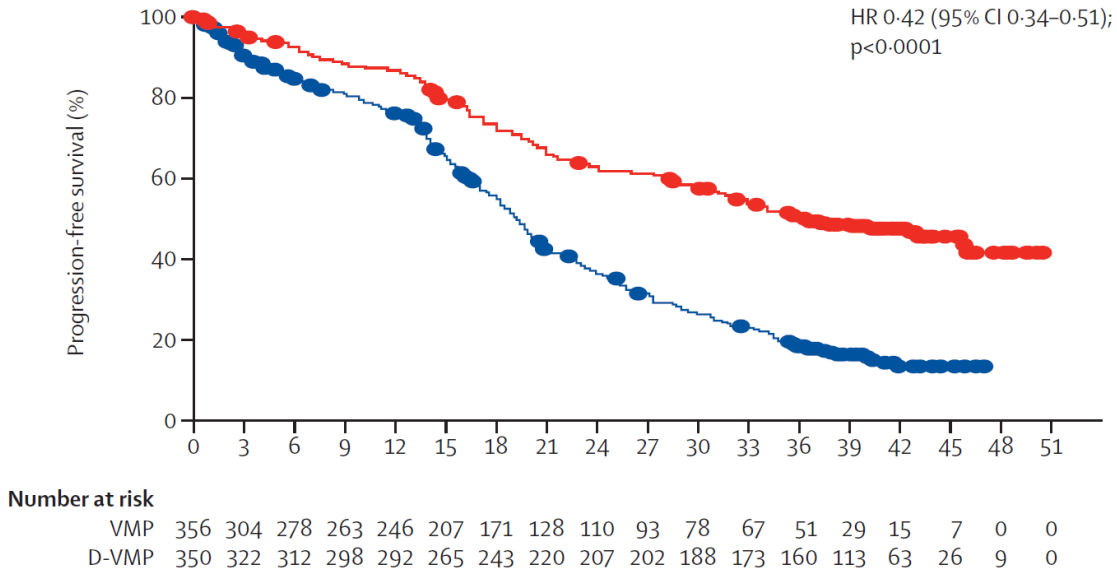


Figure reprinted from: Mateos, M. V., Cavo, M., Blade, J., Dimopoulos, M. A., Suzuki, K., Jakubowiak, A., ... & Pour, L. (2020). Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. The Lancet, 395(10218), 132-141.
D-VMP: DaraBorMelPred; VMP: BorMelPred.

6.1.2.1.1.1 Data maturity

In addition, the Expert Committee has requested the applicant to assess the data maturity. Examining the Kaplan-Meier curve for PFS and the relationship between the number of censored patients and numbers of patients at risk, the PFS data for the ALCYONE trial is assessed to be sufficiently mature, and the median has been reached for the intervention as well as the comparator.

Health related quality of life

HRQoL data was collected in the ALCYONE trial. Due to limited HRQoL data published (only a single abstract is published (27)) and considering the recent guidance from the Medicines Council (28), data-on-file is presented in the following section. It should be noted that the applicant expects a peer-reviewed manuscript to be published around the time of the assessment focusing on PROs for the ALCYONE trial.

The Expert Committee has requested data from the EORTC QLQ-C30 scale. The EORTC QLQ-C30 has five functional scales (physical, role, emotional, cognitive and social functioning), one Global Health Status (GHS) scale, three symptom scales (fatigue, nausea and vomiting, and pain) and six single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). Higher scores indicate better GHS and functioning, and more symptoms, respectively.

The applicant has consulted with the Secretariat regarding which of the EORTC QLQ-C30 scales are of interest for the Expert Committee. The Secretariat expressed that the Expert Committee is mainly interested in the Global Health Status (GHS). The results from the GHS scale is therefore presented below.

At baseline, compliance rates for completion of the EORTC QLQ-C30 were 91% in the BorMelPred arm and 90% in the DaraBorMelPred arm; after 24 months, compliance rates were 36% in the BorMelPred and 62% in the DaraBorMelPred arm.

Baseline values for GHS were descriptively comparable for patients treated with DaraBorMelPred and BorMelPred (Table 12).

TABLE 12: BASELINE VALUES FOR ALL SUBSCALES OF THE EORTC QLQ-C30 (ALCYONE; INTENT-TO-TREAT ANALYSIS SET; MEDIAN FOLLOW-UP 40.1 MONTHS)

Mean ± SD	BorMelPred	DaraBorMelPred
Global Health Status	52.40 ± 22.615	50.66 ± 21.012

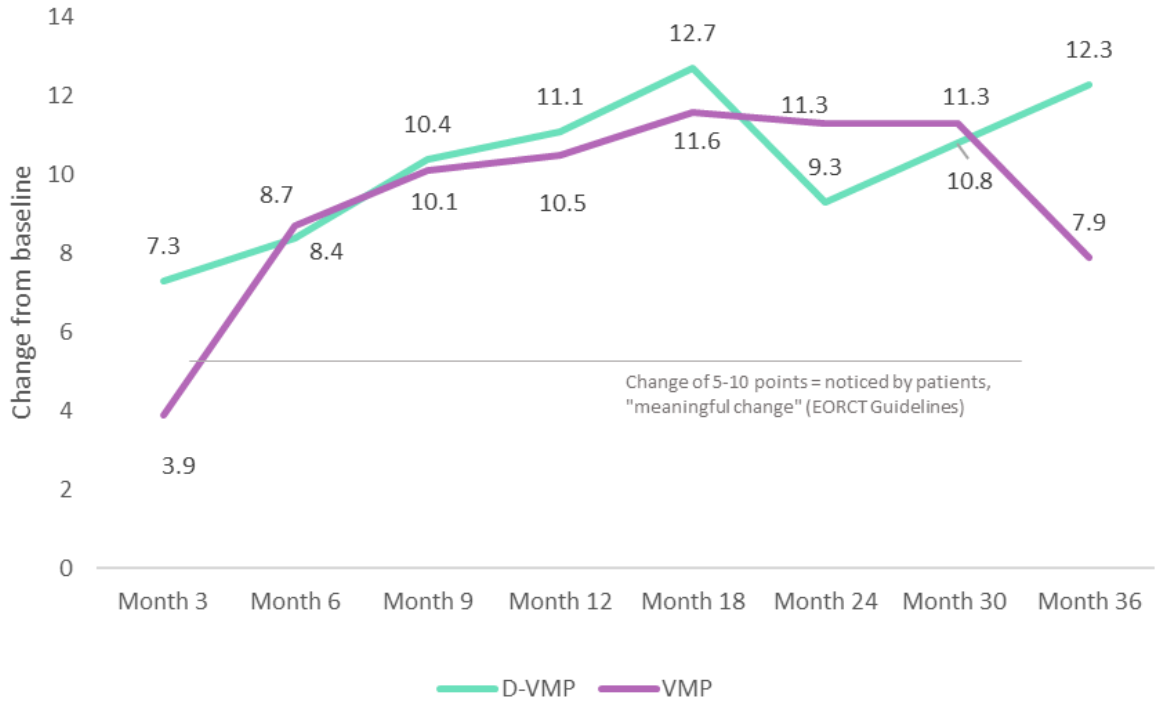
SD = standard deviation; Source: Janssen, data-on-file, median follow-up of 40.1 months.

Treatment benefit on the GHS scale

Treatment benefit was assessed using mixed-effects repeated measures analyses of least-squares (LS) mean change from baseline. A within-group change of between 5 and 10 points on the 100-point scale was defined as a difference that patients regard as “significant changes” and therefore represents a clinically meaningful change.

At month 3, there was a significant difference in the mean change from baseline for the GHS scale; patients treated with DaraBorMelPred reported greater improvements in HRQoL compared with patients treated with BorMelPred (LS mean change from baseline for DaraBorMelPred = 7.3 (95% CI: 5.1-9.5) BorMelPred = 3.9 (95% CI: 1.6-6.2) LS mean difference = 3.4 (95% CI: 0.5-6.4) p=0.0240; Figure 7). For DaraBorMelPred, the mean change from baseline was >5 points by Month 3 and was maintained at >10 points from month 9 and onwards (except at month 24), indicating a rapid meaningful change for patients and ongoing improvements (Figure 7 and Table 13). For BorMelPred, the mean change from baseline was >5 points by month 6 and was maintained up to month 34 (Figure 7 and Table 13).

FIGURE 7: EORTC-QLQ-C30 GLOBAL HEALTH SCALE AMONG PATIENTS TREATED WITH EITHER DARABORMELPRED OR BORMELPRED (ALCYONE; INTENT-TO-TREAT ANALYSIS SET; MEDIAN FOLLOW-UP 40.1 MONTHS)



D-VMP = DaraBorMelPred; VMP: BorMelPred
Source: Janssen, data-on-file, median follow-up of 40.1 months.

TABLE 13: MIXED MODEL FOR CHANGE IN EORTC QLQ-C30 GLOBAL HEALTH SCALE AMONG PATIENTS TREATED WITH EITHER DVMP OR VMP (ALCYONE; INTENT-TO-TREAT ANALYSIS SET; MEDIAN FOLLOW-UP 40.1 MONTHS)

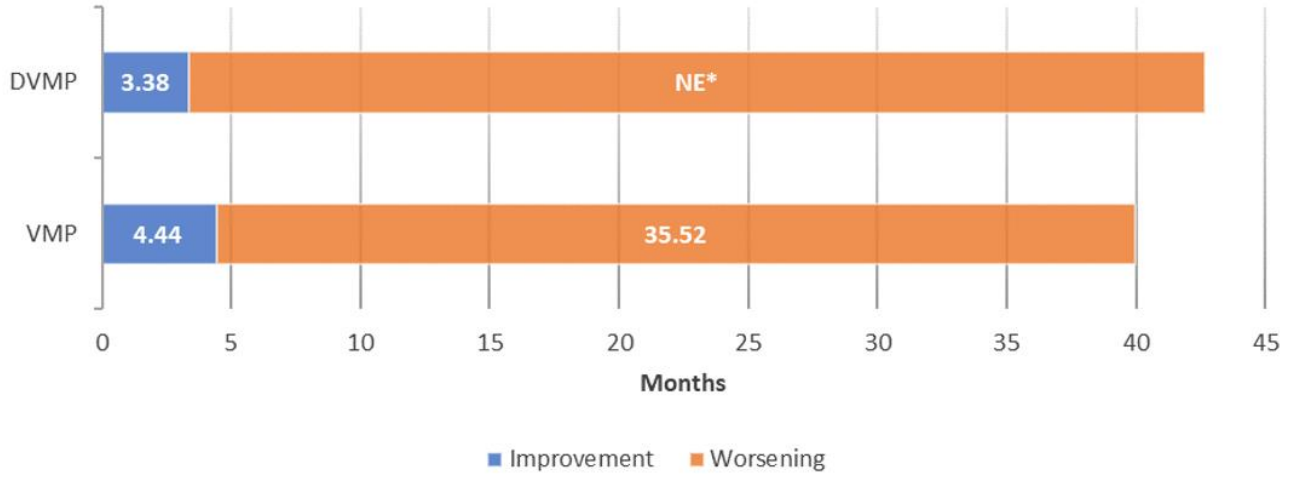
	n	BorMelPred LS Means of Change from Baseline (95% CI)	n	DaraBorMelPred LS Means of Change from Baseline (95% CI)	Difference Mean (95% CI)	p-value
Month 3	245	3.9 (1.6, 6.2)	262	7.3 (5.1, 9.5)	3.4 (0.5, 6.4)	0.0240
Month 6	213	8.7 (6.3, 11.2)	235	8.4 (6.1, 10.7)	–0.3 (–3.5, 2.8)	0.8284
Month 9	189	10.1 (7.6, 12.6)	228	10.4 (8.0, 12.7)	0.3 (–3.0, 3.5)	0.8691
Month 12	185	10.5 (8.0, 13.1)	222	11.1 (8.8, 13.5)	0.6 (–2.7, 3.9)	0.7172
Month 18	136	11.6 (8.7, 14.4)	194	12.7 (10.2, 15.1)	1.1 (–2.5, 4.7)	0.5643
Month 24	83	11.3 (7.9, 14.8)	152	9.3 (6.6, 12.0)	–2.0 (–6.3, 2.2)	0.3471
Month 30	48	11.3 (6.9, 15.7)	119	10.8 (7.8, 13.7)	-0.5 (-5.7, 4.7)	0.8445
Month 36	31	7.9 (2.5, 13.2)	80	12.3 (8.8, 15.8)	4.4 (-1.8, 10.7)	0.1656

CI = confidence interval; EORTC QLQ = European Organisation for Research and Treatment of Cancer quality of life questionnaire; LS = least squares
Source: Janssen, data-on-file, median follow-up of 40.1 months.
Least square means are derived based on the mixed effects model with repeated measures, in which the dependent variable is change from baseline in score and independent variables are baseline, visit, treatment, visit by treatment interaction and randomisation stratification factors - ISS staging (I, II, III), region (Europe vs. Other) and age (<75 years vs. ≥75 years) as fixed effects and individual subject as random effect.

Improvement in GHS occurred one month quicker with DaraBorMelPred than BorMelPred (median time to improvement = 3.38 months with DaraBorMelPred and 4.44 months with BorMelPred) (Figure 8). Changes consistent with these improvements in GHS. Median time to worsening was 35.52 (95% CI: 28.52 - NE*) for BorMelPred while it was NE* (95% CI: 39.29 - NE*) for DaraBorMelPred.

*Not estimable

FIGURE 8: MEDIAN TIME TO IMPROVEMENT OR WORSENING OF EORTC QLQ-C30 GLOBAL HEALTH STATUS SCORE



*Estimate based on 95% CI lower bound

CI = confidence interval; DVMP = DaraBorMelPred; VMP: BorMelPred EORTC QLQ = European Organisation for Research and Treatment of Cancer quality of life questionnaire; NE = not estimable

Note: Worsening is defined as a decrease in score that is at least half of standard deviation from baseline values, where standard deviation is calculated from the scores at baseline combining both treatment groups.

Source: Janssen, data-on-file, median follow-up of 40.1 months.

Treatment discontinuation due to adverse events

DaraBorMelPred is well tolerated with a lower rate of treatment discontinuations due to AEs than the comparator arm, BorMelPred. With a median follow-up of 40.1 months, a total of 24 patients in the daratumumab treatment arm (6.9%) and 33 patients in the control arm (9.3%) discontinued their treatments due to AEs.

TABLE 14: TREATMENT DISCONTINUATIONS DUE TO ADVERSE EVENTS – BORMELPRED VS. DARABORMELPRED

Treatment discontinuations due to Adverse events	BorMelPred (n=354)	DaraBorMelPred (n=346)
Treatment discontinuations due to adverse events	33 (9.3%)	24 (6.9%)
Median	NA (NA , NA)	NA (NA , NA)
Hazard ratio (95% CI), p value*		0.48 (0.26, 0.86), p = 0.0134
Relative risk (95% CI), p value*		0.75 (0.45, 1.23), p= 0.2469
Absolute difference (95% CI), p value*		-2.3% (-6.3%, 1.6%), p=0.2458

NA: Not available

*HR is based on the stratified cox proportional hazard model hazard model and the relative risk and absolute difference are also based on stratified analysis using the stratification factors used in the study.

Comparing the study arms with each other in the time-adjusted analysis of adverse events leading to treatment discontinuations shows a statistically significant reduction of 52.4% in the risk of treatment discontinuation due to AEs in favor of the DaraBorMelPred, HR=0.48 (95% CI: 0.26 - 0.86).

The absolute difference is -2.3% (95% CI: -6.3%; 1.6%) in favor of the DaraBorMelPred arm.

As stated in the protocol, an increase of approximately 10%-point in discontinuations due to adverse events is considered acceptable for the intervention. DaraBorMelPred was able to show a favorable decrease in treatment discontinuations due to adverse events compared to BorMelPred.

Qualitative assessment of adverse events

As described in the DaraBorMelPred protocol:

Fagudvalget ønsker som supplement til effektmålet behandlingsophør grundet bivirkninger en opgørelse af de hyppigste bivirkninger af enhver grad (forekommer hos > 10 % af patienterne) samt alle bivirkninger af grad 3-4, der er rapporteret i de kliniske studier, hvor DaraBorMelPred er undersøgt som behandling til nydiagnosticerede patienter med knoglemarvskræft. Fagudvalget vil ud fra denne opgørelse vurdere håndterbarhed og tyngde af bivirkningsprofilen i en narrativ sammenligning…
Ansøger bedes lave en vurdering af, om sammenligningen af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling og hvordan bivirkningerne er opgjort og rapporteret. Overvejelser om sammenlignelighed/indirekthed skal fremgå i den endelige ansøgning

Based on dialogue with the Secretariat, the Expert Committee is solely interested in an overview of the side effects/AEs and not a comparative analysis. The requested overview can be found in tables below. More specifically, the Expert Committee has requested AE data of any grade occurring in more than 10 % of the patients which is presented based on unpublished data-on-file in Table 15. In the manuscript, AEs of any grade that were reported in ≥ 20% of patients in either treatment arm are published (11).

In addition, the Expert Committee has also requested an overview of all side effects/AEs of grade 3-4 being reporting in the clinical study. To provide the most comparable results to the other specified comparators, namely LenDex18 and BorLenDex (relevant for the other clinical questions), the most common (≥5%) Grade 3 or 4 treatment emergent adverse events (TEAEs) are presented based on unpublished data-on-file in Table 16. In the manuscript, grade 3 or 4 AEs that were reported in ≥10 % of patients in either treatment arm of all treatment cycles are published (11).

Data for the review for DaraBorMelPred and BorMelPred has been extracted based on data-on-file from the ALCYONE trial with a median follow-up of 40.1 months. Data cut-off dates reported as June 2019.

Since Table 15 is reporting data from both arms, the threshold of 10% has been surpassed in at least one of the arms for the stated AE. For consistency, the number reported for the both arms have been included in the below table, but the specific number is crossed out to highlight that the 10% threshold was not surpassed. The same has been done for Table 16 reporting most common (≥5%) Grade 3 or 4 AEs.

It is important to note the low number of treatment discontinuations due to AEs for DaraBorMelPred reflecting that the majority of reported AEs could be handled without discontinuing treatment.

TABLE 15: MOST COMMON (≥10%) ADVERSE EVENTS OF ANY GRADE

Most Common (At Least 10%) Treatment-emergent Adverse Events	Proportion of patients, n (%)	
	DaraBorMelPred - ALCYONE (n=346)	BorMelPred - ALCYONE (n=354)
Reference	Janssen, data-on-file	Janssen, data-on-file
Any TEAE	337 (97.4%)	342 (96.6%)
Blood and lymphatic system disorders	**256 (74.0%)**	**269 (76.0%)**
Neutropenia	174 (50.3%)	186 (52.5%)
Thrombocytopenia	172 (49.7%)	190 (53.7%)
Anaemia	107 (30.9%)	131 (37.0%)
Leukopenia	47 (13.6%)	53 (15.0%)
Lymphopenia	39 (11.3%)	36 (10.2%)
Infections and infestations	**256 (74.0%)**	**171 (48.3%)**
Upper respiratory tract infection	106 (30.6%)	50 (14.1%)
Pneumonia	63 (18.2%)	~~18 (5.1%)~~
Bronchitis	72 (20.8%)	~~27 (7.6%)~~
Viral upper respiratory tract infection	49 (14.2%)	~~23 (6.5%)~~
Urinary tract infection	39 (11.3%)	~~12 (3.4%)~~
General disorders and administration site conditions	**212 (61.3%)**	**184 (52.0%)**
Pyrexia	89 (25 7%)	74 (20.9%)
Oedema peripheral	68 (19.7%)	39 (11.0%)
Fatigue	60 (17.3%)	51 (14.4%)
Asthenia	48 (13.9%)	43 (12.1%)
Gastrointestinal disorders	**195 (56.4%)**	**192 (54.2%)**
Diarrhoea	96 (27.7%)	87 (24.6%)
Nausea	75 (21.7%)	76 (21.5%)
Constipation	64 (18.5%)	65 (18.4%)
Vomiting	61 (17.6%)	55 (15.5%)
Nervous system disorders	**178 (51.4%)**	**181 (51.1%)**
Peripheral sensory neuropathy	100 (28.9%)	122 (34.5%)
Musculoskeletal and connective tissue disorders	**159 (46.0%)**	**116 (32.8%)**
Back pain	61 (17.6%)	42 (11.9%)
Arthralgia	39 (11.3%)	~~22 (6.2%)~~
Pain in extremity	38 (11.0%)	~~22 (6.2%)~~
Respiratory, thoracic and mediastinal disorders	**149 (43.1%)**	**74 (20.9%)**
Cough	68 (19.7%)	~~27 (7.6%)~~
Dyspnoea	44 (12.7%)	~~16 (4.5%)~~
Metabolism and nutrition disorders	**131 (37.9%)**	**125 (35.3%)**
Decreased appetite	40 (11.6%)	46 (13.0%)
Skin and subcutaneous tissue disorders	**95 (27.5%)**	**97 (27.4%)**
Rash	~~32 (9.2%)~~	38 (10.7%)
Vascular disorders	**94 (27.2%)**	**52 (14.7%)**
Hypertension	45 (13.0%)	~~11 (3.1%)~~

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Most Common (At Least 10%) Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class and Preferred Term; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months)

TABLE 16: MOST COMMON (≥5%) GRADE 3 OR 4 ADVERSE EVENTS

Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set	Proportion of patients, n (%)	
	DaraBorMelPred – ALCYONE (n=346)	BorMelPred – ALCYONE (n=354)
Reference	Janssen, data-on-file	Janssen, data-on-file
Patients with Grade 3 or 4 TEAEs	277 (80.1%)	274 (77.4%)
Blood and lymphatic system disorders	**211 (61.0%)**	**219 (61.9%)**
Neutropenia	139 (40.2%)	138 (39.0%)
Anaemia	60 (17.3%)	70 (19.8%)
Thrombocytopenia	120 (34.7%)	134 (37.9%)
Lymphopenia	27 (7.8%)	22 (6.2%)
Leukopenia	28 (8.1%)	30 (8.5%)
Infections and infestations	**92 (26.6%)**	**53 (15.0%)**
Pneumonia	45 (13.0%)	~~15 (4.2%)~~
Respiratory, thoracic and mediastinal disorders	**30 (8.7%)**	~~**13 (3.7%)**~~
Hypertension	19 (5.5%)	~~6 (1.7%)~~

Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

The Expert Committee has also requested an assessment of whether the comparison of event rates can be conducted in an acceptable manner based on study design, follow-up time, data collection and how side effects/AEs were assessed and reported. Considerations around comparison/indirectness needs be addressed in the final application.

Since the ALCYONE is a head to head trial this section is not applicable, but will be highlighted in the comparison of DaraBorMelPred vs. LenDex18 and DaraBorMelPred vs. BorLenDex

6.1.3 DaraBorMelPred compared to LenDex18

The comparison of DaraBorMelPred vs. LenDex18 is based on a network-meta analysis (NMA). The method of analysis is in line with the evaluation of the therapeutic area multiple myeloma executed by the multiple myeloma Expert Committee / Medicines Council and will be described further in the next sessions.

Presentation of relevant studies

The studies used for the NMA are:

- ALCYONE 4.4.1
- FIRST 4.4.2
- VISTA 4.4.4
- IFM 01/01 4.4.5
- IFM 99-06 4.4.6

Relevant differences between studies

See section 4.4 Table 3 for an overview of the baseline characteristics.

As mentioned in section 5.2.3, the Expert Committee for multiple myeloma assessed that the study populations for the trials included in the previously conducted NMA for primary treatment of patients that were ineligible for transplant were sufficiently similar to include an assumption regarding fixed effects for the NMA. In addition, the FIRST trial was also included in the NMA.

For the NMA conducted by the applicant, the following outcome measures were included: OS, PFS and treatment discontinuations due to AEs. As previously noted, ALCYONE was not included in the network for PFS and OS by the Expert Committee which was due immature data at the time of the analysis with a median follow-up of 16.5 months (9) p. 32. However, ALCYONE was included in the NMA for the outcome measure: treatment discontinuations due to AEs. Of relevance for the next clinical question, BorLenDex was not included in the NMA conducted by the Medicines Council due to the younger and more fit patient population in SWOG S0777.

For the network of evidence of patients that are TIE, the Expert Committee noted minor differences in study populations in terms of cytogenetic risk profile, age, and renal function. The Expert Committee stated that in terms of cytogenetic risk profile, there is variation in the share of patients with high-risk cytogenetics. One study (BorMelPredThal+BorThal cont. vs. BorMelPred) has a somewhat larger share of patients with a poorer cytogenetic risk profile, just as there are some studies where the median age is higher (MelPredThal vs. MelPred (IFM 01/01)) or renal function is better (DaraBorMelPred vs. BorMelPred (ALCYONE)) compared to other studies (9) p. 24.

Based on identified comparators by the Expert Committee in the protocol for DaraBorMelPred, the study of BorMelPredThal+BorThal cont. is not relevant for the evaluation of DaraBorMelPred. The impact of the higher age in the IFM 01/01 study investigating MelPred vs. MelPredThal and being one of the studies constructing the evidence link is not expected to have an impact on the relative efficacy for the NMA. The Expert Committee states that in the ALCYONE-study, the patients have a bit better renal function compared to the other studies (9) p.39. Regarding the slightly better renal function highlighted by the Expert Committee, this is assessed to be minor and the results from the NMA are unlikely to be affected by the slight imbalance between the trials.

In ALCYONE and SWOG S0777, patients with severe renal impairment have not been reported/included however, patients with moderate renal impairment in ALCYONE were well balanced compared with other studies. In conclusion, as stated above, smaller variations across trials are common and as such not expected to affect the results in the indirect comparison.

An overview of the renal function across studies included in the NMA has been created below. The SWOG S0777 study is used for the clinical question focusing on DaraBorMelPred vs. BorLenDex.

TABLE 17: OVERVIEW OF RENAL FUNCTION FOR STUDIES INCLUDED IN NMA

Study	Severe renal impairment < 30ml/min	Moderate renal impairment <60ml/min	Mild renal impairment >60 ml/min
ALCYONE (10)			
DaraBorMelPred	Not reported	42.9%	57.1%
BorMelPred		40.7%	59.2%
VISTA (9)			
BorMelPred	6.0%	48.0%	46.0%
MelPred	5.0%	50.0%	46.0%
IFM 01/01 (9)		-	-
MelPredThal	11.0%		
MelPred	15.0%	-	-
IFM 99-06 (9)		-	-
MelPredThal	9.0%		
MelPred	7.0%	-	-
FIRST (12)			
LenDex	8.0 %	50%	50%
LenDex18	9.0%	47%	53%
MelPredThal	10.0%	47%	53%
SWOG S0777 (EPAR) (6)			
BorLenDex	-	29.7%	70.3%
LenDex	-	30.4%	69.2%

Results per study

The studies used in the NMA is listed below. The previous section highlighted the Results per study in more detail.

- ALCYONE 6.1.1.1.1
- VISTA 6.1.1.1.3
- IFM 01/01 6.1.1.1.4
- IFM 99-06 6.1.1.1.5
- FIRST 6.1.1.1.2

Results applied in the comparative analysis for each outcome measure will be stated in the following section.

In addition, see Appendix F – Results per study for the studies included in the NMA in the requested template format. The results from these studies have been utilized in the NMA and the empirical evidence utilized in the analysis will be stated for each clinical question.

Comparative analyses

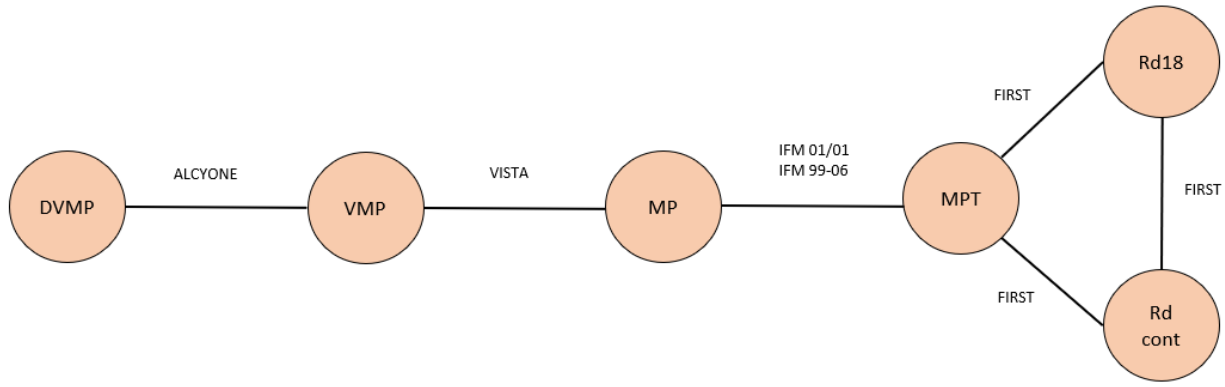
An NMA FE model for the comparison between DaraBorMelPred and LenDex18 across the outcome measures have been conducted. See previous section 5 for general considerations around the NMA conducted.

Overall survival (Median OS and OS-rate at 36 months)

6.1.3.1.1.1 Empirical Evidence

Figure 9 presents the network of evidence for OS. In total, five RCTs were included covering six treatment regimens. Table 18 presents the corresponding empirical evidence used in the analysis. As requested by the Medicines Council, the longest follow-up was used in the analysis.

FIGURE 9: NETWORK OF EVIDENCE OVERALL SURVIVAL



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex

TABLE 18: EMPIRICAL EVIDENCE BASE CASE OVERALL SURVIVAL

Trial	Treatments	Median OS (months)	OS HR	Lower bound (CI 95%)	Upper bound (CI 95%)	Follow-up time (months)
ALCYONE (11)	DaraBorMelPred versus BorMelPred	DaraBorMelPred: NR BorMelPred: NR	0.60	0.46	0.80	40.1
VISTA (19)	BorMelPred versus MelPred	BorMelPred: 56.4 MelPred: 43.1	0.70	0.57	0.85	60.1
IFM 01/01 (16)	MelPredThal versus MelPred	MelPred: 29.1 MelPredThal: 44.0	0.68	0.47	0.82	47.5
IFM 99-06 (17)	MelPredThal versus MelPred	MelPred: 33.2 MelPredThal: 51.6	0.59	0.46	0.81	51.5
FIRST (13)	LenDex versus LenDex18 LenDex vs. MelPredThal	LenDex: 59.1 LenDex18: 62.3 MelPredThal: 49.1	1.02 0.78	0.86 0.67	1.20 0.92	67.2
NR: not reached						

*Numbers are rounded for formatting purposes

6.1.3.1.1.2 NMA Assumptions

Homogeneity Assumption

In this OS network of evidence, there was one direct treatment comparison reported in multiple trials:

- MelPred versus MelPredThal, IFM 01/01 and IFM 99-06

The I2-test of MelPred versus MelPredThal showed 0%, with an Q of 0.48 and a degree of freedom of 1. There is no indication for heterogeneity in this network.

Similarity assumption

The MelPred arms in the different trials used different dosing regimens. Dosing has an impact on efficacy and safety and could therefore be a potential effect modifier. However, consistent with other NMAs in NDMM patients who are ineligible for ASCT, it was assumed that heterogeneity in dosing of MelPred would not affect the output of the NMA (29, 30).

Follow-up time (months) differed among the studies used in the analysis. Varying from median follow up time of 40.1 months in the ALCYONE trial to 67.2 months in FIRST. Additionally, the definition of OS varied among trials, see Table 19.

TABLE 19: DEFINITIONS OVERALL SURVIVAL

Trial	OS Definition
ALCYONE	Time from randomization to the date of death due to any cause
VISTA	Time from randomization until death due to any cause
IFM 01/01	Time from randomization until the date of death of any cause
IFM 99-06	Time from randomization until the date of death
FIRST	Time from randomization until death due to any cause

Consistency assumption

Inconsistency was not tested because of a lack of loops of evidence in the network.

Proportional Hazard Assumption

See 9.12 Proportional Hazard Assumption

6.1.3.1.1.3 Choice of Model

Choice of statistical model is based on DIC and on the presence of heterogeneity on the model. This network did not indicate the presence of heterogeneity. The DIC score for the FE model was lower than the DIC score of the random effects (RE) model. Therefore, a FE model was chosen for the analysis (Table 20). Additionally, the baseline characteristics of the included studies were sufficiently similar which also allowed the use of a FE model. Little difference was observed between total residual deviance between the two statistical models.

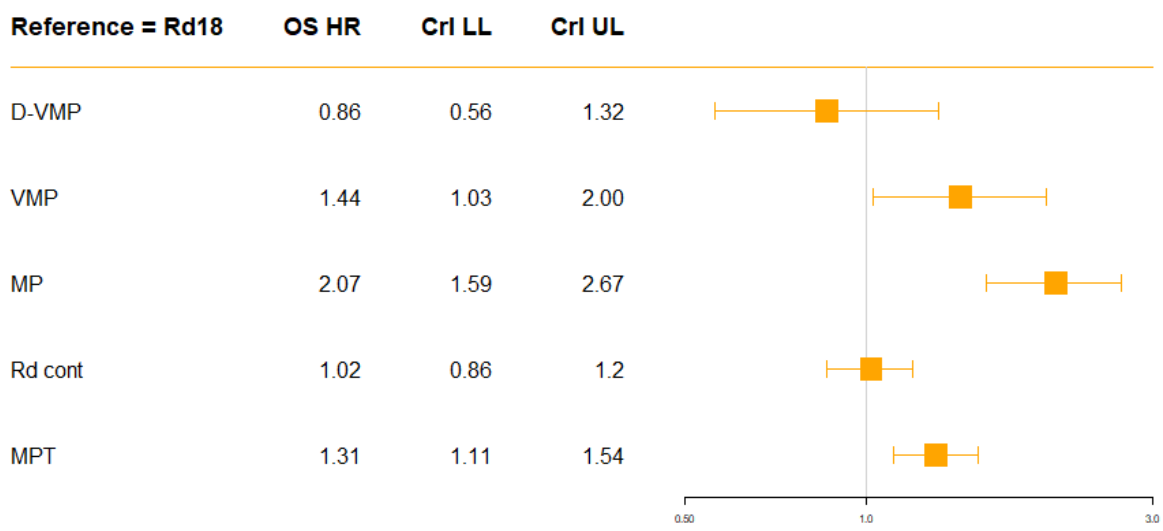
TABLE 20: STATISTICAL MODEL OVERALL SURVIVAL ANALYSIS

Model	DIC	Total residual Deviance
Fixed effects	-4.92	5.484
Random effects	-3.70	5.885

6.1.3.1.1.4 Results

Figure 10 presents a forest plot with the estimated HRs of competitor treatments against reference treatment LenDex18. A HR higher than 1 indicates that LenDex18 outperforms the comparator. Table 21 presents all the HRs of each treatment regimen against the comparators. Please note that the matrix should be read from left to right, where the first-row treatments represent the reference treatments. The HRs in bold represent the treatment comparisons from direct evidence.

FIGURE 10: FOREST PLOT OVERALL SURVIVAL, FIXED EFFECTS MODEL



Abbreviations: Rd18: LenDex18, DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, Rd cont: LenDex, MPT: MelPredThal

TABLE 21: HR MATRIX OVERALL SURVIVAL, FIXED EFFECTS MODEL

OS	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*
MelPred		1.44 (1.17-1.76)	2.02 (1.57-2.61)	2.4 (1.7-3.38)	2.07 (1.59-2.67)	1.58 (1.29-1.93)
BorMelPred	**0.7 (0.57-0.85)**		1.41 (1.01-1.95)	1.67 (1.26-2.2)	1.44 (1.03-2)	1.1 (0.83-1.46)
LenDex	0.49 (0.38-0.64)	0.71 (0.51-0.99)		1.18 (0.77-1.81)	**1.02 (0.86-1.2)**	**0.78 (0.67-0.91)**
DaraBorMelPred	0.42 (0.3-0.59)	**0.6 (0.45-0.79)**	0.84 (0.55-1.3)		0.86 (0.56-1.32)	0.66 (0.44-0.98)
LenDex18	0.48 (0.37-0.63)	0.7 (0.5-0.97)	0.98 (0.83-1.16)	1.16 (0.76-1.78)		0.76 (0.65-0.9)
MelPredThal	**0.63 (0.52-0.77)**	0.91 (0.68-1.21)	1.28 (1.09-1.5)	1.52 (1.02-2.26)	1.31 (1.11-1.54)	

The NMA shows a HR for OS of 0.86 (95% CrI: 0.56 – 1.32) in favor of DaraBorMelPred. It should be noted that the FIRST trial had a median follow-up of 67.2 months for surviving patients while the median follow-up in ALCYONE was 40.1 months. The median follow-up time (40.1 months) for ALCYONE in combination with the multiple network links in the NMA likely explains the HR and the broad confidence interval observed between DaraBorMelPred and LenDex18 for OS.

The median OS was 62.3 months for LenDex18 but since the data for the median OS has not been reached for DaraBorMelPred, the 36-months rate of overall survival is provided below as requested by the Expert Committee in the protocol for DaraBorMelPred.

The overall survival rate at 3 years was 66% for LenDex18 based on a median duration of follow-up among surviving patients of 37.0 months (range: 0 to 56.7) (12). The data for the overall survival rate at 3 years for the initial FIRST publication was similar to the follow-up in ALCYONE (40.1 month). The 3-year overall survival rate was not reported in the final FIRST publication (67.2 months follow-up for surviving patients). The overall survival rate at 3 years for DaraBorMelPred was 78.0% (73.2, 82.0). Based on a naïve unadjusted comparison, this gives DaraBorMelPred an advantage of 12 percentage points based on the 3-year overall survival rate.

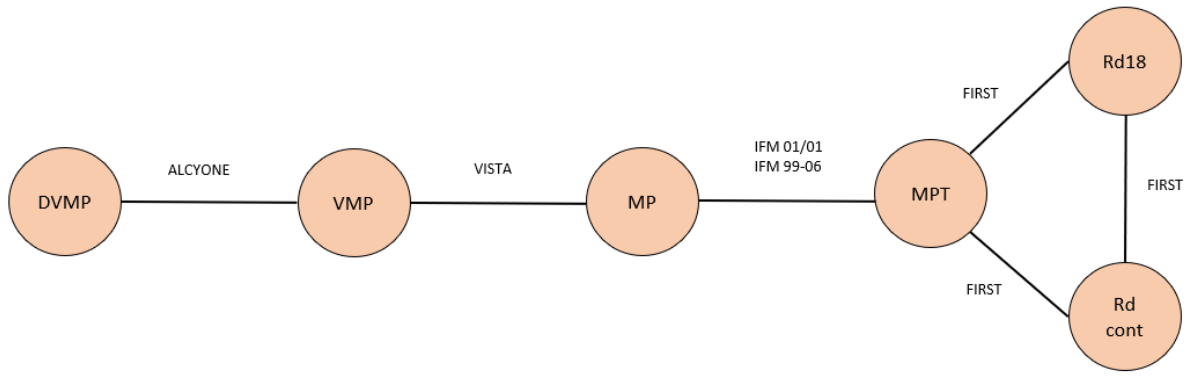
Progression free-survival (Median PFS)

Since the median OS has not been met, PFS data is provided as requested by the Expert Committee.

6.1.3.1.1.5 Empirical Evidence

Figure 11 presents the network of evidence for PFS. In total, five RCTs were included in the analyses, covering six treatment regimens. Table 22 presents the corresponding empirical evidence used in the analysis. As requested by the Medicines Council, the longest follow-up was used in the analysis.

FIGURE 11: NETWORK OF EVIDENCE PROGRESSION-FREE SURVIVAL



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex

TABLE 22: EMPIRICAL EVIDENCE BASE CASE PROGRESSION-FREE SURVIVAL

Trial	Treatments	Median PFS (months)	PFS HR	Lower bound (CI 95%)	Upper bound (CI 95%)	Follow-up time (months)
ALCYONE (11)	DaraBorMelPred versus BorMelPred	DaraBorMelPred: 36.4 BorMelPred: 19.3	0.42	0.34	0.51	40.1
VISTA (18)	BorMelPred versus MelPred	BorMelPred: 21.7 MelPred: 15.2	0.56	0.39	0.79	16.3*
IFM 01/01 (16)	MelPredThal versus MelPred	MelPred: 18.5 MelPredThal: 24.1	0.62	0.47	0.82	47.5
IFM 99–06 (17)	MelPredThal versus MelPred	MelPred: 17.8 MelPredThal: 27.5	0.51	0.39	0.66	51.5
FIRST (13)	LenDex versus LenDex18	LenDex: 26.0 LenDex18: 21.0	0.70	0.60	0.81	67.2
	LenDex versus MelPredThal	MelPredThal: 21.9	0.69	0.59	0.79	
*Please note that an earlier VISTA data-cut was used for PFS, since the latest data-cut did not PFS data. Longest follow-up is 60.1 month						

Numbers are rounded for formatting purposes

6.1.3.1.1.6 NMA Assumptions

Homogeneity Assumption

In this PFS network of evidence, there was one treatment comparison reported in multiple trials:

- MelPred versus MelPredThal, IFM 01/01 and IFM 99-06

The I2-test of MelPred versus MelPredThal showed 0%, with an Q of 1 and a degree of freedom of 1. There is no indication for heterogeneity in this network.

Similarity assumption

The MelPred arms in the different trials used different dosing regimens. Dosing has an impact on efficacy and safety and could therefore be a potential effect modifier. However, consistent with other NMAs in NDMM patients who are ineligible for ASCT, it was assumed that heterogeneity in dosing of MelPred would not affect the output of the NMA (29, 30).

Follow-up time (months) differed among the studies used in the analysis. Varying from median follow up time of 40.1 months in the ALCYONE trial to 67.2 months in FIRST. Additionally, the definition of PFS varied among trials, see Table 23.

TABLE 23: DEFINITIONS PROGRESSION-FREE SURVIVAL

Trial	PFS Definition
ALCYONE	Time from randomization until date of progression, relapse, or death
VISTA	Time from randomization until disease progression or relapse from complete response (EBMT criteria), or death due to any cause
IFM 01/01	Time from randomization until progression or death of any cause
IFM 99–06	Time from randomization until progression or death
FIRST	Time from start of the treatment until disease progression or death

Consistency assumption

Inconsistency was not tested because of a lack of loops of evidence in the network.

Proportional Hazard Assumption

See 9.12 Proportional Hazard Assumption

6.1.3.1.1.7 Choice of Model

Choice of statistical model is based on DIC and on the presence of heterogeneity on the model. This network did not indicate the presence of heterogeneity. The DIC score for the FE model was lower than the DIC score of the RE model. Therefore, a FE model was chosen for the analysis (Table 24). Additionally, the baseline characteristics of the included studies were sufficiently similar which also allowed the use of a FE model. Little difference was observed between total residual deviance between the two statistical models.

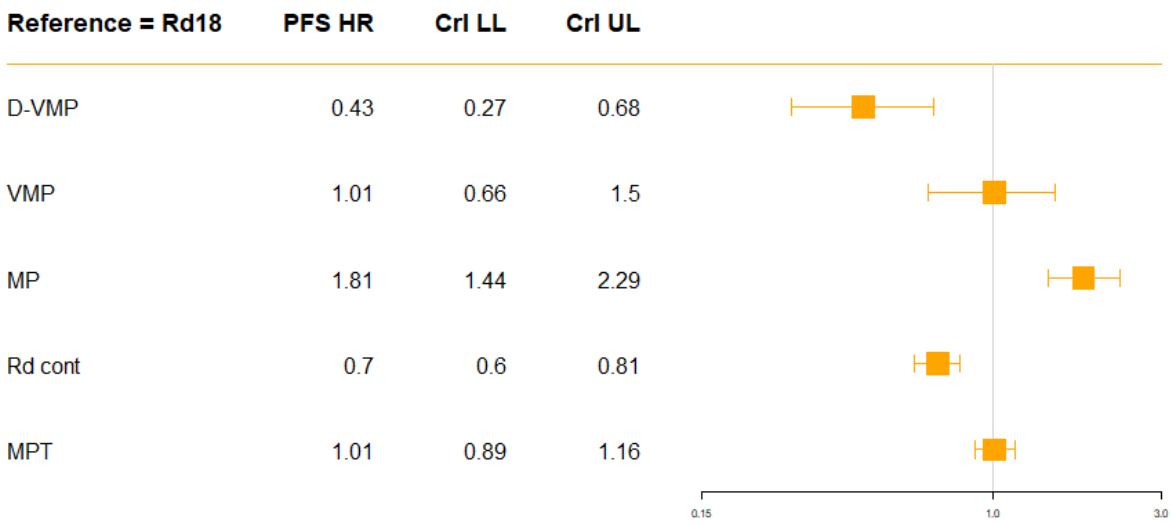
TABLE 24: STATISTICAL MODEL PROGRESSION-FREE SURVIVAL BASE CASE ANALYSIS

Model	DIC	Total residual Deviance
Fixed effects	-4.639	6.000
Random effects	-3.815	6.141

6.1.3.1.1.8 Results

Figure 12 presents a forest plot with the estimated HRs of competitor treatments against reference treatment LenDex18. A HR higher than 1 indicates that LenDex18 outperforms the comparator. Table 25 presents all the HRs of each treatment regimen against the comparators. Please note that the matrix should be read from left to right, where the first-row treatments represent the reference treatments. The HRs in bold represent the treatment comparisons from direct evidence.

FIGURE 12: FOREST PLOT PROGRESSION-FREE SURVIVAL, FIXED EFFECTS MODEL



Abbreviations: Rd18: LenDex18, DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, Rd cont: LenDex, MPT: MelPredThal

TABLE 25: HR MATRIX PROGRESSION-FREE SURVIVAL, FIXED EFFECTS MODEL

PFS	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*
MelPred		1.79 (1.26-2.55)	2.59 (2.04-3.3)	4.26 (2.84-6.4)	1.81 (1.44-2.29)	1.79 (1.48-2.17)
BorMelPred	**0.56 (0.39-0.79)**		1.45 (0.94-2.22)	2.38 (1.94-2.92)	1.01 (0.66-1.55)	1 (0.67-1.49)
LenDex	0.39 (0.3-0.49)	0.69 (0.45-1.06)		1.65 (1.03-2.64)	**0.7 (0.6-0.81)**	**0.69 (0.6-0.8)**
DaraBorMelPred	0.23 (0.16-0.35)	**0.42 (0.34-0.51)**	0.61 (0.38-0.97)		0.43 (0.27-0.68)	0.42 (0.27-0.66)
LenDex18	0.55 (0.44-0.7)	0.99 (0.65-1.51)	1.43 (1.23-1.66)	2.35 (1.47-3.75)		0.99 (0.86-1.13)
MelPredThal	**0.56 (0.46-0.68)**	1 (0.67-1.49)	1.45 (1.25-1.68)	2.38 (1.52-3.73)	1.01 (0.89-1.16)	

The NMA shows a statistically significant improvement in PFS for patients in the DaraBorMelPred arm compared with the LenDex18 arm (HR: 0.43; 95% CrI: 0.27-0.68); the risk of disease progression or death was reduced by 57%.

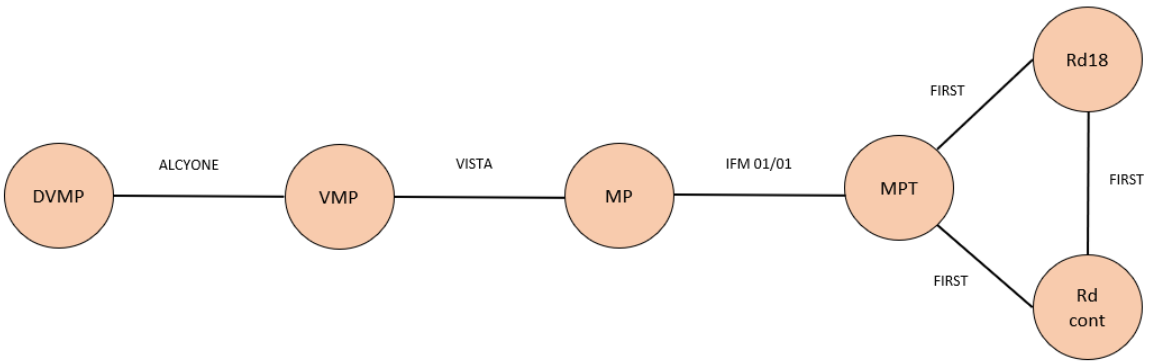
The median PFS in the DaraBorMelPred arm was 36.4 months (95% CI: 32.1–45.9) compared with 21.0 months in the LenDex18 arm. For the comparison of the two medians naively, the absolute difference between the two treatments is 15.4 months (36.4 vs. 21.0) in favor of DaraBorMelPred.

Treatment discontinuation due to adverse events

6.1.3.1.1.9 Empirical Evidence

Figure 13 presents the network of evidence for treatment discontinuation due to AEs. In total, four RCTs were included in the analyses, covering six treatment regimens. Table 26 presents the corresponding empirical evidence used in the analysis. Please note that IFM 99-06 trial did not report data on treatment discontinuation due to AEs and was therefore excluded from the network. As requested by the Medicines Council, the longest follow-up was used in the analysis, unless specified otherwise.

FIGURE 13: NETWORK OF EVIDENCE DISCONTINUATION DUE TO AES



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex

TABLE 26: EMPIRICAL EVIDENCE DISCONTINUATION DUE TO AES

Trial	Treatments	Patients in the safety population per arm (n)	Number of treatment discontinuations due to AEs per arm n	Follow-up time (months)
ALCYONE (11)	DaraBorMelPred versus BorMelPred	DaraBorMelPred: 346 BorMelPred: 354	24 33	40.1
VISTA (26)	BorMelPred versus MelPred	BorMelPred: 340 MelPred: 337	52 48	36.7*
IFM 01/01 (16)	MelPredThal versus MelPred	MelPred: 116 MelPredThal: 113	15 48	47.5
FIRST (13)	LenDex versus LenDex18 LenDex versus MelPredThal	LenDex: 532 LenDex18: 540 MelPredThal: 541	64 71 76	67.2
*Please note that an earlier VISTA data-cut was used for discontinuation due to AEs, since the latest data-cut did not include adverse event data				

6.1.3.1.1.10 NMA Assumptions

Homogeneity Assumption

In this network of evidence, there were no treatment comparisons that were reported in multiple trials. Therefore, the I2-test was not needed to be conducted.

Similarity assumption

The MelPred arms in the different trials used different dosing regimens. Dosing has an impact on efficacy and safety and could therefore be a potential effect modifier. However, consistent with other NMAs in NDMM patients who are ineligible for ASCT, it was assumed that heterogeneity in dosing of MelPred would not affect the output of the NMA (29, 30).

Follow-up time (months) differed among the studies used in the analysis. Varying from median follow up time of 36.7 months in the VISTA trial to 67.2 months in FIRST. No specific definitions on treatment discontinuation due to AEs were reported in the trial publications.

Consistency assumption

Inconsistency was not tested because of a lack of loops of evidence in the network.

6.1.3.1.1.11 Choice of Model

Choice of statistical model is based on DIC and on the presence of heterogeneity on the model. This network did not indicate the presence of heterogeneity. The DIC score for the RE model was slightly lower than the DIC score of the FE model. Yet, since this difference was limited, a FE model was chosen for the analysis (Table 27). Additionally, the baseline characteristics of the included studies were sufficiently similar which also allowed the use of a FE model. Little difference was observed between total residual deviance between the two statistical models.

TABLE 27: STATISTICAL MODEL DISCONTINUATION DUE TO AES

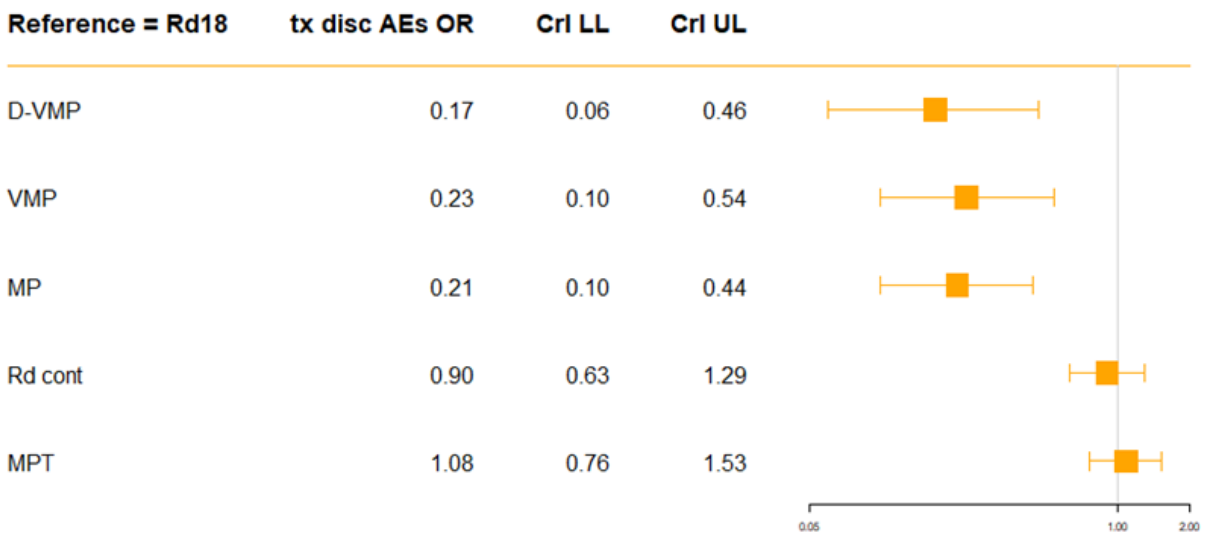
Model	DIC	Total residual Deviance
Fixed effects	66.83	9.022
Random effects	66.76	8.981

6.1.3.1.1.12 Results

Figure 14 presents a forest plot with the estimated odds ratios of treatments against reference treatment LenDex18. An odds ratio (OR) higher than 1 indicates that LenDex18 outperforms the comparator. Table 28 presents all the ORs of each treatment regimen against the comparators. Please note that the matrix should be read from left to right, where the first-row treatments represent the reference treatments.

