Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende pomalidomid i kombination med bortezomib og dexamethason som mulig standardbehandling til patienter med knoglemarvskræft der har modtaget mindst én tidligere behandling, inklusive lenalidomid

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	20. november 2019
Ikrafttrædelsesdato	20. november 2019
Dokumentnummer	63025
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 20. november 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Imnovid®
Generisk navn	Pomalidomid
Firma	Celgene Europe Ltd
ATC-kode	L04 AX06
Virkningsmekanisme	Pomalidomid 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	• Pomalidomid 4 mg (anbefalet startdosis) p.o. på dag 1-14 i gentagne 21-dages serier til progression. • I de første 8 serier gives bortezomib 1,3 mg/m^2 i.v. eller s.c. på dag 1, 4, 8 og 11. Fra serie 9 og frem gives bortezomib 1,3 mg/m^2 s.c. på dag 1 og 8. • I de første 8 serier gives dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 9, 11 og 12. Fra serie 9 og frem gives dexamethason 20 mg p.o. på dag 1, 2, 8 og 9.
EMA-indikation	Pomalidomid i kombination med bortezomib og dexamethason til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusive lenalidomid.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** pomalidomid i kombination med bortezomib og dexamethason (PomBorDex) som mulig standardbehandling til patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid. Behandlingen bør anvendes efter behandling med enten daratumumab i kombination med bortezomib og dexamethason (DaraBorDex) eller daratumumab i kombination med lenalidomid og dexamethason (DaraLenDex) eller tidligere, hvis daratumumab er kontraindiceret.

Med denne anvendelse vurderer Medicinrådet, at der er der et rimeligt forhold mellem behandlingens værdi og omkostninger.

Medicinrådet bemærker, at effekten af CarDex efter PomBorDex såvel som effekten af PomBorDex efter CarDex er ubelyst.

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

1. *Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med nuværende klinisk praksis (DaraBorDex eller DaraLenDex) til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid?*
2. *Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med DaraBorDex til behandling af patienter med knoglemarvskræft, som er refraktære overfor lenalidomid, og som har modtaget mindst én tidligere behandling?*

3. *Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med carfilzomib og dexamethason (CarDex) til behandling af patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger?*

3 Formål

Formålet med baggrund for Medicinrådets anbefaling vedrørende pomalidomid i kombination med bortezomib og dexamethason som mulig standardbehandling til patienter med knoglemarvskræft, der har modtaget mindst én tidligere behandling, inklusive lenalidomid, 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 10. februar 2019, og protokollen blev sendt til Celgene den 15. april 2019. Den endelige ansøgning blev modtaget første gang den 23. august 2019 og blev betragtet som endelig den 6. september 2019. Beslutning om anbefaling blev truffet den 20. november 2019.

Sagsbehandlingstiden er dermed 10 uger og 5 dage.

5 Medicinrådets vurdering af samlet værdi

Pomalidomid i kombination med bortezomib og dexamethason (PomBorDex) er sammenlignet med komparatorerne daratumumab i kombination med bortezomib og dexamethason (DaraBorDex), daratumumab i kombination med lenalidomid og dexamethason (DaraLenDex) og carfilzomib i kombination med dexamethason (CarDex) i tre kliniske spørgsmål:

- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med DaraBorDex og DaraLenDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid. Evidensens kvalitet vurderes at være **meget lav**.

- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med DaraBorDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling og er refraktære overfor lenalidomid. Evidensens kvalitet vurderes at være **meget lav**.

- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med CarDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger. Evidensens kvalitet vurderes at være **meget lav**.

På baggrund af sammenligningen af de absolutte effektestimater fra studierne ser PomBorDex samlet set ud til at være et dårligere behandlingsalternativ end DaraLenDex og DaraBorDex. PomBorDex ser ud til at være et ligeværdigt behandlingsalternativ sammenlignet med CarDex og bør på linje med CarDex anvendes efter DaraBorDex og DaraLenDex eller tidligere, hvis daratumumab er kontraindiceret.

Evidensens kvalitet vurderes at være **meget lav**.

6 Høring

Høringsperioden foregik fra den 16. til den 30. oktober 2019. Ansøger havde ingen kommentarer til Medicinrådets vurdering.

7 Resumé af økonomisk beslutningsgrundlag

Amgros har vurderet de gennemsnitlige meromkostninger pr. patient og budgetkonsekvenserne for regionerne ved brug af PomBorDex sammenlignet med komparatorerne DaraLenDex, DaraBorDex og CarDex.

Til patienter, der tidligere har modtaget mindst én behandling, er behandling med PomBorDex forbundet med store besparelser sammenlignet med DaraLenDex og med betydelige omkostninger sammenlignet med DaraBorDex.

Til patienter, der tidligere har modtaget mindst én behandling og er refraktære overfor lenalidomid, er behandling med PomBorDex forbundet med betydelige omkostninger sammenlignet med DaraBorDex.

Til patienter, der tidligere har modtaget mindst to behandlinger, er behandling med PomBorDex forbundet med store besparelser sammenlignet med CarDex. Der er derfor et rimeligt forhold mellem behandlingens værdi og omkostninger, når PomBorDex sammenlignes med CarDex.

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) Anette Prior Gjesing (projektdeltager) Anette Pultera Nielsen (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistisk chefkonsulent) Annemette Anker Nielsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	20. november 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Medicinrådets vurdering af pomalidomid i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft, der tidligere har modtaget mindst én behandling, inklusive lenalidomid
- Ansøgers endelige ansøgning
- Protokol for vurdering af pomalidomid i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft, der tidligere har modtaget mindst én behandling, inklusive lenalidomid

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af pomalidomid (Imnovid) i kombination med bortezomib og dexamethason (PomBorDex) som mulig standardbehandling til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusiv lenalidomid. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	20-11-2019
Firma	Celgene (ansøger)
Lægemiddel	Pomalidomid (Imnovid)
Indikation	Pomalidomid (Imnovid) i kombination med bortezomib og dexamethason (PomBorDex) er indiceret til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusiv lenalidomid

Amgros' vurdering

- Amgros **kan ikke vurdere** om der er et rimeligt forhold mellem omkostningerne og den kliniske merværdi for PomBorDex som mulig standardbehandling til patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusiv lenalidomid, sammenlignet med daratumumab i kombination med lenalidomid og dexamethason (DaraLenDex, P1a), og at der **ikke er** et rimeligt forhold mod daratumumab i kombination med bortezomib og dexamethason (DaraBorDex, P1b)

- Amgros vurderer, at der **ikke er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for PomBorDex som mulig standard behandling til patienter med knoglemarvskræft, som er refraktære overfor lenalidomid, sammenlignet med DaraBorDex (P2)

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for PomBorDex som mulig standardbehandling til patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger, sammenlignet med carfilzomib i kombination med dexamethason (CarDex, P3)

Overordnet konklusion

Medicinrådet har vurderet, at PomBorDex sammenlignet DaraLenDex og DaraBorDex giver en merværdi **der ikke kan kategoriseres**. Behandling med PomBorDex er forbundet med store besparelser sammenlignet med DaraLenDex og meromkostninger sammenlignet med DaraBorDex. Medicinrådet har dog vurderet at PomBorDex sammenlignet med DaraLenDex er et dårligere behandlingsalternativ, vurderet på den mediane PFS mellem de to behandlingskombinationer. Ligeledes vurderer Medicinrådet at PomBorDex er et dårligere behandlingsalternativ sammenlignet med DaraBorDex, og kun bør foretrækkes til patienter, hvor daratumumab er kontraindiceret. Amgros **kan ikke vurdere** om der er rimeligt forhold mellem den kliniske merværdi og besparelserne sammenlignet med DaraLenDex. Amgros vurderer, at der **ikke er** et rimeligt forhold mellem den kliniske merværdi for PomBorDex sammenlignet med DaraBorDex.

Medicinrådet har vurderet, at PomBorDex sammenlignet CarDex giver en merværdi **der ikke kan kategoriseres**. Medicinrådet har dog vurderet at behandling med PomBorDex ikke er et dårligere behandlingsalternativ sammenlignet med CarDex. Behandling med PomBorDex er forbundet med store besparelser sammenlignet med CarDex. Amgros vurderer, der **er** et rimeligt forhold mellem den kliniske merværdi og besparelserne.

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
P1: Voksne patienter med knoglemarvskræft, som har modtaget mindst en tidligere behandling, inklusive lenalidomid.	**P1a:** DaraLenDex	Kan ikke kategoriseres	Meget lav	Kan ikke vurdere
	P1b: DaraBorDex	Kan ikke kategoriseres	Meget Lav	Ikke rimeligt
P2: Voksne patienter med knoglemarvskræft, som har modtaget mindst en tidligere behandling og som vurderes at være refraktære overfor lenalidomid.	DaraBorDex	Kan ikke kategoriseres	Meget Lav	Ikke rimeligt
P3: Voksne patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger, og som har modtaget enten DaraLenDex eller DaraBorDex.	CarDex	Kan ikke kategoriseres	Meget Lav	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 PomBorDex er forbundet med store besparelser sammenlignet med DaraLenDex og CarDex og meromkostninger sammenlignet med DaraBordex

I Tabel 2,3 og 4 ses de inkrementelle omkostninger for PomBorDex og komparatorer.

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med DaraLenDex for P1a estimeres til at være ca. [redacted] DKK.

Tabel 2: Resultatet af Amgros hovedanalyse for P1a, SAIP, DKK

	PomBorDex	DaraLenDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	242.579	103.731	138.848
Patientomkostninger	33.968	25.895	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med DaraBorDex for P1b og P2 estimeres til at være ca. [redacted] DKK.

Tabel 3: Resultatet af Amgros hovedanalyse for P1b og P2, SAIP, DKK

	PomBorDex	DaraBorDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	242.579	176.942	65.636
Patientomkostninger	33.968	37.628	-3.660
Totale omkostninger	[redacted]	[redacted]	[redacted]

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med CarDex for P3 estimeres til at være ca. [redacted] DKK.

Tabel 4: Resultatet af Amgros hovedanalyse for P3, SAIP, DKK

	PomBorDex	CarDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	242.579	353.553	-110.974
Patientomkostninger	33.968	64.038	-30.069
Totale omkostninger	[redacted]	[redacted]	[redacted]

Laves analysen med AIP, er de inkrementelle omkostninger ca. -765.000 DKK for P1a, ca. -110.000 DKK for P1b og P2, og ca. -474.000 DKK for P3.

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af PomBorDex som standardbehandling vil være ca. [redacted] DKK for P1 ved år 5, ca. [redacted] mio. DKK for P2 ved år 5 og ca. [redacted] mio. DKK for P3 ved år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. -6,7 mio. DKK for P1, ca. -10,4 mio. DKK for P2 og ca. -31,6 mio. DKK for P3 ved år 5.

POMALIDOMID (IMNOVID) I KOMBINATION MED BORTEZOMIB OG DEXAMETHASON

2. LINJEBEHANDLING AF KNOGLEMARVSKRÆFT

AMGROS 25. oktober 2019

AMGROS

OPSUMMERING

Baggrund

Pomalidomid (Imnovid) i kombination med bortezomib og dexamethason (PomBorDex) er indiceret til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusiv lenalidomid. Ca. 320 nye patienter per år kandiderer til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af Celgene.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med PomBorDex til patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling inklusiv lenalidomid. I analysen sammenlignes behandling med PomBorDex med en kombination af daratumumab + lenalidomid + dexamethason (DaraLenDex), daratumumab + bortezomib + dexamethason (DaraBorDex) og carfilzomib + dexamethason (CarDex).

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af PomBorDex sammenlignet med henholdsvis DaraLenDex(P1a), DaraBorDex(P1b og P2) og CarDex(P3). De inkrementelle omkostninger er angivet i SAIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger for PomBorDex sammenlignet med komparatorene:

- P1a: ca. [redacted] DKK per patient
- P1b og P2: ca. [redacted] DKK per patient
- P3: ca. [redacted] DKK per patient

Hvis analysen udføres med AIP bliver de inkrementelle omkostninger til sammenligning ca. -765.000 DKK for P1a, ca. -110.000 DKK for P1b og P2 og ca. -474.000 DKK for P3.

Amgros vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af PomBorDe som standardbehandling vil være ca. [redacted] DKK for P1 ved år 5, ca. [redacted] DKK for P2 ved år 5 og ca. [redacted] DKK for P3 ved år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. -6,7 mio. DKK for P1, ca. -10,4 mio. DKK for P2 og ca. -31,6 mio. DKK for P3 ved år 5.

Konklusion

Behandling med PomBorDex er forbundet med store besparelser for P1a og P3 og betydelige meromkostninger for P1b og P2. Meromkostningerne og besparelserne drives af lægemiddelomkostningerne og hospitalsomkostninger.

Liste over forkortelser

AIP	Apotekernes indkøbspris
Bor	Bortezomib
Car	Carfilzomib
Dar	Daratumumab
Dex	Dexamethason
DKK	Danske kroner
DMSG	Dansk Myelomatose Studiegruppe
DRG	Diagnose Relaterede Grupper
HDT/STS	Højdosis kemoterapi med stamcellestøtte
KM	Kaplan-Meier
Len	Lenalidomid
Por	Pomalidomid
SAIP	Sygehusapotekernes indkøbspriser
SPC	Produktresumé
ToT	Time on treatment

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Celgene
Handelsnavn:	Imnovid
Generisk navn:	Pomalidomid
Indikation:	Pomalidomid (Imnovid) i kombination med bortezomib og dexamethason til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusive lenalidomid.
ATC-kode:	L04AX06

Proces	
Ansøgning modtaget hos Amgros:	16-09-2019
Endelig rapport færdig:	25-10-2019
Sagsbehandlingstid fra endelig ansøgning:	39 dage
Arbejdsgruppe:	**Louise Greve Dal** Line Brøns Jensen Lianna Geertsen Mark Friborg Pernille Winther Johansen

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

Pomalidomid (Imnovid) i kombination med bortezomib og dexamethason (PomBorDex) er indiceret til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusiv lenalidomid. Celgene (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af pomalidomid (Imnovid) og har den 16.09.2019 indsendt en ansøgning til Medicinrådet om anbefaling af PomBorDex som standardbehandling på danske hospitaler. 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 inkrementelle omkostninger forbundet med behandling med PomBorDex til den angivne indikation og de samlede budgetkonsekvenser for regionerne ved anbefaling af PomBorDex som standardbehandling. I analyserne sammenlignes behandling med PomBorDex med en behandling med DaraLenDex, DaraBorDex og CarDex.

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(1).

Knoglemarvskræft er den næst hyppigste 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. 320 patienter om året vil skulle modtage deres første relapsbehandling(1). Prognosen er afhængig af patientens alder og komorbiditeter ved diagnosetidspunktet. De patienter, der som primærbehandling behandles med højdosiskemoterapi med stamcellestøtte (HDT/STS), har en væsentlig bedre prognose end de, der ikke er egnede 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(1). Denne gruppe omfatter især patienter over 70 år og inkluderer de ældste patienter. 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.

1.3 Nuværende behandling

Behandling af knoglemarvskræft varetages af de hæmatologiske afdelinger og består udover HDT/STS af medicinsk behandling med flere lægemidler i kombination. Ved at kombinere flere lægemidler angribes kræftcellerne på flere måder, og effekten er generelt større end ved behandling med et enkelt lægemiddel(1). 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.

Til patienter, der skal have deres første relapsbehandling, og som ikke er refraktære overfor lenalidomid (ca. 270 patienter årligt), anbefales ifølge Dansk Myelomatose Studiegruppes (DMSG)(2) retningslinje en kombination af daratumumab, lenalidomid og dexamethason (DaraLenDex). Til patienter, der er refraktære overfor lenalidomid (ca. 50 patienter årligt), anbefales en kombination af daratumumab, bortezomib og dexamethason (DaraBorDex) (1).

Valg af behandling foretages i samråd mellem læge og patient under hensyntagen til effekt af tidligere behandling, bivirkninger til tidligere behandlinger, performancestatus, komorbiditet og patientpræferencer, herunder antallet af behandlingsfremmøder. Der tages også hensyn til eventuel refraktæritet overfor lægemidler, der har indgået i tidligere behandlinger og særligt lenalidomid, da det oftest anvendes indtil progression.

Patienter, der er behandlet med DaraLenDex eller DaraBorDex, som igen bliver behandlingskrævende, behandles hovedsageligt med en kombination af carfilzomib og dexamethason (CarDex)(1). De patienter, der tidligere er behandlet med carfilzomib, vil ikke igen være kandidater til en bortezomib behandlingskombination, fordi carfilzomib er den mest potente af proteasominhibitorerne og anvendes til progression. Derfor vurderer fagudvalget vedr. knoglemarvskræft, at PomBorDex (den ansøgte intervention) ikke kan være en standardbehandlingsmulighed i senere linjer.

1.4 Behandling med pomalidomid (Imnovid) i kombination med bortezomib og dexamethason

Indikation

Pomalidomid (Imnovid) er indiceret som kombinationterapi med bortezomib og dexamethason til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusive lenalidomid

Pomalidomid (Imnovid) er desuden indiceret som kombinationterapi med dexamethason til behandling af patienter der har modtaget mindst to tidligere behandlinger.

Virkningsmekanisme

Pomalidomid (Imnovid) 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(1).

Dosering

- Pomalidomid (Imnovid) 4 mg (anbefalet startdosis) p.o. på dag 1-14 i gentagne 21-dages serier til progression
- I de første 8 serier gives bortezomib 1,3 mg/m2 i.v. eller s.c. på dag 1, 4, 8 og 11. Fra serie 9 og frem gives bortezomib 1,3 mg/m2 s.c. på dag 1 og 8
- I de første 8 serier gives dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11 og 12. Fra serie 9 og frem gives dexamethason 20 mg p.o. på dag 1, 2, 8, og 9

1.4.1 Komparator

Medicinrådet har defineret DaraLenDex (P1a), DaraBorDex (P1b og P2) og CarDex (P3) som komparatorer, se tabel 1.

Tabel 1: Definerede populationer og komparator.

Population	Komparator
P1: Voksne patienter med knoglemarvskræft, som har modtaget mindst en tidligere behandling, inklusive lenalidomid.	**P1a:** DaraLenDex
	P1b: DaraBorDex
P2: Voksne patienter med knoglemarvskræft, som har modtaget mindst en tidligere behandling og som vurderes at være refraktære overfor lenalidomid.	DaraBorDex
P3: Voksne patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger, og som har modtaget enten DaraLenDex eller DaraBorDex.	CarDex

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af pomalidomid (Imnovid) som behandling for følgende populationer:

- **P1:** Hvad er den kliniske merværdi af pomalidomid (Imnovid) i kombination med bortezomib og dexamethason (PomBorDex) sammenlignet med nuværende klinisk praksis til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusiv lenalidomid?
- **P2:** Hvad er den kliniske merværdi af pomalidomid (Imnovid) i kombination med bortezomib og dexamethason (PomBorDex) sammenlignet med daratumumab i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft, som er refraktære overfor lenalidomid, og som har modtaget mindst én tidligere behandling?
- **P3:** Hvad er den kliniske merværdi af pomalidomid (Imnovid) i kombination med bortezomib og dexamethason (PomBorDex) sammenlignet med CarDex til patienter, som har modtaget mindst to tidligere behandlinger?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af inkrementelle omkostninger per patient sammenlignes behandling med PomBorDex med DaraLenDex (P1a), DaraBorDex (P1b og P2) og CarDex (P3). Analysen inkluderer omkostninger til lægemidler, administration, patienttid og -transport.

Ansøger har indsendt en analyse der sammenligner med PomBorDex med DaraLenDex, DaraBorDex og CarDex. Det er kun den seneste indsendte analyse der vurderes i følgende afsnit.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en model for behandling af patienter i de nævnte populationer, hvor tiden patienten er i behandling defineres ud fra Kaplan-Meier (KM)-kurve fra det kliniske studie, OPTIMISMM-studiet(3).Alle patienter starter i modellen i en progressionsfri tilstand på behandling (time on treatment, ToT). Der er ikke signifikant forskel i tiden til progression mellem PomBorDex, DaraLenDex, DaraBorDex og CarDex, og derfor har ansøger antaget samme behandlingslængde for alle alternativer. Behandlingslængden er bestemt via ToT KM kurve fra OPTIMISMM-studiet(3). ToT KM kurven er estimeret på en patientpopulation i OPTIMISMM-studiet, som varierer fra de populationer, som er blevet præciseret i Medicinrådets protokol ift. tidligere behandlinger med lenalidomid og lenalidomidrefraktæritet(1,3).

Ansøger antager, at bivirkningsprofilen for PomBorDex, DaraLenDex, DaraBorDex og CarDex er ens, og derfor er omkostninger til bivirkninger ikke inkluderet i ansøgers hovedanalyse.

Ansøger inkluderer ikke omkostninger til efterfølgende behandling, da den nuværende behandlingsvejledning for knoglemarvskræft ligger op til at behandlingsmulighederne i første relapsbehandling bør være udtømt, før man overvejer behandlinger under 'anden relapsbehandling'. Ingen af de efterfølgende behandlinger er ligestillet, men overvejes til patienten under hensyn til toksicitet, komorbiditet, tidligere behandlinger og patientpræferencer. En anbefaling af PomBorDex vil derfor ikke ændre på efterfølgende behandlinger(4).

Amgros' vurdering

Amgros vurderer at ansøgers modeltilgang er acceptabel.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 5 år. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4% per år jf. Amgros' metodevejledning.

Amgros' vurdering

Ansøgers analyseperspektiv er i tråd med Amgros' metodevejledning, men ændre tidshorisonten til 10 år.

Amgros accepterer ansøgers tilgang men ændrer tidshorisonten til 10 år.

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. Anvendte doser er hentet i de respektive produkters produktresuméer og priserne er baseret på sygehusapotekernes indkøbspriser (SAIP) fra Amgros. Alle anvendte lægemiddelpriser er i SAIP, se tabel 2.

Tabel 2: Anvendte lægemiddelpriser, SAIP (oktober 2019).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Pomalidomid	4 mg	21	[redacted]	Amgros
Pomalidomid	3 mg	21	[redacted]	Amgros
Pomalidomid	2 mg	21	[redacted]	Amgros
Pomalidomid	1 mg	21	[redacted]	Amgros
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
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
Dexamethason	4 mg	20	[redacted]	Amgros
Dexamethason	1 mg	100	[redacted]	Amgros

Ansøger antager at en patient gennemsnitlig vejer 73,4 kg og har et gennemsnitligt overfladeareal på 1,84 m^2.

Amgros' vurdering

Amgros ændrer priserne i analysen til SAIP.

Amgros accepterer ansøgers valg af lægemiddelomkostninger.

Hospitalsomkostninger

Ansøger har inkluderet omkostninger forbundet med administration af lægemidler, der ikke gives oralt. Omkostningerne er inkluderet i form af sygeplejersketid og kliniktid, som vist i tabel 3.

Tabel 3: Omkostninger til lægemiddeladministration

	Estimeret tidsforbrug	Enhedsomkostning	Anvendt omkostning [DKK]	Kilde
Sygeplejersketid	30 min.	8,7 DKK/min.	261	Amgros' vejledning: Værdisætning af enhedsomkostninger
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 anvender DRG-taksten 17MA98 MC17.

Amgros ændrer de anvendte enhedsomkostninger til relevante DRG-takster.

Omkostninger til bivirkninger

Da der ikke er statistisk signifikant forskel mellem PomBorDex og komparatorerne, antager ansøger at bivirkningsprofilen for PomBorDex, DaraLenDex, DaraBorDex og CarDex er ens, og inkluderer derfor ikke omkostninger til bivirkninger i ansøgers hovedanalyse.

Amgros' vurdering

Amgros har bedt ansøger indsende en følsomhedsanalyse hvor bivirkninger inkludere. Resultatet viste at ansøgers tilgang ikke har betydning for analysens resultat.

Amgros accepterer ansøgers tilgang.

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. Ansøgers estimerede patienttid kan ses i tabel 4.

Tabel 4: Ansøgers estimat af effektiv patienttid.

	Patienttid	Enhedsomkostning	Kilde
Kliniktid	30 min. (for bortezomib) 150 min. (for daratumumab) 45 min. (for carfilzomib)	180 DKK/time	Amgros' vejledning: Værdisætning af enhedsomkostninger
Patient transporttid	90 min.	100 DKK/pr. besøg	Amgros' vejledning: Værdisætning af enhedsomkostninger

Amgros' vurdering

Amgros accepterer ansøgers antagelse af patientomkostninger.

2.2 Følsomhedsanalyser

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

- Inkludering af lægemiddelspild
- Tidshorisont 10 år
- Subpopulation valgt fremfor ITT population
- Fast behandlingslængde på 96 uger undersøges
- Forskellige parametriske funktioner for PFS undersøges

Amgros' vurdering

Amgros vurderer at ansøgers følsomhedsanalyser og usikkerheden af de forskellige parametre i analysen er relevante. Amgros vurderer, at ansøgers følsomhedsanalyse, hvor det bedste fit for PFS-data fra OPTIMISMM-studiet er anvendt og ekstrapoleret er mest relevant, og anvender denne i Amgros' hovedanalyse samt en tidshorisont på 10 år. Da lægemiddelspild og en fast behandlingslængde på 96 uger har størst betydning på analysens resultat, viser Amgros disse følsomhedsanalyser som Amgros' følsomhedsanalyser. Andre følsomhedsanalyser har dog meget lille betydning for analysens resultat og præsenteres ikke.

Amgros accepterer ansøgers valg af følsomhedsanalyser.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 5, 6 og 7.

Ansøger estimerer i analysen de inkrementelle omkostninger per patient for PomBorDex sammenlignet med DaraLenDex for P1a til at være ca. [redacted] DKK.

Tabel 5: Resultatet af ansøgers hovedanalyse for P1a, SAIP, DKK

	PomBorDex	DaraLenDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	15.079	7.574	7.505
Patientomkostninger	25.690	20.295	5.394
Totale omkostninger	[redacted]	[redacted]	[redacted]

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med DaraBorDex for P1b og P2 estimerer ansøger til at være ca. [redacted] DKK.

Tabel 6: Resultatet af ansøgers hovedanalyse for P1b og P2, SAIP, DKK

	PomBorDex	DaraBorDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	15.079	12.869	2.209
Patientomkostninger	25.690	29.972	-4.282
Totale omkostninger	[redacted]	[redacted]	[redacted]

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med CarDex for P3 estimerer ansøger til at være ca. [redacted] DKK.

Tabel 7: Resultatet af ansøgers hovedanalyse for P3, SAIP, DKK

	PomBorDex	CarDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	15.079	22.007	-6.928
Patientomkostninger	25.690	47.702	-22.012
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.2 Amgros' hovedanalyse

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

- Ekstrapolerede bedste fit PFS-data anvendt
- Tidshorisonten ændres fra 5 år til 10 år
- Hospitalsomkostninger er opdateret med relevante DRG-takster

Resultaterne fra Amgros' hovedanalyse præsenteres i 8, 9 og 10

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med DaraLenDex for P1a estimeres til at være ca. [redacted] DKK.

Tabel 8: Resultatet af Amgros hovedanalyse for P1a, SAIP, DKK

	PomBorDex	DaraLenDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	242.579	103.731	138.848
Patientomkostninger	33.968	25.895	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med DaraBorDex for P1b og P2 estimeres til at være ca. [redacted] DKK.

Tabel 9: Resultatet af Amgros hovedanalyse for P1b og P2, SAIP, DKK

	PomBorDex	DaraBorDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	242.579	176.942	65.636
Patientomkostninger	33.968	37.628	-3.660
Totale omkostninger	[redacted]	[redacted]	[redacted]

De inkrementelle omkostninger per patient for PomBorDex sammenlignet med CarDex for P3 estimeres til at være ca. [redacted] DKK.

Tabel 10: Resultatet af Amgros hovedanalyse for P3, SAIP, DKK

	PomBorDex	CarDex	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	242.579	353.553	-110.974
Patientomkostninger	33.968	64.038	-30.069
Totale omkostninger	[redacted]	[redacted]	[redacted]

Laves analysen med AIP, er de inkrementelle omkostninger ca. -765.000 DKK for P1a, ca. -110.000 DKK for P1b og P2, og ca. -474.000 DKK for P3.

3.2.1 Amgros' følsomhedsanalyse

Jf. afsnit 2.2 havde følsomhedsanalyserne inklusiv lægemiddelspild, og behandlingslængde størst betydning for analysens resultat. Amgros udarbejder derfor to følsomhedsanalyser. Følsomhedsanalyser bygger på samme antagelser som ansøgers følsomhedsanalyser, men baseret på Amgros hovedanalyse. Følsomhedsanalysen inkl. lægemiddelspild, viser at der kan være mere spild forbundet med pomalidomid (Imnovid) end lægemidlerne i kombinationsbehandlingerne i komparator-armene. Følsomhedsanalysen med en behandlingslængde på 96 uger har en længere behandlingslængde end hovedanalysen. Følsomhedsanalyserne ses i tabel 11.

Tabel 11: Resultatet af Amgros' følsomhedsanalyser, SAIP, DKK

	Amgros' hoved-analyse	Inkl. lægemiddelspild	Behandlingslængde 96 uger
P1a	[redacted]	[redacted]	[redacted]
P1b	[redacted]	[redacted]	[redacted]
P2	[redacted]	[redacted]	[redacted]
P3	[redacted]	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at PomBorDex til 2. linjebehandling knoglemarvskræft vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

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

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Ansøger har estimeret patientantallet til at være 270 patienter for P1, 50 patienter for P2, og 156 patienter for P3. Ansøger estimat af patientantallet for P1 og P2, er baseret på Medicinrådets protokol for PomBorDex(1). Ansøger har baseret deres antagelse for patientantallet i P3 på et observationsstudie fra 2016(5), hvor 62% behandlet med DaraLenDex eller DaraBorDex i P1 og P2, vil blive tilbudt en endnu en behandling(P3).

Ansøger antager, at et gradvist markedsoptag for alle 3 patientgrupper, hvor 60% behandles i år 1 og markedsoptaget stiger med 10% per år, hvormed det når 100% markedsoptag i år 5. Ansøger antager at 90 % af patienterne i P1 vil være egnet til behandling med PomBorDex, vurderet ud fra behandlingsvejledningen for knoglemarvskræft(4), hvor 20% i P1 vil være kontraindiceret for daratumumab, og derfor behandles med andre behandlinger. Ansøger har antaget en simpel tilgang, hvor andre behandlinger i dette tilfælde er CarDex, og at 10% af patienterne ikke vil være egnet for PomBorDex, hvis anbefales.
Ansøger antager at 90% af patienterne i P2 og P3 vil være egnet til behandling med PomBorDex, vurderet ud fra at 10% vil være behandlet med CarDex, og derfor ikke er egnet til indikationen.

Tabel 12 viser procentfordelingen mellem de inkluderede behandlingsmuligheder for de 3 populationer.

Tabel 12: Ansøgers estimat af andelen af patienter fordelt mellem behandlingerne for P1, P2 og P3

	P1	P2	P3
	Anbefales ikke		
PomBorDex	-	-	-
DaraLenDex	80%	-	-
DaraBorDex	-	70%	-
CarDex	20%	30%	100%
	Anbefales		
PomBorDex	90%	90%	90%
DaraLenDex	0%	-	-
DaraBorDex	-	0%	-
CarDex	10%	10%	10%

Amgros' vurdering af estimeret antal patienter

Amgros anerkender at ansøgers estimater er baseret på Medicinrådets protokol for vurdering af pomalidomid (Imnovid) i kombination bortezomib og dexamethason. Der er den 25. september 2019 blevet godkendt Medicinrådets anbefaling 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(6). I Medicinrådets vurdering af klinisk værdi for lenalidomid i kombination med bortezomib og dexamethason(7) til denne indikation, står der beskrevet, at fordelingen af DaraBorDex, DaraLenDex og CarDex vil være henholdsvis ca. 65%, 20% og 15%. Hvis man har modtaget behandling med LenDex vil fordelingen af efterfølgende modtagelse af DaraBorDex, DaraLenDex og CarDex være henholdsvis ca. 25%, 60% og 15% eller 80%, 5% og 15%, afhængig af om man har modtaget LenDex til progression eller i 18 måneder. Har patienten modtaget bortezomib i kombination med melphalan og prednison, vil man efterfølgende modtage 80% DaraLenDex og 20% DaraBorDex. Det er ud fra tidligere vurderingsrapporter og behandlingsvejledningen, estimeret at patientestimerne i stedet vil være 157 for P1 og 163 for P2(4).

I Medicinrådets vurderingsrapport af PomBorDex, menes PomBorDex ikke at være bedre end DaraLenDex, og en negativ værdi sammenlignet med DaraBorDex(8). Det er derfor Amgros' vurdering, hvis PomBorDex anbefales, at behandling med PomBorDex ikke vil tag markedsandel fra behandling med henholdsvis DaraLenDex eller DaraBorDex, men i stedet CarDex i både P1 og P2. Da fordelingen mellem behandling med PomBorDex og CarDex vil være ens for P1 og P2, vil der i P3 derfor være en lige fordeling af disse to behandlinger. Se tabel 13, for Amgros' vurdering af andelen for behandling, hvis PomBorDex anbefales til de forskellige populationer.

Tabel 13: Amgros' estimat af andelen af patienter fordelt mellem behandlingerne for P1, P2 og P3, hvis anbefales

	P1	P2	P3
		Anbefales	
PomBorDex	10%	15%	50%
DaraLenDex	80%	-	-
DaraBorDex	-	70%	-
CarDex	10%	15%	50%

Amgros mener ikke markedsoptaget er realistisk, da det antal patienter der har mulighed for at modtage pomalidomid per år er 100%, og der forventes dermed ikke et langsomt markedsoptag ved anbefaling af PomBorDex.

Ansøger har kun inkluderet behandlingerne DaraLenDex, DaraBorDex, CarDex og PomBorDex, selvom der er flere lægemidler anbefalet i Medicinrådets behandlingsvejledning for knoglemarvskræft(4). Der er stor usikkerhed omkring fordelingen af behandlingen for yderligere behandlingskombinationer, og Amgros accepterer derfor ansøgers simplificerede tilgang.

Amgros ændrer patientantallet så dette svarer til det estimerede patientantal i Medicinrådets anbefaling for lenalidomid i kombination med bortezomib og dexamethason og på baggrund af behandlingsvejledningen for myelomatose.
Amgros ændrer markedsoptaget til 100%.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen foruden diskontering jf. Amgros' metodevejledning. Resultaterne ses i tabel 14, 15 og 16 for hhv. P1, P2 og P3.

Tabel 14: Ansøgers hovedanalyse for totale budgetkonsekvenser for P1, 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]

Tabel 15: Ansøgers hovedanalyse for totale budgetkonsekvenser for P2, 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]

Tabel 16: Ansøgers hovedanalyse for totale budgetkonsekvenser for P3, 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]

Med de indlagte antagelser estimerer ansøger, at anvendelse af PomBorDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK, ca. [redacted] DKK og ca. [redacted] DKK ved år 5 for hhv. P1, P2 og P3.

Amgros' vurdering

Ansøger har inkluderet patientomkostninger, hvilket ikke er i overensstemmelse med Amgros' Metodevejledning.
Da ansøgers budgetkonsekvensanalyse er baseret på ansøgers hovedanalyse, udarbejder Amgros en ny budgetkonsekvensanalyse baseret på Amgros' hovedanalyse.

Amgros ekskluderer patientomkostninger.
Amgros udarbejder egen budgetkonsekvensanalyse baseret på Amgros' hovedanalyse og de antagelser foretaget af Amgros i afsnit 4.1.1.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Budgetkonsekvenserne baseres på omkostninger og antagelser, der ligger til grund for Amgros' hovedanalyse

Resultaterne for Amgros' budgetkonsekvenser ses i tabel 17, 18 og 19 for hhv. P1, P2 og P3.

Tabel 17: Amgros' hovedanalyse for totale budgetkonsekvenser for P1, 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]

Med de indlagte antagelser estimerer Amgros, at anvendelse af PomBorDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK ved år 5 for P1.

Tabel 18: Amgros' hovedanalyse for totale budgetkonsekvenser for P2, 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]

Med de indlagte antagelser estimerer Amgros, at anvendelse af PomBorDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK ved år 5 for P2. Den negative budgetkonsekvens skyldes, antagelsen at PomBorDex kun vil tage markedsandel fra CarDex, som har en højere omkostning end PomBorDex.

Tabel 19: Amgros' hovedanalyse for totale budgetkonsekvenser for P3, 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]

Med de indlagte antagelser estimerer Amgros, at anvendelse af PomBorDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK ved år 5 for P3.

Angives analysen i AIP bliver budgetkonsekvenserne i år 5 ca. -6,7 mio. DKK for P1, ca. -10,4 mio. DKK for P2 og ca. -31,6 mio. DKK for P3.

Budgetkonsekvenserne for P3 er afhængig af behandlingsfordelingen for P1 og P2.

5 DISKUSSION

Behandling med PomBorDex er forbundet med store besparelser sammenlignet med DaraLenDex (P1a) og CarDex (P3), og betydelige meromkostninger sammenlignet med DaraBorDex (P1b og P2). De inkrementelle omkostninger drives især af lægemiddelpriserne og hospitalsomkostningerne.
Betydningen af hospitalsomkostninger skyldes administrationsfrekvensen af de forskellige lægemidler. Desuden har lægemiddelspild stor indflydelse på analysens resultat, dog vurderes at dette ikke har stor betydning i dansk klinisk praksis.

Ansøger har anvendt samme data til beregning af behandlingslængderne mellem lægemidlerne, da der ikke var statistisk signifikant forskel mellem PFS i de anvendte studier. PomBorDex sammenlignet med DaraLenDex er vurderet ud fra en narrativ sammenligning og der er umodne data for DaraLenDex.
PomBorDex er sammenlignet med DaraBorDex indirekte ud fra buchers metode, som indikerer en kortere progressionsfri overlevelse for PomBorDex, men ikke statistisk signigfikant. PomBorDex er sammenlignet med CarDex ud fra en indirekte analyse, men data er umodne. Dermed er det usikkert om der er forskel i PFS, og dermed behandlingslængden mellem de sammenlignende behandlingskombinationer. Da lægemiddelpriserne, og dermed behandlingslængden har stor betydning for analysens resultatet, skal tolkninger på disse tages med en vis forsigtighed.

Der er ikke inkluderet efterfølgende behandlinger i analysen, da man ud fra behandlingsvejledningen vil udtømme de behandlingskombinationer der overvejes i 2. linjebehandling, inden der vil blive anbefalinger for 3. linjebehandling. Dermed er det usikkert hvilken behandling patienten vil modtage efterfølgende, da dette afhænger af tidligere kombinationsbehandlinger, patientens toksicitet og komorbiditet. Da forskellige behandlingskombinationer er forsøgt udtømt i 2. linjebehandling, vurderes det ikke at have betydning for analysens resultat.

Det er svært at vurdere det estimerede markedsoptag, der er derfor stor usikkerhed forbundet med markedsoptaget hvis PomBorDex anbefales. Ansøger har antaget et markedsoptag på 90% hvis PomBorDex anbefales. Ud fra Medicinrådets vurderingsrapport af PomBorDex, vurderer Amgros at et markedsoptag på 90%, hvis PomBorDex anbefales, er optimistisk, og at Amgros' budgetkonsekvensanalyse er mere realistisk, men bør tolkes med forsigtighed.

6 REFERENCER

1. Medicinrådet. Medicinrådets protokol for vurdering af pomalidomid i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft der har modtaget mindst én tidligere behandling. :0–18.

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6. Medicinrådet. 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.

7. 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.

8. Medicinrådet. Medicinrådets vurdering af pomalidomid i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft der har modtaget mindst én tidligere behandling. :0–18.

AMGROS

REGIONERNES
LÆGEMIDDELORGANISATION

AMGROS I/S
DAMPFÆRGEVEJ 27-29
2100 KØBENHAVN Ø

TLF: 8871 3000
WWW.AMGROS.DK

Fra: [redacted]@celgene.com>
Sendt: 25. oktober 2019 11:12
Til: [redacted]
Emne: RE: Høring over godkendt vurdering af lægemidlets værdi for pomalidomid i kombination med bortezomib og dexamethason

Hej [redacted]

Tak for fremsendte.

Vedr. høringssvar, Celgene har ingen kommentarer til rådet vurdering.

Mange hilsner / Kind regards

[redacted]

Medicinrådet

Medicinrådets vurdering af pomalidomid i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft der har modtaget mindst én tidligere behandling, inklusive lenalidomid

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	23. oktober 2019
Ikrafttrædelsesdato	23. oktober 2019
Dokumentnummer	60921
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. oktober 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Imnovid®
Generisk navn	Pomalidomid
Firma	Celgene Europe Ltd
ATC-kode	L04 AX06
Virkningsmekanisme	Pomalidomid 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	• Pomalidomid 4 mg (anbefalet startdosis) p.o. på dag 1-14 i gentagne 21-dages serier til progression. • I de første 8 serier gives bortezomib 1,3 mg/m^2 i.v. eller s.c. på dag 1, 4, 8 og 11. Fra serie 9 og frem gives bortezomib 1,3 mg/m^2 s.c. på dag 1 og 8. • I de første 8 serier gives dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 9, 11 og 12. Fra serie 9 og frem gives dexamethason 20 mg p.o. på dag 1, 2, 8, og 9.
EMA-indikation	Pomalidomid i kombination med bortezomib og dexamethason til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusive lenalidomid.

2 Medicinrådets konklusion

Pomalidomid i kombination med bortezomib og dexamethason (PomBorDex) er sammenlignet med komparatorene daratumumab i kombination med bortezomib og dexamethason (DaraBorDex), daratumumab i kombination med lenalidomid og dexamethason (DaraLenDex) og carfilzomib i kombination med dexamethason (CarDex) i tre kliniske spørgsmål.

- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med DaraBorDex og DaraLenDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med DaraBorDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling og er refraktære overfor lenalidomid. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med CarDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger. Evidensens kvalitet vurderes at være **meget lav**.

På baggrund af sammenligningen af de absolutte effektestimater fra studierne ser PomBorDex samlet set ud til at være et dårligere behandlingsalternativ end DaraLenDex og DaraBorDex. PomBorDex ser ud til at være et ligeværdigt behandlingsalternativ sammenlignet med CarDex og bør på linje med CarDex anvendes efter DaraBorDex og DaraLenDex eller tidligere, hvis daratumumab er kontraindiceret.

Evidensens kvalitet vurderes at være **meget lav**.

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

CarDex:	Carfilzomib + dexamethason
CI:	Konfidensinterval
DaraBorDex:	Daratumumab + bortezomib + dexamethason
DaraLenDex:	Daratumumab + lenalidomid + dexamethason
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*
ISS:	*International staging system*
ITT:	*Intention to treat*
MRD:	*Mimimal residual disease*
OR:	*Odds ratio*
ORR:	*Overall response rate*
OS:	*Overall survival*
PFS:	Progressionsfri overlevelse
PICO:	Population, intervention, komparator, effektmål
PomBorDex:	Pomalidomid i kombination med bortezomib og dexamethason
QLQ-C30:	*Quality of Life Questionnaire Core-30*
RR:	Relativ risiko
SMD:	*Standardized mean difference*
VGPR:	*Very good partial response*

4 Formål

Formålet med Medicinrådets vurdering af pomalidomid i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft, der tidligere har modtaget mindst én behandling, 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 pomalidomid i kombination med bortezomib og dexamethason kan anbefales som mulig standardbehandling.

5 Baggrund

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 ondartede celler 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. 320 patienter om året vil skulle modtage deres første relapsbehandling [2].

Prognosen er afhængig af patientens alder og komorbiditeter ved diagnosetidspunktet. De patienter, der som primærbehandling behandles med højdosis kemoterapi med stamcellestøtte (HDT/STS), har en væsentlig bedre prognose end de, der ikke er egnede 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 [2]. Den sidstnævnte gruppe omfatter især patienter over 70 år og inkluderer de ældste patienter. 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.

