Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende lenalidomid i kombination med bortezomib og dexamethason som mulig standardbehandling til tidligere ubehandlede patienter med knoglemarvskræft der ikke er kandidater til højdosis kemoterapi med stamcellestøtte

Versionsnr.: 1.0

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 anbefalingen

Anbefalingen er Medicinrådets vurdering af, om lægemidlets samlede pris er rimelig, når man sammenligner den med lægemidlets værdi for patienterne.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	25. september 2019
Ikrafttrædelsesdato	25. september 2019
Dokumentnummer	57708
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 25. september 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Revlimid®
Generisk navn	Lenalidomid
Firma	Celgene Europe Ltd
ATC-kode	L04AX04
Virkningsmekanisme	Lenalidomid binder til proteinet cereblon og hæmmer dets funktion. Proteinet findes i knoglemarvens celler og er involveret i blandt andet cellens stofskifte, signalering og i dannelsen af nye blodkar.
Administration/dosis	I de første 8 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 til progression med: • Lenalidomid 25 mg p.o. på dag 1-21 • Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22
EMA-indikation	Lenalidomid i kombination med bortezomib og dexamethason til voksne patienter med tidligere ubehandlet knoglemarvskræft som ikke er egnede til stamcelletransplantation.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** lenalidomid i kombination med bortezomib og dexamethason som mulig standardbehandling til tidligere ubehandlede patienter med knoglemarvskræft, der ikke er kandidater til højdosis kemoterapi med stamcellestøtte.

Medicinrådet vurderer at der er et rimeligt forhold mellem meromkostninger og værdi, når de efterfølgende behandlinger tages i betragtning.

Effekten af behandling med LenDex til progression i denne population er ikke veldokumenteret, og Medicinrådet henstiller derfor til, at behandlingsvarigheden løbende tages op til overvejelse ved anvendelse af LenDex og BorLenDex.

Det kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

1. *Hvilken værdi giver BorLenDex sammenlignet med LenDex til patienter med tidligere ubehandlet knoglemarvskræft, der ikke er kandidater til HDT/STS?*
2. *Hvilken værdi giver BorLenDex sammenlignet med BorMelPred til patienter med tidligere ubehandlet knoglemarvskræft, der ikke er kandidater til HDT/STS?*

3 Formål

Formålet med *Baggrund for Medicinrådets anbefaling vedrørende lenalidomid i kombination med bortezomib og dexamethason som mulig standardbehandling til tidligere ubehandlede patienter med knoglemarvskræft der ikke er kandidater til højdosis kemoterapi med stamcellestøtte* er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Knoglemarvskræft er en uhelbredelig, livstruende og livsforkortende, men behandlingsfølsom hæmatologisk kræftsygdom.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 7. marts 2019, og protokollen blev sendt til Celgene den 15. april 2019. Den endelige ansøgning blev modtaget første gang den 3. juni 2019 og blev betragtet som endelig den 24. juni 2019. Beslutning om anbefaling blev truffet den 25. september 2019.

Sagsbehandlingstiden er dermed 13 uger og 2 dage.

5 Medicinrådets vurdering af samlet værdi

Medicinrådet vurderer, at lenalidomid i kombination med bortezomib og dexamethason (BorLenDex):

- Giver en merværdi af ukendt størrelse sammenlignet med lenalidomid og dexamethason (LenDex). Evidensens kvalitet vurderes at være meget lav.
- Ikke kan kategoriseres, men at kombinationen samlet set ikke har dårligere effekt eller sikkerhedsprofil sammenlignet med bortezomib, melphalan og prednison (BorMelPred). Evidensens kvalitet kan ikke vurderes.

6 Høring

Høringsperioden foregik fra den 21. august til 4. september 2019. Ansøger havde ikke kommentarer til vurderingen.

7 Resumé af økonomisk beslutningsgrundlag

Amgros har vurderet de gennemsnitlige meromkostninger per patient og budgetkonsekvenserne for regionerne ved brug af BorLenDex sammenlignet med komparatorerne LenDex og BorMelPred. Amgros' vurdering af meromkostninger og budgetkonsekvenser er baseret på SAIP.

Baseret på Amgros' hovedanalyse vurderer Medicinrådet, at der er et rimeligt forhold mellem omkostninger og lægemidlets værdi i sammenligningen med LenDex.

Baseret på Amgros' hovedanalyse vurderer Medicinrådet, at der ikke er et rimeligt forhold mellem omkostninger og lægemidlets værdi i sammenligningen BorMelPred. Amgros har foretaget en

følsomhedsanalyse, der inkluderer efterfølgende behandlingslinjer, hvilket medfører en reduktion i lægemidlets meromkostninger, da meromkostningerne især er drevet af lenalidomid, og patienter, der i første linje behandles med BorMelPred, vil blive behandlet med lenalidomid senere.

I Medicinrådets behandlingsvejledning er de to komparatorer ligestillet.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

9 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**
Asta Svirskaite Overlæge	Region Nordjylland
Anja Klostergaard Afdelingslæge	Region Midtjylland
Per Trøllund Pedersen Specialeansvarlig overlæge	Region Syddanmark
Carsten Helleberg Overlæge	Region Hovedstaden
Lisbeth Egeskov Patient/patientrepræsentant	Danske Patienter
Lise Heimark Patient/patientrepræsentant	Danske Patienter
Anne Kærsgaard Mylin Afdelingslæge, ph.d.	Dansk Myelomatose Studiegruppe
Jennifer A. F. Andresen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Tonny Studsgaard Pedersen Overlæge, klinisk lektor	Dansk Selskab for Klinisk Farmakologi

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Karen Kleberg Hansen (projekt- og metodeansvarlig) Louise Klokker Madsen (projektdeltager) Annette Pultera Nielsen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistisk chefkonsulent) Annemette Anker Nielsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	25. september 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Medicinrådets vurdering af klinisk værdi for lenalidomid i kombination med bortezomib og dexamethason til behandling af tidligere ubehandlede patienter med knoglemarvskræft der ikke er kandidater til højdosis kemoterapi med stamcellestøtte – version 1.0
- Ansøgers endelige ansøgning
- Medicinrådets protokol for vurdering af lenalidomid i kombination med bortezomib og dexamethason til behandling af tidligere ubehandlede patienter med knoglemarvskræft – version 1.0

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af lenalidomid (Revlimid) i kombination med bortezomib og dexamethason (BorLenDex) som mulig standardbehandling til patienter med ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	25-09-2019
Firma	Celgene (ansøger)
Lægemiddel	Lenalidomid (Revlimid)
Indikation	Lenalidomid i kombination med bortezomib og dexamethason til voksne patienter med tidligere ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation.

Amgros' vurdering

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for BorLenDex som mulig standardbehandling til patienter med ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation sammenlignet med lenalidomid i kombination med dexamethason (LenDex), (P1)
- Amgros vurderer, at der **ikke** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for BorLenDex som mulig standardbehandling til patienter med ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation sammenlignet med bortezomib i kombination med melphalan og prednisolon (BorMelPred), (P2)

Overordnet konklusion

Medicinrådet har vurderet, at BorLenDex sammenlignet med LenDex (P1) giver **merværdi af ukendt størrelse**.

Medicinrådet har vurderet, at merværdien for BorLenDex sammenlignet med BorMelPred (P2) **ikke kan kategoriseres**, men at kombinationen samlet set ikke har dårligere effekt eller sikkerhedsprofil end komparatoren. Fagudvalget fremhæver at komparatorene LenDex og BorMelPred er effektmæssigt sammenlignelige og ligestillet i Medicinrådets behandlingsvejledning, som inkluderer en indirekte sammenligning af LenDex og BorMelPred.

Behandling med BorLenDex er forbundet med meromkostninger sammenlignet med LenDex (P1) og BorMelPred (P2) til nævnte indikation. Amgros vurderer, at der **er** et rimeligt forhold mellem den kliniske merværdi for BorLenDex sammenlignet med LenDex, og at der **ikke** er rimeligt forhold mellem den kliniske merværdi for BorLenDex sammenlignet med BorMelPred. Meromkostninger drives næsten udelukkende af prisen på lenalidomid (Revlimid).

Andre overvejelser

Amgros har efter udbud indgået en aftale med Celgene om indkøb af lenalidomid (Revlimid) til en SAIP, som er lavere end AIP. Kontrakten løber indtil 31.12.2019. Der er et nyt udbud til tilbudsgivning nu, med deadline den 30.09.2019. Kontrakten for dette udbud vil træde i kraft 01.01.2020.

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Lenalidomid i kombination med bortezomib og dexamethason til voksne patienter med tidligere ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation	LenDex	Ukendt størrelse	Meget lav evidens	Rimeligt
	BorMelPred	Kan ikke kategoriseres	Kan ikke vurderes	Ikke rimeligt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med BorLenDex er forbundet med meromkostninger sammenlignet med behandling med komparatorerne. I tabel 2 ses de inkrementelle omkostninger for BorLenDex sammenlignet med LenDex (P1) og BorMelPred (P2).

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for BorLenDex sammenlignet med LenDex (P1) på ca. [redacted] DKK, og sammenlignet med BorMelPred (P2) på ca. [redacted] DKK.

Tabel 2: Resultat af Amgros hovedanalyse for BorLenDex sammenlignet med komparatorer, DKK, SAIP

	BorLenDex	LenDex (P1)	BorMelPred (P2)
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administration	123.755	59.446	90.582
Bivirkninger	6.746	4.761	6.039
Patientomkostninger	13.965	9.904	14.688
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger vs. BorLenDex	-	[redacted]	[redacted]

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for BorLenDex ca. 733.000 DKK, mens de total inkrementelle omkostninger bliver ca. 42.000 DKK per patient sammenlignet med LenDex (P1) og ca. 715.000 DKK sammenlignet med BorMelPred (P2).

Hvis efterfølgende behandlingslinjer inkluderes i analysen, reduceres meromkostningerne betydeligt. Meromkostningerne vil dog i høj grad drives af valget af efterfølgende behandlingslinjer, da den største omkostningsbyrde vil tilfalde den intervention, hvor der benyttes mest lenalidomid (Revlimid). Antagelserne omkring effekt og behandlingslængde af efterfølgende behandlingslinjer, der ligger til grund for følsomhedsanalyserne, er dog forbundet med store usikkerheder.

Tabel 3: Resultaterne af Amgros' følsomhedsanalyser, SAIP, DKK.

Følsomhedsanalyse	BorLenDex vs. LenDex (P1)	BorLenDex vs. BorMelPred (P2)
Amgros' hovedanalyse	[redacted]	[redacted]
Inklusiv efterfølgende behandlingslinjer baseret på klinikerestimater	[redacted]	[redacted]
Inklusiv efterfølgende behandlingslinjer baseret på ansøgers estimater	[redacted]	[redacted]

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer, at anvendelse af BorLenDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK ved år 5, ved et markedsoptag på 60%. Patientfordelingen på LenDex og BorMelPred er 50%/50%.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 54 mio. ved år 5.

LENALIDOMID (REVLIMID) I KOMBINATION MED BORTEZOMIB OG DEXAMETHASON

1. LINJE BEHANDLING AF KNOGLEMARVSKRÆFT

AMGROS

AMGROS 4. september 2019

OPSUMMERING

Baggrund

Lenalidomid (Revlimid) i kombination med bortezomib og dexamethason (BorLenDex) er som indiceret til 1. linje behandling af voksne patienter med tidligere ubehandlet knoglemarvskræft, som ikke er egnede til stamcelle-transplantation. Omkring 240 nye patienter per år kandiderer årligt til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Celgene.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med BorLenDex sammenlignet med lenalidomid + dexamethason (LenDex, P1) og bortezomib + melphalan + prednisolon (BorMelPred, P2) som 1. linje behandling af patienter med knoglemarvskræft.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af BorLenDex sammenlignet med LenDex (P1) og BorMelPred (P2). De inkrementelle omkostninger er angivet i SAIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for BorLenDex ca. [redacted] sammenlignet med LenDex, og [redacted] DKK sammenlignet med BorMelPred. Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning hhv. 42.000 DKK og 715.000 DKK per patient.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af BorLenDex som standardbehandling vil være ca. [redacted] ved år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 54 mio. DKK om året.

Konklusion

Behandling med BorLenDex er forbundet med begrænsede meromkostninger sammenlignet med behandling med LenDex (P1) og med betydelige meromkostninger sammenlignet med BorMelPred (P2). De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for lenalidomid (Revlimid).

Hvis efterfølgende behandlingslinjer inkluderes i analysen, reduceres de inkrementelle omkostninger betydeligt. Disse analyser bør dog tolkes med stor forsigtighed, da antagelserne der ligger til grund for disse resultater er forbundet med stor usikkerhed.

Liste over forkortelser

AIP	Apotekernes indkøbspris
BorLenDex	Lenalidomid + bortezomib + dexamethason
BorMelPred	Bortezomib + melphalan + prednisolon
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
HDT/STS	Højdosis kemoterapi med stamcellestøtte
LenDex	Lenalidomid + dexamethason
OS	Overall survival, samlet overlevelse
PFS	Progressionsfri overlevelse
SAIP	Sygehusapotekernes indkøbspriser
ToT	Time on treatment, behandlingslængde
TTNT	Time to next treatment, tid til næste behandlingslinje

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Celgene
Handelsnavn:	Revlimid
Generisk navn:	Lenalidomid
Indikation:	Lenalidomid i kombination med bortezomib og dexamethason til voksne patienter med tidligere ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation.
ATC-kode:	L04AX04

Proces	
Ansøgning modtaget hos Amgros:	24-06-2019
Endelig rapport færdig:	04-09-2019
Sagsbehandlingstid fra endelig ansøgning:	65 dage
Arbejdsgruppe:	**Line Brøns Jensen** Louise Greve Dal Pernille Winther Johansen Lianna Geertsen Mark Friborg

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Lenalidomid (Revlimid) i kombination med bortezomib og dexamethason (BorLenDex) er som indiceret til 1. linje behandling af voksne patienter med tidligere ubehandlet knoglemarvskræft, som ikke er egnede til stamcelle-transplantation. Celgene (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af lenalidomid (Revlimid) og har den 24.06.2019 indsendt en ansøgning til Medicinrådet om anbefaling af BorLenDex som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af BorLenDex som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med BorLenDex med behandling med LenDex (P1) og BorMelPred (P2).

1.2 Patientpopulation

Knoglemarvskræft er en uhelbredelig, livstruende og livsforkortende, men behandlingsfølsom hæmatologisk kræftsygdom. Sygdommen skyldes, at en type af hvide blodlegemer 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 maligne plasmaceller og er et ikkefunktionelt immunoglobulin eller dele heraf. Hos nogle patienter vil M-komponenten give anledning til nyreskader eller egentligt nyresvigt.

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 behandlingskrævende patienter årligt, der skal have deres første behandling (1).

1.3 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. Behandlingen er ikke kurativ, men målet med behandlingen er at opnå længst mulig overlevelse med færrest mulige bivirkninger, perioder med symptomfrihed, længerevarende behandlingsfri perioder 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, hvis de ønsker det. Denne behandling er internationalt anerkendt som det bedste valg uden ligeværdige alternativer.

Patienter med behandlingskrævende knoglemarvskræft, som ikke er kandidater til HDT/STS, tilbydes andre medicinske kombinationsbehandlinger. Patientpopulationen udgør ca. 240 patienter årligt. Blandt de nuværende

behandlingsmuligheder anvendes oftest en kombination af enten bortezomib, melphalan og prednisolon (BorMelPred) eller lenalidomid og dexamethason (LenDex). Samlet set har disse patienter en median progressionsfri overlevelse på ca. 18 måneder (1).

De patienter, der behandles med HDT/STS, har en væsentlig bedre prognose end de, der ikke er kandidater til denne behandling. Halvdelen af de patienter, der behandles med HDT/STS, er fortsat i live efter ca. 7 år (den mediane overlevelse), mens patienter, der ikke er kandidater til HDT/STS, har en median overlevelse på ca. 3 år. Denne gruppe omfatter især patienter over 70 år og inkluderer de ældste patienter. 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 (1).

1.4 Behandling med lenalidomid (Revlimid) i kombination med bortezomib og dexamethason

Indikation

Lenalidomid (Revlimid) er indiceret som kombinationsterapi med bortezomib og dexamethason til 1. linje behandling af voksne patienter med tidligere ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation.

Lenalidomid har været godkendt til behandling af knoglemarvskræft siden 2007, og indgår som det ene lægemiddel i mange behandlingskombinationer.

Virkningsmekanisme

Lenalidomid (Revlimid) tilhører gruppen af immunmodulerende stoffer, som binder til proteinet cereblon og hæmmer dets funktion. Proteinet findes i knoglemarvens celler og er involveret i blandt andet cellens stofskifte, signalering og i dannelsen af nye blodkar. Behandling med immunmodulerende stoffer hæmmer derfor både kræftcellernes deling og deres forsyning af næringsstoffer fra blodet.

Dosering

BorLenDex skal til behandling af patienter, der ikke er kandidater til HDT/STS, doseres som følger:

Først 8 serier af 21 dage med:

- 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 af 28 dage til progression med:

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

1.4.1 Komparator

Medicinrådet har defineret LenDex og BorMelPred som komparatorer for hhv. P1 og P2, se tabel 1 (1).

Lenalidomid og dexamethason doseres som følger:

Serier af 28 dages varighed i minimum 18 måneder eller til progression

- 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 doseres som følger:

9 serier af 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 og 4
- Prednisolon p.o. 100 mg på dag 1, 2, 3 og 4

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
P1: Tidligere ubehandlede patienter med behandlingskrævende knoglemarvskræft der ikke er kandidater til HDT/STS.	Lenalidomid + dexamethason
P2: Tidligere ubehandlede patienter med behandlingskrævende knoglemarvskræft der ikke er kandidater til HDT/STS.	Bortezomib + melphalan + dexamethason

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af BorLenDex som 1. linje behandling for følgende populationer:

- **P1:** Hvad er værdien af lenalidomid i kombination med bortezomib og dexamethason (BorLenDex) sammenlignet med lenalidomid + dexamethason (LenDex) til tidligere ubehandlede behandlingskrævende patienter med knoglemarvskræft, der ikke er kandidater til HDT/STS?
- **P2:** Hvad er værdien af lenalidomid i kombination med bortezomib og dexamethason (BorLenDex) sammenlignet med bortezomib + melphalan + prednisolon (BorMelPred) til tidligere ubehandlede behandlingskrævende patienter med knoglemarvskræft, der ikke er kandidater til HDT/STS?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af inkrementelle omkostninger per patient sammenlignes behandling med BorLenDex med behandling med LenDex og BorMelPred. Analysen inkluderer omkostninger til lægemidler, efterfølgende behandlingslinjer, administration, patienttid, transport og behandlingsrelaterede bivirkninger.

Ansøger har indsendt en analyse der sammenligner BorLenDex med behandling med LenDex og BorMelPred. Amgros havde flere indvendinger mod den første indsendte analyse. Det er kun den seneste indsendte analyse, der præsenteres.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en økonomisk model, hvor tiden patienten er i behandling defineres ud fra Kaplan-Meier kurver fra de kliniske studier. Ansøger har desuden tilføjet omkostninger forbundet med efterfølgende behandlingslinjer. Modellen estimerer således tiden til progression (progressionsfri overlevelse, PFS), tid på behandling (ToT) samt tid til næste behandling (TTNT) fra SWOG S0777-studiet (2). For komparator-kombinationen med bortezomib, melphalan og prednisolon benyttes data fra ALCYONE-studiet (3).

Ansøger har i deres hovedanalyse anvendt en subgruppe fra SWOG 0777-studiet, da de argumenterer for, at denne population bedst reflekterer dansk klinisk praksis og Medicinrådets protokol for vurdering af den kliniske merværdi (1,2). Subgruppen har en højere medianalder (70 vs. 63 år), og en større del af patienterne har dårlig performance status sammenlignet med den samlede studiepopulation (2).

Amgros' vurdering

Ansøger har valgt at inkludere efterfølgende behandlingslinjer i deres analyse. Amgros vurderer der er stor usikkerhed ved at inkludere efterfølgende behandlinger, da studierne kun rapporterer overlevelsesdata, og ikke tager højde for effekten af forskellige efterfølgende behandlingskombinationer.

Amgros' udarbejder derfor egen hovedanalyse uden efterfølgende behandlingslinjer.

Amgros vælger at ekskludere efterfølgende behandlingslinjer fra ansøgers analyse og præsenterer dette som Amgros' hovedanalyse. Modellens andre valg accepteres.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 10 år. Dette er valgt, da ansøger argumenterer, at den gennemsnitlige behandlingslængde med BorLenDex og komparatorer ligger inden for denne tidshorisont. Omkostninger der ligger efter det første år, er diskonteret med en rate på 4%.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv og diskonteringsrate er i tråd med Amgros' retningslinjer og accepteres.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen.

Lægemiddelomkostninger

Ansøger har inkluderet omkostninger til lægemidler. De anvendte doser er hentet i de respektive lægemidlers produktresuméer og priserne er fra Amgros, se tabel 2 (4,5). For bortezomib er det dog præciseret i Medicinrådets protokol for vurdering af den kliniske merværdi, at bortezomib skal administreres subkutant, selvom produktresuméet beskriver intravenøs administration. Ansøger har valgt at følge Medicinrådets protokol i dette tilfælde, og har desuden suppleret med en følsomhedsanalyse, hvor bortezomib administreres intravenøst jf. produktresuméet (1,4).

Tabel 2: Anvendte lægemiddelpriser pr. 15.07.2019, SAIP.

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Lenalidomid	25 mg	21	[redacted]	Amgros
Lenalidomid	20 mg	21	[redacted]	Amgros
Lenalidomid	15 mg	21	[redacted]	Amgros
Lenalidomid	10 mg	21	[redacted]	Amgros
Lenalidomid	7,5 mg	21	[redacted]	Amgros
Lenalidomid	5 mg	21	[redacted]	Amgros
Lenalidomid	2,5 mg	21	[redacted]	Amgros
Bortezomib	3,5 mg	1	[redacted]	Amgros
Dexamethason	4 mg	20	[redacted]	Amgros
Dexamethason	1 mg	100	[redacted]	Amgros
Melphalan	2 mg	25	[redacted]	Amgros
Prednisolon	25 mg	100	[redacted]	Amgros
Prednisolon	5 mg	100	[redacted]	Amgros
Carfilzomib	60 mg	1	[redacted]	Amgros
Carfilzomib	30 mg	1	[redacted]	Amgros
Carfilzomib	10 mg	1	[redacted]	Amgros
Daratumumab	400 mg	1	[redacted]	Amgros
Daratumumab	100 mg	1	[redacted]	Amgros

Ansøgers analyse inkluderer udover omkostninger til intervention og komparator også omkostninger til efterfølgende behandlingslinjer, hvorfor lægemiddelpriser på carfilzomib og daratumumab også fremgår i tabellen.

Amgros' vurdering

Amgros accepterer ansøgers antagelser om lægemiddelomkostninger i 1. linje.

Efterfølgende behandlingslinjer

Ansøger har inkluderet omkostninger forbundet med efterfølgende behandlingslinjer. Lægemiddelpriserne ses i Tabel 2.

Ansøger antager, at patienterne fordeles på efterfølgende behandlingslinjer jf. Tabel 3. Fordelingen er baseret på Medicinrådets protokol for vurdering af pomalidomid i kombination med bortezomib og dexamethason indikeret til 2. linjebehandling af knoglemarvskræft, eftersom denne ansøgning er blevet udarbejdet før Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft blev godkendt (6).

Tabel 3: Fordeling af efterfølgende behandlingslinjer ved progression.

	2. linjebehandling		
1. linjebehandling	DaraBorDex	DaraLenDex	CarDex
BorLenDex	65%	5%	30%
LenDex	80%	5%	15%
BorMelPred	5%	90%	5%

Amgros' vurdering

Amgros vurderer der er stor usikkerhed ved at inkludere efterfølgende behandlinger, da studierne kun rapporterer overlevelsesdata, og ikke tager højde for effekten af forskellige efterfølgende behandlingskombinationer. Amgros ekskluderer derfor omkostninger forbundet med efterfølgende behandlingslinjer, men tilføjer en følsomhedsanalyse, hvor efterfølgende behandlingslinjer alligevel medregnes.

Amgros vurderer, at fordelingen af efterfølgende behandlingslinjer bør reflektere Medicinrådets nye behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (7). Amgros har desuden fået regionerne til at udpege klinikere med ekspertise indenfor det pågældende terapiområde, og bedt dem validere ansøgers estimater og antagelser. På baggrund af den nye behandlingsvejledning samt klinikernes udtalelser ændrer Amgros derfor fordelingen i Amgros' følsomhedsanalyse, jf. Tabel 4.

Tabel 4: Amgros' fordeling af efterfølgende behandlingslinjer benyttet i Amgros' følsomhedsanalyse.

	2. linjebehandling		
1. linjebehandling	DaraBorDex	DaraLenDex	CarDex
BorLenDex	65%	20%	15%
LenDex	25%	60%	15%
BorMelPred	10%	80%	10%

Hospitalsomkostninger

Ansøger har ikke inkluderet omkostninger for oral administration af lægemidlerne i den ansøgte linje. Dog administreres bortezomib subkutant på hospitalet, hvorfor omkostninger til administration af dette lægemiddel er inkluderet. Daratumumab og carfilzomib i efterfølgende behandlingslinjer administreres intravenøst, hvorfor

omkostninger forbundet med infusion af disse lægemidler er inkluderet i ansøgers analyse. Omkostningerne er inkluderet i form af sygeplejersketid og kliniktid, som vist i Tabel 5.

Tabel 5: Omkostninger til lægemiddeladministration ved efterfølgende behandlingslinjer.

	Estimeret tidsforbrug	Enhedsomkostning [DKK]	Anvendt omkostning [DKK]	Kilde
Sygeplejersketid	30 min.	8,7 DKK/min.	261	Amgros vejledning: Værdisætning af enhedsomkostninger (8)
Kliniktid	30 min. (for bortezomib) 150 min. (for daratumumab) 45 min. (for carfilzomib)	0,3 DKK/min.	9 45 13,5	Ansøgers antagelse

Amgros' vurdering

Amgros vurderer, at det vil være mere retvisende at benytte relevante DRG-takster for estimeringen af omkostninger forbundet med administration af bortezomib, daratumumab og carfilzomib på hospitalet.

Amgros har desuden konsulteret klinikere for at validere ansøgers estimater. Klinikerne vurderer, at alle patienter uanset behandling vil ses på hospitalet i forbindelse med opstart af en ny serie. Da serielængderne er forskellige mellem behandlingerne, tilføjer Amgros et besøg ved seriestart for de orale behandlinger. Opfølgningsbesøgene vurderes at lægges sammen med administrationsbesøg ved subkutane og intravenøse lægemidler, hvorfor der ikke tilføjes yderligere besøg for disse behandlinger.

Amgros ændrer de anvendte enhedsomkostninger til relevante DRG-takster og tilføjer administrationsbesøg for orale lægemidler. Amgros ekskluderer desuden omkostninger forbundet med efterfølgende behandlingslinjer fra Amgros' hovedanalyse, men benytter dog estimaterne i Amgros' følsomhedsanalyse, hvor efterfølgende behandlingslinjer inkluderes.

Omkostninger til bivirkninger

Omkostninger til behandlingsrelaterede bivirkninger er inkluderet i ansøgers analyse.

Ansøgers model benytter sandsynligheder for bivirkninger af grad 3 eller mere. For BorLenDex og LenDex (P1) har ansøger benyttet de rapporterede bivirkningsrater fra SWOG-0777-studiet (2). For BorMelPred (P2) har ansøger inkluderet bivirkningsrater fra VISTA-studiet (9). Bivirkningsfrekvenserne ses i tabel 6.

Ressourcerne brugt i forbindelse med bivirkninger har ansøger baseret på DRG-taksten 17MA98 MDC17, hvilket giver en omkostning per event på 3.285 DKK.

Tabel 6: Rapporterede bivirkningsfrekvenser ved behandling med BorLenDex og komparatorer

Bivirkning	BorLenDex	LenDex	BorMelPred
Akut nyresvigt	2,7%	5,5%	
Anæmi	12,2%	16,0%	18,8%
Dehydrering	8,4%	2,3%	
Diarré	9,2%	1,6%	7,9%
Dyspnø	6,1%	1,2%	
Embolisme	6,9%	6,3%	
Træthed	14,5%	10,2%	7,9%
Hyperglykæmi	7,3%	9,4%	
Hypokalkæmi	6,5%	8,2%	
Hypokaliæmi	11,5%	4,7%	6,8%
Hyponatriæmi	6,5%	6,3%	
Hypotension	7,6%	0,0%	
Leukopæni	8,8%	11,3%	23,8%
Lungeinfektion	7,3%	5,5%	7,1%
Lymfopæni	18,7%	15,2%	20,0%
Muskelsvækkelse	8,4%	4,3%	
Neutropæni	9,9%	16,4%	40,0%
Perifer motorisk neuropati	6,5%	1,2%	
Perifer sensorisk neuropati	20,6%	1,6%	13,5%
Synkope	8,8%	2,7%	
Trombocytopæni	17,2%	15,2%	37,9%

Amgros' vurdering

Amgros finder ansøgers tilgang acceptabel.

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid. Dette er gjort på baggrund af den tid patienterne benytter på administration af lægemidlerne ved besøg på hospitalet, og inkluderer den effektive tid på hospitalet,

ventetid og transporttid. Ansøger inkluderer også omkostninger til patienttid forbundet med behandling af bivirkninger. Ansøgers estimerede patienttid kan ses i tabel 7.

Tabel 7: Ansøgers estimat af effektiv patienttid.

	Patienttid [minutter]	Enhedsomkostning [DKK]
Kliniktid	30 min. (for bortezomib) 150 min. (ved daratumumab) 45 min. (ved carfilzomib)	180
Patient transporttid	90	100
Behandling af bivirkninger	240 min.	180

Amgros' vurdering

Amgros ekskluderer omkostninger i forbindelse med efterfølgende behandlingslinjer fra Amgros' hovedanalyse, men inkluderer disse i Amgros' følsomhedsanalyse. Amgros accepterer ansøgers antagelser.

2.2 Følsomhedsanalyser

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende sensitivitetsanalyser er udført:

- ITT population valgt fremfor subpopulation
- BorMelPred dosering ændres fra den protokoldefinerede dosering til doseringen defineret i produktresuméet
- Parametriske kurvers funktioner undersøges
- Direkte omkostninger forbundet med administration af bortezomib, daratumumab og carfilzomib +/- 20%
- Patientvægt og -overfladeareal +/- 20%
- Andelen af patienter, der modtager DaraLenDex i efterfølgende behandlingslinjer
- Behandlingslængderne for efterfølgende behandlingslinjer +/- 20%
- Omkostninger til bivirkninger +/- 20 %

Amgros' vurdering

Da ansøger har inkluderet efterfølgende behandlingslinjer i alle følsomhedsanalyser, vælger Amgros ikke at præsentere disse. Amgros udarbejder egne følsomhedsanalyser til Amgros' hovedanalyse, hvor efterfølgende behandlingslinjer inkluderes. Amgros udarbejder to følsomhedsanalyser med efterfølgende behandlingslinjer, hvor estimater for fordelingen af efterfølgende behandlingslinjer justeres.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 8.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for BorLenDex sammenlignet med LenDex til at være ca. [redacted] DKK, og sammenlignet med BorMelPred ca. [redacted] DKK.

Tabel 8: Resultatet af ansøgers hovedanalyse, SAIP, DKK.

	BorLenDex	LenDex (P1)	BorMelPred (P2)
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administration	6.883	0	7.445
Bivirkninger	6.746	4.761	6.039
Efterfølgende behandlingslinjer	[redacted]	[redacted]	[redacted]
Patientomkostninger	13.965	1.580	14.688
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger vs. BorLenDex	-	[redacted]	[redacted]

3.2 Amgros' hovedanalyse

Amgros hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, med undtagelse af følgende parametre:

- Efterfølgende behandlingslinjer ekskluderes
- Hospitalsomkostninger er opdateret med relevante DRG-takster

Resultaterne fra Amgros' hovedanalyse præsenteres i tabel 9.

Amgros' hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for BorLenDex sammenlignet med LenDex (P1) på ca. [redacted] DKK, og sammenlignet med BorMelPred (P2) på ca. [redacted] DKK.

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for BorLenDex ca. 733.000 DKK, mens de total inkrementelle omkostninger bliver ca. 42.000 DKK per patient sammenlignet med LenDex (P1) og ca. 715.000 DKK sammenlignet med BorMelPred (P2).

Tabel 9: Resultatet af Amgros' hovedanalyse ved sammenligning med komparatorer (P1 + P2), SAIP, DKK.

	BorLenDex	LenDex	BorMelPred
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Administration	123.755	59.446	90.582
Bivirkninger	6.746	4.761	6.039
Patientomkostninger	13.965	9.904	14.688
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger vs. BorLenDex	-	[redacted]	[redacted]

3.2.1 Amgros' følsomhedsanalyser

Amgros har som tidligere beskrevet tilføjet efterfølgende behandlingslinjer i en Amgros følsomhedsanalyse. Amgros udarbejder to følsomhedsanalyser, hvor fordelingen af de efterfølgende behandlingslinjer undersøges. Den første benytter klinikerestimater, jf. Tabel 4, hvilket er i overensstemmelse med Medicinrådets vurderingsrapport for vurdering af den kliniske merværdi. Den anden følsomhedsanalyse benytter ansøgers estimater på fordelingen af efterfølgende behandlingslinjer, jf. Tabel 3.

Resultaterne af de to analyser ses i Tabel 10.

Tabel 10: Resultaterne af Amgros' følsomhedsanalyser, SAIP, DKK.

Følsomhedsanalyse	BorLenDex vs. LenDex (P1)	BorLenDex vs. BorMelPred (P2)
Amgros' hovedanalyse	[redacted]	[redacted]
Inklusiv efterfølgende behandlingslinjer baseret på klinikerestimater	[redacted]	[redacted]
Inklusiv efterfølgende behandlingslinjer baseret på ansøgers estimater	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

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

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

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Tabel 11 viser ansøgers estimat af antal patienter årligt. Ansøger har estimeret budgetkonsekvenserne samlet for LenDex (P1) og BorMelPred (P2).

Tabel 11: Ansøgers estimat af antal nye patienter per år.

	Anbefales som standardbehandling					Anbefales ikke som standardbehandling				
	År 1	År 2	År 3	År 4	År 5	År 1	År 2	År 3	År 4	År 5
BorLenDex	144	144	144	144	144	0	0	0	0	0
LenDex	29	29	29	29	29	72	72	72	72	72
BorMelPred	67	67	67	67	67	168	168	168	168	168

Amgros' vurdering af estimeret antal patienter

Amgros accepterer ansøgers antagelser vedrørende markedsoptag, men tilføjer en følsomhedsanalyse, hvor 100% af patienterne ved anbefaling som mulig standardbehandling vil behandles med BorLenDex.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen.

Med de indlagte antagelser estimerer ansøger, at anvendelse af BorLenDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK ved år 5.

Ansøgers estimat af budgetkonsekvenserne fremgår af

tabel 12.

Tabel 12: Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede 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 budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Ansøgers estimater inddrager som sagt omkostninger til efterfølgende behandlingslinjer, og derfor udarbejder Amgros egen budgetkonsekvensanalyse, hvor disse omkostninger er ekskluderet.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros beregner budgetkonsekvenserne med udgangspunkt i Amgros' hovedanalyse.

Med de indlagte antagelser estimerer Amgros, at anvendelse af BorLenDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK ved år 5, ved et markedsoptag på 60%, se tabel 13. Patientfordelingen på LenDex og BorMelPred er 50%/50%.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 54 mio. ved år 5.

Tabel 13: Amgros' analyse af totale budgetkonsekvenser ved et markedsoptag på 60 %, mio. DKK, ikke-diskonterede 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 budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.2.1 Amgros' følsomhedsanalyse af budgetkonsekvenserne

Ved samme antagelser som i Amgros' hovedanalyse for budgetkonsekvenser, men med efterfølgende behandlingslinjer inkluderet, vil de årlige budgetkonsekvenser være ca. [redacted] DKK ved anbefaling af BorLenDex som mulig standardbehandling, se tabel 14.

Ved 100% markedsoptag vil de årlige budgetkonsekvenser være ca. [redacted] DKK ved år 5.

Tabel 14: Amgros' analyse af totale budgetkonsekvenser ved inklusion er efterfølgende behandlingslinjer, mio. DKK, ikke-diskonterede tal.

	År 1	År 2	År 3	År 4	År 5
Amgros' hovedanalyse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inklusiv efterfølgende behandlingslinjer baseret på klinikerestimater	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inklusiv efterfølgende behandlingslinjer baseret på ansøgers estimater	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100% markedsoptag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 DISKUSSION

Behandling med BorLenDex er forbundet med begrænsede meromkostninger sammenlignet med LenDex (P1), men betydelige meromkostninger sammenlignet med BorMelPred (P2). Meromkostningerne drives særligt af lægemiddelomkostningerne for lenalidomid (Revlimid) samt hospitalsomkostningerne forbundet med administration af bortezomib, der gives subkutant.