Please note that in case LenDex to progression was not included in the analysis, the NMA results would ***not*** *change. However, inclusion of LenDex to progression was relevant for the link with BorLenDex in the NMA analysis for the clinical question focusing on BorLenDex.*

FIGURE 14: FOREST PLOT DISCONTINUATION DUE TO AES, FIXED EFFECTS MODEL



Abbreviations: Rd18: LenDex18, DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, Rd cont: LenDex, MPT: MelPredThal

TABLE 28: OR MATRIX DISCONTINUATION DUE TO AES, FIXED EFFECTS MODEL

Discontinuation due to AEs	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*
MelPred		0.92 (0.6-1.41)	0.24 (0.11-0.49)	1.28 (0.64-2.57)	0.21 (0.1-0.44)	0.2 (0.1-0.38)
BorMelPred	1.09 (0.71-1.66)		0.26 (0.11-0.6)	1.39 (0.8-2.42)	0.23 (0.1-0.54)	0.21 (0.1-0.47)
LenDex	4.25 (2.03-9.16)	3.91 (1.66-9.43)		5.42 (1.95-15.33)	0.9 (0.63-1.29)	0.84 (0.58-1.19)
DaraBorMelPred	0.78 (0.39-1.57)	0.72 (0.41-1.25)	0.18 (0.07-0.51)		0.17 (0.06-0.46)	0.15 (0.06-0.4)
LenDex18	4.71 (2.25-10.08)	4.33 (1.85-10.41)	1.11 (0.77-1.59)	6.01 (2.18-16.95)		0.93 (0.65-1.31)
MelPredThal	5.09 (2.67-10.05)	4.67 (2.15-10.44)	1.2 (0.84-1.71)	6.49 (2.49-17.2)	1.08 (0.76-1.53)	

Conversion of Odds Ratio to Relative Risk

For the categorization of the added clinical, the Medicines Council prefers that relative efficacy outcomes are reported in Relative Risk (RR) or HR for negative efficacy outcomes. Therefore, a conversion of the estimated ORs (including the confidence intervals) in has been conducted using the following formula provided by the Medicines Council (31):

$$RR = \frac{OR}{1 - ACR * (1 - OR)}$$

This formula assumed a control rate (ACR) which was defined as the rate of events (i.e. treatment discontinuations due to AEs) per control arm. The ACR was calculated per comparator (i.e. first row of matrices above in base case and is presented in Table 29. Please note that the number of events and the number of patients in the safety population per trial were also reported in Table 26.

TABLE 29: ACR PER TRIAL COMPARATOR

Trial	Comparator arm from matrices	N of events (N of patients in safety population)	ACR
VISTA (BorMelPred versus MelPred)	MelPred*	48 (337)	**0.1424**
	BorMelPred*	52 (340)	**0.1529**
IFM 01/01 (MelPredThal versus MelPred)	MelPred*	15 (116)	**0.1293**
	MelPredThal*	48 (113)	**0.4248**
ALCYONE (DaraBorMelPred versus BorMelPred)	BorMelPred*	33 (354)	**0.0932**
	DaraBorMelPred	24 (346)	**0.0694**
FIRST (LenDex vs. LenDex18 vs. MelPredThal)	LenDex	64 (532)	**0.1203**
	LenDex18	71 (540)	**0.1315**
	MelPredThal*	76 (541)	**0.1405**

*These treatments overlap across different trials (i.e. MelPred, DaraBorMelPred, MelPredThal)

Since the NMA included overlapping treatments from different trials, the ACR for MelPred (VISTA and IFM 01/01), BorMelPred (VISTA and ALCYONE), and MelPredThal (IFM 01/01 and FIRST) was based on a weighted ACR. The weighted ACR was calculated using the safety population for the overlapping treatments, the total safety population, and the calculated ACR per arm. See Table 30 for calculations and the weighted ACRs for MelPred, BorMelPred and MelPredThal.

TABLE 30: WEIGHTED ACRS FOR OVERLAPPING TREATMENTS IN THE NMA

Trial	Treatment	Safety population per arm	Total safety population	Weight of ACR per trial	Calculated ACR per trial	Weighted ACR
VISTA	MelPred	337	453	0.7439	0.1424	**0.1391**
IFM 01/01		116		0.2561	0.1293	
VISTA	BorMelPred	340	694	0.4899	0.1529	**0.1225**
ALCYONE		354		0.5101	0.0932	
FIRST	MelPredThal	541	654	0.8272	0.1405	**0.1896**
IFM 01/01		113		0.1728	0.4248	

Table 31 presents the RR, that were calculated using the ACR and the ORs. The calculation was done using the provided formula by the Medicines Council. Please note that the matrix should be read from left to right, where the first-row treatments represent the reference treatments.

TABLE 31: RR MATRIX DISCONTINUATION DUE TO AES BASE CASE, FIXED EFFECTS MODEL

Discontinuation due to AEs	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*
MelPred		0.94 (0.64-1.35)	0.26 (0.12-0.52)	1.27 (0.66-2.35)	0.24 (0.11-0.47)	0.22 (0.11-0.41)
BorMelPred	1.07 (0.73-1.51)		0.28 (0.12-0.62)	1.36 (0.82-2.22)	0.25 (0.11-0.57)	0.24 (0.11-0.5)
LenDex	2.93 (1.78-4.29)	2.91 (1.55-4.65)		4.21 (1.87-7.74)	0.91 (0.66-1.24)	0.86 (0.62-1.17)
DaraBorMelPred	0.8 (0.42-1.44)	0.74 (0.44-1.21)	0.2 (0.07-0.53)		0.18 (0.07-0.48)	0.17 (0.07-0.43)
LenDex18	3.12 (1.93-4.47)	3.11 (1.7-4.86)	1.1 (0.8-1.49)	4.54 (2.06-8.12)		0.94 (0.69-1.27)
MelPredThal	3.24 (2.16-4.44)	3.24 (1.9-4.85)	1.16 (0.85-1.57)	4.74 (2.29-8.14)	1.06 (0.78-1.42)	

The NMA shows statistically significant lower treatment discontinuations due to AEs for the patients in the DaraBorMelPred arm compared with the LenDex18 arm (RR: 0.18; 95% Crl: 0.08-0.48). These results are very similar to what was reported for the evaluation of the therapeutic area of multiple myeloma. The findings by the Medicines Council showed a RR: 0.17 (95% Crl: 0.07-0.39) in favor of the DaraBorMelPred arm compared to LenDex18 arm (see Appendix D – NMA conducted by the Medicines Council, Figure 22).

The small differences between the estimated RR ratios could be explained by the number of treatment comparators, and the number of studies that were included in the NMA conducted by the Medicines Council compared to the present NMA. Also, the length of follow-up could explain this slight difference. However, based on the previous NMA conducted by the Medicines Council and the current NMA, the estimated RR values demonstrate a dominant results for DaraBorMelPred over the considered comparators.

For the calculation of the absolute difference based on RR the following formula is applied as stated in the Medicines Council method handbook (31).

$$RD = ACR * RR - ACR$$

This formula assumed a control rate (ACR) which was defined as the rate of events (i.e. treatment discontinuations due to AEs) for the comparator arm (LenDex18).

The absolute difference between DaraBorMelPred and LenDex18 is calculated to be -10.78% (-12.23%, -6.84%) in favor DaraBorMelPred with fewer treatment discontinuations due to adverse events.

Health related quality of life

Health-related quality of life data (EORTC QLQ-C30) was identified for a pooled LenDex and LenDex18 patient population (14) as well as LenDex18 solely (from clinicaltrials.gov) (15) based on the FIRST trial. There were no baseline values available for LenDex18 in isolation, only change from baseline. The results from the FIRST trial can be found in the appendix, section 11.1.2. It was not possible to make an anchored indirect treatment comparison due to missing data in the network of evidence. Due to the risk of bias, a

naive comparison was not conducted. The option of making unanchored analyses - matching-adjusted indirect comparisons or a simulated trial comparison was not investigated further.

Qualitative assessment of adverse events

As described in the previous clinical question in the section 6.1.2, the Expert Committee is requesting overview of the side effects/adverse events and not a comparative analysis. The Expert Committee has requested adverse event data of any grade occurring in more than 10% of the patients and an overview of all side effects/adverse of grade 3-4 being reporting in the clinical study.

The data available data for LenDex18 regarding adverse event data of any grade occurring in more than 10% of the patients originates from the in the EPAR with a median follow-up for surviving patients of 37.0 months (range, 0 to 56.7), data cutoff 24th of May 2013 (7). These TEAE's were described as: *TEAE reported by at least 10% of patients in any study arm*. As for the previous clinical question, the following unpublished data for DaraBorMelPred is presented: *The Most common (At least 10%) treatment-emergent adverse events by treatment cycle (total) is presented (40.1 months follow-up).*

In addition, the Expert Committee has also requested an overview of any adverse events of grade 3-4. The available data for LenDex18 originates from the Benboubker et al. 2014 manuscript (median duration of follow-up among surviving patients was 37.0). *Benboubker et al. 2014: The grade 3 or 4 adverse events listed here were those reported by the investigator in at least 5% of any study group in the safety population, which was defined as all the patients who underwent randomization and received at least one dose of the study treatment (lenalidomide, dexamethasone, melphalan, prednisone, or thalidomide) (12).* In order to present somewhat comparable data to the data for LenDex18 and meeting the request from the Expert Committee as close as possible, the *Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events* will be presented for DaraBorMelPred (data-on-file) as done for the clinical question focusing on DaraBorMelPred vs. BorMelPred. Data-on-file is presented for DaraBorMelPred since the published manuscript for ALCYONE is reporting grade 3 or 4 adverse events that were reported in ≥10% of patients in either treatment arm (11).

Table 32 provides an overview of the most common AEs of any grade for at least 10% of patients. The LenDex18 data is based on reported data from the EPAR (7). The original table in the EPAR also reports data for LenDex to progression and data for MelPredThal. The table below is created based on the data from the EPAR but only including the data for LenDex18. Since the original table in the EPAR is reporting data from multiple arms, the percentage threshold has been surpassed in at least one of the other study arms for the stated AE. For consistency, the number reported for the LenDex18 arm (based on the EPAR) has been kept in the below table, but the specific number is crossed out to highlight that the 10% was not surpassed for the LenDex18 arm. The same has been done for table Table 33 reporting most common (≥5%) Grade 3 or 4 adverse events. The same has been done for DaraBorMelPred in both overviews.

TABLE 32: MOST COMMON ADVERSE EVENTS / SIDE EFFECTS OF ANY GRADE FOR AT LEAST 10% OF PATIENTS

TEAE reported in at least 10% of patients	DaraBorMelPred (n=346) – ALCYONE *Most common (At least 10%) treatment-emergent adverse events by treatment cycle – total* *Median overall follow-up: 40.1 months (data-on-file)*	LenDex18 (n=540) – FIRST *TEAE reported by at least 10% of patients in any study arm* *Median overall follow-up for surviving patients: 37 months*
Reference	Janssen, data-on-file	EPAR. table 24 p. 60-61 (7)
Analysis set: safety	346	540
Total number of subjects with TEAE	337	536
MedDRA system organ class / preferred term		
Blood and lymphatic system disorders	256 (74.0%)	325 (60.2%)
Neutropenia	174 (50.3%)	178 (33.0%)
Thrombocytopenia	172 (49.7%)	100 (18.5%)
Anaemia	107 (30.9%)	193 (35.7%)
Leukopenia	47 (13.6%)	60 (11.1%)
Lymphopenia	39 (11.3%)	~~43 (8.0%)~~
Infections and infestations	256 (74.0%)	377 (69.8%)
Upper respiratory tract infection	106 (30.6%)	~~53 (9.8%)~~
Bronchitis	72 (20.8%)	59 (10.9%)
Pneumonia	63 (18.2%)	68 (12.6%)
Nasopharyngitis	-	54 (10.0%)
Viral upper respiratory tract infection	49 (14.2%)	-
Urinary tract infection	39 (11.3%)	63 (11.7%)
General disorders and administration site conditions	212 (61.3%)	430 (79.6%)
Pyrexia	89 (25.7%)	102 (18.9%)
Oedema peripheral	68 (19.7%)	169 (31.3%)
Fatigue	60 (17.3%)	177 (32.8%)
Asthenia	48 (13.9%)	123 (22.8%)
Gastrointestinal disorders	195 (56.4%)	411 (76.1%)
Diarrhoea	96 (27.7%)	208 (38.5%)
Nausea	75 (21.7%)	128 (23.7%)
Constipation	64 (18.5%)	212 (39.3%)
Vomiting	61 (17.6%)	68 (12.6%)
Dyspepsia	-	~~28 (5.2%)~~
Abdominal pain	-	~~41 (7.6%)~~
Dry mouth	-	~~38 (7.0%)~~
Nervous system disorders	178 (51.4%)	333 (61.7%)
Peripheral sensory neuropathy	100 (28.9%)	92 (17.0%)
Peripheral neuropathy	-	~~22 (4.1%)~~
Tremor	-	73 (13.5%)
Headache	-	~~52 (9.6%)~~
Dizziness	-	70 (13.0%)
Paraesthesia	-	74 (13.7%)

Musculoskeletal and connective tissue disorders	159 (46.0%)	367 (68.0%)
Back pain	61 (17.6%)	145 (26.9%)
Arthralgia	39 (11.3%)	71 (13.1%)
Pain in extremity	38 (11.0%)	66 (12.2%)
Musculoskeletal chest pain	-	~~51 (9.4%)~~
Musculoskeletal pain	-	59 (10.9%)
Bone pain	-	77 (14.3%)
Muscle spasms	-	102 (18.9%)
Respiratory, thoracic and mediastinal disorders	149 (43.1%)	259 (48.0%)
Cough	68 (19.7%)	94 (17.4%)
Dyspnoea	44 (12.7%)	89 (16.5%)
Metabolism and nutrition disorders	131 (37.9%)	274 (50.7%)
Decreased appetite	40 (11.6%)	115 (21.3%)
Hyperglycaemia	-	~~52 (9.6%)~~
Hypocalcaemia	-	56 (10.4%)
Hypokalaemia	-	62 (11.5%)
Skin and subcutaneous tissue disorders	95 (27.5%)	276 (51.1%)
Rash	~~32 (9.2%)~~	131 (24.3%)
Vascular disorders	94 (27.2%)	148 (27.4%)
Deep vein thrombosis	-	~~36 (6.7%)~~
Hypertension	45 (13.0%)	-
Psychiatric disorders	-	**234 (43.3%)**
Depression	-	~~46 (8.5%)~~
Insomnia	-	127 (23.5%)
Eye Disorders	-	**126 (23.3%)**
Cataract	-	~~31 (5.7%)~~
Investigations	-	**173 (32.0%)**
Weight decreased	-	78 (14.4%)

ALCYONE: Most Common (At Least 10%) Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class and Preferred Term; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months)

TABLE 33: MOST COMMON (≥5%) GRADE 3 OR 4 ADVERSE EVENTS

Grade 3 or 4 adverse events reported in at least 5% of study population	DaraBorMelPred (n=346) – ALCYONE *Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events for all treatment cycles* *Median overall follow-up: 40.1 months (data-on-file)*	LenDex18 (n=540) – FIRST *Grade 3 or 4 adverse events reported by the investigator in at least 5% of any study group in the safety population* *Median overall follow-up for surviving patients: 37 months*
Reference	Janssen, data-on-file	BenBoubker et al. 2014. table 3 p. 915 (12)
Analysis set: safety	346	540
Total number of subjects with toxicity grade 3 or 4 TEAE	277 (80.1%)	433 (80%)
MedDRA system organ class / preferred term		
Blood and lymphatic system disorders	**211 (61.0%)**	-
Neutropenia	139 (40.2%)	143 (26%)
Thrombocytopenia	120 (34.7%)	43 (8%)
Anaemia	60 (17.3%)	85 (16%)
Leukopenia	28 (8.1%)	30 (6%)
Lymphopenia	27 (7.8%)	~~18 (3%)~~
Infections and infestations	**92 (26.6%)**	**118 (22%)**
Pneumonia	45 (13.0%)	45 (8%)
Respiratory, thoracic and mediastinal disorders	**30 (8.7%)**	-
Dyspnea	-	22 (4%)
Hypertension	**19 (5.5%)**	-
Cardiac disorder	-	**39(7%)**
Fatigue	-	**46 (9%)**
Asthenia	-	**33 (6%)**
Back pain	-	**34 (6%)**
Hypokalemia	-	~~**20 (4%)**~~
Hyperglycemia	-	~~**23 (4%)**~~
Rash	-	**28 (5%)**
Cataracts	-	~~**14 (3%)**~~
Constipation	-	~~**10 (2%)**~~
Peripheral sensory neuropathy	-	~~**2 (<1%)**~~

ALCYONE: Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

The Expert Committee has also requested an assessment of whether the comparison of event rates can be conducted in an acceptable manner based on study design, follow-up time, data collection and how side effects were assessed and reported. Considerations around comparison/indirectness needs be addressed in the final application.

TABLE 34: CROSS TRIAL COMPARISONS – OVERVIEW TABLES OF AES

	ALCYONE	FIRST
Study design	Multicenter, randomized, open-label, active controlled phase 3 trial. Two-arm study Interventional (Phase 3 Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	Open-label, phase 3 randomized trial. Three arm study. Interventional (Phase 3 Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)
Median follow-up	40.1 months	67 months AE data applied uses previous data-cut (based on 37 months follow up for surviving patients)
Data collection on adverse events	All AEs and special reporting situations, are reported from the time a signed ICF until 30 days after the last dose of study treatment unless the subject withdraws consent for study participation or starts subsequent anti-myeloma therapy.	All AEs are collected from the time of the first dose of study treatment, through the study and until the end-of-study visit (30 days after completion of therapy).
Reporting of side effects / adverse events	All reported AEs with onset during the treatment phase will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4)	AE information will be obtained at each contact with the participant. Version 3.0 of the CTCAE has been used to determine the grade of each AE. (http://ctep.info.nih.gov).

The ALCYONE and the FIRST study are open-label randomized clinical trials with similar study designs, in which the treatment arm is compared to the current standard of care at the time of conduct of the study, with the ALCYONE trial including two arms compared to the FIRST trial, with a three arm study design. Regarding the follow-up then the two trials are similar. The AE data from the FIRST trial is based on a median follow-up of 37 months for surviving patients (12) (requested data was not available in the final analysis for the FIRST trial (13)) and a median overall follow-up for ALYCONE of 40.1 months.

Data collection and reporting of side effects are comparable between the two studies; all AEs were collected and reported from time of signed ICF in ALCYONE versus from time of first dose of study treatment in FIRST however both trials included a 30-day period after study completion. Also, AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events.

6.1.4 DaraBorMelPred compared to BorLenDex

A narrative comparison of DaraBorMelPred vs. BorLenDex has been conducted based on the ALCYONE trial and the SWOG S0777 trial across outcome measures as well as an indirect comparison in the form of an NMA (treatment discontinuations due to AEs). The narrative approach has been selected for OS and PFS due to important differences in patient characteristics between the trials which will be highlighted in more detail in the following sections.

The precise results for the NMA for the critical outcome measure *treatment discontinuations due to AEs* should be interpreted with care due to the differing patient populations. This analysis is most likely biased in favor for BorLenDex due to the younger and more fit patient population in the SWOG S0777 trial which is evident based on subgroup data from the EPAR, but it will provide strong evidence for decision making as described in the respective section, Treatment discontinuation due to adverse events since it will provide a conservative estimate. The section will also address that bortezomib was administered intravenously in the SWOG S0777 trial, while it is administered subcutaneously in Danish clinical practice.

Presentation of relevant studies

The studies used for the narrative comparison are:

- ALCYONE (DaraBorMelPred vs. BorMelPred) 4.4.1 and SWOG S0777 (BorLenDex vs. LenDex) 4.4.3

The studies used for the NMA are mentioned below and the studies were presented in section 4.4

- ALCYONE 4.4.1
- FIRST 4.4.2
- SWOG S0777 4.4.3
- VISTA 4.4.4
- IFM 01/01 4.4.5

Relevant differences between studies

ALCYONE (DaraBorMelPred vs. BorMelPred) vs. SWOG S0777 (BorLenDex vs. LenDex)

Differences in study characteristics exists for the comparison of DaraBorMelPred vs. BorLenDex which includes length of follow-up (median follow-up of 40.1 months in ALCYONE vs. median follow-up of 69 months for all surviving subjects based on the EPAR for SWOG S0777. However, the main challenges for the narrative/naïve comparison and an NMA are the differences in the patient study populations which will be described in detail below.

Due to the lack of comparative trial data and important differences between the patient populations enrolled in ALCYONE and the SWOG S0777, the comparison of the clinical data for DaraBorMelPred vs. BorLenDex when used in NNMM patients who are ineligible for autologous stem cell transplantation (ASCT) is challenging.

The pivotal clinical trial supporting the approval of BorLenDex was SWOG S0777, a randomized, multicenter trial which included 139 participating institutions with the vast majority (or all) in the United States (20). The trial enrolled patients with NDMM who had the presence of “CRAB” criteria (calcium level elevated, renal failure, anemia, bone lesions) and for whom stem cell transplantation was *not immediately intended* (6, 20). This eligibility criteria resulted in SWOG S0777 enrolling a mixed patient population including both those where there was a subsequent intent to undergo ASCT after relapse and those where there was no

intent for a subsequent transplant. In comparison, the ALCYONE Phase III study evaluated the use of DaraBorMelPred specifically in NDMM patients who were considered *ineligible for ASCT* and included study sites worldwide. Patients were assessed to be ineligible for ASCT if they were age ≥65 years of age or <65 years of age with comorbid conditions that would have a negative impact on tolerability to high-dose chemotherapy used in ASCT (10, 11).

The important differences in the baseline characteristics of patients enrolled in the SWOG S0777 and the ALCYONE trial, specifically age and transplant-eligibility status, makes an indirect treatment comparison problematic of the two regimens and such a comparison may be biased against DaraBorMelPred. Table 35 provides an overview of the baseline characteristics between the two trials focusing solely on the regimens of interest to the clinical question, namely, BorLenDex and DaraBorMelPred.

TABLE 35: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN THE INTENTION-TO-TREAT POPULATION AT BASELINE.

Characteristic	BorLenDex N=263 (6) *SWOG S0777 based on ITT population with data lock of December 1, 2016 as reported in the Clinical Study Report*	DaraBorMelPred N=350 (10) *ALCYONE based on ITT population*
Age, Median (min,max)	**63 (35, 85)**	**71.0 (40, 93)**
Age ≤ 65, n (%) Age < 65, n (%)	167 (63.5%)	 36 (10.3%)
Age > 65, n (%) Age ≥ 65, n (%)	93 (36.5%)	 (210+104) = (89.7%)
Age > 65 and ≤ 75 Age 65 – 74	68 (25.9%)	 210 (60.0%)
Age > 75 Age ≥ 75	28 (10.6%)	 104 (29.7%)
Sex		
Male	164 (62.4%)	160 (45.7%)
Female	99 (37.6%)	190 (54.3%)
ISS Stage		
I	78 (29.7%)	69 (19.7%)[a]
II	99 (37.6%)	139 (39.7%)[a]
III	86 (32.7%)	142 (40.6%)[a]
ISS Stage (Revised)		
I	54 (20.5%)	47 (14.1%)[b]
II	155 (58.9%)	226 (67.9%)[b]
III	26 (9.9%)	60 (18.0%)[b]
Missing	28 (10.6%)	NA
Intent to Transplant at Progression		
Yes	182 (69.2%)	NA
No	81 (30.8%)	NA
Cytogenetic Status		
High t(4;14), t(14;16) or del(17p).	30 (11.4%)	53/314 (16.9%)
Not High/Standard	210 (79.8%)	261/314 (83.1%)
Missing	23 (8.7%)	NA

BorLenDex: Cytogenetic risk assessment was not required by the protocol		
Frailty Group		
Not Frail	206 (78.3%)	NA
Frail	56 (21.3%)	NA
Missing	1 (0.4%)	NA
Performance Status (ECOG)		
0	106 (40.3%)	78 (22.3%)
1	128 (48.7%)	182 (52.0%)
2	19 (7.2%)	90 (25.7%)
3	10 (3.8%)	NA
Creatine clearance		
< 60 mL/min ≤ 60 ml/min	78 (29.7%)	150 (42.9%)
≥ 60 mL/min > 60 ml/min	185 (70.3%)	200 (57.1%)

Source: recreated table based on the EPAR for BorLenDex (6) where data for DaraBorMelPred has been inserted based on data from ALCYONE (10)
a: The International Staging System (ISS) disease stage is derived on the basis of the combination of serum β 2-microglobulin and albumin levels. Higher stages indicate more severe disease. ISS stage inserted from ALCYONE (10)
b: IMWG revised ISS staging in MM – ITT. Determination is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4;14), t(14;16), or del17p by FISH or Kyrotype testing and serum lactate dehydrogenase (LDH) at baseline (8)
SWOG S0777: Baseline Clinical Characteristics as of 1st of December 2016 (ITT Population-Study SWOG S0777)
One subject in the BorLenDex arm with a missing frailty is counted in the category age > 65 years and/or frail.
NA: Not available

Compared to patients receiving BorLenDex and enrolled in the SWOG S0777 trial, DaraBorMelPred patients in ALCYONE were older (median age: 71 vs. 63), with 89.7% of DaraBorMelPred patients being ≥ 65 years old compared to 36.5% (>65 years) of BorLenDex patients in SWOG S0777 (6). Regarding patients over 75 years old; 10.6% in the SWOG S0777 (6) while it was 29.7% (≥75 years) in the ALCYONE trial (10).

Importantly, for 69.2% of BorLenDex patients in SWOG S0777 study there was an intent to undergo a transplant at first progression (20). As stated by the by the Expert Committee in the evaluation of the therapeutic area of multiple myeloma, the SWOG S0777-study is not consistent with the Danish patient population as the SWOG S0777 study' patient population is both younger and has better performance status than the Danish population. On the other hand, the ALCYONE study population was considered consistent with the Danish population (9).

Undergoing an ASCT procedure has a significant impact on patients' outcomes, with transplant ineligible patients experiencing significantly inferior progression-free survival (PFS) and overall survival (OS) compared to transplant eligible patients (32-37). This has also been demonstrated in real-world evidence from Denmark where NDMM patient who underwent ASCT had improved overall survival (in first line though) (38). The pan-Canadian Oncology Drug Review (pCODR) reported some more concrete numbers regarding how many patient who proceeded to transplant after disease progression in the SWOG S0777 trial (24) p. 53. In addition to Denmark, only very few HTA agencies seems to have evaluated BorLenDex so far, namely, France (HAS) (39) and Canada (pCODR). pCODR seems to be the only HTA agency that has published additional details (data-on-file) compared to the publication and the EPAR.

The statement from the pCODR report of BorLenDex can be found below:

Durie et al. 2017

In the SWOG publications, with the eligible analysable population per protocol, 168/242 (69%) of BorLenDex *and 156/229 (68%) of* LenDex *patients had an intent to transplant. As of the November 5th, 2015 cutoff date, 46/471 (10%) patients are estimated to have proceeded to stem-cell harvest and planned transplant*[a]*, the number per arm and whether they proceeded to transplant with or without disease progression was not reported.* (24) p. 53)

Clinical Summary Report

In the clinical summary report with the intention to treat population,182/263 (69.2%) of BorLenDex *and 179/260 (68.8%) of* LenDex *patients had an intent to transplant at progression. As of the December 1, 2016 cutoff date, 44/163 (27%) of* BorLenDex *patients and 31/187 (16.6%)* LenDex *patients proceeded to transplant after disease progression The number of patients without disease progression who also proceeded to transplant after* BorLenDex *treatment was 37/75 (49.3%) and* LenDex *treatment was 21 (25.6%)* (24) p. 53)

a: text from Durie 2017 publication: *At the time of this report, at least 46 (10%) of 471 patients are estimated to have proceeded to stem-cell harvest and planned transplant after leaving the study.*

Given the impact of ASCT on OS and the proportion of BorLenDex patients in the SWOG S0777 trial who subsequently received transplant, it is one additional aspect of why it is not appropriate to compare BorLenDex overall survival data to DaraBorMelPred overall survival data from the ALCYONE study.

Results per study

The studies used in the NMA is listed below for treatment discontinuations due to AEs. The previous section highlighted the Results per study in more detail.

- ALCYONE 6.1.1.1.1
- VISTA 6.1.1.1.3
- IFM 01/01 6.1.1.1.4
- FIRST 6.1.1.1.2
- SWOG S0777 6.1.1.1.6

Results applied in the comparative analysis for treatment discontinuations due to AEs will be stated in the following section.

Specifically, for the SWOG S0777 other data will also be presented in the comparative analysis (narrative), but this is not inserted in Appendix F – Results per study. This is specific subgroup data from the EPAR and some data from a conference abstract and a conference presentation.

In addition, see Appendix F – Results per study for the studies included in the NMA in the requested template format.

Comparative analyses

In the following section, data will be presented for DaraBorMelPred vs. BorLenDex. For some outcome measures, subgroup analyses will be presented and emphasized below. However, it is important to note that no comparable subgroup analyses to the ALCYONE population have to our knowledge been published based on the SWOG S0777 trial.

The lack of comparative trial data in the transplant ineligible population hampers the indirect treatment comparison against DaraBorMelPred. Despite missing BorLenDex RCT efficacy/safety data in the same population (transplant ineligible population only), BorLenDex has been included in an NMA based on the ITT population for treatment discontinuation due to AEs. No OS/PFS HR data is presented in Durie et al. 2017 (20) or the EPAR (6) for a patient population that directly resembles the other studies in the network of evidence, including the ALCYONE population (10, 11). It should be noted that part of the patient population in SWOG S0777 (intent to transplant at progression: no) is not the same as transplant ineligible patient population in the rest of the trials.

- ITT population of SWOG S0777 is different from ALCYONE
- SWOG S0777 ITT includes less severe intent-to-transplant patients (~70%) and no-intent-to-transplant patients (~30%) which is believed to impact the relative efficacy observed between BorLenDex and LenDex
- Patients in SWOG ITT are younger than the patients of ALCYONE

Overall survival (Median OS and OS-rate at 36 months)

6.1.4.1.1.1 Narrative comparison

The median OS for DaraBorMelPred has not been reached so a direct naïve comparison is not possible for this outcome measure. In addition, it would not be appropriate due to differing patient populations.

Regarding the OS-rate at 36 months, this has not to our knowledge been reported for the SWOG S0777 study and thus not feasible for a narrative comparative analysis.

Progression free-survival (Median PFS)

6.1.4.1.1.2 Narrative comparison

The median PFS was reached at 36.4 months for DaraBorMelPred based on the ALCYONE trial (median follow-up 40.1 months). The median PFS was reached at 41.7 months (95% CI: 33.1-51.1) for BorLenDex based on the none-comparable ITT population (EMA censoring rules for ITT population, cut-off 1st of December 2016). Based on a previous data-cut, the median PFS was reported as 40.5 months (95% CI: 33.1-50.3) for BorLenDex (EMA censoring rules for ITT population, cut-off 5th of November 2015). As previously mentioned, the patient population within SWOG S0777 is younger and fitter than the patients in ALCYONE and thus a comparison of the medians is not appropriate.

The data from the SWOG S0777 is not consistent with the Danish population as stated by the Expert Committee in the evaluation of BorLenDex (25) *p. 49 in the merged PDF*. In general, the patient population is not consistent with the definition of being ineligible for ASCT. Consequently, it is not comparable with the patient population in ALCYONE. An exploratory endpoint-subgroup analysis for PFS with intent to transplant at progression (yes/no) was presented in the EPAR based on the SWOG S0777 data, see Table 36. However, there was no OS data reported for this subgroup. Despite being more comparable than the ITT population, it is not fully comparable and there are different definitions in the literature of the patient populations.

In the Pan-Canadian oncology drug review of BorLenDex, it was mentioned that the definition of 'intent for/no intent for' stem cell transplantation as compared to 'eligible/ineligible' for stem cell transplantation was not all the way clear. In this case, the clinical guidance panel used the following definitions (24) p.30:

- *Transplant eligible: At the time of initial diagnosis the patient requires treatment and does not have a specific contraindication to high dose chemotherapy and autologous stem cell transplantation.*
- *Transplant ineligible: At the time of initial diagnosis the patient requires treatment and has a specific contraindication to high dose chemotherapy and autologous stem cell transplantation (e.g. age, heart weakness, liver function inadequate for safe exposure to transplantation)*
- *Intent to transplant: The patient is not ineligible for autologous stem cell transplantation and may be offered autologous stem cell transplantation in the future, either as part of primary treatment or at the time of relapse*
- *No intent to transplant: The patient is either ineligible for autologous stem cell transplantation or, for some other reason, will never be offered autologous stem cell transplantation at any time in the future, either as part of primary treatment or at the time of relapse.*

TABLE 36: PROGRESSION-FREE SURVIVAL BY IRAC REVIEW AND EMA CENSORING RULES FOR ITT POPULATION, BY INTENT TO TRANSPLANT AT PROGRESSION (6) P. 26

Table 13 : Progression-free survival by IRAC review and EMA censoring rules for ITT population, by intent to transplant at progression, data cut-off:1 Dec 2016 (Study SWOG S0777)

Intent to Transplant at progression	Yes (n = 361)		No (n = 162)	
Regimen	RVd (n = 182)	Rd (n = 179)	RVd (n = 81)	Rd (n = 81)
Median PFS (months) (95% CI)	43,0 (33,2 ; 56,4)	35,3 (28,9 ; 43,1)	37,5 (22,6 ; 50,3)	22,5 (15,6 ; 28,6)
HR (95% CI)	0,79 (0,61 ; 1,02) ; p = 0,06582		0,70 (0,49 ; 1,00) ; p = 0,04938	

Table reprinted from: European Medicines Agency (2019). Assessment report. Revlimid (BorLenDex). Procedure No. EMEA/H/C/000717/II/0102/G. 28 March 2019. (6)
RVd: BorLenDex, Rd: LenDex

This analysis from the EPAR (6) showed that patients with intent to transplant at progression had a median PFS of 43.0 months (BorLenDex) while it was 37.5 months for the patients with no intent to transplant at progression in the BorLenDex arm. This is 5.5 months (-12.8%) shorter for the patients where there was no intent to transplant at progression compared to the patients where there was an intent to transplant at progression. For LenDex, it was 12.8 months (-36.6%) shorter for the patients where there was no intent to transplant at progression compared to the patients where there was an intent.

The data was based on the IRAC assessment and using EMA censoring rules for ITT population (cut-off 1st of December 2016). However, this sub-group analysis is neither fully comparable to the patient population within ALCYONE. In the ALCYONE trial, patients were considered TIE if they were ≥65 years of age or <65 years of age with comorbid conditions that would have a negative impact on tolerability to high dose chemotherapy used in ASCT.

Another alternative comparison may be based on age >65 and/or frail. However, no PFS data is available (only for 65+) based on a conference presentation, see Table 37. However, this data is presumably based on the patient population analyzed by Durie et al. which is different the population evaluated in the EPAR

(see previous section 4.4.3, Table 4 for the two different patient populations) and the use of EMA censoring rules.

TABLE 37: IMPACT OF AGE IN SWOG S0777 TRIAL (MEDIAN PFS) – CONFERENCE PRESENTATION (23)

Median PFS (months)		
Age (years)	**BorLenDex**	**LenDex**
<65	48	34
≥65	34	24
>75	34	17

Table reproduced based on: Best of ASH: What are the takeaways? Thursday, January 10, 2019 Los Angeles, CA. Impact of Age in SWOG 0777 Trial (23)

Treatment discontinuation due to adverse events

6.1.4.1.1.3 Narrative comparison

Different data is available for BorLenDex. Serving as a conservative approach, the data for the ITT in the SWOG S0777 has been utilized (initial treatment only) for the BorLenDex arm for the indirect comparison vs. DaraBorMelPred presented in the next section, 6.1.4.1.1.4.

Different subgroup analyses are reported in the EPAR (based on the CSR) for treatment discontinuations due to TEAE. One analysis is focusing on initial treatment (24 weeks) + continued LenDex treatment as according to label for BorLenDex. Another analysis focuses on intent to transplant (yes/no) for BorLenDex and LenDex for the initial treatment. Lastly, an analysis presented in the EPAR focuses on initial treatment by age group. These subgroup analyses may be more comparable (but still not fully comparable) to the patient population in ALCYONE than the ITT population within SWOG S0777. However, in order to provide a conservative estimate, the data from the ITT population within the SWOG S0777 (initial treatment only, 24 weeks) (20) has been utilized in the quantitative NMA. The data presented from ALCYONE covers the full treatment duration. This will serve as a conservative estimate as more treatment discontinuation due to adverse events should be expected for longer treatment durations.

As presented in Table 38, when accounting for the full drug exposure period, the treatment discontinuations due to TEAEs are higher for BorLenDex compared to the initial treatment only (37.0% vs. 22.8%) (6).

As previously described, it should be noted that there are slight differences in the patient population analyzed in the CSR (EPAR) (6) vs. Durie et al. 2017 (20) see 4.4.3.

In Table 39, the BorLenDex arm without intent for immediate transplant at progression (no), 32.1% discontinued treatment due to TEAE while the number was 18.8% for the group where there was an intent (yes) for immediate transplant at progression (6).

The same pattern is true when examining the subgroup population by age in the EPAR. The patients aged ≤ 65 years who discontinued treatment due to TEAE was 19.2% in the BorLenDex-arm while it was 29.5% for patients aged > 65 year in the BorLenDex arm, see Table 40 (6).

The data seems to indicate that utilizing a longer period to account for AEs (not only initial treatment) may be associated with a higher frequency of treatment discontinuations due to adverse events. The same seems to be indicated by the subgroup data where immediate transplant at progression was not intended as well as higher age.

The patients in the ALCYONE trial were considered ineligible for transplant at enrollment. The patients in the ALCYONE trial were older than the patients in the SWOG S0777 (median age 71 vs. 63). Therefore, in the case where DaraBorMelPred can show an advantage compared to BorLenDex despite the likely bias in favor of BorLenDex, the indirect comparison should serve as solid evidence for rewarding an added clinical benefit. In the case where the patient population would be biased in favor of DaraBorMelPred then such a conclusion would be problematic. It should be noted that bortezomib was administered intravenously in the SWOG S0777 trial where it is administered subcutaneously in a Danish clinical practice (25). This could influence the treatment discontinuations due to AEs for BorLenDex. The Expert Committee has commented on this in the evaluation of BorLenDex. It is stated that the intravenous administration in the SWOG S0777 study may affect the discontinuations in a negative direction (more discontinuations when administered intravenously compared to subcutaneously). However, a study mentioned in the evaluation (Moreau et al. 2011, (40)) of BorLenDex by the Expert Committee compared the subcutaneous and intravenous administration of bortezomib directly, and there was not a significantly higher risk of discontinuing treatment when bortezomib is administered intravenously compared to subcutaneously. Furthermore, there was significantly higher frequency of peripheral neuropathy and gastrointestinal disorders. The Expert Committee specifically emphasizes the differences in the incidence of peripheral neuropathy, which is seen in higher rates by intravenous administration, also the cause of discontinuing treatment or dose adjusting bortezomib in the clinic. In Danish clinical practice, the first step is to try handling the AE by dose reduction instead of discontinuing treatment (25).

The ITT results presented in the NMA is based on Durie et al. 2017 includes initial treatment only, younger patients (median age 63), and patients where there was an intent for immediate transplant at progression (~69% of population the study population).

TABLE 38: OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS DURING INITIAL TREATMENT + CONTINUED LENDEX BY TREATMENT ARM AS OF 01 DEC 2017 (STUDY SEOG S0777, SAFETY POPULATION (6) P. 51

Table 36: Overview of Treatment-emergent Adverse Events During Initial Treatment + Continued Rd by Treatment Arm as of 01 Dec 2016 (Study SWOG S0777, Safety Population)

Subjects With at Least One:	RVd (N = 262) n (%)	Rd (N = 256) n (%)
TEAE	255 (97.3)	250 (97.7)
TEAE related to study drug[a]	251 (95.8)	245 (95.7)
Treatment-emergent SAE	133 (50.8)	111 (43.4)
Grade 3 or 4[b] TEAE	222 (84.7)	212 (82.8)
Grade 3 or 4[b] TEAE related to study drug [a]	210 (80.2)	190 (74.2)
Grade 5[b] TEAE	10 (3.8)	7 (2.7)
Treatment discontinuation due to TEAEs[c]	97 (37.0)	64 (25.0)

CTCAE = Common Terminology Criteria for Adverse Events; Rd = lenalidomide and dexamethasone;
RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Definition of related: possibly, probably, or definitely related to study drug as deemed by the investigator.
b Graded using CTCAE Version 4.0.
c The AEs leading to treatment discontinuation were recorded on the Off Treatment Form.
Note: Treatment-emergent adverse events include adverse events that started between the date of the first dose and 30 days after the date of the last dose. A subject with multiple occurrences of a TEAE was counted only once in that TEAE category.

Table reprinted from: European Medicines Agency (2019). Assessment report. Revlimid (BorLenDex). Procedure No. EMEA/H/C/000717/II/0102/G. 28 March 2019, table 36 p. 51 (6).

TABLE 39: OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS DURING INITIAL TREATMENT BY INTENT TO TRANSPLANT AT PROGRESSION (6) P. 62

Table 51 : Overview of Treatment-emergent Adverse Events During Initial Treatment by Intent to Transplant at Progression (Safety Population)

Subjects with at Least One:	Yes		No	
	RVd (N = 181) n (%)	Rd (N = 177) n (%)	RVd (N = 81) n (%)	Rd (N = 79) n (%)
TEAE	177 (97.8)	167 (94.4)	78 (96.3)	78 (98.7)
TEAE related[a] to study drug	173 (95.6)	162 (91.5)	78 (96.3)	78 (98.7)
Serious TEAE	68 (37.6)	41 (23.2)	37 (45.7)	32 (40.5)
Grade 3 or 4[b] TEAE	133 (73.5)	111 (62.7)	67 (82.7)	65 (82.3)
Grade 3 or 4[b] TEAE related[a] to study drug	123 (68.0)	90 (50.8)	62 (76.5)	57 (72.2)
Grade 5[b] TEAE	5 (2.8)	2 (1.1)	1 (1.2)	1 (1.3)
Treatment discontinuations due to TEAE[c]	34 (18.8)	15 (8.5)	26 (32.1)	9 (11.4)

Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event.
a Definition of related: possible, probable, or definitely related to study drug as deemed by investigator.
b Graded using Common Terminology Criteria for Adverse Events, Version 4.0
c The adverse events leading to treatment discontinuation were recorded on the Off Treatment Notice Form.

Table reprinted from: European Medicines Agency (2019). Assessment report. Revlimid (BorLenDex). Procedure No. EMEA/H/C/000717/II/0102/G. 28 March 2019, table 51 p. 62 (6).

TABLE 40: OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS DURING INITIAL TREATMENT BY AGE GROUP – STUDY SWOG S0777 (SAFETY POPULATION) (6) P. 63

Table 52 : Overview of Treatment-emergent Adverse Events During Initial Treatment by Age Group – Study SWOG S0777 (Safety Population)

	SWOG S0777			
	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)
Subjects with at least 1:	≤ 65 years		≤ 75 years	
	N = 167 n (%)	N = 149 n (%)	N = 234 n (%)	N = 232 n (%)
TEAE	164 (98.2)	141 (94.6)	228 (97.4)	226 (97.4)
Grade 3 or 4 TEAE[a]	120 (71.9)	89 (59.7)	178 (76.1)	157 (67.7)
Grade 5 TEAE[a]	5 (3.0)	1 (0.7)	10 (4.3)	6 (2.6)
Treatment-emergent SAE	57 (34.1)	35 (23.5)	90 (38.5)	63 (27.2)
Treatment Discontinuation Due to TEAE[b]	32 (19.2)	11 (7.4)	51 (21.8)	19 (8.2)
Subjects with at least 1:	> 65 years		> 75 years	
	N = 95 n (%)	N = 107 n (%)	N = 28 n (%)	N = 24 n (%)
TEAE	91 (95.8)	104 (97.2)	27 (96.4)	24 (100.0)
Grade 3 or 4 TEAE[a]	80 (84.2)	87 (81.3)	22 (78.6)	19 (79.2)
Grade 5 TEAE[a]	1 (1.1)	2 (1.9)	0 (0.0)	1 (4.2)
Treatment-emergent SAE	48 (50.5)	38 (35.5)	15 (53.6)	10 (41.7)
Treatment Discontinuation Due to TEAE[b]	28 (29.5)	13 (12.1)	9 (32.1)	5 (20.8)

Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Graded using Common Terminology Criteria for Adverse Events, Version 4.0
b The adverse events leading to treatment discontinuation were recorded on the Off Treatment Notice Form.
Note: Treatment-emergent adverse events include adverse events that started between the date of first dose and 30 days after the date of last dose.
Data cutoff date = 01 Dec 2016.

Table reprinted from: European Medicines Agency (2019). Assessment report. Revlimid (BorLenDex). Procedure No. EMEA/H/C/000717/II/0102/G. 28 March 2019, table 52 p. 63 (6).

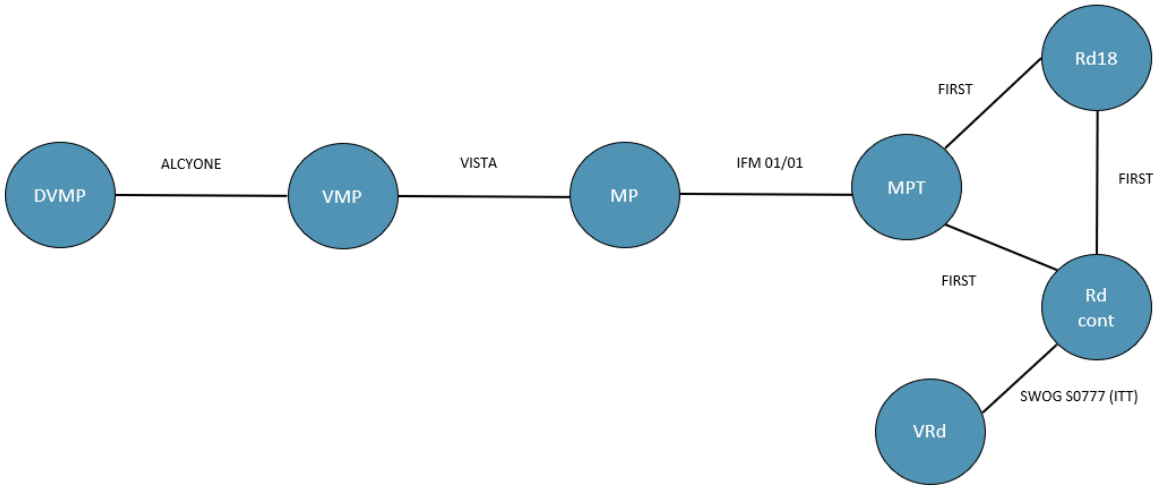
With a median follow-up of 40.1 months, 6.9% discontinued DaraBorMelPred due to AEs (including all treatment cycles). BorLenDex shows differing results depending on whether to consider initial treatment only, data based on Durie et al. 2017 or other subgroup data from the EPAR. To provide a conservative estimate based on the ITT from Durie et al. 2017 (initial treatment only) (20), 22.8% (55/241) discontinued treatment due to AEs for BorLenDex which is a 15.9 percentage points difference (22.8% - 6.9%) in favor of DaraBorMelPred. If a comparison were made based on the BorLenDex data accounting for the full treatment period (however still the younger and fitter ITT population), the difference would be 30.1 percentage point (37% - 6.9%). For the patient population with no intent to transplant at progression (initial treatment only) for BorLenDex, the difference would be 25.2 percentage points (32.1% - 6.9%).

6.1.4.1.1.4 Treatment discontinuation due to adverse events

6.1.4.1.1.4.1 Empirical Evidence Analysis

Figure 15 presents the network of evidence for treatment discontinuation due to AEs. In total, five RCTs were included in the analysis, covering seven treatment regimens. Table 41 presents the RCTs included the analysis. The empirical evidence included is identical to the data presented for LenDex18 except for the addition of SWOG S0777, ITT. As requested by the Medicines Council, the longest follow-up was used in the analysis, unless specified otherwise.

FIGURE 15: NETWORK OF EVIDENCE DISCONTINUATION DUE TO AES



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex, VRd: BorLenDex

TABLE 41: EMPIRICAL EVIDENCE DISCONTINUATION DUE TO AES

Trial	Treatments	Patients in the safety population per arm (n)	Number of treatment discontinuations due to AEs per arm n	Follow-up time (months)
ALCYONE (11)	DaraBorMelPred versus BorMelPred	DaraBorMelPred: 346 BorMelPred: 354	24 33	40.1
VISTA (26)	BorMelPred versus MelPred	BorMelPred: 340 MelPred: 337	52 48	36.7*
IFM 01/01 (16)	MelPredThal versus MelPred	MelPred: 116 MelPredThal: 113	15 48	47.5
FIRST (13)	LenDex versus LenDex18 LenDex versus MelPredThal	LenDex: 532 LenDex18: 540 MelPredThal: 541	64 71 76	67.2
SWOG S0777 (ITT) (20)	BorLenDex versus LenDex	BorLenDex: 241** LenDex: 226**	55 22	69.0
*Please note that an earlier VISTA data-cut was used for discontinuation due to AEs, since the latest data-cut did not include adverse event data				
**Patients in safety population: 241 evaluable for toxic effects (BorLenDex); 226 evaluable for toxic effects (LenDex) p. 522 (20) p. 522, Durie 2017				

6.1.4.1.1.4.2 NMA Assumptions

Homogeneity Assumption

In this network of evidence, there were no treatment comparisons that were reported in multiple trials. Therefore, the I2-test was not needed to be conducted.

Similarity assumption

The MelPred arms in the different trials used different dosing regimens. Dosing has an impact on efficacy and safety and could therefore be a potential effect modifier. However, consistent with other NMAs in NDMM patients who are ineligible for ASCT, it was assumed that heterogeneity in dosing of MelPred would not affect the output of the NMA (29, 30).

SWOG S0777 is a RCT which investigated BorLenDex in a different population than the other trials in the NMA. The trial included younger and more fit patients compared to the other included RCTs. For instance, the median age in the SWOG trial was 63 years, compared to a median age of 71 years in ALCYONE (10, 11). Especially in the NMA analysis in which the discontinuation due to AEs events of the SWOG S0777 ITT population is used, this non-similarity (in terms of age, transplant eligibility, and time period where treatment discontinuations due to AEs are accounted for) may be biasing the NMA results for BorLenDex as emphasized in the narrative comparison.

Consistency assumption

Inconsistency was not tested because of a lack of loops of evidence in the network.

6.1.4.1.1.4.3 Choice of Model

Choice of statistical model is based on DIC and on the presence of heterogeneity on the model. This network did not indicate the presence of heterogeneity. The DIC score for the RE model was slightly lower than the DIC score of the FE model. Yet, since this difference was limited, a FE model was chosen for the analysis (Table 42). Additionally, the baseline characteristics of the included studies were sufficiently similar which also allowed the use of a FE model. Little difference was observed between total residual deviance between the two statistical models.

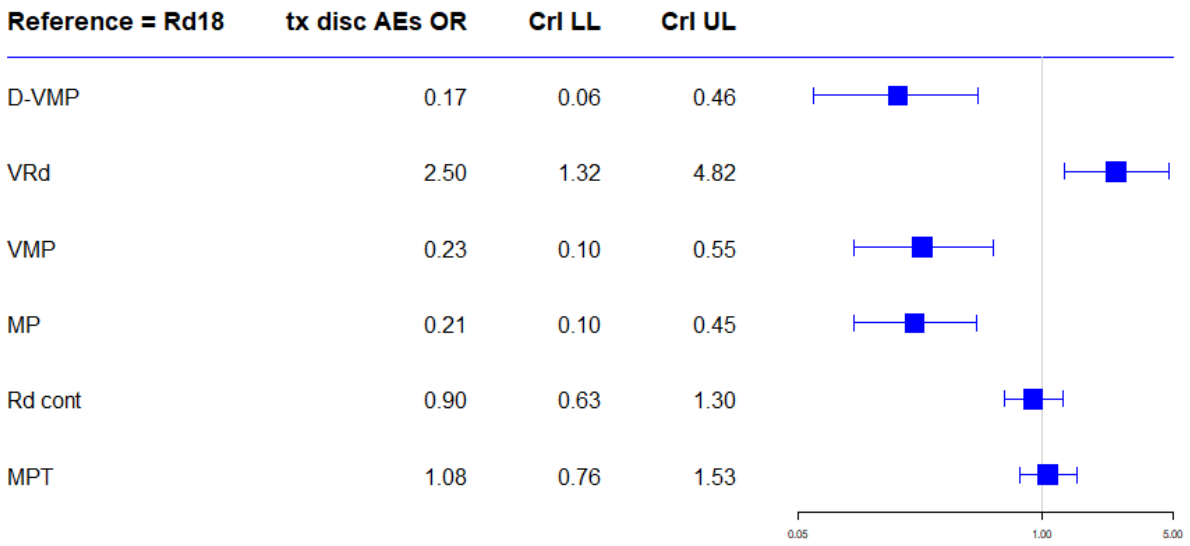
TABLE 42: STATISTICAL MODEL DISCONTINUATION DUE TO AES

Model	DIC	Total residual Deviance
Fixed effects	81.23	13.5
Random effects	81.14	13.3

6.1.4.1.1.4.4 Results

Figure 16 presents a forest plot with the estimated HRs of comparator treatments against reference treatment LenDex18. An OR higher than 1 indicates that LenDex18 outperforms the comparator. Table 43 presents all the ORs of each treatment regimen against the comparators. Please note that the matrix should be read from left to right, where the first-row treatments represent the reference treatments.

FIGURE 16: FOREST PLOT DISCONTINUATION DUE TO AES, FIXED EFFECTS MODEL



Abbreviations: Rd18: LenDex18, DVMP = DaraBorMelPred, VRd: BorLenDex, VMP: BorMelPred, MP: MelPred, Rd cont: LenDex, MPT: MelPredThal

TABLE 43: OR MATRIX DISCONTINUATION DUE TO AES, FIXED EFFECTS MODEL

Discontinuation due to AEs	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*	*BorLenDex*
MelPred		0.92 (0.6-1.41)	0.24 (0.11-0.5)	1.28 (0.64-2.57)	0.21 (0.1-0.45)	0.2 (0.1-0.38)	0.09 (0.03-0.21)
BorMelPred	1.09 (0.71-1.67)		0.26 (0.11-0.61)	1.39 (0.8-2.42)	0.23 (0.1-0.55)	0.21 (0.1-0.47)	0.09 (0.03-0.25)
LenDex	4.25 (2.01-9.12)	3.9 (1.65-9.34)		5.41 (1.95-15.21)	0.9 (0.63-1.3)	0.83 (0.58-1.19)	0.36 (0.21-0.61)
DaraBorMelPred	0.78 (0.39-1.57)	0.72 (0.41-1.25)	0.18 (0.07-0.51)		0.17 (0.06-0.46)	0.15 (0.06-0.4)	0.07 (0.02-0.21)
LenDex18	4.7 (2.24-10.05)	4.32 (1.83-10.32)	1.11 (0.77-1.59)	6 (2.16-16.81)		0.92 (0.65-1.31)	0.4 (0.21-0.76)
MelPredThal	5.08 (2.65-10.02)	4.67 (2.13-10.39)	1.2 (0.84-1.72)	6.48 (2.49-17.15)	1.08 (0.76-1.53)		0.43 (0.23-0.82)
BorLenDex	11.76 (4.71-29.96)	10.8 (3.94-30.14)	2.77 (1.64-4.79)	15 (4.74-48.09)	2.5 (1.32-4.82)	2.31 (1.22-4.44)	

Conversion of Odds Ratio to Relative Risk

As described for LenDex18, the OR needs to be converted to RR (see previous section Conversion of Odds Ratio to Relative Risk). Compared to the data presented for the previous clinical question focusing on LenDex18, SWOG S0777 is now included in the below tables. The addition of the SWOG S0777 is described in the following section.