Nuværende behandling

Behandling af knoglemarvskræft varetages af de hæmatologiske afdelinger og består udover HDT/STS af medicinsk behandling med flere lægemidler i kombination. Ved at kombinere flere lægemidler angribes kræftcellerne 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.

Til patienter, der skal have deres første relapsbehandling, og som ikke er refraktære overfor lenalidomid (ca. 270 patienter årligt), anbefales i Medicinrådets behandlingsvejledning en kombination af daratumumab, lenalidomid og dexamethason (DaraLenDex) [4]. Til patienter, der er refraktære overfor lenalidomid (ca. 50 patienter årligt), anbefales en kombination af daratumumab, bortezomib og dexamethason (DaraBorDex) [1].

Behandlingsvalget foretages i samråd mellem læge og patient under hensyntagen til effekt af tidligere behandling, bivirkninger til tidligere behandlinger, performancestatus, komorbiditet og patientpræferencer, herunder antallet af behandlingsfremmøder. Der tages også hensyn til eventuel refraktæritet overfor lægemidler, der har indgået i tidligere behandlinger og særligt lenalidomid, da det oftest anvendes indtil progression.

Patienter, der er behandlet med DaraLenDex eller DaraBorDex, som igen bliver behandlingskrævende, behandles hovedsageligt med en kombination af carfilzomib og dexamethason (CarDex) [1].

Anvendelse af det nye lægemiddel

Den ansøgte indikation er en indikationsudvidelse. Pomalidomid er i forvejen godkendt i kombination med dexamethason til behandling af patienter, der har modtaget mindst to tidligere behandlinger, dvs. senere i behandlingsforløbet end den ansøgte indikation.

Pomalidomid 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.

PomBorDex skal doseres som følger:

- Pomalidomid 4 mg (anbefalet startdosis) p.o. på dag 1-14 i gentagne 21-dages serier til progression.
- I de første 8 serier gives bortezomib 1,3 mg/m^2 i.v. eller s.c. på dag 1, 4, 8 og 11. Fra serie 9 og frem gives bortezomib 1,3 mg/m^2 s.c. på dag 1 og 8.
- I de første 8 serier gives dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11 og 12. Fra serie 9 og frem gives dexamethason 20 mg p.o. på dag 1, 2, 8, og 9.

I Danmark administreres bortezomib subkutant. Administrationen af bortezomib håndteres af en sygeplejerske og foregår ambulant. Administrationen tager få minutter.

Den samlede behandlingstid løber til progression eller intolerable bivirkninger. Fagudvalget estimerer, at behandlingstiden svarer til den mediane PFS i studiet [5], som er ca. 11 måneder.

6 Metode

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

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet den 12. april 2019. Ansøger har foretaget indirekte kvantitative analyser i form af Buchers analyser for effektmålene overlevelse, PFS og behandlingsophør hvor der har været tilgængelige data. Hvis der har været data for de relevante subgrupper, er der også lavet analyser herfor.

Ansøgningen afviger på følgende områder:

- Den kvalitative gennemgang af bivirkninger baserer sig på en opgørelse af uønskede hændelser, da der ikke er bivirkningsdata tilgængeligt. Fagudvalget vurderer, at effektmålet *bivirkninger* kan basere sig på opgørelsen af uønskede hændelser. Opgørelsen af uønskede hændelser kan være mindre påvirket af forskelle i opgørelser på tværs af studier end 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 fulgt protokollens anvisninger for litteratursøgning. Ansøger har identificeret 4 studier med tilhørende 10 publikationer, der er relevante for besvarelse af de tre kliniske spørgsmål. Ansøger anvender desuden data fra EPAR'ene for pomalidomid, bortezomib, dexamethason, daratumumab og carfilzomib. Medicinrådet baserer sin vurdering på data fra disse studier og de angivne EPAR'er.

De 4 studier og tilhørende publikationer er:

OPTIMISMM [5]: PomBorDex vs. BorDex (alle tre kliniske spørgsmål)

POLLUX [6,7]: DaraLenDex vs. LenDex (klinisk spørgsmål 1)

CASTOR [8,9]: DaraBorDex vs. BorDex (klinisk spørgsmål 1 og 2)

ENDEAVOR [10–14]: CarDex vs. BorDex (klinisk spørgsmål 3)

8 Databehandling

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger. Dog har Medicinrådets sekretariat selv beregnet de absolutte forskelle i de indirekte kvantitative analyser for effektmålet *behandlingsophør* i henhold til appendix 5 i metodehåndbogen.

Fagudvalget har vurderet PomBorDex i tre kliniske spørgsmål. I alle tre spørgsmål indgår en kvalitativ gennemgang af uønskede hændelser, som i afsnit 9.4 beskrives fælles for de tre kliniske spørgsmål på baggrund af studiedata fra de i alt 4 kliniske studier.

8.1 Datamodenhed

Ansøger angiver i deres ansøgning, at effektestimaterne for overlevelse er umodne i OPTIMISMM, CASTOR og POLLUX. Derfor er data for PFS inddraget i vurderingerne for at supplere data for overlevelse. Sekretariatet har foretaget en vurdering af modenheden af data på PFS i studierne. Vurderingen er foretaget ud fra Kaplan-Meier kurverne og forholdet mellem antal censureringer og numbers at risk. Det er sekretariatets vurdering, at data for PFS heller ikke er fuldt ud modne, og estimaterne derfor er behæftet med usikkerhed og skal tolkes med forsigtighed.

9 Lægemidlets værdi

Fagudvalget har stillet tre kliniske spørgsmål. De første to spørgsmål omhandler patienter, som skal have den første behandling for deres første relaps. Selvom patienterne tidligere er behandlet med lenalidomid, er de ikke nødvendigvis refraktære, og derfor er der to behandlingsmuligheder til den samlede gruppe af patienter, nemlig DaraBorDex og DaraLenDex. De er komparatorer i det første kliniske spørgsmål, der omhandler hele patientpopulationen, der skal behandles for deres første relaps. Det andet spørgsmål omhandler de patienter der efter deres første behandling er lenalidomidrefraktære. Her er DaraBorDex komparator. Det tredje spørgsmål omhandler de patienter, der efter behandling med enten DaraLenDex eller DaraBorDex igen skal have behandling. Her er komparatoren CarDex.

9.1 Konklusion klinisk spørgsmål 1

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med nuværende klinisk praksis (DaraBorDex eller DaraLenDex) til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid?

Sammenligning med DaraBorDex

I tabel 1 herunder fremgår resultater og kategorier for sammenligningen mellem PomBorDex og DaraBorDex.

Fagudvalget vurderer, at værdien af PomBorDex sammenlignet med DaraBorDex til patienter med knoglemarvskræft, der tidligere har modtaget mindst én tidligere behandling, **ikke kan kategoriseres**. Fagudvalget bemærker dog at data, med forbehold for usikkerheden, tyder på, at PomBorDex er et lidt dårligere behandlingsvalg end DaraBorDex. På den baggrund finder fagudvalget, at kun hos patienter, hvor daratumumab er kontraindiceret, vil PomBorDex være at foretrække.

Evidensens kvalitet vurderes at være **meget lav**.

Sammenligningen med DaraLenDex

Det var ikke muligt at foretage kvantitative sammenlignende analyser mellem PomBorDex og DaraLenDex, hvorfor vurderingen er narrativ.

Værdien af PomBorDex sammenlignet med DaraLenDex **kan ikke kategoriseres**. Fagudvalget vurderer, at studiepopulationerne er dårligt sammenlignelige og datamodenheden lav. Fagudvalget vurderer dog, at det tyder på, at PomBorDex er et dårligere behandlingsalternativ end DaraLenDex, da den mediane PFS for DaraLenDex ikke er nået ved en opfølgningstid på 25,4 måneder, mens den er 11 måneder for PomBorDex.

Evidensens kvalitet vurderes kan ikke vurderes.

Tabel 1: Kategorier og resultater for klinisk spørgsmål 1 – sammenligningen med DaraBorDex

Effektmål	Måleenhed (MKRF)	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 (3 mdr,)	Kritisk	Medianer ikke nået	Kan ikke kategoriseres[b]	HR: 1,18 (0,68;2,06)	Kan ikke kategoriseres[c]	Kan ikke kategoriseres
	Median PFS (3 mdr,)	Vigtig	Medianer ikke nået	Kan ikke kategoriseres[b]	HR: 1,61 (1,03;2,51)	Negativ værdi[d]	
Behandlingsophør	Andel af patienter der ophører behandling (10 % point)	Kritisk	4,5 %-point (-2,37;17,2)[a]	Kan ikke kategoriseres[a]	RR: 1,44 (0,77;2,67)	Kan ikke kategoriseres[c]	Kan ikke kategoriseres
Livskvalitet	Antal points ændring over tid målt med EORTC QLQ-C30 (10 point)	Vigtig	Kan ikke beregnes	Kan ikke kategoriseres	Ikke rapporteret	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Kvalitativ gennemgang	Vigtig					
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres					
Kvalitet af den samlede evidens		Meget lav					

[a]*Beregnet i henhold til appendix 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser på baggrund af den relative forskel RR og behandlingsophøret i DaraBorDex-armen i CASTOR (se tabel 4).*
[b]*Da der ikke findes konfidensintervaller om forskellene i medianer.*
[c]*Da den øverste grænse i konfidensintervallet overskrider kriteriet for ingen dokumenteret merværdi, kan de foreløbige værdier ikke kategoriseres.*
[d]*Da den nedre grænse i konfidensintervallet er over 1 (LL > 1).*

9.1.1 Gennemgang af studier

Til besvarelse af klinisk spørgsmål 1 anvendes data fra OPTIMISM, POLLUX og CASTOR.

Studiekarakteristikken er beskrevet for hvert enkelt studie og baselinekarakteristika er opsummeret i tabel 2 nedenfor.

Tabel 2: Baselinekarakteristik i de 3 studier

	OPTIMISMM	CASTOR	POLLUX
Medianalder	67	64	65
Alder over 65 år	56 %	50 %	50-54 %
Tid siden diagnose (median)	4 år	3,9 år	3,6 år
Tidligere HDT/STS	58 %	60%	86 %
Antal tidligere behandlinger (median)	2 (1-5)	2 (1-9)	1 (1-11)
Tidligere ≥ 2 behandlinger	60 %	55 %	i.o
Tidligere behandling med lenalidomid	100 %	42 %	18 %
Lenalidomidrefraktæritet	70%	21 % (seneste linje)	0%
ECOG performancestatus 0	51 %	42 %	52 %
Højrisiko cytogenetik	20 %	23 %	16 %
Creatinin clearance ≥ 60 mL/min	70 %	i.o.	i.o.

i.o.: ikke oplyst

OPTIMISMM

Karakteristika

Studiet er et ublindet randomiseret fase 3-studie, som var stratificeret efter alder, antallet af tidligere behandlinger og koncentrationen af β2 microglobulin. Studiet sammenligner effekten af PomBorDex (281 patienter) med effekten af BorDex (278 patienter). Den mediane opfølgningstid er 15,9 måneder for PFS og 26,2 måneder for overlevelse (data i EPAR). Studiets primære endepunkt er PFS, de sekundære endepunkter er OS, uønskede hændelser, ORR og responsvarighed. Analyser af primært og sekundære effektmål blev lavet i ITT-populationen.

Bortezomib blev administreret intravenøst indtil en protokolændring, hvorefter det kunne administreres enten intravenøst eller subkutant. 15 patienter i PomBorDex-armen fik bortezomib i.v. og 4 skiftede til s.c. efter protokolændringen. I BorDex-armen fik 19 patienter bortezomib i.v., hvoraf 4 skiftede til s.c. efter protokolændringen.

Population

Baselinekarakteristika er overordnet ligeligt fordelt i de to arme og er opsummeret i tabel 2.

Patientpopulationen stemmer godt overens med den definerede population i klinisk spørgsmål 1, da alle patienter tidligere er blevet behandlet med lenalidomid. Der er en høj andel af lenalidomidrefraktære patienter, hvilket adskiller sig fra CASTOR- og POLLUX-studierne. Det øger usikkerheden på sammenligningen mellem effektestimaterne fra OPTIMISMM i forhold til POLLUX og CASTOR.

CASTOR

Karakteristika

Studiet er et ublindet randomiseret fase 3-studie, som var stratificeret efter antallet af tidligere behandlinger, ISS-stadie og tidligere behandling med bortezomib. Studiet sammenligner effekten af DaraBorDex (251 patienter) med effekten af BorDex (247 patienter). Den mediane opfølgningstid er 19,4 måneder. Studiets primære endepunkt er PFS, og de sekundære endepunkter er OS, ORR, tid til respons, andel af patienter med negativ MRD, andel af patienter med minimum VGPR, tid til progression.

DaraBorDex og BorDex administreres som angivet i protokollen.

- Daratumumab 16 mg/kg i.v. på dag 1, 8, og 15 i serie 1-3, dag 1 i serie 4-9 og dag 1 i serier af 28 dage fra serie 9 og frem til progression
- Bortezomib 1,3 mg/m^2 s.c. på dag 1, 4, 8 og 11 i serie 1-9
- Dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11 og 12 i serie 1-9

Behandlingen med bortezomib og dexamethason stopper altså dermed efter 9 serier (ca. 8 måneder).

Population
Baselinekarakteristika er overordnet ligeligt fordelt i de to arme og opsummeret i tabel 2. Refraktæritet overfor bortezomib var et eksklusionskriterie.

Populationen i klinisk spørgsmål 1 er defineret som patienter, der har fået mindst en tidligere behandling, inklusive lenalidomid. En relativt høj andel må derfor formodes at være lenalidomidrefraktære. Studiepopulationen adskiller sig fra populationen i det kliniske spørgsmål, idet kun 42 % tidligere er behandlet med lenalidomid, og 21 % er refraktær overfor lenalidomid i seneste linje. Den samlede lenalidomidrefraktæritet må formodes at være større, idet patienterne også kan være refraktære overfor lenalidomid anvendt i tidligere linjer.

Fagudvalget vurderer, at effektestimaterne fra studiet kan anvendes til at besvare spørgsmålet, idet tidligere lenalidomidbehandling og lenalidomidrefraktæritet må forventes af mindre betydning for effekten af bortezomib og daratumumab. Der er forskel i behandlingsvarigheden af bortezomib i forhold til OPTIMISMM, hvor behandlingen med bortezomib fortsætter indtil progression. Ansøger bemærker, at komparatorarmene i de to studier derfor ikke er helt ens, og at det kan øge usikkerheden på effektestimaterne i de indirekte analyser.

POLLUX
Karakteristika
Studiet er et ublindet randomiseret fase 3-studie, som var stratificeret efter antallet af tidligere behandlinger, ISS-stadie og tidligere behandling med lenalidomid. Studiet sammenligner effekten af DaraLenDex (286 patienter) med effekten af LenDex (283 patienter). Den mediane opfølgningstid er 25,4 måneder. Studiets primære endepunkt er PFS, og de sekundære endepunkter er OS, ORR, tid til respons, responsvarighed, andel af patienter med negativ MRD, andel af patienter med minimum VGPR og tid til progression. Analyser af primære og sekundære effektmål blev lavet i ITT-populationen.

DaraLenDex og LenDex administreres som angivet i protokollen indtil progression.

- Daratumumab 16 mg/kg i.v. på dag 1, 8, 15 og 22 i serie 1-2, dag 1 og 15 i serie 3-6 og dag 1 fra serie 7.
- Lenalidomid 25 mg p.o. på dag 1-21.
- Dexamethason 40 mg p.o. på dag 1, 8, 16 og 22.

Population
Baselinekarakteristika er overordnet ligeligt fordelt i de to arme og er opsummeret i tabel 2. Refraktæritet overfor lenalidomid var et eksklusionskriterie i studiet.

Populationen i klinisk spørgsmål 1 er defineret som patienter, der har fået mindst en tidligere behandling, inklusive lenalidomid. En relativt høj andel må derfor formodes at være lenalidomidrefraktære. Studiepopulationen adskiller sig dermed, idet kun 18 % tidligere er behandlet med lenalidomid, og 0 % er refraktære. Det øger usikkerheden ved overførbarheden til populationen i det kliniske spørgsmål og gør sammenligningen af effektestimaterne med dem fra OPTIMISMM vanskelig.

9.1.2 Resultater og vurdering

Nedenfor følger resultater og vurdering af de enkelte effektmål angående klinisk spørgsmål 1:

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med nuværende klinisk praksis (DaraLenDex eller DaraBorDex) til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid?

Overlevelse (kritisk)

Ansøger har for effektmålet overlevelse leveret data fra studierne OPTIMISMM, CASTOR og POLLUX. For alle tre studier gælder, at overlevelsesdata endnu ikke er modent, hvorfor der i vurderingen inddrages data for PFS, hvor det er muligt.

De absolutte effektestimater for overlevelse og PFS er angivet i tabel 3.

Tabel 3: Absolutte effektestimater for overlevelse og PFS fra studierne. Overlevelse er fra ITT-populationerne og PFS er fra subgrupperne der tidligere er behandlet med lenalidomid.

	Overlevelse (mdr.)			**PFS (mdr.)**		
	OPTIMISMM [5]	*CASTOR* [8]	*POLLUX* [6]	*OPTIMISMM* [5]	*CASTOR* [9]	*POLLUX* [7]
PomBorDex	40,5			11,2		
BorDex	30,5			7,1		
DaraBorDex		Ingen data*			9,5	
BorDex		Ingen data*			6,1	
DaraLenDex			Ingen data*			Ingen data*
LenDex			20,3			18,6

*Ansøger angiver, at værdierne er angivet som "kan ikke evalueres" i de anvendte referencer.

Sammenligning med DaraBorDex

Da data for overlevelse ikke er rapporteret for subgrupperne, der tidligere er behandlet med lenalidomid i CASTOR, har ansøger for sammenligningen med DaraBorDex udført en indirekte sammenligning ved en Buchers analyse mellem effektestimaterne (HR) fra ITT-populationerne. Med udgangspunkt i studiepopulationernes forskellighed foretog fagudvalget en vurdering af den indirekte sammenligning mellem effektestimaterne for overlevelse i OPTIMISMM og CASTOR. Fagudvalget ønsker at medtage analysen trods forskellene i studiepopulationerne, fordi det er uklart, i hvilken retning forskellene påvirker resultatet og forskellene efter fagudvalgets bedømmelse ikke afgørende for effektestimaternes størrelse. Det øger dog usikkerheden i tolkningen af effektestimatet fra den indirekte sammenligning.

På baggrund af de absolutte forskelle for overlevelse kan værdien af PomBorDex ikke kategoriseres, da der ikke kan beregnes en forskel mellem medianerne eller et konfidensinterval omkring forskellen. Ansøgers indirekte analyse mellem PomBorDex og DaraBorDex viser en relativ risiko (RR) på 1,18 [0,68-2,06]. Værdien af PomBorDex kan ikke kategoriseres på baggrund af dette, da konfidensintervallet er meget bredt og usikkerheden dermed stor.

Ansøger har for sammenligningen med DaraBorDex udført en indirekte sammenligning ved en Buchers analyse mellem effektestimaterne for PFS (HR) fra ITT-populationen i OPTIMISMM, som alle tidligere er behandlet med lenalidomid og den subgruppe i CASTOR-studiet, som tidligere har fået lenalidomid. Det giver en HR på 1,61 (1,03-2,51) og tildeler PomBorDex en foreløbig negativ værdi baseret på data for PFS. Fagudvalget bemærker dog, at der er usikkerhed om datamodenheden også for PFS, hvorfor den negative værdi skal tolkes med forsigtighed.

Sammenligning med DaraLenDex

Da der ingen fælles komparator findes mellem OPTIMISMM og POLLUX, kan værdien ikke kategoriseres for sammenligningen med DaraLenDex. Sammenligningen bliver dermed udelukkende narrativ. Fagudvalget bemærker, at median PFS er nået i alle tre studier, på nær i DaraLenDex-armen i POLLUX-studiet. Det er ikke muligt at tildele en foreløbig kategori på baggrund af medianerne, da der ikke kan beregnes konfidensintervaller omkring forskellene.

Fagudvalgets vurdering af sammenligningen med DaraLenDex baserer sig også for PFS på de absolutte effektestimater (tabel 3) fra de enkelte studier, hvor data er sparsomt. Den foreløbige og aggregerede værdi kan ikke kategoriseres. PFS i DaraLenDex-armen i POLLUX-studiet er efter 25,4 måneder endnu ikke nået. Med forbehold for datamodenhed og den vanskelige sammenligning på tværs af studier tyder data på, at PomBorDex i hvert fald ikke er bedre end DaraLenDex.

Behandlingsophør (kritisk)

For behandlingsophør findes kun data fra studiernes safety populationer, som ligesom studiepopulationerne adskiller sig fra hinanden, ved at ikke alle patienter i CASTOR og POLLUX tidligere er behandlet med lenalidomid.

Tabel 4: Absolutte effektestimater på behandlingsophør i studierne

	Behandlingsophør		
	OPTIMISMM	*CASTOR*	*POLLUX*
PomBorDex	28,8 %*		
BorDex	18,9 %*		
DaraBorDex		10,3 %**	
BorDex		9,7 %**	
DaraLenDex			11,9 %*
LenDex			12,7 %*

*Behandling til progression
**Behandlingen med BorDex stoppes efter 9 serier

Sammenligning med DaraBorDex

Ansøger har udført en indirekte sammenligning mellem behandlingsophøret i OPTIMISMM og CASTOR. Den relative forskel RR er 1,44 (0,77-2,67). Da konfidensintervallet er meget bredt, og usikkerheden dermed er stor, kan forskellen ikke kategoriseres. På baggrund af den relative risiko og andelen i DaraBorDex-armen i CASTOR, der ophører behandling, kan den absolutte forskel beregnes til 4,5 %-point (-2,37;17,2), baseret på hændelsesraten i DaraBorDex-armen i CASTOR (10,3 %). Beregningen er foretaget i henhold til appendix 5 i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser 2.0.* Da konfidensintervallet er meget bredt, og usikkerheden dermed er stor, kan forskellen ikke kategoriseres.

Sammenligning med DaraLenDex

På baggrund af de absolutte effektestimater i studierne (tabel 4) vurderer fagudvalget, at der generelt er et højere behandlingsophør i OPTIMISMM, og at behandlingsophøret i OPTIMISMM er højere for PomBorDex-armen end for BorDex-armen. I de to andre studier er der ikke forskel mellem studiearmene, og fagudvalget formoder på den baggrund at tillægget af pomalidomid til BorDex påvirker behandlingsophøret i negativ retning, hvilket ikke ser ud til at være tilfældet for tillægget af daratumumab til enten BorDex eller LenDex.

Kvalitativ gennemgang af bivirkninger (vigtig)

Den generelle gennemgang af uønskede hændelser fremgår af afsnit 9.4. De uønskede hændelser er ikke specifikt for patienter, der tidligere har modtaget lenalidomidbehandling i andre studier end OPTIMISMM. Fagudvalget vurderer, at de hæmatologiske bivirkninger er håndterbare i klinikken. Forekomsten af lungeembolier er muligvis forhøjet ved PomBorDex og forekomsten af hypertension muligvis lidt lavere. Af bivirkninger, der er særligt generende for patienten, fremhæves perifer sensorisk neuropati, som forekommer i samme grad i sammenligning med DaraBorDex og i højere grad i sammenligning med DaraLenDex. Forekomsten af træthed vurderes også at være lidt højere. Diarré af grad 3-4 forekommer i mindre grad end ved behandling med DaraLenDex.

Livskvalitet (vigtig)

Der findes data fra QLQ-C30 fra alle tre studier, men ansøger angiver, at ændringer i livskvalitet er målt med forskellige værktøjer eller data opgjort forskelligt, og at det derfor ikke er muligt at sammenligne PomBorDex med komparatorerne på tværs af studierne.

I OPTIMISMM er livskvalitet målt med QLQ-C30, men der er ikke publicerede kvantitative data tilgængeligt. Studiet rapporterer dog, at der ikke er observeret signifikante ændringer i livskvalitet over tid, hverken i de enkelte arme eller imellem armene. I CASTOR er data for livskvalitet opgjort som mediantid til forbedring målt med både QLQ-C30 og EQ5D-5L. Fagudvalget har ikke defineret en mindste klinisk relevant forskel i median tid til forbedring i protokollen. Der er ingen signifikante forskelle i mediantid til forbedring mellem PomBorDex og DaraBorDex. I POLLUX er livskvalitet opgivet som mediantid til forbedring målt med QLQ-C30 og EQ5D-5L. Der er ingen signifikante forskelle i mediantid til forbedring mellem DaraLenDex og komparatoren LenDex.

Den aggregerede værdien af PomBorDex for effektmålet livskvalitet kan ikke kategoriseres.

9.1.3 Evidensens kvalitet

Sammenligning med DaraBorDex

Evidensens kvalitet for klinisk spørgsmål 1 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende ”risk of bias” fremgår af bilag 1 afsnit 17.1.1 (OPTIMISMM) og 17.1.2 (CASTOR). GRADE-vurdering af evidensens kvalitet kan ses i bilag 1 afsnit 17.2.1.

Sammenligning med DaraLenDex

Da sammenligningen er narrativ, kan evidensens kvalitet ikke vurderes. Overvejelser vedrørende ”risk of bias” fremgår af bilag 1 afsnit 17.1.3 (POLLUX).

9.2 Konklusion klinisk spørgsmål 2

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med daratumumab i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft, som er refraktære overfor lenalidomid, og som har modtaget mindst én tidligere behandling?

Resultater og kategorier af de sammenlignende analyser mellem PomBorDex og DaraBorDex fremgår af tabel 5.

Fagudvalget vurderer, at værdien af pomalidomid i kombination med bortezomib og dexamethason til patienter med knoglemarvskræft sammenlignet med DaraBorDex **ikke kan kategoriseres.** Evidensens kvalitet vurderes at være **meget lav**.

Tabel 5: Kategorier og resultater – Klinisk spørgsmål 2 – sammenligning med DaraBorDex

Effektmål	Måleenhed (MKRF)	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 PFS (3 mdr.)	Vigtig	Medianer ikke nået	Kan ikke kategoriseres[a]	1,81 (0,98; 3,31)	Kan ikke kategoriseres[b]	Kan ikke kategoriseres
Behandlingsophør	Andel af patienter der ophører behandling (10 % point)	Kritisk	4,5 %-point (-2,37; 17,2)	Kan ikke kategoriseres[b]	1,44 (0,77; 2,67)	Kan ikke kategoriseres[b]	Kan ikke kategoriseres
Livskvalitet	Antal points ændring over tid målt med EORTC QLQ-C30 (10 point)	Vigtig	Kan ikke beregnes	Kan ikke kategoriseres	Ikke rapporteret	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Kvalitativ gennemgang						
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres						
Kvalitet af den samlede evidens	Meget lav						

[a] *Da der ikke findes konfidensintervaller om forskellene i medianer.*
[b] *Da den øverste grænse i konfidensintervallet overskrider kriteriet for ingen dokumenteret merværdi, kan de foreløbige værdier ikke kategoriseres.*

9.2.1 Gennemgang af studier

Til besvarelse af klinisk spørgsmål 2 anvendes data fra OPTIMISM og CASTOR. Studiekarakteristikken for OPTIMISMM og CASTOR er beskrevet tidligere under spørgsmål 1.

OPTIMISMM
Karakteristik

(se gennemgang under klinisk spørgsmål 1).

Population

Baselinekarakteristikken fremgår af tabel 2. Studiepopulationen adskiller sig fra populationen defineret i det kliniske spørgsmål, idet ikke alle patienterne i studiet er refraktære overfor lenalidomid. Der er dog data for subgrupperne, der er lenalidomidrefraktære, hvad angår PFS.

CASTOR
Karakteristik

(se gennemgang under klinisk spørgsmål 1).

Population

Baselinekarakteristikken fremgår af tabel 2. Studiepopulationen adskiller sig fra populationen defineret i det kliniske spørgsmål, idet ikke alle patienterne i studiet er refraktære overfor lenalidomid (21 % i seneste linje). Der er dog data for subgrupperne, der er lenalidomidrefraktære, hvad angår PFS.

9.2.2 Resultater og vurdering

Nedenfor følger resultater og vurdering af de enkelte effektmål angående klinisk spørgsmål 2:

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med DaraBorDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling og er refraktære overfor lenalidomid?

Overlevelse (kritisk)

Populationerne i de to studier svarer dårligt til populationen i det spørgsmål, der ønskes besvaret (de lenalidomidrefraktære patienter), og der findes ikke overlevelsesdata fra subgrupperne, der er lenalidomidrefraktære. Derfor vurderer fagudvalget, at den indirekte sammenligning på overlevelsesdata fra de to studier er forbundet med så stor usikkerhed, at den bør udgå.

For PFS findes data fra subgrupperne, der er refraktære overfor lenalidomid i begge studier, og det er derfor relevant at foretage en indirekte analyse for PFS, om end også data for PFS vurderes at være umodent. Den relative forskel for sammenligningen mellem PomBorDex og DaraBorDex er RR = 1,81 (0,98-3,31). Da konfidensintervallet er meget bredt, kan den foreløbige værdi for den relative forskel ikke kategoriseres. Den absolutte forskel er en forskel mellem medianer, hvor der ikke kan beregnes konfidensintervaller og derfor kan den foreløbige værdi for den absolutte forskel heller ikke kategoriseres. Den mediane PFS er 9,3 måneder i DaraBorDex armen i subgruppen, der er lenalidomidrefraktær og 9,5 måneder i PomBorDex-armen i subgruppen, der er lenalidomidrefraktær.

Øvrige effektmål

Fagudvalget bemærker, at vurderingen af de andre effektmål ikke er anderledes end for klinisk spørgsmål 1, om end usikkerheden er større, fordi populationerne adskiller sig mere fra det kliniske spørgsmål. Fagudvalget forventer ikke, at bivirkningsprofilen for de lenalidomidrefraktære adskiller sig fra den samlede population, hvorfor effektestimaterne fra den indirekte analyse af behandlingsophør og den kvalitative gennemgang af uønskede hændelser kan anvendes til at belyse klinisk spørgsmål 2.

Fagudvalget vurderer, at det tyder på, at PomBorDex på baggrund af punktestimaterne i tabel 5 er et lidt dårligere behandlingsvalg. Kun hvor daratumumab er kontraindiceret, vil PomBorDex være at foretrække. Dertil kommer, at behandling med bortezomib indtil progression er en belastning for patienten på grund af bivirkninger og administrationsform, der kræver fremmøde, hvilket er en yderligere årsag til at foretrække DaraBorDex.

9.2.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 2 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende ”risk of bias” fremgår af bilag 1 afsnit 17.1.1 (OPTIMISMM) og 17.1.2 (CASTOR). GRADE-vurdering af evidensens kvalitet kan ses i bilag 1 afsnit 17.2.2.

9.3 Konklusion klinisk spørgsmål 3

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med carfilzomib og dexamethason til behandling af patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger?

Resultater for de sammenlignende analyser mellem PomBorDex og CarDex fremgår af tabel 6.

Fagudvalget vurderer, at værdien af PomBorDex sammenlignet med CarDex til patienter med knoglemarvskræft **ikke kan kategoriseres**, men at PomBorDex samlet set ikke er dårligere, hvad angår effekt og sikkerhedsprofil. Evidensens kvalitet vurderes at være **meget lav**.

Tabel 6: Kategorier og resultater – Klinisk spørgsmål 3 – sammenligning med CarDex

Effektmål	Måleenhed (MKRF)	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 (3 mdr.)	Kritisk	Medianer ikke nået	Kan ikke kategoriseres[c]	HR: 1,21 (0,85-1,73)	Kan ikke kategoriseres[a]	Kan ikke kategoriseres
	Median PFS (3 mdr.)	Vigtig	Kan ikke beregnes	Kan ikke kategoriseres[c]	HR: 0,86 (0,57-1,32)[b]	Kan ikke kategoriseres[a]	
Behandlingsophør	Andel af patienter der ophører behandling (10 % point)	Kritisk	12,8 % (-0,23 %-33,1 %)[d]	Kan ikke kategoriseres[a]	RR: 1,57 (0,99-2,47)	Kan ikke kategoriseres[a]	Kan ikke kategoriseres
Livskvalitet	Antal points ændring over tid målt med EORTC QLQ-C30 (10 point)	Vigtig	Kan ikke beregnes	Kan ikke kategoriseres	Ikke rapporteret	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Kvalitativ gennemgang	Vigtig			NA		
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres					
Kvalitet af den samlede evidens		Meget lav					

[a]*Da den øverste grænse i konfidensintervallet overskrider kriteriet for ingen dokumenteret merværdi, kan de foreløbige værdier ikke kategoriseres.*
[b]*Sammenligning mellem subgruppen i OPTIMISMM der har modtaget over én tidligere behandling og subgruppen i ENDEAVOR, der har modtaget 2-3 tidligere behandlinger, inklusive lenalidomid.*
[c]*Da der ikke findes konfidensintervaller om forskellene i medianer.*
[d]*Beregnet i henhold til appendix 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser på baggrund af den relative forskel RR og behandlingsophøret i CarDex-armen i ENDEAVOR som antaget hændelsesrate (se tabel 9).*

9.3.1 Gennemgang af studier

Til besvarelse af klinisk spørgsmål 3 anvendes data fra OPTIMISM og ENDEAVOR. Studiekarakteristikken for OPTIMISMM er beskrevet tidligere. For ENDEAVOR er den beskrevet nedenfor. Baselinekarakteristika for de to studier er angivet i tabel 7.

Tabel 7: Baselinekarakteristik for OPTIMISMM og ENDEAVOR

	OPTIMISMM	ENDEAVOR
Median alder	67	65
Alder over 65 år	56 %	50-55
Tid siden diagnose (median)	4 år	3,7 år
Tidligere HDT/STS	58 %	i.o.
Antal tidligere behandlinger (median)	2 (1-5)	2 (1-2)
Tidligere ≥ 2 behandlinger	60 %	50 %
Tidligere behandling med lenalidomid	100 %	38 %
Lenalidomidrefraktæritet	70 %	25 %
ECOG performancestatus 0	51 %	48 %
Højrisiko cytogenetik	20 %	21 %
Creatinin clearance ≥ 60 mL/min	70 %	82 % (≥ 50 mL/min)

i.o.: ikke oplyst.

OPTIMISMM
Karakteristika

(Se gennemgang under klinisk spørgsmål 1).

Population

Baselinekarakteristik fremgår af tabel 7, og for OPTIMISMM beskrevet nærmere under klinisk spørgsmål 1. Studiepopulationen adskiller sig fra populationen i de kliniske spørgsmål, idet ikke alle (60 %) har modtaget 2 behandlinger eller derover. Fagudvalget vurderer dog, at studiet alligevel kan anvendes i vurderingen af klinisk spørgsmål 3.

ENDEAVOR
Karakteristika

Studiet er et ublindet randomiseret fase 3-studie, som var stratificeret efter antallet af tidligere behandlinger, ISS-stadie, tidligere behandling med en proteasomhæmmer og planlagt administrationsvej for bortezomib (i.v. eller s.c.). Studiet sammenligner effekten af CarDex (464 patienter) med effekten af BorDex (465 patienter). Den mediane opfølgningstid er 11,1-11,9 måneder. Studiets primære endepunkter er PFS, de sekundære endepunkter er OS, ORR, responsvarighed, andel af patienter med perifær neuropati (≥ grad 2), andel af patienter med signifikant reduktion i LVEF, ændring i fra baseline i FAC og ændring fra baseline i PASP. Analyser af effekt blev lavet i ITT-populationen, og analyser af sikkerhed blev lavet i safety-populationen.

CarDex administreres som angivet i protokollen i serier af 21 dage indtil progression:

- Carfilzomib 20 mg/m^2 i.v. på dag 1 og 2 i serie 1.
  56 mg/m^2 på dag 8, 9, 15, og 16 i serie 1.
  56 mg/m^2 på dag 1, 2, 8, 9, 15, og 16 fra serie 2.
- Dexamethason 20 mg p.o. på dag 1, 2, 8, 9, 15, 16, 22 og 23.

BorDex administreres i serier af 21 dage indtil progression:

- Bortezomib 1,3 mg/m^2 i.v. eller 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.

Population

Baselinekarakteristika er overordnet ligeligt fordelt i de to arme og opsummeret i tabel 7. Myokardieinfarkt eller klasse 3 eller 4 hjertesvigt (ifølge New York Heart Association) indenfor de seneste 4 måneder var et eksklusionskriterie i studiet. Patientpopulationen adskiller sig fra populationen defineret i det kliniske spørgsmål, idet kun 38 % tidligere er behandlet med lenalidomid, og kun 50 % tidligere har modtaget 2-3 behandlinger. I OPTIMISSM er 100 % tidligere behandlet med lenalidomid, og ca. 60 % har fået to eller flere tidligere behandlinger. I praksis vil mange patienter være lenalidomidrefraktære på dette tidspunkt i behandlingsforløbet, mens det kun er 25 % i studiet. Refraktæriteten overfor lenalidomid har ikke betydning for behandlingsvalget mellem PomBorDex og CarDex, hvorfor det vurderes at være af mindre betydning. Der er ikke dokumentation for, at andelen af lenalidomidrefraktære patienter forventes at påvirke effektestimaterne. Effekten på overlevelse og PFS vil muligvis være mindre i en population, der er længere fremme i behandlingsforløbet, men effektestimaterne i de to studier OPTIMISMM og ENDEAVOR vil være påvirket ens af den forskel i forhold til patientpopulationen i det kliniske spørgsmål.

9.3.2 Resultater og vurdering

Overlevelse (kritisk)

I ENDEAVOR findes data for overlevelse i subgruppen af patienter, der tidligere har modtaget 2-3 behandlinger. I OPTMISMM findes overlevelsesdata kun for ITT-populationen, hvor ca. 60 % har modtaget to eller flere behandlinger. Ansøger har foretaget en indirekte sammenligning mellem effektestimaterne (HR) fra de to studier ved Buchers analyse og får HR = 1,21 (0,85-1,73). På trods af forskelle mellem studiepopulationerne vurderer fagudvalget, at analysen for overlevelse bør indgå i vurderingen, med forbehold også for datamodenhed. Da konfidensintervallet er for bredt, kan den foreløbige værdi ikke kategoriseres. Data for overlevelse er umodent og forbundet med stor usikkerhed. Derfor inddrages PFS i vurderingen.

For PFS er der data for den prædefinerede subgruppe i OPTIMISMM, der har modtaget mere end én tidligere behandling, og i ENDEAVOR er der data for subgrupperne, der har modtaget mindst to tidligere behandlinger samt gruppen, der har modtaget mindst to tidligere behandlinger inklusive lenalidomid. Ansøger har foretaget en sammenligning mellem subgruppen i OPTIMISMM og begge subgrupper i ENDEAVOR. Der er ikke information om, hvorvidt subgrupperne i ENDEAVOR var prædefinerede. PFS-data vurderes at være umodent, hvilket øger usikkerheden i tolkningen af effektestimaterne.

De absolutte effektestimater fra studiearmene fremgår af tabel 8.

Tabel 8. Effektestimater for overlevelse og PFS i OPTIMISMM og ENDEAVOR.

	Overlevelse (mdr.)			**PFS (mdr.)**		
	OPTIMISMM (ITT)	*ENDEAVOR (ITT)*	*ENDEAVOR* 2-3 tidligere behandling	*OPTIMISMM* > 1 tidligere behandling	*ENDEAVOR* ≥ 2 tidligere behandlinger	*ENDEAVOR* ≥ 2 tidligere beh. (inkl. Len)
PomBorDex	40,5			i.o.*		
BorDex	30,5			i.o.*		
CarDex		47,8	39,5 mdr		18,7 mdr.	9,7 mdr
BorDex		41,9	28,4 mdr.		9,4 mdr.	6,6 mdr

*Kun relativt effektestimat (HR: 0,63 (0,48-0,83)). i.o.: ikke oplyst.

Fagudvalget vurderer, at sammenligningen mellem OPTIMISMM og den subgruppe i ENDEAVOR, der har modtaget to-tre tidligere behandlinger inklusive lenalidomid, bør vægtes tungest, idet populationerne her ligner hinanden mest. For den indirekte sammenligning er HR = 0,86 (0,57-1,32), hvilket ikke kan kategoriseres, da konfidensintervallet er for bredt,

Fagudvalget vurderer, at effektestimaterne for overlevelse og PFS generelt ikke giver anledning til at antage, at PomBorDex er dårligere end CarDex, på trods af at de er forbundet med stor usikkerhed, også hvad angår datamodenhed.

Behandlingsophør (kritisk)

I ENDEAVOR findes der data for behandlingsophør for subgruppen, der har modtaget mindst to tidligere behandlinger. Ansøger har udført en indirekte sammenligning med ITT-populationen i OPTIMISMM-studiet ved en Buchers analyse og får RR = 1,57 (0,99-2,47), hvilket tildeles kategorien 'kan ikke kategoriseres' pga. for brede konfidensintervaller. Med udgangspunkt i den relative forskel og andelen, der ophører behandling i CarDex-armen i ENDEAVOR (22,5 %), beregnes den absolutte effektforskel til 6,5 %-point (-0,23 %-33,1 %), hvilket heller ikke kan kategoriseres på grund af stor usikkerhed, afspejlet i det brede konfidensinterval. Beregningen er foretaget i henhold til appendix 5 i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser 2.0.*

På baggrund af de absolutte effektestimater fra studierne angivet i tabel 9 vurderer fagudvalget, at behandlingsophøret er sammenligneligt i de to studier, men at tillægget af pomalidomid til BorDex forhøjer behandlingsophøret. Udskiftning af bortezomib med carfilzomib påvirker derimod ikke behandlingsophøret.

Tabel 9. Absolutte effektestimater for behandlingsophør fra studierne. OPTIMISMM: ITT-populationen. ENDEAVOR: subgruppen der tidligere har modtaget 2-3 behandlinger.

	Behandlingsophør	
	OPTIMISMM	*ENDEAVOR*
PomBorDex	28,8 %	
BorDex	18,9 %	
CarDex		22,5 %
BorDex		23,1 %

Fagudvalget vurderer at den aggregerede værdi for behandlingsophøret ikke kan kategoriseres.

Kvalitativ gennemgang af bivirkninger (vigtig)

CarDex er en velkendt behandlingskombination, som tåles af de fleste patienter med knoglemarvskræft. Der forekommer ikke mange hæmatologiske bivirkninger i sammenligning med PomBorDex, ligesom forekomsten af perifer sensorisk neuropati er lav. CarDex er især forbundet med hypertension og er ikke velegnet til patienter med kendt hjertesvigt eller nylig blodprop i hjerte, som også blev ekskluderet i ENDEAVOR. Andelen af patienter, der får grad 3-4 hjertesvigt, er lidt højere i CarDex-armen i ENDEAVOR (2,6 %) end i PomBorDEx-armen i OPTIMISMM (1,1 %).

Livskvalitet (vigtig)

Der er ikke data for dette effektmål for subgrupperne, der har modtaget 2 eller flere behandlinger. Data for livskvalitet er målt med QLC-C30 i begge studier. I ingen af studierne er der forskelle i livskvalitet mellem PomBorDex eller CarDex og den fælles komparator BorDex for ITT-populationerne.

9.3.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 2 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende "risk of bias" fremgår af bilag 1 afsnit 17.1.1 (OPTIMISMM) og 17.1.4 (ENDEAVOR). GRADE-vurdering af evidensens kvalitet kan ses i bilag 1 afsnit 17.2.3.

9.4 Kvalitativ gennemgang af uønskede hændelser

Ansøger har opgjort de uønskede hændelser på følgende måde:

- Hyppige hændelser (andel patienter der oplever hændelser, der forekommer hos mindst 10 % af patienterne).
- Grad 3-4 hændelser (andel patienter der oplever hændelser af grad 3-4).

Fagudvalget har i tabel 10 nedenfor opsummeret de væsentligste hændelser, det vil sige hændelser med forskellig forekomst mellem interventionsarmene i studierne og hændelser, der enten er meget generende for patienterne, eller som har behandlingsmæssige konsekvenser.

