Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. dostarlimab, version 1.0
2. Forhandlingsnotat fra Amgros vedr. dostarlimab
3. Høringssvar fra ansøger, inkl. efterfølgende dialog
4. Medicinrådets vurdering vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Dostarlimab

dMMR/MSI-high kræft i livmoderslimhinden

Version 1.0

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 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.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

Dokumentoplysninger	
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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspris
dMMR	Defekt mismatch repair (*mismatch repair deficient*)
MSI-H	Høj mikrosatellit ustabilitet (*microsatellite instability-high*)
MAIC	*Matching-Adjusted Indirect Comparisons*
KM	Kaplan-Meier
OS	Samlet overlevelse
PD	Post-progression (*progressed disease*)
PFS	Progressionsfri overlevelse
ToT	*Time on treatment*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser

Patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for dostarlimab ca. [redacted] DKK pr. patient sammenlignet med platinbaseret kemoterapi. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 750.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af dostarlimab som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 6,2 mio. DKK i det femte år.

Patienter, der er progredieret under eller efter platinbaseret kemoterapi

I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for dostarlimab ca. [redacted] DKK pr. patient sammenlignet med placebo og ca. [redacted] DKK pr. patient sammenlignet med pegyleret liposomalt doxorubicin. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning hhv. ca. 801.000 DKK pr. patient og ca. 768.000 DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af dostarlimab som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 6,3 mio. DKK i det femte år.

For begge sammenligninger driver lægemiddelomkostningerne for dostarlimab de inkrementelle omkostninger.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af dostarlimab som mulig standardbehandling på danske hospitaler til behandling af dMMR/MSI-high kræft i livmoderslimhinden.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra GlaxoSmithKline. Medicinrådet modtog ansøgningen den 21. september 2021.

3.1 Patientpopulation

Livmoderkræft er den 5. hyppigste kræftform blandt kvinder i Danmark, og den hyppigste form for gynækologisk kræft [1]. Omkring 800 kvinder får hvert år konstateret livmoderkræft, hvor den hyppigste form (> 90 %) er kræft i livmoderslimhinden (endometriecancer) [1,2]. Sygdommen rammer typisk ældre kvinder (median alder 63 år) [3], og knap 11.000 patienter i Danmark lever efter at have fået diagnosen [2].

Mismatch repair (MMR)-systemet er et cellulært system, der bl.a. reparerer fejl i DNA-strengene [4]. En arvelig eller somatisk mutation i et af generne MLH1, MSH2, MSH6 eller PMS2 kan medføre *defekt mismatch repair* (dMMR). I væv med dMMR ophobes mutationer. Dette sker særligt i de såkaldte mikrosatellitregioner af DNA, hvorved dMMR ofte kan identificeres ved en høj grad af ustabilitet i disse DNA-regioner (MSI-H/*Microsatelite instability-High*) [4].

Ca. 22-30 % af tilfældene med endometriecancer har ifølge litteraturen dMMR/MSI-H, uanset sygdomsstadie [5,6]. Fagudvalget vurderer dog, at andelen er noget lavere hos patienter med avanceret eller recidiverende endometriecancer, men der findes ikke studier, der belyser dette. Fagudvalget vurderer, at der vil være ca. 20 nye patienter med dMMR/MSI-H pr. år, der er kandidater til 2. linjebehandling.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af dostarlimab på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har dostarlimab sammenlignet med platinbaseret kemoterapi for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling?

Klinisk spørgsmål 2:

Hvilken værdi har dostarlimab sammenlignet med placebo for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?

Klinisk spørgsmål 3:

Hvilken værdi har dostarlimab sammenlignet med pegyleret liposomalt doxorubicin for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for dostarlimab sammenlignet med platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi

Sammenligningen mellem dostarlimab og platinbaseret kemoterapi er lavet på baggrund af en naiv sammenligning, hvor data fra GARNET-studiet [7] anvendes for dostarlimab, hvilket er et igangværende ikke-kontrolleret, fase I/II-studie, der undersøger effekten og sikkerheden af dostarlimab hos patienter med solide tumorer. For platinbaseret kemoterapi anvendes data fra en *Matching-Adjusted Indirect Comparisons* (MAIC)-analyse, som ansøger har udført, hvor effekten for platinbaseret kemoterapi sættes i forhold til dostarlimab. MAIC-analysen tager udgangspunkt i data fra Mazgani et al. 2018 [8] for OS og PFS. Mazgani et al. er en retrospektiv analyse af 200 patienter med endometriecancer, der har fået carboplatin i kombination med paclitaxel, hvor effektiviteten af genbehandling med carboplatin i kombination med paclitaxel undersøges.

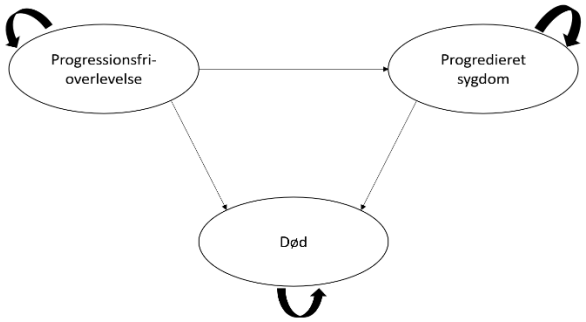
Patienter, der er progredieret under eller efter platinbaseret kemoterapi

Sammenligningen mellem dostarlimab og placebo og pegyleret liposomalt doxorubicin er ligeledes lavet på baggrund af en naiv sammenligning, hvor data fra GARNET-studiet anvendes for dostarlimab, mens data fra MAIC-analysen anvendes for placebo og pegyleret liposomalt doxorubicin. MAIC-analysen tager udgangspunkt i data fra Julius et al. 2013 [9] for OS for både placebo og pegyleret liposomalt doxorubicin. Julius et al. er et retrospektivt studie, der undersøger effekten og sikkerheden ved pegyleret liposomalt doxorubicin ud fra optegnelser af patienter behandlet på the University of Texas M. D.

Anderson Cancer Center mellem 1996 og 2006. Grundet manglende PFS-data for patienter behandlet med pegyleret liposomalt doxorubicin, anvender ansøger PFS-estimater fra MAIC-analysen, der tager udgangspunkt i patienter behandlet med platinbaseret kemoterapi, for både placebo og pegyleret liposomalt doxorubicin.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival model* til at estimere omkostningerne forbundet med behandlingen med dostarlimab. Modellen indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af tre stadier: progressionsfri overlevelse, post-progression og stadiet død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event-data. For patienter, der modtager dostarlimab, bestemmes tiden i stadiet progressionsfri overlevelse ud fra PFS-data fra GARNET-studiet. For patienter i behandling med platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin har ansøger udarbejdet en MAIC-analyse og udledt en hazard ratio mellem dostarlimab og komparatorerne. Disse hazard ratioer anvender ansøger til at generere PFS-data for platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin.

Fra progressionsfri overlevelse kan patienten bevæge sig videre til stadiet post-progression og til stadiet død. Patienter, der er progredieret, men ikke døde, vil befinde sig i post-progression. Tiden, patienterne befinder sig i dette stadie, estimeres ud fra PFS- og OS-data som den andel af patienter, der hverken er i præ-progression eller død. Fra post-progression kan patienten udelukkende bevæge sig til det absorberende stadie død. Andelen af patienter i behandling med dostarlimab i stadiet død bliver estimeret ud fra OS-data fra GARNET-studiet. For patienter i behandling med platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin anvender ansøger hazard ratioer udledt fra MAIC-analysen til at generere OS-data.

Modellen har en cykluslængde på 28 dage og ansøger har anvendt *half-cycle correction*.

Medicinrådets vurdering af ansøgers model

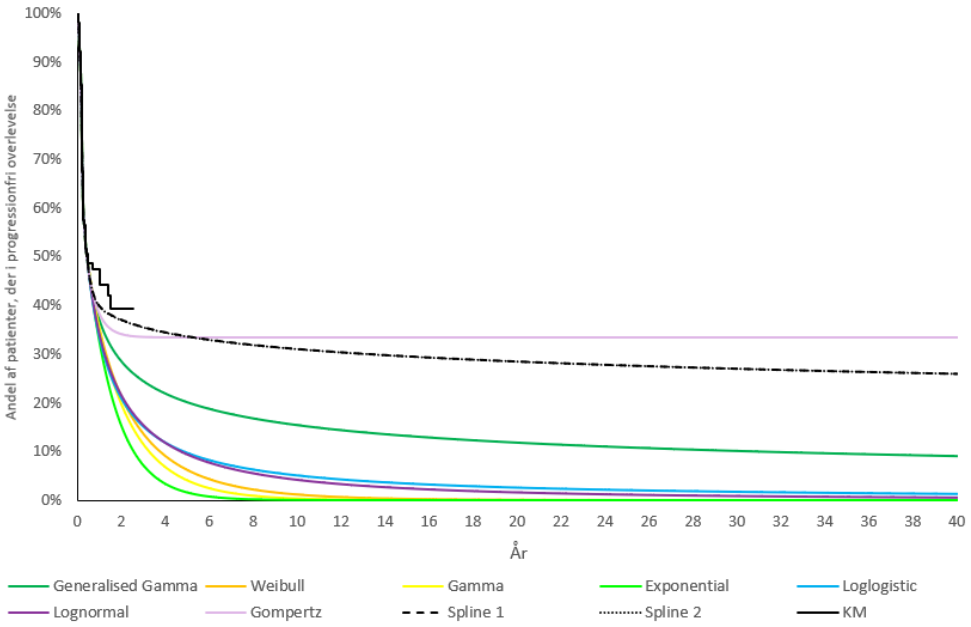
Medicinrådet vurderer, at der er betydelig usikkerhed ved de anvendte studier i ansøgers analyse, da disse er baseret på en indirekte sammenligning af studier. Medicinrådet accepterer dog ansøgers tilgang, da kvantitative estimater er nødvendige i sundhedsøkonomiske analyser, og da det tilgængelig data ikke tillader en anderledes tilgang. Derfor accepteres resultaterne fra MAIC-analysen også, selvom de vurderes at være behæftet med meget usikkerhed.

Medicinrådet accepterer ansøgers tilgang vedr. ansøgers model.

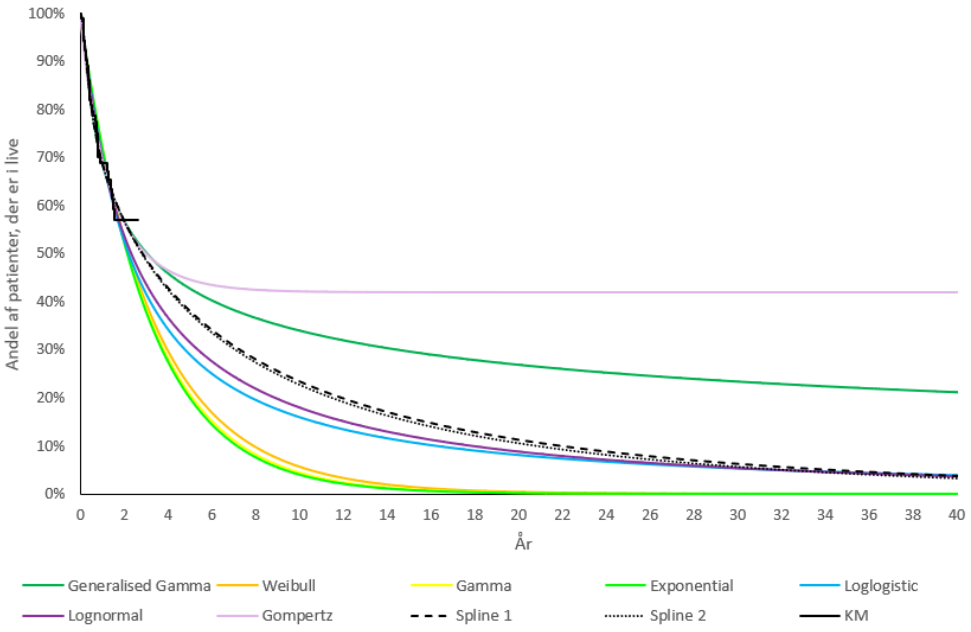
4.1.2 Modelantagelser og -beskrivelse

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i GARNET-studiet er kortere end den anvendte tidshorisont.

Ansøger har anvendt en log-normal-funktion til at ekstrapolere PFS for dostarlimab, se Figur 2. Da de ekstrapolerede PFS-kurver har dårligt fit på KM-data de første 6 måneder, vælger ansøger at anvende observeret KM-data til at estimere progression de første 6 måneder efterfulgt af log-normal-funktionen. For OS har ansøger valgt ligeledes at ekstrapolere data med en log-normal-funktion for dostarlimab, se Figur 3. Disse parametriske funktioner er valgt, da de, jf. AIC- og BIC-værdierne, har det bedste statistiske fit samt vurderes klinisk plausible. Den ekstrapolerede OS-kurve er korrigeret for den generelle mortalitetsrate, således at risikoen for at dø ikke kan være lavere end for den generelle befolkning uanset alder.



Figur 2. Ekstrapolerede PFS-kurver for dostarlimab med anvendelse af 6 måneder som skæringspunkt for overgang til de ekstrapolerede kurver



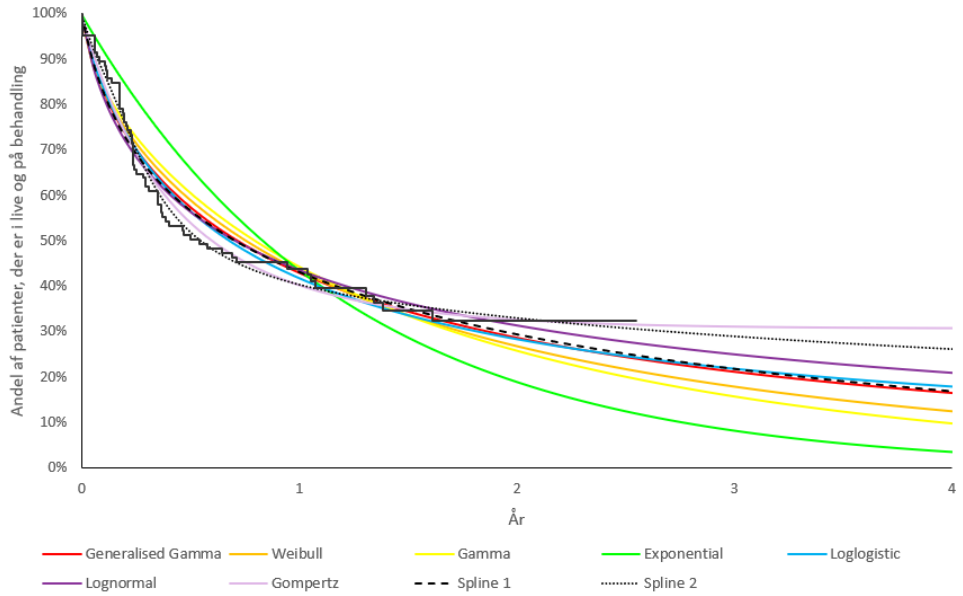
Figur 3. Ekstrapolerede OS-kurver for dostarlimab

For patienter i behandling med platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin har ansøger som tidligere beskrevet udført en MAIC-analyse og udledt hazard ratioer for platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin overfor dostarlimab. Disse hazard ratioer anvender ansøger til at generere PFS- og OS-data for platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin. De estimerede hazard ratioer udledt af MAIC-analysen er præsenteret i Tabel 1.