Hvis efterfølgende behandlingslinjer inkluderes i analysen, reduceres meromkostningerne betydeligt. Meromkostningerne vil dog i høj grad drives af valget af efterfølgende behandlingslinjer, da den største omkostningsbyrde vil tilfalde den intervention, hvor der benyttes mest lenalidomid (Revlimid). Ved inklusion af efterfølgende behandlingslinjer bliver det dermed stadig lægemiddelprisen på lenalidomid (Revlimid), der er altafgørende for det endelige resultat. Hvis fordelingen af efterfølgende behandlingslinjer vil være anderledes i dansk klinisk praksis end i Amgros' følsomhedsanalyser, vil resultatet altså potentielt også blive markant anderledes. Det bør altså understreges, at antagelserne vedrørende fordeling af patienter på efterfølgende behandlingslinjer samt behandlingslængden af efterfølgende behandlingslinjer, der ligger til grund for modelleringen af disse, er forbundet med store usikkerheder. Det er dermed særdeles usikkert, hvad de reelle meromkostninger vil være ved inklusion af efterfølgende behandlingslinjer i dansk klinisk praksis.

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AMGROS

REGIONERNES
LÆGEMIDDELORGANISATION

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4. september 2019

Medicinrådets sekretariat
Dampfærgevej 22
2100 Kbh. Ø

Høringssvar vedrørende Medicinrådets kategorisering af lenalidomid i kombination med bortezomib og dexamethason

Tak for muligheden for at afgive høringssvar i forhold til Medicinrådets kategorisering af behandlingsværdien af lenalidomid i kombination med bortezomib og dexamethason til behandling af tidligere ubehandlede patienter med knoglemarvskræft, der ikke er kandidater til højdosis kemoterapi med stamcellestøtte.

Vurderingen giver ikke anledning til yderligere kommentarer fra Celgene. Vi står naturligvis til rådighed for eventuelle spørgsmål eller kommentarer.

Med venlig hilsen

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Medicinrådet

Medicinrådets vurdering af klinisk værdi for lenalidomid i kombination med bortezomib og dexamethason til behandling af tidligere ubehandlede patienter med knoglemarvskræft der ikke er kandidater til højdosis kemoterapi med stamcellestøtte

Versionsnr.: 1.0

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 og indikationsudvidelser 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 vurderingen

Vurderingen af et nyt lægemiddel er Medicinrådets vurdering af, hvor effektiv og sikkert lægemidlet er i forhold til andre lægemidler til den samme gruppe patienter.

Vurderingen indgår, når Medicinrådet skal beslutte, om lægemidlet anbefales som mulig standardbehandling.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	28. august 2019
Ikrafttrædelsesdato	28. august 2019
Dokumentnummer	55706
Versionsnummer	1.0

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

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Revlimid®
Generisk navn	Lenalidomid
Firma	Celgene Europe Ltd
ATC-kode	L04AX04
Virkningsmekanisme	Lenalidomid binder til proteinet cereblon og hæmmer dets funktion. Proteinet findes i knoglemarvens celler og er involveret i blandt andet cellens stofskifte, signalering og i dannelsen af nye blodkar.
Administration/dosis	I de første 8 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 til progression med: • Lenalidomid 25 mg p.o. på dag 1-21 • Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22
EMA-indikation	Lenalidomid i kombination med bortezomib og dexamethason til voksne patienter med tidligere ubehandlet knoglemarvskræft som ikke er egnede til stamcelletransplantation.

2 Medicinrådets konklusion

Medicinrådet har sammenlignet lenalidomid i kombination med bortezomib og dexamethason til tidligere ubehandlede patienter med knoglemarvskræft, der ikke er kandidater til højdosis kemoterapi med stamcellestøtte. Der er sammenlignet med to komparatorer – lenalidomid i kombination med dexamethason og bortezomib i kombination med melphalan og prednisolon.

Medicinrådet vurderer, at lenalidomid i kombination med bortezomib og dexamethason giver en merværdi af ukendt størrelse sammenlignet med lenalidomid og dexamethason. Evidensens kvalitet vurderes at være meget lav.

Medicinrådet finder, at den samlede værdi af lenalidomid i kombination med bortezomib og dexamethason sammenlignet med bortezomib, melphalan og prednisolon ikke kan kategoriseres, men at kombinationen samlet set ikke har dårligere effekt eller sikkerhedsprofil end komparatoren. Evidensens kvalitet kan ikke vurderes.

I behandlingsvejledningen er de to komparatorer ligestillet på baggrund af en indirekte sammenligning.

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.

3 Forkortelser

BorLenDex:	Lenalidomid i kombination med bortezomib og dexamethason
BorMelPred:	Lenalidomid i kombination med melphalan og prednison
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
EORTC:	*European Organisation for Research and Treatment of Cancer*
EPAR:	*European Public Assessment Report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HDT/STS:	Højdosis kemoterapi med stamcellestøtte
HR:	*Hazard ratio*
ITT:	*Intention to treat*
LenDex:	Lenalidomid + dexamethason
LL:	Lower limit (nedre grænse af konfidensintervallet)
OR:	*Odds ratio*
PFS:	Progressionsfri overlevelse
PICO:	Population, Intervention, Komparator, Effektmål
QLQ-C30:	*Quality of Life Questionnaire Core-30*
RR:	Relativ risiko
SMD:	*Standardized mean difference*
TEAE:	*Treatment emergent adverse event*
UL:	Upper limit (øvre grænse af konfidensintervallet)

4 Formål

Formålet med Medicinrådets vurdering af lenalidomid i kombination med bortezomib og dexamethason til tidligere ubehandlede patienter med knoglemarvskræft, der ikke er egnede til højdosis kemoterapi med stamcellestøtte (HDT/STS) er at vurdere den værdi, lægemidlet har i forhold til et eller flere lægemidler til samme patientgruppe (komparator(er)).

Med udgangspunkt i vurderingen og en omkostningsanalyse udarbejdet af Amgros beslutter Medicinrådet, om lenalidomid i kombination med bortezomib og dexamethason kan anbefales som mulig standardbehandling.

5 Baggrund

5.1 Knoglemarvskræft

Knoglemarvskræft er en uhelbredelig, livstruende og livsforkortende, men behandlingsfølsom hæmatologisk kræftsygdom. Sygdommen skyldes, at en type af hvide blodlegemer 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 myelomatose kan der påvises et protein i blod og urin, som kaldes M-komponent. M-komponenten dannes af de maligne 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 behandlingskrævende patienter årligt, der skal have deres første behandling [2].

5.2 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, perioder med symptomfrihed, længerevarende behandlingsfri perioder 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]. Patientpopulationen udgør ca. 240 patienter årligt. Blandt de nuværende behandlingsmuligheder anvendes oftest en kombination af enten bortezomib, melphalan og

prednison (BorMelPred) eller lenalidomid og dexamethason (LenDex) [8]. Samlet set har disse patienter en median progressionsfri overlevelse på ca. 18 måneder [2].

De patienter, der behandles med HDT/STS, har en væsentlig bedre prognose end de, der ikke er kandidater til denne behandling. Halvdelen af de patienter, der behandles med HDT/STS, er fortsat i live efter ca. 7 år (den mediane overlevelse), mens patienter, der ikke er kandidater til HDT/STS, har en medianoverlevelse på ca. 3 år. Denne gruppe omfatter især patienter over 70 år og inkluderer de ældste patienter. 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.

5.3 Anvendelse af lenalidomid i kombination med bortezomib og dexamethason

Lenalidomid tilhører gruppen af immunmodulerende stoffer, som binder til proteinet cereblon og hæmmer dets funktion. Proteinet findes i knoglemarvens celler og er involveret i blandt andet cellens stofskifte, signalering og i dannelsen af nye blodkar. Behandling med immunmodulerende stoffer hæmmer derfor både kræftcellernes deling og deres forsyning af næringsstoffer fra blodet. Lenalidomid har været godkendt til behandling af myelomatose siden 2007 og indgår som det ene lægemiddel i mange behandlingskombinationer.

Lenalidomid i kombination med bortezomib og dexamethason (BorLenDex) skal til behandling af patienter, der ikke er kandidater til HDT/STS, doseres som følger:

Først 8 serier a 21 dage med:

- 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 til progression med:

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

Fagudvalget anslår, at den gennemsnitlige behandlingsvarighed ligger tæt på den mediane PFS, som er ca. 40 mdr. baseret på studiedata [10]. Det kan være overestimeret, da nogle patienter ønsker at ophøre behandlingen forud for progression.

Fagudvalget har i behandlingsvejledningen for knoglemarvskræft anbefalet BorLenDex til 60 % af patientpopulationen (tidligere ubehandlede patienter der ikke er kandidater til HDT/STS), såfremt Medicinrådet vurderer, at der er et rimeligt forhold mellem værdien af kombinationen og omkostningerne forbundet med behandlingen og dermed anbefaler den som standardbehandling [9].

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådet.

Den endelige ansøgning blev modtaget den 14. juni 2019. Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet den 12. april 2019.

Ansøgningen indeholder sammenligninger mellem BorLenDex og to komparatorer, som defineret i protokollen; lenalidomid + dexamethason (LenDex) og bortezomib + melphalan + prednison (BorMelPred).

BorLenDex og LenDex er sammenlignet direkte i et randomiseret fase 3-studie. BorLenDex og BorMelPred er sammenlignet narrativt, da der ikke findes et studie med direkte sammenligning. Ansøger beskriver, at selvom der er en mulighed for at sammenligne behandlingerne i en netværksmetaanalyse, ville antagelserne for denne ikke være opfyldt på grund af forskelle mellem studierne. Medicinrådets sekretariat og fagudvalget er enige i dette og vurderer, at kategoriseringen kan basere sig på de indsendte analyser med følgende bemærkninger:

- Ansøger har ikke leveret data på effektmålet livskvalitet. Ansøger oplyser, at der ikke findes publicerede data til belysning af sammenligningen med komparatorerne for dette effektmål.
- Ansøger har leveret data for progressionsfri overlevelse (PFS) for alle sammenligninger, uanset om der findes data for overlevelse. I protokollen er det specificeret, at data for PFS kun medtages, hvis data for overlevelse ikke er modne. Fagudvalget vil således kun medtage PFS i vurderingen, hvis effekten på overlevelse ikke kan belyses. Da der er leveret data for overlevelse, er der ikke anvendt data for PFS i vurderingen.
- I dataekstraktionstabellerne er der i to tilfælde angivet data for behandlingsophør grundet bivirkninger i stedet for uønskede hændelser. Data for behandlingsophør grundet uønskede hændelser er angivet i ansøgningens tabel 18 og er anvendt i vurderingen.
- Den narrative gennemgang af bivirkninger er baseret på data for uønskede hændelser og bivirkninger.

Fra evidens til kategori. Medicinrådet vurderer værdien af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som ”kritiske”, ”vigtige” og ”mindre vigtige”. I vurderingen vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Både den relative og absolutte effekt indgår i kategoriseringen af et lægemiddel. Dette foregår i en trinvis proces. Fagudvalget kategoriserer først den relative foreløbige kategori på baggrund af væsentlighedskriterierne og den absolutte foreløbige kategori på baggrund af de præspecificerede mindste klinisk relevante forskelle. Her er der tale om en ren kvantitativ proces. Herefter fastlægger fagudvalget den aggregerede kategori for hvert effektmål ved at sammenholde de foreløbige kategorier. Her kan fagudvalget inddrage deres kliniske indsigt. Når den samlede kategori for lægemidlets værdi skal fastlægges, sammenvejer fagudvalget alle effektmål. Effektmålenes kategorier kombineres med effektmålenes vægt, og eventuelle kliniske overvejelser inddrages. Den samlede kategorisering af lægemidlets værdi er således delvis en kvantitativ og delvis en kvalitativ proces, hvor der foretages en klinisk vurdering af det foreliggende datagrundlag. Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk værdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har foretaget litteratursøgning efter publicerede, randomiserede studier med data på sammenligningen mellem BorLenDex og de to komparatorer som angivet i protokollen. Der blev identificeret 472 referencer, som blev screenet på titel/abstractniveau. 27 artikler blev screenet på fuldtekstniveau, og heraf blev 7 studier inkluderet med resultater publiceret i 12 artikler. De 7 studier er:

- SWOG S0777 (NCT0064428) [10]
- VISTA (NCT00111319) [11–13]
- GIMEMA (NCT01063179) [14–16]
- ALCYONE (NCT02195479) [17]
- GEM 2005 (NCT00443235) [18,19]
- UPFRONT (NCT00507416) [20]
- CLARION (NCT01818752) [21]

SWOG S0777 er en direkte sammenligning mellem BorLenDex og den ene af de to komparatorer i det kliniske spørgsmål, LenDex. Det kan derfor anvendes til at besvare den del af det kliniske spørgsmål. De øvrige studier anvendes til at besvare sammenligningen med BorMelPred, hvor der ikke er identificeret direkte sammenligninger. Desuden inddrages data fra EPAR'en. Til at besvare den narrative gennemgang af bivirkninger anvender ansøger også data fra følgende to studier gengivet i EPAR'en [22]:

- IFM 2009
- PETHEMA GEM2012

De to studier undersøger effekten af BorLenDex som induktionsbehandling til patienter, der er kandidater til HDT/STS og danner sammen med SWOG-S0777 grundlag for EPAR'ens gennemgang af sikkerhed og bivirkninger [22].

8 Databehandling

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

9 Lægemidlets værdi

Fagudvalget har angivet ét klinisk spørgsmål med to komparatorer (LenDex og BorMelPred). Resultaterne gennemgås nedenfor som et klinisk spørgsmål for hver komparator.

9.1 Konklusion klinisk spørgsmål 1 (komparator LenDex)

Hvilken værdi giver BorLenDex sammenlignet med LenDex til patienter med tidligere ubehandlet knoglemarvskræft, der ikke er kandidater til HDT/STS?

Fagudvalget vurderer, at BorLenDex til populationen giver en merværdi af ukendt størrelse sammenlignet med LenDex. Evidensens kvalitet vurderes at være meget lav.

9.1.1 Gennemgang af studier

SWOG S0777

Karakteristika
SWOG S0777 er et randomiseret ublindet fase 3-studie med 523 patienter og en median opfølgningstid på 60,6 måneder, rapporteret i EPAR'en [22]. Studiet er en direkte sammenligning mellem behandlingerne BorLenDex og LenDex. BorLenDex doseres som angivet i protokollen. Bortezomib administreres intravenøst. LenDex doseres som i protokollen med dosering af lenalidomid til progression.

Studiets primære effektmål er PFS, og de sekundære effektmål er overlevelse og responsrater.

Population
Patienterne er nyligt diagnosticerede med knoglemarvskræft. Medianalder er 63 år, og 57,6 % er mænd. Patienterne fordeler sig som følger i henhold til den prognostiske stadieinddeling, ISS: stadie I (29,3 %), stadie II (37,7 %) og stadie III (33,1 %). Ca. 13 % har højrisiko cytogenetisk sygdom. Ca. 30 % har kreatinin clearance under 60 mL/min. Populationen omfatter også patienter, der er tiltænkt en senere HDT/STS (69 %). Kun 43 % er ældre end 65, og kun 14 % har dårlig performancestatus (ECOG PS > 1). Populationen stemmer derfor ikke overens med den danske population, idet den samlet set er både yngre og har bedre performancestatus end den danske population. Fagudvalget vurderer dog, at data fra studiet kan anvendes til at foretage vurderingen af lægemidlets værdi, men at der i vurderingen af evidensens kvalitet skal nedjusteres for indirekthed.

9.1.2 Resultater og vurdering

I tabel 1 herunder fremgår den samlede kategori for lægemidlet og kvaliteten af en samlede evidens. Tabellen angiver også de absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 1. Kategorier og resultater for BorLenDex i sammenligning med komparatoren LenDex.

Effektmål	Måleenhed	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi pr. effektmål
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse	Median overlevelse	Kritisk	21,9 mdr.	Kan ikke kategoriseres	HR: 0,75 (0,58-0,97)	Merværdi af ukendt størrelse	Merværdi af ukendt størrelse
Behandlingsophør grundet uønskede hændelser	Andel af patienter der ophører behandling pga. uønskede hændelser	Kritisk	13,5 procentpoint (7,3-20)	Negativ værdi	RR: 2,44 (1,57-3,80)	Negativ værdi	Negativ værdi
Livskvalitet	Ændring i point målt med EORTC QLQ-C30	Vigtigt	Ingen data	Kan ikke kategoriseres	Ingen data	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Kvalitativ gennemgang	Vigtigt	Se afsnit 9.1.2 for kvalitativ gennemgang	Kan ikke kategoriseres	Se afsnit 9.1.2 for kvalitativ gennemgang	Kan ikke kategoriseres	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi sammenlignet med LenDex		Merværdi af ukendt størrelse					
Kvalitet af den samlede evidens		Meget lav					

Overlevelse tilhører effektmålsgruppen dødelighed. Den absolutte forskel overstiger den retningsgivende mindste klinisk relevante forskel på 3 mdr. Merværdi af ukendt størrelse har for denne effektmålsgruppe væsentlighedskriterierne 0,95 ≤ UL < 1,00 og LL < 0,85.

Behandlingsophør grundet uønskede hændelser tilhører effektmålsgruppen livskvalitet samt alvorlige symptomer og bivirkninger. Den foreløbige kategori for den absolutte forskel er negativ værdi, idet den nederste grænse i konfidensintervallet omkring den absolutte forskel er større end den justerede mindste klinisk relevante forskel (5 procentpoint). Negativ værdi for den relative forskel har væsentlighedskriterierne LL > 1.

Overlevelse (kritisk)
Den mediane overlevelse er i SWOG S0777-studiet 89,1 måneder (7,4 år) for BorLenDex ved den seneste opfølgningstid publiceret i EPAR'en. For LenDex er den 67,2 måneder (5,6 år). Det giver en absolut forskel på 21,9 måneder (1,8 år), som overstiger den mindste klinisk relevante forskel på 3 mdr. Den foreløbige værdi for den absolutte forskel kan ikke kategoriseres, da der ikke kan beregnes et konfidensinterval omkring forskellen mellem medianerne. Den relative forskel er opgjort som HR 0,75 (0,58-0,97), hvilket tildeler BorLenDex en foreløbig merværdi af ukendt størrelse sammenlignet med LenDex for den relative forskel. Den foreløbige værdi afspejler det brede konfidensinterval omkring effektestimatet, som betyder, at risikoen for at dø er mellem 3 og 42 % lavere med behandling med BorLenDex end ved behandling med LenDex og derfor rummer både lille, moderat og stor merværdi. Den aggregerede værdi for effektmålet tager udgangspunkt i effektestimatet for den relative forskel, hvor der findes mest information. Fagudvalget bemærker, at overlevelsen i komparatorarmen er bedre end i den danske population, hvilket hænger sammen med, at populationen i studiet er yngre og har bedre performancestatus. Derfor tages der forbehold for effektstørrelsen, som må formodes mindre i den danske population. Fagudvalget bemærker desuden, at patienter, der indgår i studier generelt, er en selekteret gruppe, der er mindre skrøbelige end den gennemsnitlige patient i klinikken. I studiet er overlevelsen i subgruppen af patienter, der er ældre end 75 år også rapporteret [10]. Her er den mediane overlevelse 63 måneder for BorLenDex og 31 måneder for LenDex, hvilket stemmer overens med overlevelsen på ca. 3 år i den danske population. Denne subgruppe udgør dog kun ca. 10 % af den samlede population i studiet. Fagudvalget vurderer, at den aggregerede værdi for effektmålet overlevelse er merværdi af ukendt størrelse. Baseret på punktestimatet for den absolutte forskel i medianoverlevelse, som er væsentligt større end den mindste klinisk relevante forskel på 3 måneder i både den samlede population og i subgruppen af patienter, der er ældre end 75 år, vurderer fagudvalget samtidig, at effekten må forventes at være klinisk relevant.

Evidensens kvalitet vurderes at være lav for effektmålet overlevelse (se bilag 1, afsnit 17).

Behandlingsophør grundet uønskede hændelser (kritisk)
I SWOG S0777 ophører 22,9 % af patienterne, der behandles med BorLenDex, mens 9,4 % af patienterne, der behandles med LenDex, ophører med behandlingen. Det giver en forskel på 13,5 procentpoint (7,3 – 20). Den nedre grænse i konfidensintervallet er større end den justerede mindste klinisk relevante forskel på 5 procentpoint, hvilket giver BorLenDex en foreløbig negativ værdi for den absolutte forskel. Den relative forskel er opgjort som RR 2,44 (1,57 – 3,80), hvilket ligeledes tildeler BorLenDex en foreløbig negativ værdi for den relative forskel for effektmålet. Effektestimatet for den en relative risiko betyder, at mellem 1,57 og 3,80 gange så mange patienter ophører behandlingen, når de behandles med BorLenDex, end når de behandles med LenDex. Forskellen mellem studiepopulationen og den danske population kan muligvis medføre en underestimering af behandlingsophøret, da patienterne i den danske patientgruppe er ældre og har dårligere performancestatus. Da den foreløbige kategori for både den absolutte og relative forskel er negativ, er den aggregerede værdi for effektmålet negativ. Ansøger bemærker, at bortezomib i studiet administreres intravenøst i modsætning til dansk klinisk praksis, hvor bortezomib administreres subkutant, hvilket er forbundet med færre bivirkninger og ubehag for patienten [23]. Fagudvalget er enige i ansøgers betragtning og vurderer, at den intravenøse administration kan påvirke frafaldet i negativ retning, så det er større i studiet, end det ville være i dansk klinisk praksis. I et klinisk studie, der direkte sammenligner subkutan vs. intravenøs administration af bortezomib, vises der ikke signifikant forhøjet risiko for at ophøre behandlingen, når bortezomib administreres intravenøst, men der er signifikant højere forekomst af perifer neuropati og gastrointestinale gener [23]. Fagudvalget fremhæver særligt forskelle i forekomsten af perifer neuropati, som er højere ved intravenøs administration, og som i klinikken ofte er årsag til at stoppe behandlingen eller reducere dosis af bortezomib. I dansk praksis vil man i første omgang håndtere bivirkningerne ved dosisreduktion fremfor at ophøre behandlingen [24].

Evidensens kvalitet vurderes at være meget lav for effektmålet behandlingsophør grundet uønskede hændelser (se bilag 1, afsnit 17.2).

Livskvalitet (vigtig)
Fagudvalget beklager, at ansøgende virksomhed ikke har leveret data for effektmålet. Livskvalitet var ikke defineret som et effektmål i studiet, og der findes derfor ikke data for effektmålet. Derfor kan værdien for effektmålet livskvalitet ikke kategoriseres.

Livskvalitet indeholder blandt andet information om grad 1-2 bivirkninger, som kan have stor betydning for patienterne, men som sjældnere har konsekvenser for behandlingen i form af dosisjustering, pause eller ophør. Fagudvalget vurderer, at den samlede vurdering af behandlingens effekt bliver mere usikker, når data for livskvalitet mangler, men at det ikke bør påvirke den samlede vurdering negativt.

Narrativ gennemgang af bivirkninger (vigtigt)
Ansøger har med udgangspunkt i SWOG S0777-studiet og EPAR'en (baseret på studierne IFM-2009 og PETHEMA GEM2012) beskrevet de ønskede hændelser og/eller bivirkninger, der er rapporteret i studier hvor der indgår behandling med BorLenDex. Datagrundlaget udgøres dermed af 3 studier med i alt 1076 patienter, som fik BorLenDex i serier af enten 28 eller 21 dage. Safety populationen var alle randomiserede patienter, der havde fået mindst én dosis af behandlingen.

I PETHEMA er der rapporteret bivirkninger, det vil sige uønskede hændelser som er vurderet at have relation til behandlingen. I IFM-2009, og SWOG S0777 er der rapporteret uønskede hændelser. I protokollen efterspørger fagudvalget data på bivirkninger, som forekommer i mindst 10 % af populationen. Ansøger har fremsendt data for uønskede hændelser, der forekommer i mindst 5 % af populationen og i mindst 20 % af populationen. Fagudvalget vurderer, at det tilgængelige datagrundlag er tilstrækkeligt til den narrative gennemgang af bivirkninger.

Fagudvalget tager udgangspunkt i data fra den direkte sammenligning mellem BorLenDex og LenDex i SWOG-S0777, som generelt understøttes af data fra IFM-2009. PETHEMA rapporterer bivirkninger, og data herfra kan derfor ikke direkte sammenlignes med data fra de øvrige studier. Der er rapporteret flere grad 3 og 4 TEAE'er (*treatment emergent adverse events*) hos den patientgruppe, der blev behandlet med BorLenDex (76 %), sammenlignet med gruppen der blev behandlet med LenDex (69 %). Blandt de hændelser der forekom i mindst 20 % af patienterne, vurderer fagudvalget, at de væsentligste forskelle ses for perifer sensorisk neuropati, gastrointestinale gener og dyspnø. Fagudvalget fremhæver de samme hændelser i data for hændelser af grad 3-4, der forekommer hos mindst 5 % af patienterne. Her fremhæver fagudvalget også hypotension som en væsentlig bivirkning. Se tabel 2 som opsummerer andelene for de væsentligste hændelser.

Tabel 2. TEAE'er fremhævet af fagudvalget og deres forekomst i SWOG-S0777.

	TEAE'er (alle grader) rapporteret i mindst 20 % af patienterne		TEAE'er (grad 3-4) rapporteret i mindst 5 % af patienterne	
	BorLenDex	LenDex	BorLenDex	LenDex
Perifer sensorisk neuropati	70 %	33 %	21 %	2 %
Gastrointestinale gener	81 %	65 %	18 %	7 %
Dyspnø	31 %	26 %	6 %	1 %
Hypotension	-	-	8 %	0 %

I SWOG-S0777 blev bortezomib administreret intravenøst, hvilket ikke svarer til nuværende dansk praksis, hvor bortezomib administreres subkutant. Der findes studiedata, som sammenligner effekt og bivirkninger ved intravenøs og subkutan administration. Effekten er den samme, men bivirkninger i form af neuropati og gastrointestinale gener er signifikant reduceret ved subkutan administration [23].

Fagudvalget vurderer på baggrund af det tilgængelige data, at de vil forvente flere bivirkninger hos patienterne, der behandles med BorLenDex, men ikke i samme grad som rapporteret i SWOG-S0777-studiet. Bivirkningerne er overvejende reversible og må betragtes som håndterbare. Dyspnø, hypotension og de gastrointestinale bivirkninger vil typisk forsvinde, når dosis nedsættes, eller behandlingen stoppes. Neuropati vil ligeledes væsentligt aftage eller helt forsvinde, når behandlingen stoppes, selvom der kan være vedvarende gener.

Fagudvalget fremhæver desuden, at patienterne ved begge behandlinger generelt oplever udmattende træthed, som er meget generende for patienten. Det er imidlertid ikke en bivirkning, som har konsekvenser for behandlingen, og de fleste patienter lever med det for at kunne få den bedst mulige behandling.

Ansøger skriver i deres ansøgning, at der er højere forekomst af grad 3-4 AE'er hos de skrøbelige patienter, ældste patienter og de med dårligst performancestatus (ECOG-status minimum 2). Det er i overensstemmelse med fagudvalgets erfaring og er reflekteret i behandlingsvejledningens anbefaling, at BorLenDex bør anvendes til de 60 % af populationen, som er de yngre og de med bedst performancescore.

Da effektmålet ikke kan kvantificeres, kan den foreløbige værdi ikke kategoriseres.

Da vurderingen er narrativ, kan evidensens kvalitet ikke vurderes.

9.1.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 1 er samlet set vurderet som værende **meget lav**. Der er kun et studie, hvilket fører til nedgradering for inkonsistens. Studiepopulationen afviger som tidligere beskrevet fra den danske population ved at være yngre og have bedre performance, hvorfor der nedgraderes for indirekthed. SWOG-studiet er ublindet, hvilket indebærer risiko for bias. Det har mindre betydning for effektmålet overlevelse end for behandlingsophør grundet uønskede hændelser, men samlet set medfører det, at evidensens kvalitet er meget lav

9.2 Konklusion klinisk spørgsmål 2 (komparator BorMelPred)

Hvilken værdi giver BorLenDex sammenlignet med BorMelPred til patienter med tidligere ubehandlet knoglemarvskræft, der ikke er kandidater til HDT/STS?

Da sammenligningen er narrativ, kan den samlede værdi af BorLenDex sammenlignet med BorMelPred ikke kategoriseres. Fagudvalget vurderer, at BorLenDex samlet set ikke har dårligere effekt eller sikkerhedsprofil end BorMelPred.

Evidensens samlede kvalitet kan ikke vurderes.

9.2.1 Gennemgang af studier

VISTA

Karakteristika

VISTA er et randomiseret ublindet fase 3-studie i 682 patienter, med en median opfølgningstid på 60,1 måneder. Studiet har to grupper, der behandles med enten BorMelPred eller MelPred.

Studiets primære effektmål er tid til sygdomsprogression. De præspecificerede sekundære effektmål er komplet responsrate, responsvarighed, tid til næste behandling og overlevelse. Andre sekundære effektmål er PFS, komplet plus partiel responsrate, tid til respons og EORTC QLQC30 questionnaire.

Population
Patienterne er tidligere ubehandlede patienter, der ikke er kandidater til HDT/STS. Medianalder er 71 år, og 50 % er mænd. Patienterne fordeler sig som følger i henhold til den prognostiske stadieinddeling ISS: stadie I (19 %), stadie II (47 %) og stadie III (34 %). Ca. 8 % har højrisiko cytogenetik (data kun rapporteret for patienter, der behandles med BorMelPred). Ca. 55 % har kreatinin-clearance under 60 mL/min. Populationen stemmer overens med den danske population.

GIMEMA

Karakteristika
GIMEMA er et randomiseret ublindet fase 3-studie i 511 patienter. Den mediane opfølgningstid er 54 måneder. Patienterne er randomiseret til to grupper, der behandles med enten BorMelPred eller BorMelPred plus bortezomib og thalidomid som efterfølgende vedligeholdelsesbehandling.

Det primære endepunkt er PFS. De sekundære endepunkter er responsrate, overlevelsesrate, responsvarighed.

Population
Patienterne er tidligere ubehandlede patienter med knoglemarvskræft, der ikke er kandidater til HDT/STS. Medianalder er 71 år, og ca. 50 % er mænd (51% og 47 % i hhv. intervention og komparatorgruppen). Patienterne fordeler sig som følger i henhold til den prognostiske stadieinddeling ISS: stadie I (23 vs. 22 %), stadie II (39 vs. 34 %) og stadie III (19 vs. 22 %). Det er ikke angivet, hvor mange patienter der samlet set har højrisiko cytogenetik, men risikoen er opgjort for mutationerne enkeltvis (t(4;14): 14 %, t(14;16) 11 % og del17: 13 %). Ca. 72 % har kreatinin-clearance på under 60 mL/min. Populationen stemmer overens med den danske population.

ALCYONE

Karakteristika
ALCYCONE er et randomiseret ublindet fase 3-studie med 706 patienter randomiseret til enten interventionen BorMelPred plus daratumumab eller komparator BorMelPred. Den mediane opfølgningstid er 16,5 måneder. Det primære endepunkt er PFS. De sekundære endepunkter er responsrater.

Population
Patienterne er nyligt diagnosticerede patienter, der ikke er kandidater til HDT/STS. Medianalder er 71 år. Patienterne fordeler sig som følger i henhold til den prognostiske stadieinddeling ISS: stadie I (20 vs. 19 %), stadie II (40 vs. 45 %) og stadie III (41 vs. 36 %). Der er ca. 16 % af patienterne, der har højrisiko cytogenetik. Der er ikke angivet information om nyrefunktion. Populationen stemmer overens med den danske population.

GEM 2005

Karakteristika
GEM 2005 er et ublindet randomiseret fase 3-studie i 260 patienter, der blev randomiseret til behandling med først enten BorMelPred eller bortezomib, thalidomid og prednisolon, efterfulgt af vedligeholdelsesbehandling med enten bortezomib og prednisolon eller bortezomib og thalidomid i op til 3

år. Behandlingen adskiller sig dermed fra den i protokollen definerede komparator ved at være efterfulgt af vedligeholdelsesbehandling.

Det primære endepunkt er responsrate under den indledende behandling og under vedligeholdelsesbehandlingen. Sekundære effektmål er tid til progression, PFS og overlevelse. Den mediane opfølgningstid er 6 år.

Population
Patienterne er nyligt diagnosticerede og tidligere ubehandlede patienter med knoglemarvskræft, der er over 65 år. Medianalderen er 73 år. Patienterne fordeler sig som følger i henhold til den prognostiske stadieinddeling ISS: stadie I (30 vs. 20 %), stadie II (40 vs. 43 %) og stadie III (30 vs. 37 %). Ca. 14 % i BorMelPred-gruppen har højrisiko cytogenetik Der er ikke angivet information om nyrefunktion. Populationen stemmer overens med den danske population.

UPFRONT

Karakteristika
UPFRONT er et ublindet randomiseret studie i 502 patienter, randomiseret til 3 behandlinger, enten bortezomib og dexamethason (BorDex), bortezomib, thalidomid og dexamethason (BorThalDex) eller BorMelPred efterfulgt af vedligeholdelsesbehandling med bortezomib. Behandlingen adskiller sig dermed fra den i protokollen definerede komparator ved at være efterfulgt af vedligeholdelsesbehandling.

Studiet har en median opfølgningstid på 42,7 måneder. Det primære endepunkt er PFS; de sekundære endepunkter inkluderer responsrater, tid til næste behandling, andel der oplever uønskede hændelser og livskvalitet.

Population
Patienterne er tidligere ubehandlede patienter, der ikke er kandidater til HDT/STS. Medianalderen er ca. 73 år. I de tre arme (BorDex vs. BorThalDex vs. BorMelPred) er henholdsvis 22 % vs. 33 % vs. 25 % på ISS-stadie I, 46 % vs. 35 % vs. 39 % på stadie II og 33 % vs. 32 vs. 36 % på stadie III. Der er ingen information om, hvor mange patienter der har højrisiko cytogenetik i de tre grupper. Populationen stemmer overens med den danske population.

CLARION

Karakteristika
CLARION er et ublindet randomiseret fase 3-studie i 955 patienter randomiseret til enten carfilzomib, melphalan og prednisolon eller BorMelPred. Studiet er stratificeret efter ISS-stadie. Studiet har en median opfølgningstid på 22 måneder. Det primære endepunkt er PFS. De sekundære endepunkter er overlevelse, responsrater, andel patienter der oplever neuropati og livskvalitet målt med værktøjerne GHS/QoL og EORT QLQ-C30.

Population
Patienterne er nyligt diagnosticerede, tidligere ubehandlede patienter, som ikke er egnede til HDT/STS. Medianalderen er 72 år, og fordelingen på ISS-stadier er 19 % i stadie I, 43 % i stadie II og 38 % i stadie III. Ca. 13 % har højrisiko cytogenetik. Ca. 35 % har kreatinin-clearance på under 50 mL/min. Populationen stemmer overens med den danske population.

9.2.2 Resultater og vurdering

Der findes ingen direkte sammenligninger mellem BorLenDex og BorMelPred, og det er ikke muligt at foretage en indirekte analyse på baggrund af data fra de studier, hvor enten intervention eller komparator er sammenlignet direkte med en anden behandling. Ansøger gør opmærksom på, at intervention og komparator kan forbindes i et netværk, som kan danne grundlag for en netværksmetaanalyse. Ansøger vurderer dog, at studierne er væsentligt forskellige og har derfor ikke foretaget analysen. Fagudvalget er enigt i den betragtning. Netværket vil inkludere sammenligningen mellem BorLenDex og LenDex (SWOG S0777), som adskiller sig fra de øvrige studier ved en væsentligt yngre og mere 'fit' patientpopulation. Netværket vil desuden indeholde flere forbindelser med irrelevante komparatorer, som vil øge usikkerheden på effektestimaterne, så det er vanskeligt at drage meningsfulde konklusioner. For de effektmål, hvor der er data, vil fagudvalget derfor foretage en vurdering på baggrund af ansøgers narrative analyse af data fra de studier, ansøger har identificeret.

Overlevelse (kritisk)
Vurderingen baserer sig på en naiv sammenligning af de absolutte værdier fra armene i de studier, hvor enten BorLenDex (interventionen) eller BorMelPred (komparator) er undersøgt.

Resultaterne fremgår af tabel 3, hvor også den anvendte komparator i studiet er angivet.