Samlet set vurderer fagudvalget, at den generelle bivirkningsprofil af PomBorDex ikke adskiller sig væsentligt fra eksisterende behandlingsmuligheder til patientpopulationerne.

Tabel 10: Andel af patienter med hyppige hændelser (> 10 %) og andel af patienter med grad 3-4 hændelser. Opgørelsen indeholder de hændelser, hvor der er forskelle mellem interventionsarmene i studierne, og de hændelser, som fagudvalget har erfaring for, optræder som bivirkninger i klinikken. IO: ikke oplyst. I få tilfælde har Medicinrådet udtrukket bivirkningsdata fra clinicaltrial.gov. I disse tilfælde er data markeret som enten SAE (serious adverse event) eller NSAE (non-serious adverse event). Data er opgjort som antal (%).

Bivirkning	**OPTIMISMM (PomBorDex, N = 281)**		**CASTOR (DaraBorDex, N = 251)**		**POLLUX (DaraLenDex, N = 286)**		**ENDEAVOR (CarDex, N = 464)**	
	(> 10 %)	**Grad 3 + 4**	**(> 10 %)**	**Grad 3 + 4**	**(> 10%)**	**Grad 3 + 4**	**(> 10 %)**	**Grad 3 + 4**
Infektioner og manifestationer								
Øvre luftvejsinfektioner	58 (20,9)	i.o.	76 (31,3)	6 (2,5)	105 (37,1)	4 (1,4)	111 (24,0)	10 (2,2)
Bronkitis	39 (14,0)	i.o.	28 (11,5)	i.o.	53 (18,7)	6 (2,1)	95 (20,5)	13 (2,8)
Lungebetændelse	53 (19,1)	32 (11,5)	36 (14,8)	24 (9,9)	58 (20,5)	34 (12,0)	24 (5,2) (NSAE)	39 (8,4)
Gastrointestinale bivirkninger								
Forstoppelse/obstipation	102 (36,7)	7 (2,5)	53 (21,8)	0 (0,0)	88 (31,1)	3 (1,1)	73 (15,8)	2 (0,4)
Diarré	94 (33,8)	20 (7,2)	85 (35,0)	9 (3,7)	144 (50,9)	20 (7,1)	150 (32,4)	18 (3,9)
Hæmatologiske bivirkninger								
Neutropeni	130 (46,8)*	116 (41,7)	46 (18,9)	33 (13,6)	172 (60,8)	153 (54,1)	27 (5,8) (NSAE)	11 (2,4)
Trombocytopeni	102 (36,7)	76 (27,3)	145 (59,7)	111 (45,7)	81 (28,6)	39 (13,8)	59 (12,7)	43 (8,9)
Anæmi	79 (28,4)	39 (14,0)	69 (28,4)	37 (15,2)	104 (36,7)	44 (15,5)	121 (26,1)	76 (16,4)
Lymfopeni	32 (11,5)	12 (4,3)	32 (13,2)	24 (9,9)	18 (6,4)	15 (5,3)	31 (6,7) (NSAE)	22 (4,8)

Leukopeni	i.o.	15 (5,4)	19 (7,8) (NSAE)	i.o.	21 (7,4) (NSAE)	i.o.	i.o.	i.o.
Neurologiske bivirkninger								
Perifer sensorisk neuropati	133 (47,8)	23 (8,3)	121 (49,8)	11 (4,5)	0 (0,0)	i.o.	28 (6,0)	6 (1,3)
Kardiovaskulære bivirkninger								
Hypertension	i.o.	8 (2,9)	21 (8,6) (NSEA)	16 (6,6)	20 (7,0) (NSAE)	1 (0,35) (SAE)	82 (17,7)	67 (14,5)
Hjertesvigt*	i.o.	3 (1,1)	i.o.	1 (0,41) (SAE)	i.o.	1 (0,35)	i.o.	12 (2,6)
Lungeemboli*	i.o.	11 (4,0)	i.o.	1 (0,41) (SAE)	i.o.	7 (2,5)	i.o.	10 (2,2) (SAE)
Generelle gener								
Træthed (Fatigue)	103 (37,1)	23 (8,3)	53 (21,8)	12 (4,9)	103 (36,4)	0 (0) (SAE)	118 (25,5)	3 (0,65) (SAE)

*Tilføjet af FU selvom hyppigheden ikke overstiger 10 % i nogen af studiearmene. i.o.: ikke oplyst.

Infektioner og manifestationer

Antallet af hændelser relateret til infektioner er generelt sammenligneligt mellem interventionsarmene i studierne. Dog bemærker fagudvalget, at der er let reduceret antal af øvre luftvejsinfektion hos patienter i behandling med PomBorDex.

Gastrointestinale hændelser

Blandt patienterne i behandling med PomBorDex oplevede 36,7 % forstoppelse eller obstipation, hvoraf 2,5 % var grad 3 og 4. Denne andel var let forhøjet sammenlignet med patienter i interventionsarmene i de øvrige studier. DaraLenDex er forbundet med en højere andel af diarré sammenlignet med de andre interventioner. For diarré af grad 3-4 er der ikke forskelle mellem DaraLenDex og PomBorDex.

Hæmatologiske hændelser

Hæmatologiske bivirkninger er en direkte konsekvens af behandlingens virkning og ses dermed generelt ofte hos patienter i behandling for knoglemarvskræft.

Generelt var der et stort antal hæmatologiske hændelser. 46,8 % og 36,7 % af patienterne i behandling med PomBorDex udviklede hhv. neutropeni (nedsat antal hvide blodlegemer) og trombocytopeni (nedsat antal blodplader). Til sammenligning udviklede kun 10,7 % af patienterne i BorDex-armen neutropeni, men 38,1 % af patienterne trombocytopeni. Det må derfor antages, at en hyppig bivirkning af tilføjelse af pomalidomid til BorDex er neutropeni, men ikke trombocytopeni.

Neutropeni øger risikoen for infektioner og indlæggelser, men kan afhjælpes med G-CSF-behandling (vækstfaktor) eller dosisjustering af pomalidomid eller lenalidomid, som især er forbundet med forekomst af neutropeni. Trombocytopeni øger risikoen for blødning og indlæggelser og kræver dosisreduktion eller transfusion. Trombocytopeni er især forbundet med behandling med bortezomib.

Fagudvalget lægger mest vægt på grad 3-4 bivirkninger, da grad 1 og 2 hæmatologiske bivirkninger ikke har behandlingsmæssige konsekvenser i form af dosisjustering eller behandlingsophør. Andelen, der oplever neutropeni grad 3-4 ved behandling med PomBorDex (41,7 %), er lavere end DaraLenDex (54,1 %), men højere end ved DaraBorDex (13,6 %) og CarDex (2,4 %). For trombocytopeni var forekomsten lavere for

PomBorDex (27,3 %) end for DaraBorDex (45,7 %), men højere end for DaraLenDex (13,8 %) og CarDex (8,9 %). Generelt er forekomsten af neutropeni og trombocytopeni væsentligt lavere ved behandling med CarDex, hvilket er i overensstemmelse med fagudvalgets erfaring.

Neurologiske hændelser

Perifer sensorisk neuropati (føleforstyrrelser, særligt i hænder og fødder) er en bivirkning, der især er forbundet med behandling med bortezomib. I overensstemmelse hermed optrådte perifær sensorisk neuropati ikke som en hyppig hændelse ved behandling med DaraLenDex. Perifer sensorisk neuropati optrådte hos 47,8 % af patienterne ved behandling med PomBorDex. Til sammenligning optrådte perifer sensorisk neuropati hos 49,8 % af patienterne, som modtog DaraBorDex, og hos hhv. 37,0 % (OPTIMISMM) og 38,0 % (CASTOR) af patienterne som modtog BorDex. Grad 3 og 4 perifer sensorisk neuropati forekom hos 8,3 % af patienterne under behandling med PomBorDex og hos 4,5 % og 1,3 % hos patienter i behandling med hhv. DaraBorDex og CarDex. Fagudvalget bemærker, at forekomsten af perifer sensorisk neuropati kan være forhøjet, når bortezomib gives intravenøst i forhold til subkutant. I OPTIMISSM havde 15 patienter (ca. 5 %) fået bortezomib intravenøst. I CASTOR blev bortezomib udelukkende administreret subkutant, og i ENDEAVOR fik 23 % intravenøst bortezomib i løbet af studiet. Den lidt højere andel af grad 3-4 perifer sensorisk neuropati kan dermed ikke entydigt tilskrives administrationsvejen af bortezomib.

Kardiovaskulære hændelser

Blandt de kardiovaskulære bivirkninger bemærker fagudvalget, at antallet af lungeembolier blandt patienter i behandling med PomBorDex er 4 %, sammenlignet med hhv. 0,41 %, 2,5 % og 2,2 % af patienterne i de resterende interventionsarme. Lungeemboli kan være alvorligt og kræver antikoagulationsbehandling.

Forekomsten af hypertension ser ud til at være lavere for PomBorDex end for de øvrige behandlinger. Fagudvalget vurderer, at der er en øget forekomst af ødemer, men bemærker at det kan være relateret til dexamethason, som gives hyppigere ved behandling med PomBorDex end de øvrige behandlinger.

Generelle gener

Af generelle gener oplevede 8,3 % af patienterne grad 3 og 4 træthed, hvilket var en let forhøjet andel sammenlignet med de resterende interventionsarme (4,9, 0,0 og 0,6 %). Træthed er en kendt bivirkning ved behandling med immunmodulerende stoffer. Trætheden kan eventuelt afhjælpes ved at tage tabletten om aftenen.

10 Andre overvejelser

Fagudvalget bemærker, at det kan have indflydelse på de efterfølgende behandlinger, hvis PomBorDex anbefales som mulig standardbehandling til patienter, der tidligere har modtaget mindst en behandling. Patienter, der i dag behandles med CarDex, vil efterfølgende kunne behandles med PomDex eller PomBorDex. Patienter, der vil blive behandlet med PomBorDex, vil efterfølgende kunne behandles med CarDex.

11 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

11.1 Fagudvalget vurdering – klinisk spørgsmål 1

Fagudvalget har vurderet PomBorDex sammenlignet med DaraBorDex og DaraLenDex til patienter, der tidligere har modtaget mindst én behandling, inklusive lenalidomid. To kritiske og to vigtige effektmål indgår i vurderingen.

Sammenligningen med DaraBorDex

Data på det første kritiske effektmål, *overlevelse*, var ikke modent, hvorfor data for PFS blev medtaget i vurderingen som et vigtigt effektmål. Den aggregerede værdi for de umodne effektestimater på overlevelse kunne ikke kategoriseres. For PFS kunne den foreløbige kategori for den absolutte effektforskel ikke kategoriseres. Den foreløbige værdi for den relative effektforskel var negativ, men da data for PFS ikke blev vurderet modent, bør den negative værdi for det relative effektestimat for PFS ikke veje tungt i den samlede vurdering. Den aggregerede værdi for effektmålet kan ikke kategoriseres.

På det andet kritiske effektmål, *behandlingsophør*, kunne den aggregerede værdi af PomBorDex ikke kategoriseres på grund af konfidensintervallernes bredde omkring de absolutte og relative effektestimater.

Den kvalitative gennemgang af bivirkninger er et vigtigt effektmål i vurderingen. Her lægger fagudvalget vægt på, at bivirkningsprofilen for PomBorDex er velkendt. De hæmatologiske bivirkninger er håndterbare i klinikken. Forekomsten af lungeembolier er muligvis forhøjet og forekomsten af hypertension muligvis lidt lavere. Af bivirkninger, der er særligt generende for patienten, fremhæves perifær sensorisk neuropati, hvor forekomsten er sammenlignelig med forekomsten ved behandling med DaraBorDex, men højere end forekomsten ved behandling med DaraLenDex. Forekomsten af træthed vurderes også at være lidt højere. Diarré af grad 3-4 forekommer i mindre grad end ved behandling med DaraLenDex. På denne baggrund vurderer fagudvalget, at PomBorDex er hverken mere eller mindre bivirkningstung end andre behandlingsregimer til denne patientgruppe.

På det vigtige effektmål *livskvalitet* kunne den aggregerede værdi af PomBorDex ikke kategoriseres, da datagrundlaget ikke muliggjorde en sammenligning. Det manglende datagrundlag tæller hverken positivt eller negativt, da ingen af lægemidlerne i studierne har vist forskelle i livskvalitet overfor den fælles komparator (BorDex).

Der er ikke for nogen af effektmålene vist en positiv værdi af PomBorDex, hvorimod der for det vigtige effektmål *PFS* er vist en negativ værdi på den relative effektforskel, omend usikkerheden på effektestimatet er stor.

Fagudvalget bemærker desuden, at PomBorDex indbefatter behandling med bortezomib indtil progression, hvorimod behandlingen med bortezomib stoppes efter 9 serier ved behandling med DaraBorDex. Den kontinuerte behandling med bortezomib er en belastning for patienten, hvilket kan have en negativ betydning for patientens livskvalitet i form af flere bivirkninger og samt flere hospitalsbesøg.

Samlet set vurderer fagudvalget, at værdien af PomBorDex **ikke kan kategoriseres**. Fagudvalget vurderer dog på baggrund af effektestimaterne fra de indirekte analyser, at det tyder på, at PomBorDex er et dårligere behandlingsalternativ, hvad angår overlevelse, PFS og behandlingsophør.

Evidens kvalitet vurderes at være **meget lav**.

Sammenligningen med DaraLenDex

Sammenligningen med DaraLenDex er narrativ. Fagudvalget vurderer, at det er vanskeligt at foretage en vurdering af sammenligningen mellem PomBorDex og DaraLenDex, da studiepopulationerne er forskellige.

Den samlede værdi **kan ikke kategoriseres**. Fagudvalget vurderer dog på baggrund af de absolutte effektestimater fra studierne OPTIMISMM og POLLUX, at DaraLenDex ser ud til at være bedre end PomBorDex.

Evidens kvalitet kan ikke vurderes.

11.2 Fagudvalget vurdering – klinisk spørgsmål 2

For effektmålet *overlevelse* baseres vurderingen på PFS, da der her findes data for de lenalidomidrefraktære patienter. De foreløbige og den aggregerede værdi kan ikke kategoriseres, da konfidensintervallerne er for brede. Med forbehold for datamodenheden bemærker fagudvalget dog, at den nedre grænse i konfidensintervallet (0,98) kun akkurat krydser 1 og derfor tyder på, at PomBorDex for dette effektmål er et dårligere behandlingsalternativ end DaraBorDex.

Vurderingen af de øvrige effektmål er den samme som for klinisk spørgsmål 1, omend overførbarheden til de lenalidomidrefraktære patienter gør vurderingen mere usikker.

Samlet set vurderer fagudvalget, at værdien af PomBorDex sammenlignet med DaraBorDex **ikke kan kategoriseres.** Fagudvalget vurderer dog på baggrund af effektestimaterne fra de indirekte analyser, at det tyder på, at PomBorDex er et dårligere behandlingsalternativ.

Evidens kvalitet vurderes at være **meget lav**.

11.3 Fagudvalgets vurdering – klinisk spørgsmål 3

Vurderingen af det kritiske effektmål *overlevelse* baserer sig på en indirekte analyse mellem ITT-populationen i OPTIMISMM, hvor 60 % har fået 2 eller flere behandlinger og subgruppen i ENDEAVOR, som alle har fået 2 eller flere forudgående behandlinger. De foreløbige og aggregerede værdier kan ikke kategoriseres, da konfidensintervallerne er for brede. Da data for overlevelse er umodent, inddrages data for PFS. Her findes effektestimater for subgruppen i OPTIMISMM, der har modtaget mere end en behandling og subgrupperne i ENDEAVOR, der har fået to eller flere behandlinger inklusive lenalidomid. De foreløbige og aggregerede værdier kan ikke kategoriseres. Fagudvalget bemærker, at punktestimaterne alle ligger i nærheden af 1, og at datagrundlaget for effektmålet overlevelse ikke giver grundlag for at vælge det ene fremfor det andet, baseret på effektestimaterne.

For det andet kritiske effektmål *behandlingsophør* er vurderingen baseret på en indirekte sammenligning mellem ITT-populationen i OPTIMISMM og populationen i ENDEAVOR, der tidligere har modtaget to eller flere behandlinger. De foreløbige og aggregerede værdier kan ikke kategoriseres, men fagudvalget vurderer, at behandlingsophøret ved behandling med PomBorDex tyder på at være højere og kan være forbundet med pomalidomid.

På de vigtige effektmål livskvalitet var der ikke data, der muliggjorde en sammenligning.

I forhold til den kvalitative gennemgang af bivirkninger vurderer fagudvalget ikke, at bivirkningsprofilerne for PomBorDex og CarDex giver anledning til at vælge den ene fremfor den anden. Valget af behandling afhænger dermed af patientens komorbiditet og tidligere bivirkninger.

Samlet set vurderer fagudvalget, at værdien af PomBorDex sammenlignet med CarDex **ikke kan kategoriseres**, men at PomBorDex ikke er et dårligere behandlingsalternativ, hvad angår effekt og sikkerhedsprofil. Fagudvalget vurderer, at PomBorDex og CarDex er ligeværdige behandlingsalternativer.

Behandlingsvalget mellem de to bør tage udgangspunkt i en vurdering af patienternes komorbiditet og bivirkningshistorik.

Evidens kvalitet vurderes at være **meget lav**.

12 Rådets vurdering af samlet værdi og samlet evidensniveau

Pomalidomid i kombination med bortezomib og dexamethason (PomBorDex) er sammenlignet med komparatorene daratumumab i kombination med bortezomib og dexamethason (DaraBorDex), daratumumab i kombination med lenalidomid og dexamethason (DaraLenDex) og carfilzomib i kombination med dexamethason (CarDex) i tre kliniske spørgsmål.

- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med DaraBorDex og DaraLenDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med DaraBorDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling og er refraktære overfor lenalidomid. Evidensens kvalitet vurderes at være **meget lav**.
- Værdien af PomBorDex **kan ikke kategoriseres** sammenlignet med CarDex til behandling af patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger. Evidensens kvalitet vurderes at være **meget lav**.

På baggrund af sammenligningen af de absolutte effektestimater fra studierne ser PomBorDex samlet set ud til at være et dårligere behandlingsalternativ end DaraLenDex og DaraBorDex. PomBorDex ser ud til at være et ligeværdigt behandlingsalternativ sammenlignet med CarDex og bør på linje med CarDex anvendes efter DaraBorDex og DaraLenDex eller tidligere, hvis daratumumab er kontraindiceret.

Evidensens kvalitet vurderes at være **meget lav**.

13 Relation til eksisterende behandlingsvejledning

Fagudvalget indplacerer PomBorDex som en behandlingsmulighed til patienter, der tidligere har modtaget mindst én behandling, men som et behandlingsvalg der på linje med CarDex bør anvendes efter DaraLenDex og DaraBorDex. Det vil typisk være patienter som ved første relaps er behandlet med enten DaraLenDex eller DaraBorDex, og som oplever et nyt behandlingsbehov. Fagudvalget vurderer, at PomBorDex og CarDex er ligeværdige behandlingsalternativer.

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15 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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16 Versionslog

Version	Dato	Ændring
1.0	23. oktober 2019	Godkendt af Medicinrådet.

17 Bilag 1: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

17.1.1 OPTIMISMM

Richardson et al., 2019. (NCT01734928).

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Low**	*…using a validated interactive response technology system. Randomisation was done using a permutated blocked design with a block size of four, stratified according to age (≤75 years vs >75 years), number of previous regimens (1 vs >1), and the concentration of β2 microglobulin at screening (<3,5 mg/L vs 3,5–5,5 mg/L vs >5,5 mg/L)..*
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Some concerns**	*Because the trial was open label, study centre personnel and enrolled patients were not masked to treatment assignment. The funder of the study was unaware of aggregate treatment assignments in the statistical analyses and treatment-level analysis results.* Comment: not known whether participants chose to seek non-protocol interventions based on known assigned treatment.
Missing outcome data	**Some concerns**	*Primary, secondary, and prespecified exploratory analyses were done in the intention-to-treat population, which included all patients who were randomly assigned. Safety assessments were done in the safety population, which included all patients who received at least one dose of study medication.* Comment: no details about analysis plan (imputation). Only 80 % of participants reported QoL data.
Risk of bias in measurement of the outcome	**Some concerns**	*Myeloma response and progression were assessed by an independent review adjudication committee (IRAC) according to IMWG criteria.23 IRAC reviewers were masked to treatment assignment, demographic information, study site, and investigator assessment. Safety and efficacy data were monitored by an independent data monitoring committee (IDMC), who reviewed unmasked data at predetermined times throughout the trial.* Comment: For OS and PFS there is low risk of bias. For adverse events there are some concerns for risk of bias. For QoL and drop-out due to adverse reactions, there are high risk of bias. This is supported by the difference in proportion of drop-out due to adverse events which are higher for BorDex (49) vs. PomBorDex (30) – when you would think it was the other way around.
Risk of bias in selection of the reported result	**Low**	Clinicaltrials.gov: PFS, OS, ORR, DoR, Adverse events Comment: HRQOL as exploratory outcome, measured on day 1 in each cycleand at end of treatment. Baseline scores reported, but no changes or follow-up scores. It is reported: *Scores were maintained over time for both treatment groups, with no statistically significant or clinically meaningful differences recorded between treatments at any cycle.* No reason to assume that the analysis plan was not followed for the reported outcomes.
Overall risk of bias	**Some concerns**	The overall risk of bias is judged to be of some concern. There are some concerns due to the open-label design and uncertainty about the analysis plan. Even though for the critical outcome OS, the risk of bias is low, there may have been an effect of treatment assignment on the critical outcome, drop-out due to adverse events. This is supported by the uneven distribution across groups, where there are fewer drop-outs due to adverse events in the group that receives three drugs compared to the two-drug combination.

Fagudvalget bemærker at:

- *The funder contributed to study design, data collection, data analysis, and data interpretation, and funded a professional medical writer to assist with preparation of the report.*

17.1.2 CASTOR

Palumbo et al., 2016 og Spencer 2018. (NCT02136134).

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Some concerns**	*Randomization was stratified according to International Staging System (ISS) disease stage at the time of screening (stage I, II, or III, with higher stages indicating more severe disease; definitions are provided in the Supplementary Appendix), the number of previous lines of therapy (1 vs. 2 or 3 vs. >3), and previous treatment with bortezomib (no vs. yes).* Comment: no information about randomization sequence and allocation concealment. However, there seems to be no serious baseline imbalances.
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Some concerns**	*Open-label study.* Comment: Not known whether participants chose to seek non-protocol interventions based on known assigned treatment.
Missing outcome data	**Some concerns**	*Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations.* Comment: No information about missing data (suppl. not available from NEJM). ITT and safety population used. Higher dropout rate in the control group (BorDex: 43,9 %) than in the daratumumab group (DaraBorDex: 30,5 %).
Risk of bias in measurement of the outcome	**Some concerns**	*An independent data and safety monitoring committee periodically reviewed the safety data.* *Protocol: An IDMC, consisting of 2 clinicians and 1 statistician, will be established to review efficacy and safety results at the planned interim analyses.* Comment: For PFS and adverse events there are some concerns for risk of bias. For drop-out due to adverse reactions, there are high risk of bias. This is supported by the difference in proportion of drop-out due to adverse events which are higher for BorDex (9,7 %) vs. DaraBorDex (7,8 %) – when you would think it was the other way around.
Risk of bias in selection of the reported result	**Some concerns**	*The sponsor and investigators were jointly responsible for the trial design and the statistical analysis plan,* *Representatives of the sponsor who were involved in data collection and analyses.* *Protocol: Statistical analysis will be done by the sponsor or under the authority of the sponsor.* Comment: As the sponsor is responsible for the statistical analysis, there is a risk of bias in the reported results. However, there is no evidence that the analysis plan was not followed for the reported outcomes. Overall survival was not reported as data were not mature at interim – and after interim analysis, the control group was offered daratumumab. Therefore OS data will not be available at any timepoint.
Overall risk of bias	**High**	The overall risk of bias is judged to be high. There are some concerns due to the open-label design and uncertainty about the involvement of the sponsor in most aspects of the conduct of the trial. There may have been an effect of treatment assignment on the critical outcome, drop-out due to adverse events. This is supported by the uneven distribution across groups, where there are fewer drop-outs due to adverse events in the group that receives three drugs compared to the two-drug combination.

17.1.3 POLLUX

Dimopoulos et al., 2016 og 2018. (NCT02076009).

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Low**	Protocol: *Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by ISS (I, II, or III) at screening, number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.*
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Some concerns**	*Open-label study.* Comment: not known whether participants chose to seek non-protocol interventions based on known assigned treatment.
Missing outcome data	**Low**	Protokol: *Analysis of PFS and OS will be based on the ITT population. … the number and percentage of subjects who had a PFS/OS event or were censored will be reported. The Kaplan-Meier PFS curve will also be plotted by treatment group.* *Safety population: is defined as subjects who have received at least 1 administration of any study treatment (partial or complete). This population will be used for all safety analyses. The safety analyses grouping will be according to treatment actually received.* *There is no imputation planned for missing efficacy endpoint values.*
Risk of bias in measurement of the outcome	**Some concerns**	*An independent data and safety monitoring committee was established to periodically review unblinded efficacy and safety data.* Comment: For OS and PFS there is low risk of bias. For adverse reactions there are some concerns for risk of bias. For drop-out due to adverse reactions, there is high risk of bias.
Risk of bias in selection of the reported result	**Low**	Predefined outcomes are reported: PFS, OS, Response (CR, VGPR, PR, MR, SD, PD, TTR, Duration of Response) Comment: Quality of life was defined as an outcome in the protocol, but not reported in this article. No reason to assume that the analysis plan was not followed for the reported outcomes.
Overall risk of bias	**Low**	The overall risk of bias is judged low even though there are some concerns and the study is unblinded. However, for the critical outcome OS, the risk of bias is low and for the critical outcome, drop-out due to adverse events, there is no clear indication of in which direction the risk of bias will affect the outcome.

Fagudvalget bemærker at:

- *The investigators and the sponsor (Janssen Research and Development) were responsible for the trial design and statistical analysis. Data were collected by the investigators and associated research teams and were compiled and maintained by the sponsor. All the investigators had access to the data on request and were not restricted by confidentiality agreements. Professional medical writers prepared the manuscript and were funded by the sponsor.*
- En stor del af medforfatterne har økonomiske interessekonflikter.

17.1.4 ENDEAVOR

Dimopoulos et al., 2016 og 2017 og Chang 2017. (NCT01568866).

Bias	Risk of bias	Elaboration
Risk of bias arising from the randomization process	**Low**	*Randomisation was stratified by baseline factors (ISS I vs II–III, previous lines of treatment (1 vs 2–3), previous proteasome inhibitor therapy (yes vs no), and planned route of bortezomib administration if assigned to the bortezomib group (intravenous vs subcutaneous)). Within each stratum, patients were randomly assigned to treatment by use of a blocked randomisation design in blocks of four. An interactive voice and web response system was used to randomly assign patients to treatment groups.*
Risk of bias due to deviations from the intended interventions		
Effect of assignment to intervention	**Some concerns**	*Because of the different dosing schedules, the study was designed as an open-label study; therefore neither patients nor providers were masked to assigned treatment.* Comment: not known whether participants chose to seek non-protocol interventions based on known assigned treatment.
Missing outcome data	**Low**	*The primary endpoint was progression-free survival in the intention-to-treat population. All participants who received at least one dose of study drug were included in the safety analyses.* *Survival status was not assessable in patients who were lost to follow-up or withdrew consent for follow-up; in these cases, we censored survival data at the patient's date of last contact.* *Participants with no baseline disease assessments, starting a new anticancer therapy before documentation of disease progression or death, death or disease progression immediately after more than 1 consecutively missed disease assessment visit, or alive without documentation of disease progression before the data cut-off date were censored (clintrials).* Comment: Balanced drop-out rate between study arms. Fewer participants have reported QoL data in the BorDex arm, which can cause risk of bias in an unblinded study.
Risk of bias in measurement of the outcome	**Some concerns**	*Potential bias in the assessment of the primary endpoint (PFS) was mitigated by use of an independent review committee that was masked to treatment allocation. The funder remained masked to survival results during the study, and the success of masking was not assessed.* Comment: For OS and PFS there is low risk of bias. For adverse reactions and drop-out due to adverse reactions, there is high risk of bias.
Risk of bias in selection of the reported result	**Low**	Predefined outcomes are reported (some only at www.clinicaltrials.gov). In the publication (2017): PFS, Overall Survival, Overall Response, Duration of Response, Percentage of Participants With ≥ Grade 2 Peripheral Neuropathy, Safety. No reason to assume that the analysis plan was not followed.
Overall risk of bias	**Low**	The overall risk of bias is judged low even though there are some concerns and the study is unblinded. However, for the critical outcome OS, the risk of bias is low and for the critical outcome, drop-out due to adverse events, there is no clear indication of in which direction the risk of bias will affect the outcome. There is missing data for QoL in the comparator group, however as QoL is an important outcome, the risk of bias for this domain will not affect the overall risk of bias judgement.

Fagudvalget bemærker at:

- *The funder collaborated with the authors in the interpretation of the data.*
- En stor del af medforfatterne har økonomiske interessekonflikter.

17.2 GRADE-evaluering af evidenskvaliteten

17.2.1 Klinisk spørgsmål 1

PomBorDex vs. DaraBorDex til patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid.

GRADE-profil PomBorDex vs. BorDex (OPTIMISMM)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**lenalidomid**	**komparator**	**Relativ [95 % CI]**	**Absolut**		
Overlevelse, median (måneder)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	281	278	HR: 0,91 (0,70-1,18)		⨁⨁◯◯ LOW	CRITICAL
PFS, median (måneder)												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	281	278	HR: 0,61 (0,49-0,77)		⨁⨁⨁◯ MODERATE	IMPORTANT
Behandlingsophør på grund af uønskede hændelser												
1	randomised trials	serious [c]	serious [a]	not serious	not serious	none	80/278 (28,8 %)	51/270 (18,9 %)	HR: 1,52 (1,12-2,07)		⨁⨁◯◯ LOW	CRITICAL
Livskvalitet												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard ration; RR: Risk ratio
a. Der er kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens.
b. Der er et bredt konfidensinterval på HR for overlevelse. Derfor nedgraderes ét niveau for unøjagtighed.
c. Studiet er ublindet, hvilket kan påvirke andelen, der ophører behandlingen på grund af bivirkninger, hvorfor der er nedgraderet ét niveau på grund af risiko for bias.

GRADE-profil DaraBorDex vs. BorDex (CASTOR)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**lenalidomid**	**komparator**	**Relativ [95 % CI]**	**Absolut**		
Overlevelse, median (måneder)												
1	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	251	247	HR: 0,77 (0,47-1,26)		⨁◯◯◯ VERY LOW	CRITICAL
PFS, median (måneder)												
1	randomised trials	serious [a]	serious [b]	not serious	not serious	none	89	120	HR: 0,38 (0,26-0,56)		⨁⨁◯◯ LOW	IMPORTANT
Behandlingsophør på grund af uønskede hændelser												
1	randomised trials	Very serious [d]	serious [b]	not serious	serious [e]	none	25/243 (10,3 %)	23/237 (9,7 %)	RR:1,06 (0,62-1,81)		⨁◯◯◯ VERY LOW	CRITICAL
Livskvalitet												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard ration; RR: Risk ratio
a. Studiet er ublindet, hvilket dog ikke forventes at påvirke overlevelsen. Der var ingen information om randomiseringen, dog ser baselinekarakteristika ud til at være velbalanceret mellem de 2 arme. Sponsor var involveret i alle aspekter af studiet inkl. analyseplan og databearbejdning. Derfor er der nedgraderet ét niveau for risiko for bias.
b. Der er kun data fra ét studie. Derfor nedgraderes der ét niveau for inkonsistens.
c. Der er et bredt konfidensinterval på HR for overlevelse i dette studie, hvilket omfatter forskellige konklusioner. Derfor er der nedgraderet ét niveau for unøjagtighed.
d: Studiet er ublindet, hvilket kan påvirke andelen af patienter, der ophører behandlingen pga. uønskede hændelser. Der var ingen information om randomiseringen, dog ser baselinekarakteristika ud til at være velbalanceret mellem de 2 arme. Sponsor var involveret i alle aspekter af studiet inkl. analyseplan og databearbejdning. Derfor er der nedgraderet 2 niveauer for risiko for bias.
e: Der er et bredt konfidensinterval på RR for behandlingsophør i dette studie, hvilket omfatter forskellige konklusioner. Derfor er der nedgraderet ét niveau for unøjagtighed.

17.2.2 Klinisk spørgsmål 2

PomBorDex vs. DaraBorDex til patienter med knoglemarvskræft, *som er refraktære overfor lenalidomid, og som har modtaget mindst én tidligere behandling?*

GRADE-profil PomBorDex vs. BorDex (OPTIMISMM)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**lenalidomid**	**komparator**	**Relativ [95 % CI]**	**Absolut**		
Overlevelse, median (måneder)												
												CRITICAL
PFS, median (måneder)												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	200	191	HR:0,65 (0,50-0,84)		⨁⨁⨁◯ MODERATE	IMPORTANT
Behandlingsophør på grund af uønskede hændelser												
1	randomised trials	serious [b]	serious [a]	not serious	not serious	none	80/278 (28,8 %)	51/270 (18,9 %)	RR: 1,52 (1,12-2,07)		⨁⨁◯◯ LOW	CRITICAL
Livskvalitet												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard ration; RR: Risk ratio
a. Der er kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens.
b. Studiet er ublindet, hvilket kan påvirke andelen, der ophører behandlingen på grund af bivirkninger. Derfor er der nedgraderet ét niveau på grund af risiko for bias.

GRADE-profil DaraBorDex vs. BorDex (CASTOR)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**lenalidomid**	**komparator**	**Relativ [95 % CI]**	**Absolut**		
Overlevelse, median (måneder)												
												CRITICAL
PFS, median (måneder)												
1	randomised trials	serious [a]	serious [b]	not serious	not serious	none	45	60	0,36 (0,21-0,63)		⨁⨁◯◯ LOW	IMPORTANT
Behandlingsophør på grund af uønskede hændelser												
1	randomised trials	very serious [c]	serious [b]	serious [d]	serious [e]	none	25/243 (10,3 %)	23/237 (9,7 %)	RR:1,06 (0,62-1,81)		⨁◯◯◯ VERY LOW	CRITICAL
Livskvalitet												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard ration; RR: Risk ratio
a. Studiet er ublindet, hvilket dog ikke forventes at påvirke overlevelsen. Der var ingen information om randomiseringen, dog ser baselinekarakteristika ud til at være velbalanceret mellem de 2 arme. Sponsor var involveret i alle aspekter af studiet inkl. analyseplan og databearbejdning. Derfor er der nedgraderet ét niveau for risiko for bias.
b. Der er kun data fra ét studie. Derfor nedgraderes der ét niveau for inkonsistens.
c: Studiet er ublindet, hvilket kan påvirke andelen af patienter, der ophører behandlingen pga. uønskede hændelser. Der var ingen information om randomiseringen, dog ser baselinekarakteristika ud til at være velbalanceret mellem de 2 arme. Sponsor var involveret i alle aspekter af studiet inkl. analyseplan og databearbejdning. Derfor er der nedgraderet 2 niveauer for risiko for bias.
d. Der er et bredt konfidensinterval på RR for behandlingsophør i dette studie, hvilket omfatter forskellige konklusioner. Derfor er der nedgraderet ét niveau for unøjagtighed.
e. Studiepopulationen (ITT) adskiller sig fra den population, som indgår i det kliniske spørgsmål i forhold til andelen af lenalidomidrefraktære patienter. Derfor nedgraderes 1 niveau.

17.2.3 Klinisk spørgsmål 3

PomBorDex vs. CarDex til patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger?

GRADE-profil PomBorDex vs. BorDex (OPTIMISMM)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	Studiedesign	Risk of bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	lenalidomid	komparator	Relativ [95 % CI]	Absolut		
Overlevelse, median (måneder)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	281	278	HR:0,91 (0,70-1,18)		⨁⨁◯◯ LOW	CRITICAL
PFS, median (måneder)												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	170	163	HR: 0,63 (0,48-0,83)		⨁⨁⨁◯ MODERATE	IMPORTANT
Behandlingsophør på grund af uønskede hændelser												
1	randomised trials	serious [c]	serious [a]	serious	not serious	none	80/278 (28,8 %)	51/270 (18,9 %)	HR: 1,52 (1,12-2,07)		⨁◯◯◯ VERY LOW	CRITICAL
Livskvalitet												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard ration; RR: Risk ratio
a. Der er kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens.
b. Usikkerheden på medianoverlevelser er stor: 40,5 (29,8-ikke opnået). Derfor nedgraderes ét niveau for unøjagtighed.
c. Studiet er ublindet, hvilket kan påvirke andelen, der ophører behandlingen på grund af bivirkninger. Derfor er der nedgraderet ét niveau på grund af risiko for bias.
d. Studiepopulationen adskiller sig fra populationen til det kliniske spørgsmål. Derfor nedgraderes ét niveau for indirekthed.

GRADE-profil CarDex vs. BorDex (ENDEAVOR)

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**lenalidomid**	**komparator**	**Relativ [95 % CI]**	**Absolut**		
Overlevelse, median (måneder)												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	233	236	HR: 0,75 (0,59 – 0,96)		⨁⨁◯◯ LOW	CRITICAL
PFS, median (måneder)												
1	randomised trials	not serious	serious [a]	not serious	serious [c]	none	126	132	HR: 0,86 (0,57-1,32)		⨁⨁◯◯ LOW	IMPORTANT
Behandlingsophør på grund af uønskede hændelser												
1	randomised trials	serious [d]	serious [a]	not serious	serious [e]	none	52/231 (22,5 %)	53/229 (23,1 %)	RR: 1,57 (0,99-2,47)		⨁◯◯◯ VERY LOW	CRITICAL
Livskvalitet												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; HR: Hazard ration; RR: Risk ratio
a. Der er kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens.
b. Patientpopulationen adskiller sig fra populationen defineret i det kliniske spørgsmål, idet kun 38 % tidligere er behandlede med lenalidomid, og kun 50 % tidligere har modtaget 2-3 behandlinger.
c. Der er et bredt konfidensinterval på HR for PFS i dette studie, hvilket omfatter forskellige konklusioner.
d. Studiet er ublindet, hvilket kan påvirke andelen, der ophører behandlingen på grund af bivirkninger, Derfor er der nedgraderet ét niveau på grund af risiko for bias.
e. Der er et bredt konfidensinterval på RR for behandlingsophør i dette studie, hvilket omfatter forskellige konklusioner.

Application for the assessment of Imnovid® (pomalidomide) in combination with bortezomib and dexamethasone (PomBorDex) for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

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1 Basic information

Table 1 Contact information

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Title	Associate Director Market Access
Area of responsibility	Primary contact
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E-mail	nfik@celgene.com

Table 2 Overview over the pharmaceutical

Proprietary name	Imnovid®
Generic name	Pomalidomide
Marketing authorization holder in Denmark	Celgene Europe Ltd, 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom
ATC code	L04 AX06
Pharmacotherapeutic group	Other immunosuppressants
Active substance(s)	Pomalidomide
Pharmaceutical form(s)	Hard capsules for oral administration
Mechanism of action	Pomalidomide has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma tumour cell growth. Specifically, pomalidomide inhibits proliferation and induces apoptosis of haematopoietic tumour cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergises with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumour cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. Pomalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and Roc1, and can inhibit the auto-ubiquitination of CRBN within the complex. E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate [SmPC]
Dosage regimen	The recommended dose of pomalidomide is 4 mg orally once daily on Days 1 to 14 of repeated 21-day cycles. Bortezomib (1.3 mg/m^2)should be given on days 1, 4, 8 and 11 of 21 day cycles for the first 8 cycles, and on days 1 and 8 of 21 days cycles thereafter. Dexamethasone 20 mg should be given on days 1, 2, 4, 5, 8,9 11, and 12 for the first 8 cycles and days 1,2, 8 and 9 thereafter.

	Treatment with pomalidomide combined with bortezomib and dexamethasone should be given until disease progression or until unacceptable toxicity occurs.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Imnovid in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.
Other approved therapeutic indications	Imnovid is currently indicated in combination with dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received *at least two prior* treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.
Will dispensing be restricted to hospitals?	Yes, BEGR
Combination therapy and/or co-medication	For the indication to be assessed pomalidomide is to be administered in combination with bortezomib and dexamethasone.
Packaging – types, sizes/number of units, and concentrations	Imnovid (pomalidomide) is provided as hard capsules in the strengths 1, 2, 3, and 4 mg per capsules in pack sizes of 14 or 21 hard capsules in blisters.
Orphan drug designation	No.
Reference: [1]	

2 Abbreviations

Table 3 Abbreviations

BorDex	Bortezomib + Dexamethasone
CarDex	Carfilzomib+Dexamethasone
DaraBorDex	Daratumumab+Bortezomib+Dexamethasone
DaraLenDex	Daratumumab+Lenalidomide+Dexamethasone
DRd	Daratumumab+lenalidomide+Dexamethasone
DVd	Daratumumab+Bortezomib+Dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HRQoL	Health-related quality of life
IMiD	Immunomodulatory drug
ITC	Indirect Treatment Comparison

ITT	Intention to Treat
Kd	Carfilzomib+dexamtehasone
LenDex	Lenalidomide+dexamethasone
MM	Multiple myeloma
NDMM	Newly Diagnosed Multiple Myeloma
NMA	Network meta-analysis
OS	Overall survival
PFS	Progression Free Survival
PomBorDex	Pomalidomide+bortezomib+dexamethasone
PVd	Pomalidomide+bortezomib+dexamethasone
RRMM	Relapsed/refractory multiple myeloma
Vd	Bortezomib+dexamethasone

3 Summary

This is an application for assessment of the combination of pomalidomide + bortezomib+ dexamethasone as standard treatment for adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

The application focuses on three populations each with separate comparators as defined in the Medicines Council protocol.[2]

1. Adult patients with multiple myeloma who have received at least one prior treatment, including lenalidomide. The comparators are DaraBorDex and DaraLenDex.
2. Adult patients with multiple myeloma who have received at least one prior treatment and who are considered refractory to lenalidomide. The comparator is DaraBorDex.
3. Adult patients with multiple myeloma who have received at least two previous treatments and who have received either DaraLenDex or DaraBorDex. The comparator is CarDex.

As no data were available for population #3 (patients having received DaraLenDex or DaraBorDex), data have been included for adult patients with multiple myeloma who have received at least two previous treatments.

A systematic literature search was conducted according to the definitions in the Medicines Council protocol identifying four clinical studies reported in a total of 12 eligible publications.

No head to head studies comparing the intervention and the pre-defined comparators were identified. An indirect treatment comparison has been conducted with between PomBorDex and DaraBorDex and PomBorDex and CarDex.

It should be noted that the BorDex regimen in the DaraBorDex study is for a fixed schedule of maximum 8 cycles, while the schedule for PomBorDex is until progression, which may impact the outcome of the analysis.

For DaraLenDex no common comparator could be identified, why this is described narratively.

There are several important differences between the study designs and baseline characteristics causing reason to caution when making comparisons.

In the OPTIMISMM study all patients had received lenalidomide in prior lines, and approx. 70% were lenalidomide refractory. The study was statistically powered to assess results also in this subgroup.

In the study PomBorDex showed statistically significant improvement in PFS as compared to BorDex alone in both the ITT-population of lenalidomide exposed patients and in patients refractory to lenalidomide both when administered in patients who had received only one prior line of therapy as well as in patients having received two or more lines of treatment.

The other included studies (CASTOR, POLLUX and ENDEAVOR) had a markedly lower proportion of patients previously exposed to lenalidomide and even lower proportion of patients who were refractory to lenalidomide, which impacts the validity of the comparative analyses due to the size of subgroups compared.

When assessing the discontinuation rate not only the different study designs (fixed versus continuous treatment), but also the extent of previous bortezomib exposure in the populations should be taken into account.

