Medicinrådet

Baggrund for Medicinrådets anbefaling af elotuzumab i kombination med pomalidomid og dexamethason til behandling af patienter med knoglemarvskræft der tidligere har modtaget mindst to behandlinger

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om Baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

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

Indhold

1 Anbefaling vedrørende elotuzumab i kombination med pomalidomid og dexamethason til behandling af patienter med knoglemarvskræft der tidligere har modtaget mindst to behandlinger

Medicinrådet anbefaler ikke elotuzumab i kombination med pomalidomid og dexamethason (EloPomDex) som mulig standardbehandling til patienter med knoglemarvskræft, der tidligere har modtaget mindst to behandlinger.

Medicinrådet anbefaler ikke EloPomDex, fordi sundhedsvæsenets omkostninger til lægemidlet vil være urimeligt høje i forhold til de behandlinger, man anvender i dag; også selvom lægemidlet sandsynligvis er bedre end en af de behandlinger, man anvender i dag og ikke er dårligere end de øvrige.

2 Værdi for patienterne

Medicinrådet vurderer, at EloPomDex har en **merværdi af ukendt størrelse** sammenlignet med PomDex. Evidensens kvalitet vurderes at være meget lav.

Den samlede værdi **kan ikke kategoriseres**, jf. Medcinrådets metoder sammenlignet med PomBorDex. Medicinrådet vurderer, at EloPomDex ikke er et dårligere behandlingsalternativ end PomBorDex, hvad angår effekt. Bivirkningsprofilen er muligvis lettere.

Den samlede værdi **kan ikke kategoriseres**, jf. Medicinrådets metoder, sammenlignet med CarDex. Medicinrådet vurderer, at EloPomDex ikke er dårligere end CarDex, hvad angår effekt og bivirkninger.

Ansøger har ikke indsendt et høringssvar.

Læs mere i Medicinrådets vurdering af klinisk værdi og den bagvedliggende protokol (bilag).

3 Omkostninger for sundhedsvæsenet

Lægemiddelfirmaet har givet en fortrolig rabat, så den reelle pris for EloPomDex er lavere end den officielle pris. Medicinrådets vurdering baserer sig på den reelle pris.

Medicinrådet vurderer, at forholdet mellem klinisk værdi og pris i sammenligning med de behandlinger, der anvendes i dag, er:

- Ikke rimeligt i sammenligning med PomDex
- Ikke rimeligt i sammenligning med PomBorDex
- Rimeligt i sammenligning med CarDex

Det rimelige forhold mellem EloPomDex og CarDex forudsætter, at behandling med EloPomDex erstatter behandling med CarDex. Det vurderer Medicinrådet ikke vil være tilfældet. Derfor vurderer Medicinrådet, at det vil være forbundet med urimeligt høje udgifter at anvende EloPomDex. Læs mere i den sundhedsøkonomiske afrapportering (bilag).

4 Alvorlighed

Medicinrådet har ikke anvendt alvorlighedsprincippet i beslutningsgrundlaget for anbefalingen af EloPomDex.

5 Anbefalingen betyder

Regionerne bør i udgangspunktet ikke bruge EloPomDex til mulig behandling af patienter med knoglemarvskræft, der tidligere har modtaget mindst to behandlinger.

6 Sagsbehandlingstid

Medicinrådet har brugt 14 uger og 5 dage på sit arbejde med EloPomDex til behandling af patienter med knoglemarvskræft der tidligere har modtaget mindst to behandlinger

7 Kontaktinformation til Medicinrådet

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8 Versionslog

Version	**Dato**	**Ændring**
1.0	18. maj 2020	Godkendt af Medicinrådet.

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- Bilag 2 - Amgros' forhandlingsnotat for EloPomDex
- Bilag 3 - Ansøgers høringssvar
- Bilag 4 - Medicinrådets vurdering af elotuzumab i kombination med pomalidomid og dexamethason til behandling af patienter med knoglemarvskræft der tidligere har modtaget mindst to behandlinger - version 1.0
- Bilag 5 - Ansøgers endelige ansøgning
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Medicinrådet

Sundhedsøkonomisk afrapportering

Elotuzumab i kombination med pomalidomid og dexamethason

Patienter med knoglemarvskræft der tidligere har modtaget mindst to behandlinger

Version 1.0

Indholdsfortegnelse

Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for elotuzumab kombineret med pomalidomid og dexamethason (EloPomDex) til patienter med relaps eller behandlingsrefraktær knoglemarvskræft, som tidligere har modtaget mindst to tidligere behandlinger inklusive lenalidomid og en proteasomhæmmer, samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under "*Sekretariatets vurdering*". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.
Afsnit 2.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

Opsummering

Baggrund

I den ansøgte behandlingskombination er elotuzumab kombineret med pomalidomid og dexamethason (EloPomDex) indiceret til patienter med relaps eller behandlingsrefraktær knoglemarvskræft, som tidligere har modtaget mindst to tidligere behandlinger inklusive lenalidomid og en proteasomhæmmer.
Omkring 200 nye patienter pr. år vil modtage anden relapsbehandling og er kandidater til den ansøgte indikation i Danmark. Medicinrådets sekretariats vurdering tager udgangspunkt i dokumentation indsendt af Bristol-Myers Squibb (BMS).

Analyse

Analysen estimerer de inkrementelle omkostninger pr. patient ved behandling med EloPomDex sammenlignet med pomalidomid i kombination med dexamethason (PomDex), pomalidomid i kombination med bortezomib og dexamethason (PomBorDex) og carfilzomib i kombination med dexamethason (CarDex), over en tidshorisont på otte år. Analysens resultat præsenteres med SAIP.

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, Medicinrådets sekretariat mener er mest sandsynligt, er de inkrementelle omkostninger pr. patient for EloPomDex ca. [redacted]. DKK sammenlignet med PomDex, ca. [redacted] DKK sammenlignet med PomBorDex og ca. [redacted] DKK sammenlignet med CarDex, over en tidshorisont på otte år. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger pr. patient til sammenligning ca. 1,3 mio. DKK sammenlignet med PomDex, ca. 250.000 DKK sammenlignet med PomBorDex, og ca. -220.000 DKK sammenlignet med CarDex. Der er 200 patienter per år der er kandidater til behandlingerne. Ved nuværende fordeling er der antaget at 10 patienter modtager PomDex, 95 patienter modtager PomBorDex og 95 patienter modtager CarDex. Medicinrådets sekretariat vurderer, at budgetkonsekvenserne for regionerne i år 5 vil være på ca. [redacted] DKK sammenlignet med PomDex, ca. [redacted] DKK sammenlignet med PomBorDex og ca. [redacted] DKK sammenlignet med CarDex. Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 10,4 mio. DKK, ca. 24,1 mio. DKK og ca. – 1,6 mio. DKK i år 5 sammenlignet med hhv. PomDex, PomBorDex og CarDex.

Konklusion

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne.

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Arbejdsgruppe	Louise Greve Dal, Camilla Nybo Holmberg

Liste over forkortelser

AIP	Apotekernes indkøbspris
BorDex	Bortezomib i kombination med dexamethason
CarDex	Carfilzomib i kombination med dexamethason
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
I.v	Intravenøs
KM	Kaplan-Meier
OS	Overlevelse
PD	Progression
PH	*Proportional Hazard*
PFS	Progressionsfri overlevelse
PomBorDex	Pomalidomid i kombination med bortezomib og dexamethason
PomDex	Pomalidomid i kombination med dexamethason
SAIP	Sygehusapotekernes indkøbspriser
S.c	Subkutant

1. Baggrund for den økonomiske analyse

BMS (herefter omtalt som ansøger) er indehaver af markedsføringstilladelsen for Elotuzumab og har den 7. februar 2020 indsendt en ansøgning til Medicinrådet om anbefaling af elotuzumab i kombination med pomalidomid og dexamethason som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den økonomiske analyse, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Sekretariatets vurdering af den fremsendte økonomiske analyse (herefter omtalt som analysen).

1.1 Patientpopulation

Knoglemarvskræft er den næsthyppigste hæmatologiske kræftsygdom i Danmark, hvor i alt ca. 2.300 patienter anslås at leve med sygdommen. Der diagnosticeres ca. 380 behandlingskrævende patienter om året i Danmark, og medianalder ved diagnose er ca. 71 år[1]. For egnede patienter vil primærbehandling være højdosiskemoterapi med stamcellestøtte (HDT/STS). Patienter, som modtager denne behandling, har en væsentlig bedre prognose end de, der ikke er egnede. Halvdelen af de patienter, der behandles med HDT/STS, er fortsat i live efter ca. syv år (mediane overlevelse), mens patienter, der ikke er kandidater til HDT/STS, har en medianoverlevelse på ca. tre år [1]. Denne gruppe omfatter især de ældste patienter (over 70 år). Prognosen er, udover patientens alder, afhængig af komorbiditeter ved diagnosetidspunktet. Uafhængig af hvilken primærbehandling patienten modtager, vil en lille andel af patienterne være refraktære over for primærbehandling, og alle patienterne vil på et tidspunkt få behandlingskrævende relaps. Årligt vil ca. 380 myelomatosepatienter modtage primær behandling, og 320 vil modtage første relapsbehandling [1]. Fagudvalget vurderer, at ca. 200 vil modtage anden relapsbehandling. Patientgruppen er heterogen, og prognosen afhænger af tidligere behandling.

I henhold til behandlingsvejledningen for knoglemarvskræft vil behandlingsvalget til første relaps typisk være DaraLenDex eller DaraBorDex. Alternativt trestofkombinationerne EloLenDex, CarLenDex eller IxaLenDex. Ved andet behandlingskrævende relaps, dvs. når patienten har modtaget mindst to tidligere behandlinger og vil modtage 3. linjebehandling, vil behandlingsvalget typisk være CarDex eller PomDex. Medicinrådet anbefalede i november 2019 PomBorDex til patienter, der har modtaget mindst én tidligere behandling, og som derfor også kan være et behandlingsvalg.

1.1.1 Komparator

Medicinrådet har defineret carfilzomib i kombination med dexamethason (CarDex), pomalidomid i kombination med dexamethason (PomDex) og pomalidomid i kombination med bortezomib og dexamethason (PomBorDex) som komparatorer til EloPomDex, for patientpopulationen defineret i 1.1, se Tabel 1. Komparatorerne er alternative

behandlingsmuligheder, baseret på en individuel vurdering af patientens tidligere behandlinger, komorbiditeter, patientpræferencer og tidligere bivirkninger.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
Patienter med knoglemarvskræft, som tidligere har modtaget mindst to behandlinger inklusive lenalidomid og en proteasomhæmmer, og som har haft progression på den seneste behandlingslinje	CarDex
	PomDex
	PomBorDex

1.2 Problemstilling

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

Klinisk spørgsmål 1*:*

Hvad er værdien af elotuzumab i kombination med pomalidomid og dexamethason sammenlignet med eksisterende standardbehandling til behandling af patienter med knoglemarvskræft, som tidligere har modtaget mindst to behandlinger inklusive lenalidomid og en proteasomhæmmer, og som har haft progression på den seneste behandlingslinje?

2. Vurdering af den økonomiske analyse

Ansøger har indsendt en økonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for EloPomDex, sammenlignet med CarDex, PomDex og PomBorDex. I det nedenstående vil den økonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

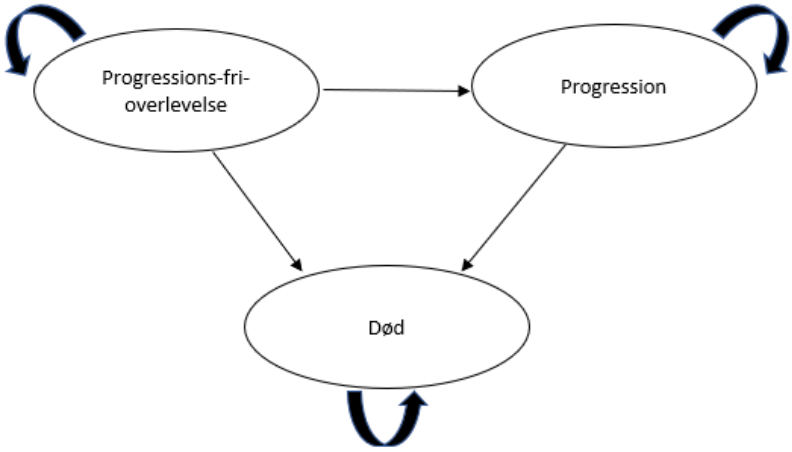
2.1 Antagelser og forudsætninger for model

Den økonomiske model har til formål at estimere de inkrementelle omkostninger pr. patient for EloPomDex sammenlignet med CarDex, PomDex og PomBorDex ved 3. linjebehandling af knoglemarvskræft.

Sammenligningen med EloPomDex er lavet på baggrund af data fra det kliniske studie ELOQUENT-3[2], der sammenligner EloPomDex med PomDex. Det har ikke været muligt at undersøge den kliniske effekt i en indirekte analyse mellem EloPomDex og CarDex, samt EloPomDex og PomBorDex, da der ikke findes studier med en fælles komparator. Der er yderligere stor forskel i patientpopulationerne mellem studierne. Sammenligningen af EloPomDex med CarDex og PomBorDex er derfor baseret på en narrativ sammenligning mellem studierne ELOQUENT-3[2], ENDEAVOR[3–7] og OPTIMISMM[8]. Ansøger antager på baggrund af studierne, at behandlingslængden baseret på progressionsfri overlevelse (PFS) for EloPomDex i ELOQUENT-3[2] er tilsvarende for behandling med CarDex og PomBorDex.

2.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival model* for behandling af patienter i de nævnte populationer, hvor tiden patienten er i behandling, defineres ud fra PFS Kaplan-Meier (KM)-kurve fra det kliniske studie ELOQUENT-3[2]. Alle patienter starter i PFS-stadiet og bevæger sig ud fra studiedata, videre til progressionsstadie (PD) eller død, som estimeres ud fra overlevelsesdata (OS) og dermed KM-kurven for OS. Tiden, hvor patienter befinder sig i PD-stadiet, er defineret ud fra PFS og OS, og er den procentdel, der ikke indgår i disse stadier.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen.

Ansøger har testet for proportional hazard (PH), som antages at være opfyldt, og der vælges derfor den samme parametriske funktion til at fremskrive effektkurverne for intervention og komparatorer i modellen. Ansøger har ekstrapoleret KM-kurverne i studiet, og testet alle parametriske kurvers fit på studiedata, hvorefter den parametriske funktion med bedste statistiske fit og klinisk validitet er valgt. Der er for PFS valgt eksponentiel funktion som er gældende for alle behandlingerne. Den gennemsnitlige behandlingslængde bliver baseret på PFS og er hhv. [redacted] måneder for EloPomDex, CarDex og PomBorDex og [redacted] måneder for PomDex. Se Figur 22 for PFS ud fra ekstrapolerede kurver.

For OS-kurverne er der ligeledes valgt den eksponentielle parametriske funktion for både EloPomDex og komparator-arme, se figur 3.

Ansøger antager, at bivirkningsprofilen for EloPomDex, PomDex, CarDex og PomBorDex er overvejende 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 lægger 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 EloPomDex vil ikke ændre væsentligt på efterfølgende behandlinger. Andelen af de forskellige behandlinger patienten har modtaget tidligere, gør resultaterne for efterfølgende behandling meget usikkert. Usikkerheden er blevet undersøgt i en følsomhedsanalyse.[1]

Figur 2: Ekstrapolerede PFS-kurver af PomDex og EloPomDex baseret på KM-data

Figur 3: Ekstrapolerede OS-kurver for PomDex og EloPomDex baseret på KM-data

Sekretariatets vurdering

Fagudvalget vurderer, at valgte parametriske funktioner er klinisk plausible.

Sekretariatet vurderer, at det på grund af forskelle i patientpopulationerne i studierne er svært at sammenligne bivirkningerne for lægemidlerne. Ansøger antager, at

bivirkningsprofilen er ens i alle behandlinger. Ansøger har inkluderet bivirkningerne i en følsomhedsanalyse.

Da det er usikkert, hvilke lægemidler patienterne i denne behandlingslinje har modtaget før behandling med EloPomDex, er efterfølgende behandling meget usikker, og sekretariatet mener derfor, at ansøgers antagelse om ikke at inkludere efterfølgende behandlingslinjer i hovedanalysen er acceptabel. Betydning af efterfølgende behandlingslinje vises i en følsomhedsanalyse.

Sekretariatet accepterer ansøgers tilgang.

2.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv. Analysen har en tidshorisont på ti år. Ansøger argumenterer for, at tidshorisonten på ti år er en overestimering af de reelle omkostninger og har vist flere følsomhedsanalyser, der belyser en kortere tidshorisont. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 % jf. Medicinrådets metodehåndbog.

Sekretariatets vurdering

Sekretariatet har på baggrund af dialog med fagudvalget vurderet, at tidshorisonten er meget usikker, men vurderer samtidig, at en tidshorisont på ti år kan overestimere omkostningerne, og at en tidshorisont på otte år vil være mere realistisk. Sekretariatet anvender en tidshorisont på otte år i sin hovedanalyse.

Sekretariatet anvender en tidshorisont på otte år i hovedanalysen.

2.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den økonomiske analyse af EloPomDex sammenlignet med PomDex, CarDex og PomBorDex. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Ansøger har ikke inkluderet bivirkningsrelaterede omkostninger, da forskel i bivirkninger ikke kunne vurderes og bivirkningerne antages at være overvejende ens i de forskellige behandlinger. Ansøgers estimering af lægemiddelomkostninger bygger altid på AIP, hvilket sekretariatets udskifter med SAIP i den endelige afrapportering.

2.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive produkters produktresuméer (SPC'er). Se Tabel 2 for lægemiddelpriser.

Behandlingerne EloPomDex, CarDex og PomDex gives i serier af 28 dage til progression.
PomBorDex gives i serier af 21 dage til progression.
EloPomDex doseres som følgende:

- Elotuzumab 10 mg/kg i.v. på dag 1,8,15 og 22 i serie 1-2. Efterfølgende serier: 20 mg/kg på dag 1.
- Pomalidomid: 4 mg p.o på dag 1-21
- Dexamethason: ≤75 år: 29 mg p.o på dag 1, 8, 15 og 22 i serie 1-2. efterfølgende serier: 28 mg på dag 1 og 40 mg på dag 8,15 og 22. Derudover gives 8 mg i.v. på dag 1, 8, 15 og 22 i serie 1-2, derefter kun dag 1.

CarDex doseres som følgende:

- 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.

PomDex doseres som følgende:

- Pomalidomid: 4 mg p.o. på dag 1-21
- Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22.

PomBorDex doseres som følgende:

- Pomalidomid: 4 mg p.o. på dag 1-14 i serier af 21 dage til progression.
- Bortezomib gives 1,3 mg/m^2 i.v eller s.c. på dage 1, 4, 8 og 11 i serie 1-8. fra serie 9 gives 1,3 mg/m^2 s.c. på dag 1 og 8.
- Dexamethason gives 20 mg på dag 1, 2, 4, 5, 8, 9, 11 og 12 i serie 1-8. Fra serie 9 og frem gives 20 mg p.o. på dag 1, 2, 8 og 9

Tabel 2: Anvendte lægemiddelpriser, SAIP, februar 2020.

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Elotuzumab	300 mg	1 stk.	[redacted]	Amgros
	400 mg	1 stk.	[redacted]	
Pomalidomid	1 mg	21 stk.	[redacted]	Amgros
	2 mg	21 stk.	[redacted]	
	3 mg	21 stk.	[redacted]	
	4 mg	21 stk.	[redacted]	
Dexamethason	1 mg	100 stk.	[redacted]	Amgros
	4 mg	20 stk	[redacted]	
Bortezomib	3,5 mg	1 htgl.	[redacted]	Amgros
Carfilzomib	10 mg	1 stk.	[redacted]	

	30 mg	1 stk.	[redacted]	Amgros
	60 mg	1 stk.	[redacted]	

Sekretariatets vurdering

Sekretariatet vurderer, at doserne er retvisende.

Sekretariatet accepterer ansøgers antagelser for lægemiddelomkostninger.

2.2.2 Hospitalsomkostninger

Ansøger har opdelt monitoreringsomkostninger ud fra, om patienten befinder sig i PFS-stadie eller PD-stadie, samt hvilken behandling patienten får. I PFS-stadiet er hospitalsomkostninger forbundet med administration af lægemidlerne og det antal administrationer, patienten får ved behandling med lægemidlerne inden for de forskellige behandlingsregimer. Omkostningerne er opgjort ved hjælp af DRG-taksten 17MA98 MC17 2020 for behandlingerne EloPomDex, CarDex og PomBorDex. For behandling med PomDex baseres estimeringen af omkostninger på Amgros' udvidede sammenligningsgrundlag til Medicinrådets behandlingsvejledning for knoglemarvskræft. Herfra anvendes omkostningerne forbundet med behandling med lenalidomid i kombination med dexamethason (LenDex), da disse lægemidler er orale ligesom PomDex, se Tabel 3.

Tabel 3: Hospitalsomkostninger til monitorering og administration, i PFS-stadiet

Behandling	Enhedsomkostning per besøg [DKK]	Omkostning per måned [DKK]	Kode	Kilde
EloPomDex		4.411		
CarDex	3.235	21.175	17MA98 MC17	Ambulante DRG-takser 2020
PomBorDex		11.764		
PomDex	1.759,25	1.955	-	Amgros' udvidede sammenligningsgrundlag for knoglemarvskræft

Ansøger antager, at patienter i progression (PD-stadiet) ses hver 14. dag og anvender samme DRG-takst for besøg, se Tabel 4.

Tabel 4: Hospitalsomkostninger til monitorering og administration, i PD-stadiet

	Enhedsomkostning pr. besøg [DKK]	Omkostning per måned [DKK]	Kode	Kilde
Ressourceforbrug for patienter I PD-stadie	3.235	7.033,24	17MA98 MC17	DRG-takser 2020

Sekretariatets vurdering

Der er stor usikkerhed omkring det præcise estimat for ressourceomkostningerne. Det er på baggrund af dialog med fagudvalget vurderet, at lægemidler administreret intravenøst er mere ressourcekrævende en subkutan behandling. Elotuzumab og carfilzomib gives intravenøst og bortezomib gives subkutant, og derfor kan den anvendte DRG-takst være overestimeret for PomBorDex. Sekretariatet udarbejder derfor en følsomhedsanalyse, hvor hospitalsomkostninger justeres -20 % for PomBorDex.

Sekretariatet accepterer ansøgers tilgang, men udarbejder en følsomhedsanalyse på hospitalsomkostninger, hvor der justeres med -20 % for administrationsomkostningerne for PomBorDex.

2.2.3 Bivirkningsomkostninger

Ansøger har ikke inkluderet bivirkningsomkostninger, da ansøger vurderer, at der ikke er forskel på bivirkningsfrekvensen mellem behandlingerne. Sammenligningen af bivirkninger er desuden vanskelig grundet forskelle i studiepopulationerne.

Sekretariatets vurdering

Sekretariatet accepterer ansøgers tilgang.

2.2.4 Patientomkostninger

Patientomkostninger er omkostninger forbundet med den tid, patienterne bruger til at komme til ambulante besøg, og den tid de bruger på administration af lægemidlerne på hospitalet. Patientomkostninger er estimeret på baggrund af Amgros' udvidede sammenligningsgrundlag til Medicinrådets behandlingsvejledning for knoglemarvskræft. Patientomkostninger er ligesom monitoreringsomkostninger beregnet for både patienter i behandling (PFS) og i progression (PD). Ansøger antager, at patienttiden for behandling med EloPomDex kan estimeres ud fra patienttiden for behandling med EloLenDex. EloLenDex er en behandlingskombination, der er beskrevet i det udvidede sammenligningsgrundlag. Antagelsen baserer sig på, at både lenalidomid og pomalidomid er orale lægemidler, og omkostninger til behandlingerne er ens. Ansøger antager, at samme antagelse kan benyttes for sammenligningen med PomBorDex, da både elotuzumab og bortezomib kan gives intravenøst.

Ansøger antager, at patienttiden for PomDex kan estimeres ud fra patienttiden for LenDex, da alle lægemidler er orale, og derfor forventes patientens tidsforbrug på hospitalet at være den samme.
Ansøger antager, at patienttiden for CarDex er den samme som patienttiden for CarLenDex, som også er beskrevet i det udvidede sammenligningsgrundlag, hvor behandlingen kun differentierer på lenalidomid, som er et oralt lægemiddel. Ansøgers estimerede patienttid for patienter i behandling kan ses i Tabel 5.

Tabel 5: Ansøgers estimat af patientomkostninger i PFS-stadiet

Behandling	Enhedsomkostning pr. besøg [DKK]	Omkostning pr. måned [DKK]	Kilde og antagelse (Udvidede sammenligningsgrundlag i Medicinrådets behandlingsvejledning for knoglemarvskræft)
EloPomDex	769,83	1.049,76	Baseret på EloLenDex
PomBorDex	769,83	2.799,37	Baseret på EloLenDex
PomDex	651,75	724,17	Baseret på LenDex
CarDex	656,42	4.296,55	Baseret på CarLenDex

Patientomkostninger for PD-stadiet er beregnet på baggrund af Amgros' udvidede sammenligningsgrundlag for bortezomib i kombination med melphalan og prednisolon (BorMelPred), se Tabel 6.

Tabel 6: Ansøgers estimat af patientomkostninger i PD-stadiet

Behandling	Enhedsomkostning pr. besøg [DKK]	Omkostning pr. måned [DKK]	Kilde og antagelse (Udvidede sammenligningsgrundlag i Medicinrådets behandlingsvejledning for knoglemarvskræft)
Alle	606,56	1.213,11	Baseret på BorMelPred

Sekretariatets vurdering

I PFS-stadiet gives Dexamethason i behandlingskombinationen EloPomDex også intravenøst samme dage som elotuzumab gives. Estimeringen af patienttid ved behandling med EloPomDex kan derfor være underestimeret. Sekretariatet udarbejder en følsomhedsanalyse på dette estimat med +50 % på patienttid.

Da bortezomib kan gives subkutant og dermed er forbundet med færre omkostninger end elotuzumab, kan disse patienttidsomkostninger være overestimerede, og sekretariatet foretager en følsomhedsanalyse på estimatet for bortezomib på -50 % på patienttid.

Patienttiden for PD-stadiet er baseret på patienttiden for behandling med BorMelPred i det udvidede sammenligningsgrundlag til Medicinrådets behandlingsvejledning for knoglemarvskræft. Sammen med fagudvalget er det vurderet, at patienttiden i PD-stadiet er højere end patienttiden estimeret for BorMelPred. Fagudvalget vurderer, at patienter i PD-stadiet vil blive set hver 14. dag. Sekretariatet foretager derfor en følsomhedsanalyse på dette estimat på +50 % på patienttid. Dette vil kun have betydning for sammenligningen med PomDex, da patienternes tidsforbrug i PD-stadiet er ens mellem de andre behandlinger.

Sekretariatets accepterer ansøgers tilgang.

Sekretariatet udarbejder en følsomhedsanalyse, hvor patienttid i PFS-stadiet for EloPomDex justeres med +50 % på baggrund af den ekstra tid, patienten observeres i forbindelse med indgivning af dexamethason. Patienttiden for behandling med PomBorDex justeres med -50 %, da subkutan bortezomib forventes at blive givet mindre hyppigt end intravenøs elotuzumab.

Sekretariatet udarbejder en følsomhedsanalyse hvor patienttid i PD-stadiet justeres med +50 %.

2.2.5 Omkostninger til efterfølgende behandling

Ansøger inkluderer ikke omkostninger til efterfølgende behandlinger, da der er store forskelle i, hvilke tidligere behandlinger patienterne har fået inden behandling i 3. linje. Da disse tidligere behandlinger er afgørende for de efterfølgende valg, er det for usikkert at estimere de sandsynlige omkostninger til efterfølgende behandling. Ansøger har lavet en følsomhedsanalyse, hvor de inkluderer omkostninger til efterfølgende behandlinger.

For at estimere omkostninger til efterfølgende behandling har ansøger antaget, at de fleste patienter har modtaget CarDex i 3. linje, og at behandlingsregimer med pomalidomid anvendes efter CarDex. Behandling efter 3. linje vil afhænge af tidligere behandlinger, alder, respons til tidligere behandlinger, komorbiditeter og patientens præferencer. Ansøger antager, at patienter i 4. og 5. linje behandling af knoglemarvskræft vil blive behandlet med behandlingsregimer som BorDex og daratumumab monoterapi.

Ud fra studiet ELOQUENT-3 får 94 % af patienterne i EloPomDex-armen efterfølgende behandling og 88 % af patienterne i PomDex armen. Der gælder samme antagelser for CarDex og PomBorDex som for EloPomDex.

Det antages i ansøgers følsomhedsanalyse, at 80 % af patienterne får BorDex og 20 % daratumumab monoterapi i den efterfølgende behandlingslinje, se Tabel 7.

Tabel 7: Andel af patienter der modtager efterfølgende behandling

	Andel af patienter der modtager efterfølgende behandling			
	EloPomDex	PomBorDex	PomDex	CarDex
BorDex	80 %	80 %	80 %	80 %
Daratumumab mono-terapi	20 %	20 %	20 %	20 %

Den gennemsnitlige behandlingslængde for efterfølgende behandling antages at være den samme som for PomDex i studiet ELOQUENT-3, da patientpopulationen her har modtaget 3 tidligere behandlinger.

I Tabel 8 ses dosis og lægemiddelpriser for efterfølgende behandling.

Tabel 8: Anvendte lægemiddelpriser, SAIP, februar 2020.

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Bortezomib	3,5 mg	1 htgl.	[redacted]	Amgros
Dexamethason	1 mg	100 stk.	[redacted]	Amgros
	4 mg	10 stk.	[redacted]	
Daratumumab	20 mg/ml	5 ml	[redacted]	Amgros
	20 mg/ml	20 ml	[redacted]	

Sekretariatets vurdering

Sekretariatet er enig med ansøger i, at inkludering af efterfølgende behandling er for usikkert. Sekretariatet har efter dialog med fagudvalget vurderet, at den efterfølgende behandling, som er valgt i analysen, ikke afspejler den kliniske praksis, og at de fleste patienter vil modtage behandlinger, patienten ikke har modtaget tidligere. Få vil kunne få daratumumab monoterapi. Hvis EloPomDex anbefales som mulig standardbehandling til ansøgte indikation vil dette dog få betydning for efterfølgende behandling. Umiddelbart introduceres endnu et behandlingsregime til patienter i 3. linjebehandling, men behandlingsregimer med pomalidomid kan kun anvendes en gang. Dvs. at EloPomDex, PomBorDex og PomDex ikke kan anvendes efter hinanden. Desuden skal man være opmærksom på, at behandlingsregimer med pomalidomid kan anvendes før CarDex og omvendt. I klinisk praksis vil det have stor betydning at anvende billigste regime først, da behandlingslængden efter endnu et relaps antages at være kortere.

Sekretariatet accepterer ansøgers antagelser om, at inkludering af efterfølgende behandlingslinjer er for usikkert og inkluderer kun efterfølgende behandling i en følsomhedsanalyse, der ifølge fagudvalget ikke afspejler klinisk praksis.

2.3 Følsomhedsanalyser

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

- Inkludering af bivirkninger
- Forskellige tidshorisonter for modellen
- Inkludering af efterfølgende behandling

Sekretariatets vurdering

Sekretariatet mener, at ansøgers følsomhedsanalyser er relevante. Også ansøgers følsomhedsanalyse for efterfølgende behandling er relevant, selvom denne ikke afspejler klinisk praksis. Dette hænger sammen med, at patienter stadig vil modtage efterfølgende behandling, og det er derfor kun typen af behandling, der er usikker. Fagudvalget har vurderet, at der er stor usikkerhed omkring tidshorisonten og derfor præsenteres en kortere tidshorisont.

Sekretariatet vælger kun at præsentere følgende følsomhedsanalyser::

- *Inkludering af efterfølgende behandling*
- *Tidshorisont på fem år for modellen*
- *Ændring af hospitalsomkostningerne for behandlingerne med PomBorDex -20 %.*
- *Ændring på patientomkostningerne for behandlingerne med EloPomDex +50 %, PomBorDex -50 % i PFS-stadiet og patientomkostningerne i PD-stadiet med +50 %.*

Sekretariatet præsenterer ikke følsomhedsanalyserne med bivirkninger.

2.4 Opsummering af basisantagelser

I Tabel 9 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som Sekretariatet har lavet i egen hovedanalyse.

Tabel 9: Basisantagelser for ansøgers og Sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Komparator	PomDex CarDex PomBorDex	PomDex CarDex PomBorDex
Modeltype	Partitioned survival model	Partitioned survival model
Tidshorisont	10 år	8 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostning Hospitalsomkostning Patientomkostning	Lægemiddelomkostning Hospitalsomkostning Patientomkostning
Behandlingslængde	16,3 måneder (EloPomDex, PomBorDex, CarDex) 7,8 måneder (PomDex)	16,3 måneder (EloPomDex, PomBorDex, CarDex) 7,8 måneder (PomDex)
Dosering	Som angivet i SPC	Som angivet i SPC
Effektmål	PFS	PFS
Håndtering af usikkerhed	One-way følsomhedsanalyse	One-way følsomhedsanalyse
Monitoreringsomkostninger	DRG-takst 2020	DRG-takst 2020

3. Resultater

3.1 Resultatet af sekretariatets hovedanalyse

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

- Tidshorisont på otte år

Sekretariatets hovedanalyse viser, at de inkrementelle omkostninger pr. patient bliver ca. [redacted] DKK sammenlignet med PomDex, ca. [redacted] DKK sammenlignet med PomBorDex, og ca. [redacted] DKK sammenlignet med CarDex, over en tidshorisont på otte år. Udføres analysen med AIP bliver den inkrementelle omkostning pr. patient ca. 1,3 mio. DKK, ca. 250.000 DKK, og ca. -220.000 DKK for sammenligningen mellem hhv. PomDex, PomBorDex og CarDex.
Resultaterne fra Sekretariats hovedanalyse præsenteres i Tabel 10.

Tabel 10: Resultatet af Medicinrådets sekretariats hovedanalyse, DKK, diskonterede tal.