Udover SWOG-S0777-studiet, hvor komparator er LenDex er ingen af komparatorerne i de andre studier behandlinger, der anvendes som standard i dansk klinisk praksis. Fagudvalget fremhæver forskellene i studiepopulationerne, hvor patienterne i SWOG-S0777 er yngre end patienterne i de andre studier, hvorfor der tages forbehold for effektstørrelsen, som forventes at være mindre i den danske population. Fagudvalget bemærker desuden, at behandlingen med BorMelPred i tre af studierne efterfølges af vedligeholdelsesbehandling, hvilket må formodes at forbedre effekten. I en subgruppeanalyse af de ældste patienter, som er ældre end 75 år, er den mediane overlevelse 63 måneder for de patienter, der behandles med BorLenDex [10]. Denne patientgruppe ligner de andre studiepopulationer og den danske population mere, omend den er ældre. Fagudvalget vurderer, at den naive narrative sammenligning indikerer, at BorLenDex ikke er dårligere end BorMelPred, idet den mediane overlevelse er længere for BorLenDex i SWOG-S0777 end for BorMelPred i de andre studier, også når data for den ældre subpopulation i SWOG-S0777 inddrages.

Tabel 3. Data for den mediane overlevelse i de studier der udgør sammenligningsgrundlaget for den naive sammenligning mellem BorLenDex og BorMelPred, inkl. opfølgningstid, patientpopulationernes medianalder og information om studiets komparator.

Studie	Opfølgningstid Måneder	Alder Median	Behandling	Overlevelse Median mdr.	Komparator
SWOG-S0777	55	63	BorLenDex	89,1	LenDex med median overlevelse på 67,2 måneder
VISTA	60,1	71	BorMelPred	56,4	MelPred med median overlevelse på 43,1 måneder
GIMEMA	54	71	BorMelPred (+ BorThal vedligehold)	60,6	BorMelPred + BorThal vedligehold – median overlevelse ikke nået
ALCYONE	16,5	71	BorMelPred	Ikke nået	BorMelPred + Dara – median overlevelse ikke nået
GEM2005	72	73	BorMelPred (+ BorPred el. BorThal vedligehold)	63	BorThalPred med median overlevelse på 43 måneder (+ BorPred el. BorThal vedligehold)
UPFRONT	42,7	73	BorMelPred (+ Bor vedligehold)	53,1	BorDex med median overlevelse på 49,8 måneder BorThalDex + Bor vedligehold med median overlevelse på 51,5 måneder
CLARION	22	72	BorMelPred	Ikke nået	CarMelPred – median overlevelse ikke nået

Behandlingsophør grundet uønskede hændelser (kritisk)

Vurderingen baserer sig på en naiv sammenligning af de absolutte værdier fra armene i de studier, hvor enten BorLenDex eller BorMelPred er undersøgt. Resultaterne fremgår af tabel 4.

Tabel 4. Data for behandlingsophør grundet uønskede hændelser i de studier der udgør sammenligningsgrundlaget for den naive sammenligning mellem BorLenDex og BorMelPred, inkl. opfølgningstid, patient-populationernes medianalder og information om studiets komparator samt administrationsvejen for bortezomib.

Studie	Opfølgningstid median mdr.	Alder median	Behandling	i.v. eller s.c. adm. af bortezomib	Behandlings-ophør grundet uønskede hændelser (%)	Komparator
SWOG-S0777	55	63	BorLenDex	i.v.	22,9	LenDex (9,4 %)
VISTA	60,1	71	BorMelPred	i.v.	15	MelPred (14 %)
GIMEMA	54	71	BorMelPred (+ BorThal vedligehold)	i.v.	16,7	BorMelPred+BorThal (23 %)
ALCYONE	16,5	71	BorMelPred	s.c.	9,3	BorMelPred+ Dara (4,9 %)
GEM2005	72	73	BorMelPred (+BorPred el. BorThal vedligehold)	i.v.	12	BorThalPred (+BorPred el. BorThal vedligehold) (17 %)
UPFRONT	42,7	73	BorMelPred (+ Bor vedligehold)	i.v.	38,3	BorDex (34,5 %) BorThalDex + Bor vedligehold (40,1 %)
CLARION	22	72	BorMelPred	i.v./s.c.	14,7	CarMelPred (16,7 %)

Fagudvalget vurderer, at flere stopper behandlingen med BorLenDex frem for BorMelPred. Fagudvalget bemærker desuden, at der er væsentlig forskel på opfølgningstiden i studierne, hvilket har betydning for antallet af rapporterede hændelser, som er stigende gennem opfølgningstiden. ALCYONE og CLARION har væsentligt kortere opfølgningstid end de øvrige studier og har samtidig også den laveste andel af patienter, der ophører med behandlingen. Fagudvalget har i vurderingen lagt mindst vægt på studierne med kort opfølgningstid og taget højde for at nogle af studierne inkluderer vedligeholdelsesbehandling, hvilket adskiller sig fra behandling med BorMelPred i dansk klinisk praksis.

Fagudvalget bemærker, at datagrundlaget ikke giver en klar indikation på, om den mindste klinisk relevante forskel på 10 procentpoint er overskredet, og om forskellene mellem BorLenDex og BorMelPred på den baggrund kan betragtes som klinisk relevant.

Livskvalitet (vigtig)
Det er ikke muligt at foretage en sammenlignende analyse af effektmålet livskvalitet, da der ikke findes data for effektmålet for interventionen (BorLenDex). Der er data for livskvalitet i enkelte af de studier, der undersøger komparator, men det kan ikke alene danne grundlag for vurderingen. Fagudvalget beklager, at datagrundlaget ikke er tilstrækkeligt til at foretage en meningsfuld vurdering.

Narrativ gennemgang af bivirkninger (vigtigt)
Der findes ingen direkte sammenligning. Ansøger har baseret den narrative gennemgang på data for bivirkninger fra PETHEMA og uønskede hændelser fra SWOG-S0777 og IFM-2009, hvad angår BorLenDex. Der er sammenlignet med uønskede hændelser fra VISTA-studiet, som også danner grundlag for EPAR'ens gennemgang af sikkerhedsprofilen for BorMelPred [25]. Fagudvalget vurderer, at det indsendte datagrundlag er tilstrækkeligt til at foretage den narrative gennemgang.

Fagudvalget har fremhævet de samme hændelser til sammenligningsgrundlaget som i sammenligningen med LenDex. Herudover har de tilføjet hæmatologiske bivirkninger (se tabel 5). Fagudvalget vurderer, at BorLenDex og BorMelPred ikke adskiller sig væsentligt i forhold til bivirkninger, og at valg af behandling beror på en individuel vurdering, hvor der tages hensyn til patientens præferencer, alder og almene tilstand. Der er en højere forekomst af perifære neuropatier ved behandling med BorLenDex i forhold til BorMelPred. Dette skyldes formentlig, at doseringen af bortezomib er højere ved behandling med BorLenDex. Det er fagudvalgets erfaring, at neuropatien overvejende er reversibel og vil fortage sig eller forsvinde ved ophør af behandlingen, hvilket også er understøttet af en subanalyse af VISTA-studiet [26]. De gastrointestinale, hæmatologiske og respiratoriske bivirkninger er reversible og håndterbare i klinikken.

Tabel 5. TEAE'er fremhævet af fagudvalget.

	TEAE'er (alle grader) rapporteret i mindst 20 % af patienterne	
	BorLenDex*	BorMelPred[#]
Perifær sensorisk neuropati	52-70 %	44 %
Gastrointestinale gener	77-81 %	77 %
Dyspnø	10-31 %	15 %
Hæmatologiske	78-79 %	82 %

*Data fra IFM og SWOG-S0777
[#]Data fra VISTA

Fagudvalget bemærker, at der for BorLenDex er 6,3 % med embolier blandt TEAE'er rapporteret i mindst 5 % af patienterne. Der er ikke rapporteret data for embolier for BorMelPred. Tromboembolier kan hos nogle

give anledning til vedvarende gener og antikoagulationsbehandling. Desuden vil det for patienter, som har fået blodprop i lungen, betyde at de må ophøre eller pausere behandlingen med lenalidomid, som minimum indtil de er stabiliseret med antikoagulationsbehandling.

Det stemmer overens med fagudvalgets erfaringer, at der vil være flere embolier ved behandling med BorLenDex end ved BorMelPred. Dog vurderer fagudvalget, at den høje forekomst i SWOG-S0777- studiet kan skyldes, at der blev givet en mindre målrettet tromboseprofylakse. I SWOG-studiet fik alle aspirin, mens man i dansk praksis anvender lavmolekylær heparin til patienter med høj risiko for tromboembolier.

9.2.3 Evidensens kvalitet

Da der ikke er grundlag for at foretage en direkte eller indirekte sammenligning, kan evidensens kvalitet i alle tilfælde ikke vurderes. Af den årsag er der ikke foretaget en GRADE-vurdering af evidensgrundlaget for sammenligningen med komparator BorMelPred. Vurdering af risk of bias for de enkelte studier fremgår af bilag 1, afsnit 17.

10 Andre overvejelser

Fagudvalget vurderer, at anbefaling af BorLenDex som standardbehandling til patienter med knoglemarvskræft, der ikke er kandidater til HDT/STS, vil påvirke efterfølgende behandlingslinjer, idet flere patienter vil blive behandlet med lenalidomid i første linje.

I anden linje er de mest anvendte behandlinger DaraBorDex, DaraLenDex og CarDex. DaraLenDex er førstevalg til 80 % af de patienter, der ikke er refraktære overfor lenalidomid, og som kan tåle behandlingen. En patient betragtes som refraktær overfor lenalidomid, når vedkommende er progredieret under behandling med stoffet i fuld dosis.

For komparatoren LenDex skelner fagudvalget mellem, om der er behandlet til progression eller ej, idet komparatoren er defineret som behandling i 18 måneder eller til progression.

Fagudvalget vurderer, at der ved behandling med LenDex til progression vil være ca. 80 %, 5 % og 15 %, der i anden linje behandles med henholdsvis DaraBorDex, DaraLenDex og CarDex. Ved behandling med LenDex i 18 måneder vil ca. 25 %, 60 % og 15 % behandles med henholdsvis DaraBorDex, DaraLenDex og CarDex.

For komparatoren BorMelPred vil ca. 80 % af patienterne behandles med DaraLenDex, og resten vil behandles med enten DaraBorDex, CarLenDex, EloLenDex eller IxaLenDex.

Ved behandling med BorLenDex vil fordelingen mellem DaraBorDex, DaraLenDex og CarDex blive henholdsvis ca. 65 %, 20 % og 15 %.

Fagudvalget har ikke et data- eller erfaringsbaseret grundlag for at udtale sig om, hvordan førstelinjebehandlingerne påvirker andenlinjebehandlingernes effekt og varighed.

11 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

Fagudvalget vurderer, at BorLenDex til behandling af tidligere ubehandlede patienter med knoglemarvskræft, der ikke er kandidater til højdosis kemoterapi med stamcellestøtte, giver en:

- Merværdi af ukendt størrelse i forhold til komparatoren LenDex (evidensens kvalitet er meget lav)

- Værdien kan ikke kategoriseres i forhold til BorMelPred (evidensens kvalitet kan ikke vurderes)

Fagudvalget vurderer, at BorLenDex er et bedre behandlingsalternativ i forhold til LenDex. Vurderingen er baseret på data fra SWOG-S0777-studiet for effektmålene overlevelse og behandlingsophør grundet uønskede hændelser samt en narrativ gennemgang af bivirkninger og uønskede hændelser. Effektmålet overlevelse gav en aggregeret værdi i kategorien merværdi af ukendt størrelse, som spænder over kategorierne lille, moderat og stor merværdi. Fagudvalget vurderer ikke, at den negative værdi for behandlingsophør grundet uønskede hændelser vægter højt nok til at trække den samlede værdi for lægemidlet ned på ingen dokumenteret merværdi, idet ophøret delvist kan forklares ved administrationsvejen for bortezomib. Desuden er de rapporterede bivirkninger overvejende forbigående og håndterbare. Derfor vurderer fagudvalget, at den samlede værdi er merværdi af ukendt størrelse i sammenligningen med LenDex.

Datagrundlaget for sammenligningen med komparatoren BorMelPred giver ikke mulighed for at kategorisere BorLenDex. Fagudvalget vurderer dog, at effekten på overlevelse opvejer det højere behandlingsophør og den tungere bivirkningsprofil. Bivirkningerne er velkendte, overvejende reversible og håndterbare. Derfor vurderer fagudvalget, at BorLenDex ikke er et dårligere behandlingsalternativ end BorMelPred. Fagudvalget fremhæver at komparatorene LenDex og BorMelPred er effektmæssigt sammenlignelige og ligestillet i Medicinrådets behandlingsvejledning, som inkluderer en indirekte sammenligning af LenDex og BorMelPred.

12 Rådets vurdering af samlet værdi og samlet evidensniveau

Rådet vurderer, at BorLenDex til behandling af tidligere ubehandlede patienter med knoglemarvskræft, der ikke er kandidater til højdosis kemoterapi med stamcellestøtte, giver en:

- Merværdi af ukendt størrelse i forhold til komparatoren LenDex (evidensens kvalitet er meget lav)

Værdien kan ikke kategoriseres i forhold til komparatoren BorMelPred (evidensens kvalitet kan ikke vurderes)

13 Relation til eksisterende behandlingsvejledning

Medicinrådet har allerede taget stilling til placeringen af BorLenDex i behandlingsvejledningen for knoglemarvskræft. Her er BorLenDex førstevalg til 60 % af ikketidligere behandlede patienter med knoglemarvskræft, som ikke er kandidater til HDT/STS. LenDex og BorMelPred er ligestillede som andetvalg. Placeringen af BorLenDex forudsætter, at Medicinrådet anbefaler lægemidlet som standardbehandling.

Fagudvalget vurderer, at resultaterne af vurderingen er i overensstemmelse med behandlingsvejledningens anbefalinger.

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende knoglemarvskræft (myelomatose)

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16 Versionslog

Version	Dato	Ændring
1.0	28. august 2019	Godkendt af Medicinrådet.

17 Bilag 1: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

17.1.1 SWOG S-0777

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	We used a dynamic allocation algorithm developed by Pocock and Simon to balance treatment assignment by the stratification factors.
Allocation concealment	**Low**	
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Overlevelse	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Overlevelse	**Low**	Ikkeblindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager. Det vurderes ikke at have indflydelse på vurdering af overlevelse.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Det kan ikke udelukkes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	Der er forskel i andelen, der bliver i behandling/modtager anden behandling og i andelen af dropouts.
Reporting bias: selective reporting outcome data.	**Low**	Alle effektmål er rapporteret i publikationen, og der er data i clinical trials.gov.
Other bias	**High**	Mange af forfatterne er associerede med Celgene og/eller Jansson.
Overall bias	**Unclear**	Samlet vurderes risiko for bias at være unclear.

17.1.2 VISTA

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Unclear**	Metode for randomisering fremgår ikke.
Allocation concealment	**Unclear**	Umiddelbart ikke beskrevet.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Overlevelse	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Overlevelse	**Low**	Ikke-blindet studie. Patienter og personale har kendskab til hvilken behandling patienterne modtager. Det vurderes ikke at have indflydelse på vurdering af overlevelse.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Det kan ikke udelukkes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	supplement giver consort med overblik over frafald. Hhv. 40 % og 49 % ophører med behandling. Primære årsager er progression eller AE.
Reporting bias: selective reporting outcome data.	**Low**	Kan ikke se protokol, men i forhold til effektmål på clinicaltrials.gov er alt rapporteret i forskellige publikationer.
Other bias	**High**	Data were collected by the sponsors and analyzed in collaboration with the senior academic authors, who vouch for the completeness and accuracy of the data and the analyses. The first draft of the manuscript was developed by the senior academic investigators with editorial assistance from representatives of Johnson & Johnson Pharmaceutical Research & Development. Additional writing assistance was provided by both sponsors.
Overall bias	**High**	Samlet vurderes risiko for bias at være high.

17.1.4 GEM-2005

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	The treatment codes were generated by a central contract research organisation with a computerised random number generator, with dynamic balancing used to maintain treatment balance within the four groups.
Allocation concealment	**Low**	The treatment codes were generated by a central contract research organisation with a computerised random number generator, with dynamic balancing used to maintain treatment balance within the four groups.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Overlevelse	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Overlevelse	**Low**	Ikkeblindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager. Det vurderes ikke at have indflydelse på vurdering af overlevelse.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Det kan ikke udelukkes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	
Reporting bias: selective reporting outcome data.	**Low**	alle effektmål rapporteret.
Other bias	**Low**	
Overall bias	**Unclear**	Samlet vurderes risiko for bias at være unclear.

17.1.5 GIMEMA

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Computer-generated randomization schedule (ifølge protokol).
Allocation concealment	**Low**	Computer-generated.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Overlevelse	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Overlevelse	**Low**	Ikkeblindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager. Det vurderes ikke at have indflydelse på vurdering af overlevelse.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Det kan ikke udelukkes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Ca. 35 % i begge arme stoppede behandling i studiet, hyppigst grundet bivirkninger, dernæst pga. progression (altså ikke noget som giver anledning til missing data). Ca. 5% i begge arme var lost to FU eller tilbagetrak deres samtykke.
Reporting bias: selective reporting outcome data.	**Low**	Protokol: PFS,OS, EFS, ORR, time to response, duration of respons, HRQOL. HRQOL er ikke rapporteret.
Other bias	**Low**	
Overall bias	**Unclear**	Samlet vurderes risiko for bias at være unclear.

17.1.6 ALCYONE

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Interactive voice response system on the basis of a computer-generated randomization schedule prepared by the sponsor. system.
Allocation concealment	**Low**	Interactive voice response.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Overlevelse	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Overlevelse	**Low**	Ikkeblindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager. Det vurderes ikke at have indflydelse på vurdering af overlevelse.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Det kan ikke udelukkes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**High**	Hhv. 20 og 33 % stoppede før de planlagte 9 cyklusser; de fleste grundet progression, næsthyppigst bivirkninger. Der var lige mange dødsfald i hver gruppe.
Reporting bias: selective reporting outcome data.	**Low**	Protokol: PFS, TTP, sCR, CR, PFS2, MRD, TTNT, ORR, > VGPR, DoR, OS, subgruppe (højrisiko), PRO global health, safety.
Other bias	**High**	Representatives of the sponsor who were involved in data collection and analyses (2 medforfattere er affilieret til Janssen Research and Development, der er ingen COI statement fra dem).
Overall bias	**High**	Samlet vurderes risiko for bias at være high.

17.1.8 UPFRONT

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Interactive Web-response system.
Allocation concealment	**Low**	Interactive Web-response system.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Overlevelse	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Overlevelse	**Low**	Ikke-blindet studie. Patienter og personale har kendskab til hvilken behandling patienterne modtager. Det vurderes ikke at have indflydelse på vurdering af overlevelse.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Det kan ikke udelukkes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	I VTD-gruppen er der færre, der får maintenance (VD = 49 %, VTD = 36 %, VMP = 41 %) og færre i gruppen, der evalueres ift. respons (VD = 88 %, VTD = 79 %, VMP = 86 %). Det vurderes af mindre betydning for denne vurdering.
Reporting bias: selective reporting outcome data.	**Low**	Alle outcome-data er rapporteret i artiklen og tilgængelige på clinicaltrials.gov.
Other bias	**Unclear**	Mange af forfatterne er associerede med Takeda - enten som ansatte eller fordi de har aktier (Takeda has entered into a co-promotion agreement with Janssen Pharmaceutical K.K. ("Janssen Pharma") for VELCADE (bortezomib)).
Overall bias	**Unclear**	Samlet vurderes risiko for bias at være unclear.

17.1.9 CLARION

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Randomization was stratified by International Staging System stage.
Allocation concealment	**Low**	To mitigate potentional bias, a validated computer algorithm ORCA was used to determine disease status with masking treatment information.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Overlevelse	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Ublindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Overlevelse	**Low**	Ikkeblindet studie. Patienter og personale har kendskab til, hvilken behandling patienterne modtager. Det vurderes ikke at have indflydelse på vurdering af overlevelse
Øvrige effektmål (Behandlingsophør pga. uønskede hændelser)	**High**	Det kan ikke udelukkes, at patientens og personalets kendskab til behandlingsallokering kan påvirke udfaldet for effektmålene.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Percentages of patients not receiving the entire treatment was similar in both treatment groups; almost all patients were included in the efficacy analyses.
Reporting bias: selective reporting outcome data.	**Low**	All prespecified outcomes are reported.
Other bias	**High**	Mange af forfatterne er associerede med Celgene.
Overall bias	**Unclear**	Samlet vurderes risiko for bias at være unclear.

17.2 GRADE-evaluering af evidenskvaliteten

Tabel 6. Grade-evaluering af evidensens kvalitet for klinisk spørgsmål 1, sammenligningen mellem BorLenDex og LenDex.

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**BorLenDex**	**LenDex**	**Relativ**	**Absolut**		
Overlevelse (median opfølgningstid 60,6 måneder)												
1	Randomiseret forsøg	Ikke[a] alvorlig	Alvorlig[b]	Alvorlig[c]	Ikke alvorlig[d]	Ingen	263	260	0,75 [0,58;0,97]	Median: 21,9 måneder	⨁⨁◯◯ LAV	KRITISK
Behandlingsophør grundet uønskede hændelser (medianopfølgningstid 60,6 måneder)												
1	Randomiseret forsøg	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ikke alvorlig[e]	Ingen	262	256	RR: 2,44 [1,57;3,80]	13,5 %-point	⨁◯◯◯ MEGET LAV	KRITISK
Livskvalitet												
0											⨁◯◯◯ MEGET LAV	VIGTIGT
Bivirkninger, kvalitativ gennemgang												
3	Randomiserede forsøg											VIGTIGT

CI: Confidence interval; HR: Hazard ration; RR: Risk ratio
a. Studiet er ublindet, hvilket indebærer risiko for bias. Det vurderes at have mindre betydning for effektmålet overlevelse end for behandlingsophør grundet uønskede hændelser.
b. Der er kun et studie.
c. Populationen er væsentligt yngre og mere 'fit' end populationen defineret i det kliniske spørgsmål. Populationen inkluderer også patienter, som er kandidater til transplantation.
d. Der er ikke tilstrækkelige informationer til at beregne optimal information size på det angivne data. Data fra et tidligere og senere cut-off giver indikation på, at optimal information size ikke er opfyldt, men da det ikke kan bekræftes, nedgraderes ikke for unøjagtighed.
e. Optimal information size er opfyldt.

Application for the assessment of Revlimid® (lenalidomide) as combination treatment with bortezomib and dexamethasone for the treatment of adult patients with previously untreated multiple myeloma (MM), who are not eligible for transplant.

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1 Basic information

Table 1 Contact information

Name	Nicolai Fik
Title	Senior Market Access Manager
Area of responsibility	Primary contact
Phone	M: +45 51 70 08 76, T: +45 35 27 16 00
E-mail	nfik@celgene.com

Table 2 Overview over the pharmaceutical

Proprietary name	Revlimid®
Generic name	Lenalidomide
Marketing authorization holder in Denmark	Celgene Europe Ltd, Winthontlaan 6 N, 3526 KV Utrecht, Netherlands
ATC code	L04 AX04
Pharmacotherapeutic group	Other immunosuppressants
Active substance(s)	Lenalidomide
Pharmaceutical form(s)	Hard capsules
Mechanism of action	The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of micro vessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. [SmPC]
Dosage regimen	Lenalidomide co-administered with bortezomib and dexamethasone. *Initial treatment:* The recommended starting dose is lenalidomide 25 mg orally once daily on Days 1 to 14 of each 21-day cycle.[SmPC] Bortezomib should be administered via subcutaneous injection (1.3 mg/m^2 body surface area) twice weekly on days 1, 4, 8 and 11 of each 21-day cycle. The dosage of dexamethasone is not defined in the SmPC, however in the clinical study underlying the regulatory approval of this indication the used administered

	dose of dexamethasone was 20 mg/day orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of 21-day cycles. *Continued treatment:* Series of 28 days until progression with • Lenalidomide 25 mg orally on days 1-21 • Dexamethason 40 mg orally on days 1, 8, 15 og 22 [1]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Revlimid as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant [SmPC]
Other approved therapeutic indications	Multiple myeloma Revlimid® as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Revlimid® as combination therapy (melphalan + prednisone) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Revlimid® in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Myelodysplastic syndromes Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Mantle cell lymphoma Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).[SmPC]
Will dispensing be restricted to hospitals?	Yes, BEGR
Combination therapy and/or co-medication	For the indication to be assessed lenalidomide is to be administered in combination with bortezomib and dexamethasone. [SmPC]
Packaging – types, sizes/number of units, and concentrations	Revlimid is provided in 2,5 mg/5 mg/7,5 mg/10 mg/15 mg/20 mg/25 mg hard capsules in a pack size of 21 capsules. [SmPC]
Orphan drug designation	No.

2 Abbreviations

Table 3 Abbreviations

ASCT	Autologous stem cell transplantation
BorLenDex	Bortezomib+lenalidomide+dexamethasone
BorMelPred	Bortezomib+melphalan+predsisolone
BorThalDex	bortezomib, thalidomide, and high-dose dexamethasone
CR	Complete Response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HDT/STS	High dose chemo therapy with stem cell support
HRQoL	Health-related quality of life
IFM	Intergroupe Francais du Myélome
IRAC	Independent response adjudication committee
ITT	Intention to Treat
LenDex	Lenalidomide+dexamethasone
MM	Multiple myeloma
MRD	Minimum Residual Disease
NDMM	Newly Diagnosed Multiple Myeloma
OS	Overall survival
OS	Overall Survival
PETHEMA	Programa para el Tratamiento de Hemopatías Malignas
PFS	Progression Free Survival
Rd	Lenalidomide+dexamethasone
RVd	Lenalidomide+bortezomib+dexamethasone (BorLenDex)
TE	Transplant eligible
TEAE	Treatment Emergent Adverse Event
TNE	Transplant non-eligible
VGPR	Very Good Partial Response
VMP	bortezomib, melphalan, and prednisone (BorMelPred)
VMP	Bortezomib+melphalan+predsisolone (BorMelPred)
VTd	bortezomib, thalidomide, and high-dose dexamethasone (BorThalDex)

3 Summary

This is an application for assessment of the combination of bortezomib+lenalidomide+dexamethasone (BorLenDex) as standard treatment for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

In the defined population the application provides data for a comparison with two comparators, lenalidomide+ dexamethasone (LenDex) and bortezomib+melphalan+ prednisone (BorMelPred).

The comparison of BorLenDex to LenDex is done based on the SWOG S0777 study which is a phase III head to head study comparing BorLenDex with LenDex as defined by the Medicines Council.[1]

As no head to head studies exist between BorLenDex and BorMelPred, Celgene investigated if a network meta-analysis was possible. While it was possible to identify a connecting network allowing for a network meta-analysis for the two main outcomes (Overall Survival and Progression Free Survival) the heterogeneity in both study design, patient populations and other parameters would make the outcome of such an analysis questionable. Therefore, the comparison between BorLenDex and BorMelPred has been conducted narratively.

For the third outcome (Discontinuation due to TEAEs) a narrative comparison is provided.

The fourth outcome (Health Related Quality of Life) has not been addressed since data for HRQoL are not available as this was not collected in the SWOG study.

A qualitative review is provided in response to the Medicines Councils request for information on side effects in studies where BorLenDex has been studied.

The comparison of BorLenDex to LenDex in the SWOG study showed that BorLenDex was significantly superior to LenDex for both Overall Survival and Progression Free survival.

The absolute median Overall Survival for BorLenDex was 89.1 (76.1-NE) months for BorLenDex as compared to 67.2 (58.4-90.8) months for LenDex, a difference in favour of BorLenDex of 21 (1.13-42.67) months with a hazard ratio of 0.75 (0.58-0.97), p=0.02786) in favour of BorLenDex using EMA censoring rules.

The absolute median Progression Free Survival for BorLenDex was 41.7 (33.1-51.5) months for BorLenDex as compared to 29.7 (24.2-37.8) months for LenDex, a difference in favour of BorLenDex of 10.7 (0.52-23.48) months with a hazard ratio of 0.76 (0.62-0.94), p=0.00996) in favour of BorLenDex using EMA censoring rules.

Treatment with BorLenDex resulted in discontinuations in 22.7% of patients as compared to 9.6% in the LenDex group, a difference of 13.1 percentage points. This was to be expected due to the well-known safety profile of bortezomib. The difference is emphasized by the fact that bortezomib in the SWOG S0777 study was administered intravenously as compared to the current standard of subcutaneous administration which is known to have a more favourable side profile than intravenous bortezomib.

Collection of data on quality of life was not included in the study design of the SWOG S0777 study, why no data can be presented.

A qualitative review of the adverse event profile of BorLenDex has been provided. The entity of data confirms the expected, well known and manageable adverse event profile of the drugs included in the regimen.

In summary BorLenDex has been shown to improve both Overall Survival and Progression Free survival as compared to LenDex.

The rate of discontinuation due to TEAE is higher than for LenDex. However, the current clinical practice of using subcutaneous bortezomib rather than intravenous bortezomib as in the SWOG study, the discontinuation rate in daily clinical practice can be assumed to be lower than reported in the study. The qualitative review of the adverse event profile indicates that the profile is well known and clinically manageable.

The narrative comparison to BorMelPred indicate that treatment with BorLenDex results in longer Overall Survival and Progression Free Survival than BorMelPred.

The discontinuation rate for BorLenDex seems at a comparable level with BorMelPred. Overall the data show that BorLenDex is more efficacious than both LenDex and BorMelPred.

4 Literature search

4.1 Systematic literature review

The systematic literature review was executed according to the guidance provided by the Danish Medicine Council in the protocol.

4.1.1 Eligibility criteria

Study eligibility criteria as applied to abstract and full-text screening were defined in terms of the population, interventions, comparisons, outcomes, and study design (PICOS) structure, outlined in Table 4.

Table 4: Trial inclusion and exclusion criteria for the systematic literature review

Criteria	Inclusion	Exclusion
Population	• Treatment-requiring multiple myeloma • Previously untreated, not candidates for HDT / STS • Men and women • Adults (≥ 18 years of age)	Studies with other populations than defined in the inclusion criteria
Interventions	• Lenalidomide + bortezomib + dexamethasone	Any treatment other than those listed in the inclusion are ineligible
Comparisons	The following controls/interventions are considered eligible comparisons: • Lenalidomide and dexamethasone • Bortezomib, melphalan and prednisolone	Any treatment other than those listed in the inclusion are ineligible
Outcomes	At least one of the following outcomes: • Overall survival • Progression free survival • Treatment discontinuation due to adverse events • Quality of Life • Adverse events for the treatment arm RVd	Studies that do not report any outcomes of interest
Study Design	• Randomized controlled trials (RCTs)	• Non-RCTs • Single-arm trials • Observational studies • Phase I and IIa studies
Other	• Inclusion language: English, Danish	Exclusion language: any other than English and Danish

4.1.2 Literature review

Relevant studies were identified by searching the following databases: MEDLINE via PubMed and CENTRAL via Cochrane library. The study search strategies used to identify studies were provided by the Danish Medicines Council. The search was executed on April 23, 2019. The search strategies are found in sections 7.1.3 and 7.1.4 on p. 53**.**

4.1.3 Included trials

Study selection criteria are enumerated in Table 4. All records identified by the search strategies were screened by two reviewers with discrepancies mediated by a third reviewer. Full-text articles corresponding to potentially relevant abstracts were then screened, also in duplicate. The trials excluded at the full-text screening phase are described in section 7.1.5, Table 23.

In all, twelve publications pertaining to seven trials were identified.

4.1.4 Data extraction

Two investigators independently extracted data for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two data extractors was resolved by involving a third reviewer and coming to a consensus. Data was stored and managed in Microsoft Excel Workbooks.

Data on study characteristics, interventions, patient characteristics, and outcomes were extracted where available. Criteria for data extraction is listed in section 7.1.1.

4.1.5 Study identification and selection

In the SLR (search executed April 23, 2019), 472 records were identified through MEDLINE via Pubmed and Central via Cochrane library. During abstract screening, 445 publications were excluded, and 27 records progressed to the full-text screening phase. Of these 27 publications, 3 were excluded due to inappropriate study design, 6 due to lack of reporting on outcomes of interest, 5 due to other reasons (such as commentary, editorial, letters, reviews, subsequent papers with no novel usable data), and 1 due to population not of interest. A PRISMA diagram of the study flow for the SLR is presented in section 7.1.2, Figure 2. In total, the SLR identified 12 publications pertaining to 7 unique trials (some trials were associated with more than one publication). The final included studies and their associated publications are presented in Table 5 below.

In addition to the above results of the systematic literature search two studies (IFM 2009 and PETHEMA 2012) were added manually for the qualitative review of adverse events as these studies form the basis for the European Medicines Agency's assessment of the safety profile of lenalidomide in the current context.

4.2 Relevant studies

Table 5 Main studies included in the application

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Main study for comparison with LenDex				
Durie B, Hoering A, Abidi M, 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. [1]	SWOG S0777	NCT00644228	01APR2008-01JULY2016	1
Main studies for comparison with BorMelPred				
San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. The New England journal of medicine. 2008;359(9):906-917. [2] *Mateos M-V, Richardson PG, Schlag R, et al.* Bortezomib Plus Melphalan and Prednisone Compared With Melphalan and Prednisone in Previously Untreated Multiple Myeloma: Updated Follow-Up and Impact of Subsequent Therapy in the Phase III VISTA Trial. Journal of Clinical Oncology. 2010;28(13):2259-2266[3] *San Miguel JF, Schlag R, Khuageva NK, et al.* Persistent overall survival benefit and no	VISTA	NCT00111319	DEC2004-JULY2007	1

increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(4):448-455[4]				
Palumbo A, Bringhen S, Larocca A, Rossi D, Di Raimondo F, Magarotto V, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: Updated follow-up and improved survival. J Clin Oncol. 2014;32(7):634–40.[5] *Palumbo A, Bringhen S, Rossi D, et al:* Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol 28:5101-5109, 2010. [6] *Bringhen S, Larocca A, Rossi D, et al.* Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010;116(23):4745-4753. [7]	GIMEMA	NCT01063179	MAY2006-JULY2014	1
Mateos MV, Dimopoulos MA, Cavo M, et al. ALCYONE Trial Investigators. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018 Feb 8;378(6):518-528[8]	ALCYONE	NCT02195479	09DEC2014-21NOV2017	1
Mateos MV, Oriol A, Martínez-López J, et al. GEM2005 trial update comparing BorMelPred/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? Blood. 2014 Sep 18;124(12):1887-93. *Mateos MV, Oriol A, Martınez-Lopez J, et al.* 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. Lancet Oncol. 2010; 11(10):934-941.	GEM 2005	NCT00443235	MAR2005- MAR2007	1
Niesvizky R, Flinn IW, Rifkin R, et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. J Clin Oncol. 2015 Nov 20;33(33):3921-9. [9]	UPFRONT	NCT00507416	JUN2007-Mar2010	1
Facon T, Lee JH, Moreau P, et al. Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma. Blood. 2019 May;133(18):1953-1963.[10]	CLARION	NCT01818752	JUL2013-JUL2016	1
Studies used for qualitative review on adverse events for BorLenDex				
Attal M, et al.; IFM 2009 Study. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017 Apr 6;376(14):1311-1320. [11]	IFM 2009	NCT01191060.	NOV2010-NOV2012	1 (safety review)
Rosinol L, Oriol A, Rios R, et al. Bortezomib, Lenalidomide and Dexamethasone (VRD-GEM) As	PETHEMA 2012	NCT01916252	SEP2103-NOV2016	1 (safety review)

Induction Therapy Prior Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma (MM): Results of a Prospective Phase III Pethema/GEM Trial. Blood. 2017;130:2017-[Abstract]. [12]				

In addition to the studies above, the EPARs for lenalidomide and for bortezomib have been consulted.

4.3 Main characteristics of included studies

In the protocol, the Expert Committee has stated that it wishes to distinguish between whether the comparators are time-limited or continuous treatment, as the committee expects a greater effect difference when the intervention is compared with a comparator, where the treatment is time-limited.

In the relevant population it has not been possible to identify any data for comparisons going further than 6 months as reported in the SWOG S0777 study. [1]

Therefore, the comparison between BorLenDex and LenDex has been based solely on data from the SWOG study and the EPAR as agreed with the Medicines Council secretariat.

No clinical studies have compared BorLenDex with BorMelPred. Celgene has therefore performed a narrative comparison between BorLenDex and BorMelPred based on data from the separate studies.

The main studies with BorMelPred in the narrative comparison between BorLenDex and BorMelPred are VISTA, GIMEMA, GEM2005, ALCYONE, UPFRONT and CLARION. [2, 5, 8-10, 13]

4.3.1 SWOG S0777

Data from this study is used for a) direct comparison to LenDex, b) the narrative comparison to BorMelPred in the NMA, and c) the qualitative narrative of adverse events.