In addition to the comparative analysis of the predefined outcomes an overview of adverse events in ≥10% of patients and grade 3/4 adverse events in all patients has been provided.

A formal comparison for overall survival was not possible for PomBorDex compared to DaraBorDex and DaraLenDex in the predefined populations in clinical questions 1 and 2 due to lack of mature data.

For clinical question # 1 in patients who have received at least one prior line including lenalidomide an indirect comparison was performed in spite of the different dosing regimens for PomBorDex (until

progression) and DaraBorDex (maximum 8 cycles). The analysis showed that DaraBorDex improves PFS as compared to PomBorDex while no difference could be shown with regard to discontinuations due to TEAEs. Due to lack of common comparator between PomBorDex and DaraLenDex a narrative description of data has been provided.

For clinical question # 2 in patients having at least one prior treatment and who are considered refractory to lenalidomide, the indirect treatment comparison did not show any statistically significant difference between PomBorDex and DaraBorDex with regard to PFS.

For clinical question # 3 in patients who have received at least two previous treatments the indirect treatment comparison did not show any statistically significant difference between PomBorDex and DaraBorDex with regard to PFS and discontinuations due to TEAEs.

These results should be assessed with caution as the dosing schedule was different in the underlying studies, and the size of the subgroups of lenalidomide exposed and in particular the lenalidomide refractory patients were small.

The qualitative review of the adverse event profile confirms the already well documented adverse event profile of pomalidomide, bortezomib and dexamethasone with no apparent clinically significant differences.

In conclusion data supports the use of PomBorDex as a valid treatment option in patients who have received one or more previous lines of therapy including lenalidomide.

4 Literature search

A systematic literature search was conducted on according to the guidance provided by the Danish Medicines Council.[2]

See section 7.1.2 for details on the systematic literature search including in- and exclusion criteria, search strings, PRISMA Diagram and list of excluded studies after full text review.

4.1.1 Databases and search strategy

To identify relevant studies addressing the research questions of interest, the following electronic databases below were searched:

- MEDLINE, MEDLINE-IN-PROCESS (via PubMed)
- Embase (via EMBASE.com)

The search strings are listed in Table 14 (p. 40) and Table 15 (p. 42).

4.1.2 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 as outlined in section 7.1.2 (p. 38).

4.1.3 Study selection

Titles and abstracts of studies identified from the search strategy, where available, were reviewed by two reviewers in parallel according to the pre-specified inclusion/exclusion criteria shown in Table 13 (p. 38). Any discrepancies were resolved by discussion.

Articles identified as potentially relevant were then reviewed in full and selected according to the list of pre-specified inclusion/exclusion criteria. A second reviewer independently reviewed the titles and abstracts according to the screening criteria

A total of 489 records were identified during the searches. After review 18 articles were retrieved for full text review, of which were excluded (see Table 16 on p. 43).
A total of 10 publications are included in the current application.
In addition

4.2 Relevant studies

Table 4 Relevant 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>*
***Richardson PG, Oriol A, Beksac M, et al.**; OPTIMISMM trial investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019 Jun;20(6):781-794.[3]*	*OPTIMISMM*	*NCT01734928*	*07JAN2013 – MAY2022 (for OS data)*	*1, 2, 3*
***Dimopoulos MA, Oriol A, Nahi H et al.** Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:1319-31. [4]* ***Dimopoulos MA, San-Miguel J, Belch A et al.** Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica 2018;103:2088-96. [5]*	*POLLUX*	*NCT02076009*	*23MAY2014-07MAR2016 (primary outcome)*	*1*
***Palumbo A, Chanan-Khan A, Weisel K et al.** Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:754-66. [6]* ***Spencer A, Lentzsch S, Weisel K et al.** Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica 2018;103:2079-87. [7]*	*CASTOR*	*NCT02136134*	*15AUG2014-11JAN2016 (primary outcome)*	*1, 2,*
***Dimopoulos MA, Moreau P, Palumbo A et al.** Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016;17:27-38.[8]*	*ENDEAVOR*	*NCT01568866*	*20JUN2012-10NOV2014 (primary outcome)*	*3*

***Dimopoulos MA, Goldschmidt H, Niesvizky R et al**. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:1327-1337.[9]* ***Moreau P, Joshua D, Chng WJ, et al.** Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia. 2017 Jan;31(1):115-122. [10]* ***Orlowski RZ, Moreau P, Niesvizky R, et al.** Carfilzomib-Dexamethasone Vs Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups. Clinical Lymphoma Myeloma and Leukemia. 2019. [11]* ***Ludwig H, Moreau P, Dimopoulos MA, et al.** Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma. Blood Cancer J. 2019 Feb 22;9(3):23. [12]*				
**when multiple clinical questions are defined in the protocol*				

In addition, the following EPARs have been consulted:

PomBorDex	Imnovid Procedure No. EMEA/H/C/002682/II/0031/G (EMA/CHMP/674052/2018)
DaraBorDex DaraLenDex	Darzalex Procedure No. EMEA/H/C/004077/II/0002 (EMA/193295/2017)
CarDex	Kyprolis Procedure No. EMEA/H/C/003790/II/0001/G (EMA/517040/2016)

4.3 Main characteristics of included studies

The main characteristics of the included studies are presented in the appendix as follows:

OPTIMISMM - Table 17 (p. 44)

POLLUX - Table 18 (p. 46)

CASTOR - Table 19 (p. 49)

ENDEAVOR - Table 20 (p. 52)

4.3.1 Main differences in study design and baseline characteristics

An overview of study design and baseline data across the four studies in this application is provided in Table 5 (p. 12).

The following points should be considered during the assessment.

Number of prior treatments

The number of prior treatments differ between studies with the highest proportion of patients having received two lines or more seen in the OPTIMISMM study.

Treatment exposure in prior treatment lines

In the OPTIMISMM study all (100%) patients had to have received lenalidomide during one of their previous treatments, while this was not mandatory in the other three studies.

This is also reflected in the baseline demographics where all patients in the OPTIMISMM study had received lenalidomide, while in CASTOR (35.5%), POLLUX (17.6%) and ENDEAVOR (38%) the percentage of patients having received lenalidomide previously was markedly lower (details are provided in Table 5 (p. 12)).

Among the bortezomib containing studies, the number of patients that previously have received bortezomib seems lower in the ENDEAVOR (54%) compared with OPTIMISMM (72%) and with CASTOR (66%) in between.[13-15]

Refractory status

A marked difference is also visible regarding the proportion of patients who were refractory to lenalidomide in each of the studies. While a high proportion of the patients enrolled in the OPTIMISMM (69.9%) trial were lenalidomide refractory, this subgroup is relatively small in the CASTOR (21.1% as last line therapy) and ENDEAVOR (15.3%) studies. In the POLLUX (0%) study prior refractoriness to lenalidomide was an exclusion criterion.

Of note is that reporting of data for certain subgroups based on e.g. previous lenalidomide treatment and lenalidomide refractoriness varies between publications, which should be considered during the assessment.

The CASTOR study excluded patients, who were refractory to bortezomib, while such patients were permitted to be included into OPTIMISMM. Patients who progressed on or within 60 days of a once-weekly bortezomib schedule or on a lower dose of bortezomib were eligible to participate and were regarded as the bortezomib-refractory patient population in OPTIMISMM.[3]

A significantly higher proportion of patients in the OPTMISMM study were refractory to last prior line of therapy (68%), compared to the CASTOR (32.3%), POLLUX (27.4%) and ENDEAVOR (40%).[3] [7, 15]

Dosing schedule

In the CASTOR study bortezomib treatment was administered as a fixed dose (maximum 8 cycles), while study drug was dosed until progression in the other three studies.

Statistical power of the studies

Due to the limited size of the subgroups across studies, any comparisons should be interpreted with caution.

Table 5 Study design and baseline demographics - overview

	OPTIMISMM	**CASTOR**	**POLLUX [**	**ENDEAVOR**
Reference	[3] [14] [EPAR, table 15, 16, 17]	[6, 7, 13]	[4, 5, 13]	[8, 9, 11]
Number of patients	559	498	569	929
Study design	Randomized open-label multicentre phase 3	Randomized open-label multicentre phase 3	Randomized open-label multicentre phase 3	Randomized open-label multicentre phase 3
Intervention	PomBorDex administered in 21 days cycles Pomalidomide 4 mg orally on days 1-14 Bortezomib 1.3 mg/m2 i.v./s.c. on days 1, 4, 8 and 11 for cycles 1 -8 then days 1, 8 for cycles 9 and onward until disease progression plus Dexamethasone 20 mg/day [≤ 75 years old] or 10 mg/day [> 75 years old] orally on days 1, 2, 4, 5, 8, 9, 11, 12 for cycles 1-8 on days 1, 2,8, 9 of 21 days for cycles 9 and onward until disease progression	DaraBorDex administered in 21 day cycles Daratumumab i.v. 16 mg/kg /week for the first 3 cycles, on Day 1 of Cycles 4-9, then every 4 weeks thereafter. Bortezomib s.c. 1.3 mg/m^2 on Days 1, 4, 8 and 11 for up to eight cycles (note limited duration) Dexamethasone orally 20 mg on Days 1, 2, 4, 5, 8, 9, 11 and 12 of the first 8 bortezomib cycles	DaraLenDex Daratumumab i.v. 16 mg/kg on days 1, 8, 15, and 22) for 8 weeks during cycles 1 and 2, every 2 weeks (on days 1 and 15) for 16 weeks (cycles 3-6), and every 4 weeks thereafter. Lenalidomide 25 mg orally days 1 to 21 of each cycle (if CrCl >60 ml/min) or 10 mg daily (if CrCl 30-60 ml/min) Dexamethasone 40 mg/week	CarDex administered in 28 day cycles as Carfilzomib 20mg/m^2 days 1 and 2 of cycle 1; 56 mg/m^2 on days 1, 2, 8, 9, 15, 16 Dexamethasone 20mg (oral/i.v.) on days 1, 2, 8, 9, 15, 16, 22, and 23
Comparator	BorDex dosed as above	BorDex dosed as above	LenDex dosed as above	BorDex administered in 21 day cycles Bor 1.3mg/m^2; (i.v. bolus or s.c.) on days 1, 4, 8, and 11, Dexamethasone 20 mg (oral/ i.v.) on days 1, 2, 4, 5, 8, 9, 11, and 12.
Time since diagnosis (median)	4.2 (0.2; 25.9)	3.87 (0.7-20.7) years	3.6 years	44.0 (4.0, 306.2) months
Previous treatments, number	Median 2 (1-5) 1: 40.4.% 2: 39.5% 3: 19.9% >3: 0.2%	Median: 2 (1-9) 1: 48.6% 2: 29.9% 3: 14.7% >3: 8.8%	Median: 1 (1-11) Previous ≥3: 19.2 %	Median (IQR): 2 (1-2) 1: 50% 2: 34% 3: 16%

	OPTIMISMM	CASTOR	POLLUX [	ENDEAVOR
Previous treatments, type	Len: 100% Thal, Len, Corticosteroids: 25% Len+PI: 76.0% Len+ Bor: 72.3% BorDex: 71.0%	Len: 42.0% Alkylating: 95.6% Proteasome inh.: 67.3% IMiD: 71.1% PI+IMiD: 44.6%	Len: 17.6% Prev. proteasome-inh.: 85.6% Prev. alkylating: 94.6% Prev. IMiD: 55.2 % Prev. Bor and Len: 15%	Len: 38% Bor: 54% Car: <1% Thal: 45%
Primary treatment	No info	No info	No info	No info
Age	68 (27-89)	64 (30-88)	65 (35-89) years >65 years: 52.0%	65 (35-89)
Cytogenetic risk status	High risk: 19.7% Non-high risk: 48.1% Missing/not evaluable: 32.2%	Standard: 77.3% High: 22.7%	High: 15.9% Standard: 84.1%	High: 21% Standard: 61% Unknown/Missing: 18%
ISS disease stage	I: 51.3% II: 31.3% III: 17.4%	I: 39.0% II: 37.5% III: 23.5%	I: 48.7% II: 31.5% III: 19.9%	I: 44% II-III: 56%
ECOG performance status	0: 51.2% 1: 42.9% 2: 5.9%	0: 42.4% 1: 52.4% 2: 5.2%	0: 51.7% 1 or 2: 48.3%	0: 48% 1: 45% 2: 7%
Refractory status	*To last line: 68%* *IMiDs: 70.7%* Len: 69.9% Thal: 4.3% *Prot. Inhib.: 13.2%* Bor: 10.0% Car: 1.6% Ixa: 1.8%	To last line: 32.3% (DaraBorDex 30.3%, BorDex 34.4%) To Len as last line: DaraBorDex 17.9%, BorDex 24.3% (21.1% for total pop)	Bor: 20.5% IMid: 3.7% Prot.-inh-+IMiD: 3.8% To Len: 0% Last line 27.4%	Len: 25.3% Bor: 6% To last line: 40.0%
Renal function	<30: 3.8% 30<45: 9.7% 45<60: 16.5% 60<80: 27.0% ≥80: 43.1%	Unknown	>30 ml/min: 100%	Mean (SD): 76.7 (31.8) ml <30: 6% 30<50: 12% 50<80: 40% ≥80: 42%
Subsequent treatments	163 (59%) of 278 patients allocated bortezomib and dexamethasone received subsequent treatments and 109 (39%) received pomalidomide. Thus, of 163 patients allocated bortezomib and dexamethasone who received subsequent treatment, two-thirds (109 [67%]	No info	No info	No info

	OPTIMISMM	CASTOR	POLLUX [	ENDEAVOR
	of 163) received pomalidomide. Of note, 21 (7%) of 281 patients assigned pomalidomide, bortezomib, and dexamethasone received pomalidomide as subsequent treatment.			
Median follow-up	PFS: 15.9 (IQR 9.9-21.7) months OS: 26.2 months (Not mature)	19.4 months	PFS: 13.5 months OS: 25.4 (0-32.7)	PFS: 11.9 months OS: 44.3 months in the Kd56 group and 43.7 months in the Vd group
Numbers for CASTOR, POLLUX and ENDEAVOR have been sourced from references listed and cross-checked with the data in the Medicines Council background document, table D, p. 91 (POLLUX) and table E, p. 93 (CASTOR/ENDEAVOR).				

5 Clinical questions

5.1 PomBorDex compared to DaraBorDex and DaraLenDex in patients who have received at least one prior treatment, including lenalidomide

What is the value of pomalidomide in combination with bortezomib and dexamethasone compared to current clinical practice for the treatment of multiple myeloma in patients who have received at least one prior treatment, including lenalidomide?

5.1.1 Presentation of relevant studies

The following studies are used in the assessment of clinical question #1:

OPTIMISMM (PomBorDex vs. BorDex)

This was a phase III, randomized (1:1), open-label, parallel clinical trial with the purpose of comparing the efficacy and safety of bortezomib and low dose dexamethasone with or without pomalidomide in participants with relapsed/refractory multiple myeloma who had received 1-3 previous lines of treatments including at least two cycles of lenalidomide. Patients were eligible to participate in the study if they were aged 18 years or older and had a diagnosis of multiple myeloma, had measurable disease based on serum (≥0.5 g/dL) or urine (≥200 mg/24 h) protein levels, and had an Eastern Cooperative Oncology Group performance status of 0–2.[3]

Two important points should be noted:

- The proportion of patients previously treated with lenalidomide was 100.0% and 69.9% were refractory to lenalidomide. [3]
- Bortezomib was administered with a continuous dose schedule until progression. [3]

CASTOR (DaraBorDex vs. BorDex)

This was a multicentre, randomized (1:1), open-label, active-controlled, phase 3 trial with the purpose of the study of assessing the effects of administration of daratumumab when combined with fixed dose bortezomib and dexamethasone compared with bortezomib and dexamethasone alone, for participants with relapsed or refractory multiple myeloma who had received at least one previous line of therapy for multiple myeloma, had at least a partial response to one or more of their previous therapies, and had documented progressive disease, according to International Myeloma Working Group (IMWG) criteria during or after the completion of their last regimen as well as having measurable disease on the basis of assessments of the serum, urine, or both or to have measurable disease as assessed by the serum free light-chain assay, in accordance with the criteria specified by the IMWG at screening. [6]

Two important points should be noted:

- The proportion of patients previously treated with lenalidomide was 42.0%, and 21.1% were refractory to lenalidomide. [7, 13]
- Bortezomib was administered with a fixed dose schedule for a maximum of 8 cycles. [7]

POLLUX (DaraLenDex vs. LenDex)

This was a randomized open-label multicentre phase III trial with the purpose of this study of comparing the effectiveness of daratumumab when combined with lenalidomide and dexamethasone (DaraLenDex) to that of lenalidomide and dexamethasone (LenDex), in terms of progression-free survival in participants who had measurable disease at screening according to serum or urinary M-protein levels or serum free light-

chain levels and abnormal serum immunoglobulin free light-chain ratios and relapsed or refractory multiple myeloma according to IMWG criteria during or after the receipt of their last regimen, and who had received and had a response to one or more lines of previous therapy. [4]

Two important points should be noted

- the proportion of patients previously treated with lenalidomide was only 17.6%. [5]
- patients, who were refractory to lenalidomide were excluded from study participation[5]

An overview of the patient characteristics and baseline characteristics are presented in Table 5 (p. 12).

5.1.2 Results per study

The results per study for OS, PFS, QoL and discontinuations due to TEAES are available in Table 24 (OPTIMISMM) (p. 64), Table 25 (CASTOR) (p. 74) and Table 26 (POLLUX) (p.80).

OPTIMISMM

Data for overall survival (ITT-population) were not mature at the original cut-off date of 26OCT2017. However, an updated OS analysis (15SEP2018) submitted to the EMA based on an event rate of 43.3% and after a median follow-up of 26.2 months has shown a positive trend in favour of PomBorDex as compared to BorDex (please see the pomalidomide EPAR, tables 33 (p. 57) and 51 (p. 83)). [14]

Data for the ITT-population, regardless of previous lines of treatment, showed a significant improvement in PFS for PomBorDex (n=281) as compared to BorDex (n=278) with a HR of 0.61 (95% CI 0.49-0.77, p<0.0001). [3]

In patients who had received only 1 previous line of therapy, PFS was also significantly better for PomBorDex (n=111) compared to BorDex (n=115) with a HR 0.54 (95% CI 0.36-0.82, p=0.0027). [3]

This improvement in PFS was consistent across other analysed subgroups, e.g. patients with high risk cytogenetics, patients previously exposed to proteasome inhibitors, and as will be discussed in separate section in patients refractory to lenalidomide (section 5.2) and patients who have received two previous treatment lines or more (section 5.2). [3]

Baseline scores for the global health status/QoL domain of the EORTC QLQ-C30 were similar between groups for PomBorDex and for bortezomib and dexamethasone. Scores were maintained over time for both treatment groups with no statistically significant or clinically meaningful differences recorded between treatments at any cycle. [3]

Discontinuations of any study drug (either pomalidomide, bortezomib or dexamethasone) because of at least one adverse event occurred in 28.8% (80 of 278) patients who received PomBorDex vs 18.9% of (51 of 270) patients treated with BorDex. [14]

However, discontinuation of pomalidomide alone occurred in 11.2% (31 of 278 patients) in the PomBorDex arm. In contrast discontinuation of bortezomib alone occurred in 24.1% (67 of 278) of patients in the PomBorDex arm and 18.5% (50 of 270) in the BorDex arm. [14]

This may very well be caused not only by the longer duration of exposure to bortezomib, but also the difference in the cumulative dose of bortezomib between the study arms. See Richardson 2019 (supplementary table 3) for details on treatment exposure and dosing information in the safety population in the OPTIMISMM study. [14]

It is thus apparent that the known adverse event profile of bortezomib has a marked impact on the discontinuation rate in both study arms.

Tables for a qualitative overview of adverse events in ≥10% of patients (Table 21) as well as grade 3/4 adverse events (Table 23) are available in sections 7.3 and 7.4.

CASTOR

Data for Overall Survival in patients previously treated with lenalidomide (the predefined population) has not been reported for DaraBorDex. In the latest available publication (Spencer 2018), data for overall survival was reported still to be immature. [7] Data for OS for the ITT-population can be found in Table 25.

For patients previously treated with lenalidomide DaraBorDex (n=89) showed a significant improvement in PFS compared to BorDex (n=120) with a HR of 0.38 (0.26-0.56). The treatment (BorDex) in the comparator arm was stopped no later than after cycle number 8.[7]

These results are consistent with the significant improvement in PFS for the ITT-population in the CASTOR study with a HR of 0.31 for DaraBorDex compared to BorDex. [7]

There was no statistically significant difference on EORTC QLQ-C30 Quality of Life scores between the study groups (ITT-population). [7]

Discontinuations of any study drug because of at least one adverse event occurred in 10.3% of patients who received DaraBorDex as compared to 9.7% patients treated with BorDex. [7]

Tables for a qualitative overview of adverse events in ≥10% of patients (Table 21) as well as grade 3/4 adverse events (Table 23) are available in sections 7.3 and 7.4.

POLLUX

Data for Overall Survival in patients previously treated with lenalidomide (the predefined population) has not been reported for DaraLenDex. In the latest available publication, data were reported still to be immature. [5] Data for OS for the ITT-population can be found in Table 26.

For patients previously treated with lenalidomide DaraLenDex (n= 50) showed a significant improvement in PFS compared to LenDex (n=50) with a HR of 0.32 (DaraLenDex not reached vs LenDex 18.6 months). [5]

The outcome for the ITT-population showed a HR of 0.41 (DaraLenDex Not Reached vs. LenDex 17.5 months) for DaraLenDex compared to LenDex. [5]

With the EORTC QLQ-C30 Global Health Status Score (ITT-population), statistically significant differences in the change from baseline were observed in favour of DaraLenDex at Weeks 40, 48, 52, 68, 84, and 116. However, these improvements did not last beyond 3 consecutive assessments for either questionnaire. [5]

Discontinuations of any study drug because of at least one adverse (ITT-population) event occurred in 11.9% of patients who received DaraLenDex vs 12.7% of patients treated with LenDex. [5]

Tables for a qualitative overview of adverse events in ≥10% of patients (Table 21) as well as grade 3/4 adverse events (Table 23) are available in sections 7.3 and 7.4.

5.1.3 Comparative analyses

To perform the comparison between PomBorDex and the two comparators, a feasibility analysis was performed to identify if an indirect comparison was possible.

OPTIMISMM vs POLLUX

An indirect treatment comparison could not be conducted between OPTIMISMM and POLLUX as there is not common comparator (comparators in the studies were BorDex and LenDex, respectively). A narrative comparison is provided below.

OPTIMISMM (PomBorDex) vs. CASTOR (DaraBorDex)

Data for the comparison is provided in Table 28 on p. 95 and details on the methodology of the ITC in section 1.1 on p. 100f.

The CASTOR trial presented a significant difference in the BorDex arm design when compared to OPTIMISMM. Indeed, the BorDex arm in the CASTOR trial had a fixed schedule, with a maximum medication time of 24 weeks (8 cycles), whereas OPTIMISMM relied on continuous treatment over the trial duration. [6] As a result, the comparators could not be pooled between CASTOR on the one hand and OPTIMISMM on the other hand.

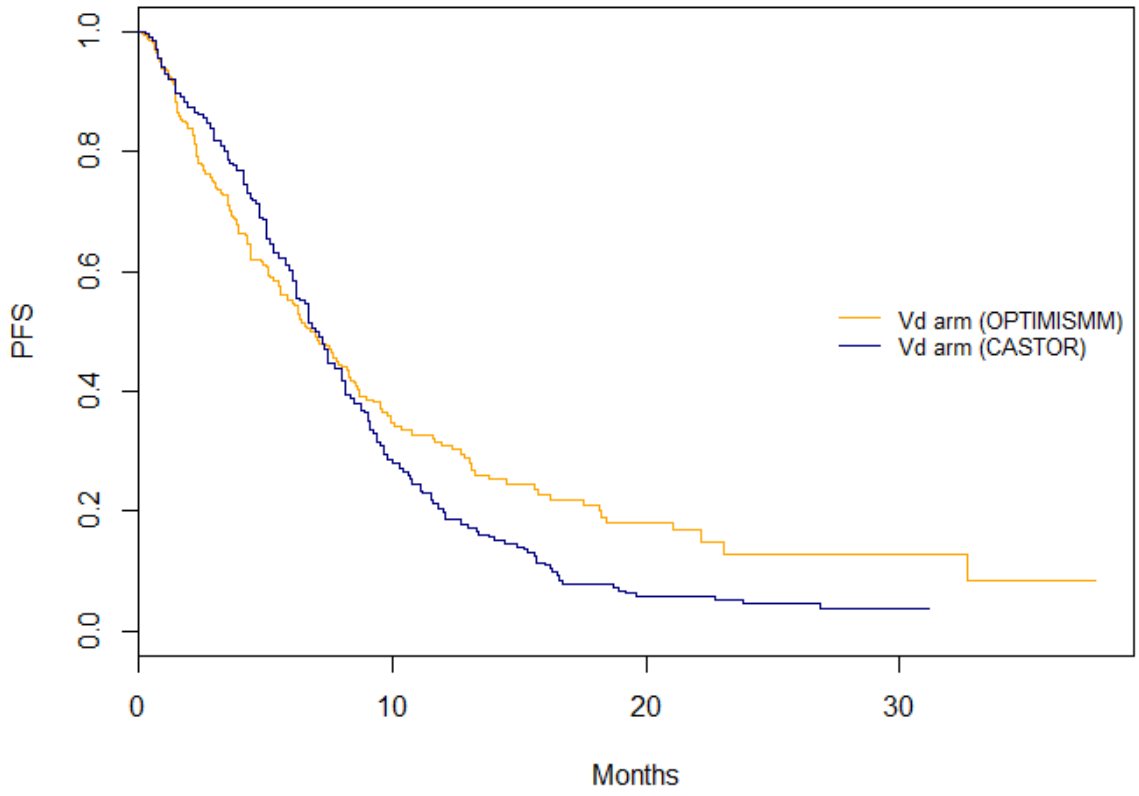
The impact of using a fixed dose of BorDex can been seen on the Kaplan-Meier curves below, which present the time to PFS reported in the OPTIMISMM and CASTOR trials. Indeed, there is an acceleration in the rate of progression of disease in patients randomised to BorDex in the CASTOR trial compared to OPTIMISMM, resulting in the two PFS curves crossing at approximately 7 months. Considering these two treatment regimens comparable would penalise PomBorDex, given the fact that the comparator arm of OPTIMISMM (BorDex continuous) is performing better than the comparator arm of CASTOR (BorDex fixed).

Heterogeneity assessments were also performed for age, sex, ECOG status, ISS stage, and number of prior therapies.

Although not methodologically justified, a Bucher comparison was estimated as a scenario analysis to generate a hazard ratio comparing PomBorDex to DaraBorDex.

For further description of the methodology, please refer to section 7.9 on p. 100f.

Figure 1 PFS KM curves of BorDex comparator arms in OPTIMISMM and CASTOR trials



Overall survival

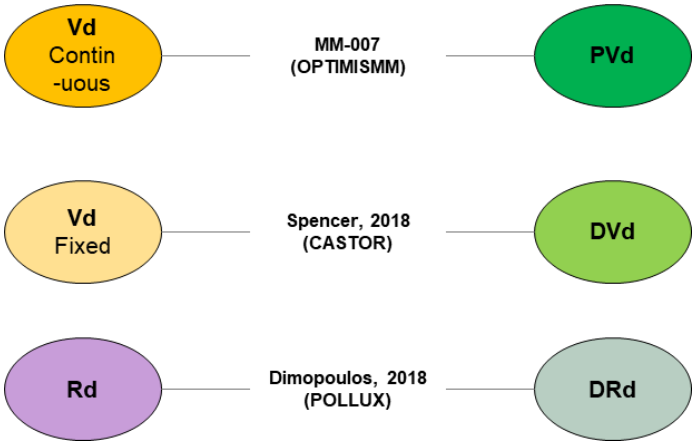
Estimates for Overall Survival in the lenalidomide exposed population (= ITT-population) was only reported for OPTIMISMM, but not for CASTOR.

An indirect comparison of the available immature data for the ITT-population in both studies showed a HR of 1.18 (0.68-2.06) in favour of DaraBorDex (Table 28, p. 92).

Progression Free Survival

The network of evidence, displaying the treatments of interest and included studies for PFS within the lenalidomide-exposed population is presented in Figure 2.

Figure 2 Network of evidence for PFS – Lenalidomide-exposed population



Inputs

The inputs, HR and 95%CI associated with PFS, of the three included studies are displayed below.

Table 6 HR inputs for PFS - Lenalidomide-exposed population

Study	Comparator	Reference	HR 95% CI
Richardson, 2019	PomBorDex (N=281)	BorDex (N=278)	0.61 [0.49, 0.77]
Spencer, 2018	DaraBorDex (N=89)	BorDex (N=120)	0.38 [0.26, 0.56]

Note: An HR<1 indicates comparator is associated with longer PFS when compared to reference. An HR>1 indicates reference is associated with longer PFS vs. comparator.

Results

As shown on Figure 2, due to the disconnected nature of the network, a quantitative analysis was not possible.

A sensitivity analysis relying on a Bucher indirect comparison was undertaken to generate the hazard ratio comparing DaraBorDex vs PomBorDex. As mentioned earlier this analysis needs to be interpreted with caution as the CASTOR trial had a fixed BorDex duration as a comparator arm while patients randomized to BorDex in OPTIMISMM had a continuous treatment.

The hazard ratio of PomBorDex vs DaraBorDex from the indirect comparison was 1.61, and the 95% CI was [1.03-2.51].

Quality of Life

The relative treatment effect on quality of life was assessed inconsistently across trials, thereby making the quantitative synthesis impossible.

In OPTIMISMM, the QoL assessable population included 240 (85%) of 281 patients assigned with PomBorDex and 209 (75%) of 278 patients allocated with BorDex. Based on the number of patients expected to complete the EORTC QLQ-C30 at each visit, QoL compliance exceeded 80% up to cycle 20 among both treatment groups. Baseline scores for the global health status/QoL domain of the EORTC QLQ-C30 were similar between groups (mean 61.0 [standard deviation 23.2] for PomBorDex and 63.5 [21.3] for BorDex). Scores were maintained over time for both treatment groups, with no statistically significant or clinically meaningful differences recorded between treatments at any cycle. [3]

In CASTOR, the EORTC QLQ-C30 and EQ-5D-5L results showed that QoL was maintained during treatment for patients in both groups. Significant differences in the least squares mean changes from baseline were not observed between DaraBorDex and BorDex at any time for the EORTC QLQ-C30 Global Health Status Scores or the EQ-5D-5L Utility Score. A significant difference was observed solely at Week 21 in favor of DaraBorDex for the Visual Analog Scale Score (P=0.0185). No significant differences in EORTC QLQ-C30 Global Health Status were observed for median time to improvement (5.0 vs 5.1 months; HR: 0.99; 95% CI, 0.76-1.29; p=0.9163). Similarly, no significant difference in the median time to improvement was observed for either the EQ-5D-5L Utility Score (7.7 vs 3.5 months; HR: 0.82; 95% CI, 0.62-1.08; p=0.1469) or the Visual Analog Scale Score (5.0 vs 5.0 months; HR: 1.03; 95% CI, 0.79-1.35; p=0.8072). [7]

Discontinuations due the TEAEs

For safety outcomes, the analyses were based on the safety population.

Inputs

Table 7 Proportion of patients discontinuing treatment due to an adverse event

Study	Study arm	Safety population (N)	Patients discontinuing due to adverse events (n)	Proportion	RR 95% CI
Imnovid EPAR	PomBorDex	278	80	28.8%	1.52 [1.12, 2.07]
	BorDex	270	51	18.9%	
Spencer, 2018	DaraBorDex	243	25	10.3%	1.06 [0.62, 1.81]
	BorDex	237	23	9.7%	

Results

A sensitivity analysis relying on a Bucher indirect comparison was undertaken to generate the hazard ratio comparing DaraBorDex vs PomBorDex. As mentioned earlier this analysis needs to be interpreted with caution as the CASTOR trial had a fixed BorDex duration as a comparator arm while patients randomized to BorDex in OPTIMISMM had a continuous treatment.

The RR of PomBorDex vs DaraBorDex from the indirect comparison was 1.44 [0.77-2.67]..

The numerical difference in discontinuation rate seems to be caused by bortezomib as the numerical discontinuation rate in the OPTIMISMM study in the BorDex arm is almost twice as high as in the CASTOR study BorDex arm.

In addition to the potential impact of the fixed versus continuous dosing, data show that dose modification/interruption occurred in a higher proportion of patients receiving daratumumab (36%) in the CASTOR study than in dose modification/interruption of pomalidomide (7.6%) in the OPTIMISMM study. For details please refer to the Pomalidomide EPAR (table 44) [13]and Daratumumab EPAR (table 45, and pages 79-80). [14]

Qualitative review of adverse events

Overview of the frequency of adverse events occurring in ≥10% of patients, and of all grade 3/4 AEs is provided in Table 21 (p. 57) and Table 23 (p.61), respectively.

The data seem to indicate a safety profile consistent with the known safety profiles of the individual components of the regimens.

OPTIMISMM (PomBorDex) vs. POLLUX (DaraLenDex)

Due to lack of a common comparator between PomBorDex and DaraLenDex this is described narratively. Data for the comparison is provided in Table 28 on p. 95.

Overall survival

Mature data for Overall survival has not been reported neither for PomBorDex nor DaraLenDex.

Progression Free Survival

Due to the lack of common comparator, an indirect comparison cannot be made between PomBorDex and DaraLenDex.

The data from OPTIMISMM and POLLUX are show below.

Study	**Comparator**	**Reference**	**HR** **95% CI**
Richardson, 2019	PomBorDex (N=281)	BorDex (N=278)	0.61 [0.49, 0.77]
Dimopoulos, 2018	DaraLenDex (N=50)	LenDex (N=50)	0.32 [0.16, 0.64]

Any comparison of these numbers should be done with caution due to the difference in comparator arms, the limited sized of the lenalidomide treated subgroup in the POLLUX study, and the heterogeneity in the severity of disease (e.g. ISS stage) between the populations.

Quality of Life

The relative treatment effect on quality of life was assessed inconsistently across trials, thereby making a quantitative synthesis impossible.

In OPTIMISMM, the QoL assessable population included 240 (85%) of 281 patients assigned with PomBorDex and 209 (75%) of 278 patients allocated with BorDex. Based on the number of patients expected to complete the EORTC QLQ-C30 at each visit, QoL compliance exceeded 80% up to cycle 20 among both treatment groups. Baseline scores for the global health status/QoL domain of the EORTC QLQ-C30 were similar between groups (mean 61.0 [standard deviation 23.2] for PomBorDex and 63.5 [21.3] for BorDex). Scores were maintained over time for both treatment groups, with no statistically significant or clinically meaningful differences recorded between treatments at any cycle. [3]

In POLLUX, there was no decline in QoL measures with the addition of daratumumab to LenDex. Statistically significant differences in the change from baseline were observed in favor of DaraLenDex at Weeks 8 and 56 with the Utility Score and at Weeks 40, 48, and 56 with the Visual Analog Scale Score of the EQ-5D-5L questionnaire. With the EORTC QLQ-C30 Global Health Status Score, statistically significant differences in the change from baseline were observed in favour of DaraLenDex at Weeks 40, 48, 52, 68, 84, and 116. However, these improvements did not last beyond 3 consecutive assessments in either questionnaire. No significant differences for median time to improvement (6.6 months vs 6.5 months; HR: 1.03; 95% CI, 0.81-1.30; p=0.820) were reported for EORTC QLQ-C30 Global Health Status Scores in the DaraLenDex and LenDex groups. Similarly, no significant differences in median time to improvement were observed between treatment groups for either the EQ-5D-5L Utility Score (6.6 months vs 10.2 months; HR: 1.23; 95% CI, 0.97-1.57; p=0.089) or Visual Analog Scale Score (6.9 months vs 9.3 months; HR: 1.14; 95% CI, 0.89-1.45; p=0.283). [5]

Discontinuations due to TEAEs

Due to the different comparators in the OPTIMISMM and POLLUX studies, a direct comparison of discontinuation rates is difficult.

Study	Study arm	Safety population (N)	Patients discontinuing due to adverse events (n)	Proportion	RR 95% CI
Imnovid EPAR	PomBorDex	278	80	28.8%	1.52 [1.12, 2.07]
	BorDex	270	51	18.9%	
Dimopoulos, 2018	DaraLenDex	286	34	11.9%	0.93 [0.60, 1.45]
	LenDex	283	36	12.7%	

In the OPTIMISMM study the rate for discontinuation of pomalidomide only was 11.2% in the PomBorDex arm while the discontinuation rate of bortezomib only in the PomBorDex arm was 24.1%.[14]

The main cause of discontinuation due to TEAEs in the OPTIMISMM study can thus be considered to be caused by the well-known adverse event profile of bortezomib. It should be noted that bortezomib was dosed continuously until progression.

When comparing to the discontinuation rate in the POLLUX study, it therefore seems relevant to compare the discontinuation rate between PomBorDex and DaraLenDex based on the discontinuation rate for pomalidomide of 11.2% and the discontinuation rate for DaraLenDex of 11.9%.

In addition, data show that dose modification/interruption occurred in a higher proportion of patients receiving daratumumab (37%) in the POLLUX study than in dose modification/interruption of pomalidomide (7.6%) in the OPTIMISMM study. For details please refer to the Pomalidomide EPAR (table 44) and Daratumumab EPAR (table 45, and pages 79-80). [14]

Qualitative review of adverse events

Overview of the frequency of adverse events occurring in ≥10% of patients, and of all grade 3/4 AEs is provided in Table 21 (p. 57) and Table 23 (p.61), respectively.

The data seem to indicate a safety profile consistent with the known safety profiles of the individual components of the regimens.

5.2 PomBorDex compared to DaraBorDex in patients who are refractory to lenalidomide and who have received at least one prior treatment

What is the value of pomalidomide in combination with bortezomib and dexamethasone compared to daratumumab in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who are refractory to lenalidomide and who have received at least one prior treatment?

5.2.1 Presentation of relevant studies

In the context of assessing the results for clinical question #2, it is important to bear in mind the marked difference in patients who have previously received lenalidomide (100% vs. 42.0%) and patients who are refractory to lenalidomide (69.9% vs. 21.1% (as last line)) in the OPTIMISMM and the CASTOR studies respectively.

Additionally, the difference in the bortezomib dosing schedule between OPTIMISMM (continuous until progression) and CASTOR (fixed maximum 8 cycles) should be considered.

Taken all these differences into account, it makes the comparison very difficult and the interpretation of the data should be done with great caution.

OPTIMISMM (PomBorDex vs. BorDex)

Please refer to the study description on p. 15.[3]

CASTOR (DaraBorDex vs. BorDex)

Please refer to the study description on p. 15. [6]

5.2.2 Results per study

A brief narrative overview of the general results for both OPTIMISMM and CASTOR and can be found in section 5.1.1 on p. 15. The results per study for are available in Table 24 (OPTIMISMM) (p. 64), and Table 25 (CASTOR) (p. 74).

OPTIMISMM

In lenalidomide refractory patients who had received one or more prior lines of treatment, PomBorDex (n=200) improved PFS significantly as compared to BorDex (n=191) with a HR of 0.65 (0.50-0.84, p=0.0008).

In lenalidomide refractory patients who had received only one prior line of treatment, PomBorDex (n=64) improved PFS significantly as compared to BorDex (n=65) with a HR of 0.55 (0.33-0.94, p=0.03). [3]

Data for Overall Survival, Quality of Life and Discontinuations due to TEAEs have not been reported separately for this subgroup.

CASTOR

In patients who were refractory to lenalidomide as last line of therapy, PomBorDex (n=45) improved PFS significantly as compared to BorDex (n=60) with a HR of 0.36 (0.21-0.63, p=0.0002). [7]

5.2.3 Comparative analyses

Data for the comparison is provided in Table 28 on p. 95 and details on the methodology of the ITC in section 1.1 on p. 100f.

Comparison of PomBorDex to DaraBorDex

The reservations for comparison due to the different types of dosing (continuous vs. fixed) between the OPTIMISMM and the CASTOR studies are described on p. 18.

Overall survival

OS estimates for the subgroup of patients who are refractory to lenalidomide have not been reported.

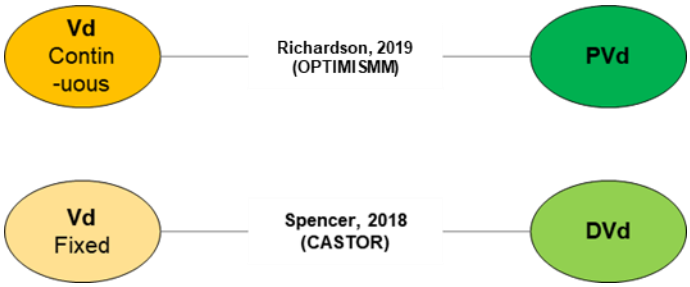
Even though an ITC was considered questionable the results of such an analysis, based on immature data for the ITT-population as a proxy, is shown in Table 29, p. 95.

Progression Free Survival

Network of evidence

The network of evidence related to study including PFS estimates in the lenalidomide refractory population is presented on Figure 3.

Figure 3 Network of evidence for PFS – Lenalidomide-refractory population



Inputs

The inputs, HR and 95%CI, of the two included studies are displayed in Table 8.

Table 8 HR inputs for PFS - Lenalidomide- refractory population

Study	Comparator	Reference	HR 95% CI
Richardson, 2019	PomBorDex (N=200)	BorDex (N=191)	0.65 [0.50, 0.84]
Spencer, 2018	DaraBorDex (N=45)	BorDex (N=60)	0.36 [0.21, 0.63]

Note: An HR<1 indicates comparator is associated with longer PFS when compared to reference. An HR>1 indicates reference is associated with longer PFS vs. comparator.

Results

As mentioned earlier, due to the disconnected nature of the network, an indirect treatment comparison was not feasible.

Despite its limitation, an indirect comparison was estimated and the corresponding hazard ratio of PomBorDex vs DaraBorDex was estimated at 1.81 [95% CI 0.98-3.31]..

Quality of Life

Quality of life data was not reported separately for the subgroup of lenalidomide refractory patients.

Reference is made to the data for the overall lenalidomide exposed population, cf. clinical question #1 (p. 20).

Discontinuations due to TEAEs

The rate of discontinuation due to TEAEs was not reported separately for the subgroup of lenalidomide refractory patients.

Reference is made to the data for the overall population of lenalidomide exposed patients, cf. clinical question #1 (p. 21).

Qualitative review of adverse events

Adverse events have not been reported separately for the for the subgroup of lenalidomide refractory patients.

Reference is made to the data for the overall lenalidomide exposed population, cf. the overview of the frequency of adverse events occurring in ≥10% of patients, and of all grade 3/4 AEs is provided in Table 21 (p. 57) and Table 23 (p.61), respectively.

The data seem to indicate a safety profile consistent with the known safety profiles of the individual components of the regimens.

5.3 PomBorDex compared to CarDex in patients who have received at least two previous treatments

What is the value of pomalidomide in combination with bortezomib and dexamethasone compared to CarDex in patients who have received at least two previous treatments?

The population defined by the Medicines Council is:

Adult patients with multiple myeloma who have received at least two previous treatments and who have received either DaraLenDex or DaraBorDex.

It has however not been possible to identify any published data for a group of patients having received DaraLenDex or DaraBorDex. [2]

The response to clinical question #3 is therefore based on a population defined as: Adult patients with multiple myeloma who have received at least two previous treatments.

5.3.1 Presentation of relevant studies

In the context of this clinical question, it is important to note that all patients (n=) in the OPTIMISMM study had received lenalidomide in previous line. However, in the ENDEAVOR study only 38% had received lenalidomide in previous lines.

In OPTIMISSM 59.6% of the patients had received ≥2 lines of previous treatment as compared to ENDEAVOR where 50% of the patients had received ≥2 lines of previous treatment.