Tabel 1. Estimerede hazard ratio mellem komparatorerne og dostarlimab

Behandling	PFS	OS
Platinbaseret kemoterapi	0,78	1,79
Placebo	0,78	3,48
Pegyleret liposomalt doxorubicin	0,78	3,48

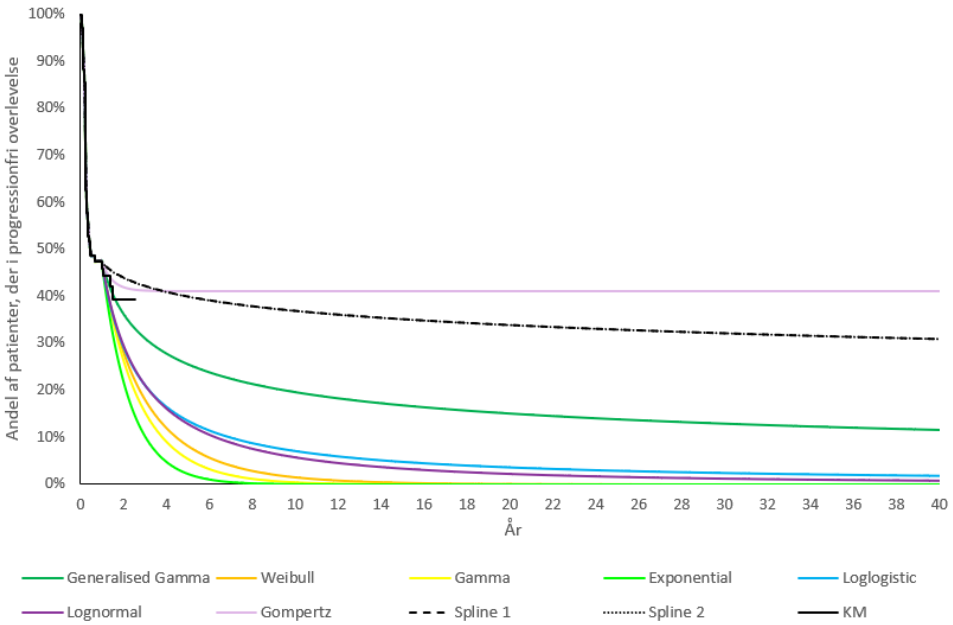
Ansøger har baseret behandlingsvarighed for dostarlimab på den gennemsnitlige tid til behandlingsophør (ToT) fra GARNET-studiet. For dostarlimab antager ansøger, at dostarlimab maksimalt må anvendes i to år i henhold til protokollen for GARNET-studiet. Ansøger har anvendt en generaliseret gamma-funktion til at ekstrapolere behandlingsvarigheden for dostarlimab, se Figur 4. Behandling med komparatorerne gives i serier, hvorfor der ikke anvendes data for tid til behandlingsophør for komparatorerne.



Figur 4. Ekstrapolerede ToT-kurver for dostarlimab

Medicinrådets vurdering af ansøgers modelantagelser

Fagudvalget vurderer, at skæringspunktet for overgangen mellem KM-data og ekstrapolerede kurve skal ske ved 12 måneder, da ekstrapoleringerne dermed stemmer bedre overens med de kliniske data, se Figur 5. Ved anvendelse af et skæringspunkt ved 6 måneder synes PFS underestimeret i forhold til det observerede data, se Figur 2. Samtidig vurderer fagudvalget, at halen på log-normal-funktionen ikke vil estimere den andel af patienter, der vil være langtidsprogressionsfri, hvilket det observerede data ellers antyder. Medicinrådet vælger derfor at ekstrapolere PFS ved anvendelse af en generaliseret gamma-funktion, der modellerer en gennemsnitlig tid til progression på 4,9 år for dostarlimab. På grund af store usikkerheder vedr. det forventede forløb af de observerede data, vælger Medicinrådet at udarbejde en følsomhedsanalyse, hvor kurven for PFS ekstrapoleres med en log-normal-funktion for at belyse effekten af den valgte ekstrapolering på analysens resultat. Derudover udarbejder Medicinrådet en følsomhedsanalyse, hvor skæringspunktet ændres til 6 måneder. Fagudvalget vurderer, at ansøgers anvendte ekstrapolerede OS-kurve for dostarlimab kan være rimelig på trods af, at forløbet er forbundet med stor usikkerhed grundet umodent data. Fagudvalget accepterer ansøgers valg, da de forventer, at patienter, der behandles med dostarlimab, vil være i post-progression-overlevelse i ca. 9-12 måneder.



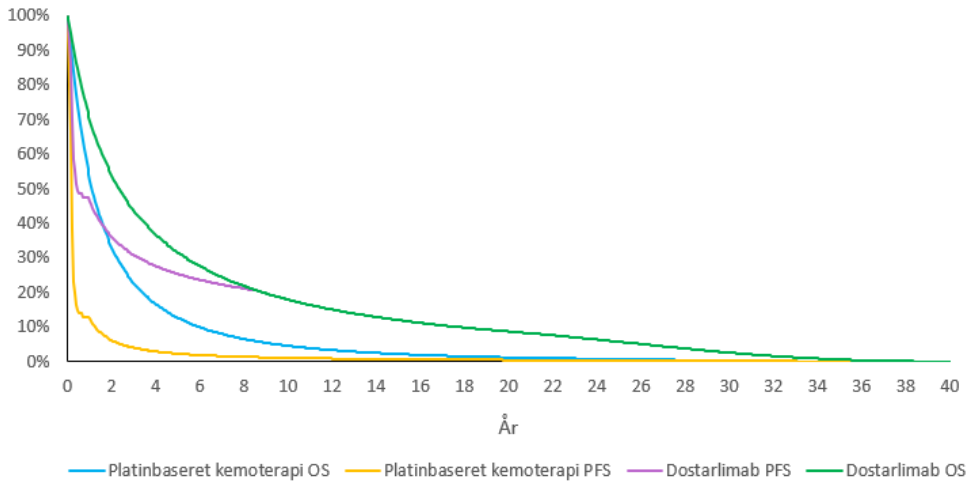
Figur 5. Ekstrapolerede PFS-kurver for dostarlimab med anvendelse af 12 måneder som skæringspunkt for overgang til de ekstrapolerede kurver

Fagudvalget vurderer, at de anvendte hazard ratioer for PFS ikke er klinisk plausible, da de estimerer, at patienter, der behandles med dostarlimab, progredierer hurtigere end patienter, der behandles med én af de tre komparatorer. Dette stemmer ikke overens med de kliniske data, der indikerer, at der vil være en væsentlig andel langtidsprogressionsfrie patienter ved behandling med dostarlimab. Ligeledes estimerer ansøgers MAIC-analyse, at *proportional hazards* ikke kan antages, hvilket betyder, at PFS-data for dostarlimab har et anderledes forløb end PFS-data for komparatorerne, hvorfor en fast hazard ratio ikke kan anvendes. Fagudvalget er dog opmærksomme på det begrænsede data, hvorfor fagudvalget accepterer anvendelsen af hazard ratioer til at generere PFS-data for komparatorerne. Fagudvalget ændrer dog hazard ratioerne, således at den gennemsnitlige tid til progression for de forskellige komparatorer stemmer overens med fagudvalgets kliniske erfaring, svarende til ca. 9 måneder i PFS for platinbaseret kemoterapi og ca. 5 måneder i PFS for placebo og pegyleret liposomalt doxorubicin, se Tabel 2.

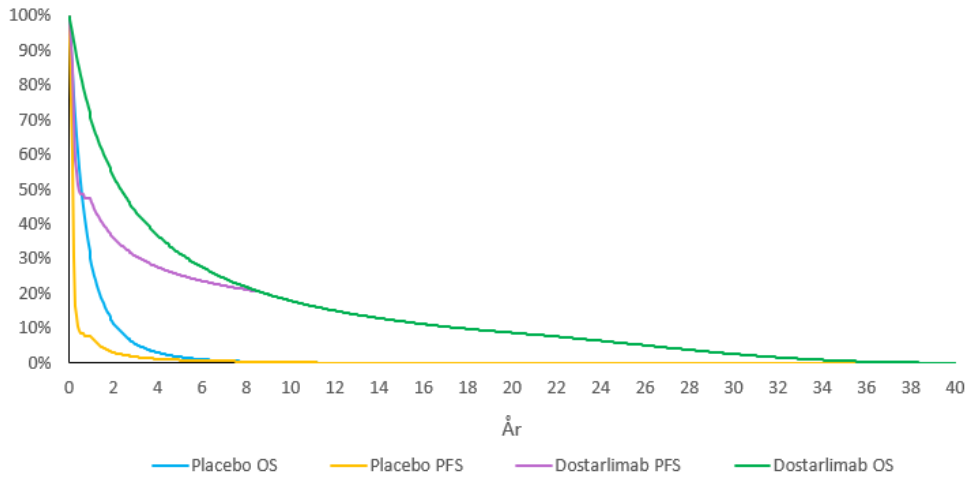
Modsat data for PFS, kan *proportional hazards* for OS ikke forkastes, hvilket betyder, at OS-data for dostarlimab og komparatorernes vurderes at have et proportionalt forløb. Fagudvalget kan desuden ikke afvise, at ansøgers estimerede hazard ratioer til at generere OS-data for komparatorerne er rimelige. Medicinrådet vælger derfor at acceptere ansøgers hazard ratioer for OS for komparatorerne, se Tabel 2. De estimerede PFS- og OS-kurver for hhv. platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin kan ses i Figur 6, Figur 7 og Figur 8.

Tabel 2. Fagudvalgets estimerede hazard ratioer mellem komparatorerne og dostarlimab

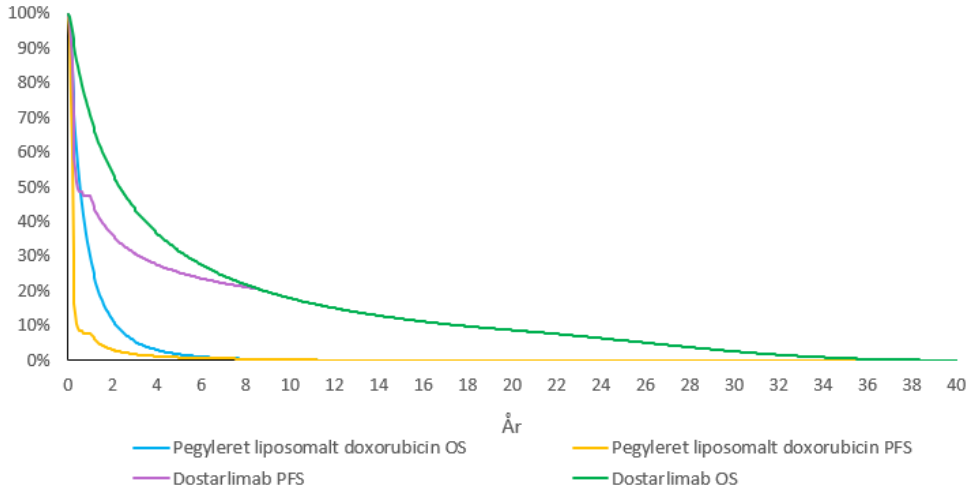
Behandling	PFS	OS
Platinbaseret kemoterapi	2,72	1,79
Placebo	3,39	3,48
Pegyleret liposomalt doxorubicin	3,39	3,48



Figur 6. Anvendte kurver for PFS og OS for dostarlimab og platinbaseret kemoterapi i Medicinrådets hovedanalyse



Figur 7. Anvendte kurver for PFS og OS for dostarlimab og placebo i Medicinrådets hovedanalyse



Figur 8. Anvendte kurver for PFS og OS for dostarlimab og pegyleret liposomalt doxorubicin i Medicinrådets hovedanalyse

Patienter, der indgik i GARNET-studiet, blev behandlet med dostarlimab i op til to år, med forbehold for uacceptabel toksicitet eller sygdomsprogression. Det var dog muligt at fortsætte behandling ud over de to år, hvis det blev vurderet gavnligt af den behandlende læge. Fagudvalget vurderer dog, at alle patienter, der stadig er i behandling med dostarlimab efter to år, vil blive seponeret, hvis ikke der er tungtvejende kliniske grunde til at fortsætte behandlingen. Medicinrådet accepterer derfor ansøgers estimater for behandlingsvarighed.

Estimaterne for tid i behandling, tid i PFS, post-progression (PD) og samlet overlevelse i modellen er præsenteret i Tabel 3. Estimaterne er baseret på meget usikre observerede data, hvorfor der er stor usikkerhed omkring patienternes samlede overlevelse samt den faktiske varighed af stadierne, PFS og PD.

Tabel 3. Gennemsnitlig tid i behandling, tid til progression og samlet overlevelse i modellen. Estimaterne er baseret på meget usikre observerede data, hvorfor der er stor usikkerhed omkring patienternes samlede overlevelse samt den faktiske varighed af stadierne, PFS og PD

Behandling	Behandlingsvarighed [måneder]	PFS [måneder]	PD [måneder]	OS [måneder]
Dostarlimab	10,4	59,3	10,6	69,9
Platinbaseret kemoterapi	2,6	9,0	21,5	30,5
Placebo	-	5,0	6,9	11,9
Pegyleret liposomalt doxorubicin	2,3	5,0	6,9	11,9

*Progressionsfri overlevelse (PFS), post-progression (PD), samlet overlevelse (OS).

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser. Dog ændrer Medicinrådet skæringspunktet og ekstrapoleringen for PFS. Medicinrådet vælger ligeledes at udarbejde følsomhedsanalyser, hvor betydningen af skæringspunktet og ekstrapoleringen for PFS undersøges.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 40 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år. Omkostninger, der ligger efter år 35, bliver diskonteret med en rate på 2,5 % pr. år

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont.

Tidshorisonten er valgt, da den gennemsnitlige behandlingslængde ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med dostarlimab i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem dostarlimab og komparatorerne set over en tidshorisont på 40 år.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af dostarlimab sammenlignet med platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, testomkostninger og patientomkostninger. Omkostninger til efterfølgende behandling er ikke inkluderet, da ansøger antager, at der ikke er forskel i efterfølgende behandling mellem dostarlimab, platinbaseret kemoterapi og pegyleret liposomalt doxorubicin.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i de forskellige sygdomsstadier i modellen.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Den anbefalede dosis af dostarlimab er 500 mg i.v. hver 3. uge over 4 cyklusser og derefter 1000 mg i.v. hver 6. uge.

Den anbefalede dosis af platinbaseret kemoterapi er:

- Paclitaxel: 175 mg/m2 i.v. hver 3. uge i op til 6-9 serier.

- Carboplatin: AUC5 (5 x arealet under kurven for koncentration i forhold til tid)

Ansøger antager, at patienter i gennemsnit modtager 8 serier platinbaseret kemoterapi.

Den anbefalede dosis af pegyleret liposomalt doxorubicin er 40-50 mg/m2 i.v. hver 4. uge i op til 6-8 serier. Ansøger antager, at patienter i gennemsnit modtager 8 serier pegyleret liposomalt doxorubicin.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 4.

Tabel 4. Anvendte lægemiddelpriser, SAIP (september 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Dostarlimab	50 mg/ml	10 ml	[redacted]	Amgros
Paclitaxel	6 mg/ml	16,7 ml	[redacted]	Amgros
	6 mg/ml	50 ml	[redacted]	Amgros
Carboplatin	10 mg/ml	15 ml	[redacted]	Amgros
	10 mg/ml	45 ml	[redacted]	Amgros
Pegyleret liposomalt doxorubicin	2 mg/ml	10 ml	[redacted]	Amgros

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger for dostarlimab og komparatorerne i form af DRG-takster, da alle lægemidlerne administreres intravenøst. Ansøger anvender DRG-taksten (MDC12 1-dagsgruppe, pat. mindst 7 år, DRG-takster 2021), svarende til 1.636 kr. som enhedsomkostning for et administrationsbesøg.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger. Anvendte enhedsomkostninger kan ses i Tabel 5.