This was a phase 3 open label randomized study to evaluate whether the addition of bortezomib to lenalidomide and dexamethasone would improve progression-free survival in patients with previously untreated multiple myeloma who were not planned for immediate autologous stem-cell transplant. [1]

Data from this study is used to support the regulatory approval of the indication for first line treatment of TNE-patients with BorLenDex.

The main study characteristics can be found in Table 24.

4.3.2 VISTA

Data from this study is used for the comparison between BorLenDex and BorMelPred in the narrative comparison.

This was a randomized, open-label phase 3 study evaluating the effect on the primary endpoint on Time To Progression, and amongst the secondary endpoint PFS and OS of addition of bortezomib to melphalan and prednisone in 682 previously untreated patients with multiple myeloma who were ineligible for high-dose therapy. [2]

The main study characteristics can be found in Table 25.

4.3.3 GIMEMA

Data from this study is used for the comparison between BorLenDex and BorMelPred in the narrative comparison.

This was a phase III, multi-center, randomized open label study comparing BorLenMelThal induction followed by bortezomib thalidomide maintenance (BorLenThal-BorThal) with BorMelPred in patients with newly diagnosed multiple myeloma.[5]

The main study characteristics can be found in Table 26.

4.3.4 ALCYONE

Data from this study is used for the comparison between BorLenDex and BorMelPred in the narrative comparison.

This was a phase 3, randomized, controlled, open-label study to determine if the addition of daratumumab to BorMelPred will prolong progression-free survival (PFS) compared with BorMelPred alone in participants with previously untreated multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant (ASCT). [8]

The main study characteristics can be found in Table 27.

4.3.5 GEM 2005

Data from this study is used for the comparison between BorLenDex and BorMelPred in the narrative comparison.

This was a phase III randomized open-label study to compare BorMelPred with BorThalPred as induction in elderly MM patients, and those who completed the induction therapy were subsequently randomly assigned in approximately equal numbers to maintenance therapy with either BorPred or BorThal.[13]

The main study characteristics can be found in Table 28.

4.3.6 UPFRONT

Data from this study is used for the comparison between BorLenDex and BorMelPred in the narrative comparison.

This was a phase III, open-label randomized study designed to compare BorThalDex-Bor with BorMelPred-Bor and BorDex-Bor in transplantation-ineligible patients with myeloma.[9]

The main study characteristics can be found in Table 29.

4.3.7 CLARION

Data from this study is used for the comparison between BorLenDex and BorMelPred in the narrative comparison.

The CLARION study was a randomized, open-label, phase III study with the objective of comparing the progression-free survival of transplant ineligible patients newly diagnosed with multiple myeloma who were treated with carfilzomib, melphalan and prednisone (CarMelDex) or with bortezomib, melphalan and prednisone (BorMelPred).[10]

The main study characteristics can be found in Table 30.

4.3.8 IFM 2009

This study is used for the narrative review of adverse events for BorLenDex.

This randomized, open-label, phase 3 trial was to compare the effect of induction therapy with three cycles of BorLenDex and then consolidation therapy with either five additional cycles of BorLenDex (350 patients) or high-dose melphalan plus stem-cell transplantation followed by two additional cycles of BorLenDex. [11]

The main study characteristics can be found in Table 31.

4.3.9 PETHEMA GEM 2012

This study is used for the narrative review of adverse events for BorLenDex.

This was an open-label, randomized, multicentre, national study that compared two pretransplant conditioning regimens (Bu-Mel versus MEL200) in subjects who received BorLenDex as initial (induction) treatment to evaluate CR rate after induction, post-transplant and post-consolidation, evaluation of minimal residual disease (MRD) after each treatment step, progression-free survival, overall survival and toxicity. [12, 14]

The main study characteristics can be found in Table 32.

5 Clinical questions

5.1 What is the value of lenalidomide in combination with bortezomib and dexamethasone compared to current clinical practice in previously untreated patients requiring treatment for multiple myeloma who are not candidates for HDT/STS?

5.1.1 Presentation of relevant studies

The Expert Committee has defined two comparators:

a) lenalidomide plus dexamethasone (LenDex) and
b) bortezomib + melphalan + dexamethasone (BorMelPred).

Studies used for comparator 1 – LenDex

The study used for this comparator is the SWOG study (see section 4.3.1 and Table 24). [1]

Study characteristics

The comparison of BorLenDex and LenDex is based on one study only (SWOG S0777). There are therefore no differences in the study characteristics. [1]

Patient characteristics

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 EMA concludes that the slight numeric differences in cytogenetic risk, frailty, and age between the two treatment arms were not considered clinically meaningful. [EPAR p. 45] *[1, 14]*

Studies used for comparator 2 - BorMelPred

The main studies used for the narrative comparison between BorLenDex and BorMelPred are

BorLenDex

- SWOG S007 (see section 4.3.1 and Table 24) [1]

BorMelPred

- VISTA study (see section 4.3.2 and Table 25), [2]
- GIMEMA study (see section 4.3.3 and Table 37), [5]
- ALCYONE study (see section 4.3.4 and Table 38), [8]
- GEM2005 study (see section 4.3.5 and Table 36), [13]
- UPFRONT study (see section 4.3.6 and Table 29), [9]
- CLARION study (see section 4.3.7 and Table 30). [9]

Study characteristics and baseline demographics

The study characteristics and baseline demographics are summarized in Table 6 and Table 7 below. A detailed description of each study is available in appendix 7.3 – Main Study Characteristics.

For information on baseline demographics, the Expert committee has specifically asked for characteristics of the patients' cytogenetics, stage division (ISS), the number and type of previous treatments and renal function. These data have to the extent available been included in the data tables below.

Table 6 Study characteristics - BorMelPred studies

Study characteristics	UPFRONT [9]	ALCYONE[8]	GIMEMA[5]	VISTA[2, 4]	GEM2005[3, 13]	CLARION [10]	SWOG S0777[1]
Number of patients	502	706	511	682	260	950	525
Study design	RCT, open-label	RCT, open-label	RCT	RCT, open-label	RCT, open-label. Randomisation first to induction, then to maintenance	RCT, open-label	RCT, open-label
Median follow-up	42.7	16,5 mths	54 mths	60,1 mths	6 years	22 mths	55 mths
Intervention A	***BorThalDex-Bor 8 cycles (of 21 days)*** **bortezomib** i.v. 1,3 mg/m2 for 4 days/cycle) + **dexamethasone** (p.o. 20 mg for 8 days of cycle 1-4, thereafter for 4 days) + **thalidomid** (p.o. 100 mg for 21 days/cycle) ***Maintenance (5 cycles of 35 days) :*** **bortezomib** i.v. 1,6 mg/m2 for 4 days/cycle	-	-	-	-		-
Intervention B	***BorMelPred-Bor*** **bortezomib as intervention A + melphalan** (p.o. 9 mg/m2, 4 days every second cycle) **+ prednisone** (p.o. 60 mg/m2, 4 days every second cycle) Maintenance as Intervention A.	DaraBorMelPred-Dara ***Up to 9 cycles of 42 days of*** **bortezomib** (s.c. 1,3 mg/m2, 1 time/week in the first cycle, then twice weekly) + **melphalan** (p.o. 9 mg/m2, 1 time/day for 4 days/cycle) + **prednisone** (p.o. 60 mg/m2, 1 time/day for 4 days/cycle) + **daratumumab** (p.o or i.v. 16 mg/kg; 20 mg once weekly in 1. cycle, every 3. Week in cycle 2-9, and then every 4 weeks until progression or unacceptable side effects,	BorMelPred-BorThal ***9 cycles (of 42 days)*** **bortezomib** (i.v. 1,3 mg/m2 for 8 days in cycle 1-4 og 4 days in cycle 5-9) + **melphalan** (p.o. 9 mg/m2 for 4 days/cycle) + **prednisone** (p.o. 60 mg/m2 for 4 days/cycle) + **thalidomide** (50 mg/day for 2 years or until progression or death) ***OBS: dose reduction after inclusion of 139 patients:*** 9 cycles of 5 weeks bortezomib for 5 weeks, bortezomib for 4 days/cycle.	BorMelPred ***BorMelPred* 9 cycles of 42 days** **bortezomib** (i.v. 1,3 mg/m2; 8 days for 1.-4. cycle, 4 days i 5.-9. cycle + **melphalan** (9 mg/m2/day for 4 days/cycle) + **prednisone** (60 mg/m2/day i 4 days/cycle)	***BorMelPred -BorThal / BorMelPred -BorPred 6 cycles (of 42 days)*** **bortezomib** (i.v. 1,3 mg/m2, twice weekly, in 1. cycle, then once weekly) + **melphalan** (p.o. 9 mg/m2, 4 days/cycle) + prednisone (p.o. 60 mg/m2, 4 Days/cycle) ***Maintenance up to 3 years:*** **bortezomib** (1,3 mg/m2, 4 days every 3rd month) AND **prednisone** (50 mg every second day) OR **thalidomide** (50 mg/day)	**CarMelPred** (9 cycles of 42 days) **Carfilzomib iv** on days 1, 2, 8, 9, 22, 23, 29, and 30 of each 42-day cycle. 20 mg/m² on cycle 1, days 1 and 2 followed by 36 mg/m² thereafter. **Melphalan** 9 mg/m² days 1-4 of each cycle **Prednisone** 60 mg/m² days 1-4 of each cycle	***BorLenDex*** ***8 cycles (of 21 days)*** **bortezomib** (i.v. 1,3 mg/m2 for 4 days/cycle) **+ lenalidomid** (p.o. 25 mg/day for 14 days/cycle) **+ dexamethason** (p.o. 20 mg/day for 8 days/cycle) **continuously in cycles of 28 days** lenalidomid 25 mg/day for 21 days/cycle + dexamethason 40 mg on days 1,8,15,22

Study characteristics	UPFRONT [9]	ALCYONE[8]	GIMEMA[5]	VISTA[2, 4]	GEM2005[3, 13]	CLARION [10]	SWOG S0777[1]
Comparator C	***BorDex-Bor*** **bortezomib + dexamethason** as in intervention A. **Maintenance as in Intervention A**	***BorMelPred*** **bortezomib + melphalan + prednisone** as in the intervention group	***BorMelPred*** **bortezomib + melphalan + prednisone** as in the intervention group	*MelPred* melphalan + prednisone as in the intervention group	***BorPredThal-BorThal / BorPredLen-BorPred*** **bortezomib + prednisone as** invervention B **+ thalidomid** (50 mg/day i 15 days of first cycle, then 100 mg/day) ***Maintenance as in intervention B.***	***BorMelPred*** ***Bortezomib*** *(either iv or sc) 1.3 mg/m² during cycles 1 to 4 on days 1, 4, 8, 11, 22, 25, 29, and 32 followed by 1.3 mg/m² during cycles 5 to 9 on days 1, 8, 22, and 29.* ***Melphalan and Prednisone*** *as in the intervention group*	***LenDex*** ***6 cycles (of 28 days)*** **lenalidomide** (p.o. 25 mg/day for 21 days/cycle) **+ dexamethason** (p.o. 40 mg/day for 4 days/cycle) **continuously in cycles of 28 days** lenalidomid 25 mg/day for 21 days/cycle + dexamethason
Inclusion criteria	> 65 years NDDM (as per protocol ≥18 yrs), not previously treated	> 65 years ELLER < 65 years and not eligible for HDT, NDDM, not eligible for HDT	> 65 years NDDM, not eligible for HDT	> 18 years NDDM, not eligible for HDT, not previously treated	> 65 years NDDM, not previously treated	≥18years, previously untreated	> 18 years. Newly diagnosed (NDMM)
Neutrophils	≥1000 cells/mm3	≥ 1,0 x 10^9/l	-	-	> 1,0 x 10^9/l	> 1,0 x 10^9/l	> 1,0 x 103 cells/mm3
ASAT/ALAT	≤2 times ULN	≤2.5 x upper limit of norm.	-	-	-	<3 x ULN	-
Total bilirubin	-	≤1.5 x upper limit of norm.l	-	-	-	<1.5 x ULN	-
CrCl	≤2mg/dl	≥40 ml/min	-	-	< 176,8 mmol/l	≥15 ml/min	> 30 ml/min
Corr. seCal		<3.5 mmol/l	-	-		-	
Thrombocytes	≥100.000 x 10^9/l	≥70x$10^{9/l}$	-	-	> 50 x 10^9/l	> 50 x 10^9/l	> 80.000 /mm3
Hemoglobin	-	≥7,5 mmol/l	-	-	> 80 g/l	8 g/dL	> 9 g/dl
Performance status	Karnofsky ≥50%	ECOG 0-2	Karnofsky ≥60%	-	ECOG < 3	0-2	ECOG 0-3
Adapted from: [15]							

Table 7 Baseline demographics - BorMelPred studies

Baseline data		UPFRONT [9]	ALCYONE[8]	GIMEMA[5]	VISTA[2, 4]	GEM2005[3, 13]	CLARION [10]	SWOG S0777[1, 14]
Age, median, range	A	73 (66-77)	-					
	B	72 (68-77)	71 (40-93)	71	71 (57-90)	73 (68-77)	72 (42-89)	63 [56-70]
	C	74.5 (67-79)	71 (50-91)	71	71 (48-91)	73 (69-76)	72 (43-91)	63 [56-71]
Hemoglobin, median (range)	A	-	-	-	-	-		-
	B	-	-	-	-	-		-
	C	-	-	-	-	-		-
Thrombocytes	A	-	-	-	-	-		-
	B	-	-	-	-	-		-
	C	-	-	-	-	-		-
β-microglobulin, median (Range, IQR)	A	3.9 (2.8-6.2)	-	-				
	B	4.1 (3.0-6.2)	-	3,8 (IQR 2,7-5,2)	>5,5 mg/l: 33%	< 2,5: 22 % 2,5-5,5: 48 % > 5,5: 29 %	< 2,5: 8.4 % 2,5-5,5: 53.6 % > 5,5: 38.1 %	> 3,5 mg/l: 60 %
	C	4.5 (3.1-6.2)	-	4 (IQR 3,0-5,6)		< 2,5: 13 % 2,5-5,5: 53 % > 5,5: 34 %	< 2,5: 8.2 % 2,5-5,5: 53.7 % > 5,5: 38.2 %	> 3,5 mg/l: 63 %
Cytogenetic risk status	A							
	B	-	standard: 83 % high risk: 17 %	t(4;14): 17% t(14;16): 5 % Del17: 17 %	-	High-risk:14%	High: 11.3% Standard: 66.9% Unknown: 21.8%	High-risk:33%
	C	-	standard: 85 % high risk: 15 %	t(4;14): 14 % t(14;16): 11 % Del17: 13 %	-	High-risk:7%	High: 14.0% Standard:67.9% Unknown:18.0%	
ISS stage	A	I: 25 % II: 39 % III: 36 %	-	-	-	-		-
	B	I: 25 % II: 39 % III: 36 %	I: 20 % II: 40 % III: 41 %	I: 59 23% II: 100 39% III: 47 19% Data missing: 19%	I: 19% II: 47% III: 35%	I: 30% II: 40 % III: 30 %	I: 17.6% II: 44.1% III: 38.1% Unknown: 0.2%	I: 29.7% II: 37.6% III: 32.7%
	C	I: 22 % II: 46 % III: 33 %	I: 19 % II: 45 % III: 36 %	I: 22% II: 34% III: 22% Data missing: 22%	I: 19% II: 47% III: 34%	I: 20 % II: 43 % III: 37 %	I: 19.7% II: 42.6% III: 37.7% Unknown: 0%	I: 28.8 II: 37.7 III: 33.1%
ECOG performance status	A	Karnofsky < 70 %: 8 %	-	-	-	-		-
	B	Karnofsky < 70 %: 12 %	0: 22 % 1: 52 % 2: 26 %	-	Karnofsky performance status < 70: 35 %	-	0-1: 81.4% (389/478) 2: 18.6 (89/478)	0: 40.3% 1: 48.7% 2: 7.2% 3: 3.8%

Baseline data		UPFRONT [9]	ALCYONE[8]	GIMEMA[5]	VISTA[2, 4]	GEM2005[3, 13]	CLARION [10]	SWOG S0777[1, 14]
	C	Karnofsky < 70 %: 11 %	0: 28 % 1: 49 % 2: 24 %	-	Karnofsky performance status < 70: 33 %	-	0-1: 78.6% (375/477) 2: 21.1% (101/477)	0: 38.8% 1: 46.2% 2: 12.3% 3: 2.7%
Renal function	A	median [IQR] 1,0 [0,8-1,4]	-	-	-	-		-
	B	median [IQR] 1,0 [0,8-1,3]	-	< 30 ml/min: 8 % 30-60 ml/min: 58% > 60 ml/min: 34 %	< 30 ml/min: 6 % 30-60 ml/min: 48% >60 ml/min: 46 %	-	< 30 ml/min: 8.8% (42/478) ≥30-<50 ml/min: 23.6% (113/478) ≥50-<80 ml/min: 46.0% (220/478) <80 ml/min: 21.1%(101/478)	< 60 ml/min: 29.7% >60 ml/min: 70.3% Missing: 0%
	C	median [IQR] 1,1 [0,9-1,4]	-	< 30 ml/min: 9 % 30-60 ml/min: 62% > 60 ml/min: 28 %	< 30 ml/min: 5 % 30-60 ml/min: 50% >60 ml/min: 46 %	-	< 30 ml/min:7.6% (37/477) ≥30-<50 ml/min: 26.4%(126/477) ≥50-<80 ml/min: 41.1%(196/477) <80 ml/min: 24.7% (118/477)	< 60 ml/min: 30.4% >60 ml/min: 69.2% Missing: 0.4%
Adapted from: [15]								

5.1.2 Results per study

The study results are presented in Table 33 through Table 39.

The comparison of BorLenDex to LenDex showed that BorLenDex was significantly superior to LenDex for both Overall Survival and Progression Free survival.

SWOG S0777 – study results

See Results per study - tables

Table 33.

Data from the SWOG study has been analysed with a number of different cut-off dates and censoring principles.

The response to the clinical question regarding both comparators has been provided using data from the main publication of SWOG and the EPAR. [1, 14]

Data presented in the principal publication for SWOG (Durie et al.) is based on the eligible analysable population without IRAC review and censoring. In the EPAR several different data cut-offs are presented. In this application data based in the EMA censoring rules for the ITT-population is shown.

An overview of the different available data cut-off dates is available in Appendix 7.2.

Overall survival

In the EMA analysis applying EMA censoring rules (cut-off date 01DEC2016) Overall Survival for BorLenDex was 89.1 (76.1-NE) months for BorLenDex as compared to 67.2 (58.4-90.8) months for LenDex, a difference in favour of BorLenDex of 21 months with a hazard ratio of 0.75 (0.58-0.97), p=0.002786) in favour of BorLenDex. [14]

In the primary analysis of the eligible population of the SWOG study (cut-off date 05NOV2015) the absolute median Overall Survival for BorLenDex was 75 (65-NR) months for BorLenDex as compared to 64 (56-NR) months for LenDex, a difference in favour of BorLenDex of 11 months with a hazard ratio of 0.71 (0.560-0.906), p=0.0018) in favour of BorLenDex. [1]

Progression Free Survival

In the EMA analysis applying EMA censoring rules (cut-off date 01DEC2016)) the absolute median Progression Free Survival for BorLenDex was 41.7 (33.1-51.5) months for BorLenDex as compared to 29.7 months (24.2-37.8) for LenDex, a difference in favour of BorLenDex of 10.7 months with a hazard ratio of 0.76 (0.62-0.94), p=0.00996) in favour of BorLenDex. [14]

In the primary analysis of the eligible population of the SWOG study (cut-off date 05NOV2015) the absolute median Progression Free Survival for BorLenDex was 43 (39-52) months for BorLenDex as compared to 30 months (25-39) for LenDex, a difference in favour of BorLenDex of 13 ((6.49-19.51), p<0.001)) months with a hazard ratio of 0.709 (0.524-0.0.959), p=0.0125) in favour of BorLenDex. [1]

Discontinuations due to adverse events

When assessing this outcome, it is important to bear in mind that bortezomib was administered intravenously in the SWOG study in contrast to the current standard of subcutaneous administration which

has a more favourable safety profile. [16] Further details on the difference in safety profile depending on method of administration are available on p.34.

In the SWOG study treatment with BorLenDex resulted in discontinuations in 22.7% of patients as compared to 9.6% in the LenDex group, a difference of 13.1 percentage points with a Relative Risk Ratio of 2.37 (1.49-3.75); p≤0.001). [1]

This difference was to be expected due to the well-known adverse event profile of intravenous bortezomib. [1, 14]

Health Related Quality of Life

Collection of data on quality of life was not included in the study design of the SWOG S0777 study, why no results can be presented.

Qualitative review of adverse events.

The Expert Committee has requested a qualitative review of adverse events (occurring in> 10% of patients) and all grade 3 and 4 adverse reactions, which can be found in a separate section below (see p. 26).

The entity of data confirms the expected, well known and manageable adverse event profile of the drugs included in the combination.

VISTA

See Table 35 for results. Data has been sourced from the publications as it has not been possible to identify the EPAR-version which contains the follow-up data with the longest duration.

The VISTA study was designed to compare BorMelPred to MelPred and does therefore not support a direct comparison with BorLenDex. [2, 4]

Overall survival

The absolute median Overall Survival was 43.1 months for MelPred as compared to 56.4 months for BorMelPred, a difference in favour of BorMelPred of 13.3 months with a hazard ratio of 0.695 (0.567-0.852), p<0.001) in favour of BorMelPred. [2, 4]

Progression Free Survival

The absolute median Progression Free Survival was 15.2 months for MelPred as compared to 21.7 months for BorMelPred, a difference in favour of BorMelPred of 6.5 months with a hazard ratio of 0.558 (0.430-0.720), p<0.001) in favour of BorMelPred. [2] Data for follow-up were not reported in the 2013-publication. [4]

Discontinuations due to adverse events

Treatment with BorMelPred resulted in discontinuation in 14% (47/338) patients as compared to 15% (50/344) in the MelPred group. This is a relative difference of 1.05 (0.72-1.51), p=0.814. [2, 4]

It is a confounding factor, however, that the investigators had the option of discontinuing only bortezomib in the BorMelPred group of patients, allowing the patient to continue on MelPred alone. Thus, these number do not fully reflect the discontinuation rate due to adverse events for bortezomib. Data from the bortezomib EPAR shows the following picture:

Table 8 Discontinuations due to TEAEs - VISTA

	BorMelPred (N=340) N (%)	**MelPred (N=337) N (%)**
Terminated treatment due to AEs	50 (15)	47 (14)
At least one related	37 (11)	35 (10)
At least on bortezomib related	33 (10)	NA
Discontinued bortezomib due to AEs	108 (32)	NA
Source: EPAR [14]		

Including these numbers in the assessment, the full or partly discontinuation rate for the BorMelPred regimen was actually 46.5% (158 patients) as compared 14% (14 patients) in the MelPred group. [14]

Health Related Quality of Life

Data for health-related quality of life has not been included in the analysis as such data are not available for BorLenDex, rendering a comparison impossible.

Qualitative review of adverse events

As per the Medicines Council protocol this outcome is relevant only for studies where BorLenDex in combination has been used for newly diagnosed patients with NDMM. Therefore, the outcome is not relevant for the indirect comparison between BorLenDex and BorMelPred, and no data have been provided.

GEM2005

The GEM 2005 study was designed to compare BorMelPred to BorThalPred and does therefore not support a direct comparison with BorLenDex.

The median Overall Survival was 63 months for BorMelPred as compared to 43 months for BorThalPred, with a hazard ratio of 0.67 [0.49-0.91] in favour of BorMelPred. [13]

The median Progression Free Survival was 32 months for BorMelPred as compared to 24 months for BorThalPred, which was non-significant (p=0.1). [13]

Treatment with BorMelPred resulted in treatment discontinuation in 12% of the patients as compared to 17% in the BorThalPred group, a relative risk of 0.60 (0.18-1.97; p=0.393). [13]

GIMEMA

The GIMEMA study was designed to compare BorMelPredThal to BorMelPred and does therefore not support a direct comparison with BorLenDex.

The median Overall Survival was Not Reached for BorMelPredThal as compared to 60.6 months for BorMelPred, with a hazard ratio of 0.70 [0.52-0.92] in favour of BorMelPredThal.[5]

The median Progression Free Survival was 35.3 months for BorMelPredThal as compared to 24.8 months for BorMelPred, with a hazard ratio of 0.58 [0.47-0.71] in favour of BorMelPredThal. [5]

Treatment with BorMelPredThal resulted in treatment discontinuation in 30% of the patients as compared to 16.7% in the BorMelPred group. [5]

ALCYONE

The ALCYONE study was designed to compare DaraBorMelPred to BorMelPred and does therefore not support a direct comparison with BorLenDex. The data below are from a published prespecified interim analysis. [8]

The median Overall Survival was not reported in the publication as data were not yet mature.[8]

The median Progression Free Survival was 35.3 months for DaraBorMelPred as compared to 24.8 months for BorMelPred, with a hazard ratio of 0.50 [038-0.65] in favour of DaraBorMelPred.[8]

Treatment with DaraBorMelPred resulted in treatment discontinuation in 4.9% of the patients as compared to 9.3% in the BorMelPred group. [8]

UPFRONT

The UPFRONT study was designed to compare BorThalDex-Bor with BorMelPred-Bor and BorDex-Bor and does therefore not provide a direct comparison with BorLenDex.

The median Overall Survival was 51.5 months for BorThalDex-Bor, as compared to 53.1 months for BorMelPred-Bor and 49.8 months for BorDex-Bor respectively.[9]

The median Progression Free Survival was 15.4 months for BorThalDex-Bor, as compared to 17.3 months for BorMelPred-Bor and 14.7 months for BorDex-Bor respectively.[9]

Treatment with BorThalDex-Bor resulted in treatment discontinuation in 40.1% of the patients as compared to 38.3% for BorMelPred-Bor and 34.5% months for BorDex-Bor respectively. [9]

CLARION

The CLARION study was designed to compare CarMelPred with BorMelPred-Bor and does therefore not provide a direct comparison with BorLenDex.

The median Overall Survival is not reported as data are not mature.[10]

The median Progression Free Survival was 22.3 months for CarMelPred, as compared to 22.1 months for BorMelPred, respectively. [10]

Treatment with CarMelPred resulted in treatment discontinuation in 16.7% of the patients as compared to 14.7% months for BorMelPred-Bor. [10]

5.1.3 Qualitative review of adverse events

The Expert Committee has requested a qualitative review of

- the most common side effects of any degree (occurring in> 10% of patients) and
- any grade 3-4 adverse reactions

reported in the clinical studies in which lenalidomide in combination with bortezomib has been studied as a treatment for newly diagnosed MM patients.

The adverse event profile of lenalidomide has been evaluated by the Medicines Council in connection with the assessment of lenalidomide for maintenance treatment of patients with multiple myeloma.

The conclusion was that the adverse event profile is well-known from clinical use and are manageable. The following qualitative review supplements the previously submitted information with focus on the population relevant for the population relevant for the present application.

Data sources

Data for the review for BorLenDex has been sourced from the EPAR and the SWOG S0777 study. [1, 14]

Additional safety data for patients treated with BorLenDex has been identified in the EPAR based on PETHEMA GEM study and the IFM 2009 study [see Table 31 and Table 32 for study descriptions]. [11] [14]

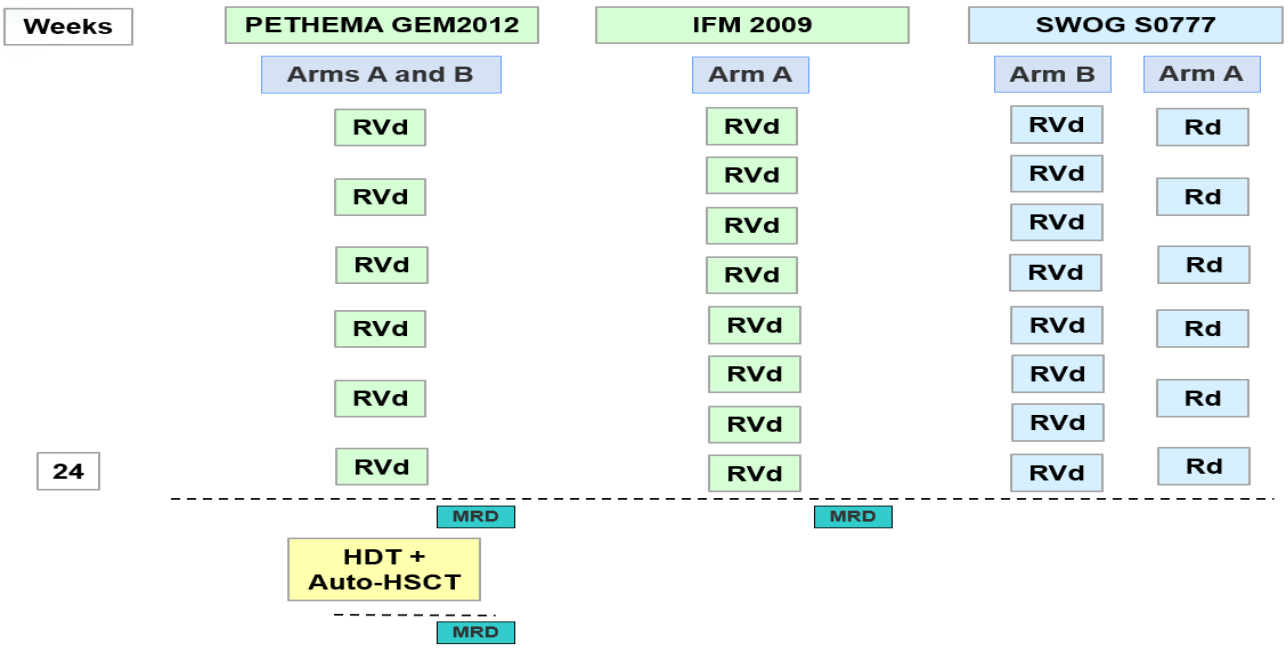
The IFM-2009 and PETHEMA GEM studies were designed to assess BorLenDex as induction therapy in newly diagnosed transplant eligible MM patients and are as such not relevant for the efficacy outcomes of this application.

However, these studies are included in the safety assessment performed by the EMA, why it seems reasonable to include those data in the qualitative review of adverse events in a patient population of previously untreated newly diagnosed MM patients to the extent that data are available for the period prior to ASCT. [11] [14]

The safety data provided to EMA in connection with the regulatory submission focused on 24 weeks of BorLenDex initial treatment for the safety populations of the following studies:

- SWOG S0777 (BorLenDex and LenDex arms),
- PETHEMA GEM 2012 (both BorLenDex arms combined), and
- IFM 2009 Arm A (BorLenDex no transplant arm).

Figure 1 Overview of the design of Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777



auto-HSCT = autologous hematopoietic stem cell transplantation; HDT = high-dose therapy; MRD = minimal residual disease; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; TE = transplant eligible.
Notes:
1) Each box represents one 4-week cycle of BorLenDex in the PETHEMA GEM2012 study and Rd in Arm A of the SWOG S0777 study, one 3-week cycle of BorLenDex in the IFM 2009 study, and one 3-week cycle of BorLenDex in Arm B of the SWOG S0777 study.
2) Bortezomib was given subcutaneously in the PETHEMA GEM2012 study and intravenously in the IFM 2009 and SWOG S0777 studies.
Figure reproduced from the EMA lenalidomide EPAR.

A total of 1076 subjects were included in the safety population to assess the safety profile of BorLenDex as initial treatment: SWOG S0777 (262 subjects), PETHEMA GEM2012 (458 subjects), and IFM 2009 (356 subjects). BorLenDex dosing regimens in these studies were either six 28-day cycles or eight 21-day cycles. The data cut-off dates reported are 31 March 2017 for the PETHEMA GEM2012 study and 1 December 2016 for the IFM 2009 and SWOG S0777 studies. [14]

In the context of assessing the adverse event profile, it is important to note that bortezomib was administered intravenously in the SWOG and IFM-2009 studies and subcutaneously in the PETHEMA GEM study.[1, 11, 14] It is well documented that subcutaneous administration of bortezomib is associated with a more favourable safety profile in particularly regarding peripheral neuropathy. [16, 17] This is described in more detail on p. 34.

The safety population includes all subjects who were randomized and received at least one dose of study drug. If a subject received study drug other than the subject's randomized treatment assignment, then the subject was assigned to the treatment arm reflecting the treatment that the subject actually received during the study. The extent of patient exposure can be found in Table 9. [14] Please note that the nomenclature for the intervention and comparator has been maintained in these tables as they are reproduced from the Assessment Report (RVd = BorLenDex; Rd = LenDex).

Table 9: Duration of Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 Arm A), and SWOG S0777 (Safety Population)

Source: EPAR [14]	**PETHEMA GEM2012**	**IFM 2009**	**SWOG S0777**	
	RVd[a] (4-week cycles × 6 = 24 weeks) (N = 458) n (%)	**RVd[b] (3-week cycles × 8 = 24 weeks) (N = 356) n (%)**	**RVd (3-week cycles × 8 = 24 weeks) (N = 262) n (%)**	**Rd (4-week cycles × 6 = 24 weeks) (N = 256) n (%)**
Treatment Duration (weeks)				
Median	27.0	24.1	24.0	24.1
Minimum, maximum	0.6, 60.0	3.0, 36.0	0.4, 36.6	1.3, 35.1

Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone.
[a] Both RVd arms combined. For the PETHEMA GEM2012 study.[b] For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment." Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

General adverse event profile

The overall incidence of adverse events for the initial treatment period is summarized in Table 10 below.

Table 10 : Overview of TEAEs – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

Subjects With ≥ 1:	**PETHEMA GEM2012**	**IFM 2009**	**SWOG S0777**	
	RVd[a] (4-week cycles × 6 = 24 weeks)	RVd[b] (3-week cycles × 8 = 24 weeks)	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6= 24 weeks) (N = 256) n (%)
TEAE	402 (87.8)	354 (99.4)	255 (97.3)	245 (95.7)
Grade 3 or 4 TEAE[c]	183 (40.0)	306 (86.0)	200 (76.3)	176 (68.8)
Grade 5 TEAE[c]	9 (2.0)	1 (0.3)	6 (2.3)	3 (1.2)
Treatment-emergent SAE	147 (32.1)	108 (30.3)	105 (40.1)	73 (28.5)
Treatment Discontinuation Due to TEAE[d]	14 (3.1)	30 (8.4)	60 (22.9)	24 (9.4)
Source: Table 35 EPAR [14]				

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] Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
[b] For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
[c] Graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies.
[d] "Discontinuation" refers to study discontinuation for the PETHEMA GEM2012 study and treatment discontinuation for the IFM 2009 and SWOG S0777 studies. The TEAEs leading to treatment discontinuation were recorded on the Off Treatment Notice Form for the SWOG S0777 study.

Notes: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study. A subject with multiple occurrences of a TEAE was counted only once in that TEAE category.

Adverse events in ≥10 % of the patients

The Expert Committee has asked for data for adverse events occurring in more than 10 % of the patients. Such data are not specified neither in the identified publications not in the EPAR. The EPAR provides the most detailed information which is however with a cut-off at more than 20 % of the patients for the comparison of BorLenDex vs LenDex.