[DKK]	EloPomDex	CarDex	PomDex	PomBorDex
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	237.481	500.713	141.295	352.933
Patientomkostninger	45.498	96.482	27.369	72.972
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

3.1.1 Resultatet af sekretariatets følsomhedsanalyser

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

- Tidshorisont på fem år
- Efterfølgende behandling inkluderet
- Justeret hospitalsomkostninger for PomBorDex
- Justeret patientomkostninger for EloPomDex, PomBorDex og PD-stadiet

Følsomhedsanalyserne har lille betydning for analysens resultat.

Resultatet af følsomhedsanalysen med efterfølgende behandling viser, at inddragelse af efterfølgende behandlinger har lille betydning for analysens resultat. Dette kan dog hænge sammen med ansøgers antagelser om, hvilke lægemidler der udgør efterfølgende

behandling. Det har stor betydning for eventuelle meromkostninger eller besparelser hvilken behandlingsrække, der vælges i klinisk praksis. Anvendelse af billigste behandlingsregime først vil resultere i mindre inkrementelle omkostninger pr. patient, da behandlingslængden sandsynligt vil være kortere, jo flere relaps patienten har oplevet. Desuden vil pomalidomidholdige kombinationer kun kunne anvendes én gang. Efterfølgende behandling i dansk klinisk praksis vurderes ud fra en individuel vurdering af patientens tidligere behandlinger, komorbiditeter, patientpræferencer og tidligere bivirkninger og er derfor for usikker til at kunne estimeres.

Tabel 11: Resultatet af Sekretariatets følsomhedsanalyse med en tidshorisont på 5 år

	EloPomDex	CarDex	PomDex	PomBorDex
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	193.611	451.925	127.648	306.907
Patientomkostninger	37.846	87.878	25.014	64.807
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 12: Resultatet af Sekretariatets følsomhedsanalyse med efterfølgende behandling

	EloPomDex	CarDex	PomDex	PomBorDex
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	237.481	500.713	141.295	352.933
Patientomkostninger	45.498	96.482	27.369	72.972
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 13:Resultatet af Sekretariatets følsomhedsanalyse med justering af hospitalsomkostninger

	EloPomDex	CarDex	PomDex	PomBorDex
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	237.481	500.713	141.295	315.989
Patientomkostninger	45.498	96.482	27.369	72.972
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 14: Resultatet af Sekretariatets følsomhedsanalyse med justering af patienttidsomkostninger

	EloPomDex	CarDex	PomDex	PomBorDex
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	237.481	500.713	141.295	352.933
Patientomkostninger	68.246	110.988	38.249	65.499
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

4. Budgetkonsekvenser

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

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

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers budgetkonsekvensanalyse

4.1.1 Ansøgers estimat af patientantal og markedsandel

Ansøger estimerer et samlet patientantal på 200 patienter årligt, baseret på Medicinrådets protokol for vurdering af EloPomDex til nævnte indikation.
Ansøger antager, at hvis EloPomDex anbefales, vil behandlingen, i år 1, opnå en markedsandel på 60 % af den markedsandel, PomDex har i dag, stigende til 90 % i år 5.
Ansøger antager endvidere, at en anbefaling vil betyde, at EloPomDex vil opnå 11,5 % i år 1 stigende til 20 % i år 5 af den markedsandel, som hhv. PomBorDex og CarDex har i dag.

Tabel 15 viser ansøgers estimat for det årlige nye patientantal.

Tabel 15: Ansøgers estimat af antal nye patienter pr. år.

Anbefales					
	År 1	År 2	År 3	År 4	År 5
EloPomDex	28	38	47	47	47
PomDex	4	2	1	1	1
CarDex	84	80	76	76	76
PomBorDex	84	80	76	76	76
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
EloPomDex	0	0	0	0	0
PomDex	10	10	10	10	10

CarDex	95	95	95	95	95
PomBorDex	95	95	95	95	95

Sekretariatets vurdering

Ansøger har inkluderet samme omkostninger, som indgår i deres hovedanalyse inkl. omkostninger til patienttid, men uden diskontering. Sekretariatet anvender sin egen hovedanalyse til beregning af budgetkonsekvenserne men inkluderer ikke patienttidsomkostninger.
Sekretariatet anvender fagudvalgets antagelse om at EloPomDex vil erstatte 80 % af behandlingerne med PomDex, 90 % af PomBorDex og 10 % af CarDex, og disse estimater anvendes i sekretariatets hovedanalyse for budgetkonsekvenserne for alle fem år.

Sekretariatet udfører egen budgetkonsekvensanalyse, hvor omkostninger er baseret på sekretariatets hovedanalyse og hvor markedsandelen ændres til estimaterne baseret på fagudvalget for knoglemarvskræft.

4.2 Sekretariatets budgetkonsekvensanalyse

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

- Markedsandel 10 % af CarDex populationen
- Markedsandel 80 % af PomDex populationen
- Markedsandel 90 % af PomBorDex population

Beregningen af budgetkonsekvenser tager udgangspunkt i de omkostninger, der i dag er forbundet med behandling af det antal patienter, som jf. Tabel 15 behandles med hhv. CarDex, PomDex og PomBorDex sammenlignet med omkostningerne til behandling af samme antal patienter, hvor EloPomDex har overtaget den angivne markedsandel fra de pågældende lægemidler. Medicinrådets sekretariat estimerer, at en anbefaling af EloPomDex vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 i forhold til de omkostninger, der i dag er forbundet med behandling med CarDex, ca. [redacted] DKK i forhold til PomDex og ca. [redacted] DKK i forhold til PomBorDex. Resultatet er præsenteret i Tabel 16, Tabel 17 og Tabel 18. Samlet vil en anbefaling af EloPomDex resultere i budgetkonsekvenser på [redacted] DKK i år 5.
Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. -1,6 mio. DKK, ca. 10,4 mio. DKK og ca. 24,1 mio. DKK i år 5 sammenlignet med det nuværende forbrug af hhv. CarDex, PomDex og PomBorDex.

[redacted]

Tabel 16: Sekretariatets analyse af totale budgetkonsekvenser for EloPomDex over for CarDex, 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 budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 17: Sekretariatets analyse af totale budgetkonsekvenser for EloPomDex over for PomDex, 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 budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 18: Sekretariatets analyse af totale budgetkonsekvenser for EloPomDex over for PomBorDex, 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 budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5. Diskussion

Behandling med EloPomDex er forbundet med betydelige inkrementelle besparelser sammenlignet CarDex, og meget høje inkrementelle meromkostninger sammenlignet med PomDex og PomBorDex. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for de forskellige behandlinger.

5.1 Usikkerheder

Der er stor usikkerhed omkring efterfølgende behandling, da patienter i denne fase af sygdommen allerede har været udsat for adskillige behandlingsregimer. Både forudgående behandlinger og efterfølgende behandlinger er afhængig af patientens komorbiditet, præferencer, tidligere bivirkninger og refraktæritet, og der er derfor ikke ét bestemt behandlingsregime før og efter progression ved 2. og/eller 3. relaps. Ansøger har indsendt en følsomhedsanalyse, der afspejler efterfølgende behandling, da mange patienter vil modtage et behandlingsregime efterfølgende. Det ser ikke ud til, at inddragelse af efterfølgende behandling har nogen særlig betydning for resultatet. Dette kan dog hænge sammen med, at de valgte lægemidler til efterfølgende behandling ikke er i overensstemmelse med dansk klinisk praksis. Det har stor betydning for eventuelle meromkostninger eller besparelser hvilken behandlingsrækkefølge, der vælges i klinisk praksis. Anvendelse af billigste behandlingsregime først vil resultere i mindre inkrementelle omkostninger pr. patient, da behandlingslængden sandsynligt vil være kortere, jo flere relaps patienten har oplevet. Desuden vil pomalidomidholdige kombinationer kun kunne anvendes én gang. Efterfølgende behandling i dansk klinisk praksis vurderes ud fra en individuel vurdering af patientens tidligere behandlinger, komorbiditeter, patientpræferencer og tidligere bivirkninger og er derfor for usikker til at kunne estimeres.

Der er usikkerhed omkring tidshorisonten for behandlingerne, da de ekstrapolerede kurver fra studiedata kan være overestimerede sammenlignet med den danske kliniske praksis. Fagudvalget har ikke viden om den nøjagtige relevante tidshorisont på baggrund af studiedata, men forventer at forskel i omkostninger mellem behandlingerne vil ligge med en tidshorisont på fem til otte år. Tidshorisonten har lille betydning for analysens resultat.

Estimaterne for hospitalsomkostninger og patienttid er meget usikre, og der er både anvendt mikroomkostninger og DRG-takster for estimering af ressourcer. Hospitalsomkostninger har betydning for de inkrementelle omkostninger i sammenligningen med PomBorDex og patienttidsomkostningerne har en lille betydelig forskel i inkrementelle omkostninger i sammenligningen med både CarDex, PomDex og PomBorDex.

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7. Bilag

7.1 Resultatet af ansøgers hovedanalyse

Ansøger estimerer i analysen de inkrementelle omkostninger pr. patient for EloPomDex sammenlignet med CarDex, PomDex og PomBorDex.

Tabel 19: Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal.

[DKK]	EloPomDex	CarDex	PomDex	PomBorDex
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	252.178	515.828	144.026	367.814
Patientomkostninger	48.040	99.105	27.840	75.557
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

7.2 Resultatet af ansøgers budgetkonsekvensanalyse

I nedenstående tabeller ses ansøgers resultat af budgetkonsekvensanalysen.

Tabel 20: Ansøger analyse af totale budgetkonsekvenser for EloPomDex over for CarDex, 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 budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 21: Ansøgers analyse af totale budgetkonsekvenser for EloPomDex over for PomDex, 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 budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 22: Ansøgers analyse af totale budgetkonsekvenser for EloPomDex over for PomBorDex, 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 budgetkonse-kvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	13.05.2020
Leverandør	BMS
Lægemiddel	Elotuzumab (Empliciti) i komb. med pomalidomid og dexamethason (EloPomDex)
EMA-indikation	Patienter med knoglemarvskræft, der har modtaget mindst to tidligere behandlinger (dvs. passer i behandlingsvejledningen for behandling ved 2. relaps)

Forhandlingsresultat

Amgros har opnået følgende pris på elotuzumab (Empliciti). Prisen er betinget af, at Medicinrådet anbefaler EloPomDex som mulig standardbehandling:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Gældende SAIP	Ny SAIP	Rabatprocent ift. AIP
Empliciti	300 mg	1 stk.	7.289,19	[redacted]	[redacted]	[redacted]
Empliciti	400 mg	1 stk.	9.718,92	[redacted]	[redacted]	[redacted]

Elotuzumab er en del af et eksisterende udbud med udløb d. 31.12.2020. Det nuværende udbud indeholder muligheden for at ændre priser ved brug af en indbygget prisreguleringsmekanisme. Amgros har igangsat denne prisreguleringsmekanisme, så det er muligt for alle leverandører i udbuddet at tilbyde en ny og lavere pris med frist den 29.05.2020.

[redacted]

Det er kun prisen på elotuzumab der vises, da hverken pomalidomid eller dexamethason har været en del af prisforhandlingerne.

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt **har** opnået den bedst mulige pris. Denne vurdering baserer vi på følgende punkter:

[redacted]

- Leverandøren vurderer, at EloPomDex er klinisk ligeværdigt med carfilzomib+dexamethason (CarDex), hvor de er billigere, og at de har bedre data vedr. bivirkninger sammenlignet med pomalidomid +bortezomib+dexamethason (PomBorDex), samt har bedre effekt end pomalidomid+dexamethason (PomDex).

[redacted]

Konklusion

Amgros vurderer, at vi har opnået en pris, der kan skabe mere konkurrence, da de er billigere end CarDex [redacted] Amgros' konklusion er, at man kun vil opnå mere sundhed for pengene ved at anbefale EloPomDex, hvis det bruges i stedet for CarDex, da EloPomDex er et billigere behandlingsalternativ end CarDex. EloPomDex er en markant dyrere behandling end både PomBorDex og PomDex

[redacted]

Relation til markedet

Elotuzomab bruges allerede i dag i behandlingen af knoglemarvskræft,

[redacted]

Medicinrådet

25. marts 2020

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Karen Kleberg Hansen

Ang. Høring vedr. vurdering af vedrørende elotuzumab i kombination med pomalidomid og dexamethason til behandling af patienter med knoglemarvskræft der tidligere har modtaget mindst to behandlinger

Ansøger meddeler, at de ikke indsender høringssvar.

Medicinrådet

Medicinrådets vurdering af elotuzumab i kombination med pomalidomid og dexamethason til behandling af patienter med knoglemarvskræft der tidligere har modtaget mindst to behandlinger

Version 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

Lægemidlet er vurderet efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser.

Godkendt af Medicinrådet 18. marts 2020
Dokumentnummer: 72542
Versionsnummer: 1.0

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

Indhold

1 Medicinrådets konklusion

Medicinrådet vurderer, at EloPomDex har en **merværdi af ukendt størrelse** sammenlignet med PomDex. Evidensens kvalitet vurderes at være meget lav.

Den samlede værdi **kan ikke kategoriseres** sammenlignet med PomBorDex. Medicinrådet vurderer, at EloPomDex ikke er et dårligere behandlingsalternativ end PomBorDex, hvad angår effekt. Bivirkningsprofilen er muligvis lettere.

Den samlede værdi **kan ikke kategoriseres** sammenlignet med CarDex. Medicinrådet vurderer, at EloPomDex ikke er dårligere end CarDex, hvad angår effekt og bivirkninger.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

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

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

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

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

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

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

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

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

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

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

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

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

2 Begreber og forkortelser

Bor:	Bortezomib
CAR:	Carfilzomib
CI:	Konfidensinterval
Dex:	Dexamethason
Elo:	Elotuzumab
EMA:	*European Medicines Agency*
EORTC-QLQ-C30:	*European Organisation for Research and Treatment Quality of Life Questionnaire – Cancer (30 items)*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HDT/STS:	Højdosiskemoterapi med stamcellestøtte
HR:	*Hazard ratio*
i.v.:	Intravenøs
Len:	Lenalidomid
NK:	*Natural killer*
OR:	*Odds ratio*
Pom:	Pomalidomid
RR:	Relativ risiko
s.c.:	Subkutan
SLAMF7:	*Signaling lymphocytic activation molecule family member 7* (et protein)

3 Introduktion

Formålet med Medicinrådets vurdering af elotuzumab i kombination med pomalidomid og dexamethason (EloPomDex) til behandling af patienter med knoglemarvskræft, der tidligere har modtaget mindst to behandlinger, er at vurdere den værdi, behandlingen har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Bristol-Myers Squibb. Vi modtog ansøgningen den 5. februar 2020.

Det kliniske spørgsmål er:

Hvad er værdien af elotuzumab i kombination med pomalidomid og dexamethason sammenlignet med eksisterende standardbehandling til behandling af patienter med knoglemarvskræft, som tidligere har modtaget mindst to behandlinger inklusive lenalidomid og en proteasomhæmmer, og som har haft progression på den seneste behandlingslinje?

Vurderingen inkluderer følgende tre komparatorer;

- pomalidomid i kombination med dexamethason (PomDex)
- pomalidomid i kombination med bortezomib og dexamethason (PomBorDex)
- carfilzomib i kombination med dexamethason (CarDex)

3.1 Knoglemarvskræft

Knoglemarvskræft (myelomatose) er en uhelbredelig, livstruende og livsforkortende, men behandlingsfølsom hæmatologisk kræftsygdom. Sygdommen skyldes, at én type af hvide blodlegemer (plasmaceller) i knoglemarven ændrer karakter og herved bliver ondartede. Patienten kan på grund af nedsat funktion af knoglemarven opleve symptomer på svækket immunforsvar som infektioner og på blodmangel, som medfører, at patienten oplever bl.a. træthed og åndenød. Ændringerne i knoglemarven fremmer aktiviteten af celler, som nedbryder knoglerne og reducerer aktiviteten af de celler, som opbygger knoglevæv. Derfor nedbrydes knoglerne, og patienten får øget risiko for knoglebrud, oplever knoglesmerter og får forhøjet kalk i blodet. Hos størstedelen af patienter med 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 immunglobulin 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. 2.300 patienter anslås at leve med sygdommen [2]. Der diagnosticeres ca. 380 behandlingskrævende patienter om året i Danmark, og medianalder ved diagnose er ca. 71 år [3].

Patienter med god almentilstand, uden betydende komorbiditet og som er yngre end ca.70 år, behandles med højdosiskemoterapi med stamcellestøtte (HDT/STS) som primærbehandling. Patienter, som modtager denne behandling, har en væsentlig bedre prognose end de, der ikke er kandidater til behandlingen. 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 [4]. Denne gruppe omfatter især de ældste patienter. Uafhængigt af hvilken primærbehandling patienten modtager, vil en lille andel af patienterne ikke respondere (være refraktære) på primærbehandling, og alle patienterne vil på et tidspunkt få et behandlingskrævende tilbagefald (relaps). Årligt vil ca. 380 myelomatosepatienter modtage primærbehandling, heraf vil 320 på et tidspunkt få relaps og modtage første relapsbehandling [3]. Fagudvalget vurderer, at ca. 200 vil få relaps igen og modtage anden relapsbehandling. Patientgruppen er

heterogen i forhold til komorbiditet og respons på tidligere behandlinger, og prognosen afhænger bl.a. af disse faktorer. Den mediane overlevelse for patienter, der er refraktære overfor det immunmodulerende stof lenalidomid og bortezomib, som er en proteasomhæmmer, er i et studie fra 2012 angivet at være ca. 9 måneder [5]. Med nyere behandlingsmuligheder vurderer fagudvalget, at overlevelsen er forbedret og må ligge tættere på den mediane overlevelse på ca. 17 måneder i studiet, der danner grundlag for denne vurdering af EloPomDex [6]. I den danske population vil den forventes lidt lavere, da den indeholder flere patienter med høj alder og komorbiditet.

3.2 Elotuzumab

Elotuzumab er et kendt lægemiddel til behandling af knoglemarvskræft, hvor det i kombination med lenalidomid og dexamethason er godkendt til patienter, der har modtaget mindst én tidligere behandling. I Medicinrådets behandlingsvejledning anbefales denne behandlingskombination (EloLenDex) til behandling af patienter ved første relaps, hvor anvendelse af daratumumab er kontraindiceret.

Elotuzumab er et monoklonalt antistof, der binder sig til proteinet signaling lymphocytic activation molecule family member 7 (SLAMF7). SLAMF7 er udtrykt på knoglemarvskræftceller og natural killer (NK)-celler. Aktivering af NK-celler sker ved binding af SLAMF7. De aktiverede NK-celler medfører apoptose (programmeret celledød) af omkringliggende knoglemarvskræftceller [6].

I den ansøgte behandlingskombination er elotuzumab kombineret med pomalidomid og dexamethason (EloPomDex). Kombinationen har markedsføringstilladelse til patienter med relaps eller behandlingsrefraktær knoglemarvskræft, som tidligere har modtaget mindst to tidligere behandlinger, inklusive lenalidomid og en proteasomhæmmer (bortezomib, ixazomib eller carfilzomib). EloPomDex er vurderet i en accelereret proces hos EMA. Til denne indikation skal EloPomDex doseres som følger:

I serier a 28 dage til progression:

- Elotuzumab 10 mg/kg i.v. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 20 mg/kg på dag 1.
- Pomalidomid 4 mg p.o. på dag 1-21.
- Dexamethason:
    - ≤ 75 år: 28 mg p.o. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 28 mg på dag 1 og 40 mg på dag 8, 15, og 22.
    - > 75 år: 8 mg p.o. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 8 mg på dag 1 og 20 mg på dag 8, 15, og 22.
    - Herudover: 8 mg i.v. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 8 mg i.v. på dag 1.

3.3 Nuværende behandling

Behandlingen ved relaps af knoglemarvskræft er medicinsk. Behandlingen er oftest en kombination af flere lægemidler, som angriber kræftcellerne på forskellige måder [7]. Behandlingen er ikke kurativ, så ud over forlænget overlevelse er målet med behandlingen at give patienterne længst mulige perioder med lav sygdomsbyrde og bedst mulig livskvalitet.

I henhold til Medicinrådets behandlingsvejledning vedr. knoglemarvskræft vil behandlingsvalget til første relaps typisk være kombinationen DaraLenDex (daratumumab, lenalidomid og dexamethason) eller DaraBorDex (daratumumab, bortezomib og dexamethason). Alternativt trestofkombinationerne, EloLenDex (elotuzumab, lenalidomid og dexamethason), CarLenDex (carfilzomib, lenalidomid og dexamethason) eller IxaLenDex (ixazomib, lenalidomid og dexamethason). Ved andet behandlingskrævende relaps, dvs. når patienten har modtaget mindst to tidligere behandlinger, vil behandlingsvalget typisk være CarDex (carfilzomib og dexamethason), PomBorDex (pomalidomid, bortezomib og dexamethason) eller PomDex (pomalidomid og dexamethason).

Behandlingsvalget foretages i samråd mellem læge og patient under hensyntagen til effekt af tidligere behandling, bivirkninger til tidligere behandlinger, alment funktionsniveau (performance status), komorbiditet og patientpræferencer, herunder antallet af behandlingsfremmøder. Der tages også hensyn til eventuel manglende respons overfor lægemidler, der er indgået i tidligere behandlinger. I henhold til Medicinrådets behandlingsvejledning bør et lægemiddel ikke bruges ved fremtidige behandlinger, hvis en patient er behandlingsrefraktær overfor lægemidlet givet i fuld dosering.

4 Metode

Medicinrådets protokol for vurdering af elotuzumab i kombination med pomalidomid og dexamethason beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

Det kliniske spørgsmål er:

Hvad er værdien af elotuzumab i kombination med pomalidomid og dexamethason sammenlignet med eksisterende standardbehandling til behandling af patienter med knoglemarvskræft, som tidligere har modtaget mindst to behandlinger inklusive lenalidomid og en proteasomhæmmer, og som har haft progression på den seneste behandlingslinje?

Vurderingen inkluderer følgende effektmål (tabel 1), som er beskrevet nærmere i protokollen.

Tabel 1: Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire effektmålsgrupper (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikkealvorlige symptomer og bivirkninger).

Effektmål*	**Vigtighed**	**Effektmålsgruppe**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Samlet overlevelse	*Kritisk*	*Dødelighed*	Median overlevelse	3 mdr.
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger**	Median PFS	3 mdr.
Behandlingsophør/ bivirkninger	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel der ophører behandling pga. uønskede hændelser	*Forskel på 10 %-point mellem grupperne*
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger*	*Kvalitativ gennemgang*	-
Livskvalitet	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	*Antal points ændring over tid målt med EORTC QLQC30*	*Forskel på 10 point mellem grupperne*

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

5 Resultater

5.1 Hvad er værdien af Elotuzumab i kombination med pomalidomid og dexamethason?

5.1.1 Litteratur

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

Ansøger har foretaget litteratursøgning i overensstemmelse med protokollen og identificeret syv publicerede artikler med data fra i alt tre studier. De inkluderede studier fremgår af tabel 2. Sammen med EPAR'ene for elotuzumab (Empliciti), pomalidomid (Imnovid) og carfilzomib (Kyprolis) vil de tre studier danne grundlag for Medicinrådets vurdering.

Tabel 2: Oversigt over inkluderede artikler

Titel	Forfatter og publikationsår	Intervention	Komparator	Studienavn (NCT-nummer)
Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma.	Dimopoulos et al. NEJM, 2018. [6]	EloPomDex	PomDex	ELOQUENT-3 (NCT02654132)
Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open label, multicentre study *Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial.* *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.* *Carfilzomib-Dexamethasone vs Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups.* *Health-related quality of life in the ENDEAVOR study: Carfilzomib dexamethasone vs bortezomib dexamethasone in relapsed/refractory multiple myeloma*	Dimopoulos et al. Lancet Oncol., 2016. [8] Dimopoulos et al. Lancet Oncol., 2017. [9] Moreau et al., Leukemia, 2017. [10] Orlowski et al., Clinical Lymphoma Myeloma and Leukemia. 2019. [11] Ludwig et al., Blood Cancer J. 2019. [12]	CarDex	BorDex	ENDEAVOR (NCT01568866)
Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial.	Richardson et al., Lancet Oncol., 2019. [13]	PomBorDex	BorDex	OPTIMISMM (NCT01734928)

5.1.2 Databehandling og analyse

Nedenfor beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål.

Ansøger baserer deres ansøgning på data fra tre studier. Det ene studie (ELOQUENT-3) er en direkte sammenligning mellem EloPomDex og den ene komparator PomDex. De to andre studier sammenligner bortezomib og dexamethason med henholdsvis PomBorDex (OPTIMISMM) og CarDex (ENDEAVOR). Studierne gennemgås enkeltvis nedenfor.

For den direkte sammenligning mellem EloPomDex og den ene komparator PomDex (ELOQUENT-3) er der direkte sammenlignende analyser for effektmålene *overlevelse*, *PFS* og *behandlingsophør grundet bivirkninger*. Ansøger har beregnet den absolutte forskel i medianoverlevelse og PFS ud fra HR som angivet i metodehåndbogen. Der er uoverensstemmelse mellem de observerede absolutte forskelle mellem studiearmene i studiet og de forskelle, der er beregnet ud fra de relative forskelle, hvilket skyldes at data stammer fra ét studie. Medicinrådet baserer vurderingen på de observerede forskelle, hvor det er muligt og anvender ikke de beregnede forskelle i vurderingen. For effektmålene kvalitativ gennemgang af bivirkninger og livskvalitet er sammenligningen mellem EloPomDex og PomDex narrativ.

For de øvrige komparatorer findes der ikke studier med en direkte sammenligning eller studier med en fælles komparator, der tillader en indirekte sammenligning. Derfor er vurderingen baseret på narrative sammenligninger mellem EloPomDex og de øvrige komparatorer ud fra data i studierne ENDEAVOR og OPTIMISMM.

Studiekarakteristik og baselinekarakteristik for de tre studier er opsummeret i tabel 3 og 4.

Tabel 3: Studiekarakteristik for de tre inkluderede studier

	ELOQUENT-3	OPTIMISMM	ENDEAVOR
Studiedesign	Fase 2, randomiseret, ublindet	Fase 3, randomiseret, ublindet.	Fase 3, randomiseret, ublindet
Start **Slut**	Marts 2016 December 2020	Januar 2013 Maj 2022	Juni 2012 Februar 2018
Intervention (antal pt.) **Komparator (antal pt.)**	EloPomDex (60) PomDex (57)	PomBorDex (281) BorDex (278)	CarDex (464) BorDex (465)
Population	≥ 2 tidligere behandlinger	≥ 1 tidligere behandlinger	1-3 tidligere behandlinger
Stratificering	• Antal tidligere behandlinger • ISS sygdomsstadie	• Antal tidligere behandlinger • Alder • β2-microglubolin-koncentration ved screening	• Antal tidligere behandlinger • ISS sygdomsstadie • Tidligere PI-behandling • I.v. eller s.c. adm. af bortezomib
Primært endepunkt	PFS	PFS	PFS
Sekundære endepunkter	OS, ORR	OS, ORR, sikkerhed	OS, ORR, responsvarighed, andel af patienter med ≥ grad 2 perifer neuropati, sikkerhed
Eksplorative endepunkter	Tid til respons, responsvarighed, sikkerhed og livskvalitet	Livskvalitet	Livskvalitet
Længste opfølgningstid	18,3 mdr.	26,2 mdr.	44,3 mdr.

Tabel 4: Baselinekarakteristik for de tre inkluderede studier

	ELOQUENT-3	OPTIMISMM	ENDEAVOR
Medianalder, år	69	67	65
Alder over 65 år, %	62	56	50-55
Tid siden diagnose, år (median)	4,8	4,0	3,7 år
Tidligere HDT/STS, %	52	58	i.o.
Antal tidligere behandlinger (median)	3 (2-8)	2 (1-5)	2 (1-2)
Tidligere ≥ 2 behandlinger, %	100	60	50
Tidligere behandling med lenalidomid, %	98	100	38
Lenalidomidrefraktæritet, %	90	71	24
Proteasomhæmmerrefraktæritet, %	78	13,2	3,2 (bortezomib)
ECOG performancestatus 0*	i.o.	51	48
Højrisiko cytogenetik, %	22	22	21
Creatinin clearance ≥ 60 mL/min	i.o.**	70 %	82 % (≥ 50 mL/min)

*i.o.: ikke oplyst. IMID: Immunmodulerende stof. PI: proteasomhæmmer. *Alle tre studier inkluderede kun patienter med performance status 0-2. **Patienter med creatinin clearence < 45 mL/min blev ekskluderet.*

ELOQUENT-3

Karakteristika

Studiet er et ublindet randomiseret fase 2-studie, som sammenligner effekten af EloPomDex (60 patienter) med PomDex (57 patienter). Opfølgningstiden er minimum 9,1 måneder for PFS og minimum 18,3 måneder for overlevelse (data i EPAR).

EloPomDex og PomDex blev doseret som anført under *nuværende behandling*, afsnit 5.

Analyser af primært (PFS) og sekundære effektmål (OS) blev lavet i ITT-populationen.

Fagudvalget bemærker, at studiepopulationen er lille, og at der er kort opfølgningstid, hvilket øger usikkerheden - særligt på bivirkningsdata.

Population

Patienterne i ELOQUENT-3 havde fået mindst to tidligere behandlinger, inklusive mindst to serier lenalidomid og en proteasomhæmmer. Patienterne var refraktære overfor deres seneste behandlingslinjer og enten refraktære overfor lenalidomid og en proteasomhæmmer eller havde haft progression under seks måneder efter behandling med lenalidomid eller en proteasomhæmmer.

Patientpopulationen stemmer overens med det kliniske spørgsmål og svarer godt til den danske population af patienter, der har modtaget 2-3 tidligere behandlinger, omend patienterne i studiet er lidt yngre, har bedre performance status og nyrefunktion som det ofte er tilfældet for kliniske studier. I studiet er patienter med creatinin clearence under 45 mL/min ekskluderet, selv om der ikke er kliniske årsager til at udelukke patienter med dårlig nyrefunktion, da hverken elotuzumab eller pomalidomid er forbundet med nyrepåvirkning.

Sammenlignet med ENDEAVOR og OPTIMISMM er patienterne længere henne i deres behandlingsforløb. 90 % af patienterne er refraktære overfor lenalidomid, og knap 80 % er refraktære overfor en proteasomhæmmer.

OPTIMISMM

Karakteristika
Studiet er et ublindet randomiseret fase 3-studie, som 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).

PomBorDex blev administreret indtil progression:

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

BorDex blev administreret som i interventionsarmen. 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. Analyser af primært (PFS) og sekundære effektmål (OS) blev lavet i ITT-populationen.

Population
Det var et inklusionskriterie, at patienterne tidligere var behandlet med lenalidomid i mindst to serier, og de måtte gerne være lenalidomidrefraktære. Patienterne måtte gerne være behandlet med og være refraktære overfor bortezomib. Baselinekarakteristika er overordnet set ligeligt fordelt i de to arme og er opsummeret i tabel 3.

Patientpopulationen adskiller sig fra populationen i det kliniske spørgsmål, idet patienterne er tidligere i deres behandlingsforløb, og 40 % kun har modtaget én tidligere behandling.

Ligesom i ELOQUENT-studiet er der en høj andel af lenalidomidrefraktære patienter (71 %), men kun 13 % er refraktære overfor en proteasomhæmmer mod 78 % i ELOQUENT-studiet.

For PFS er der data for subgruppen af patienter, der tidligere har modtaget mindst to tidligere behandlinger. Da den subgruppe må forventes at ligne den danske population bedre, fordi den er længere i behandlingsforløbet, inkluderes data herfra i vurderingen, hvor det er muligt.

ENDEAVOR

Karakteristika
ENDEAVOR er et ublindet randomiseret fase 3-studie, som sammenligner effekten af CarDex (464 patienter) med effekten af BorDex (465 patienter).

CarDex administreres i serier a 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 a 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.

Analyser af effekt (PFS, OS) blev lavet i ITT-populationen, og analyser af sikkerhed blev lavet i safety-populationen.

Population
De inkluderede patienter skulle have dokumenteret partielt repons på mindst én tidligere behandling. Tidligere behandling måtte gerne inkludere en proteasomhæmmer (carfilzomib eller bortezomib), hvis de havde opnået mindst partielt respons på den behandling, ikke var ophørt pga. toksicitet og ikke havde modtaget behandling med en proteasomhæmmer i mindst seks måneder før inklusion i studiet. Myokardieinfarkt eller klasse 3 eller 4 hjertesvigt (ifølge New York Heart Association) indenfor de seneste fire måneder var et eksklusionskriterie i studiet. Baselinekarakteristika er overordnet set ligeligt fordelt i de to arme og opsummeret i tabel 4.

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 ELOQUENT og OPTIMISSM er henholdsvis 98 og 100 % tidligere behandlet med lenalidomid, og 100 henholdsvis 60 % af patienterne i de to studier har fået to eller flere tidligere behandlinger. Patienterne i den samlede patientpopulation i ENDEAVOR er dermed tidligere i deres behandlingsforløb end patientpopulationen i ELOQUENT-3. I overensstemmelse hermed er andelen af patienter, der er refraktære overfor lenalidomid og/eller en proteasomhæmmer, væsentlig mindre i ENDEAVOR end i de to andre studier.

I ENDEAVOR er der publicerede subgruppeanalyser for subgruppen, der har modtaget 2-3 behandlinger inklusive lenalidomid. Den subgruppe må forventes at ligne patientpopulationen i ELOQUENT-3 og den danske population defineret i det kliniske spørgsmål bedre, hvorfor data fra denne subgruppe vil anvendes i vurderingen, hvor det er muligt. Hvorvidt subgruppen var prædefineret er uklart.

5.1.3 Evidensens kvalitet

Fagudvalget har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1).

GRADE-profilen for den direkte sammenligning mellem EloPomDex og PomDex kan ses i bilag 1. Der er ikke foretaget GRADE-vurderinger af de narrative sammenligninger. Risk of bias er vurderet for alle tre studier ved Cochranes Risk of bias 2.0-værktøjet og fremgår ligeledes af bilag 1.