OPTIMISMM (PomBorDex vs. BorDex)

Please refer to the study description on p. 15.[3]

ENDEAVOR (CarDex vs. BorDex)

This was a phase III, randomized, open-label compare progression-free survival in patients with multiple myeloma who relapsed after 1 to 3 prior therapies treated with carfilzomib plus dexamethasone or bortezomib plus dexamethasone. Eligible patients were aged 18 years or older with relapsed or refractory multiple myeloma, measurable disease (ie, serum M-protein of at least 5 g/L or urine M-protein of at least 200 mg/24 h; or in patients without detectable serum or urine M-protein, serum free light chain of at least 100 mg/L [involved light chain] and an abnormal serum κ:λ ratio), Eastern Cooperative Oncology Group performance status of 0 to 2, one to three previous treatments, and at least a partial response to at least one previous treatment.[8]

5.3.2 Results per study

The general results per study for OS, PFS and discontinuations due to TEAES are available in Table 24 (OPTIMISMM) (p. 64) and Table 27 (ENDEAVOR) (p. 86).

OPTIMISMM

Data for Overall Survival in this population has not been reported. Reference is made to the data provided for the ITT-population, cf. clinical question #1.

In patients having received 2 or more lines of previous treatment PomBorDex (n=170) improved PFS significantly as compared to BorDex (n=163) with a HR of 0.63 (0.48-0.83). [3]

In patients having received only 2 lines of previous treatment PomBorDex (n=117) improved PFS significantly as compared to BorDex (n=104) with a HR of 0.67 (0.48-0.94). [3]

The general results per outcome for the OPTIMISMM study are also described narratively in section 5.1.2 (p. 16).

ENDEAVOR

In previously lenalidomide exposed patients having received at least two prior lines of treatment, CarDex compared to BorDex improved both PFS (HR 0.73 [0.53, 1.01]) [10] and OS (0.752 [0.589, 0.959]. [11]

Discontinuations due TEAEs occurred in 52 (22.5%) of 231 patients in the CarDex group and 53 (23.1%) of 229 in BorDex group, having received ≥2 prior lines of therapy. [10]

In ENDEAVOR, CarDex was associated with statistically significantly higher GHS/QoL scores compared with BorDex ($p < 0.0001$). However, the overall treatment difference point estimate of 3.51 (95% CI 1.97 to 5.06) did not reach the predefined minimum important difference (5.0). [16, 17]

For data on adverse events occurring in more than 10% of patients and grade 3/4 adverse events, please refer to Table 21 (p. 57) and Table 23 (p. 61), respectively.

5.3.3 Comparative analyses (PomBorDex vs CarDex)

The comparative data for PFS and OS in the third- and fourth-line lenalidomide exposed population is based on a network meta-analysis. The methodology is described in the appendix in section 1.1 on p. 100).

The results per PICO are provided in Table 30 (p. 98).

Overall survival

OS estimates for the population in question were only available from ENDEAVOR, while data for the ITT-population from OPTIMISMM is used as proxy.and are displayed in Table 9.

Table 9 HR inputs for OS - At least two previous treatments population

Study	**Comparator**	**Reference**	**HR** **95% CI**
Richardson, 2019	PomBorDex (N=281)	BorDex (N=278)	0.91 (0.70-1.18)
Orlowski, 2019	CarDex (N = 233)	BorDex (N = 236)	0.752 [0.589, 0.959]

The data show a HR for PomBorDex vs CarDex of 1.21 (0.85-1.73).

Progression Free Survival

Network of evidence

The network of evidence related to study including PFS estimates in the population with at least two previous treatments is presented on Figure 4.

In the OPTIMISMM trial, PFS results were available for patients having received exactly two previous treatments (third line (3L)) and for patients having received more than three previous treatments (after third line (3L+)). The HR in these two populations were pooled to obtain the HR in the population with at least two previous treatments, as follows:

$$\ln\left(HR_{pooled}\right) = \frac{\frac{\ln(HR_{3L})}{Var(\ln(HR_{3L}))} + \frac{\ln(HR_{3L+})}{Var(\ln(HR_{3L+}))}}{\frac{1}{Var(\ln(HR_{3L}))} + \frac{1}{Var(\ln(HR_{3L+}))}}$$

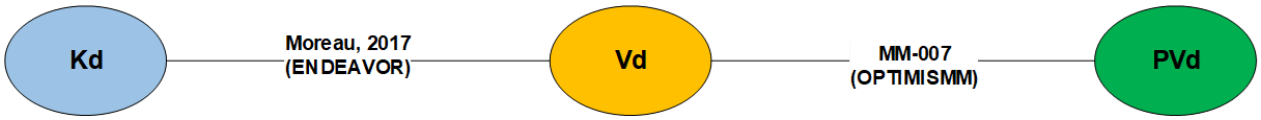
$Var(\ln(HR_{3L}))$ and $Var(\ln(HR_{3L+}))$ were calculated based on the published 95% CI of the HR. The standard error (SE) corresponding to $\ln\left(HR_{pooled}\right)$ was estimated using the following formula:

$$SE(\ln\left(HR_{pooled}\right)) = \frac{1}{\frac{1}{Var(\ln(HR_{3L}))} + \frac{1}{Var(\ln(HR_{3L+}))}}$$

In the ENDEAVOR trial, PFS results were available for patients with at least two previous treatments. The corresponding HR was used for the indirect comparison between PomBorDex and CarDex in this

population. However, as in the OPTIMISMM trial all patients had been previously exposed to lenalidomide, a sensitivity analysis was performed using the HR from the ENDEAVOR estimated in the subgroup of patients with two or three previous lines and a prior lenalidomide exposure.

Figure 4 Network of evidence for PFS – At least two previous treatments population



Note: in yellow, the anchoring treatment, in green the treatment of interest, in blue the comparator treatment

Inputs

The inputs, HR and 95%CI, of the two included studies are displayed in Table 10.

Table 10 HR inputs for PFS – At least two previous treatments population

Study	Comparator	Reference	HR 95% CI
Richardson, 2019 (>1line)	PomBorDex (N = 170)	BorDex (N = 163)	0.63 [0.48, 0.83]
Moreau, 2017 (at least two previous treatments)	CarDex (N = 232)	BorDex (N = 233)	0.604 [0.466, 0.783]
Moreau, 2017 (two or three previous treatments a prior lenalidomide exposure)	CarDex (N = 126)	BorDex (N = 132)	0.73 [0.53, 1.01]

Results

Based on the above inputs, a base case indirect treatment comparison was conducted in the population with at least two previous treatments and the results were not significantly different between PomBorDex and CarDex (PomBorDex vs. CarDex HR =1.04, 95% CI [0.72-1.52]).

In the sensitivity analysis using the population of patients with two or three previous treatments and a prior lenalidomide exposure of the ENDEAVOR trial, the results were numerically different but still not significant (PomBorDex vs. CarDex HR =0.86, 95% CI [0.57-1.32]).

Discontinuation due to adverse events

For safety outcomes, the analysis was based on the safety population sin ENDEAVOR and OPTIMISMM.

Inputs

The proportion of patients discontinuing due to adverse events per treatment arm of the four included studies and the corresponding RR are displayed in Table 11.

Table 11 Proportion of patients discontinuing treatment due to an adverse event

Study	Study arm	Safety population (N)	Patients discontinuing due to adverse events (n)	Proportion	RR 95% CI
Pomalidomide EPAR	PomBor Dex	278	80	28.8%	1.52 [1.12, 2.07]
	BorDex	270	51	18.9%	
Moreau, 2017	CarDex	231	52	22.5%	0.97 [0.70-1.36]
	BorDex	229	53	23.1%	

Results

Based on the connected network shown in Figure 4, an indirect treatment comparison was conducted between CarDex and PomBorDex (PomBorDex vs. CarDex RR=1.57, 95% CI [0.99, 2.47]).

As previously described the rate of discontinuation due to TEAEs is mainly driven by a high discontinuation rate for bortezomib, whilst the discontinuation rate for pomalidomide alone is relatively low (cf. clinical question #1 (p. 21)). The cumulative dose of (total mg/m^2) for bortezomib in the PomBorDex arm was numerical higher with 37.2 (20.8–54.1) vs 29.5 ((15.6–46.8) [3]. Furthermore, the difference between the two study in the proportion of patients prior exposed to bortezomib (ENDEAVOR 54% (Table 20) and OPTIMISMM 72% (Table 17) should be taken into account as well, as this potentially could have influenced the tolerability towards bortezomib in the studies.

Qualitative review of adverse events

Adverse events have not been reported separately for the lenalidomide exposed 3-4-line population.

Reference is made to the data for the overall lenalidomide exposed population, cf. the overview of the frequency of adverse events occurring in ≥10% of patients, and of all grade 3/4 AEs is provided in Table 21 (p. 57) and Table 23 (p.61), respectively.

The data seem to indicate a safety profile consistent with the known safety profiles of the individual components of the regimens.

5.4 Other considerations

The subject 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 relapsing/refractory multiple myeloma even in the not very remote future is a challenge considering the quickly changing treatment landscape.

Our guess is that PomBorDex mainly will be used in for lenalidomide refractory patients, a group from whom scientific data is very limited for other currently approved therapeutic options. This would result in an increased number of IMiD refractory patients, i.e. patients that are refractory to both approved IMiDs (lenalidomide and pomalidomide). The scientific evidence in the double IMID exposed and IMID refractory population is very limited. Furthermore, a large majority of these patients will also be bortezomib refractory. This makes it difficult to predict how an implementation of PomBorDex will affect the subsequent treatment. The decision on the exact use of the available different combinations should depend on the availability of data as well as the clinical assessment for the individual patient.

The suggested subsequent treatment options listed below is an attempt to shed light on possible treatment options well aware that it is without strong evidence.

1. Adult patients with multiple myeloma who have received at least one prior treatment, including lenalidomide.

According to the recently published guideline by the Medicine Council, the majority (80%) of patients, who are not refractory to lenalidomide, should continue with lenalidomide in combination with daratumumab and dexamethasone. [18]We would consider this to be an effective possible treatment option for patients that are candidates for daratumumab. At progression on DaraLenDex, PomBorDex could then be considered as a treatment option (due to the robust data in lenalidomide refractory patients) possibly followed by subsequent treatment with CarDex or any of the newer drugs that are about to be introduced in the coming years (even if data on IMiD refractory patients is currently sparse).

2. Adult patients with multiple myeloma who have received at least one prior treatment and who are considered refractory to lenalidomide.

This is probably the population where PomBorDex is going to be mostly used. The implementation of PomBorDex would then generate an increase in patients that are exposed to and refractory to both lenalidomide and pomalidomide and many of them to bortezomib as well. Again, data on IMiD refractory patients is very limited for all currently used combinations but if the patients are considered to be non-refractory towards bortezomib, DaraBorDex might be considered. However, if the patients are considered to be refractory towards bortezomib or wouldn't be able to tolerate additional bortezomib, CarDex might be an option.

3. Adult patients with multiple myeloma who have received at least two previous treatments and who have received either DaraLenDex or DaraBorDex.

These are also patients that could be eligible if lenalidomide refractor (after DaraLenDex) but not bortezomib refractory (after DaraBorDex, a maximum of eight cycles of bortezomib given with this combination) According to the recently published guideline by the Medicine Council, CarDex could be an option for patients who have received at least 2 prior treatment and progress on DaraLenDex or

DaraBorDex. With the implementation of PomBorDex in this patient population, one could speculate if CarDex could be an option at progression on PomBorDex.

5.5 Conclusion

In conclusion data supports the use of PomBorDex as a valid treatment option in patients who have received one or more previous lines of therapy including lenalidomide.

PomBorDex has shown significant improvement in PFS compared to BorDex in both lenalidomide exposed and lenalidomide refractory patients, regardless if the patients have received one or more previous lines of treatment.

PomBorDex is thus a relevant treatment option for second line treatment of patients with multiple myeloma, having received at least one prior line of treatment including lenalidomide regardless if refractory to lenalidomide or not.

PomBorDex is similarly a relevant standard treatment option in patients who have received at least two prior lines of treatment.

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7 Appendices

7.1 Literature search

7.1.1 Methods

Research questions

The systematic review aimed at answering three specific clinical research questions, which were set by the Council in the context of assessment of the clinical added value of PomBorDex. Each of the three research questions was formalised according to the PICOS (population, intervention, comparator, outcome, study type) framework.

Search strategy

Electronic searches

To identify relevant studies addressing the research questions of interest, the following electronic databases below were searched:

- MEDLINE, MEDLINE-IN-PROCESS (via PubMed)
- Embase (via EMBASE.com)

The exact search terms (including MeSH/EMTREE terms and free text searches) are presented in Table 14 and Table 15.

Hand searches

In addition to searches of electronic databases, hand searches were also conducted to capture data from recent published European public assessment reports (EPARs) on the European Medicines Agency website. [19]

There are six EPARs identified, which were summarized in Table 12**.**

Table 12 Hand search

International non-proprietary name	Procedure No.	European public assessment report URL
Pomalidomide	EMEA/H/C/002682	https://www.ema.europa.eu/en/documents/variation-report/imnovid-h-c-2682-ii-0031-g-epar-assessment-report-variation_en.pdf
Bortezomib	EMEA/H/C/000539/II/0079	https://www.ema.europa.eu/en/documents/variation-report/velcade-h-c-539-ii-0079-epar-assessment-report-variation_en.pdf
Lenalidomide	EMEA/H/C/000717/II/0102/G	https://www.ema.europa.eu/en/documents/variation-report/revlimid-h-c-717-ii-0102-g-epar-assessment-report-variation_en.pdf
Daratumumab	EMEA/H/C/004077/0000	https://www.ema.europa.eu/en/documents/assessment-report/darzalex-epar-public-assessment-report_en.pdf
Dexamethasone	EMEA/H/C/001140	https://www.ema.europa.eu/en/documents/variation-report/ozurdex-h-c-1140-ii-0015-epar-assessment-report-variation_en.pdf

Carfilzomib	EMEA/H/C/003790/0000	https://www.ema.europa.eu/en/documents/assessment-report/kyprolis-epar-public-assessment-report_en.pdf

7.1.2 Study selection

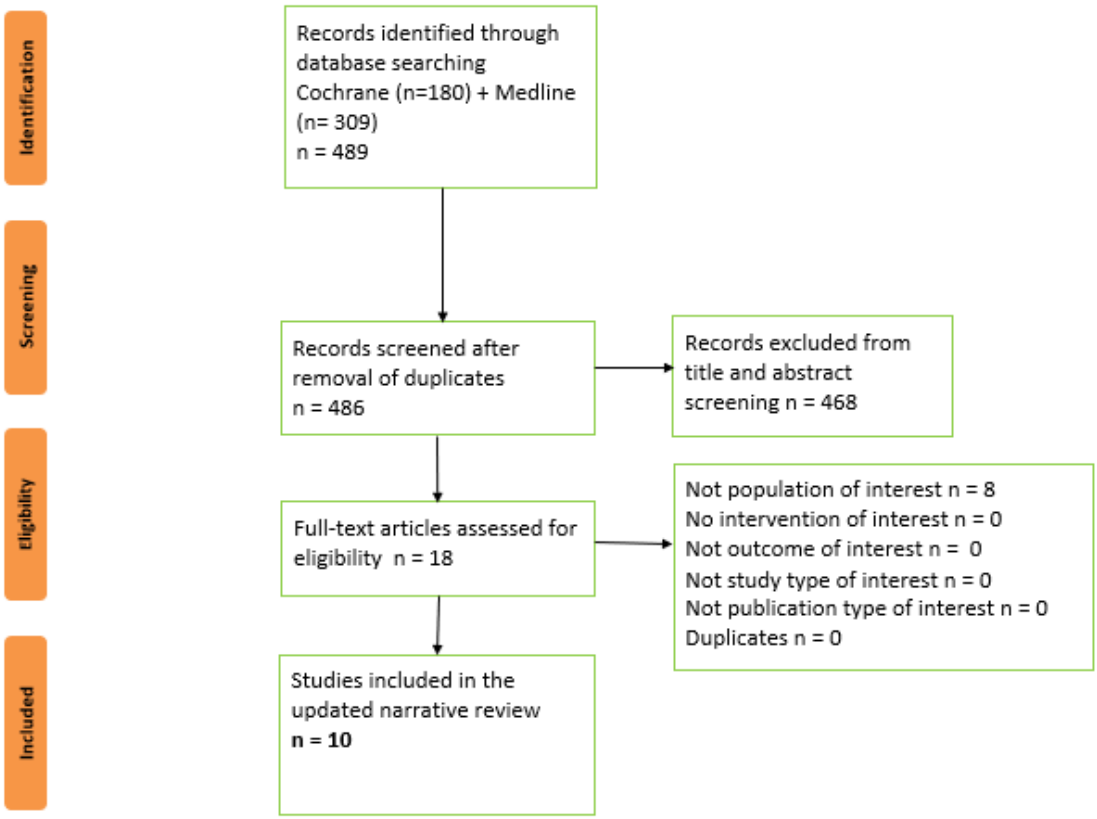
Titles and abstracts of studies identified from the search strategy, where available, were reviewed by two reviewers in parallel according to the pre-specified inclusion/exclusion criteria (Table 13). Any discrepancies were resolved by discussion. Articles identified as potentially relevant were then reviewed in full and selected according to the list of pre-specified inclusion/exclusion criteria. A second reviewer independently reviewed the titles and abstracts according to the screening criteria.

Table 13 Literature search – Study selection criteria

Category	Inclusion criteria	Exclusion criteria
Population	▪ Adult patients with multiple myeloma who have received at least one prior treatment, including lenalidomide ▪ Adult patients with multiple myeloma who have received at least one prior treatment and who are considered refractory to lenalidomide ▪ Adult patients with multiple myeloma who have received at least two previous treatments and who have received either DaraLenDex or DaraBorDex [as this population probably does not exist, the search should be performed without the DaraLenDex and DaraBorDex modifier]	Any population other than those listed in the inclusion are ineligible
Inverventions	▪ PomBorDex	Any other intervention/combination of interventions will be excluded
Comparators	▪ DaraLenDex ▪ DaraBorDex ▪ CarDex	Any other intervention/combination of interventions will be excluded
Study Type	▪ Randomized controlled trials (RCTs) ▪ Phase III	▪ Non-RCTs ▪ Single-arm trials ▪ Observational studies ▪ Phase I and II studies
Publication type	Peer reviewed published in journals or retrieved via hand searches on payer relevant website	Letters, editorials and conference abstracts
Language	Full text version available in English or Danish	Full text version not available in English or Danish will be excluded
Publication date	No restriction	No restriction
Countries	No restriction	No restriction

7.1.3 PRISMA flow diagram

Figure 5 PRISMA flow diagram



7.1.4 Search string MEDLINE

Search terms for MEDLINE and MEDLINE-IN-PROCESS via www.pubmed.com

Date of the search: 18/07/2019.

Table 14 Search string MEDLINE

#	Search terms	Results
1	"Multiple Myeloma"[Mesh]	39431
2	Myeloma*[tiab] OR ndmm*[tiab] OR (khaler*[tiab] AND (disease[tiab] OR morbus[tiab]))	51614
3	#1 OR #2	58624
4	"pomalidomide"[nm]	329
5	pomalidomide*[tiab] OR cc4047*[tiab] OR cc-4047*[tiab] OR imnovid*[tiab] OR pomalyst*[tiab] OR actimid*[tiab]	611
6	#4 or #5	653
7	"bortezomib"[Mesh]	5251
8	Bortezomib*[tiab] OR velcade*[tiab] OR mg-341*[tiab] OR mln-341*[tiab] OR mln341*[tiab] OR ldp-341*[tiab] OR ldp341*[tiab] OR PS-341*[tiab] OR PS341*[tiab]	7687
9	#7 OR #8	8389
10	"dexamethasone"[Mesh]	50070
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 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]	56447
12	#10 OR #11	70740
13	#6 AND #9 AND #12	112
14	"lenalidomide"[Mesh]	2373
15	lenalidomid*[tiab] OR revlimid*[tiab] OR revimid*[tiab] OR cc-5013*[tiab] OR cc5013*[tiab] OR cdc-501*[tiab] OR cdc501*[tiab] OR cdc5013*[tiab] OR enmd-0997*[tiab] OR enmd0997*[tiab] OR imid-3*[tiab] OR imid3*[tiab]	3872
16	#14 OR #15	4211
17	"daratumumab"[nm]	183
18	"daratumumab"*[tiab] OR darzalex*[tiab] OR "humax cd38" *[tiab]	410
19	#17 and #18	449
20	"carfilzomib"[nm]	400
21	carfilzomib*[tiab] or kyprolis*[tiab] or pr-171*[tiab]	785
22	#20 OR #21	844
23	#19 AND #16 AND #12	70
24	#19 AND #9 AND #12	68
25	#22 AND #12	195

26	#23 OR #24 OR #25	260
27	#13 OR #26	331
28	#3 AND #27	309

7.1.5 Search string CENTRAL

Search terms EMBASE via www.embase.com

Date of the search: 18/07/2019

Table 15 Search string CENTRAL

Search	Query	Hits
#1	[mh "Multiple Myeloma"]	1369
#2	(myeloma* or ndmm* or ((Kahler or kahler's or Kahler*) next (disease or morbus))):ti,ab,kw	5078
#3	{or #1-#2}	5078
#4	(pomalidomid* or cc4047* or cc-4047* or imnovid* or pomalyst* or actimid*):ti,ab,kw	269
#5	[mh Bortezomib]	341
#6	(bortezomib* or velcade* or mg-341* or mln-341* or ldp-341* or ldp341* or PS-341* or PS341*):ti,ab,kw	1783
#7	{or #5-#6}	1783
#8	[mh Dexamethasone]	3992
#9	(dexametason* or dexamethason* or Adexon* or Aeroseb-dex* or Aphthasolone* or Decaderm* or Decadron* or Decajet* 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 Ispoto-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	0
#10	{or #8-#9}	1572992
#11	#4 and #7 and #10	154
#12	[mh Lenalidomide]	158
#13	(lenalidomide* or revlimid* or revimid* or cc-5013* or cc5013* or cdc-501* or cdc-5013* or cdc501* or cdc5013* or enmd-0997* or imid-3* or imid3*):ti,ab,kw	1688
#14	[20-#13]	1688
#15	(daratumumab* or darzalex* or "humax cd38"):ti,ab,kw	195
#16	(carfilzomib* or kyprolis* or pr-171):ti,ab,kw	306
#17	#15 and #14 and #10	100
#18	#15 and #7 and #10	103
#19	#16 and #10	306
#20	#17 OR 18 OR #19	268655
#21	#11 OR #18 OR #19	469
#22	#3 AND #21	446
#23	"conference abstract":pt	148967
#24	#22 NOT #23	185

7.1.6 Excluded studies after full text review

Table 16 Excluded studies after full text review

Reference	Reason for exclusion
Ludwig H, Dimopoulos MA, Moreau P, et al. Carfilzomib and dexamethasone vs bortezomib and dexamethasone in patients with relapsed multiple myeloma: results of the phase 3 study ENDEAVOR (NCT01568866) according to age subgroup. Leuk Lymphoma. 2017 Oct;58(10).[21]	Not population of interest
Mateos MV, Goldschmidt H, San-Miguel J, et al. Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: A subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials. Hematol Oncol. 2018 Apr;36(2):463-470.[22]	Not population of interest
Dimopoulos M, Siegel D, White DJ, et al. Carfilzomib vs bortezomib in patients with multiple myeloma and renal failure: a subgroup analysis of ENDEAVOR. Blood. 2019 Jan 10;133(2):147-155.[23]	Not population of interest
Goldschmidt H, Moreau P, Ludwig H, et al. Carfilzomib-dexamethasone versus subcutaneous or intravenous bortezomib in relapsed or refractory multiple myeloma: secondary analysis of the phase 3 ENDEAVOR study. Leuk Lymphoma. 2018 Jun;59(6):1364-1374.[24]	Not population of interest
Chng WJ, Goldschmidt H, Dimopoulos MA, et al. Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. Leukemia. 2017 Jun;31(6):1368-1374. [25]	Not population of interest
Suzuki K, Dimopoulos MA, Takezako N, et al. Daratumumab, lenalidomide, and dexamethasone in East Asian patients with relapsed or refractory multiple myeloma: subgroup analyses of the phase 3 POLLUX study. Blood Cancer J. 2018 May 1;8(4):41. [26]	Not population of interest
Mateos MV, Spencer A, Nooka AK, et al. Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies. Haematologica. 2019 Jun 20. [27]	Not population of interest
Hari P, Mateos MV, Abonour R, et al. Efficacy and safety of carfilzomib regimens in multiple myeloma patients relapsing after autologous stem cell transplant: ASPIRE and ENDEAVOR outcomes. Leukemia. 2017 Dec;31(12):2630-2641. [28]	Not population of interest

7.2 Main characteristics of included studies

Study characteristics

Table 17 OPTIMISMM Study characteristics

Trial name	OPTIMISMM
NCT number	NCT01734928
Objective	The purpose of this study is to compare the efficacy of the combination of pomalidomide, bortezomib and low dose dexamethasone to the combination of bortezomib and low dose dexamethasone in participants with relapsed/refractory multiple myeloma. This study will also assess how safe the combination of pomalidomide, bortezomib and low dose dexamethasone is compared to the combination of bortezomib and low dose dexamethasone.
Publications – title, author, journal, year	Richardson PG, Oriol A, Beksac M, et al.; OPTIMISMM trial investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019 Jun;20(6):781-794.[3]
Study type and design	Phase III, randomized (1:1), open-label, parallel clinical trial. Eligible patients were randomly assigned 1:1 to bortezomib and dexamethasone with or without pomalidomide (appendix p 2), using a validated interactive response technology system. Randomisation was done using a permutated blocked design with a block size of four, stratified according to age (≤75 years vs >75 years), number of previous regimens (1 vs >1), and the concentration of β2 microglobulin at screening (<3.5 mg/L vs 3.5–5.5 mg/L vs >5.5 mg/L).
Follow-up time	Median follow-up of 15.9 months (IQR 9·9–21·7).
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Must be ≥ 18 years at the time of signing informed consent. • Must have documented diagnosis of multiple myeloma and have measureable disease by serum and urine protein electrophoresis. • Must have had at least 1 but no greater than 3 prior anti-myeloma regimens. • Must have documented disease progression during or after their last anti-myeloma therapy. • All subjects must have received prior treatment with a lenalidomide containing regimen for at least 2 consecutive cycles. Exclusion Criteria: • Documented progressive disease during therapy or within 60 days of the last dose of a bortezomib-containing therapy under the 1.3 mg/m^2 dose twice weekly dosing schedule. • Peripheral neuropathy Grade 3, Grade 4 or Grade 2 with pain within 14 days prior to randomization. • Non-secretory multiple myeloma. • Subjects with severe renal impairment requiring dialysis. • Previous therapy with pomalidomide.
Intervention	Intervention (N=281): Pomalidomide 4 mg orally on Days 1-14 of a 21-day cycle plus Bortezomib 1.3 mg/m2 s.c. • Days 1, 4, 8 and 11 of 21 day cycles 1 -8 • Days 1, 8 of 21 days for cycle 9 and onward until disease progression plus Dexamethasone 20 mg/day [≤ 75 years old] or 10 mg/day [> 75 years old] orally • days 1, 2, 4, 5, 8, 9, 11, 12 of 21 days for cycles 1-8 • days 1, 2,8, 9 of 21 days for cycles 9 and onward until disease progression Comparator (N=278): • Bortezomib and dexamethasone as above.

Baseline characteristics		PomBorDex (n=281)	BorDex (n=278)
	Age (years)	67 (60–73)	68 (59–73)
	≤65	123 (44%)	120 (43%)
	>65	158 (56%)	158 (57%)
	≤75	235 (84%)	231 (83%)
	>75	46 (16%)	47 (17%)
	Sex		
	Male	155 (55%)	147 (53%)
	Female	126 (45%)	131 (47%)
	ECOG performance status		
	0	149 (53%)	137 (49%)
	1	121 (43%)	119 (43%)
	2	11 (4%)	22 (8%)
	ISS disease stage		
	I	149 (53%)	138 (50%)
	II	85 (30%)	90 (32%)
	III	47 (17%)	50 (18%)
	Cytogenetic profile by FISH		
	Standard risk	137 (49%)	132 (47%)
	High risk	61 (22%)	49 (18%)
	Time since diagnosis (years)	4·0 (2·6–6·5)	4·3 (2·5–6·4)
	Previous lines of treatment	2 (1–2)	2 (1–2)
	Lines of treatment		
	1	111 (40%)	115 (41%)
	2	117 (42%)	104 (37%)
	≥3*	53 (19%)	59 (21%)
	Previous stem-cell transplant	161 (57%)	163 (59%)
	Creatinine clearance (mL/min)		
	<60	91 (32%)	76 (27%)
	≥60	190 (68%)	202 (73%)
	Previous immunomodulatory treatment	281 (100%)	278 (100%)
	Lenalidomide	281 (100%)	278 (100%)
	Previous alkylating agent	237 (84%)	232 (83%)
	Previous proteasome inhibitor	212 (75%)	213 (77%)
	Bortezomib	201 (72%)	203 (73%)
	Carfilzomib	8 (3%)	11 (4%)
	Ixazomib	9 (3%)	5 (2%)
	Refractory disease to immunomodulatory drug	202 (72%)	193 (69%)
	Lenalidomide	200 (71%)	191 (69%)
	Lenalidomide in the last previous antimyeloma regimen before study entry	178 (63%)	167 (60%)
	Refractory disease to proteasome inhibitor	37 (13%)	37 (13%)
	Bortezomib	24 (9%)	32 (12%)
	Refractory disease to last previous regimen	196 (70%)	184 (66%)
Primary and secondary endpoints	Primary endpoints: Progression Free Survival defined as the length of time during and after the treatment that participants in the study live without the disease getting worse. Secondary endpoints: • Overall Survival [Time Frame: Up to 5 years] • Adverse Event [Time Frame: Up to 1 year] • Overall Response Rate [Time Frame: Up to 1 year] • Duration of Response [Time Frame: Up to 1 year]		

Method of analysis	Primary, secondary, and prespecified exploratory analyses were done in the intention-to-treat population, which included all patients who were randomly assigned. Safety assessments were done in the safety population, which included all patients who received at least one dose of study medication. The intention-to treat population, efficacy-assessable population (which included all patients who received at least one dose of study medication and had a baseline and at least one post-baseline efficacy assessment), and all efficacy analyses except for duration of response were adjusted by stratification factors (age, number of previous regimens, and concentration of β2 microglobulin at screening). However, subgroup analyses for efficacy endpoints were not adjusted by stratification factors. A sensitivity analysis for progression-free survival was done based on the investigator's assessment to support the robustness of the primary data. We used the Kaplan-Meier method to estimate progression-free survival. The treatment effect (measured by HR and 95% CI) was estimated using a stratified Cox proportional hazards model. A stratified Cochran- Mantel-Haenszel test was used to compare responses. If the study primary endpoint was significant at the final analysis, overall responses and overall survival were to be sequentially tested using a step-down approach. Specifically, if the value of the log-rank statistic for progression-free survival was significant, then the overall response would be tested next, at the same significance level of 0.05 (two-sided). If the overall response was significant, then the interim overall survival analysis would be done, with Lan-DeMets implementation of the Pocock boundaries. Type I error was controlled for these endpoints and analyses. The observed change in HRQOL score from baseline was calculated using a mixed-model repeated measure approach, using baseline covariates where appropriate to estimate the least square means (95% CI and p value) for changes from baseline across all scheduled visits (excluding the visit at the end of treatment) and on day 1 of cycles five, nine, 19, and 25 within each treatment group, as well as the difference in the least square means between treatment groups.
Subgroup analyses	The primary analysis addressed the ITT-population relevant for the clinical question # 1. Prespecified subgroup analyses was performed for PFS for the relevant populations in clinical question # 2 (lenalidomide refractory patients) and clinical question # 3 (patient having received at least 2 prior lines of therapy). Refractory patients were defined as those with disease that was non-responsive to treatment (failure to achieve minimum response or development of progressive disease) or progression within 60 days of the last dose, inclusive. The subgroup of patients having received at least two prior lines is not specified in detail in the publication. The method of analysis is described in the section above under "Method of analysis" – however the subgroup analyses for efficacy endpoints were not adjusted by stratification factors. The statistical validity of the subgroup analysis is not specified separately from the general statistical methodology above.

Table 18 POLLUX study characteristics

Trial name	POLLUX
NCT number	NCT02076009
Objective	The purpose of this study is to compare the effectiveness of daratumumab when combined with lenalidomide and dexamethasone (DaraLenDex) to that of lenalidomide and dexamethasone (LenDex), in terms of progression-free survival in participants with relapsed or refractory multiple myeloma
Publications – title, author, journal, year	Dimopoulos MA, Oriol A, Nahi H et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:1319-31. [4] Dimopoulos MA, San-Miguel J, Belch A et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica 2018;103:2088-96. [5]

	Mateos MV, Spencer A, Nooka AK, et al. Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies. Haematologica. 2019 Jun 20.[27] Suzuki K, Dimopoulos MA, Takezako N, et al. Daratumumab, lenalidomide, and dexamethasone in East Asian patients with relapsed or refractory multiple myeloma: subgroup analyses of the phase 3 POLLUX study. Blood Cancer J. 2018 May 1;8(4):41. [26]
Study type and design	Randomized open-label multicentre phase III trial. Randomization (in a 1:1 ratio) was conducted by means of a central schedule and was balanced with the use of randomly permuted blocks and stratified according to the number of lines of previous therapy (1 vs. 2 or 3 vs. >3), International Staging System disease stage (I vs. II vs. III, with higher stages indicating more advanced disease; see the Supplementary Appendix) at screening, and previous receipt of lenalidomide (no vs. yes).
Follow-up time	Median follow-up: 25.4 months. [5]
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Must have documented multiple myeloma and measurable disease • Must have received at least 1 prior line of therapy for multiple myeloma and achieved a response (partial response or better) to at least one prior regimen • Must have documented evidence of progressive disease as defined by the International Myeloma Working Group criteria on or after their last regimen • Must have an Eastern Cooperative Oncology Group Performance Status score of 0, 1, or 2 • If a participant has received subsequent anticancer therapy (salvage therapy), the participant must have a "wash-out period" defined as 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the planned start date of daratumumab monotherapy. The only exception is the emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 milligram per day for a maximum of 4 days) before Daratumumab monotherapy Exclusion Criteria: • Has received any of the following therapies: daratumumab or other anti-CD38 therapies • Has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment • Disease shows evidence of refractoriness or intolerance to lenalidomide or if previously treated with a lenalidomide-containing regimen the participant is excluded if he or she discontinued due to any adverse event related to prior lenalidomide treatment • Has received autologous stem cell transplantation within 12 weeks before the date of randomization, or previously received an allogenic stem cell transplant (regardless of timing), or planning to undergo a stem cell transplant prior to progression of disease • History of malignancy (other than multiple myeloma) within 5 years before the first dose of daratumumab monotherapy (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or breast, or other non-invasive lesion, that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years)
Intervention	*Intervention:* Daratumumab 16mg/kg IV infusion (N=286) • once a week during treatment cycles 1 and 2; • every 2 weeks during treatment cycles 3 to 6 • every 4 weeks for cycles 7 and onwards. Lenalidomide 25 mg orally on Days 1 through 21 of each treatment cycle. Dexamethasone 40 mg orally weekly (or 20 mg weekly for participants > 75 years old or with a body mass index < 18.5) *Comparator (N=283)* • Lenalidomide and dexamethasone as above.

Baseline characteristics	**Characteristic**	**DaraLenDex (N = 286)**	**LenDex (N = 283)**
	Age		
	Median (range) — yr	65 (34–89)	65 (42–87)
	Distribution — no. (%)		
	<65 yr	133 (46.5)	140 (49.5)
	65 to 74 yr	124 (43.4)	108 (38.2)
	≥75 yr	29 (10.1)	35 (12.4)
	Race — no. (%)†		
	White	207 (72.4)	186 (65.7)
	Black	5 (1.7)	11 (3.9)
	Asian	54 (18.9)	46 (16.3)
	Other or unreported	20 (7.0)	40 (14.1)
	ECOG performance-status score — no. (%)‡		
	0	139 (48.6)	150 (53.0)
	1 or 2	147 (51.4)	133 (47.0)
	ISS disease stage — no. (%)§		
	I	137 (47.9)	140 (49.5)
	II	93 (32.5)	86 (30.4)
	III	56 (19.6)	57 (20.1)
	Cytogenetic profile — no./total no. (%)¶		
	Standard risk	193/228 (84.6)	176/211 (83.4)
	High risk	35/228 (15.4)	35/211 (16.6)
	Median time since diagnosis (range) — yr	3.5 (0.4–27.0)	4.0 (0.4–21.7)
	Median no. of previous lines of therapy (range)	1 (1–11)	1 (1–8)
	Previous therapy — no. (%)		
	Autologous stem-cell transplant	180 (62.9)	180 (63.6)
	Proteasome inhibitor	245 (85.7)	242 (85.5)
	Immunomodulatory drug	158 (55.2)	156 (55.1)
	Glucocorticoid	280 (97.9)	281 (99.3)
	Alkylating agent	268 (93.7)	270 (95.4)
	Proteasome inhibitor and immunomodulatory drug	125 (43.7)	125 (44.2)
	Proteasome inhibitor, immunomodulatory drug, and alkylating agent	118 (41.3)	121 (42.8)
	Bortezomib and lenalidomide	44 (15.4)	43 (15.2)
	Refractory disease — no. (%)		
	To last line of therapy	80 (28.0)	76 (26.9)
	To proteasome inhibitor only	57 (19.9)	46 (16.3)
	To immunomodulatory drug only	10 (3.5)	11 (3.9)
	To proteasome inhibitor and immunomodulatory drug	7 (2.4)	14 (4.9)
Primary and secondary endpoints	Primary endpoint: Progression Free Survival Secondary endpoints: • Time to Disease Progression (TTP) • Percentage of Participants Who Achieved Very Good Partial Response (VGPR) or Better • Percentage of Participants With Negative Minimal Residual Disease (MRD) • Overall Response Rate • Overall Survival (OS) • Time to Response • Duration of Response (DOR		
Method of analysis	For the primary end point, the O'Brien–Fleming stopping boundary at the interim analysis was calculated with the use of the Lan-DeMets alphaspending function on the basis of the numbers of observed events at the clinical cut-off date. If the primary end point was significant at the interim analysis, the major efficacy secondary end points of time to disease progression, rate of very good partial response, rate of results below the threshold for minimal residual disease, overall response rate, and overall survival, as ordered here, were sequentially tested, each with an overall two-sided alpha of 0.05. Progression-free survival was compared between groups on		

	the basis of a stratified logrank test. The Kaplan–Meier method was used to estimate the distributions and 12-month rates of progression-free survival. Hazard ratios and 95% confidence intervals were estimated with the use of a Cox regression model, with treatment as the sole explanatory variable. Stratified Cochran–Mantel–Haenszel tests were used to compare overall response rates, rates of very good partial response or better, and other binary end points. Duration of response was assessed by means of the Kaplan–Meier method.
Subgroup analyses	The subgroup of patients having received lenalidomide were subject to the same inclusion and exclusion criteria as the ITT- population, hereunder that patients who were excluded.. The analysis of the subgroup having received lenalidomide was pre-specified. The method for subgroup analysis is not specified in the publication or clinicaltrials.gov, why reference is made to the section of the general statistical method above is made. The statistical validity of the subgroup analysis is not specified separately from the general statistical methodology above.

Table 19 CASTOR study characteristics

Trial name	CASTOR
NCT number	NCT02136134
Objective	The purpose of this study is to assess the effects of administration of daratumumab when combined with VELCADE (bortezomib) and dexamethasone compared with bortezomib and dexamethasone alone, for participants with relapsed or refractory multiple myeloma.
Publications – title, author, journal, year	Palumbo A, Chanan-Khan A, Weisel K et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:754-66. [6] Spencer A, Lentzsch S, Weisel K et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica 2018;103:2079-87. [7] Mateos MV, Spencer A, Nooka AK, et al. Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies. Haematologica. 2019 Jun 20.[27]
Study type and design	This was a multicenter, randomized (1:1), open-label, active-controlled, phase 3 trial. Randomization was stratified according to International Staging System (ISS) disease stage at the time of screening (stage I, II, or III, with higher stages indicating more severe disease; the number of previous lines of therapy (1 vs. 2 or 3 vs. >3), and previous treatment with bortezomib (no vs. yes).
Follow-up time	Median follow-up for PFS was 7.4 months.
Population (inclusion and exclusion criteria)	Inclusion criteria • Must have had documented multiple myeloma • Must have received at least 1 prior line of therapy for multiple myeloma • Must have had documented evidence of progressive disease as defined based on Investigator's determination of response of International Myeloma Working Group (IMWG) criteria on or after their last regimen • Must have an Eastern Cooperative Oncology Group Performance Status score of 0, 1, or 2 • Must have achieved a response (partial response [PR] or better based on investigator's determination of response by the IMWG criteria) to at least 1 prior regimen in the past Exclusion Criteria: • Has received daratumumab or other anti-CD38 therapies previously

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Is refractory to VELCADE or another PI, like ixazomib and carfilzomib (had progression of disease while receiving VELCADE therapy or within 60 days of ending VELCADE therapy or another PI therapy, like ixazomib and carfilzomib
Is intolerant to VELCADE (ie, discontinued due to any adverse event while on VELCADE treatment)
Has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization. The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 milligram per day [mg/day] for a maximum of 4 days) before treatment. A list of anti-myeloma treatments with the corresponding pharmacokinetic half-lives is provided in the Site Investigational Product Procedures Manual (IPPM).
Has a history of malignancy (other than multiple myeloma) within 3 years before the date of randomization
Has any concurrent medical condition or disease (eg, active systemic infection) that is likely to interfere with study procedures

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<tr><td>Intervention</td><td>Daratumumab+bortezomib+dexamethasone (DaraBorDex) (n=251)
Daratumumab IV 16 mg/kg weekly for the first 3 cycles, on Day 1 of Cycles 4-9, and then every 4 weeks thereafter.
Bortezomib
Bortezomib sc 1.3 mg/m2 on Days 1, 4, 8 and 11 of each 21-day cycle for eight cycles
Dexamethasone
Dexamethasone orally 20 mg on Days 1, 2, 4, 5, 8, 9, 11 and 12 of the first 8 bortezomib cycles

Bortezomib+dexamethasone (BorDex) (n=247)
As above</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic</th><th>DaraBorDex (N = 251)</th><th>BorDex (N = 247)</th></tr>
<tr><td>Age</td><td></td><td></td></tr>
<tr><td>Median (range) — yr</td><td>64 (30–88)</td><td>64 (33–85)</td></tr>
<tr><td>Distribution — no. (%)</td><td></td><td></td></tr>
<tr><td><65 yr</td><td>132 (52.6)</td><td>125 (50.6)</td></tr>
<tr><td>65–74 yr</td><td>96 (38.2)</td><td>87 (35.2)</td></tr>
<tr><td>≥75 yr</td><td>23 (9.2)</td><td>35 (14.2)</td></tr>
<tr><td>Type of measurable disease — no. (%)</td><td></td><td></td></tr>
<tr><td>IgG</td><td>125 (49.8)</td><td>138 (55.9)</td></tr>
<tr><td>IgA</td><td>56 (22.3)</td><td>54 (21.9)</td></tr>
<tr><td>Other</td><td>5 (2.0)</td><td>4 (1.6)</td></tr>
<tr><td>Detected in urine only</td><td>40 (15.9)</td><td>36 (14.6)</td></tr>
<tr><td>Detected in serum free light-chains only</td><td>25 (10.0)</td><td>14 (5.7)</td></tr>
<tr><td>Not evaluated</td><td>0</td><td>1 (0.4)</td></tr>
<tr><td>ISS disease staging — no. (%)†</td><td></td><td></td></tr>
<tr><td>I</td><td>98 (39.0)</td><td>96 (38.9)</td></tr>
<tr><td>II</td><td>94 (37.5)</td><td>100 (40.5)</td></tr>
<tr><td>III</td><td>59 (23.5)</td><td>51 (20.6)</td></tr>
<tr><td>Cytogenetic profile — no. (%)‡</td><td></td><td></td></tr>
<tr><td>Standard-risk cytogenetic abnormality</td><td>140/181 (77.3)</td><td>137/174 (78.7)</td></tr>
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	High-risk cytogenetic abnormality	41/181 (22.7)	37/174 (21.3)
	Del17p	28/181 (15.5)	21/174 (12.1)
	t(4;14)	14/181 (7.7)	15/174 (8.6)
	t(14;16)	4/181 (2.2)	5/174 (2.9)
	Median time since initial diagnosis of multiple myeloma (range) — yr	3.87 (0.7–20.7)	3.72 (0.6–18.6)
	Number of previous lines of therapy — no. (%)		
	1	122 (48.6)	113 (45.7)
	2	70 (27.9)	74 (30.0)
	3	37 (14.7)	32 (13.0)
	>3	22 (8.8)	28 (11.3)
	Median no. of previous lines of therapy (range)	2 (1–9)	2 (1–10)
	Previous autologous stem-cell transplantation — no. (%)	156 (62.2)	149 (60.3)
	Previous alkylating agent therapy — no. (%)	240 (95.6)	224 (90.7)
	Previous proteasome inhibitor therapy — no. (%)	169 (67.3)	172 (69.6)
	Previous immunomodulatory drug therapy — no. (%)	179 (71.3)	198 (80.2)
	Previous proteasome inhibitor + immunomodulatory drug therapy — no. (%)	112 (44.6)	129 (52.2)
	Disease refractory to last line of therapy — no. (%)	76 (30.3)	85 (34.4)

Primary and secondary endpoints	Primary outcome: • Progression Free Survival Secondary outcomes • Time to Disease Progression (TTP) • Percentage of Participants with a Very Good Partial Response (VGPR) or Better • Overall Response Rate (ORR) • Percentage of Participants with Negative Minimal Residual Disease (MRD) • Overall Survival (OS)
Method of analysis	The end points of progression-free survival, which included disease status and deaths, and time to disease progression, which included disease status only, were compared between the daratumumab group and the control group with the use of a stratified log-rank test. Hazard ratios and corresponding 95% confidence intervals were estimated with the use of a stratified Cox regression model, with treatment as the sole explanatory variable. The Kaplan–Meier method was used to estimate the distributions. A stratified Cochran–Mantel–Haenszel chi-square test was used to test between-group differences in the overall response rate, the rate of very good partial response or better (i.e., very good partial response, complete response, or stringent complete response), and the rate of complete response or better (i.e., complete response or stringent complete response). The duration of response was summarized by means of the Kaplan–Meier method.
Subgroup analyses	Subgroup analyses for patients previously having received lenalidomide (not defined) and patient who were refractory to lenalidomide at last line of therapy (not defined) were exploratory, post hoc secondary analyses. The statistical methodology for the subgroup analyses is not specified in the publication (Spencer 2018).