The frequencies of subjects with TEAEs (any grade) reported in ≥ 20% of subjects in any treatment arm by study and by System Organ Class (SOC) for the studies SWOG S0777, PETHEMA GEM 2012 and IFM2009 are

presented in the tables below. [EPAR T38] These data are supplemented with information and conclusions sourced from the EPAR and three relevant publications.[1, 11, 14]

Data for the PETHEMA GEM and the IFM 2009 studies for adverse events occurring in more than 10 % of patients are tabularized in the EPAR tables and reproduced below in tables Table 12 and Table 13 respectively. [14]

Table 11: TEAEs (Any Grade) Reported in at Least 20% of Subjects in Any Treatment Arm – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	**PETHEMA GEM2012**	**IFM 2009**	**SWOG S0777**	
	RVd[b] (4-week cycles × 6 = 24 weeks)	RVd[c] (3-week cycles × 8 = 24 weeks)	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)
Subjects With ≥ 1 TEAE	402 (87.8)	354 (99.4)	255 (97.3)	245 (95.7)
Blood and Lymphatic System Disorders	229 (50.0)	276 (77.5)	208 (79.4)	203 (79.3)
Neutropenia	146 (31.9)	163 (45.8)	77 (29.4)	99 (38.7)
Thrombocytopenia	116 (25.3)	71 (19.9)	151 (57.6)	117 (45.7)
Anemia	69 (15.1)	62 (17.4)	179 (68.3)	175 (68.4)
Leukopenia	41 (9.0)	128 (36.0)	109 (41.6)	126 (49.2)
Lymphopenia	21 (4.6)	186 (52.2)	67 (25.6)	62 (24.2)
Nervous System Disorders	192 (41.9)	290 (81.5)	219 (83.6)	145 (56.6)
Neuropathy peripheral	160 (34.9)	16 (4.5)	2 (0.8)	0
Dizziness	7 (1.5)	18 (5.1)	76 (29.0)	41 (16.0)
Paresthesia	5 (1.1)	80 (22.5)	3 (1.1)	2 (0.8)
Dysgeusia	0	13 (3.7)	79 (30.2)	48 (18.8)
Peripheral sensory neuropathy	0	186 (52.2)	184 (70.2)	85 (33.2)
Infections and Infestations	129 (28.2)	188 (52.8)	92 (35.1)	74 (28.9)
Infection	129 (28.2)	5 (1.4)	3 (1.1)	1 (0.4)
Gastrointestinal Disorders	125 (27.3)	273 (76.7)	211 (80.5)	166 (64.8)
Diarrhea	59 (12.9)	120 (33.7)	104 (39.7)	79 (30.9)
Constipation	55 (12.0)	136 (38.2)	147 (56.1)	115 (44.9)
Nausea	13 (2.8)	109 (30.6)	98 (37.4)	69 (27.0)
General Disorders and Administration Site Conditions	102 (22.3)	258 (72.5)	221 (84.4)	191 (74.6)
Pyrexia	21 (4.6)	72 (20.2)	37 (14.1)	22 (8.6)
Edema peripheral	15 (3.3)	90 (25.3)	122 (46.6)	65 (25.4)
Edema	2 (0.4)	4 (1.1)	0	0
Fatigue	0	154 (43.3)	193 (73.7)	167 (65.2)
Respiratory, Thoracic, and Mediastinal Disorders	68 (14.8)	115 (32.3)	150 (57.3)	117 (45.7)
Cough	3 (0.7)	43 (12.1)	77 (29.4)	51 (19.9)
Dyspnea	1 (0.2)	34 (9.6)	80 (30.5)	65 (25.4)
Musculoskeletal and Connective Tissue Disorders	23 (5.0)	195 (54.8)	185 (70.6)	166 (64.8)
Back pain	4 (0.9)	68 (19.1)	87 (33.2)	71 (27.7)
Muscular weakness	1 (0.2)	4 (1.1)	64 (24.4)	45 (17.6)
Skin and Subcutaneous Tissue Disorders	21 (4.6)	172 (48.3)	113 (43.1)	104 (40.6)
Rash	4 (0.9)	78 (21.9)	49 (18.7)	52 (20.3)
Psychiatric Disorders	18 (3.9)	126 (35.4)	113 (43.1)	110 (43.0)
Insomnia	0	86 (24.2)	86 (32.8)	74 (28.9)
Metabolism and Nutrition Disorders	19 (4.1)	61 (17.1)	201 (76.7)	202 (78.9)
Hyperglycemia	11 (2.4)	8 (2.2)	127 (48.5)	142 (55.5)
Decreased appetite	2 (0.4)	16 (4.5)	90 (34.4)	59 (23.0)
Hyponatremia	2 (0.4)	4 (1.1)	80 (30.5)	65 (25.4)

Hypokalemia	1 (0.2)	14 (3.9)	76 (29.0)	53 (20.7)
Hypoalbuminemia	0	1 (0.3)	78 (29.8)	67 (26.2)
Hypocalcemia	0	9 (2.5)	131 (50.0)	111 (43.4)
Investigations	28 (6.1)	37 (10.4)	163 (62.2)	144 (56.3)
ALT increased	7 (1.5)	7 (2.0)	67 (25.6)	49 (19.1)
Blood creatinine increased	2 (0.4)	2 (0.6)	48 (18.3)	64 (25.0)
Blood alkaline phosphatase	1 (0.2)	2 (0.6)	66 (25.2)	48 (18.8)
AST increased	1 (0.2)	4 (1.1)	56 (21.4)	38 (14.8)
Weight decreased	1 (0.2)	12 (3.4)	53 (20.2)	54 (21.1)
Source: EPAR [14]				

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[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 for the RVd column in the PETHEMA GEM2012 study.

[b] Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.

[c] For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."

Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.

Data cut-off date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

Table 12: TEAEs Reported in at Least 10 Percent of Subjects in Any Cohort – Initial Treatment – PETHEMA GEM2012 (Safety Population)

System Organ Class Preferred Term[a]	**RVd[b] (PETHEMA GEM2012); 4-week cycles × 6 = 24 weeks) (N = 458) n (%)**
Subjects With ≥ 1 TEAE	402 (87.8)
Blood and Lymphatic System Disorders	229 (50.0)
Neutropenia	146 (31.9)
Thrombocytopenia	116 (25.3)
Anemia	69 (15.1)
Nervous System Disorders	192 (41.9)
Neuropathy peripheral	160 (34.9)
Neuralgia	25 (5.5)
Dizziness	7 (1.5)
Paresthesia	5 (1.1)
Peripheral sensory neuropathy	0
Infections and Infestations	129 (28.2)
Infection	129 (28.2)
Gastrointestinal Disorders	125 (27.3)
Diarrhea	59 (12.9)
Constipation	55 (12.0)
General Disorders and Administration Site Conditions	102 (22.3)
Asthenia	56 (12.2)
Pyrexia	21 (4.6)
Edema peripheral	15 (3.3)
Edema	2 (0.4)
Injury, Poisoning, and Procedural Complications	93 (20.3)
Skin toxicity	91 (19.9)
Respiratory, Thoracic, and Mediastinal Disorders	68 (14.8)
Pneumonia	24 (5.2)
Nasopharyngitis	4 (0.9)

MedDRA = Medical Dictionary for Regulatory Activities; RVd= lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.

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 for the RVd column.

b Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.

Notes: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study.

Table 13 : TEAEs Reported in at Least 10 Percent of Subjects in Any Cohort – Initial Treatment – IFM 2009 (Arm A) (Safety Population)

System Organ Class Preferred Term[a]	**RVd[b] (IFM 2009 Arm A); 3-week cycles × 4 = 12 weeks) (N = 356) n (%)**
Subjects With ≥ 1 TEAE	354 (99.4)
Blood and Lymphatic System Disorders	269 (75.6)
Lymphopenia	178 (50.0)
Neutropenia	158 (44.4)
Leukopenia	125 (35.1)
Thrombocytopenia	70 (19.7)
Anemia	60 (16.9)
Nervous System Disorders	267 (75.0)
Peripheral sensory neuropathy	157 (44.1)
Paresthesia	67 (18.8)
Headache	50 (14.0)
Neuropathy peripheral	13 (3.7)
Gastrointestinal Disorders	257 (72.2)
Constipation	126 (35.4)
Nausea	106 (29.8)
Diarrhea	101 (28.4)
Vomiting	54 (15.2)
General Disorders and Administration Site Conditions	236 (66.3)
Fatigue	129 (36.2)
Edema peripheral	81 (22.8)
Pyrexia	65 (18.3)
Asthenia	3 (0.8)
Musculoskeletal and Connective Tissue Disorders	159 (44.7)
Back pain	59 (16.6)
Muscle spasms	38 (10.7)
Skin and Subcutaneous Tissue Disorders	155 (43.5)
Rash	69 (19.4)
Psychiatric Disorders	115 (32.3)
Insomnia	81 (22.8)
Source: EPAR [14]	

MedDRA = Medical Dictionary for Regulatory Activities; RVd = lenalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event; VTD = bortezomib, thalidomide, and dexamethasone.
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 for the RVd column.
Note: Treatment-emergent adverse events in each treatment phase were defined as any adverse events that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days (IFM 2009) after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 01 Dec 2016 for IFM 2009.

For the SWOG study the author highlights the following in the discussion section:

> *The trial was conceived in 2007 and accrued patients between 2008 and 2012. It encompassed a time in which bortezomib was given if possible, at maximum doses twice a week intravenously. This resulted in almost a quarter of patients assessable for toxic effects stopping BorLenDex induction treatment prematurely and 10% of those in the LenDex group.*

Associated with this was the significantly increased grade 3 or worse neuropathic and gastrointestinal adverse events with the BorLenDex regimen versus the LenDex regimen.

If bortezomib had been given subcutaneously as it is now, some more serious neuropathic side-effects could have been avoided and additional benefit might have been realised. [1]

PETHEMA GEM 2012 has so far only been published in an abstract. In the abstract the author does not draw any conclusions specifically for the patient population relevant for the present application. [12]

In the publication for IFM 2009, the author makes no specific remarks to the adverse event profile for the patient population relevant for this application, apart from the fact that the side effect profile was more favourable in the non-transplanted group than in the transplanted group. [11]

In the discussion on clinical safety in the EPAR, EMA states the following:

"With regard to the frailer and older population for the subjects of SWOG S0777, although the proportion of treatment discontinuation due to TEAE was higher than in other studies, especially in the BorLenDex arm, this can be partly attributed to study conduct including management of discontinuations during the initial treatment period, the receipt of subsequent AMT, and the management of toxicities, which was consistent with standard clinical practice. [14]

In SWOG S07777 study, BorLenDex is associated with more Grade 3 or 4 TEAE related to study drug and greater treatment discontinuation due to TEAEs during the entire treatment period compared to LenDex. [14]

The BorLenDex regimen was associated with comparable rates of TEAEs, for all grades as well as grades 3 and 4, with the VTD regimen. Fewer treatment discontinuations or dose reductions due to TEAE were reported in PETHEMA GEM2012. [14]

TEAEs (any grade) frequencies by SOC reported in SWOG S0777 for the Rd arm were consistent with the well-known lenalidomide + dexamethasone association safety profile. No new risk has been identified. [14]

TEAEs frequencies with BorLenDex were variable throughout the studies but addition of bortezomib to lenalidomide and dexamethasone led to an overall similar safety profile, notably with particularly increased risk for peripheral sensory neuropathy. This adverse effect, which occurs at a very common frequency as described in the bortezomib SmPC, may be reduced with a subcutaneous administration (SC) instead of intravenous infusion of the product. Due to differences in reporting of adverse effects, it seems that the preferred term "peripheral neuropathy" for PETHEMA GEM2012 actually might contain both peripheral sensory neuropathy and peripheral neuropathy and was not clearly reported. PETHEMA GEM2012 was the only study where subjects received SC bortezomib. [14]

In study SWOG S0777, subjects showed an increase in some TEAEs frequencies compared to the other studies, such as metabolism and nutrition disorders, investigations, musculoskeletal and connective tissue disorders and respiratory, thoracic, and mediastinal disorders, for both arms. [14]

Safety data from the integrated analysis comparing TEAE between BorLenDex and VTD should be assessed with caution as bortezomib route of administration, and so subsequent toxicity profile, was different for PETHEMA GEM2012 and IFM 2009 studies. Furthermore, some of TEAE rates in the BorThalDex cohorts (for example "Blood and Lymphatic System Disorders"), are not consistent between studies. For IFM studies, the comparison was made on a 12 weeks duration of therapy which is quite short. The safety data are mostly supportive. However, no new safety concerns seem to emerge from these data. [14]

The Grade 3 or 4 TEAEs frequencies were allocated similarly to the All grades frequencies. BorLenDex was associated with higher adverse events frequencies than LenDex, although these frequencies have to be considered taking into account the frailty and age of the population of the studies. Same grade 3 or 4 TEAEs were reported but at a lower frequency in studies PETHEMA GEM2012 and IFM 2009. [14]

Both PETHEMA GEM2012 and IFM 2009 studies in the integrated analysis showed an increase in grades 3 or 4 TEAEs for Blood and Lymphatic System Disorders for the BorLenDex regimen compared to the VTD regimen." [14]

Grade 3 and 4 adverse events

The Expert Committee has requested a qualitative review of all Grade 3 and 4 adverse events. The identified sources do not provide a complete overview of all such adverse events.

The most detailed data set is provided in the EPAR for Grade 3 and 4 adverse events occurring in more ≥5% of patients. These data are shown in Table 14 below.

In the narrative below information and conclusions sourced from the EPAR and two relevant publications will be included. [1, 11, 14]

Table 14 : Grade 3 or 4 TEAEs Reported in at Least 5% of Subjects in Any Treatment Arm – Initial Treatment – Studies PETHEMA GEM2012, IFM 2009 (Arm A), and SWOG S0777 (Safety Population)

System Organ Class Preferred Term[a]	**PETHEMA GEM2012**	**IFM 2009**	**SWOG S0777**	
	RVd[b] (4-week cycles × 6 = 24 weeks)	RVd[c] (3-week cycles × 8 = 24 weeks)	RVd (3-week cycles × 8 = 24 weeks)	Rd (4-week cycles × 6 = 24 weeks)
Subjects With ≥ 1 Grade 3 or 4 TEAE[d]	183 (40.0)	306 (86.0)	200 (76.3)	176 (68.8)
Blood and Lymphatic System Disorders	89 (19.4)	262 (73.6)	104 (39.7)	106 (41.4)
Neutropenia	59 (12.9)	159 (44.7)	26 (9.9)	42 (16.4)
Thrombocytopenia	29 (6.3)	66 (18.5)	45 (17.2)	24 (9.4)
Anemia	9 (2.0)	27 (7.6)	32 (12.2)	41 (16.0)
Lymphopenia	7 (1.5)	185 (52.0)	49 (18.7)	39 (15.2)
Leukopenia	5 (1.1)	127 (35.7)	23 (8.8)	29 (11.3)
Infections and Infestations	45 (9.8)	28 (7.9)	36 (13.7)	24 (9.4)
Infection	45 (9.8)	1 (0.3)	1 (0.4)	0
Lung infection	0	3 (0.8)	19 (7.3)	14 (5.5)
Nervous System Disorders	22 (4.8)	30 (8.4)	89 (34.0)	24 (9.4)
Syncope	1 (0.2)	1 (0.3)	23 (8.8)	7 (2.7)
Peripheral sensory neuropathy	0	18 (5.1)	54 (20.6)	4 (1.6)
Peripheral motor neuropathy	0	1 (0.3)	17 (6.5)	3 (1.2)
Respiratory, Thoracic, and Mediastinal Disorders	21 (4.6)	10 (2.8)	26 (9.9)	9 (3.5)
Dyspnea	0	2 (0.6)	16 (6.1)	3 (1.2)
Vascular Disorders	15 (3.3)	9 (2.5)	41 (15.6)	18 (7.0)
Hypotension	3 (0.7)	1 (0.3)	20 (7.6)	0
Embolism	0	0	18 (6.9)	16 (6.3)
Gastrointestinal Disorders	12 (2.6)	21 (5.9)	46 (17.6)	18 (7.0)
Diarrhea	4 (0.9)	7 (2.0)	24 (9.2)	4 (1.6)
General Disorders and Administration Site Conditions	10 (2.2)	21 (5.9)	49 (18.7)	29 (11.3)
Fatigue	0	9 (2.5)	38 (14.5)	26 (10.2)
Investigations	9 (2.0)	8 (2.2)	29 (11.1)	22 (8.6)
Alanine aminotransferase increased	3 (0.7)	3 (0.8)	13 (5.0)	4 (1.6)
Renal and Urinary Disorders	8 (1.7)	2 (0.6)	8 (3.1)	17 (6.6)
Renal failure acute	3 (0.7)	0	7 (2.7)	14 (5.5)

Musculoskeletal and Connective Tissue Disorders	6 (1.3)	22 (6.2)	45 (17.2)	30 (11.7)
Muscular weakness	0	0	22 (8.4)	11 (4.3)
Metabolism and Nutrition Disorders	4 (0.9)	18 (5.1)	85 (32.4)	70 (27.3)
Hyperglycemia	2 (0.4)	4 (1.1)	19 (7.3)	24 (9.4)
Hyponatremia	1 (0.2)	3 (0.8)	17 (6.5)	16 (6.3)
Hypokalemia	0	3 (0.8)	30 (11.5)	12 (4.7)
Hypocalcemia	0	2 (0.6)	17 (6.5)	21 (8.2)
Dehydration	0	0	22 (8.4)	6 (2.3)
Source: EPAR [14]				

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; Rd = lenalidomide and dexamethasone; RVd = lenalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[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 for the RVd column in the PETHEMA GEM2012 study.
[b] Both RVd arms combined. For the PETHEMA GEM2012 study, TEAEs include all SAEs plus non-SAEs that the investigator considered related to study treatment.
[c] For the purpose of comparison to the PETHEMA GEM2012 and SWOG S0777 studies, the 8 cycles (24 weeks) of initial RVd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment."
[d] Graded using CTCAE Version 4.03 for the PETHEMA GEM2012 study and Version 4.0 for the IFM 2009 and SWOG S0777 studies.
Note: Treatment-emergent adverse events in each treatment phase were defined as any AEs that began on or after the start of study drug in that phase through the day before the start date of the next phase, or through 30 days after the last dose of study drug if the phase was the last phase in the study.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 and SWOG S0777 studies.

In the EPAR discussion on clinical safety EMA concludes the following: *The Grade 3 or 4 TEAEs frequencies were allocated similarly to the All grades frequencies. BorLenDex was associated with higher adverse events frequencies than LenDex, although these frequencies have to be considered taking into account the frailty and age of the population of the studies. Same grade 3 or 4 TEAEs were reported but at a lower frequency in studies PETHEMA GEM2012 and IFM 2009.* [14]

Difference between intravenous and subcutaneous bortezomib

In the assessment of the adverse event profile of the combination of bortezomib, lenalidomide and dexamethasone, it is important to consider the fact that bortezomib was administered intravenously (i.v.) rather than subcutaneously (s.c.) in the SWOG study, and the authors emphasize the potential impact of i.v. rather than s.c. bortezomib administration.[1].

A randomised open-label phase 3 study by Moreau et al. [16] investigated the efficacy (non-inferiority) and safety of s.c. vs. i.v. administration of bortezomib .

The study confirmed non-inferiority for the efficacy outcomes (primary endpoint ORR), while the safety profile was found to improve with s.c. administration.

Grade 3 and higher AEs were reported in 57% (84/147) in the s.c. group and 70% (52/74) in the i.v. group.

Overall rates of e.g. gastrointestinal (including diarrhoea), respiratory, and nervous system disorders were 10% lower or more in the s.c. group.

Rates of peripheral neuropathy (PN) were also lower. PN of any grade (56 [38%] vs 39 [53%]; p=0·044), grade 2 or worse (35 [24%] vs 30 [41%]; p=0·012), and grade 3 or worse (nine [6%] vs 12 [16%]; p=0·026) was significantly less common with s.c. vs. i.v.

Risk factors for PN were well balanced between the groups. Subcutaneous administration was locally well tolerated.

Nowadays s.c. administration is included in the SmPC for bortezomib and is routine practice in the clinical setting. [17]

The SWOG trial was conceived in 2007 and accrued patients between 2008 and 2012. It encompassed a time in which bortezomib was given, if possible, at maximum doses twice a week and i.v. If bortezomib had been given subcutaneously as it is now, some more serious neuropathic side-effects could have been avoided and additional benefit might have been realised. [1]

In the Assessment Report the EMA concludes that:

TEAEs frequencies with BorLenDex were variable throughout the studies but addition of bortezomib to lenalidomide and dexamethasone led to an overall similar safety profile, notably with particular increased risk for peripheral sensory neuropathy. This adverse effect, which occurs at a very common frequency as described in Velcade SmPC, may be reduced with a subcutaneous administration (SC) instead of intravenous infusion of the product. [14],

This information should thus be taken into consideration when assessing the overall adverse event profile of BorLenDex.

Other relevant safety information for BorLenDex

The frequency and causes of deaths were consistent with the profile of the patient population and the underlying disease. [14]

There were no findings of an increase in secondary primary malignancies associated with adding bortezomib to the lenalidomide-dexamethasone combination. [14]

The higher age of subjects was associated with more TEAEs of any grade and also more TEAEs of grades 3 or 4, in the BorLenDex arm as well as in the LenDex arm. The safety profile the treatments seems to converge with advanced age, probably more related to the associated comorbidities rather than with the regimen of treatment itself. [14]

A more advanced disease, as characterized by the ISS Stage III, was associated with more grades 3 or 4 TEAE, treatment-emergent SAE or treatment discontinuation due to TEAE for all groups (BorLenDex or LenDex). [14]

Lower baseline creatinine clearance was associated with more grades 3 or 4 TEAE, treatment-emergent SAE or treatment discontinuation due to TEAE for all groups (BorLenDex or LenDex), which is consistent with the safety profile of lenalidomide. [14]

Frailer subjects (with an ECOG status ≥ 2) seem to be at higher risk for TEAEs of grades 3, 4, or 5 and treatment emergent SAEs. The small number of patients, precluding a robust assessment, should however be highlighted. [14]

Conclusion on adverse event profile

The AEs reported for RVd are consistent with the well-known safety profiles for bortezomib and lenalidomide respectively. As expected, there were more discontinuations in the BorLenDex arm mainly due to more peripheral neuropathy and gastrointestinal AEs, well-known side effects from bortezomib. These side effects that is expected to decrease with subcutaneous administration.

Even if great caution should be taken doing cross-trial comparisons, the lower rates of e.g. peripheral neuropathy and gastrointestinal AEs for RVd in the PETHEMA trial (s.c. administrations of bortezomib) compared to IFM and SWOG further supports this.

5.1.4 Qualitative review of adverse events for BorMelPred

The Expert Committee has requested a qualitative review of

- the most common side effects of any degree (occurring in> 10% of patients) and
- any grade 3-4 adverse reactions

reported in the clinical studies in which lenalidomide in combination with bortezomib has been studied as a treatment for newly diagnosed MM patients.

In addition, the Expert Committee has requested a similar review for BorMelPred.

The review for BorMelPred below is based on the version of the EMA EPAR for bortezomib where the pivotal phase III trial (VISTA) underlying the approval of the BorMelPred combination is assessed. [18]

In addition, data from the other BorMelPred studies included in this application has been included where relevant data are reported.

Patient exposure

The assessment by the EMA was based on the VISTA study and safety data from integrated safety data from 5 previous studies as described below.

Of the 682 subjects randomized into VISTA (VISTA), 677 subjects received at least 1 dose of study medication and are included in the safety population (340 treated with BorMelPred combination therapy and 337 treated with MelPred therapy).

In addition, the safety data from the BorMelPred treatment group in VISTA (VISTA) were compared with integrated safety data from 5 previous studies of single-agent bortezomib, used at the approved dose of 1.3 mg/m2, in subjects with previously treated multiple myeloma. The 5 studies included Studies M34100-024 (26 subjects), M34100-025 (202 subjects), M34101-039 (331 subjects), M34101-040 (449 subjects), and JPN-MM-101 (25 subjects). A combined total of 1,033 subjects with multiple myeloma received single-agent bortezomib in these studies. [18]

In addition, the additional studies identified for included in this application (UPFRONT, ALCYONE, GEM2005, GIMEMA and CLARION) report data for more than 1300 patients treated with BorMelPred.

Adverse events – overall incidence

The incidence of treatment-emergent adverse events is summarized in Table 15 for the BorMelPred and MelPred treatment groups in VISTA, as well as for single-agent bortezomib included in prior studies. As exposure was longer in VISTA than in prior studies in relapsed subjects, the incidence of adverse events was adjusted for length of exposure. [18]

Table 15 TEAEs for BorMelPred

	Previously Untreated				Previously Treated	
	Vc-MP (N=340)		MP (N=337)		VELCADE (N=1033)	
Description	Unadjusted, N (%)	Exposure-Adjusted[a]	Unadjusted, N (%)	Exposure-adjusted[a]	Unadjusted, N (%)[d]	Exposure-adjusted[a]
Any TEAE	338 (99)	2.2472	326 (97)	0.9310	1031 (>99)	4.6573
At least one Related[b]	331 (97)	1.2636	283 (84)	0.3255	1002 (97)	2.2450
At least one VELCADE-related	331 (97)	1.1354			1002 (97)	2.2450
Any Serious TEAE	155 (46)	0.0655	121 (36)	0.0477	541 (52)	0.1307
Grade 1	2 (1)	0.0006	12 (4)	0.0040	16 (2)	0.0027
Grade 2	32 (9)	0.0104	47 (14)	0.0170	174 (17)	0.0335
Grade 3	181 (53)	0.0901	148 (44)	0.0630	615 (60)	0.1708
Grade 4	96 (28)	0.0365	92 (27)	0.0351	225 (22)	0.0414
Grade 5	27 (8)	0.0082	27 (8)	0.0088	1 (<1)	0.0002
Grade≥3	304 (89)	0.2268	267 (79)	0.1398	841 (81)	0.2677
Terminated Treatment Due to AEs [c]	50 (15)	0.0076	47 (14)	0.0077	356 (34)	0.0650
At least one related[b]	37 (11)	0.0056	35 (10)	0.0057	236 (23)	0.0423
At least one VELCADE-related	33 (10)	0.0050	NA	NA	236 (23)	0.0423
Discontinued VELCADE Due to AEs	108 (32)	0.0379	NA	NA	356 (34)	0.0650

Vc-MP=VELCADE-melphalan-prednisone; MP=melphalan-prednisone; TEAE=treatment emergent adverse event; AE=adverse event

[a] Exposure-adjusted incidence rate equals the number of subjects with events divided by the sum of time to first event (in patient-months).

[b] For Study MMY-3002, it includes all adverse events that were related to 1 of the 3 study drugs: VELCADE, melphalan, or prednisone.

[c] For Study MMY-3002, it includes those subjects indicated as having discontinued treatment due to an adverse event on the treatment termination case report form page.

[d] In the VELCADE group, Grade 5 is only available in the JPN-MM-101 study (total N for JPN-MM-101 is 25).

In VISTA, nearly all subjects in both treatment groups were reported to have at least 1 treatment-emergent adverse event. [18]

Adverse events in ≥10 % of the patients

The Expert Committee has asked for data for adverse events occurring in more than 10 % of the patients. Such data are not specified neither in the identified publications not in the bortezomib EPAR.

The EPAR provides the most detailed information which is however with a cut-off at more than 20 % of the patients for BorMelPred.

The most common treatment-emergent adverse events (≥20% of subjects in any group) for the BorMelPred, MelPred, and pooled single-agent bortezomib treatment groups are summarized in Table 16. [18]

Table 16 TEAEs in ≥ 20% of patients for BorMelPred

	---------- Previously Untreated ----------		Previously Treated
	Vc-MP	MP	VELCADE
MedDRA System Organ Class	(N=340)	(N=337)	(N=1033)
Preferred Term	n (%)	n (%)	n (%)
Total no. Subjects with TEAE	338 (99)	326 (97)	1031 (>99)
Blood and Lymphatic System Disorders	279 (82)	259 (77)	629 (61)
Anaemia	147 (43)	187 (55)	344 (33)
Leukopenia	113 (33)	100 (30)	75 (7)
Lymphopenia	83 (24)	58 (17)	51 (5)
Neutropenia	165 (49)	155 (46)	201 (19)
Thrombocytopenia	178 (52)	159 (47)	408 (39)
Gastrointestinal Disorders	262 (77)	185 (55)	907 (88)
Constipation	125 (37)	54 (16)	432 (42)
Diarrhoea	157 (46)	58 (17)	570 (55)
Nausea	164 (48)	94 (28)	593 (57)
Vomiting	112 (33)	55 (16)	359 (35)
General Disorders and Administration Site Conditions	239 (70)	199 (59)	862 (83)
Asthenia	73 (21)	60 (18)	205 (20)
Fatigue	98 (29)	86 (26)	486 (47)
Oedema Peripheral	68 (20)	34 (10)	196 (19)
Pyrexia	99 (29)	64 (19)	393 (38)
Metabolism and Nutrition Disorders	159 (47)	124 (37)	554 (54)
Anorexia	77 (23)	34 (10)	268 (26)
Nervous System Disorders	253 (74)	122 (36)	775 (75)
Headache	49 (14)	35 (10)	241 (23)
Neuralgia	121 (36)	5 (1)	77 (7)
Neuropathy Peripheral	11 (3)	1 (<1)	281 (27)
Peripheral Sensory Neuropathy	151 (44)	16 (5)	87 (8)
Psychiatric Disorders	112 (33)	76 (23)	411 (40)
Insomnia	69 (20)	43 (13)	208 (20)
Respiratory, Thoracic and Mediastinal Disorders	133 (39)	123 (36)	585 (57)
Cough	71 (21)	45 (13)	213 (21)
Dyspnoea	50 (15)	44 (13)	220 (21)
Skin and Subcutaneous Tissue Disorders	140 (41)	80 (24)	487 (47)
Rash	66 (19)	24 (7)	205 (20)

MedDRA=Medical Dictionary for Regulatory Activities; Vc-MP=VELCADE-melphalan-prednisone; MP=melphalan-prednisone; no.=number; TEAE=treatment emergent adverse event
Note: Percentages calculated with the number of subjects in each group as denominator.

Grade 3/4 adverse events

Data for this narrative is primarily sourced from the bortezomib EPAR. [18]

Please refer to Danish Medicines Council Background for The Medicines Council treatment guideline for multiple myeloma (attachment 7, table T) [15] for data for the UPFRONT, ALCYONE, GEM2005, VISTA and GIMEMA studies.

As the CLARION study [10] had not been published at the time of the Medicines Council assessment, data for this study is provided in Table 17 in a format similar to tabularization used by the Medicines Council for ease of comparison.

Grade 3/4 adverse events for BorMelPred based on the EPAR

In the VISTA study the incidence rate was higher in the BorMelPred treatment group than the MelPred treatment group for Grade 3 adverse events (53% vs. 44%) and serious adverse events (46% vs. 36%). However, the incidences were similar for Grade 4 adverse events (28% vs. 27%), Grade 5 adverse events (8% for both), and adverse events leading to treatment termination (15% vs. 14%).[18]

Comparison of the BorMelPred and single agent bortezomib groups revealed a similar incidence of bortezomib related events (97% for both) and serious adverse events (46% vs. 52%) (Table 4). However, when analyzed by length of exposure, the incidence rates (per patient-months) appeared to be lower for BorMelPred than for single-agent bortezomib for these 2 types of events. [18]

Exposure-adjusted incidence rates for the BorMelPred and single-agent bortezomib treatment groups were 1.1354 vs. 2.2450 events per patient month for bortezomib related adverse events, and 0.0655 and 0.1307 events per patient-month for serious adverse events. [18]

The incidence of Grade ≥3 adverse events was 89% for BorMelPred and 81% for single-agent bortezomib. The exposure-adjusted incidence rate of Grade ≥3 events appeared to be lower for BorMelPred than for single-agent bortezomib (0.2268 vs. 0.2677 events per patient-month). The incidence of termination of all study treatment because of adverse events was 15% for the BorMelPred treatment group and 34% for the single-agent bortezomib treatment group, corresponding to exposure-adjusted incidence rates of 0.0076 and 0.0650 events per patient-month, respectively. The incidence of adverse events leading to bortezomib discontinuation was similar with BorMelPred treatment (32%) and single-agent bortezomib (34%). The exposure-adjusted incidence rate again appeared to be lower for BorMelPred than for single-agent bortezomib (0.0379 vs. 0.0650 events per patient-month, respectively). [18]

In conclusion, for all adverse event groups summarized in Table 15, the exposure-adjusted incidence rates were similar (and for several groups even lower) for the BorMelPred treatment group as compared with the single-agent bortezomib treatment group.

Safety in special populations

Subgroup analyses were performed with respect to adverse events to evaluate the safety of BorMelPred in different special populations. These analyses showed a similar safety profile across age and gender. For the BorMelPred regimen, the adverse event profile for subjects with moderate renal function impairment (30 to 60 mL/min creatinine clearance) was similar to the profile for subjects without renal function impairment (>60 mL/min creatinine clearance). [18]

Discussion on clinical safety

The EMA concludes the following on the safety profile of BorMelPred:

The safety profile of bortezomib in combination with MelPred in VISTA was consistent with the known safety profiles of both bortezomib and MelPred. No new safety concerns emerged for BorMelPred relative to what has been observed for each of its components. [18]

The safety profile of MelPred was as expected in this patient population: major side effects of MelPred were consistent with those described in previous studies. [18]

The safety profile was comparable between BorMelPred and single-agent bortezomib used in prior studies, despite the older patient population in the BorMelPred treatment group as compared with the single-agent bortezomib treatment group (median age, 71 and 60 years, respectively). [18]

The most frequently reported adverse events for the BorMelPred treatment group were as expected based on the known toxicity profile of each of the 3 individual agents. [18]

Although peripheral neuropathy events were more common with BorMelPred treatment than with single-agent bortezomib treatment (47% vs. 37%, respectively), the incidence of Grade ≥3 peripheral neuropathy events was similar (13% and 11%) and serious events were uncommon for both groups (1% each). Exposure-adjusted incidence rates, as well as relationship to cumulative dose and time to onset of peripheral neuropathy events, were similar between treatment groups. The reversibility of peripheral neuropathy has been documented in the majority of cases for subjects receiving BorMelPred (74% improvement or recovery). [18]

The addition of MelPred to bortezomib treatment did not appear to affect the cumulative dose at onset or the time to onset of peripheral neuropathy events. [18]

Overall, the number of serious adverse events was 10% higher in the BorMelPred group than in the MelPred group in this study as well as the number of deaths and adverse events Grade>3. Particularly, in the beginning of the treatment (Cycles 1-4) there were more adverse events in the BorMelPred group than in the control group. However, during the next cycles (5-9) the tolerability of BorMelPred treatment was similar to that of MelPred treatment group. Therefore, no new safety concerns arise with the longer duration of treatment of 54 weeks. [18]

Grade 3/4 adverse events in the CLARION study

Data for adverse events reported in the CLARION study has been sourced from Facon et al. [10]

For ease of comparison with data from other relevant studies the data has been tabularized in line with the tabularization in the Medicines Council's Background for The Medicines Council treatment guideline for multiple myeloma (attachment 7, table T). [15]

Table 17 Grade 3/4 AEs in the CLARION study

CLARION safety population		**BorMelPred**		**CarMelPred**	
Number of patients, n		470		474	
	AE term used in publication*	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Neutropenia		146 (31.1)	64 (13.6)	170 (35.9)	107 (22.6)
Peripheral neuropathy	PN and peripheral sensory neuropathy	219 (46.6)	44 (9.4)	37 (7.8)	1 (0.2)
Edema		NR	NR	NR	NR
Heart failure	Cardiac failure	10 (2.1)	7 (1.5)	31 (6.5)	24 (5.1)
Hypertension		32 (6.8)	14 (3.0)	104 (21.9)	43 (9.1)
Dyspnoea		36 (7.7)	3 (0.6)	76 (16.0)	16 (3.4)
Ischemic heart disease		NR	NR	NR	NR
Muscle cramps		NR	NR	NR	NR
Viral infection	Upper respiratory tract infection	51 (10.9)	7 (1.5)	51 (10.8)	4 (0.8)
Infusion related reactions		NR	NR	NR	NR
Lymphocytopenia	Lymphopenia/lymphocyte count decreased	34 (7.2)	24 (5.1)	37 (7.8)	23 (4.9)
Lymphopenia	Leukopenia/white blood cell count decreased	94 (20.0)	60 (12.8)	81 (17.1)	42 (8.9)
Thrombocytopenia	Thrombocytopenia/platelet count decreased	151 (32.1)	99 (21.1)	127 (26.8)	73 (15.4)
Anemia		146 (31.1)	64 (13.6)	174 (36.7)	80 (16.9)

Hypogammaglobulinemia		NR	NR	NR	NR
Pneumonia	Lung infection	17 (3.6)	13 (2.8)	12 (2.5)	10 (2.1)
Herpes zoster		NR	NR	NR	NR
Diarrhoea		133 (28.3)	27 (5.7)	96 (20.3)	6 (1.3)
Obstipation	Constipation	114 (24.3)	6 (1.3)	66 (13.9)	2 (0.4)
Nausea		133 (28.3)	2 (0.4)	168 (35.4)	6 (1.3)
Vomiting		91 (19.4)	6 (1.3)	118 (24.9)	7 (1.5)
Insomnia		65 (13.8)	2 (0.4)	49 (10.3)	1 (0.2)
Cataract		NR	NR	NR	NR
SPM		NR	NR	NR	NR
Confusion		NR	NR	NR	NR
Agitation		NR	NR	NR	NR
Irritability		NR	NR	NR	NR
Mood disturbances		NR	NR	NR	NR
Psychosis		NR	NR	NR	NR
Depression		NR	NR	NR	NR
Thrombosis, leg		NR	NR	NR	NR
Thrombosis, lung		NR	NR	NR	NR
Fatigue		85 (18.1)	17 (3.6)	79 (16.7)	6 (1.3)
Other					
Pyrexia		86 (18.3)	2 (0.4)	172 (36.3)	10 (2.1)
Peripheral edema		54 (11.5)	2 (0.4)	84 (17.7)	4 (0.8)
Asthenia		85 (18.1)	17 (3.6)	72 (15.2)	18 (3.8)
Decreased appetite		88 (18.7)	7 (1.5)	67 (14.1)	1 (0.2)
Hypokalemia		63 (13.4)	28 (6.0)	53 (11.2)	16 (3.4)
Cough		63 (13.4)	0 (0)	63 (13.3)	0 (0)
Back pain		59 (12.6)	5 (1.1)	57 (12.0)	7 (1.5)
Rash		49 (10.4)	4 (0.9)	26 (5.5)	1 (0.2)
Acute kidney injury		13 (2.8)	7 (1.5)	30 (6.3)	20 (4.2)
Renal failure		7 (1.5)	3 (0.6)	29 (6.1)	14 (3.0)
Hyponatriemia		26 (5.5)	15 (3.2)	17 (3.6)	9 (1.9)
Hypotension		42 (8.9)	16 (3.4)	20 (4.2)	3 (0.6)
* if different from the term used in the Medicines Council tabularization [15] Source: table 3 [10]					

Overall the safety profile for BorMelPred as used in the CLARION study is consistent with the safety profile of BorMelPred in the other BorMelPred studies included in this application (UPFRONT, ALCYONE, GEM2005, VISTA and GIMEMA).