Dette er nedgraderet for inkonsistens og unøjagtighed for alle effektmål. Det skyldes, at datagrundlaget udgøres af kun ét studie, og dermed kan resultaterne være inkonsistente i forhold til fremtidige sammenlignelige studier. Da studiepopulationen er lille, er effektestimaterne behæftet med usikkerhed; det vil sige, at de resultater, der er i studiet, er unøjagtige. Studiet er ublindet, hvilket giver en risiko for bias for effektmålet *behandlingsophør på grund af uønskede hændelser*, da behandlingsophøret kan være påvirket af patienternes viden om, hvilken behandling de får. Derfor er der også nedgraderet for risk of bias for effektmålet *behandlingsophør*.

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.4 Effektestimater og kategorier

Sammenligning med PomDex
I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for sammenligningen mellem EloPomDex og PomDex.

Fagudvalget vurderer, at EloPomDex til patienter med knoglemarvskræft giver en **merværdi af ukendt størrelse** sammenlignet med PomDex. Evidensens kvalitet vurderes at være meget lav.

I tabel 5 herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede værdier, den samlede kategori for lægemidlet og kvaliteten af den samlede evidens.

Tabel 5: Kategorier og resultater for sammenligning mellem EloPomDex og PomDex

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	Ikke beregnet*	Kan ikke kategoriseres	HR: 0,54 (0,30-0,96)	Merværdi af ukendt størrelse	Merværdi af ukendt størrelse
	Median PFS	Vigtigt	5,6 mdr.	Kan ikke kategoriseres	HR: 0,54 (0,34-0,86)	Moderat merværdi	
Behandlings-ophør / bivirkninger	Andel der ophører behandling på grund af uønskede hændelser (10 %-point)	Kritisk	-5,3 %-point (-14,7-13,8)	Kan ikke kategoriseres	RR: 0,78 (0,39-1,59)	Kan ikke kategoriseres	Kan ikke kategoriseres
	Kvalitativ gennemgang	Vigtigt	Ikke relevant da vurderingen er kvalitativ				
Livskvalitet	Antal points ændring over tid målt med EORTC QLQC30 (10 point)	Vigtigt	Ingen data	Kan ikke kategoriseres	Ingen data	Kan ikke kategoriseres	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi		Merværdi af ukendt størrelse					
Kvalitet af den samlede evidens		*Meget lav*					

**Medianen er kun nået i komparatorarmen.*

Sammenligning med PomBorDex
Den samlede værdi af EloPomDex sammenlignet med PomBorDex **kan ikke kategoriseres**, da vurderingen er baseret på en narrativ sammenligning, jf. Medicinrådets metoder. Fagudvalget vurderer, at EloPomDex samlet set ikke har dårligere effekt eller sikkerhedsprofil end PomBorDex.

Effektestimaterne fra de to studier, der udgør datagrundlaget præsenteres under gennemgangen af hvert effektmål.

Sammenligning med CarDex
Den samlede værdi af EloPomDex sammenlignet med CarDex **kan ikke kategoriseres**, da vurderingen er baseret på en narrativ sammenligning, jf. Medicinrådets metoder. Fagudvalget vurderer, at EloPomDex samlet set ikke har dårligere effekt eller sikkerhedsprofil end CarDex.

Effektestimaterne fra de to studier, der udgør datagrundlaget præsenteres under gennemgangen af hvert effektmål.

Overlevelse

Fagudvalget ønskede at se effektmålet *overlevelse* opgjort som medianoverlevelse. Såfremt overlevelsesdata ikke var modent, ønskede fagudvalget at supplere med data for PFS som et vigtigt effektmål. I ELOQUENT-3 er data for medianoverlevelse ikke modent, hvorfor både overlevelse og PFS vil indgå i vurderingen. Modenheden blev vurderet ud fra, om medianerne er nået, og om der er mange censureringer, der ligger omkring medianen på Kaplan-Meier-kurven. Kun i PomDex-armen er PFS-data modent ved opfølgningstiden på minimum 9,1 måneder, hvorfor data skal tolkes med forsigtighed.

De mediane overlevelser og PFS-værdier for de tre studier er vist i tabel 6.

Tabel 6: Data for overlevelse (OS) og PFS fra de tre studier.

	ELOQUENT-3		OPTIMISMM		ENDEAVOR	
	EloPomDex	PomDex	PomBorDex	BorDex	CarDex	BorDex
Medianoverlevelse, måneder	i.n. (24,9-NE)	17,4 (13,8-NE)	40,5 (29,83-NE)	30,5 (24,6-35,9)	39,5*	28,4*
HR for overlevelse	0,54 (0,30-0,96)		0,91 (0,70-1,18)		0,75 (0,59-0,96)	
Median PFS, måneder	10,3 (6,5-NE)	4,7 (2,8-7,6)	11,2 (6,66-13,73)	7,1 (5,88-8,48)	9,7*	6,6*
HR for PFS	0,54 (0,34-0,86)		0,61 (0,49-0,77)**		0,73 (0,53-1,01)	

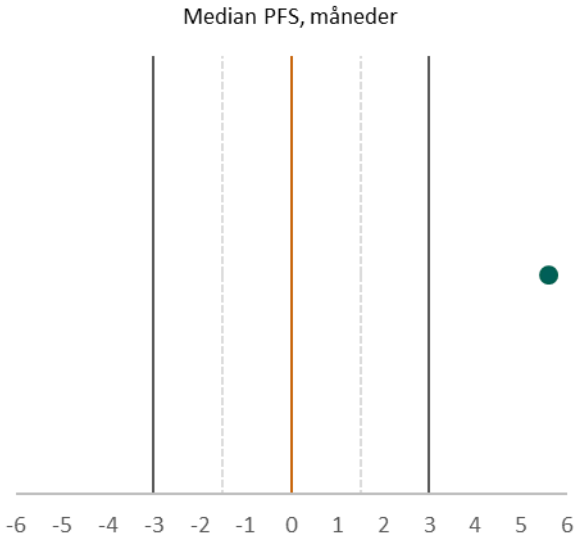
**Data fra subgruppen der har modtaget 2-3 behandlinger. NE = not estimatable. ** HR for subgruppen der har modtaget > 1 tidligere behandling er HR: 0,63 (0,48-0,83).*

Sammenligning med PomDex

Forskellen i medianoverlevelse mellem de to arme kan ikke beregnes, da medianen kun er nået i komparatorarmen. Derfor kan den foreløbige værdi for den absolutte forskel ikke kategoriseres efter Medicinrådets metoder.

Den relative effektforskel for overlevelse baseret på det seneste data cut-off med en opfølgningstid på minimum 18,3 måneder (data fra EPAR) er HR 0,54 (0,30-0,96), hvilket kategoriserer EloPomDex med en foreløbig merværdi af ukendt størrelse.

For PFS er den absolutte forskel mellem den mediane PFS i de to arme 5,6 måneder, afbildet i figur 1 herunder. Punktestimatet afspejler en klinisk relevant forskel, men da der ikke kan beregnes et konfidensinterval omkring forskellen, kan den foreløbige værdi ikke kategoriseres. Den relative effektforskel baseret på en opfølgningstid på 9,1 måned er HR 0,54 (0,34-0,86), hvilket giver en foreløbig moderat merværdi.



Figur 1. Punktestimat for den absolutte forskel mellem EloPomDex og PomDex for median PFS (5,6 mdr.). Den midterste linje indikerer ingen forskel (0). De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Data for både overlevelse og PFS er umodent, idet der er mange censureringer før medianen, hvilket gør det sandsynligt, at tidspunktet for medianen ændrer sig ved en længere opfølgningstid. Den usikkerhed bør afspejles i den aggregerede kategori for effektmålet, som fagudvalget derfor vurderer at være merværdi af ukendt størrelse.

Sammenligning med PomBorDex
Sammenligningen med PomBorDex er narrativ baseret på data fra ELOQUENT-3 og OPTIMISMM. Derfor kan den samlede værdi ikke kategoriseres. Data for overlevelse og for PFS er umodent, og studiepopulationerne er forskellige, hvilket vanskeliggør en sammenligning.

Sammenligning med CarDex
Sammenligningen med CarDex er narrativ, baseret på data fra ELOQUENT-3 og ENDEAVOR. Data for overlevelse og for PFS er umodent. Studiepopulationerne er forskellige, hvilket vanskeliggør en sammenligning. Den samlede værdi kan ikke kategoriseres.

Baseret på data for medianoverlevelse og PFS vurderer fagudvalget, at EloPomDex ikke ser ud til at være dårligere end hverken PomBorDex eller CarDex. Baseret på den nedre grænse i konfidensintervallet for den mediane overlevelse (tabel 5) vurderer fagudvalget, at der er en høj sandsynlighed for, at medianen ligger over 25 måneder. Dette er en god effekt i sammenligning med PomBorDex og CarDex, når der tages højde for, at populationen er senere i behandlingsforløbet end populationerne i de andre studier.

Data for PFS ligger i samme størrelsesorden på tværs af de tre studier, hvilket understøtter, at EloPomDex ikke er dårligere end hverken PomBorDex eller CarDex.

Behandlingsophør grundet uønskede hændelser (kritisk)

Data for behandlingsophør fra de tre studier er gengivet i tabel 7.

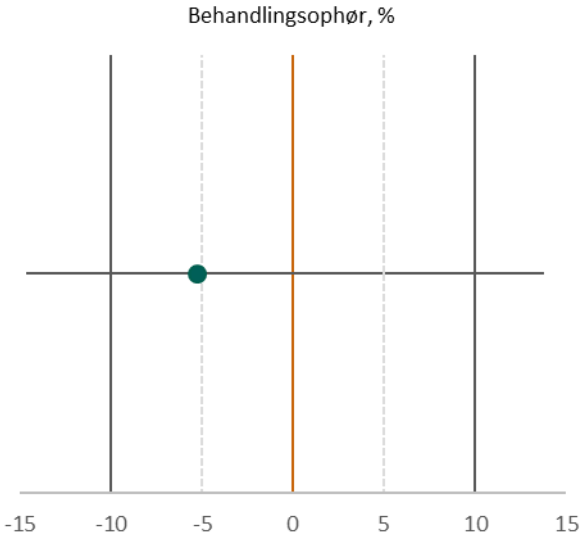
Tabel 7: Data for behandlingsophør fra de tre studier.

	ELOQUENT-3		OPTIMISMM		ENDEAVOR	
	EloPomDex	PomDex	PomBorDex	BorDex	CarDex	BorDex
Behandlingsophør grundet uønskede hændelser (%)	18,3	23,6	28,8	18,9	22,5*	23,1*
RR	0,78 (0,39-1,59)		1,52 (1,12-2,07)		0,97 (0,70-1,36)**	

**Data fra subgruppen der har modtaget 2-3 behandlinger. **Beregnet på baggrund af data i den endelige ansøgning.*

Sammenligning med PomDex

Sammenligningen med PomDex baserer sig på data fra den direkte sammenligning i ELOQENT-3. Der ses et højere frafald i PomDex-armen og den absolutte forskel mellem de to studiearme er -5,3 %- point (-14,7-13,8), afbildet på figur 2 herunder. Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervaller ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi ikke kategoriseres efter Medicinrådets metode.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel mellem EloPomDex og PomDex (-5,3 %-point) for behandlingsophør grundet uønskede hændelser. Den midterste linje indikerer ingen forskel (0).
De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den relative forskel mellem de to studiearme er RR 0,78 (0,39-1,59). På grund af det brede konfidensinterval, der rummer både positiv og negativ værdi, kan den foreløbige værdi ikke kategoriseres.

De tilsyneladende færre tilfælde af behandlingsophør i EloPomDex-armen kan skyldes færre sygdomsrelaterede hændelser pga. en mere effektiv behandling. Fagudvalget bemærker, at der også er forhold vedrørende studiedesignet, der bidrager til usikkerheden, f.eks. det ublindede design, det lille antal patienter og den korte opfølgningstid.

Sammenligning med PomBorDex

Sammenligningen med PomBorDex er narrativ og baserer sig på data fra studierne ELOQUENT-3 og OPTIMISMM. Værdien for effektmålet kan ikke kategoriseres.

Data for behandlingsophør fra OPTIMISMM-studiet indikerer, at tillæg af pomalidomid til bortezomib og dexamethason øger behandlingsophøret sammenlignet med bortezomib og dexamethason alene. Tillæg af elotuzumab til pomalidomid og dexamethason ser ikke ud til at have samme negative effekt i en ellers lidt ældre og mere syg population.

Sammenligning med CarDex
Sammenligningen med CarDex er narrativ og baserer sig på data fra studierne ELOQUENT-3 og ENDEAVOR. Værdien for effektmålet kan derfor ikke kategoriseres.

Kvalitativ gennemgang af bivirkninger (vigtigt)

Ansøger har indsendt data for uønskede hændelser i stedet for bivirkninger. Bivirkninger udgør den delmængde af uønskede hændelser, som vurderes at være relateret til behandlingen og er derfor følsom overfor risiko for bias, hvis studiet er ublindet. Da alle tre inkluderede studier er ublindede, vurderer fagudvalget, at det indsendte data for uønskede hændelser kan danne grundlag for vurderingen. Ansøger har indsendt en opgørelse med uønskede hændelser, der optræder hos mere end 10 % af patienterne i en af studiearmene fra de tre studier. Fagudvalget har medtaget de væsentligste hændelser i tabel 8.

Fagudvalget bemærker, at sammenligningen på tværs af de tre studier er vanskelig pga. de forskellige opfølgningstider, og at forskelle mellem studiearmene er forbundet med stor usikkerhed. ELOQUENT-3 er et væsentligt mindre studie end de to andre, hvilket betyder, at sandsynligheden for at detektere sjældne bivirkninger er mindre for EloPomDex.

Andelen af patienter med hæmatologiske hændelser er høj, men sammenlignelige for de fire behandlingstyper. Fagudvalget bemærker, at den tilsyneladende højere hæmatologiske toksicitet i PomDex-armen kan skyldes en dårligere effekt af PomDex i patientpopulationen. Andelen af patienter med grad 3/4 lymfopeni er højere for EloPomDex, men tilsyneladende ikke forbundet med flere infektioner. Fagudvalget vurderer, at de hæmatologiske bivirkninger er håndterbare, da de ofte kan afhjælpes ved dosisreduktion, transfusioner og ved neutropeni GCSF.

Perifer sensorisk neuropati, som er generende for patienten og kan være irreversibel, er typisk forbundet med bortezomibholdige behandlinger. Der er ikke data for neuropati for EloPomDex.

Behandling med EloPomDex ser ud til at være forbundet med en lavere andel af patienter, som oplever diarré, træthed og øvre luftvejsinfektioner sammenlignet med CarDex og PomBorDex. Dette er også gældende for træthed af sværhedsgrad 3 og 4, mens andelen af de resterende grad 3 og 4 bivirkninger er sammenlignelig mellem behandlingerne på nær hypertension, som er hyppigere ved behandling med CarDex.

Generelt vurderer fagudvalget, at bivirkningsprofilen ikke er dårligere for EloPomDex end for de tre komparatorer, og at EloPomDex ser ud til at være forbundet med færre bivirkninger end PomBorDex og CarDex, hvilket stemmer overens med den kliniske erfaring med elotuzumab som et veltolereret stof. Usikkerheden vedrørende data er dog stor på grund af ELOQUENT-3's korte opfølgningstid og lille størrelse. Derfor er der ikke grundlag for at skelne mellem de fire behandlinger, hvad angår bivirkningstyngden.

Tabel 8: Udvalgte uønskede hændelser af relevans for vurderingen.

Udvalgte uønskede hændelser af relevans for vurderingen								
	Alle hændelser, % (hyppighed > 10 %)				Grad 3+4 hændelser, %			
	ELOQUENT 3		OPTIMISMM	ENDEAVOR	ELOQUENT 3		OPTIMISMM	ENDEAVOR
	EloPomDex	**PomDex**	**PomBorDex**	**CarDex**	**EloPomDex**	**PomDex**	**PomBorDex**	**CarDex**
Infektioner og manifestationer								
Øvre luftvejsinfektioner	11,7	14,5	20,9	20,3	0	1,8	i.o.	1,7
Bronkitis	10	9	14	16,4	1,7	1,8	i.o.	2,8
Lungebetændelse	6,7	10,9	19,1	8,9	5,0	9,1	11,5	8,4
Gastrointestinale bivirkninger								
Forstoppelse /obstipation	21,7	10,9	36,7	14,7	1,7	0	2,5	0,4
Diarré	18,3	9,1	33,8	30,9	i.o.	i.o.	7,2	3,9
Hæmatologiske bivirkninger								
Neutropeni	23,3	30,9	46,8	5,4	13,3	27,3	41,7	2,4
Trombocytopeni	15	18,2	36,7	20,5	8,3	5,5	27,3	8,9
Anæmi	25	36,4	28,4	39,3	10	20	14,0	16,4
Lymfopeni	10,0	1,8	i.o.	5,6	8,3	1,8	4,3	4,8
Leukopeni	8,3	5,5	11,5	i.o.	8,3	3,6	5,4	1,1
Neurologiske bivirkninger								
Perifer sensorisk neuropati	i.o.	i.o.	47,8	5,8	i.o.	i.o.	8,3	0,2
Kardiovaskulære bivirkninger								
Hypertension	1,7	3,6	6,5	24,8	1,7	0	2,9	14,5
Hjertesygdom	12	11	22,7	i.o.	i.o.	i.o.	1,1	2,6
Lungeemboli	i.o.	i.o.	4,0	1,9	i.o.	i.o.	4,0	1,9
Generelle gener								
Træthed (Fatigue)	15	16,4	37,1	29,4	0	3,6	8,3	6,7
Muskelkramper	13,3	5,5	18,6	9,4	i.o.	i.o.	i.o.	i.o.

i.o. ikke oplyst

Livskvalitet (vigtigt)

Sammenligningen med PomDex
Data for livskvalitet i ELOQUENT-3-studiet er ikke publiceret. Livskvalitet blev målt med EQ-5D-3L. Værdien for effektmålet kan ikke kategoriseres, da der ikke er publicerede data.

Sammenligningen med PomBorDex.
Livskvalitet blev målt med det cancerspecifikke spørgeskema EORTC-QLQ-C30 i OPTIMISMM. Der var ingen forskel mellem de to studiearme (PomBorDex og BorDex). Da der ikke er data fra ELOQUENT-3-studiet, er det ikke muligt at sammenligne effekten på livskvalitet mellem behandlingerne. Derfor kan værdien for effektmålet ikke kategoriseres.

Sammenligningen med CarDex
Livskvalitet blev målt med det cancerspecifikke spørgeskema EORTC-QLQ-C30 i ENDEAVOR-studiet. Der var ingen forskel mellem de to studiearme (CarDex og BorDex). Da der ikke er data fra ELOQUENT-3-studiet, er det ikke muligt at sammenligne effekten på livskvalitet mellem behandlingerne. Derfor kan værdien for effektmålet ikke kategoriseres.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at EloPomDex sammenlignet med PomDex har en **merværdi af ukendt størrelse**. Evidensens kvalitet er meget lav.

Værdien af EloPomDex sammenlignet med PomBorDex og CarDex **kan ikke kategoriseres**, da det ikke er muligt at gennemføre statistiske sammenlignende analyser, jf. Medicinrådets metoder. Evidensens kvalitet kan ikke vurderes.

Sammenligningen med PomDex
Fagudvalget vurderer, at data for overlevelse og PFS tilsammen giver EloPomDex en merværdi af ukendt størrelse sammenlignet med PomDex, usikkerheden vedrørende datamodenhed taget i betragtning.

Værdien for effektmålet *behandlingsophør* kan ikke kategoriseres pga. stor usikkerhed om effektestimatet. Tillægget af elotuzumab til pomalidomid og dexamethason ser ikke ud at påvirke behandlingsophøret i en negativ retning, hvilket indikerer, at EloPomDex tolereres godt.

Den kvalitative gennemgang af bivirkninger viser ikke væsentlige forskelle mellem de to behandlinger, hvilket er i overensstemmelse med fagudvalgets kliniske erfaring, som er at elotuzumab generelt er veltolereret.

Der er ingen data for livskvalitet, hvorfor værdien for det effektmål ikke kan kategoriseres.

Samlet set vurderer fagudvalget at EloPomDex har en **merværdi af ukendt størrelse** sammenlignet med PomDex. Fagudvalget har lagt vægt på merværdien for det kritiske effektmål *overlevelse* i kombination med en bivirkningsprofil, der ikke er væsentligt forskellig fra PomDex. Evidensens kvalitet vurderes at være meget lav.

Kun for de patienter, der ikke ønsker en intravenøs behandling, vil PomDex være at foretrække.

Sammenligningen med PomBorDex
Fagudvalget vurderer, at effekten af EloPomDex på *overlevelse* og *PFS* er sammenlignelig med effekten af PomBorDex, usikkerheden på sammenligningen hvad angår forskelle i studiepopulationer taget i betragtning.

Hvor tillægget af pomalidomid til bortezomib og dexamethason i OPTIMISMM øger behandlingsophøret, ser tillægget af elotuzumab til pomalidomid og dexamethason ikke ud til at øge behandlingsophøret i ELOQUENT-3. Det er i overensstemmelse med fagudvalgets kliniske erfaring, at elotuzumab generelt er veltolereret.

Hvad angår bivirkninger, tyder data for uønskede hændelser på, at bivirkningsprofilen er sammenlignelig, muligvis mindre generende for EloPomDex i forhold til PomBorDex. Sammenligningen er dog vanskelig og på usikkert grundlag på grund af forskelle i studiepopulationer, kort opfølgningstid og lille studiepopulation i ELOQUENT-3-studiet.

Den samlede værdi **kan ikke kategoriseres** sammenlignet med PomBorDex. Samlet set vurderer fagudvalget, at EloPomDex ikke er et dårligere behandlingsalternativ end PomBorDex, hvad angår effekt. EloPomDex har muligvis en lettere bivirkningsprofil, og det er en fordel, at behandlingskombinationen ikke indeholder bortezomib, som mange patienter vil være behandlet med tidligere.

Sammenligningen med CarDex
Fagudvalget vurderer, at effekten af EloPomDex på *overlevelse* og *PFS* ikke er dårligere sammenlignet med effekten af CarDex. CarDex er undersøgt i en population, der er tidligere i behandlingsforløbet og med lavere andel af proteasomhæmmerrefraktære patienter, og det er derfor rimeligt at antage, at effekten af

CarDex ville være mindre i studiepopulationen fra ELOQUENT og den danske population svarende til indikationen.

Data tyder ikke på at der er forskel på, hvor mange patienter der ophører behandlingen på grund af uønskede hændelser.

Data for uønskede hændelser tyder på, at bivirkningstyngden for EloPomDex er sammenlignelig med bivirkningstyngden for CarDex, omend sammenligningen er vanskelig på grund af forskelle i studiepopulationer, kort opfølgningstid og lille studiepopulation i ELOQUENT-3-studiet.

Den samlede værdi **kan ikke kategoriseres** sammenlignet med CarDex. Samlet set vurderer fagudvalget, at EloPomDex ikke er dårligere end CarDex, hvad angår effekt og bivirkninger.

Samlet vurdering
Fagudvalget vurderer, at EloPomDex er at foretrække fremfor PomDex i den danske population, der tidligere har modtaget mindst to behandlinger. Vurderingen er baseret på en bedre effekt og bedre bivirkningsprofil. Typisk vil de patienter, der i dag behandles med PomDex, have modtaget tre tidligere behandlinger, hvilket svarer til det mediane antal tidligere behandlinger i ELOQUENT-3.

Fagudvalget vurderer, at EloPomDex ikke er et dårligere behandlingsalternativ end PomBorDex og CarDex, som i dansk klinisk praksis typisk anvendes til patienter, der tidligere har modtaget to behandlinger. De to forudgående behandlinger er oftest en primærbehandling indeholdende bortezomib og lenalidomid efterfulgt af et daratumumabholdigt regime. EloPomDex er i ELOQUENT-3-studiet vist at være effektiv i en population med høj andel af proteasomhæmmer- og lenalidomidrefraktæritet. Fagudvalget vurderer på den baggrund, at EloPomDex vil være et egnet behandlingsvalg i den danske population, der efter to eller tre behandlinger igen er behandlingskrævende.

En patient på det behandlingsstadie vil typisk være behandlingsnaiv overfor både pomalidomid og elotuzumab. Samtidig tyder data på, at elotuzumab er skånsom for patienten og derfor velegnet til patienter, som er sent i deres sygdomsforløb, og som har været behandlet med bortezomib.

Forudgående behandling med et pomalidomidholdigt regime vil udelukke en ny behandling indeholdende pomalidomid.

6 Andre overvejelser

Fagudvalget har i protokollen stillet spørgsmål til ansøger vedrørende valg af behandlinger efter EloPomDex, hvorvidt der er et alternativ til H2-blokker, hvilken administrationsvej der anvendes ved dexamethason præmedicinering og effekten af elotuzumab efter behandling med daratumumab.

Påvirkning af efterfølgende behandlingslinjer
Ansøger har ikke data, der viser, hvordan anvendelse af EloPomDex påvirker valg af efterfølgende behandlinger. Ansøger har i den sundhedsøkonomiske analyse angivet daratumumab-monoterapi og BorDex som mulige behandlingsvalg efter EloPomDex. Fagudvalget vurderer, at en meget lille andel af den danske patientpopulation vil være kandidater til daratumumab, da langt de fleste vil have været behandlet med et daratumumabholdigt regime i 2. linje. Så godt som ingen patienter vil blive behandlet med BorDex på dette tidspunkt i behandlingsforløbet. Efter EloPomDex vil eneste tilbageværende behandlingsmuligheder reelt være nye lægemidler i protokol eller ældre behandlinger som thalidomid og cyclofosfamid.

Fagudvalget skønner, at såfremt EloPomDex tages i brug, vil det forventeligt erstatte 80 % af PomDex, 10 % af CarDex og 90 % af PomBorDex.

Administrationsvej for dexamethason i forbindelse med præmedicinering
Fagudvalget bad ansøger redegøre for, hvorfor det i SPC'et er angivet, at dexamethason som præmedicinering til elotuzumab skal gives intravenøst, når det ellers doseres oralt. Ansøger angiver, at de ikke har data for infusionsrelaterede bivirkninger ved elotuzumab, hvis dexamethason som præmedicinering doseres oralt. Fagudvalget bemærker, at der i de forskellige regioner er lidt forskellig praksis og baseret på fagudvalgets erfaring, er der ikke forskel på, om det gives oralt eller intravenøst.

Alternativ H2-blokker
Udover dexamethason gives præmedicinering med en H1- og en H2-blokker samt paracetamol for forebyggelse af infusionsrelaterede reaktioner. Fagudvalget ønskede belyst, om ansøger anbefaler en alternativ H2-blokker, hvis ikke ranitidin er tilgængelig.

Ansøger angiver, at der i EMAs produktresumé står, at præmedicinering inkluderer ranitidin eller tilsvarende (f.eks. cimetidin eller famotidin). Fagudvalget bemærker, at cimetidin er forbundet med mange lægemiddelinteraktioner. I situationer, hvor ranitidin ikke har været tilgængeligt, bemærker fagudvalget, at der ikke er dårlige erfaringer med at udelade en H2-blokker fra præmedicineringen.

Erfaring med behandlingskombinationer indeholdende elotuzumab efter behandling med et daratumumabholdigt regime
Fagudvalget efterspørger data for effekten af elotuzumab efter daratumumab, idet det bedst afspejler et behandlingsforløb i dansk klinisk praksis, men kun ca. 2 % af patienter i ELOQUENT-3 tidligere var behandlet med daratumumab.

Ansøger angiver, at der ikke findes data fra randomiserede studier, men henviser til et observationelt studie for at belyse effekten af elotuzumab efter behandling med daratumumab. Baseret på real world-data er elotuzumab i studiet en af de behandlinger, der anvendes i længst tid efter et daratumumabholdigt regime, hvilket indikerer, at elotuzumab har effekt efter behandling med daratumumab.

7 Relation til behandlingsvejledning

Fagudvalget har foreløbig placeret EloPomDex under 'anvend' til 2. relapsbehandling i Medicinrådets behandlingsvejledning for knoglemarvskræft. Det kan få betydning for lægemiddelrekommandationen.

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9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende knoglemarvskræft

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
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10 Versionslog

Version	Dato	Ændring
1.0	18. marts 2020	Godkendt af Medicinrådet.

11 Bilag 1: Evidensens kvalitet

11.1 Cochrane, Risk of Bias

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

	ELOQUENT-3*	OPTIMISMM**	ENDEAVOR***
Risiko for bias i randomiseringsprocessen	*lav*	*lav*	*lav*
Risiko for bias grundet afvigelser fra tilsigtet intervention (effekt af tildeling til intervention)	*forbehold*	*forbehold*	*forbehold*
Manglende data for effektmål	*lav*	*forbehold*	*forbehold*
Risiko for bias ved indsamlingen af data	*forbehold*	*forbehold*	*forbehold*
Risiko for bias ved udvælgelse af resultater der rapporteres	*Lav*	*lav*	*lav*
Overordnet risiko for bias	*forbehold*	*forbehold*	*lav*

* Det bemærkes at *The investigators collected the data, which were maintained by the sponsors. The manuscript was prepared with assistance from professional medical writers who were funded by Bristol-Myers Squibb. The authors contributed to the development of the manuscript, approved the final version, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.*

** Det bemærkes 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.*

*** Det bemærkes, at en stor del af medforfatterne har økonomiske interessekonflikter og *The funder collaborated with the authors in the interpretation of the data.*

11.2 GRADE-Tabel

GRADE-profil EloPomDex vs. PomDex (ELOQUENT-3)

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	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ingen	60	57	HR: 0,54 [0,30; 0,96]	-	⨁⨁◯◯ LAV	KRITISK
PFS, median (måneder)												
1	Randomiseret undersøgelse	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ingen	60	57	HR: 0,54 [0,34; 0,86]	5,6	⨁⨁◯◯ LAV	VIGTIGT
Behandlingsophør på grund af uønskede hændelser (%-point)												
1	Randomiseret undersøgelse	Alvorlig[c]	Alvorlig[a]	Ikke alvorlig	Alvorlig[b]	Ingen	60	55	RR: 0,78 [0,39; 1,59]	-5,3 (-14,7 – 13,8)	⨁◯◯◯ MEGET LAV	KRITISK
Livskvalitet												
0	-	-	-	-	-	-	-	-	-	-	⨁◯◯◯ MEGET LAV	VIGTIGT

CI: Konfidensinterval; HR: Hazard ratio; RR: Relativ risiko
a. Der er kun data fra ét studie. Derfor nedgraderes ét niveau for inkonsistens.
b. Der er et bredt konfidensinterval, hvilket indikerer stor usikkerhed om estimatet. 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.

Bristol-Myers Squibb

APPLICATION FOR THE ASSESSMENT OF ELOTUZUMAB IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE FOR ADULT PATIENTS WITH MULTIPLE MYELOMA WHO HAVE RECEIVED AT LEAST TWO PRIOR THERAPIES INCLUDING LENALIDOMIDE AND A PROTEASOME INHIBITOR

CONTENTS

1 BASIC INFORMATION

TABLE 1. CONTACT INFORMATION

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Title	Market Access Manager
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Name	Stephanie Serre
Title	Scientific Advisor
Area of responsibility	clinical/medical
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TABLE 2. OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Empliciti®
Generic name	Elotuzumab
Marketing authorization holder in Denmark	Bristol-Myers Squibb Denmark, subsidiary of Bristol-Myers Squibb AB, Sweden
ATC code	L01XC23
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies
Active substance(s)	Elotuzumab
Pharmaceutical form(s)	Powder for concentrate for solution for infusion
Mechanism of action	Elotuzumab is an immunostimulatory humanised, IgG1κ monoclonal antibody that specifically targets the signalling lymphocyte activation molecule family member 7 (SLAMF7) protein. The SLAMF7 protein is highly expressed on multiple myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on natural killer cells (NK cells), normal plasma cells, and other immune cells including some T cell subsets, monocytes, B cells, macrophages, and plasmacytoid dendritic cells, but is not detected on normal solid tissues or haematopoietic stem cells.[1] Elotuzumab directly activates NK cells through both the SLAMF7 pathway and Fc receptors enhancing anti-myeloma activity in vitro. Elotuzumab also targets SLAMF7 on myeloma cells and through interactions with Fc receptors on specific immune cells, promotes the killing of myeloma cells through NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and macrophage-mediated antibody-dependent cellular phagocytosis (ADCP). In nonclinical models, elotuzumab has

	demonstrated synergistic activity when combined with lenalidomide, pomalidomide or bortezomib.[1]
Dosage regimen[1]	The recommended dosing schedule for elotuzumab in combination with pomalidomide and dexamethasone differs from the dosing schedule for elotuzumab in combination with lenalidomide and dexamethasone. The length of each treatment cycle is 28 days (see below the table Recommended dosing schedule of elotuzumab in combination with pomalidomide and dexamethasone). Treatment should continue until disease progression or unacceptable toxicity. **Elotuzumab:** The recommended dose of elotuzumab is 10 mg/kg administered intravenously every week on days 1, 8, 15, and 22 of each treatment cycle for the first two cycles, and then 20 mg/kg administered on day 1 of each treatment cycle thereafter. **Pomalidomide:** The recommended dose of pomalidomide is 4 mg orally once daily on days 1 – 21 of repeated 28-day cycles, and at least 2 hours after elotuzumab infusion when administered on the same day. **Dexamethasone:** • On days that elotuzumab is administered, patients ≤ 75 years old are recommended to take dexamethasone 28 mg orally between 3 and 24 hours before elotuzumab, plus 8 mg intravenously between 45 and 90 minutes before elotuzumab, and patients > 75 years old are recommended to take dexamethasone 8 mg orally between 3 and 24 hours before elotuzumab, plus 8 mg intravenously between 45 and 90 minutes before elotuzumab • On days that elotuzumab is not administered, but a dose of dexamethasone is scheduled (Days 8, 15 and 22 of cycle 3 and all subsequent cycles), 40 mg orally is recommended for patients ≤ 75 years old, and 20 mg orally is recommended for patients > 75 years old **Premedication for prevention of infusion reaction:** Patients must be administered with the following pre-medications 45 – 90 minutes prior to elotuzumab infusion for prevention of infusion reaction: • Dexamethasone 8 mg intravenous • H1 blocker: diphenhydramine (25 – 50 mg orally or intravenous) or equivalent H1 blocker • H2 blocker: ranitidine (50 mg intravenous or 150 mg orally) or equivalent H2 blocker • Paracetamol (650 – 1000 mg orally) Prophylaxis against thromboembolism was required for all patients in the ELOQUENT-3 study.