Tabel 5. Omkostninger til lægemiddeladministration

	Enhedsomkostning [DKK]	Frekvens	Kilde
Administration af dostarlimab	1.636	Hver 3. uge de første 12 uger og derefter hver 6. uge.	2021 DRG: 13MA98

	Enhedsomkostning [DKK]	Frekvens	Kilde
Administration af platinbaseret kemoterapi	1.636	Hver 3. uge	2021 DRG: 13MA98
Administration af pegyleret liposomalt doxorubicin	1.636	Hver 4. uge	2021 DRG: 13MA98

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostning

Ansøger har inkluderet monitoreringsomkostninger for dostarlimab og komparatorerne i form af DRG-takster og differentierer mellem, om patienter modtager aktiv behandling eller ej, når de er progressionsfrie eller progredieret. Ansøger antager ikke forskellige monitoreringsfrekvenser, alt efter hvilken behandling patienterne modtager.

For patienter, der er progressionsfri og modtager aktiv behandling, antager ansøger, at patienterne har ét ambulant monitoreringsbesøg og blodprøvetagning hver 3. uge samt én CT-scanning hver 9. uge. Patienter, der derimod ikke modtager aktiv behandling eller er progredieret, har ét ambulant monitoreringsbesøg, blodprøvetagning og én CT-scanning hver 9. uge.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af monitoreringsomkostninger. Medicinrådet ekskluderer dog omkostninger til blodprøvetagning, da disse vil være inkluderet i DRG-taksten anvendt som enhedsomkostning for et ambulant besøg i forbindelse med monitorering. Denne ændring er gældende for patienter i både aktiv og inaktiv behandling og vurderes at have minimal betydning for analysens resultat.

Anvendte ressourceforbrug for PFS og PD kan ses i Tabel 6, og enhedsomkostningerne kan ses i Tabel 7.

Tabel 6. Ressourceforbrug til monitorering i PFS og PD pr. måned

Stadie	Behandling	Ambulant besøg	CT-scanning	Blodprøve
PFS	I aktiv behandling	2,0	0,3	4,0
	Ikke i aktiv behandling	1,0	0,3	1,0
PD		1,0	0,3	2,0

Tabel 7. Enhedsomkostninger til monitorering

	Enhedsomkostning [DKK]	Kilde
Ambulant besøg	1.636	2021 DRG: 13MA98
CT-scanning	2.433	2021 DRG: 36PR07
Blodprøvetagning	31	Rigshospital Labportal

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men ekskluderer omkostningerne til blodprøvetagning.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger og anvender grad 3+ bivirkninger med en frekvens på mindst 5 % i en af behandlingsarmene som mål for bivirkningerne. For dostarlimab har ansøger anvendt de rapporterede behandlingsrelaterede bivirkningsrater i GARNET-studiet. Ansøger har ikke kunne finde relevant litteratur, der har opgjort behandlingsrelaterede bivirkninger af grad 3+ for komparatorerne. Derfor anvender ansøger behandlingsrelaterede bivirkningsrater af doxorubicin som proxy for platinbaseret kemoterapi, placebo og pegyleret liposomalt doxorubicin.

Ressourcerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på 2021 DRG-takster og timeomkostninger for sundhedspersonale.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ikke ansøgers tilgang til estimering af bivirkningsomkostninger, da platinbaseret kemoterapi og pegyleret liposomalt doxorubicin ifølge fagudvalgets erfaringer generelt er mindre bivirkningstungt end doxorubicin. Medicinrådet har fundet to kliniske fase III-studier for hhv. carboplatin-paclitaxel og pegyleret liposomalt doxorubicin, som kan bidrage med at give et skøn over bivirkningsrater for platinbaseret kemoterapi og pegyleret liposomalt doxorubicin. I begge studier er der opgjort bivirkninger, der er forekommet under behandling, men som ikke er direkte relateret til lægemidlet. Medicinrådet vælger derfor ligeledes at tage udgangspunkt i bivirkninger opstået i GARNET-studiet, som ikke er direkte relateret til dostarlimab i Medicinrådets hovedanalyse for at sikre større sammenlignelighed mellem bivirkningsopgørelserne for de tre lægemidler. Der er dog stor usikkerhed, da opgørelserne kan indeholde en stor andel af bivirkninger, som ikke er relateret til lægemidlerne, og der er derfor risiko for at bivirkningsomkostningerne overestimeres. Disse ændringer vurderes at have minimal betydning for analysens resultat.

For platinbaseret kemoterapi anvender Medicinrådet bivirkningsfrekvenser fra et studie af Miller et al. [10], der rapporterer bivirknings- og effektdata fra et klinisk fase III-studie, GOG0209, hvori to forskellige kemoterapiregimer undersøges til 1. linjebehandling af avanceret eller recidiverende endometriecancer. Medicinrådet antager, at uønskede hændelser vil være sammenlignelige, uanset om behandlingen bruges i 1. eller 2. linjebehandling. Dog er doseringen af carboplatin AUC6 (6 x arealet under kurven for

koncentration i forhold til tid) i studiet af Miller et al., mens en dosering på AUC5 anvendes i dansk klinisk praksis. Derfor er bivirkningsfrekvenser forbundet med stor usikkerhed. For pegyleret liposomalt doxorubicin anvender Medicinrådet bivirkningsfrekvenser fra et studie af Gordon et al. [11], der rapporterer effekt og bivirkningsdata fra studiet, hvor pegyleret liposomalt doxorubicin undersøges overfor topotecan til behandling af recidiverende ovariecancer. Fagudvalget vurderer, at bivirkningerne vil være relativt sammenlignelige, uanset om man behandler avanceret ovariecancer eller endometriecancer med pegyleret liposomalt doxorubicin. Derudover er doseringen af pegyleret liposomalt doxorubicin 50 mg/m^2 i studiet af Gordon et al., mens den almindelige dosering i dansk klinisk praksis er 40 mg/m^2. Derfor er bivirkningsfrekvenser forbundet med stor usikkerhed.

Bivirkningsfrekvenser og anvendte takster kan ses i Tabel 8 og Tabel 9.

Tabel 8. Rapporterede bivirkningsfrekvenser ved behandling med dostarlimab og komparatorerne

	Dostarlimab [%]	Platinbaseret kemoterapi [%]	Pegyleret liposomalt doxorubicin [%]
Mavesmerter	5,4 %	-	-
Anæmi	14,7 %	16,6 %	5,4 %
Udmattelse	0,8 %	9,6 %	-
Kvalme	0,0 %	5,6 %	-
Neutropeni	1,6 %	79,8 %	12,1 %
Opkastning	0,0 %	3,5 %	-
Leukopeni	1,6 %	49,7 %	10,0 %
Febril neutropeni	-	5,4 %	-
Hånd-fod-syndrom	-	-	29,0 %
Stomatitis	-	0,2 %	8,4 %

Tabel 9. Anvendte enhedsomkostninger for bivirkningerne

	Enhedsomkostning [DKK]	Kilde
Mavesmerter	5.130	DRG 2021: 06MA11
Anæmi	3.987	DRG 2021: 23MA03
Udmattelse	3.114	DRG 2021: 16MA98
Kvalme	3.114	DRG 2021: 16MA98 + domperidon

	Enhedsomkostning [DKK]	Kilde
Neutropeni	0	Ikke behandlingskrævende
Opkastning	5.130	DRG 2021: 06MA11
Leukopeni	0	Ikke behandlingskrævende
Febril neutropeni	16.737	DRG 2021: 13MA01
Hånd-fod-syndrom	3.114	DRG 2021: 16MA98
Stomatitis	3.114	DRG 2021: 16MA98

Medicinrådet vælger at ændre bivirkningsfrekvenserne for platinbaseret kemoterapi og pegyleret liposomalt doxorubicin. Derudover anvender Medicinrådet opgjorte bivirkninger, der er forekommet under behandling, men som ikke er direkte relateret til lægemidlet for dostarlimab.

Testomkostninger

På nuværende tidspunkt testes der ikke rutinemæssigt for dMMR/MSI-H-tumorstatus, men dette vil være en forudsætning for ibrugtagning af dostarlimab. Derfor inkluderer ansøger omkostninger til test for dMMR/MSI-H-tumorstatus og antager, at alle patienter skal testes via immunhistokemi. Ansøger inkluderer dog ikke testomkostninger for de patienter, som vil blive testet, men som ikke har dMMR/MSI-H.

Ansøger anvender en pris på 631 DKK for MMR-test via immunhistokemi.

Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger

Fagudvalget vurderer, at 22-30 % af alle patienter med endometriecancer vil have dMMR/MSI-H. Det er således i den fulde population, at man skal identificere de patienter, som kan være kandidater til behandling med dostarlimab. Derfor skal testomkostninger også inkluderes for de patienter, som vil blive testet, men som ikke har dMMR/MSI-H. Medicinrådet antager, at 26 % af patienterne med endometriecancer har dMMR/MSI-H. Dermed bliver den gennemsnitlige testomkostning 2.369 DKK pr. patient med dMMR/MSI-H. Denne ændring vurderes at have minimal betydning for analysens resultat.

Medicinrådet accepterer ansøgers tilgang vedr. testomkostninger, men vælger at inkludere omkostninger for de patienter, som testes, men som ikke har dMMR/MSI-H.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 99 DKK pr. besøg, jf. Medicinrådets værdisætning af enhedsomkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers estimerede patienttid, som kan ses i Tabel 10.

Tabel 10. Estimat af effektiv patienttid i forbindelse med administration og monitorering

	Patienttid [timer]
Administration	
Administration af dostarlimab	0,5
Administration af platinbaseret kemoterapi	4
Administration af pegyleret liposomalt doxorubicin	1
Monitoring	
Ambulant besøg	1
CT-scanning	1
Blodprøvetagning	0,5

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

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

Tabel 11. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Tidshorisont	Tidshorisont ændres til 20 år eller 30 år
Half-cycle correction	*Half-cycle correction* anvendes ikke
Ekstrapolering af OS for dostarlimab	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion log-logistisk, eksponentiel, generaliseret gamma, Weibull, gompertz, gamma, spline model med 1 knudepunkt eller spline model med 2 knudepunkter

Følsomhedsanalyse	Beskrivelse
Ekstrapolering af PFS for dostarlimab	Data for PFS ekstrapoleres ved anvendelse af den parametriske funktion log-logistisk, eksponentiel, generaliseret gamma, Weibull, gompertz, gamma, spline model med 1 knudepunkt eller spline model med 2 knudepunkter
Ekstrapolering af ToT for dostarlimab	Data for ToT ekstrapoleres ved anvendelse af den parametriske funktion log-logistisk, log-normal, eksponentiel, Weibull, gompertz, gamma, spline model med 1 knudepunkt eller spline model med 2 knudepunkter
ToT lig PFS	Behandlingsvarigheden for dostarlimab antages at være lig tid til PFS
Skæringspunktet for overgangen mellem KM-data og ekstrapolerede kurve for PFS	Skæringspunktet for overgangen mellem KM-data og ekstrapolerede kurve for PFS varieres til efter 0 måneder, 12 måneder, 18 måneder eller 24 måneder
Skæringspunktet for overgangen mellem KM-data og ekstrapolerede kurve for ToT	Skæringspunktet for overgangen mellem KM-data og ekstrapolerede kurve for ToT varieres til efter 6 måneder, 12 måneder, 18 måneder eller 24 måneder
Ekskludering af testomkostninger	Omkostninger til test af dMMR/MSI-H-status ekskluderes

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vurderer, at det ikke er relevant at udarbejde følsomhedsanalyser med alternative tidshorisonter, da tidshorisonten skal være så lang, at den opfanger alle forskelle i omkostninger mellem intervention og komparator.

På trods af usikkerheder vedr. det forventede forløb af de observerede data for PFS, vurderer fagudvalget, at størstedelen af ekstrapoleringerne for PFS ikke er klinisk plausible. Derfor vælger Medicinrådet kun at præsentere følsomhedsanalysen, hvor data for PFS ekstrapoleres ved anvendelse af den parametriske funktion log-normal. Ved anvendelse af log-normal falder den gennemsnitlige tid til progression for dostarlimab fra 4,9 år til 2,6 år. Derudover vælger Medicinrådet at præsentere følsomhedsanalyser, hvor skæringspunktet for overgang mellem KM-data og ekstrapolering for PFS sættes til 6 måneder, hvormed den gennemsnitlig tid til progression for dostarlimab falder fra 4,9 år til 4,4 år.

For OS vælger Medicinrådet at præsentere ansøgers følsomhedsanalyser, der undersøger betydningen af valg af parametrisk funktion til ekstrapolering af OS-data. Hertil præsenterer Medicinrådet følsomhedsanalyser, hvor data for OS ekstrapoleres ved anvendelse af den parametriske funktion log-logistisk, hvilket er den kurve, der ligger tættest på kurven for overlevelsen anvendt i Medicinrådets hovedanalyse. Ved anvendelse af log-logistisk ekstrapolation falder den gennemsnitlige overlevelse for dostarlimab fra 5,8 år til 5,5 år.

Da Medicinrådet vurderer, jf. vurderingsrapporten, at værdien af dostarlimab overfor platinbaseret kemoterapi ikke kan kategoriseres, vælger Medicinrådet i en følsomhedsanalyse at udarbejde en omkostningsminimeringsanalyse. Hertil antages effekten og bivirkningsprofilen for dostarlimab og platinbaseret kemoterapi at være ens. Medicinrådet vælger derfor at udarbejde en følsomhedsanalyse, hvor de mest konservative ekstrapoleringer for PFS og OS for dostarlimab anvendes til at estimere effekten af dostarlimab. Samtidig sættes hazard ratioen mellem dostarlimab og platinbaseret kemoterapi til 1,0 for både PFS og OS. Medicinrådet vælger at ekstrapolere data for PFS og OS ved anvendelse af den parametriske funktion eksponentiel, hvormed den gennemsnitlig tid til progression bliver 1 år, og den gennemsnitlige overlevelse bliver 3,1 år.

Det skal dog nævnes, at den parameter, der har størst indflydelse på resultaterne, er den pris, dostarlimab indkøbes til.

Medicinrådet vælger at præsentere et par af ansøgers følsomhedsanalyser, hvor ekstrapoleringerne for OS og PFS undersøges. Derudover udarbejder Medicinrådet en følsomhedsanalyse, der antager ens effekt mellem dostarlimab og platinbaseret kemoterapi.

4.4 Opsummering af basisantagelser

I Tabel 12 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 12. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	40 år	40 år
Diskonteringsrate	1-35 år: 3,5 % 36-70 år: 2,5 %	1-35 år: 3,5 % 36-70 år: 2,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger (inkl. testomkostninger) Patient- og transportomkostninger	Lægemiddelomkostninger Hospitalsomkostninger (inkl. testomkostninger) Patient- og transportomkostninger
Behandlingslinje	2. linjebehandling	2. linjebehandling
Stop-regel for dostarlimab	Ja, efter to år	Ja, efter to år

Basisantagelser	Ansøger	Medicinrådet
Behandlingsvarighed		
Dostarlimab:	10,0 måneder	10,4 måneder
Platinbaseret kemoterapi:	4,3 måneder	2,6 måneder
Pegyleret liposomalt doxorubicin:	4,3 måneder	2,3 måneder
Parametriske funktioner for dostarlimab		
ToT:	Generaliseret gamma	Generaliseret gamma
PFS:	Log-normal	Generaliseret gamma
OS:	Log-normal	Log-normal
Skæringspunktet for overgangen mellem KM-data og ekstrapolerede kurve for PFS	6 måneder	12 måneder
Hazard ratioer for platinbaseret kemoterapi overfor dostarlimab		
PFS:	HR: 0,78	HR: 2,72
OS:	HR: 1,79	HR: 1,79
Hazard ratioer for pegyleret liposomalt doxorubicin (og placebo) overfor dostarlimab		
PFS:	HR: 0,78	HR: 3,39
OS:	HR: 3,48	HR: 3,48
Inkludering af spild	Ja	Ja

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyser bygger på samme antagelser som ansøgers hovedanalyser med undtagelse af de væsentligste ændringer, der fremgår af Tabel 12.

Patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor dostarlimab sammenlignes med platinbaseret kemoterapi. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 750.000 DKK. Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 13.