Summary of adverse events for BorMel Pred

The overall safety profile of BorMelPred has been well described by the EMA (see above) when assessing the data from the phase III VISTA study.

Safety data from the other studies identified for use in this application (UPFRONT, ALCYONE, GEM2005, GIMEMA and CLARION) is consistent with the safety profile described and assessed by the EMA.

5.1.5 Comparative analyses

The comparative analysis should be viewed in light of a recent meta-analysis by Weisel et al, where LenDex was associated with a significant PFS and survival advantage versus other first-line treatments, including BorMelPred.[19]

The meta-analysis showed that the Hazard Ratio (95% CI) for Overall Survival for LenDex compared to BorMelPred was 0.66 (0.46-0.93), and for Progression Free Survival was 0.70 (0.49-0.99). [19]

As BorLenDex as shown in the SWOG study is significantly more effective than LenDex, there is a strong indication that BorLenDex is also superior to BorMelPred.

BorLenDex vs LenDex

As the comparison between BorLenDex and LenDex is based on the SWOG S0777 study only, the data for comparison is described in the study data section above on p. 22 and in the study data table Results per study - tables

Table 33 below.

BorLenDex vs BorMelPred

Data for OS, PFS and Discontinuation rates due to TEAEs from the identified studies with a study arm receiving BorMelPred has been tabularised in the table below. Similar data for BorLenDex has been included for the sake of comparison.

Table 18 Overview of data for OS, PFS and Discontinuation rates due to TEAEs for BorMelPred studies

Study name	**Study arm**	**Follow-up time, months**	**Overall survival, months**	**Progression Free Survival, months**	**Discontinuation rate**
SWOG	BorLenDex	55	89.1	41.7	22.7%*
UPFRONT	BorMelPred	42.7	53,1	17,3	38.3%
GEM2005	BorMelPred	72	63	32	12%
ALCYONE	BorMelPred	16.5	NR	18.1	9.3%
GIMEMA	BorMelPred	54	60.6	24.8	16.7%
VISTA	BorMelPred	60.1	56.4	21.7	15%
CLARION	BorMelPred	22	NR	22.1	14.7%
NR: Not reached * During the induction period[14]					

In the Medicines Council's recently published guideline the Medicines Council has highlighted the important points of notice for each of the relevant studies.

Emphasis should be put on the following

- Administration form and schedule of bortezomib (i.v. versus s.c. and once weekly vs. twice weekly may impact the adverse event profile and thereby the discontinuation rate due to TEAEs)
- Baseline demographics for the study population in the studies differ in several parameters (see Table 6 and Table 7)
    - While inconsistently reported in most studies it should be noted that 33% of the patients in the SWOG study have a high risk cytogenetic profile.[14]
- Follow-up time for the studies ranges from 16.5 to 60.1 months
- The discontinuation due to TEAEs may be reported with great variability as in the VISTA study where discontinuation of bortezomib alone did not count as discontinuation. (see details below).

Overall survival

The above data on overall survival show that Overall Survival for BorLenDex with 89.1 months is more than 20 months longer than all the BorMelPred arms (53.1-63), except for ALCYONE and UPFRONT where OS is not yet reported.

This in addition to the already presented data where BorLenDex is significantly better than LenDex alone.

Progression Free Survival

The above data on Progression Free Survival show that Progression Free Survival for BorLenDex with 41.7 months is close to 10 months longer than all the BorMelPred arms (17.2-32).

Discontinuations due to TEAEs

When assessing this outcome, it is important to bear in mind that the bortezomib was administered intravenously in most of these studies in contrast to the current standard of subcutaneous administration which has a more favourable safety profile. [16] Further details on the difference in safety profile depending on method of administration are available on p. 34.

Table 19 Discontinuation rates in the BorMelPred arms of the comparator studies

	Discontinuation rate	Bor admin.	Bor Once or twice weekly
SWOG[14]	22.7%	i.v.	8 cycles of 21 days 1,3 mg/m2 for 4 days/cycle
VISTA[2]	15%	i.v.	9 cycles of 42 days 1,3 mg/m2; 8 days in 1.-4. cycle, 4 days i 5.-9. cycle
GEM2005[13]	12 %	i.v.	6 cycles of 42 days 1,3 mg/m2, twice weekly, in 1. cycle, then once weekly
GIMEMA[5]	16.7%	i.v.	9 cycles of 42 days 1.3 mg/m2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9; Changed to 9 35-day cycles where the bortezomib dose was modified to 1.3 mg/m2 on days 1, 8, 15, and 22 (cycles 1-9).
ALCYONE[8]	9.3 %	i.c.	9 cycles of 42 days 1,3 mg/m^2, 1 time/week in the first cycle, then twice weekly
UPFRONT[9]	38.3%	i.v.	8 cycles, 21 days 1,3 mg/m2 i 4 days/cycle followed by maintenance (five 35-day cycles) 1.6 mg/m^2, days 1, 8, 15, and 22).
CLARION	14.7%	i.v. or s.c.	9 cycles of 42 days IV or subcutaneously at 1.3 mg/m² during cycles 1 to 4 on days 1, 4, 8, 11, 22, 25, 29, and 32 followed by 1.3 mg/m² during cycles 5 to 9 on days 1, 8, 22, and 29.

There is a relatively broad range of frequency of discontinuation due to TEAEs. This may be caused by several factors

- Timing of reporting e.g. following induction therapy only or including the subsequent maintenance therapy (when applicable)
- The possibility of partial discontinuation not being reported as full discontinuation – see below for the VISTA study

In the SWOG study treatment with BorLenDex resulted in discontinuations in 22.7% of patients as compared to 9.6% in the LenDex group, a difference of 13.1 percentage points with reporting for the period patients were in treatment with BorLenDex.[1, 14]

In the VISTA study treatment with BorMelPred resulted in discontinuation in 14% (47/338) patients as compared to 15% (50/344) in the MelPred group. This is a relative difference of 1.053 (0.669-1.659), p=0.8.[2]

In the VISTA study the investigator had the option of discontinuing bortezomib only in the BorMelPred group of patients, allowing the patient to continue on MelPred alone, why the numbers above not necessarily fully reflect the discontinuation rate due to adverse event for bortezomib. [2]

Data from the bortezomib EPAR are tabularized below:

Table 20 Discontinuations due to TEAE - VISTA study

	BorMelPred (N=340) N (%)	**MelPred (N=337) N (%)**
Terminated treatment due to AEs	50 (15)	47 (14)
At least one related	37 (11)	35 (10)
At least on bortezomib related	33 (10)	NA
Discontinued bortezomib due to AEs	108 (32)	NA
Source: EPAR Bortezomib [18]		

Including numbers for bortezomib discontinuation only in the assessment, full or partly discontinuation rate for the BorMelPred regimen can be calculated to 46.5% (158 patients) as compared to 14% (47 patients) in the MelPred group. [18]

This should be seen in the light of the 22.7% discontinuation rate for BorLenDex in the SWOG study. [1, 14]

Health Related Quality of Life

Collection of data on quality of life was not included in the study design of the SWOG S0777 study, why no results can be presented.

Qualitative review of adverse events.

The Expert Committee has requested a qualitative review of adverse events (occurring in> 10% of patients) and all grade 3 and 4 adverse reactions for BorLenDex (see p. 26) and BorMelPred (see p. 37).

The safety profiles of BorLenDex and BorMelPred are as expected from the AE profile of the individual treatments, and choice of treatment should be based on an individual assessment of the patients needs.

Summary of the narrative comparison

In summary BorLenDex has been shown to improve both Overall Survival and Progression Free Survival as compared to LenDex.

The rate of discontinuation due to TEAE is higher than for LenDex. However, the current clinical practice of using subcutaneous bortezomib rather than intravenous bortezomib as in the SWOG study, the discontinuation rate in daily clinical practice can be assumed to be lower that reported in the study. The qualitative review of the adverse event profile indicates that, that the profile is well known and clinically manageable.

The narrative comparison to BorMelPred indicate that treatment BorLenDex results in longer Overall Survival and Progression Free Survival than BorMelPred.

As a recent meta-analysis by Weisel et al showed that the Hazard Ratio (95% CI) for Overall Survival for LenDex compared to BorMelPred was 0.66 (0.46-0.93), and for Progression Free Survival was 0.70 (0.49-0.99). [19] As BorLenDex, as shown in the SWOG study, is significantly more effective than LenDex, there is a strong indication that BorLenDex is also superior to BorMelPred.

The discontinuation rate for BorLenDex seems at a comparable level with BorMelPred.

5.2 Other considerations

The expert committee wants information that can shed light on an assessment of whether and how the introduction of the applied intervention in Danish clinical practice will affect treatments in subsequent treatment lines in terms of type, duration and expected effect.

Prediction of the management of patients with multiple myeloma even in the not very remote future is a challenge considering the quickly changing treatment landscape.

The assumption for this response is that BorLenDex in previously untreated patients who are not eligible for transplant is administered according to the SmPC for 8 cycles, followed by LenDex maintenance treatment until progression (or discontinuation due to adverse events or other).

The implementation of this treatment approach will result in more patient treated with Len in first line which is likely to result in an increasing number of patients considered refractory to lenalidomide at 1st relapse.

In the recently published guideline by the Medicine Council refractory patients are defined as patients who progressed during full-dose treatment or within 60 days of discontinuation of full-dose treatment. At first relapse, the majority (70%) of lenalidomide refractory patients should, as recommended in the guideline, be treated with daratumumab in combination with bortezomib, and dexamethasone (DaraBorDex). Carfilzomib + dexamethasone (CarDex) is to be considered for the remainder of patients. [15]

These recommendations are based on the CASTOR (DaraBorDex vs. BorDex) and ENDEAVOR (CarDex vs. BorDex) studies respectively [20-23]. These studies, however, enrolled only a smaller percentage of lenalidomide exposed patients (19-38%) and only a few lenalidomide refractory patients (24%).

To our knowledge, the only randomized phase III trial to include a population where 100% of the patients had been previously been treated with lenalidomide, a substantial proportion (70%) were lenalidomide refractory, and hence the only randomized phase III trial to provide robust scientific evidence for the treatment of this specific group of patients, is the OPTIMISMM trial (PomBorDex vs. BorDex). [24] The trial showed that PomBorDex significantly improved PFS (11.2 vs 7.1 months, HR 0.61) compared to BorDex. In the pre-specified subgroup of patients having received only one prior line of therapy PFS was 20.73 months for PomBorDex (95% CI 15.11–27·99) vs 11.63 months for BorDex 7.52–15.74) (HR 0·54, 95% CI 0.36–0.82; p=0·0027). [24]

In summary the introduction of BorLenDex as 1st line treatment in Danish clinical practice, will increase the number of lenalidomide refractory patients and thereby increase the need for combinations that do not include lenalidomide. Thus, the use of e.g. DaraLenDex can be expected to decrease, while the use of combinations containing proteasome inhibitors (e.g. DaraBorDex, CarDex, and PomBorDex) can be assumed to increase. The current Medicine Council's guideline recommends DaraBorDex as the first choice in lenalidomide refractory patients after 1st relapse, but recent data from the OPTIMISMM trial support the introduction of a pomalidomide-based regimen (PomBorDex) immediately after lenalidomide treatment failure for management of relapsed or refractory multiple myeloma [24], and may challenge this recommendation The decision on the exact use of the available different combinations should depend on the availability of robust data as well as the clinical assessment for the individual patient.

6 References

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7 Appendices

7.1 Systematic literature review

An overview of the general methodology has been provided in section 4.

7.1.1 Data extraction criteria

The following data extraction criteria were applied.

Study characteristics:

- Study name
- Study design (e.g. number of arms, double blind, open label, crossover of control group after disease progression, etc.)
- Study inclusion criteria (including line of treatment)
- Study exclusion criteria
- Year of study initiation and study close
- Location of study
- Follow-up period
- Median follow up overall, and by treatment arm
- Sample size, total and by intervention
- Outcome definitions
- Quality appraisal

Intervention:

- Treatment regimen
- Type of therapy
- Treatment dose
- Frequency of administration/number of doses
- Duration of treatment
- Mean number of cycles received
- Route of administration
- Concomitant/background therapies

Patient characteristics:

- Sample size at baseline
- Age
- Gender
- Race and ethnicity
- ECOG performance status/WHO performance status/Karnofsky performance status
- International staging system stage (ISS)
- Smoking status (historical and current)
- History of bone lesions
- Creatinine clearance, anaemia, hypercalcaemia,
- Cytogenetics, light chains, paraprotein class

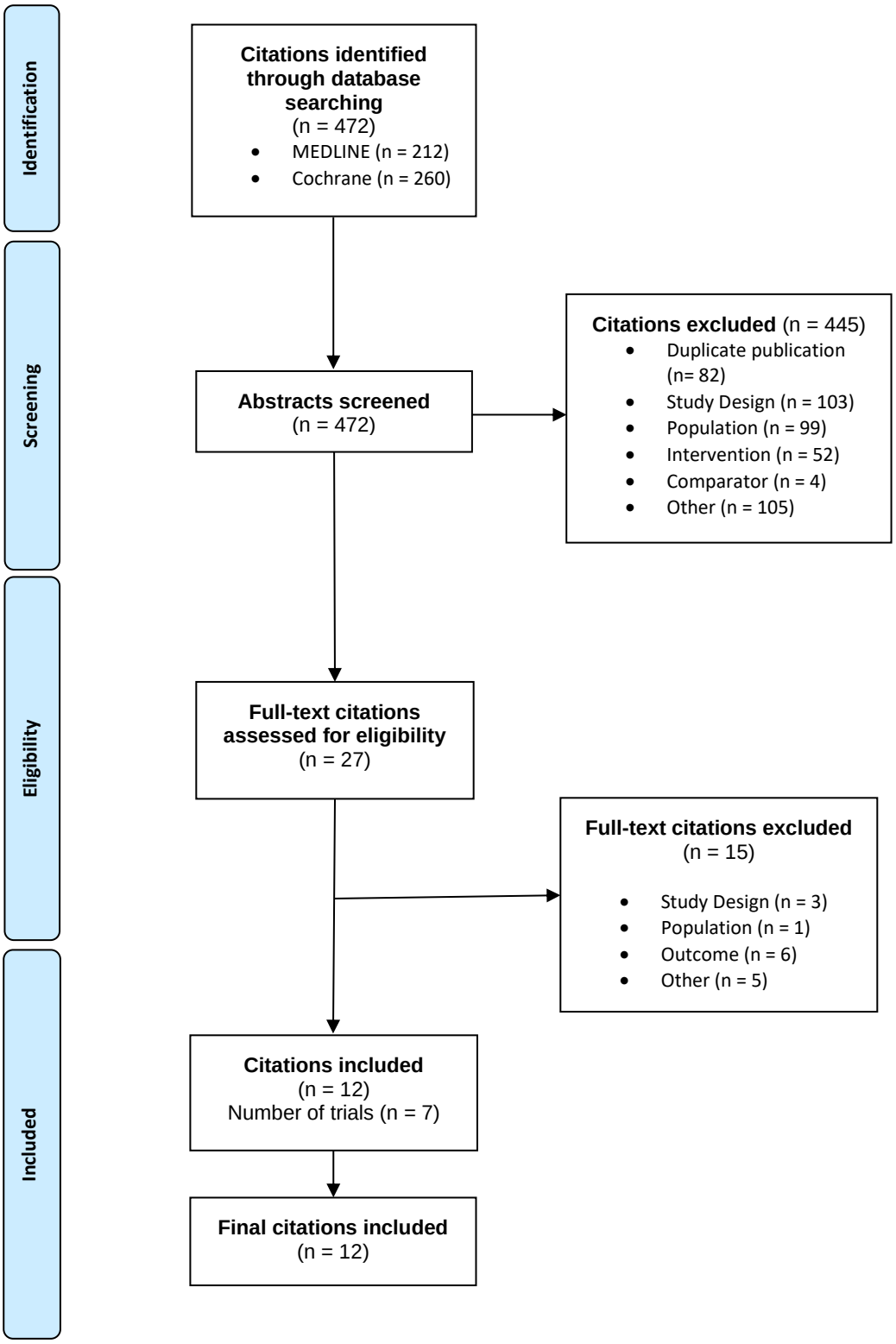
Outcomes:

With regards to efficacy, we extracted the following:

- Overall survival
- Progression-free survival
- Response rate (according to RECIST criteria)
    - Complete response
    - Very good partial response
    - Partial response
    - Stable disease
    - Progressive disease

7.1.2 PRISMA diagram for SLR

Figure 2 PRISMA diagram for SLR



7.1.3 MEDLINE – Search strategy

The search was executed on 23. April 2019 using the search string provided by the Medicines Council.

Table 21 MEDLINE search string

Line	Search term	Hits
1	"Multiple Myeloma"[Mesh]	38944
2	myeloma*[tiab] OR ndmm*[tiab] OR (kahler*[tiab] AND (disease[tiab] OR morbus[tiab]))	51080
3	#1 OR #2	58055
4	"lenalidomide"[Mesh]	2292
5	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]	3778
6	#4 OR #5	4103
7	"bortezomib"[Mesh]	5143
8	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]	7559
9	#7 OR #8	8243
10	"dexamethasone"[Mesh]	49763
11	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]	55921
12	#10 OR #11	70158
13	#6 AND #9 AND #12	652
14	Melphalan[Mesh]	7547
15	melphalan*[tiab] or melphelan*[tiab] or melfalan*[tiab] or medphalan*[tiab] or merphalan*[tiab] or sarcolysin*[tiab] or sarkolysin*[tiab] or alkeran*[tiab] or "phenylalanine mustard"[tiab]	8042
16	#14 OR #15	10758
17	Prednisone[Mesh]	38365
18	prednisone*[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 decortin*[tiab] or dacortin*[tiab] or decortisyl*[tiab] or deltason*[tiab] or encorton*[tiab] or liquid-pred*[tiab] or meticorten*[tiab] or panasol*[tiab] or prednidib*[tiab] or pronison*[tiab] or sone*[tiab]	28379
19	#17 OR #18	52053
20	#16 AND #9 AND #19	253
21	#13 OR #20	811
22	#3 AND #21	747
23	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans [mh])	1155204
24	#22 AND #23	212

7.1.4 COCHRANE Central Register of Controlled Trials – search string

The search was executed on 23. April 2019 using the search string provided by the Medicines Council.

Table 22 COCHRANE search string

Line	Search term	Hits
1	[mh "Multiple Myeloma"]	1339
2	(myeloma* or ndmm* or ((kahler or kahler's or kahler*) next (disease or morbus))):ti,ab,kw	4983
3	{or # 1 - # 2}	4983
4	[mh Lenalidomide]	141
5	(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	1644
6	{or # 3 - # 4}	1644
7	[mh Bortezomib]	330
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	1739
9	{or # 7 - # 8}	1739
10	[mh Dexamethasone]	3899
11	(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	10300
12	{or #10 - #11}	10318
13	#6 and #9 and #12	443
14	[mh Melphalan]	636
15	(melphalan* or melphelan* or melfalan* or medphalan* or merphalan* or sarcolysin* or sarkolysin* or alkeran* or "phenylalanine mustard"):ti,ab,kw	2006
16	{or # 14 - # 15}	2021
17	[mh Prednisone]	3650
18	(prednisone* 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	8968
19	{or #17-#18}	8968
20	#16 and #9 and #19	188
21	#13 or #20	561
22	#3 and #21	546
23	conference abstract:pt	143005
24	#22 not #23	260

7.1.5 Excluded publications after full text review

Table 23 Studies excluded after full text review

Author	Year	Title	Reason for exclusion
Delforge et al	2012	Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with vmp vs. Mp: Results from the vista trial	Outcomes
Delforge et al	2011	Fewer bone disease events, improvement in bone remodeling, and evidence of bone healing with bortezomib plus melphalan-prednisone vs. Melphalan-prednisone in the phase iii vista trial in multiple myeloma	Outcomes
Dimopoulos et al	2009	Vmp (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: Cohort analysis of the phase iii vista study	Outcomes
Facon et al	2018	Final analysis of survival outcomes in the phase 3 first trial of up-front treatment for multiple myeloma	Other
Gentile et al	2017	Lenalidomide and low-dose dexamethasone (rd) versus bortezomib, melphalan, prednisone (vmp) in elderly newly diagnosed multiple myeloma patients: A comparison of two prospective trials	Study design
Harousseau et al	2010	Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: Analysis of the phase 3 vista study of bortezomib plus melphalan-prednisone versus melphalan-prednisone	Outcomes
Mateos et al	2015	Effect of cumulative bortezomib dose on survival in multiple myeloma patients receiving bortezomib-melphalan-prednisone in the phase iii vista study	Study design
Morabito et al	2011	Safety and efficacy of bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (vmpt-vt) versus bortezomib-melphalan-prednisone (vmp) in untreated multiple myeloma patients with renal impairment	Population
Nair et al	2010	Superior results of total therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with vrd maintenance	Study design
Palumbo et al	2008	Prolonged therapy with bortezomib plus melphalan-prednisone (vmp) results in improved quality and duration of response in the phase iii vista study in previously untreated multiple myeloma (mm)	Other
Richardson et al	2011	Characterization of haematological parameters with bortezomib-melphalan-prednisone versus melphalan-prednisone in newly diagnosed myeloma, with evaluation of long-term outcomes and risk of thromboembolic events with use of erythropoiesis-stimulating agents: Analysis of the vista trial	Outcomes
San-Miguel et al	2007	Mmy-3002: A phase 3 study comparing bortezomib-melphalan-prednisone (vmp) with melphalan-prednisone (mp) in newly diagnosed multiple myeloma	Outcomes
San-Miguel et al	2011	Continued overall survival benefit after 5 years' follow-up with bortezomib-melphalan-prednisone (vmp) versus melphalan-prednisone (mp) in patients with previously untreated multiple myeloma, and no increased risk of second primary malignancies: Final results of the phase 3 vista trial	Other
San-Miguel et al	2008	Updated follow-up and results of subsequent therapy in the phase iii vista trial: Bortezomib plus melphalan-prednisone versus melphalan-prednisone in newly diagnosed multiple myeloma	Other
San-Miguel et al	2008	Superior efficacy with bortezomib plus melphalan-prednisone (vmp) versus melphalan-prednisone (mp) alone in previously untreated multiple myeloma (mm): Results of the phase iii mmy-3002 vista study	Other

7.2 Overview of data cut-off and censoring differences

The first patient in the SWOG study was randomized on July 28, 2008 and the last patient was randomized on February 2, 2012. Results of the primary analysis performed by SWOG based on the eligible (per protocol) patient population were published with the data cutoff date of November 5, 2015. Data were collected according to SWOG and NIH standards. In the original SWOG protocol, patients who discontinued treatment were followed for disease progression or survival for a maximum of 6 years after initial registration.

The SWOG S0777 study was a cooperative group study not originally designed to support regulatory application for marketing authorization. Celgene has obtained rights to the data for this study in order to develop a dataset appropriate to support submissions to health authorities. To enable a complete, updated analysis of a more mature dataset, with longer follow-up, and to ensure a standard of data quality consistent with the requirements of regulatory authorities, the following monitoring and collection procedures were implemented:

- The protocol was amended to extend the duration of follow-up until the end of 2018.
- Celgene collaborated with SWOG to collect additional elements and conduct retrospective source document verification (SDV) to enable a more detailed and updated analysis of the dataset.
- Intent-to-treat (ITT) population: Of the 525 randomized patients in the SWOG publication, 21 patients in the BorLenDex arm and 31 patients in the LenDex arm were deemed ineligible based mainly on missing, insufficient, or early or late baseline laboratory data. Celgene worked with SWOG to complete a comprehensive update of the database, analysing all randomized patients.
- Independent response adjudication committee (IRAC) review: An IRAC, consisting of hematologists with expertise and experience in the diagnosis and management of MM, was established to review the data and provide a retrospective, independent, verifiable, objective, and documented assessment of each randomized patient's response and date of PD. The members of the IRAC remained blinded to treatment assignment.
- PFS censoring: To support the robustness of the primary PFS results as determined by the protocol-prespecified SWOG censoring rules, sensitivity analyses were also performed using EMA and FDA censoring rules.

The primary analysis of PFS in the SWOG S0777 CSR is based on the ITT population, disease assessment as determined by the IRAC using SWOG censoring rules and the November 5, 2015 data cutoff date. The SWOG publication used the same data cutoff date but assessed the eligible analysable population, without IRAC review and censoring rules.

7.3 Appendix - Main characteristics of included studies

Study characteristics

Table 24 SWOG S0777 Study characteristics

Trial name	SWOG S0777
NCT number	NCT00644228
Objective	The overall objective of the study was to study whether the addition of bortezomib to lenalidomide and dexamethasone would improve progression-free survival and provide better response rates in patients with previously untreated multiple myeloma who were not planned for immediate autologous stem-cell transplant.
Publications – title, author, journal, year	Durie BG, 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 Feb 4;389(10068):519-527.[1]
Study type and design	This was phase 3 open label randomized study. Patients were randomly assigned (1:1) to receive initial treatment of bortezomib with lenalidomide and dexamethasone (BorLenDex) or lenalidomide and dexamethasone (LenDex) using a dynamic allocation algorithm developed by Pocock and Simon to balance treatment assignment by the stratification factors. The randomisation was stratified based on International Staging System stage (I, II, or III) and intent to transplant (yes vs no).17 Patients at participating NCTN institutions were randomly assigned upon registration. Randomisation procedures were developed and maintained by the SWOG statistics and data management centre. There was no masking to treatment interventions
Follow-up time	At the time of prespecified primary efficacy analyses, 66 patients (14% of eligible patients) were still on maintenance therapy. 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.[Durie Lancet 2017] Subsequent analysis has been performed for the EMA submission (cut-off date 01DEC2016) with a follow up of 60.6 months. [EMA submission ?] A later analysis was performed with a cut-off date of 15MAY2018 with a follow-up of 84 months (7 years) [Durie abstract #1992, ASH 2018]
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 [EPO]) >= 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 • 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 criteria • 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 favourable 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 [SQ] daily if patient is unable to take aspirin) as prophylactic anticoagulation; exception: patients receiving

<table>
<tr><td></td><td>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>INDUCTION THERAPY: Patients are randomized to 1 of 2 treatment arms.

ARM I (LenDex): Patients (n=242) received dexamethasone orally (PO) once daily (QD) on days 1, 8, 15, and 22 and lenalidomide PO QD on days 1-21. Treatment was repeated every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.

ARM II (BorLenDex): Patients (229) received dexamethasone PO QD on days 1, 2, 4, 5, 8, 9, 11, and 12; lenalidomide PO QD on days 1-14; and bortezomib intravenously (IV) over 3-5 seconds on days 1, 4, 8, and 11. Treatment was repeated every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity.

MAINTENANCE THERAPY: After the completion of at least 4 courses (Arm I) or at least 6 courses (Arm II) of induction therapy, patients received maintenance therapy comprising dexamethasone PO QD on days 1, 8, 15, and 22 and lenalidomide PO QD on days 1-21. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity</td></tr>
<tr><td>Baseline characteristics</td><td>Tables 5 and 6 from the EPAR p. 21-21

<table>
<tr><th>Parameter</th><th>BorLenDex (N = 263)</th><th>LenDex (N = 260)</th><th>Total (N = 523)</th></tr>
<tr><td>Age (years)</td><td></td><td></td><td></td></tr>
<tr><td>Median</td><td>63.0</td><td>63.0</td><td>63.0</td></tr>
<tr><td>Min, Max</td><td>35.0, 85.0</td><td>28.0, 87.0</td><td>28.0, 87.0</td></tr>
<tr><td>Age Group 1 (years), n (%)</td><td></td><td></td><td></td></tr>
<tr><td>≤ 65</td><td>167 (63.5)</td><td>150 (57.7)</td><td>317 (60.6)</td></tr>
<tr><td>> 65</td><td>96 (36.5)</td><td>110 (42.3)</td><td>206 (39.4)</td></tr>
<tr><td>Age Group 2 (years), n (%)</td><td></td><td></td><td></td></tr>
<tr><td>≤ 65</td><td>167 (63.5)</td><td>150 (57.7)</td><td>317 (60.6)</td></tr>
<tr><td>> 65 and ≤ 75</td><td>68 (25.9)</td><td>85 (32.7)</td><td>153 (29.3)</td></tr>
<tr><td>> 75</td><td>28 (10.6)</td><td>25 (9.6)</td><td>53 (10.1)</td></tr>
<tr><td>Sex, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Male</td><td>164 (62.4)</td><td>137 (52.7)</td><td>301 (57.6)</td></tr>
<tr><td>Female</td><td>99 (37.6)</td><td>123 (47.3)</td><td>222 (42.4)</td></tr>
</table></td></tr>
</table>

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)
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 (Strat. 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 missing)	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; BorLenDex = 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 BorLenDex 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

Secondary endpoints:

- Overall survival
- Response rates

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 was 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 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. 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. 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

Table 25 VISTA Study characteristics

Trial name	VISTA (MMY-3002)
NCT number	NCT00111319
Objective	The objective of this phase 3 study was to compare the use of melphalan and prednisone with or without bortezomib in previously untreated patients with multiple myeloma who were ineligible for high-dose therapy.
Publications – title, author, journal, year	San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. The New England journal of medicine. 2008;359(9):906-917.[2] Mateos M-V, Richardson PG, Schlag R, et al. Bortezomib Plus Melphalan and Prednisone Compared With Melphalan and Prednisone in Previously Untreated Multiple Myeloma: Updated Follow-Up and Impact of Subsequent Therapy in the Phase III VISTA Trial. Journal of Clinical Oncology. 2010;28(13):2259-2266[3] San Miguel JF, Schlag R, Khuageva NK, 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(4):448-455[4]
Study type and design	This was a randomized (1:1), open-label, parallel-group phase 3 study. Randomization was stratified according to baseline levels of β2-microglobulin (<2.5, 2.5 to 5.5, or >5.5 mg per liter [<212, 212 to 466, or >466 nmol per liter]), serum albumin (<3.5 or ≥3.5 g per deciliter), and region (North America, Europe, or other region).
Follow-up time	Initial data cut-off: Median follow-up of 16.3 months. [2] Subsequent data cut-off: 60.1 months. [4]
Population (inclusion and exclusion criteria) [clinicaltrials.gov (NCT00111319)]	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. Asymptomatic multiple myeloma-related organ or tissue damage can include presence of asymptomatic lytic bone lesion or plasmacytoma, or presence of anemia, renal function impairment, or hypercalcemia, as long as the criteria for pre-treatment clinical laboratory values indicated below are met. • Presence of measurable disease, defined as: o For secretory multiple myeloma, measurable disease is defined as any quantifiable serum monoclonal protein value. o 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

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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:

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

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, plasmapheresis or 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.

</td></tr>
<tr><td>Intervention</td><td>Nine 6-week cycles of either

melphalan (9 mg/m^2 body-surface area) + prednisone (60 mg/m^2) on days 1 to 4 alone

or

as above plus bortezomib (1.3 mg/m^2) on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9.