<table>
<tr><td></td><td>
Recommended dosing schedule of Elotuzumab in combination with pomalidomide and dexamethasone[1]
<table>
<tr><td>Cycle</td><td colspan="4">28-Day Cycles 1 and 2</td><td colspan="4">28-Day Cycles 3+</td></tr>
<tr><td>Day of Cycle</td><td>1</td><td>8</td><td>15</td><td>22</td><td>1</td><td>8</td><td>15</td><td>22</td></tr>
<tr><td>Premedication</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>Elotuzumab (mg/kg) intravenously</td><td>10</td><td>10</td><td>10</td><td>10</td><td>20</td><td></td><td></td><td></td></tr>
<tr><td>Pomalidomide (4 mg) orally</td><td colspan="4">Days 1-21</td><td colspan="4">Days 1-21</td></tr>
<tr><td>Dexamethasone (mg) intravenously</td><td>8</td><td>8</td><td>8</td><td>8</td><td>8</td><td></td><td></td><td></td></tr>
<tr><td>Dexamethasone (mg) orally ≤ 75 years old</td><td>28</td><td>28</td><td>28</td><td>28</td><td>28</td><td>40</td><td>40</td><td>40</td></tr>
<tr><td>Dexamethasone (mg) orally > 75 years old</td><td>8</td><td>8</td><td>8</td><td>8</td><td>8</td><td>20</td><td>20</td><td>20</td></tr>
<tr><td>Day of Cycle</td><td>1</td><td>8</td><td>15</td><td>22</td><td>1</td><td>8</td><td>15</td><td>22</td></tr>
</table>
</td></tr>
<tr><td>Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)</td><td>Elotuzumab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.[1]</td></tr>
<tr><td>Other approved therapeutic indications</td><td>Elotuzumab is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.[1]</td></tr>
<tr><td>Will dispensing be restricted to hospitals?</td><td>Yes (BEGR)</td></tr>
<tr><td>Combination therapy and/or co-medication</td><td>Elotuzumab in combination with pomalidomide and dexamethasone</td></tr>
<tr><td>Packaging – types, sizes/number of units, and concentrations</td><td>20 ml Type I glass vial containing either 300 mg or 400 mg elotuzumab.
The flip-off seal button colour is ivory for the 300 mg presentation and blue for the 400 mg presentation.
Pack size of 1 vial.</td></tr>
<tr><td>Orphan drug designation</td><td>This product is no longer an orphan medicine. The designation was withdrawn in April 2016, at the time of the granting of the initial marketing authorization (elotuzumab in combination with lenalidomide and dexamethasone).</td></tr>
</table>

2 ABBREVIATIONS

Abbreviation	Term
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
ANC	Absolute neutrophil count
BEGR	Begrænset udlevering
BMS	Bristol-Myers Squibb
Bor	Bortezomib
BorDex	Bortezomib and dexamethasone
Car	Carfilzomib
CarDex	Carfilzomib and dexamethasone
CI	Confidence interval
Dara	Daratumumab
Dex	Dexamethasone
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EloPomDex	Elotuzumab in combination with pomalidomide and dexamethasone
GHS/QoL	Global Health Status/ Quality of Life
HR	Hazard ratio
HRQoL	Health related quality of life
IQR	Interquartile range
IRC	Independent review committee
ISS	International Staging System
ITT	Intent to treat
IMiDs	Immunomodulatory drugs
IMWG	International Myeloma Working Group
IR	Infusion reaction
I.V.	intravenous
Ixa	Ixazomib
Len	Lenalidomide
MCID	Minimal clinical relevant difference
MM	Multiple myeloma
NA	Not applicable
NK cells	Natural killer cells
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
pDCs	Plasmacytoid dendritic cells
PFS	Progression-free survival
PI	Proteasome inhibitor
Pom	Pomalidomide
PomBorDex	Pomalidomide in combination with bortezomib and dexamethasone
PomDex	pomalidomide and dexamethasone
PR	Partial response
PRO	Patient reported outcome
RCT	Randomized controlled trial
RR	Relative risk
RRMM	Relapsed refractory multiple myeloma
SLAMF7	Signalling lymphocyte activation molecule family member 7
SmPC	Summary of product characteristics
Thal	Thalidomide
TTR	Time to response

3 SUMMARY

The European Medicines Agency (EMA) approved elotuzumab (Empliciti®) in combination with pomalidomide and dexamethasone (EloPomDex) on 23 August 2019 with the indication: "Empliciti is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy".

In Denmark, multiple myeloma (MM) patients are extensively exposed to lenalidomide (Len) and bortezomib (Bor) in earlier stages of disease and are expected to be refractory to Len at their second relapse, which is used until disease progression in the prior line(s) of therapy.[2-4] As a consequence, non-Len-containing regimens are currently the cornerstone of third- and fourth-line therapy in Denmark. Such options include pomalidomide (Pom) and dexamethasone (PomDex), pomalidomide in combination with bortezomib and dexamethasone (PomBorDex; OPTIMISMM study) or carfilzomib and dexamethasone (CarDex, ENDEAVOR study). These 3 combinations constitute the relevant comparators for EloPomDex.

The ELOQUENT-3 study of EloPomDex versus PomDex included patients who were refractory or relapsed and refractory to Len and a proteasome inhibitor (PI). The selected patients were in an advanced stage of relapse with a median of 3 prior lines of therapy (range 2-8) and they had to be refractory to their last line. All patients had received prior treatment with Bor, 90% were refractory to Len and 68% were refractory to Len and a PI.[5] Patients in the pivotal trials of CarDex and PomBorDex were less heavily pretreated compared to the ELOQUENT-3 study.[6,7]

EloPomDex demonstrated a statistically significant and clinically meaningful 46% reduction in the risk of progression or death compared to PomDex (Hazard Ratio HR [95% CI], 0.54 [0.34, 0.86]) and the estimated absolute difference in median progression free survival (PFS) of 4.0 months (estimated 95% CI: 0.8-9.1) exceeds the minimal clinical relevant difference (MCID) of 3 months. The median PFS of 10.3 months in the EloPomDex arm is comparable to the median PFS observed for CarDex (Len-exposed with 2-3 prior lines) and PomBorDex (intent to treat, ITT) in patient populations that were most comparable to the ELOQUENT-3 trial.

A favorable trend in OS was seen for patients receiving EloPomDex versus PomDex, with an HR of 0.54 (95% CI 0.30-0.96) and an estimated absolute difference in OS of 14.8 months (estimated 95% CI: 0.7-40.6), which exceeds the MCID by almost 5 times. Comparison of the OS benefit of EloPomDex compared to CarDex (Len-refractory) or PomBorDex (ITT) is inconclusive considering the immaturity of the OS data, the lack of common comparator and the differences in the characteristics of the patient populations rendering cross-trial comparison uncertain.

In ELOQUENT-3, the benefits in efficacy observed with the addition of elotuzumab to PomDex did not translate into increased severe toxicity. All-cause Grade 3-4 adverse events (AEs) were reported in 57% versus 60% of patients with EloPomDex and PomDex, respectively. In ENDEAVOR, Grade ≥3 AEs were reported in 76.6% of patients with 2-3 prior lines of therapy and Grade 3-4 AEs were reported in 90.3% of patients treated with PomBorDex.[8,9] Discontinuation rates due to AEs were 18.3% with EloPomDex and 23.6% for PomDex with a relative risk (RR) 0.78 (95% CI, 0.38-1.59). Moreover, the discontinuation rate due to AEs of EloPomDex was numerically lower compared to the rate reported for the subgroup of patients with 2-3 prior lines of therapy treated with CarDex (22.5%) in the ENDEAVOR study and for the safety population treated with PomBorDex (28.8%) in the OPTIMISMM study.[8,9]

Overall, compared to PomDex, EloPomDex is a more efficacious treatment option with a similar safety profile for adult patients with multiple myeloma who have received at least two prior therapies including Len and a PI and have progressed on their last line of therapy. Despite a more heavily pretreated patient population in ELOQUENT-3, the PFS results suggest that EloPomDex might be equally effective as CarDex or PomBorDex with a safety profile associated with a numerically lower rate of discontinuation due to AEs and numerically fewer grade 3-4 AEs. However, the clinical added value of EloPomDex versus PomBorDex or CarDex is inconclusive considering the absence of head to head trial, the lack of common comparator for indirect comparison and the differences in the characteristics of the patient populations enrolled in the relevant studies rendering cross-trial comparison uncertain.

4 LITERATURE SEARCH

A systematic literature review was conducted to identify relevant publications to assess the clinical added value of EloPomDex in adults patients with MM who have received at least 2 previous therapies including lenalidomide and a PI.

The systematic literature review included the search string as defined in the protocol provided by the Medicines Council. The results from the systematic search performed on 25 November 2019 in both CENTRAL and Medline are presented in Table 3 and Table 4, respectively.

TABLE 3. SEARCH STRING AND RESULTS OF THE SYSTEMATIC SEARCH IN CENTRAL (VIA COCHRANE LIBRARY)

#	Query	Search facet	No. of hits
#1	[mh "Multiple Myeloma"]	Population	1391
#2	(myeloma OR myelomatosis OR "kahler* disease"):ti,ab,kw		5144
#3	#1 OR #2		5144
#4	(elotuzumab OR Empliciti*):ti,ab,kw	Intervention/ comparators	108
#5	(pomalidomid* OR Imnovid* OR Pomalyst* OR Actimid*):ti,ab,kw		275
#6	[mh Dexamethasone]		4064
#7	dexamethason*:ti,ab,kw		10771
#8	#4 AND #5 AND (#6 OR #7)		18
#9	(carfilzomib OR Kyprolis*):ti,ab,kw		314
#10	(#6 OR #7) AND #9		237
#11	[mh Bortezomib]		350
#12	(bortezomib OR Velcade*):ti,ab,kw		1821
#13	#5 AND (#6 OR #7) AND (#11 OR #12)		136
#14	#3 AND (#8 OR #10 OR #13)	Indirect comparison	330
#15	("conference abstract" OR review):pt	Exclusion of non-relevant publication types	180209
#16	NCT*:au		145578
#17	("clinicaltrials.gov" OR trialsearch):so		275250
#18	#15 OR #16 OR #17		455558
#19	#14 NOT #18		72

TABLE 4. SEARCH STRING AND RESULTS OF THE SYSTEMATIC SEARCH IN MEDLINE (VIA PUBMED)

#	Query	Search facet	No. of hits
#1	Multiple Myeloma[mh]	Population	39975
#2	myeloma[tiab] OR myelomatosis[tiab] OR kahler disease[tiab]		51336
#3	#1 OR #2		58700
#4	elotuzumab[nm]	Intervention/ comparators	107
#5	elotuzumab[tiab] OR Empliciti*[tiab]		218
#6	pomalidomide[nm]		356
#7	pomalidomid*[tiab] OR Imnovid*[tiab] OR Pomalyst*[tiab] OR Actimid*[tiab]		622
#8	Dexamethasone[mh]		50506
#9	dexamethason*[tiab]		55614
#10	(#4 OR #5) AND (#6 OR #7) AND (#8 OR #9)		19
#11	carfilzomib[nm]		430
#12	carfilzomib[tiab] OR Kyprolis*[tiab]		829
#13	(#8 OR #9) AND (#11 OR #12)		209
#14	Bortezomib[mh]		5372
#15	bortezomib[tiab] OR Velcade*[tiab]		7743
#16	(#6 OR #7) AND (#8 OR #9) AND (#14 OR #15)		119
#17	#3 AND (#10 OR #13 OR #16)	Indirect comparison	277
#18	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	RCT (Cochrane filter)	1194436
#19	#17 AND #18	Exclusion of non-relevant publication types	88
#20	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt]		6082029
#21	#19 NOT #20		60

The eligibility criteria used for the systematic literature review are defined in terms of the Population, Interventions, Comparisons, Outcomes, and study design (PICOS) framework, as well as language and time frame (Table 5).

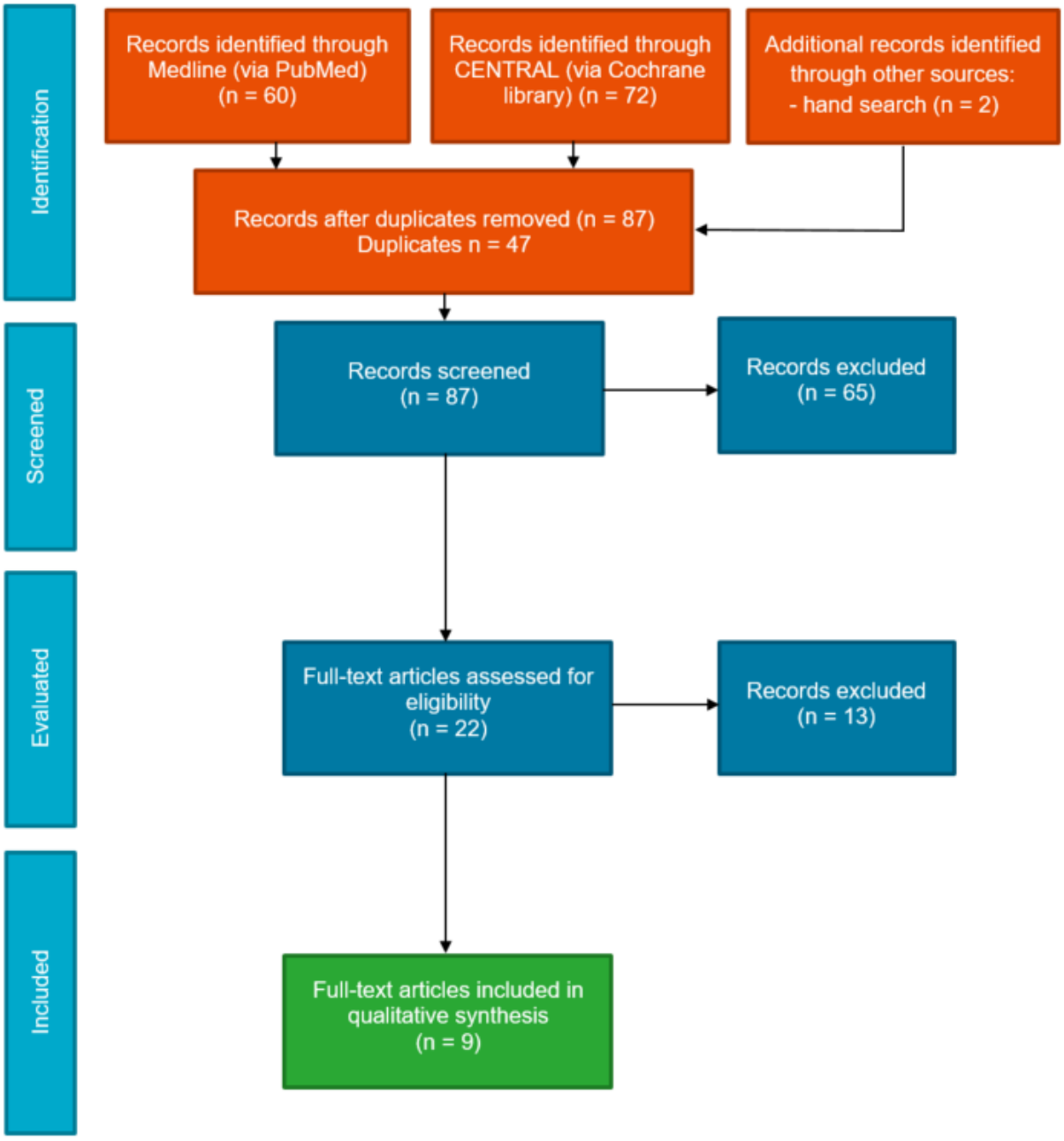
TABLE 5. INCLUSION AND EXCLUSION CRITERIA FOR SEARCH STRATEGY

	Inclusion criteria	Exclusion criteria
Population	Relapsed or refractory multiple myeloma having received two prior therapy lines including lenalidomide and a proteasome inhibitor.	
Intervention	Elotuzumab in combination with pomalidomide and dexamethasone.	
Comparator	CarDex PomDex PomBorDex	Other dosage and administration schedules than indicated in the protocol for the Danish Medicines Council.
Outcomes	Overall survival o PFS o Mortality Treatment end point o Discontinuation reason QoL o Using validated tool (e.g. EORTC QLQ C30)	
Trial design/study type	Randomised control trials Phase II studies were only considered when no phase III studies are available	Non RCTs Single-arm trials Case reports Editorials & opinion pieces Reviews Conference abstract poster
Language	English, Norwegian, Swedish, Danish	Not English, Norwegian, Danish or Swedish

A total of 132 records were identified through CENTRAL and MEDLINE. Two reviewers, working independently reviewed the identified records according to the PICO selection criteria. Two additional studies were identified through hand search and included for data completeness for the ELOQUENT-3 study. After removal of the duplicates (n=47), 87 records were screened for relevance by title and abstract. Out of these, 22 studies were then screened at a full-text stage by the same two reviewers. Following reconciliation between the two investigators, a third reviewer was included to reach consensus for any remaining discrepancies. As a result, 9 studies were selected for this application, which include data from 3 randomized controlled trials (RCTs), further described in Table 6. The process of study identification and selection are summarized in Figure 1 with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

All excluded articles with reasons for exclusion are listed in Table 18 in the Appendix.

FIGURE 1. PRISMA FLOW DIAGRAM OF MEDLINE (VIA PUBMED) AND CENTRAL (VIA COCHRANE LIBRARY)



4.1 RELEVANT STUDIES

The 9 studies identified via the systematic literature search are described in Table 6. Seven of these are peer-reviewed articles. For the ELOQUENT-3 study, 2 abstracts presented in 2019 at 2 international congresses have been included for data completeness for the PICO and as supportive literature. For clarity, data disclosed only in these abstracts are highlighted by blue font colour in the application.

TABLE 6. RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question 1
<u>Peer-reviewed</u> Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. **Dimopoulos et al. NEJM, 2018.**[5] <u>Abstracts at international congresses</u> Elotuzumab Plus Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Efficacy Results After Additional Follow-Up of the Phase 2, Randomized ELOQUENT-3 Study. **Dimopoulos et al., poster at the 24th Congress of the EHA, 2019, Abs #PS1370.**[10] **Impact of Elotuzumab Plus Pomalidomide and Dexamethasone on Health-Related Quality of Life in Patients With Relapsed/Refractory Multiple Myealoma Enrolled in the ELOQUENT-3 Study. Weisel et al., poster at the 61st ASH Annual meeting, 2019, Abs #3480.**[11]	ELOQUENT-3	NCT02654132	Start: 16 March 2016 Expected Completion: 1 December 2020	Yes
Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. **Dimopoulos et al. Lancet Oncol., 2016.**[6] Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. **Dimopoulos et al. Lancet Oncol., 2017.**[12] 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. **Moreau et al., Leukemia, 2017.**[9] Carfilzomib-Dexamethasone Vs Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups. **Orlowski et al., Clinical Lymphoma Myeloma and Leukemia. 2019.**[13]	ENDEAVOR	NCT01568866	Start: 20 June 2012 Completion: 5 February 2018	Yes

Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma. **Ludwig et al., Blood Cancer J. 2019.**[14]				
Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. **Richardson et al., Lancet Oncol., 2019.**[7]	OPTIMISMM	NCT01734928	7 January 2013 – May 2022 (for OS data)	yes

In addition, the following European Public Assessment Reports (EPARs) have been consulted:

EloPomDex Empliciti Procedure No. EMEA/H/C/003967/II/0012 (EMA/CHMP/455667/2019)[15] https://www.ema.europa.eu/en/documents/variation-report/empliciti-h-c-003967-ii-0012-epar-assessment-report-variation_en.pdf

PomBorDex Imnovid Procedure No. EMEA/H/C/002682/II/0031/G (EMA/CHMP/674052/2018)[8] https://www.ema.europa.eu/en/documents/variation-report/imnovid-h-c-2682-ii-0031-g-epar-assessment-report-variation_en.pdf

CarDex Kyprolis Procedure No. EMEA/H/C/003790/II/0001/G (EMA/517040/2016)[16] https://www.ema.europa.eu/en/documents/variation-report/kyprolis-h-c-3790-ii-0001-g-epar-assessment-report-variation_en.pdf

CA204-142, supportive multi-cohort study investigating EloPomDex

The assessment of the efficacy and safety of EloPomDex in patients with MM by the EMA is based on the results of one pivotal phase II study (ELOQUENT-3, CA204-125), supported by the data of the EloPomDex cohort of the phase II CA204-142 study.[15]

Study CA204142 is a non-randomized phase II, multi-cohort multi-center, open-label study conducted in the United States, which includes a cohort investigating the combination of EloPomDex. The objective of the EloPomDex cohort was to explore the clinical benefit and tolerability of this combination in subjects with MM who received at least 1 prior therapy and were relapsed, refractory, or intolerant to prior treatment with Len. PFS was the primary endpoint. Secondary endpoints included overall response rate (ORR), duration of response (DoR), time to response (TTR) and overall survival (OS).[15]

Based on both studies' inclusion/exclusion criteria, baseline demographics and disease characteristics of the enrolled patients, the population included in study CA204-142 appeared to be at an earlier stage of disease with less previously treated (1-2 prior lines of therapy) compared to the patient population of the ELOQUENT-3 study (≥2 lines of therapy, median of 3 prior therapies). The study has not been published in a peer-reviewed journal. Data from the CA204-142 at minimum follow-up of 16 months are found in the Empliciti EPAR.[15] As it is a non-randomized trial, this study was not in the scope of the systematic literature search and the results from CA204-142 are therefore not described in this application.

4.2 MAIN CHARACTERISTICS OF INCLUDED STUDIES

Overall, the treatments investigated and the ITT population enrolled in the 3 RCTs relevant for this application differ. This can be appreciated in Table 7 and in Table 8, which are providing an overview of the study design and baseline characteristics of special interest.

The main characteristics of the 3 included RCTs are presented in the Appendix as indicated in Table 7.

TABLE 7. OVERVIEW OF THE RCTS INCLUDED IN THE ASSESSMENT

	ELOQUENT-3 (CA204-125)	**OPTIMISMM (MM-007)**	**ENDEAVOR**
Table # in Appendix and corresponding page	Table 19, page 45	Table 21, page 53	Table 20, page 49
Number of patients in the investigational arm	60	281	464
Study design	Randomized open-label multicentre phase II	Randomized open-label multicentre phase III	Randomized open-label multicentre phase III
Intervention (investigational arm)	EloPomDex administered in 28 day cycles	PomBorDex administered in 21 day cycles	CarDex administered in 28 day cycles
Comparator (control arm)	PomDex	BorDex	BorDex

5 CLINICAL QUESTION 1

A single clinical question has been defined in the protocol from the Medicines Council, including 3 comparators (i.e. PomDex, CarDex and PomBorDex):

"*What is the added clinical value of Elotuzumab in combination with pomalidomide and dexamethasone compared to the current standard treatments for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy?*"

5.1 PRESENTATION OF RELEVANT STUDIES

5.1.1 ELOQUENT-3

Elotuzumab is an immunostimulatory humanised, IgG1κ monoclonal antibody that specifically targets the SLAMF7 (signaling lymphocyte activation molecule family member 7) protein (also known as CS1, CD319).[1] Elotuzumab activates the patient´s immune system via the direct activation of NK cells through both the SLAMF7 pathway and Fc receptors enhancing anti-myeloma activity.[15,17] Elotuzumab also promotes the killing of myeloma cells through NK cell-mediated ADCC.[1,17] Recently, killing of myeloma cells through a novel immune-mediated mechanism of elotuzumab whereby macrophage-mediated ADCP was identified.[1,18]

Primarily based on the results of the ELOQUENT-3 study, the EMA approved elotuzumab in combination with pomalidomide and dexamethasone on 23 August 2019 with the indication: "Empliciti is indicated in

combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy".[1]

The ELOQUENT-3 (CA204-125) study is a multicentre, randomised, open-label phase II trial, with the objective to determine if adding elotuzumab to Pom and low-dose dex is a more effective treatment of relapsed and refractory multiple myeloma (RRMM) compared to pomalidomide and low-dose dexamethasone.[5]
The aim of the study was to enrol patients with similar characteristics to the PomDex registrational phase III MM-003 study. Patient eligible to enter the ELOQUENT-3 study had to have received ≥2 previous lines of therapy, including at least two consecutive cycles of lenalidomide and a PI alone or in combination. Eligible patients had MM that was refractory (disease progressed while the patient was receiving treatment or within 60 days after treatment discontinuation) or relapsed and refractory (disease progressed within 6 months after treatment discontinuation after the patient had at least a partial response) to Len and a PI. In addition, all patients had MM that was refractory to their last therapy.[5]

Patients were randomly assigned in a 1:1 ratio to receive EloPomDex (intervention group) or PomDex (control group). Randomisation was stratified according to the number of previous lines of therapy (2 or 3 vs. ≥4) and the International Staging System (ISS) disease stage at the time of trial enrolment. The patients were treated until disease progression, intolerable side effects, withdrawal of consent, or death.[5]

The primary endpoint was investigator-assessed PFS, defined as the time from randomisation to the first occurrence of disease progression or death from any cause. The secondary endpoints were overall response ORR and OS. Additional exploratory endpoints included time to response, DoR, safety, and health related quality of life (HRQoL).[5]

An independent review committee (IRC) assessed PFS and ORR to confirm the results of the investigator assessment.

The results of the primary analysis are published in a peer-reviewed article from Dimopoulos et al. in 2018 in the New England Journal of Medicine, with a minimum follow-up period of 9.1 months (database lock 21 February 2018).[5] The results of an extended analysis with a minimum follow up of 18.3 months (cut off 29 November 2018) were presented in a poster at the EHA 2019 congress and the OS data are also included in the Empliciti EPAR.[10,15] A short description of the HRQoL data are available in the EPAR and have been further described in abstracts presented at International congress.[11,15] Data only presented in these abstracts are highlighted by blue font color in the application.

The main inclusion and exclusion criteria, baseline characteristics as well as additional details about the ELOQUENT-3 study are presented in Table 19.

5.1.2 ENDEAVOR

The ENDEAVOR study is a phase III, randomised, open-label (completed study), with the objective to compare PFS in patients with multiple myeloma who relapsed after 1-3 prior therapies, treated with CarDex or BorDex. Patients had to have documented ≥ partial response to at least 1 line of prior therapy. They were allowed to

have received previous therapy with a PI (Car or Bor) if they achieved at least a partial response to treatment, did not discontinue the proteasome inhibitor because of toxicity, and did not receive treatment with a PI for an interval of 6 months or more before enrolment.[6]

Patients were randomly assigned 1:1 to receive CarDex or BorDex until disease progression, intolerable side effects, withdrawal of consent, or deaths. Randomization was stratified by the following baseline factors: ISS stage (I vs II–III), previous lines of treatment, previous PI therapy, and planned route of Bor administration if assigned to the BorDex group (intravenous vs subcutaneous). Within each stratum, patients were randomly assigned to treatment by use of a blocked randomisation design in blocks of four.[6]

The primary endpoint was PFS assessed by IRC. The secondary endpoints included OS, overall response, duration of response, percentage of participants with ≥ Grade 2 peripheral neuropathy, and safety.[6] HRQoL was assessed as an exploratory endpoint in ENDEAVOR.[14]

For the primary analysis, median follow-up was 11.9 months (IQR 9.3 - 16.1) in the CarDex group and 11.1 months (IQR 8.2 - 14.3) in the BorDex group.[6] For the extended analysis, the median follow-up was 37.5 months (IQR 34.4-41.9) in the CarDex group and 36.9 months (IQR 33.4-40.6) in the BorDex group.[12] Updated OS, safety and subgroup analysis were recently published by Orlowski et al. at a median follow-up time for OS of 44.3 months in the CarDex group.[13]

The inclusion and exclusion criteria, baseline characteristics, and additional details are provided in Table 20.

5.1.3 OPTIMISMM

The OPTIMISMM study is a phase III, randomised, open-label, with the objective to compare PFS in patients with MM who relapsed after 1-3 prior therapies treated with PomBorDex or BorDex.[7]

Patients must have received prior treatment with lenalidomide-containing regimen for at least 2 consecutive cycles. Patients refractory to Len, including those who received Len in their last previous regimen, were eligible. 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. Patients exposed to bortezomib were eligible for the study as long as they did not have progressive disease during treatment or within 60 days of the last dose of a bortezomib-containing regimen (dosing schedule 1.3 mg/m2 of body surface area twice weekly). 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 this trial.[7]

Eligible patients were randomly assigned 1:1 to BorDex with or without Pom using a validated interactive response technology system. Randomization 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).[7]

The primary endpoint was PFS, defined as time from randomization to disease progression or death assessed by IRC. Prespecified secondary endpoints were OS (time from randomization to death due to any cause),

overall response (partial response or better) according to IMWG criteria,DoR (time of first documented response to confirmed progressive disease or death due to any cause for all responders), and safety. HRQoL was a prespecified exploratory endpoint.[7]

The median follow up time for the primary analysis was 15.9 months (IQR, 9.9-21.7) from a database lock from the 26 October 2017.[7] An updated OS analysis based on a database lock from the 15 September 2018 after a median follow-up period of 26.2 months is provided in the Imnovid EPAR.[8]

The inclusion and exclusion criteria, baseline characteristics, and additional details are provided in Table 21.

5.1.4 IMPORTANT CONSIDERATIONS ABOUT THE HETEROGENEITY OF THE INCLUDED STUDIES

Overall, the treatments investigated and the ITT population enrolled in the ELOQUENT-3, ENDEAVOR and OPTIMISMM RCTs differ (Table 8).

The selection of later lines of therapy is driven by multiple factors such as patient preferences, the patient comorbidities and disease-related characteristics, tolerability to prior treatment, treatment until progression or fixed number of cycles, number of prior lines of therapy, quality of response (depth and duration) to the prior regimens and the relapsed or refractory status of the disease. MM patients are extensively exposed to lenalidomide and bortezomib in earlier stages of disease. Thus, number of previous line of therapies as well as prior-exposure and relapse/refractory status to these 2 agents are important baseline characteristics to consider in the late relapse/refractory setting.

At the second relapse, most of the patients are expected to be refractory to Len, which is used until disease progression in the prior line(s) of therapy.[2,4] As a results, the non-lenalidomide containing regimen CarDex, which is indicated for patients at first relapse, is recommended and used for most patients as third line therapy in the Danish clinical practice[2,4]. The CarDex registrational phase III trial ENDEAVOR enrolled patients between 2012 and 2014 who had 1-3 prior therapies with 50% having received only 1 prior line of treatment.[6] In line with this, about one fourth of patients was lenalidomide-refractory (24.4%) and 54% had been previously treated with bortezomib (3.2% refractory).[6,16] The registrational phase III OPTIMISMM study also enrolled patients between 2013 and 2017 who had 1-3 prior therapies, of whom 40% had received 1 prior line of treatment.[7] Seventy-one percent of the patients were refractory to Len and 72% have been previously treated with Bor (8.5% refractory).[7] The ELOQUENT-3 study is focusing on subjects who were refractory or relapsed and refractory to Len and a PI. The selected patients were in a more advanced stage of relapse with a median of 3 prior lines of therapy (range 2-8). All patients had received prior treatment with bortezomib (63.3% bortezomib-refractory; 78.3% refractory to a PI) and 98% of patients had been treated with Len, of whom 90% were lenalidomide-refractory.[5]

In regards to study design, patients in the control arm of the ELOQUENT-3 study were treated with PomDex. Thus, the results from the ELOQUENT-3 study have been used to assess the added clinical value of EloPomDex compared to PomDex. For CarDex and PomBorDex, BorDex was the control arm of the 2 relevant RCTs investigating these treatments (ENDEAVOR and OPTIMISMM, respectively). Thus, an indirect comparison was precluded by the lack of a common comparator and a narrative synthesis of the data is provided for these 2

comparators. In addition, in the OPTIMISMM study, the administration schedule of Pom was adjusted to fit bortezomib administration schedule and differ from the approved dosing schedule for PomDex and thus from the ELOQUENT-3 study. Additional caution should be taken when assessing the added value of elotuzumab or bortezomib to PomDex.