Patienter, der er progredieret under eller efter platinbaseret kemoterapi

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor dostarlimab sammenlignes med placebo. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 801.000 DKK. Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 14.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor dostarlimab sammenlignes med pegyleret liposomalt doxorubicin. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 768.000 DKK. Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 15.

Tabel 13. Resultatet af Medicinrådets hovedanalyse ved sammenligning med platinbaseret kemoterapi, DKK, diskonterede tal

	Dostarlimab	Platinbaseret kemoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	129.590	61.721	67.869
Testomkostninger	2.369	0	2.369
Patientomkostninger	39.701	10.222	29.479
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 14. Resultatet af Medicinrådets hovedanalyse ved sammenligning med placebo, DKK, diskonterede tal

	Dostarlimab	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	129.590	19.827	109.764
Testomkostninger	2.369	0	2.369
Patientomkostninger	39.701	3.781	35.919
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 15. Resultatet af Medicinrådets hovedanalyse ved sammenligning med pegyleret liposomalt doxorubicin, DKK, diskonterede tal

	Dostarlimab	Pegyleret liposomalt doxorubicin	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	129.590	28.683	100.907
Testomkostninger	2.369	0	2.369
Patientomkostninger	39.701	4.136	35.565
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 16.

Tabel 16. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling	
Resultatet af hovedanalysen	[redacted]
PFS-ekstrapolering – log-normal	[redacted]
PFS-skæringspunkt – 6 måneder	[redacted]
OS-ekstrapolering – log-logistisk	[redacted]
Ens effekt mellem dostarlimab og platinbaseret kemoterapi	[redacted]
Patienter, der er progredieret under eller efter platinbaseret behandling	
Resultatet af hovedanalysen sammenlignet med pegyleret liposomalt doxorubicin	[redacted]
PFS-ekstrapolering – log-normal	[redacted]
PFS-skæringspunkt – 6 måneder	[redacted]
OS-ekstrapolering – log-logistisk	[redacted]

6. Budgetkonsekvenser

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

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

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

Ansøger antager, at der vil være ca. 20 nye patienter med dMMR/MSI-H pr. år, der ved en anbefaling er kandidater til behandling med dostarlimab. Heraf er 15 patienter progredieret ca. 6 måneder eller mere efter platinbaseret behandling, og 5 patienter er progredieret under eller mindre end 6 måneder efter platinbaseret behandling. Ansøger antager, at dostarlimab har et markedsoptag på 80 % fra år 1 stigende til 90 % fra år 2 for begge patientpopulationer.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis dostarlimab anbefales som mulig standardbehandling, og hvis ikke dostarlimab anbefales. Fagudvalget er enigt i ansøgers estimering af det totale patientantal. Fagudvalget vurderer dog, at der nærmere er en ligelig fordeling af patienter mellem de to patientpopulationer, således at 10 patienter er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi, og 10 patienter er progredieret under eller mindre end 6 måneder efter platinbaseret kemoterapi. I forhold til markedsoptaget for dostarlimab, er fagudvalget enig med ansøger. Se patientantallet og markedsoptaget for hver patientpopulation i Tabel 17 og Tabel 18.

Tabel 17. Medicinrådets estimat af antal nye patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Dostarlimab	8	9	9	9	9
Platinbaseret kemoterapi	2	1	1	1	1
			Anbefales ikke		
Dostarlimab	0	0	0	0	0
Platinbaseret kemoterapi	10	10	10	10	10

Tabel 18. Medicinrådets estimat af antal nye patienter, der er progredieret under eller efter platinbaseret kemoterapi pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Dostarlimab	8	9	9	9	9
Pegyleret liposomalt doxorubicin	2	1	1	1	1
			Anbefales ikke		
Dostarlimab	0	0	0	0	0
Pegyleret liposomalt doxorubicin	10	10	10	10	10

Medicinrådet accepterer ansøgers antagelser vedr. budgetkonsekvenserne.

6.2 Medicinrådets budgetkonsekvensanalyse

Patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi

Medicinrådet estimerer, at anvendelse af dostarlimab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 19. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 6,2 mio. DKK i år 5.

Patienter, der er progredieret under eller efter platinbaseret kemoterapi

Medicinrådet estimerer, at anvendelse af dostarlimab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 20. Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 6,3 mio. DKK i år 5.

Tabel 19. Medicinrådets analyse af totale budgetkonsekvenser for patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 20. Medicinrådets analyse af totale budgetkonsekvenser for patienter, der er progredieret under eller efter platinbaseret kemoterapi, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med dostarlimab til patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret kemoterapi, er forbundet med inkrementelle omkostninger på [redacted] DKK sammenlignet med behandling med platinbaseret kemoterapi. Behandling med dostarlimab til patienter, der er progredieret under eller efter platinbaseret kemoterapi, er forbundet med inkrementelle omkostninger på [redacted] DKK sammenlignet med behandling med pegyleret liposomalt doxorubicin. For begge sammenligninger er de inkrementelle omkostninger næsten udelukkende drevet af lægemiddelomkostningerne for dostarlimab.

Der er store usikkerheder vedr. det forventede forløb af de observerede data for PFS, da de observerede data antyder, at nogle patienter vil være langtidsprogressionsfri. Hvis PFS ekstrapoleres med en log-normal funktion, som ikke estimerer samme andel af patienter, der er langtidsprogressionsfri, falder de inkrementelle omkostninger til hhv. [redacted] sammenlignet med platinbaseret kemoterapi og [redacted] sammenlignet med pegyleret liposomalt doxorubicin. Hvis skæringspunktet for overgangen mellem KM-data og den ekstrapolerede kurve for PFS ændres til 6 måneder, falder den gennemsnitlige tid til progression for patienter, der behandles med dostarlimab, fra 4,9 år til 4,4 år. Dermed falder de inkrementelle omkostninger også til hhv. [redacted] sammenlignet med platinbaseret kemoterapi og [redacted] sammenlignet med pegyleret liposomalt doxorubicin. Grundet umodent OS-data er der ligeledes usikkerhed vedr. patienternes overlevelse. Hvis data for OS ekstrapoleres med en log-logistisk funktion, som reducerer overlevelsen med 3,5 måneder for patienter, der behandles med dostarlimab, falder de inkrementelle omkostninger med hhv. [redacted] sammenlignet med platinbaseret kemoterapi og [redacted] sammenlignet med pegyleret liposomalt doxorubicin.

Ovenstående usikkerheder vedr. PFS og OS har mindre betydning for analysens resultat, hvilket skyldes, at analysens resultat primært er drevet af lægemiddelomkostningerne for dostarlimab, og dermed behandlingsvarigheden for dostarlimab. Ændringerne i PFS og OS, der er undersøgt i følsomhedsanalyserne, har ikke stor betydning for behandlingsvarigheden for dostarlimab, fordi behandlingen seponeres for patienter, der behandles i mere end to år.

Hvis effekten mellem dostarlimab og platinbaseret kemoterapi sættes til at være ens, falder de inkrementelle omkostninger til [redacted] DKK pr. patient sammenlignet med platinbaseret kemoterapi. Denne følsomhedsanalyse har, sammenlignet med de øvrige følsomhedsanalyser, større betydning for analysens resultat, da den gennemsnitlige tid i PFS sænkes til 1 år, hvilket derfor nedsætter den gennemsnitlige behandlingsvarighed med ca. 1 måned.

8. Referencer

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	15. december 2021	Godkendt af Medicinrådet

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

Patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 40 år sammenlignet med platinbaseret kemoterapi. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 21.

Patienter, der er progredieret under eller efter platinbaseret behandling

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 40 år sammenlignet med placebo. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 22.

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 40 år sammenlignet med pegyleret liposomalt doxorubicin. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 23.

Tabel 21. Resultatet af ansøgers hovedanalyse sammenlignet med platinbaseret kemoterapi, DKK, diskonterede tal

	Dostarlimab	Platinbaseret kemoterapi	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	129.097	67.426	61.671
Testomkostninger	616	0	616
Patientomkostninger	24.712	12.864	11.848
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 22. Resultatet af ansøgers hovedanalyse sammenlignet med placebo, DKK, diskonterede tal

	Dostarlimab	Placebo	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	129.097	19.978	109.119
Efterfølgende behandling	616	0	616
Patientomkostninger	24.712	3.781	20.930
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 23. Resultatet af ansøgers hovedanalyse sammenlignet med pegyleret liposomalt doxorubicin, DKK, diskonterede tal

	Dostarlimab	Pegyleret liposomalt doxorubicin	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	129.097	37.038	92.059
Efterfølgende behandling	616	0	616
Patientomkostninger	24.712	5.580	19.132
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Patienter, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling

Ansøger estimerer, at anvendelse af dostarlimab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 24.

Patienter, der er progredieret under eller efter platinbaseret behandling

Ansøger estimerer, at anvendelse af dostarlimab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 25.

Tabel 24. Ansøgers hovedanalyse for totale budgetkonsekvenser sammenlignet med platinbaseret kemoterapi, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 25. Ansøgers hovedanalyse for totale budgetkonsekvenser sammenlignet med pegyleret liposomalt doxorubicin, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	År 1	År 2	År 3	År 4	År 5
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	15. december 2021
Leverandør	GlaxoSmithKline (GSK)
Lægemiddel	Dostarlimab (Jemperli)
Ansøgt indikation	Som monoterapi til behandling af voksne patienter med recidiverende eller avanceret endometriecancer med dMMR/MSI-high, som er progredieret under eller efter platinbaseret behandling

Forhandlingsresultat

Amgros har opnået følgende pris på dostarlimab (Jemperli):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Dostarlimab	50 mg/ml i.v.	10 ml	[redacted]	[redacted]	[redacted]

[redacted]

Informationer fra forhandlingen

Amgros vurderer, at det **IKKE** er muligt at opnå en bedre pris. Denne vurdering baseres på nedenstående punkter fra forhandlingen:

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen godkendte konkurrerende lægemidler i 2. linje. Dog er lenvatinib i kombination med pembrolizumab under behandling i Medicinrådet (anmodning om vurdering indsendt 2. august 2021). Pegyleret liposomalt doxorubicin (PLD) bruges off-label som standard ved progression under eller op til et halvt år efter behandling med carboplatin og paclitaxel.

Tabel 2: Behandlingspris og rene lægemiddelpriser for behandling med dostarlimab i 10,4 måneder

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/ 10,4 måneder	Årlig lægemiddelpris SAIP pr. år (DKK)
Dostarlimab	50 mg/ml i.v.	10 ml	[redacted]	15	[redacted]

Status fra andre lande

Norge: Ansøgning er under udarbejdelse.
Sverige: Ansøgning er under udarbejdelse.
England: Dostarlimab er på nuværende tidspunkt under vurdering. Forventet anbefaling 26. januar 2022[1].

Konklusion

Det er Amgros' vurdering, at vi **IKKE** kan opnå en bedre pris på dostarlimab på nuværende tidspunkt på grund af den manglende konkurrence, og eftersom dostarlimab er det første godkendte lægemiddel til denne indikation.

[1] https://www.nice.org.uk/guidance/indevelopment/gid-ta10670

Vallensbæk d. 30.11.2021

Høringssvar – GSK – Vedr. udkast til vurderingsrapport for dostarlimab

Kære Hans Christian

Tak for udkast til vurdering af værdien af dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden (ca. 20 patienter årligt uden andre godkendte behandlingsmuligheder).

Evidensgrundlaget for små populationer, såsom patienter med recidiverende/avanceret dMMR/MSI-high kræft i livmoderslimhinden er ofte udfordret af et sparsomt datagrundlag samt begrænsede eller ingen komparative studier.

På den baggrund anerkender GSK fagudvalgets arbejde og kliniske vurdering af dostarlimab, hvor den deskriptive gennemgang fremhæver dostarlimabs potentiale til at have langvarig effekt hos en betydelig andel af patienterne, en favorabel bivirkningsprofil og positiv indvirkning på patienternes livskvalitet.

Af vurderingsrapporten fremgår flg:

Klinisk spørgsmål 1: Fagudvalget kan ikke vurdere, om effekten af dostarlimab er forskellig fra platinbaseret kemoterapi men konkluderer, **at dostarlimab er mindre bivirkningstungt end platinbaseret kemoterapi**.

Ved vurdering af dostarlimabs effekt, mener GSK, det er vigtigt at tage højde for, at de inkluderede studier for platinbaseret kemoterapi generelt, havde en længere cut-off periode for det platinfrie interval (PFI) i forhold til protokollens definition på > 6 måneder. Den længere PFI vil potentielt overvurdere effekten af platinbaseret kemoterapi hos platinfølsomme patienter, da patienter med længere PFI har bedre mulighed for respons, når de genbehandles med platinbaseret kemoterapi.

GSK bemærker, at fagudvalget gentagne gange påpeger, at PFS-raten ved 24 måneder indikerer, at dostarlimab har et potentiale til at have en langvarig effekt hos en stor andel af patienterne. Dette observeres ikke på samme måde hos patienter, der får genbehandling med platinbaseret kemoterapi, hvilket stemmer overens med fagudvalgets kliniske erfaring med behandling med komparatorerne.

GSK er enig med fagudvalgets vurdering af, at dostarlimab er mindre bivirkningstungt end platinbaseret kemoterapi og undrer os over, at dette aspekt ikke nævnes i medicinrådets konklusion. I vurderings-rapporten nævnes eksplicit, at neuropati, der opstår hos 20-25 % af patienterne, som har været i behandling med platinbaseret kemoterapi, kan have en livslang påvirkning af patienterne. Derudover, at hæmatologiske bivirkninger som febril neutropeni, kvalme, træthed og påvirkning af slimhinder kan være generende for patienterne og påvirke deres daglige funktionsniveau.

Klinisk spørgsmål 3: Fagudvalget vurderer at **dostarlimab er mere effektivt og mindre bivirkningstungt end PLD/doxorubicin.**

GSK er enig i fagudvalgets vurdering, at dostarlimab er mere effektivt og mindre bivirkningstungt end PLD/doxorubicin.

I den endelige vurdering af dostarlimab som standardbehandling, mener GSK, det er vigtigt at have nedenstående for øje*:*

- Patientpopulationen for dostarlimab er af beskeden størrelse på blot 20 patienter/år.
- PFS-raten ved 24 måneder indikerer, at dostarlimab har et potentiale til at have en langvarig effekt hos en stor andel af patienterne.
- Patienter uden respons på dostarlimab identificeres hurtigt, hvorved langtidsbehandling kun vil finde sted for patienter, der har gavn af det.
- Responsvarighed for dostarlimab indikerer, at dMMR/MSI-H er en god markør til selektion af hvilke patienter med endomtriecancer, der har størst mulighed for god effekt af immunterapi.

Med venlig hilsen

Birgit Andersen
Market Access Manager & Tender Manager

GSK
2665 Vallensbæk Strand

Fra: Hans Christian Cederberg Helms
Sendt: 1. december 2021 08:38
Til: Birgit Andersen <birgit.x.andersen@gsk.com>
Cc: Helle Hellberg <helle.a.hellberg@gsk.com>
Emne: SV: Høringssvar dostarlimab

Kære Birgit

Tak for jeres høringssvar angående Medicinrådets vurdering af dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden.

Vi har gennemgået jeres høringssvar sammen med fagudvalgsformanden, og vi finder ikke anledning til at ændre den nuværende vurdering.

Jeres kommentarer indgår i den videre behandling og bliver offentliggjort sammen med den endelige anbefaling.

Mvh

Hans Christian Cederberg Helms

Sundhedsvidenskabelig specialkonsulent

Cand.pharm., ph.d.

hce@medicinraadet.dk

+45 21 34 08 76

Medicinrådet

Dampfærgevej 21-23, 3. sal

2100 København Ø

+45 70 10 36 00

medicinraadet@medicinraadet.dk

www.medicinraadet.dk

Medicinrådet

Medicinrådet

Medicinrådets vurdering vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden

Version 1.0

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 bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

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

Dokumentoplysninger	
Godkendelsesdato	24. november 2021
Dokumentnummer	130207
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet har vurderet dostarlimab til patienter med tilbagefald af kræft i livmoderslimhinden efter tidligere behandling med platinbaseret kemoterapi.