</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td colspan="3">Table 1. Baseline Characteristics of the Patients.* [San Miguel 2008]</td></tr>
<tr><td></td><td>Bortezomib Group</td><td>Control Group</td></tr>
<tr><td>Variable</td><td>(N = 344)</td><td>(N = 338)</td></tr>
<tr><td>Age</td><td></td><td></td></tr>
<tr><td>Median — yr</td><td>71</td><td>71</td></tr>
<tr><td>Range — yr</td><td>57–90</td><td>48–91</td></tr>
<tr><td>Subgroup — no. (%)</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<65 yr	14 (4)	9 (3)
≥75 yr	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	0.6–60.9
Subgroup — %‡		
<2.5 mg/liter	12	12
2.5–5.5 mg/liter	55	55
>5.5 mg/liter	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	104.00	106.00
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)
Cytogenetics		
High risk (t(4;14), t(14;16)), 17 p deletion, no. (%)	26 (7.6)	NR
Standard risk	142 (41.3)	NR

Primary and secondary endpoints	Primary endpoint: Time to disease progression. Prespecified secondary endpoints: Rate of complete response, the duration of response, the time to subsequent myeloma therapy, and overall survival. Additional secondary efficacy end points included progression-free survival (defined as the time between randomization and either disease progression or relapse from complete response by EBMT criteria, or death due to any cause, whichever occurred first.), complete plus partial response rate by EBMT criteria, complete response rate by EBMT criteria, time to first response, and time to subsequent myeloma therapy, EORTC QLQC30 questionnaire.
Method of analysis	The time to progression, the time to subsequent myeloma therapy, and overall survival from randomization was analyzed and compared the differences between groups using stratified log-rank tests in the intention-to-treat population (all randomized patients). Distributions were estimated with use of the Kaplan–Meier method. For time to- progression analyses, data from patients in whom there was no disease progression were censored at the last assessment or at the start of subsequent therapy. Hazard ratios were estimated with the use of the stratified Cox proportional hazards model for the intention-to-treat population, as well as within subgroups that were defined according to baseline characteristics in order to assess the consistency of treatment effects (seven prespecified analyses according to age, sex, race, baseline β2-microglobulin level, baseline albumin level, region, and disease stage and one post hoc analysis according to creatinine clearance). Response rates were analyzed in the population of patients who could be evaluated for a response and were compared between groups on the basis of a stratified Cochran–Mantel–Haenszel chi-square test.
Subgroup analyses	n/a

Table 26 GIMEMA Study characteristics

Trial name	GIMEMA
NCT number	NCT01063179
Objective	This randomized trial compared BorMelPred plus thalidomide (BorMelPredThal) induction followed by bortezomib thalidomide maintenance (BorMelPredThal -VT) with BorMelPred in patients with newly diagnosed multiple myeloma.
Publications – title, author, journal, year	Palumbo A, Bringhen S, Larocca A, Rossi D, Di Raimondo F, Magarotto V, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: Updated follow-up and improved survival. J Clin Oncol. 2014;32(7):634–40.[5] Palumbo A, Bringhen S, Rossi D, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-

	prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol 28:5101-5109, 2010. [6] Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood.* 2010;116(23):4745-4753. [7]
Study type and design	A phase III, multi-center, randomized open label study. Patients were randomized 1:1 to the intervention and the komparator.
Follow-up time	Median follow-up 54 months
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Age > 65 year old and not a candidate for stem cell transplant, or younger who refuses or is not eligible for high-dose therapy • Symptomatic multiple myeloma or asymptomatic multiple myeloma with related organ or tissue damage • Presence of measurable disease • Karnofsky performance status (PS) > 60% • Able to read and complete the HRQOL instruments • Agrees to use an acceptable barrier method for contraception for the duration of the study • Pretreatment clinical laboratory values within 14 days of randomization: platelet count ≥ 100x109/L • hemoglobin ≥ 8 g/dL • absolute neutrophil count (ANC) ≥ 1.0x109/L • AST ≤ 2.5 times the upper limit of normal • ALT ≤ 2.5 times the upper limit of normal • total bilirubin ≤ 1.5 times the upper limit of normal • serum creatinine ≤ 2.5mg/dL • corrected serum calcium <14 mg/dL (<3.5 mmol/L) • 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. • Women of child-bearing potential must agree to use 2 methods of contraception: 1 effective (for example hormonal or tubal ligation) and 1 barrier (for example latex condom, diaphragm) for at least 4 weeks before starting the therapy, during the Treatment Period, and for 4 weeks after the last dose; • Males must agree to use barrier contraception (latex condoms) when engaging in reproductive activity during the Treatment Period and for 4 weeks after the last dose. Exclusion Criteria: • Diagnosis of smoldering multiple myeloma or MGUS. • Diagnosis of Waldenstrom's disease • Prior or current systemic therapy for multiple myeloma including steroids (with exception of emergency use of a short course [maximum 4 days] of steroids before randomization or prior or current use of biphosphonates) • 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, or to Thalidomide • Peripheral neuropathy Grade 2 or higher, as defined by National Cancer Institute Common Toxicity Criteria (NCI CTC) 3.0

	• Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis • Other malignancy within the past 5 years. Exceptions: basal cell or non metastatic squamous cell carcinoma of the skin, cervical carcinoma in situ or FIGO Stage 1 carcinoma of the cervix • Concurrent medical condition or disease (e.g., active systemic infection, uncontrolled diabetes, pulmonary disease) 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. • Pregnant or lactating women. A serum β-hCG pregnancy test must be performed at the Screening visit, for female patients of child-bearing potential. If the test is positive, the patient must be excluded from the study. Confirmation that the patient is not pregnant must be established by a negative serum or urinary pregnancy test with the result obtained 1 day prior to the Baseline visit (or the day of the visit if results are available before drug delivery).
Intervention	A. BorMelPred-BorThal 9 cycles (of 42 days) bortezomib (i.v. 1,3 mg/m2 for 8 days in cycle 1-4 og 4 days i cycle 5-9) + melphalan (p.o. 9 mg/m2 i 4 days/cycle) + prednisone (p.o. 60 mg/m2 i 4 days/cycle) + thalidomid (50 mg/day for 2 years or until progression or death) OBS: dose reduction aftrer inclusion of 139 patients: 9 cycles of 5 weeks bortezomib for 5 weeks, bortezomib for 4 days/cycle. B. BorMelPred bortezomib + melphalan + prednisone as in the intervention group
Baseline characteristics	

Characteristic	VMPT-VT (n=254) No	%	VMP (n=257) No.	%
Age				
Median, years	71		71	
IQR, years	68-75		68-75	
Subgroup				
< 65 years	12	5	6	2
65-74 years	174	68	182	71
≥75 years	68	27	69	27
Male sex	130	51	122	47
Serum β2-microglobulin level				
Median, mg/L	3.8		4	
IQR, mg/L	2.7-5.2		3.0-5.6	
Subgroup				
< 3.5 mg/L	93	37	84	33
> 3.5 mg/L	118	46	125	49
Data missing	43	17	48	18
Albumin				
Median, g/L	37.9		37.5	
IQR, g/L	33.1-41.0		33.7-41.0	
Data missing	32	12.5	34	13
ISS stage				
I	59	23	56	22
II	100	39	88	34
III	47	19	57	22
Data missing	48	19	56	22
Creatinine clearance (calculated)				

	< 30 mL/min	21		8	24	9
	30-60 mL/min	147		58	160	62
	> 60 mL/min	86		34	73	28
	LDH					
	Median, UI/L		277		293	
	IQR, UI/L		193-355		203-368	
	Data missing	51		20	36	14
	Chromosome abnormalities'					
	Del13	101/192		53	86/184	47
	t(4;14)	33/192		17	26/184	14
	t(11;14)	31/192		16	20/184	11
	t(14;16)	9/192		5	6/184	3
	Del17	32/192		17	23/184	13
	Bortezomib schedule					
	Twice per week	73		29	66	26
	Once per week	181		71	191	74
Primary and secondary endpoints	Primary endnpoint was PFS. Secondary endpoints were Response rate, Overall Survival rate, Time and duration of response, Assess the safety, Assessment of the prognostic factors.					
Method of analysis [Palumbo 2010]	A sample size of 500 patients (250 per group) was determined to provide a power of 80% to detect a hazard ratio (HR) of PFS ≤ 0.75 comparing patients receiving BorMelPredThal-VT with those receiving BorMelPred, by using a log-rank test with a two-sided alpha of .05. An interim analysis of safety was planned when approximately 80 patients had received at least one treatment. Patients were analyzed on an intention-to-treat basis for all time-to-event end points. Times of observation were censored on February 1, 2010. Response rates and safety were analyzed in patients who received at least one dose of study drugs. Response rates and the incidence of any adverse event were compared with the _2 test or Fisher's exact test when appropriate. Survival data were analyzed with the Kaplan-Meier method, and treatment groups were compared with the log-rank test.27 Time to event was expressed as median with interquartile range (IQR). The Cox proportional hazard model was used to estimate the HR values and the 95% CIs for the intention-to-treat population28 as well as within subgroups defined according to baseline characteristics to assess the consistency of treatment effects (three prespecified analyses according to albumin, β2-microglobulin, and high-risk cytogenetic profile [presence of a t(4;14), t(14,16), or a 17p deletion] and five post hoc analyses according to sex, age, creatinine clearance, lactate dehydrogenase, and bortezomib schedule). Subgroup analyses were performed by introducing an interaction term between the treatment group variable and the subgroup variables.					
Subgroup analyses	See above					

Table 27 ALCYONE Study characteristics

Trial name	ALCYONE
NCT number	NCT02195479
Objective	The purpose of this study is to determine if the addition of daratumumab to velcade (bortezomib) melphalan-prednisone (BorMelPred) will prolong progression-free survival (PFS)

	compared with BorMelPred alone in participants with previously untreated multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant (ASCT).
Publications – title, author, journal, year	Mateos MV, Dimopoulos MA, Cavo M, et al. ALCYONE Trial Investigators. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018 Feb 8;378(6):518-528
Study type and design	A Phase 3, Randomized, Controlled, Open-label Study. Randomized 1:1 with interactive web system.
Follow-up time	Median follow-up 16.5 months
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Participant must have documented multiple myeloma satisfying the calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB) diagnostic criteria, monoclonal plasma cells in the bone marrow greater than or equal to 10 percent (%) or presence of a biopsy proven plasmacytoma, and measurable secretory disease, as assessed by the central laboratory, and defined in protocol • Participants who are 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 • Participant must have an 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. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy Exclusion Criteria: • Participant has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma • Participant has a 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 • Participant has 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 • Participant has peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the national cancer institute common terminology criteria for adverse events (NCI CTCAE) Version 4 • Participant has a 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) • Participant has had radiation therapy within 14 days of randomization • Participant has had plasmapheresis within 28 days of randomization • Participant has known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second [FEV1] <50% of predicted normal), 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) • Participants with known or suspected COPD must have a FEV1 test during screening • Participant is known to be seropositive for human immunodeficiency virus (HIV), known to have hepatitis B surface antigen positivity, or history of to have a history of hepatitis C • Participant has any concurrent medical or psychiatric condition or disease (example active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study
Intervention	DaraBorMelPred-Dara (N=350) Up to 9 cycles of 42 days of bortezomib (s.c. 1,3 mg/m2, 1 time/week in the first cycle, then twice weekly) + melphalan (p.o. 9 mg/m2, 1 time/day i 4 days/cycle) + prednisone (p.o. 60 mg/m2, 1 time/day i 4 days/cycle) + daratumumab (p.o or i.v. 16 mg/kg; 20 mg once weekly in 1. cycle, hver 3. Week in cycle 2-9, and the every 4 weeks until progression or unacceptable side effects. BorMelPred bortezomib + melphalan + prednisone (N=356) as in the intervention group
Baseline characteristics	**Characteristic** / **Daratumumab Group (N = 350)** / **Control Group (N = 356)** Age Median (range) — yr: 71.0 (40–93) / 71.0 (50–91) Distribution — no. (%) <65 yr: 36 (10.3) / 24 (6.7) 65–74 yr: 210 (60.0) / 225 (63.2) ≥75 yr: 104 (29.7) / 107 (30.1) 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) — mo: 0.8 (0.1–11.4) / 0.8 (0.1–25.3)‖
Primary and secondary endpoints	The primary end point was progression-free survival, defined as the time from randomization to either disease progression or death. Key efficacy secondary end points were the overall response rate and the rates of very good partial response or better (comprising very good partial, complete, and stringent complete responses).
Method of analysis	The primary analysis population was the intention- to-treat population of all the patients who underwent randomization. The safety population comprised patients who received any dose of trial treatment. 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. Response to trial treatment was determined with the

	use of a validated computer algorithm, as described previously. 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. If the between-group difference in the primary end point was significant at the time of the second interim analysis, the efficacy secondary end points of overall response rate and rates of very good partial response or better, complete response or better, and negative status for minimal residual disease, as ordered here, were sequentially tested, each with an overall two-sided alpha level of 0.05.
Subgroup analyses	NA

Table 28 GEM2005 Study characteristics

Trial name	GEM 2005
NCT number	NCT00443235
Objective	To compare BorMelPred with bortezomib plus thalidomide and prednisone (VTP) as induction in elderly MM patients.
Publications – title, author, journal, year	*Mateos MV, Oriol A, Martínez-López J, et al. GEM2005 trial update comparing BorMelPred/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? Blood. 2014 Sep 18;124(12):1887-93.* *Mateos MV, Oriol A, Martınez-Lopez J, et al. 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. Lancet Oncol. 2010; 11(10):934-941.*
Study type and design	Phase III open label study where patients were randomly 1:1 assigned to receive either BorMelPred or VTP as induction therapy, and those who completed the induction therapy were subsequently randomly assigned in approximately equal numbers to maintenance therapy with either bortezomib plus prednisone (VP) or bortezomib plus thalidomide (VT).
Follow-up time	6 years
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Must be able to comply with the protocol requirements. • Must voluntary sign the informed consent before performance of any study-related procedure not part of normal medical care, with the understanding it can be withdrawn at any time without prejudice to future medical care. • Age > 65 years. • Patient recently diagnosed with symptomatic Multiple Myeloma based on standard criteria28 and that has not received any previous chemotherapy treatment for Multiple Myeloma Some steroid doses or bisphosphonates are allowed for emergencies before starting induction treatment. • Patient has measurable disease, defined as follows: For secretory multiple myeloma, measurable disease is defined as any quantifiable serum monoclonal protein value and, where applicable, urine light-chain excretion of ≥ 200 mg/24 hours. • Patient has a ECOG performance status < 2 • Patient has a life-expectancy >3 months. • Patient has the following laboratory values before beginning induction treatment: Platelet count ≥ 50000/mm3, hemoglobin ≥ 8 g/dl and absolute neutrophil count ≥ 1000/mm3. Lower values are allowed if they are due to marrow infiltration.

<table>
<tr><td></td><td>Corrected serum calcium <14mg/dl. Aspartate transaminase (AST): ≤ 2.5 x the upper limit of normal. Alanine transaminase (ALT):): ≤ 2.5 x the upper limit of normal. Total bilirubin: ≤1.5 x the upper limit of normal. Serum creatinine ≤ 2 mg/dl.
Exclusion Criteria:
Patients previously received treatment to Multiple Myeloma, except steroids doses for urgency or bisphosphonates.
Non-secretor Myeloma
Patients with < Grade 2 peripheral neuropathy within 14 days before enrolment.
Patient had major surgery within 4 weeks before enrolment.
Patient has hypersensitivity to bortezomib, boron or mannitol.
Patient has received other investigational drugs within 30 days before enrolment.
Patient is known to be seropositive for the human immunodeficiency virus (HIV), Hepatitis B surface antigen-positive or active hepatitis C infection.
Patient had a myocardial infarction within 6 months of enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
Patient is enrolled in another clinical research study and/or is receiving an investigational agent for any reason.</td></tr>
<tr><td>Intervention</td><td>BorMelPred -BorThal / BorMelPred -BorPred 6 cycles (of 42 days) bortezomib (i.v. 1,3 mg/m2, twice weekly, in 1. cycle, then once weekly) + melphalan (p.o. 9 mg/m2, 4 days/cycle) + prednisone (p.o. 60 mg/m2, 4 Days/cycle)

Maintenance up to 3 years: bortezomib (1,3 mg/m2, 4 days every 3rd month) AND prednisone (50 mg every second day) OR thalidomid (50 mg/day)

BorPredThal-BorThal / BorPredLen-BorPred bortezomib + prednisone as invervention B + thalidomid (50 mg/day i 15 days of first cycle, then 100 mg/day)

Maintenance as in the intervention.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>VMP (N=130)</th><th>VTP (N=130)</th></tr>
<tr><td>Men</td><td>69 (53%)</td><td>61 (47%)</td></tr>
<tr><td>Age (years)</td><td>73 (68–77)</td><td>73 (69–76)</td></tr>
<tr><td>Age ≥75 years</td><td>41 (32%)</td><td>47 (36%)</td></tr>
<tr><td>M protein</td><td></td><td></td></tr>
<tr><td>IgG</td><td>81 (62%)</td><td>72 (55%)</td></tr>
<tr><td>IgA</td><td>37 (28%)</td><td>42 (32%)</td></tr>
<tr><td>Light chain</td><td>12 (9%)</td><td>16 (12%)</td></tr>
<tr><td>ISS stage</td><td></td><td></td></tr>
<tr><td>I</td><td>39 (30%)</td><td>26 (20%)</td></tr>
<tr><td>II</td><td>52 (40%)</td><td>56 (43%)</td></tr>
<tr><td>III</td><td>39 (30%)</td><td>48 (37%)</td></tr>
<tr><td>β2-microglobulin (mg/L)</td><td></td><td></td></tr>
<tr><td><2·5</td><td>29 (22%)</td><td>17 (13%)</td></tr>
<tr><td>2·5–5·5</td><td>63 (48%)</td><td>69 (53%)</td></tr>
<tr><td>>5·5</td><td>38 (29%)</td><td>44 (34%)</td></tr>
<tr><td>Median albumin <35 g/L</td><td>56 (43%)</td><td>68 (52%)</td></tr>
<tr><td>Plasma cells bone-marrow infiltration >35%</td><td>52 (40%)</td><td>60 (46%)</td></tr>
<tr><td>High-risk [t(4;14), t(14;16), del 17p] by FISH</td><td>18 (14%)</td><td>9 (7%)</td></tr>
</table>
Data are number (%) or median (IQR). VMP=bortezomib plus melphalan and prednisone. VTP=bortezomib plus thalidomide and prednisone. ISS=international staging system. FISH=fluorescence in-situ hybridisation.</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary endpoint was to assess the response rate in both the induction and maintenance phase.</td></tr>
</table>

	Secondary objectives were to assess time to progression (time from random isation to disease progression), PFS (time from random isation to disease progression or death from any cause), and overall survival (time from randomisation to death from any cause).
Method of analysis	The ITT analysis of the eff ect of induction therapy on survival was measured from the time of first randomisation. The analysis of the eff ect of maintenance was measured from the time of the second randomisation. Survival analyses were done with the Kaplan-Meier method, and we used the Cox proportional hazards regression model to estimate hazard ratios (HRs) and 95% CIs. Differences between survival curves were tested for statistical significance with the two-sided logrank test.13 To avoid any potential eff ect on the comparison between induction treatments by maintenance therapy regimens, we did a stratifi ed Cox regression analysis with inverse probability weighting14–17 appropriate for two-stage randomisation designs as a sensitivity analysis. All statistical analyses were done with SPSS (version 15.0).
Subgroup analyses	NA

Table 29 UPFRONT Study characteristics

Trial name	UPFRONT
NCT number	NCT00507416
Objective	This is a randomized, open label, multicenter clinical trial to compare the efficacy and safety of Velcade (bortezomib) and dexamethasone versus Velcade, thalidomide, and dexamethasone versus Velcade, melphalan, and prednisone in patients with previously untreated multiple myeloma not considered candidates for high-dose chemotherapy and autologous stem cell transplantation.
Publications – title, author, journal, year	*Niesvizky R, Flinn IW, Rifkin R, et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. J Clin Oncol. 2015 Nov 20;33(33):3921-9. [9]*
Study type and design	Randomized, open-label, parallel group allocated 1:1:1 to three treatment groups.
Follow-up time	Median follow-up 42.7 months (IQR, 26.3 to 52.8 months)
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Male or female 18 years of age or older • Not a candidate for high-dose chemotherapy and stem cell transplantation (HDT/SCT) due to age, presence of important comorbid condition(s) likely to have a negative impact on tolerability of HDT-SCT, or subject preference. • A Karnofsky Performance Status score of ≥50% • Symptomatic multiple myeloma or asymptomatic multiple myeloma with related organ or tissue damage. • Asymptomatic multiple myeloma-related organ or tissue damage can include presence of an asymptomatic lytic bone lesion or plasmacytoma, the presence of anemia (hemoglobin <10 g/dL), renal function impairment (serum creatinine > upper limit of normal [ULN]) or hypercalcemia (serum calcium >ULN). • Must have measurable disease requiring systemic therapy. Measurable disease is defined by at least 1 of the following criteria: o Quantifiable serum M-protein value (>1 g/dL of immunoglobulin (Ig)G or IgM M-protein, >0.5g/dL of IgA M-protein, >0.5 g/dL of IgD M-protein) o Urine light-chain excretion ≥200 mg/24 hours

	• Voluntary written informed consent must be given before performance of any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care. Exclusion Criteria: • Diagnosis of smoldering multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS). Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of lytic bone lesions. MGUS is defined by presence of serum monoclonal protein <3 g/dL; absence of lytic bone lesions, anemia, 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 immunoglobulin M (IgM) M-protein is present in the absence of a clonal plasma cell infiltration or lytic bone lesions. • Previously or currently treated with any systemic therapy for multiple myeloma. Prior treatment of hypercalcemia or spinal cord compression with corticosteroids or radiation therapy, respectively, does not disqualify the subject (the dose of corticosteroids should not exceed the equivalent of 160 mg of dexamethasone in 2-week period). • Radiation therapy within 2 weeks before randomization. Enrollment of patients who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 2 weeks have elapsed since the last date of therapy. • Major surgery within 30 days before randomization (Kyphoplasty is not considered major surgery) • History of allergy to any of the study medications, their analogues, or excipients in the various formulations • ≥Grade 2 peripheral neuropathy on clinical examination within 21 days before enrollment. • Any of the following clinical laboratory values within 21 days prior to enrollment: ○ Absolute neutrophil count (ANC) <1000 cells/mm^3 ○ Platelets <100,000 × 10^9/L, or <70 × 10^9/L if thrombocytopenia is considered by the investigator to be due to myeloma infiltration of bone marrow ○ Aspartate aminotransferase [serum glutamic oxaloacetic transaminase] (AST [SGOT]) or alanine aminotransferase [serum glutamic-pyruvic transaminase] (ALT [SGPT]) >2× the upper limit of normal (ULN) ○ Serum creatinine >2 mg/dL (>176.8 µmol/L); if the rise in creatinine is related to myeloma and there has been demonstrated a response to hydration, the subject may be enrolled. • Myocardial infarction within 6 months prior to enrollment or New York Hospital Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or significant conduction system abnormalities in the opinion of the investigator. Prior to study entry, any abnormality on electrocardiogram at screening must be determined and documented by the investigator as not medically relevant. • Any condition, including laboratory abnormalities, that in the opinion of the Investigator places the patient at unacceptable risk if he/she were to participate in the study. This includes but is not limited to serious medical conditions or psychiatric illness likely to interfere with participation in this clinical study. • Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, in situ breast cancer, in situ prostate cancer, or other cancer for which the patient has been disease-free for at least 3 years.

	• Female who is pregnant or breastfeeding. Female participants of childbearing potential must have a negative pregnancy test with a sensitivity of at least 50 mIU/mL during Screening. • Use of any investigational drugs within 30 days before randomization.
Intervention	Group A: BorThalDex-Bor 8 cyklusser (a 21 dage) bortezomib i.v. 1,3 mg/m2 i 4 days/cycle) + dexamethasone (p.o. 20 mg i 8 days of cycle 1-4, thereafter for 4 days) + thalidomid (p.o. 100 mg for 21 days/cycle) Maintenance (5 cycles of 35 days) : bortezomib i.v. 1,6 mg/m2 for 4 days/cycle Group B: BorMelPred-Bor bortezomib as intervention A + melphalan (p.o. 9 mg/m2, 4 days every second cycle) + prednisone (p.o. 60 mg/m2, 4 days every second cycle) Maintenance as Intervention A. Group C: BorDex-Bor bortezomib + dexamethason as in intervention A. Maintenance as in Intervention A
Baseline characteristics	

Demographic or Characteristic	**VD** (n = 168)	**VTD** (n = 167)	**VMP** (n = 167)
Age, years			
Median (IQR)	74.5 (67.0-79.0)	73.0 (66.0-77.0)	72.0 (68.0-77.0)
Age subgroup, No. (%)			
≥75	84 (50)	64 (38)	62 (37)
≥80	40 (24)	27 (16)	23 (14)
Male, No. (%)	101 (60)	70 (42)	90 (54)
Race,' No. (%)			
White	131 (78)	124 (74)	118 (71)
Black	23 (14)	31 (19)	29 (17)
Asian	2 (1)	1 (< 1)	0
Other†	10 (6)	11 (7)	19 (11)
Not reported	2 (1)	0	1 (< 1)
Charlson comorbidity index, No. (%)			
0	88 (53)	94 (59)	89 (54)
1	39 (24)	41 (26)	47 (28)
≥2	38 (23)	24 (15)	29 (18)
Myeloma type, No. (%)			
IgG	101 (62)	89 (58)	100 (62)
IgA	41 (25)	43 (28)	40 (25)
IgD	0	1 (< 1)	0
IgM	0	1 (< 1)	1 (< 1)
Light chain	21 (13)	20 (13)	18 (11)
Biclonal	1 (< 1)	0	2 (1)
ISS disease stage, No. (%)			
I	33 (22)	50 (33)	41 (25)
II	70 (46)	53 (35)	63 (39)
III	50 (33)	49 (32)	58 (36)
Karnofsky performance status < 70%, No. (%)	18 (11)	13 (8)	19 (12)
Serum albumin level, g/dL			
Median (IQR)	3.5 (3.1-4.0)	3.7 (3.3-3.9)	3.5 (3.1-3.8)
Subgroup, No. (%)			
< 3.5	75 (45)	56 (35)	78 (48)
≥3.5	90 (55)	103 (65)	86 (52)
Serum β2-microglobulin level, mg/L			
Median (IQR)	4.5 (3.1-6.2)	3.9 (2.8-6.2)	4.1 (3.0-6.6)
Subgroup, No. (%)			
< 2.5	20 (13)	27 (18)	24 (15)
2.5 to 5.5	84 (55)	76 (50)	80 (49)
> 5.5	49 (32)	49 (32)	58 (36)
Serum creatinine level, mg/dL			
Median (IQR)	1.1 (0.9-1.4)	1.0 (0.8-1.4)	1.0 (0.8-1.3)

Primary and secondary endpoints	The primary end point was progression-free survival (PFS; time from randomization to date of progression, relapse, or death, whichever came first). Patients without events were censored at the date of last response assessment. Prespecified secondary end points were as follows: overall response rate (ORR; partial response [PR] or better); complete response (CR) rate; CR plus very good PR (CR_VGPR) rate; duration of response; time to alternate anti-MM therapy; OS; safety, including rates of grade_3 adverse events (AEs), serious AEs, and PN; and patient-reported quality of life (QoL).
Method of analysis	Intent-to-treat, safety, and response-evaluable populations are defined in the Data Supplement. Kaplan-Meier method was used for time-to-event analyses; global differences among arms were based on the Wald test. Potential prognostic factors for PFS (age, sex, race, International Staging System [ISS] stage, myeloma type, Charlson comorbidity index, and Karnofsky performance status [KPS]) were analyzed using Cox regression modeling. Reasons for patient censoring in PFS analysis are summarized in the Data Supplement. The chi^2 test was used for response rate comparisons. EORTCQLQ-C30 scores were collected within 1 year of randomization, regardless of discontinuation. For patients dying within 1 year, missing assessments were assigned the worst possible score. A linear mixed model was used to assess changes from baseline in scores within and between arms. Sensitivity analyses, incorporating post-treatment data or last observation carried forward, were performed to investigate the impact of missing scores.
Subgroup analyses	NA

Table 30 CLARION Study characteristics

Trial name	CLARION
NCT number	NCT01818752.
Objective	The primary objective was to compare the progression-free survival of transplant ineligible patients newly diagnosed with multiple myeloma who were treated with carfilzomib, melphalan and prednisone or with bortezomib, melphalan and prednisone.
Publications – title, author, journal, year	Facon T, Lee JH, Moreau P, Niesvizky R, Dimopoulos M, Hajek R, Pour L, Jurczyszyn A, Qiu L, Klippel Z, Zahlten-Kumeli A, Osman M, Paiva B, San-Miguel J. Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma. Blood. 2019 May 2;133(18):1953-1963. doi: 10.1182/blood-2018-09-874396. Epub 2019 Feb 28. PubMed PMID: 30819926.[10]
Study type and design	Randomized, open-label, phase III. Patient were randomized 1:1 stratified by ISS (I vs II-III), administration route of bortezomib (iv vs sc), age and geography.
Follow-up time	Median follow-up time: 22 months

Population (inclusion and exclusion criteria)	Inclusion Criteria:
	• Newly diagnosed symptomatic multiple myeloma (per International Myeloma Working Group [IMWG] diagnostic criteria)
	• Transplant ineligibility
	• Measurable disease, as defined by 1 or more of the following (assessed within 21 days prior to randomization):
	  ○ Serum M-protein ≥ 0.5 g/dL, or
	  ○ Urine M-protein ≥ 200 mg/24 hours, or
	  ○ In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal kappa lambda ratio (SFLC kappa lambda ratio < 0.26 or > 1.65)
	• No prior treatment for multiple myeloma

<table>
<tr><td></td><td>
Eastern Cooperative Oncology Group (ECOG) performance status 0-2
Exclusion Criteria:

Multiple myeloma of IgM (immunoglobulin M) subtype
Glucocorticoid therapy within 14 days prior to randomization that equals or exceeds a cumulative dose of 160 mg of dexamethasone
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
Plasma cell leukemia (> 2.0 × 10^9/L circulating plasma cells by standard differential)
Waldenström macroglobulinemia (WM)
Known amyloidosis

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<tr><td>Intervention</td><td>
Max. 9 cycles of 42 days (or until disease progression/death/withdrawal/ toxicity).
Group A: Carfilzomib, Melphalan, Prednisone (N=478)
Participants received carfilzomib administered in combination with melphalan and prednisone for nine 42-day cycles.
Carfilzomib iv on days 1, 2, 8, 9, 22, 23, 29, and 30 of each 42-day cycle. Carfilzomib dose: 20 mg/m² on cycle 1, days 1 and 2 followed by 36 mg/m² thereafter.
Melphalan 9 mg/m² days 1-4 of each cycle
Prednisone 60 mg/m² days 1-4 of each cycle
Group B: Bortezomib, Melphalan, Prednisone (n=477)
Bortezomib was administered either IV or subcutaneously at 1.3 mg/m² during cycles 1 to 4 on days 1, 4, 8, 11, 22, 25, 29, and 32 followed by 1.3 mg/m² during cycles 5 to 9 on days 1, 8, 22, and 29.
Melphalan 9 mg/m² days 1-4 of each cycle
Prednisone 60 mg/m² days 1-4 of each cycle
</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic</th><th>Carfilzomib (n=478)</th><th>Bortezomib (n=477)</th><th>Total (N=955)</th></tr>
<tr><td>Age</td><td></td><td></td><td></td></tr>
<tr><td>Median, y</td><td></td><td></td><td></td></tr>
<tr><td>Range, y</td><td>72</td><td>72</td><td>72</td></tr>
<tr><td>Distribution, no. of patients (%)</td><td>42-89</td><td>43-91</td><td>42-91</td></tr>
<tr><td><65</td><td>16 (3.3)</td><td>35 (7.3)</td><td>51 (5.3)</td></tr>
<tr><td>65-74</td><td>311 (65.1)</td><td>297 (62.3)</td><td>608 (63.7)</td></tr>
<tr><td>>75</td><td>151 (31.6)</td><td>145 (30.4)</td><td>296 (31.0)</td></tr>
<tr><td>Sex, no. (%)</td><td></td><td></td><td></td></tr>
<tr><td>Male</td><td>243 (50.8)</td><td>239 (50.1)</td><td>482 (50.5)</td></tr>
<tr><td>Female</td><td>235 (49.2)</td><td>238 (49.9)</td><td>473 (49.5)</td></tr>
<tr><td>International Staging System stage, no. (%)</td><td></td><td></td><td></td></tr>
<tr><td>Stage 1</td><td>84 (17.6)</td><td>94 (19.7)</td><td>178 (18.6)</td></tr>
<tr><td>Stage 2</td><td>211 (44.1)</td><td>203 (42.6)</td><td>414 (43.4)</td></tr>
<tr><td>Stage 3</td><td>182 (38.1)</td><td>180 (37.7)</td><td>362 (37.9)</td></tr>
<tr><td>Unknown</td><td>1 (0.2)</td><td>0</td><td>1 (0.1)</td></tr>
<tr><td>Cytogenetics, no. (%)*</td><td></td><td></td><td></td></tr>
<tr><td>High risk</td><td>54 (11.3)</td><td>67 (14.0)</td><td>121 (12.7)</td></tr>
<tr><td>Standard risk</td><td>320 (66.9)</td><td>324 (67.9)</td><td>644 (67.4)</td></tr>
<tr><td>Unknown</td><td>104 (21.8)</td><td>86 (18.0)</td><td>190 (19.9)</td></tr>
<tr><td>Race, no. (%)</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>329 (68.8)</td><td>339 (71.1)</td><td>668 (69.9)</td></tr>
<tr><td>Asian</td><td>123 (25.7)</td><td>121 (25.4)</td><td>244 (25.5)</td></tr>
<tr><td>American Indian or Alaska Native</td><td>1 (0.2)</td><td>2 (0.4)</td><td>3 (0.3)</td></tr>
<tr><td>Other</td><td>6 (1.3)</td><td>3 (0.6)</td><td>9 (0.9)</td></tr>
</table>
</td></tr>
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	Not reported	19 (4.0)	12 (2.5)	31 (3.2)
	Serum b2 microglobulin, mg/L, no. (%)			
	<2.5	40 (8.4)	39 (8.2)	79 (8.3)
	2.5 to ,5.5	256 (53.6)	256 (53.7)	512 (53.6)
	>5.5	182 (38.1)	182 (38.2)	364 (38.1)
Primary and secondary endpoints	The primary endpoint was PFS (based on ORCA-assessed outcomes). Secondary endpoints included OS, ORR (≥ partial response [PR]), CR rate (CR or stringent complete response [sCR]), neuropathy events (defined as an incident of grade ≥ 2 PN by standardized MedDRA query narrow search), GHS/Quality of Life (GHS/QoL) as measured by the EORTC QLQ-C30 GHS/QoL scale, and safety/tolerability.			
Method of analysis	PFS and OS were compared between treatment groups using a log-rank test stratified by the randomization stratification factors. The corresponding HRs and their 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model stratified by the same randomization stratification factors. The graphical approach by Maurer and Bretz was used to adjust for multiplicity in the primary and secondary endpoint testing, such that overall type I error rate was strongly controlled under 0.025 (1-sided). Rates of overall response and ≥CR were calculated by treatment group, and the associated 95% CIs were estimated using the Clopper-Pearson method. These rates were compared between treatment groups using stratified Cochran-Mantel-Haenszel chi^2 tests. The incidence of grade ≥ 2 PN was compared between treatment groups using a Pearson chi^2 test. Overall differences between treatment groups in the EORTC QLQ-C30 and QLQMY20 scores were compared using a linear mixed model for repeated measures (supplemental data). Safety and tolerability, including PN rates, were assessed in the safety population (all randomized patients who received ≥1 dose of study treatment). All other secondary endpoints were assessed in the intent-to treat population (all randomized patients). The distribution of time-to-event endpoints were summarized descriptively using the Kaplan-Meier method. Corresponding 95% CIs for the medians were constructed using the method of Klein and Moeschberger with log-log transformation. All reported P values are 1-sided.			
Subgroup analyses	NA			

Table 31 IFM 2009 Study characteristics

Trial name	IFM 2009
NCT number	NCT01191060
Objective	The objective of this study was to compare the effect of induction therapy with three cycles of BorLenDex and then consolidation therapy with either five additional cycles of BorLenDex (350 patients) or high-dose melphalan plus stem-cell transplantation followed by two additional cycles of BorLenDex.
Publications – title, author, journal, year	Attal M, et al.; IFM 2009 Study. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017 Apr 6;376(14):1311-1320.[11]
Study type and design	This randomized, open-label, phase 3 trial was conducted at 69 centers in France, Belgium, and Switzerland. Patients were recruited from November 2010 through November 2012 and were randomly assigned, in a 1:1 ratio, to one of two treatment groups during the first cycle of induction therapy. Randomization was stratified according to International Staging System disease stage (stage I, II, or III, with higher stages indicating more severe disease) and cytogenetic risk profile (standard risk, high risk, or risk undetermined because of test failure; high risk was defined by the presence of a t[4;14] translocation, t[14;16] translocation, or 17p deletion, as determined by fluorescence in situ hybridization).

Follow-up time	Median follow up was 44 and 43 months respectively.
Population (inclusion and exclusion criteria)	Inclusion Criteria for registration : (with labs performed within 21 days of initiation of protocol therapy): • Patients diagnosed with multiple myeloma based on International Myeloma Foundation 2003 Diagnostic Criteria. • Patients must have symptomatic myeloma with myeloma-related organ damage. • Patients must have myeloma that is measurable by either serum or urine evaluation of the monoclonal component or by assay of serum free light chains. • Age between 18 and 65 years at the time of signing the informed consent document. • ECOG performance status <2 (Karnofsky ≥ 60%) • Negative HIV blood test Exclusion Criteria for registration: • Participants must not have been treated with any prior systemic therapy for multiple myeloma. Treatment by localized radiotherapy is not an exclusion criterion if an interval of at least two weeks between the end of radiotherapy and initiation of protocol therapy entry in the study is observed. Similarly, the dose of corticosteroids received by the participant should not exceed the equivalent of 160 mg of dexamethasone over a two-week period before initiation of protocol therapy. • Primary amyloidosis (AL) or myeloma complicated by amylosis. • Participants may not be receiving any other study investigational agents. • Participants with known brain metastases • Poor tolerability or known allergy to any of the study drugs or compounds of similar chemical or biologic composition to study agents • Platelet count < 50,000/mm3 per µLwithin 21 days of initiation of protocol therapy. Transfusion within 7 days of screening is not allowed to meet platelet eligibility criteria. • ANC < 1,000 cells/mm3 within 21 days of initiation of protocol therapy. Growth factor within 7 days of screening is not allowed to meet ANC eligibility criteria. • Hemoglobin < 8.0 g/dL within 21 days of initiation of protocol therapy. Transfusion may be used to meet hemoglobin eligibility criteria. • Hepatic impairment, defined a bilirubin > 1.5 x institutional upper limit of normal (ULN) > 2 mg/dL (Patients with benign hyperbilirubinemia (e.g., Gilbert's syndrome) are eligible) and or AST (SGOT), or ALT (SGPT), or alkaline phosphatase > 2 x ULN • Renal insufficiency, defined as serum creatinine > 2.5 mg/dl and/or creatinine clearance < <40 60 ml/min (actual or calculated). The Cockgroft-Gault formula should be used for calculating creatinine clearance values. • Respiratory compromise, defined as ventilation tests and with DLCO < 50% • Participant must not demonstrate with clinical signs of heart or coronary failure, or evidence of LVEF < 40%. Participant must not have with myocardial infarction within 6 months prior to enrolment or have New York Heart Association (NYHA Appendix VII) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant. • Intercurrent illness including, but not limited to ongoing or active severe infection, known (active or not) infection with hepatitis B or C virus, poorly controlled diabetes, severe uncontrolled psychiatric disorder or psychiatric illness/social situations that would limit compliance with study requirements.

	• Participant with previous history of another malignant condition, except for basal cell carcinoma and stage I cervical cancer • Female participant who is pregnant or breast-feeding • Inability to comply with an anti-thrombotic treatment regimen • Peripheral neuropathy ≥ Grade 2 peripheral neuropathy on clinical examination within 21 days of initiation of protocol therapy • Mental illness likely to interfere with participation in the study and Adults under juridical protection
Intervention	All the patients received induction therapy with three 21-day cycles of BorLenDex, which consisted of lenalidomide (25 mg, administered orally on days 1 through 14), bortezomib (1.3 mg per square meter of body-surface area, administered intravenously on days 1, 4, 8, and 11), and dexamethasone (20 mg, administered orally on days 1, 2, 4, 5, 8, 9, 11, and 12). After the induction phase, all the patients underwent stem-cell mobilization with cyclophosphamide and granulocyte colony-stimulating factor. During the consolidation phase, the patients received either five cycles of BorLenDex (n=350) with a reduced daily dose of dexamethasone of 10 mg (BorLenDex-alone group) or melphalan (n=350) at a dose of 200 mg per square meter plus autologous stem-cell transplantation followed by two cycles of BorLenDex with a reduced daily dose of dexamethasone of 10 mg (transplantation group). In both treatment groups, maintenance therapy with lenalidomide (10 mg per day for the first 3 months, with a possible dose increase to 15 mg thereafter, depending on side effects) was initiated within the first 3 weeks after the completion of consolidation therapy and was continued for 1 year or until the occurrence of disease progression or unacceptable adverse events.
Baseline characteristics	**Characteristic** / **RVD-Alone Group (N = 350)** / **Transplantation Group (N = 350)** Country — no. (%) France: 343 (98) / 345 (99) Belgium: 6 (2) / 5 (1) Switzerland: 1 (<1) / 0 Age — yr Median: 59 / 60 Range: 29–66 / 30–66 Male sex — no. (%): 208 (59) / 214 (61) Type of myeloma — no. (%) IgG: 209 (60) / 223 (64) IgA: 71 (20) / 73 (21) Light chain: 57 (16) / 46 (13) Other: 13 (4) / 8 (2) International Staging System disease stage — no. (%) I: 115 (33) / 118 (34) II: 170 (49) / 171 (49) III: 65 (19) / 61 (17) Serum β2-microglobulin level — no. (%) <3.5 mg/liter: 169 (48) / 178 (51) 3.5–5.5 mg/liter: 116 (33) / 111 (32) >5.5 mg/liter: 65 (19) / 61 (17) Cytogenetic abnormalities — no./total no. of patients who could be evaluated† t(4;14) translocation: 26/256 / 28/259 17p deletion: 15/256 / 16/258 t(14;16) translocation: 6/256 / 6/258 t(4;14) or t(14;16) translocation or 17p deletion: 44/256 / 46/259
Primary and secondary endpoints	The primary end point was progression-free survival.