TABLE 8. OVERVIEW OF THE STUDY DESIGN AND BASELINE DEMOGRAPHICS OF SPECIAL INTEREST OF THE RELEVANT RCTS

	ELOQUENT-3	**OPTIMISMM**	**ENDEAVOR**
Reference	[5,15]	[7,8]	[6,9,12,13,16]
Number of patients in the investigational arm	60	281	464
Study design	Randomized open-label multicentre phase II	Randomized open-label multicentre phase III	Randomized open-label multicentre phase III
Intervention and pomalidomide dosage	EloPomDex administered in 28 day cycles Pomalidomide 4 mg orally on days 1-21	PomBorDex administered in 21 day cycles Pomalidomide 4 mg orally on days 1-14	CarDex administered in 28 day cycles NA
Comparator	PomDex	BorDex	BorDex
Time since diagnosis, median (range)	4.8 years (0.5-21.9)	4.0 years (0.2; 25.9)	44.0 months (4.0, 306.2)
Age, median (range)	69 (43–81)	67 (27-87)	65 (35-89)
ISS disease stage	I 53.3% II 35.0% III 11.7%	I: 53.0% II: 30.2% III: 16.7%	I: 44% II-III: 56%
Cytogenetic risk status High risk is defined as the presence of one abnormality in at least one of the following: Del(17p), t(4;14), t(14;16).	High risk: 22% Non-high risk: 52% not evaluable: 27%	High risk: 21.7% Non-high risk: 48.8% Missing/not evaluable: 29.5%	High: 21% Standard: 61% Unknown/Missing: 18%
Previous treatments, number	**Median (range): 3 (2-8)** 1: 0% 2: 23.3% 3: 36.7% ≥4: 40.0%	**Median (IQR): 2 (1-2)** 1: 39.5% 2: 41.6% 3: 18.9% >3: 0%	**Median (IQR): 2 (1-2)** 1: 50% 2: 34% 3: 16%
Previous treatments with immunomodulatory drugs (IMiDs) and PI	Len: 98% Thal: 42% Bor: 100% Car: 15% Ixa: 8% Len and Bor: 98%[¥]	Len: 100% Thal, Len, corticosteroids: 25.6% Bor: 72% Car: 3% Ixa: 3% Len and Bor: 71.5% Len and PI: 75.4% BorDex: 70.1%	Len: 38% Thal: 45% Bor: 54% Car: <1% IMiDs and Bor: 34%
Refractory status to lenalidomide and/or a proteasome inhibitors (PI)	To last line: 100% (inclusion criteria) Len: 90% <u>PI: 78%</u> Bor: 63.3% Car:15.0% Ixa: 8.3% Len and a PI: 68%	To last line: 70% Len: 71.2% <u>PI: 13.2%</u> Bor: 8.5% Car: 1.8% Ixa: 2.8%	To last line: 40% Len: 24.4% Bor: 3.2%

	ELOQUENT-3	OPTIMISMM	ENDEAVOR
Subsequent treatments	55% of the patients in the EloPomDex arm received subsequent systemic therapies. The most common subsequent systemic therapies were*: Dara: 30% Cyclophosphamide : 17% Car: 13% Pom: 13% Bor : 10% Bendamustine: 10% Len: 7%	37.4% of (105/281) patients assigned PomBorDex received subsequent treatment. Agents received by >5% of the patients are shown below. The full list of subsequent therapies can be found in table 32 the EPAR. Dex: 23.1% Dara. 14.2% Cyclophosphamide: 11% Car: 10.3% Bor: 9.3% Pom: 7.5% Len: 6.0% Melphalan: 5.3%	262 (67%) of 391 patients who entered long-term follow up following discontinuation of CarDex received any additional lines of therapy. Agents received by >10% of the patients are shown below. The full list of subsequent therapies can be found in table 2 of Dimopoulos et al. 2017.[12] Dex: 48% Len: 32% Bor: 25% Cyclophosphamide: 22% Pom: 16% Melphalan: 13%
Follow-up	Primary analysis: Minimum follow-up of 9.1 months Extended follow-up: minimum follow-up of 18.3 months	Median follow-up PFS: 15.9 months (IQR 9.9-21.7) Extended OS analysis: median follow-up of 26.2 months	Primary analysis: median follow-up PFS: 11.9 months (IQR 9.3–16.1) Planned interim and final OS analysis: median follow-up of 37.5 months (IQR 34·4–41·9) Updated OS, safety and subgroup analysis: median follow-up of 44.3 months

¥ calculated based on the number of patients who have received prior lenalidomide and bortezomib. *Data highlighted in blue have only been reported in a poster by Dimopoulos et al., which was presented at EHA 2019.[10]
Bor, bortezomib; Car, carfilzomib; Dex, dexamethasone; Dara, daratumumab; Elo, elotuzumab; IMiD, immunomodulatory drug; IQR, interquartile range; Ixa, ixazomib; Len, lenalidomide, OS, overall survival; PFS, progression free survival; Pom, pomalidomide; PI, proteasome inhibitor; Thal, thalidomide.

5.2 RESULTS PER STUDY

The results per study are provided for the 3 relevant RCTs in the following tables.

ELOQUENT-3 – Table 22, page 57.

ENDEAVOR – Table 23, page 60.

OPTIMISMM - Table 24, page 63.

5.3 COMPARATIVE ANALYSIS AND NARRATIVE SYNTHESIS

As indicated above, the results from the ELOQUENT-3 study have been used to assess the added clinical value of EloPomDex compared to PomDex. For CarDex and PomBorDex, BorDex was the control arm of the 2 relevant RCTs investigating these treatments. Thus, an indirect comparison was precluded by the absence of a common comparator and a narrative synthesis of the data is provided for these 2 comparators.

The ITT population of the ELOQUENT-3 study corresponds to the population of the PICO. Consequently, for the comparison of EloPomDex with PomDex, the results of the ITT population of the ELOQUENT-3 study have been used for the comparative analysis of all outcomes.

As outlined above, the ITT population enrolled in the phase III trial investigating CarDex (ENDEAVOR) and PomBorDex (OPTIMISMM) differ from the population of the PICO i.e. patients who have received at least 2 prior therapies including lenalidomide and a PI (see Section 5.1.4, page 16). Consequently, efficacy and safety analyses for this specific subgroup of patients are not available for these 2 comparators. For CarDex, numerous subgroup analyses have been done in ENDEAVOR but data are not consistently available for all the outcomes of the PICO. Thus, the rational for selecting a specific subgroup of patients and the associated results are described for each outcome for CarDex. In the OPTIMISMM study, 75.4% of the ITT population has been previously exposed to Len and a PI. In addition, results available for subgroup analysis per prior lines of therapy is limited to a HR for PFS. Thus, the results of the ITT population have been used for the narrative synthesis of all the outcomes for PomBorDex.

5.3.1 OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

Overall Survival (OS)

Subgroup analysis of patients who have had ≥2 prior lines of therapy, including Len and a PI have not been carried out in neither the ENDEAVOR nor the OPTIMISMM study.

In the ENDEAVOR study, data for the subgroup of patients (i) with prior lenalidomide exposure, (ii) who are lenalidomide-refractoy or (iii) who had received 2-3 prior lines of therapy are available (Table 23).[13] In this study, a limited number of patients have been exposed to Len (38%) of whom 24.4% are refractory, 54% had prior bortezomib and 34% have been exposed to an IMiD (lenalidomide and/or thalidomide) and bortezomib.[6,16] In contrast, 90% of the patients were refractory to lenalidomide and all patients have been exposed to bortezomib in the ELOQUENT-3 study.[5] Multiple myeloma patients are extensively exposed to lenalidomide in earlier stages of disease and patients who have received at least 2 prior therapies are expected to be lenalidomide-refractory.[2,4] Thus, the data for the lenalidomide-refractory patients in the ENDEAVOR study were chosen for the narrative synthesis of the data.[13]

The data selected for the comparative analysis and the narrative description of this outcome are shown in Table 9.

TABLE 9. OVERVIEW OF OS DATA OF THE RELEVANT STUDIES USED FOR THE COMPARISON

Treatment	EloPomDex	PomDex	CarDex	PomBorDex
Population used	ITT (n=60)	ITT (n=57)	Len-refractory (n=113)	ITT (n=281)
Number of previous lines of therapy	Median (range) 3 (2-8)	Median (range) 3 (2-8)	Not reported	Median (IQR) 2 (1-2)
Len-refractory	90%	84%	100%	71%
Prior bortezomib	100%	100%	Not reported	72%
Prior IMiD and PI	Prior Len and Bor 98%	Prior Len and Bor 100%	Not reported	Prior Len and a PI 75.4%
Data cutoff	29 November 2018		19 July 2017	15 September 2018
Follow up	Minimum 18.3 months		Median 44.3 months	Median 26.2 months
Events reached for final planned OS analysis (ITT)	61.5% deaths (48/78 events) required for the final analysis (cut off 29 November 2018)		final OS data at a median follow-up of 37.5 months (cutoff 3 January 2017)[12]	63.8% deaths (242/379 events) required for the final analysis (cutoff 15 September 2018)
Median OS	Not reached	17.4 months	29.2 months	40.5 months
HR for OS	0.54 (95% CI, 0.30-0.96)		NA	NA
12-months OS rate	79%*	68%*	Not reported	75.9%
References	5,10,15		13	7,8

*Data in blue font color have only been reported in the poster by Dimopoulos et al. at EHA 2019.[10] The 12-months OS rate at the primary OS analysis after a minimum follow-up of 9.1 months and 40% of deaths required for final OS analysis (cut off 21 February 2018) reported in the Empliciti EPAR were 77% for EloPomDex versus 67% for PomDex.[15] Bor, bortezomib; Len, lenalidomide.

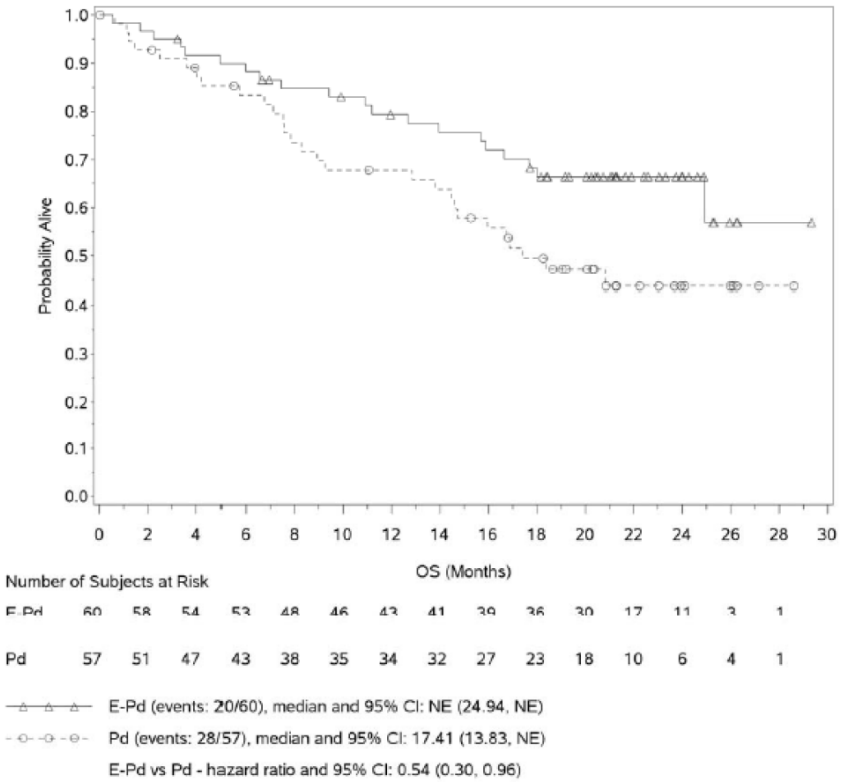
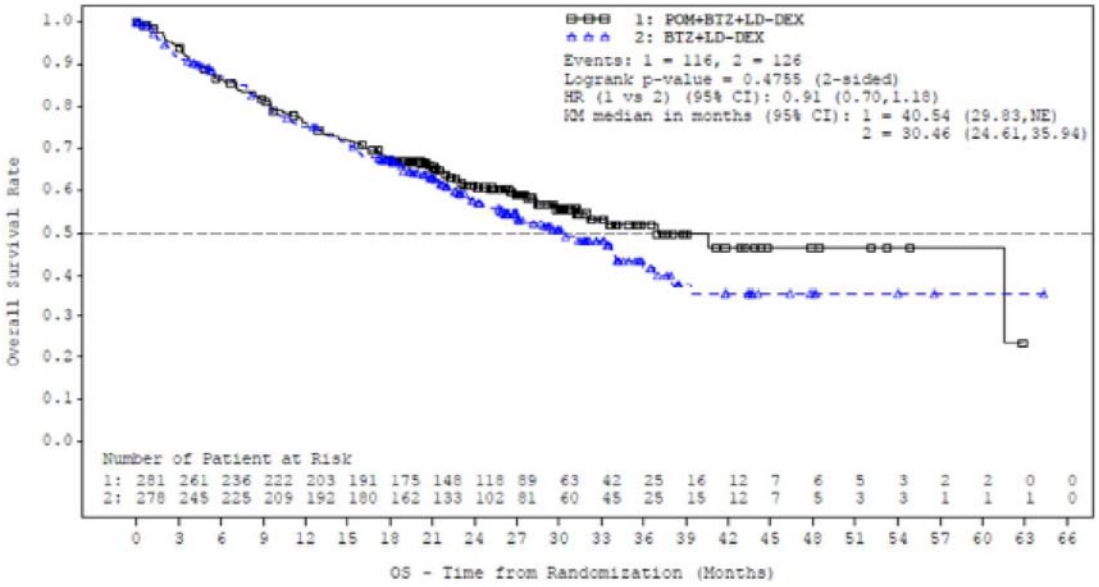


FIGURE 2. KAPLAN-MEIER CURVE OF OVERALL SURVIVAL IN THE ELOQUENT-3 STUDY (ITT, CUTOFF 29 NOV 2018)[15]

After a minimum follow-up of 18.3 months at which 61.5% of the requested OS events for the planned final analysis had occurred (48/78 events), a favorable trend in OS for patients receiving EloPomDex was seen compared to PomDex, with an HR of 0.54 (95% CI 0.30-0.96) (Figure 2).[15] The curves are separating within the first 2 months in the advantage of the EloPomDex combination. The median OS was not reached for patients treated with EloPomDex versus 17.41 months in the PomDex arm. The estimated absolute difference in OS is 14.8 months (estimated 95% CI: 0.7-40.6) and exceeds by almost 5 times the MCID of 3 months defined by the Medicines Council. The estimation of the absolute difference in medians was based on formula 6, page 55, of the Methods Guideline from the Medicines Council (v.2.3).

In the ENDEAVOR study, the difference in median OS between CarDex and BorDex for the patients refractory to Len was 7.8 months (29.2 vs 21.4 months, respectively) at a median follow-up of approx. 44 months (6 months of additional follow up compared to final OS data reported by Dimopoulos et al.).[12] As observed for the ITT population, there is a late separation of the curves in the advantage of CarDex occurring at around 18 months for this subgroup (see figure 3E from Orlowski et al.).[12,13] The HR was 0.86 (95% CI, 0.62-1.18).

In the OPTIMISMM study, the difference in median OS between PomBorDex and BorDex for the ITT population was 10.1 months (40.54 vs 30.46 months, respectively) at a median follow-up of 26.2 months at which 63.8% of the events required for the final OS analysis had occurred (242/379 events).[8] The curves are separating at around 16 months in the advantage of PomBorDex. The HR was 0.91 (95% CI, 0.70-1.18).



BTZ = bortezomib; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; LD-DEX = low-dose dexamethasone; NE = not estimable; OS = overall survival; POM = pomalidomide.

FIGURE 3. KAPLAN-MEIER CURVE FOR OVERALL SURVIVAL IN THE OPTIMISMM STUDY (ITT, CUTOFF 15 SEPT 2018)[8]

Overall, a favorable trend in OS was seen for patients treated with EloPomDex versus PomDex, with an HR of 0.54 (95% CI 0.30-0.96) and an estimated absolute difference in OS of 14.8 months (estimated 95% CI: 0.7-40.6), which exceeds the MCID by almost 5 times. At an approximately similar number of OS events required for the planned final OS analysis (EloPomDex 61.5% vs PomBorDex 63.8%), the median OS was not reached for EloPomDex and 40.5 months for PomBorDex (ITT populations). The lenalidomide-refractory patients

treated with CarDex had a median OS of 29.2 months at the longest follow-up period between the 3 RCTs. No conclusion on the added OS value of EloPomDex compared to CarDex or PomBorDex can be made considering the immaturity of the OS data, the lack of common comparator and the differences in the characteristics of the patient populations rendering cross-trial comparison highly uncertain.

Progression-free Survival (PFS)

PFS subgroup analysis of patients who have had ≥2 prior lines of therapy, including Len and a PI have not been carried out in neither the ENDEAVOR nor the OPTIMISMM study. For the narrative comparison with PomBorDex, the PFS data for the ITT population in the OPTIMISMM study were used (see rational above). In ENDEAVOR, a PFS subgroup analysis of patients who have had 2-3 prior lines of therapy and have been exposed to Len has been carried out.[9] This subgroup is considered the most relevant in regards to the population of the PICO and was selected for the narrative synthesis of this outcome.

The data selected for the comparative analysis and the narrative description for this outcome are shown in Table 10.

TABLE 10. OVERVIEW OF PFS DATA FOR THE RELEVANT STUDIES

Treatment	EloPomDex	PomDex	CarDex	PomBorDex
Population used	ITT (n=60)	ITT (n=57)	Prior Len, 2-3 prior lines (n=126)	ITT (n=281)
Median number of previous lines of therapy	Median (range) 3 (2-8)	Median (range) 3 (2-8)	Not reported	Median (IQR) 2 (1-2)
Len-refractory	90%	84%	Not reported	71%
Prior bortezomib	100%	100%	Not reported	72%
Prior IMiD and PI	Prior Len and Bor 98%	Prior Len and Bor 100%	Not reported	Prior Len and a PI 75.4%
Data cutoff	21 February 2018		10 November 2014	26 October 2017
Follow up	Minimum 9.1 months		Median 11.9 months	Median 15.9 months
Median PFS	10.3 months	4.7 months	9.7 months	11.2 months
Estimated absolute difference in median PFS	4.0 months¥ 95% CI, 0.8-9.1		0.6 months‡	-0.9 months‡
HR for PFS	0.54 (95% CI, 0.34-0.86) P=0.008		NA	NA
12-month PFS rate	40% 95% CI, 0.26-0.54	19% 95% CI, 0.09-0.31	Not reported	49.47%
18 month PFS rate	34%*	11%*	Not reported	Not reported
References	5,15		9	7,8

* Data from a minimum follow up of 18.3 months. Data in blue font color have only been reported in the poster by Dimopoulos et al. at EHA 2019.[10] The 12-month PFS rates at the extended analysis after a minimum follow-up of 18.3 months (cut off 29 November 2018) were consistent with the previous analysis and were 43% for EloPomDex versus 20% for PomDex.[10]

¥ The estimation of the absolute difference in medians between EloPomDex and PomDex was based on formula 6, page 55, of the Methods Guideline from the Medicines Council (v.2.3)

‡ The absolute difference was calculated by subtracting the median PFS of (i) CarDex or (ii) PomBorDex from the median PFS reported for EloPomDex. NA, not applicable.

At a minimum follow-up of 9.1 months, EloPomDex demonstrated a statistically significant and clinically meaningful 46% reduction in the risk of progression or death compared to PomDex (HR [95% CI], 0.54 [0.34, 0.86]).[5] This benefit was maintained at a minimum follow-up of 18.3 months.[10] The estimated absolute difference in medians between EloPomDex and PomDex was 4.0 (estimated 95% CI: 0.8-9.1), which exceeds the MCID defined by the Medicines Council (Table 22). As for OS, the estimation of the absolute difference in medians was based on formula 6, page 55, of the Methods Guideline from the Medicines Council (v.2.3).

In the ENDEAVOR study at a median follow up of 11.9 months, the median PFS of 9.7 months for patients who have received prior Len and 2-3 prior lines of therapy was similar to EloPomDex. The difference in median PFS between CarDex and BorDex for this patient group was 3.1 months (9.7 vs 6.6 months, respectively).[9] Despite the fact that lenalidomide-refractory is not the population of interest in this PICO, it is worth noting that regardless of the number of prior lines of therapy, patients who were refractory to prior lenalidomide had a median PFS of 8.6 months when treated with CarDex.[9] The effect on PFS of EloPomDex was demonstrated in a patient population refractory to lenalidomide (90%) with a median of 3 prior lines of therapy.

In the OPTIMISMM study at a median follow up of 15.9 months, the median PFS of 11.2 months for the ITT population was similar to EloPomDex. The difference in median PFS between PomBorDex and BorDex for the ITT population was 4.1 months (11.2 vs 7.1 months, respectively). Despite the fact that lenalidomide-refractory is not the population of interest in this PICO, it is worth noting that regardless of the number of prior lines of therapy, patients who were refractory to prior Len had a median PFS of 9.5 months when treated with PomBorDex.

Thus, a statistically significant and clinically meaningful benefit in PFS is provided by the addition of elotuzumab to PomDex in the ELOQUENT-3 study. The median PFS for patients with prior lenalidomide-exposure and 2-3 prior therapies treated with CarDex and the median PFS for the ITT population for PomBorDex were similar to the median PFS reported for EloPomDex (ITT). However, caution should be taken when assessing the added PFS value of EloPomDex compared to CarDex or PomBorDex considering the differences and limitations previously described.

5.3.2 DISCONTINUATION RATE DUE TO ADVERSE EVENTS

PomDex being the comparator in the ELOQUENT-3 study, the rate of treatment discontinuation due to any AEs of any grade reported for the safety population (all treated patients) of the study were used for the comparison of EloPomDex with PomDex.[5,15] The RR was calculated and used to estimate the absolute difference in effect using formula 4, page 54, of the Methods Guideline from the Medicines Council (v.2.3).

For PomBorDex, safety data have only been reported for the overall safety population of the OPTIMISMM study (n=278). Thus, the rate of treatment discontinuation due to any AEs of any grade of the safety population was used for the narrative comparison between PomBorDex and EloPomDex.

For CarDex, the rate of treatment discontinuation due to any AEs of any grade is available for (i) the entire safety population and (ii) for the subgroup of patients who have received 2-3 prior lines of therapy at a median follow up of 11.9 months.[9] The latest was selected for the narrative synthesis of the data since one of the characteristics of the population of the PICO is to have received ≥2 prior lines of therapy.

The data selected for the comparative analysis and the narrative description for this outcome are shown in Table 11.

TABLE 11. OVERVIEW OF THE RATE OF TREATMENT DISCONTINUATION DUE TO ANY-CAUSE AES OF ANY GRADE REPORTED IN THE RELEVANT STUDIES USED FOR THE COMPARISON

Treatment	EloPomDex	PomDex	CarDex	PomBorDex
Population used	Safety population (n=60)	Safety population (n=55)	2-3 prior lines (n=231)	Safety population (n=278)
Rate of treatment discontinuation due to any-cause AEs	18.3%	23.6%	22.5%	28.8%
Estimated Absolute difference	-5.3%-points¥ 95% CI, -14.7%-13.8%		-4.2%ǂ	-10.5%ǂ
Estimated Relative Risk (RR)	0.78 95% CI, 0.38-1.59		NA	NA
Data Cutoff	21 February 2018		10 November 2014	26 October 2017
Follow up	Minimum 9.1 months		Median 11.9 months	Median 15.9 months
References	[5,15] (Table 9 in Empliciti EPAR, page 55)		[9]	[8] (Table 35 in the Imnovid EPAR, page 60)

¥ For the comparison of EloPomDex with PomDex, the relative risk (RR) were calculated and used to estimate the absolute difference in effect using formula 4, page 54, of the Methods Guideline from the Medicines Council (v.2.3).

ǂ The absolute difference was calculated by subtracting the rate of discontinuation due to AEs of (i) CarDex or (ii) PomBorDex from the rate of discontinuation due to AEs reported for EloPomDex. NA, not applicable.

The discontinuation rate due to any AEs of any grade was 18.3% with EloPomDex and 23.6% for PomDex.[15] The indirect treatment comparison showed a RR = 0.78 (95% CI, 0.38-1.59) suggesting that the addition of elotuzumab to PomDex does not seem to increase treatment discontinuation due to AEs. The estimated absolute risk reduction is -5.3%-points (95% CI, -14.7-13.8) and is below the MCID of 10%-points defined by the Medicines Council.

The discontinuation rate due to any AEs of any grade of EloPomDex (18.3%) was numerically lower compared to the rate reported for patients with 2-3 prior lines of therapy treated with CarDex (22.5%). A similar rate was reported for the safety population of the ENDEAVOR study (n=463) at the same data cutoff, which increased to 29.6% at an extended follow up (data cutoff of 19 July 2017).[13,16] Further, the discontinuation rate due to *drug-related* AEs of any grade was lower with EloPomDex (8.3%) compared to CarDex (13.0%) in the overall safety population (cutoff 10 November 2014).[15,16]

The difference between the discontinuation rate due to AEs of any grade reported for the overall safety population treated with PomBorDex (28.8%) compared with EloPomDex (18.3%) was -10.5%, favoring EloPomDex. This difference exceeds the 10%-points defined by the Medicines Council as MCID.

Caution should be taken in interpreting these results in regards to the differences in study design and patient population enrolled in these 3 RCTs, which were described in the previous sections.

5.3.3 SAFETY PROFILE

Any grade AEs reported in at least 10% of patients in the ELOQUENT-3, ENDEAVOR and OPTIMISMM study are shown in Table 25, page 67.

The Grade 3-4 AEs reported in the ELOQUENT-3, ENDEAVOR and OPTIMISMM study are show in Table 26, page 70.

TABLE 12. OVERVIEW OF SEVERE AES REPORTED IN THE ELOQUENT-3, ENDEAVOR AND OPTIMISMM STUDIES

Treatment	EloPomDex	PomDex	CarDex		PomBorDex
Population	Safety population (n=60)	Safety population (n=55)	2-3 prior lines (n=231)	Safety population (n=463)	Safety population (n=278)
Data Cutoff	21 February 2018		10 November 2014	3 January 2017	26 October 2017
Follow up	Minimum 9.1 months		Median 11.9 months	Median 37.5 months	Median 15.9 months
Any severe AEs	Grade 3-4 56.7%	Grade 3-4 60.1%	Grade ≥3 76.6%	Grade ≥3 81.4%	Grade 3-4 90.3%
Absolute difference in severe AEs between EloPomDex and comparators*	NA	-3.4%	-19.9%	-24.7%	-33.6%
References	[5,15] (Table 9 in Empliciti EPAR, page 55)		[9]	[12]	[8] (Table 35 in the Imnovid EPAR, page 60)

NA, not applicable.

* The absolute difference in rate of severe AEs was calculated by subtracting the rate of AEs reported with (i) PomDex, (ii) CarDex or (PomBorDex) from the rate of severe AEs reported with EloPomDex.

In the ELOQUENT-3 study, the median number of treatment cycles was 9 (IQR, 4-13) in the EloPomDex group and 5 (IQR, 3-10) in the PomDex group. The benefits in efficacy observed with the addition of elotuzumab to PomDex did not translate into increased severe toxicity at the primary analysis. All-cause Grade 3-4 AEs were reported in 57% vs. 60% of patients with EloPomDex vs PomDex, respectively. The most common Grade 3-4 events were neutropenia (13% in the EloPomDex group vs. 27% in the PomDex group), anemia (10% vs. 20%), hyperglycemia (8% vs. 7%), thrombocytopenia (8% vs 6%), lymphopenia (8% vs 2%) and leukopenia (8% vs 4%).[5]

Infections of any grade were reported in 65% of the patients in each of the two groups, with grade 3-4 infections occurring in 13% of the patients in the EloPomDex group and in 22% in the PomDex group.[5] Herpes zoster occurred more frequently in the EloPomDex group than in the PomDex group (5% vs 1.8%).

The most common treatment-related AEs were neutropenia (18% in the EloPomDex group vs. 20% in the PomDex group), hyperglycemia (18% vs. 11%), and anemia (10% vs. 15%) (Table S2 in Dimopoulos et al., 2018).[5]

Three infusion reactions (IRs) had occurred (deafness, chest discomfort, and an unspecified infusion-related reaction occurred in one patient each). All the infusion reactions were Grade 1 or 2.[5]

Thus, the safety profile of EloPomDex was manageable and similar to that of PomDex alone, with the exception of infusion reactions.[5]

Patients were treated with CarDex for a median of 12 cycles (IQR 6–22). Grade ≥3 AEs were reported in 76.6% of the patients who had 2-3 prior lines of therapy and in 81.4% of the safety population.[9,12] Compared to EloPomDex, this corresponds to a difference of 20% and 25% in favor of EloPomDex. Frequent Grade ≥3 AEs reported with CarDex (preferred term) were anaemia (16%), hypertension (15%), pneumonia (9%), and thrombocytopenia (9%).[12] Grade ≥3 cardiac failure (MedDRA grouped term) occurred in 6% of patients in the CarDex group and grade ≥3 acute renal failure (grouped term) occurred in 26 (6%) patients in the CarDex group.[12]

Patients were treated with PomBorDex for a median of 12 (IQR 6–21) cycles. Grade 3-4 AEs reported for patient treated with PomBorDex was 90.3%, which is increased by 34% compared to EloPomDex. PomBorDex seems to be associated with the highest incidence of hematologic AEs compared to EloPomDex, PomDex and CarDex. The most common Grade 3-4 haematological AEs were neutropenia (42%) and thrombocytopenia (27%).The most common Grade 3-4 non-haematological AEs was infection (31%) in the PomBorDex group.

Overall, the lowest rate of severe AEs was reported with EloPomDex and PomDex. No new AEs were identified with EloPomDex compared to PomDex (except for infusion reactions). An increase of 20-34% in the rate of severe AEs is seen with CarDex and PomBorDex compared to EloPomDex, suggesting that EloPomDex may have a more favourable safety profile. Nevertheless, these treatment options have not been compared head to head and caution should be taken in interpreting the results.

The safety profile of elotuzumab, pomalidomide, bortezomib, carfilzomib are well known. The safety profile of the combinations seems to be consistent with the known safety profile of the individual agents of the regimens.

5.3.4 HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Different patient-reported outcome (PRO) instruments were used in the ELOQUENT-3 study compared to the ENDEAVOR and OPTIMISMM studies. In addition, caution should be taken in interpreting the results due to the open-label design of the 3 RCTs.

In ELOQUENT-3, the difference in change from baseline in EQ-5D-3L scores between EloPomDex and PomDex are statistically and clinically non-significant, but a positive trend favoring EloPomDex with a gain versus baseline on the EQ-5D VAS of 4.7 points (95% CI: -0.9-10.2) and 0.046 (95% CI: -0.035-0.127) on the EQ-5D index score was observed. As the results are neither statistically significant nor meets the predefined MCID, no difference can be claimed from the addition of elotuzumab (infusion) to PomDex (oral administration) compared to PomDex alone. These data has only been presented in posters at international congresses.[11]

In the ENDEAVOR study, CarDex resulted in statistically but not clinically significant improvements in mean Global Health Status/ Quality of Life (GHS/QoL) scores versus BorDex (QLQ-C30).

In the OPTIMSMM study, scores for the GHS/QoL domain of the EORTC QLQ-C30 were maintained over time for both treatment groups, with no statistically significant or clinically meaningful differences recorded between treatments at any cycle.

Thus, no clinically significant improvement in HRQoL were observed with EloPomDex, CarDex or PomBorDex compared to their respective treatment control.

6 OTHER CONSIDERATIONS

6.1 IMPLEMENTATION OF ELOPOMDEX IN THE DANISH CLINICAL PRACTICE

The Medicines Council requested an assessment of how the implementation of EloPomDex will impact the Danish clinical practice.

The current Danish clinical practice is defined in this application as described in the latest available version of the Danish Myeloma Study Group guidelines for treatment of multiple myeloma relapse (publically available since 20 November 2019)[4] and from the guidelines from the Medicines Council approved on 11 October 2019[2].

For the growing population of patients who have failed several lines of therapies including a PI and Len, there is a high unmet need for novel and effective treatments with relatively low toxicity to allow continued disease control with acceptable quality of life. Few treatment options are available for this patient population and are supported by sparse evidences. Further, the patient populations enrolled in the relevant studies in the relapse/refractory setting are heterogeneous and therefore, not comparable (see sections above). Further, both Danish treatment guidelines highlight the fact that the choice of relapse treatment should be made in dialogue with the patient and based on factors such as comorbidity, complications from previous treatments, refractory-status and the biology of the disease.[2,4] The recent guidelines from the Medicines Council state that treatment is so individualized for patients with a relapse after minimum 2 prior lines of therapy, that it is not possible to compare the treatment options. Consequently, no treatment is recommended; however, the 2 regimens approved by the European Commission, PomDex and Daratumumab (Dara) monotherapy, are suggested treatment options. However, Dara monotherapy is only suggested for the treatment of the very few patients, who have not been previously treated with a dara-containing regimen.[2]

Patients are extensively exposed to bortezomib and lenalidomide in earlier lines of therapy and most of them are expected to be refractory to Len at their second relapse (third line of therapy). Therefore, CarDex is currently recommended and used for most patients at second relapse.[4] Pomalidomide-containing regimens are currently recommended as third relapse treatment for most patients in the latest available treatment guidelines. No studies have specifically assessed the optimal sequencing of EloPomDex and CarDex.

Overall, EloPomDex is a new pomalidomide-containing treatment option associated with a statistically significant benefit in PFS with a manageable safety profile for patients who have received at least two prior therapies including Len and a PI.[5] The consequences of the implementation of this new treatment option on the following treatment lines is unknown in regards to type, length and expected effect. In addition, the highly individualized treatment decision made in these latter lines of therapy renders such assessment difficult.

6.2 PREMEDICATION PRIOR INFUSION OF ELOTUZUMAB

Equivalent H2 blocker

In the Empliciti Summary of product characteristics (SmPC), the premedication for the prevention of infusion reaction (IR) is as follows.

Patients must be administered with the following premedications 45-90 minutes prior to Empliciti infusion.

- Dexamethasone 8 mg intravenous (i.v.)
- H1 blocker: diphenhydramine (25-50 mg orally or intravenous) or equivalent H1 blocker.
- H2 blocker: ranitidine (50 mg intravenous or 150 mg orally) or equivalent H2 blocker.
- Paracetamol (650-1000 mg orally).

Based on the SmPC, ranitidine or equivalent H2 blocker can be used in premedication for the prevention of IRs. Several other H2 blockers equivalent to ranitidine are available in Europe (e.g. cimetidine and famotidine). Bristol-Myers Squibb (BMS) does not have data supporting the use of one other specific equivalent H2 blocker.

The Empliciti SmPC does not provide any information regarding the use of elotuzumab without premedicating with a H2 blocker. BMS recommends administration of elotuzumab in accordance with the SmPC information. Any deviation from this instruction is at the discretion of the treating physician.

To date, BMS has not conducted any controlled clinical trials/studies where these premedications were omitted or modified prior to an elotuzumab infusion. Therefore, BMS has no relevant information regarding the impact of altering the premedication regimen on the likelihood of developing an IR due to elotuzumab administration. In the event diphenhydramine, ranitidine (or equivalent H2 blocker), acetaminophen, or dexamethasone are unavailable, or a patient is allergic or intolerant to any of these premedications, it is at the treating physician's discretion to evaluate the risks/benefits to determine whether to proceed with administration of elotuzumab.