Medicinrådet vurderer, at dostarlimab ikke er mere effektivt end genbehandling med platinbaseret kemoterapi. Medicinrådet kan ikke vurdere effekten af dostarlimab i forhold til ingen behandling, da der ikke findes data for dette. Rådet noterer sig fagudvalgets vurdering af, at dostarlimab synes væsentligt mere effektivt end pegyleret liposomalt doxorubicin (PLD), blandt andet tyder data på, at patienterne lever længere. Samtidig er dostarlimab mindre bivirkningstungt. PLD er ikke godkendt til indikationen, men er i dag standardbehandling til patienter, der ikke kan genbehandles med platinbaseret kemoterapi.

Vurderingerne er baseret på en deskriptiv sammenligning af effektestimater fra et ukontrolleret studie af dostarlimab med effektestimater fra en blanding af prospektive kliniske studier og retrospektive kohortestudier af komparatorerne. Den samlede værdi af dostarlimab kan ikke kategoriseres efter Medicinrådets metoder, fordi datagrundlaget er for usikkert.

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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.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

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

AUC 5	5 x arealet under kurven for koncentration i forhold til tid *(Area under the curve)*
CR	Komplet respons (*complete response*)
DGCG	Dansk Gynækologisk Cancer Gruppe
dMMR:	Defekt mismatch repair (*mismatch repair deficient)*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EORTC-QLQ-C30	Spørgeskema til vurdering af livskvalitet (*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*)
EORTC-QLQ-EN24:	Spørgeskema til vurdering af livskvalitet ved endometriecancer (*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Endometrial Cancer Module 24*)
ESGO:	*European Society of Gynaecological Oncology*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
iORR	Immunrelateret objektiv responsrate
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention to treat*
MAIC	Matched adjusted indirect comparison
MKRF:	Mindste klinisk relevante forskel
MMR	*Mismatch repair*
MSI-H:	Høj mikrosatellit-ustabilitet (*microsatellite instability-high)*
NICE:	*The National Institute for Health and Care Excellence*
ORR:	Objektiv responsrate
OS:	Samlet overlevelse (*Overall survival*)
PFS:	Progressionsfri overlevelse (*progression free survival*)

PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PD:	Receptor (*Programmed death*)
PD-L:	Ligand (*Programmed death ligand*)
PLD	Pegyleret liposomalt doxorubicin
PP:	*Per Protocol*
PR:	Partielt respons
PS	*Performance status*
RECIST:	*Response Evaluation Criteria in Solid Tumors*
RR:	Relativ risiko
SMD:	*Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af dostarlimab til dMMR/MSI-high kræft i livmoderslimhinden er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra GSK. Medicinrådet modtog ansøgningen den 21. september 2021.

Det kliniske spørgsmål er:

1. Hvilken værdi har dostarlimab sammenlignet med platinbaseret kemoterapi for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling?
2. Hvilken værdi har dostarlimab sammenlignet med placebo for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?
3. Hvilken værdi har dostarlimab sammenlignet med pegyleret liposomalt doxorubicin for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?

Der findes ikke en godkendt behandling til patienter med avanceret eller recidiverende endometriecancer, som er progredieret under eller inden for 6 måneder efter platinbaseret behandling. Derfor vil dostarlimab blive sammenlignet med placebo, og Medicinrådets anbefaling vil tage udgangspunkt i denne sammenligning. Medicinrådets fagudvalg vil derudover foretage en vurdering af værdien af dostarlimab sammenlignet med dansk standardbehandling, uanfægtet at denne er off-label.

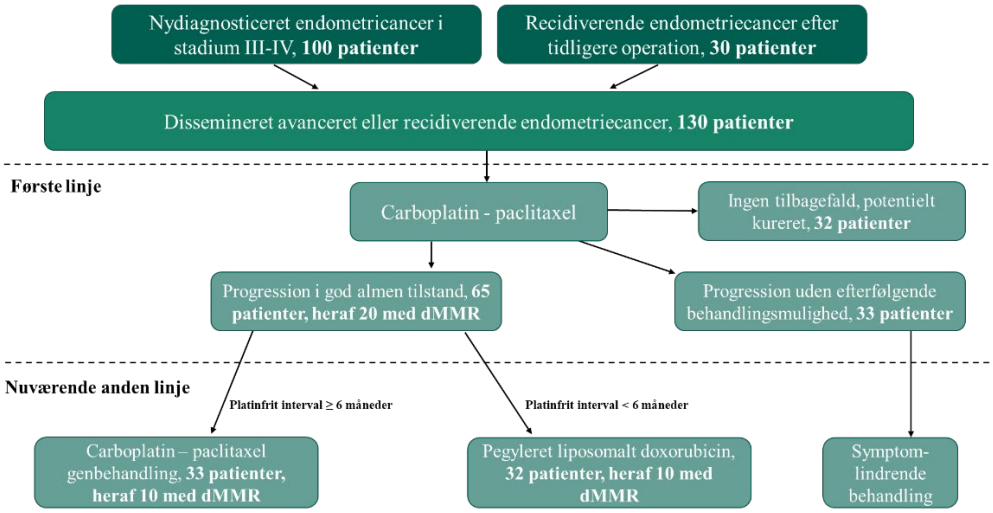
3.1 Kræft i livmoderslimhinden (endometriecancer)

Livmoderkræft er den 5. hyppigste kræftform blandt kvinder i Danmark, og den hyppigste form for gynækologisk kræft [1]. Omkring 800 kvinder får hvert år konstateret livmoderkræft, hvor den hyppigste form (> 90 %) er kræft i livmoderslimhinden (endometriecancer) [1,2]. Sygdommen rammer typisk ældre kvinder (median alder 63 år) [3], og knap 11.000 patienter i Danmark lever efter at have fået diagnosen [2].

Endometriecancer diagnosticeres i ca. 80 % af tilfældene tidligt (lokaliseret til livmoderen), pga. tydelige symptomer [4]. Konstateres sygdommen i et tidligt stadie, betragtes den som kirurgisk helbredelig med en 5-års overlevelse på omkring 80-85 % [4]. Lokalavanceret eller metastatisk endometriecancer (samlet benævnt avanceret endometriecancer) har en dårligere prognose med 5-års overlevelse på hhv. 49 % og 28 % for stadie III og IV [4].

Nogle patienter vil opleve tilbagefald af sygdommen inden for få år efter endt primærbehandling. Dette karakteriseres som oftest som uhelbredelig endometriecancer med en median overlevelse på omkring 12 måneder [5]. I Danmark er der ca. 100 patienter om året med nydiagnosticeret avanceret endometriecancer [1] samt ca. 30

patienter med recidiverende endometriecancer [1,6]. Omkring halvdelen af disse patienter vil opleve progression efter førstelinjebehandling og stadig være i en almen tilstand til at kunne modtage andenlinjebehandling. Resten er enten kureret (omkring 20-30 %) eller progredierer uden at kunne modtage andenlinjebehandling. Disse tilbydes symptomlindrende behandling. Patientflowet er skitseret i Figur 3-1.



Figur 3-1: Oversigt over patientantal og nuværende behandlingsforløb ved avanceret eller recidiverende endometriecancer. dMMR = defekt *mismatch repair.*

Mismatch repair (MMR)-systemet er et cellulært system, der bl.a. reparerer fejl i DNA-strengene [7]. En arvelig eller somatisk mutation i et af generne MLH1, MSH2, MSH6 eller PMS2 kan medføre dMMR. I væv med dMMR ophobes mutationer. Dette sker særligt i de såkaldte mikrosatellitregioner af DNA, hvorved dMMR ofte kan identificeres ved en høj grad af ustabilitet i disse DNA-regioner (MSI-H/*Microsatelite instability-High*) [7]. Funktionelle defekter i MMR-systemet i tumorvæv medfører en ophobning af såkaldt mutations-associerede neoantigener, som kan genkendes af immunsystemet [8]. Neoantigener er tumorspecifikke og dermed også patientspecifikke. Derved spiller et aktivt immunrespons en vigtig rolle i at bekæmpe dMMR/MSI-H-tumorer, hvilket giver et rationale for immunterapi til patienter med disse tumorer. dMMR/MSI-H skyldes oftest somatiske forandringer men kan også være arvelige (Lynch syndrom).

Ca. 22-30 % af tilfældene med endometriecancer har ifølge litteraturen dMMR/MSI-H, uanset sygdomsstadie [9,10]. Fagudvalget vurderer dog, at andelen er noget lavere hos patienter med avanceret eller recidiverende endometriecancer, men der findes ikke studier, der belyser dette. Fagudvalget vurderer, at der vil være ca. 20 nye patienter med dMMR/MSI-H pr. år, der er kandidater til andenlinjebehandling.

Det er uvist i hvilken grad MMR/MSI-status påvirker patientens prognose. Der findes dog en række faktorer med vigtig prognostisk betydning. Disse er bl.a. histologien (endometrioid/serøst eller clearcelle adenokarcinom eller karcinosarkom), molekylær biologiske faktorer (særligt POLE og p53) og hormonreceptorpositivitet [11].

3.2 Dostarlimab

Dostarlimab er et monoklonalt antistof, der binder til receptoren, *programmed death-1* (PD-1) og derved hæmmer dets binding til liganderne *programmed death-ligand-1 og -2* (PD-L1 og -2). PD-1-receptoren er til stede på overfladen af immunceller, og når receptoren aktiveres via PD-L1-binding medfører det et negativt feedback respons, der hæmmer T-celle-medieret celledød [12]. PD-L1 er overudtrykt på mange tumorceller, hvilket beskytter tumorcellerne fra immunsystemets reaktion. Ved at bryde PD-L1/PD-1-interaktionen i tumorceller kan dostarlimab modvirke denne beskyttelse [10], hvilket øger T-cellemedieret celledød i tumorer med mange mutations-associerede neoantigener.

Dostarlimab er godkendt af EMA til indikationen:

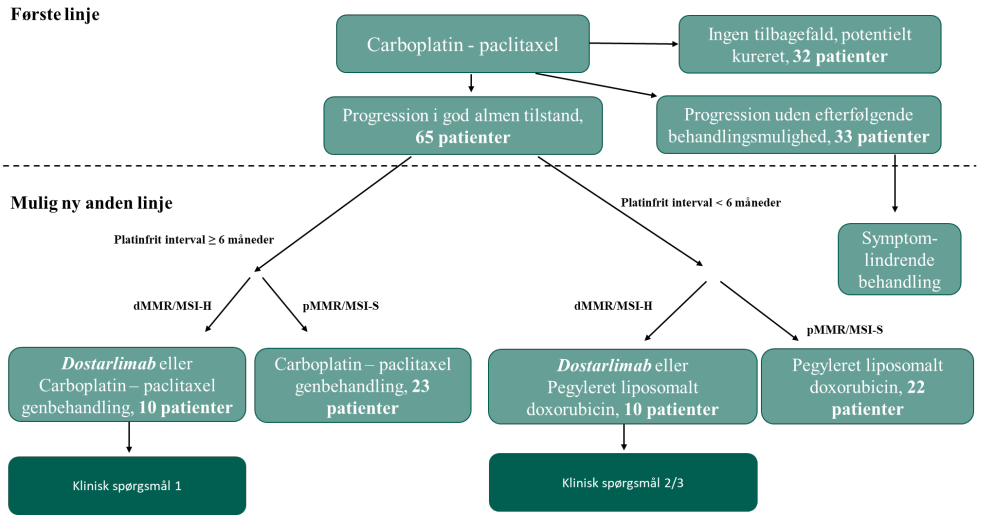
- monoterapi til behandling af voksne patienter med recidiverende eller avanceret endometriecancer med dMMR/MSI-high, som er progredieret under eller efter platinbaseret behandling.

Dostarlimab administreres som intravenøst over 30 minutter. Forventet dosis er 500 mg hver tredje uge over 4 cyklusser og derefter 1000 mg hver 6. uge indtil sygdomsprogression.

I EMAs godkendelse fremgår det, at effekt og bivirkningsdata for dostarlimab skal bekræftes ved yderligere opfølgningsdata fra registreringsstudiet (GARNET), og at data fra et igangværende fase III-studie (RUBY) skal indsendes til EMA senest den 31. december 2022.

3.3 Nuværende behandling

Behandlingen af endometriecancer er beskrevet i kliniske retningslinjer fra Dansk Gynækologisk Cancer Gruppe (DGCG) [5,13]. Størstedelen af patienter med endometriecancer i de tidlige stadier behandles med operation med kurativt (helbredende) sigte [1,13]. Behandlingen herefter, samt hvorledes dostarlimab kan indtræde i behandlingsalgoritmen, er skitseret i Figur 3-2.



Figur 3-2: Oversigt over nuværende behandling af avanceret eller recidiverende endometriecancer, samt hvorledes dostarlimab kan indtræde i behandlingsalgortiment. dMMR = *mismatch repair deficient*, pMMR = *mismatch repair proficient*.

Avanceret og recidiverende endometriecancer kan behandles med operation og/eller strålebehandling, suppleret med carboplatin og paclitaxel i op til 6 serier [5]. Formålet med denne behandling er at forlænge overlevelsen ved at begrænse yderligere sygdomsprogression. Herved opnås medianoverlevelse fra 15 måneder til over 3 år [14,15]. Patienter, der progredierer ca. 6 måneder eller mere efter afsluttet platinbehandling, betragtes som platinsensitive og kan efter progression genbehandles med platinbaseret kemoterapi [3,16]

Ved progression under eller op til et halvt år efter behandling med carboplatin og paclitaxel gives som standard pegyleret liposomalt doxorubicin (PLD). Denne behandling er ikke godkendt af EMA til indikationen, hvorfor brugen kan betragtes som off-label. Behandlingen er dog standard i dansk klinisk praksis [5], og klinikerne i Danmark har flere års erfaring med brugen af PLD til disse patienter. Anvendelsen af PLD er også beskrevet som behandling til denne patientpopulation i de danske kliniske retningslinjer fra DGCG [5]. Den kliniske effekt af denne behandling er begrænset, og fagudvalget vurderer, at patienter, der modtager behandling med PLD, har en median overlevelse på ca. 12 måneder [17].

Nogle patienter kan også behandles med antihormonel behandling, særligt ved tumorer med østrogenreceptor-positiv status.

Fordi patienter behandles forskelligt, alt efter om de forventes at respondere på genbehandling med platinbaseret kemoterapi, har fagudvalget valgt at dele patienterne op i to underpopulationer i de kliniske spørgsmål. Fagudvalget har derudover valgt to kliniske spørgsmål til populationen af patienter, der progredierer under eller efter platinbaseret kemoterapi, fordi nuværende standardbehandling ikke er godkendt af EMA. Da der ikke findes et godkendt lægemiddel til behandling af voksne patienter med recidiverende eller avanceret endometriecancer med dMMR/MSI-high, som er

progredieret under eller efter platinbaseret behandling, vil Medicinrådets vurdering af den kliniske merværdi og dermed endelige anbefaling for denne population bero på en sammenligning med placebo (klinisk spørgsmål 2).

4. Metode

Medicinrådets protokol for vurdering vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Klinisk spørgsmål 1:

Hvilken værdi har dostarlimab sammenlignet med platinbaseret kemoterapi for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling?

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt ni fuldtekstartikler (Tabel 5-1), baseret på otte studier. Ét af studierne undersøgte dostarlimab, og syv undersøgte platinbaseret kemoterapi.