TABLE 44: ACR PER TRIAL COMPARATOR

Trial	Comparator arm from matrices	N of events (N of patients in safety population)	ACR
VISTA (BorMelPred vs. MelPred)	MelPred*	48 (337)	**0.1424**
	BorMelPred*	52 (340)	**0.1529**
IFM 01/01 (MelPredThal vs. MelPred)	MelPred*	15 (116)	**0.1293**
	MelPredThal*	48 (113)	**0.4248**
ALCYONE (DaraMelPred vs. BorMelPred)	BorMelPred*	33 (354)	**0.0932**
	DaraBorMelPred	24 (346)	**0.0694**
FIRST (LenDex vs. Len18 vs. MelPredThal)	LenDex	64 (532)	**0.1203**
	LenDex18	71 (540)	**0.1315**
	MelPredThal*	76 (541)	**0.1405**
SWOG S0777 (BorLenDex vs. LenDex)	**LenDex**	**22 (226)**	**0.0973**
	BorLenDex	**55 (241)**	**0.2282**

*These treatments overlap across different trials (i.e. MelPred, BorMelPred, MelPredThal)

By adding the SWOG S0777 trial on top of the analysis, another overlapping treatment (LenDex) emerged in the treatment comparisons. The ACR used for LenDex was thus based on a weighted ACR that was calculated using the safety population for the overlapping treatments, the total safety population, and the calculated ACR per arm presented in Table 44 (LenDex: SWOG S0777 & FIRST). See Table 45 for calculations and the weighted ACR of LenDex.

TABLE 45: WEIGHTED ACRS FOR OVERLAPPING TREATMENTS IN THE NMA

Trial	Treatment	Safety population per arm	Total safety population	Weight of ACR per trial	Calculated ACR per trial	Weighted ACR
VISTA IFM 01/01	MelPred	337 116	453	0.7439 0.2561	0.1424 0.1293	**0.1391**
VISTA ALCYONE	BorMelPred	340 354	694	0.4899 0.5101	0.1529 0.0932	**0.1225**
FIRST IFM 01/01	MelPredThal	541 113	654	0.8272 0.1728	0.1405 0.4248	**0.1896**
SWOG S0777 FIRST	**LenDex**	**226 532**	**758**	**0.2982 0.7018**	**0.0973 0.1203**	**0.1135**

Table 46 presents the RR ratios, that were calculated using the ACR and the ORs. The calculation was done using the provided formula by the Medicines Council (31). Please note that the matrix should be read from left to right, where the first-row treatments represent the reference treatments.

TABLE 46: RR MATRIX DISCONTINUATION DUE TO AES, FIXED EFFECTS MODEL

Discontinuation due to AEs SA	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*	*BorLenDex*
MelPred		0.93 (0.63-1.34)	0.26 (0.12-0.53)	1.25 (0.65-2.32)	0.24 (0.11-0.48)	0.23 (0.12-0.43)	0.11 (0.04-0.26)
BorMelPred	1.07 (0.74-1.53)		0.28 (0.12-0.63)	1.35 (0.81-2.21)	0.26 (0.11-0.58)	0.25 (0.12-0.52)	0.12 (0.04-0.31)
LenDex	2.93 (1.76-4.28)	2.88 (1.53-4.62)		4.14 (1.83-7.66)	0.91 (0.66-1.25)	0.86 (0.63-1.15)	0.42 (0.25-0.67)
DaraBorMelPred	0.81 (0.42-1.45)	0.75 (0.44-1.21)	0.2 (0.07-0.54)		0.19 (0.07-0.5)	0.18 (0.07-0.45)	0.08 (0.03-0.26)
LenDex18	3.1 (1.91-4.45)	3.07 (1.66-4.82)	1.09 (0.79-1.49)	4.46 (2-8.02)		0.94 (0.7-1.24)	0.46 (0.25-0.8)
MelPredThal	3.24 (2.15-4.45)	3.22 (1.87-4.83)	1.17 (0.85-1.59)	4.7 (2.26-8.09)	1.07 (0.79-1.43)		0.5 (0.27-0.85)
BorLenDex	4.71 (3.11-5.96)	4.91 (2.89-6.6)	2.31 (1.53-3.35)	7.61 (3.76-11.27)	2.09 (1.27-3.21)	1.85 (1.17-2.69)	

The NMA shows statistically significant lower treatment discontinuations due to AEs for the patients in the DaraBorMelPred arm compared with the BorLenDex arm (RR: 0.08; 95% CrI: 0.03-0.26). BorLenDex was not included in the analysis for evaluation of the whole therapeutic area. For the specific outcome measure, treatment discontinuations due to AEs, BorLenDex was probably not included due to the younger and more fit patient population potentially biasing the results in the favor of BorLenDex. However, the overall findings by the Medicines Council showed that DaraBorMelPred was statistically significantly better than all other treatments except for MelPred (Appendix D – NMA conducted by the Medicines Council Figure 22).

For the calculation of the absolute difference based on RR the following formula is applied as stated in the Medicines Council method handbook (31).

$$RD = ACR * RR - ACR$$

This formula assumed a control rate (ACR) which was defined as the rate of events (i.e. treatment discontinuations due to AEs) for the comparator arm (BorLenDex).

The absolute difference between DaraBorMelPred and BorLenDex is calculated to be -21.00% (-22.14%, -16.89%) in favor DaraBorMelPred with fewer treatment discontinuations due to AEs.

Health related quality of life

No health-related quality of life data has been reported for BorLenDex based on the SWOG S0777 trial. Thus, it will not be possible to make a narrative or indirect comparison.

Qualitative assessment of adverse events

As described in the clinical question focusing on DaraBorMelPred and BorMelPred, the Expert Committee is requesting an overview of the AEs and not a comparative analysis. The Expert Committee has requested adverse event data of any grade occurring in more than 10% of the patients and an overview of all AEs of grade 3-4 being reporting in the clinical study.

Regarding AE data of any grade occurring in more than 10% of the patient population, such data has to our knowledge not been published for BorLenDex based on the SWOG S0777 trial. The published data for

BorLenDex that is closest to what the Expert Committee has requested is assessed to be the data published in the EPAR assessment report. The data reported for BorLenDex covers initial treatment *TEAEs (Any Grade) Reported in at Least 20% of Subjects in Any Treatment Arm – Initial Treatment – SWOG S0777 (Safety Population)* BorLenDex *(3-week cycles × 8 = 24 weeks) (N = 262) n (%)* (6) p. 52. To provide somewhat comparable data to what has been published for SWOG S0777 (included in the EPAR assessment report), DaraBorMelPred data is presented based on the published manuscript (supplementary appendix) with 40.1 months follow-up. The data can be found in Table 47.

As previously mentioned, it should be noted that data for BorLenDex is based on a younger and more fit patient population compared to the patient population in ALCYONE which may affect the frequency and severity of AEs. This can be observed in the tables provided for the narrative comparison of treatment discontinuations due to AEs in the previous section 6.1.4.1.1.3 where data is provided for the total number of TEAEs, treatment-emergent serious adverse events (SAE), Grade 3 or 4 TEAE, and grade 5 TEAE based on the different analyses; induction + continued treatment Table 38, intent to transplant at progression (yes/no) Table 39, and analyses based on age group Table 40. In addition, Appendix E provides the following table based on transplant eligibility and initial treatment only based on the EPAR: Table 62: TEAEs (Any Grade) Reported in at Least 20% of Subjects in Any Treatment Arm by Transplant Eligibility – Initial Treatment – Study SWOG S0777 (Safety Population) (6) p.61

For the second overview focusing on all side effects/AEs of grade 3-4 being reporting in the clinical study, no comparable data is available. However, some data is available from the EPAR. Once again, the data for BorLenDex covers initial treatment *Grade 3 or 4 TEAEs Reported in at Least 5% of Subjects in Any Treatment Arm – Initial Treatment - SWOG S0777 (Safety Population)* - BorLenDex *(3-week cycles × 8 = 24 weeks) (N = 262) n (%).* For DaraBorMelPred, *Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events* is presented with 40.1 months follow-up as presented the previous clinical questions. The data can be found in Table 48: Most common (≥5%) Grade 3 or 4 adverse events

The tables provided is based data reported in the EPAR. The original table in the EPAR reports data based on different studies with BorLenDex (including the SWOG S0777) as reported below. The table is created based on the table in the EPAR excluding the data reported separately for PETHEMA GEM 2012, IFM 2009 as well as the LenDex arm in SWOG S0777. Since the tables in the EPAR is reporting data from different trials, for Table 47, the threshold of 20% have been surpassed in at least one of the other study arms. For consistency, the number reported for the BorLenDex arm (based on SWOG S0777) has been kept in the below table, but the specific number is crossed out to highlight that the 20% was not surpassed for the BorLenDex arm. The same has been done for Table 48 and it has also been done for DaraBorMelPred in both tables.

TABLE 47: ADVERSE EVENTS OF ANY GRADE FOR AT LEAST 20% OF PATIENTS

Any grade adverse events during treatment in safety population	DaraBorMelPred (n=346) - ALCYONE *The safety population included all patients who received ≥1 dose of trial treatment. Adverse events of any grade that were reported in ≥20% of patients in either treatment group for all treatment cycles. n (%) Median overall follow-up: 40.1 months*	BorLenDex (n=262) -SWOG S0777 *TEAEs (Any Grade) Reported in at Least 20% of Subjects in Any Treatment Arm – Initial Treatment – SWOG S0777 (Safety Population) RVd (3-week cycles × 8 = 24 weeks) n (%)*
Reference	Mateos et al 2019; Supplementary appendix. Table S4 p. 13 (11)	EPAR. Cutoff 01. December 2016, table 38 p. 52-53 (6)
Treatment arm	DaraBorMelPred	BorLenDex
Number of patients	346	262
Grade	All	All
Blood and Lymphatic System Disorders		**208 (79.4%)**
Neutropenia	174 (50.3%)	77 (29.4%)
Thrombocytopenia	172 (49.7%)	151 (57.6%)
Anemia	107 (30.9%)	179 (68.3%)
Leukopenia	-	109 (41.6%)
Lymphopenia	-	67 (25.6%)
Nervous System Disorders	-	**219 (83.6%)**
Neuropathy peripheral	-	~~2 (0.8%)~~
Dizziness	-	76 (29.0%)
Paresthesia	-	~~3 (1.1%)~~
Dysgeusia	-	79 (30.2%)
Peripheral sensory neuropathy	100 (28.9%)	184 (70.2%)
Infections and Infestations		**92 (35.1%)**
Infection	-	~~3 (1.1%)~~
Upper respiratory tract infection	106 (30.6%)	-
Bronchitis	72 (20.8%)	-
Pneumonia	~~63 (18.2%)~~[a]	-
Gastrointestinal Disorders	-	**211 (80.5%)**
Diarrhea	96 (27.7%)	104 (39.7%)
Constipation	-	147 (56.1%)
Nausea	75 (21.7%)	98 (37.4%)
General Disorders and Administration Site Conditions	-	**221 (84.4%)**
Pyrexia	89 (25.7%)	~~37 (14.1%)~~
Edema peripheral	-	122 (46.6%)
Edema	-	0
Fatigue	-	193 (73.7%)
Respiratory, Thoracic, and Mediastinal Disorders	-	**150 (57.3%)**
Cough	-	77 (29.4%)
Dyspnea	-	80 (30.5%)
Musculoskeletal and Connective Tissue Disorders	-	**185 (70.6%)**
Back pain	-	87 (33.2%)
Muscular weakness	-	64 (24.4%)
Skin and Subcutaneous Tissue Disorders	-	**113 (43.1%)**
Rash	-	~~49 (18.7%)~~
Psychiatric Disorders	-	113 (43.1%)
Insomnia	-	86 (32.8%)
Metabolism and Nutrition Disorders	-	**201 (76.7%)**

Hyperglycemia	-	127 (48.5%)
Decreased appetite	-	90 (34.4%)
Hyponatremia	-	80 (30.5%)
Hypokalemia	-	76 (29.0%)
Hypoalbuminemia	-	78 (29.8%)
Hypocalcemia	-	131 (50.0%)
Investigations	-	**163 (62.2%)**
ALT increased	-	67 (25.6%)
Blood creatinine increased	-	48 (18.3%)
Blood alkaline phosphatase increased	-	66 (25.2%)
AST increased	-	56 (21.4%)
Weight decreased	-	53 (20.2%)

a: despite being below 20%, the number has been kept since it is reported in the publication, supplementary appendix (10)

TABLE 48: MOST COMMON (≥5%) GRADE 3 OR 4 ADVERSE EVENTS

	DaraBorMelPred (n=346) – ALCYONE *Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events for all treatment cycles* *Median overall follow-up: 40.1 month*	BorLenDex (n=262) – SWOG S0777 *Grade 3 or 4 TEAEs Reported in at Least 5% of Subjects in Any Treatment Arm – Initial Treatment - SWOG S0777 (Safety Population) - RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)* *Cutoff 01. December 2016*
Reference	Janssen, data-on-file	EPAR. Cutoff 01. December 2016, table 41 p. 55 (6)
Number of patients	346	262
Total number of subjects with toxicity grade 3 or 4 TEAE	277 (80.1%)	200 (76.3%)
Blood and lymphatic system disorders	**211 (61.0%)**	**104 (39.7%)**
Neutropenia	139 (40.2%)	26 (9.9%)
Thrombocytopenia	120 (34.7%)	45 (17.2%)
Anaemia	60 (17.3%)	32 (12.2%)
Leukopenia	28 (8.1%)	23 (8.8%)
Lymphopenia	27 (7.8%)	49 (18.7%)
Infections and infestations	**92 (26.6%)**	**36 (13.7%)**
Infection	-	~~1 (0.4%)~~
Lung infection	-	19 (7.3%)
Pneumonia	45 (13.0%)	-
Respiratory, thoracic and mediastinal disorders	**30 (8.7%)**	**26 (9.9%)**
Dyspnea	-	16 (6.1%)
Vascular disorders	-	**41 (15.6%)**
Hypertension	19 (5.5%)	-
Hypotension	-	20 (7.6%)
Embolism	-	18 (6.9%)
Nervous System Disorders	**-**	**89 (34.0%)**
Syncope	-	23 (8.8%)
Peripheral sensory neuropathy	-	54 (20.6%)
General Disorders and Administration Site Conditions	-	**49 (18.7%)**
Fatigue	-	38 (14.5%)
Investigations	-	**29 (11.1%)**
Alanine aminotransferase increased	-	13 (5.0%)
Renal and Urinary Disorders	-	~~8 (3.1%)~~
Renal failure acute	-	~~7 (2.7%)~~
Musculoskeletal and Connective Tissue Disorders	-	**45 (17.2%)**
Muscular weakness	-	22 (8.4%)
Metabolism and Nutrition Disorders	-	**85 (32.4%)**
Hyperglycemia	-	19 (7.3%)
Hyponatremia	-	17 (6.5%)
Hypokalemia	-	30 (11.5%)
Hypocalcemia	-	17 (6.5%)
Dehydration	-	22 (8.4%)

ALCYONE: Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by Treatment Cycle (New Onset), MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set. ALCYONE; safety analysis set from median follow-up 40.1 months
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

In the evaluation for BorLenDex it is important to note that the TEAE's presented is based on initial treatment only while the TEAE presented for DaraBorMelPred represents the daratumumab monotherapy phase as well.

The Expert Committee has also requested an assessment of whether the comparison of event rates can be conducted in an acceptable manner based on study design, follow-up time, data collection and how side effects /AEs were assessed and reported. Considerations around comparison/indirectness needs be addressed in the final application.

TABLE 49: CROSS TRIAL COMPARISONS – OVERVIEW TABLES OF AES

	ALCYONE	SWOG S0777
Study design	Multicenter, randomized, open-label, active controlled phase 3 trial. Two-arm study. Interventional (Phase 3 Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	Randomised, open-label phase 3 trial. Two-arm study. Interventional (Phase 3 Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)
Median follow-up	40.1months	69 months for surviving patients NB: Only initial treatment reported (24 weeks)
Data collection	All AEs and special reporting situations, are reported from the time a signed ICF until 30 days after the last dose of study treatment unless the subject withdraws consent for study participation or starts subsequent anti-myeloma therapy.	Data was collected for AEs every 3 months while on treatment and again at the end of induction and maintenance treatment.
Reporting of side effects /AEs	All reported AEs with onset during the treatment phase will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4)	All AEs were initially graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. From April 6, 2011, serious AEs were graded according to CTCAE version 4.0

ALCYONE and the SWOG S0777 study are both open-labeled randomized clinical trials with similar study designs, in which the treatment arm is compared to the current standard of care at the time of conduct of the study.
Regarding the follow up time, the SWOG S0777 trial has a longer follow up time compared to the ALCYONE trial. In addition, the data reported for BorLenDex includes initial treatment only (24 weeks) and for the overall ITT population, which represents a younger and more fit population compared to the DaraBorMelPred arm. Hence, the reported results may be biased in favor of BorLenDex.

7 Other considerations

7.1 Treatments in the ALCYONE study

The Expert Committee requested the applicant to inform, as far as possible, what treatments the patients included in the ALCYONE study receive, including the proportion of patients in the intervention and control arm who receive daratumumab in subsequent treatment lines, respectively.

ALCYONE is a multicenter, randomized, open-label, active controlled phase III trial. Patients were enrolled between 9th of February 2015, and 14th of July 2016, at 162 sites in 25 countries across North and South America, Europe, and the Asia–Pacific region. At the initial clinical cutoff date (12th of June , 2017), a total of 276 patients (79.8%) in the daratumumab arm and 220 patients (62.1%) in the control arm had completed all nine cycles of bortezomib, melphalan, and prednisone; 17 patients in each group were still receiving treatment with bortezomib, melphalan, and prednisone (10).

As of any multicenter trial conducted in the past (the ALCYONE trial started enrollment February 2015), it is important to consider the subsequent treatments available at that time for respective Regions/countries which will differ. The second (and third) line treatments currently used in the Danish clinical setting may or may not have been regulatory approved at that point in time for respective Regions, and there could be a potential lack of national recommendation/reimbursement for various second- and third-line treatments. To provide an example for the Europe Region, daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy was approved by the European Commission in April 2017 (41). The initial Marketing Authorization was granted in May 2016 for daratumumab as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy (42). For Europe, the number of patients receiving daratumumab in subsequent lines would be influenced by the European Commission date and whether the daratumumab combinations would have been recommended nationally which in some countries are a longer process.

Regarding the ALCYONE trial and the most recent data available (median follow-up of 40.1 months), 115 (33%) of 350 patients in the DaraBorMelPred arm and 202 (57%) of 356 patients in the BorMelPred arm received subsequent therapy. Among the 317 patients who received second-line therapy, an immunomodulatory drug-containing regimen without a proteasome inhibitor was the most common first subsequent therapy (55 [48%] of 115 patients in the DaraBorMelPred arm and 108 [54%] of 202 in the BorMelPred arm). The most common immunomodulatory drug-containing regimen was lenalidomide and dexamethasone. Other common subsequent therapies included a proteasome inhibitor plus an immunomodulatory drug (29 [25%] patients in the DaraBorMelPred arm and 25 [12%] in the BorMelPred arm) and a proteasome inhibitor-containing regimen without an immunomodulatory drug (14 [12%] patients in the DaraBorMelPred arm and 28 [14%] in the BorMelPred arm). The most common proteasome inhibitor plus immunomodulatory drug combination regimen was carfilzomib, lenalidomide, and dexamethasone, and the most common proteasome inhibitor-containing regimen without an immunomodulatory drug was bortezomib and dexamethasone.

21 (10.4%) patients in the BorMelPred arm and one (0.9%) in the DaraBorMelPred arm received a daratumumab-containing regimen as first subsequent therapy. For the BorMelPred arm:

- 12 patients received daratumumab/lenalidomide/dexamethasone
- Five patients received daratumumab/bortezomib/dexamethasone
- Two patients received daratumumab/carfilzomib/dexamethasone
- Two patients received daratumumab monotherapy

Regarding other regimens containing a CD38 antibody (reported if received by ≥3 patients in either arm)

- 3 patients received Carfilzomib/dexamethasone/isatuximab in the BorMelPred arm

For the DaraBorMelPred arm

- One patient received daratumumab/lenalidomide/dexamethasone

7.2 DaraBorMelPred in Danish clinical practice

The Expert Committee has requested information to support the assessment of whether and how the introduction of DaraBorMelPred in a Danish clinical practice will influence the treatments in subsequent lines regarding type, duration and expected efficacy.

The introduction of DaraBorMelPred in the first-line setting is expected to influence both the choice of first line treatment and subsequent treatments. As previously mentioned, the comparators specified in the DaraBorMelPred protocol are BorMelPred, LenDex18 and BorLenDex. A recommendation by the Medicines Council may be based on a recommendation across all specified comparators or specific treatments depending on the decision.

The applicant would expect the majority of patients receiving DaraBorMelPred in the first line setting to receive a lenalidomide containing regimen in the second line setting which may be elotuzumab+lenalidomid+dexamethason (EloLenDex) based on the current drug recommendation (May 2020), where EloLenDex is the first choice for patients where daratumumab is contraindicated in the second line setting. The carfilzomib+lenalidomid+dexamethason (CarLenDex) regimen is currently the second choice in the drug recommendation and this regimen is also expected to be used. There may also be specific preference for administration at home and some patients are expected to be offered LenDex despite more effective combinations being available. The applicant also expect that some patients will not be treated with a lenalidomide containing regimen in the second line setting and be offered a pomalidomide containing regimen such as pomalidomide+bortezomib+dexamethason (PomBorDex) or carfilzomib and dexamethasone (CarDex).

The treatment duration and efficacy would unlikely be negatively affected by first line regimen, DaraBorMelPred, considering the switch of mechanisms of action in which adding an immunomodulatory drug such as lenalidomide or pomalidomide with multifactorial mechanisms of action in combination with Elotuzumab (EloLenDex) targeting SLAMF7 on the myeloma cells, or with proteasome inhibitors such as Carfilzomib (CarLenDex) or Bortezomib (PomBorDex) in second line. The DaraBorMelPred treatment regimen does not preclude the later use of proteasome inhibitors (for example bortezomib) in subsequent lines as the bortezomib regimen in the DaraBorMelPred arm is a fixed treatment duration.

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9 Appendices

9.1 Search syntax

Appendix A – Primary SLR

The following search syntax was run in PubMed. This search protocol in Table 50 was set-up and approved by the Danish Medicines Council (1).

TABLE 50: SEARCH SYNTAX PUBMED

#	Search terms	Hits
1	"Multiple Myeloma"[Mesh]	40267
2	myeloma*[tiab] OR ndmm*[tiab] OR (kahler*[tiab] AND (disease[tiab] OR morbus[tiab]))	52957
3	#1 OR #2	60031
4	refractory[ti] OR relapsed[ti] OR recurrent[ti]	115833
5	#3 NOT #4	58342
6	"daratumumab"(14)	247
7	daratumumab*[tiab] OR darzalex*[tiab] OR "humax cd38"[tiab]	489
8	#6 OR #7	536
9	"bortezomib"[Mesh]	5451
10	Bortezomib*[tiab] OR velcade*[tiab] OR mg-341*[tiab] OR mg341*[tiab] OR mln-341*[tiab] OR mln341*[tiab] OR ldp-341*[tiab] OR ldp341*[tiab] OR PS-341*[tiab] OR PS341*[tiab]	8034
11	#9 OR #10	8759
12	"melphalan"[Mesh]	7666
13	melphalan*[tiab] or melphelan*[tiab] or melphalon*[tiab] or melfalan*[tiab] or medphalan*[tiab] or merphalan*[tiab] or sarcolysin*[tiab] or sarkolysin*[tiab] or alkeran*[tiab] or "phenylalanine mustard"[tiab]	8232
14	#12 OR #13	10975
15	"prednisone"[Mesh]	38938
16	prednison*[tiab] or dehydrocortison*[tiab] or delta-cortison*[tiab] or rectodelt*[tiab] or sterapred*[tiab] or ultracorten*[tiab] or winpred*[tiab] or cortan*[tiab] or panafcort*[tiab] or cutason*[tiab] or decortin*[tiab] or dacortin*[tiab] or decortisyl*[tiab] or deltason*[tiab] or encorton*[tiab] or enkortolon*[tiab] or kortancyl*[tiab] or liquid-pred*[tiab] or meticorten*[tiab] or orison*[tiab] or panasol*[tiab] or predni-tablinen*[tiab] or prednidib*[tiab] or predniment*[tiab] or pronison*[tiab] or sone*[tiab]	29149
17	#15 OR #16	53160
18	#8 AND #11 AND #14 AND #17	14
19	"lenalidomide"[Mesh]	2511
20	lenalidomid*[tiab] OR revlimid*[tiab] OR revimid*[tiab] OR cc-5013*[tiab] OR cc5013*[tiab] OR cdc-501*[tiab] OR cdc-5013*[tiab] OR cdc501*[tiab] OR cdc5013*[tiab] OR enmd-0997*[tiab] OR enmd0997*[tiab] OR imid-3*[tiab] OR imid3*[tiab]	4096
21	#19 OR #20	4455
22	"dexamethasone"[Mesh]	50762

#	Search terms	Hits
23	dexametason*[tiab] OR dexamethason*[tiab] OR Adexon*[tiab] OR Aeroseb-dex*[tiab] OR Decaderm*[tiab] OR Decadron*[tiab] OR Decaject*[tiab] OR Decameth*[tiab] OR Decaspray*[tiab] OR Dectancyl*[tiab] OR Dexacort*[tiab] OR Dexafarm*[tiab] OR Dexafree*[tiab] OR Dexapos*[tiab] OR Dexa-Rhinospray*[tiab] OR Dexa-sine*[tiab] OR Dexason*[tiab] OR Dexone*[tiab] OR dexpak*[tiab] OR Dexsol*[tiab] OR Fortecortin*[tiab] OR Gammacorten*[tiab] OR Hexadecadrol*[tiab] OR Hexadrol*[tiab] OR Isopto-Dex*[tiab] OR Loverine*[tiab] OR Luxazone*[tiab] OR Maxidex*[tiab] OR Maxitrol*[tiab] OR Methylfluorprednisolone*[tiab] OR Millicorten*[tiab] OR oradexon*[tiab] OR Ozurdex*[tiab] OR Sofradex*[tiab] OR Superprednol*[tiab] OR Visumetazone*[tiab]	57560
24	#22 OR #23	71982
25	#21 AND #24	1350
26	#11 AND #25	717
27	#18 OR #25 OR #26	1357
28	#5 AND #27	879
29	(randomized controlled trial(43) OR controlled clinical trial(43) OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	1207142
30	#28 AND #29	**224**

The following search syntax was run in Cochrane. The search protocol in Table 51 was set-up and approved by the Medicines Council (1).

TABLE 51: SEARCH SYNTAX COCHRANE

#	Search terms	Hits
1	[mh "Multiple Myeloma"]	1551
2	(myeloma* or ndmm* or ((kahler or kahler's or kahler*) next (disease or morbus))):ti,ab,kw	5490
3	1 - #2	5490
4	(refractory or relapsed or recurrent):ti	18391
5	#3 not #4	4559
6	(daratumumab* or darzalex* or "humax cd38"):ti,ab,kw	255
7	[mh Bortezomib]	420
8	(bortezomib* or velcade* or mg-341* or mg341* or mln-341* or mln341* or ldp-341* or ldp341* or PS-341* or PS341*):ti,ab,kw	1994
9	{or #7-#8}	1994
10	[mh Melphalan]	692
11	(melphalan* or melphelan* or melfalan* or medphalan* or merphalan* or sarcolysin* or sarkolysin* or alkeran* or "phenylalanine mustard"):ti,ab,kw	2132
12	2 - #11	2147
13	[mh Prednisone]	3910
14	(prednison* or dehydrocortison* or delta-cortison* or rectodelt* or sterapred* or ultracorten* or winpred* or cortan* or panafcort* or decortin* or dacortin* or decortisyl* or deltason* or encorton* or liquid-pred* or meticorten* or panasol* or prednidib* or pronison* or sone*):ti,ab,kw	9625
15	{or #13-#14}	9625
16	#6 AND #9 AND #12 AND #15	25
17	[mh Lenalidomide]	365
18	(lenalidomide* or revlimid* or revimid* or cc-5013* or cc5013* or cdc-501* or cdc-5013* or cdc501* or cdc5013* or enmd-0997* or enmd0997* or imid-3* or imid3*):ti,ab,kw	1945
19	{or #17-#18}	1945
20	[mh Dexamethasone]	4376
21	(dexametason* or dexamethason* or Adexon* or Aeroseb-dex* or Aphthasolone* or Decaderm* or Decadron* or Decaject* or Decameth* or Decaspray* or Dectancyl* or Degabina* or Dexabion* or Dexacen* or Dexacort* or Dexafarm* or Dexafree* or Dexair* or Dexalaf* or Dexalergin* or Dexameral* or Dexamonozon* or Dexapos* or Dexa-Rhinospray* or Dexa-sine* or Dexason* or Dexatotal* or Dexone* or dexpak* or Dexsol* or Dropodex* or Flourmethylprednisolone* or Fortecortin* or Gammacorten* or Hexadecadrol* or Hexadrol* or Isopto-Dex* or Loverine* or Luxazone* or Martapan* or Maxidex* or Maxitrol* or Methylfluorprednisolone* or Millicorten* or Monopex* or Neofordex* or Oradexon* or Ozurdex* or Sofradex* or Superprednol* or Visumetazone*):ti,ab,kw	11428
22	{or #20-#21}	11448
23	#19 AND #22	1048
24	#9 AND #23	535
25	#16 OR #23 OR #24	1061
26	#5 AND #25	630
27	("conference abstract" or review):pt OR NCT*:au	370171
28	(clinicaltrials.gov or trialsearch or meeting):so	334116
29	abstract:ti	7809

#	Search terms	Hits
30	{or #27- #29}	519009
31	#26 NOT #30	**133**

9.2 Main characteristics of included studies

An overview of the main study characteristics per included study is presented below.

9.2.1 ALCYONE

TABLE 52: ALCYONE MAIN STUDY CHARACTERISTICS

Trial name	**ALCYONE**
Clinical trial ID	**NCT02195479**
Objective	Updated efficacy and safety results from a prespecified, interim, overall survival analysis of a randomized, phase 3 trial (ALCYONE) of bortezomib, melphalan, and prednisone with or without daratumumab in patients with newly diagnosed multiple myeloma who were ineligible for ASCT with more than 36 months of follow-up
Publications – author, title, journal, year	**Main Publication** Mateos M-V, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. The New England journal of medicine 2018; 378:518–28 (10). **Follow-up publication** Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, Knop S et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomized, open-label, phase 3 trial. Lancet. 2020;395(10218):132–141 (11).
Study type and design	Interventional (Phase 3 Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)
Follow-up time	Median follow-up 40.1 months (longest follow-up time)
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Documented multiple myeloma, as assessed by the central laboratory, and defined in protocol • Newly diagnosed and not considered candidate for high-dose chemotherapy with stem cell transplantation (SCT) due to: being age >=65 years, or in participants <65 years: presence of important comorbid conditions likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation • Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 • Meet the clinical laboratory criteria as specified in the protocol • A woman of childbearing potential must have a negative serum pregnancy test at screening within 14 days prior to randomization • Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. Exclusion Criteria: • Diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma • Diagnosis of Waldenstrom's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions • Prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment • Peripheral neuropathy or neuropathic pain Grade 2 or higher • History of malignancy (other than multiple myeloma) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years) • Radiation therapy within 14 days of randomization • Plasmapheresis within 28 days of randomization • Participant has known chronic obstructive pulmonary disease (COPD), known moderate or severe persistent asthma within the last 2 years or currently has uncontrolled asthma of any classification (controlled intermittent asthma or controlled mild persistent asthma is allowed) • Known or suspected COPD must have a FEV1 test during screening Seropositive for human immunodeficiency virus (HIV), known to have hepatitis B surface antigen positivity, or history of to have a history of hepatitis C • Any concurrent medical or psychiatric condition or disease
Intervention	Experimental arm: DaraBorMelPred (N=350) • Daratumumab:16 mg/kg as intravenous infusion, once weekly, for 6 weeks in Cycle 1 and then once every 3 weeks, in Cycle 2 to 9 and thereafter, once every 4 weeks + Velcade: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9 + Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9 + Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. Active Comparator: BorMelPred (N=356)

<table>
<tr><td></td><td>

- Velcade: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9 + Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9 + Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.

</td></tr>
<tr><td>Baseline characteristics</td><td>

	DaraBorMelPred	BorMelPred
N	350	356
Age		
Median (range) — year	71.0 (40–93)	71.0 (50–91)
Distribution — no. (%)		
<65 year	36 (10.3)	24 (6.7)
65–74 year	210 (60.0)	225 (63.2)
≥75 year	104 (29.7)	107 (30.1)
Sex- no. (%)		
Male	160 (45.7%)	167 (46.9%)
Female	190 (54.3%)	189 (53.1%)
ECOG performance status — no. (%) †		
0	78 (22.3)	99 (27.8)
1	182 (52.0)	173 (48.6)
2	90 (25.7)	84 (23.6)
ISS disease stage — no. (%) ‡		
I	69 (19.7)	67 (18.8)
II	139 (39.7)	160 (44.9)
III	142 (40.6)	129 (36.2)
Cytogenetic profile — no./total no. (%) §		
Standard risk	261/314 (83.1)	257/302 (85.1)
High risk¶	53/314 (16.9)	45/302 (14.9)
Median time since initial diagnosis of multiple myeloma (range) — months	0.8 (0.1–11.4)	0.8 (0.1–25.3) ‖

* The intention-to-treat population was defined as all the patients who had undergone randomization. Post hoc analyses showed no significant differences between the two groups in the characteristics evaluated at baseline. Percentages may not sum to 100 because of rounding.
† Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
‡ The International Staging System (ISS) disease stage is derived on the basis of the combination of serum β2-microglobulin and albumin levels. Higher stages indicate more severe disease.
§ Cytogenetic risk was based on fluorescence in situ hybridization or karyotype testing. Cytogenetic data assessed by means of next-generation sequencing for the total intention-to-treat population were not available at the data cutoff date, and analysis is ongoing.
¶ These patients had at least one high-risk abnormality: del17p, t (4;14), or t(14;16).
‖ At the time of initial diagnosis, the patient with a time since initial diagnosis of multiple myeloma of 25.3 months did meet International Myeloma Working Group diagnostic criteria for multiple myeloma with a hemoglobin level of less than 10 g per deciliter and at least 10% plasma cells on examination of the bone marrow. A decision was made by the physician not to initiate treatment at the time of diagnosis. The patient's disease was stable and actively monitored until treatment was begun at a later date.

</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint:
PFS, defined as time from date of randomization to either progressive disease (PD), or death, whichever occurs first. PD will be determined according to International Myeloma Working Group (IMWG) criteria
Secondary endpoints:
TTP, CR, MRD Negativity Rate, Progression Free Survival on Next Line of Therapy (PFS2), Time to Next Treatment ORR, sCR, VGPR, VGPR or better, Time to Response, Duration of Response, OS, EORTC-QLQ-C30, EQ-5D-5L</td></tr>
<tr><td>Method of analysis</td><td>All efficacy analyses were intention-to-treat analyses. Continuous variables were summarized with descriptive statistics, and categorical variables were summarized in frequency tables. Time-to-event variables were evaluated with the Kaplan–Meier method. Binary end points, such as response rate, were assessed with a stratified Cochran–Mantel– Haenszel test, and an odds ratio and two-sided 95% confidence interval were calculated. The primary efficacy end point was estimated with the Kaplan– Meier method, and the treatment effect (hazard ratio) and its two-sided 95% confidence interval were estimated with a stratified Cox regression model. Statistical significance was evaluated with a stratified log-rank test based on the predetermined alpha level at the clinical cut-off date.</td></tr>
<tr><td>Subgroup analyses</td><td>For PFS, subgroup analysis was performed by sex, age (<75/>=75 years), race (white/other), Geographic region (Europe/other), Baseline creatinine clearance (≤60 ml/min/ >60 ml/min), Baseline hepatic function (Normal/impaired), ISS disease stage (I/II/III), Type of MM (IgG/Non-IgG), Cytogenetic profile at trial entry (High risk/Standard risk), ECOG PS (0/1 or 2). Analyses were conducted on prespecified subgroups. PFS analysis was performed on the intention-to-treat population. PFS was estimated with the Kaplan– Meier method, and the treatment effect (hazard ratio) and its two-sided 95% confidence interval were estimated with a stratified Cox regression model. Statistical significance was evaluated with a</td></tr>
</table>

	stratified log-rank test based on the predetermined alpha level at the clinical cut-off date. Validity of subgroup analysis including statistical power is not reported.

9.2.2 FIRST

Please note that this study would be included in both cases when LenDex18 or LenDex is considered a comparator.

TABLE 53: FIRST MAIN STUDY CHARACTERISTICS

Trial name	**FIRST trial**
Clinical trial ID	**NCT00689936**
Objective	To compare the efficacy and safety of lenalidomide–dexamethasone, given until disease progression or for a fixed number of cycles, with MelPredThal given for a fixed number of cycles in patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation.
Publications – author, title, journal, year	**Main Publication** Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906–17 (12). **Follow-up publication** Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood, 131(3), 301–310 (13).
Study type and design	Interventional (Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)
Follow-up time	LenDex: treatment until disease progression; LenDex18: treatment for 18 (four-week) cycles; MelPredThal: treatment for 12 (six-week) cycles. Response to treatment was assessed after each treatment cycle and every 28 days during follow-up. Median follow-up: 67.2 months (longest follow-up time)

Population (inclusion and exclusion criteria)	Inclusion Criteria:
	• Must understand and voluntarily sign informed consent form
	• Age ≥ 18 years at the time of signing consent
	• Previously untreated, symptomatic multiple myeloma as defined by the 3 criteria below:
	  ○ MM diagnostic criteria (all 3 required):
	  ○ AND have measurable disease by protein electrophoresis analyses as defined by the following:
	  ○ AND are at least 65 years of age or older or, if younger than 65 years of age, are not candidates for stem cell transplantation
	• ECOG performance status of 0, 1, or 2
	• Able to adhere to the study visit schedule and other protocol requirements
	• Females of child-bearing potential (FCBP)^2:
	• Must agree to undergo two medically supervised pregnancy tests prior to starting study therapy with either LenDex or MelPredThal.
	• Must commit to either continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use and be able to comply with effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including during periods of dose interruptions), and for 28 days after discontinuation of study therapy.
	
	Male Patients:
	• Must agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy.
	• Must agree to not donate semen during study drug therapy and for a period after end of study drug therapy.
	• Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.
	
	All patients must:
	• Have an understanding that the study drug could have a potential teratogenic risk.
	• Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy.
	• Agree not to share study medication with another person. All FCBP and male patients must be counseled about pregnancy precautions and risks of fetal exposure.
	
	Exclusion Criteria:
	• Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid [i.e., less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of randomization]).
	• Any serious medical condition that places the patient at an unacceptable risk if he or she participates in this study.
	• Pregnant or lactating females.
	• Any of the following laboratory abnormalities:

<table>
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Absolute neutrophil count (ANC) < 1,000/µL (1.0 x 109/L)
Untransfused platelet count < 50,000 cells/µL (50 x 10^9/L)
Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN)

Renal failure requiring hemodialysis or peritoneal dialysis.
Prior history of malignancies, other than multiple myeloma, unless the patient has been free of the disease for ≥ 3 years. Exceptions include the following:

Basal cell carcinoma of the skin
Squamous cell carcinoma of the skin
Carcinoma in situ of the cervix
Carcinoma in situ of the breast
Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)

Patients who are unable or unwilling to undergo antithrombotic therapy.
Peripheral neuropathy of > grade 2 severity.
Known HIV positivity or active infectious hepatitis, type A, B, or C. Primary AL (immunoglobulin light chain) amyloidosis and myeloma complicated by amyloidosis.

</td></tr>
<tr><td>Intervention</td><td>
Active Comparator: MelPredThal (N=547)

Melphalan: 0.25 mg/kg/day on days 1 to 4 in 42-day cycles for 72 weeks- 12 cycles + Prednisone: 2 mg/kg/day on days 1 to 4 in 42-day cycles for 72 weeks-12 cycles + Thalidomide: 200 mg/day in 42-day cycles for 72 weeks-12 cycles.

Experimental arm (1): LenDex (N=535)

Revlimid: 25 mg/day on days 1 to 21 of each 28-day cycles until disease progression + Dexamethasone: 40 mg/day on days 1, 8, 15, and 22 of each 28-day cycles until disease progression.

Experimental arm (2): LenDex18 (N=541)

Revlimid: 25 mg/day on days 1 to 21 of each 28-day cycles for 72 weeks- 18 cycles + Dexamethasone: 40 mg/day on days 1, 8, 15, and 22 of each 28-day cycles for 72 weeks- 18 cycles

</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>LenDex</th><th>LenDex18</th><th>MelPredThal</th></tr>
<tr><td>N</td><td>535</td><td>541</td><td>547</td></tr>
<tr><td>Age</td><td></td><td></td><td></td></tr>
<tr><td>Median — yr</td><td>73</td><td>73</td><td>73</td></tr>
<tr><td>Range — yr</td><td>44–91</td><td>40–89</td><td>51–92</td></tr>
<tr><td>≥65 yr — no. (%)</td><td>504 (94)</td><td>507 (94)</td><td>520 (95)</td></tr>
<tr><td>>75 yr — no. (%)</td><td>186 (35)</td><td>193 (36)</td><td>188 (34)</td></tr>
<tr><td>Sex — no. (%)</td><td></td><td></td><td></td></tr>
<tr><td>Male</td><td>294 (55)</td><td>273 (50)</td><td>287 (52)</td></tr>
<tr><td>Female</td><td>241 (45)</td><td>268 (50)</td><td>260 (48)</td></tr>
<tr><td>Race or ethnic group — no. (%) †</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>474 (89)</td><td>480 (89)</td><td>491 (90)</td></tr>
<tr><td>Asian</td><td>40 (7)</td><td>43 (8)</td><td>44 (8)</td></tr>
<tr><td>Black</td><td>9 (2)</td><td>6 (1)</td><td>5 (1)</td></tr>
<tr><td>Native Hawaiian or Pacific Islander</td><td>1 (<1)</td><td>0</td><td>1 (<1)</td></tr>
<tr><td>Other</td><td>6 (1)</td><td>11 (2)</td><td>3 (1)</td></tr>
<tr><td>Undisclosed</td><td>5 (1)</td><td>1 (<1)</td><td>3 (1)</td></tr>
<tr><td>ECOG performance-status score — no. (%) ‡</td><td></td><td></td><td></td></tr>
<tr><td>0</td><td>155 (29)</td><td>163 (30)</td><td>156 (29)</td></tr>
<tr><td>1</td><td>257 (48)</td><td>263 (49)</td><td>275 (50)</td></tr>
<tr><td>2</td><td>119 (22)</td><td>113 (21)</td><td>111 (20)</td></tr>
<tr><td>3</td><td>2 (<1)</td><td>2 (<1)</td><td>2 (<1)</td></tr>
<tr><td>Data not available</td><td>2 (<1)</td><td>0</td><td>3 (1)</td></tr>
<tr><td>International Staging System stage — no. (%) §</td><td></td><td></td><td></td></tr>
<tr><td>I or II</td><td>319 (60)</td><td>322 (60)</td><td>323 (59)</td></tr>
<tr><td>III</td><td>216 (40)</td><td>219 (40)</td><td>224 (41)</td></tr>
<tr><td>Myeloma subtype — no. (%)</td><td></td><td></td><td></td></tr>
<tr><td>IgA</td><td>138 (26)</td><td>142 (26)</td><td>123 (22)</td></tr>
<tr><td>IgD</td><td>4 (1)</td><td>7 (1)</td><td>4 (1)</td></tr>
<tr><td>IgG</td><td>334 (62)</td><td>331 (61)</td><td>350 (64)</td></tr>
<tr><td>IgM</td><td>3 (1)</td><td>1 (<1)</td><td>1 (<1)</td></tr>
<tr><td>IgA and IgG</td><td>7 (1)</td><td>6 (1)</td><td>8 (1)</td></tr>
</table>
</td></tr>
</table>

	IgA and IgM	0	0	1 (<1)
	Light-chain only	46 (9)	54 (10)	57 (10)
	Data not available	3 (1)	0	3 (1)
	Lactate dehydrogenase — no. (%)			
	<200 U/liter	448 (84)	442 (82)	434 (79)
	≥200 U/liter	86 (16)	99 (18)	112 (20)
	Missing data	1 (<1)	0	1 (<1)
	Creatinine clearance — no. (%)			
	<30 ml/min	45 (8)	47 (9)	55 (10)
	<60 ml/min	267 (50)	254 (47)	258 (47)
	≥60 ml/min	268 (50)	287 (53)	289 (53)
	History of bone lesions — no. (%)			
	Present	380 (71)	382 (71)	394 (72)
	Absent	154 (29)	158 (29)	153 (28)
	Unknown	1 (<1)	1 (<1)	0
	High-risk cytogenetic profile — no./total no. (%) ¶	43/248 (17)	52/261 (20)	47/253 (19)
	* There were no significant between-group differences at baseline. MelPredThal denotes melphalan–prednisone–thalidomide. † Race and ethnic group were self-reported. ‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability.16 Six patients across the three study groups had worsening of their ECOG performance-status score from 2 to 3 during the screening period. § Higher stages indicate more severe disease. ¶A high-risk cytogenetic profile was defined as translocations (4;14) or (14;16) or deletion 17p.			
Primary and secondary endpoints	Primary endpoint: PFS: Defined as the time from randomization to the first documented PD or death due to any cause during the study, which ever occurred first based on the International Myeloma Working Group Uniform Response criteria (IMWG). Secondary endpoints: OS, ORR, duration of response, time to first response, Time to Treatment Failure, Time to Second-line Anti-myeloma Treatment, Time to Second Line Therapy, Quality of life (EORTC QLQ-C30. EORTC QLQ-MY20), Healthcare Resource Utilization (HRU), Adverse events, Postbaseline Value in Creatinine Clearance (CrCl), Postbaseline Value in Absolute Neutrophil Count, Postbaseline Value in Haemoglobin, Postbaseline Value in Platelet Count, Infection Rate			
Method of analysis	All efficacy analyses were intention-to-treat analyses. PFS and OS were analysed using Kaplan-Meier methods and the O'Brien–Fleming boundary was used for PFS and the Pocock boundary was used for OS. Fisher's exact test was used for comparison response outcomes among the treatment arms.			
Subgroup analyses	For PFS, subgroup analysis was performed by response rate (Patients with CR/ Patients with >=VGPR/ Patients with >=PR/ Patients with <=SD), RI (Normal RI CrCl >= 80 mL/min/ Mild RI CrCl >= 50 < 80 mL/min/ Moderate RI CrCl >= 30 < 50 mL/min/ Severe RI < 30 mL/min), age (<75/>=75), risk status (high risk/ standard risk), Asian subgroup, ISS status (ISS stage: I or II/ ISS stage: III), ECOG (ECOG PS 0/ ECOG PS 1/ ECOG PS 2), Lactate dehydrogenase (< 200 U/L/ ≥ 200 U/L). Subgroup analyses according to age (<75/>=75) was prespecified; other subgroup analyses were post-hoc analyses. PFS was analysed using Kaplan-Meier methods and the O'Brien–Fleming boundary was used. Validity of subgroup analysis including statistical power is not reported. For OS, subgroup analysis was performed by CrCL level (Normal RI CrCl >= 80 mL/min/ Mild RI CrCl >= 50 < 80 mL/min/ Moderate RI CrCl >= 30 < 50 mL/min/ Severe RI < 30 mL/min), age (<75/>=75), Asian subgroup, response rate (Patients with CR/ Patients with >=VGPR/ Patients with >=PR/ Patients with <=SD), risk status (high risk/ standard risk), second line treatment, ISS status (ISS stage: I or II/ ISS stage: III), ECOG (ECOG PS 0/ ECOG PS 1/ ECOG PS 2), Lactate dehydrogenase (< 200 U/L/ ≥ 200 U/L). Subgroup analyses according to age (<75/>=75) was prespecified; other subgroup analyses were post-hoc analyses. OS was analysed using Kaplan-Meier methods and the Pocock boundary was used for. Validity of subgroup analysis including statistical power is not reported. For response rate, subgroup analysis was performed by risk status (high risk/ standard risk), age (<75/>=75), Asian subgroup, second line treatment. Subgroup analyses according to age (<75/>=75) was prespecified; other subgroup analyses were post-hoc analyses. Fisher's exact test was used for comparison of treatment arms. Validity of subgroup analysis including statistical power is not reported.			

9.2.3 IFM 01/01

TABLE 54: IFM 01/01 MAIN STUDY CHARACTERISTICS

Trial name	**IFM 01/01**
Clinical trial ID	**NCT00644306**
Objective	This randomized, placebo-controlled, phase III trial investigated the efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed myeloma.
Publications – author, title, journal, year	**Main Publication** Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, Dib M, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. Journal of Clinical Oncology, 3664-3670 (16).
Study type and design	Interventional (Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double
Follow-up time	Median follow-up: 47.5 months (longest follow-up time)
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Stage II or III multiple myeloma according to Durie and Salmon criteria • Patients older than 75 years • Previously untreated patients. Exclusion Criteria: • Prior history of another neoplasm (except basocellular cutaneous or cervical epithelioma) • Primary or associated amyloïdosis • World Health organisation performance index of at least 3 • Significant renal insufficiency with creatinine serum levels of 5.0 mg per deciliter or more • Cardiac or hepatic dysfunction • Cerebral circulatory insufficiency • Absolute contraindication to corticosteroids • Peripheral neuropathy clinically significant • History of venous thrombosis during the last 6 months • HIV or hepatitis B or C positivity • Patients who had geography, social, or psychological conditions which might prevent adequate follow-up.
Intervention	Comparator arm: 12 cycles every 6 weeks: melphalan 0.2 mg/kg day 1 to 4, prednisone 2 mg/kg/d day 1 to 4 plus placebo 100mg/d continuously for 18 months Experimental arm: melphalan, prednisone, thalidomide; 12 cycles every 6 weeks: melphalan 0.2 mg/kg day 1 to 4, prednisone 2 mg/kg/d day 1 to 4 plus thalidomide 100mg/d continuously for 18 months
Baseline characteristics	MelPred / MelPredThal N: 116 / 113 Men: 53% / 38% Median age: 78.5 (75-89) Age ≥80 years: 40 (34%) / 43 (38%) 93 (82%) / 87 (78%) Bone lesions M protein IgA: 34 (30%) / 31 (28%) ISS stage I: 26/104 (25%) / 25/98 (25%) II: 47/104 (45%) / 39/98 (40%) III: 31/104 (30%) / 34/98 (35%) B2 microglobulin (mg/L) ≥3.5: 73/107 (68%) / 70/101 (69%) Albumin, <3.5 g/dL: 34/113 (30%) / 27/110 (25%) Clearance creatinine ≤ 30 mL/min: 16/105 (15%) / 11/105 (11%)
Primary and secondary endpoints	Primary endpoint: To evaluate whether the MP plus thalidomide combination prolonged survival in patients age 75 years or older with previously untreated multiple myeloma (OS) Secondary endpoints: Safety, response rates, PFS

Method of analysis	Assuming a median survival time of 22 months in the control (MP plus placebo) group and with a global type I error rate of 5%, the sample size was estimated to be 280 patients to guarantee, in a two-sided test, a power of 80% to detect an increase in the median survival time of 6 months. With this method, a P value of .05 at the final analysis would be regarded as significant. No interim analysis was initially planned. However, the IFM board decided to perform an interim analysis based on the confirmed efficacy of MP plus thalidomide in two other trials.10,11 Recruitment into this trial was stopped on December 2006, due to the finding of a clear survival advantage with MP plus thalidomide in the IFM 99-06 trial,11 and because MP plus thalidomide had been made available to newly diagnosed myeloma patients ineligible for high-dose therapy by the French Autorisation Temporaire d'Utilisation. The distribution of parameters at inclusion or during follow-up was described overall or by treatment group through number and percentage of patients. Distributions of parameters assessed at inclusion were compared globally between treatment groups using χ2 tests for categoric variables and Kruskal-Wallis rank test for continuous variables. Best response rates at 12 months were compared using the χ2 test. Overall survival was calculated from random assignment to death from any cause. Data on patients who were alive at the time of analysis were censored in the survival analysis on the last date they were known to be alive. Progression-free survival was calculated from random assignment to progression or death. Data on patients who had not experienced disease progression were censored on the last date they were known to be alive and progression free. Survival was estimated with the Kaplan-Meier product limit method and curves were compared with the stratified log-rank test on an intention-to-treat basis. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model for the intention-to-treat population. Adverse events rates were compared between groups using the χ2 test.
Subgroup analyses	NA

9.2.4 IFM 99-06

TABLE 55: IFM 99-06 MAIN STUDY CHARACTERISTICS

Trial name	**IFM 99-06**
Clinical trial ID	**NCT00367185**
Objective	To assess the relative efficacy and safety of MelPred versus MelPredThal or versus MEL100. Additionally, the relative efficacy of MPT versus MEL100 was evaluated
Publications – author, title, journal, year	**Main Publication** Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, Renaud M, Harousseau JL, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial. Lancet 2007; 370: 1209–18 (17).
Study type and design	Interventional (Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open label)
Follow-up time	Median follow-up: 51.5 months (longest follow-up time)
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Stage II or III multiple myeloma according to Durie and Salmon criteria. • Patients between 65 and 75 years of age • Previously untreated patients Exclusion Criteria: • Prior history of another neoplasm (except basocellular cutaneous or cervical epithelioma) • Primary or associated amyloidosis • World Health organisation performance index of at least 3 • Significant renal insufficiency with creatinine serum levels of 5.0 mg per deciliter or more • Cardiac or hepatic dysfunction • Cerebral circulatory insufficiency • Absolute contraindication to corticosteroids • Peripheral neuropathy • HIV or hepatitis B or C positivity • Patients who had geographic, social or psychological conditions which might prevent adequate follow-up
Intervention	Comparator arm: • Melphalan: 0.25 mg/kg • Prednisone: 2 mg/kg Experimental arm: • Melphalan: 0.25 mg/kg • Prednisone: 2 mg/kg • Thalidomide: not exceeding 400 mg (Thalidomide was stopped at day 4 of the last melphalan and prednisone cycle)

Baseline characteristics	MelPred	MelPredThal
N	196	125
Men	109 (66%)	63 (50%)
Age (≥70 years)	84 (43%)	50 (40%)
Bone lesions	154 (79%)	90 (76%)
M protein		
IgA	43 (22%)	25 (20%)
ISS stage		
I	61/182 (34%)	38/112 (34%)
II	67/182 (37%)	42/112 (38%)
III	54/182 (30%)	32/112 (29%)
B2 microglobulin (mg/L)		
≥3.5	110/182 (60%)	69/112 (62%)
Albumin, <3.5 g/dL	45/194 (23%)	24 (19%)
Creatinine ≥20 mg/L	13 (7%)	11/124 (9%)
Translocation (11;14)	11/95 (12%)	11/58 (19%)
Translocation (4;14)	7/95 (7%)	10/57 (18%)

Primary and secondary endpoints	Primary endpoint: To evaluate whether the MP plus thalidomide combination prolonged survival in patients age 75 years or older with previously untreated multiple myeloma (OS) Secondary endpoints: Safety, response rates, PFS
Method of analysis	Parameter distribution at inclusion or during follow-up was described generally or per treatment group through number (percentage) of patients. Distributions of parameters assessed at inclusion were compared globally between treatment groups through χ^2 test for categorical variables and Kruskal-Wallis rank test for continuous variables. Best response rates at 12 months were compared between treatment groups through χ^2 test or Fisher's exact test, when necessary. Curves for overall survival, progression-free survival, and survival after progression were calculated from randomization and from progression (for survival after progression) with use of the Kaplan-Meier method.17 Time to event (death, progression or death without progression, death after progression) was expressed as median (SE and IQR). Comparison between treatment groups and hazard ratios (HR) for death, progression or death without progression, or death after progression were estimated through the unstratified proportional hazards model,18 with 95% CI. Adverse events rates were compared between treatment groups through χ^2 test or Fisher's exact test, when necessary. Comparisons of overall survival between groups were adjusted on prognostic factors through a stepwise multivariate proportional hazards model, by forward selection with likelihood ratio test.19 In these prognostic analyses, every continuous variable was first divided into five categories at roughly the 20th, 40th, 60th, and 80th percentiles. If the relative death rates (ratio of the observed number of deaths to the excepted number of deaths in each category, assuming no variation of death rate across categories) in two or more adjacent categories were not substantially different, these categories were collapsed.20,21 If no clear pattern was recorded, the median was used as the cut-off point. Usual limits (e.g., 3 mg/L or 6 mg/L for CRP concentration) were also tested. As a result, two to three categories were used for every continuous variable. After univariate analysis, all variables with a p value of less than 0·20 were proposed in several steps to multivariate analyses, first including all variables with no missing values, and then successively proposing variables with an increasing number of missing values. At every step, the stability of the previously derived model was checked, and no further analysis was done in case of instability. All analyses were done on the intention-to-treat population with a date of point of Oct 8, 2005. A confirmatory analysis of the primary endpoint was done on the per-protocol population, and adverse events were analyzed on the safety population. Furthermore, overall survival, progression-free survival, and survival after progression analyses on the intention-to-treat population were updated on Jan 8, 2007, to present the most up-to-date survival findings. All analyses were done on SPSS software (version 13).
Subgroup analyses	NA

*MEL100 not described as it is not relevant for the clinical question.