Table 20 ENDEAVOR study characteristics

Trial name	ENDEAVOR
NCT number	NCT01568866
Objective	The primary objective of this study was to compare progression-free survival in patients with multiple myeloma who relapsed after 1 to 3 prior therapies treated with carfilzomib plus dexamethasone or bortezomib plus dexamethasone
Publications – title, author, journal, year	Dimopoulos MA, Moreau P, Palumbo A et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016;17:27-38.[8] Dimopoulos MA, Goldschmidt H, Niesvizky R et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:1327-1337.[9] Moreau P, Joshua D, Chng WJ, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia. 2017 Jan;31(1):115-122.[10] Orlowski RZ, Moreau P, Niesvizky R, Ludwig H, Oriol A, Chng WJ, et al. Carfilzomib-Dexamethasone Vs Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups. Clinical Lymphoma Myeloma and Leukemia. 2019. [11] Ludwig H, Moreau P, Dimopoulos MA, Mateos MV, Kaiser M, Hajek R, Feng S, Cocks K, Buchanan J, Weisel K. Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma. Blood Cancer J. 2019 Feb 22;9(3):23.[12] Ludwig H, Dimopoulos MA, Moreau P, et al. Carfilzomib and dexamethasone vs bortezomib and dexamethasone in patients with relapsed multiple myeloma: results of the phase 3 study ENDEAVOR (NCT01568866) according to age subgroup. Leuk Lymphoma. 2017 Oct;58(10).[21] Mateos MV, Goldschmidt H, San-Miguel J, et al. Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: A subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials. Hematol Oncol. 2018 Apr;36(2):463-470.[22] Dimopoulos M, Siegel D, White DJ, et al. Carfilzomib vs bortezomib in patients with multiple myeloma and renal failure: a subgroup analysis of ENDEAVOR. Blood. 2019 Jan 10;133(2):147-155.[23] Goldschmidt H, Moreau P, Ludwig H, et al. Carfilzomib-dexamethasone versus subcutaneous or intravenous bortezomib in relapsed or refractory multiple myeloma: secondary analysis of the phase 3 ENDEAVOR study. Leuk Lymphoma. 2018 Jun;59(6):1364-1374.[24] Chng WJ, Goldschmidt H, Dimopoulos MA, et al. Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. Leukemia. 2017 Jun;31(6):1368-1374. Hari P, Mateos MV, Abonour R, et al. Efficacy and safety of carfilzomib regimens in multiple myeloma patients relapsing after autologous stem cell transplant: ASPIRE and ENDEAVOR outcomes. Leukemia. 2017 Dec;31(12):2630-2641.[28]
Study type and design	Phase III randomized (1:1, interactive voice/web) open-label. Randomisation was stratified by previous proteasome inhibitor therapy(yes vs no), previous lines of treatment (one vs two or three), International Staging System stage (I vs II–III),and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group. Within each stratum, patients were randomly assigned using a block randomisation scheme(block size of four).
Follow-up time	Median follow-up for progression-free survival was 11.9 months (IQR .3–16.1) in the carfilzomib group and 11.1 months (8.2–14.3) in the bortezomib group.

Population (inclusion and exclusion criteria)	Inclusion Criteria: 1. Multiple myeloma with relapsing or progressing disease at study entry. 2. Patients must have evaluable multiple myeloma with, at least one of the following (assessed within 21 days prior to randomization): o Serum M-protein ≥ 0.5 g/dL, or o Urine M-protein ≥ 200 mg/24 hour, or o In patients without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) and an abnormal serum kappa/lamda ratio, or o For immunoglobulin (Ig) A patients whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA) ≥ 750 mg/dL (0.75 g/dL). 3. Patients must have documented at least partial response (PR) to at least 1 line of prior therapy. PR documentation can be based on Investigator assessment. 4. Received 1, but no more than 3 prior treatment regimens or lines of therapy for multiple myeloma. (Induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as one line of therapy). 5. Prior therapy with Velcade is allowed as long as the patient had at least a PR to prior Velcade therapy, was not removed from Velcade therapy due to toxicity, and will have at least a 6 months Velcade treatment-free interval from last dose received until first study treatment. (Patients may receive maintenance therapy with drugs that are not in the proteasome inhibitor class during this 6 months Velcade treatment-free interval). 6. Prior therapy with carfilzomib is allowed as long as the patient had at least a PR to prior carfilzomib therapy, was not removed from carfilzomib therapy due to toxicity, and had at least a 6-month carfilzomib treatment-free interval from last dose received until first study treatment. (Patients may receive maintenance therapy with drugs that are not in the proteasome inhibitor class during this 6 months carfilzomib treatment-free interval). The exception to this is patients randomized or previously randomized in any other Onyx-Sponsored Phase 3 trial. 7. Males and females ≥ 18 years of age. 8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2. 9. Adequate hepatic function within 21 days prior to randomization, with bilirubin < 1.5 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 times the ULN. 10. Left ventricular ejection fraction (LVEF) ≥ 40%. 11. Absolute neutrophil count (ANC) ≥ 1000/mm³ within 21 days prior to randomization. Screening ANC should be independent of growth factor support for ≥ 1 week. 12. Hemoglobin ≥ 8.0 g/dL within 21 days prior to randomization. Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed, however most recent RBC transfusion may not have been done within 7 days prior to obtaining screening hemoglobin. 13. Platelet count ≥ 50,000/mm³ (≥ 30,000/mm³ if myeloma involvement in the bone marrow is > 50%) within 21 days prior to randomization. Patients should not have received platelet transfusions for at least 1 week prior to obtaining the screening platelet count. 14. Calculated or measured creatinine clearance (CrCl) of ≥ 15 mL/min within 21 days prior to randomization. Calculation should be based on standard formula such as the Cockcroft and Gault: [(140 - Age) x Mass (kg) / (72 x Creatinine mg/dL)]; multiply result by 0.85 if female. 15. Written informed consent in accordance with federal, local, and institutional guidelines. 16. Female patients of child-bearing potential (FCBP) must have a negative serum pregnancy test within 21 days prior to randomization and agree to use an effective method of contraception during and for 3 months following last dose of drug (more frequent pregnancy tests may be conducted if required per local regulations). FCBP is defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12

	consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months). 17. Male patients must use an effective barrier method of contraception during study and for 3 months following the last dose if sexually active with a FCBP. Exclusion Criteria: 1. Multiple Myeloma of IgM subtype. 2. Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 14 days prior to randomization. 3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). 4. Plasma cell leukemia or circulating plasma cells ≥ 2 × 10^9/L. 5. Waldenstrom's Macroglobulinemia. 6. Patients with known amyloidosis. 7. Chemotherapy with approved or investigational anticancer therapeutics within 21 days prior to randomization. 8. Patients randomized or previously randomized in any other Onyx-Sponsored Phase 3 trial. 9. Focal radiation therapy within 7 days prior to randomization. Radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to randomization (i.e., prior radiation must have been to less than 30% of the bone marrow). 10. Immunotherapy within 21 days prior to randomization. 11. Major surgery (excluding kyphoplasty) within 28 days prior to randomization. 12. Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, or conduction abnormalities uncontrolled by conventional intervention. Myocardial infarction within four months prior to randomization. 13. Acute active infection requiring systemic antibiotics, antiviral (except antiviral therapy directed at hepatitis B) or antifungal agents within 14 days prior to randomization. 14. Known human immunodeficiency (HIV) seropositive, hepatitis C infection, and/or hepatitis B (except for patients with hepatitis B surface antigen [SAg] or core antibody receiving and responding to antiviral therapy directed at hepatitis B: these patients are allowed). 15. Patients with known cirrhosis. 16. Second malignancy within the past 3 years except: ○ adequately treated basal cell or squamous cell skin cancer ○ carcinoma in situ of the cervix ○ prostate cancer < Gleason score 6 with stable prostate-specific antigen (PSA) over 12 months ○ breast carcinoma in situ with full surgical resection ○ treated medullary or papillary thyroid cancer 17. Patients with myelodysplastic syndrome. 18. Significant neuropathy (Grades 3 to 4, or Grade 2 with pain) within 14 days prior to randomization. 19. Female patients who are pregnant or lactating. 20. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib). 21. Patients with hypersensitivity to carfilzomib, Velcade, boron, or mannitol. 22. Patients with contraindication to dexamethasone. 23. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment. 24. Ongoing graft-vs-host disease. 25. Patients with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomization.
Intervention	<u>Carfilzomib plus Dexamethasone (CarDex)</u> – administered in 21 days cycles (N=464) • Carfilzomib 20 mg/m² IV on Days 1 and 2 of Cycle 1, followed by Carfilzomib 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. • 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle. <u>Bortezomib plus Dexamethasone</u> (BorDex) – administered in 21 days cycles (N=465) • Bortezomib 1.3 mg/m² IV or SC on Days 1, 4, 8, and 11 of a 21-day cycle

	• Dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

Baseline characteristics

	CarDex (n=464)	BorDex (n=465)
Age (years)		
Median (range)	65 (35–89)	65 (30–88)
<65	223 (48%)	210 (45%)
65–74	164 (35%)	189 (41%)
≥75	77 (17%)	66 (14%)
Sex		
Male	240 (52%)	229 (49%)
Female	224 (48%)	236 (51%)
ECOG performance status		
0	221 (48%)	232 (50%)
1	211 (45%)	203 (44%)
2	32 (7%)	30 (6%)
ISS stage		
I	205 (44%)	204 (44%)
II–III	259 (56%)	261 (56%)
Cytogenetics		
High risk	97 (21%)	113 (24%)
Standard risk	284 (61%)	291 (63%)
Unknown	55 (12%)	30 (6%)
Missing	28 (6%)	31 (7%)
Race		
White	348 (75%)	353 (76%)
Black	8 (2%)	9 (2%)
Asian	58 (13%)	57 (12%)
Not reported	50 (11%)	45 (10%)
Multiple	0	1 (<1%)
Geographical region		
Eastern Europe	135 (29%)	121 (26%)
Western Europe	182 (39%)	169 (36%)
North America	35 (8%)	49 (11%)
South America	10 (2%)	15 (3%)
Asia-Pacific	102 (22%)	111 (24%)
Creatinine clearance (mL/min)		
Mean (SD)	76·7 (31·8)	75·1 (32·4)
<30	28 (6%)	28 (6%)
30 to <50	57 (12%)	71 (15%)
50 to <80	186 (40%)	177 (38%)
80	193 (42%)	189 (41%)
Serum β2 microglobulin (mg/L)		
Mean (SD)	4·6 (3·0)	4·8 (3·9)
<3·5	220 (47%)	216 (46%)
≥3·5	244 (53%)	249 (54%)
Previous regimens*		
Median (IQR)	2 (1–2)	2 (1–2)
One	232 (50%)	232 (50%)
Two	157 (34%)	145 (31%)
Three	75 (16%)	87 (19%)
History of peripheral neuropathy		
No	249 (54%)	221 (48%)
Yes	215 (46%)	244 (52%)
Ongoing peripheral neuropathy at screening		
Grade 1	133 (29%)	159 (34%)
Grade 2	10 (2%)	10 (2%)

	Previous proteasome inhibitor treatment†		
	Bortezomib	250 (54%)	252 (54%)
	Carfilzomib	2 (<1%)	1 (<1%)
	None	212 (46%)	212 (46%)
	Previous immunomodulatory agent treatment		
	Lenalidomide	177 (38%)	177 (38%)
	Thalidomide	211 (45%)	247 (53%)
Primary and secondary endpoints	Primary endpoint: • Progression-free Survival Secondary endpoints: • Overall Survival • Overall Response • Duration of Response • Percentage of Participants With ≥ Grade 2 Peripheral Neuropathy • Percentage of Participants With a Significant Reduction in Left Ventricular Ejection Fraction (LVEF) • Change From Baseline in Right Ventricular Fractional Area Change (FAC) • Change From Baseline in Pulmonary Artery Systolic Pressure (PASP)		
Method of analysis	Progression-free survival and overall survival were compared between treatment groups using a log-rank test and the corresponding hazard ratio (HR) was estimated using a Cox regression model. The overall response was compared between groups using a Mantel-Haenszel test, and the associated odds ratio (OR) and 95% CI were estimated. A Pearson $\chi 2$ test was used to compare the incidence of grade 2 or higher peripheral neuropathy between treatment groups, and the OR and 95% CI were estimated. For the distribution of time-to-event endpoints, the medians and 95% CIs were estimated using the Kaplan-Meier point estimates. For median follow-up data, the IQR was calculated. All reported p values are two-sided.		
Subgroup analyses	The subgroup analysis of patients having received at least 2 prior lines of therapy was a secondary analysis. [Moreau 2017]{Moreau, 2017 #17927} In general, patient demographic and baseline characteristics were well balanced between treatment arms in both subgroups, including age, presence of high-risk cytogenetics, and prior exposure to lenalidomide or bortezomib The intent-to-treat population was used for efficacy analyses, and all patients who received at least one dose of study treatment were used for safety analyses. The Kaplan–Meier method was used to assess PFS and DOR. Disease responses were evaluated by an independent review committee that was blinded to treatment arm. PFS was compared between treatment groups using a log-rank test, and a Cox regression model was used to estimate the corresponding HR. No adjustments were made for multiple comparisons of the subgroup analysis, and the P-values reported for the subgroup analysis are descriptive in nature. No assessment of the validity of the analysis is provided. The analysis for Overall Survival in patients having received 2 or more lines of therapy is reported in Orlowski 2019.{Orlowski, 2019 #17926} It is not reported, if the subgroup analysis of Overall Survival in patients having received at least 2 prior lines of therapy was prespecified. Median OS was estimated using the Kaplan-Meier method. Cis for the median were estimated using the method by Klein and Moeschberger with log-log transformation. For the comparison of OS between treatment groups, HRs and corresponding 95% CIs were estimated using stratified or unstratified Cox proportional hazards models for the primary intent-to-treat (ITT) population and subgroup OS analyses, respectively. Exposure-adjusted patient incidences per 100 patient-years were calculated. Total person-time in each treatment group was the sum of the time to first treatment emergent AE for each patient, or the entire time of exposure to study drug if a patient had no event.		

7.3 Adverse events in ≥10% of patients

Adverse events occurring in ≥10% of patients in the intervention and comparators arms defined by the Medicines Council (PomBorDex, DaraLenDex, DaraBorDex and CarDex) are listed in the table below.

The following data sources have been used:

PomBorDex (OPTIMISMM)– table 36 in the pomalidomide EPAR. [14]This source has been chosen as a) data are listed for all grades (1-4) of AEs, in contrast to table 3 in the publication where grade 1-2 AEs are reported separately from grade 3-4 AE. [3]

DaraBorDex (CASTOR) – Data for AEs occurring in ≥15 % of patients of patients in the DaraBorDex arm has been sourced from the latest available data in Spencer 2018 (table 3).[7] Data for AEs occurring in ≥10%, but<15% of patients has been sourced from daratumumab EPAR (table 35). [13]

DaraLenDex (POLLUX) – data for AEs occurring in ≥15% of patients has been sourced from the latest available data are reported in Dimopoulos 2018 (table 3). [5] Data for AEs occurring in 10% to ≤15% of patients has been sourced from daratumumab EPAR (table 35). [13] It should be noted that data have not been reported separately for POLLUX but are presented pooled with data from the daratumumab phase Ib study (GEN 503). This approach was agreed telephonically with the Medicines Council secretariat.

CarDex (ENDEAVOR) – data for AEs occurring in ≥10% of patients has been sourced from Dimopoulos 2017 (table S4) [9] as this provides data that meets the Medicines Council requirement. For a few AEs, more recent data are available in Orlowski 2019 (table 2).[11] However as the format of reporting in Orlowski (all grades) differs from the main reporting in Dimopoulos 2017, the Orlowski 2019 data has been provided in Table 22 (p. 60) below the main Table 21.

The data seem to indicate a safety profile consistent with the known safety profiles of the individual components of the regimens.

Table 21 Adverse events in ≥10% of patients

Study	**OPTIMISMM**		**CASTOR**		**POLLUX**		**ENDEAVOR**[d]	
Reference	Pomalidomide EPAR (table 36)		Spencer 2018, Daratumumab EPAR[7, 13]		Dimopoulos 2018, Daratumumab EPAR [5, 13]		Dimopoulos 2017 [9]	
Treatment arm	**PomBorDex**	**BorDex**	**DaraBorDex**	**BorDex**	**DaraLenDex**	**LenDex**	**CarDex**	**BorDex**
Number of patients	278	270	243	237	283	281	463	456
Grade	All	All	All	All	All	All	1-2	1-2
Data are n (%)								

Infections and infestations								
Bronchitis	39 (14.0)	19 (7.0)	28 (11.5)[y]	13 (5.5)[y]	53 (18.7)[‡]	46 (16.4)[‡]	95 (20.5)	44 (9.6)
Nasopharyngitis					84 (29.7)[‡]	54 (19.2)[‡]	80 (17.3)	60 (13.2)
Pneumonia	53 (19.1)	37 (13.7)	36 (14.8)[z]	31 (13.1)[z]	58 (20.5)[‡]	42 (14.9)[‡]		
Upper respiratory tract infection	58 (20.9)	48 (17.8)	76 (31.3)[z]	43 (18.1)[z]	105 (37.1)[‡]	74 (26.3)[‡]	111 (24.0)	79 (17.3)
Respiratory tract infection					33 (10.4)[§]	22 (7.8)[§]		
Viral infections	31 (11.2)[a]	14 (5.2)[a]						
Gastrointestinal disorders								
Diarrhoea	94 (33.8)	81 (30.0)	85 (35.0)[z]	53 (22.4)[z]	144 (50.9)[‡]	89 (31.7)[‡]	150 (32.4)	146 (32.0)
Nausea	49 (17.6)	54 (20.0)	34 (14.0)[y]	26 (11.0)[y]	76 (26.9)[‡]	50 (17.8)[‡]	100 (21.6)	88 (19.3)
Obstipation/Constipation	102 (36.7)	65 (24.1)	53 (21.8)[z]	38 (16.0)[z]	88 (31.1)[‡]	74 (26.3)[‡]	73 (15.8)	118 (25.9)
Vomiting	32 (11.5)	27 (10.0)	26 (10.7)[y]	9 (3.8)[y]	52 (18.4)[‡]	19 (6.8)[‡]	70 (15.1)	38 (8.3)
Blood and lymphatic disorders								
Anaemia	79 (28.4)	73 (27.0)	69 (28.4)[z]	75 (31.6)[z]	104 (36.7)[‡]	109 (38.8)[‡]	121 (26.1)[‡]	83 (18.2)
Febrile neutropenia					17 (6.0)[‡]	8 (2.8)[‡]		
Lymphopenia	32 (11.5)[c]	9 (3.3)[c]	32 (13.2)[z]	9 (3.8)[z]	18 (6.4)[‡]	16 (5.7)[‡]		
Neutropenia	130 (46.8)	29 (10.7)	46 (18.9)[z]	23 (9.7)[z]	172 (60.8)[‡]	127 (45.2)[‡]		
Thrombocytopenia	102 (36.7)	103 (38.1)	145 (59.7)[z]	105 (44.3)[z]	81 (28.6)[‡]	87 (31.0)[‡]	59 (12.7)	41 (9.0)
General disorders and administration site conditions								
Asthenia	48 (17.3)	48 (17.8)	24 (9.9)[z]	37 (15.6)[z]	51 (18.0)[‡]	43 (15.3)[‡]	86 (18.6)	65 (14.3)
Fatigue	103 (37.1)	71 (26.3)	53 (21.8)[z]	58 (24.5)[z]	103 (36.4)[‡]	85 (30.2)[‡]	118 (25.5)	105 (23.0)
Oedema, peripheral	94 (33.8)	54 (20.0)	45 (18.5)[z]	20 (8.4)[z]	53 (18.7)[‡]	43 (15.3)[‡]	111 (24.0)	84 (18.4)
Pyrexia	64 (23.0)	32 (11.9)	43 (17.9)[z]	28 (11.8)[z]	67 (23.7)[‡]	36 (12.8)[‡]	136 (29.4)	66 (14.5)
Respiratory, thoracic and mediastinal disorders								
Cough	57 (20.5)	40 (14.8)	68 (28.0)[z]	30 (12.7)[z]	91 (32.2)[‡]	40 (14.2)[‡]	128 (27.6)	71 (15.6)
Dyspnoea	56 (20.1)	33 (12.2)	46 (18.9)[z]	21 (8.9)[z]	59 (20.8)[‡]	35 (12.5)[‡]	120 (25.9)	52 (11.4)
Musculoskeletal and connective tissue disorders								
Arthralgia	32 (11.5)	31 (11.5)					57 (12.3)	48 (10.5)
Back pain	52 (18.7)	36 (13.3)	47 (19.3)[z]	24 (10.1)[z]	58 (20.5)[‡]	53 (18.9)[‡]	97 (21.0)	67 (14.7)
Muscle spasms					81 (28.6)[‡]	59 (21.0)[‡]	91 (19.7)	25 (5.5)
Muscular weakness	38 (13.7)	13 (4.8)						
Pain in extremity	33 (11.9)	36 (13.3)			26 (8.2)[§]	30 (10.7)[§]	52 (11.2)	46 (10.1)
Nervous system disorders								
(Peripheral) neuropathy							43 (9.3)	102 (22.4)
Dizziness	48 (17.3)	28 (10.4)					41 (8.9)	67 (14.7)
Headache	31 (11.2)	25 (9.3)	25 (10.3)[y]	14 (5.9)[y]	43 (15.2)[‡]	22 (7.8)[‡]	91 (19.7)	46 (10.1)
Neuralgia			33 (13.6)[y]	26 (11.0)[y]			9 (1.9)	63 (13.8)
Paraesthesia							40 (8.6)	74 (16.2)
Peripheral sensory neuropathy	133 (47.8)[b]	100 (37.0)[b]	121 (49.8)[z]	90 (38.0[z])			28 (6.0)	(64 (14.0)

Tremor	30 (10.8)	8 (3.0)						
Metabolism and nutrition disorders								
Hyperglycaemia	40 (14.4)	30 (11.1)						
Hypokalaemia	43 (15.5)	30 (11.1)			33 (10.4) [§]	29 (10.3) [§]	49 (10.6)	34 (7.5)
Decreased appetite					34 (10.7) [§]	29 (10.3) [§]	46 (9.9)	56 (12.3)
Psychiatric disorders								
Insomnia	45 (16.2)	53 (19.6)	42 (17.3) [z]	36 (15.2) [z]	67 (23.7) [‡]	61 (21.7) [‡]	113 (24.4) [‡]	110 (24.1)
Cardiac disorders								
Hypertension							82 (17.7) [‡]	30 (6.6)
Renal and urinary disorders								
Increased blood creatinine							49 (10.6) [‡]	26 (5.7)
Skin and subcutaneous tissue disorders								
Rash					38 (11.9) [§]	29 (10.3) [§]		
Pruritus					29 (9.1) [§]	29 (10.3) [§]		
Data are n (%).	[a] Viral Upper Respiratory infection; [b] Peripheral sensory neuropathy [c] Leukopenia Data sourced from the EPAR (table 36) as Richardson et al reports data for grad 1/2 and 3/4 separately		[z]Spencer 2018 (table 3) for AEs occurring ≥15%. [y]Daratumumab EPAR table 35 for 10 to<15%		[‡]Data is for AEs occurring in **≥15 %** of patients sourced from Dimo 2018. [§]The EPAR (table 35) presents data for ≥10%, but presents POLLUX data combined with another study (GEN503).		Sourced from Dimopoulos 2017 2017, table S4 [d] Data presented are for grade 1-2 AEs as the publication (and the EPAR) have reported grades 1-2, 3, 4 and 5 separately.	

For ENDEAVOR more recent data have been reported for a few selected adverse events in Orlowski 2019 (table 2). These are listed in the table below.

Table 22 ENDEAVOR latest data for adverse events

Ref.: Orlowski 2019, table [11]	CarDex (n=463)		BorDex (n=456)	
Most Common Events, n (%)[a]	**All grades**	**Grade 3 or higher**	**All grades**	**Grade 3 or higher**
Anemia	202 (43.6)	80 (17.3)	130 (28.5)	46 (10.1)
Diarrhea	170 (36.7)	19 (4.1)	185 (40.6)	40 (8.8)
Pyrexia	151 (32.6)	14 (3.0)	70 (15.4)	3 (0.7)
Hypertension	150 (32.4)	69 (14.9)	46 (10.1)	15 (3.3)
Fatigue	149 (32.2)	32 (6.9)	140 (30.7)	35 (7.7)
Dyspnea	149 (32.2)	29 (6.3)	62 (13.6)	10 (2.2)
Events of Interest, n (%)				
Cardiac failure (SMQN)	51 (11.0)	28 (6.0)	16 (3.5)	9 (2.0)
Ischemic heart disease (SMQN)	18 (3.9)	12 (2.6)	9 (2.0)	7 (1.5)
Peripheral neuropathy (SMQN)	97 (21.0)	11 (2.4)	249 (54.6)	44 (9.6)
Acute renal failure (SMQN)	50 (10.8)	27 (5.8)	29 (6.4)	16 (3.5)
Hematopoietic thrombocytopenia (SMQN)	148 (32.0)	58 (12.5)	123 (27.0)	67 (14.7)
Neutropenia (PT)	29 (6.3)	12 (2.6)	26 (5.7)	10 (2.2)
[a] Adverse events (preferred terms) are included if reported in ≥30% of patients in either treatment group. Abbreviations: PT = preferred term; SMQN = standardized Medical Dictionary for Regulatory Activities query, narrow scope.				

7.4 Grade 3/4 adverse events in all patients

The frequency of grade 3/4 adverse event is listed in the table below.

The following data sources have been used:

PomBorDex (OPTIMISMM)– data has been sourced from table 38 in the pomalidomide EPAR. [14] This source has been chosen as data are listed for grade 3-4 events occurring in ≥2% of patients, while the Richardson 2018 publication lists grade 3 and grade 4 separately and only for events in ≥5% of patients. [3, 14]

DaraBorDex (CASTOR) – the latest available data are presented in the Spencer 2018 publication (table 3), where data are reported for grade 3/4 adverse events occurring in more than 5 % of patients. The daratumumab EPAR also reports grade 3/4 adverse events occurring in more than 5 % of patients. However, as the cut-off date for data in the Spencer 2018 publication is more recent than the EPAR, data from the Spencer publication has been listed. [7, 13]

DaraLenDex (POLLUX) – data for grade 3/4 AEs occurring in ≥5% of patients has been sourced from the latest available data that are reported in Dimopoulos 2018 (table 3). [5] The EPAR does not provide any additional data and has an earlier cut-off date.

CarDex (ENDEAVOR) – data for grade 3/4 AEs occurring in ≥2% of patients has been sourced from Dimopoulos 2017 (table S43). [9] For a few grade 3/4 AEs, more recent data are available in Orlowski 2019 (table 2).[11] In order not to confuse the picture too much these data have been listed in a separate table see above

The data seem to indicate a safety profile consistent with the known safety profiles of the individual components of the regimens.

Table 23 Grade 3/4 adverse events

Study	**OPTIMISMM**		**CASTOR**		**POLLUX**		**ENDEAVOR**	
Data source	EPAR (table 38)		Spencer 2018, table 3		[Dimo 2018, table 3]		[Dimo 2017, table S4]	
Treatment arm	**PomBorDex**	**BorDex**	**DaraBorDex**	**BorDex**	**DaraLenDex**	**LenDex**	**CarDex**	**BorDex**
Number of patients	278	270	243	237	283	281	463	456
Grade	≥3/4	≥3/4	≥3/4	≥3/4	≥3/4	≥3/4	≥3/4 [D]	≥3/4 [E]
Incidence cut off for reporting in the source	≥2%		≥5%					
Data are n(%)								
Infections and infestations								

Study	OPTIMISMM		CASTOR		POLLUX		ENDEAVOR	
Bronchitis					6 (2.1)	7 (2.5)	13 (2.8)	4 (0.9)
Pneumonia	32 (11.5)	17 (6.3)	24 (9.9)	24 (10.1)	34 (12.0)	24 (8.5)	39 (8.4)	37 (8.1)
Influenza	7 (2.5)	4 (1.5)						
Sepsis	6 (2.2)	1 (0.4)						
Upper respiratory infection			6 (2.5)	1 (0.4)	4 (1.4)	4 (1.4)	10 (2.2)	4 (0.9)
Urinary tract infection							11(3.3)	3 (0.7)
Gastrointestinal disorders								
Diarrhoea	20 (7.2)	9 (3.3)	9 (3.7)	3 (1.3)	20 (7.1)	9 (3.2)	18 (3.9)	39 (8.6)
Nausea					5 (1.8)	2 (0.7)	9 (1.9)	3 (0.7)
Obstipation/Constipation	7 (2.5)	1 (0.4)	0 (0.0)	2 (0.8)	3 (1.1)	2 (0.7)	2 (0.4)	8 (1.8)
Vomiting					3 (1.1)	4 (1.4)	7 (1.5)	7 (1.5)
Blood and lymphatic disorders								
Anaemia	39 (14.0)	38 (14.1)	37 (15.2)	38 (16.0)	44 (15.5)	60 (21.4)	76 (16.4)	46 (10.1)
Febrile neutropenia	9 (3.2)	0 (0.0)			17 (6.0)	8 (2.8)		
Lymphocytopenia (decreased lymphocyte count)							29 (6.3)[c]	9 (2.0)[c]
Leukopenia	15 (5.4)	5 (1.9)						
Lymphopenia	12 (4.3)	8 (3.0)	24 (9.9)	6 (2.5)	15 (5.3)	11 (3.9)	22 (4.8)	14 (3.1)
Neutropenia	116 (41.7)	23 (8.5)	33 (13.6)	11 (4.6)	153 (54.1)	112 (39.9)	11 (2.4)	10 (2.2)
Thrombocytopenia	76 (27.3)	79 (29.3)	111 (45.7)	78 (32.9)	39 (13.8)	44 (15.7)	43 (8.9)	43 (9.4)
General disorders and administration site conditions								
Fatigue	23 (8.3)	10 (3.7)	12 (4.9)	8 (3.4)	18 (6.4)	10 (3.6)	31 (6.7)	35 (7.7)
Asthenia	8 (2.9)	8 (3.0)	2 (0.8)	5 (2.1)	10 (3.5)	8 (2.8)	21 (4.5)	14 (3.1)
Pyrexia	6 (2.2)	2 (0.7)	3 (1.2)	3 (1.3)	7 (2.5)	5 (1.8)	14 (3.0)	3 (0.7)
Oedema, peripheral			1 (0.4)	0 (0.0)	2 (0.7)	4(1.4)	5 (1.1)	3 (0.7)
General health deterioration	3 (1.1)	7 (2.6)						
Respiratory, thoracic and mediastinal disorders								
Cough					1 (0.4)	0 (0.0)		
Dyspnoea	8 (2.9)	3 (1.1)	9 (3.7)	2 (0.8)	12 (4.2)	2 (0.7)	29 (6.3)	10 (2.2)
Musculoskeletal and connective tissue disorders								
Back pain			5 (2.1)	3 (1.3)	6 (2.1)	5 (1.8)	10 (2.2)	14 (3.1)
Muscle spasms					3 (1.1)	4 (1.4)	1 (0.2)	3 (0.7)
Nervous system disorders								
(Peripheral) neuropathy	23 (8.3)	12 (4.4)	11 (4.5)	16 (6.8)			6 (1.3)	28 (6.1)
Headache							4 (0.9)	3 (0.7)
Syncope	14 (5.0)	6 (2.2)						
Metabolism and nutrition disorders								
Hyperglycaemia	25 (9.0)	14 (5.2)					22 (4.8)	17 (3.9)

Study	OPTIMISMM		CASTOR		POLLUX		ENDEAVOR	
Hypokalaemia	17 (6.1)	11 (4.1)					11 (2.4)	17 (3.7)
Hypophosphatemia	11 (4.0)	5 (1.9)					15 (3.2)	6 (1.3)
Hyponatriemia	7 (2.5)	2 (0.7)					12 (2.6)	6 (1.3)
Hyperkalaemia	7 (2.5)	2 (0.7)						
Hyperuricaemia	2 (0.7)	2 (2.6)						
Psychiatric disorders								
Insomnia			2 (0.8)	3 (1.3)	4 (1.4)	(4 (1.4)	12 (2.6)	12 (2.6)
Cardiac disorders								
Heart failure	3 (1.1)	2 (0.7)					12 (2.6)	3 (0.7)
Atrial fibrillation	9 (3.2)	2 (0.7)						
Hypertension	8 (2.9)	4 (1.5)	16 (6.6)	2 (0.8)			67 (14.5)	15 (3.3)
Pulmonary embolus	11 (4.0)	1 (0.4)						
Eye disorders								
Cataract							11 (2.4)	9 (2.0)
Neoplasms								
Secondary Primary Malignancy					16 (5.7)	16 (5.7)		
Renal and urinary disorders								
Acute kidney injury	9 (3.2)	4 (1.5)					11 (2.4)	7 (1.5)
Creatinine clearance decreased							10 (2.2)	3 (0.7)
Skin and subcutaneous tissue disorders								
Rash	6 (2.2)	0 (0.0)						
Data are n (%).	Grade 3/4 [a] Leukopenia		Grade 3/4		Grade 3/4 %		Grade 3/4 % Has been grouped and percentage recalculated.	[c] Decreased lymphocyte count [D] Grade 5: Pneumonia 3 (0.6), cardiac failure 1 (0.2) [E] Grade 5: Pneumonia 2 (0.4)

7.5 Results per study

Table 24 Results of OPTIMISMM (PomBorDex vs BorDex)

Trial name:	*OPTIMISMM*									
NCT number:	*NCT01734928*									
				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	Pomalidomide + Bortezomib+ Dexamethasone (ITT)	281	40.54 months (29.83-NE[a])	10.1 months	NR[c]	NR[c]	HR: 0.91	0.70-1.18	0.4755	*The median is based on Kaplan-Meier estimate. Hazard ratio is based on Cox proportional hazards model comparing the hazard functions associated with treatment*	Imnovid EPAR; p.57; table 33
	Bortezomib + Dexamethasone (ITT)	278	30.46 months (24.61-35.94)								

				groups, stratified by age, prior number of antimyeloma regimens, and β2-macroglobulin at screening. P value is based on a stratified log-rank test with stratification factors as in the above Cox model. Absolute differences in median OS were not reported but were calculated by subtraction of reported medians. 95% CIs were not calculated as the calculations of confidence	

										intervals for differences in median survival are not well defined.	
	Pomalidomide + Bortezomib+ Dexamethasone (ITT)	281	11.2 months (9.66-13.73)	4.1 months	NR[c]	NR[c]	HR: 0.61	0.49 - 0.77	<0.0001	*Kaplan-Meier method was used to estimate progression-free survival. The treatment effect (measured by HR and 95% CI) was estimated using a stratified Cox proportional hazards model. Absolute differences in median PFS were not*	Richardson, 2019; p.786 and Richardson, 2019; p.787; figure 2
	Bortezomib + Dexamethasone (ITT)	278	7.1 months (5.88-8.48)								
	Pomalidomide + Bortezomib+ Dexamethasone (refractory to lenalidomide)	200	9.53 months (8.05 - 11.30)	3.94 months	NR[c]	NR[c]	HR: 0.65	0.50 - 0.84	0.0008		
	Bortezomib + Dexamethasone (refractory to lenalidomide)	191	5.59 months (4.44 - 7.00)								

	Pomalidomide + Bortezomib+ Dexamethasone (1 previous LOT)	111	20.73 months (15.11 - 27.99)	9.1 months	NR[c]	NR[c]	HR: 0.54	0.36 - 0.82	0.0027	*reported but were calculated by subtraction of reported medians. 95% CIs were not calculated as the calculation of confidence intervals for differences in median survival are not well defined.*	
	Bortezomib + Dexamethasone (1 previous LOT)	115	11.63 months (7.52 - 15.74)								
	Pomalidomide + Bortezomib+ Dexamethasone (1 previous LOT + refractory to lenalidomide)	64	17.84 months (12.02 - NE[a])	8.35 months	NR[c]	NR[c]	HR: 0.55	0.33 - 0.94	0.03		Richardson, 2019; p.788 and appendix p. 3 and p.788 figure 3
	Bortezomib + Dexamethasone (1 previous LOT + refractory to lenalidomide)	65	9.49 months (6.34 - 16.20)								
Median Progression Free Survival	Pomalidomide + Bortezomib+ Dexamethasone (previous exposure to proteasome inhibitors)	212	10.91 months (8.41 - 13.73)	4.6 months	NR[c]	NR[c]	HR: 0.57	0.44 - 0.73	<0.0001		

Bortezomib + Dexamethasone (previous exposure to proteasome inhibitors)	213	6.31 months (5.19 to 8.31)								
Pomalidomide + Bortezomib+ Dexamethasone (>1 previous lines of treatment)	170	NR[b]	NR[c]	NR[c]	NR[c]	HR: 0.63	0.48-0.83	NR[c]		Richardson, 2019; p. 788; figure 3
Bortezomib + Dexamethasone (patients with >1 previous lines of treatment)	163	NR[b]								
Pomalidomide + Bortezomib+ Dexamethasone (after next-line treatment)	NR[b]	22.44 months (18.06 - NE[a])	5.49 months	NR[c]	NR[c]	HR: 0.76	0.59 - 0.99	0.04		Richardson, 2019; p.789
Bortezomib + Dexamethasone (after next-line treatment)	NR[b]	16.95 months (14.69 - 21.09)								

	Pomalidomide + Bortezomib+ Dexamethasone (3L)	117	NR[b]	NR[c]	NR[c]	NR[c]	HR: 0.67	0.48-0.94	NR[c]		Richardson, 2019; p.788; figure 3
	Bortezomib + Dexamethasone (3L)	104	NR[b]								
	Pomalidomide + Bortezomib+ Dexamethasone (3L+)	53	NR[b]	NR[c]	NR[c]	NR[c]	HR: 0.60	0.38-0.95	NR[c]		
	Bortezomib + Dexamethasone (3L+)	59	NR[b]								
HRQoL mean baseline scores, QLQ-C30	Pomalidomide + Bortezomib+ Dexamethasone (ITT)	240	Baseline score: 61.0 (SD: 23.2)	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	*The observed change in HRQOL score from baseline was calculated using a mixed-model repeated measure approach, using baseline covariates*	Richardson, 2019; p.791
	Bortezomib + Dexamethasone (ITT)	209	Baseline score: 63.5 (SD: 21.3)								

				where appropriate to estimate the least square means (95% CI and p value) for changes from baseline across all scheduled visits, as well as the difference in the least square means between treatment groups. *Quantitative results not reported, authors note that 'scores were maintained over time for both treatment groups, with no statistically*	

										significant or clinically meaningful differences recorded between treatments at any cycle'	
Discontinuations due to TEAEs	Pomalidomide + Bortezomib+ Dexamethasone (TEAE leading to discontinuation of any study drug)	278	28.8 % (80 patients)	-9.9%	-17.3% ; -2.4%	0.009	RR: 1.52	1.12, 2.07	0.008	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-value were calculated using two sample z-test for proportions. Relative risk*	Imnovid EPAR; p.73; table 46
	Bortezomib+ Dexamethasone (TEAE leading to discontinuation of any study drug)	270	18.9% (51 patients)								
	Pomalidomide + Bortezomib+ Dexamethasone (TEAE leading to discontinuation of pomalidomide)	278	11.2% (31 patients)	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]		

	Bortezomib+ Dexamethasone (TEAE leading to discontinuation of pomalidomide)	270	NR[b]						*(RR), along with its confidence interval and p value, were calculated using standard methods.*	
	Pomalidomide + Bortezomib+ Dexamethasone (TEAE leading to discontinuation of bortezomib)	278	24.1% (67 patients)	-5.6%	-12.8% ; 1.6%	0.14	RR: 1.30	0.94, 1.80	0.11	
	Bortezomib+ Dexamethasone (TEAE leading to discontinuation of bortezomib)	270	18.5% (50 patients)							
	Pomalidomide + Bortezomib+ Dexamethasone (TEAE leading to discontinuation of dexamethasone)	278	16.9% (47 patients)	2.0%	-4.8% ; 8.8%	0.62	RR: 0.90	0.63, 1.28	0.54	
	Bortezomib+ Dexamethasone (TEAE leading to discontinuation of dexamethasone)	270	18.9% (51 patients)							

Qualitative review of AEs	See narrative
	[a] Results were reported as not evaluable in the reference [b] Results were not reported in the EPAR or the identified full publications [c] Results were not reported in the EPAR or the identified full publications and were not calculated as per DMC's protocol (section 5.4)

Table 25 Results of CASTOR (DaraBorDex vs BorDex)