Tabel 5-1 Oversigt over studier

Publikationer	Klinisk forsøg, NCT-nummer	Population	Studietype, intervention og eventuel komparator	Inkluderede effektmål	Median opfølgningstid
Oaknin A et al. 2020 [18] EPAR [19] og produktresume [20] for dostarlimab	GARNET, NCT02715284	Patienter med avanceret eller recidiverende endometriecancer, der tidligere er behandlet med platinbaseret kemoterapi. Alle patienter har dMMR/MSI-H	Fase I-II, ikke-kontrolleret klinisk studie. Dostarlimab	Median OS, OS-rate, median PFS, PFS-rate livskvalitet ved EORTC QLQ-C30, ORR, Uønskede hændelser	16,3 måneder
Mazgani et al. 2008 [21]	-	Patienter med avanceret eller recidiverende endometriecancer	Retrospektivt kohortestudie.	Median OS, OS-rate, median PFS, PFS-rate, ORR	Ikke rapporteret
Miyake et al. 2011 [22]	-	Patienter med avanceret eller recidiverende endometriecancer	Retrospektivt kohortestudie	Median PFS, PFS-rate, ORR	Ikke rapporteret
Rubinstein et al. 2019 [16]	-	Patienter med avanceret eller recidiverende endometriecancer	Retrospektivt studie	Median OS, OS-rate, median PFS, PFS-rate, ORR	Ikke rapporteret
Nagao et al. 2013 [23]. Nagao et al. 2015 [24]	SGSG012/GOTIC004/Intergroup study	Patienter med avanceret eller recidiverende endometriecancer	Retrospektivt kohortestudie	Median OS, OS-rate, median PFS, PFS-rate, ORR	Ikke rapporteret
Ueda et al. 2011 [25]	-	Patienter med avanceret eller recidiverende endometriecancer	Retrospektivt kohortestudie	Median OS, median PFS, ORR	Ikke rapporteret

Publikationer	Klinisk forsøg, NCT-nummer	Population	Studietype, intervention og eventuel komparator	Inkluderede effektmål	Median opfølgningstid
Nomura et al. 2011 [26]	-	Patienter med avanceret eller recidiverende endometriecancer, hvoraf nogle har modtaget behandling i første linje med kemoterapi	Fase II-studie	Median PFS, PFR-rate, ORR	Ikke rapporteret
Vergote et al. 2015 [27]	-	Patienter med avanceret eller recidiverende endometriecancer, hvoraf nogle har modtaget behandling i første linje med kemoterapi	Fase II-studie	Median OS, OS-rate, median PFS, PFS-rate, ORR	Ikke rapporteret

OS: samlet overlevelse (*overall survival*), PFS: progressionsfri overlevelse (*progression free survival*), ORR: objektiv responsrate.

Dostarlimab er undersøgt i ét klinisk studie (GARNET), og data herfra er rapporteret i én fuldtekstartikel [18]. EPAR'en [19] og produktresumeet [20] for dostarlimab indeholder data fra et senere data cut-off med en større patientpopulation og længere opfølgningstid (16,3 måneders opfølgning i marts 2020 overfor 11,2 måneders opfølgning i juli 2019). I denne rapport anvendes udelukkende data fra data cut-off i marts 2020.

Ansøger har ikke identificeret studier, hvori der udføres en direkte sammenligning af dostarlimab og platinbaseret kemoterapi. I stedet har ansøger fundet syv studier, der undersøger effekten af komparatorerne, enten i prospektive studier eller i retrospektive kohortestudier. De syv studier er beskrevet i otte artikler.

GARNET

GARNET er et igangværende ikke-kontrolleret, fase I/II-studie, der undersøger effekten og sikkerheden af dostarlimab hos patienter med solide tumorer. Studiet består af to dele:

- Del 1, der undersøger sikkerhed, farmakokinetik, farmakodynamik og dosering.
- Del 2, der er yderligere inddelt i to dele:
    - Del 2A, der undersøger sikkerhed af dostarlimab ved 500 mg hver 3. uge og 1000 mg hver 6. uge.
    - Del 2B, der undersøger sikkerhed og kliniske effektivitet hos patienter med forskellige avancerede eller recidiverende solide tumorer. Del 2B består af to

kohorter, hvoraf den relevante er kohorte A1. I denne kohorte havde patienterne dMMR/MSI-H avanceret eller recidiverende endometriecancer.

Patienterne blev behandlet med 500 mg dostarliamb hver 3. uge i 4 serier efterfulgt af 1000 mg hver 6. uge indtil progression. Det primære endemål var objektiv responsrate (ORR) og responsvarighed (*duration of response*, DoR) målt ved RECIST 1.1. Sekundære endemål var immunrelateret ORR (iORR) målt ved irRECIST, samlet overlevelse (*overall survival*, OS) og progressionsfri overlevelse (*progression free* survival, PFS). Sikkerhed og livskvalitet blev også undersøgt i studiet.

129 patienter i den relevante kohorte fik dostarlimab. 20 patienter blev ekskluderet fra analysen, fordi de ikke havde målbar sygdom ved baseline. Én blev ekskluderet, fordi MMR-status var ukendt. To patienter var inkluderet i studiet med ukendt MMR-status, men med MSI-high bekræftet.

Komparatorstudier

Ansøger har fundet syv studier, der undersøger effekten af komparatorerne, enten i prospektive studier eller i retrospektive kohortestudier. Fem af komparatorstudierne, bestående af et fase II-klinisk studie og fire retrospektive kohortestudier, undersøger effekten af carboplatin i kombination med paclitaxel ved andenlinjebehandling af avanceret eller recidiverende endometriecancer. Fagudvalget har valgt at ekskludere de resterende to studier. Ét af komparatorstudierne (Vergote et al. 2015) undersøger effekt og bivirkninger ved en højere dosis af platinbaseret kemoterapi. Det andet studie (Nomura et al. 2011) er et faseII-studie, der undersøger effekten og sikkerheden af platinbaseret kemoterapi som første- eller andenlinjebehandling. Studiet indeholdt dog kun 4 ud af 30 patienter, der blev genbehandlet med carboplatin i kombination med paclitaxel. Da resultaterne kun er rapporteret for den samlede gruppe, er de ikke repræsentative for dette kliniske spørgsmål. De enkelte studier er kort beskrevet i bilaget (afsnit 11.2).

Baselinekarakteristika for patienterne i de inkluderede studier er angivet i tabellen nedenfor.

Tabel 5-2 Baselinekarakteristika

Lægemiddel		Dostarlimab	Platinbaseret kemoterapi					
Studie		**GARNET**	**Mazgani**	**Rubinstein**	**Nagao 2015**	**Miyake**		**Ueda**
Patientantal i relevant arm		108	31	20	127	12 (behandlings frit interval på 6-12 måneder)	17 (behandlin gs-frit interval >12 måneder)	40
Alder, median (range)		64,5 (39-80) år	-	67 (40-83) år	65 (37-80) år	-	-	-
Tumor histologi	Endometrioid	66 %			50 %			80 %
	Andre	34 %			50 %			20 %
ECOG performance status	0	39 %	-	-	-	-	-	-
	1	61 %	-	-	-	-	-	-
	≥ 2	0 %	-	-	-	-	-	-
Antal tidligere behandlings-linjer	0	0 %	-	-	-	-	-	-
	1	64 %	100 %	100 %	100 %	100 %	100 %	100 %
	2	25 %	-	-	-	-	-	-

Lægemiddel		Dostarlimab	Platinbaseret kemoterapi					
Studie		**GARNET**	**Mazgani**	**Rubinstein**	**Nagao 2015**	**Miyake**		**Ueda**
	> 2	11 %	-	-	-	-	-	-
	Median (range)	1	-	-	-	-	-	-
Progressionsfrit interval ved sidste forudgående behandlingslinje (median)		6,6 måneder	-Deler efter mere eller mindre end 12 måneder, men kun for ORR	Ingen under 6 måneder (range 7-78 måneder)	6-12 måneder: 27 % 12-24 måneder: 30 % ≥ 24 måneder: 27 %	7 måneder	12 måneder	-

Patienternes alder er sammenlignelig på tværs af studierne i de studier, hvor det er rapporteret. Ingen af studierne inkluderer behandlingsnaive patienter, hvilket er vigtigt for sammenligningen, da disse patienter generelt har en bedre prognose. Derudover er det vanskeligt at vurdere populationernes sammenlignelighed, da flere af komparatorstudierne angiver sparsomme baselinekarakteristika. Dette kan have stor betydning for vurderingen af resultaterne, da forskelle i prognostiske faktorer, bl.a. histologien (endometrioid/serøst eller clearcelle adenokarcinom eller karcinosarkom), molekylærbiologiske faktorer (særligt POLE og p53) og hormonreceptorpositivitet kan påvirke studieestimaterne i meget høj grad [11].

Samlet set kan det ikke konkluderes, om patientpopulationen i GARNET er forbundet med bedre eller dårligere prognose end populationerne i komparatorstudierne.

Fagudvalget vurderer, at der overordnet set ikke er væsentlige forskelle mellem studiepopulationen i GARNET og den forventede population i dansk klinisk praksis. Fagudvalget bemærker dog, at der i dansk klinisk praksis måske vil være flere patienter med mere komorbiditet, eventuelt flere patienter i performance status > 1. Brug af dostarlimab til disse patienter er kort berørt under 'andre overvejelser' (afsnit 6).

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt data fra de ovennævnte studier for effektmålene, OS, PFS, ORR og uønskede hændelser. Livskvalitet er kun undersøgt i GARNET. Ansøger har desuden indsendt fortrolige data for PFS-raten og livskvalitet samt Kaplan-Meier kurverne for OS og PFS fra GARNET fra samme data cut-off som i EMAs EPAR. Disse data besvarer effektmål i protokollens kliniske spørgsmål og lever op til Medicinrådets principper for anvendelse af upublicerede data, jf. Princippapir for anvendelse af upublicerede data i vurderinger af nye lægemidler og indikationsudvidelser.

Ansøger har udført en *matched adjusted indirect comparison* (MAIC)-analyse med udgangspunkt i data fra GARNET og Mazgani et al. for effektmålene OS, PFS og ORR. Ansøger har også foretaget en deskriptiv sammenligning af data fra de enkelte studier.

Medicinrådet kan ikke vurdere, i hvor høj grad ansøgers justerede analyser (MAIC) medfører en mere retvisende sammenligning end en deskriptiv analyse. Dette skyldes, at der kun har været meget begrænsede baselinekarakteristika tilgængelige til at foretage justeringerne i MAIC-analyserne. Medicinrådet finder derfor ikke, at MAIC-analyserne giver et mere retvisende billede af dostarlimabs effekt end en deskriptiv sammenligning af effektestimaterne fra studierne. Fagudvalget vælger derfor at lægge størst vægt på en deskriptiv gennemgang af studiedata og anvender alene resultaterne fra de justerede analyser som supplerende information. Fagudvalget er beviste om, at alle konklusioner er behæftet med stor usikkerhed.

I den deskriptive gennemgang fokuserer fagudvalget på samlede estimater for komparatoren på tværs af studierne, når flere studier rapporterer data for effektmålene. De samlede effektestimater er fremkommet ved at tage medianen af effektestimaterne

fra de enkelte studier. Medicinrådet vurderer, at analysen skal tages med store forbehold, men vurderer alligevel, at fremgangsmåden giver det mest komplette samlede billede af, hvilken effekt man kan forvente ved behandling med komparatorerne.

5.1.3 Evidensens kvalitet

Da vurderingen af dostarlimab er baseret på en deskriptiv sammenligning med platinbaseret kemoterapi, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Fraværet af data fra randomiserede kliniske undersøgelser medfører, at Medicinrådet vurderer evidensens kvalitet som meget lav.

Medicinrådet vurderer normalt studierne ved Cochrane risk of bias tool 2.0. Dette værktøj er designet til randomiserede kliniske studier, og kan derfor ikke anvendes meningsfuldt på studierne til klinisk spørgsmål 1.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra GARNET og de samlede estimater fra de studier, der undersøger behandling med platinbaseret kemoterapi. De samlede effektestimater for platinbaseret kemoterapi er fremkommet ved at tage medianen af de relevante effektestimater fra hvert studie. Skemaet indeholder dermed ikke estimater for absolutte eller relative forskelle mellem dostarlimab og platinbaseret kemoterapi. Effektestimaterne fra de enkelte studier af platinbaseret kemoterapi er tilgængelige i bilag 3 (Tabel 11-3).

Tabel 5-3 Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Dostarlimab (GARNET) Punktestimat [95 % konfidensinterval]	Samlet komparator (platinbaseret kemoterapi) Median (range)
			n = 108 / 129*	5 studier, n = 20-127
Overlevelse (OS)	Median OS (3 måneder)	Kritisk	Ikke nået [17,1 måneder; ikke nået]	21 måneder (13-48 måneder)
	OS-rate ved 12 måneder (5 %-point)		69,2 % [58,6; 77,6 %]	84 % (56-95 %)
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Kritisk	5,5 måneder [3,3 måneder; ikke nået]	10 måneder (5,5-13 måneder)
	PFS-rate ved 24 måneder (10 %-point)		[redacted]	18,5 % (6-50 %)
Livskvalitet	EORTC QLQ-EN24 i tillæg til EORTC-QLQ-C30. Gennemsnitlig ændring i post-basislinje relativt til basislinjen (10 point)	Vigtig	[redacted]	Ikke undersøgt
Objektiv responsrate (ORR)	Andel, der opnår komplet eller partielt respons (20 %-point)	Vigtig	43,5 % [34,0; 53,4 %]	53 % (42-59 %)
Uønskede hændelser	Andel, der oplever mindst én bivirkning af grad 3-4 (10 %-point)	Vigtig	13,2 %	Ikke angivet
	Deskriptiv gennemgang		Se gennemgang	Se gennemgang
Konklusion				

Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget kan ikke vurdere, om effekten af dostarlimab er forskellig fra effekten af platinbaseret kemoterapi, men fagudvalget vurderer, at dostarlimab er mindre bivirkningstungt end platinbaseret kemoterapi.
Kvalitet af den samlede evidens	Meget lav.

* Data for bivirkninger stammer fra sikkerhedspopulationen i EPAR, hvilket inkluderer 129, der alle er behandlet med minimum én dosis dostarlimab.

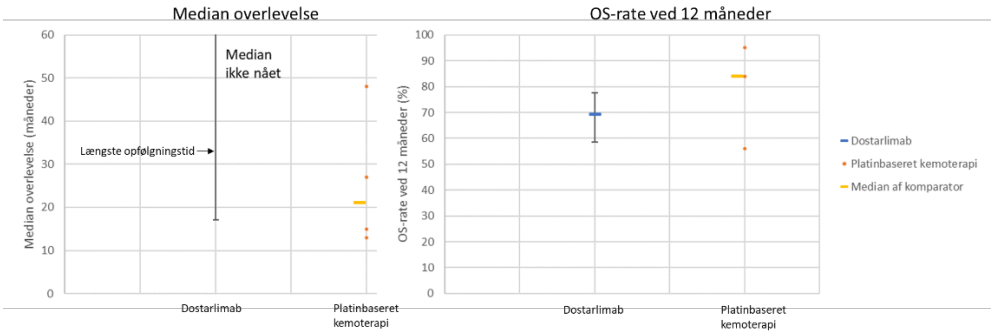
Samlet overlevelse (OS)
Som beskrevet i protokollen er effektmålet samlet overlevelse kritisk for vurderingen af lægemidlets værdi for patienterne, fordi forbedret OS med mindst mulig toksicitet er det optimale mål for kræftbehandling.

Patienterne behandlet med dostarlimab havde en median overlevelse, der ikke var nået (17,1 måneder; ikke nået) og en 12-måneders OS-rate på 69,2 % [58,6; 77,6 %]. Estimaterne er dog meget usikre, da der ved 16,3 måneders median opfølgningstid blot er indtruffet 35 dødsfald. Kaplan-Meier kurven for dostarlimab ses nedenfor.

Figur 5-1: Kaplan-Meier kurven for samlet overlevelse ved dostarlimab ved data cut-off i marts 2020. Median opfølgningstid er på dette tidspunkt 16,3 måneder.

Kurven indikerer, at der muligvis indtræffer et plateau i overlevelsesraten. Fagudvalget kan ikke på det nuværende grundlag vurdere, om dette er stabilt, da data stadig er umodne.