9.2.5 VISTA

TABLE 56: VISTA MAIN STUDY CHARACTERISTICS

Trial name	**VISTA trial**
Clinical trial ID	**NCT00111319**
Objective	To compare bortezomib plus melphalan– prednisone with melphalan–prednisone alone in patients with newly diagnosed myeloma who were ineligible for high-dose therapy.
Publications – author, title, journal, year	**Main Publication** San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906–17 (18). Follow-up publication **Follow-up publication** San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M,, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple Myeloma. 2013. J Clin Oncol 448-455 (19).
Study type and design	Interventional (Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)
Follow-up time	Nine 6-week cycles of treatment. Blood and 24-hour urine samples were collected every 3 weeks during the 54-week treatment phase and then every 8 weeks until disease progression. Patients were followed for survival and subsequent myeloma therapy at least every 12 weeks after disease progression. Safety was evaluated throughout the study and until 30 days after the administration of the last dose of a study drug. Median follow-up: 60.1 months (longest follow-up time)

Population (inclusion and exclusion criteria)	Inclusion Criteria:
	• Male or female
	• Not a candidate for HDT/SCT due to: age - subject is 65 years or older or in subjects less than 65 years of age - presence of important comorbid condition(s) likely to have a negative impact on tolerability of HDT/SCT.
	• Symptomatic multiple myeloma or asymptomatic multiple myeloma with related organ or tissue damage.
	• Presence of measurable disease, defined as:
	  ○ For secretory multiple myeloma, measurable disease is defined as any quantifiable serum monoclonal protein value.
	  ○ For oligosecretory or nonsecretory multiple myeloma, measurable disease is defined by the presence of measurable soft tissue or organ (not bone) plasmacytomas as determined by clinical examination or applicable radiographs.
	• Karnofsky performance status score of equal or greater than 60%.
	• Willing and able to complete the PRO instruments
	• Agrees to use an acceptable barrier method for contraception for the duration of the study (for male subjects); If female subjects are still having menstrual periods and are not surgically sterile, they must be practicing an effective method of birth control before entry, and throughout the study, and have a negative serum B-HCG pregnancy test at screening.
	• Have pretreatment clinical laboratory values meeting the criteria as described in the protocol within 14 days before randomization.
	• Subjects (or their legally acceptable representatives) must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
	
	Exclusion Criteria:
	• Diagnosis of smoldering multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS, hypercalcemia, and renal insufficiency related to the monoclonal protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less.
	• Diagnosis of Waldenström's disease or other conditions in which IgM M protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions
	• Prior or current systemic therapy for multiple myeloma including steroids (with the exception of emergency use of a short course [maximum of 4 days] of steroids before randomization or of prior or current use of bisphosphonates)
	• Radiation therapy within 30 days before randomization
	• Plasmapheresis within 30 days before randomization
	• Major surgery within 30 days before randomization (kyphoplasty is not considered major surgery)
	• History of allergic reaction attributable to compounds containing boron or mannitol
	• Peripheral neuropathy or neuropathic pain Grade 2 or higher.
	• Uncontrolled or severe cardiovascular disease, including myocardial infarction, within 6 months of enrollment, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
	• Other malignancy within the past 5 years. Exceptions if treated and not active include the following: basal cell or nonmetastatic squamous cell carcinoma of the skin, cervical carcinoma in situ or International Federation of Gynecology and Obstetrics (FIGO) Stage 1 carcinoma of the cervix

	• Concurrent medical condition or disease (e.g., active systemic infection, uncontrolled diabetes) that is likely to interfere with study procedures or results, or that, in the opinion of the investigator would constitute a hazard for participating in this study • Use of any investigational drugs within 30 days before randomization • Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, or family members of the employees or the investigator.
Intervention	Active Comparator: MP (N=338) • Melphalan: 9 mg/m² on days 1 to 4, during each of nine 6-week cycles + Prednisone: 60 mg/m² on days 1 to 4, during each of nine 6-week cycles. Experimental arm: BorMelPred (N=344) • Velcade: Twice weekly during cycles 1 to 4 and once weekly during cycles 5 to 9 (all 6-week cycles) + Melphalan: 9 mg/m² on days 1 to 4, during each of nine 6-week cycles + Prednisone: 60 mg/m² on days 1 to 4, during each of nine 6-week cycles.

Baseline characteristics

	BorMelPred	MelPred
N	344	338
Age		
Median — year	71	71
Range — year	57–90	48–91
Subgroup — no. (%)		
<65	14 (4)	9 (3)
>=75	107 (31)	101 (30)
Male sex — no. (%)	175 (51)	166 (49)
Race — no. (%) †		
White	304 (88)	295 (87)
Asian	33 (10)	36 (11)
Black	5 (1)	7 (2)
Other	2 (1)	0
Region — %‡		
Europe	79	78
North America	9	9
Other	11	13
Karnofsky performance status ≤70 — no. (%)	122 (35)	111 (33)
Type of myeloma — %		
IgG	64	62
IgA	24	26
IgD	1	1
IgM	1	1
Light chain	8	8
Biclonal	2	2
Lytic bone lesions — no./total no. (%)	224/343 (65)	222/336 (66)
Median plasma cells on bone marrow biopsy — %	40	41
International Staging System stage — %		
I	19	19
II	47	47
III	35	34
Serum β2-microglobulin level		
Median — mg/liter	4.2	4.3
Range — mg/liter	1.7–21.6	1.7–21.6
Subgroup — %‡		
<2.5 mg/l	12	12
2.5-5.5 mg/l	55	55
>5.5 mg/l	33	33
Albumin level		
Median — g/dl	3.3	3.3
Range — g/dl	1.3–4.7	1.4–5.0
Subgroup — %‡		
<3.5 g/dl	58	62
>=3.5 g/dl	42	38

	Hemoglobin — g/liter		
	Median	104	106
	Range	64.0–159.0	73.0–165.0
	Platelet count/mm3		
	Median	221,500	221,500
	Range	68,000–515,000	33,000–587,000
	Creatinine clearance (calculated) — %		
	<30 ml/min	6	5
	30-60 ml/min	48	50
	>60 ml/min	46	46
	History of cardiac condition — no. (%)	121 (35)	105 (31)
	* Percentages may not total 100 because of rounding. To convert the values for serum β2-microglobulin to nanomoles per liter, multiply by 84.75. † Race was self-reported. ‡ Patients were stratified on the basis of this subgroup at randomization.		
Primary and secondary endpoints	Primary endpoint: TTP: response was assessed using criteria of the European Group for Blood and Marrow Transplantation (EBMT) and a prespecified computer algorithm that was validated in a previous trial. Secondary endpoints: PFS, ORR, OS, time to first response, duration of response, CR rate, and patient reported outcomes as assessed using the EORTC QLQ-C30, FACIT-F and EQ-5D instruments.		
Method of analysis	All time-to-event end points were intention-to-treat analyses. Response rates were analysed in the population of patients who could be evaluated for a response (a total of 14 patients, 7 in each study group, could not be evaluated for a response: 5 did not receive a study drug, and 9 had no measurable disease at baseline. Among the patients who could be evaluated, responses were not determined for 4 patients in the BorMelPred group and 4 in the MelPred group) TTP, time to subsequent myeloma therapy, and OS were analysed from randomization and the differences between groups were compared using stratified log-rank tests. Distributions were estimated with use of the Kaplan–Meier method. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model. Response rates were compared between groups based on a stratified Cochran–Mantel–Haenszel chi-square test. Treatment differences were tested at a two-sided alpha level of 0.05.		
Subgroup analyses	For OS, subgroup analysis was performed by Glomerular filtration rate (<=30 ml/min/ 31-50 ml/min/ <=50 ml/min/ >50 ml/min), patients who had received subsequent therapy, ESA (Yes/no), RBC transfusion (Yes/No), Response (CR/PR/Early CR/Late CR), age (<75/>=75 years), Gender (Male/Female), Race (White/Asian/Other race), B-2-Microglobulin level (<2.5 mg/dl/2.5–5.5 mg/dl/>5.5 mg/dl), Albumin level (<3.5 g/dl/>= 3.5 g/dl), Region (North America/Europe/Other region), ISS (I/II/III), Creatinine clearance (>= 60 ml/min/< 60 ml/min), risk status (Standard cytogenetic risk/ High cytogenetic risk). Analyses were conducted on prespecified subgroups. Distributions were estimated with use of the Kaplan–Meier method. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model. The validity of subgroup analysis including statistical power is not reported. For TTP, subgroup analysis was performed by age (<75/>=75 years), Gender (Male/Female), Race (White/Asian/Other race), B-2-Microglobulin level (<2.5 mg/dl/2.5–5.5 mg/dl/>5.5 mg/dl), Albumin level (<3.5 g/dl/>= 3.5 g/dl), Region (North America/Europe/Other region), ISS (I/II/III), Creatinine clearance (>= 60 ml/min/< 60 ml/min), Glomerular filtration rate (<=30 ml/min/ 31-50 ml/min/ <=50 ml/min/ >50 ml/min), ESA (Yes/no), RBC transfusion (Yes/No), Response (CR/PR/Early CR/Late CR). Distributions were estimated with use of the Kaplan–Meier method. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model. Subgroup analysis of TTP according to ESA (Yes/no) was a post-hoc analysis. For others, information on whether analyses were prespecified or post-hoc is not reported. The validity of subgroup analysis including statistical power is not reported. For response rate, subgroup analysis was performed by Glomerular filtration rate (<=30 ml/min/ 31-50 ml/min/ <=50 ml/min/ >50 ml/min). Response rates were compared between groups based on a stratified Cochran–Mantel–Haenszel chi-square test. Treatment differences were tested at a two-sided alpha level of 0.05. Information on whether analyses were prespecified or post-hoc is not reported. The validity of subgroup analysis including statistical power is not reported.		

9.2.6 SWOG S0777

Despite of not fully complying to the population inclusion criteria, this study has been included due to an overlapping patient population (TIE patients) and since this is the only study evaluating BorLenDex in the NDMM patient population.

TABLE 57: SWOG S0777 MAIN STUDY CHARACTERISTICS

Trial name	**SWOG S0777**
Clinical trial ID	**NCT00644228**
Objective	We hypothesized that the addition of bortezomib to lenalidomide and dexamethasone would provide better response rates and improve progression-free survival. This report is the first prospective randomized phase 3 trial of the three-drug combination bortezomib, lenalidomide, and dexamethasone versus the two drug combination lenalidomide and dexamethasone in newly diagnosed myeloma without intent for immediate autologous stem-cell transplantation (ASCT)
Publications – author, title, journal, year	**Main publication** Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519–527 (20).
Study type and design	Interventional (Clinical Trial) Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)
Follow-up time	Overall median follow-up: 55 months (Durie et al. 2017) (20) Data is presented in the EPAR assessment report with a data cut-off of 01. Dec 2016. The median follow-up (based on Kaplan-Meier estimate) for all surviving subjects was 69 months (6). Additional data is presented in the EPAR assessment report with a data cut-off of 15 May 2018. The median follow-up (based on Kaplan-Meier estimate) for all surviving subjects was 84.2 months (6).
Population (inclusion and exclusion criteria)	Inclusion criteria • Patients must have newly diagnosed multiple myeloma with measurable disease; patients with non-secretory multiple myeloma (MM) based upon standard M-component criteria (i.e., measurable serum/urine M-component) are not eligible for this study; exception: patients with non-secretory MM will be eligible only if the baseline serum Freelite is elevated (Note that serum Freelite must be drawn; serum light chains are not acceptable); all tests for establishing baseline disease status must be completed within 28 days prior to registration and documented on the baseline and follow-up tumor assessment form for multiple myeloma • Patients must have received no prior chemotherapy for this disease; patients must have received no prior radiotherapy to a large area of the pelvis (more than half of the pelvis); prior steroid treatment is allowed provided treatment was not more than 2 weeks in duration; patients must not have received any prior treatment with bortezomib or lenalidomide • Patients must have a Zubrod performance status (PS) of 0 - 3; NOTE: patients with PS 3 are eligible only if it is documented by the treating physician that the patient's multiple myeloma is the central cause of his/her disability; patients who have a PS of 3 due to other concurrent medical conditions are not eligible for this trial • Platelet count >= 80 x 10^3/mcL; must be obtained within 28 days prior to registration; exception: patients with biopsy-proven heavy-marrow involvement, as defined by having at least 30% marrow cellularity, with > 50% of the cells being malignant plasma cells (documented marrow results required); in this case, although there are no required lower limits of normal for the blood counts, the treating physician must use his/her medical judgment as to the appropriateness of this study therapy for these patients • Absolute neutrophil count (ANC) >= 1 x 10^3/mcL; must be obtained within 28 days prior to registration; exception: patients with biopsy-proven heavy-marrow involvement, as defined by having at least 30% marrow cellularity, with > 50% of the cells being malignant plasma cells (documented marrow results required); in this case, although there are no required lower limits of normal for the blood counts, the treating physician must use his/her medical judgment as to the appropriateness of this study therapy for these patients • Hemoglobin (including patients who have been either transfused or treated with erythropoietin (44)) >= 9 g/dL; must be obtained within 28 days prior to registration; exception: patients with biopsy-proven heavy-marrow involvement, as defined by having at least 30% marrow cellularity, with > 50% of the cells being malignant plasma cells (documented marrow results required); in this case, although there are no required lower limits of normal for the blood counts, the treating physician must use his/her medical judgment as to the appropriateness of this study therapy for these patients • Patients must be offered participation in the Myeloma Specimen Repository for banking and future research; with the patient's consent, bone marrow aspirates and serum specimens will be submitted to the Myeloma Specimen Repository for additional testing and banking (including SNP testing); patient consent must be obtained before specimens may be submitted

<table>
<tr><td></td><td>

Patients must have baseline skeletal survey to include lateral skull, anterior-posterior (AP) pelvis and posterior-anterior (PA) chest within 28 days prior to registration
Institutions must submit a local cytogenetics report and fluorescence in situ hybridization (FISH) analysis report obtained prior to enrollment to S0777; for FISH analysis two probes will be utilized: LSI 13 (RBI) 13q14 SpectrumOrange Probe for detection of chromosome 13 deletion and LSI p53 (17p13.1) SpectrumOrange probe for detection of tumor protein (p)53 locus on chromosome 17; if these exact probes are not available locally, it is acceptable to submit results using local protocol; this must be noted on the prestudy form; NOTE: it is not required that the results of the FISH analysis be known prior to registration, only that pre-registration specimens be drawn and sent for analysis prior to registration, and the FISH analysis report be submitted
Patients with pathologic fractures, pneumonia at diagnosis or symptomatic hyperviscosity must have these conditions attended to prior to registration (i.e., intramedullary rod, I.V. antibiotics, plasmapheresis)
Patients must have a calculated or measured creatinine clearance > 30 cc/min; measured creatinine clearance or serum creatinine used in calculation must be obtained within 28 days prior to registration

Exclusion critera

Patients must not have uncontrolled, active infection requiring intravenous antibiotics, New York Heart Association (NYHA) class III or class IV heart failure, myocardial infarction within the last 6 months, history of treatment for clinically significant ventricular cardiac arrhythmias, poorly controlled hypertension, or poorly controlled diabetes mellitus; patients must have undergone an electrocardiogram (EKG) within 28 days prior to registration
Patients must not have any psychiatric illness that could potentially interfere with the completion of treatment according to this protocol
Patients must not be hepatitis B, hepatitis C or human immunodeficiency virus (HIV) positive; patients must have a negative hepatitis B and HIV test performed within 28 days prior to registration; exception: treatment-sensitive HIV infection patients will be eligible provided that immunological and virologic indices are indicative of favorable long-term survival prospects on the basis of HIV infection, but whose life expectancy is limited predominantly by multiple myeloma rather than HIV infection in the judgment of the treating physician
Patients must not have a history of cerebral vascular accident with persistent neurologic deficits
Patients must be able to take aspirin 325 mg daily (or enoxaparin 40 mg subcutaneously (36) daily if patient is unable to take aspirin) as prophylactic anticoagulation; exception: patients receiving anticoagulation therapy such as Coumadin or heparin will NOT receive aspirin, and therefore need not be able to take it
Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 - 14 days and again within 24 hours prior to starting cycle 1 of lenalidomide; further, they must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control: one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting lenalidomide; FCBP must also agree to ongoing pregnancy testing; men must agree to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy; a FCBP is a sexually mature woman who: has not undergone a hysterectomy or bilateral oophorectomy; or has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months); all patients must be counseled by a trained counselor every 28 days about pregnancy precautions and risks of fetal exposure
No prior malignancy is allowed except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer or other cancer for which the patient has been disease-free for five years
Patients must be offered participation in gene expression profiling (GEP) molecular studies for the evaluation of genetic polymorphisms
All patients must be informed of the investigational nature of this study and must sign and give written consent in accordance with institutional federal guidelines
At the time of patient registration, the treating institution's name and identification (ID) number must be provided to the statistical center in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base

</td></tr>
<tr><td>Intervention</td><td>Experimental arm (dexamethasone, lenalidomide, bortezomib)
Patients receive dexamethasone PO QD on days 1, 2, 4, 5, 8, 9, 11, and 12; lenalidomide PO QD on days 1-14; and bortezomib IV over 3-5 seconds on days 1, 4, 8, and 11. Treatment repeats every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity.
Comparator arm: (dexamethasone and lenalidomide)

Patients receive dexamethasone PO QD on days 1, 8, 15, and 22 and lenalidomide PO QD on days 1-21. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics based on Durie et al 2017
<table>
<tr><td></td><td>BorLenDex</td><td>LenDex</td></tr>
<tr><td>N</td><td>264</td><td>261</td></tr>
<tr><td>Age ≥65 years</td><td>93/242 (38%)</td><td>109/229 (48%)</td></tr>
<tr><td>Female</td><td>89/242 (37%)</td><td>107/229 (47%)</td></tr>
<tr><td>Intent to transplant</td><td>168/242 (69%)</td><td>156/229 (68%)</td></tr>
<tr><td>ECOG performance status > 1</td><td>28/242 (12%)</td><td>36/229 (16%)</td></tr>
<tr><td>International Staging System stage III</td><td>78/242 (32%)</td><td>79/229 (34%)</td></tr>
<tr><td>Albumin concentration <3·5 g/dL</td><td>98/239 (41%)</td><td>99/227 (44%)</td></tr>
<tr><td>Haemoglobin concentration <10 g/dL</td><td>79/242 (33%)</td><td>72/229 (31%)</td></tr>
</table>
</td></tr>
</table>

Platelet count <150 × 10^9/L	11/241 (5%)	10/228 (4%)
Creatinine concentration ≥2 mg/dL	11/242 (5%)	11/229 (5%)

Baseline characteristics based on EPAR (CSR) (6)

Table 5 : Demographic Characteristics as of 1 Dec 2016 (ITT Population-Study SWOG S0777)

Parameter	RVd (N = 263)	Rd (N = 260)	Total (N = 523)
Age (years)			
Median	63.0	63.0	63.0
Min, Max	35.0, 85.0	28.0, 87.0	28.0, 87.0
Age Group 1 (years), n (%)			
≤ 65	167 (63.5)	150 (57.7)	317 (60.6)
> 65	96 (36.5)	110 (42.3)	206 (39.4)
Age Group 2 (years), n (%)			
≤ 65	167 (63.5)	150 (57.7)	317 (60.6)
> 65 and ≤ 75	68 (25.9)	85 (32.7)	153 (29.3)
> 75	28 (10.6)	25 (9.6)	53 (10.1)
Sex, n (%)			
Male	164 (62.4)	137 (52.7)	301 (57.6)
Female	99 (37.6)	123 (47.3)	222 (42.4)
Race Group, n (%)			
Caucasian	210 (79.8)	207 (79.6)	417 (79.7)
Non-Caucasian	46 (17.5)	47 (18.1)	93 (17.8)
Unknown	7 (2.7)	6 (2.3)	13 (2.5)

ITT = intent to treat; Max = maximum; Min = minimum; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.
Data cutoff date = 1 Dec 2016.

Table 6 : Baseline Clinical Characteristics as of 1 Dec 2016 (ITT Population-Study SWOG S0777)

Parameter	RVd (N = 263)	Rd (N = 260)	Total (N = 523)
ISS Stage, n (%)			
I	78 (29.7)	75 (28.8)	153 (29.3)
II	99 (37.6)	98 (37.7)	197 (37.7)
III	86 (32.7)	87 (33.5)	173 (33.1)
Revised ISS Stage, n (%)			
I	54 (20.5)	55 (21.2)	109 (20.8)
II	155 (58.9)	161 (61.9)	316 (60.4)
III	26 (9.9)	23 (8.8)	49 (9.4)
Missing	28 (10.6)	21 (8.1)	49 (9.4)
Intent to Transplant at Progression (Stratification Factor), n (%)			
No	81 (30.8)	81 (31.2)	162 (31.0)
Yes	182 (69.2)	179 (68.8)	361 (69.0)
Cytogenetic Risk, n (%)			
High[a]	30 (11.4)	36 (13.8)	66 (12.6)
Not High	210 (79.8)	207 (79.6)	417 (79.7)
Missing[b]	23 (8.7)	17 (6.5)	40 (7.6)
Frailty Group, n (%)			
Not Frail	206 (78.3)	188 (72.3)	394 (75.3)
Frail	56 (21.3)	72 (27.7)	128 (24.5)
Missing	1 (0.4)	0 (0.0)	1 (0.2)
Frailty and Age Group, n (%)			
Age ≤ 65 years and Not Frail	142 (54.0)	120 (46.2)	262 (50.1)
Age > 65 years and/or Frail	121 (46.0)[c]	140 (53.8)	261 (49.9)[c]
Performance Status (ECOG) Category 1, n (%)			
0 - Fully active	106 (40.3)	101 (38.8)	207 (39.6)
1 - Restricted activity	128 (48.7)	120 (46.2)	248 (47.4)
2 - No work, ambulatory	19 (7.2)	32 (12.3)	51 (9.8)
3 - Limited self-care	10 (3.8)	7 (2.7)	17 (3.3)
Creatinine Clearance Group 1, n (%)			
< 60 mL/min	78 (29.7)	79 (30.4)	157 (30.0)
≥ 60 mL/min	185 (70.3)	180 (69.2)	365 (69.8)
Missing	0 (0.0)	1 (0.4)	1 (0.2)
Creatinine Clearance Group 2, n (%)			

< 50 mL/min	46 (17.5)	45 (17.3)	91 (17.4)
≥ 50 mL/min	217 (82.5)	214 (82.3)	431 (82.4)
Missing	0 (0.0)	1 (0.4)	1 (0.2)
Hemoglobin Group, n (%)			
< 10 g/dL	89 (33.8)	76 (29.2)	165 (31.5)
≥ 10 g/dL	174 (66.2)	184 (70.8)	358 (68.5)
B2 Microglobulin Group, n (%)			
≤ 5.5 mg/L	176 (66.9)	174 (66.9)	350 (66.9)
> 5.5 mg/L	85 (32.3)	84 (32.3)	169 (32.3)
Missing	2 (0.8)	2 (0.8)	4 (0.8)
Lactate Dehydrogenase Group, n (%)			
Not High (LDH ≤ 280 IU/L and not	214 (81.4)	224 (86.2)	438 (83.7)
High (LDH > 280 IU/L)	44 (16.7)	32 (12.3)	76 (14.5)
Missing	5 (1.9)	4 (1.5)	9 (1.7)
Albumin Group, n (%)			
≤ 35 g/L	128 (48.7)	129 (49.6)	257 (49.1)
> 35 g/L	135 (51.3)	128 (49.2)	263 (50.3)
Missing	0 (0.0)	3 (1.2)	3 (0.6)

ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; ITT = intent to treat; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; t(4;14) = translocation involving chromosomes 4 and 14; t(14;16) = translocation involving chromosomes 14 and 16.
a High Risk: t(4;14), t(14;16) or del(17p).
b Cytogenetic risk assessment was not required by the protocol.
c One subject in the RVd arm with a missing frailty is counted in the category age > 65 years and/or frail.
Data cutoff date = 1 Dec 2016.

Primary and secondary endpoints

Primary endpoint

- Progression-free Survival [Time Frame: From date of registration to date of first documentation of progression or symptomatic deterioration, or death due to any cause, assessed up to 6 years]
  - Unstratified median progression-free survival in months.

Secondary endpoint

- Overall Survival [Time Frame: Up to 6 years]
  - Unstratified median overall survival in months.
- Response Rates () [Time Frame: Up to 6 years]
  - The response rate was calculated as the number of patients with documented confirmed partial response (PR) or better, which includes confirmed/unconfirmed stringent complete response (sCR), confirmed/unconfirmed complete response (CR), confirmed/unconfirmed very good partial response (VGPR), or confirmed partial response (PR), as best response divided by the total number of evaluable patients, in each arm. Patients with measurable disease, as defined in the protocol, are evaluable. Response rates were compared between the two treatment arms using a stratified Cochran-Mantel-Haenszel test. Response designations were based on the International Uniform Response Criteria for Multiple Myeloma. Due to the complexity of these criteria, the details of these criteria have been omitted.

Method of analysis

The sample size was based on the assumption of an eligible patient accrual rate of 110 patients per year (440 eligible patients over 4 years), a median progression-free survival of about 3 years in the control group, exponential distribution of progression-free survival, and roughly 2·5 years of additional follow up. The study was designed to detect a hazard ratio of 1·5, with approximately 87% power and an overall study alpha of 0·05. Thus, to allow for an interim analysis, a one-sided 0·02 significance level was used to assess the primary progression-free survival endpoint. The primary endpoint was evaluated with the use of a group-sequential design, with two planned interim analyses at 1/3 and 2/3 of the total number of events. A Haybittle–Peto approach was used for alpha spending and a one-sided alpha of 0·0025 was used for each interim analysis. At the final analysis, a one-sided stratified log-rank test was done at the 0·02 significance level for an overall one-sided alpha of 0·025. We compared progression-free survival and overall survival between treatment groups using a log-rank test stratified according to the factors used for randomisation. Hazard ratios were estimated by means of a stratified Cox proportional-hazards model. The multivariate analysis were done with a model that was not stratified by, rather adjusted for stratification factors, to provide some idea as to how the stratification factors were associated with outcome. We used the Kolmogorov-Smirnov test to assess assumptions of proportional hazards. There was no evidence of violation of proportional hazards for any of the covariates. Survival curves were based on the Kaplan-Meier method. We compared the overall response rate between groups using a stratified Cochran-Mantel-Haenszel test. The odds ratio and corresponding 95% confidence interval were

	estimated with the use of the Mantel-Haenszel method. Duration of response was summarised by means of the Kaplan-Meier method. All primary and secondary endpoint analyses were predefined within the protocol. Analyses were done on an intention to treat basis that incorporated all eligible patients. Patients with missing parameters of interest were excluded from multivariate analyses. We used SAS (version 4) for all analyses. Baseline variables were compared using Fisher's exact test. The safety analysis included all eligible patients who received at least one dose of study treatment and who were evaluated for toxic effects.
Subgroup analyses	NA

9.3 List of excluded studies

A list of studies that were excluded at full-text screening is presented below in Table 58.

TABLE 58: LIST OF EXCLUDED STUDIES AT FULL-TEXT STAGE

Source	Study ID	Title	Reason for exclusion
PubMed	20739218	Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators?	INTERVENTION OUT OF SCOPE
PubMed	26500339	Sequential vs alternating administration of VMP and Rd in elderly patients with newly diagnosed MM	INTERVENTION OUT OF SCOPE
PubMed	31327689	Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomized, open-label, phase 3 trial	INTERVENTION OUT OF SCOPE
PubMed	31701481	Elotuzumab plus lenalidomide and dexamethasone for newly diagnosed multiple myeloma: a randomized, open-label, phase 2 study in Japan.	INTERVENTION OUT OF SCOPE
PubMed	26729895	Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma.	INTERVENTION OUT OF SCOPE
PubMed	31141632	Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma.	INTERVENTION OUT OF SCOPE
PubMed	31771382	Clinical outcomes with fixed-duration therapy (UK real-world data) compared with continuous lenalidomide and low-dose dexamethasone therapy (FIRST trial; MM-020) for transplant-ineligible patients with newly-diagnosed multiple myeloma	PUBLICATION TYPE OUT OF SCOPE
PubMed	30606791	Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation: a network meta-analysis	PUBLICATION TYPE OUT OF SCOPE
PubMed	31765002	Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in adults with transplant-ineligible multiple myeloma: a network meta-analysis	PUBLICATION TYPE OUT OF SCOPE
PubMed	31248973	First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients: a pooled analysis of two randomized trials	PUBLICATION TYPE OUT OF SCOPE
PubMed	28017406	Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial	POPULATION OUT OF SCOPE
PubMed	26518211	Phase 3 trial of three thalidomide-containing regimens in patients with newly diagnosed multiple myeloma not transplant-eligible	INTERVENTION OUT OF SCOPE
Cochrane	CN-00625431	Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma	POPULATION OUT OF SCOPE

		(NDMM): results of the randomized, double-blinded, placebo-controlled SWOG trial S0232	
Cochrane	CN-00643527	A randomized Southwest Oncology Group study comparing dexamethasone (D) to lenalidomide + dexamethasone (LD) as treatment of newly-diagnosed multiple myeloma (NDMM): impact of cytogenetic abnormalities on efficacy of LD, and updated overall study results	OUTCOMES OUT OF SCOPE

Appendix B – Secondary SLR

9.4 Search syntax and hits

The syntaxes below were run in Medline and CENTRAL via Cochrane. The adjusted syntaxes were based on the provided syntaxes by the Medicines Council (9) which used broader inclusion criteria. This means that this search was not limited solely to the combination treatments DaraBorMelPred, BorMelPred, LenDex and BorLenDex. This broader search would ensure that all relevant trials in the indication of NDMM with TIE patients would be captured.

Please note that these searches have been adjusted on date (limited from 25th of October 2018 to 27th of February 2020) as described in 4.1.4. Additionally, the Cochrane search has been adjusted on indication (TIE specifically). This was not done in the initial Danish search strategy conducted by the Medicines Council since the search was covering the whole therapeutic area (multiple lines of treatment and different patient populations). Setting date limits was done manually in Cochrane as this is a feature in the search engine. The date limit was performed in the end of the syntax. As a result, the following text was presented at line 31: *with Publication Year from 2018 to 2020, with Cochrane Library publication date from Oct 2018 to Mar 2020, in Trials*.

TABLE 59: SEARCH SYNTAX MEDLINE

#	Search terms	Search hits
1	exp Multiple Myeloma/	40779
2	(myeloma$ or ndmm$ or ((kahler or kahler's or kahler$) adj1 (disease or morbus))).ti,ab,kf.	54006
3	1 or 2	61128
4	Bortezomib/	5579
5	(bortezomib$ or velcade$ or mg-341$ or mg341$ or mln-341$ or mln341$ or ldp-341$ or ldp341$ or PS341$ or PS341$).ti,ab,kf.	8174
6	4 or 5	9015
7	Lenalidomide.nm.	2591
8	(lenalidomid$ or revlimid$ or revimid$ or cc-5013$ or cc5013$ or cdc-501$ or cdc-5013$ or cdc501$ or cdc5013$ or enmd-0997$ or enmd0997$ or imid-3$ or imid3$).ti,ab,kf.	4266
9	7 or 8	4633
10	exp Melphalan/	7718
11	(melphalan$ or melphelan$ or melphalon$ or melfalan$ or medphalan$ or merphalan$ or sarcolysin$ or sarkolysin$ or alkeran$ or phenylalanine mustard).ti,ab,kf.	8336
12	10 or 11	11090
13	Daratumumab.nm.	277
14	(daratumumab$ or darzalex$ or humax cd38$).ti,ab,kf.	568
15	13 or 14	619
16	exp Dexamethasone/	51112
17	(dexametason$ or dexamethason$ or Adexon$ or Aeroseb-dex$ or Aphthasolone$ or Decaderm$ or Decadron$ or Decaject$ or Decameth$ or Decaspray$ or Dectancyl$ or Degabina$ or Dexabion$ or Dexacen$ or Dexacort$ or Dexafarm$ or Dexafree$ or Dexair$ or Dexalaf$ or Dexalergin$ or Dexameral$ or Dexamonozon$ or Dexapos$ or Dexa-Rhinospray$ or Dexa-sine$ or Dexason$ or Dexatotal$ or Dexone$ or dexpak$ or Dexsol$ or Dropodex$ or Flourmethylprednisolone$ or Fortecortin$ or Gammacorten$ or Hexadecadrol$ or Hexadrol$ or Isopto-Dex$ or Loverine$ or Luxazone$ or Martapan$ or Maxidex$ or Maxitrol$ or Methylfluorprednisolone$ or Millicorten$ or Monopex$ or Neofordex$ or Oradexon$ or Ozurdex$ or Sofradex$ or Superprednol$ or Visumetazone$).ti,ab,kf.	58390
18	16 or 17	72875
19	Carfilzomib.nm.	458
20	(carfilzomib$ or kyprolis$ or pr-171$ or pr171$).ti,ab,kf.	970

21	19 or 20	1033
22	Pomalidomide.nm.	380
23	(pomalidomid$ or cc4047$ or cc-4047$ or imnovid$ or pomalyst$ or actimid$).ti,ab,kf.	704
24	22 or 23	758
25	Thalidomide/	8853
26	(thalidomid$ or sedoval$ or thalomid$ or contergan$ or distaval$ or isomin$ or kedavon$ or kevadon$ or neurosedin$ or neurosedyne$ or nsc 66847$ or nsc66847$ or sedalis$ or softenon$ or synovir$ or talimol$ or talizer$ or telaga$n or telargan$ or thado??? or thalimodide$ or thalix$).ti,ab,kf.	8123
27	25 or 26	11476
28	exp Cyclophosphamide/	53346
29	(cyclophosphamid$ or cytophosphan$ or cyclophosphan$ or endoxan$ or enduxan$ or neosar$ or procytox$ or sendoxan$ or cytoxan$ or alkyroxan$ or carloxan$ or ciclofosfamid$ or ciclolen$ or cicloxal$ or clafen$ or cyclo-cell$ or cycloblastin$ or cyclophar$ or cyclostin$ or cycloxan$ or cyphos$ or genoxal$ or ledoxan$ or ledoxina$ or mitoxan$ or neosan$ or noristan$ or procytoxide$ or semdoxan$ or syklofosfamid$ or nsc26271$ or nsc-26271$ or nsc-2671$ or nsc2671$ or B518$ or B-518$).ti,ab,kf.	54920
30	28 or 29	78914
31	exp Prednisone/	39191
32	(prednison$ or dehydrocortison$ or delta-cortison$ or rectodelt$ or sterapred$ or ultracorten$ or winpred$ or cortan$ or panafcort$ or cutason$ or decortin$ or dacortin$ or decortisyl$ or deltason$ or encorton$ or enkortolon$ or kortancyl$ or liquid-pred$ or meticorten$ or orison$ or panasol$ or predni-tablinen$ or prednidib$ or predniment$ or pronison$ or sone$).ti,ab,kf.	29558
33	31 or 32	53707
34	Prednisolone/	32687
35	(prednisolon$ or predate$ or predonin$ or di-adreson-f$ or diadresonf$).ti,ab,kf.	31238
36	34 or 35	49316
37	Elotuzumab.nm.	115
38	(elotuzumab$ or empliciti$ or huluc63$ or pdl 063$ or pdl063$).ti,ab,kf.	245
39	37 or 38	274
40	Ixazomib.nm.	141
41	(ixazomib$ or mln9708$ or mln-9708$ or mln-2238$ or mln2238$ or ninlaro$).ti,ab,kf.	346
42	40 or 41	364
43	Panobinostat.nm.	499
44	(panobinostat$ or farydak$ or lbh589$ or lbh-589$ or nvp-lbh589$).ti,ab,kf.	823
45	43 or 44	883
46	exp Doxorubicin/	56264
47	(doxorubicin$ or dox#rubin$ or dexorubicin$ or adrubicin$ or amminac$ or farmiblastina$ or ribodoxo$ or rubex$ or adriacin$ or adriamycin$ or adriamicin$ or adriblastin$ or adriablastin$ or adrimedac$ or doxocell$ or doxolem$ or doxotec$ or myocet$ or onkodox$ or cael#x$ or carcinocin$ or dox-sl$ or doxil$ or doxolem$ or doxor lyo$ or doxil$ or evacet$ or fi-106$ or fi106$ or ifadox$ or lipodox$ or mcc-465$ or mcc465$ or nsc-123127$ or nsc123127$ or rastocin$ or resmycin$ or rp-25253$ or rp25253$ or rubidox$ or sarcodoxome$ or tlc-d-99$).ti,ab,kf.	58711
48	46 or 47	77720
49	6 or 9 or 12 or 15 or 18 or 21 or 24 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48	305365
50	3 and 49	12912
51	exp animals/ not humans/	4701352
52	50 not 51	12674
53	randomized controlled trial.pt.	506268
54	controlled clinical trial.pt.	93688
55	randomi?ed.ab.	575092
56	placebo.ab.	208034
57	clinical trials as topic/	191315
58	randomly.ab.	333912
59	trial.ti.	218930

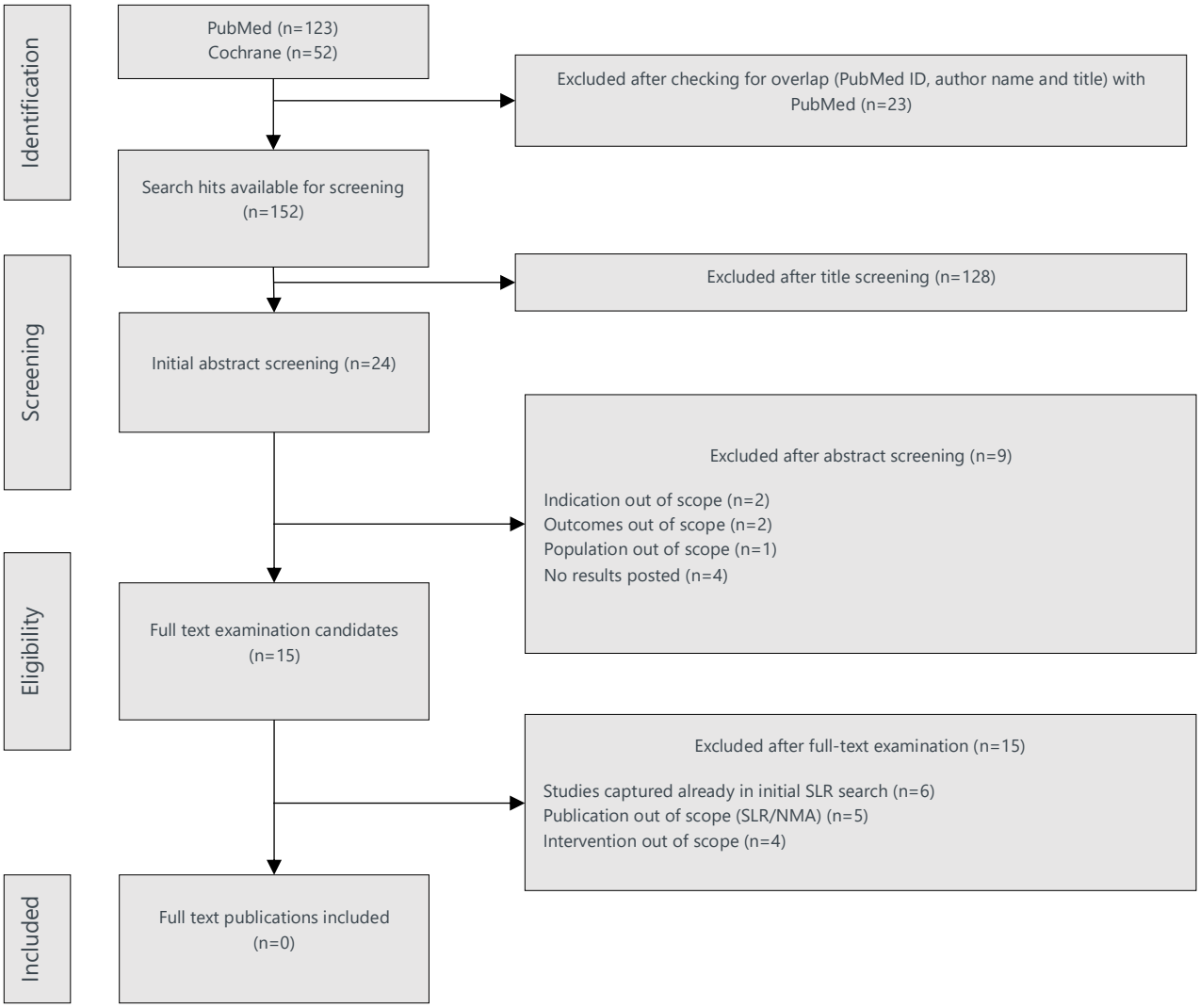
60	or/53-59	1326506
61	52 and 60	1883
62	(systematic review or systematic literature review or drug class review or meta synthesis or meta-analy$ or metaanaly$).ti. or this systematic review.ab. or (systematic review.ab. and review.pt.)	215328
63	(practice guideline or guideline or meta-analysis).pt. or (clinical guideline.ti,ab. and review.pt.)	149234
64	(cochrane database of systematic reviews or health technology assessment winchester england or evidence report technology assessment summary or "jbi database of systematic reviews and implementation reports").jn.	17356
65	limit 52 to systematic reviews	80
66	or/62-65	285192
67	limit 66 to dt=20181025-20200226 [October 25th, 2018 to February 26th, 2020]	42986
68	52 and 67	24
69	61 or 68	1895
70	remove duplicates from 69	1886
71	limit 70 to (danish or english or norwegian or swedish or italian or french or german or spanish)	1811
72	limit 71 to dt=20181025-20200226 [October 25th, 2018 to February 26th, 2020]	**123**

TABLE 60: SEARCH SYNTAX COCHRANE

#	Cochrane Search	Hits
1	[mh "Multiple Myeloma"]	1544
2	(myeloma* or ndmm* or ((kahler or kahler's or kahler*) next (disease or morbus))):ti,ab,kw	5188
3	(novo* or first* AND line* OR naive* or first-line* or newly diagnosed* or frontline* or front* AND line* or front-line* or untreated* or ndmm* or newly diagnosed mm*, or newly diagnosed multiple myeloma*):ti,ab,kw	77154
4	(transplant AND ineligible* or TIE* or ASCT* AND ineligible* or autologous* AND stem* AND cell* AND transplant* AND ineligible* or autologous* AND stem-cell* transplant* AND ineligible*):ti,ab,kw	11165
5	{or #1-#2} AND #3 AND #4	653
6	[mh Bortezomib]	423
7	(bortezomib* or velcade* or mg-341* or mg341* or mln-341* or mln341* or ldp-341* or ldp341* or PS341* or PS341*):ti,ab,kw	1875
8	(lenalidomide* or revlimid* or revimid* or cc-5013* or cc5013* or cdc-501* or cdc-5013* or cdc501* or cdc5013* or enmd-0997* or enmd0997* or imid-3* or imid3*):ti,ab,kw	1858
9	[mh Melphalan]	695
10	(melphalan* or melphalan* or melphalon* or melfalan* or medphalan* or merphalan* or sarcolysin* or sarkolysin* or alkeran* or "phenylalanine mustard" *):ti,ab,kw	0
11	(daratumumab* or darzalex* or "humax cd38" *):ti,ab,kw	0
12	[mh Dexamethasone]	4409
13	(dexametason* or dexamethason* or Adexon* or Aeroseb-dex* or Aphthasolone* or Decaderm* or Decadron* or Decaject* or Decameth* or Decaspray* or Dectancyl* or Degabina* or Dexabion* or Dexacen* or Dexacort* or Dexafarm* or Dexafree* or Dexair* or Dexalaf* or Dexalergin* or Dexameral* or Dexamonozon* or Dexapos* or Dexa-Rhinospray* or Dexa-sine* or Dexason* or Dexatotal* or Dexone* or dexpak* or Dexsol* or Dropodex* or Flourmethylprednisolone* or Fortecortin* or Gammacorten* or Hexadecadrol* or Hexadrol* or Isopto-Dex* or Loverine* or Luxazone* or Martapan* or Maxidex* or Maxitrol* or Methylfluorprednisolone* or Millicorten* or Monopex* or Neofordex* or Oradexon* or Ozurdex* or Sofradex* or Superprednol* or Visumetazone*):ti,ab,kw	11333
14	(carfilzomib* or kyprolis* or pr-171* or pr171*):ti,ab,kw	321
15	(pomalidomid* or cc4047* or cc-4047* or imnovid* or pomalyst* or actimid*):ti,ab,kw	300
16	[mh Thalidomide]	849

17	(thalidomide* or sedoval* or thalomid* or contergan* or distaval* or isomin* or kedavon* or kevadon* or neurosedin* or neurosedyne* or nsc-66847* or nsc66847* or sedalis* or softenon* or synovir* or talimol* or talizer* or telagan* or telargan* or thado* or thalimodide* or thalix*):ti,ab,kw	1749
18	[mh Cyclophosphamide]	5403
19	(cyclophosphamid* or cytophosphan* or cyclophosphan* or endoxan* or enduxan* or neosar* or procytox* or sendoxan* or cytoxan* or alkyroxan* or carloxan* or ciclofosfamid* or ciclolen* or cicloxal* or clafen* or cyclo-cell* or cycloblastin* or cyclophar* or cyclostin* or cycloxan* or cyphos* or genoxal* or ledoxan* or ledoxina* or mitoxan* or neosan* or noristan* or procytoxide* or semdoxan* or syklofosfamid* or nsc26271* or nsc-26271* or nsc-2671* or nsc2671* or B518* or B-518*):ti,ab,kw	12933
20	[mh Prednisone]	3909
21	(prednisolon* or predate* or predonin* or di-adreson-f* or diadresonf*):ti,ab,kw	7041
22	(elotuzumab* or empliciti* or huluc63* or pdl-063* or pdl063*):ti,ab,kw	108
23	(ixazomib* or mln9708* or mln-9708* or mln-2238* or mln2238* or ninlaro*):ti,ab,kw	167
24	(panobinostat* or farydak* or lbh589* or lbh-589* or nvplbh589* or nvp-lbh589*):ti,ab,kw	104
25	[mh Doxorubicin]	4728
26	(doxorubicin* or dox*rubin* or dexorubicin* or adrubicin* or amminac* or farmiblastina* or ribodoxo* or rubex* or adriacin* or adriamycin* or adriamicin* or adriblastin* or adriablastin* or adrimedac* or doxocell* or doxolem* or doxotec* or myocet* or onkodox* or caelyx* or carcinocin* or dox-sl* or doxil* or doxolem* or "doxor lyo" * or doxil* or evacet* or fi-106* or fi106* or ifadox* or lipodox* or mcc-465* or mcc465* or nsc-123127* or nsc123127* or rastocin* or resmycin* or rp-25253* or rp25253* or rubidox* or sarcodoxome* or tlc-d-99*):ti,ab,kw	0
27	{or #6-#26}	1628644
28	#5 and #27	653
29	"conference abstract":pt	153136
30	#28 not #29	332
31	#30	**52**

9.5 PRISMA Flow diagram



9.6 List of excluded studies

Source	Study ID	Title	Reason for exclusion
PubMed	31709875	Relative efficacy of treatment options in transplant-ineligible newly diagnosed multiple myeloma: results from a systematic literature review and network meta-analysis.	PUBLICATION OUT OF SCOPE
PubMed	31765002	Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in adults with transplant-ineligible multiple myeloma: a network meta-analysis. (24)	PUBLICATION OUT OF SCOPE
PubMed	31444819	Daratumumab added to standard of care in patients with newly diagnosed multiple myeloma: A network meta-analysis.	PUBLICATION OUT OF SCOPE
PubMed	30606791	Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation: a network meta-analysis.	PUBLICATION OUT OF SCOPE
PubMed	31130487	Treatment Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Stem-Cell Transplantation: Systematic Review and Network Meta-analysis. (24)	PUBLICATION OUT OF SCOPE
PubMed	31701481	Elotuzumab plus lenalidomide and dexamethasone for newly diagnosed multiple myeloma: a randomized, open-label, phase 2 study in Japan.	CAPTURED ALREADY IN PRIMARY SLR SEARCH
PubMed	31836199	Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial.	CAPTURED ALREADY IN PRIMARY SLR SEARCH
PubMed	31620815	Daratumumab plus bortezomib, melphalan, and prednisone in East Asian patients with non-transplant multiple myeloma: subanalysis of the randomized phase 3 ALCYONE trial.	CAPTURED ALREADY IN PRIMARY SLR SEARCH
PubMed	31327689	Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial.	CAPTURED ALREADY IN PRIMARY SLR SEARCH
PubMed	31141632	Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma.	CAPTURED ALREADY IN PRIMARY SLR SEARCH
PubMed	29150421	Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma	CAPTURED ALREADY IN PRIMARY SLR SEARCH
PubMed	31325152	Report of phase I and II trials of melphalan, prednisolone, and thalidomide triplet combination therapy versus melphalan and prednisolone doublet combination therapy in Japanese patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplantation	INTERVENTION OUT OF SCOPE
PubMed	31515355	Health-related quality of life in transplant ineligible newly diagnosed multiple myeloma patients treated with either thalidomide or lenalidomide-based regimen until progression: a prospective, open-label, multicenter, randomized, phase 3 study.	INTERVENTION OUT OF SCOPE
PubMed	30819926	Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma.	INTERVENTION OUT OF SCOPE
PubMed	30471652	All-oral ixazomib, cyclophosphamide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma.	INTERVENTION OUT OF SCOPE

Appendix C – NMA conducted by applicant

9.7 NMA assumptions

To ensure reliability of an NMA, three assumptions should be met: the homogeneity assumption, the similarity assumption, and the consistency assumption. These are described in the paragraphs below.

9.7.1 Homogeneity Assumption

Homogeneity assumes that there is no significant difference (or if present, it is due to random chance) in treatment effects among studies of the same comparison. In other words, it assumes that all pairwise comparison trials are "comparable" and are estimating the same treatment effect.

Heterogeneity in treatment effects is an indication of the presence of effect-modifying mechanisms—in other words, interactions—between the treatment effect and the trial-level characteristics (45). The I^2-test was applied to indicate whether there was heterogeneity among the studies with the same treatment comparison. The I^2-test formula is as follows:

$$I^2 = 100\% \, x \, (Q - df)/Q$$

Where Q is Cochran's Q (chi-square) which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies; the degree of freedom (df) is the number of studies with a specific treatment comparison. In case there are multiple evidence of a specific treatment comparison present, the results of the I^2-test over this specific treatment comparison will be presented for each endpoint.