Trial name:	*CASTOR*									
NCT number:	*NCT02136134*									
				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 (interim)	Daratumumab + Bortezomib+ Dexamethasone (ITT)	251	NE[a]	NR[c]	NR[c]	NR[c]	HR: 0.77	0.47-1.26	0.30	*The HR is based on a Cox proportional hazards model.*	*Palumbo, 2016; Supplementary Appendix p.27; figure s7*
	Bortezomib + Dexamethasone (ITT)	247	NE[a]								
Median Progression Free Survival	Daratumumab + Bortezomib+ Dexamethasone (ITT)	251	16.7 months	9.6 months	NR[c]	NR[c]	HR: 0.31	0.24-0.39	<0.0001	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.*	*Spencer, 2018; p. 2082; figure 1 (A)*
	Bortezomib + Dexamethasone (ITT)	247	7.1 months								

Daratumumab + Bortezomib+ Dexamethasone (2-3 prior treatments)	107	9.8 months	3.5 months	NR[c]	NR[c]	HR: 0.51	0.36-0.71	<0.0001	*Absolute differences in median PFS were not reported but were calculated by subtraction of reported medians, where applicable. 95% CIs were not calculated as the calculations of confidence intervals for differences in median survival are not well defined.*	*Spencer, 2018; p. 2082; figure 1 (C)*
Bortezomib + Dexamethasone (2-3 prior treatments)	106	6.3 months								
Daratumumab + Bortezomib+ Dexamethasone (>3 prior treatments)	22	8.1 months	2.7 months	NR[c]	NR[c]	HR: 0.37	0.17-0.80	NR[c]		*Spencer, 2018; p. 2083; figure 2*
Bortezomib + Dexamethasone (>3 prior treatments)	28	5.4 months								
Daratumumab + Bortezomib+ Dexamethasone (prior lenalidomide exposure)	89	9.5 months	3.4 months	NR[c]	NR[c]	HR: 0.38	0.26-0.56	NR[c]		

	Bortezomib + Dexamethasone (prior lenalidomide exposure)	120	6.1 months								
	Daratumumab + Bortezomib+ Dexamethasone (refractory to lenalidomide at the last prior line of treatment)	45	9.3 months	4.9 months	NR[c]	NR[c]	HR: 0.36	0.21-0.63	0.0002		*Spencer, 2018; p. 2083; figure 2 and Spencer, 2018; p. 2082; col. 1*
	Bortezomib + (refractory to lenalidomide at the last prior line of treatment)	60	4.4 months								
HRQoL	Daratumumab + Bortezomib+ Dexamethasone (ITT), EORTC QLQ C30, median time to improvement	NR[b]	5.0 months	-0.1 months	NR[c]	NR[c]	HR: 0.99	0.76-1.29	0.9163	*Health-related quality of life (HRQoL) was assessed by the European Organization*	*Spencer, 2018; p. 2085; col. 1*

Bortezomib + Dexamethasone (ITT), EORTC QLQ C30, median time to improvement	NR[b]	5.1 months							*for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC-QLQC30) and the EuroQol 5 Dimensions Questionnaire (EQ-5D-5L) tools. Median time to improvement was estimated. Absolute differences in median time to improvement were calculated by subtraction of reported median.*
Daratumumab + Bortezomib+ Dexamethasone (ITT), EQ-5D-5L, median time to improvement	NR[b]	7.7 months	4.2 months	NR[c]	NR[c]	HR: 0.82	0.62-1.08	0.1469	
Bortezomib + Dexamethasone (ITT), EQ-5D-5L, median time to improvement	NR[b]	3.5 months							
Daratumumab + Bortezomib+ Dexamethasone (ITT), VAS, median time to improvement	NR[b]	5.0 months	0 months	NR[c]	NR[c]	HR: 1.03	0.79-1.35	0.8072	
Bortezomib + Dexamethasone (ITT), VAS,	NR[b]	5.0 months							

	median time to improvement										
Discontinuations due to TEAEs	Daratumumab + Bortezomib+ Dexamethasone (ITT)	243	10.3% (25 patients)	-0.4%	-6.47%-5.20%	0.95	RR: 1.06	0.62-1.81	0.83	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-value were calculated using two sample z-test for proportions. Relative risk (RR), along with its confidence interval and p value, were calculated using standard methods.*	*Spencer, 2018; Appendix p. 5; figure S1*
	Bortezomib + Dexamethasone (ITT)	237	9.7% (23 patients)								

Qualittative review of AEs	See narrative
	[a] Results were reported as not evaluable in the reference [b] Results were not reported in the EPAR or the identified full publications [c] Results were not reported in the EPAR or the identified full publications and were not calculated as per DMC's protocol (section 5.4)

Table 26 Results of POLLUX (DaraLenDex vs LenDex)

Trial name:	*POLLUX*										
NCT number:	*02076009*										
				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	Daratumumab + Lenalidomide + Dexamethasone (ITT)	286	NE[a]	NR[c]	NR[c]	NR[c]	HR: 0.64	(0.40-1.01)	0.0534	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.*	Dimopoulos, 2016; Supplementary Appendix p.23; figure s7
	Lenalidomide + Dexamethasone (ITT)	283	20.3								
Median Progression Free Survival	Daratumumab + Lenalidomide + Dexamethasone (ITT)	286	NE[a]	NR[c]	NR[c]	NR[c]	HR: 0.41	(0.31-0.53)	<0.0001	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for study arm. Absolute*	Dimopoulos, 2018; p.2091; figure 1 (B)
	Lenalidomide + Dexamethasone (ITT)	283	17.5								
	Daratumumab + Lenalidomide	149	NE[a]	NR[c]	NR[c]	NR[c]	HR: 0.39	(0.26-0.58)	<0.0001		

+ Dexamethasone (1 prior line) Lenalidomide + Dexamethasone (1 prior line)	146	19.6							*differences in median PFS were not reported but were calculated by subtraction of reported medians, where applicable. 95% CIs were not calculated as the calculations of confidence intervals for differences in median survival are not well defined.*
Daratumumab + Lenalidomide + Dexamethasone (2-3 prior lines) Lenalidomide + Dexamethasone (2-3 prior lines)	123 118	28.9 15.7	13.2	NR[c]	NR[c]	HR: 0.38	(0.26-0.56)	<0.0001	
Daratumumab + Lenalidomide + Dexamethasone (1-3 prior lines) Dexamethasone (1-3 prior lines)	272 264	NE[a] 17.5	NR[c]	NR[c]	NR[c]	HR: 0.39	(0.30-0.52)	<0.0001	

	Lenalidomide + Dexamethasone (1-3 prior lines)									
	Daratumumab + Lenalidomide + Dexamethasone (prior lenalidomide)	50	NE[a]	NR[c]	NR[c]	NR[c]	HR: 0.32	(0.16-0.64)	0.0008	
	Lenalidomide + Dexamethasone (prior lenalidomide)	50	18.6							
HRQoL	Daratumumab + Lenalidomide + Dexamethasone (ITT), EORTC QLQ-C30, median time to improvement	NR[b]	6.6 months	0.1 months	NR[c]	NR[c]	HR: 1.03	(0.81-1.30)	0.82	*Health-related quality of life (HRQoL) was assessed using the EuroQol 5-Dimension Questionnaire (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life*	Dimopoulos, 2018; p. 2093; col. 1
		NR[b]	6.5 months							

	Lenalidomide + Dexamethasone (ITT), EORTC QLQ-C30, median time to improvement								*Questionnaire Core-30 (EORTC QLQ-C30). Absolute differences in median time to improvement were calculated by subtraction of reported median.*
	Daratumumab + Lenalidomide + Dexamethasone (ITT), EQ-5D-5L, median time to improvement	NR[b]	6.6 months	-3.6 months	NR[c]	NR[c]	HR: 1.23	(0.97-1.57)	0.089	
	Lenalidomide + Dexamethasone (ITT), EQ-5D-5L, median time to improvement	NR[b]	10.2 months							
	Daratumumab + Lenalidomide + Dexamethasone (ITT), VAS, median time to improvement	NR[b]	6.9 months	-2.4 months	NR[c]	NR[c]	HR: 1.14	(0.89-1.45)	0.283	

	Lenalidomide + Dexamethasone (ITT), VAS, median time to improvement	NR[b]	9.3 months						
Discontinuations due to TEAEs	Daratumumab + Lenalidomide + Dexamethasone (ITT)	286	11.9% (34 patients)	0.8%	-4.9%-6.6%	0.86	RR: 0.93	(0.60-1.45) 0.762	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-value were calculated using two sample z-test for proportions. Relative risk (RR), along with its confidence interval and p value, were calculated using standard methods.*	Dimopoulos, 2018; Appendix p.7; figure 1
	Lenalidomide + Dexamethasone (ITT)	283	12.7% (36 patients)							
Qualitative	Intervention			See narrative						

review of AEs	Comparator				

[a] Results were reported as not evaluable in the reference

[b] Results were not reported in the EPAR or the identified full publications

[c] Results were not reported in the EPAR or the identified full publications and were not calculated as per DMC's protocol (section 5.4)

Table 27 Results of ENDEAVOR (CarDex vs BorDex)

Trial name:	*ENDEAVOR*									
NCT number:	*NCT01568866*									
				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	Carfilzomib + Dexamethasone (ITT)	464	47.8 months (41.9 to NE[a])	9.0 months	NR[c]	NR[c]	HR: 0.761	0.633-0.915	0.0017	*Median OS was estimated using the Kaplan-Meier method and CIs for median PFS were estimated using the method by Klein and Moeschberger with log-log transformation. Hazard ratio and corresponding 95% CI were estimated using a Cox proportional hazard model. Absolute differences in median OS were not reported but were calculated by subtraction of reported medians.*	Orlowski, 2019; p. 524; figure 2 and Orlowski, 2019; p. 526, col. 2
	Bortezomib + Dexamethasone (ITT)	465	38.8 months (31.7 to 42.7)								
	Carfilzomib + Dexamethasone (2-3 prior treatments)	233	39.5 months	11.1 months	NR[c]	NR[c]	HR: 0.752	0.589-0.959	NR[c]		Orlowski, 2019; p. 526; figure 3 (C)
	Bortezomib + Dexamethasone (2-3 prior treatments)	236	28.4 months								

										95% CIs were not calculated as the calculations of confidence intervals for differences in median survival are not well defined.	
Median Progression Free Survival	Carfilzomib + Dexamethasone (ITT)	464	18.7 months (15.63 to NE[a])	9.3 months	NR[c]	NR[c]	HR: 0.53	0.437-0.651	<0.0001	*Median PFS was estimated using the Kaplan-Meier method and CIs for median PFS were estimated using the method by Klein and Moeschberger with log-log transformation. Hazard ratio and corresponding 95% CI were estimated using a stratified Cox proportional hazard model. P value was calculated using a stratified log-rank test. Absolute differences in median*	Kyprolis EPAR; p. 47; table 10
	Bortezomib + Dexamethasone (ITT)	465	9.4 months (8.39 to 10.39)								
	Carfilzomib + Dexamethasone (at least 2 prior treatments)	232	14.9 months	6.5 months	NR[c]	NR[c]	HR: 0.604	0.466-0.783	<0.0001		Moreau, 2017; p.118; figure 1 (b)
	Bortezomib + Dexamethasone (at least 2 prior treatments)	233	8.4 months								

	Carfilzomib + Dexamethasone (2-3 prior treatments & prior bortezomib exposure)	153	13.1 months	5.7 months	NR[c]	NR[c]	HR: 0.62	0.45-0.85	NR[c]	*PFS were not reported but were calculated by subtraction of reported medians. 95% CIs were not calculated as the calculations of confidence intervals for differences in median survival are not well defined.*	Moreau, 2017; p.119; table 4
	Bortezomib + Dexamethasone (2-3 prior treatments & prior bortezomib exposure)	154	7.4 months								
	Carfilzomib + Dexamethasone (2-3 prior treatments & no prior bortezomib exposure)	80	15.7 months	6.3 months	NR[c]	NR[c]	HR: 0.56	0.36-0.89	NR[c]		
	Bortezomib + Dexamethasone (2-3 prior treatments & no prior bortezomib exposure)	82	9.4 months								

Carfilzomib + Dexamethasone (2-3 prior treatments & prior lenalidomide exposure) Bortezomib + Dexamethasone (2-3 prior treatments & prior lenalidomide exposure)	126 132	9.7 months 6.6 months	3.1 months	NR[c]	NR[c]	HR: 0.73	0.53-1.01	NR[c]	
Carfilzomib + Dexamethasone (2-3 prior treatments & no prior lenalidomide exposure) Bortezomib + Dexamethasone (2-3 prior treatments & no prior lenalidomide exposure)	107 104	NE[a] 10.4 months	NR[c]	NR[c]	NR[c]	HR: 0.45	0.29-0.70	NR[c]	

HRQoL *(Treatment Difference Over Time in QLC-C30 Global Health Status/Quality of Life Based on Mixed Model for Repeated Measures)*	Carfilzomib + Dexamethasone (ITT)	459	60.66	3.51	1.97-5.06	<0.0001	NR[c]	NR[c]	NR[c]	*HRQoL was measured by EORTC Quality of Life Questionnaire QLQ-C3. The least squares mean estimates and their difference were obtained from the analysis based on a linear mixed effects model, and the overall estimates were reported assuming that the treatment effect was the same across visits.*	Kyprolis EPAR; p. 54; table 17 and Ludwig, 2019; p.7; figure 2
	Bortezomib + Dexamethasone (ITT)	452	57.15								
Discontinuations due to TEAEs	Carfilzomib + Dexamethasone (ITT)	463	21.8% (101 patients)	-0.7%	-6.29%-4.76%	0.84	RR: 1.04	0.81-1.33	0.78	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-value were calculated using two sample z-test for proportions. Relative risk (RR), along with its*	Orlowski, 2019; p.523; figure 1
	Bortezomib + Dexamethasone (ITT)	456	21.1% (96 patients)								
	Carfilzomib + Dexamethasone (at least 2 prior treatments)	231	22.5% (52 patients)	0.6%	-7.60%-8.27%	1.00	RR: 0.97	0.70 - 1.36	0.87		Moreau, 2017; p.119; table 3

	Bortezomib + Dexamethasone (at least 2 prior treatments)	229	23.1% (53 patients)			*confidence interval and p value, were calculated using standard methods.*
Qualitative review of AEs	See narrative					
	[a] Results were reported as not evaluable in the reference [b] Results were not reported in the EPAR or the identified full publications [c] Results were not reported in the EPAR or the identified full publications and were not calculated as per DMC's protocol (section 5.4)					

7.6 Results per PICO -Clinical question #1

The table below addresses the PICO for the comparison of PomBorDex with DaraBorDex in the population of adult patients with multiple myeloma who have received at least one prior treatment, including lenalidomide.

Table 28 Clinical question #1 - Results per PICO

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Description of methods used for estimation
		Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Overall survival	OPTIMISMM (PVd versus Vd continuous), Imnovid EPAR CASTOR (DVd versus Vd fixed), Palumbo 2016	NA	NA	NA	HR(PVd vs Vd): 0.91 HR(DVd vs Vd): 0.77 HR(PVd vs DVd): 1.18	(0.70-1.18) (0.47-1.26) (0.68-2.06)	0.4755 0.30	*The HRs for the included studies were used to compare PVd versus DVd using an indirect comparison with the Bucher method. The Vd arm was considered as the common comparator even if the schedule was different. HRs for the ITT population were used for both studies. In the OPTIMISMM trial, the ITT population corresponded to the population of interest (clinical question 1) but in the CASTOR trial not all patients had been exposed to lenalidomide. The HR for the ITT population has been used as a proxy as it was the only HR available.*
Overall survival	OPTIMISMM (PVd versus Vd continuous), Imnovid EPAR	NA	NA	NA	HR(PVd vs Vd): 0.91 HR(DRd vs Rd): 0.64	(0.70-1.18) (0.40-1.01)	0.4755 0.0534	*HRs for the ITT population are presented for both studies. In the OPTIMISMM trial, the ITT population corresponded to the population of interest (clinical question 1) but in the*

	POLLUX (DRd versus Rd), Dimopoulos 2016						*POLLUX trial not all patients had been exposed to lenalidomide. The HR for the ITT population has been presented as a proxy as it was the only HR available.* *No indirect comparison between PVd and DRd was performed as no common comparator was available.*
Progression free survival	OPTIMISMM (PVd versus Vd continuous), Richardson 2019 CASTOR (DVd versus Vd fixed), Spencer 2018	NA	NA	NA	HR(PVd vs Vd): 0.61 HR(DVd vs Vd): 0.38 HR(PVd vs DVd): 1.61	(0.49-0.77) (0.26-0.56) (1.03-2.51)	<0.0001 NR	*The HRs for the included studies for the population of interest (clinical question 1) were used to compare PVd versus DVd using an indirect comparison with the Bucher method. The Vd arm was considered as the common comparator even if the schedule was different.*
Progression free survival	OPTIMISMM (PVd versus Vd continuous), Richardson 2019 POLLUX (DRd versus Rd), Dimopoulos 2018	NA	NA	NA	HR(PVd vs Vd): 0.61 HR(DRd vs Rd): 0.32	(0.49-0.77) (0.16-0.64)	<0.0001 0.0008	*No indirect comparison between PVd and DRd was performed as no common comparator was available.*
Discontinuations due to TEAEs	OPTIMISMM (PVd versus Vd	PVd vs Vd: -9.9%	-17.3%; -2.4%	0.009	RR(PVd vs Vd): 1.52 RR(DVd vs Vd): 1.06	(1.12-2.07) (0.62-1.81)	0.008 0.83	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-*

	continuous), Imnovid EPAR CASTOR (DVd versus Vd fixed), Spencer 2018	DVd vs Vd: -0.4% -6.47%; 5.20% 0.95	RR(PVD vs DVd): 1.44 (0.77-2.67)	*value were calculated using two sample z-test for proportions. Relative risk (RR), along with its confidence interval and p value, were calculated using standard methods. The RRs were used to compare PVd versus DVd using an indirect comparison with the Bucher method. The Vd arm was considered as the common comparator even if the schedule was different. RRs for the safety population were used for both studies. In the OPTIMISMM trial, the safety population included only patients of the population of interest (clinical question 1) but in the CASTOR trial not all patients had been exposed to lenalidomide. The RR for the safety population has been used as a proxy as it was the only result available.*
Discontinuations due to TEAEs	OPTIMISMM (PVd versus Vd continuous), Imnovid EPAR POLLUX (DRd versus Rd), Dimopoulos 2018	PVd vs Vd: -9.9% -17.3%; -2.4% 0.009 DRd vs Rd: 0.8% -4.9%; 6.6% 0.86	RR(PVd vs Vd): 1.52 (1.12-2.07) 0.008 RR(DRd vs Rd): 0.93 (0.60-1.45) 0.762	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-value were calculated using two sample z-test for proportions. Relative risk (RR), along with its confidence interval and p value, were calculated using standard methods.*

								RRs for the safety population are presented for both studies. In the OPTIMISMM trial, the safety population included only patients from the population of interest (clinical question 1) but in the POLLUX trial not all patients had been exposed to lenalidomide. The RR for the safety population has been presented as a proxy as it was the only result available. *No indirect comparison between PVd and DRd was performed as no common comparator was available.*
Quality of life	OPTIMISMM CASTOR POLLUX	NA	NA	NA	NR	NR	NR	*The relative treatment effect on quality of life was assessed inconsistently across trials, thereby making the indirect comparison impossible. Different questionnaires were used and different measure parameters were reported.*

7.7 Results per PICO -Clinical question #2

The table below addresses the PICO for the comparison of PomBorDex with DaraBorDex in the population Adult patients with multiple myeloma who have received at least one prior treatment and who are considered refractory to lenalidomide.

Table 29 Clinical question #2 - Results pr PICO

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Description of methods used for estimation
		Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Overall survival	OPTIMISMM (PVd versus Vd continuous), Imnovid EPAR CASTOR (DVd versus Vd fixed), Palumbo 2016	NA	NA	NA	HR(PVd vs Vd): 0.91 HR(DVd vs Vd): 0.77 HR(PVd vs DVd): 1.18	(0.70-1.18) (0.47-1.26) (0.68-2.06)	0.4755 0.30	*The HRs for the included studies were used to compare PVd versus DVd using an indirect comparison with the Bucher method. The Vd arm was considered as the common comparator even if the schedule was different. HRs for the ITT population were used for both studies. In both trials not all patients were refractory to lenalidomide. However, the HRs for the ITT population have been used as proxies as they were the only HRs available.*
Progression free survival	OPTIMISMM (PVd versus Vd continuous), Richardson 2019 CASTOR (DVd versus Vd fixed), Spencer 2018	NA	NA	NA	HR(PVd vs Vd): 0.65 HR(DVd vs Vd): 0.36 HR(PVd vs DVd): 1.81	(0.50-0.84) (0.21-0.63) (0.98-3.31)	0.0008 0.0002	*The HRs for the included studies for the population of interest (clinical question 2) were used to compare PVd versus DVd using an indirect comparison with the Bucher method. The Vd arm was considered as the common comparator even if the schedule was different.*

Discontinuations due to TEAEs	OPTIMISMM (PVd versus Vd continuous), Imnovid EPAR CASTOR (DVd versus Vd fixed), Spencer 2018	PVd vs Vd: -9.9% DVd vs Vd: -0.4%	-17.3%; -2.4% -6.47%; 5.20%	0.009 0.95	RR(PVd vs Vd): 1.52 RR(DVd vs Vd): 1.06 RR(PVD vs DVd): 1.44	(1.12-2.07) (0.62-1.81) (0.77-2.67)	0.008 0.83	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-value were calculated using two sample z-test for proportions. Relative risk (RR), along with its confidence interval and p value, were calculated using standard methods. The RRs were used to compare PVd versus DVd using an indirect comparison with the Bucher method. The Vd arm was considered as the common comparator even if the schedule was different. RRs for the safety population were used for both studies. . In both trials not all patients were refractory to lenalidomide. However, the HRs for the safety population have been used as proxies as they were the only HRs available.*
Quality of life	OPTIMISMM CASTOR	NA	NA	NA	NR	NR	NR	*The relative treatment effect on quality of life was assessed inconsistently across trials, thereby making the indirect comparison impossible. Different questionnaires were used and different measure parameters were reported.*

7.8 Results per PICO -Clinical question #3

The table below addresses the PICO for the comparison of PomBorDex with CarDex in adult patients with multiple myeloma who have received at least two previous treatments and who.

Table 30 Clinical question #3 - Results per PICO

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Description of methods used for estimation
		Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Overall survival	OPTIMISMM (PVd versus Vd), Richardson 2019 ENDEAVOR (Kd versus Vd), Orlowski 2019	NA	NA	NA	HR(PVd vs Vd): 0.91 HR(Kd vs Vd): 0.752 HR(PVd vs Kd): 1.21	(0.70-1.18) (0.589-0.959) (0.85-1.73)	0.4755 NR	*The HRs for the included studies were used to compare PVd versus Kd using an indirect comparison with the Bucher method. The HR for the ITT population was used as a proxy for the OPTIMISMM trial as it was the only HR available.*
Progression free survival (base case)	OPTIMISMM (PVd versus Vd), Richardson 2019 ENDEAVOR (Kd versus Vd), Moreau 2017	NA	NA	NA	HR(PVd vs Vd): 0.63 HR(Kd vs Vd): 0.604 HR(PVd vs Kd): 1.04	(0.48-0.83) (0.466-0.783) (0.72-1.52)	NA <0.0001	*The HRs for the included studies were used to compare PVd versus Kd using an indirect comparison with the Bucher method.*
Progression free survival (sensitivity analysis)	OPTIMISMM (PVd versus Vd), Richardson 2019 ENDEAVOR (Kd versus Vd), Moreau 2017	NA	NA	NA	HR(PVd vs Vd): 0.63 HR(Kd vs Vd): 0.73 HR(PVd vs Kd): 0.86	(0.48-0.83) (0.53-1.01) (0.57-1.32)	NA NR	*The HRs for the included studies were used to compare PVd versus Kd using an indirect comparison with the Bucher method. The HR from the ENDEAVOR estimated in the subgroup of patients with two or three previous lines and a prior lenalidomide exposure was used to have more comparable populations between the two studies.*

Discontinuations due to TEAEs	OPTIMISMM (PVd versus Vd), Richardson 2019 ENDEAVOR (Kd versus Vd), Moreau 2017	PVd vs Vd: -9.9% Kd vs Vd: -0.6%	-17.3%; -2.4% -7.60%; 8.27%	0.009 1.00	RR(PVd vs Vd): 1.52 RR(Kd vs Vd): 0.97 RR(PVD vs Kd): 1.57	(1.12-2.07) (0.70-1.36) (0.99-2.47)	0.008 0.87	*Absolute difference was calculated by subtraction of reported event rates and was presented as absolute risk reduction (ARR). The 95% CI and p-value were calculated using two sample z-test for proportions. Relative risk (RR), along with its confidence interval and p value, were calculated using standard methods. The RRs were used to compare PVd versus Kd using an indirect comparison with the Bucher method. RR for the safety population was used as a proxy for the OPTIMISMM trial as it was the only result available.*
Quality of life	OPTIMISMM ENDEAVOR	NA	NA	NA	NR	NR	NR	*The relative treatment effect on quality of life was assessed inconsistently across trials, thereby making the indirect comparison impossible. Different questionnaires were used and different measure parameters were reported.*

7.9 Treatment comparison – methodology

7.9.1 Network meta-analysis

Three PICO questions have been outlined by the DMC and were used to assess the feasibility of conducting a network meta-analysis (NMA) or indirect treatment comparisons (ITC). These questions are outlined in Table 31.

Table 31 Population, intervention, comparators, and outcomes (PICO) for each research question

Criteria	Description
Population	Research question 1: ▪ Adult patients with multiple myeloma who have received at least one prior treatment, including lenalidomide Research question 2: ▪ Adult patients with multiple myeloma who have received at least one prior treatment and who are considered refractory to lenalidomide Research question 3: ▪ Adult patients with multiple myeloma who have received at least two previous treatments and who have received either DRd or DVd
Interventions	▪ PVd dosed as follows: ▪ Pomalidomide 4 mg (recommended starting dose) p.o. on day 1-14 in repeated 21-day series for progression. ▪ During the first 8 cycles given bortezomib 1.3 mg/m2 i.v. or s.c. on days 1, 4, 8, and 11. From the series of 9 and above given bortezomib 1.3 mg/m2 s.c. on days 1 and 8. ▪ During the first 8 cycles dexamethasone 20 mg p.o. is administered on days 1, 2, 4, 5, 8, 9, 11 and 12. From cycle 9 and beyond dexamethasone 20 mg p.o. is administered on days 1, 2, 8, and 9.
Comparators	Research question 1: ▪ DRd dosed as follows in series of 28 days until progression: ▪ Daratumumab 16 mg/kg i.v. on days 1, 8, 15 and 22 in series 1-2, days 1 and 15 in series 3-6 and day 7 of series 7 ▪ Lenalidomide 25 mg p.o. on day 1-21 ▪ Dexamethasone 40 mg p.o. on days 1, 8, 16 and 22 ▪ DVd dosed as follows in series of 28 days until progression: ▪ Daratumumab 16 mg/kg i.v. on day 1, 8, 15 in series 1 -3, day 1 in series 4-9 and day 1 in series of 28 days from series 9 and until progression ▪ Bortezomib 1.3 mg/m2 s.c. on days 1, 4, 8 and 11 in series 1-9

	▪ Dexamethasone 20 mg p.o. on day 1, 2, 4, 5, 8, 9, 11, and 12 in series 1-9 Research question 2: ▪ DVd dosed as above Research question 3: ▪ Kd dosed as follows in series of 28 days until progression: ▪ Carfilzomib 20 mg/m2 i.v. on days 1 and 2 in series 1. 56 mg/m2 on days 8, 9, 15, and 16 in series 1. 56 mg/m2 on days 1, 2, 8, 9, 15, and 16 of series 2. ▪ Dexamethasone 20 mg p.o. on days 1, 2, 8, 9, 15, 16, 22 and 23.
Outcomes	▪ Overall survival (OS) ▪ Progression free survival (PFS) ▪ Treatment discontinuation due to adverse events ▪ Quality of Life

DRd: daratumumab in combination with lenalidomide and dexamethasone; DVd: daratumumab in combination with bortezomib and dexamethasone; PVd: pomalidomide in combination with bortezomib and dexamethasone; Kd: carfilzomib in combination with dexamethasone

Populations

The feasibility of conducting a NMA or an ITC for each endpoint was assessed in the populations corresponding to each research question of the DMC:

- Adults with MM who have received **at least one prior treatment, including lenalidomide**
- Adults with MM who have received **at least one prior treatment** and who are considered **refractory to lenalidomide**
- Adults with MM who have received **at least two previous treatments** and who have received either DRd or DVd (relaxing the criterion related to DRd or DVd if needed as recommended by the DMC)

Outcomes

The feasibility of conducting a NMA or an ITC was assessed for the following outcomes:

- Overall Survival
  - Time from randomisation or initiation of treatment to death, regardless of cause
- Progression free survival
  - Time from randomisation to progression or death, where progression is determined by the standardised response criterion
  - PFS is included as a surrogate goal for OS
- Treatment discontinuation due to AE
- Health-related quality of life
  - EORTC QLQ-C30
  - Other validated instruments (EQ-5D or other disease specific tools)

Heterogeneity assessment & treatment effect modifiers

Descriptive statistics were prepared to describe the main characteristics of the study populations at baseline (e.g. age, sex, cancer stage, prior exposure) and study designs (length of follow-up, definition of endpoints, etc.) of studies of interest for the research questions.

The following descriptive analyses were planned:

- Study characteristics
  - Study design
  - Follow-up period
  - Sample size
  - Duration of treatment
  - Regimen (dose, frequency, cycle length)
- Demographic characteristics
  - Age
  - Gender
  - Ethnicity
  - Age at diagnosis
- Medical characteristics
  - Disease stage
  - Performance status
  - Genetic expression profiles
  - Comorbidities
  - Prior treatment exposure
    - Prior lenalidomide exposure
    - Refractory to lenalidomide
    - Prior IMiD exposure
    - Refractory to IMiD
    - Line of therapy
  - Eastern Cooperative Oncology Group (ECOG) performance status
  - WHO performance status
  - Karnofsky performance status
  - ISS stage
  - B2M level
  - Lactate dehydrogenase level

However, only five of those baseline characteristics were consistently reported among included studies: age, gender, ECOG status, ISS stage and number of prior therapies.

These findings were used as a basis to identify potential sources of heterogeneity and more specifically to detect any potential outliers in the selected studies. Discussion with clinicians was organised to discuss and identify potential treatment confounders among study characteristics.

The analysis of treatment effect modifiers was conducted according to the ISPOR recommendations, whereby histograms are presented per treatment arm to identify potential imbalance between trials according to those characteristics.[i]

Robustness and consistency of the findings were investigated by comparing the results in the different populations.

Network connectivity

Network of evidence were drawn for each outcome. Studies not connected by any direct or indirect link to OPTIMISMM trial were excluded according to the NICE guidelines[ii].

Proportional hazard assumption investigation

In line with the National Institute for Health and Clinical Excellence Decision Support Unit Technical Support Document (NICE DSU TSD) per guidelines[iii], the assumption of proportional hazard assumption (PHA) was investigated for the two survival endpoints of interest: PFS and OS for all studies included in the network of evidence.

The PHA validity was investigated in each population of interest according to the steps below.

1. Publications identified in the SLR were screened for Kaplan Meier (KM) curves
2. The Guyot's algorithm[iv] was used to reconstruct individual patient level data (IPD) from identified Kaplan-Meier curves
3. The proportional hazard assumption was investigated based on
    a. The Grambsch and Therneau test
    b. The cumulative hazard plot and Schoenfeld residual plots

7.9.2 Statistical method

Network meta-analysis

Outcomes

For both survival outcomes (PFS and OS), the log hazard ratio (HR) vs. reference arm and its associated variance were used as inputs for the NMA. Log HRs were used instead of HRs since it is normally distributed. For a binary outcome (proportion of patients discontinuing due to AE), the log odds ratio (OR) vs. reference arm and its associated variance were used as inputs for the NMA. Log ORs were used instead of ORs since it is normally distributed.

Missing data

Hazard ratio

If HR and its 95% confidence interval were available but not the standard error of the log hazard ratio, the following formula was used to calculate the standard error (se) of the log-HR:[v]

$$se_{\log(HR)} = \frac{\log\left(HR_{UCI,\alpha}\right) - \log\left(HR_{LCI,\alpha}\right)}{2 * q\left(1 - \frac{\alpha}{2}\right)}$$

With:

- α: confidence level
- q: the quantile function of a normal distribution of mean 0 and variance 1

If HRs were not reported in a publication but the corresponding KM curves were available, the algorithm provided by Guyot (2012)[iv] was used to re-construct the IPD from digitised KM curves, alongside optional information such as number-at-risk at given time points and/or the total number of events, where available. More details on the approach are available in Appendix A: Guyot's algorithm. Once the IPD were reconstructed, a classic Cox model was applied to obtain an estimate of the HR and associated 95% confidence interval (CI) vs. the reference arm in the study.

In case no Kaplan-Meier curve was reported but the median survival times were reported per treatment arm, the HR was estimated assuming the distribution of event per treatment arm is an exponential distribution, using the following formula:

$$HR_{a\ vs\ b} = \frac{MS_a}{MS_b}$$

$$HR_{a\ vs\ b,LCI} = \frac{MS_{a,LCI}}{MS_{b,UCI}}$$

$$HR_{a\ vs\ b,UCI} = \frac{MS_{a,UCI}}{MS_{b,LCI}}$$

With:

- MS_a: Median survival of treatment a
- $MS_{a,LCI}$: Lower bound of the median survival of treatment a
- $MS_{a,UCI}$: Upper bound of the median survival of treatment a
- MS_b: Median survival of treatment b
- $MS_{b,LCI}$: Lower bound of the median survival of treatment b
- $MS_{b,UCI}$: Upper bound of the median survival of treatment b

In case of the HR, KM curves and median survival times were not reported but the number of events per treatment arm was reported, the risk ratio was calculated and used as a proxy for the HR. This estimate is valid if the hazards are proportional and the same length of follow-up is observed between treatment arms

$$HR_{a\ vs\ b} = \frac{e_a}{e_b}$$

$$se(\log(HR_{a\ vs\ b})) = \sqrt{\frac{1}{e_a} + \frac{1}{e_b} - (\frac{1}{n_a} + \frac{1}{n_b})}$$

With:

- e_a: number of events in arm a
- e_b: number of events in arm b
- n_a: number of patients in arm a
- n_b: number of patients in arm b

Relative risk

The relative risk can be calculated using the number of events reported per treatment arm

$$RR_{a\ vs\ b} = \frac{e_a/n_a}{e_b/n_b}$$

$$se(\log(RR_{a\ vs\ b})) = \sqrt{\left(\frac{1}{e_a}+\frac{1}{e_b}\right)-\left(\frac{1}{n_a}+\frac{1}{n_b}\right)}$$

With:

- e_a: number of events in arm a
- e_b: number of events in arm b
- n_a: number of patients in arm a
- n_b: number of patients in arm b

Indirect treatment comparison

Indirect treatment comparison were carried out using Bucher et al.[vi] The model aims to provide an estimation of the indirect treatment effect of a treatment A relatively to B when both are compared to the same treatment C. The model can be summarized through the following set of equation:

$$\log(\theta_{AB}) = \log(\theta_{AC}) - \log(\theta_{BC})$$

With:

$$\sigma^2_{AB} = \sigma^2_{AC} + \sigma^2_{BC}$$

And θ_{xy}: Hazard ratio or relative risk of x versus y

σ^2_{xy}: variance of the log hazard ratio or log relative risk of x versus y

7.9.3 Heterogeneity assessment

Vd arm design

A summary of the common reference arm (Vd) and standard of care has been provided in Table 32. The CASTOR trial presented a significant difference in the Vd arm design when compared to other included trials: ENDEAVOR and MM-07. Indeed, the Vd arm in the CASTOR trial had a fixed schedule, with a maximum medication time of 24 weeks, whereas the other included trials relied on continuous treatment over the trial duration. As a result, the comparators could not be pooled between CASTOR on the one hand and ENDEAVOR and OPTIMISMM on the other hand.

Table 32. Vd arm design

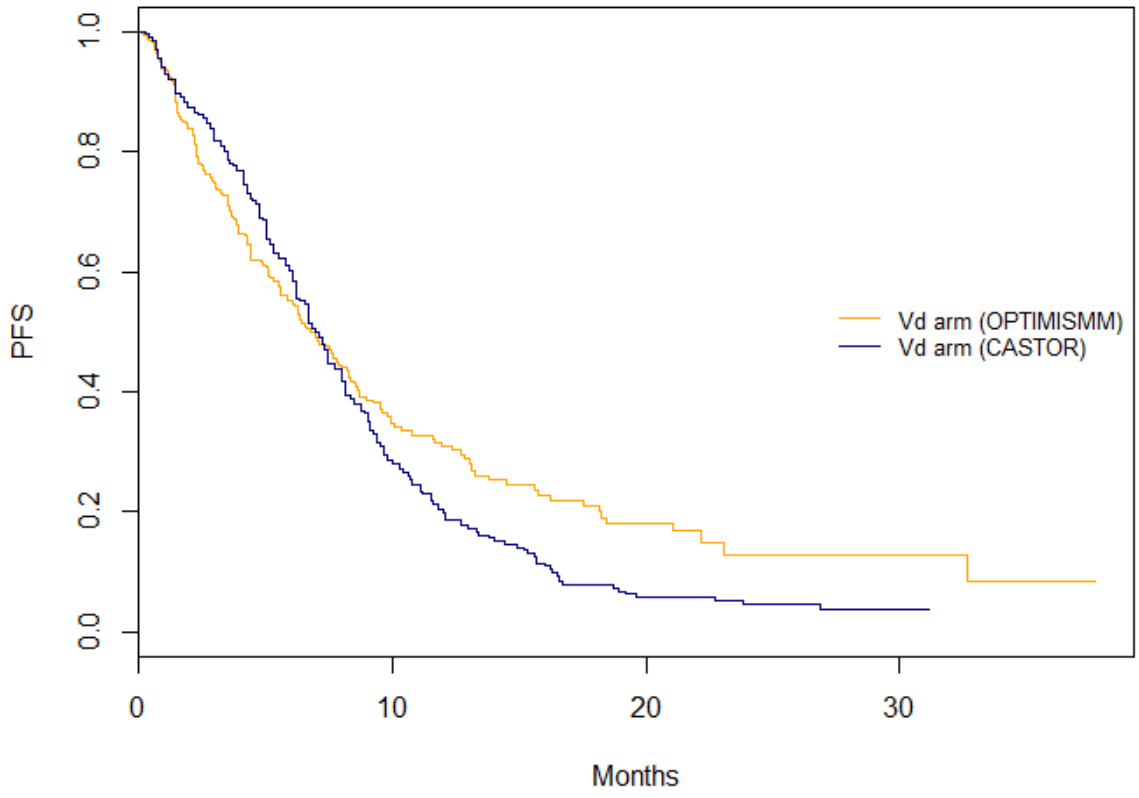
Study	**Bortezomib (Velcade) regimen**	**Dexamethasone regimen**
Orlowski, 2019 (ENDEAVOR)[vii]	Dose: 1.3mg/m² Route: IV or SC Schedule: Days 1, 4, 8, and 11 of a 21-day cycle	Dose: 20mg/d Route: Oral Schedule: Days 1, 2, 4, 5, 8, 9, 11, and 12

Richardson, 2019 (OPTIMISMM)[viii]	Dose: 1.3mg/m^2 Route: SC Schedule: Days 1, 4, 8 and 11 of 21 days for cycles 1 -8 and on Days 1, 8 of 21 days for cycle 9 and onward until disease progression	Dose: 20 mg/d Route: Oral Schedule: Days 1, 2, 4, 5, 8, 9, 11, 12 of 21 days for cycles 1-8 and on Days 1, 2, 8, 9 of 21 days for cycles 9 and onward until disease progression
Palumbo, 2016 (CASTOR)[ix]	Dose: 1.3mg/m2 Route: SC Schedule: Days 1, 4, 8, and 11 Number of cycle: 8 21-day cycles	Dose: 20mg/d Route: Oral or IV Schedule: Days 1-2, 4-5, 8-9, and 11-12

The impact of using a fixed dose of Vd can been seen on the Kaplan-Meier curves below, which present the time to PFS reported in the OPTIMISMM and CASTOR trials. Indeed, there is an acceleration in the rate of progression of disease in patients randomised to Vd in the CASTOR trial compared to OPTIMISMM, resulting in the two PFS curves crossing at approximately 7 months. Considering these two treatment regimen comparable would penalise PVd, given the fact that the comparator arm of OPTIMISMM (Vd continuous) is performing better than the comparator arm of CASTOR (Vd fixed).

Although not methodologically justified, a Bucher comparison was estimated as a scenario analysis to generate a hazard ratio comparing PVd to DVd.

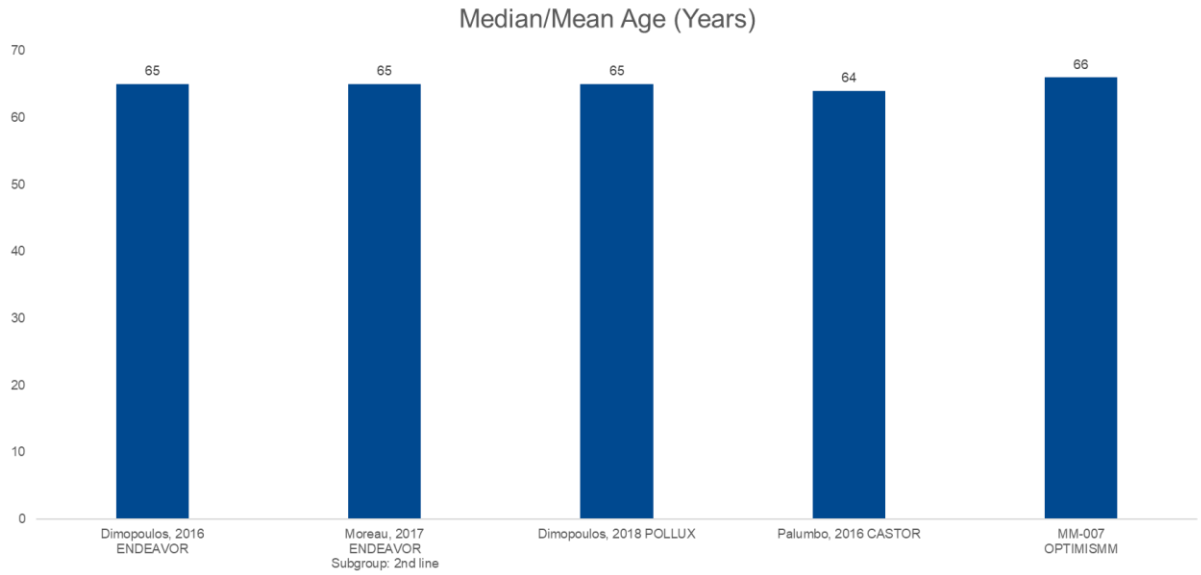
Figure 6 PFS KM curves of Vd in OPTIMISMM and CASTOR trials



Age

The median/mean age distribution was homogenous among included studies, ranging from 64 years to 66 years.