Medianen af estimaterne for median OS i komparatorstudierne var 21 måneder (13-48 måneder), og medianen af estimaterne for OS-raten ved 12 måneder for komparatorstudierne var 85 % (56-95 %) (se Figur 5-2). Kontrolestimaterne adskiller sig samlet set ikke klart fra dostarlimab. Derudover indikerer ansøgers MAIC-analyse ikke, at dostarlimab medfører en signifikant bedre overlevelse end platinbaseret kemoterapi (HR = 0,56 [0,26; 1,22].



Figur 5-2: Samlede estimater for dostarlimab og platinbaseret kemoterapi i forhold til median overlevelse (venstre) og OS-raten ved 12 måneder (højre). De vandrette streger viser punktestimaterne for medianerne/OS-raterne, fejllinjerne viser 95 % konfidensinterval omkring medianen for dostarlimab, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Dostarlimabs værdi overfor platinbaseret kemoterapi kan ikke kategoriseres for samlet overlevelse, pga. manglende komparative data. Fagudvalget kan ikke vurdere, om dostarlimab har en anderledes effekt på den samlede overlevelse end platinbaseret kemoterapi. Den store forskel i overlevelsesestimaterne mellem komparatorstudierne gør det svært for fagudvalget at vurdere dostarlimabs effekt, når der ikke kan laves en direkte sammenligning med komparatoren. Desuden er overlevelsesdata for dostarlimab umodne, hvorved der er stor usikkerhed om estimaterne for interventionen.

Progressionsfri overlevelse

Som beskrevet i protokollen er effektmålet progressionsfri overlevelse (PFS) kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det afspejler sygdomsbyrden samt varigheden af effekten.

Kaplan-Meier kurven for PFS ved behandling med dostarlimab er vist nedenfor (Figur 5-3).

Figur 5-3: Kaplan-Meier kurven for progressionsfri overlevelse ved dostarlimab ved data cut-off i marts 2020. Median opfølgningstid er på dette tidspunkt 16,3 måneder.

[redacted] hvilket stemmer overens med en lang responsvarighed forbundet med dostarlimab (80 % [57; 92 %] opretholder deres respons efter 18 måneder). Dette kunne indikere, at dMMR/MSI-H er en god selektionsmarkør for immunterapis effekt ved endometriecancer, da fagudvalget ville forvente væsentlig færre langtidsrespondere i en ikke-selekteret population.

Patienterne behandlet med dostarlimab havde en median PFS på 5,5 måneder (3,3 måneder; ikke nået) og en 24-måneders PFS-rate på [redacted]). Punktestimaterne er dog behæftet med stor usikkerhed, hvilket tydeliggøres af konfidensintervallet omkring PFS-medianen og det lille patientantal i opfølgning ved 24 måneder [redacted]

Medianen af estimaterne for median PFS i komparatorstudierne var 10 måneder (5,5-13 måneder), og medianen af estimaterne for PFS-raten ved 24 måneder for komparatorstudierne var 18,5 % (6-50 %) (Figur 5-4). Fagudvalget har set bort fra ansøgers MAIC-analyser vedr. PFS, da behandlingerne medfører vidt forskellige forløb, hvor *proportional hazards* mellem forløbene ikke kan antages.

Figur 5-4: Samlede estimater for dostarlimab og platinbaseret kemoterapi i forhold til median progressionsfri overlevelse (venstre) og PFS-raten ved 24 måneder (højre). De vandrette streger viser punktestimaterne for medianerne/OS-raterne, fejllinjerne viser 95 % konfidensinterval omkring medianen for dostarlimab, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Dostarlimabs værdi overfor platinbaseret kemoterapi kan ikke kategoriseres for PFS, pga. manglende komparative data. Det store konfidensinterval omkring PFS-medianen for dostarlimab, og den store forskel i PFS mellem komparatorstudierne gør det svært for fagudvalget at vurdere dostarlimabs effekt overfor platinbaseret kemoterapi.

Fagudvalget bemærker dog, at især PFS-raten ved 24 måneder peger i retning af, at en væsentlig andel af patienterne har vedvarende gavn af behandling med dostarlimab. Dette observeres ikke på samme måde hos patienter, der får genbehandling med platinbaseret kemoterapi, hvilket stemmer overens med fagudvalgets kliniske erfaring med behandling med komparatorerne.

Livskvalitet

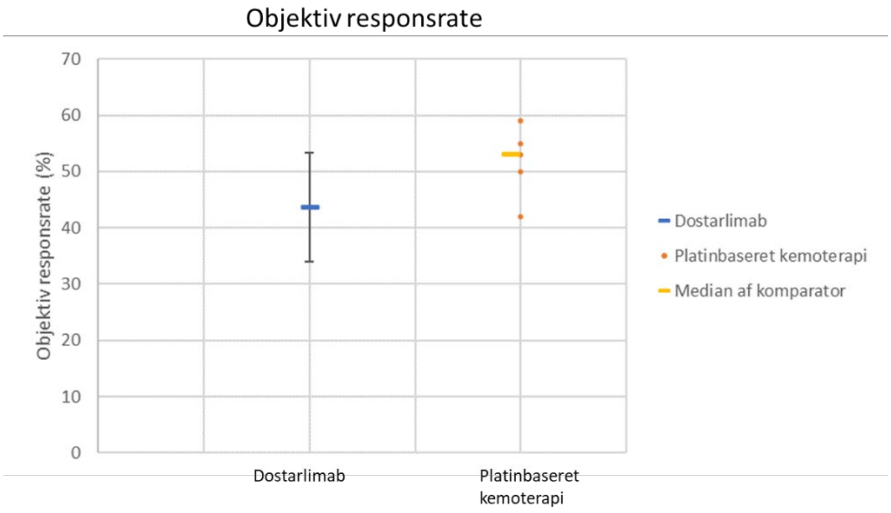
Som beskrevet i protokollen er effektmålet livskvalitet vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi behandling med dostarlimab er livsforlængende og ikke-kurativ.

Behandling med dostarlimab [redacted]

Dostarlimabs værdi overfor platinbaseret kemoterapi kan ikke kategoriseres for livskvalitet, pga. manglende komparative data. Fagudvalget fremhæver, at den overordnede livskvalitet udvikler sig positivt ved behandling med dostarlimab, hvilket ikke forventes ved behandling med platinbaseret kemoterapi. Den positive udvikling, som ses ved behandling med dostarlimab, understreges af de underliggende domæner, der alle udvikles i positiv retning. Det er dog svært at vurdere dostarlimabs effekt på livskvaliteten, da der kun foreligger ikke-kontrollerede data, og det er svært at vurdere, om de er repræsentative for studiepopulationen pga. manglende svar fra nogle patienter. Fagudvalget fremhæver dog, at de nuværende data afkræfter, at behandling med dostarlimab kunne medføre et generelt fald i patienternes livskvalitet.

Objektiv responsrate

Som beskrevet i protokollen er effektmålet objektiv responsrate (ORR) vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi tumorsvind ofte vil afspejles i patienternes sygdomsbyrde, hvilket kan associeres med forventet øget livskvalitet.



Figur 5-5: Samlede estimater for dostarlimab og platinbaseret kemoterapi for ORR. De vandrette streger viser punktestimaterne for ORR, fejllinjen viser 95 % konfidensintervallet omkring ORR

for dostarlimab, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

ORR var 43,5 % (34,0; 53,4 %) for patienter, der modtog dostarlimab. Medianen af estimaterne for ORR i komparatorstudierne var 53 % (42-59 %) (Figur 5-5).

Dostarlimabs værdi overfor platinbaseret kemoterapi kan ikke kategoriseres for ORR, pga. manglende komparative data. Fagudvalget vurderer, at intet i det nuværende datagrundlag indikerer, at ORR for dostarlimab adskiller sig nævneværdigt fra platinbaseret kemoterapi. Fagudvalget bemærker dog, at responsvarigheden ved dostarlimab er usædvanlig lang (80 % [57; 92 %] ved 18 måneder), og at de ikke forventer en lignende responsvarighed ved platinbaseret kemoterapi.

Bivirkninger og uønskede hændelser
Som beskrevet i protokollen er effektmålet bivirkninger/uønskede hændelser vigtigt for vurderingen af lægemidlets værdi for patienterne.

Kvantitativ sammenligning
Ved dostarlimab oplevede 13,2 % af patienterne minimum én uønsket hændelse af grad 3-4, der var relateret til lægemidlet (bivirkning/*adverse reaction*). Ingen af studierne af komparatorerne har opgjort dette, og fagudvalget kan derfor ikke lave en kvantitativ bedømmelse af bivirkningerne ved dostarlimab overfor komparatorerne.

Deskriptiv sammenligning
Af EMA's produktresumé fremgår det, at de hyppigste bivirkninger ved behandling med dostarlimab var anæmi, kvalme, diarré, opkast, ledsmerter, hudkløe, udslæt, feber og lavt stofskifte. Bivirkninger førte til behandlingsophør hos 3,3 % af patienterne. I de fleste tilfælde var årsagen immunrelaterede hændelser.

Immunrelaterede hændelser opstod hos 179 ud af 515 patienter (34,8 %), der modtog behandling med dostarlimab. De hyppigste immunrelaterede hændelser var diarré (7,2 %) og nedsat stofskifte (7,2 %). De fleste hændelser, uanset sværhedsgraden, var reversible efter behandlingsophør eller medicinsk behandling af hændelsen. Fagudvalget bemærker, at konsekvensen af immunrelaterede hændelser normalt er pausering og i alvorlige tilfælde behandlingsophør.

Fagudvalget har stor klinisk erfaring med behandling med platinbaseret kemoterapi, hvilket ligger til grund for den deskriptive gennemgang. De hyppigste bivirkninger ved platinbaseret kemoterapi er hæmatologiske bivirkninger, heriblandt febril neutropeni. Derudover er kvalme, træthed, nyrepåvirkning, neuropati og påvirkning af slimhinder hyppige. Fagudvalget vurderer, at disse bivirkninger kan være generende for patienterne og påvirke deres daglige funktionsniveau. Fagudvalget bemærker særligt neuropati, der opstår hos 20-25 % af patienterne, særligt pga. paclitaxel. Neuropati påvirker ofte patientens daglige funktionsniveau og forårsager smerte. Fagudvalget gør opmærksom på, at behandling med kemoterapi ofte gives i serier, hvorfor de fleste bivirkninger vil være begrænset til en kortere periode. Dette gælder dog ikke for neuropati, hvor påvirkningerne kan være livslange.

Samlet set kan dostarlimabs værdi ift. bivirkninger overfor platinbaseret kemoterapi ikke kategoriseres. Fagudvalget vurderer, at dostarlimab er mindre bivirkningstungt, baseret på bivirkningsprofilerne og fagudvalgets kliniske erfaring med checkpoint inhibitor-immunterapi og platinbaseret kemoterapi.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af dostarlimab sammenlignet med genbehandling med platinbaseret kemoterapi til patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret 6 måneder eller mere efter behandling med platinbaseret kemoterapi, **ikke kan kategoriseres**.

Fagudvalget har sammenlignet effekten af dostarlimab med komparatorerne ved at foretage en deskriptiv sammenligning af effektestimater fra et ukontrolleret studie af dostarlimab med effektestimater fra en blanding af prospektive kliniske studier og retrospektive kohortestudier af komparatorerne. Derved er der stor usikkerhed omkring effektestimaterne, og i hvor høj grad de er sammenlignelige.

Fagudvalget er tilbageholdende med at udtale sig om den samlede effekt af dostarlimab på det nuværende usikre datagrundlag. Samlet set indikerer de nuværende data ikke, at effekten af dostarlimab er væsentlig forskellig fra effekten af platinbaseret kemoterapi til denne patientgruppe. Fagudvalget bemærker dog, at PFS-raten ved 24 måneder indikerer, at dostarlimab har et potentiale til at have en langvarig effekt hos en stor andel af patienterne. Derudover progredierer patienter uden respons hurtigt på dostarlimab, hvorved langtidsbehandling kun vil finde sted for patienter, der har gavn af det.

Den høje andel af langtidsprogressionsfri patienter kan have en positiv effekt på den samlede overlevelse, men overlevelsesdata er imidlertid for umodne til at vurdere, om dette er tilfældet. Fagudvalget vurderer, at sikkerhedsprofilen er bedre for dostarlimab end platinbaseret kemoterapi.

Fagudvalget bemærker, at det ikke-kontrollerede studie af dostarlimab (GARNET) stadig er igangværende, og forventer derfor, at yderligere data med længere opfølgningstid vil blive tilgængelige efter indsendelse til EMA i slutningen af 2022. Ydermere er fagudvalget bekendt med, at dostarlimab undersøges i kombination med platinbaseret kemoterapi som førstelinjebehandling til dMMR-MSI-high avanceret eller recidiverende endometriecancer i et fase III-randomiseret klinisk studie. Selvom dette er en kombinationsbehandling, og patientpopulationen har en bedre prognose, forventer fagudvalget, at dette studie vil højne evidenskvaliteten for dostarlimabs effekt på sygdommen betragteligt. Data fra dette studie forventes indsendt til EMA i slutningen af 2022.

5.2 Klinisk spørgsmål 2

Klinisk spørgsmål 2:

Hvilken værdi har dostarlimab sammenlignet med placebo for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?

Ansøger har ikke identificeret studier, der belyser effekten af placebo eller ingen behandling for denne patientgruppe. Ansøger har derved ikke indleveret data, der kan besvare dette spørgsmål, og fagudvalget afstår fra at vurdere det kliniske spørgsmål. Fagudvalget bemærker dog, at patienter, der ikke modtager behandling, samlet set vil klare sig marginalt dårligere end patienterne i klinisk spørgsmål 3. Derfor kan vurderingen i klinisk spørgsmål 3 afspejle en konservativ vurdering af dostarlimabs effekt ift. klinisk spørgsmål 2.

5.3 Klinisk spørgsmål 3

Klinisk spørgsmål 3:

Hvilken værdi har dostarlimab sammenlignet med pegyleret liposomalt doxorubicin for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?

5.3.1 Litteratur

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

I Medicinrådets protokol for vurdering vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden er komparatoren for klinisk spørgsmål 3 defineret som pegyleret liposomalt doxorubicin (PLD) [28]. Denne behandling er ikke godkendt af EMA til indikationen, men anses som standard i dansk klinisk praksis [5]. Fagudvalget angiver endvidere, at de ønsker at få data, der beskriver effekt og bivirkning af doxorubicin, hvis der ikke findes tilstrækkelige data til at beskrive PLD. Dette skyldes, at fagudvalget vurderer, at den antineoplastiske effekt af doxorubicin og PLD er sammenlignelig, baseret på et tidligere komparativt studie [29].

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt 5 fuldtekstartikler samt én klinisk rapport fra et studie, der ikke medførte en publiceret fuldtekstartikel.