	Secondary end points included response rate, time to disease progression, overall survival, and adverse event rates.
Method of analysis	Progression-free survival was defined as the time from randomization until either the first documentation of disease progression or death from any cause. Censoring rules for progression-free survival followed the Food and Drug Administration guidance on end points in cancer trials. Time to progression was defined as the time from randomization until either the first documentation of disease progression or death owing to myeloma. Overall survival was defined as the time from randomization until death from any cause. Duration of follow-up after randomization was estimated by means of the reverse Kaplan–Meier method. Time-to-event end points were analyzed by means of the Kaplan–Meier method, with the use of a two-sided stratified log-rank test to compare the treatment groups and a multivariate Cox proportional-hazards model adjusted for stratification factors to estimate adjusted hazard ratios and 95% confidence intervals. A competing-risk analysis was performed to assess the effect of censoring events on progression-free survival.
Subgroup analyses	n/a

Table 32 PETHEMA GEM 2012 Study characteristics

Trial name	PETHEMA GEM 2012
NCT number	NCT01916252
Objective	The objectives of the study were to evaluate CR rate after induction, post-transplant and post-consolidation, evaluation of minimal residual disease (MRD) after each treatment step, progression-free survival, overall survival and toxicity
Publications – title, author, journal, year	Rosinol L, Oriol A, Rios R, et al. Bortezomib, Lenalidomide and Dexamethasone (VRD-GEM) As Induction Therapy Prior Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma (MM): Results of a Prospective Phase III Pethema/GEM Trial. Blood. 2017;130:2017- [Abstract] [12] Not yet published in a full publication. Data from the EPAR will be used in the application.
Study type and design	This was an open-label, randomized, multicenter, national study that compared 2 pretransplant conditioning regimens (Bu-Mel versus MEL200) in subjects who received BorLenDex as initial (induction) treatment. [14]
Follow-up time	The induction with BorLenDEx had a duration of 6 cycles of 4 weeks.
Population (inclusion and exclusion criteria)	Inclusion Criteria: The patient must, in the opinion of the investigator, be capable of complying with all requirements of the trial Have signed the informed consent form Be between 18 and 65 years of age and a candidate for autologous stem cell transplant Have an ECOG Performance Status > 2 (or 3 if the ECOG is due to myeloma) Newly diagnosed patient with symptomatic multiple myeloma based on standard criteria, who has not received any prior chemotherapy treatment for Multiple Myeloma. Patient must have measurable disease, defined by the following criteria: For secretory MM, measurable disease is defined by any quantifiable value of serum M-protein (IgG ≥ 10 g/L or IgA > 5 g/L) and/or, when applicable, an excretion of light chain in urine ≥ 200 mg/24 hours. For oglio- or non-secretory multiple myeloma, measurable disease is defined by the presence of soft tissue (not bone) plasmacytomas, which is determined by clinical exam or radiographic techniques. Life expectancy > 3 months. The patient must have the following laboratory values in the 21 days prior to initiation of treatment (day 1, cycle 1): Platelet count ≥ 100 x 109/L and absolute neutrophil count of ≥ 1.0 x 109/L Corrected serum calcium < 14 mg/dL. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x the upper limit of normal (ULN). Total

<table>
<tr><td></td><td>bilirubin within normal limits. Serum creatinine ≤ 2 mg/dL - Women of childbearing potential and men (including vasectomized men whose partners are women of childbearing potential), must use two methods of contraception during the entire course of treatment, during dose interruptions and for up to three months after receiving the final dose Exclusion Criteria: Non-secretory myeloma without measurable plasmacytomas. Patients who have undergone prior treatment for multiple myeloma, with the exception of emergency treatment using steroid pulses, bisphosphonates, or radiotherapy received before beginning induction treatment. Peripheral neuropathy ≥ grade 2 in the 21 days prior to inclusion. Known hypersensitivity to bortezomib, boric acid, mannitol or lenalidomide. Patients that have received any investigational agent in the 28 days prior to inclusion in the study. Patients who have had a myocardial infarction in the six months prior to inclusion in this study or who are a class III or IV according to the New York Heart Association (NYHA) functional classification system, heart failure, unstable angina, uncontrolled ventricular arrhythmias or acute ischemia detected by electrocardiogram, or nervous system disorders. Patients currently enrolled in another clinical trial or receiving any type of investigational agent. Patients who are seropositive for HBV, HCV or HIV</td></tr>
<tr><td>Intervention [EPAR]</td><td>BorLenDex (BorLenDex) induction for all patients (N=458) consisted of bortezomib 1.3 mg/m2/sc on days 1,4,8,11 of each cycle, lenalidomide 25 mg/day on days 1 to 21 and dexamethasone 40 mg on days 1-4 and 9-12 at 4-week intervals for 6 cycles. This was followed by Arm A: Six 4-week cycles (24 weeks) of BorLenDex initial treatment followed by melphalan 200 mg/m2 (MEL200)7 conditioning, auto-HSCT, and two 4-week cycles of BorLenDex consolidation Arm B: Six 4-week cycles (24 weeks) of BorLenDex initial treatment followed by busulfan with melphalan (Bu-Mel) conditioning, auto-HSCT, and two 4-week cycles of BorLenDex consolidation</td></tr>
<tr><td>Baseline characteristics

[Reproduced from the EPAR]</td><td>
<table>
<tr><th>Characteristic</th><th>RVd/ Bu-Mel/ RVd (N = 230)</th><th>RVd/ MEL200/ RVd (N = 228)</th><th>Total (N = 458)</th></tr>
<tr><td>ISS Stage, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>95 (41.3)</td><td>84 (36.8)</td><td>179 (39.1)</td></tr>
<tr><td>II</td><td>78 (33.9)</td><td>88 (38.6)</td><td>166 (36.2)</td></tr>
<tr><td>III</td><td>53 (23.0)</td><td>54 (23.7)</td><td>107 (23.4)</td></tr>
<tr><td>Missing</td><td>4 (1.7)</td><td>2 (0.9)</td><td>6 (1.3)</td></tr>
<tr><td>Revised ISS Stage, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>37 (16.1)</td><td>38 (16.7)</td><td>75 (16.4)</td></tr>
<tr><td>II</td><td>91 (39.6)</td><td>86 (37.7)</td><td>177 (38.6)</td></tr>
<tr><td>III</td><td>16 (7.0)</td><td>16 (7.0)</td><td>32 (7.0)</td></tr>
<tr><td>Missing</td><td>86 (37.4)</td><td>88 (38.6)</td><td>174 (38.0)</td></tr>
<tr><td>ECOG performance status, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Fully active (Grade 0)</td><td>94 (40.9)</td><td>101 (44.3)</td><td>195 (42.6)</td></tr>
<tr><td>Restricted activity (Grade 1)</td><td>94 (40.9)</td><td>88 (38.6)</td><td>182 (39.7)</td></tr>
<tr><td>No work, ambulatory (Grade 2)</td><td>29 (12.6)</td><td>33 (14.5)</td><td>62 (13.5)</td></tr>
<tr><td>Limited self-care (Grade 3)</td><td>11 (4.8)</td><td>5 (2.2)</td><td>16 (3.5)</td></tr>
<tr><td>Missing</td><td>2 (0.9)</td><td>1 (0.4)</td><td>3 (0.7)</td></tr>
<tr><td>Cytogenetic risk[a], n (%)</td><td></td><td></td><td></td></tr>
<tr><td>High</td><td>50 (21.7)</td><td>42 (18.4)</td><td>92 (20.1)</td></tr>
<tr><td>Not high</td><td>106 (46.1)</td><td>107 (46.9)</td><td>213 (46.5)</td></tr>
<tr><td>Other</td><td>42 (18.3)</td><td>52 (22.8)</td><td>94 (20.5)</td></tr>
<tr><td>All missing</td><td>32 (13.9)</td><td>27 (11.8)</td><td>59 (12.9)</td></tr>
<tr><td>Creatinine clearance, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>< 60 mL/min</td><td>35 (15.2)</td><td>35 (15.4)</td><td>70 (15.3)</td></tr>
<tr><td>≥ 60 mL/min</td><td>186 (80.9)</td><td>184 (80.7)</td><td>370 (80.8)</td></tr>
<tr><td>Missing</td><td>9 (3.9)</td><td>9 (3.9)</td><td>18 (3.9)</td></tr>
<tr><td>β2 microglobulin, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>≤ 5.5 mg/L</td><td>179 (77.8)</td><td>172 (75.4)</td><td>351 (76.6)</td></tr>
<tr><td>> 5.5 mg/L</td><td>49 (21.3)</td><td>54 (23.7)</td><td>103 (22.5)</td></tr>
<tr><td>Missing</td><td>2 (0.9)</td><td>2 (0.9)</td><td>4 (0.9)</td></tr>
<tr><td>Lactate dehydrogenase elevated, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>32 (13.9)</td><td>33 (14.5)</td><td>65 (14.2)</td></tr>
<tr><td>No</td><td>188 (81.7)</td><td>188 (82.5)</td><td>376 (82.1)</td></tr>
<tr><td>Missing</td><td>10 (4.3)</td><td>7 (3.1)</td><td>17 (3.7)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary Outcome Measures : Progression Free Survival to measure the treatment efficacy Secondary Outcome Measures : Complete response rates to measure the treatment</td></tr>
</table>

	efficacy Evaluation of minimal residual disease immunofixation negative-CR after each phase of treatment Overall survival Describe the adverse events to evaluate the safety and tolerability
Method of analysis	Not reported in the abstract nor in the EPAR. The study in this application is used only for a qualitative description of the safety profile, why information on efficacy analysis is not relevant.
Subgroup analyses	n/a

7.4 Results per study - tables

Table 33 Results per study Table A3a Results of the SWOG S0777 study – Primary analysis

Trial Name: SWOG S0777 NCT Number: NCT00644228												
				Estimated absolute difference in effect			Estimated relative difference in effect					
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Hazard/Odds/ Risk Ratio (**)	95% CI	P value	Description of methods used for estimation	References
Median overall survival	Bortezomib + Lenalidomide + Dexamethasone	242	75 (65-NR) months	11	--	--	HR: 0.71	0.560-0.906	0.0018	Overall 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 Cox proportional-hazards model.	Durie 2017[1]
	Lenalidomide + Dexamethasone	229	64 (56-NR) months								
Median progression-free survival	Bortezomib + Lenalidomide + Dexamethasone	242	43 (39-52) months	13	--	--	HR: 0.709	0.524-0.959	0.0125	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 Cox proportional-hazards model.	Durie 2017[1]
	Lenalidomide + Dexamethasone	229	30 (25-39) months								

Discontinuations due to treatment-related adverse events	Bortezomib + Lenalidomide + Dexamethasone	242	55 (22.7%)	13.1 %	6.59%-19.6%--	--	RR: 2.37	1.49-3.75	<0.001	All adverse events were initially graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. From April 6, 2011, serious adverse events were graded according to CTCAE version 4.0.	Durie 2017[1]
	Lenalidomide + Dexamethasone	229	22 (9.6%)								

(*) Hazard/Odds/Risk ratios are calculated as BorLenDex vs. Rd

(**) Risk ratio compares groups RVd vs. Rd; confidence interval calculated using statistical software

Note: P-values for difference effect was calculated using standard p-value formula while log transformation was used for ratio p-values appropriately

Table 34 Results per study Table A3a Results of the SWOG S0777 study – Longest follow-up (EMA Censored)

Trial name:	SWOG S0777 (Longest follow up – EMA Censoring)										
NCT number:	NCT00644228										
				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		
Overall survival	Bortezomib + Lenalidomide + Dexamethasone	263	89.1 (76.1-NE)	21.9	--	--	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.	Cut-off:01DEC2016 EPAR table 14, p. 27 (EMA censoring rules)
	Lenalidomide + Dexamethasone	260	67.2 (58.4-90.8)								do.
Progression Free Survival	Bortezomib + Lenalidomide + Dexamethasone	263	41.7 (33.1-51.5)	12	--	--	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.	Cut-off:01DEC2016 EPAR table 14, p. 27
	Lenalidomide + Dexamethasone	260	29.7 (24.2-37.8)								do.
HRQoL				No data available							
Discontinuations due to TEAEs	Bortezomib + Lenalidomide + Dexamethasone	262	60 (22.9%)	13.5 %	7.3-19.7%	-	RR: 2.44	1.57-3.80	<0.001	Risk ratio compares BorLenDex to LenDex	Cut-off: 01DEC2016 EPAR table 35, p. 50
	Lenalidomide + Dexamethasone	256	24 (9.4%)								
Qualitative review of AEs	Intervention Comparator			See narrative							

Table 35 Results per study Table A3b Results of the VISTA study

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	Melphalan + Prednisone	338	43.1 months	13.3	--	--	HR: 0.695	0.567-0.852	<0.001	Overall survival was analyzed by using Kaplan-Meier methodology. Data were compared between arms by using stratified log-rank tests, and hazard ratios (HRs) with 95% CIs were calculated.	San-Miguel 2013[4]
	Bortezomib + Melphalan + Prednisone	344	56.4 months								
Median progression-free survival	Melphalan + Prednisone	338	15.2 months	6.5	--	--	HR: 0.558	0.430-0.720	<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 2008 Appendix Figure 2A[2]
	Bortezomib + Melphalan + Prednisone	344	21.7 months								
Discontinuations due to treatment-related adverse events	Melphalan + Prednisone	338	47 (14%)	1%	0-6.3%	--	RR: 1.05	0.72-1.51	0.814	Adverse events were graded with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Serious adverse events were monitored monthly by the independent data and safety monitoring committee.	San Miguel 2008[2]
	Bortezomib + Melphalan + Prednisone	344	50 (15%)								

(*) Hazard/Odds/Risk ratios are calculated as BorMelPred vs. MP

(**) Risk ratio compares BorMelPred vs. MP, confidence interval calculated using statistical software
Note: P-values for difference effect was calculated using standard p-value formula while log transformation was used for ratio p-values appropriately

Table 36 Results per study Table A3b Results of the GEM2005 study

Trial Name: GEM05 NCT Number: NCT00443235											
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	130	63 (NR) months	20	--	--	HR: 0.67	0.49-0.91	0.01	Overall survival analyses were done with the Kaplan-Meier method, and we used the Cox proportional hazards regression model to estimate hazard ratios (HRs) and 95% CIs. HR is BorMelPred vs. VTP	Mateos et al 2014[13]
	VTP	130	43 (NR) months								
Median progression-free survival	BorMelPred	130	24 (21-27) months	8	--	--	HR: 1.4	0.8-2.1	0.1	Progression-free survival analyses were done with the Kaplan-Meier method, and we used the Cox proportional hazards regression model to estimate hazard ratios (HRs) and 95% Cis. HR is BorMelPred vs. VTP.	Mateos et al 2010[3]
	VTP	130	32 (29-35) months								
Discontinuations due to treatment-related adverse events	BorMelPred	87	4 (5%)	3%	0-10.2%	--	RR: 0.60	0.18-1.97	0.393	All adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events,version 3.0).	Mateos et al 2010[3]
	VTP	91	7 (8%)								
(*) Hazard/Odds/Risk ratios are calculated as BorMelPred vs. VTP (**) Risk ratio compares BorMelPred vs. VTP; confidence intervals calculated using statistical software Note: P-values for difference effect was calculated using standard p-value formula while log transformation was used for ratio p-values appropriately											

Table 37 Results per study Table A3b Results of the GIMEMA study

Trial Name: GIMEMA-MM-03-05 NCT Number: NCT01063179											
				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	VMPT-VT	254	--	--	--	--	HR for VMPT-VT vs. VMP: 0.70	0.52-0.92	0.01	Overall survival data were analyzed with the Kaplan-Meier method, and treatment groups were compared with the log-rank test. The Cox proportional hazard model was used to estimate the HR values and the 95% CIs for the intention-to-treat population	Palumbo et al 2014[5]
	VMP	257	--								
Median progression-free survival	VMPT-VT	254	35.3 months (NR)	10.5	--	--	HR for VMPT-VT vs. VMP: 0.58	0.47-0.71	<0.001	Progression-free survival data were analyzed with the Kaplan-Meier method, and treatment groups were compared with the log-rank test. The Cox proportional hazard model was used to estimate the HR values and the 95% CIs for the intention-to-treat population	Palumbo et al 2014[5]
	VMP	257	24.8 months (NR)								
Discontinuations due to treatment-related adverse events	VMPT-VT	254	57 (23%)	6%	0-12.9%	--	RR: 1.37	0.96-1.97	0.081	Adverse events were graded with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.	Palumbo et al 2010[6]
	VMP	257	42 (17%)								
(*) Hazard/Odds/Risk ratios are calculated as VMPT-VT vs. VMP (**) Risk ratio compares VMPT-VT vs. VMP; confidence interval calculated using statistical software Note: P-values for difference effect was calculated using standard p-value formula while log transformation was used for ratio p-values appropriately											

Table 38 Results per study Table A3b Results of the ALCYONE study

Trial Name: ALCYONE NCT Number: NCT02195479											
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 progression-free survival	VMP	356	18.1 months (16.5-19.9)	--	--	--	HR for Dara + VMP vs. VMP: 0.50 (**)	0.38-0.65	<0.001	Time-to-event variables were evaluated with the Kaplan–Meier method. 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 cutoff date.	Mateos et al 2018[8]
	Dara + VMP	350	NR								
Discontinuations due to treatment-related adverse events	VMP	356	9.3%	4.4%	0.63-6.3%	--	RR: 0.53 (**)	0.30-0.93	0.023	Safety assessments included evaluation of adverse events graded in accordance with the NCI CTCAE (version 4), clinical laboratory testing, electrocardiograms, measurement of vital signs, and physical examinations.	Mateos et al 2018[8]
	Dara + VMP	350	4.9%								
(*) Hazard/Odds/Risk ratios are calculated as Dara + VMP vs. VMP (**) Risk ratio compares Dara + VMP vs. VMP; confidence interval calculated using statistical software Note: P-values for difference effect was calculated using standard p-value formula while log transformation was used for ratio p-values appropriately											

Table 39 Results per study Table A3b Results of the UPFRONT study

Trial Name: UPFRONT NCT Number: NCT00507416											
Outcome	Study Arm	N	Result (CI)	Estimated absolute difference in effect Difference	95% CI	P value	Estimated relative difference in effect Hazard/Odds/ Risk Ratio (**)	95% CI	P value	Description of methods used for estimation	References
Median progression-free survival	VD	168	14.7 months (12.0-18.6)	VMP - VD 2.6	--	--	HR VMP vs. VD 0.95	--	--	Kaplan-Meier method was used for time-to-event analyses	Niesvizky et al 2015[9]
	VTD	167	15.4 months (12.6-24.2)	VMP - VTD 1.9	--	--	HR: VMP vs. VTD 1.17	--	--		
	VMP	167	17.3 months (14.8-20.3)								
Median overall survival	VD	168	49.8 months (35.7-NR)	VMP – VD 3.3	--	--	HR: VMP vs. VD 0.97	--	--	Kaplan-Meier method was used for time-to-event analyses	Niesvizky et al 2015[9]
	VTD	167	51.5 months (38.5-NR)	VMP – VTD 1.6	--	--	HR: VMP vs. VTD 1.06	--	--		
	VMP	167	53.1 months (41.1-NR)								
Discontinuations due to treatment-related adverse events	VD	165	37 (22%)	VMP – VD 6.0% VMP – VTD 2.0%	0-15.4% 0-11.7%	--	RR for VMP vs. VD: 1.23 RR for VMP vs. VTD: 1.06	0.84-1.79 0.74-1.53	0.279 0.7378	Adverse events were assessed per the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0.	Niesvizky et al 2015[9]
	VTD	158	41 (26%)								
	VMP	163	45 (28%)								

(*) Hazard/Odds/Risk ratios are calculated using the reference treatment as noted in the table
(**) Risk ratio compares VMP vs. VTD or VMP vs. VD; confidence interval calculated using statistical software
Note: P-values for difference effect was calculated using standard p-value formula while log transformation was used for ratio p-values appropriately

Table 40 Results per study Table A3b Results of the CLARION study

Trial Name: CLARION NCT Number: NCT01818752											
				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	KMP	478	NR	--	--	--	HR for KMP vs. VMP: 1.084	0.819-1.434	0.7128	Overall survival was compared between treatment groups using a log-rank test stratified by the randomization stratification factors. The corresponding HRs and their 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model stratified by the same randomization stratification factors. The distribution of time-to-event endpoints were summarized descriptively using the Kaplan-Meier method. Corresponding 95% CIs for the medians were constructed using the method of Klein and Moeschberger12 with log-log transformation.	Facon et al 2019[10]
	VMP	477	NR								
Median progression-free survival	KMP	478	22.3 months (20.9-26.7)	KMP – VMP 0.20	--	--	HR for KMP vs. VMP: 0.906	0.746-1.101	0.1590	Progression-free survival was compared between treatment groups using a log-rank test stratified by the randomization stratification factors. The corresponding HRs and their 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model stratified by the same randomization stratification factors. The distribution of time-to-event endpoints were summarized descriptively using the Kaplan-Meier method. Corresponding 95% CIs for the medians were constructed using	Facon et al 2019[10]
	VMP	477	22.1 months (20.8-24.4)								

										the method of Klein and Moeschberger12 with log-log transformation.	
Discontinuations due to treatment-related adverse events	KMP	478	16.7%	2.0%	0-6.6%	--	RR: 1.14	0.85-1.53	0.396	The National Cancer Institute Common Terminology Criteria for adverse events version 4.03 was used to describe and assess adverse event severity.	Facon et al 2019[10]
	VMP	477	14.7%								
(*) Hazard/Odds/Risk ratios are calculated as KMP vs. VMP (**) Risk ratio compares KMP vs. VMP; confidence interval calculated using statistical software Note: P-values for difference effect was calculated using standard p-value formula while log transformation was used for ratio p-values appropriately											

Medicinrådet

Medicinrådets protokol for vurdering af lenalidomid i kombination med bortezomib og dexamethason til behandling af tidligere ubehandlede patienter med knoglemarvskræft

Versionsnr.: 1.0

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 nye indikationer 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 ansøger 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	12. april 2019
Ikrafttrædelsesdato	15. april 2019
Dokumentnummer	46990
Versionsnummer	1.0

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, 15. april 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Revlimid®
Generisk navn	Lenalidomid
Firma	Celgene
ATC-kode	L04 AX04
Virkningsmekanisme	Lenalidomid binder til proteinet cereblon og hæmmer dets funktion. Proteinet findes i knoglemarvens celler og er involveret i blandt andet cellens stofskifte, signalering og i dannelsen af nye blodkar.
Administration/dosis	Først 8 serier af 21 dage med • 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 af 28 dage til progression med • Lenalidomid 25 mg p.o. på dag 1-21 • Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22
Forventet EMA-indikation	Lenalidomid i kombination med bortezomib og dexamethason til voksne patienter med tidligere ubehandlet knoglemarvskræft, som ikke er egnede til stamcelletransplantation.

2 Forkortelser

BorLenDex:	Lenalidomid i kombination med bortezomib og dexamethason
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
EORTC:	*European Organisation for Research and Treatment of Cancer*
EPAR:	*European Public Assessment Report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HDT/STS:	Højdosis kemoterapi med stamcellestøtte
HR:	*Hazard ratio*
ITT:	*Intention to treat*
OR:	*Odds ratio*
PFS:	Progressionsfri overlevelse
PICO:	Population, Intervention, Komparator, Effektmål
QLQ-C30:	*Quality of Life Questionnaire Core-30*
RR:	Relativ risiko
SMD:	*Standardized mean difference*

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes besvaret i vurderingen af lenalidomid i kombination med bortezomib og dexamethason (BorLenDex) som mulig standardbehandling af behandlingsnaive patienter med knoglemarvskræft. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres 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 BorLenDex modtaget den 7. marts 2019.

Protokollen danner grundlag for den endelige ansøgning vedrørende vurdering af BorLenDex, sammenlignet med dansk standardbehandling (komparator). For alle effektmål, der er opgivet i denne protokol, skal der foretages sammenlignende analyser mellem BorLenDex og komparator, af både absolutte og relative værdier for de specificerede populationer i de angivne måleenheder (se tabel 1 og 2). 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 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 myelomatose kan der påvises et protein i blod og urin, som kaldes M-komponent. M-komponenten dannes af de maligne 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 behandlingskrævende patienter årligt, der skal have deres første behandling [2].

4.1 Nuværende behandling

Behandling af myelomatose 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, perioder med symptomfrihed, længerevarende behandlingsfri perioder 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]. Patientpopulationen udgør ca. 240 patienter årligt. Blandt de nuværende behandlingsmuligheder anvendes oftest en kombination af enten bortezomib, melphalan og

prednison (BorMelPred) eller lenalidomid og dexamethason (LenDex) [8]. Samlet set har disse patienter en median progressionsfri overlevelse på ca. 18 måneder [2].

De patienter, der behandles med HDT/STS, har en væsentlig bedre prognose end de, der ikke er kandidater til denne behandling. Halvdelen af de patienter, der behandles med HDT/STS, er fortsat i live efter ca. 7 år (den mediane overlevelse), mens patienter, der ikke er kandidater til HDT/STS, har en median overlevelse på ca. 3 år. Denne gruppe omfatter især patienter over 70 år og inkluderer de ældste patienter. Den samlede medianoverlevelse for hele gruppen af patienter med myelomatose 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 Lenalidomid i kombination med bortezomib og dexamethason

Lenalidomid tilhører gruppen af immunmodulerende stoffer, som binder til proteinet cereblon og hæmmer dets funktion. Proteinet findes i knoglemarvens celler og er involveret i blandt andet cellens stofskifte, signalering og i dannelsen af nye blodkar. Behandling med immunmodulerende stoffer hæmmer derfor både kræftcellernes deling og deres forsyning af næringsstoffer fra blodet. Lenalidomid har været godkendt til behandling af myelomatose siden 2007 og indgår som det ene lægemiddel i mange behandlingskombinationer.

BorLenDex skal til behandling af patienter, der ikke er kandidater til HDT/STS, doseres som følger:

Først 8 serier af 21 dage med

- 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 af 28 dage til progression med

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

5 Kliniske spørgsmål

Det kliniske spørgsmål, fagudvalget ønsker at besvare i vurderingen af den kliniske merværdi for lenalidomid i kombination med bortezomib og dexamethason, fremgår nedenfor og indeholder en specifikation af patientgruppen, interventionen, alternativet til interventionen (komparator) og effektmål.

5.1 Klinisk spørgsmål

Hvad er værdien af lenalidomid i kombination med bortezomib og dexamethason sammenlignet med nuværende klinisk praksis til tidligere ubehandlede behandlingskrævende patienter med knoglemarvskræft, der ikke er kandidater til HDT/STS?

Population
Tidligere ubehandlede patienter med behandlingskrævende knoglemarvskræft der ikke er kandidater til HDT/STS.

Intervention
Lenalidomid i kombination med bortezomib og dexamethason.

Komparator
Fagudvalget vil gerne sammenligne interventionen med nuværende dansk klinisk praksis, som er enten lenalidomid og dexamethason i minimum 18 måneder eller bortezomib i kombination med melphalan og prednisolon.

Lenalidomid og dexamethason, doseret som følger:

Serier af 28 dages varighed i minimum 18 måneder eller til progression

- 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 doseret som følger:

9 serier af 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 effektmål, fagudvalget ønsker at vurdere, fremgår af tabel 1.

5.2 Valg af effektmål

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 derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er fremkommet på samme måde som under den tidligere metode og afspejler den mindste forskel, som, fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende mindste klinisk relevante forskel* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

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 håndbog. 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 håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1 summerer de effektmål fagudvalget ønsker at se data for i vurderingen af lenalidomid i kombination med bortezomib og dexamethason som behandling af tidligere ubehandlede patienter, der ikke er kandidater til HDT/STS. Tabellen angiver effektmålenes vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og kategori for det kliniske spørgsmål.

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 (retningsgivende og evt. justeret) samt indplacering i de tre kategorier ("dødelighed" "livskvalitet, alvorlige symptomer og bivirkninger" og "ikkealvorlige symptomer og bivirkninger").

Effektmål	Vigtighed	Kategori	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret mindste klinisk relevante forskel
Samlet overlevelse	*Kritisk*	*Dødelighed*	Median overlevelse	3 mdr. ved behandlinger af samme varighed 6 mdr. ved behandlinger af forskellig varighed	-
	Vigtig	*Livskvalitet, alvorlige symptomer og bivirkninger**	Median PFS	3 mdr. ved behandlinger af samme varighed 6 mdr. ved behandlinger af forskellig varighed	-
Behandlingsophør	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel der ophører behandling pga. uønskede hændelser	*Forskel på 10 %-point mellem grupperne*	*Forskel på 5 %-point mellem grupperne*
Livskvalitet	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Antal pointændring over tid målt med EORTC QLQ-C30	*Forskel på 10 point mellem grupperne*	*Forskel på 5 point mellem grupperne*
Bivirkninger	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Kvalitiativ gennemgang	-	-

* Da PFS er et sammensateffektmål, som indeholder både progression og død anvendes væsentlighedskriterierne for katergorien *Livskvalitet, alvorlige symptomer og bivirkninger*.

5.2.1 Kritiske effektmål

Samlet overlevelse

Samlet overlevelse (overall survival, OS) er et præcist effektmål, der enten kan opgøres som sandsynligheden for at dø indenfor en fast opfølgningstid eller som en median overlevelsesperiode. Overlevelse defineres som tiden fra randomisering eller opstart af behandling til død, uanset årsag. Da behandlingsmålet ved knoglemarvskræft er at sikre længst mulig overlevelse under hensyntagen til patientens livskvalitet, er overlevelse et kritisk effektmål for vurderingen af nye lægemidler. Fagudvalget ønsker effektmålet opgjort som median overlevelse. Fagudvalget ønsker at skelne mellem, hvorvidt komparator er en tidsbegrænset eller kontinuert behandling, idet de forventer en større effektforskel, når interventionen sammenlignes med en komparator, hvor behandlingen er tidsbegrænset. Derfor vurderer fagudvalget, at den mindste klinisk relevante forskel er 3 måneder, hvis intervention og komparator har

samme varighed og 6 måneder, hvis intervention og komparator har forskellig varighed. Dette er fastsat på baggrund af den mediane overlevelse på ca. 3 år.

Fagudvalget ønsker at medtage PFS som et surrogatmål for samlet overlevelse, såfremt data for overlevelse ikke er modne. For patienter, der ikke er kandidater til HDT/STS, er den mediane PFS ca. 18 måneder [9]. Fagudvalget vurderer, at PFS bør være et vigtigt effektmål. Fagudvalget vurderer, at mindste klinisk relevante forskel i PFS er 6 måneder, når komparator er tidsbegrænset og 3 måneder, når komparator er tidsubegrænset behandling.

Fagudvalget ønsker at vurdere data for den længst mulige opfølgningstid i studierne.

PFS defineres som tiden fra randomisering til progression eller død, hvor progression bestemmes efter det standardiserede responskriterie [10]. PFS er i en metaanalyse vist at korrelere med overlevelse indenfor behandling af myelomatose [11,12] 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.

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 myelomatose er relativt bivirkningstunge, og 10-20 % ophører behandlingen pga. uønskede hændelser. Fagudvalget vurderer, at en forskel på 10 %-point mellem grupperne er klinisk relevant. Fagudvalget ønsker at vurdere data for den længst mulige opfølgningstid i studierne.

5.2.2 Vigtige effektmål

Helbredsrelateret livskvalitet
Livskvalitet er et vigtigt effektmål i vurderingen af behandling af knoglemarvskræft, fordi sygdommen manifesterer sig ved en række symptomer og behandlingsmulighederne ved en række bivirkninger, som direkte påvirker patientens livskvalitet. Desuden findes endnu ingen kurative behandlingsformer, og en række af lægemidlerne gives kontinuerligt indtil relaps. 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 [13,14]. 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 [15]. 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 [16]. 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.

Kvalitativ gennemgang af bivirkninger
Fagudvalget ønsker som supplement til effektmålet behandlingsophør grundet bivirkninger en kvalitativ gennemgang 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 lenalidomid i kombination med bortezomib er undersøgt som behandling til nydiagnosticerede patienter med knoglemarvskræft. Fagudvalget

vil ud fra denne gennemgang vurdere håndterbarhed og tyngde af bivirkningsprofilen. Fagudvalget vurderer, at den kvalitative gennemgang er vigtig for kategoriseringen af den kliniske merværdi.

6 Litteratursøgning

Vurderingen af klinisk merværdi 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 BorLenDex er sammenlignet direkte med komparatorerne. Sekretariatet fandt følgende artikel, som er relevant, og som kan anvendes til direkte sammenligning af interventionen og komparatoren lenalidomid i kombination med dexamethason:

- Durie BGM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, 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):519–27. [17]

Virksomheden skal derfor søge efter yderligere studier, der kan anvendes til en indirekte sammenligning med den anden komparator, bortezomib i kombination med melphalan og prednisolon. Det betyder, at der både skal søges efter primærstudier af interventionens effekt og efter primærstudier af effekten af komparator. 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.

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. Studier, der ikke er fase 3-studier, ekskluderes.

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, stadieinddeling (ISS), antallet og type af tidligere behandlinger og nyrefunktion.

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 informationer, der kan belyse en vurdering af, hvorvidt og hvordan indførelsen af den ansøgte intervention i dansk klinisk praksis vil påvirke behandlinger 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 Specialeansvarlig overlæge	Region Syddanmark
Carsten Helleberg Overlæge	Region Hovedstaden
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En patient/patientrepræsentant	Danske Patienter
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Jennifer A. F. Andresen Farmaceut	Dansk Selskab for Sygehusapoteksledelse
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Medicinrådets sekretariat

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11 Bilag 1 – Søgeprotokol

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	Population
4	"lenalidomide"[Mesh]	
5	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]	
6	#4 OR #5	
7	"bortezomib"[Mesh]	
8	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]	
9	#7 OR #8	
10	"dexamethasone"[Mesh]	
11	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]	
12	#10 OR #11	
13	#6 AND #9 AND #12	Intervention
14	"Melphalan"[Mesh]	
15	melphalan*[tiab] or melphelan*[tiab] or melfalan*[tiab] or medphalan*[tiab] or merphalan*[tiab] or sarcolysin*[tiab] or sarkolysin*[tiab] or alkeran*[tiab] or "phenylalanine mustard"[tiab]	
16	#14 OR #15	
17	"Prednisone"[Mesh]	
18	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 decortin*[tiab] or dacortin*[tiab] or decortisyl*[tiab] or deltason*[tiab] or encorton*[tiab] or liquid-pred*[tiab] or meticorten*[tiab] or panasol*[tiab] or prednidib*[tiab] or pronison*[tiab] or sone*[tiab]	
19	#17 OR #18	
20	#16 AND #9 AND #19	Komparator #2
21	#13 OR #20	Intervention **eller** komparator #2
22	#3 AND #21	
23	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[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
24	#22 AND #23	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}	Population
4	[mh Lenalidomide]	
5	(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	
6	{or #4-#5}	
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 Dexamethasone]	
11	(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	
12	{or #10-#11}	
13	#6 and #9 and #12	Intervention
14	[mh Melphalan]	
15	(melphalan* or melphelan* or melfalan* or medphalan* or merphalan* or sarcolysin* or sarkolysin* or alkeran* or "phenylalanine mustard"):ti,ab,kw	
16	{or #14-#15}	
17	[mh Prednisone]	
18	(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	
19	{or #17-#18}	
20	#16 and #9 and #19	Komparator #2
21	#13 or #20	Intervention **eller** komparator
22	#3 and #21	
23	"conference abstract":pt	
24	#22 not #23	Endelig søgning

12 Versionslog

Version	Dato	Ændring
1.0	12. april 2019	Godkendt af Medicinrådet.