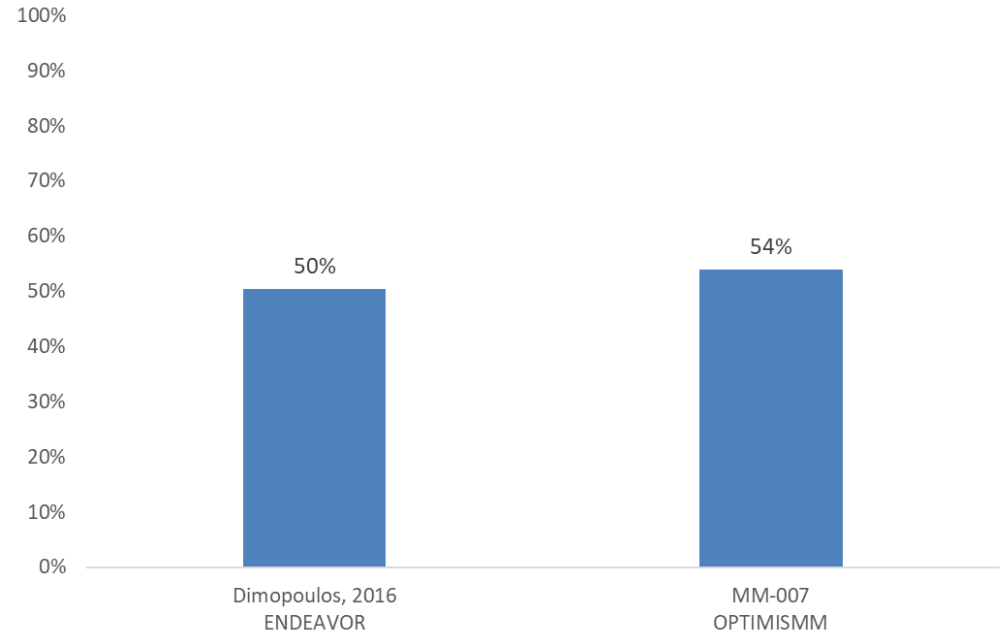
Figure 7 Heterogeneity assessment – Median/Mean Age (Years)



Sex

Two studies reported the distribution by sex. These studies included 50% and 54% of male patients. The distribution by sex was therefore considered consistent across trials.

Figure 8 Heterogeneity assessment – Sex (Proportion of Male %)



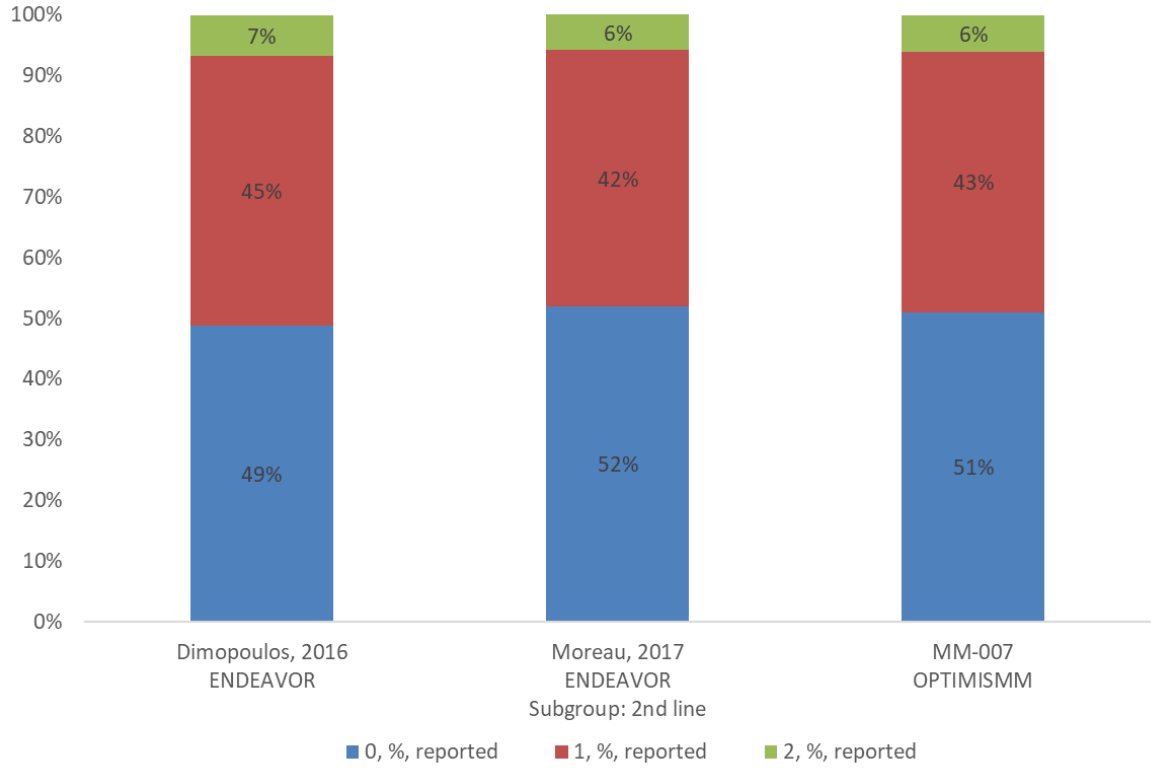
ECOG status

The ECOG performance status describes how the disease impacts a patient's daily living abilities. Grade 0 means the patients are able to carry on all pre-disease performance without restriction. Grade 1 relates to the patients who are restricted in physically intense activity but ambulatory and able to carry out work of a light or sedentary nature, such as office work or light house work. Grade 2 corresponds to patients, who are

capable of all self-care but unable to carry out any work activities. Grade 3 refers to patients, who are capable of only limited self-care and grade 4 to patients, who are completely disabled. Finally grade 5 corresponds to death.[x]

Three studies (two trials) reported ECOG grade at baseline. The proportion of study participants reporting an ECOG grade of 0 ranged from 49% to 52%, making it the most commonly reported ECOG grade. The second most frequent ECOG grade was grade 1 with a range from 42% to 45%, followed by ECOG grade 2 with 6% or 7% of study population. After review and discussion with clinical expert, no significant heterogeneity was found on ECOG status between included studies.

Figure 9 Heterogeneity assessment – ECOG status

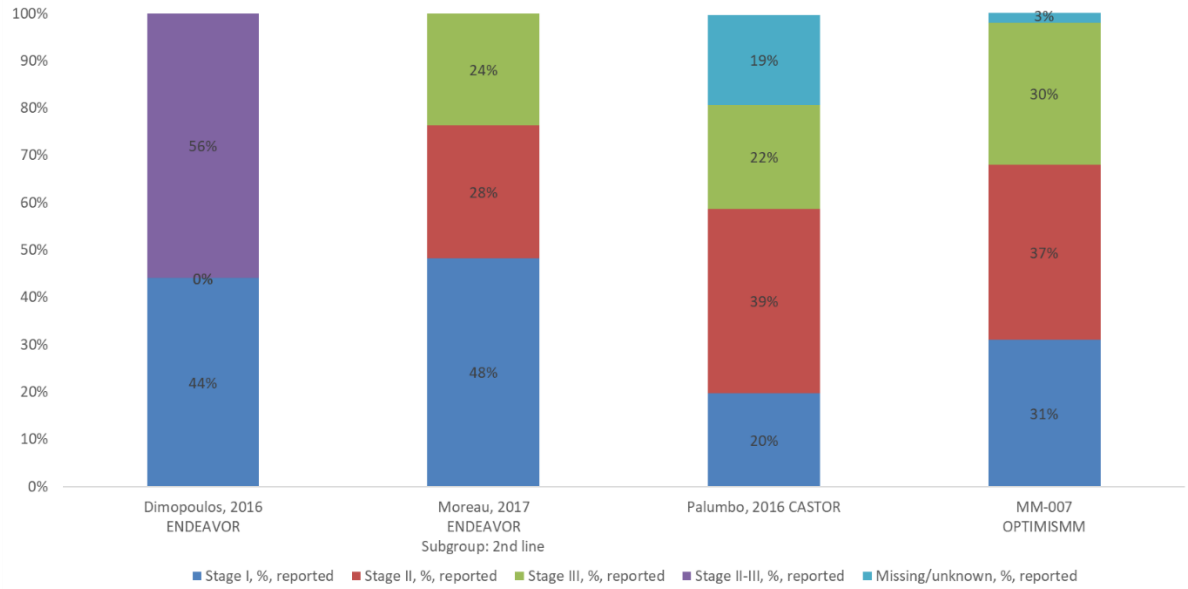


ISS stage

The ISS for multiple myeloma defines three prognostic subgroups with expected overall survival: stage 1 represents 62 months; stage 2 represents 44 months and stage 3 represents 29 months.[xi]

Four studies reported ISS stage at baseline. Proportion of study participants with ISS stage 1 ranged from 20% to 48% and with stage 2 from 28% to 39%. Upon review, significant heterogeneity was identified between included studies on ISS stage at baseline. However, due to the low number of studies included in the networks and the lack of set of studies comparing the same treatments, no adjustment could be made to tackle this issue.

Figure 10 Heterogeneity assessment – ISS stage

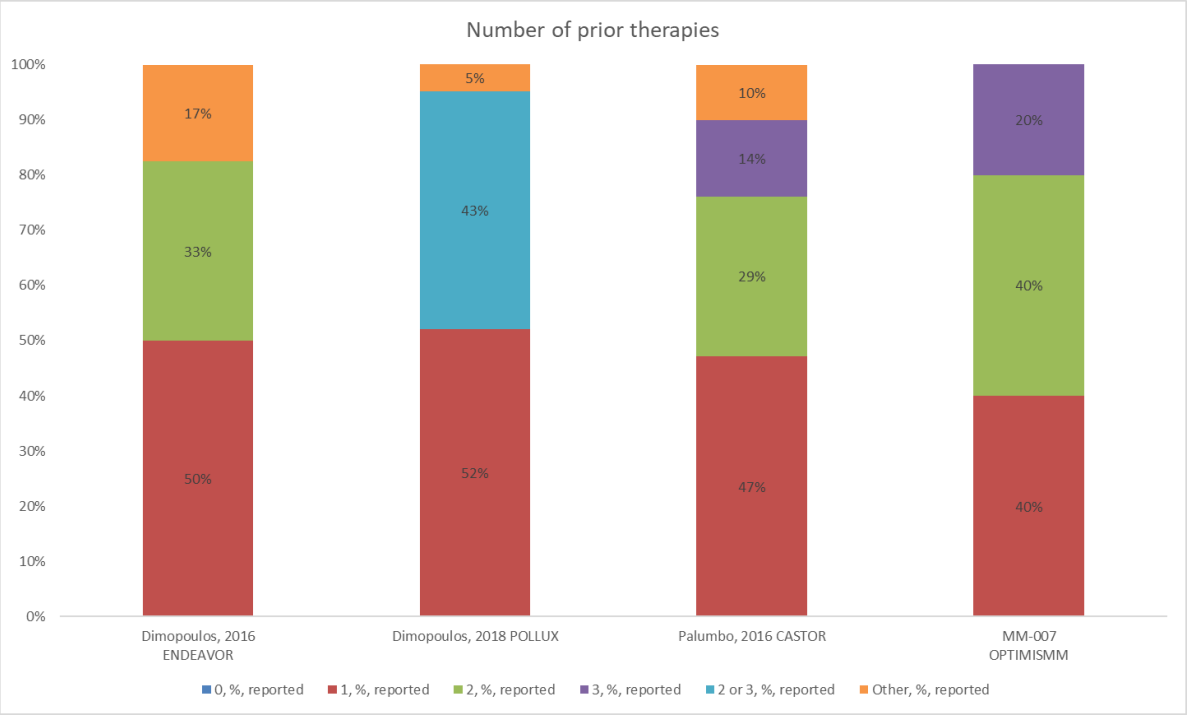


Number of prior therapies

Four studies reported the number of prior therapies received by patients enrolled in the selected clinical trials. The majority of study participants were receiving their second-line treatment (ranging from 40% to 50%). From 29% to 40% of patients had received two prior therapies and less than 24% reported at least three prior therapies. Given the differences between trials with regard to the number of prior treatment lines, additional analyses on second line only populations were carried out.

OPTIMISMM involved patients more heavily pre-treated as it was associated with the lowest proportion of patients who had received only one prior therapy (40%) and the highest proportion of patients who had received three therapies (20%).

Figure 11 Heterogeneity assessment – Number of prior therapies



PFS definition

PFS definitions among trials are summarized in Table 33 below. The ENDEAVOR, OPTIMISMM and CASTOR trials used the same definition and set of rules to define PFS (IMWG-URC IRAC).

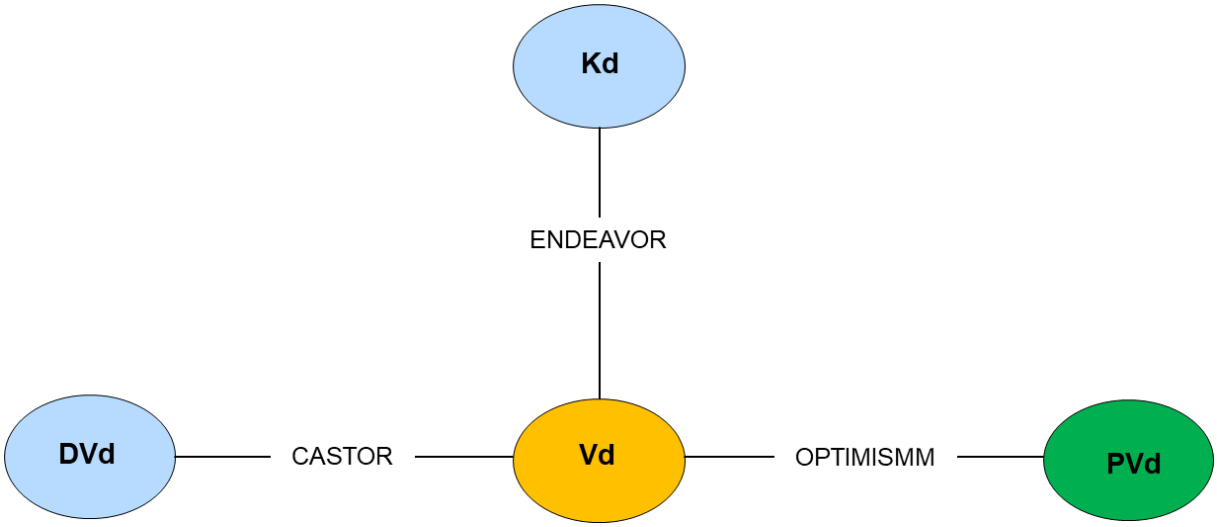
Table 33 Summary of PFS definition

Trial name	**Treatment arm**	**PFS Definition**
ENDEAVOR	Kd, Vd	PFS was evaluated in accordance to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) as assessed by an Independent Review Committee (IRC).
OPTIMISMM	PVd, Vd	PFS was evaluated in accordance to the IMWG-URC as assessed by IRAC
CASTOR	DVd, Vd	PFS was evaluated in accordance to the International Myeloma Working Group (IMWG) guidelines

7.9.4 Proportional hazard assumption (PHA) validity check

Based on the results of the SLR, the following network of evidence was constructed and is presented in Figure 12. In total three therapies were connected (Kd, PVd and Vd) through the OPTIMISMM and ENDEAVOR trials. As mentioned earlier, the Vd arms of the CASTOR and OPTIMISMM trials were not comparable due to the treatment duration, however a sensitivity analysis based on the Bucher method was conducted to generate a hazard ratio comparing PVd to DVd despite the major limitation of the analysis.

Figure 12. Overall network of evidence



Therefore the PHA was tested in the OPTIMISMM, ENDEAVOR and CASTOR trials.

Based on data availability, the assumption was tested for OPTIMISMM and CASTOR for PFS and for the three trials (OPTIMISMM, ENDEAVOR and CASTOR) for OS. Upon generation of the Grambsch and Therneau tests and qualitative assessment of the plots, no study was identified as violating the PHA hypothesis (Appendix C).

7.9.5 Appendix A: Guyot's algorithm

If HRs are not reported in a publication but the corresponding KM curves are available, the algorithm described by Guyot (2012)[iv] will be used to re-construct the individual level patient data (IPD) from digitised KM curves, alongside optional information such as number-at-risk at given time and/or the total number of events.

The algorithm assumes a uniform distribution of censoring cases per time interval identified by number-at-risk time points. When both number at risk table and the total number of events are available, the algorithm estimates the number of censored cases and the number of events at each time interval (excluding the last) using the following steps:

1. Derive the number at risk at the end of the time interval using KM survival formula, while assuming no censoring. The difference between this number and the reported number at risk is the first estimate of the number of cases censored which is then assumed distributed evenly within the current time interval
2. Estimate the number of events that occurs at every "step" of the digitised KM curve within the current time interval and update the number at risk for this interval to equal to the sum of number of censored events
3. Compare the updated number at risk to the reported value. If they are not the same, adjust the number of censored (i.e. second part of step 1) and repeat step 2 and 3 until the estimated value matches the reported value

For the last time interval, an initial estimate of the number of censored is calculated as the total number of estimated censoring that happened in all previous time intervals weighted by the relative time in the last time interval. Step 2 is performed to estimate the total number of events, which is then compared with the

reported value. An underestimation (i.e. estimated value < reported value) will lead to adjustment of the censoring and events within this interval similar to step 3.

In the case where only the total number of events per treatment is available (i.e. the number-at-risk table is missing), a single time interval is assumed and treated as the last time interval.

In the case where only the number-at-risk table is available (i.e. the total number of events per treatment arm is missing), the estimated total number of events cannot be verified and the first estimated values will be used.

In the case where both the number-at-risk table and the total number of events per treatment arm are missing, the algorithm assumes no censoring (i.e. the first part of step 1) and a single time interval will be used.

As a final step, IPD are reconstructed based on the estimated censoring and event distributions over time.

7.9.6 Appendix B: Proportional Hazard Assumption validation

Publications and conference presentations related to the trials identified as part of the systematic literature review (i.e. ENDEAVOR, CASTOR and ENDEAVOR) were screened to retrieve Kaplan-Meier curves for PFS and OS outcomes. For OPTIMISMM, the individual patient level data from the trial were directly analysed. Given the absence of common comparator for POLLUX, the PHA was not tested.

Table 34 PHA validity check - PFS - KM curves availability

Trials	**Publications**	**ITT**	**Adult patients with MM who were lenalidomide exposed**	**Adult patients with MM who are refractory to lenalidomide**
ENDEAVOR	Moreau, 2017[xii]			
	Dimopoulos, 2017[xiii]			
CASTOR	Spencer, 2018[xiv]			
	Mateos, 2018[xv]	✓		
	Lentzsch, 2017[xvi]			
	Usmani, 2018[xvii]			
OPTIMISMM		✓	✓	✓

Note: a check sign indicates availability of KM curves in the population

Table 35 PHA validity check - OS - KM curves availability

Trials	**Publications**	**ITT**
ENDEAVOR	Moreau, 2017	
	Dimopoulos, 2017	✓
CASTOR	Spencer, 2018	
	Mateos, 2018	

	Lentzsch, 2017	✓
	Usmani, 2018	
OPTIMISMM		✓

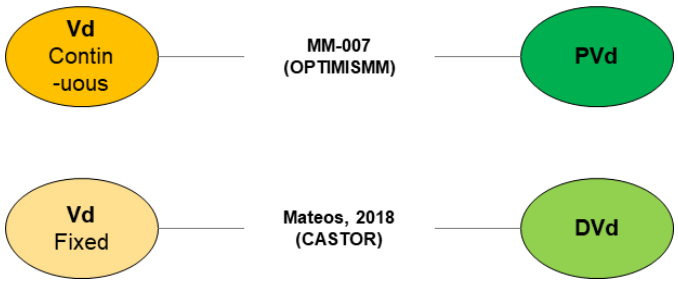
Note: a check sign indicates availability of KM curves in the population

PFS

The investigation of the validity of the PHA for the PFS outcome was carried out on the ITT population as per availability.

The network displaying the source of the Kaplan-Meier curves and the included comparators is available in the figure**Error! Reference source not found.** below.

Figure 13 Availability of KM curves in the ITT population - PFS



Once individual patient level data were generated based on the Guyot algorithm[iv] for the CASTOR trial, the Grambsch and Therneau test was carried out to test the PHA. All p-values exceeded 0.10 and the PHA was therefore not rejected for any of the trials.

No Kaplan Meier curve was available from ENDEAVOR and the assumption could therefore not be tested.

Table 36 Summary of Grambsch and Therneau test for the PFS

Study	**Treatment vs. Vd**	**P-value**
MM-07	PVd	0.58
CASTOR	DVd	0.10

In addition, the cumulative log hazard graphs and Schoenfeld residuals have been plotted per study and are displayed below.

Figure 14 Mateos, 2018 - DVd & Vd – PFS Cumulative log hazard & Schoenfeld residual plots

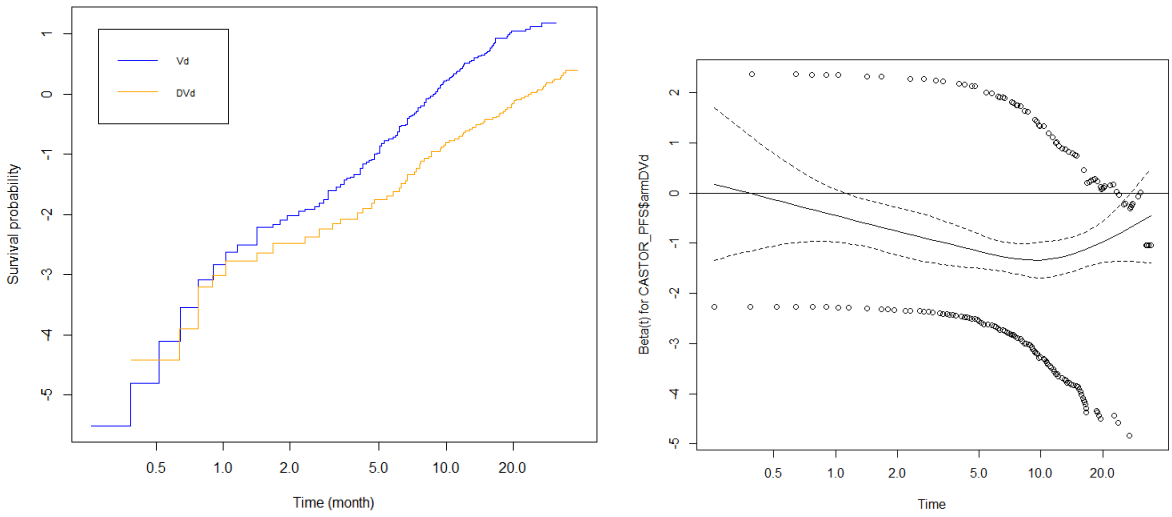
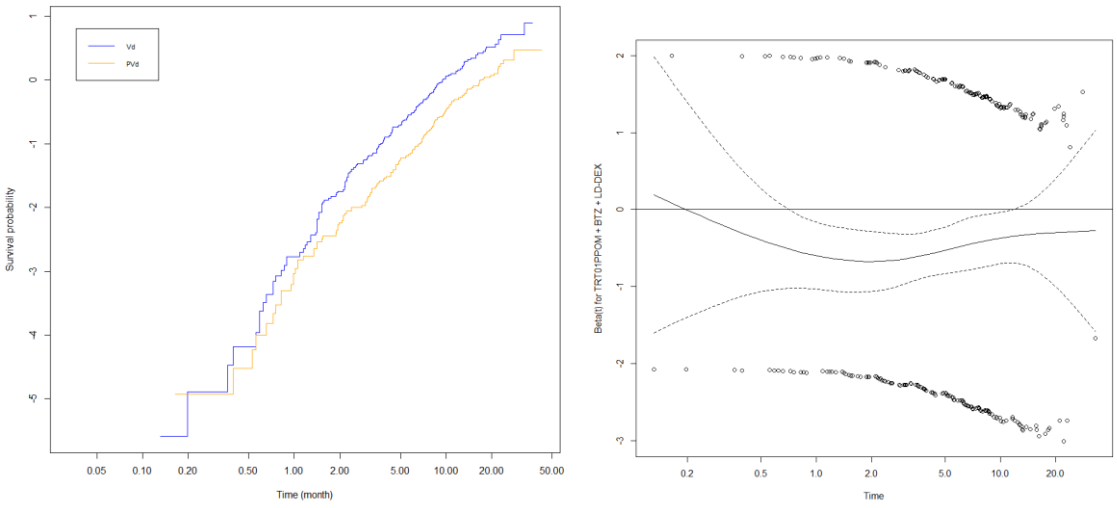


Figure 15 MM-07 2018 - PVd & Vd – PFS Cumulative log hazard & Schoenfeld residual plots



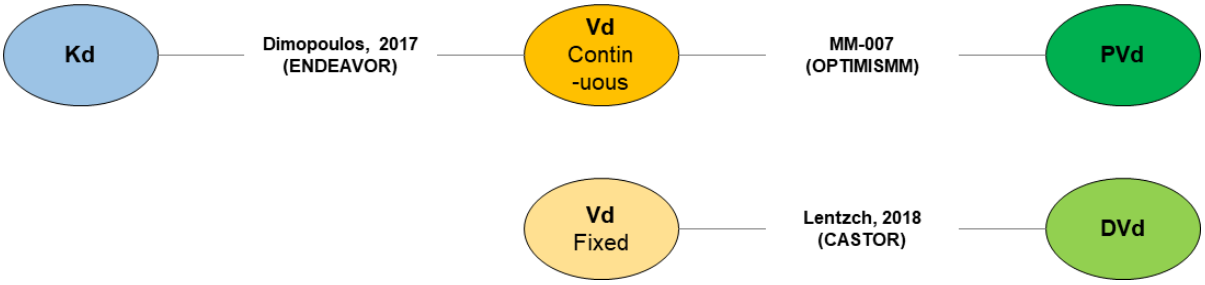
Upon qualitative assessment the plots, no study was identified as violating the PHA hypothesis.

OS

The investigation of the validity of the PHA for the OS outcome was carried out on the ITT population.

The networks displaying the source of the Kaplan-Meier curves and the included comparators is available in the figure below.

Figure 16 Availability of KM curves in the ITT population - OS



As for PFS, the Grambsch and Therneau tests were carried out to identify significant PHA violation. None of the included studies had significant p-value and the PHA was therefore not rejected.

Table 37 Summary of Grambsch and Therneau test

Study	Treatment vs. Vd	P-value
Dimopoulos, 2017 (ENDEAVOR)	Kd	0.62
MM-07	PVd	0.89
Lentzch, 2017 (CASTOR)	DVd	0.66

In addition, the cumulative log hazard graphs and Schoenfeld residuals have been plotted per study and are displayed below.

Figure 17 Dimopoulos 2017 - Kd & Vd – OS Cumulative log hazard & Schoenfeld residuals plots

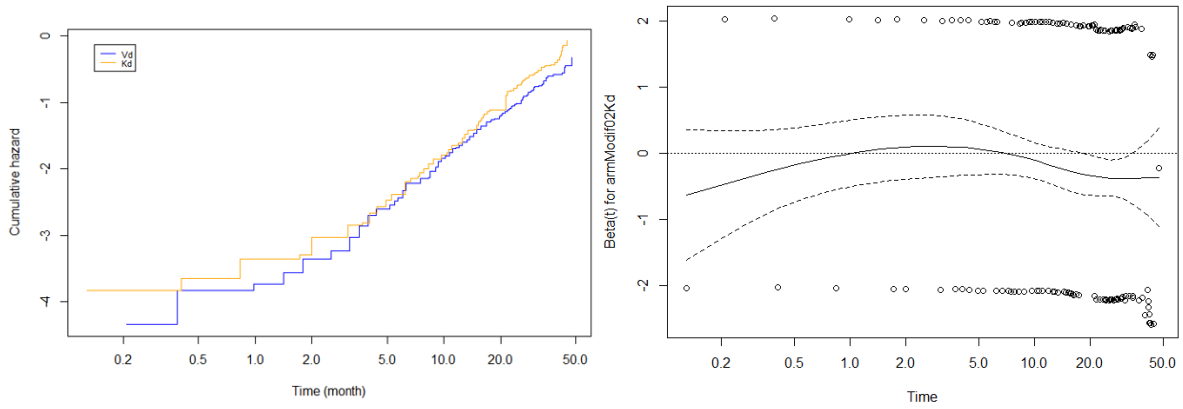


Figure 18 MM-07 2018 - PVd & Vd – OS Cumulative log hazard & Schoenfeld residuals plots

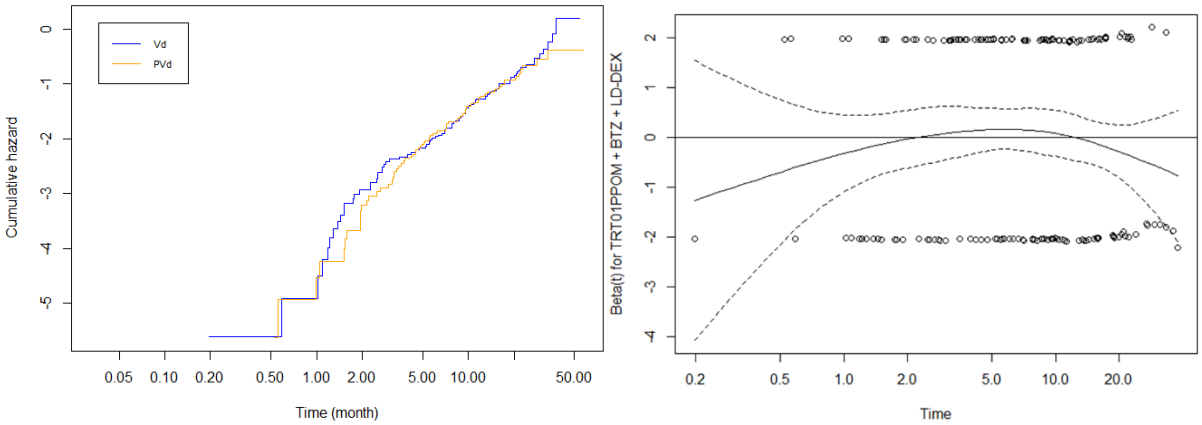
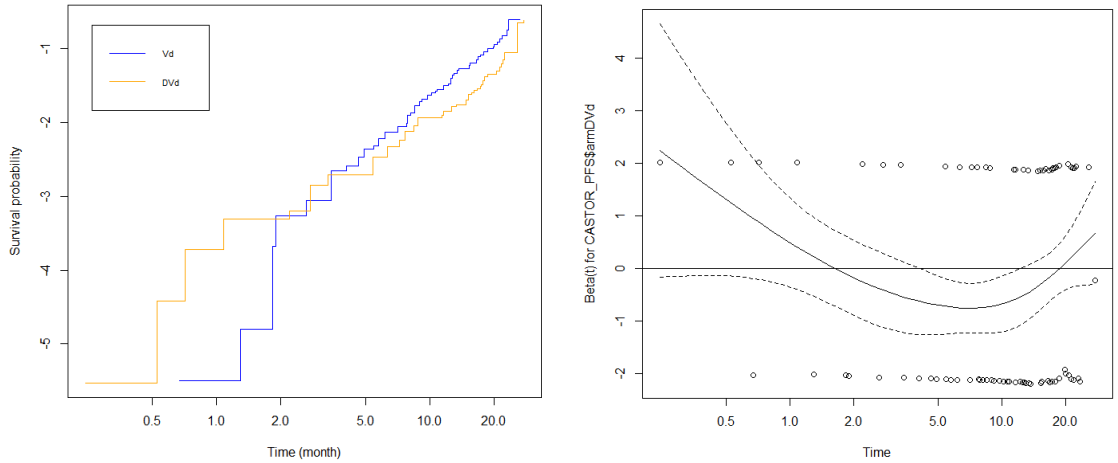


Figure 19 Lentzsch 2017 – DVd & Vd – OS Cumulative log hazard & Schoenfeld residuals plots



Upon qualitative assessment of the plots, no study was identified as violating the PHA hypothesis.

- 0 -

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[viii] Richardson PG, Oriol A, Beksac M, Liberati AM, Galli M, Schjesvold F, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2019;20(6):781-94.

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[x] ECOG Performance Status ECOG-ACRIN cancer reseach group2018 [Available from: https://ecog-acrin.org/resources/ecog-performance-status.]

[xi] Multiple Myeloma Internaltional Staging System (ISS) MD+CALC [Available from: https://www.mdcalc.com/multiple-myeloma-international-staging-system-iss.]

[xii] Moreau P, Joshua D, Chng W, Palumbo A, Goldschmidt H, Hájek R, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia. 2017;31(1):115.

[xiii] Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, Chng W-J, Oriol A, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. The Lancet Oncology. 2017;18(10):1327-37.

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Medicinrådet

Medicinrådets protokol for vurdering af pomalidomid i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft der har modtaget mindst én tidligere behandling

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	46991
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	Imnovid®
Generisk navn	Pomalidomid
Firma	Celgene A/S
ATC-kode	L04AX06
Virkningsmekanisme	Pomalidomid 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	• Pomalidomid 4 mg (anbefalet startdosis) p.o. på dag 1-14 i gentagne 21-dages serier til progression. • I de første 8 serier gives bortezomib 1,3 mg/m^2 i.v. eller s.c. på dag 1, 4, 8 og 11. Fra serie 9 og frem gives bortezomib 1,3 mg/m^2 s.c. på dag 1 og 8. • I de første 8 serier gives dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 9, 11 og 12. Fra serie 9 og frem gives dexamethason 20 mg p.o. på dag 1, 2, 8, og 9.
Forventet EMA-indikation	Pomalidomid i kombination med bortezomib og dexamethason til voksne patienter med knoglemarvskræft som har modtaget mindst én tidligere behandling inklusive lenalidomid.

2 Forkortelser

CarDex:	Carfilzomib + dexamethason
CI:	Konfidensinterval
DaraBorDex:	Daratumumab + bortezomib + dexamethason
DaraLenDex:	Daratumumab + lenalidomid + dexamethason
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
PomBorDex:	Pomalidomid i kombination med bortezomib og dexamethason
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 pomalidomid i kombination med bortezomib og dexamethason (PomBorDex) som mulig standardbehandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling. I protokollen angives en definition af de 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 PomBorDex modtaget den 10. februar 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af PomBorDex sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal analyseres med en sammenlignende analyse mellem PomBorDex og komparator af både absolutte og relative værdier for de specificerede populationer i de angivne måleenheder (se tabel 1). 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. 320 patienter om året vil skulle modtage deres første relapsbehandling [2].

Prognosen er afhængig af patientens alder og komorbiditeter ved diagnosetidspunktet. De patienter, der som primærbehandling behandles med højdosiskemoterapi med stamcellestøtte (HDT/STS), har en væsentlig bedre prognose end de, der ikke er egnede 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 [2]. Denne gruppe omfatter især patienter over 70 år og inkluderer de ældste patienter. 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.

4.1 Nuværende behandling

Behandling af knoglemarvskræft varetages af de hæmatologiske afdelinger og består udover HDT/STS af medicinsk behandling med flere lægemidler i kombination. Ved at kombinere flere lægemidler angribes kræftcellerne 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.

Til patienter, der skal have deres første relapsbehandling, og som ikke er refraktære overfor lenalidomid (ca. 270 patienter årligt), anbefales ifølge DMSG's retningslinje en kombination af daratumumab, lenalidomid og dexamethason (DaraLenDex). Til patienter, der er refraktære overfor lenalidomid (ca. 50 patienter årligt), anbefales en kombination af daratumumab, bortezomib og dexamethason (DaraBorDex) [1].

Behandlingsvalget foretages i samråd mellem læge og patient under hensyntagen til effekt af tidligere behandling, bivirkninger til tidligere behandlinger, performancestatus, komorbiditet og patientpræferencer, herunder antallet af behandlingsfremmøder. Der tages også hensyn til eventuel refraktæritet overfor lægemidler der har indgået i tidligere behandlinger og særligt lenalidomid, da det oftest anvendes indtil progression.

Patienter, der er behandlet med DaraLenDex eller DaraBorDex, som igen bliver behandlingskrævende, behandles hovedsageligt med en kombination af carfilzomib og dexamethason (CarDex) [1]. De patienter, der tidligere er behandlet med carfilzomib, vil ikke igen være kandidater til en bortezomibholdig behandlingskombination, fordi carfilzomib er den mest potente af proteasominhibitorerne og anvendes til progression. Derfor vurderer fagudvalget, at PomBorDex (den ansøgte intervention) ikke kan være en standardbehandlingsmulighed i senere linjer.

4.2 Pomalidomid i kombination med bortezomib og dexamethason

Pomalidomid er ikke et nyt lægemiddel. Det er godkendt i kombination med dexamethason til behandling af patienter der har modtaget mindst to tidligere behandlinger, dvs. senere i behandlingsforløbet end den ansøgte indikation.

Pomalidomid 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.

PomBorDex skal doseres som følger:

- Pomalidomid 4 mg (anbefalet startdosis) p.o. på dag 1-14 i gentagne 21-dages serier til progression.
- I de første 8 serier gives bortezomib 1,3 mg/m^2 i.v. eller s.c. på dag 1, 4, 8 og 11. Fra serie 9 og frem gives bortezomib 1,3 mg/m^2 s.c. på dag 1 og 8.
- I de første 8 serier gives dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11 og 12. Fra serie 9 og frem gives dexamethason 20 mg p.o. på dag 1, 2, 8, og 9.

5 Kliniske spørgsmål

De kliniske spørgsmål fagudvalget ønsker at besvare i vurderingen af den kliniske merværdi for pomalidomid 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 1

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med nuværende klinisk praksis til behandling af patienter med knoglemarvskræft, som har modtaget mindst én tidligere behandling, inklusive lenalidomid?

Population
Voksne patienter med knoglemarvskræft, som har modtaget mindst en tidligere behandling, inklusive lenalidomid.

Intervention
Pomalidomid i kombination med bortezomib og dexamethason.

Komparator

DaraLenDex doseret som følger i serier af 28 dage indtil progression:

- Daratumumab 16 mg/kg i.v. på dag 1, 8, 15 og 22 i serie 1-2, dag 1 og 15 i serie 3-6 og dag 1 fra serie 7
- Lenalidomid 25 mg p.o. på dag 1-21
- Dexamethason 40 mg p.o. på dag 1, 8, 16 og 22

DaraBorDex doseret som følger i serier af 21 dage

- Daratumumab 16 mg/kg i.v. på dag 1, 8, 15 i serie 1-3, dag 1 i serie 4-9 og dag 1 i serier af 28 dage fra serie 9 og frem til progression
- Bortezomib 1,3 mg/m^2 s.c. på dag 1, 4, 8 og 11 i serie 1-9
- Dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11, og 12 i serie 1-9

Effektmål
De effektmål, fagudvalget ønsker at vurdere, fremgår af tabel 1.

5.2 Klinisk spørgsmål 2

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med daratumumab i kombination med bortezomib og dexamethason til behandling af patienter med knoglemarvskræft, som er refraktære overfor lenalidomid, og som har modtaget mindst én tidligere behandling?

Population
Voksne patienter med knoglemarvskræft, som har modtaget mindst en tidligere behandling og som vurderes at være refraktære overfor lenalidomid.

Intervention
Pomalidomid i kombination med bortezomib og dexamethason.

Komparator
Fagudvalget definerer følgende komparatorer:

DaraBorDex doseret som følger i serier af 21 dage

- Daratumumab 16 mg/kg i.v. på dag 1, 8, 15 i serie 1-3, dag 1 i serie 4-9 og dag 1 i serier af 28 dage fra serie 9 og frem til progression
- Bortezomib 1,3 mg/m^2 s.c. på dag 1, 4, 8 og 11 i serie 1-9
- Dexamethason 20 mg p.o. på dag 1, 2, 4, 5, 8, 9, 11, og 12 i serie 1-9

Effektmål
De effektmål, fagudvalget ønsker at vurdere, fremgår af tabel 1.

5.3 Klinisk spørgsmål 3

Hvad er værdien af pomalidomid i kombination med bortezomib og dexamethason sammenlignet med CarDex til patienter, som har modtaget mindst to tidligere behandlinger?

Population
Voksne patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger, og som har modtaget enten DaraLenDex eller DaraBorDex.

Intervention
Pomalidomid i kombination med bortezomib og dexamethason.

Komparator
Fagudvalget definerer følgende komparatorer:

CarDex doseret som følger i serier af 28 dage indtil progression

- Carfilzomib 20 mg/m^2 i.v. på dag 1 og 2 i serie 1. 56 mg/m^2 på dag 8, 9, 15, og 16 i serie 1. 56 mg/m^2 på dag 1, 2, 8, 9, 15, og 16 fra serie 2.
- Dexamethason 20 mg p.o. på dag 1, 2, 8, 9, 15, 16, 22 og 23.

Effektmål
De effektmål, fagudvalget ønsker at vurdere, fremgår af tabel 1.

5.4 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og kategori. 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. Oversigt over de valgte effektmål. For hvert effektmål er angivet deres vigtighed og 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.	-
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger**	Median PFS	3 mdr.	-
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 points ændring 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 kategorien *Livskvalitet, alvorlige symptomer og bivirkninger*.

5.4.1 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. Den mediane overlevelse, baseret på studiedata, er med de nuværende behandlingsmuligheder ca. 4 år [4–6]. Fagudvalget har vurderet, at den mindste klinisk relevante forskel i median overlevelse mellem intervention og komparator er 3 måneder.

Fagudvalget ønsker at medtage PFS som et surrogatmål for samlet overlevelse, såfremt data for overlevelse ikke er modne for samtlige sammenligninger mellem intervention og komparatorer. Fagudvalget vurderer, at PFS som surrogat for overlevelse er et vigtigt effektmål. For patienter, der har modtaget mindst en tidligere behandling, er den mediane PFS ca. 18 måneder, baseret på studiedata [4–9]. Fagudvalget vurderer, at mindste klinisk relevante forskel i PFS er 3 måneder.

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. De behandlinger, der i dag anvendes til behandling af patienter, der tidligere har modtaget mindst én behandling, er bivirkningstunge, og 10-15 % ophører behandlingen pga. uønskede hændelser, baseret på studiedata [4,8,9]. 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.

5.4.2 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 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 pomalidomid i kombination med bortezomib og dexamethason er sammenlignet direkte med de valgte komparatorer.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af pomalidomid i kombination med bortezomib og dexamethason og de valgte komparatorer

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af pomalidomid i kombination med bortezomib og dexamethason og komparatorerne. Det betyder, at der både skal søges efter primærstudier af effekten af pomalidomid i kombination med bortezomib og dexamethason og efter primærstudier af effekten af komparatorerne. 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 et relevant effektmål. Studier, som 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), nyrefunktion samt antal og type af tidligere behandlinger, herunder hvor mange patienter der har modtaget HDT/STS.

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**
Asta Svirskaite Overlæge	Region Nordjylland
Anja Klostergaard Afdelingslæge	Region Midtjylland
Per Trøllund Specialeansvarlig overlæge	Region Syddanmark
Carsten Helleberg Overlæge	Region Hovedstaden
Lisbeth Egeskov Patient/patientrepræsentant	Danske Patienter
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	"pomalidomide"[nm]	
5	pomalidomide*[tiab] OR cc4047*[tiab] OR cc-4047*[tiab] OR imnovid*[tiab] OR pomalyst*[tiab] OR actimid*[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	“lenalidomide”[Mesh]	
15	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]	
16	#14 OR #15	
17	“daratumumab”[nm]	
18	daratumumab*[tiab] OR darzalex*[tiab] OR “humax cd38”[tiab]	
19	#17 OR #18	
20	"carfilzomib" [nm]	
21	carfilzomib*[tiab] or kyprolis*[tiab] or pr-171*[tiab]	
22	#20 OR #21	
23	#19 AND #16 AND #12	Komparator Klinisk spg. 1
24	#19 AND #9 AND #12	Komparator Klinisk spg. 2
25	#22 AND #12	Komparator Klinisk spg. 3
26	#23 OR #24 OR #25	Alle komparatorer
27	#13 OR #26	Intervention **eller** Komparatorer
28	#3 AND #27	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	(pomalidomid* or cc4047* or cc-4047* or imnovid* or pomalyst* or actimid*):ti,ab,kw	
5	[mh Bortezomib]	
6	(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	
7	{or #5-#6}	
8	[mh Dexamethasone]	
9	(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	
10	{or #8-#9}	
11	#4 and #7 and #10	Intervention
12	[mh Lenalidomide]	
13	(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	
14	{or #12-#13}	
15	(daratumumab* or darzalex* or "humax cd38"):ti,ab,kw	
16	(carfilzomib* or kyprolis* or pr-171):ti,ab,kw	
17	#15 and #14 and #10	Komparator spg. 1
18	#15 and #7 and #10	Komparator spg. 2
19	#16 and #10	Komparator spg. 3
20	#17 OR #18 OR #19	Alle komparatorer
21	#11 OR #20	Intervention **eller** Komparatorer
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.