Cochrane provides a rough interpretation of an I^2 as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100% considerable heterogeneity

According to Cochrane, when there is heterogeneity that cannot readily be explained, one analytical approach is to incorporate it into a random effects model (46). Therefore, in case of an I^2-test result above 60%, a random effects model will be used. In case of an I^2-test results above 50%, the source of the heterogeneity is further investigated. When 50%-60% heterogeneity is found with significant heterogeneity results, a random effects model might be used. Choice of statistical model will be discussed further in 9.10.1

9.7.2 Similarity Assumption

Similarity assumes there is no bias due to effect modification between the set of trials included in the indirect comparison. Below a list of potential treatment effect modifiers is presented (45):

- Baseline characteristics
- Length of follow-up
- The way in which outcomes are defined/measured
- Dosing protocols

Please note, these variables are not necessarily all effect modifiers. Only those that affect the relative outcome between the active intervention and the placebo intervention are the treatment effect modifiers. A statistical assessment to determine whether a variable is an effect modifier for instance based on the patient level data of the ALCYONE study was not conducted. Only qualitative assessment was conducted for each variable. They are described below.

Baseline Characteristics

Serving as an example, the ALCYONE trial concluded that the subgroup analyses for OS and PFS were consistent over all pre-specified subgroups. Meaning, treatment effect of DaraBorMelPred over BorMelPred was consistent over the tested subgroups. This is an indication that any differences across baseline characteristics over the trials included in the NMA will not have a substantial impact on the relative treatment effect.

Within trial differences

All studies are randomized trials and therefore randomization of patients should be safeguarded. However, differences were noted between the treatment arms within a trial. Table 3 in section 4.4 provides overview of relevant baseline characteristics per included trial in the SLR. Examples of substantial within trial differences based on Table 3 may be:

- IFM 01/01: the proportion of females in the study population
  - 47% in MelPred arm and 62% in the MelPredThal arm
- IFM 99-06: the proportion of females in the study population
  - 34% in MelPred arm and 50% in the MelPredThal arm
- SWOG S0777: the proportion of females in the study population
  - 37% in BorLenDex arm and 47% in LenDex arm

Between trial differences

As Table 3 in section 4.4 also shows, there were differences observed in baseline characteristics between the trials in terms of for example:

- Proportion of female: it varied from 34% in the MelPred arm of IFM 99-06 to 62% in the MelPredThal arm of IFM 01/01

Despite these differences, the impact of potential effect modification is limited, as the trial publications concluded that the findings for HRs of OS and PFS were consistent across subgroups.

Length of Follow-up and Outcome Definition

Length of follow-up impacts the assessment of long-term endpoints (e.g. OS and PFS), and consequently impacts the HR. Therefore, follow-up time might be an effect modifier. Moreover, different definitions of OS may impact the time that is considered as survival. Therefore, the definition of survival (e.g. the starting time from which OS is measured) might also be an effect modifier. The length of follow-up and the outcome definitions used in each trial are presented and discussed in the results section of this report.

Dosing Protocols

Dosing protocols of the treatments over the trials might be prognostic and/or effect modifier for the outcomes considered in this NMA. An overview table of dosing protocols for all treatments is presented in section 9.11, Table 61. However, consistent with other NMAs in NDMM patients who are ineligible for ASCT, it was assumed that heterogeneity in dosing of MP would not affect the output of the NMA (29, 30).

9.7.3 Consistency Assumption

This assumption is needed when both direct and indirect evidence are combined for a pairwise comparison. According to the consistency assumption, there should not be any discrepancy between the direct and the indirect comparisons (the indirect estimate should not be biased) (47). This can only be assessed in the presence of loops of evidence. Due to the absence of loops in the network of evidence, the consistency assumption is not tested in this NMA.

9.8 Missing Data

All the considered studies for the network reported all data for endpoint analyses on OS and PFS and treatment discontinuation due to AEs, except for one study. IFM 99-06, did not include any data on treatment discontinuation due to AEs, and was therefore excluded from this specific analysis.

9.9 Zero Correction Assumption

For endpoints with binomial likelihoods (i.e. discontinuation due to AEs), a zero-event rate would make the interpretation of the NMA results difficult. A zero-event rate means zero response in a treatment arm or both treatment arms, i.e. no discontinuation due to AEs in a treatment arm or both treatment arms. This is specifically challenging in sparse networks, in which there is only one trial making the comparison X versus Y, and treatment Y only appears in this specific trial.

Zero event rates appeared in none of the trials included in this NMA.

9.10 Statistical Programming

The NMAs were conducted within a Bayesian framework. This involves a formal combination of a prior probability distribution reflecting a prior belief of the possible values of the model parameters (priors), and a likelihood distribution of these parameters based on the observed data (48, 49). The prior beliefs that we used were non-informative (i.e. non-informative priors), as we assumed no treatment effect in the base case of the Bayesian framework. All NMAs were performed using both fixed effects (FE) models and random effects (RE) models. All NMAs were conducted in BUGS (WinBUGS, OpenBUGS or MultiBUGS), and the I2-tests were conducted in Cran-R.

9.10.1 Choice of Model

FE models assume that there is no variation in relative treatment effects across studies for a pairwise comparison. FE models give an answer to the question “what is the true treatment effect?”. By contrast, RE models assume that there is a variation in treatment effects across studies (i.e. studies are heterogenous). RE models treat the inputs as a sample from a normal distribution of which the mean is the pooled relative effect and the standard error reflects the heterogeneity. The variance reflecting heterogeneity is assumed to be constant for all pairwise comparisons. RE models give an answer to the following questions: “what is the average of the true treatment effects, and how much do these effects vary across trials?”.

Both FE and RE models were fitted on the available data per endpoint. The goodness of fit was assessed using the deviance information criterion (DIC). The DIC is the sum of the posterior mean of the residual deviance, and the effective number of parameters. The model with the lowest DIC score was considered as the best fit on the data (50). In the case that the differences between the DICs of the FE model and the RE model were very small the FE model was chosen as its results are better interpretable(51) (e.g. FE model resulted in narrower credible intervals (CrI)). The DIC scores and the total residual deviance, which should be approximately around 1 are reported for each datapoint, for both FE and RE models.

All WinBUGS models were retrieved from NICE DSU Technical Support Unit (51). For OS and PFS, a normal likelihood with identity link model was used. Variance of the baseline in the multi-arm trial was estimated and included to adjust for correlation (51, 52). For treatment discontinuation due to AEs-, a binomial likelihood with logit link model was used.

9.10.2 Running Analyses

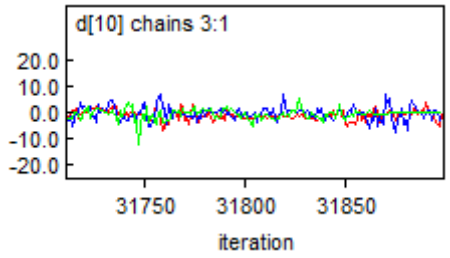
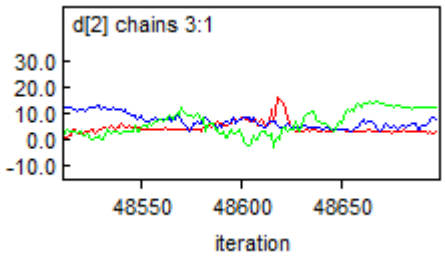
All analyses were performed with 100.000 iterations after a burn-in of 100.000 unless the model and data were not sufficiently converged. Three lines of inits were used in each analysis. These were either set up manually or generated by BUGS.

Diagnostics

To ensure that the results are reliable, the analyses in BUSG were assessed by using a few program build-in diagnostic tools, such as trace, quantiles, auto cor (53). These tools facilitated in face validating the analyses of the parameters mu, d, lhr and lor.

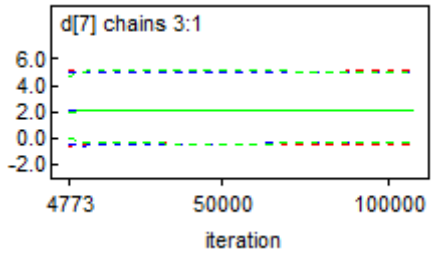
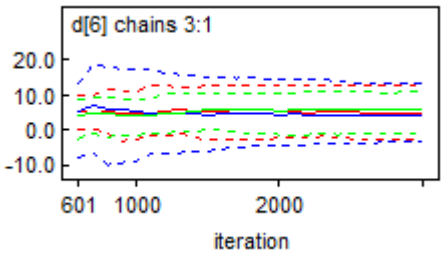
Trace plots the variable value against the iteration number. Although the trace is dynamic, it is supposed to converge around a certain range (53), see Figure 17. In Figure 17A the chains are converging, whereas the chains in Figure 17B are not. The results presented in this NMA report were all based on converged traces.

FIGURE 17: EXAMPLES OF TRACE PLOTS

A. In this example, the three chains of inits for parameter *d[3]* (baseline effect for treatment with label number 3) seem to converge well for this data and model.	**B. In this example, the three chains of inits for parameter *d[10]* (baseline effect for treatment with label number 10) does not seem to converge well for this data and model.**
	

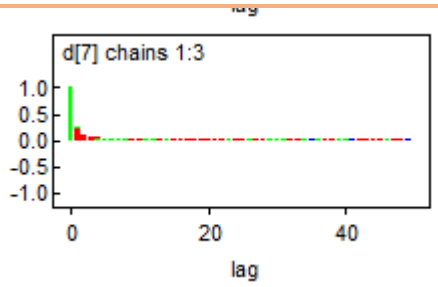
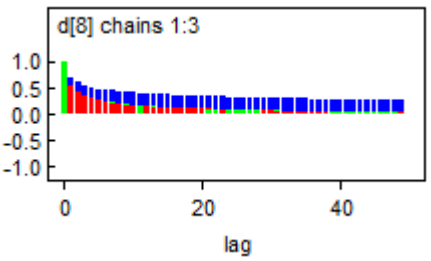
Quantiles plots out the running mean with running 95% CI against iteration number. Quantiles were used as face validation (53), see Figure 18. In Figure 18A the chains are converging, whereas the chains in Figure 18B are not. The results presented in this NMA report were all based on converged quantile plots.

FIGURE 18: EXAMPLES OF QUANTILES PLOTS

A. In this example, the three chains of inits for parameter *d[7]* (baseline effect for treatment with label number 7) seem to converge well for this data and model.	B. In this example, the three chains of inits for parameter *d[6]* (baseline effect for treatment with label number 6) do not seem to converge well for this data and model. This can be explained due to small amount of iterations,
	

Auto cor plots the autocorrelation function of the variable out to lag-50, see Figure 19A shows limited correlation, whereas Figure 19B shows substantial correlation. In case the auto cor-plots show high autocorrelation in the analyses, new analyses were conducted with a higher thin number. Thin is the numeric value used to enable that only every k^{th} iteration (k = thin value) of each chain contributes to the statistic being calculated (53). The results presented in this NMA analysis did not show autocorrelation. In case autocorrelation was present, thin has been used to solve the autocorrelation.

FIGURE 19: EXAMPLES OF AUTO COR PLOTS

A. In this example, the three chains of inits for parameter *d[7]* (baseline effect for treatment with label number 7) show little correlation of effects between the iterations. No need to use *thin.*	B. In this example, the three chains of inits for parameter *d[8]* (baseline effect for treatment with label number 8) show large correlation of effects between the iterations. *Thin* needs to be applied.
	

9.11 Additional tables and figures related to NMA

TABLE 61: DOSING OF IDENTIFIED TREATMENTS PER TRIAL

Trial	Trial arm	Dosing
ALCYONE	Comparator arm (BorMelPred)	Velcade: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9 + Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9 + Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.
	Experimental arm (DaraBorMelPred)	Daratumumab:16 mg/kg as intravenous infusion, once weekly, for 6 weeks in Cycle 1 and then once every 3 weeks, in Cycle 2 to 9 and thereafter, once every 4 weeks + Velcade: 1.3 mg/m^2, as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9 + Melphalan: 9 mg/m^2, orally, once daily on Days 1 to 4 of each cycle up to Cycle 9 + Prednisone: 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9.
FIRST	Comparator arm (MelPredThal)	Melphalan: 0.25 mg/kg/day on days 1 to 4 in 42-day cycles for 72 weeks- 12 cycles + Prednisone: 2 mg/kg/day on days 1 to 4 in 42-day cycles for 72 weeks-12 cycles + Thalidomide: 200 mg/day in 42-day cycles for 72 weeks-12 cycles.
	Experimental arm (LenDex)	Revlimid: 25 mg/day on days 1 to 21 of each 28-day cycles until disease progression + Dexamethasone: 40 mg/day on days 1, 8, 15, and 22 of each 28-day cycles until disease progression.
	Experimental arm (LenDex18)	Revlimid: 25 mg/day on days 1 to 21 of each 28-day cycles for 72 weeks- 18 cycles + Dexamethasone: 40 mg/day on days 1, 8, 15, and 22 of each 28-day cycles for 72 weeks- 18 cycles
IFM 01/01	Comparator arm (MelPred)	12 cycles every 6 weeks: melphalan 0.2 mg/kg day 1 to 4, prednisone 2 mg/kg/d day 1 to 4 plus placebo 100mg/d continuously for 18 months
	Experimental arm (MelPredThal)	Melphalan, prednisone, thalidomide; 12 cycles every 6 weeks: melphalan 0.2 mg/kg day 1 to 4, prednisone 2 mg/kg/d day 1 to 4 plus thalidomide 100mg/d continuously for 18 months
IFM 99/06	Comparator arm (MelPred)	Melphalan: 0.25 mg/kg, Prednisone: 2 mg/kg
	Experimental arm (MelPredThal)	Melphalan: 0.25 mg/kg, Prednisone: 2 mg/kg, Thalidomide: not exceeding 400 mg (Thalidomide was stopped at day 4 of the last melphalan and prednisone cycle)
VISTA	Comparator arm (MelPred)	Melphalan: 9 mg/m² on days 1 to 4, during each of nine 6-week cycles + Prednisone: 60 mg/m² on days 1 to 4, during each of nine 6-week cycles.
	Experimental arm (BorMelPred)	Velcade: Twice weekly during cycles 1 to 4 and once weekly during cycles 5 to 9 (all 6-week cycles) + Melphalan: 9 mg/m² on days 1 to 4, during each of nine 6-week cycles + Prednisone: 60 mg/m² on days 1 to 4, during each of nine 6-week cycles.
SWOG S0777	Comparator arm (LenDex)	Dexamethasone PO QD on days 1, 8, 15, and 22 and lenalidomide PO QD on days 1-21. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.
	Experimental arm (BorLenDex)	Dexamethasone PO QD on days 1, 2, 4, 5, 8, 9, 11, and 12; lenalidomide PO QD on days 1-14; and bortezomib IV over 3-5 seconds on days 1, 4, 8, and 11. Treatment repeats every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity.

9.12 Proportional Hazard Assumption

HR NMAs require proportional hazards. Therefore, for the conducted HR NMAs on OS and PFS, the proportional hazard assumption was assumed to hold. This assumption can be visually assessed by the log cumulative hazard plot (54). In case the lines of the treatments in the log cumulative hazard plots cross, there is an indication that the PH assumption is violated. However, crossing log cumulative hazard plots can also be observed when there is no real treatment benefit. Therefore, in case of crossing log cumulative hazard plots, the Schoenfeld test can additionally be conducted, which quantitatively assesses whether proportional hazard assumption is violated. For both the log cumulative hazard plot and the Schoenfeld test, individual patient level data are required, which are not available at this stage for most trials. Patient level data may be constructed for those trials that reported Kaplan Meier plots of treatment comparisons that showed crossing survival curves, indicating proportional hazard assumption violation.

For the considered trials ALCYONE, VISTA, IFM 01/01, and IFM 99-06, the Kaplan Meier plots did not present crossing curves. Therefore, the proportional hazard assumption was not tested as this was assumed to hold based on visual inspection. Whether the proportional hazard assumption holds were investigated further in the economic submission. However, the Kaplan Meier plots of FIRST presented crossing curves (12, 13). In this case, the proportional hazard assumption appeared to be violated. For OS, the Kaplan Meier curves showed more constant HRs based on visual assessment.

Appendix D – NMA conducted by the Medicines Council

9.13 Analyses results – relative efficacy estimates from NMA, NDMM TIE patients

FIGURE 20: RESULTS FROM NMA CONDUCTED BY THE MEDICINES COUNCIL - OS

Bilag 6: Analyseresultater - relative effektestimater fra netværksmetaanalyserne

Primærbehandling, patienter der ikke er kandidater til HDT/STS

Tabel N: indirekte analyse (hazard ratio) af data for OS, der ligger til grund for netværksmetaanalysen.

OS, HR	BorMelPred	BorMelPredThal + BorThal cont.	LenDex cont.	LenDex	MelPredThal	MelVinDoxDex	MelPred	MelPredThal + Thal cont.
BorMelPred	1							
BorMelPredThal + BorThal cont.	0,7 (0,53; 0,93)*	1						
LenDex cont.	0,73 (0,51; 1,03)	1,04 (0,66; 1,63)	1					
LenDex	0,69 (0,48; 0,98)*	0,98 (0,62; 1,55)	0,95 (0,80; 1,13)	1				
MelPredThal	0,88 (0,65; 1,19)	1,25 (0,82; 1,90)	1,21 (1,02; 1,43)*	1,27 (1,07; 1,51)*	1			
MelVinDoxDex	1,24 (0,88; 1,75)	1,77 (1,13; 2,77)*	1,71 (1,19; 2,46)*	1,81 (1,26; 2,59)*	1,42 (1,03; 1,94)*	1		
MelPred	1,43 (1,16; 1,74)*	2,04 (1,44; 2,88)*	1,97 (1,47; 2,61)*	2,08 (1,54; 2,76)*	1,63 (1,29; 2,04)*	1,15 (0,87; 1,52)	1	
MelPredThal + Thal cont.	1,38 (1,05; 1,79)*	1,96 (1,33; 2,90)*	1,89 (1,35; 2,65)*	2,00 (1,42; 2,80)*	1,57 (1,18; 2,10)*	1,11 (0,79; 1,55)	0,96 (0,81; 1,15)	1

**statistisk signifikant resultat. OS = samlet overlevelse, HR = hazard ratio*

Figure reprinted from: Medicinrådet (2020). Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose). Version 1.2. Bilag 6 tabel N, page 112 (9).

FIGURE 21: RESULTS FROM NMA CONDUCTED BY THE MEDICINES COUNCIL - PFS

Tabel O: indirekte analyse (hazard ratio) af data for PFS, der ligger til grund for netværksmetaanalysen.

PFS, HR	MelPredThal	MelPred	LenDex cont.	LenDex	MelPredLen	MelVinDoxDex	MelPredLen + Len cont.	MelPredThal + Thal cont.
MelPredThal	1							
MelPred	1,71 (1,37; 2,12)*	1						
LenDex cont.	0,84 (0,71; 1,00)	0,49 (0,37; 0,65)*	1					
LenDex	1,04 (0,88; 1,24)	0,61 (0,46; 0,81)*	1,24 (1,04; 1,47)*	1				
MelPredLen	1,58 (1,07; 2,34)*	0,92 (0,67; 1,28)	1,87 (1,23; 2,88)*	1,51 (0,99; 2,33)	1			
MelVinDoxDex	1,56 (1,19; 2,05)*	0,91 (0,71; 1,16)	1,85 (1,34; 2,55)*	1,49 (1,08; 2,06)*	0,99 (0,66; 1,49)	1		
MelPredLen + Len cont.	0,72 (0,49; 1,06)	0,42 (0,30; 0,58)*	0,85 (0,56; 1,31)	0,69 (0,45; 1,06)	0,46 (0,33; 0,63)*	0,46 (0,31; 0,69)*	1	
MelPredThal + Thal cont.	1,27 (0,96; 1,67)	0,74 (0,63; 0,88)*	1,50 (1,09; 2,08)*	1,22 (0,88; 1,68)	0,80 (0,56; 1,16)	0,81 (0,61; 1,10)	1,77 (1,23; 2,54)*	1

**statistisk signifikant resultat. PFS = progressionsfri overlevelse, HR = hazard ratio*

Figure reprinted from: Medicinrådet (2020). Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose). Version 1.2. Bilag 6 tabel O, page 113 (9).

FIGURE 22: RESULTS FROM NMA CONDUCTED BY THE MEDICINES COUNCIL - TREATMENT DISCONTINUATIONS DUE TO AES

Tabel P: indirekte analyse (relativ risiko) af data for beh. Oph., der ligger til grund for netværksmetaanalysen.

Beh.oph. RR	BorMelPred	DaraBorMel Pred+ Dara cont.	LenDex cont.	LenDex	MelPredThal + Thal cont.	MelPredThal	MelPred	BorMelPredThal +Thal cont.	MelPredLen + Len cont.	MelPredLen
BorMelPred	1	1.91 (1.09, 3.46)*	0.36 (0.19, 0.67)*	0.33 (0.18, 0.60)*	0.31 (0.18, 0.52)*	0.32 (0.20, 0.53)*	1.07 (0.74, 1.54)	0.56 (0.40, 0.77)*	0.39 (0.18, 0.78)*	0.47 (0.21, 0.95)*
DaraBorMel Pred+Dara cont.		1	0.19 (0.08, 0.43)*	0.17 (0.07, 0.39)*	0.16 (0.07, 0.34)*	0.17 (0.08, 0.36)*	0.561 (0.28, 1.09)	0.29 (0.15, 0.56)*	0.20 (0.08, 0.49)*	0.24 (0.09, 0.60)*
LenDex cont.			1	0.91 (0.66, 1.25)	0.86 (0.63, 1.17)	0.90 (0.50, 1.62)	2.97 (1.84, 4.88)*	1.54 (0.77, 3.10)	1.08 (0.47, 2.36)	1.29 (0.55, 2.86)
LenDex				1	0.94 (0.70, 1.27)	0.99 (0.55, 1.77)	3.27 (2.05, 5.30)*	1.70 (0.85, 3.40)	1.19 (0.52, 2.57)	1.42 (0.61, 3.10)
MelPredThal + Thal cont.					1	1.05 (0.64, 1.72)	3.46 (2.45, 5.08)*	1.80 (0.98, 3.36)	1.27 (0.59, 2.56)	1.51 (0.69, 3.10)
MelPredThal						1	3.29 (2.42, 4.70)*	1.71 (0.95, 3.12)	1.20 (0.57, 2.38)	1.44 (0.67, 2.91)
MelPred							1	0.52 (0.32, 0.85)*	0.36 (0.19, 0.66)*	0.44 (0.22, 0.81)*
BorMelPred Thal+Thal cont.								1	0.70 (0.30, 1.51)	0.84 (0.36, 1.84)
MelPredLen + Len cont.									1	1.20 (0.76, 1.91)
MelPredLen										1

**statistisk signifikant resultat. BO = behandlingsophør grundet ønskede hændelser, RR = relativ risiko*

Figure reprinted from: Medicinrådet (2020). Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose). Version 1.2. Bilag 6 tabel P, page 114 (9).

10 Appendix E

TABLE 62: TEAES (ANY GRADE) REPORTED IN AT LEAST 20% OF SUBJECTS IN ANY TREATMENT ARM BY TRANSPLANT ELIGIBILITY – INITIAL TREATMENT – STUDY SWOG S0777 (SAFETY POPULATION) (6) P.61

Table 50 : TEAEs (Any Grade) Reported in at Least 20% of Subjects in Any Treatment Arm by Transplant Eligibility – Initial Treatment – Study SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	TNE		TE	
	RVd (3-week cycles × 8 = 24 weeks) (N = 120) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 137) n (%)	RVd (3-week cycles × 8 = 24 weeks) (N = 142) n (%)	Rd (4-week cycles × 6 = 24 weeks) (N = 119) n (%)
Subjects With ≥ 1 TEAE	115 (95.8)	133 (97.1)	140 (98.6)	112 (94.1)
Nervous System Disorders	**100 (83.3)**	**82 (59.9)**	**119 (83.8)**	**63 (52.9)**
Peripheral sensory neuropathy	80 (66.7)	47 (34.3)	104 (73.2)	38 (31.9)
Dizziness	36 (30.0)	23 (16.8)	40 (28.2)	18 (15.1)
Dysgeusia	35 (29.2)	29 (21.2)	44 (31.0)	19 (16.0)
Gastrointestinal Disorders	**99 (82.5)**	**93 (67.9)**	**112 (78.9)**	**73 (61.3)**
Constipation	63 (52.5)	69 (50.4)	84 (59.2)	46 (38.7)
Diarrhea	52 (43.3)	45 (32.8)	52 (36.6)	34 (28.6)
Nausea	40 (33.3)	36 (26.3)	58 (40.8)	33 (27.7)
Dyspepsia	19 (15.8)	17 (12.4)	31 (21.8)	16 (13.4)
General Disorders and Administration Site Conditions	**99 (82.5)**	**103 (75.2)**	**122 (85.9)**	**88 (73.9)**
Fatigue	84 (70.0)	90 (65.7)	109 (76.8)	77 (64.7)
Edema peripheral	57 (47.5)	41 (29.9)	65 (45.8)	24 (20.2)
Blood and Lymphatic System Disorders	**96 (80.0)**	**118 (86.1)**	**112 (78.9)**	**85 (71.4)**
Anemia	82 (68.3)	101 (73.7)	97 (68.3)	74 (62.2)
Thrombocytopenia	77 (64.2)	77 (56.2)	74 (52.1)	40 (33.6)
Leukopenia	46 (38.3)	76 (55.5)	63 (44.4)	50 (42.0)
Neutropenia	35 (29.2)	58 (42.3)	42 (29.6)	41 (34.5)
Lymphopenia	34 (28.3)	37 (27.0)	33 (23.2)	25 (21.0)
Metabolism and Nutrition Disorders	**93 (77.5)**	**111 (81.0)**	**108 (76.1)**	**91 (76.5)**
Hypocalcemia	66 (55.0)	63 (46.0)	65 (45.8)	48 (40.3)
Hyperglycemia	58 (48.3)	81 (59.1)	69 (48.6)	61 (51.3)
Decreased appetite	43 (35.8)	35 (25.5)	47 (33.1)	24 (20.2)
Hypoalbuminemia	43 (35.8)	40 (29.2)	35 (24.6)	27 (22.7)
Hyponatremia	41 (34.2)	42 (30.7)	39 (27.5)	23 (19.3)
Hypokalemia	36 (30.0)	31 (22.6)	40 (28.2)	22 (18.5)
Dehydration	25 (20.8)	13 (9.5)	18 (12.7)	4 (3.4)
Musculoskeletal and Connective Tissue Disorders	**87 (72.5)**	**96 (70.1)**	**98 (69.0)**	**70 (58.8)**

Muscular weakness	36 (30.0)	29 (21.2)	28 (19.7)	16 (13.4)
Back pain	35 (29.2)	37 (27.0)	52 (36.6)	34 (28.6)
Investigations	**73 (60.8)**	**83 (60.6)**	**90 (63.4)**	**61 (51.3)**
Blood AP increased	31 (25.8)	29 (21.2)	35 (24.6)	19 (16.0)
Blood creatinine increased	30 (25.0)	38 (27.7)	18 (12.7)	26 (21.8)
Weight decreased	26 (21.7)	41 (29.9)	27 (19.0)	13 (10.9)
ALT increased	24 (20.0)	21 (15.3)	43 (30.3)	28 (23.5)
AST increased	18 (15.0)	21 (15.3)	38 (26.8)	17 (14.3)
Respiratory, Thoracic, and Mediastinal Disorders	**69 (57.5)**	**74 (54.0)**	**81 (57.0)**	**43 (36.1)**
Dyspnea	43 (35.8)	38 (27.7)	37 (26.1)	27 (22.7)
Cough	36 (30.0)	30 (21.9)	41 (28.9)	21 (17.6)
Skin and Subcutaneous Tissue Disorders	**47 (39.2)**	**55 (40.1)**	**66 (46.5)**	**49 (41.2)**
Rash	20 (16.7)	25 (18.2)	29 (20.4)	27 (22.7)
Vascular Disorders	**47 (39.2)**	**44 (32.1)**	**54 (38.0)**	**29 (24.4)**
Hypotension	24 (20.0)	11 (8.0)	19 (13.4)	2 (1.7)
Psychiatric Disorders	**45 (37.5)**	**64 (46.7)**	**68 (47.9)**	**46 (38.7)**
Insomnia	35 (29.2)	40 (29.2)	51 (35.9)	34 (28.6)

AE = adverse event; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TE = transplant eligible; TEAE = treatment-emergent adverse event; TNE = transplant non-eligible.
a System organ classes and preferred terms were coded using MedDRA Version 15.1. A subject with multiple events was counted only once in each preferred term and system organ class. System organ classes and preferred terms are listed in decreasing order of frequency by the TNE RVd column.

Table reprinted from: European Medicines Agency (2019). Assessment report. Revlimid (BorLenDex). Procedure No. EMEA/H/C/000717/II/0102/G. 28 March 2019. Table 50 p.61 (6)

11 Appendix F – Results per study

11.1 Results per study

Results from the reported studies have been included. Absolute differences and relative differences were calculated when necessary for the evaluation of the added clinical benefit of DaraBorMelPred. Absolute and relative differences have not been calculated in case they were irrelevant for the assessment of DaraBorMelPred (except if they were directly reported in the publication).

11.1.1 DaraBorMelPred and BorMelPred study

TABLE 63: RESULTS PER STUDY – ALCYONE

Trial name:	**ALCYONE**										
NCT number:	NCT02195479										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Median overall survival	DaraBorMelPred	350	NE (NE-NE)	NA	NA	NA	HR: 0.60	0.46–0.80	0.0003	The primary endpoint and other time-to-event variables were estimated using the Kaplan-Meier method. A Cox regression model was used to estimate treatment effect, presented as hazard ratios (HRs) with two-sided 95% CIs.	Mateos et al. 2019 (11) Lower confidence interval for BorMelPred: Janssen, Data-on-file
	BorMelPred	356	NE (43.9-NE)								
OS-rate at 3 years	DaraBorMelPred	350	78.0% (73.2%-82.0%)	10.1%	(5.4%, 14.8%)	NA				36-months survival rate is analyzed for the ITT population. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. Absolute difference calculated by naïve	Mateos et al. 2019 (11)
	BorMelPred	356	67.9% (62.6%-72.6%)								

										unadjusted subtraction. The 95% CI is approximated using the WALD type confidence intervals.	
Median progression-free survival	DaraBorMelPred	350	36.4 months (32.1–45.9)	17.1 months	NA	NA	HR: 0.42	0.34–0.51	<0.0001	The primary endpoint and other time-to-event variables were estimated using the Kaplan-Meier method. A Cox regression model was used to estimate treatment effect, presented as hazard ratios (HRs) with two-sided 95% CIs. Absolute difference calculated by naïve unadjusted subtraction	Mateos et al. 2019 (11)
	BorMelPred	356	19.3 months (18.0–20.4)								
Treatment discontinuation due to adverse events	DaraBorMelPred	346	24/N = 6.94%	-2.3%	(-6.3%, 1.6%)	p=0.2458	HR: 0.48	0.26, 0.86	0.0134	HR is based on the stratified cox proportional hazard model hazard model and the relative risk and absolute difference are also based on stratified analysis using the stratification factors used in the study.	Mateos et al. 2019 (11)
	BorMelPred	354	33/N = 9.32%								
HRQoL *EORTC QLQ-C30* *Global Health scale*	DaraBorMelPred	317	Baseline value Mean ± SD 50.66 ± 21.012	NA	NA	NA	NA	NA	NA	Treatment benefit was assessed using mixed-effects repeated measures analyses of least-squares (LS) mean change from baseline.	Janssen, Data-on-file
	BorMelPred	327	Baseline value Mean ± SD 52.40 ± 22.615								
	DaraBorMelPred	262	Month 3	3.4	0.5, 6.4	0.0240	NA	NA	NA		

Least-squares (LS) mean change from baseline.			7.3 (5.1, 9.5)							Least square means are derived based on the mixed effects model with repeated measures, in which the dependent variable is change from baseline in score and independent variables are baseline, visit, treatment, visit by treatment interaction and randomisation stratification factors - ISS staging (I, II, III), region (Europe vs. Other) and age (<75 years vs. ≥75 years) as fixed effects and individual subject as random effect.	
	BorMelPred	245	Month 3 3.9 (1.6, 6.2)								
	DaraBorMelPred	235	Month 6 8.4 (6.1, 10.7)	– 0.3	– 3.5, 2.8	0.8284	NA	NA	NA		
	BorMelPred	213	Month 6 8.7 (6.3, 11.2)								
	DaraBorMelPred	228	Month 9 10.4 (8.0, 12.7)	0.3	– 3.0, 3.5	0.8691	NA	NA	NA		
	BorMelPred	189	Month 9 10.1 (7.6, 12.6)								
	DaraBorMelPred	222	Month 12 11.1 (8.8, 13.5)	0.6	– 2.7, 3.9	0.7172	NA	NA	NA		
	BorMelPred	185	Month 12 10.5 (8.0, 13.1)								
	DaraBorMelPred	194	Month 18 12.7 (10.2, 15.1)	1.1	– 2.5, 4.7	0.5643	NA	NA	NA		
	BorMelPred	136	Month 18 11.6 (8.7, 14.4)								
	DaraBorMelPred	152	Month 24 9.3 (6.6, 12.0)	– 2.0	– 6.3, 2.2	0.3471	NA	NA	NA		
	BorMelPred	83	Month 24 11.3 (7.9, 14.8)								
	DaraBorMelPred	119	Month 30 10.8 (7.8, 13.7)	– 0.5	– 5.7, 4.7	0.8445	NA	NA	NA		
	BorMelPred	48	Month 30 11.3 (6.9, 15.7)								
	DaraBorMelPred	80	Month 36 12.3 (8.8, 15.8	4.4	– 1.8, 10.7	0.1656	NA	NA	NA		
	BorMelPred	31	Month 36 7.9 (2.5, 13.2)								

Notes: Median follow-up: 40.1 months (95% CI: 37.4-43.1). Median follow-up not reported per arm; NE: Not evaluable; NA: Not available
Qualitative assessment of AEs, see 6.1.2

11.1.2 LenDex18 studies

TABLE 64: RESULTS PER STUDY – FIRST

Trial name:	**FIRST**										
NCT number:	NCT00689936										
Outcome	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
				Difference	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Median overall survival	LenDex	535	59.1 months (53.9-65.9)	NA	NA	NA	LenDex vs. LenDex18 HR: 1.02	LenDex vs. LenDex18 0.86-1.20	0.829	The O'Brien–Fleming boundary was used for progression-free survival and the Pocock boundary was used for overall survival.	Facon et al. 2018 (13) HR for LenDex18 vs. MelPredThal: Clinicaltrials.gov (15), see "study results", 3 secondary outcome, statistical analysis 3
	LenDex18	541	62.3 months (53.6-68.7)				LenDex vs. MelPredThal HR: 0.78	LenDex vs. MelPredThal 0.67-0.92	0.0023		
	MelPredThal	547	49.1 months (44.3-53.5)				LenDex18 vs. MelPredThal HR: 0.77	LenDex18 vs. MelPredThal 0.66-0.90*	0.001		
*OS-rate at 3 years***	LenDex	535	70.0%	NA	NA	NA	NA	NA	NA		Benboubker et al. 2014 (12)
	LenDex18	541	66.0%								
	MPT	547	62.0%								
*OS-rate at 4 years****	LenDex	535	59.0%	NA	NA	NA	See median overall survival	See median overall survival	See median overall survival		Facon et al. 2018 (13)
	LenDex18	541	58.0%								
	MelPredThal	547	51.7%								

Median progression-free survival	LenDex	535	26.0 months	NA	NA	NA	LenDex vs LenDex18 HR: 0.70 LenDex vs MelPredThal HR: 0.69 LenDex18 vs. MelPredThal HR: 0.99*	0.60-0.81 0.59-0.79 0.86-1.14*	<0.0001 <0.0001 0.91	The O'Brien–Fleming boundary was used for progression-free survival and the Pocock boundary was used for overall survival.	Facon et al. 2018 (13) HR for LenDex18 vs. MelPredThal: Clinicaltrials.gov (FIRST study) (15). See "Study results", 2.Primary, Outcome, Statistical Analysis 3
	LenDex18	541	21.0 months								
	MelPredThal	547	21.9 months								
*Treatment discontinuation due to adverse events*****	LenDex	532	64/N = 12.03%	NA	NA	NA	NA	NA	NA		Benboubker et al. 2014 (12)
	LenDex18	540	71/N = 13.15%								
	MelPredThal	541	76/N = 14.05%								
*HRQoL EORTC QLQ-C30 Global Health scale***** *Change from baseline*	LenDex & LenDex18 pooled[a]	1015	Baseline value Mean (SD) 51.7 (24.36)	NA	NA	NA	NA	NA	NA	Constructed scale and change from baseline are calculated based on the mean scale linear transformation of raw score.	LenDex & LenDex18 pooled (Baseline values and GHS results)[a]: Delforge et al. 2015 (14). Supplementary appendix, table 1, page 2. Only pooled data for LenDex and LenDex18 available as well as separate data for MelPredThal.[a] GHS results (LenDex, LenDex18, MelPredThal)[b]: Clinicaltrials.gov (FIRST study).
	MelPredThal[a,b]	508	Baseline value Mean (SD) 50.8 (24.16)								
	LenDex[b]	438	Month 1 0.4 (23.98)	NA	NA	NA	NA	NA	NA		
	LenDex18[b]	441	Month 1 -1.3 (23.93)								
	LenDex & LenDex18 pooled[a]	879	Month 1 -0.4 (23.96)								
	MelPredThal[a,b]	415	Month 1 1.0 (23.68)								
	LenDex[b]	421	Month 3 4.8 (24.15)	NA	NA	NA	NA	NA	NA		
	LenDex18[b]	413	Month 3 4.7 (25.15)								

LenDex & LenDex18 pooled[a]	834	Month 3 4.8 (24.64)								(15). See "study results", 19. Secondary outcome". No baseline values available for the treatment arms.[b]
MelPredThal[a,b]	396	Month 3 4.3 (26.04)								
LenDex[b]	369	Month 6 5.9 (25.93)	NA	NA	NA	NA	NA	NA		
LenDex18[b]	376	Month 6 5.4 (23.88)								
LenDex & LenDex18 pooled[a]	745	Month 6 5.6 (24.90)								
MelPredThal[a,b]	351	Month 6 6.1 (25.98)								
LenDex[b]	302	Month 12 4.8 (26.42)	NA	NA	NA	NA	NA	NA		
LenDex18[b]	299	Month 12 3.2 (25.38)								
LenDex & LenDex18 pooled[a]	601	Month 12 4.0 (25.90)								
MelPredThal[a,b]	252	Month 12 6.5 (25.90)								
LenDex[b]	246	Month 18 6.4 (28.02)	NA	NA	NA	NA	NA	NA		
LenDex18[b]	238	Month 18 5.7 (24.86)								
LenDex & LenDex18 pooled[a]	484	Month 18 6.0 (26.49)								
MelPredThal[a,b]	178	Month 18 4.8 (27.05)								
LenDex[b]	203	Study discon. -0.1 (27.07)	NA	NA	NA	NA	NA	NA		
LenDex18[b]	261	Study discon. 5.0 (27.33)								

	LenDex & LenDex18 pooled[a]	464	Study discon. 2.8 (27.31)								
	MelPredThal[a,b]	257	Study discon. 0.3 (28.07)								

Median duration of follow-up for surviving patients (months): 67.2 (range: 0-86.8). Median follow-up not reported per arm. Discon: discontinuation visit. NA: Not available
Absolute differences between the treatment arms are not calculated as these are not relevant for the clinical questions
Reporting of AEs, see 6.1.3
* For the comparison of LenDex18 vs. MelPredThal for OS and PFS, the latest values were obtained from clinicaltrials.gov (data cut-off date of 21 January 2016; median follow-up 48.3 and 17.7 months, respectively). The PFS HR and 95% CI is identical to the one reported in the EPAR (7) (table 15, p. 45) with a data cutoff of 03 Mar 2014. For OS, the data from clinicaltrials.gov represents the longest follow-up. For the other comparisons (LenDex vs LenDex18 and LenDex vs MelPredThal), the latest values were obtained from the latest publication for FIRST trial (Facon et al, 2018), after a median follow-up of 67.2 months.
**With a data cutoff of 24th of May 2013, the median duration of follow-up among surviving patients was 37.0 months (range, 0 to 56.7) (12). The 3-year OS rate was not reported in the final analysis. 36 months OS-rate is also reported in the EPAR at a data cuttoff of 03 Mar 2014. The 36 months OS-rate rounds to the same numbers as stated in the table above (reported in Benboubker et al. 2014).
EPAR (7) (table 16, p. 47), 36 months OS-date (SE): Cutoff of 24 May 2013: LenDex 69.94 (2.09); LenDex18 65.62 (2.17); MelPredThal 62.44 (2.20). Cutoff of 03 Mar 2014: LenDex 70.09 (2.03); LenDex18 66.30 (2.07); MelPredThal 62.15 (2.13).
***Data based on median follow-up for surviving patients of 67.2 months (range: 0-86.8).
****Values based on a median follow-up for surviving patients of 37 months (range, 0 to 56.7)

11.1.3 BorLenDex studies

TABLE 65: RESULTS PER STUDY – SWOG S0777 (DURIE ET AL. 2017)

Trial name:	**SWOG S0777**											
NCT number:	NCT00644228											
Outcome	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
				Difference	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Median overall survival	BorLenDex	242	75 months (65-NR)	11 months*	NA	NA	HR: 0.712	0.560-0.906	0.0018	Stratified hazard ratio and one-sided stratified log-rank (96% Wald confidence interval) Overall survival between treatment groups using a log-rank test stratified according to the factors used for randomisation. Hazard ratios were estimated by means of a stratified Cox proportional-hazards model	Durie et al. 2017 (20)
	LenDex	229	64 months (56-NR)								
Median progression-free survival	BorLenDex	242	43 months (39-52)	13 months*	NA	NA	HR: 0.709	0.524-0.959	0.0125	Unstratified median progression free survival Progression-free survival between treatment groups is based using a log-rank test stratified according to the factors used for randomisation. Hazard ratios were estimated by means of a stratified	Durie et al. 2017 (20)
	LenDex	229	30 months (25-39)								

										Cox proportional-hazards model.	
Treatment discontinuation due to adverse events	BorLenDex	241**	55 (22.82%)	NA	NA	NA	NA	NA	NA		Durie et al. 2017 (20)
	LenDex	226**	22 (9.73%)								

The median overall follow up was 55 months (IQR 48–68), 54 months (IQR 47–66) for BorLenDex and 56 months (50–70) for the LenDex group. NR: Not reached; NA: Not available
Absolute differences between the treatment arms are not calculated as these are not relevant for the clinical questions
Reporting of AEs, see 6.1.4
*Stated in manuscript: *The progression-free survival was improved by 13 months and overall survival by 11 months*.
**Patients in safety population: 241 evaluable for toxic effects (BorLenDex); 226 evaluable for toxic effects (LenDex) figure 1, p. 522 (20) Durie et al. 2017. Induction only (24 weeks).
The stated number of treatment discontinuations due to adverse events have been utilized in the comparative analysis based on Durie et al. 2017.

TABLE 66: RESULTS PER STUDY – SWOG S0777 (EPAR)

Trial name:	**SWOG S0777 (Longest follow up – EMA Censoring)**											
NCT number:	NCT00644228											
Outcome	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
				Difference	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Median overall survival	BorLenDex	263	89.1 months (76.1-NR)	NA	NA	NA	HR: 0.75	0.58-0.97	0.02786	The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	BorLenDex EPAR (6) Table 14, p. 28
	LenDex	260	67.2 months (58.4-90.8)								
Median progression-free survival	BorLenDex	263	41.7 months (33.1-51.5)	NA	NA	NA	HR: 0.76	0.62-0.94	0.00996	The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	BorLenDex EPAR (6) Table 14, p. 28
	LenDex	260	29.7 months (24.2-37.8)								
Treatment discontinuation due to adverse events	BorLenDex	262*	(37.0%)	NA	NA	NA	NA	NA	NA		BorLenDex EPAR (6) Table 36, p.51
	LenDex	256*	64 (25.0%)								

The median follow-up (based on Kaplan-Meier estimate) for all surviving subjects was 69 months, data cut-off date: 01 Dec 2016 (6). The median follow-up for all patients in the BorLenDex arm was 61.6 months (min, max: 0.2, 99.4) and 59.4 months (min, max: 0.4-99.1) for LenDex (4). NR: Not reached; NA: Not available.
Absolute differences between the treatment arms are not calculated as these are not relevant for the clinical questions
Reporting of AEs, see 6.1.4
*Patients in safety population: 241 evaluable for toxic effects (BorLenDex); 226 evaluable for toxic effects (LenDex) p. 522 (20) p. 522, Durie et al. 2017. Induction only.
To estimate the relative difference for treatment discontinuations due to adverse events, the data from Durie et al. 2017 was applied (see table above).

11.1.4 Other studies (used in NMA)

VISTA

TABLE 67: RESULTS PER STUDY – VISTA

Trial name:	**VISTA**											
NCT number:	NCT00111319											
Outcome	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
				Difference	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Median overall survival	BorMelPred	344	56.4 months	NA	NA	NA	HR: 0.695	0.567-0.852	<0.001	OS was analysed from randomization and the differences between groups were compared using stratified log-rank tests. Distributions were estimated with use of the Kaplan–Meier method. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model.	San Miguel et al. 2013 (19)
	MelPred	338	43.1 months								
OS-rate at 5 years	BorMelPred	344	46.0 % (40.3-51.8%)	NA	NA	NA					San Miguel et al. 2013 (19)
	MelPred	338	34.4 % (28.9%-39.9%)								
Median progression-free survival	BorMelPred	344	21.7 months	NA	NA	NA	HR: 0.56	0.39-0.79*	<0.001	Progression-free survival were compared between treatment groups by stratified log-rank test based on the intent-to-treat population (all randomized patients). Distributions were estimated using Kaplan-Meier methodology. Hazard ratios were estimated using the stratified Cox proportional hazards model	San Miguel et al. 2008 (18), supplementary appendix, figure 2
	MelPred	338	15.2 months								

Treatment discontinuation due to adverse events	BorMelPred	340	52/N =15.29%**	NA	NA	NA	NA	NA	NA		Mateos et al. 2010 (26)
	MelPred	337	48/N = 14.24%**								

Median follow-up: 60.1 months (longest follow-up time). PFS based on previous data-cut (median follow-up of 16.3 months), since PFS could not be updated at this final analysis because they were based on central laboratory assessment and, because of the highly significant initial benefit observed for these outcome measures. For treatment discontinuations due to AEs, the data is based on a previous data-cut (36.7 months follow-up) since the latest data cut did not include adverse event data. NA: Not available

Absolute differences between the treatment arms are not calculated as these are not relevant for the clinical questions

* The CI was calculated based on the HRs and the reported p-values following the methodology reporting in Altman, D. G., & Bland, J. M. (2011). How to obtain the confidence interval from a P value. BMJ (55)

**Data represent discontinuation of all treatment

Absolute differences not calculated as these are not relevant for the clinical questions

IFM01/01

TABLE 68: RESULTS PER STUDY – IFM01/01

Trial name:	**IFM01/01**											
NCT number:	NCT00644306											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Median overall survival	MelPred	116	29.1 months (26.4-34.9)	NA	NA	NA	HR: 0.68	0.47-0.82*	0.028	Survival was estimated with the Kaplan-Meier product limit method and curves were compared with the stratified log-rank test on an intention-to-treat basis. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model for the intention-to-treat population.	Hulin et al, 2009 (16)
	MelPredThal	113	44.0 months (33.4-58.7)								
Median progression-free survival	MelPred	116	18.5 months (14.6-21.3)	NA	NA	NA	HR: 0.62	0.47-0-82*	0.001	Progression-free survival was calculated from random assignment to progression or death. Data on patients who had not experienced disease progression were censored on the last date they were known to be alive and progression free.	Hulin et al, 2009 (16)
	MelPredThal	113	24.1 months (19.4-29.0)								
Treatment discontinuation due to adverse events	MelPred	116	15/N = 12.93%	NA	NA	NA	NA	NA	NA		Hulin et al, 2009 (16)
	MelPredThal	113	48/N = 42.48%								

Median follow-up: 47.5 months (longest follow-up time). OS-rate at 3 years not available. NR: Not reached; NA: Not available

Absolute differences between the treatment arms are not calculated as these are not relevant for the clinical questions

* The CI was calculated based on the HRs and the reported p-values following the methodology reporting in Altman, D. G., & Bland, J. M. (2011). How to obtain the confidence interval from a P value. BMJ (55)

IFM99-06

TABLE 69: RESULTS PER STUDY – IFM99-06

Trial name:	**IFM99-06**											
NCT number:	NCT00367185											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Hazard/Odds/ Risk ratio**	**95% CI**	***P* value**		
Median overall survival	MelPred	196	33.2 months (13.8-54.8)	NA	NA	NA	HR: 0.59	0.46-0.81	0.0006	Curves for overall survival were calculated from randomization and from progression (for survival after progression) with use of the Kaplan-Meier method	Facon et al. 2007 (17)
	MelPredThal	125	51.6 months (26.6-NR)								
Median progression-free survival	MelPred	196	17.8 months	NA	NA	NA	HR: 0.51	0.39-0.66	<0.0001	Curves for progression-free survival, and survival after progression were calculated from randomization and from progression (for survival after progression) with use of the Kaplan-Meier method. Comparison between treatment groups and hazard ratios (HR) for death, progression or death without progression, or death after progression were estimated through the unstratified proportional hazards model with 95% CI.	Facon et al. 2007 (17)
	MelPredThal	125	27.5 months								
Treatment discontinuation	MelPred	193	Not reported	NA	NA	NA	NA	NA	NA		Facon et al. 2007 (17)

due to adverse events	MelPredThal	124	45%								

Median follow-up: 51.5 months (95% CI: 34.4-63.2) (longest follow-up time). OS-rate at 3 years not available. NR: Not reached. NA: Not available
Absolute differences between the treatment arms are not calculated as these are not relevant for the clinical questions
*MEL100 not reported as it is irrelevant for the clinical question.

11.2 Results per PICO (clinical question)

11.2.1 DaraBorMelPred compared with BorMelPred

TABLE 70: RESULTS PER PICO – DARABORMELPRED VS. BORMELPRED

Results per outcome		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Median overall survival	ALCYONE DaraBorMelPred vs. BorMelPred	NA	NA	NA	HR: 0.60	0.46–0.80	0.0003	Kaplan-Meier method. Head to head study.
OS-rate at 3 years	ALCYONE DaraBorMelPred vs. BorMelPred	10.1 months	(5.4%, 14.8%)	NA				Kaplan-Meier method. Head to head study. Absolute difference calculated by naïve unadjusted subtraction. The 95% CI is approximated using the WALD type confidence intervals.
Median progression-free survival	ALCYONE DaraBorMelPred vs. BorMelPred	17.1 months	NA	NA	HR: 0.42	0.34–0.51	<0.0001	Kaplan-Meier method. Head to head study.
Treatment discontinuation due to adverse events	ALCYONE DaraBorMelPred vs. BorMelPred	-2.3% (favoring DaraBorMelPred)	-6.3%, 1.6%	0.2458	HR: 0.48	0.26; 0.86	0.0134	HR is based on the stratified cox ph model and OR/RR/RD are also based on stratified analysis using the stratification factors used in this study.

NA: Not available

11.2.2 DaraBorMelPred compared with LenDex18

TABLE 71: RESULTS PER PICO – DARABORMELPRED VS. LENDEX18

Results per outcome		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Median overall survival	ALCYONE & FIRST (+NMA links) DaraBorMelPred vs. LenDex18	NA	NA	NA	HR: 0.86	0.56–1.32	NA	Derived based on NMA
OS-rate at 3 years	ALCYONE & FIRST (+NMA links) DaraBorMelPred vs. LenDex18	12%	NA	NA				Absolute difference: naïve unadjusted subtraction (78%-66%)
Median progression-free survival	ALCYONE & FIRST (+NMA links) DaraBorMelPred vs. LenDex18	15.4 months	NA	NA	HR: 0.43	0.27–0.68	NA	Absolute difference: naïve unadjusted subtraction (36.4 months – 21 months) HR: Derived based on NMA
Treatment discontinuation due to adverse events	ALCYONE & FIRST (+NMA links) DaraBorMelPred vs. LenDex18	-10.78% (favoring DaraBorMelPred)	-12.23%, -6.84%		RR: 0.18	0.08–0.48	NA	RR derived from NMA. Absolute difference and 95% CrI calculated according to the Medicines Council method handbook (31)

NA: Not available

11.2.3 DaraBorMelPred compared with BorLenDex

TABLE 72: RESULTS PER PICO – DARABORMELPRED VS. BORLENDEX

Results per outcome		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	CrI	*P* value	
Median overall survival	NA	NA	NA	NA	NA	NA	NA	Absolute difference and relative difference were not estimated due to bias
OS-rate at 3 years	NA	NA	NA	NA				OS-rate at 3 years not reported. If OS-rate at 3 years were reported, it would be subject to bias
Median progression-free survival	NA	NA	NA	NA	NA	NA	NA	Absolute difference and relative difference were not estimated due to bias
Treatment discontinuation due to adverse events	ALCYONE & SWOG S0777 (+NMA links) DaraBorMelPred vs. BorLenDex	-21.00% (favoring DaraBorMelPred)	-22.14%, -16.89%	NA	RR: 0.08	0.03 - 0.26	NA	RR derived from NMA. Absolute difference and 95% CrI calculated according to the Medicines Council method handbook.