A multicenter, open-label, phase 1, dose-escalation 1 study investigating elotuzumab monotherapy reported on the rates of IRs before and after implementation of a premedication protocol. Following a protocol amendment, acetaminophen and an antihistamine were administered before and during each elotuzumab infusion. In addition, an i.v. corticosteroid was administered prior to the first dose in patients in the 20 mg/kg cohort. This was used as pretreatment for infusion-related reactions. Patients were evaluated for AEs at 30 and 60 days after the last dose of elotuzumab.[19]
Before implementation of revised infusion reaction management guidelines, 13 of 25 treated patients experienced IRs, which with one exception (grade 3 hypersensitivity reaction) were grade 1 or 2 in severity. Five patients had at least one infusion interrupted, discontinued, or rate of infusion reduced in response to an IR. Following a protocol amendment to require IR premedication immediately before a first dose of elotuzumab, no further serious or Grade 3 and 4 IRs were observed, and Grade 1 and 2 IRs either resolved spontaneously or were managed as clinically indicated.[19]

Additionally, relevant information can be found in the protocols of the ELOQUENT-2 (page 19) and ELOQUENT-3 (page 23) clinical trials.

Formulation of dexamethasone in premedication for prevention of infusion reaction prior elotuzumab administration

BMS does not have any data on the incidence or severity of IRs following the use of oral dexamethasone instead of i.v. dexamethasone in premedication required before elotuzumab infusion. BMS recommends administration of elotuzumab in accordance with the Empliciti SmPC.[1]

6.3 EFFECT OF ELOTUZUMAB AFTER DARATUMUMAB

Over the last years, remarkable progress has been made in the treatment of multiple myeloma. Nevertheless, the rapidly evolving treatment paradigm comes with its challenges in regards to treatment sequencing, lack of head-to-head comparison and high heterogeneity of the patient population enrolled in the clinical trials.

Daratumumab (Dara) is a human IgG1κ monoclonal antibody targeting CD38, which is expressed on a majority of NK cells.[20] Dara anti-myeloma effect is mediated by several mechanisms, including NK-cell mediated ADCC.[21] Based on data from 2 clinical studies (GEN501 and SIRIUS), treatment with dara monotherapy has been shown to reduce the total and activated NK-cell counts.[22] The reduction in NK cells was reversible with some recovery at 3 months after the last dose of dara and significant recovery at 6 months.[22]
The effect on NK cells of dara combined with IMiDs, which have immunostimulating properties, is not well described. Consistent with dara monotherapy studies, treatment with DaraLenDex and DaraPomDex resulted in a reduction of circulating NK cells in samples collected within the first 2 cycles of treatment (no data were provided beyond).[23-25] Nevertheless, with DaraPomDex, of the total number of NK cells, the proportion of proliferating NK cells increased at the same time.[23] The observed proliferation might overcome NK cell depletion and was suggested to be a possible mechanism by which Pom enhance the ADCC activity of the monoclonal antibody.[23] In addition, NK cells that persisted with DaraLenDex treatment (POLLUX study) had a distinct phenotype suggesting that these cells may remain competent to elicit ADCC.[24] In line with this, others showed that the remaining NK cells in MM patients who have undergone dara therapy are $CD38^{-/low}$, which were superior at acting cooperatively with dara to kill MM cells via ADCC compared to CD38+ NK cells.[26] Also, the NK cells derived from $CD38^{-/low}$ NK progenitors from peripheral blood of healthy donors were more proliferative compared with those derived from CD38+ NK progenitors.[26]

Thus, NK cells are not completely depleted during dara treatment.[22-24,26] In addition, the remaining NK cells are capable of eradicating MM cells via ADCC and retain cytotoxic functionality,[26] suggesting that these cells are able to kill MM cells via ADCC mediated by elotuzumab. Importantly, the depletion of NK cells was reversible and recovery occurred within 3-6 months after the last dose of dara monotherapy.[22] Moreover, the impact of NK cells proliferation observed in patients treated with dara combined with an IMiD and dex on the recovery of NK cells is unknown. At last, elotuzumab has been shown to induce phenotypic activation of macrophages and mediates ADCP of myeloma cells though CD16 similarly to dara.[18]

Daratumumab (Darzalex) was first conditionally approved in Europe in May 2016 as monotherapy for the treatment of relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy. At the same time, EloLenDex was approved

for patients who have had at least one prior therapy. In April 2017, the combination of DaraLenDex or DaraBorDex was approved for the treatment of patients with MM who have received at least one prior therapy. The first approval of a dara-containing regimen for newly-diagnosed MM patients was granted in August 2018. Adding to this the time necessary for the national reimbursement processes and local implementation, dara-based combinations are not yet expected to be established standard of care in the newly diagnosed setting. Supporting this, the first dara-containing regimens recommended in Denmark are for patients at first relapse (DaraLenDex or DaraBorDex), despite rapid national reimbursement processes.[2] Similarly, EloPomDex has just received a market authorization in August 2019.

As a results, clinical data on optimal sequencing of elotuzumab in combination with lenalidomide and dexamethasone (EloLenDex) or EloPomDex with daratumumab are sparse.

To date, BMS has not conducted any clinical trials evaluating the use of elotuzumab after daratumumab. In the ELOQUENT-3 trial enrolling from March 2016 through April 2017, 3 patients (EPd, n=1; Pd, n=2) had received prior daratumumab. However, data from an ongoing, observational, prospective real-world study (PREAMBLE, NCT01838512) and the McKesson electronic medical record (EMR) database are available and summarized below (Vij et al.).[27]

6.3.1 REAL-WORLD DATA ON TREATMENT SEQUENCING IN PATIENTS WITH RELPASED/REFRACTORY MULTIPLE MYELOMA AFTER DARATUMUMAB

The objective of the study reported by Vij et al. at ASH 2018 was to evaluate treatment sequences among patients with RRMM after failure of dara-based therapy in a real-world setting.[27]

Study design and statistical analysis

Vij et al. identified patients ≥18 years with RRMM who received dara in their 2nd to 6th line of therapy from these 2 sources from November 2015 onward. Database lock for the PREAMBLE study and the McKesson EMR were April 2018 and May 2018, respectively.

Descriptive statistics were used to summarize patient demographics and clinical characteristics. Statistical comparisons were made using *t* or Mann–Whitney *U* tests (continuous variables) and chi-square tests (categorical variables). Kaplan–Meier analyses were used to estimate duration of therapy.

Demographics and baseline characteristics

At the time of analysis, 86% (n = 1016) of the 1179 enrolled patients received dara as their first monoclonal antibody in their 2nd to 6th line of therapy (Table 13).

TABLE 13. DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF PATIENTS WHO RECEIVED DARA IN LINE OF THERAPY 2–6

Characteristics	Patients (n=1016)
Age, years	
Median (range)	69 (36-91)
<65	367 (36)
65-74	347 (34)
≥75	292 (29)
Unknown	10 (1)

Male	545 (54)
ISS stage	
I	240 (24)
II	261 (26)
III	378 (37)
Unknown	137 (13)
Prior therapies, median (range)	2 (1-5)
LoT in which dara was received	
2	283 (28)
3	306 (30)
4	311 (31)
5	76 (7)
6	40 (4)

Data are n (%) unless stated otherwise; Dara, daratumumab; ISS, International Staging System; LoT, line of therapy

Baseline Treatment Regimens

Dara was most commonly used in combination with an IMiD. Dara-based regimens at enrollment are shown in Table 14.

TABLE 14. DARATUMUMAB-BASED REGIMENS AT ENROLLMENT

Daratumumab-based regimen, n (%)	Patients (n = 1016)
PI	272 (27)
IMiD	377 (37)
Plus pomalidomide	187 (50)
PI + IMiD	36 (4)
Dexamethasone and/or chemotherapy	325 (32)
Panobinostat	6 (1)

Adapted from Vij et al.[27]

In this study, the median (range) follow-up for enrolled patients was 6.5 (2.6–12.6) months. At database lock, 433 (43%) patients were still on treatment, and 354 (35%) switched to subsequent therapy.

Switching treatment after daratumumab

In total 354 patients (35%) of patients switched to a subsequent therapy after dara of which 76 patients (21%) received an elotuzumab-based regimen and are detailed in Table 15.

TABLE 15. ELOTUZUMAB-CONTAINING REGIMENS RECEIVED AFTER DARA

Subsequent therapy	Unique patients post-dara (n=354)	Unique regimens post-dara (n=521)
Elotuzumab (Elo) regimen	76 (21)	79 (15)
Elo + IMiD	63 (83)	65 (82)
Elo + Len	48 (63)	48 (61)
Elo + Pom	17 (22)	17 (22)
Elo + Pi + IMiD	5 (7)	5 (6)
Elo + PI	4 (5)	4 (5)

Data are n (%). Adapted from Vij et al.[27] Elo, elotuzumab, IMiD, immunomodulatory drug; PI, proteasome inhibitor; Pom, pomalidomide

The most common elotuzumab-based regimens after dara were elotuzumab plus an IMiD (n = 63, 83%), elotuzumab plus an IMiD and a PI (n = 5, 7%), and elotuzumab plus a PI (n = 4, 5%).

- Of patients receiving elotuzumab plus an IMiD, 63% received Len and 22% received Pom.

Most patients who switched to elotuzumab after dara had previously received a PI (93%) or an IMiD (91%).

Duration of treatment with regimens received after daratumumab

Median duration of subsequent treatment at any time after dara was higher in patients receiving elotuzumab-based regimens (Table 16). Similarly, median duration of subsequent therapies immediately after dara was higher among patients receiving elotuzumab-based regimens (151 days) with an equivalent median from the end of the dara treatment to the start of the elotuzumab-therapy (140 days) (Table 17).

TABLE 16. DURATION OF SUBSEQUENT THERAPIES ANY TIME AFTER DARATUMUMAB

Subsequent Therapy, n (%)	Unique Patients (n = 354)	Median (95% CI) Duration of Treatment, Days*
IMiD	139 (39)	50 (40-64)
PI + IMiD	92 (26)	117 (88-145)
PI	81 (23)	74 (45-113)
Elotuzumab regimen	**76 (21)**	**151 (100-204)**
Chemotherapy	39 (11)	36 (22-46)
Daratumumab retreatment	28 (8)	94 (57-150)
Panobinostat regimen	24 (7)	78 (33-97)

Adapted from Vij et al.[27] *Calculated using Kaplan-Meier methods. IMiD, immunomodulatory drug; PI, proteasome inhibitor

TABLE 17. DURATION OF SUBSEQUENT THERAPIES IMMEDIATELY AFTER DARATUMUMAB

Subsequent Therapy, n (%)	Unique Patients Post-Daratumumab (n = 354)	Median (IQR) From End of Daratumumab to Start of Subsequent Therapy, Days*	Median (95% CI) Duration of Treatment, Days†
IMiD	120 (34)	116 (59-240)	22 (12-40)
PI + IMiD	70 (20)	168 (92-250)	115 (87-153)
PI	60 (17)	167 (83-281)	58 (43-113)
Elotuzumab regimen	**51 (14)**	**140 (85-272)**	**151 (100-218)**
Chemotherapy	24 (7)	109 (71-179)	43 (24-85)
Daratumumab retreatment	16 (5)	229 (157-238)	104 (43-225)
Panobinostat regimen	13 (4)	125 (84-245)	81 (53-129)

Adapted from Vij et al.[27] *Descriptive analysis; †Calculated using Kaplan-Meier methods.

In conclusion, patients with RRMM after failure of daratumumab switched to a variety of regimens. The majority of patients received regimens containing IMiDs and/or PIs despite having been exposed to those agents in the past. These data suggest an unmet need in this patient population.

In total, 21% of patients with RRMM after failure of dara received elotuzumab-based regimens, most commonly elotuzumab plus lenalidomide. Elotuzumab-based regimens were associated with a longer median duration of therapy (151 days) after dara than other regimens.

Hoylman et al.

Recently, Hoylman et al. compared retrospectively the clinical outcomes in 37 patients who received daratumumab before elotuzumab (n=23) or vice versa (n=14) in order to investigate the optimal sequence of daratumumab and elotuzumab in relapse/refractory MM.[28] In addition to several limitations, most of the patients included in this single-center retrospective cohort study were treated with various experimental combinations containing elotuzumab for which efficacy and safety has not been well characterized. Therefore, this study is not further described here.[28]

Overall, pre-clinical and clinical data suggest that EloPomDex is an effective therapy option for patients with RRMM who have received at least two prior therapies including lenalidomide, a proteasome inhibitor and potentially daratumumab. Caution should be taken as the potential effect of prior dara-containing treatment has not been investigated prospectively in clinical trials and current evidence are sparse and mostly indirect. Additional data are warranted.

7 CONCLUSIONS

In conclusion, EloPomDex is associated with a statistically and clinically meaningful clinical benefit versus PomDex given the superior efficacy with a similar safety profile.

Despite a more heavily pretreated patient population in ELOQUENT-3, results suggest that EloPomDex might be as effective as CarDex or PomBorDex in patients populations most similar to the one in ELOQUENT-3. In addition, the safety profile of EloPomDex was associated with a numerically lower number of grade 3-4 AEs and discontinuation rate due to AEs compared to CarDex and PomBorDex. However, the added value of EloPomDex versus PomBorDex or CarDex is inconclusive considering the lack of head-to-head study, the absence of a common comparator precluding indirect comparison and the great differences in the characteristics of the patient populations enrolled in the 3 RCTs rendering cross-trial comparison highly uncertain.

Overall, the availability of EloPomDex as a treatment option would be beneficial to cater to the highly individualized treatment decisions made in these later lines of therapy.

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9 APPENDICES

9.1 LITERATURE SEARCH

TABLE 18. ALL EXCLUDED ARTICLES IDENTIFIED DURING THE LITERATURE SEARCH WITH REASON FOR EXCLUSION ACCORDING TO THE PICO CRITERIA

Ref	Article	Exclusion Reason
29	panobinostat (FARYDAK degrees). Multiple myeloma: too toxic! Prescrire Int, 2016. 25(176): p. 257-259.	Review
30	Avet-Loiseau, H., et al., Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. Blood, 2016. 128(9): p. 1174-80.	Therapy combination not in scope
31	Baertsch, M.A., et al., Efficacy and tolerability of the histone deacetylase inhibitor panobinostat in clinical practice. Hematol Oncol, 2018. 36(1): p. 210-216.	Therapy combination not in scope
32	Brown, S., et al., The MUK five protocol: a phase II randomised, controlled, parallel group, multi-centre trial of carfilzomib, cyclophosphamide and dexamethasone (CCD) vs. cyclophosphamide, bortezomib (Velcade) and dexamethasone (CVD) for first relapse and primary refractory multiple myeloma. BMC Hematol, 2016. 16: p. 14.	Therapy combination not in scope
33	Brown, S., et al., The MUK five protocol: a phase II randomised, controlled, parallel group, multi-centre trial of carfilzomib, cyclophosphamide and dexamethasone (CCD) vs. cyclophosphamide, bortezomib (Velcade) and dexamethasone (CVD) for first relapse and primary refractory multiple myeloma. BMC Hematol, 2016. 16: p. 14.	Therapy combination not in scope
34	Campioni, M., et al., Methodology and results of real-world cost-effectiveness of carfilzomib in combination with lenalidomide and dexamethasone in relapsed multiple myeloma using registry data. Eur J Health Econ, 2019.	Not a clinical trial
35	Chari, A., et al., Phase 1 trial of ibrutinib and carfilzomib combination therapy for relapsed or relapsed and refractory multiple myeloma. Leuk Lymphoma, 2018. 59(11): p. 2588-2594.	Therapy combination not in scope
36	Chng, W.J., et al., Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. Leukemia, 2017. 31(6): p. 1368-1374.	Wrong outcome measure
37	Danhof, S., et al., 'Real-life' experience of preapproval carfilzomib-based therapy in myeloma - analysis of cardiac toxicity and predisposing factors. Eur J Haematol, 2016. 97(1): p. 25-32.	Not a clinical trial
38	Dimopoulos, M.A., et al., Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. Blood, 2016. 128(4): p. 497-503.	Therapy combination not in scope
39	Dimopoulos, M.A., et al., Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. Haematologica, 2015. 100(10): p. 1327-33.	Therapy combination not in scope
40	Dimopoulos, M., et al., Carfilzomib vs bortezomib in patients with multiple myeloma and renal failure: a subgroup analysis of ENDEAVOR. Blood, 2019. 133(2): p. 147-155.	Subgroup analysis of patients with renal failure only
41	Dimopoulos, M., et al., Response and progression-free survival according to planned treatment duration in patients with relapsed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in the phase III ASPIRE study. J Hematol Oncol, 2018. 11(1): p. 49.	Therapy combination not in scope
42	Dimopoulos, M.A., et al., Outcomes for Asian patients with multiple myeloma receiving once- or twice-weekly carfilzomib-based therapy: a subgroup analysis of the randomized phase 3 ENDEAVOR and A.R.R.O.W. Trials. Int J Hematol, 2019. 110(4): p. 466-473.	Subgroup analysis of Asian patients only
43	Dimopoulos, M.A., et al., International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment. J Clin Oncol, 2016. 34(13): p. 1544-57.	Recommendation
44	Dimopoulos, M.A., et al., Carfilzomib, lenalidomide, and dexamethasone in patients with relapsed multiple myeloma categorised by age: secondary analysis from the phase 3 ASPIRE study. Br J Haematol, 2017. 177(3): p. 404-413.	Therapy combination not in scope
45	Dimopoulos, M.A., et al., Carfilzomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. Blood Cancer J, 2017. 7(4): p. e554.	Therapy combination not in scope
46	Fenichel, M.P., FDA approves new agent for multiple myeloma. J Natl Cancer Inst, 2015. 107(6): p. djv165.	Review
47	Garderet, L., et al., Upfront autologous stem cell transplantation for newly diagnosed elderly multiple myeloma patients: a prospective multicenter study. Haematologica, 2016. 101(11): p. 1390-1397.	Therapy combination not in scope

Ref	Article	Exclusion Reason
48	Garderet, L., et al., Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. Blood, 2018. 132(24): p. 2555-2563.	Therapy combination not in scope
49	Goldschmidt, 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. 59(6): p. 1364-1374.	Secondary analysis of trial data, only therapy not in scope was analysed
50	Gupta, N., et al., A pharmacokinetics and safety phase 1/1b study of oral ixazomib in patients with multiple myeloma and severe renal impairment or end-stage renal disease requiring haemodialysis. Br J Haematol, 2016. 174(5): p. 748-59.	Therapy combination not in scope
51	Hajek, R., et al., Design and rationale of FOCUS (PX-171-011): a randomized, open-label, phase 3 study of carfilzomib versus best supportive care regimen in patients with relapsed and refractory multiple myeloma (R/R MM). BMC Cancer, 2012. 12: p. 415.	Therapy combination not in scope
52	Hajek, R., et al., A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia, 2017. 31(1): p. 107-114.	Therapy combination not in scope
53	Hanaizi, Z., et al., The European medicines agency review of pomalidomide in combination with low-dose dexamethasone for the treatment of adult patients with multiple myeloma: summary of the scientific assessment of the committee for medicinal products for human use. Oncologist, 2015. 20(3): p. 329-34.	Review
54	Herndon, T.M., et al., U.s. Food and Drug Administration approval: carfilzomib for the treatment of multiple myeloma. Clin Cancer Res, 2013. 19(17): p. 4559-63.	Review
55	Ito, S., [Novel agents in multiple myeloma treatment]. Rinsho Ketsueki, 2015. 56(10): p. 2066-73.	Review
56	Jagannath, S., et al., Heterogeneity of Second-Line Treatment for Patients With Multiple Myeloma in the Connect MM Registry (2010-2016). Clin Lymphoma Myeloma Leuk, 2018. 18(7): p. 480-485 e3.	Registry study
57	Kapoor, P., Another bidder (BDR) revisits. Blood, 2017. 129(4): p. 398-400.	Therapy combination not in scope
58	Kazandjian, D., et al., Remission and Progression-Free Survival in Patients With Newly Diagnosed Multiple Myeloma Treated With Carfilzomib, Lenalidomide, and Dexamethasone: Five-Year Follow-up of a Phase 2 Clinical Trial. JAMA Oncol, 2018. 4(12): p. 1781-1783.	Therapy combination not in scope
59	Kumar, S.K., et al., Randomized phase 2 trial of ixazomib and dexamethasone in relapsed multiple myeloma not refractory to bortezomib. Blood, 2016. 128(20): p. 2415-2422.	Therapy combination not in scope
60	Larocca, A., et al., Current treatment strategies with lenalidomide in multiple myeloma and future perspectives. Future Oncol, 2012. 8(10): p. 1223-38.	Therapy combination not in scope
61	Leleu, X., et al., Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009-02. Blood, 2013. 121(11): p. 1968-75.	Therapy combination not in scope
62	Lonial, S., et al., Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet, 2016. 387(10027): p. 1551-1560.	Therapy combination not in scope
63	Ludwig, H., 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. 58(10): p. 2501-2504.	Post hoc analysis of trial data stratified by patient age
64	Luo, X.W., et al., Treatment options for refractory/relapsed multiple myeloma: an updated evidence synthesis by network meta-analysis. Cancer Manag Res, 2018. 10: p. 2817-2823.	Not a clinical trial
65	Maciocia, N., et al., Real-world use of pomalidomide and dexamethasone in double refractory multiple myeloma suggests benefit in renal impairment and adverse genetics: a multi-centre UK experience. Br J Haematol, 2017. 176(6): p. 908-917.	Not a clinical trial
66	Majer, I.M., et al., Modeling Covariate-Adjusted Survival for Economic Evaluations in Oncology. Pharmacoeconomics, 2019. 37(5): p. 727-737.	Not a clinical trial
67	Mateos, M.V., et al., Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial. Lancet Haematol, 2019. 6(9): p. e459-e469.	Therapy combination not in scope
68	Mateos, M.V., 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. 36(2): p. 463-470.	Indirect comparison of two trials with carfilzomib in combination
69	Matsue, K., et al., Pomalidomide alone or in combination with dexamethasone in Japanese patients with refractory or relapsed and refractory multiple myeloma. Cancer Sci, 2015. 106(11): p. 1561-7.	Phase I cohort study evaluating dose escalation
70	Matsumura, I., [Positioning of autoPBSCT in the treatment of multiple myeloma in the era of new drugs]. Nihon Rinsho, 2015. 73(1): p. 80-4.	Review

Ref	Article	Exclusion Reason
71	Miguel, J.S., et al., Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol, 2013. 14(11): p. 1055-1066.	Therapy combination not in scope
72	Mikhael, J.R., et al., Phase Ib/II trial of CYKLONE (cyclophosphamide, carfilzomib, thalidomide and dexamethasone) for newly diagnosed myeloma. Br J Haematol, 2015. 169(2): p. 219-27.	Therapy combination not in scope
73	Moreau, P., et al., Adverse event management in patients with relapsed and refractory multiple myeloma taking pomalidomide plus low-dose dexamethasone: A pooled analysis. Eur J Haematol, 2017. 99(3): p. 199-206.	Not a clinical trial
74	Moreau, P., et al., Convenience, satisfaction, health-related quality of life of once-weekly 70 mg/m(2) vs. twice-weekly 27 mg/m(2) carfilzomib (randomized A.R.R.O.W. study). Leukemia, 2019.	Secondary analysis of HRQoL for two treatment groups
75	Moreau, P., et al., Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncol, 2018. 19(7): p. 953-964.	Therapy combination not in scope
76	Moreau, P., et al., Relationship of response and survival in patients with relapsed and refractory multiple myeloma treated with pomalidomide plus low-dose dexamethasone in the MM-003 trial randomized phase III trial (NIMBUS). Leuk Lymphoma, 2016. 57(12): p. 2839-2847.	Secondary analysis of NIMUS trial data - not all patients were double refractory
77	Morgan, G., et al., Overall survival of relapsed and refractory multiple myeloma patients after adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone. Br J Haematol, 2015. 168(6): p. 820-3.	Secondary analysis of NIMUS trial data - not all patients were double refractory
78	Niesvizky, R., et al., Phase Ib dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Clin Cancer Res, 2013. 19(8): p. 2248-56.	Therapy combination not in scope
79	Orlowski, R.Z. and S. Lonial, Integration of Novel Agents into the Care of Patients with Multiple Myeloma. Clin Cancer Res, 2016. 22(22): p. 5443-5452.	Review
80	Papadopoulos, K.P., et al., Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. J Clin Oncol, 2015. 33(7): p. 732-9.	Not a clinical trial
81	Richardson, P.G., et al., Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood, 2014. 123(12): p. 1826-32.	Therapy combination not in scope
82	Richardson, P.G., D. Siegel, and R. Baz, A phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib. Blood, 2010. 116.	Short report of Phase I dose escalation. Full trial data included elsewhere
83	Richardson, P.G., et al., Randomized, Open Label Phase 1/2 Study of Pomalidomide (POM) Alone or in Combination with Low-Dose Dexamethasone (LoDex) in Patients (Pts) with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide (LEN) and Bortezomib (BORT): Phase 2 Results. Blood, 2011. 118(21): p. 634-634.	Abstract only. Full trial data included elsewhere
84	San Miguel, J.F., et al., Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica, 2015. 100(10): p. 1334-9.	Secondary analysis of trial data. Outcome stratified by prior therapy
85	Saunders, G., Overview of drug therapy for multiple myeloma. J Oncol Pharm Pract, 2005. 11(3): p. 83-100.	Review
86	Schmitz, S., et al., The use of single armed observational data to closing the gap in otherwise disconnected evidence networks: a network meta-analysis in multiple myeloma. BMC Med Res Methodol, 2018. 18(1): p. 66.	Meta-analysis of observational data
87	Schroeder, M.A., et al., A Phase I/II Trial of Carfilzomib, Pegylated Liposomal Doxorubicin, and Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma. Clin Cancer Res, 2019. 25(13): p. 3776-3783.	Therapy combination not in scope
88	Siegel, D.S., et al., Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. J Clin Oncol, 2018. 36(8): p. 728-734.	Therapy combination not in scope
89	Soekojo, C.Y., et al., Pomalidomide and dexamethasone combination with additional cyclophosphamide in relapsed/refractory multiple myeloma (AMN001)-a trial by the Asian Myeloma Network. Blood Cancer J, 2019. 9(10): p. 83.	Therapy combination not in scope
90	Sonneveld, P., et al., Phase 2 study of carfilzomib, thalidomide, and dexamethasone as induction/consolidation therapy for newly diagnosed multiple myeloma. Blood, 2015. 125(3): p. 449-56.	Therapy combination not in scope
91	Spencer, A., et al., A phase 1 clinical trial evaluating marizomib, pomalidomide and low-dose dexamethasone in relapsed and refractory multiple myeloma (NPI-0052-107): final study results. Br J Haematol, 2018. 180(1): p. 41-51.	Therapy combination not in scope
92	Stewart, A.K., Novel therapeutics in multiple myeloma. Hematology, 2012. 17 Suppl 1: p. S105-8.	Review

Ref	Article	Exclusion Reason
93	Stewart, A.K., Carfilzomib for the treatment of patients with relapsed and/or refractory multiple myeloma. Future Oncol, 2015. 11(15): p. 2121-36.	Review
94	Stewart, A.K., et al., Health-Related Quality-of-Life Results From the Open-Label, Randomized, Phase III ASPIRE Trial Evaluating Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients With Relapsed Multiple Myeloma. J Clin Oncol, 2016. 34(32): p. 3921-3930.	Therapy combination not in scope
95	Stewart, A.K., et al., Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med, 2015. 372(2): p. 142-52.	Therapy combination not in scope
96	Suzuki, K., et al., Carfilzomib, lenalidomide and dexamethasone in patients with heavily pretreated multiple myeloma: A phase 1 study in Japan. Cancer Sci, 2017. 108(3): p. 461-468.	Therapy combination not in scope
97	Touzeau, C. and P. Moreau, Pomalidomide in the management of relapsed multiple myeloma. Future Oncol, 2016. 12(17): p. 1975-83.	Review
98	Tzogani, K., et al., The European Medicines Agency Review of Carfilzomib for the Treatment of Adult Patients with Multiple Myeloma Who Have Received at Least One Prior Therapy. Oncologist, 2017. 22(11): p. 1339-1346.	Review
99	Van Sanden, S., et al., Comparative Efficacy of Daratumumab Monotherapy and Pomalidomide Plus Low-Dose Dexamethasone in the Treatment of Multiple Myeloma: A Matching Adjusted Indirect Comparison. Oncologist, 2018. 23(3): p. 279-287.	Indirect comparison of daratuzumab vs PomDex
100	Voorhees, P.M. and S.Z. Usmani, The role of high-dose melphalan and autologous stem cell transplant in the rapidly evolving era of modern multiple myeloma therapy. Clin Adv Hematol Oncol, 2016. 14(9): p. 719-28.	Therapy combination not in scope
101	Waldschmidt, J.M., et al., CXCL12 and CXCR7 are relevant targets to reverse cell adhesion-mediated drug resistance in multiple myeloma. Br J Haematol, 2017. 179(1): p. 36-49.	Therapy combination not in scope
102	Weisel, K., et al., Pomalidomide and Low-Dose Dexamethasone Improves Health-Related Quality of Life and Prolongs Time to Worsening in Relapsed/Refractory Patients With Multiple Myeloma Enrolled in the MM-003 Randomized Phase III Trial. Clin Lymphoma Myeloma Leuk, 2015. 15(9): p. 519-30.	Secondary analysis of NIMUS trial data - not all patients were double refractory
103	Weisel, K., et al., Health-related quality of life of carfilzomib- and daratumumab-based therapies in patients with relapsed/refractory multiple myeloma, based on German benefit assessment data. Qual Life Res, 2019.	Not a clinical trial
104	Weisel, K.C., et al., Analysis of renal impairment in MM-003, a phase III study of pomalidomide + low - dose dexamethasone versus high - dose dexamethasone in refractory or relapsed and refractory multiple myeloma. Haematologica, 2016. 101(7): p. 872-8.	Subgroup analysis of patients with renal impairment only
105	Wester, R., et al., Phase II study of carfilzomib, thalidomide, and low-dose dexamethasone as induction and consolidation in newly diagnosed, transplant eligible patients with multiple myeloma; the Carthadex trial. Haematologica, 2019. 104(11): p. 2265-2273.	Therapy combination not in scope

9.2 MAIN CHARACTERISTICS OF INCLUDED STUDIES

Study characteristics

TABLE 19. MAIN STUDY CHARACTERISTICS FOR ELOQUENT-3

Trial name	Eloquent-3
NCT number	NCT02654132
Objective	The purpose of this study is to determine if adding Elotuzumab to Pomalidomide and low-dose dexamethasone is a more effective treatment of relapsed and refractory multiple myeloma compared to pomalidomide and low-dose dexamethasone by itself
Publications – title, author, journal, year	Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma, Dimopoulos MA, Dytfeld D, Grosicki S et al., N. Engl. J. Med., 2018. Elotuzumab Plus Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Efficacy Results After Additional Follow-Up of the Phase 2, Randomized ELOQUENT-3 Study, Dimopoulos MA, Dytfeld D, Grosicki S et al., Poster at the 24th Congress of the European Hematology Association (EHA), Abstract PS1370, 2019.
Study type and design	Multicentre, randomised, open label, phase II trial. Patients were randomly assigned, in a 1:1 ratio, to receive elotuzumab plus pomalidomide and dexamethasone (EPd, intervention group) or pomalidomide and dexamethasone (Pd, control group). Randomisation was stratified according to the number of previous lines of therapy (2 or 3 vs. ≥4) and the ISS disease stage at the time of trial enrolment.
Follow-up time	• Minimum follow-up time in the primary analysis was 9.1 months (Dimopoulos 2018) • Minimum follow-up time in the extended follow-up period was 18.3 months (Dimopoulos 2019 and EMPLICITI EPAR)
Population (inclusion and exclusion criteria)	Below are listed the main inclusion and exclusions criteria of the Eloquent-3 study. The full list of the study criteria is available in the Eloquent-3 study protocol at the New England Journal of Medicine website. Main Inclusion Criteria: • Measurable disease at screening • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 • ≥ 2 prior lines of therapy which must have included at least 2 consecutive cycles of lenalidomide and a proteasome inhibitor alone or in combination • Documented refractory or relapsed and refractory multiple myeloma • Refractory (progressed on or within 60 days of treatment) to their last treatment. • Subjects must have failed treatment with a proteosome inhibitor and lenalidomide in one of the following ways: - Refractory to proteosome inhibitor and lenalidomide, and to their last treatment. - Relapsed and refractory defined as patients, who had achieved at least a partial response to previous treatment with proteosome inhibitor or

<table>
<tr><td></td><td>lenalidomide, or both, but progressed within 6 months, and were refractory to their last treatment.

Main Exclusion Criteria:
• Prior treatment with pomalidomide
• Subjects with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
• Subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), amyloidosis, Waldenstrom's macroglobulinemia, or POEMS syndrome
• Subjects with active plasma cell leukemia
• Any uncontrolled or severe cardiovascular or pulmonary disease determined by the investigator
• Creatinine clearance < 45 ml/min according to the Cockroft-Gault formula
• Unable to tolerate thromboembolic prophylaxis while on the study
• Grade ≥2 peripheral neuropathy (per NCI CTCAE v3.0)
• Active infection that requires parenteral anti-infective treatment >14 days
• Prior participation in an elotuzumab clinical trial regardless of treatment assignment
• Prior autologous stem cell transplant within 12 weeks
• Treatment with melphalan or monoclonal antibodies within 6 weeks of the first dose of study drug
• Use of any anti-myeloma drug therapy, within 14 days of the initiation of study drug treatment or use of any experimental drug therapy or plasmapheresis within 28 days (or 5 half-lives) whichever is longer) of the initiation of study drug treatment (includes dexamethasone). Bisphosphonate use permitted.</td></tr>
<tr><td>Intervention</td><td>Elotuzumab + Pomalidomide + Dexamethasone arm (EPd)
60 patients were randomised into the arm and were all treated

Pomalidomide + Dexamethasone arm (Pd)
57 patients were randomised into the arm of which 55 were treated

(for dosing, see "Dosage regimen" section in Table 2)</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic*</th><th></th><th>Elotuzumab + Pomalidomide + Dexamethasone (n=60)</th><th>Pomalidomide + Dexamethasone (n=57)</th></tr>
<tr><td rowspan="5">Age (years)</td><td>Median</td><td>69</td><td>66</td></tr>
<tr><td><65</td><td>37</td><td>39</td></tr>
<tr><td>≥65</td><td>63</td><td>61</td></tr>
<tr><td><75</td><td>78</td><td>79</td></tr>
<tr><td>≥75</td><td>22</td><td>21</td></tr>
<tr><td>Sex (%)</td><td></td><td>47 female</td><td>39 female</td></tr>
<tr><td rowspan="4">Race/ethnicity (%)</td><td>White</td><td>75</td><td>79</td></tr>
<tr><td>Black</td><td>0</td><td>2</td></tr>
<tr><td>Asian</td><td>25</td><td>16</td></tr>
<tr><td>Other</td><td>0</td><td>3</td></tr>
<tr><td rowspan="2">ISS Stage Measure Type† (%)</td><td>Stage I</td><td>88</td><td>88</td></tr>
<tr><td>Stage II or III</td><td>12</td><td>12</td></tr>
<tr><td rowspan="3">Serum lactate dehydrogenase level (%)</td><td><300 U/litre</td><td>72</td><td>72</td></tr>
<tr><td>≥300 U/ litre</td><td>23</td><td>26</td></tr>
<tr><td>Data not available</td><td>5</td><td>2</td></tr>
<tr><td></td><td>Yes</td><td>22</td><td>25</td></tr>
</table>
</td></tr>
</table>

	Cytogenetic abnormalities‡ (%)	Del17p, t(4;14), or t(14;16)	No	52	47
			Data not available	27	28
		1q21	Yes	42	47
			No	33	23
			Data not available	25	30
	Lines of Prior Treatment		Median (range)	3 (2 –8)	3 (2 –8)
			2 or 3 (%)	60	63
			≥4 (%)	40	37
	Previous stem-cell transplantation (%)			52	58
	Previous therapies§ (%)		Bortezomib	10	100
			Lenalidomide	98	100
			Melphalan	63	63
			Thalidomide	42	33
			Doxorubicin	30	26
			Carfilzomib	15	28
			Ixazomib	8	4
			Daratumumab	2	4
	Refractory status of disease to lenalidomide (%)		Refractory	90	84
			Relapsed and refractory	8	12
	Refractory status of disease to a proteasome inhibitor (%)		Refractory	78	82
			Relapsed and refractory	22	14
	Refractory status of disease to lenalidomide and a proteasome inhibitor¶ (%)		Refractory to both	68	72
			Relapsed and refractory to both	0	5
			Refractory to one, relapsed and refractory to the other	30	16
	Median time since diagnosis of multiple myeloma (range) (years)			4.8 (0.5 – 21.9)	4.4 (0.7 – 17.5)

*Included are all patients who underwent randomisation.
†The International Staging System consists of three stages, with higher stages indicating more severe disease: stage I, serum β2-microglobulin level lower than 3.5 mg per litre (300 nmol per litre) and albumin level 3.5 g per decilitre or higher; stage II, neither stage I nor III; and stage III, serum β2-microglobulin 5.5 mg per litre or higher (470 nmol per litre).
‡Fluorescence in situ hybridization was performed at a central laboratory to detect cytogenetic mutations. Positivity for each cytogenetic mutation was based on the identification of at least 1 abnormal cell out of a minimum of 100 cells examined, with the exception of del17p, which required at least 60% abnormal cells. Positivity for 1q21 required at least three copies of 1q21 in 1 cell.
§Only previous therapies of interest are reported. As a result of a protocol deviation, one patient in the elotuzumab group did not receive previous treatment with lenalidomide.
¶A total of five patients (one in the elotuzumab group and four in the control group) had disease with an unknown status with respect to either lenalidomide or a proteasome inhibitor (protocol deviations)

Primary and secondary endpoints	**Primary endpoint** • Investigator-assessed PFS, which was defined as the time from randomisation to the first occurrence of disease progression (not including clinical deterioration) or death from any cause, whichever occurred first (primary definition) **Secondary endpoints** • ORR (partial response or better) as assessed by the investigator • OS An independent review committee (IRC) also assessed PFS and ORR to confirm the results of the investigator assessment.

	Exploratory end points • Time to response • Duration of response (DoR) • Safety and tolerability • HRQoL by assessing the patient-reported outcomes in disease-related symptoms using MDASI-MM and EQ-5D • The pharmacokinetics and immunogenicity of elotuzumab in presence of pomalidomide and dexamethasone • To assess the relationship between (a) changes in soluble SLAMF7 (sSLAMF7) from baseline and response and (b) baseline measurements of sSLAMF7 and PFS (c) baseline levels of SLAMF7 expression on MM cells and NK cells and response to treatment (d) the gene expression profile at baseline and while on therapy to clinical response (e) M-protein and molecular Minimal Residual Disease (MRD) status • The changes from baseline of SLAMF7 expression on MM cell and NK cells at time of progression • The association between cytogenetic risk and response An ad-hoc endpoint of Time to Next Treatment (TTNT) was analyzed. TTNT was defined as the time from randomization to the earliest start date of subsequent myeloma systemic therapy or death, whichever occurred first.
Method of analysis	Investigator-assessed PFS was based on the ITT population. Kaplan-Meier method was used to estimate PSF and its median. PFS was compared with the use of a two-sided stratified log-rank test, stratified by number of prior lines of therapy (2–3 vs. ≥4) and ISS stage (I–II vs. III) at study entry; the hazard ratio of the elotuzumab group to the control group was estimated with a stratified Cox proportional-hazards model with treatment as the single covariate. The ORR in the 2 groups was compared with the use of a Cochran–Mantel–Haenszel test and its corresponding estimate of treatment odds ratio. Preliminary OS was estimated by the Kaplan–Meier method; a preliminary HR was estimated with the use of a stratified Cox proportional-hazards model, with treatment as the single covariate. An IRC-assessed PFS and ORR to confirm the results of the investigator assessment. Response assessments were based on International Myeloma Working Group (IMWG) consensus criteria, except for assessment of minor (minimal) response, which was derived from European Society for Blood and Marrow Transplantation criteria. Definitions of responses and progression are provided in the supplemental material from Dimopoulos et al., 2018, NEJM.
Subgroup analyses	Results from subgroup analyses should be taken with caution in view of the very limited number of patients included in most of the subgroups examined. The majority of the performed investigator-assessed PFS subgroup analyses on ITT are presented in Figure 3-5 of the EMPLICITI EPAR. In addition, some subset analyses are shown in Dimopoulos et al., 2018, NEJM and associated supplemental material. Kaplan-Meier analyses of PFS of key patient subgroup were performed for patients who were refractory to both lenalidomide and a proteasome inhibitor; according to the number of prior lines of therapy received (2–3 vs. ≥4); in patients with high-risk disease (ISS stage II–III and t(4;14) or del(17p) abnormality) according to IMWG risk stratification; in patients with at least one del(17p), t(4;14), or t(14;16) abnormality; and in patients with at least one del(17p), t(4;14), or t(14;16) abnormality or LDH levels ≥300 IU/L). See Figure S3 from Dimopoulos et al., 2018, NEJM.

	Subset analysis of PFS described in the Eloquent-3 protocol (page 29) The influence of baseline and demographic characteristics on the treatment effect were explored via exploratory subset analyses for the following factors: • Age (< 75 years, ≥ 75 years) and Age (< 65 years, ≥ 65 years) • Race (White, Black, Asian, Other) • Gender (Male, Female) • Baseline β2 microglobulin (mg/L) (< 3.5, ≥3.5) • ISS Stage at study entry (I-II, III) • Baseline LDH (< 300IU/L, ≥300IU/L) • Baseline creatinine clearance (ml/min) (< 60, ≥60) • Number of lines of prior therapy (2-3, ≥4) • Region (North America, Europe, Japan, And Australia) • Baseline ECOG performance status (0-1, 2) • Prior stem cell transplant (Yes, No) • Myeloma risk category (High risk, Low risk and Other) • High risk [ISS stage II or III and t(4;14) or del(17p) abnormality], Low risk [ISS stage I or II and absence of t(4;14), del(17p) and 1q21 abnormalities and age < 55 years] and Standard risk (any subjects not meeting the definition of high or low risk and enough data to be classified as standard risk) • Individual FISH abnormalities (del 17p, t(14; 16), t(4; 14), del(1q), and del(1p)) The HR of EPd to Pd and the associated 95% CI for each subgroup category are presented in a forest plot. The estimate of each hazard ratio and CI were generated using an unstratified Cox proportional hazards model with treatment as the only covariate.

TABLE 20. MAIN STUDY CHARACTERISTICS FOR ENDEAVOR

Trial name	ENDEAVOR
NCT number	NCT01568866
Objective	The primary objective of this study was to compare PFS 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	Dimopolous et al. 2016. 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 Oncology, 17: 27 – 38. Dimopolous et al. 2017. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncology, 18:1327 – 37.
Study type and design	Randomised, open-label, phase 3, completed study. Patients were randomly assigned (1:1) to receive carfilzomib and dexamethasone (carfilzomib group) or bortezomib and dexamethasone (bortezomib group), and were stratified by the following baseline factors: ISS stage (I vs II–III), previous lines of treatment, previous proteasome inhibitor therapy, 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.

Follow-up time	• For the primary analysis, median follow-up was 11·9 months (IQR 9·3–16·1) in the carfilzomib group and 11·1 months (IQR 8·2–14·3) in the bortezomib group (Dimopoulos 2016) • For the follow-up analysis, median follow-up of 37·5 months (IQR 34·4–41·9) in the carfilzomib group and 36·9 months (IQR 33·4–40·6) in the bortezomib group (Dimopoulos 2017)
Population (inclusion and exclusion criteria)	Inclusion Criteria • Multiple myeloma with relapsing or progressing disease at study entry • Evaluable multiple myeloma with at least one of the following (assessed within 21 days prior to randomisation): o Serum M-protein ≥ 0.5 g/dL; or urine M-protein ≥ 200 mg/24 hour; or in patients without detectable serum or urine M-protein, serum free light chain > 100 mg/L (involved light chain) and an abnormal serum kappa/lamda ratio; or for IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA) ≥ 750 mg/dL (0.75 g/dL). • At least a (partial response) PR to at least 1 line of prior therapy; PR documentation can be based on investigator assessment • Received 1 to 3 prior treatment regimens or lines of therapy for multiple myeloma • Prior therapy with Velcade is allowed if: 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-month Velcade treatment-free interval from last dose received until first study treatment • Prior therapy with carfilzomib is allowed if: 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. • ≥ 18 years of age • ECOG Performance Status of 0 to 2 • Adequate hepatic function within 21 days prior to randomisation, with bilirubin < 1.5 times the ULN, and aspartate aminotransferase and alanine aminotransferase < 3 times the ULN • Left ventricular ejection fraction ≥ 40% • Absolute neutrophil count (ANC) ≥ 1000/mm³ within 21 days prior to randomisation; screening ANC should be independent of growth factor support for ≥ 1 week • Haemoglobin ≥ 8.0 g/dL within 21 days prior to randomisation; most recent red blood cell transfusion may not have been done within 7 days prior to obtaining screening haemoglobin • Platelet count ≥ 50,000/mm³ (≥ 30,000/mm³ if myeloma involvement in the bone marrow is > 50%) within 21 days prior to randomisation • Calculated or measured creatinine clearance of ≥ 15 mL/min within 21 days prior to randomisation Exclusion Criteria • Multiple Myeloma of IgM subtype • Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 14 days prior to randomisation • POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) • Plasma cell leukaemia or circulating plasma cells ≥ 2×10^9/L • Waldenstrom's Macroglobulinemia • Known amyloidosis

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Chemotherapy with approved or investigational anticancer therapeutics within 21 days prior to randomisation
Randomised or previously randomised in any other Onyx-Sponsored Phase 3 trial
Focal radiation therapy within 7 days prior to randomisation; radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to randomisation
Immunotherapy within 21 days prior to randomisation
Major surgery (excluding kyphoplasty) within 28 days prior to randomisation
New York Heart Association Class III to IV, symptomatic ischemia, or conduction abnormalities uncontrolled by conventional intervention; Myocardial infarction within four months prior to randomisation
Acute active infection requiring systemic antibiotics, antiviral (except antiviral therapy directed at hepatitis B) or antifungal agents within 14 days prior to randomisation
Known HIV, hepatitis C infection, and/or hepatitis B (except for patients with hepatitis B surface antigen or core antibody receiving and responding to antiviral therapy directed at hepatitis B)
Known cirrhosis
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 over 12 months; breast carcinoma in situ with full surgical resection; treated medullary or papillary thyroid cancer

Myelodysplastic syndrome
Significant neuropathy (Grades 3 to 4, or Grade 2 with pain) within 14 days prior to randomisation
Female patients who are pregnant or lactating
Known history of allergy to Captisol
Patients with hypersensitivity to carfilzomib, Velcade, boron, or mannitol
Patients with contraindication to dexamethasone
Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs, or intolerance to hydration due to pre-existing pulmonary or cardiac impairment
Ongoing graft-vs-host disease
Pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomisation

</td></tr>
<tr><td>Intervention</td><td>Drug: Carfilzomib
n=464
Administered over 30 minutes as an infusion
Drug: Bortezomib
n=465
Administered as a 3-5 second bolus intravenous injection or subcutaneously injection
Drug: Dexamethasone
n=929
Tablet for oral administration; On days when carfilzomib or bortezomib was administered, the dexamethasone was to be given 30 minutes to 4 hours prior to the carfilzomib or bortezomib dose</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic</th><th></th><th>Bortezomib + DEX (n=465)</th><th>Carfilzomib + DEX (n=464)</th></tr>
<tr><td rowspan="4">Age (years)</td><td>Median</td><td>65</td><td>65</td></tr>
<tr><td><65</td><td>45</td><td>48</td></tr>
<tr><td>65 – 74</td><td>41</td><td>35</td></tr>
<tr><td>≥75</td><td>14</td><td>17</td></tr>
<tr><td>Sex (%)</td><td></td><td>51 (female)</td><td>48 (female)</td></tr>
<tr><td rowspan="2">Race/ethnicity (%)</td><td>White</td><td>76</td><td>75</td></tr>
<tr><td>Black</td><td>2</td><td>2</td></tr>
</table>
</td></tr>
</table>

		Asian	12	13
		Not reported	10	11
		Multiple	<1	0.0
	ECOG Performance Status (%)	0 (fully active)	50	48
		1 (restrictive but ambulatory)	44	45
		2 (ambulatory but unable to work)	6	7
	Lines of Prior Treatment* (%)	1 line	50	50
		2 lines	31	34
		3 lines	19	16
	ISS Stage Measure Type (%)	Stage I	44	44
		Stage II or III	56	56
	Cytogenetics (%)	High risk	24	21
		Standard risk	63	61
		Unknown	6	12
		Missing	7	6
	Creatinine clearance (mL/min) (%)	Mean	75.1	76.7
		<30	6	6
		30 – 50	15	12
		50 – 80	38	40
		≥80	41	42
	Serum β2 microglobulin (mg/L) (%)	Mean	4.8	4.6
		<3.5	46	47
		≥3.5	54	53
	History of peripheral neuropathy (%)	No	48	54
		Yes	52	46
	Ongoing peripheral neuropathy at screening (%)	Grade 1	34	29
		Grade 2	2	2
	Prior Proteasome Inhibitor Treatment Measure Type† (%)	Bortezomib	54	54
		Carfilzomib	<1	<1
		No prior carfilzomib or bortezomib	46	46
	Previous Immunomodulatory Agent Treatment (%)	Lenalidomide	38	38
		Thalidomide	45	53

*One patient in the Bortezomib group had received four prior treatments (a protocol deviation). †Defined as patients who achieved at least a partial response and had at least 6 months since last proteasome inhibitor treatment; all patients who had received previous carfilzomib and all except one patient (a protocol deviation in the carfilzomib group) who had received previous bortezomib met the above entry criteria for previous proteasome inhibitor therapy.

Primary and secondary endpoints	Primary Endpoint • PFS, defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first Secondary Endpoint • OS • Overall response (partial response or better) • Duration of response • Percentage of participants with ≥ Grade 2 peripheral neuropathy • Safety
Method of analysis	Efficacy analyses were ITT analyses. A stratified log-rank test was used for PFS and OS, and median values for both were estimates using the Kaplan-Meier method. Stratified Cochran-Mantel-Haeszel test was used for overall response. Median duration of response was estimates using the Kaplan-Meier method.

	The overall response was compared between groups using a Mantel-Haenszel test, and the associated OR and 95% CI were estimated. A Pearson χ^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 echocardiogram sub-study, a mixed model for repeated measures was used under the assumption of missing-at-random to estimate longitudinal differences between the treatment groups in the reduction of left ventricular ejection fraction and right ventricular function. 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.
Subgroup analyses	Pre-planned exploratory analyses of PFS have been done in subgroups: age, baseline ECOG, performance status, baseline creatine clearance, ISS stage, risk group by fluorescence in-situ hybridisation, and previous treatment with bortezomib and immunomodulatory drugs. Overall survival (HR with 85% CI) was compared between treatment groups using a stratified log-rank test, the corresponding HR was estimated using a stratified Cox regression model. One-sided significance level was determined by the O'Brien-Fleming–type α spending function based on the actual number of events (α=0·0123). The Kaplan-Meier method was used to summarise time to next treatment and survival beyond disease progression.

TABLE 21. MAIN STUDY CHARACTERISTICS FOR OPTIMISMM

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.
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)	The full list of the study criteria is available in the OPTIMISMM study protocol included in the supplemental material of Richardson et al., 2019, Lancet Oncol. Main 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.

<table>
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All subjects must have received prior treatment with a lenalidomide containing regimen for at least 2 consecutive cycles.
Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2

Main 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.
≥ Grade 3 rash during prior thalidomide or lenalidomide therapy
Subjects with any one of the following:

Clinically significant abnormal ECG finding at screening
Congestive heart failure (New York Heart Association Class III or IV)
Myocardial infarction within 12 months prior to starting study treatment
Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris

Subjects who received any of the following within the last 14 days of initiation of study treatment:

Plasmapheresis
Major surgery (kyphoplasty is not considered major surgery)
Radiation therapy other than local therapy for myeloma associated bone lesions
Use of any systemic anti-myeloma drug therapy

Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of treatment

</td></tr>
<tr><td>Intervention</td><td>
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.

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<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>PomBorDex (n=281)</th><th>BorDex (n=278)</th></tr>
<tr><td>Age (years)</td><td>67 (60–73)</td><td>68 (59–73)</td></tr>
<tr><td>≤65</td><td>123 (44%)</td><td>120 (43%)</td></tr>
<tr><td>>65</td><td>158 (56%)</td><td>158 (57%)</td></tr>
<tr><td>≤75</td><td>235 (84%)</td><td>231 (83%)</td></tr>
<tr><td>>75</td><td>46 (16%)</td><td>47 (17%)</td></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>Male</td><td>155 (55%)</td><td>147 (53%)</td></tr>
<tr><td>Female</td><td>126 (45%)</td><td>131 (47%)</td></tr>
<tr><td>ECOG performance status</td><td></td><td></td></tr>
<tr><td>0</td><td>149 (53%)</td><td>137 (49%)</td></tr>
<tr><td>1</td><td>121 (43%)</td><td>119 (43%)</td></tr>
<tr><td>2</td><td>11 (4%)</td><td>22 (8%)</td></tr>
<tr><td>ISS disease stage</td><td></td><td></td></tr>
<tr><td>I</td><td>149 (53%)</td><td>138 (50%)</td></tr>
<tr><td>II</td><td>85 (30%)</td><td>90 (32%)</td></tr>
<tr><td>III</td><td>47 (17%)</td><td>50 (18%)</td></tr>
<tr><td>Cytogenetic profile by FISH</td><td></td><td></td></tr>
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</table>

	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. Prespecified subgroup analyses was performed for PFS for lenalidomide refractory patients and 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. 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.

9.3 RESULTS PER STUDY

TABLE 22. RESULTS OF THE ELOQUENT-3 STUDY

Trial name:	ELOQUENT-3									
NCT number:	NCT02654132									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value	
Investigator-assessed progression-free survival (Primary endpoint)	Elotuzumab + PomDex	60	10.3 months (5.6–NE)	4.0	0.8-9.1	NA	HR: 0.54	0.34-0.86	0.008	Progressive-free survival was estimated by the Kaplan–Meier method. The HR is based on a log rank test. The estimation of the absolute difference in medians was based on formula 6, page 55, of the Methods Guideline from the Medicines Council (v.2.3).
	PomDex	57	4.7 months (2.8–7.2)							
Independent review assessed progression-free survival	Elotuzumab + PomDex	60	10.3 months (6.5–NE)				HR: 0.51	0.32-0.82		
	PomDex	57	4.7 months (2.8–7.6)							
Overall Survival	Elotuzumab + PomDex	60	No reached (24.9 months – NE)	14.8	0.7-40.6	NA	HR: 0.54	0.30– 0.96		Overall survival was estimated by

	PomDex	57	17.4 months (13.8 – NE)							the Kaplan–Meier method. For the absolute difference in median was estimated using formula 6, p.55 of the methods guideline (v.2.3) from the Medicines Council
Discontinuation due to AEs	**Any AEs** Elotuzumab + PomDex	60	18.3% (11 patients)	-5,3%	-14.7%-13.8%	NA	RR: 0.78	0.38-1.59	NA	Reference EPAR Table 9. Safety assessments occurred prior to and during dosing, up to 60 days after the last dose was administered, and throughout long-term follow-up post treatment (every 12 weeks or more). Safety was summarized using Common Terminology Criteria for Adverse Events, version 3.0. The relative risk (RR) were calculated and
	PomDex	55	23.6% (13 patients)							

								used to estimate the absolute difference in effect using formula 4, page 54, of the Methods Guideline from the Medicines Council (v.2.3).
	Drug-related AEs Elotuzumab + PomDex	60	8.3% (5 patients)					
	PomDex	55	5.5% (3 patients)					
Healt-related Quality of Life EQ-5D-3L[a]	**Visual analog scale (VAS)** Elotuzumab + PomDex	55	Baseline score (mean, [SD]) 65.6 (18.6)	4.7	-0.9-10.2	0.098		The minimally important difference was based on UK index scores. Patient-reported outcome data were collected at baseline, at the start of each cycle, end of treatment, and during long-term follow-up
	PomDex	51	Baseline score (mean, [SD]) 69.2 (20.9)					

	Utility Index Elotuzumab + PomDex	55	Baseline score (mean, [SD]) 0.698 (0.283)			(approx. every 12 cycles) Randomized patients with baseline and at least 1 post-baseline assessments were included in the analysis. Analysis of change from baseline used a longitudinal mixed-effects model, with PRO score as the dependant variable, and baseline score and stratification factors as covariates.
	PomDex	51	Baseline score (mean, [SD]) 0.677 (0.291)	0.046	-0.035-0.127	0.259	
Qualitative review of AEs	See narrative						

a, HRQoL data shown here have been only presented in abstracts at international congresses and are highlighted in blue.[11]
CI, confidence interval; NA, not applicable

TABLE 23. RESULTS FROM THE ENDEAVOR STUDY

Trial name:	ENDEAVOR			
NCT number:	NCT01568866			
		Estimated absolute difference in effect	Estimated relative difference in effect	Description of methods used for estimation

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Progression-free survival	**ITT population** Bortezomib + Dex	465	9.4 months (8.4–10.4)				HR: 0.53	0.44–0.65	< 0.0001	The median PFS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model stratified by prior proteasome inhibitor treatment, lines of prior treatment, ISS stage, and choice of route of bortezomib administration.
	Carfilzomib + Dex	464	18.7 months (15.6–NA)							
	Prior LEN and 2-3 prior lines Bortezomib + Dex	132	6.6 months				0.73	0.53-1.01		
	Carfilzomib + Dex	126	9.7 months							
	Refractory to any prior LEN treatment Bortezomib + Dex	122	6.6 months				0.80	0.573-1.110	0.0891 (1-sided)	
	Carfilzomib + Dex	113	8.6 months							
Overall survival	**ITT population** Bortezomib + Dex	465	40.0 months (32.6–42.3)				HR: 0.791	0.648–0.964	0.010	The median OS rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model stratified by prior proteasome inhibitor treatment, lines of prior
	Carfilzomib + Dex	464	47.6 months (42.5–NA)							

	With prior lenalidomide Bortezomib + Dex	178	29.4 months		0.88	0.67-1.16	treatment, ISS stage, and choice of route of bortezomib administration.
	Carfilzomib + Dex	177	35.4 months				
	Refractory to LEN Bortezomib + Dex	123	21.4 months		0.857	0.62-1.18	
	Carfilzomib + Dex	113	29.2 months				
	2-3 prior lines of therapy Bortezomib + Dex	236	28.4 months		0.75	0.59-0.96	
	Carfilzomib + Dex	233	39.5 months				
Discontinuation due to AEs	**Any AEs** Bortezomib + Dex	456	26.5% (121 patients)[13]				Adverse event and laboratory data were collected until 30 days after last dose of study treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
	Carfilzomib + Dex	463	29.6% (137 patients)[13]				
	Any AEs and 2-3 prior lines Bortezomib + Dex	229	23.1% (53 patients)[9]				
		231	22.5% (52 patients)[9]				

	Carfilzomib + Dex						
	Treatment-related AEs						References: [9,13,16] Table 19 of the Kyprolis EPAR (page 69).
	Bortezomib + Dex	456	16.7% (76 patients)				
	Carfilzomib + Dex	463	13.0% (60 patients)				
Health-related Quality of Life (Treatment Difference Over Time in QLC-C30 Global Health Status/Quality of Life Based on Mixed Model for Repeated Measures)	Bortezomib + Dexamethasone (ITT)	452	57.15	3.51	1.97-5.06	<0.0001	Kyprolis EPAR; p. 54; table 17 and Ludwig, 2019; p.7; figure 2 HRQoL was measured by EORTC Quality of Life Questionnaire QLQ-C30. 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.
	Carfilzomib + Dexamethasone (ITT)	459	60.66				
Qualitative review of AEs	See narrative						

TABLE 24. RESULTS OF THE OPTIMISMM STUDY

Trial name:	OPTIMISMM
NCT number:	NCT01734928

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Median Overall survival	**ITT population** Pomalidomide + Bortezomib+ Dexamethasone	281	40.54 months (29.83-NE)	10.1 months	NR	NR	HR: 0.91	0.70-1.18	0.4755	Imnovid EPAR; p.49; table 23. *Data from the updated analysis (median FU* of 26.2 months; *DBL 15 Sept 2018)* *The median is based on Kaplan-Meier estimate. Hazard ratio is based on Cox proportional hazards model comparing the hazard functions associated with treatment 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.*
	ITT population Bortezomib + Dexamethasone	278	30.46 months (24.61-35.94)							
Median Progression Free Survival	**ITT population** Pomalidomide + Bortezomib+ Dexamethasone	281	11.2 months (9.66-13.73)	4.1 months	NR	NR	HR: 0.61	0.49 - 0.77	<0.0001	Richardson, 2019; p.786 Richardson, 2019; p.787; figure 2 Richardson, 2019; p. 788; figure 3 *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*
	ITT population Bortezomib + Dexamethasone	278	7.1 months (5.88-8.48)							

	Refractory to LEN Pomalidomide + Bortezomib+ Dexamethasone **Refractory to LEN** Bortezomib + Dexamethasone (refractory to lenalidomide)	200 191	9.53 months (8.05 - 11.30) 5.59 months (4.44 - 7.00)	3.94 months	NR	NR	HR: 0.65	0.50 - 0.84	0.0008	*model. Absolute differences in median PFS were not 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.*
	>1 previous lines of treatment Pomalidomide + Bortezomib+ Dexamethasone **>1 previous lines of treatment** Bortezomib + Dexamethasone	170 163	NR NR	NR	NR	NR	HR: 0.63	0.48-0.83	NR	
HRQoL mean baseline scores, QLQ-C30	Pomalidomide + Bortezomib+ Dexamethasone Bortezomib + Dexamethasone	240 209	Baseline score: 61.0 (SD: 23.2) Baseline score: 63.5 (SD: 21.3)	NR	NR	NR	NR	NR	NR	Richardson, 2019; p.791 *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, 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 Treatment-Emergent AEs (TEAEs)	**TEAE leading to discontinuation of any study drug** Pomalidomide + Bortezomib+ Dexamethasone	278	28.8 % (80 patients)	-9.9%	-17.3% ; -2.4%	0.009	RR: 1.52	1.12, 2.07	0.008	Imnovid EPAR; p.73; table 46 Safety assessments comprised assessment of adverse events, clinical laboratory tests, electrocardiograms, measurement of vital signs, and physical examinations. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0 or higher) and were summarised by system organ class and preferred term. Second primary malignancies were monitored and reported as serious adverse events. *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.*
	TEAE leading to discontinuation of any study drug Bortezomib+ Dexamethasone	270	18.9% (51 patients)							
Qualitative review of AEs	See narrative									

9.4 ADVERSE EVENTS IN ≥10% OF PATIENTS

As requested by the Medicines Council, all Grade AEs occurring in ≥10% of patients in the intervention and comparators arms defined in the protocol (EloPomDex, PomDex, CarDex and PomBorDex) are listed in Table 25 below.

For EloPomDex and PomDex (ELOQUENT-3), Table 3 from Dimopoulos et al., 2018[5] and Table 10 from the Empliciti EPAR[15] were used.

For PomBorDex (OPTIMISMM), Table 36 in the Imnovid EPAR[8] was selected to complete Table 25. This data source was chosen as incidence of AEs are provided for any Grade, in contrast to the Table 3 in Richardson et al., 2019[7].

For CarDex (ENDEAVOR), data for AEs occurring in ≥10% of patients has been sourced from Table 20 from the Kyprolis EPAR[16] (column Cd under ENDEAVOR sNDA), which reports AEs by any Grade and meets the Medicines Council requirement. Presentation of the safety data in the peer-reviewed articles of the ENDEAVOR study were not suitable here.

The tables from the respective EPARs reports any cause AEs reported in ≥5% of subject in either treatment arm of the study.

TABLE 25. ANY ADVERSE EVENTS OF ANY GRADE REPORTED IN AT LEAST 10% OF PATIENTS IN EITHER TREATMENT GROUP

	EloPomDex n=60	**PomDex** n=55	**CarDex** n=463	**PomBorDex** n=278
Cutoff	21 February 2018		10 November 2014	26 October 2017
Follow up	min. 9.1 months		median 11.9 months	median 15.9 months
Any AEs, n (%)	58 (96.7)	52 (94.5)	455 (98.3)	277 (99.6)
Nonhematologic AEs				
Constipation	**13 (21.7)**	**6 (10.9)**	**68 (14.7)**	**102 (36.7)**
Hyperglycemia	**12 (20.0)**	**8 (14.5)**	**49 (10.6)**	**40 (14.4)**
Diarrhea	**11 (18.3)**	5 (9.1)	**143 (30.9)**	**94 (33.8)**
Fatigue	**9 (15.0)**	**9 (16.4)**	**136 (29.4)**	**103 (37.1)**
Bone pain	**9 (15.0)**	5 (9.1)	**47 (10.2)**	22 (7.9)
Dyspnea	**9 (15.0)**	4 (7.3)	**138 (28.5)**	**56 (20.1)**
Pyrexia	**8 (13.3)**	**14 (25.5)**	**130 (28.1)**	**64 (23.0)**
Insomnia	**8 (13.3)**	**6 (10.9)**	**117 (25.3)**	**45 (16.2)**
Peripheral edema	**8 (13.3)**	4 (7.3)	**101 (21.8)**	**94 (33.8)**

Muscle spasms	**8**	**(13.3)**	3	(5.5)	**86**	**(18.6)**	26	(9.4)
Asthenia	**7**	**(11.7)**	5	(9.1)	**94**	**(20.3)**	**48**	**(17.3)**
Rash	**6**	**(10.0)**	**6**	**(10.9)**	27	(5.8)	26	(9.4)
Hypokalemia	4	(6.7)	**7**	**(12.7)**	**50**	**(10.8)**	**43**	**(15.5)**
Increased blood creatinine	3	(5.0)	**6**	**(10.9)**	**47**	**(10.4)**		
Malignant neoplasm progression	1	(1.7)	**6**	**(10.9)**				
Cough	5	(8.3)	5	(9.1)	**115**	**(24.8)**	**57**	**(20.5)**
Nausea	1	(1.7)	5	(9.1)	**90**	**(19.4)**	**49**	**(17.6)**
Back pain	4	(6.7)	4	(7.3)	**86**	**(18.6)**	**52**	**(18.7)**
Headache	3	(5.0)	2	(3.6)	**79**	**(17.1)**	**31**	**(11.2)**
Vomiting	1	(1.7)	1	(1.8)	**65**	**(14.0)**	**32**	**(11.5)**
Arthralgia	1	(1.7)	4	(7.3)	**47**	**(10.2)**	**32**	**(11.5)**
Pain in Extremity					**47**	**(10.2)**	**33**	**(11.9)**
Diziness	2	(3.3)	3	(5.5)	37	(8.0)	**48**	**(17.3)**
Muscular weakness	2	(3.3)	4	(7.3)	36	(7.8)	**38**	**(13.7)**
Tremor	4	(6.7)	2	(3.6)	10	(2.2)	**30**	**(10.8)**
Hematologic AEs	31	(51.7)	30	(54.5)				
Anemia	**15**	**(25.0)**	**20**	**(36.4)**	**182**	**(39.3)**	**79**	**(28.4)**
Neutropenia	**14**	**(23.3)**	**17**	**(30.9)**	25	(5.4)	**130**	**(46.8)**
Thrombocytopenia	**9**	**(15.0)**	**10**	**(18.2)**	**95**	**(20.5)**	**102**	**(36.7)**
Lymphopenia	**6**	**(10.0)**	1	(1.8)	30	(6.5)		
Leukopenia	5	(8.3)	3	(5.5)			**32**	**(11.5)**
Platelet Count decreased					**55**	**(11.9)**		
Adverse events of special interest								
Infections and infestations	**39**	**(65.0)**	**36**	**(65.5)**			**223**	**(80.2)**
Nasopharyngitis	**10**	**(16.7)**	**8**	**(14.5)**	**66**	**(14.3)**		
Respiratory tract infection	**10**	**(16.7)**	5	(9.1)			23	(8.3)
Upper respiratory tract infection	**7**	**(11.7)**	**8**	**(14.5)**	**94**	**(20.3)**	**58**	**(20.9)**

Viral upper respiratory tract infection				**31 (11.2)**
Bronchitis	**6 (10.0)**	5 (9.1)	**76 (16.4)**	**39 (14.0)**
Pneumonia	4 (6.7)	**6 (10.9)**	41 (8.9)	**53 (19.1)**
Herpes zoster infection	3 (5.0)	1 (1.8)		8 (2.9)
Infusion reactions	3 (5.0)	NA		
Other adverse events				
Vascular disorders	**8 (13.3)**	5 (9.1)		**79 (28.4)**
Hypertension	1 (1.7)	2 (3.6)	**115 (24.8)**	18 (6.5)
Cardiac disorders	**7 (12)**	**6 (11)**		**63 (22.7)**
Neoplasms†	1 (2)	**12 (22)**		
Neuropathy Peripheral			43 (9.3)	
Peripheral Sensory Neuropathy			27 (5.8)	**133 (47.8)**
References	Table 3 in Dimopoulos et al. 2018 and Table 10 in the Empliciti EPAR		Table 20 in the Kyprolis EPAR (column sNDA, Cd)	Table 36 in the Imnovid EPAR

The sorting is done by decreasing order based on the column of the EloPomDex group. Bold numbers indicate AEs with an incidence ≥10% in each treatment group.
NA, not applicable. † This term includes malignant, benign, and unspecified neoplasms.
For EloPomDex and PomDex, AEs were coded using MedDRA version 20.1, CTC version 3.0. Included are AE and SAE with onset on or after the first dosing date and on or prior to the last dosing date +60 days.
For CarDex, AEs were coded using MedDRA version 15.1, CTC version 4.03. Treatment emergent event AEs are defined as any AEs with an onset date between the date of first dose and 30 days after the date of the last dose of any.
For PomBorDex, AEs were coded using MedDRA version 20.0. CTC version 4.0. Treatment emergent event AE is defined as any AEs occurring or worsening on or after the first treatment of study medication and within 28 days.