NA: Not available

Health economic analyses of daratumumab in combination with bortezomib, melphalan, and prednisone for the treatment of newly diagnosed patients with multiple myeloma who are ineligible for autologous stem cell transplant

Technical Report

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List of Abbreviations

Main drug combination abbreviation(s)	Drug combination
BorLenDex / VRd	Bortezomib+lenalidomide+dexamethasone
BorMelPred / VMP	Bortezomib+melphalan+prednisone
CarDex	Carfilzomib+dexamethasone
CarLenDex	Carfilzomib+lenalidomide+dexamethasone
DaraBorDex / Dara+Vd	Daratumumab+bortezomib+dexamethasone
DaraBorMelPred / Dara+VMP	Daratumumab+bortezomib+melphalan+prednisone
DaraLenDex / Dara+Rd	Daratumumab+lenalidomide+dexamethasone
EloLenDex	Elotuzumab+lenalidomide+dexamethasone
IxaLenDex	Ixazomib+lenalidomide+dexamethasone
LenDex / Rd	Lenalidomide+dexamethasone (to progression)
LenDex18 / Rd18	Lenalidomide+dexamethasone (18 cycles)
PomDex	Pomalidomide+dexamethasone
PomBorDex	Pomalidmoide+bortezomib+dexamethasone

Abbreviations	Definitions
1PL	one prior line
AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
BSA	Body surface area
CD38	cluster of differentiation 38
CI	Confidence interval
CR	Complete response
CrI	Credible interval
HR	Hazard ratio
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IPD	individual patient data
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier

MM	Multiple myeloma
MRD	Minimal residual disease
N/A	not applicable
NDMM	Newly diagnosed multiple myeloma
NICE	National Institute of Health and Care Excellence (UK)
NMA	Network meta-analysis
OS	Overall survival
pCODR	Pan-Canadian Oncology Drug Review
PFS	Progression-free survival
PI	Proteasome inhibitor
PLD	Patient-level data
PO	Oral, by mouth
PP	post-progression
PPS	Post-progression survival
QoL	Quality of life
RCT	Randomized clinical trial
RMSE	root-mean-square error
rrMM	Relapsed/refractory multiple myeloma
SAS	Statistical Analysis System
SC	Subcutaneous
SE	Standard error
SLR	Systematic literature review
TTTD	Time-to-treatment discontinuation
tx	Treatment

Executive Summary

Purpose of the Model and Report

A health economic model was adapted to the Danish setting to evaluate daratumumab in combination with bortezomib, melphalan, and prednisone (DaraBorMelPred) for the treatment of patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT), in other words, transplant ineligible (TIE) patients.

This report describes the methods, inputs, data sources, assumptions, and results of the model. The model has been tailored to the Danish setting and takes a "restricted" societal perspective. The report focuses on what has been requested by the Danish Medicines Council, namely, the incremental costs per patient (DaraBorMelPred vs. comparators) as well as the budget impact (reference case vs. alternative case). The added clinical benefit of DaraBorMelPred is assessed separately by the Medicines Council in the clinical evaluation. Health outcomes will not be presented in this report.

Methods

An economic model was developed in Microsoft Excel® to assess the incremental costs per patient and the budget impact for DaraBorMelPred versus comparators for the treatment of patients with NDMM who are ineligible for ASCT. The cost part of the model has been extracted and evaluated in the report. The comparators included in the base-case were those specified in the protocol for DaraBorMelPred (the combinations of bortezomib, melphalan, and prednisone [BorMelPred]; lenalidomide and dexamethasone for 18 cycles [LenDex18]; bortezomib, lenalidomide, and dexamethasone [BorLenDex] (1). However, lenalidomide and dexamethasone continuous treatment (LenDex) is also analyzed throughout the report serving as a scenario analysis.

Model Structure

A survival partition cohort model structure with three health states, commonly used in peer-reviewed publications for the target indication of this analysis, was selected to follow patients from an initial line of treatment after diagnosis into later lines until death. The model was developed based on the clinical and treatment pathways for patients with NDMM who are ineligible for ASCT; considerations around key clinical aspects such as progression-free survival, overall survival, and treatment duration.

The three health states modelled were pre-progression, post-progression, and death. For the adequate modelling of treatment-related costs, status (i.e., on and off treatment) in the pre- and post-progression health states was tracked over time. Patients enter the model, initiate first-line treatment, and experience an interval of PFS. Patients who experience disease progression and do not die during the initial modelled line of treatment continue to the post-progression health state, in which they may receive subsequent treatments. Patients may discontinue treatment or die at any time in the model. Costs are assigned to each health state and are accrued and summarised for each cycle of the model (one week), so the difference in cumulative cost can be analysed and compared between comparators. Costs are discounted at 4% per annum according to Danish guidelines (2).

Model Inputs

PFS and OS extrapolations

Long-term PFS extrapolations were needed for the survival partition model. [redacted]

[redacted]

Costs

Drug-acquisition costs for the treatment options in the model, including those in the first, second, and third line, were sourced from the Danish Medicines Agency database (Medicinpriser.dk). The model also considers costs of administration, concomitant and prophylactic medications (first-line), cost of handling AEs (first-line), medical resource costs for pre-progression and post-progression states, patient costs (first-line and second line) and terminal care costs. DRG codes (2020) were used to inform about relevant costs and the Medicines Council published material for how to cost patient time.

Model Outputs

Model outcomes for the incremental costs per patient include:

- Pre-progression (first-line treatment): Drug acquisition, drug administration & routine monitoring, concomitant and prophylactic medications, adverse event management, and patient costs (time spend by patients)
- Post progression
    - Second-line: Drug acquisition, administration, on-treatment monitoring, routine monitoring (off-treatment), and patient costs
    - Third-line: Drug acquisition, administration, on-treatment monitoring, routine monitoring (off-treatment)
- Terminal Care (pre- and post-progression)

Sensitivity analyses were used to test the influence of uncertainty of the model parameters on the results.

The model output for the budget impact analysis consists of a five-year period and includes the above cost outcomes except patient costs. In addition, the budget impact analysis is not discounted as per guidance from the Medicines Council (2).

Results

The base case has been created based on the general guidance from the Medicines Council around the extrapolation of time-to-event data (3). Patients with multiple myeloma require lifelong treatment and are likely to receive multiple lines of therapy. Thus, the costs associated with multiple lines of treatment are relevant. In the base case, multiple lines of therapy are considered as this provides a more comprehensive picture of the incremental costs per patients and the budgetary impact of introducing DaraBorMelPred in the first-line setting. The treatment received in the first-line setting will naturally influence the subsequent treatments received within multiple myeloma.

The modelled incremental costs per patient for DaraBorMelPred versus each comparator:

Incremental costs per patient	
DaraBorMelPred vs. BorMelPred	DKK 981,025
DaraBorMelPred vs. LenDex18	DKK 723,993
DaraBorMelPred vs. BorLenDex	DKK 328,348
DaraBorMelPred vs. LenDex	*DKK 494,601*

Drug acquisition costs included are based on list price (pharmacy purchase price)

The modelled budget impact varied depending on the recommendation scenario and can be found in section 5.1.2.

Discussion

DaraBorMelPred came with a higher lifetime total cost compared with the other treatments. The primary cost driver was first-line drug acquisition costs. Patients on DaraBorMelPred accrued more costs in the initial line given its PFS benefit.

The results of the economic analysis should be considered part of a broader assessment of DaraBorMelPred that does not solely focus on its higher incremental costs per patient versus the comparators over a treatment sequence. The findings in this report should be assessed in parallel with the clinical benefit that DaraBorMelPred delivers to patients, both from an efficacy, safety and tolerability perspective versus the comparator treatments.

1 Introduction

Purpose of the Model and Report

A health economic model was adapted to the Danish setting to evaluate daratumumab in combination with bortezomib, melphalan, and prednisone (DaraBorMelPred) for the treatment of patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT), in other words, transplant ineligible (TIE) patients.

This report describes the methods, inputs, data sources, assumptions, and results of the model. The model has been tailored to the Danish setting and takes a "restricted" societal perspective. The report focuses on what has been requested by the Medicines Council, namely, the incremental cost per patient (DaraBorMelPred vs. comparators) as well as the budget impact (reference case vs. alternative case). The added clinical benefit of DaraBorMelPred is assessed separately by the Medicines Council in the clinical evaluation and health outcomes will not be presented in this report.

The model was developed to be transparent and highly flexible to allow for easy adaptation, test uncertainty, and provide different scenarios. This report describes the methods, inputs, data sources, assumptions, and results of the model.

Epidemiology

In the protocol for DaraBorMelPred, it is estimated that approximately 450 patients are diagnosed annually with a median age at diagnosis of 71 years. Approximately 20% of the NDMM patients are not requiring treatment at the time of diagnosis which results in approximately 360 patients that are expected to start treatment annually. Of these, approximately 240 are estimated to be ineligible for ASCT accounting for 2/3 of the patients that are expected to start treatment (1).

Considerable progress in the treatment of multiple myeloma (MM) has been made during the last 15 years, improving patient survival. This development is primarily assumed to be attributed to the introduction of novel and more targeted, guideline-recommended therapies in the first-line setting. However, patients who are ineligible for ASCT demonstrate markedly worse outcomes and treatment-related toxicities compared with those who undergo ASCT. Patients with MM require lifelong treatment and are likely to receive multiple lines of therapy. In the protocol for DaraBorMelPred, it is estimated that patients who are ineligible for ASCT has a median survival of approximately 3 years. The estimated median survival for patients that are eligible for ASCT are 7 years. The median survival for the general Danish population at an age of 70 years is approximately 16 years (1).

An ongoing need remains for effective, well-tolerated frist-line treatments that improve survival and delay disease relapse. The aim of front-line treatment for MM is to induce remission, delay disease progression and relapse, prolong survival, and maximise quality of life.

Daratumumab

Daratumumab (DARZALEX®) is a first-in-class human monoclonal antibody that targets cluster of differentiation 38 (CD38), a surface glycoprotein that is universally overexpressed on myeloma cells regardless of cytogenetic status. Daratumumab operates through novel, multifactorial mechanisms of action, which are different from those associated with other therapies, including proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs).

This application is focusing on the following indication by the European Commission: Daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Based on findings from the ALCYONE study at a median follow-up of 16.5 months (clinical cut-off date of June 12, 2017) (4), DaraBorMelPred was approved on 3 September 2018, by the European Commission for use as first-line treatment of patients with NDMM who are ineligible for ASCT. At this early cut-off, DaraBorMelPred had resulted in a 50% reduction in the risk of progression or death in patients ineligible for ASCT. The overall response rate was 90.9% in the DaraBorMelPred group compared with 73.9% in the BorMelPred group and the rate of complete response or better (including stringent complete response) was 42.6% versus 24.4%, respectively. In the DaraBorMelPred group, 22.3% of the patients were negative for minimal residual disease (MRD; at a threshold of 1 tumour cell per 10^5 white cells) compared with 6.2% in the BorMelPred group (p-value <0.001)(4). DaraBorMelPred was well tolerated, and overall, the safety profile was consistent with the known toxicity of daratumumab and BorMelPred (4).

At the latter data cut-off, at a median follow-up of 40.1 months, the ALCYONE trial demonstrated that DaraBorMelPred had significant progression-free survival (PFS) benefit (hazard ratio [HR] 0.42; 95% CI 0.34, 0.51; p-value <0.0001) and survival benefit (HR 0.61; 95% CI 0.46, 0.80; p-value 0.0004) compared with BorMelPred; the median OS was not reached in either group. The overall response rate was 90.9% in the DaraBorMelPred group, compared with 73.9% in the BorMelPred group (p-value <0.0001); the rate of complete response or better (including stringent complete response) was 45.7% versus 25.3% (p-value <0.0001). DaraBorMelPred more than doubled the rate of stringent complete response (23.1%) compared with BorMelPred (7.9%). DaraBorMelPred was well tolerated, and overall, the safety profile was consistent with the known toxicity of daratumumab and BorMelPred.

2 Methods

Target Population

The target population of this analysis reflects that of the ALCYONE trial comparing DaraBorMelPred with BorMelPred (4, 5). The intention-to-treat (ITT) population was patients with newly diagnosed, documented MM, who were not eligible for high-dose chemotherapy with stem cell transplantation owing to coexisting conditions or an age ≥65 years (4).

The median age at baseline was 71.0 years in the ALYCONE trial. The median age at time for diagnosis of myeloma patients in Denmark is the same, approximately 71 years (6).

Perspective, Time Horizon and Discounting

The base case analysis was conducted from a "restricted" societal perspective. Broadly, this represents a societal perspective, including time spend by patients (and the related costs) and excluding indirect costs.

The costs include direct medical costs, drug acquisition costs for front-line and subsequent treatments, drug administration costs (including co-medications), monitoring, management of AEs, and terminal care costs. In addition, time spend by the patient (patient costs) are also considered focusing on transportation costs and time spend at the hospital for the first- and second-line setting.

The time horizon of the model is flexible. A 10-year time horizon was used in the base case scenario which is the same as used in the evaluation of lenalidomide in combination with bortezomib and dexamethasone (BorLenDex) in the evaluation of NDMM TIE patients (7). Since BorLenDex has been evaluated by the Medicines Council versus BorMelPred and LenDex (a minimum of 18 cycles) and DaraBorMelPred is being evaluated versus the same comparators (including BorLenDex), a similar time horizon was assessed to be appropriate. This time horizon was considered long enough to capture the long-term economic consequences of MM for patients who are ineligible for ASCT.

Cost outcomes were discounted at a rate of 4.0% in the base-case analysis which is the current discount rate applied by the Ministry of Finance in Denmark* and in accordance with Medicines Council guidelines (2).

Comparators

The choice of therapy for patients with NDMM depends on the eligibility of ASCT. Typically, younger (<65) or fit patients (<70 years and in good clinical condition) are eligible for ASCT. Patients >65 years are not typically eligible for ASCT (8, 9).

The model contains the primary treatments of interest specified by the Medicines Council, namely, BorMelPred, BorLenDex and LenDex18. After consulting with the Secretariat, it was made clear that the Expert Committee was requesting a comparison vs. LenDex18 (and not LenDex to progression). However, LenDex to progression has been included in the result sections and will partly serve as a scenario analysis

* fm.dk

as some physicians may aim to treat to progression if the patient tolerates the treatment rather than a fixed 18 cycles treatment duration. Both treatment strategies are according to the label.

Table 1. Overview-Therapies relevant for Denmark and Included in the Model

Comparator	Abbreviation
Daratumumab in combination with bortezomib, melphalan, and prednisone	DaraBorMelPred
Bortezomib, melphalan, and prednisone	BorMelPred
Lenalidomide and dexamethasone, 18 cycles	LenDex18
Bortezomib, lenalidomide and dexamethasone	BorLenDex
Lenalidomide and dexamethasone to progression (scenario analysis)	LenDex

Relative efficacy estimates were obtained using an network meta-analysis (NMA) for NDMM TIE patients and it was specifically tailored to the Danish comparators of interest to the Expert Committee. The NMA are described the section 2, Establishing Relative Efficacy and Appendix A.

Model Description

A health economic model was developed in Microsoft Excel® to assess DaraBorMelPred versus relevant comparators for the treatment of patients with NDMM who are ineligible for ASCT focusing on Denmark. In accordance with the current methodology from the Medicines Council, utilities/ health outcomes as an outcome of a cost-effectiveness is not considered in the evaluation. When using time-to-event data, extrapolation of cost data is required (3). In the current Danish setting, the added clinical benefit is decided in a separate clinical evaluation focusing on available data (see clinical part of this application) with no extrapolation of clinical data when the added clinical benefit is being assessed. This report focuses on what is formally assessed by the Medicines Council in the evaluation of DaraBorMelPred.

A three-health state-transition cohort model was chosen instead of an individual patient-level simulation. The main reasons for this choice are:

- No patient-level data (PLD) available for comparators (except for BorMelPred)
- Because of daratumumab's unique mechanism of action, the relationship between the patient characteristics and outcomes is different compared with those of patients treated with other regimens. Therefore, predictive equations previously developed from PLD from other trials may not be relevant.

This model structure was selected to follow patients from an initial line of treatment after diagnosis into later lines until death. The three health states modelled were pre-progression, post-progression, and death. Patients with MM require lifelong treatment and are likely to receive multiple lines of therapy. Thus, the costs associated with multiple lines of treatment are relevant. For the adequate modelling of treatment-related costs, it was necessary to keep track of treatment status in both the pre- and post-progression health states.

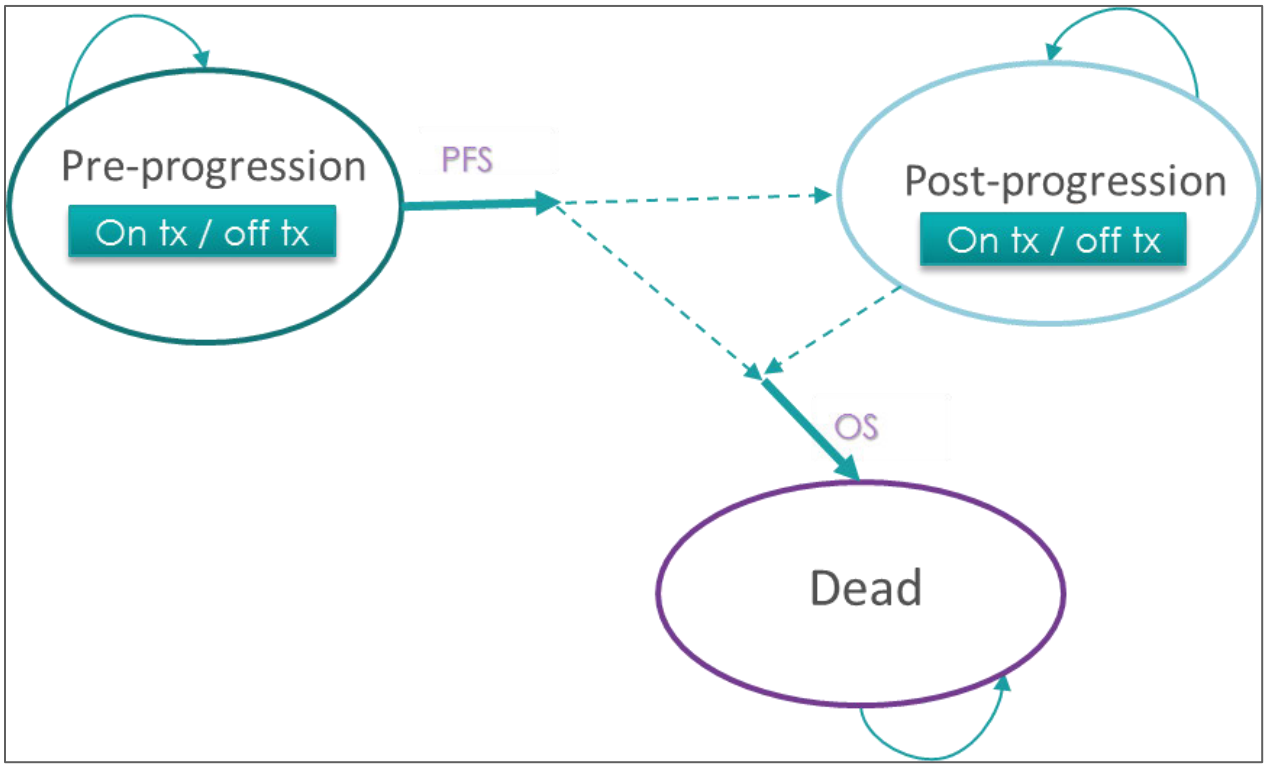
- Progression-free
    - On treatment

    - Off treatment
- Post-progression
    - On subsequent treatment(s)
    - Off treatment
- Death

Patients with NDMM who are ineligible for ASCT enter the model, initiate front-line treatment, and experience an interval of PFS. Patients who experience disease progression and do not die during the initial modelled line of treatment continue to the post-progression health state, in which they may receive subsequent treatments. Patients may discontinue treatment or die at any time in the model.

Figure 1 illustrates the survival partition health states for the model. This approach applies treatment-specific and independent OS and PFS curves for each comparator.

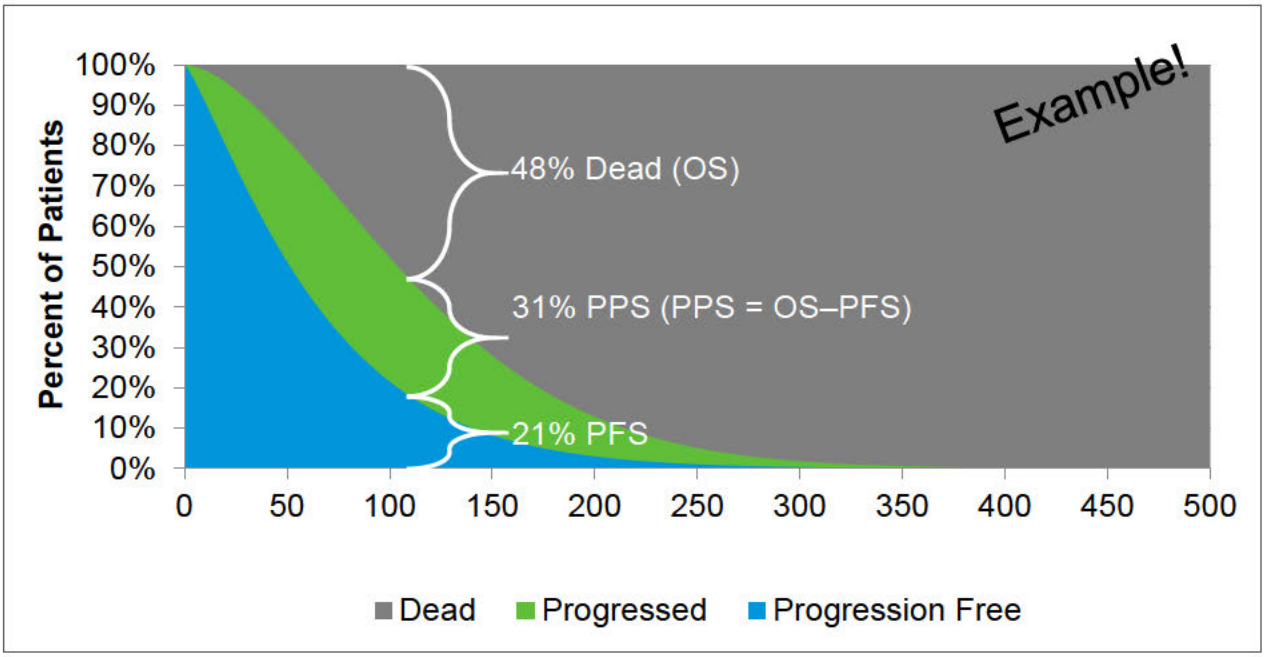
Figure 1. Model Diagram of Survival Partition Approach



Legend: Dotted lines represent the fact the transitions between health states are not directly tracked, but proportions of patients in each health state are calculated through the partition approach at each time point.
Abbreviation: OS = overall survival; PFS = progression-free survival; tx = treatment

The partition survival model (PSM) does not directly calculate transitions between health states; instead, it partitions the population into groups. The method postulates that at any timepoint, the proportion of patients falling under the PFS curve is in the pre-progression health state, the proportion of patients falling above the OS curve is in the death health state, and those remaining must be in the post-progression health state (Figure 2). In the PSM, the efficacy of treatment with respect to PFS does not directly impact OS (PFS and OS are independent).

Figure 2. Survival Partition Approach



Abbreviation: OS = overall survival; PFS = progression-free survival; PPS = post-progression survival

The model also captures the proportion of patients on and off treatment within each health state using the same partition approach: patients falling under the time-to-treatment discontinuation (TTTD) curve are on treatment, while the proportion of patients between the TTTD and PFS curves must be in the pre-progression health state but off treatment.

During pre-progression, patients could stop receiving front-line treatment based on the treatment duration and stop accruing treatment-related costs; however, these patients will not switch to second-line treatments unless they progress.

In the post-progression health state, a proportion of patients can receive second-line treatment. PFS and TTTD can be modelled explicitly for second-line treatment, or treatment-to-progression can be assumed. Treatment-related costs are accrued based on the treatment duration of the second-line treatments; however, these patients will not switch to third-line treatment unless they progress for a second time. Once patients experience progression after receiving second-line treatment, a proportion can receive third-line treatment. However, unlike with first- and second-line treatment, progression is not explicitly modelled for third-line treatment; only treatment costs are accrued while the patient is receiving third-line treatment based on the duration for this line.

In the survival partition approach, the efficacy of treatment with respect to PFS does not directly impact OS. Another factor to consider is that the efficacy of subsequent treatments is already captured by the OS data, while their costs need to be captured explicitly and consistently with the actual subsequent treatments applied in the OS of the source trial.

Costs were assigned to each health state. Costs were accrued and summarized for each cycle of the model (one week) so the difference in cumulative cost could be analysed and compared between comparators.

2.1.1 Treatments

2.1.1.1 Treatment Duration - Pre-progression

Time-to-treatment discontinuation (TTTD) curves were included for all treatment regimens to account for the fact that patients may stop treatment before progression due to other causes, such as intolerable AEs. TTTD was modelled independently from PFS in the base case since the reasons behind discontinuation were not necessarily linked to efficacy. If patients stop treatment before progression, they stop accruing treatment-related costs (e.g., drug acquisition, administration, monitoring while on treatment); however, patients only start receiving second-line treatment when progression occurs. It is possible to use the reported median treatment duration from the trials and assume an exponential distribution to predict and extrapolate duration over time.

Comparators with fixed duration of treatment (e.g. BorMelPred & LenDex18) were assumed to be discontinued at their specified maximum duration. Due to lack of data on TTTD for other comparators, assumptions needed to be made. For BorLenDex, the median duration was calculated by summing up the 24 weeks of induction and 17.4 months median LenDex, taken from the latest SWOG study follow up (10). This median was used to assign an exponential curve for TTTD.

[redacted]

Pre-progression death was modelled to avoid overestimating the proportion of patients that survive progression and go on to receive subsequent therapies, which would have a cost/resource use impact within the model. Mortality for the pre-progression health state can be modelled in two ways: 1) by assuming a constant mortality rate or 2) assuming a constant ratio of death events among PFS events. The base case uses a constant mortality rate. A constant ratio for death events among PFS events are tested in a sensitivity analysis.

2.1.1.2 Subsequent Treatments - Post-progression

Patients with MM receive multiple lines of treatment. Therefore, subsequent treatments represent a significant component of costs, and modelling is a critical aspect of the assessment. The choice and efficacy of treatment in subsequent lines may depend on the options selected and efficacy obtained in prior lines. This dependency creates a difficult modelling challenge, as there is little information available from clinical trials regarding:

- The number of subsequent treatment lines

- The treatments applied in subsequent lines
- The duration of subsequent treatments
- The clinical efficacy of subsequent treatment options, especially regarding prior treatment history

For second-line treatments, if there is a lack of TTTD data, treat-to-progression is assumed. The median treatment duration was selected due to data availability. Once progressed, patients start receiving third-line treatment.

Once patients experience progression after receiving second-line treatment, a proportion can receive third-line treatment. Patients accrue treatment-related costs based on the median duration as reported in the literature. However, disease progression and switch to subsequent lines (i.e., fourth line and above) were not considered in the model.

The costs of subsequent treatments are accrued in the model explicitly and based on expected shares of the actual subsequent treatments in the Danish setting.

2.1.2 Model Outcome Measures relevant to the Danish setting

The model aggregates costs from each health state and reports the discounted costs (discounted at 4.0% per annum):

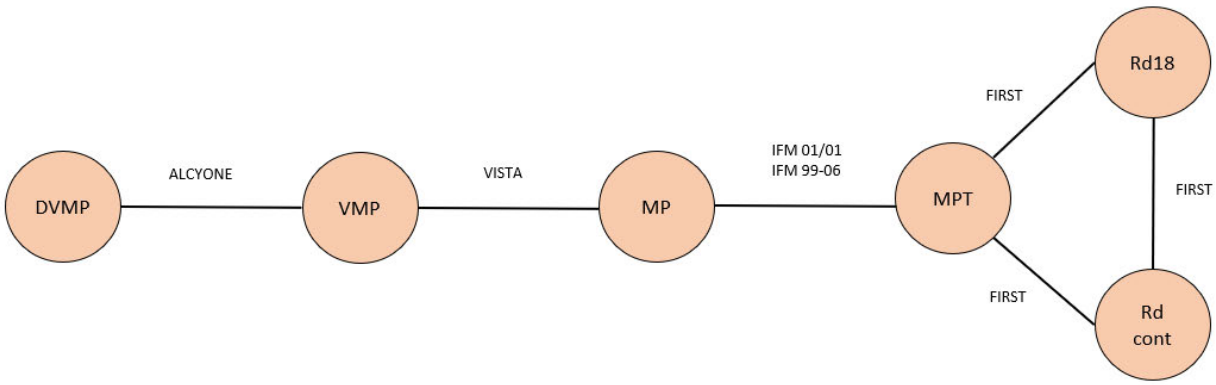
- First-, second-, and third-line drug acquisition, administration, and monitoring (on and off treatment) costs, concomitant and prophylactic medications (for first-line treatment only), AE management costs (for first-line treatment only), patient costs (first and second line), and terminal costs.

Establishing Relative Efficacy

In the absence of head-to-head clinical trial evidence comparing DaraBorMelPred to all relevant comparators, a systematic literature review (SLR) was conducted to identify clinical data for comparators in accordance with the search-strings provided by from the Medicines Council in the protocol for DaraBorMelPred (1). This is described in detail for the clinical part of this application. Furthermore, an NMA were also conducted to establish the relative efficacy versus the relevant comparators, including a sensitivity analysis vs. BorLenDex.

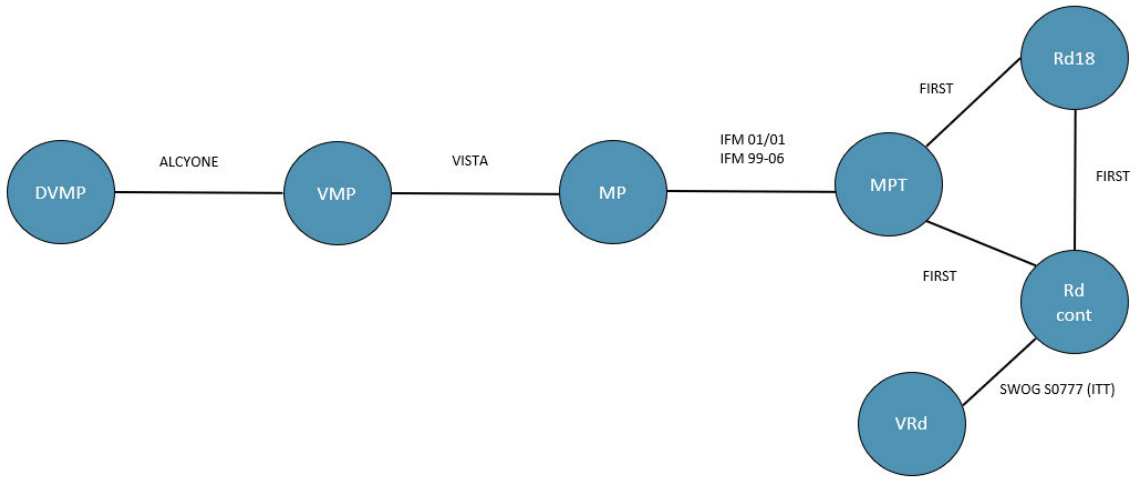
The network of evidence for PFS and OS is shown in Figure 3 and Figure 4.

Figure 3: Network of evidence of Overall Survival and Progression-free survival, excluding BorLenDex



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex,

Figure 4: Network of evidence of Overall Survival and Progression-free survival, including BorLenDex



Abbreviations: DVMP = DaraBorMelPred, VMP: BorMelPred, MP: MelPred, MPT: MelPredThal, Rd18: LenDex18, Rd cont: LenDex, VRd: BorLenDex

The NMA provides a formal, systematic framework and statistical methodology for determining the relative efficacy (e.g., HR) of different treatments using an evidence base of RCTs that individually do not compare all treatment options. The relative efficacy of different treatments connected to each other in a network can be estimated via a common comparator. The NMA performed used a Bayesian framework allowing for the ranking of treatments in terms of efficacy or safety, providing a systematic and structured approach for establishing relative outcomes of treatment arms not evaluated directly in a head-to-head trial.

This section of the economic report aims to summarise the key considerations of the NMAs relevant for modelling. A full justification of feasibility, methodology, assumptions, and results of the NMA is available in the clinical part of this application.

2.1.3 Results of the NMA

Table 2 & Table 3 shows the NMA OS results for the comparators specified in the protocol for DaraBorMelPred; excluding and including BorLenDex, considering the SWOG S0777 ITT population based on data from the EPAR (11). The same is shown for PFS in Table 4 and Table 5. It should be noted the SWOG S0777 ITT population were younger and more fit compared to the rest of the trials which is described in detailed in the clinical part of this application. Across the trials, the longest follow-up were applied as requested in the protocol for DaraBorMelPred. For the VISTA trial (12), longest follow-up for OS is a median follow-up for 60.1 months.

Table 2. OS NMA Results (VISTA median follow-up = 60.1), Network excluding BorLenDex (SWOG S0777 ITT)—HR for Relevant Comparators vs. DaraBorMelPred and BorMelPred

	vs. DaraBorMelPred			vs. BorMelPred		
Comparator	HR	Lower Limit CrL	Upper Limit CrL	HR	Lower Limit CrL	Upper Limit CrL
DaraBorMelPred	1.00	1.00	1.00	0.60	0.45	0.79
BorMelPred	1.67	1.26	2.2	1.00	1.00	1.00
LenDex18	1.16	0.76	1.78	0.70	0.50	0.97
LenDex	1.18	0.77	1.81	0.71	0.51	0.99

Abbreviations: CrL = credible interval; DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; LenDex18 = lenalidomide and dexamethasone for 18 cycles, LenDex = lenalidomide and dexamethasone; BorMelPred = bortezomib, melphalan, and prednisone

Table 3. OS NMA Results (VISTA median follow-up = 60.1), Network Including BorLenDex (SWOG S0777 ITT)—HR for Relevant Comparators vs. DaraBorMelPred and BorMelPred

	vs. DaraBorMelPred			vs. BorMelPred		
Comparator	HR	Lower Limit CrL	Upper Limit CrL	HR	Lower Limit CrL	Upper Limit CrL
DaraBorMelPred	1.00	1.00	1.00	0.60	0.45	0.79
BorMelPred	1.67	1.26	2.20	1.00	1.00	1.00
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LenDex18	1.16	0.76	1.79	0.7	0.50	0.97
LenDex	1.18	0.77	1.82	0.71	0.51	0.99

Abbreviations: CrL = credible interval; DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; LenDex18 = lenalidomide and dexamethasone for 18 cycles, LenDex = lenalidomide and dexamethasone; BorMelPred = bortezomib, melphalan, and prednisone; BorLenDex = bortezomib, lenalidomide, and dexamethasone

[redacted]

Table 4. PFS NMA Results, Network excluding BorLenDex —HR for Comparator vs. DaraBorMelPred and BorMelPred

	vs. DaraBorMelPred			vs. BorMelPred		
Comparator	HR	Lower Limit CrL	Upper Limit CrL	HR	Lower Limit CrL	Upper Limit CrL
DaraBorMelPred	1.00	1.00	1.00	0.42	0.34	0.51
BorMelPred	2.38	1.94	2.92	1.00	1.00	1.00
LenDex18	2.35	1.47	3.75	0.99	0.65	1.51
LenDex	1.65	1.03	2.64	0.69	0.45	1.06

Abbreviations: CrL = credible interval; DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; LenDex18 = lenalidomide and dexamethasone for 18 cycles, LenDex = lenalidomide and dexamethasone; BorMelPred = bortezomib, melphalan, and prednisone

Table 5. PFS NMA Results, Network Including BorLenDex —HR for Comparator vs. DaraBorMelPred and BorMelPred

	vs. DaraBorMelPred			vs. BorMelPred		
Comparator	HR	Lower Limit CrL	Upper Limit CrL	HR	Lower Limit CrL	Upper Limit CrL
DaraBorMelPred	1.00	1.00	1.00	0.42	0.34	0.51
BorMelPred	2.38	1.94	2.92	1.00	1.00	1.00
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LenDex18	2.35	1.47	3.76	0.99	0.65	1.51
LenDex	1.65	1.03	2.64	0.69	0.45	1.06

Abbreviations: CrL = credible interval; DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; LenDex18 = lenalidomide and dexamethasone for 18 cycles, LenDex = lenalidomide and dexamethasone; BorMelPred = bortezomib, melphalan, and prednisone; BorLenDex = bortezomib, lenalidomide, and dexamethasone

[redacted]

Extended results including HRs versus all treatments included in the NMA are shown in Appendix A. These were the results presented in the clinical part of this application.

3 Inputs and Data Sources

Patient Characteristics

The patient population of modelled scenarios have been adjusted to reflect data from Denmark (4, 5). Relevant patient characteristics for the economic model are presented in Table 6. These patient characteristics are used in the base case for the results.

Table 6. Population Characteristics at Baseline

Parameter	Value	Source	Purpose
Median age, years	71.0	Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose) (6) / ALCYONE (4)	Inform background population mortality
Mean weight, kg	73.4	Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose) (6)	Inform weight-based drug dosing
Mean BSA, m^2	1.84	Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose) (6)	Inform BSA-based drug dosing

Abbreviations: BSA = body surface area

Establishing the Relative Efficacy of DaraBorMelPred

The ALCYONE trial was used to derive clinical data for DaraBorMelPred and BorMelPred, as patient-level data were available. The NMA was used for the efficacy inputs of pre-specified treatment comparators, and individual clinical trials were used to inform the TTTD for the comparators not included in the ALCYONE trial. Extrapolations of PFS and OS based on patient-level data were aligned with the guidance provided by the Medicines Council (3) which follows the recommendations in the NICE Decision Support Unit (DSU) Report 14 (13). Six parametric distributions were fitted to model OS, PFS, and TTTD data, and were implemented in the model. These are the Exponential distribution, Weibull and Gompertz distributions, Log-logistic and Log-normal distributions and the Generalised Gamma distribution. Following considerations based on e.g. observed data regarding goodness-of-fit and plausibility of results the "best-fitting" distribution was selected for the base case analysis (13, 14).

- The Exponential distribution is a one-parameter function that is considered the simplest parametric model. The Exponential model is a proportional hazards model, meaning it is assumed that the HR for the two groups being compared is constant over time.
- The Weibull and Gompertz distributions are functions with two parameters—a shape and scale. Therefore, these two distributions are more flexible than the Exponential distribution. Both distributions are proportional hazards models.
- The Log-logistic and Log-normal distributions share many similarities. They have a hazard function that can be non-monotonic with respect to time. Therefore, neither of the distributions can be parameterised as a proportional hazards model. Furthermore, due to their functional forms, the Log-logistic and Log-normal models typically produce long tails in the survivor function. As a result, the clinical validity of Log-logistic and Log-normal survival models must be carefully assessed.
- The Generalised Gamma distribution is a flexible three-parameter model. The Weibull, Exponential, and Log-normal distributions are special cases of the Generalised Gamma distribution. However, due to its flexibility, the long-term projections may be unduly influenced by the end of the Kaplan-Meier

(KM) curves, which are based on a small number of patients. Therefore, similar to the Log-normal and Log-logistic distributions, the clinical validity of the projected survival must be assessed.

The process of selecting a 'best-fitting' distribution involves considerations based on the observed data regarding goodness-of-fit and plausibility of results(13, 14):

- Graphical assessment of fits
- Goodness-of-fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]). Statistically, the best fit to the observed data is the curve with the lowest AIC and BIC.
- Clinical plausibility of long-term projections
- Comparison of long-term projections with external sources (if available)

'Best fitting' does not necessarily imply good fit; the best-fitting distribution may still deviate from the observed data or produce clinically implausible long-term projections. [redacted]

The following sections list the relevant data from the fitting exercises, including predicted versus observed curves, parameters of the survival distributions, AIC and BIC values, diagnostic plots for each fit, and HRs for the comparators.

All parametric fits to survival data discussed in this section were obtained using the LIFETEST and LIREG procedures from Statistical Analysis System (SAS) version 9.4.

OS

The different modelling options for the OS curve are shown in Table 7, the approach highlighted in green is used in the base case for DaraBorMelPred, BorMelPred, LenDex18, BorLenDex, and LenDex OS. Further details on recommendations are provided in the following section.

[redacted]

[redacted]	[redacted]	LenDex18	BorLenDex	LenDex
[redacted]		HR vs. reference curve*	HR vs. reference curve*	HR vs. reference curve*
[redacted]	[redacted]			
[redacted]	[redacted]			

Green highlight: Recommended approach

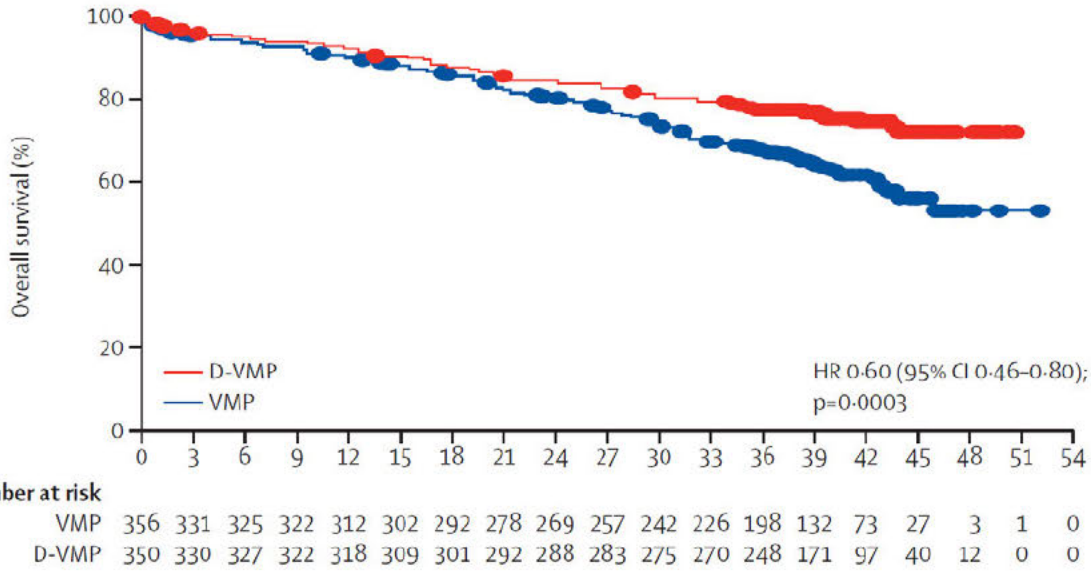
[redacted]

3.1.1 DaraBorMelPred and comparator OS

[redacted]

[redacted]

Figure 5. OS Observed—DaraBorMelPred and BorMelPred



Abbreviations: D-VMP= daratumumab in combination with bortezomib, melphalan, prednisone; OS = overall survival; VMP = bortezomib, melphalan, and prednisone

Following the recommendations from the NICE Decision Support Unit (Latimer 2013) on survival data extrapolation which is mentioned in the guidance from the Medicines Council (3) (Latimer 2013), proportionality between the DaraBorMelPred and BorMelPred OS curves was assessed to determine if individual parametric curves should be fit for DaraBorMelPred and BorMelPred, or if a proportional hazard model in which treatment is a predictor can be used (13). This assessment was done using the Schoenfeld residuals plot (Appendix B., Figure 6) for OS.

[redacted]

[redacted]

The clinical plausibility of the OS longer-term projections for BorMelPred was assessed by comparing them to the reported OS from two clinical trials and one retrospective analysis study (Appendix B. Figure 9): Palumbo et al. (2014) (15), San Miguel et al. (2013; VISTA) (12), and Mateos et al. (2014) (16). These studies were selected because the target populations (i.e., patients enrolled—with NDMM who are ineligible for ASCT) and dosing schedule for BorMelPred was similar to that of the ALCYONE trial, and because they reported KM curves for OS after at least five years of follow-up. As DaraBorMelPred is a new treatment, the OS longer-term projections cannot be compared with external data.

[redacted]

3.1.1.2 Base case choice for BorLenDex, LenDex18 and LenDex - NMA

To model OS for LenDex18, BorLenDex and LenDex, the base case is to apply the HRs versus BorMelPred based on the HRs from the NMA shown in section 2.1.3. The respective OS curves used in the base case can be found in Appendix B., Figure 18.

PFS

The following sections provide details on the different options to model PFS for first-line DaraBorMelPred, BorMelPred, LenDex18, BorLenDex, and LenDex (summarised in Table 8 with the base case approach highlighted in green). Further details are provided in the next sections.

Table 8. PFS Modelling Options Included in the Model

[redacted]	[redacted]	LenDex18	BorLenDex	LenDex
[redacted]		HR vs. reference curve*	HR vs. reference curve*	HR vs. reference curve*
[redacted]				
[redacted]				
[redacted]				

*PFS reference curves included in the model: DaraBorMelPred, BorMelPred
Green highlight: Recommended approach

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Following recommendations by the NICE Decision Support Unit on survival data extrapolation, proportionality between the DaraBorMelPred and BorMelPred PFS curves was assessed to determine if individual parametric curves should be fit for DaraBorMelPred and BorMelPred, or if a proportional hazard model in which treatment is a predictor can be used (13). This assessment was done using the Schoenfeld residuals plot (Appendix B., Figure 14) for Weeks 58-plus PFS.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]. The clinical plausibility of the longer-term PFS extrapolations for BorMelPred was assessed by comparing them to the reported PFS from one clinical trial (Palumbo et al. [2014](15)) and one retrospective analysis (Mateos et al. [2014] (16)). These studies were selected because the target populations (i.e., patients enrolled) were similar to that of the ALCYONE trial—patients with NDMM who are ineligible for ASCT; they reported KM curves for PFS after at least five years of follow-up, and the dosing schedule for BorMelPred was similar to the dosing schedule for BorMelPred in the ALCYONE trial.

The PFS KM curves from Palumbo et al. (2014) (15) and Mateos et al. (2014) (16) were digitised, and the data were extracted using the Guyot et al. (2012) (17) method.

As DaraBorMelPred is a new treatment for patients with NDMM who are ineligible for ASCT, the longer-term PFS projections cannot be compared with external data.

[redacted]

3.1.3 Base case choice for LenDex18, BorLenDex, and LenDex - NMA

BorMelPred was chosen as the reference distribution in the base case for PFS for both BorLenDex, LenDex18 and LenDex as this is consistent with the choice of using BorMelPred as the reference curve for the HRs from the NMA for OS. The respective PFS curves used in the base case can be found in Appendix B., Figure 10

Death during Second-Line PFS

The incidence of progression in each model cycle (one week) is calculated to track patients receiving second-line treatment and PPS. Some patients may die in the pre-progression state; therefore, to avoid over-estimating the incidence of progression, pre-progression death was explicitly incorporated.

Death during the pre-progression state can be modelled in two ways: by assuming a constant mortality rate, or by assuming a constant ratio of death to progression among PFS events.

The ratio and rate of mortality were calculated based on data from the DaraBorMelPred arm of the ALCYONE for DaraBorMelPred, and from the BorMelPred arm of the ALCYONE trial for BorMelPred. For other comparators, the ratio and rate of mortality were assumed equal to that calculated for BorMelPred.

The base case assumption is a constant mortality rate for DaraBorMelPred and all comparators, as it is more in line with the understanding of the role of progression in MM. The constant mortality rate can be thought of as a reflection of a background mortality, which is not necessarily directly MM-related.

- Using a constant rate of mortality:

$$Pre-progression\ Deaths(t) = PFS(t-1) \times Rate\ of\ Death\ during\ PFS$$

- Using a constant ratio of death and progression:

$$Pre-progression\ Deaths(t) = [PFS(t-1) - PFS(t)] \times Ratio\ of\ Death\ during\ PFS$$

[redacted]

Comparators	Constant Ratio of Death and Progression	Source	Constant Mortality Rate (Weekly)	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Clinical cut-off date of 24 June 2019; median follow-up 40.1 months

Abbreviations: DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; PFS = progression-free survival; BorMelPred = bortezomib, melphalan, and prednisone

[redacted]

Treatment Duration

Treatment duration is a key driver of costs. In the model, stopping treatment affects only cost outcomes, and not efficacy outcomes, which are determined by PFS/OS. However, there is a high positive correlation between TTTD and efficacy, especially for PFS. In the model, the treatment duration was modelled independently from efficacy, although the input parameters of the PFS and TTTD curves are naturally correlated.

[redacted]

Treatments with a fixed duration, the model caps TTTD at the maximum fixed duration; although, it is possible for patients to discontinue treatment before the fixed duration.

3.1.4 First-line Treatment Duration

First-line treatment costs were accrued according to the predicted duration of first-line treatment based on TTTD. The model allows for selection of a TTTD projection method from the options shown in Table 10. It should be noted that the model calculations ensure that, irrespective of the approach selected to model TTTD, the curve is never above the PFS curve; patients are assumed to discontinue treatment when progression occurs. In addition, being off treatment does not mean that patients switch to second-line treatment. Patients switch from front-line to second-line treatment only after disease progression occurs, based on PFS.

Table 10 shows the options for first line TTTD for DaraBorMelPred, BorMelPred, LenDex18, BorLenDex and LenDex. The base case approaches are highlighted in green.

Table 10. DaraBorMelPred Network: TTTD Curve Options

[redacted]	[redacted]	LenDex18	BorLenDex	LenDex
[redacted]	[redacted]	Median treatment duration per trial	Median treatment duration per trial	Median treatment duration per trial
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]				—
[redacted]				

Abbreviations: DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; BorLenDex = bortezomib, lenalidomide, and dexamethasone; HR = hazard ratio; PFS = progression-free survival; BorMelPred = bortezomib, melphalan, prednisone

[redacted]

3.1.5 Base Case for DaraBorMelPred – Segmented Parametric Survival Analysis

[redacted] For BorMelPred, as it has a fixed duration, no extrapolation is required, and the KM curve data can be used directly in the model. For BorLenDex, LenDex18 and LenDex due to lack of data on TTTD and using a consistent approach for the comparators, the median treatment duration is applied to construct the exponential treatment discontinuation curve (see section 3.1.5.1).

Appendix B., Figure 19 shows the observed PFS and TTTD KM curves from the ALCYONE trial for DaraBorMelPred. As previously mentioned, patients receiving DaraBorMelPred and BorMelPred stop receiving BorMelPred after 54 weeks.

[redacted]

[redacted]

[redacted]

The parameters of the distributions are shown in Appendix B., Distribution Parameters.

[redacted]

3.1.5.1 Fixed Duration (BorMelPred & LenDex18)

BorMelPred has a fixed regimen of nine six-week cycles. Therefore, there is no need for long-term extrapolation of the TTTD for BorMelPred, and the KM data from the ALCYONE trial can be used directly.

LenDex18 is also a fixed regimen. To model treatment duration for LenDex18 an exponential TTTD curve was estimated based on the median treatment duration (16.6 months) reported in Facon et al.2018 (18). This curve is used to estimate treatment duration until cycle 18 when LenDex18 treatment is assumed to be stopped.

3.1.5.2 Median Treatment Duration and Treat-to-Progression Approaches

For all first-line and second-line treatments, a TTTD curve can be modelled according to the following options:

- ***Median Duration per Trial:*** A constant treatment discontinuation rate is used based on the median treatment duration reported in clinical trials (Table 11). In this approach, the TTTD curves are Exponential (i.e., with a constant rate of treatment discontinuation) and match the median treatment duration reported in the corresponding trials (using the equation below). Hence, it considers treatment discontinuations for any reason, although it is not explicitly modelled. However, using the median treatment duration does not consider patients who were censored in the clinical trial due to the data cut on a specific data (i.e., some patients could continue to receive treatment after the day of the data cut that is used to report the median treatment duration).

$$Weekly\ treatment\ discontinuation\ rate = \frac{-\ln(0.5)}{median\ treatment\ duration\ (in\ weeks)}$$

- ***Treat to Progression:*** In this approach, treatment discontinuation is not modelled. The duration of treatment is determined exactly by the PFS associated with the treatment. Discontinuation due to AEs or other non-clinical reasons are not considered. This approach may overestimate treatment duration and thus treatment costs for each comparator.

Table 11. First-line Median Treatment Duration

Treatment	Median Treatment Duration (Months)	Reference
DaraBorMelPred	[redacted]	ALCYONE*
BorMelPred	[redacted]	ALCYONE*
LenDex18	16.6	Facon et al. 2018 (18)
BorLenDex	23.4	SWOG S0777 study (10)
LenDex	18.4	Facon et al. 2018 (18)

* Clinical cut-off 200 OS events, cut-off date of 24 June 2019, median follow-up of 40.1 months. Data-on-file

Abbreviations: DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; BorMelPred = bortezomib, melphalan, and prednisone; LenDex = lenalidomide and dexamethasone; ; LenDex18 = lenalidomide and dexamethasone (18 cycles) BorMelPred = bortezomib, melphalan, and prednisone

[redacted]

3.1.6 Second-line TTTD and PFS

Second-line treatment duration is required for costing purposes. For all second-line treatment comparators, a TTTD curve is assigned to each comparator arm according to the following options:

- **Median duration per trial**: in this approach, the TTTD curves are Exponential based on the median value reported per trials (i.e., with a constant rate of treatment discontinuation)
- **Treat to progression**: using second-line PFS estimates

The median treatment duration for each subsequent therapy (Table 12) is used to calculate the costs of second-line therapies for the duration the treatment is given. However, as with the first-line treatments, being off second-line treatment does not mean that patients switch to third-line therapies.

Patients switch from second to third line only after disease progression occurs, based on median PFS of the second-line treatment options (Table 12). Using the median duration reported in the trials may underestimate true TTTD due to the way censoring is handled in the calculation of this median. This is especially true for fixed-duration treatments. However, fixed treatment regimens in the second-line setting is presumably rarely used in Denmark.

As an alternative option, it is possible to assume second-line treatments are treat to progression. Median PFS for second-line treatment options are based on the NMAs for CASTOR (DaraBorMel) and POLLUX (DaraLenDex) for adults with relapsed/refractory MM who received at least one prior line of therapy (1PL). There are two NMAs available, one with LenDex as the reference and another with BorDex as the reference, as these backbones have separate populations. The HRs from the second-line NMAs are applied to the medians for LenDex and BorDex. The median for LenDex is taken from ITT population in POLLUX (DRd vs. LenDex), and the median for BorDex is taken from the ASPIRE trial (19). ASPIRE was selected as the source for median PFS for BorDex as it had been reached in this trial, whereas it has not been reached in CASTOR (i.e., the median would need to be extrapolated, which would add uncertainty). However, it should be noted that the populations included in the second-line trials do not match those included in ALCYONE, as they include patients that will appear to be healthier than ALCYONE patients.

Where treatments are fixed duration, TTTD is capped at the maximum duration; however, prior to this timepoint, TTTD is extrapolated based on the median treatment duration reported in the trial or the median PFS.

Median duration per trial is used for second-line treatment duration in the model base case due to data availability and since the NMAs reported is not based a Danish setting. Sensitivity analysis is conducted for treat to progression. Alternatively, one could use the findings from the NMA conducted by the Medicines Council for the one prior line setting. A treatment such as pomalidomide in combination with bortezomib and dexamethasone is however missing from the network since the recommendation of this treatment regimen was evaluated after the NMA was conducted by the Medicines Council.

Table 12. Second-line TTTD and PFS

Second-line Treatment	Median Duration (Reported per Trial)		Median PFS (Calculated using HRs)		
	Months	Source	Months	HR	Source
DaraLenDex	34.0	MMY3003(20) IA3*	37.7	0.44	1PL NMA ASCO 2017 data, versus LenDex
DaraBorDex	13.3	MMY3004(21) IA3†	24.1	0.32	1PL NMA ASCO 2017 data, versus Vd
CarDex	9.2	ENDEAVOR study, Dimopoulos et al. 2016(20)	14.5	0.53	1PL NMA ASCO 2017 data, versus Vd
CarLenDex	20.2	ASPIRE study, Stewart et al. 2015(19)	24.1	0.69	1PL NMA ASCO 2017 data, versus LenDex
EloLenDex	17.0	ELOQUENT-2 study, Lonial et al. 2015(22)	23.4	0.71	1PL NMA ASCO 2017 data, versus LenDex
IxaLenDex	15.6	TOURMALINE study, Moreau et al. 2016(23)	22.3	0.75	1PL NMA ASCO 2017 data, versus LenDex
PomBorDex	8.8	OPTIMISMM study (24)	11.2	0.61	OPTIMISMM study (24)
PomDex	4.2	Dimopoulus et al. 2013(25)	12.1	1.38	1PL NMA ASCO 2017 data, versus LenDex
LenDex	15.9	MMY3003(20) IA3*	16.6	1.00	ASPIRE study, Stewart et al. 2015(19)

* Treatment length is capped based on weeks or number of treatment cycles. DaraBorDex: BorDex administered for up to 54 weeks maximum; Carfilzomib+LenDex: Carfilzomib administered for up to 72 weeks maximum

Abbreviations: 1PL = one prior line; ASCO = American Society of Clinical Oncology; dexamethasone; TTTD = time-to-treatment discontinuation

As for the case of the first line setting, for second-line treatments, the incidence of progression in each model cycle (one week) is calculated to track patients receiving third-line treatment. As some patients may die directly during pre-progression on second-line treatment, death during this state was incorporated when estimating the incidence of progression. A constant weekly mortality rate of 0.14% was used, based on the average of DaraBorDex and DaraLenDex networks in the 1PL setting.

3.1.7 Third-line Treatment Duration

A median treatment discontinuation of nine months was used for all third-line treatment options, based on the study by Kumar et al. (2012) (26). The TTTD curves are Exponential (i.e., with a constant rate of treatment discontinuation).

In the model, patients accrue treatment-related costs only while they are receiving treatment. In addition, being off treatment does not mean that patients switch to subsequent therapies; treatment switch happens only when progression occurs. However, the model does not model the switch from third- to fourth-line treatment or beyond.

Once patients receive third-line treatment, they stay on treatment based on the median treatment duration of nine months, after which they continue to accrue non-treatment-related costs (e.g., monitoring) until they die or the end of the model time horizon is reached.

Adverse Events

Only grade ≥3 AEs occurring in ≥5% of study subjects in the DaraBorMelPred or BorMelPred arms of ALCYONE were considered in the model. The same was the case for the comparators. AEs for second- and third-line treatments were not considered.

This inclusion criterion was considered appropriate and sufficient to capture AEs that would impact patients with any consistency; this is to maintain validity in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting. It is also a conservative approach, because it ignores AEs that might have a higher occurrence for comparators in the model. In addition, a simplifying assumption has been made regarding the severity of the AE and whether it would require hospitalization. It is assumed that all AEs can be handled the same day. As the frequency of AEs are higher for most comparators, this will serve as a conserve approach and for BorLenDex, the AEs reported represents induction only (24 weeks) where the frequency of AEs are expected to be larger with longer follow-up. It was not feasible to collect information for each individual AE and investigate the proportion of patients that may need to be hospitalized. A similar approach was taken in the evaluation of BorLenDex and was accepted by Amgros (7). In this case, the cost was based on the DRG-code 17MA98 MDC17 giving a cost per event of DKK 3,285 across the various AEs.

AEs are assumed to occur only in the first year of treatment. Therefore, patients who remain 'on treatment' for subsequent years do not incur further AE-related costs. In addition, only AEs associated with initial (i.e., front line) treatment were considered.

The model uses the cumulative probabilities of AE occurrence during the treatment period. The cumulative probabilities of AEs are assumed to be independent of PFS and treatment duration. To account for differences in exposure time, treatment-specific cumulative probabilities for the ITT population over the entire trial duration are used to calculate an overall cost of AEs. A per-patient overall AE cost and utility decrement is applied as an on-off lump sum at the start of treatment.

3.1.8 AE Incidence

The cumulative probabilities of AE occurrence during the treatment period are shown in Table 13.

Table 13. Cumulative Probability of AEs

Adverse event (Grade 3 or 4)	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex	LenDex
Alanine aminotransferase increased	0.0%	0.0%	0.0%	5.0%	0.0%
Anemia	17.3%	19.8%	15.7%	12.2%	18.2%
Asthenia	0.0%	0.0%	6.1%	0.0%	7.7%
Back pain	0.0%	0.0%	6.3%	0.0%	7.0%
Cardiac disorder	0.0%	0.0%	7.2%	0.0%	11.8%
Cataract	0.0%	0.0%	0.0%	0.0%	5.8%
Deep-vein thrombosis, pulmonary embolism, or both	0.0%	0.0%	5.6%	0.0%	7.9%
Dehydration	0.0%	0.0%	0.0%	8.4%	0.0%
Diarrhea	0.0%	0.0%	0.0%	9.2%	0.0%
Dyspnea	0.0%	0.0%	0.0%	6.1%	5.6%
Embolism	0.0%	0.0%	0.0%	6.9%	0.0%
Fatigue	0.0%	0.0%	8.5%	14.5%	7.3%
Hyperglycemia	0.0%	0.0%	0.0%	7.3%	5.3%
Hypertension	5.5%	0.0%	0.0%	0.0%	0.0%
Hypocalcemia	0.0%	0.0%	0.0%	6.5%	0.0%
Hypokalemia	0.0%	0.0%	0.0%	11.5%	6.6%
Hyponatremia	0.0%	0.0%	0.0%	6.5%	0.0%
Hypotension	0.0%	0.0%	0.0%	7.6%	0.0%
Infection	0.0%	0.0%	21.9%	0.0%	28.9%
Leukocytopenia	8.1%	8.5%	5.6%	8.8%	0.0%
Lung infection	0.0%	0.0%	0.0%	7.3%	0.0%
Lymphopenia	7.8%	6.2%	0.0%	18.7%	5.6%
Muscular weakness	0.0%	0.0%	0.0%	8.4%	0.0%
Neutropenia	40.2%	39.0%	26.5%	9.9%	27.8%
Peripheral motor neuropathy	0.0%	0.0%	0.0%	6.5%	0.0%
Peripheral sensory neuropathy	0.0%	0.0%	0.0%	20.6%	0.0%
Pneumonia	13.0%	4.2%	8.3%	0.0%	8.1%
Rash	0.0%	0.0%	5.2%	0.0%	6.2%
Syncope	0.0%	0.0%	0.0%	8.8%	0.0%
Thrombocytopenia	34.7%	37.9%	8.0%	17.2%	8.3%
Source	ALYCONE*	ALYCONE*	FIRST**	SWOG S0777***	FIRST**

* Median follow-up of 40.1 months

** Median follow-up of surviving patients: 37 months

*** Induction only (24 weeks), younger and more fit patient population.

Costs

Disease- and treatment-related costs are applied to each health state and event in the model. Cost categories include drug acquisition and administration applied for the duration of active treatment (determined by dosing regimen and treatment duration); costs of routine follow-up care; patient costs (time spend by patient) and the costs of unplanned events, such as AEs, progression, and terminal care costs.

3.1.9 Drug Acquisition Costs

Drug acquisition cost for the treatment options included in the model have been retrieved from medicinpriser.dk. The prices reflect the pharmacy purchase price (list price) and are shown in Table 14. It includes various regimens which may be administered in the first-, second-, and/or the third-line setting.

Table 14. Drug Acquisition Cost

Drug	Strength	Pack size	AIP (Price)	Source/notes
Daratumumab	400.0	1	DKK 13,299.55	Medicinpriser.dk / Pharmacy Purchase Price
Daratumumab	100.0	1	DKK 3,396.38	Medicinpriser.dk / Pharmacy Purchase Price
Carfilzomib	60.0	1	DKK 8,656.89	Medicinpriser.dk / Pharmacy Purchase Price
Carfilzomib	30.0	1	DKK 4,328.44	Medicinpriser.dk / Pharmacy Purchase Price
Carfilzomib	10.0	1	DKK 1,442.81	Medicinpriser.dk / Pharmacy Purchase Price
Elotuzumab	400.0	1	DKK 9,718.92	Medicinpriser.dk / Pharmacy Purchase Price
Elotuzumab	300.0	1	DKK 7,289.19	Medicinpriser.dk / Pharmacy Purchase Price
Ixazomib	4.0	3	DKK 50,493.57	Medicinpriser.dk / Pharmacy Purchase Price
Ixazomib	3.0	3	DKK 50,493.57	Medicinpriser.dk / Pharmacy Purchase Price
Ixazomib	2.3	3	DKK 50,493.57	Medicinpriser.dk / Pharmacy Purchase Price
Bortezomib	3.5	1	DKK 1,940.00	Medicinpriser.dk / Pharmacy Purchase Price
Lenalidomide	25.0	21	DKK 40,845.82	Medicinpriser.dk / Pharmacy Purchase Price
Lenalidomide	10.0	21	DKK 35,383.03	Medicinpriser.dk / Pharmacy Purchase Price
Melphalan	2.0	25	DKK 540.98	Medicinpriser.dk / Pharmacy Purchase Price
Cyclophosphamide	50.0	100	DKK 907.64	Medicinpriser.dk / Pharmacy Purchase Price
Dexamethasone	4	20	DKK 157.00	Medicinpriser.dk / Pharmacy Purchase Price
Dexamethasone	1	100	DKK 492.00	Medicinpriser.dk / Pharmacy Purchase Price
Dexamethasone	100	1	DKK 70.00	Medicinpriser.dk / Pharmacy Purchase Price
Dexamethasone	200	1	DKK 130.00	Medicinpriser.dk / Pharmacy Purchase Price
Thalidomide	50.0	28	DKK 2,355.17	Medicinpriser.dk / Pharmacy Purchase Price
Prednisone (Methylprednisolone PO)	16	50	DKK 114.00	Medicinpriser.dk / Pharmacy Purchase Price
Prednisone (Methylprednisolone PO)	4	100	DKK 96.00	Medicinpriser.dk / Pharmacy Purchase Price
Panobinostat	20.0	6	DKK 29,725.33	Medicinpriser.dk / Pharmacy Purchase Price
Panobinostat	15.0	6	DKK 29,725.33	Medicinpriser.dk / Pharmacy Purchase Price
Panobinostat	10.0	6	DKK 29,725.33	Medicinpriser.dk / Pharmacy Purchase Price
Pomalidomide	4.0	21	DKK 58,467.74	Medicinpriser.dk / Pharmacy Purchase Price
Pomalidomide	3.0	21	DKK 57,591.06	Medicinpriser.dk / Pharmacy Purchase Price
Pomalidomide	2.0	21	DKK 56,714.36	Medicinpriser.dk / Pharmacy Purchase Price
Pomalidomide	1.0	21	DKK 55,836.79	Medicinpriser.dk / Pharmacy Purchase Price

Data retrieved from Medicinpriser.dk, accessed 04. May 2020. Prices are list price (pharmacy purchase price).

Dosing regimens for the front-line comparators included in the model are shown in Table 15. Dose regimens are used in the model to inform the cost of treatment.

Table 15. Summary of Front-line Dosing Regimens

Treatment Regimens		Dose/Admin	Admin/Cycle	Cycle Length	Relative Dose Intensity	Source
DaraBorMelPred						
Daratumumab	Cycle 1	16 mg/kg	6	6 weeks	[redacted]	ALCYONE*
	Cycles 2–9	16 mg/kg	2	6 weeks	[redacted]	
	Cycles 10+	16 mg/kg	1	4 weeks	[redacted]	
Bortezomib	Cycle 1	1.3 mg/m^2	8	6 weeks	[redacted]	
	Cycles 2–9	1.3 mg/m^2	4	6 weeks	[redacted]	
Melphalan	Cycles 1–9	9 mg/m^2	4	6 weeks	[redacted]	
Prednisone	Cycles 1–9	60 mg/m^2	4	6 weeks	[redacted]	
BorMelPred						
Bortezomib	Cycle 1	1.3 mg/m^2	8	6 weeks	[redacted]	ALCYONE*
	Cycles 2–9	1.3 mg/m^2	4	6 weeks	[redacted]	
Melphalan	Cycles 1–9	9 mg/m^2	4	6 weeks	[redacted]	
Prednisone	Cycles 1–9	60 mg/m^2	4	6 weeks	[redacted]	
LenDex18						
Lenalidomide	Cycles 1–18	25 mg	21	4 weeks	82.46%	Usmani et al.;(27)
Dexamethasone	Cycles 1–18	40 mg	4	4 weeks	81.31%	Usmani et al.;(27)
LenDex						
Lenalidomide	All cycles	25 mg	21	4 weeks	82.46%	Usmani et al.;(27)
Dexamethasone	All cycles	40 mg	4	4 weeks	81.31%	
BorLenDex						
Bortezomib	Cycles 1-8	1.3 mg/m^2	4	3 weeks	88.31%[5]	SWOG S0777 study; Durie et al. 2017 Lancet
Lenalidomide	Cycles 1-8	25 mg	14	3 weeks	82.46%[2]	
Lenalidomide	Cycles 9+	25 mg	21	3 weeks	82.46%[2]	Usmani et al.;(27)
Dexamethasone	Cycles 1-8	20 mg	8	3 weeks	81.31%[3]	
Dexamethasone	Cycles 9+	40 mg	4	4 weeks	81.31%[3]	

*Clinical cut-off date of 12 June 2018; median follow-up 27.5 months

**Assumed the same as melphalan in DaraBorMelPred; †Assumed the same as lenalidomide in LenDex from Usmani et al.;(27) ‡Assumed the same as dexamethasone in LenDex from Usmani et al.(27); ¥Assumed the same as bortezomib overall (Cycles 1-9) in DaraBorMelPred; ¶Assumed the same as prednisone in DaraBorMelPred.

[redacted]

3.1.9.1 Drug Wastage and dose intensity

For treatments that are dependent on weight or body surface area (BSA), some of the drug may be wasted if perfect vial sharing is not practiced. When vial sharing is used, the model calculates the exact dose needed for the patients, depending on their weight or BSA, and multiplies it by the per milligram cost of the drug.

A mean weight of 73.4 kg was applied utilised for therapies that depend on patient weight to calculate the dose. For therapies that depend on BSA to calculate dose, a value of 1.84 m^2 was utilized. The data was obtained from the evaluation of the therapeutic area of multiple myeloma conducted by the Medicines Council. The data is stated to be unpublished data from Region Capital in Denmark (6).

As in the real world, patients in clinical trials do not always receive the full doses of their assigned treatments. Data from clinical trials, therefore, may best reflect the efficacy of the received dose rather than the intended dose. To account for this, dose intensity is considered in the model and is used to adjust the drug cost in proportion to the doses received in the trial.

The model considers dose intensity and treatment discontinuation in the drug cost calculation. Treatment discontinuation accounts for discontinuation due to progression, AEs, maximum treatment duration, or other non-clinical reasons. Patients' exposure to the regimen during the on-treatment period is reflected via relative dose intensity. Relative dose intensity is calculated as the average of doses per treatment cycle received, divided by doses per cycle, according to the trial design. Applying both factors in the calculation of drug cost ensures that the drug exposure is consistent with the efficacy data from the ALCYONE trial.

Dose intensity was considered separately for each component of each combination treatment (Table 15). For the components of DaraBorMelPred and BorMelPred, the dose intensity was available from the ALCYONE clinical study report, cut-off date of 12 June 2018. For other front-line comparator therapies for which dose intensity data were not available from trial publications, the same dose intensities were assumed as for the components of DaraBorMelPred (Table 14).

The model is flexible regarding whether to consider wastage and dose intensity. The base case analysis considers dose intensity and no wastage (i.e., vial sharing is allowed). The applicant is under the impression that vial sharing is common in Danish clinical practice. In case vial sharing is not allowed, the dosing consumption per administration is rounded up to the closest integer number of vials. Wastage is considered in a sensitivity analysis.

3.1.10 Drug Administration Costs

It is assumed that a SC administration is the same cost the same as IV administration which is in line with the approach previously taken by Amgros (7, 28). The cost by mode of administration is shown in Table 16.

In the evaluation of BorLenDex, it is stated that Amgros consulted with clinicians. The clinicians assessed that all patients, no matter the treatment, will go to the hospital for the start-up of a new series. Since the series lengths are different between the treatments, Amgros added a visit at the start of the series for

oral treatments. The follow-up visits were assessed taking place at the same time as the visits where the patient would receive an administration with subcutaneous and intravenously drugs, why no additional visits are added for these treatments (7).

The treatments containing a regimen that is administered at the hospital to progression (i.e. in front line, DaraBorMelPred), the costs of regular follow-up visits are assumed to be captured in administration cost. Hence, regular follow-up visits were not accounted for in these cases to avoid double counting. This approach seems to be aligned with approach taken by Amgros for the evaluation of BorLenDex (7).

For regimens where the induction treatment requires administration at the hospital (i.e. BorLenDex), it is assumed that regular follow-up visits are required throughout all treatment cycles. Ideally, this would only be accounted for after the induction period, but it was not possible to adjust the model to reflect post induction costs only. This may be a slight overestimation of costs since the follow-up visits would not be relevant until the end of the induction period (for BorLenDex, 24 weeks) which is in alignment with the assumption made for DaraBorMelPred above. This is primarily relevant in the front-line setting as the regimens administered in the 2L setting are mainly administered at the hospital to progression.

Due to the structure of the model, it was not possible to capture administration costs of oral treatment separately without double counting. To account for this cost (LenDex18) follow-up visits have been added to the model.

Table 16. Drug Administration Costs

Procedure	Cost	DRG procedure & procedure
Administration of SC, IV, a combination SC & IV	DKK 3,235.00	DRG group: 17MA98 MDC17. Procedures: BWAA31 - Medicingivning ved subkutan injektion (DKK 3235). BWAA62 - Medicingivning ved intravenøs infusion (DKK 3235). Same assumption applied by Amgros in the evaluation of PomBorDex (28)
Oral initiation (one-time cost)	NA – Reflected in regular follow-up visits	

*Unit costs are obtained from
Abbreviations: IV = intravenous; SC = subcutaneous

3.1.11 Co-medications

Co-medications include any pre and post-medications, concomitant medications, and prophylactic medications. The requirements for additional medications for each comparator were based on the data sources available for their dosing schedule in the summaries of product characteristics.

The additional medications recommended for each comparator are summarized in Table 17. Only co-medications required for all patients were accounted for in the model. Additional medications that were provided to selected patients (e.g., patients at risk) were not included to reduce the risk of bias, as the proportion of patients was not clearly reported for all comparators.

Table 17. Required Co-medications for All Patients for Each Comparator

Treatment	Required Co-medications
Daratumumab(29)	**Administration requirement:** • Dilution with sodium chloride 9 mg/mL (0.9%) **Pre-infusion medication:** Administer approximately one hour prior to every infusion: • IV corticosteroid (methylprednisolone 100 mg) ○ Can decrease after second administration (oral or intravenous methylprednisolone 60 mg) • Oral antipyretics (paracetamol 650mg to 1000 mg) • Oral or IV antihistamine (diphenhydramine 25mg to 50 mg) **Post-infusion medication:** • Administer oral corticosteroid (20 mg methylprednisolone) to patients the first and second day after all infusions. • After >4 infusions, if no major IRRs, these post-infusion medications may be discontinued
Lenalidomide(30)	**Co-medication:** • Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors
Bortezomib(31)	**Administration requirement:** • Three- to five-second bolus IV injection followed by a flush with sodium chloride 9 mg/mL (0.9%) solution for injection **Co-medications:** • Antiviral prophylaxis is recommended in patients being treated with bortezomib

Abbreviations: IV =intravenous; mg = milligram; mL = millilitre

The drug costs of co-medications included in the model are shown in Table 18.

Table 18. Co-medication Drug Costs

Medications	Drug Units per Pack	Strength (mg)	Price per Pack (List price, pharmacy purchase price)	Dosage per Administration (mg)	Cost per Administration**	Source
Methylprednisolone IV	24	40	DKK 566	100 (29)	DKK 58.95	Medicinpriser.dk (VNR:420151) [Accessed 07. May 2020]
Paracetamol	300	500.0	DKK 35	825 (29)†	DKK 0.19	Medicinpriser.dk (VNR: 064318) [Accessed 07. May 2020]
Cetirizine	100	10	DKK 88	37.5(29)‡	DKK 3.30	Webapoteket.dk (VNR: 591795) [Accessed 07. May 2020]
Acyclovir	100	200	DKK 47	400Ŧ	DKK 0.94	Medicinpriser.dk (VNR: 467722) [Accessed 07. May 2020]
Acetylsalicylic acid	500	75	DKK 22	325§	DKK 0.19	Medicinpriser.dk (VNR: 512197) [Accessed 07. May 2020]
Saline solution	6	13,500	DKK 150	585¥	DKK 1.08	Medicinpriser.dk (VNR: 141355) [Accessed 07. May 2020]

**Calculated based on the other inputs in the table
†Average between 650 mg and 1000 mg
‡Average between 25mg and 50 mg.
ŦAssumed the same as unit strength
§Regular acetylsalicylic acid tablet strength
¥Assumption. Daratumumab is available in vials of 5 mL (100 mg of daratumumab) and 20 mL (400 mg of daratumumab), and the dose per administration is 16 mg/m². Based on the mean weight of the target population (77.24 kg), patients on DaraBorMelPred in the model will receive on average 3 vials of 20 mL and 1 vial of 5 mL per administration, for a total of 65 mL. The dilution with sodium chloride is 9 mg/mL, therefore 585 mg of sodium chloride are used for the average 65 mL of daratumumab required per administration.
Abbreviations: DaraBorMelPred = daratumumab, bortezomib, melphalan, prednisone; IV =intravenous;

The proportion of patients receiving each one of the co-medications included in the model are shown in Table 19, and are based on the required comedications for the different individual components of the combination therapies. For example, patients receiving DaraBorMelPred require methylprednisolone, paracetamol, and cetirizine because of daratumumab (29),and acyclovir because of bortezomib (31).

Table 19. Percentage of Patients Receiving Required Co-medications

Medications	DaraBorMelPred (29, 31)	BorMelPred (31)	LenDex18 (30)	BorLenDex	LenDex (30)
Methylprednisolone IV	100%			Equals LenDex and BorMelPred	
Paracetamol	100%				
Cetirizine	100%				
Acyclovir	100%	100%			
Acetylsalicylic acid			100%		100%
Saline solution	100%	100%			

Abbreviations: DaraBorMelPred = daratumumab, bortezomib, melphalan, prednisone; IV =intravenous; LenDex = lenalidomide, dexamethasone; BorMelPred = bortezomib, melphalan, prednisone

3.1.12 Routine Follow-up Care Costs

Routine follow-up care costs were accrued in each health state (i.e., pre- and post-progression) separately in the model. The types and frequencies of healthcare resource were based on those used in the NICE assessment for first-line treatment of MM (NICE TA228: bortezomib and thalidomide) (32).

In the base case analysis, it was assumed that different kind of tests (such as full blood count, biochemistry, protein electrophoresis, immunoglobin, urinary light chain excretion) were the same across treatments and thus excluded from the analysis.

The frequency of routine follow-up care is assumed to be the same for all comparators. The rationale for the difference between DaraBorMelPred and the comparators was described in section 3.1.10 (assuming the follow-up visits were already included in the continuous administration cost since daratumumab is administered at the hospital to progression).

Table 20. Frequency of Routine Follow-up Care Use (Every Four Weeks)

	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex	LenDex
Pre-progression Haematologist Initial Visit	0.00	0.00	0.00	0.00	0.00
Pre-progression Haematologist Follow-up Visit	0.00	0.69	0.69	0.69	0.69
Post-progression: On subsequent Treatment	0.92	0.92	0.92	0.92	0.92

Table 21. Unit Costs of Healthcare Resources and Tests during Routine Follow-up Care

Item	Cost	DRG procedure & procedure
Haematologist follow-up visit	DKK 3,235.00	DRG group: 17MA98 MDC17 1-dagsgruppe. Procedure: AAF21

3.1.13 Subsequent Treatment Costs

Drug costs for second- and third-line treatment after progression are also included in the model. The post-progression costs are a combination of drug costs (Table 14), administration costs (Table 16), and the monitoring costs (Table 20 and Table 21), which were assumed to be the same regardless of prior treatment. Patient costs are accounted for separately for the second-line setting (patient costs related to administration and transportation).

Wastage and dose intensity consideration for subsequent treatments are consistent with those selected for the first-line treatments. In the base case scenario, no wastage (i.e., vial sharing allowed) and dose intensity are considered.

Dose intensity was considered separately for each component of each combination treatment. Dose intensity for DaraLenDex and DaraBorDex was available from the POLLUX/CASTOR (ASCO 2017 update), respectively. Dose intensity for daratumumab monotherapy was available from the integrated analysis of MMY2002/GEN501 (cut-off date of 31 December 2015). For other front-line comparator therapies for which dose intensity data were not available from trial publications, the same dose intensities were assumed as for the components of DaraLenDex for lenalidomide-containing regimens, or as for the components of DaraBorDex for bortezomib-containing regimens.

The dosing schedules for subsequent treatments are shown in Table 22 and Table 23,

Table 22. Summary of Subsequent Treatment Regimen Dosing that could be relevant to the Danish setting (Part 1)

Treatment Regimens		Dose/Admin	Admin/Cycle	Cycle Length	Relative Dose Intensity	Source
Carfilzomib+Dexamethasone						
Carfilzomib	Cycle 1 (Days 1 & 2)	20 mg/m^2	2	1 week	[redacted]	ENDEAVOR study, Dimopoulos et al. 2016(20)
	Cycle 1 (post Days 1 & 2)	56 mg/m^2	4	3 weeks	[redacted]	
	Cycles 2+	56 mg/m^2	6	4 weeks	[redacted]	
Dexamethasone	All cycles	20 mg/m^2	8	4 weeks	[redacted]	
Carfilzomib+LenDex						
Carfilzomib	Cycle 1 (Days 1 & 2)	20 mg/m^2	2	1 weeks	[redacted]	ASPIRE study, Stewart et al. 2015(19)
	Cycle 1 (post Days 1 & 2)	27 mg/m^2	4	3 weeks	[redacted]	
	Cycles 2–12	27 mg/m^2	6	4 weeks	[redacted]	
	Cycles 13–18	27 mg/m^2	4	4 weeks	[redacted]	
Lenalidomide	All cycles	25 mg	21	4 weeks	[redacted]	
Dexamethasone	All cycles	40 mg	4	4 weeks	[redacted]	
Daratumumab						
Daratumumab	Cycles 1–2	16 mg/kg	4	4 weeks	[redacted]	MMY2002(33)
	Cycles 3–6	16 mg/kg	2	4 weeks	[redacted]	
	Cycles 7+	16 mg/kg	1	4 weeks	[redacted]	
DaraLenDex						
Daratumumab	Cycles 1–2	16 mg/kg	4	4 weeks	[redacted]	MMY3003(20)
	Cycles 3–6	16 mg/kg	2	4 weeks	[redacted]	
	Cycles 7+	16 mg/kg	1	4 weeks	[redacted]	
Lenalidomide	All cycles	25 mg	21	4 weeks	[redacted]	
Dexamethasone	All cycles	40 mg	4	4 weeks	[redacted]	

*Assumed the same as daratumumab in Dara+Vd; †Assumed the same as dexamethasone in Dara+Vd; ‡ Assumed the same as daratumumab in Dara+LenDex; ₸ Assumed the same as lenalidomide in Dara+LenDex; ¥ Assumed the same as dexamethasone in Dara+LenDex; ¶ Assumed the same as bortezomib in Dara+Vd

Abbreviations: LenDex = lenalidomide and dexamethasone

[redacted]

Table 23. Summary of Subsequent Treatment Regimen Dosing that could be relevant to the Danish setting (Part 2)

Treatment Regimens		Dose/ Admin	Admin/Cycle	Cycle Length	Relative Dose Intensity	Source
DaraBorDex						
Daratumumab	Cycles 1–3	16 mg/kg	3	3 weeks	[redacted]	MMY3004(21)
	Cycles 4–8	16 mg/kg	1	3 weeks	[redacted]	
	Cycles 9+	16 mg/kg	1	4 weeks	[redacted]	
Bortezomib	Cycles 1–8	1.3 mg/m^2	4	3 weeks	[redacted]	
Dexamethasone	Cycles 1–8	20 mg	8	3 weeks	[redacted]	
Elotuzumab+LenDex						
Elotuzumab	Cycles 1–2	10 mg/kg	4	4 weeks	[redacted]	ELOQUENT-2 study, Lonial 2015(22)
	Cycles 3+	10 mg/kg	2	4 weeks	[redacted]	
Lenalidomide	All Cycles	25 mg	21	4 weeks	[redacted]	
Dexamethasone	All Cycles (elotuzumab weeks)	28 mg	4	4 weeks	[redacted]	
		8 mg	4	4 weeks	[redacted]	
Dexamethasone	All Cycles (non-elotuzumab weeks)	40 mg	4	4 weeks	[redacted]	
Ixazomib+LenDex						
Ixazomib	All cycles	4 mg	3	4 weeks	[redacted]	TOURMALINE study, Moreau et al. 2016(23)
Lenalidomide	All cycles	25 mg	21	4 weeks	[redacted]	
Dexamethasone	All cycles	40 mg	4	4 weeks	[redacted]	
Pomalidomide+Dexamethasone						
Pomalidomide	All cycles	4 mg	21	4 weeks	[redacted]	Weisel, et al. 2013(34)
Dexamethasone (aged ≤75)	All cycles	40 mg	4	4 weeks	[redacted]	
Dexamethasone (aged >75)	All cycles	20 mg	4	4 weeks	[redacted]	
LenDex						
Lenalidomide	All cycles	25 mg	21	4 weeks	[redacted]	MMY3003(20)
Dexamethasone	Cycles 1–4	40 mg	12	4 weeks	[redacted]	
	Cycles 5+	40 mg	4	4 weeks	[redacted]	

*Assumed the same as daratumumab in Dara+Vd; †Assumed the same as dexamethasone in Dara+Vd; ‡ Assumed the same as daratumumab in Dara+LenDex; ₸Assumed the same as lenalidomide in Dara+LenDex; ǂ Assumed the same as dexamethasone in Dara+LenDex; ¶ Assumed the same as bortezomib in Dara+Vd

Abbreviations: DaraBorDex = daratumumab in combination with bortezomib, dexamethasone; LenDex = lenalidomide and dexamethasone; [redacted]

3.1.13.1 Second-line and third-line treatment Market Shares

After patients progress from a first-line treatment, a proportion of patients will receive a second-line and a third-line treatment. Of the patients starting first-line treatment, 89.9% were assumed to continue to second-line treatment. The proportion of patients receiving a second-line treatment is based on the estimates provided by the MM Expert Committee (Medicines Council) in the evaluation of multiple myeloma. A total of 360 patients are estimated to start treatment per year which includes both transplant eligible and ineligible patients. In the second-line setting, the total number is stated to be 320 (88.9% of the patients). In the protocol for elotuzumab in combination with pomalidomide and dexamethasone, the same numbers are provided as above for the first-line and second-line setting, but in addition, an estimate of 200 patients that will receive a third-line treatment (62.5% of the patients coming from the second-line continues to receive a third line treatment) (35). The lower percentage moving from second-line to third-line compared to first-line to second-line is supported by the severity of disease, and the expectation that fewer patients would be healthy enough to move to third-line treatment than from first line to second line.

The base case distribution of patients among the second-line treatment options is shown in Table 24. The base case reflects considerations around the current treatment guidelines and the drug recommendation published by the Medicines Council as well as expected clinical practice. Clinical practice is continuously evolving and a new recommendation such as PomBorDex has also been considered in the assumptions for 2nd and 3rd line subsequent treatment mix.

The applicant expects the majority of patients receiving DaraBorMelPred in the first-line setting to receive a lenalidomide containing regimen in the second-line setting which will likely be EloLenDex based on the current drug recommendation (May 2020), where EloLenDex is the first choice in for patients where daratumumab is contraindicated. The CarLenDex regimen is currently the second choice in the drug recommendation after EloLenDex and this regimen is also expected to be used. There may also be a strong patient preference for not travelling to the hospital or other patient specific conditions where LenDex is preferred despite more effective combinations being available (though mainly needing to be administered at the hospital). The applicant also expect that some patients will not be treated with a lenalidomide containing regimen in the second-line setting and will be offered a regimen such as PomBorDex or CarDex.

For patients receiving BorMelPred in the first-line setting, the majority of patients are expected to receive DaraLenDex. DaraBorDex, CarLexDex and EloLenDex are only expected to be used to a limited degree due to DaraLenDex being available. As with the case of DaraBorMelPred, some patients are expected to receive LenDex despite more effective combinations being available due to patient specific preferences. The percentage allocated to LenDex after the use of BorMelPred is slightly lower than the percentage provided for LenDex after treatment with DaraBorMelPred. This is due to the specific regimen of DaraLenDex being available for the patients that have received BorMelPred.

For BorLenDex (and LenDex to progression serving as an additional analysis), the applicant expects that a large share of patients will receive DaraLenDex in the second line setting even in the case where lenalidomide is intended to be used to progression according to label (for BorLenDex and LenDex). In clinical practice, it is the applicant's understanding that these regimens are often not used to progression. This could be explained by some patients experiencing toxicity on the continuous lenalidomide regimen, and potentially has a general preference for DaraLenDex. DaraBorDex is also expected to be a preferred choice for these patients. For both regimens, some patients are also expected to receive CarDex and PomBorDex.

Lastly, LenDex18 is a fixed treatment regimen and the majority of patients are expected to be able to receive the DaraLenDex regimen subsequently. DaraBorDex will also be a relevant regimen for some patients while only a few patients are expected to receive CarDex and PomBorDex

For the different treatment sequences, it is assumed that both CarDex and PomBorDex are used equally in the specific treatment regimen, but the percentage will very between the different treatment sequences depending on the first-line treatment.

For the third-line setting, an equal division across treatments were assumed (CarDex, PomDex, and PomBorDex). The applicant expects that only limited patients would receive a daratumumab-containing regimen in this line of treatment due to the high likelihood of already have been exposed the daratumumab regimen in a prior line. The base case distribution of patients among the third-line treatment options is shown in Table 25.

Table 24. Second-line Treatment Distribution Based on First-line Treatment Received

Second-line Treatment	First-line treatment				
	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex	LenDex
DaraLenDex	0.00%	80.00%	70.00%	40.00%	50.00%
DaraBorDex	0.00%	5.00%	20.00%	40.00%	40.00%
CarDex	15.00%	0.00%	5.00%	10.00%	5.00%
CarLenDex	15.00%	5.00%	0.00%	0.00%	0.00%
EloLenDex	45.00%	5.00%	0.00%	0.00%	0.00%
LenDex	10.00%	5.00%	0.00%	0.00%	0.00%
PomBorDex	15.00%	0.00%	5.00%	10.00%	5.00%
Total	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Abbreviations: DaraLenDex = daratumumab in combination with lenalidomide and dexamethasone; DaraBorDex = daratumumab in combination with bortezomib and dexamethasone; CarDex = carfilzomib and dexamethasone; CarLenDex = carfilzomib, lenalidomide and dexamethasone; EloLenDex = elotuzumab, lenalidomide and dexamethasone, LenDex = lenalidomide and dexamethasone; PomBorDex: pomalidomide, bortezomib and dexamethasone

Table 25. Third-line Treatment Distribution Based on First-line Treatment Received

Third-line treatment	First-line treatment				
	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex	LenDex
CarDex	33.33%	33.33%	33.33%	33.33%	33.33%
PomDex	33.33%	33.33%	33.33%	33.33%	33.33%
PomBorDex	33.34%	33.34%	33.34%	33.34%	33.34%
Total	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Abbreviation: CarDex = carfilzomib and dexamethasone; PomDex: pomalidomide and dexamethasone; PomBorDex: pomalidomide, bortezomib and dexamethasone

3.1.13.2 AE Costs

The list of AEs in the model was presented in the previous section as well as the costing approach. The DRG code applied across AEs is 17MA98 MDC17 which implies a cost of DKK 3,235 based on DRG 2020 codes per AE event.

3.1.14 Patient costs

Patient costs include the time spend on transportation to the hospital (one fixed cost) as well as the time spend at the hospital multiplied by an hourly cost. Patient costs were included for the first-line setting and second-line setting. In the first-line setting, patient costs included both transportation costs, time spend on receiving a specific regimen and waiting time as well as follow-up haematologist visits where relevant. It was assumed that all patients require an initial visit at the hospital before starting treatment and this cost was therefore excluded.

Since the most commonly used regimens in Denmark in the second-line setting are administered to progression (in a hospital setting), the patient costs were only assumed to occur in relation to the administration, waiting time and the related transportation costs. For patient costs, it was assumed that regular hematologist follow-up visits were included in the regular hospital visits due to most of the second-line treatments being administered at the hospital.

Table 26. Costing of patient time

Item	Minutes	Cost	Reference
Transportation costs	90	DKK 100	Medicinrådet: Værdisætning af enhedsomkostninger, Version 1.3 2020 (36)
Patient cost per hour	*60*	DKK 179	Medicinrådet: Værdisætning af enhedsomkostninger, Version 1.3 2020 (36)

Table 27. Patient time and related costing for hospital visits and administrations

Item	Minutes	Reference
Haematologist follow-up visit	90	Assumption
Waiting time at the hospital	30	Waiting time is assumed to be the same no matter the treatment received. However, number of hospital visits will be depended the treatment sequence.

Table 28. Patient time related to different administrations

First-line DaraBorMelPred, 1 prior line: DaraBorDex and DaraLenDex			
Administration	**Admin time (average of week 1 & 2), minutes**	**Admin time from week 3, minutes**	**Source / Notes**
Administration of single daratumumab	360	180	EPAR** / assumption
Administration of daratumumab + bortezomib (Not relevant for DaraLenDex)	375	195	EPAR** / assumption
Administration of single bortezomib (s.c)	15	15	EPAR / assumption Any administration is assumed to take a minimum of 15 minutes
Bortezomib containing regimen (regimens that require hospital administration due to bortezomib)			
Administration	**Admin time, minutes**		**Source / Notes**
BorLenDex: Administration of bortezomib in regimen	15		EPAR / assumption Any administration is assumed to take a minimum of 15 minutes
BorMelPred: Administration of bortezomib in regimen	15		
PVd: Administration of bortezomib in regimen	15		
Other regimens			
Administration	**Admin time, minutes**		**Source / Notes**
EloLenDex: administration of elotuzumab	60		EPAR / assumption
CarLenDex: Administration of carfilzomib	30		EPAR / assumption
CarDex: Administration of carfilzomib	60		EPAR / assumption

*For example: DaraBorMelPred, week 1, day 4.

** The prescribing information recommends that daratumumab be administered intravenously (IV) by a health care professional as monotherapy or as combination therapy. The first infusions is administered at an initial rate of 50mL/hour and increased up to a maximum rate of 200mL/hour in the absence of infusion reactions. However, after the second infusion, the subsequent infusions the initial infusion rate is 100mL/hour, giving a median duration time of three hours.

3.1.15 Other Costs

3.1.15.1 Terminal Care

A terminal care cost for patients who die during the progression-free or post-progression health state is accrued as a one-off cost at the time of death.

The cost applied is DKK 2,685 based on DRG 2020 code: 15MP02 *(Død eller overflyttet til anden afdeling inden 2 døgn)* which seems rather low. The cost was DKK 13,134 based on the DRG 2019 which is somewhat higher. To provide an example from another country, the one-off cost of terminal care for Sweden was estimated to be SEK 76,811 in a health technology assessment evaluation (37). The impact of the terminal care cost is tested in a sensitivity analysis.

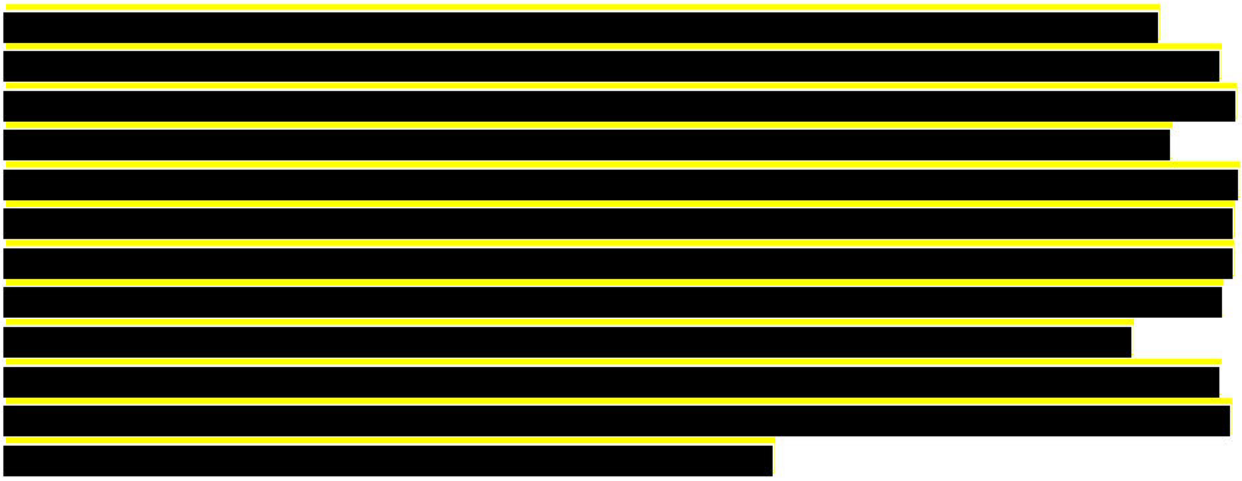
4 Budget impact model

Input and data sources

As per guidance from the Medicines Council, the budget impact model needs to be in the same Excel file as the calculation for incremental costs per patient and the budget impact model should cover five years. Based on the guidance, a budget impact model was implemented into the model accounting for incremental costs per patient allowing one single Excel file to be delivered.

The budget impact model is based on the model output described in the previous section. It is stated in the guidance by the Medicines Council that, in addition to drug costs, other cost for the regional sector should be included if possible. These costs have also been included in the budget impact analysis based on the output from the model. The budget impact calculation is excluding patient costs and is not discounted as per guidance. The budget impact model consists of a reference scenario where DaraBorMelPred is not recommended for standard treatment and an alternative scenario where DaraBorMelPred is recommended for standard treatment.

For the model input, it is possible to enter number of patients starting treatment per year as well as the expected market share in the reference scenario and the alternative scenario.



In the protocol for DaraBorMelPred, it is stated that 360 patients with multiple myeloma are expected to start treatment annually. Of these, approximately 240 are ineligible for ASCT accounting for 2/3 of the patients that are expected to start treatment (1). In the base case, the applicant has deducted the patients that is expected to start in clinical protocols. The share of newly diagnosed patients with multiple myeloma that received a first-line treatment and was included a clinical protocol were 21% in 2017, 20% in 2016, 32% in 2015 and 24% in 2014 on a national level (38). The applicant assumes that a similar share of patients will be included in clinical protocols moving forward. Based on the numbers from 2014, 2015, 2016, and 2017 the lowest percentage (20%) has been deducted (average for the four years were approximately 24%). The base case for the annual number of patients (NDMM ineligible for ASCT) starting treatment is 192 ((360*0.8) * (2/3)).

Table 29 shows the reference case which is based on current treatment guidelines where the Medicines Council estimates that 60% of patients can be treated with BorLenDex. The two preferred options after BorLenDex is BorMelPred and LenDex18. For these two regimens, an even market share of 20% for each regimen is assumed.

Table 29. Reference case – Shares and number of patients

Reference scenario (negative recommendation) - patient share and number of patients					
Reference scenario (no recommendation)	Year 1	Year 2	Year 3	Year 4	Year 5
DaraBorMelPred share	0%	0%	0%	0%	0%
DaraBorMelPred patients	0	0	0	0	0
BorMelPred share	20%	20%	20%	20%	20%
BorMelPred patients	38	38	38	38	38
BorLenDex share	60%	60%	60%	60%	60%
BorLenDex patients	115	115	115	115	115
LenDex18 share	20%	20%	20%	20%	20%
LenDex18 patients	38	38	38	38	38
Total number of patients	192	192	192	192	192

In case of a negative recommendation, 0% market share has been assumed for DaraBorMelPred. This will serve as a conservative estimate since the cost of the DaraBorMelPred sequence is estimated to be more expensive than the other regimens (presented in the results section). In case market shares were assigned to DaraBorMelPred in the reference case, it would have had to be deducted from the alternative scenario. Selected patients may start treatment with DaraBorMelPred despite of a negative recommendation. In addition, serving as another conservative estimate, it is also assumed that all patients will receive one of the stated regimens. It might be the case that some patients are not eligible for any of the treatments and neither DaraBorMelPred which would decrease the overall patient population and the estimated budget impact.

It is important to note that a positive recommendation by the Medicines Council will not necessarily imply being the first treatment choice in a subsequent drug recommendation. This will depend on the kind of recommendation (is the treatment considered equal or superior to the different comparators) as well as a subsequent update of the treatment guidelines and drug recommendation by the Medicines Council. Although DaraBorMelPred demonstrates superior efficacy, tolerability and a well-known and manageable safety profile, it should be noted that in Danish Clinical practice, there is likely specific preferences for the first-line treatment depending on the treating hematologist as well as patient preferences. The majority of hematologists may prefer treating with a lenalidomide-containing regimen as the first line treatment which will naturally decrease the patient population for DaraBorMelPred if this preference is evident after

a recommendation of DaraBorMelPred. There may also be opinions around a preferred use of daratumumab (specifically DaraLenDex) in the second line setting which is unlikely to be possible if DaraBorMelPred is administered in the first-line setting.

Lastly, it should be noted that BorLenDex regimen is currently the first choice in the Danish Drug recommendation with an estimated 60% of the patient population (NDMM patients ineligible for ASCT) that are expected to be able to be treated with the regimen.

Referring to the guidance documents from the Medicines Council, it is stated that in case there are multiple clinical questions/comparators, the budgetary consequences of a recommendation should be presented versus each comparator, all comparators, and groups of comparators (39).

DaraBorMelPred may be recommended versus BorLenDex, or alternatively, for the patient population that are not eligible for BorLenDex where BorMelPred and LenDex18 are currently recommended. In addition, it could also be a recommendation versus specific comparators and not others. The different scenarios analyzed are shown below.

Table 30. Market share per year for DaraBorMelPred in different recommendation scenarios – Base case

Estimated market share per year for DaraBorMelPred in different recommendation scenario					
DaraBorMelPred recommendation scenarios	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
A) DaraBorMelPred recommended vs. All comparators	20.0%	30.0%	35.0%	35.0%	35.0%
B) DaraBorMelPred recommended vs. BorLenDex & BorMelPred	15.0%	25.0%	30.0%	30.0%	30.0%
C) DaraBorMelPred recommended vs. BorLenDex & LenDex18	15.0%	25.0%	30.0%	30.0%	30.0%
D) DaraBorMelPred recommended vs. BorMelPred and LenDex18	10.0%	20.0%	25.0%	25.0%	25.0%
E) DaraBorMelPred recommended vs. BorLenDex	10.0%	20.0%	25.0%	25.0%	25.0%
F) DaraBorMelPred recommended vs. BorMelPred	5.0%	10.0%	15.0%	15.0%	15.0%
G) DaraBorMelPred recommended vs. LenDex18	5.0%	10.0%	15.0%	15.0%	15.0%

Table 31. Number of patients per year starting DaraBorMelPred treatment in different recommendation scenarios – Base case

Estimated number of patients per year starting DaraBorMelPred treatment in different recommendation scenarios					
DaraBorMelPred recommendation scenarios	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
A) DaraBorMelPred recommended vs. All comparators	38	58	67	67	67
B) DaraBorMelPred recommended vs. BorLenDex & BorMelPred	29	48	58	58	58
C) DaraBorMelPred recommended vs. BorLenDex & LenDex18	29	48	58	58	58
E) DaraBorMelPred recommended vs. BorLenDex	19	38	48	48	48
D) DaraBorMelPred recommended vs. BorMelPred and LenDex18	19	38	48	48	48
F) DaraBorMelPred recommended vs. BorMelPred	10	19	29	29	29
G) DaraBorMelPred recommended vs. LenDex18	10	19	29	29	29

Budget impact model – methodology

In short, the budget impact model is multiplying the cost per patient each week, estimated in the health economic model by the number of patients treated each week and the assigned market share.

The budget impact model assumes that a new cohort of patients are starting a first-line treatment every 4th week. The number of patients starting treatment is assumed to be evenly distributed throughout the year based on an entered number of patients expected to start annually.

Patients starting in a given week is tracked throughout the modelled period. Serving as examples, the patient cohort starting first-line treatment in week 1 (year one of budget impact period) will continue to be tracked on a weekly basis until the end of 5-year budget impact period (and accumulate the relevant cost for the given week they are in). A patient cohort starting treatment in week 53 (year two of the budget impact period) will continue to be tracked until end of the 5-year budget impact period. Since this specific patient cohort started treatment in the second year of the budget impact period, these patients will be tracked for a total of 4 years in the budget impact model which in turn will be year 5 for the budget impact period. The patient cohort starting in week 53 (year 2 of the budget impact period but the first year of treatment for these patients) will accumulate the week 1 costs from the model. Once this patient cohort entered week 54, they will accumulate the costs based on week 2 from the model.

The costing per week of the specific cohort is connected to the cost output from the model where the cost input and output was described in the previous section (however excluding patient costs and not discounted). For each regimen in the model (in the reference case, BorMelPred, BorLenDex, LenDex18; in the alternative case, DaraBorMelPred, BorMelPred, BorLenDex, LenDex18), the number of patients for a specific week is multiplied by the entered market share (reference scenario and alternative scenario) for

the different regimens and then multiplied by the cost of each comparator in the model based where the patient cohort is in the treatment cycle.

Model outcomes

A budget impact estimate per year for a five-year period is provided for the different recommendation scenarios.

Based on the number of patients starting treatment and the market shares for the given scenario (reference scenario and alternative scenario), the model will provide an estimate of the incremental costs per treatment regimen per year (for a five-year period) as well as a total.

[redacted]

5 Results

The reference scenario was conducted using a 10-year time horizon from the "restricted" societal perspective in the Danish setting. Cost outcomes included: first-line drug acquisition, administration and routine follow-up during pre-progression; concomitant and prophylactic medications, AE management; second- and third-line drug acquisition, administration, routine follow-up during post-progression; patient costs (first- and second line) and terminal care. Model outcomes were calculated using the life-table method for half-cycle correction (40).

Base case results

A summary of the parameters used and the costs considered in the base case scenario is presented in Table 32.

Table 32. Summary of Model Parameters Base Case Scenario

Parameter		Survival Partition
Model type		Partitioned survival model
Time horizon		10 years
Discount rate		4%
Cost outcomes included		**Pre-Progression** Drug acquisition Drug administration Concomitant and prophylactic medications Routine monitoring Adverse event management Patient costs **Post-Progression** **Second-line Treatment** Drug acquisition, administration, on-treatment monitoring Routine monitoring (off-treatment) Patient costs **Third-line Treatment** Drug acquisition, administration, on-treatment monitoring Routine monitoring (off-treatment) **Terminal Care (pre- and post-progression)**
Lines of treatments included		3 lines of treatment
OS	[redacted]	[redacted]
	[redacted]	[redacted]
	LenDex18	HR vs. BorMelPred from NMA (BorLenDex ITT)
	BorLenDex	HR vs. BorMelPred from NMA (BorLenDex ITT)
	LenDex	HR vs. BorMelPred from NMA
PFS	[redacted]	[redacted]

Parameter		Survival Partition
	[redacted]	[redacted]
	LenDex18	HR vs. BorMelPred from NMA
	BorLenDex	HR vs. BorMelPred from NMA
	LenDex	HR vs. BorMelPred from NMA
Treatment duration	[redacted]	[redacted]
	[redacted]	[redacted]
	LenDex18	Median duration per FIRST study: 16.6 months
	BorLenDex	Median duration per SWOG study: 23.4 month
	LenDex	Median duration per FIRST study: 18.4 months
	Second-line treatments	Median duration per trial (months)
	Third-line treatment	Median treatment duration: 9 months (assumed based on Kumar, et al. 2012
% receiving second-line treatment		88.9%; market shares of second-line treatments
% receiving third-line treatment		62.5% market shares of third-line treatments
Death during second-line PFS		Estimated using Constant Mortality Rate
Patient characteristics		Baseline age 71 years; mean weight 73.4 kg; mean BSA 1.84 m^2
Wastage		Not included (i.e., vial sharing allowed)
Dose intensity		Included
Terminal care cost		Included (one-time off cost)

Abbreviations: BSA = body surface area; DaraBorMelPred = daratumumab in combination with bortezomib, melphalan, and prednisone; HR = hazard ratio; KM = Kaplan-Meier;NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; LenDex = lenalidomide and dexamethasone; LenDex18 = lenalidomide and dexamethasone (18 cycles);BorMelPred = bortezomib, melphalan, and prednisone; BorLenDex= bortezomib, lenalidomide, and dexamethasone

[redacted]

5.1.1 Incremental costs per patient

Table 33 shows the results for the base case results. When interpreting the results, it is important to note that patients receiving DaraBorMelPred as the first-line treatment had improved survival compared with all other treatments and spent more time progression free (i.e., in the pre-progression state). The improved survival for the DaraBorMelPred sequence is naturally impacting the results throughout the different lines of treatment (i.e. the use of the partitioned survival approach).

The primary cost driver was drug acquisition costs. Patients treated with DaraBorMelPred in the first-line setting had higher drug administration costs primarily due to bortezomib and daratumumab being administered in the hospital setting (daratumumab to progression). The costs for LenDex18 and LenDex represent routine monitoring costs (routine visits at hospital) as lenalidomide in combination with dexamethason is administered at home. The post-progression treatment costs for DaraBorMelPred were lower compared with the other treatments which was primarily impacted by the second-line treatment mix and the related drug acquisition costs.