9.5 GRADE 3-4 ADVERSE EVENTS REPORTED IN THE ELOQEUNT-3, ENDEAVOR AND OPTIMISMM STUDIES

The Medicines Council requested a list of all Grade 3-4 AEs occurring in the relevant RCTs investigating EloPomDex, PomDex, CarDex and PomBorDex. This data was only available for the ENDEAVOR study in Table S4 of Dimopoulos et al., 2017[12], which presents data from an extended follow up compared to Table 25 above.

In Table 26 below, available safety data for Grade 3-4 AEs (any-cause) are summarized. Details about the data included here can be found in the footnote of Table 26.

TABLE 26. GRADE 3-4 AES REPORTED IN THE ELOQUENT-3, ENDEAVOR AND OPTIMISMM STUDIES

	EloPomDex n=60		**PomDex** n=55		**CarDex** n=463		**PomBorDex** n=278	
Cutoff	21 February 2018				3 January 2017		26 October 2017	
Follow up	min. 9.1 months				median 37.5 months		median 15.9 months	
Grade	Grade 3-4		Grade 3-4		Grade 3-4		Grade 3-4	
Total subjects with an event, n (%)	34	(56.7)	33	(60.0)	377	(81.4)*	251	(90.3)
Blood and lymphatic system disorders	23	(38.3)	23	(41.8)			154	(55.4)
Anemia	6	(10.0)	11	(20.0)	76	(16.4)	39	(14.0)
Neutropenia	8	(13.3)	15	(27.3)	11	(2.4)	116	(41.7)
Thrombocytopenia	5	(8.3)	3	(5.5)	41	(8.9)	76	(27.3)
Lymphopenia	5	(8.3)	1	(1.8)	22	(4.8)	12	(4.3)
Leukopenia	5	(8.3)	2	(3.6)	5	(1.1)	15	(5.4)
Ferbile neutropenia	3	(5.0)	3	(5.5)	5	(1.1)	9	(3.2)
Infections and infestations	8	(13.3)	12	(21.8)			86	(30.9)
Upper respiratory tract infection	0		1	(1.8)	8	(1.7)		
Pneumonia	3	(5.0)	5	(9.1)	39	(8.4)	32	(11.5)
Bronchitis	1	(1.7)	1	(1.8)	13	(2.8)		
Respiratory tract infection	0		1	(1.8)	10	(2.2)		
Influenza					2	(0.4)	7	(2.5)
Sepsis					6	(1.3)	6	(2.2)
Urinary tract infection					11	(2.4)		
Respiratory, thoracic and mediastinal disorders	7	(11.7)	3	(5.5)			24	(8.6)
Dyspnea	2	(3.3)	1	(1.8)	29	(6.3)	8	(2.9)
Productive cough	1	(1.7)	0		0			
Pulmonary embolism					9	(1.9)	11	(4.0)
Metabolism and nutrition disorders	7	(11.7)	12	(21.8)			71	(25.5)
Hyperglycemia	5	(8.3)	4	(7.3)	22	(4.8)	25	(9.0)

Decreased appetite	0	2 (3.6)	4 (0.9)	
Hypokalemia	0	3 (5.5)	11 (2.4)	17 (6.1)
Hypophosphataemia			15 (3.2)	11 (4.0)
Hyponatremia			12 (2.6)	7 (2.5)
Hyperkalaemia			6 (1.3)	7 (2.5)
Hyperuricaemia			5 (1.1)	2 (0.7)
Cardiac disorders	4 (7)	2 (4)		22 (7.9)
Atrial fibrillation			9 (1.9)	9 (3.2)
Cardiac failure			12 (2.6)	3 (1.1)
Psychiatric disorders	4 (6.7)	1 (1.8)		
Insomnia	1 (1.7)	0	12 (2.6)	
Anxiety	0	1 (1.8)	1 (0.2)	
Depression	1 (1.7)	0	1 (0.2)	
Gastrointestinal Disorders	2 (3.3)	1 (1.8)		36 (12.9)
Constipation	1 (1.7)	0	2 (0.4)	7 (2.5)
Diarrhoea			18 (3.9)	20 (7.2)
Musculoskeletal and connective tissue disorders	2 (3.3)	1 (1.8)		
Bone pain	2 (3.3)	0	9 (1.9)	
Back pain			10 (2.2)	
Vascular disorders	2 (3.3)	0		17 (6.1)
Hypertension	1 (1.7)	0	67 (14.5)	8 (2.9)
Investigations	2 (3.3)	8 (14.5)		
Neutrophil Count decreased	2 (3.3)	5 (9.1)	9 (1.9)	
Increased blood creatinine	0	2 (3.6)	4 (0.9)	
Platelet count decreased			18 (3.9)	
Creatinine renal clearance decreased			10 (2.2)	
Lymphocyte count decreased			29 (6.3)	
Gamma-glutamyltransferase increased			10 (2.2)	
Nervous system disorders	2 (3.3)	2 (3.6)		57 (20.5)
Peripheral sensory neuropathy			1 (0.2)	23 (8.3)
Syncope			2 (0.4)	14 (5.0)

General disorders and administration site conditions	1 (1.7)	4 (7.3)		50 (18.0)
Fatigue	0	2 (3.6)	31 (6.7)	23 (8.3)
Asthenia	1 (1.7)	2 (3.6)	21 (4.5)	8 (2.9)
Pyrexia			14 (3.0)	6 (2.2)
General physical health deterioration			4 (0.9)	3 (1.1)
Neoplasms benign, malignant and unspecified	1 (2)	6 (11)		
Malignant neoplasm progression	1 (1.7)	2 (3.6)		
Injury, poisoning and procedural complications	1 (1.7)	1 (1.8)		
Skin and subcutaneous tissue disorders	0	1 (1.8)		9 (3.2)
Rash	0	1 (1.8)	4 (0.9)	6 (2.2)
Renal and urinary disorders				19 (6.8)
Acute kidney injury				9 (3.2)
Renal failure acute			11 (2.4)	
Eye disorders				
Cataract			11 (2.4)	
References	Table 3 in Dimopoulos et al. 2018 and Table 10 in the Empliciti EPAR.[5,15]		Table S4 from Dimopoulos et al., 2017.[12]	Table 38 in the Imnovid EPAR.[8]

* Numbers here indicate Grade ≥3 AEs.

For EloPomDex and PomDex: This table was constructed based on Table 10 in the Empliciti EPAR, which shows AEs with at least 5% frequency in either treatment group in the ELOQUENT-3 trial. AEs were coded using MedDRA version 20.1, CTC version 3.0; includes AE and SAE with onset on or after the first dosing date and on or prior to the last dosing date +60 days.

For CarDex, Table S4 in Dimopoulos et al., 2017 was used. Grade 3-4 AEs with an incidence ≥2% are shown, except if an AE was reported here for one of the other treatment group to allow eventual comparison. AEs were coded using MedDRA version 15.1, CTC version 4.03. Treatment emergent event AEs are defined as any AEs with an onset date between the date of first dose and 30 days after the date of the last dose of any investigational product.

For PomBorDex, Table 38 from the Imnovid EPAR reports Grade 3-4 treatment emergent AEs reported in ≥2% of subject in either treatment arm of the OPTIMISMM study and were all reported here for PomBorDex. AEs were coded using MedDRA version 20.0. CTC version 4.0. Treatment emergent event AE is defined as any AEs occurring or worsening on or after the first treatment of study medication and within 28 days after the latest dose date of any study drug.

9.6 RESULTS PER PICO (CLINICAL QUESTION)

The table below summarizes the results for the current PICO aiming at assessing the clinical value of EloPomDex compared to PomDex, CarDex and PomBorDex for treatment of patients with relapse and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.

Results per outcome	Attach forest plots and statistical results as a separate file. Results from the comparative analysis should be given in the table below, if possible.							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	P value	Hazard/Odds/Risk ratio	CI	P value	
Overall Survival (OS) *Critical*	**EloPomDex** ITT ELOQUENT-3 vs **PomDex** ITT ELOQUENT-3	**14.8** (median Not Reached) (median 17.4 months)	**0.7-40.6**	**NA**	**HR 0.54**	**0.30-0.96**	**NA**	*EloPomDex vs PomDex*: Overall survival in the ELOQUENT-3 study was estimated by the Kaplan–Meier method. The estimation of the absolute difference in medians was based on formula 6, page 55, of the Methods Guideline from the Medicines Council (v.2.3). *EloPomDex vs CarDex and PomBorDex*: No common comparator was identified. Since the median OS for EloPomDex was not reached , the absolute difference obtained by subtracting the median OS for CarDex or PomBorDex from the median OS for EloPomDex could not be cacluclated. The median OS for each group is reported in parenthesis.
	vs **CarDex** Len-refractory ENDEAVOR	NA (median 29.2 months)						
	vs **PomBorDex** ITT OPTIMISMM	NA (median 40.5 months)						
Progression Free Survival (PFS) *Important*	**EloPomDex** ITT ELOQUENT-3 vs **PomDex** ITT ELOQUENT-3	**4.0** (median 10.3 months) (median 4.7 months)	**0.8-9.1**	**NA**	**HR 0.54**	**0.34-0.86**	**0.008**	*EloPomDex vs PomDex*: Progressive-free survival was estimated by the Kaplan–Meier method. The HR is based on a log rank test. The estimation of the absolute difference in medians was based on formula 6, page 55, of the Methods Guideline from the Medicines Council (v.2.3).
	vs	0.6 months						

	CarDex Len-exposed, 2-3 prior lines ENDEAVOR	(median 9.7 months)						*EloPomDex vs CarDex and PomBorDex*: The absolute difference was calculated by subtracting the median PFS reported for (i) the subgroup of patients with prior Len-exposure and 2-3 prior lines of therapy treated with CarDex or (ii) the ITT population of the OPTIMISMM study (PomBorDex) from the median PFS of the ITT population treated with EloPomDex in the ELOQUENT-3 study. The median PFS for each group is reported in parenthesis.
	vs **PomBorDex** ITT OPTIMISMM	-0.9 months (median 11.2 months)						
Discontinuation due to AEs *Critical*	**EloPomDex** Safety population ELOQUENT-3 vs **PomDex** Safety population ELOQUENT-3	**-5.3%** (18.3%) (23.6%)	**-14.7%-13.8%**	**NA**	**RR 0.78**	**0.39-1.59**	**NA**	*EloPomDex vs PomDex*: The relative risk (RR) were calculated and used to estimate the absolute difference in effect using formula 4, page 54, of the Methods Guideline from the Medicines Council (v.2.3). *EloPomDex vs CarDex and PomBorDex*: The absolute difference was calculated by subtracting the discontinuation rate due to AEs (i) for the subgroup of patients with 2-3 prior lines of therapy treated with CarDex or (ii) the safety population of the OPTIMISMM study (PomBorDex) from discontinuation rate due to AEs of the safety population treated with EloPomDex in the ELOQUENT-3 study. The rate of discontinuation due to any AEs for each group is reported in parenthesis.
	vs **CarDex** 2-3 prior lines ENDEAVOR	**-4.2%** (22.5%)	**NA**	**NA**				
	vs **PomBorDex** Safety population OPTIMISMM	**-10.5%** (28.8%)	**NA**	**NA**				
Health-related Quality of life (HRQoL) *Important*	**EloPomDex** ELOQUENT-3 vs **PomDex** ELOQUENT-3	EQ-5D-3L VAS 4.7 Utility Index 0.046	 -0.9-10.2 -0.035-0.127	 0.098 0.259				Different questionnaires were used in ELOQUENT-3 compared to ENDEAVOR and OPTIMISMM, thereby making impossible the comparison of the effect on HRQoL of EloPomDex with CarDex and PomBorDex. *EloPomDex vs PomDex*: The EQ-5D-3L instrument was used. Analysis of change from baseline used a longitudinal mixed-effects model, with PRO score as the dependant variable, and baseline score and stratification factors as covariates. *CarDex:* QLQ-C30 Global Health Status (GHS)/
	vs **CarDex** ENDEAVOR	(GHS/QoL QLQ-C30 Mean estimate: 60.66)						
	vs **PomBorDex** OPTIMISMM	(GHS/QoL QLQ-C30						

		Baseline Score: 61.0)						QoL scale. Questionnaires were completed prior to drug administration on day 1 of cycle 1 (baseline), then every 28 days until disease progression, withdrawal of consent, or until other anticancer treatment. Analysis was performed based on a linear mixed effect model. The least square mean estimates were the overall estimates under the assumption that the treatment effect was the same across visits. *PomBorDex*: QLQ-C30 global health status/QoL domain questionnaire on day 1 of every 21-day cycle before treatment administration and at the end of treatment.
Qualitative review of AEs *Important*	**EloPomDex** Safety population ELOQUENT-3 vs **PomDex** Safety population ELOQUENT-3	Grade 3-4 56.7% 60.1%	-3.4%					Table 25 list all Grade AEs in at least 10% of patients. Table 26 shows Grade-4 AEs reported in the ELOQUENT-3, ENDEAVOR and OPTIMISMM studies. The absolute difference was calculated by subtracting the rate of severe AEs reported for the safety population treated with (i) PomDex, (ii) CarDex or (iii) PomBorDex from subgroup of patients with 2-3 prior lines of therapy treated with CarDex or (ii) the safety population of the OPTIMISMM study (PomBorDex) from d the rate of severe AEs reported for the safety population treated with EloPomDex. The rate of severe AEs for each group is reported in parenthesis.
	vs **CarDex** 2-3 prior lines ENDEAVOR	Grade ≥3 76.6%	-19.9%					
	vs **PomBorDex** Safety population OPTIMISMM	Grade 3-4 90.3%	-33.6%					

Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for elotuzumab i kombination med pomalidomid og dexamethason til behandling af patienter med knoglemarvskræft der har modtaget mindst to tidligere behandlinger

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 lægemiddels kliniske værdi. 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 Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	6. november 2019
Ikrafttrædelsesdato	7. november 2019
Dokumentnummer	62982
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, 7. november 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Empliciti
Generisk navn	Elotuzumab
Firma	Bristol-Myers Squibb
ATC-kode	L01XC23
Virkningsmekanisme	Elotuzumab er et monoklonalt antistof, der binder til proteinet SLAM7, som findes på knoglemarvkræftsceller og immunceller (NK-celler). Denne binding medfører aktivering af NK-celler og efterfølgende celledød af knoglemarvskræftceller.
Administration/dosis	• Elotuzumab gives i kombination med pomalidomid og dexamethason indtil progression eller intolerable bivirkninger. • Elotuzumab gives som 10 mg/kg i.v. ugentligt på dag 1, 8, 15 og 22 i serie 1 og 2. • Fra serie 3 og fremefter gives 20 mg/kg i.v. på dag 1.
Forventet EMA-indikation	Elotuzumab gives i kombination med pomalidomid og dexamethason til patienter med relaps eller behandlingsrefraktær knoglemarvskræft, som har modtaget mindst to tidligere behandlinger inklusive lenalidomid og en proteasomhæmmer, og som har haft progression på den seneste behandlingslinje.

2 Forkortelser

Bor:	Bortezomib
Car:	Carfilzomib
CI:	Konfidensinterval
Dex:	Dexamethason
Elo:	Elotuzumab
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HDT/STS:	Højdosiskemoterapi med stamcellestøtte
HR:	*Hazard ratio*
OR:	*Odds ratio*
Pom:	Pomalidomid
RR:	Relativ risiko

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af elotuzumab i kombination med pomalidomid og dexamethason (EloPomDex) som mulig standardbehandling af patienter med knoglemarvskræft, der har modtaget mindst to tidligere behandlinger. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres 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 EloPomDex modtaget den 3. oktober 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af den kliniske merværdi af EloPomDex sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem EloPomDex og komparatorene af både absolutte og relative værdier for de udspecificerede 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 én 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, som medfører, at patienten oplever bl.a. træthed og åndenød. Ændringerne i knoglemarven fremmer aktiviteten af celler, som nedbryder knoglerne og reducerer aktiviteten af de celler, som opbygger knoglevæv. Derfor nedbrydes knoglerne, og patienten får øget risiko for knoglebrud, oplever knoglesmerter og får forhøjet kalk i blodet. Hos størstedelen af patienter med 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 immunglobulin 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 [2].

For egnede patienter vil primærbehandling være højdosiskemoterapi med stamcellestøtte (HDT/STS). Patienter, som modtager denne behandling, har en væsentlig bedre prognose end de, der ikke er egnede. 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 [3]. Denne gruppe omfatter især de ældste patienter (over 70 år). Prognosen er, udover patientens alder, afhængig af komorbiditeter ved diagnosetidspunktet. Uafhængigt af hvilken primærbehandling patienten modtager, vil en lille andel af patienterne være refraktære over for primærbehandling, og alle patienterne vil på et tidspunkt få et behandlingskrævende relaps. Årligt vil ca. 360 myelomatosepatienter modtage primær behandling, 320 modtage første relapsbehandling [2]. Fagudvalget vurderer, at ca. 200 vil modtage anden relapsbehandling. Patientgruppen er heterogen, og prognosen afhænger af tidligere behandling. Den mediane overlevelse for patienter, der er refraktære overfor immunmodulerende stoffer og proteasomhæmmere, er angivet at være ca. 9 måneder [4].

4.1 Nuværende behandling

Behandlingen ved relaps af knoglemarvskræft er medicinsk. Behandlingen er oftest en kombination af flere lægemidler, som angriber kræftcellerne på forskellige måder, hvorved effekten generelt er større end ved

behandling med et enkelt lægemiddel [5]. Behandlingen er ikke kurativ, så ud over forlænget overlevelse er målet med behandlingen at give patientenerne længst mulige sygdomsfrie perioder med bedst mulig livskvalitet.

I henhold til behandlingsvejledningen for myelomatose vil behandlingsvalget til første relaps typisk være DaraLenDex eller DaraBorDex. Alternativt trestofskombinationerne, EloLenDex, CarLenDex eller IxaLenDex. Ved andet behandlingskrævende relaps, dvs. når patienten har modtaget mindst to tidligere behandlinger, vil behandlingsvalget typisk være CarDex eller PomDex.

Behandlingsvalget foretages i samråd mellem læge og patient under hensyntagen til effekt af tidligere behandling, bivirkninger til tidligere behandlinger, performance status, komorbiditet og patientpræferencer, herunder antallet af behandlingsfremmøder. Der tages også hensyn til eventuel manglende respons overfor lægemidler, der er indgået i tidligere behandlinger. I henhold til Medicinrådets behandlingsvejledning bør et lægemiddel ikke bruges ved fremtidige behandlinger, hvis en patient er behandlingsrefraktær overfor lægemidlet givet i fuld dosering.

4.2 Elotuzumab i kombination med pomalidomid og dexamethason

Elotuzumab er et kendt lægemiddel i behandlingen af knoglemarvskræft, hvor det i kombination med lenalidomid og dexamethason er indiceret til patienter, der har modtaget mindst én tidligere behandling. I Medicinrådets behandlingsvejledning anbefales denne behandlingskombination (EloLenDex) til behandling af patienter ved første relaps, hvor anvendelse af daratumumab er kontraindiceret.

Elotuzumab er et monoklonalt antistof, der binder sig til proteinet signaling lymphocytic activation molecule family member 7 (SLAMF7). SLAMF7 er udtrykt på knoglemarvskræftceller og NK-celler. Aktivering af NK-celler sker ved binding af SLAM7 og medfører apoptose (programmeret celledød) af omkringliggende knoglemarvskræftceller [6].

I den ansøgte behandlingskombination er elotuzumab kombineret med pomalidomid og dexamethason (EloPomDex) og er indiceret til patienter med relaps eller behandlingsrefraktær knoglemarvskræft, som tidligere har modtaget mindst to tidligere behandlinger inklusive lenalidomid og en proteasomhæmmer. EloPomDex bliver vurderet i en accelereret proces hos EMA. Til denne indikation skal EloPomDex doseres som følger:

I serier af 28 dage til progression

- Elotuzumab 10 mg/kg i.v. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 20 mg/kg på dag 1.
- Pomalidomid 4 mg p.o. på dag 1-21.
- Dexamethason:
    - ≤ 75 år: 28 mg p.o. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 28 mg på dag 1 og 40 mg på dag 8, 15, og 22.
    - > 75 år: 8 mg p.o. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 8 mg på dag 1 og 20 mg på dag 8, 15, og 22.
    - Herudover: 8 mg i.v. på dag 1, 8, 15 og 22 i serie 1-2. Efterfølgende serier: 8 mg i.v. på dag 1.

5 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

5.1 Klinisk spørgsmål 1

Hvad er værdien af elotuzumab i kombination med pomalidomid og dexamethason sammenlignet med eksisterende standardbehandling til behandling af patienter med knoglemarvskræft, som tidligere har modtaget mindst to behandlinger inklusive lenalidomid og en proteasomhæmmer, og som har haft progression på den seneste behandlingslinje?

Population
Voksne patienter med knoglemarvskræft, som har modtaget mindst to tidligere behandlinger inklusive lenalidomid og en proteasomhæmmer, og som har haft progression på den seneste behandlingslinje.

Intervention
Elotuzumab i kombination med pomalidomid og dexamethason.

Komparator
Fagudvalget ønsker, at interventionen sammenlignes med nedenstående komparatorer, som alle vil være alternative behandlingsmuligheder, baseret på en individuel vurdering af patientens komorbiditeter og tidligere bivirkninger. Disse komparatorer er valgt, da de udgør standardbehandling til denne patientgruppe:

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.

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

- Pomalidomid 4 mg p.o. på dag 1-21.
- Dexamethason 40 mg p.o. på dag 1, 8, 15 og 22.

PomBorDex (under forudsætning af at denne behandling anbefales af Medicinrådet som standardbehandling til patienter, der har modtaget mindst én tidligere behandling).

- 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/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.

CarDex og PomDex vil være standardbehandling til denne patientgruppe, da patienterne på dette stadie typisk vil være refraktære overfor lenalidomid og daratumumab og vil være behandlet med eller refraktære overfor bortezomib, når behandlingsforløbet følger Medicinrådets behandlingsvejledning vedrørende lægemidler til knoglemarvskræft (myelomatose).

PomBorDex er under igangværende vurdering i Medicinrådet til samme patientpopulation Såfremt behandlingen bliver anbefalet som mulig standardbehandling, vil den også være en relevant komparator.

CarDex og PomBorDex er EMA-godkendt til patienter, der tidligere har modtaget mindst én tidligere behandling. PomDex er godkendt til patienter, der tidligere har modtaget mindst to tidligere behandlinger.

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

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikkealvorlige symptomer og bivirkninger).

Effektmål*	**Vigtighed**	**Effektmålsgruppe**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Samlet overlevelse	*Kritisk*	*Dødelighed*	Median overlevelse	3 mdr.
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger**	Median PFS	3 mdr.
Behandlingsophør/ bivirkninger	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel der ophører behandling pga. uønskede hændelser	*Forskel på 10 %-point mellem grupperne*
	Vigtigt	*Livskvalitet, alvorlige symptomer og bivirkninger*	*Kvalitativ gennemgang*	-
Livskvalitet	*Vigtigt*	*Livskvalitet, alvorlige symptomer og bivirkninger*	*Antal points ændring over tid målt med EORTC QLQC30*	*Forskel på 10 point mellem grupperne*

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

5.2.1 Kritiske effektmål

Samlet overlevelse

Samlet overlevelse (overall survival, OS) er et præcist effektmål, defineret 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 til vurderingen af effekten af nye lægemidler. Fagudvalget ønsker effektmålet opgjort som medianoverlevelse. Den mediane overlevelse til den pågældende population, baseret på studiedata, er med de nuværende behandlingsmuligheder ca. 9 måneder. [4]. Fagudvalget har vurderet, at den mindste klinisk relevante forskel i medianoverlevelse mellem intervention og komparator er 3 måneder.

Hvis data for overlevelse ikke er modne, ønsker fagudvalget at medtage PFS som et surrogatmål for samlet overlevelse. PFS defineres som tiden fra randomisering til progression eller død, hvor progression bestemmes efter det standardiserede responskriterie [7]. PFS er i metaanalyser vist at korrelere med overlevelse indenfor behandling af myelomatose både blandt nydiagnosticerede og hos patienter med relaps eller som er behandlingsrefraktære [8,9] og anvendes typisk som primært endepunkt i kliniske studier, fordi der ikke ved publikationstidspunktet forventes at foreligge modne data for OS. For patienter, der har

modtaget mindst to tidligere behandlinger, inklusive lenalidomid og en proteasomhæmmer, er den mediane PFS 4-9 måneder, baseret på studiedata [10,11]. Fagudvalget vurderer, at mindste klinisk relevante forskel i PFS er 3 måneder. Fagudvalget ønsker at vurdere data for den længst mulige opfølgningstid i studierne.

Behandlingsophør grundet uønskede hændelser

Fagudvalget ønsker at vurdere et effektmål, der belyser tyngden af bivirkninger. Andelen af patienter, der ophører behandlingen pga. uønskede hændelser, er et effektmål, der udtrykker, hvor godt behandlingen tolereres af patienterne, og fagudvalget vurderer, at det er et kritisk effektmål for vurderingen. De behandlinger, der i dag anvendes til behandling af patienter, der tidligere har modtaget behandling, er bivirkningstunge, og 10-15 % ophører behandlingen pga. uønskede hændelser, baseret på studiedata [12–14]. 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.

Ved indirekte sammenligninger af EloPomDex med komparatorerne bør ansøger lave en vurdering af, om sammenligningen af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling og hvordan de alvorlige uønskede hændelser er opgjort og rapporteret. Overvejelser omkring dette skal fremgå i den endelige ansøgning.

5.2.2 Vigtige effektmål

Kvalitativ gennemgang af bivirkninger

Fagudvalget ønsker som supplement til effektmålet behandlingsophør grundet bivirkninger en opgørelse af de hyppigste bivirkninger af enhver grad (forekommer hos > 10 % af patienterne) samt alle bivirkninger af grad 3-4, der er rapporteret i de kliniske studier, hvor elotuzumab i kombination med pomalidomid og dexamethason er undersøgt som behandling til patienter med knoglemarvskræft. Fagudvalget vil ud fra denne opgørelse vurdere håndterbarhed og tyngde af bivirkningsprofilen.

Ansøger bør lave en vurdering af, om sammenligningen af hændelsesfrekvenser kan foretages på forsvarlig vis på baggrund af studiedesign, opfølgningstid, dataindsamling og hvordan bivirkningerne er opgjort og rapporteret. Overvejelser omkring dette skal fremgå i den endelige ansøgning.

Fagudvalget vurderer, at den kvalitative gennemgang er et vigtigt effektmål for kategoriseringen af den kliniske merværdi.

Helbredsrelateret livskvalitet

Livskvalitet er et vigtigt effektmål i vurderingen af behandling af knoglemarvskræft, fordi sygdommen manifesterer sig ved en række symptomer og behandlingsmulighederne har en række bivirkninger, som påvirker patientens livskvalitet. Desuden findes endnu ingen kurative behandlingsformer, og der gives derfor en række lægemidler kontinuerligt indtil relaps. 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 [15,16]. 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, og undersøgelsen har vist, at de patienter, som oplevede en forbedring i livskvalitet, i gennemsnit havde en ændring på + 7,6 point, mens en forværring af livskvalitet var forbundet med en gennemsnitlig ændring på – 12,1 point [17]. Fagudvalget vurderer på den baggrund, at en forskel på mindst 10 point er klinisk relevant.

Såfremt der ikke foreligger data fra EORTC QLQ-C30, foretrækkes data fra et andet valideret instrument, som er relevant for patienter med knoglemarvskræft, eksempelvis det generiske EQ-5D eller andre generiske eller sygdomsspecifikke værktøjer. Såfremt der leveres data for et andet værktøj end EORTC-QLQ-C30, bedes ansøger indsende argumentation og dokumentation for den mindste klinisk relevante forskel.

6 Litteratursøgning

Vurderingen af klinisk merværdi baseres på data fra peer reviewede 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.

Der findes en direkte sammenligning mellem EloPomDex og PomDex:

- Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma, Dimopoulos MA, Dytfeld D, Grosicki S et al., N. Engl. J. Med., 2018 [6].

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af EloPomDex og de øvrige komparatorer.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af EloPomDex med CarDex og PomBorDex. Det betyder, at der både skal søges efter primærstudier af effekten af EloPomDex 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).

Databaser for søgningen
Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgestrenge
Søgestreng fremgår af bilag 1.

Hvis der i litteratursøgningen er afvigelser fra den angivne søgestreng, skal der redegøres herfor.

Kriterier for udvælgelse af litteratur
Der ekskluderes først 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.

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer reviewede publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report. Data skal derudover stemme overens med protokollens beskrivelser.

7 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. 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.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

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 (ORR, SAE, 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.

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.

Det skal angives, hvilke studier der benyttes til at besvare hvilke PICO-spørgsmål

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.

Ved metaanalyser og indirekte sammenligninger ønskes en vurdering af, om studierne er homogene nok til at sammenlignes.

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.

Udover dexamethason gives præmedicinering med en H1- og en H2-blokker samt paracetamol for forebyggelse af infusionsrelaterede reaktioner. Fagudvalget ønsker belyst, om der findes data for infusionsrelaterede reaktioner hos patienter, der udelukkende har fået p.o. og ikke i.v. dexamethason som præmedicinering, og om ansøger anbefaler en alternativ H2-blokker, hvis ikke ranitidin er tilgængelig.

Fagudvalget ønsker informationer om, hvorvidt der findes data, der belyser effekten af elotuzumab efter behandling med daratumumab.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende knoglemarvskræft (myelomatose)

Formand	**Indstillet af**
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11 Versionslog

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

12 Bilag 1: Søgeprotokol

MEDLINE (via PubMed)

https://www.ncbi.nlm.nih.gov/pubmed/advanced

#1	Multiple Myeloma[mh]	Søgetermer for populationen
#2	myeloma[tiab] OR myelomatosis[tiab] OR kahler disease[tiab]	
#3	#1 OR #2	
#4	elotuzumab[nm]	Søgetermer for interventionen/ komparatorer
#5	elotuzumab[tiab] OR Empliciti*[tiab]	
#6	pomalidomide[nm]	
#7	pomalidomid*[tiab] OR Imnovid*[tiab] OR Pomalyst*[tiab] OR Actimid*[tiab]	
#8	Dexamethasone[mh]	
#9	dexamethason*[tiab]	
#10	(#4 OR #5) AND (#6 OR #7) AND (#8 OR #9)	
#11	carfilzomib[nm]	
#12	carfilzomib[tiab] OR Kyprolis*[tiab]	
#13	(#8 OR #9) AND (#11 OR #12)	
#14	Bortezomib[mh]	
#15	bortezomib[tiab] OR Velcade*[tiab]	
#16	(#6 OR #7) AND (#8 OR #9) AND (#14 OR #15)	
#17	#3 AND (#10 OR #13 OR #16)	Søgestreng for indirekte sammenligning
#18	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	Afgrænsning, RCT (Cochrane filter)
#19	#17 AND #18	
#20	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR Systematic Review[pt]	Eksklusion af ikke relevante publikationstyper #21 = endelig søgning
#21	#19 NOT #20	

CENTRAL (via Cochrane Library)

https://www.cochranelibrary.com/advanced-search/search-manager

#1	[mh "Multiple Myeloma"]	Søgetermer for populationen
#2	(myeloma OR myelomatosis OR "kahler* disease"):ti,ab,kw	
#3	#1 OR #2	
#4	(elotuzumab OR Empliciti*):ti,ab,kw	Søgetermer for interventionen/ komparatorer
#5	(pomalidomid* OR Imnovid* OR Pomalyst* OR Actimid*):ti,ab,kw	
#6	[mh Dexamethasone]	
#7	dexamethason*:ti,ab,kw	
#8	#4 AND #5 AND (#6 OR #7)	
#9	(carfilzomib OR Kyprolis*):ti,ab,kw	
#10	(#6 OR #7) AND #9	
#11	[mh Bortezomib]	
#12	(bortezomib OR Velcade*):ti,ab,kw	
#13	#5 AND (#6 OR #7) AND (#11 OR #12)	
#14	#3 AND (#8 OR #10 OR #13)	Søgestreng for indirekte sammenligning
#15	("conference abstract" OR review):pt	Eksklusion af ikke relevante publikationstyper #19 = endelig søgning
#16	NCT*:au	
#17	("clinicaltrials.gov" OR trialsearch):so	
#18	#15 OR #16 OR #17	
#19	#14 NOT #18	