Table 33. Base case results

DKK cost outcomes (discounted)	DaraBorMelPred	BorMelPred	LenDex18	BorLenDex	LenDex
Pre-progression (first-line treatment)					
Drug acquisition	1,999,095	43,614	535,145	1,378,283	1,111,477
Drug administration + Routine monit.	223,351	160,131	54,956	181,251	70,905
Concomitant and prophylactic medications	3,238	62	51	233	108
AE management	4,096	3,740	4,041	6,726	5,438
Patient costs	44,196	13,686	6,260	15,991	8,077
Post-progression					
Second-line treatment					
Drug acquisition, admin., and on tx. monit.	580,841	1,599,956	1,444,254	916,942	1,117,790
Off-treatment monitoring	44,964	79,876	86,480	64,277	72,351
Patient costs	6,000	18,028	17,961	13,362	15,687
Third-line treatment					
Drug acquisition, admin., and on tx. monit.	232,344	269,323	276,750	241,809	261,659
Off-treatment monitoring	35,978	3,673	23,364	26,191	15,156
Terminal care	1,298	2,286	2,146	1,989	2,153
Total	3,175,400	2,194,374	2,451,407	2,847,052	2,680,799
Incremental costs (DaraBorMelPred vs. comparator)		**981,025**	**723,993**	**328,348**	**494,601**

Abbreviations: AE = adverse event; admin = administration; tx.= treatment; monit. = monitoring
Drug acquisition costs are based on public list prices (pharmacy purchase price)

5.1.2 Budget impact results

Results are presented per recommendation scenario. Across all presented scenarios, the reference case assumes the market shares in stated in section 4, Input and data sources. The following budget impact results are undiscounted and excluding patient costs.

The tables below show the budgetary consequences across different recommendation scenarios (A to G). A gradual market share uptake is assumed up to the end of year 2 and then a stable market share from year 3. A gradual uptake is expected due to Regional implementation, update of treatment guidelines, and hematologists gradually adapting to new treatment strategies. The below scenarios take a conservative approach assuming that no other new MM treatments in the front-line TIE setting will be recommended for standard treatment for the budget impact period ("competing regimens"). In case this would have been included, it could have decreased the assumed market share.

[redacted]

Table 34. Base case scenario – A) DaraBorMelPred recommended vs. all comparators

Estimated budget impact per year for DaraBorMelPred					
A) DaraBorMelPred recommended vs. All comparators	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
New patients treated with DaraBorMelPred	38	58	67	67	67
DaraBorMelPred % uptake	20%	30%	35%	35%	35%
BorMelPred share (if DaraBorMelPred is recommended)	*16%*	*14%*	*13%*	*13%*	*13%*
BorLenDex share (if DaraBorMelPred is recommended)	*48%*	*42%*	*39%*	*39%*	*39%*
LenDex18 share (if DaraBorMelPred is recommended)	*16%*	*14%*	*13%*	*13%*	*13%*
Reference scenario (no recommendation)*	65.877M	162.456M	259.971M	347.424M	415.729M
Alternative scenario (recommendation)*	75.830M	184.429M	288.595M	376.486M	442.735M
Incremental costs*	9.953M	21.973M	28.624M	29.062M	27.006M

*DKK million

Table 35. Base case scenario – B) DaraBorMelPred recommended vs. BorLenDex & BorMelPred

Estimated budget impact per year for DaraBorMelPred					
B) DaraBorMelPred recommended vs. BorLenDex & BorMelPred	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
New patients treated with DaraBorMelPred	29	48	58	58	58
DaraBorMelPred % uptake	15%	25%	30%	30%	30%
BorMelPred share (if DaraBorMelPred is recommended)	*16%*	*14%*	*13%*	*13%*	*13%*
BorLenDex share (if DaraBorMelPred is recommended)	*49%*	*41%*	*38%*	*38%*	*38%*
LenDex18 share (if DaraBorMelPred is recommended)	*20%*	*20%*	*20%*	*20%*	*20%*
Reference scenario (no recommendation)*	65.877M	162.456M	259.971M	347.424M	415.729M
Alternative scenario (recommendation)*	73.292M	180.486M	284.547M	372.739M	438.998M
Incremental costs*	7.414M	18.030M	24.576M	25.315M	23.270M

*DKK million

Table 36. Base case scenario – C) DaraBorMelPred recommended vs. BorLenDex & LenDex18

Estimated budget impact per year for DaraBorMelPred					
C) DaraBorMelPred recommended vs. BorLenDex & LenDex18	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
New patients treated with DaraBorMelPred	29	48	58	58	58
DaraBorMelPred % uptake	15%	25%	30%	30%	30%
BorMelPred share (if DaraBorMelPred is recommended)	*20%*	*20%*	*20%*	*20%*	*20%*
BorLenDex share (if DaraBorMelPred is recommended)	*49%*	*41%*	*38%*	*38%*	*38%*
LenDex18 share (if DaraBorMelPred is recommended)	*16%*	*14%*	*13%*	*13%*	*13%*
Reference scenario (no recommendation)*	65.877M	162.456M	259.971M	347.424M	415.729M
Alternative scenario (recommendation)*	72.192M	177.200M	280.075M	368.195M	434.910M
Incremental costs*	6.315M	14.744M	20.104M	20.771M	19.181M

*DKK million

Table 37. Base case scenario - D) DaraBorMelPred recommended vs. BorMelPred & LenDex18

Estimated budget impact per year for DaraBorMelPred					
D) DaraBorMelPred recommended vs. BorMelPred & LenDex18	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
New patients treated with DaraBorMelPred	19	38	48	48	48
DaraBorMelPred % uptake	10%	20%	25%	25%	25%
BorMelPred share (if DaraBorMelPred is recommended)	*21%*	*16%*	*14%*	*14%*	*14%*
BorLenDex share (if DaraBorMelPred is recommended)	*48%*	*48%*	*48%*	*48%*	*48%*
LenDex18 share (if DaraBorMelPred is recommended)	*21%*	*16%*	*14%*	*14%*	*14%*
Reference scenario (no recommendation)*	65.877M	162.456M	259.971M	347.424M	415.729M
Alternative scenario (recommendation)*	69.253M	175.033M	280.275M	369.848M	436.569M
Incremental costs*	3.376M	12.577M	20.304M	22.424M	20.840M

*DKK million

Table 38. Base case scenario – E) DaraBorMelPred recommended vs. BorLenDex

Estimated budget impact per year for DaraBorMelPred					
E) DaraBorMelPred recommended vs. BorLenDex	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
New patients treated with DaraBorMelPred	19	38	48	48	48
DaraBorMelPred % uptake	10%	20%	25%	25%	25%
BorMelPred share (if DaraBorMelPred is recommended)	*20%*	*20%*	*20%*	*20%*	*20%*
BorLenDex share (if DaraBorMelPred is recommended)	*50%*	*40%*	*35%*	*35%*	*35%*
LenDex18 share (if DaraBorMelPred is recommended)	*20%*	*20%*	*20%*	*20%*	*20%*
Reference scenario (no recommendation)*	65.877M	162.456M	259.971M	347.424M	415.729M
Alternative scenario (recommendation)*	69.787M	173.198M	275.711M	363.997M	430.738M
Incremental costs*	3.909M	10.743M	15.740M	16.573M	15.010M

*DKK million

Table 39. Base case scenario – F) DaraBorMelPred recommended vs. BorMelPred

Estimated budget impact per year for DaraBorMelPred					
F) DaraBorMelPred recommended vs. BorMelPred	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
New patients treated with DaraBorMelPred	10	19	29	29	29
DaraBorMelPred % uptake	5%	10%	15%	15%	15%
BorMelPred share (if DaraBorMelPred is recommended)	*15%*	*10%*	*5%*	*5%*	*5%*
BorLenDex share (if DaraBorMelPred is recommended)	*60%*	*60%*	*60%*	*60%*	*60%*
LenDex18 share (if DaraBorMelPred is recommended)	*20%*	*20%*	*20%*	*20%*	*20%*
Reference scenario (no recommendation)*	65.877M	162.456M	259.971M	347.424M	415.729M
Alternative scenario (recommendation)*	69.899M	173.678M	278.604M	368.773M	436.267M
Incremental costs*	4.021M	11.222M	18.633M	21.349M	20.538M

*DKK million

Table 40. Base case scenario - G) DaraBorMelPred recommended vs. LenDex18

Estimated budget impact per year for DaraBorMelPred					
G) DaraBorMelPred recommended vs. LenDex18	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
New patients treated with DaraBorMelPred	10	19	29	29	29
DaraBorMelPred % uptake	5%	10%	15%	15%	15%
BorMelPred share (if DaraBorMelPred is recommended)	*20%*	*20%*	*20%*	*20%*	*20%*
BorLenDex share (if DaraBorMelPred is recommended)	*60%*	*60%*	*60%*	*60%*	*60%*
LenDex18 share (if DaraBorMelPred is recommended)	*15%*	*10%*	*5%*	*5%*	*5%*
Reference scenario (no recommendation)*	65.877M	162.456M	259.971M	347.424M	415.729M
Alternative scenario (recommendation)*	68.433M	168.807M	270.529M	359.376M	427.750M
Incremental costs*	2.555M	6.351M	10.558M	11.952M	12.022M

*DKK million

Sensitivity analysis – incremental costs per patient

In the sensitivity analysis, specific parameters were changed one by one and Table 41 presents the results from the sensitivity analysis. For the scenarios analysed, the results for the incremental costs per patient were most sensitive to adjusting the time horizon, the body weight, and whether to allow for vial sharing.

Table 41. Sensitivity analysis – incremental costs per patient

Incremental costs per patient (DKK)	BorMelPred	LenDex18	BorLenDex	LenDex	Base Ref (if relevant)
DaraBorMelPred vs. comparators					
Base case	981,025	723,993	328,348	494,601	
Difference vs. base case					
15 year time horizion	1,114,709	857,899	405,934	608,467	10 years
Body weight (-5%; 69.7kg)	917,440	658,498	249,049	422,137	73.4 kg
Body weight (+5%; 77.1 kg)	1,044,611	789,489	407,646	567,064	73.4 kg
2L - Treat to progression	763,256	494,371	304,430	413,199	Median treatment duration
Higher terminal care costs (DRG 2019; DKK 13,134)	977,180	720,695	325,659	491,276	DRG 2020 DKK = 2,685
DVMP reference curve (PFS & OS)	981,025	714,977	427,274	552,790	VMP as reference curve
DVMP OS projection: Gamma	978,124	721,092	325,447	491,699	Exponential
DVMP OS projection: Weibull	984,411	727,379	331,733	497,986	Exponential
Constant ratio of death and progression, DVMP = [redacted] comparators [redacted]	1,025,054	762,190	239,718	459,970	Constant mortality rate; DVMP [redacted] comparators [redacted]
Include Wastage (i.e., no vial sharing)	1,019,408	785,817	377,802	558,493	Vial sharing allowed

Incremental costs per treatment sequence. Drug acquisition costs in the calculation reflects the list price (pharmacy purchase price)

[redacted]

Discussion and conclusion

MM is a rare cancer of the bone marrow that causes serious complications. Despite numerous treatment options and the recent launch of novel therapies, patients with MM eventually become refractory to treatment or suffer a relapse. This highlights an unmet need for new treatment options that induce deep remission, delay progression, and prolong survival, while improving or maintaining quality of life.

Daratumumab operates through novel, multifactorial mechanisms of action, different other therapies including proteasome inhibitors and immunomodulatory drugs.

In phase III trials, both DaraBorMelPred (ALCYONE) was shown to confer significant benefits in PFS, OS, depth of response, and MRD for the treatment of patients with previously untreated MM who are ineligible for ASCT (4, 5).

Summary of Analyses and Conclusion

To assess the incremental costs per patient and the budget impact for DaraBorMelPred, an economic model was developed and adapted to the Danish setting. The results from the base case analysis showed that DaraBorMelPred came with a higher incremental cost per patient of DKK 981,025 versus BorMelPred, DKK 723,993 versus LenDex18, DKK 328,348 versus BorLenDex, and DKK 494,601 versus LenDex based on the pharmacy purchase price (list price) over a treatment sequence. The primary cost driver was drug acquisition costs of DaraBorMelPred in the first-line. However, since DaraBorMelPred confers a strong benefit in prolonging PFS compared to BorMelPred, LenDex18, BorLenDex and LenDex, drug costs in the progression-free state consequently accrue.

Naturally the increased incremental cost per patient will also have budgetary consequences and the estimated budget impact depends on the specific recommendation scenario.

[redacted]

The results of the economic analysis should be considered part of a broader assessment of DaraBorMelPred that does not solely focus on its higher incremental costs per patient versus the comparators over a treatment sequence. The findings in this report should be assessed in parallel with the clinical benefit that DaraBorMelPred delivers to patients, both from an efficacy, safety and tolerability perspective versus the comparator treatments.

Appendix A.

Network Meta-analysis results

Results of the NMA are listed in tables below.

Table 42. OS NMA Results, Network Excluding VRd —HR for Comparators

OS	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*
MelPred		1.44 (1.17-1.76)	2.02 (1.57-2.61)	2.4 (1.7-3.38)	2.07 (1.59-2.67)	1.58 (1.29-1.93)
BorMelPred	**0.7 (0.57-0.85)**		1.41 (1.01-1.95)	1.67 (1.26-2.2)	1.44 (1.03-2)	1.1 (0.83-1.46)
LenDex	0.49 (0.38-0.64)	0.71 (0.51-0.99)		1.18 (0.77-1.81)	**1.02 (0.86-1.2)**	**0.78 (0.67-0.91)**
DaraBorMelPred	0.42 (0.3-0.59)	**0.6 (0.45-0.79)**	0.84 (0.55-1.3)		0.86 (0.56-1.32)	0.66 (0.44-0.98)
LenDex18	0.48 (0.37-0.63)	0.7 (0.5-0.97)	0.98 (0.83-1.16)	1.16 (0.76-1.78)		0.76 (0.65-0.9)
MelPredThal	**0.63 (0.52-0.77)**	0.91 (0.68-1.21)	1.28 (1.09-1.5)	1.52 (1.02-2.26)	1.31 (1.11-1.54)	

Table 43. OS NMA Results, Network Including VRd (ITT)—HR for Comparators

OS SA	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*	*BorLenDex*
MelPred		1.44 (1.17-1.76)	2.02 (1.57-2.61)	2.4 (1.7-3.38)	2.07 (1.59-2.67)	1.58 (1.29-1.93)	[redacted]
BorMelPred	**0.7 (0.57-0.85)**		1.41 (1.01-1.95)	1.67 (1.26-2.2)	1.44 (1.03-1.99)	1.1 (0.83-1.46)	[redacted]
LenDex	0.49 (0.38-0.64)	0.71 (0.51-0.99)		1.18 (0.77-1.82)	**1.02 (0.86-1.2)**	**0.78 (0.67-0.91)**	[redacted]
DaraBorMelPred	0.42 (0.3-0.59)	**0.6 (0.46-0.79)**	0.84 (0.55-1.3)		0.86 (0.56-1.32)	0.66 (0.44-0.98)	[redacted]
LenDex18	0.48 (0.37-0.63)	0.7 (0.5-0.97)	0.98 (0.83-1.16)	1.16 (0.76-1.79)		0.76 (0.65-0.9)	[redacted]
MelPredThal	**0.63 (0.52-0.77)**	0.91 (0.68-1.21)	1.28 (1.09-1.5)	1.52 (1.02-2.26)	1.31 (1.11-1.54)		[redacted]
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Table 44. PFS NMA Results, Network Excluding VRd —HR for Comparator

PFS	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*
MelPred		1.79 (1.26-2.55)	2.59 (2.04-3.3)	4.26 (2.84-6.4)	1.81 (1.44-2.29)	1.79 (1.48-2.17)
BorMelPred	**0.56 (0.39-0.79)**		1.45 (0.94-2.22)	2.38 (1.94-2.92)	1.01 (0.66-1.55)	1 (0.67-1.49)
LenDex	0.39 (0.3-0.49)	0.69 (0.45-1.06)		1.65 (1.03-2.64)	**0.7 (0.6-0.81)**	**0.69 (0.6-0.8)**
DaraBorMelPred	0.23 (0.16-0.35)	**0.42 (0.34-0.51)**	0.61 (0.38-0.97)		0.43 (0.27-0.68)	0.42 (0.27-0.66)
LenDex18	0.55 (0.44-0.7)	0.99 (0.65-1.51)	1.43 (1.23-1.66)	2.35 (1.47-3.75)		0.99 (0.86-1.13)
MelPredThal	**0.56 (0.46-0.68)**	1 (0.67-1.49)	1.45 (1.25-1.68)	2.38 (1.52-3.73)	1.01 (0.89-1.16)	

Table 45. PFS NMA Results, Network Including VRd —HR for Comparator

PFS SA	*MelPred*	*BorMelPred*	*LenDex*	*DaraBorMelPred*	*LenDex18*	*MelPredThal*	[redacted]
MelPred		1.79 (1.26-2.55)	2.59 (2.04-3.3)	4.27 (2.84-6.4)	1.81 (1.44-2.29)	1.79 (1.48-2.17)	[redacted]
BorMelPred	**0.56 (0.39-0.79)**		1.45 (0.94-2.22)	2.38 (1.94-2.92)	1.01 (0.66-1.55)	1 (0.67-1.49)	[redacted]
LenDex	0.39 (0.3-0.49)	0.69 (0.45-1.06)		1.65 (1.03-2.64)	**0.7 (0.6-0.81)**	**0.69 (0.6-0.8)**	[redacted]
DaraBorMelPred	0.23 (0.16-0.35)	**0.42 (0.34-0.51)**	0.61 (0.38-0.97)		0.43 (0.27-0.68)	0.42 (0.27-0.66)	[redacted]
LenDex18	0.55 (0.44-0.7)	0.99 (0.65-1.51)	1.43 (1.23-1.66)	2.35 (1.47-3.76)		0.99 (0.86-1.13)	[redacted]
MelPredThal	**0.56 (0.46-0.68)**	1 (0.67-1.5)	1.45 (1.25-1.68)	2.39 (1.52-3.74)	1.01 (0.89-1.16)		[redacted]
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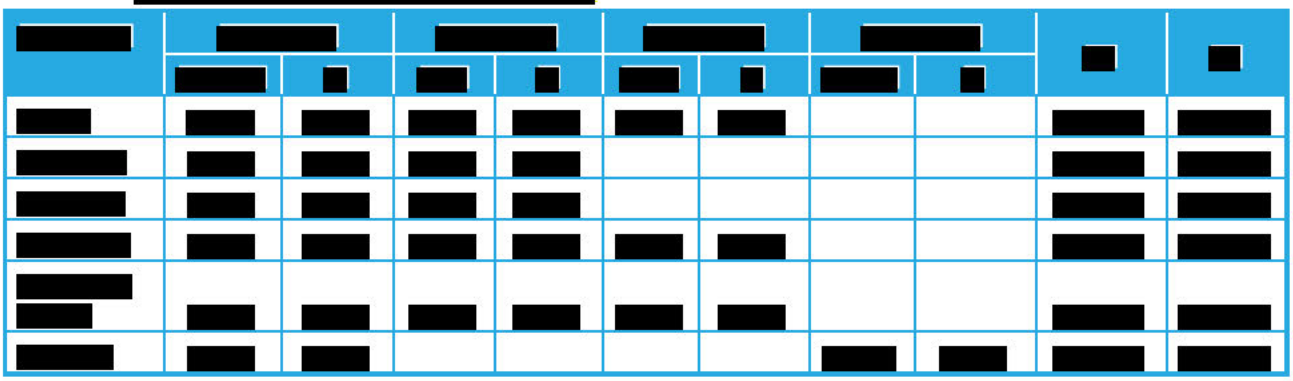

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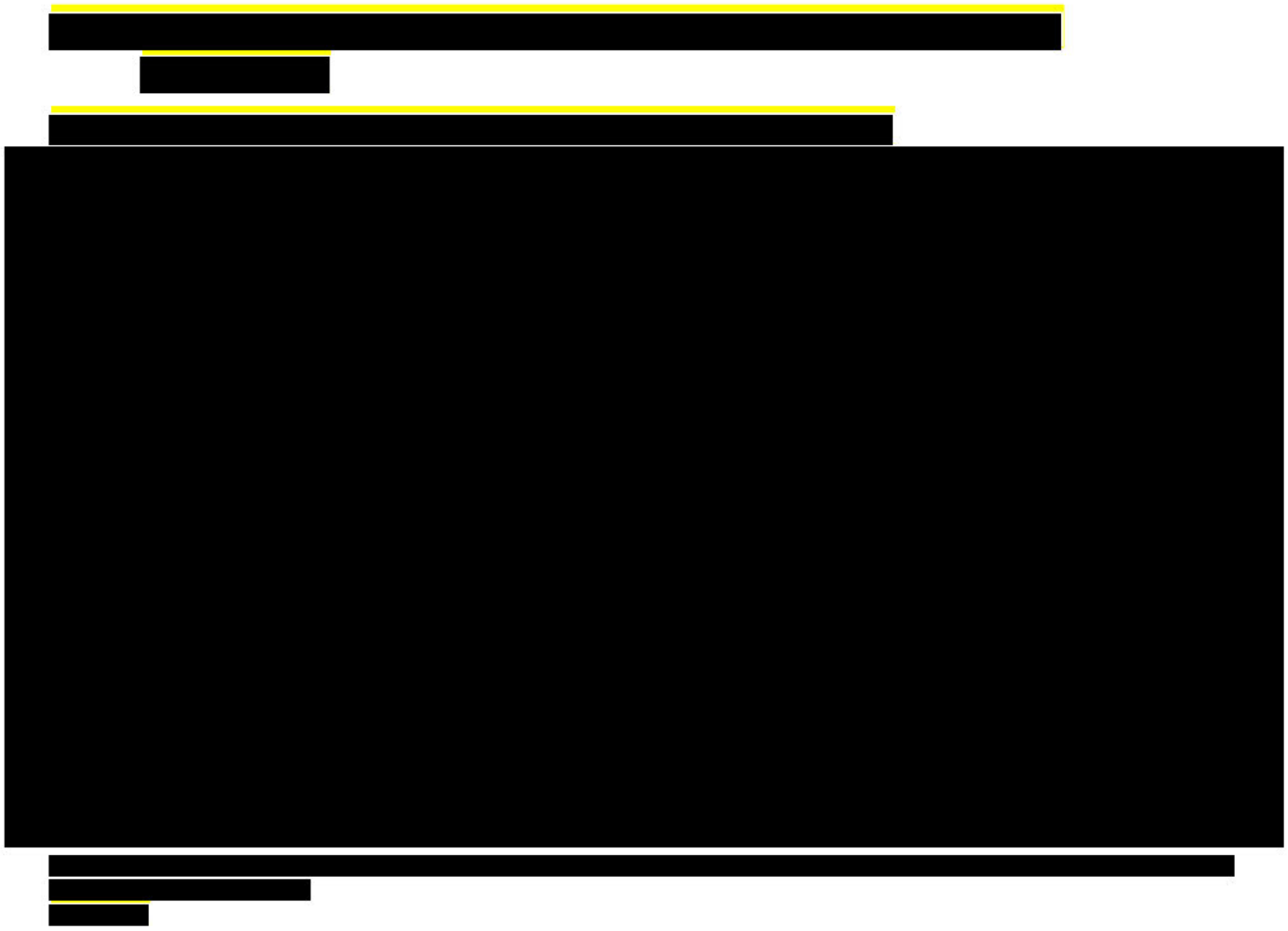

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Medicinrådet

Medicinrådets protokol for vurdering af daratumumab i kombination med bortezomib, melphalan og prednison til behandling af nydiagnosticerede patienter med knoglemarvskræft (myelomatose)

Versionsnr.: 2.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	3. februar 2020
Ikrafttrædelsesdato	4. februar 2020
Dokumentnummer	70738
Versionsnummer	2.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 4. februar 2020

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Darzalex®
Generisk navn	Daratumumab
Firma	Janssen-Cilag
ATC-kode	L01XC24
Virkningsmekanisme	Daratumumab er et humant monoklonalt IgG1κ-antistof (mAb), som binder til CD38-proteinet, der er udtrykt på højt niveau på overfladen af myelomatosetumorceller og på forskellige niveauer på andre celletyper og væv. CD38-proteinet har flere funktioner som f.eks. receptormedieret adhæsion, signalering og enzymatisk aktivitet.
Administration/dosis	Daratumumab administreres intravenøst (16 mg pr. kg) ugentligt i cyklus 1, hver tredje uge i cyklus 2-9 og efterfølgende hver fjerde uge indtil sygdomsprogression eller uacceptabel toksicitet.
EMA-indikationsudvidelse	Darzalex® er indiceret i kombination med bortezomib, melphalan og prednison til behandling af nydiagnosticerede voksne patienter med myelomatose, som ikke er egnede til højdosis kemoterapi med stamcellestøtte.

2 Forkortelser

ARR	Absolut risikoreduktion
BorLenDex	Lenalidomid i kombination med bortezomib og dexamethason
CI	Konfidensinterval
CR	Komplet respons
D-VMP	Daratumumab i kombination med bortezomib, melphalan og prednison
EMA	*European Medicines Agency*
EORTC	*European Organization for Research and Treatment of Cancer*
EPAR	*European public assessment report*
GRADE	*Grading of Recommendations Assessment, Development and Evaluation System*
HDT/STS	Højdosis kemoterapi med stamcellestøtte
HR	*Hazard ratio*
MRD	*Minimal residual disease*
OR	*Odds ratio*
ORR	*Overall response rate*
OS	*Overall survival* (samlet overlevelse)
PFS	*Progression free survival* (progressionsfri overlevelse)
QLQ-C30	*Quality of life questionnaire*
RR	Relativ risiko
SMD	*Standardized mean difference*
SPM	Sekundær primær malignitet

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af daratumumab i kombination med bortezomib, melphalan og prednison (D-VMP) som mulig standardbehandling til nydiagnosticerede patienter med knoglemarvskræft (myelomatose), som ikke er egnede til højdosis kemoterapi med stamcellestøtte. I protokollen defineres de populationer, komparatorer og effektmål, der skal indsendes data for i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende D-VMP, modtaget den 5. august 2018.

Version 1.0 af protokollen blev godkendt den 18. september 2018. Ansøger valgte efterfølgende at udskyde indsendelse af deres endelige ansøgning. Denne version 2.0 af protokollen er opdateret efter Medicinrådets metoder pr. 1. januar 2019 samt en ny foreløbig ansøgning, modtaget den 13. december 2019.

Protokollen danner grundlag for den endelige ansøgning for vurderingen af den kliniske merværdi af D-VMP sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem D-VMP og standardbehandlingen af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1**Fejl! Henvisningskilde ikke fundet.**). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Knoglemarvskræft er en uhelbredelig, livstruende og livsforkortende, men behandlingsfølsom hæmatologisk kræftsygdom. Sygdommen skyldes, at en type af hvide blodlegemer (plasmaceller) i knoglemarven ændrer karakter og herved bliver ondartede. Patienten kan på grund af nedsat funktion af knoglemarven opleve symptomer på svækket immunforsvar som infektioner og på blodmangel, for eksempel træthed og åndenød. Ændringerne i knoglemarven fremmer aktiviteten af celler, som nedbryder knoglerne og reducerer aktiviteten af celler, som opbygger knoglevæv. Derfor nedbrydes knoglerne, og patienten får øget risiko for knoglebrud, oplever knoglesmerter og får forhøjet kalk i blodet. Hos størstedelen af patienter med knoglemarvskræft kan der påvises et protein i blod og urin, som kaldes M-komponent. M-komponenten dannes af de ondartede plasmaceller og er et ikkefunktionelt immunoglobulin eller dele heraf. Hos nogle patienter vil M-komponenten give anledning til nyreskader eller egentligt nyresvigt [1].

Knoglemarvskræft er den næsthyppigste hæmatologiske kræftsygdom i Danmark, hvor i alt ca. 1.800 patienter anslås at leve med sygdommen. Der diagnosticeres ca. 450 nye patienter om året i Danmark, og medianalder ved diagnose er ca. 71 år. Ca. 20 % af de nydiagnosticerede patienter er ikke behandlingskrævende ved diagnosetidspunktet, og der er således ca. 360 patienter årligt, der skal have deres første behandling [2].

4.1 Nuværende behandling

Behandling af knoglemarvskræft varetages af de hæmatologiske afdelinger. Den medicinske behandling består ofte af flere lægemidler i kombination, da kræftcellerne på den måde angribes på flere måder, og effekten er generelt større end ved behandling med et enkelt lægemiddel [3]. Behandlingen er ikke kurativ, men målet med behandlingen er at opnå længst mulig overlevelse med færrest mulige bivirkninger og bedst mulig livskvalitet.

Nydiagnosticerede patienter inddeles overordnet i to patientgrupper, efter hvorvidt de er kandidater til højdosis kemoterapi med stamcellestøtte (HDT/STS) eller ej. Dette afgøres på baggrund af almentilstand og komorbiditet (om patienten har andre sygdomme). Patienter med knoglemarvskræft, som er yngre end 65-70

år og uden betydende komorbiditet, behandles med HDT/STS, såfremt de ønsker det. Denne behandling er internationalt anerkendt som det bedste valg uden ligeværdige alternativer [4–6].

Patienter med behandlingskrævende knoglemarvskræft, som ikke er kandidater til HDT/STS, tilbydes andre medicinske kombinationsbehandlinger [7]. Den patientpopulation udgør ca. 240 patienter årligt, svarende til ca. 2/3 af de behandlingskrævende nydiagnosticerede. Blandt de nuværende behandlingsmuligheder anvendes oftest en kombination af enten bortezomib, lenalidomid og dexamethason (BorLenDex), bortezomib, melphalan og prednison (BorMelPred) eller lenalidomid og dexamethason (LenDex) [8]. Patienter, der ikke er kandidater til HDT/STS, har en medianoverlevelse på ca. 3 år og en median progressionsfri overlevelse på ca. 18 måneder [2].

De patienter, der behandles med HDT/STS, har med en medianoverlevelse på 7 år en væsentlig bedre prognose end de, der ikke er kandidater til denne behandling. Den samlede medianoverlevelse for hele gruppen af patienter med knoglemarvskræft er 5 år. Den mediane overlevelse i baggrundsbefolkningen er for 60-årige ca. 24 år og for 70-årige ca. 16 år, baseret på beregninger af estimater fra Danmarks Statistik, www.dst.dk.

4.2 Daratumumab til nydiagnosticerede patienter

Daratumumab i kombination med bortezomib, melphalan og prednisolon (DaraBorMelPred) til nydiagnosticerede patienter, som ikke er kandidater til HDT/STS, doseres som følger i serier a 6 uger:

- Daratumumab 16 mg pr. kg i.v. ugentligt i serie 1, hver tredje uge i serie 2-9 og hver fjerde uge fra serie 10 og frem til progression
- Bortezomib 1,3 mg pr. m^2 s.c. 2 gange ugentligt i uge 1, 2, 4 og 5 i serie 1 og én gang ugentligt i uge 1, 2, 4 og 5 i serie 2-9
- Melphalan 9 mg pr. m^2 p.o. på dag 1-4 i serie 1-9
- Prednison 60 mg pr. m^2 p.o. på dag 2-4 i serie 1-9
- Desuden dexamethason 20 mg p.o. eller i.v. på dag 1 i serie 1-9.

Daratumumab har desuden følgende EMA-godkendte indikationer [9]:

- som monoterapi til behandling af voksne patienter med recidiverende og refraktær knoglemarvskræft, som tidligere har fået behandling med en proteasomhæmmer og et immunmodulerende middel, og som har vist sygdomsprogression under den sidste behandling.
- i kombination med lenalidomid og dexamethason eller bortezomib og dexamethason til behandling af voksne patienter med knoglemarvskræft, som tidligere har fået mindst én behandling.
- i kombination med lenalidomid og dexamethason til behandling af voksne patienter med nydiagnosticeret knoglemarvskræft, som ikke er kandidater til autolog stamcelletransplantation.

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål 1

Hvad er værdien af daratumumab i kombination med bortezomib, melphalan og prednison samt efterfølgende som vedligeholdelsesbehandling, sammenlignet med nuværende standardbehandling til voksne patienter med nydiagnosticeret knoglemarvskræft, som ikke er egnede til højdosis kemoterapi med stamcellestøtte?

Population
Voksne patienter med nydiagnosticeret knoglemarvskræft, som ikke er egnede til højdosis kemoterapi med stamcellestøtte.

Intervention
Daratumumab kombineret med bortezomib, melphalan og prednison samt efterfølgende vedligeholdelsesbehandling indtil progression eller intolerance.

I op til ni serier a 6 uger:

- Bortezomib 1,3 mg/m^2 s.c. to gange ugentligt i uge 1, 2, 4 og 5 (serie 1) og en gang ugentligt i uge 1, 2, 4 og 5 (serie 2 til 9)
- Melphalan 9 mg pr. m^2 p.o. dagligt på dag 1 til 4 i hver cyklus
- Prednison 60 mg pr. m^2 p.o. dagligt på dag 1 til 4 i hver cyklus
- Daratumumab 16 mg pr. kg i.v. suppleret med intravenøs eller oral dexamethason (20 mg til håndtering af de infusionsrelaterede reaktioner) ugentligt i cyklus 1, hver tredje uge i cyklus 2-9

Dernæst indtil sygdomsprogression eller uacceptabel toksicitet:

- Daratumumab 16 mg pr. kg i.v. suppleret med intravenøs eller oral dexamethason (20 mg til håndtering af de infusionsrelaterede reaktioner) hver fjerde uge

Komparator
Nedenstående kombinationsbehandlinger er alle anbefalede og anvendt i Danmark. Alle behandlingerne er relevante komparatorer, idet behandlingsvalg i høj grad afgøres af komorbiditet og patientens præferencer vedrørende forventede bivirkninger og antal fremmøder.

Bortezomib + lenalidomid + dexamethason (BorLenDex):

I de første otte serier a 21 dage

- Lenalidomid 25 mg p.o. på dag 1-14
- Bortezomib 1,3 mg/m^2 s.c. på dag 1, 4, 8 og 11
- Dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11 og 12

Dernæst serier a 28 dage indtil progression

- Lenalidomid 25 mg p.o. på dag 1-21
- Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22

Lenalidomid og dexamethason (LenDex) doseret som følger:

Serier a 28 dages varighed i minimum 18 måneder

- Lenalidomid 25 mg p.o. på dag 1-21
- Dexamethason 40 mg p.o. på dag 1, 8, 15, og 22

Bortezomib, melphalan og prednisolon (BorMelPred) doseret som følger:

9 serier a 35 dages varighed med

- Bortezomib s.c. 1,3 mg/m^2 på dag 1, 8, 15 og 22
- Melphalan p.o. 9 mg/m^2 på dag 1, 2, 3, 4
- Prednisolon p.o. 100 mg på dag 1, 2, 3, 4

Effektmål
De valgte effektmål fremgår af tabel 1.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den mindste klinisk relevante forskel og effektmålsgruppe. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er for at sikre, at absolutte og relative effektforskelle vurderes og kategoriseres med udgangspunkt i de samme overordnede principper – herunder, at der tages hensyn til den usikkerhed et punktestimat er behæftet med. For at absolutte forskelle for de enkelte effektmål kan kategorisere med merværdi af ukendt størrelse, forudsætter Medicinrådet at alle værdier i konfidensintervallet ligger tættere på den mindste klinisk relevant forskel end på ingen effekt. Kategorisering i kategorien negativ værdi forudsætter omvendt, at ingen værdier i konfidensintervallet er tættere på ingen effekt end den negative mindste klinisk relevante forskel. Derfor vil konfidensintervallets grænser blive sammenholdt med det halve af den mindste klinisk relevante forskel (i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt).

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets metodehåndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	**Vigtighed**	**Effektmålsgruppe**	**Måleenhed**	**Mindste klinisk relevante forskel**
Samlet overlevelse (OS)	Kritisk	Overlevelse	Median OS	Komparator BorLenDex Forskel på 3 måneder mellem grupperne Komparator BorMelPred: Forskel på 6 måneder mellem grupperne Komparator LenDex (18 mdr.): Forskel på 6 måneder mellem grupperne
	Kritisk	Overlevelse	Overlevelsesrate ved tre år (såfremt data for median OS ikke er modne)	Forskel på 5 procentpoint
	Vigtig	*Livskvalitet, alvorlige symptomer og bivirkninger^*	Median PFS (såfremt data for overlevelse ikke er modne)	Komparator BorLenDex Forskel på 3 måneder mellem grupperne Komparator BorMelPred: Forskel på 6 måneder mellem grupperne

				Komparator LenDex (18 mdr.): Forskel på 6 måneder mellem grupperne
Behandlingsophør	Kritisk	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel, der ophører med behandling pga. uønskede hændelser (adverse events)	Forskel på 10 procentpoint mellem grupperne
Livskvalitet	Vigtig	*Livskvalitet, alvorlige symptomer og bivirkninger*	Pointændring over tid målt med EORTC QLQ-C30	Forskel på 10 point mellem grupperne
Bivirkninger	Vigtig	*Livskvalitet, alvorlige symptomer og bivirkninger*	Kvalitativ gennemgang	-

* For alle effektmål ønskes data med længst mulig opfølgningstid.
^ Da PFS er et sammensat effektmål, som indeholder tid til både progression og død, anvendes væsentlighedskriterierne for kategorien *Livskvalitet, alvorlige symptomer og bivirkninger*.

Kritiske effektmål

Samlet overlevelse

Samlet overlevelse (Overall survival, OS) er et effektmål, der belyser patientens levetid efter en fast opfølgningstid eller som en medianoverlevelse. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død, uanset årsag. Behandlingsmålet ved knoglemarvskræft er at sikre længst mulig overlevelse under hensyntagen til patientens livskvalitet, og overlevelse er derfor et kritisk effektmål. Fagudvalget ønsker overlevelse opgjort som medianoverlevelse. Den mediane overlevelse hos patienter, der ikke behandles med højdosis kemoterapi med stamcellestøtte, er ca. 3 år [2]. Ved fastsættelsen af den mindste klinisk relevante forskel skelner fagudvalget mellem, om komparator er tidsbegrænset eller til progression. Da interventionen løber til progression, bør der være en større effektforskel, hvis der sammenlignes med en tidsbegrænset behandling. Fagudvalget har vurderet, at den mindste klinisk relevante forskel i medianoverlevelse mellem intervention og komparator er 6 måneder, når komparator er en tidsbegrænset behandling. 6 måneder er valgt på grund af den relativt lange nuværende mediane overlevelse, og at interventionen gives i 1. linje indtil progression. Hvis komparator også løber til progression, er den mindste klinisk relevante forskel 3 måneder.

Såfremt data for medianoverlevelsen ikke er modne ønsker fagudvalget data for overlevelsesraten efter tre år. Den nuværende 3-årsoverlevelse i den danske population er ca. 58 % baseret på tal fra 2014-2017 [10]. Fagudvalget vurderer, at den mindste klinisk relevante forskel for overlevelsesraten er 5 procentpoint, svarende til at ca. 12 patienter flere vil være i live efter 3 år.

Fagudvalget medtager PFS som et surrogatmål for samlet overlevelse, såfremt data for overlevelse ikke er modne. Ansøger bedes redegøre for datamodenheden. Fagudvalget vurderer, at PFS er et vigtigt effektmål, da det er et surrogatmål for et kritisk effektmål. For patienter, der ikke er kandidater til HDT/STS, er den mediane PFS ca. 18 måneder [2]. Baseret på dette vurderer fagudvalget, at den mindste klinisk relevante forskel er 3 måneder for komparator BorLenDex og 6 måneder for de to øvrige komparatorer.

PFS defineres som tiden fra randomisering til progression eller død, hvor progression bestemmes efter det standardiserede responskriterie [11]. PFS er i en metaanalyse vist at korrelere med overlevelse indenfor behandling af knoglemarvskræft [12,13] og anvendes typisk som primært endepunkt i kliniske studier, fordi der ikke ved publikationstidspunktet forventes at foreligge modne data for OS. Derudover afspejler PFS varigheden af de perioder, hvor patienterne opnår symptomfrihed og dermed formodet bedre livskvalitet.

Fagudvalget ønsker at vurdere data for den længst mulige opfølgningstid i studierne.

Behandlingsophør grundet uønskede hændelser

Fagudvalget ønsker at vurdere et effektmål, der belyser tyngden af bivirkninger. Andelen af patienter, der ophører behandlingen pga. uønskede hændelser, er et effektmål, der udtrykker, hvor godt behandlingen

tolereres af patienterne, og fagudvalget vurderer, at det er et kritisk effektmål for vurderingen. Behandlinger til knoglemarvskræft er relativt bivirkningstunge, og frafald er forventeligt. Med de nuværende behandlinger ophører ca. 10-20 % af patienterne behandlingen pga. uønskede hændelser. Selvom daratumumab, baseret på fagudvalgets erfaringer, generet er veltolereret, forventer fagudvalget ikke, at en ny behandling med 4 stoffer i stedet for 3 vil give lavere fravær, men vil acceptere en forøgelse på ca. 10 %-point. Fagudvalget vurderer derfor, at en forskel på 10 %-point mellem grupperne er klinisk relevant. Fagudvalget ønsker at vurdere data for den længst mulige opfølgningstid i studierne.

Hvis der er foretaget en indirekte sammenligning, bedes ansøger lave en vurdering af, om sammenligningen af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling og hvordan bivirkningerne er opgjort og rapporteret. Overvejelser om sammenlignelighed/indirekthed skal fremgå i den endelige ansøgning.

Vigtige effektmål

Livskvalitet

Livskvalitet er et vigtigt effektmål i vurderingen af behandling af knoglemarvskræft, fordi sygdommen manifesterer sig ved en række symptomer og behandlingsmuligheder ved en række bivirkninger, som direkte påvirker patientens livskvalitet. Desuden findes endnu ingen kurative behandlingsformer, og en række af lægemidlerne gives kontinuerligt indtil progression Målinger af livskvalitet vil dermed også udtrykke, om patienten oplever, at eventuelle bivirkninger eller behov for ambulant behandling har betydende indflydelse på livskvaliteten. Det hyppigst anvendte redskab til vurdering af livskvalitet indenfor kliniske studier af knoglemarvskræft er det cancerspecifikke EORTC QLQ-C30-skema. Redskabet indeholder fem funktionelle skalaer, tre symptomskalaer, seks enkeltsymptomer samt en overordnet status for helbred og livskvalitet [14,15]. Der findes ikke en alment anerkendt mindste klinisk relevant forskel for dette måleredskab. Det er undersøgt, hvor stor en ændring på skalaen der i gennemsnit opfattes som en ændring i livskvalitet blandt patienter med knoglemarvskræft [16]. Et studie viste, at de patienter, som oplevede en forbedring i livskvalitet, i gennemsnit havde en ændring på + 7,6 point, mens en forværring af livskvalitet var forbundet med en gennemsnitlig ændring på - 12,1 point [17]. Fagudvalget vurderer på den baggrund, at en forskel på mindst 10 point er klinisk relevant.

Såfremt der ikke foreligger data fra EORTC QLQ-C30, foretrækkes data fra et andet valideret instrument, som er relevant for patienter med knoglemarvskræft, eksempelvis det generiske EQ-5D eller andre sygdomsspecifikke værktøjer.

Fagudvalget ønsker at vurdere data for den længst mulige opfølgningstid i studierne.

Bivirkninger

Fagudvalget ønsker som supplement til effektmålet *behandlingsophør grundet bivirkninger* en opgørelse af de hyppigste bivirkninger af enhver grad (forekommer hos > 10 % af patienterne) samt alle bivirkninger af grad 3-4, der er rapporteret i de kliniske studier, hvor DaraBorMelPred er undersøgt som behandling til nydiagnosticerede patienter med knoglemarvskræft. Fagudvalget vil ud fra denne opgørelse vurdere håndterbarhed og tyngde af bivirkningsprofilen i en narrativ sammenligning. Fagudvalget vurderer, at den kvalitative gennemgang er vigtig for kategoriseringen af den kliniske merværdi.

Ansøger bedes lave en vurdering af, om sammenligningen af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling og hvordan bivirkningerne er opgjort og rapporteret. Overvejelser om sammenlignelighed/indirekthed skal fremgå i den endelige ansøgning.

6 Litteratursøgning

Vurderingen af klinisk værdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor daratumumab i kombination med bortezomib, melphalan og prednisolon er sammenlignet direkte med henholdsvis BorLenDex, BorMelPred og LenDex.

Sekretariatet fandt følgende artikel, som er relevant, og som kan anvendes til direkte sammenligning med BorMelPred:

- Mateos MV et al. *Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial.* Lancet. 2020 Jan 11;395(10218):132-141.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning med komparatorerne BorLenDex og LenDex. Virksomheden bedes derfor søge efter yderligere studier til at belyse sammenligninger med disse behandlinger. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i bilag 1. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram *(*http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx*)*.
Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram *(*http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx*)*.
Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier
De inkluderede studier skal være randomiserede kontrollerede forsøg og skal stemme overens med de kliniske spørgsmål, hvad angår de beskrevne populationer, komparatorer og indeholde minimum ét relevant effektmål.

7 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Fagudvalget ønsker udover de i ansøgningsskemaet angivne karakteristika at se

karakteristik af patienternes cytogenetik (andel med højrisiko), stadieinddeling (ISS) og nyrefunktion. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention to treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Det skal angives, hvilke studier der benyttes til at besvare hvilke PICO-spørgsmål. Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, angives og begrundes dette.

Oplysning om, hvor data på de enkelte effektmål stammer fra, begrundelse for eventuelle afvigelser fra EPAR samt beskrivelse af, hvilke analysemetoder der er blevet anvendt til hvilke effektmål, skal fremgå. Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (for eksempel responsrater, uønskede hændelser, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans. Såfremt metaanalyse vil være relevant, ønskes en vurdering af, om studierne er homogene nok til at sammenlignes i en metaanalyse eller en netværksmetaanalyse.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

8 Andre overvejelser

Fagudvalget ønsker, at ansøger så vidt muligt belyser hvilke behandlinger patienterne, der indgik i ALCYONE-studiet, får, herunder andelen af patienter i henholdsvis interventions- og kontrolarmen, der får daratumumab i senere behandlingslinjer.

Fagudvalget ønsker informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlingerne i efterfølgende behandlingslinjer, hvad angår type, varighed og forventet effekt.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende knoglemarvskræft (myelomatose)

Formand	**Indstillet af**
Ulf Christian Frølund Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Sjælland
Medlemmer	**Udpeget af**
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Anja Klostergaard Afdelingslæge	Region Midtjylland
Per Trøllund Pedersen Specialeansvarlig overlæge	Region Syddanmark
Carsten Helleberg Overlæge	Region Hovedstaden
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Lise Heimark Patient/patientrepræsentant	Danske Patienter
Anne Kærsgaard Mylin Afdelingslæge, ph.d.	Dansk Myelomatose Studiegruppe
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11 Bilag 1: søgestrategi

Protokol: **Daratumumab i kombination med bortezomib, melphalan og prednison**

MEDLINE via PubMed

#	Søgestrenge	Kommentar
1	"Multiple Myeloma"[Mesh]	
2	myeloma*[tiab] OR ndmm*[tiab] OR (kahler*[tiab] AND (disease[tiab] OR morbus[tiab]))	
3	#1 OR #2	
4	refractory[ti] OR relapsed[ti] OR recurrent[ti]	
5	#3 NOT #4	Population
6	"daratumumab"[nm]	
7	daratumumab*[tiab] OR darzalex*[tiab] OR "humax cd38"[tiab]	
8	#6 OR #7	
9	"bortezomib"[Mesh]	
10	Bortezomib*[tiab] OR velcade*[tiab] OR mg-341*[tiab] OR mg341*[tiab] OR mln-341*[tiab] OR mln341*[tiab] OR ldp-341*[tiab] OR ldp341*[tiab] OR PS-341*[tiab] OR PS341*[tiab]	
11	#9 OR #10	
12	"melphalan"[Mesh]	
13	melphalan*[tiab] or melphelan*[tiab] or melphalon*[tiab] or melfalan*[tiab] or medphalan*[tiab] or merphalan*[tiab] or sarcolysin*[tiab] or sarkolysin*[tiab] or alkeran*[tiab] or "phenylalanine mustard"[tiab]	
14	#12 OR #13	
15	"prednisone"[Mesh]	
16	prednison*[tiab] or dehydrocortison*[tiab] or delta-cortison*[tiab] or rectodelt*[tiab] or sterapred*[tiab] or ultracorten*[tiab] or winpred*[tiab] or cortan*[tiab] or panafcort*[tiab] or cutason*[tiab] or decortin*[tiab] or dacortin*[tiab] or decortisyl*[tiab] or deltason*[tiab] or encorton*[tiab] or enkortolon*[tiab] or kortancyl*[tiab] or liquid-pred*[tiab] or meticorten*[tiab] or orison*[tiab] or panasol*[tiab] or predni-tablinen*[tiab] or prednidib*[tiab] or predniment*[tiab] or pronison*[tiab] or sone*[tiab]	
17	#15 OR #16	
18	#8 AND #11 AND #14 AND #17	Intervention
19	"lenalidomide"[Mesh]	
20	lenalidomid*[tiab] OR revlimid*[tiab] OR revimid*[tiab] OR cc-5013*[tiab] OR cc5013*[tiab] OR cdc-501*[tiab] OR cdc-5013*[tiab] OR cdc501*[tiab] OR cdc5013*[tiab] OR enmd-0997*[tiab] OR enmd0997*[tiab] OR imid-3*[tiab] OR imid3*[tiab]	
21	#19 OR #20	
22	"dexamethasone"[Mesh]	
23	dexametason*[tiab] OR dexamethason*[tiab] OR Adexon*[tiab] OR Aeroseb-dex*[tiab] OR Decaderm*[tiab] OR Decadron*[tiab] OR Decaject*[tiab] OR Decameth*[tiab] OR Decaspray*[tiab] OR Dectancyl*[tiab] OR Dexacort*[tiab] OR Dexafarm*[tiab] OR Dexafree*[tiab] OR Dexapos*[tiab] OR Dexa-Rhinospray*[tiab] OR Dexa-sine*[tiab] OR Dexason*[tiab] OR Dexone*[tiab] OR dexpak*[tiab] OR Dexsol*[tiab] OR Fortecortin*[tiab] OR Gammacorten*[tiab] OR Hexadecadrol*[tiab] OR Hexadrol*[tiab] OR Isopto-Dex*[tiab] OR Loverine*[tiab] OR Luxazone*[tiab] OR Maxidex*[tiab] OR Maxitrol*[tiab] OR Methylfluorprednisolone*[tiab] OR Millicorten*[tiab] OR oradexon*[tiab] OR Ozurdex*[tiab] OR Sofradex*[tiab] OR Superprednol*[tiab] OR Visumetazone*[tiab]	
24	#22 OR #23	
25	#21 AND #24	Komparator LenDex

26	#11 AND #25	Komparator BorLenDex
27	#18 OR #25 OR #26	Intervention **eller** Komparatorer
28	#5 AND #27	Samlet søgning
29	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	Cochrane RCT filter
30	#28 AND #29	Endelig søgning

Central via Cochrane library

#	**Søgestrenge**	**Kommentar**
1	[mh "Multiple Myeloma"]	
2	(myeloma* or ndmm* or ((kahler or kahler's or kahler*) next (disease or morbus))):ti,ab,kw	
3	{or #1-#2}	
4	(refractory or relapsed or recurrent):ti	
5	#3 not #4	Population
6	(daratumumab* or darzalex* or "humax cd38"):ti,ab,kw	
7	[mh Bortezomib]	
8	(bortezomib* or velcade* or mg-341* or mg341* or mln-341* or mln341* or ldp-341* or ldp341* or PS-341* or PS341*):ti,ab,kw	
9	{or #7-#8}	
10	[mh Melphalan]	
11	(melphalan* or melphelan* or melfalan* or medphalan* or merphalan* or sarcolysin* or sarkolysin* or alkeran* or "phenylalanine mustard"):ti,ab,kw	
12	{or #10-#11}	
13	[mh Prednisone]	
14	(prednison* or dehydrocortison* or delta-cortison* or rectodelt* or sterapred* or ultracorten* or winpred* or cortan* or panafcort* or decortin* or dacortin* or decortisyl* or deltason* or encorton* or liquid-pred* or meticorten* or panasol* or prednidib* or pronison* or sone*):ti,ab,kw	
15	{or #13-#14}	
16	#6 AND #9 AND #12 AND #15	Intervention
17	[mh Lenalidomide]	
18	(lenalidomide* or revlimid* or revimid* or cc-5013* or cc5013* or cdc-501* or cdc-5013* or cdc501* or cdc5013* or enmd-0997* or enmd0997* or imid-3* or imid3*):ti,ab,kw	
19	{or #17-#18}	
20	[mh Dexamethasone]	
21	(dexametason* or dexamethason* or Adexon* or Aeroseb-dex* or Aphthasolone* or Decaderm* or Decadron* or Decaject* or Decameth* or Decaspray* or Dectancyl* or Degabina* or Dexabion* or Dexacen* or Dexacort* or Dexafarm* or Dexafree* or Dexair* or Dexalaf* or Dexalergin* or Dexameral* or Dexamonozon* or Dexapos* or Dexa-Rhinospray* or Dexa-sine* or Dexason* or Dexatotal* or Dexone* or dexpak* or Dexsol* or Dropodex* or Flourmethylprednisolone* or Fortecortin* or Gammacorten* or Hexadecadrol* or Hexadrol* or Isopto-Dex* or Loverine* or Luxazone* or Martapan* or Maxidex* or Maxitrol* or Methylfluorprednisolone* or Millicorten* or Monopex* or Neofordex* or Oradexon* or Ozurdex* or Sofradex* or Superprednol* or Visumetazone*):ti,ab,kw	
22	{or #20-#21}	
23	#19 AND #22	Komparator LenDex
24	#9 AND #23	Komparator BorLenDex

25	#16 OR #23 OR #24	Intervention **eller** Komparatorer
26	#5 AND #25	
27	("conference abstract" or review):pt OR NCT*:au	
28	(clinicaltrials.gov or trialsearch or meeting):so	
29	abstract:ti	
30	{or #27-#29}	
31	#26 NOT #30	Endelig søgning

12 Versionslog

Version	Dato	Ændring
2.0	3. februar 2020	Protokollen er opdateret ifølge Medicinrådets metodehåndbog pr. 1. januar 2019. Effektmål er tilrettet ifølge nyere protokoller for vurdering af lægemidler til knoglemarvskræft. Herunder er overlevelsesraten ved tre år tilføjet som effektmål, såfremt data for medianoverlevelse ikke er modne, og det er præciseret, at effektmålet *progressionsfri overlevelse* anses som et surrogatmål for overlevelse.
1.0	18. september 2018	Godkendt af Medicinrådet.