Tabel 5-4 Oversigt over studier til besvarelse af klinisk spørgsmål 3

Publikationer	Klinisk forsøg, NCT-nummer	Population	Studietype, intervention og eventuel komparator	Inkluderede effektmål	Median opfølgningstid
Oaknin et al. 2020 [18] EPAR [19] og produktresume [20] for dostarlimab	GARNET, NCT02715284	Patienter med avanceret eller recidiverende endometriecancer, der tidligere er behandlet med platinbaseret kemoterapi. Alle patienter har dMMR/MSI-H	Fase I-II, ikke-kontrolleret klinisk studie. Dostarlimab	Median OS, OS-rate, median PFS, PFS-rate, livskvalitet ved EORTC QLQ-C30, ORR, Uønskede hændelser	16,3 måneder
Julius et al. 2013 [30]	-	Patienter med recidiverende endometriecancer behandlet på ét center i perioden 1996-2006. Alle var tidligere behandlet med minimum et kemoterapiregime.	Retrospektivt kohorte-studie. Pegyleret liposomalt doxorubicin	Median OS, OS-rate, median PFS	-
Muggia et al. 2002 [17]	-	Patienter med recidiverende eller persisterende endometriecancer, der tidligere har gennemgået minimum én systemisk behandlingslinje.	Prospektivt fase-II studie, ikke-kontrolleret. Pegyleret liposomalt doxorubicin.	Median OS, ORR	Ikke rapporteret.
Makker et al. 2013 [31]	-	Patienter med recidiverende endometriecancer behandlet på ét center i perioden 1995-2009. Alle patienterne var tidligere behandlet med platinbaseret kemoterapi	Retrospektivt kohorte-studie. Doxorubicin	Median OS, OS-rate, median PFS, PFS-rate, ORR	Ikke rapporteret

Publikationer	Klinisk forsøg, NCT-nummer	Population	Studietype, intervention og eventuel komparator	Inklude-rede effektmål	Median opfølg-ningstid
McMeekin et al. 2015 [32]	IXAMPLE 2, NCT00883116	Patienter med avanceret eller recidiverende endometriecancer, der tidligere har gennemgået minimum én behandlingslinje med platinbaseret kemoterapi	Prospektivt fase III, randomiseret klinisk studie. Ixabepilone vs. Paclitaxel eller doxorubicin.	Median OS, OS-rate, median PFS, ORR	29,6 måneder
ZoptEC [33]	ZoptEC, NCT01767155	Patienter med avanceret eller recidiverende endometriecancer, der tidligere har gennemgået minimum én behandlingslinje med platinbaseret kemoterapi	Prospektivt fase III, randomiseret klinisk studie. zoptarelin vs. doxorubicin.	Median OS, OS-rate, median PFS, livskvalitet ved EORTC QLQ-C30	Ikke rappor-teret

OS: samlet overlevelse (*overall survival*), PFS: progressionsfri overlevelse (*progression free survival*), ORR: objektiv responsrate.

Dostarlimab er undersøgt i ét klinisk studie (GARNET), og data herfra er rapporteret i én fuldtekstartikel [18]. EPAR'en [19] og produktresumeet [20] for dostarlimab indeholder dog data fra et senere data cut-off med en større patientpopulation og længere opfølgningstid (16,3 måneders opfølgning i marts 2020 overfor 11,2 måneders opfølgning i juli 2019). I denne rapport anvendes udelukkende data fra data cut-off i marts 2020.

GARNET og den relevante patientpopulation er begge beskrevet under klinisk spørgsmål 1 (afsnit 5.1.1).

Ansøger har ikke identificeret studier, hvori der udføres en direkte sammenligning af dostarlimab og komparatorerne. I stedet har ansøger fundet fem studier, der undersøger effekten af komparatorerne. Tre af studierne er prospektive studier, mens to er retrospektive kohortestudier. To af studierne undersøger effekten af PLD (Julius et al. og Muggia et al.), mens tre studier undersøger effekten af doxorubicin (Makker et al., IXAMPLE2 og ZoptEC). De enkelte studier er kort beskrevet i Bilag 2.

Baselinekarakteristika for patienterne i de inkluderede studier er angivet i tabellen nedenfor.

Tabel 5-5 Baselinekarakteristika for patienterne i studierne, der anvendes til besvarelse af klinisk spørgsmål 2

Lægemiddel		**Dostarlimab**	**Pegyleret liposomalt doxorubicin (PLD)**		**Doxorubicin**		
Studie		**GARNET**	**Julius et al.** [30]	**Muggia et al.** [17]	**Makker et al.** [31]	**IXAMPLE2** [32]	**ZoptEC** [33]
Patientantal i relevant arm		108	41	42	17	248	255
Alder, median (range)		64,5 (39-80)	67 (34-84)	62,5 (40-79)	56 (36-78)	64 (33-88)	64 (28-87)
Tumor histologi	Endometrioid	66 %	-	-	29 %	56 %	64 %
	Andre	34 %	-	-	71 %	44 %	36 %
ECOG performance status	0	39 %	-	45 %	47 %	-	49 %
	1	61 %	-	40 %	41 %	-	46 %
	≥ 2	0 %	-	14 %	12 %	-	4 %
Antal tidligere behandlingslinjer	0	0 %	0 %	0 %	0 %	0 %	0 %
	1	64 %	-	100 %	100 %	-	-
	2	25 %	-	0 %	0 %	-	-
	> 2	11 %	-	0 %	0 %	-	-
	Median (range)	1	3 (1-5)	1 (1)	1 (1)	-	-

Lægemiddel	Dostarlimab	Pegyleret liposomalt doxorubicin (PLD)		Doxorubicin		
Studie	**GARNET**	**Julius et al.** [30]	**Muggia et al.** [17]	**Makker et al.** [31]	**IXAMPLE2** [32]	**ZoptEC** [33]
Progressionsfrit interval ved sidste forudgående behandlingslinje (median)	6,6 måneder	-	-	-	-	-

Det er vanskeligt at vurdere populationernes sammenlignelighed, da flere af komparatorstudierne angiver sparsomme baselinekarakteristika. Ingen af studierne inkluderer behandlingsnaive patienter, hvilket er vigtigt for sammenligningen, da disse patienter generelt har en bedre prognose. Derudover er patienternes alder sammenlignelig på tværs af studierne.

Tre af komparatorstudierne rapporterer ECOG performance status. Overordnet set var en marginalt større del af patienterne i performance score 0 i komparatorstudierne. Dette opvejes dog af, at komparatorstudierne inkluderede patienter med performance score 2 (4-14 %), hvorimod disse patienter var ekskluderet i GARNET. Samlet set kan det ikke konkluderes, om patientpopulationen i GARNET er forbundet med bedre eller dårligere prognose end populationerne i komparatorstudierne.

Fagudvalget vurderer, at der overordnet set ikke er væsentlige forskelle mellem studiepopulationen i GARNET og den forventede population i dansk klinisk praksis. Fagudvalget bemærker dog, at der i dansk klinisk praksis måske vil være flere patienter med mere komorbiditet, eventuelt flere patienter i performance status > 1. Brug af dostarlimab til disse patienter er kort berørt under 'andre overvejelser' (afsnit 6).

5.3.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har indsendt data fra de ovennævnte studier for alle effektmålene, selvom nogle af komparatorstudierne kun rapporterer nogle af effektmålene. Ansøger har foretaget en deskriptiv gennemgang af studierne og angivet de tilgængelige effektestimater direkte fra studierne. Desuden har ansøger foretaget justerede sammenligninger (MAIC), hvor OS ved dostarlimab sammenlignes med OS ved doxorubicin ud fra studiedata fra IXAMPLE2 og ZoptEC og med PLD ud fra studiedata fra Julius et al. Yderligere blev ORR for dostarlimab sammenlignet med ORR for doxorubicin ud fra data fra IXAMPLE2.

Medicinrådet kan ikke vurdere, i hvor høj grad ansøgers justerede analyser medfører en mere retvisende sammenligning end en deskriptiv analyse. Dette skyldes, at der er meget begrænsede informationer, angående hvilke prognostiske variable der er justeret for, og hvor meget disse prognostiske variable betyder i forhold til andre variable, der ikke er justeret for. Fagudvalget vælger derfor at lægge størst vægt på en deskriptiv gennemgang af studiedata og anvender alene resultaterne fra de justerede analyser som supplerende information. Dette betyder, at alle fagudvalgets konklusioner er behæftet med stor usikkerhed.

I den deskriptive gennemgang fokuserer fagudvalget på de samlede estimater for komparatoren på tværs af studierne, når flere studier rapporterer data for effektmålene. Fagudvalget har valgt at lave samlede effektestimater for komparatoren, uagtet om effektestimaterne er fra studier af doxorubicin eller PLD. Dette skyldes, at fagudvalget anser effekten af doxorubicin og PLD for sammenlignelig. Bivirkningsprofilerne er dog forskellige for de to stoffer, og derfor foretager fagudvalget en deskriptiv gennemgang af

dostarlimabs bivirkninger overfor både doxorubicin og PLD. De samlede effektestimater er fremkommet ved at tage medianen af effektestimaterne fra de enkelte studier. Medicinrådet vurderer, at analysen skal tages med store forbehold, men vurderer alligevel, at fremgangsmåden giver det mest komplette samlede billede af, hvilken effekt man kan forvente ved behandling med komparatorerne.

5.3.3 Evidensens kvalitet

Da vurderingen af dostarlimab er baseret på en deskriptiv sammenligning med pegyleret liposomalt doxorubicin og doxorubicin, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Fraværet af data fra randomiserede kliniske undersøgelser af dostarlimab medfører, at Medicinrådet vurderer evidensens kvalitet som meget lav.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Dette værktøj er designet til randomiserede kliniske studier. Derfor er vurderingerne kun foretaget for IXAMPLE2 (doxorubicin, Tabel 11-1) og ZoptEC (doxorubicin, Tabel 11-2).

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne fra GARNET og de samlede komparatorestimater fra studierne, der undersøger behandling med doxorubicin eller PLD. De samlede effektestimater for PLD/doxorubicin er fremkommet ved at tage medianen af de relevante effektestimater fra hvert studie. Skemaet indeholder dermed ikke estimater for absolutte eller relative forskelle mellem dostarlimab og PLD/doxorubicin. Effektestimaterne fra de enkelte studier af PLD og doxorubicin er tilgængelige i bilag 3 (Tabel 11-4).

Tabel 5-6 Resultater for klinisk spørgsmål 3

Effektmål	Målenhed (MKRF)	Vigtighed	Dostarlimab (GARNET) Punktestimat [95 % konfidensinterval]	Samlet komparator (doxorubicin og pegyleret liposomalt doxorubicin) Median (range)
			n = 108 / 129*	4 studier, n = 290 / 625
Overlevelse (OS)	Median OS (3 måneder)	Kritisk	Ikke nået [17,1 måneder; ikke nået]	8,2 måneder (5,8-12,3 måneder)
	OS-rate ved 12 måneder (5 %-point)		69,2 % [58,6; 77,6 %]	46,3 % (28-52 %)
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Kritisk	5,5 måneder [3,3 måneder; ikke nået]	4,4 måneder (2,1-7 måneder)
	PFS-rate ved 24 måneder (10 %-point)		[redacted]	0 % (kun ét estimat)
Livskvalitet	EORTC QLQ-EN24 i tillæg til EORTC-QLQ-C30. Gennemsnitlig ændring i post-basislinje relativt til basislinjen (10 point)	Vigtig	[redacted]	-11,7 point (kun ét estimat)
Objektiv responsrate (ORR)	Andel, der opnår komplet eller partielt respons (20 %-point)	Vigtig	43,5 % [34,0; 53,4 %]	11,8 % (0-15,7 %)
Uønskede hændelser	Andel, der oplever mindst én bivirkning af grad 3-4 (10 %-point)	Vigtig	13,2 %	Ikke rapporteret
	Deskriptiv gennemgang		Se gennemgang	Se gennemgang
Konklusion				

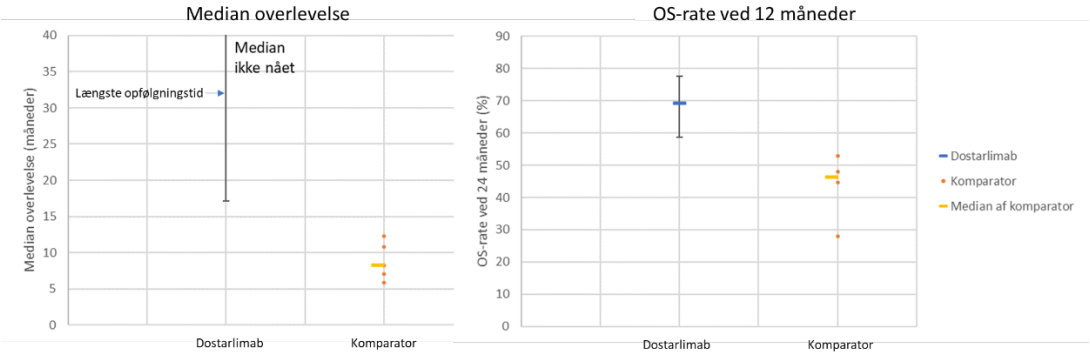
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at dostarlimab er mere effektivt og mindre bivirkningstungt end komparatorerne.
Kvalitet af den samlede evidens	Meget lav.

* Data for bivirkninger stammer fra sikkerhedspopulationen i EPAR, hvilket inkluderer 129, der alle er behandlet med minimum én dosis dostarlimab.

Overlevelse (OS)

Patienterne behandlet med dostarlimab havde en median overlevelse, der ikke var nået (17,1 måneder; ikke nået) og en 12-måneders OS-rate på 69,2 % [58,6; 77,6 %]. Estimaterne er dog meget usikre, da der ved 16,3 måneders median opfølgningstid blot er indtruffet 35 dødsfald.

For den samlede komparatorgruppe var den mediane overlevelse 8,2 måneder (5,8-12,3 måneder), og OS-raten ved 12 måneder var 46,3 % (28-52 %) (se Figur 5-6).



Figur 5-6: Samlede estimater for dostarlimab og komparatorer i forhold til median overlevelse (venstre) og OS-raten ved 12 måneder (højre). De vandrette streger viser punktestimaterne for medianerne/OS-raterne, fejllinjerne viser 95 % konfidensinterval omkring medianen for dostarlimab, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Værdien af dostarlimab overfor komparatorerne kan ikke kategoriseres ift. OS grundet manglende komparative data. Desuden er overlevelsesdata for dostarlimab stadig umodne, hvorved der er stor usikkerhed om estimaterne for interventionen. Fagudvalget vurderer alligevel, at data indikerer, at dostarlimab medfører en længere overlevelse for patientpopulationen, hvor alternativet er behandling med PLD eller doxorubicin. De nedre grænser for konfidensintervallerne omkring punktestimaterne overstiger klart den samlede median for komparatorerne, og ingen af de enkeltstående komparatorstudier rapporterer estimater inden for konfidensintervallet for dostarlimab. Fagudvalget bemærker endvidere, at ansøgers justerede analyser også indikerer, at dostarlimab medfører en længere overlevelse end komparatorerne, hvor hazard ratios er henholdsvis 0,41, 0,29 og 0,41 overfor IXAMPLE2, Julius et al. og ZoptEC (alle tre statistisk signifikante og klinisk relevante). Fagudvalget kan ikke lave en kvantitativ vurdering af, hvor meget længere overlevelse man kan forvente at opnå ved behandling med dostarlimab, grundet de umodne data for dostarlimab og de overordnede usikkerheder ved sammenligningerne.

Progressionsfri overlevelse (PFS)

Patienterne behandlet med dostarlimab havde en median PFS på 5,5 måneder (3,3 måneder; ikke nået) og en 24-måneders PFS-rate på [redacted] Punktestimaterne er dog behæftet med stor usikkerhed, hvilket tydeliggøres af konfidensintervallet omkring PFS-medianen og det lille patientantal i opfølgning ved 24 måneder [redacted]

For den samlede komparatorgruppe var median PFS 4,4 måneder (2,1-7 måneder), og PFS-raten ved 24 måneder var 0 % (kun ét estimat) (se Figur 5-7).

Figur 5-7: Samlede estimater for dostarlimab og komparatorer i forhold til median progressionsfri overlevelse (venstre) og PFS-raten ved 24 måneder (højre). De vandrette streger viser punktestimaterne for medianerne/OS-raterne, fejllinjerne viser 95 % konfidensinterval omkring medianen for dostarlimab, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Værdien af dostarlimab overfor komparatorerne kan ikke kategoriseres ift. PFS grundet manglende komparative data.

Fagudvalget vurderer, at dostarlimab er et væsentligt bedre alternativ end komparatorerne bedømt ud fra PFS som samlet effektmål. Dostarlimab medfører sandsynligvis ikke en længere progressionsfri overlevelse end komparatorerne, hvis effekten bedømmes ud fra median PFS. Derimod medfører dostarlimab tilsyneladende en betydelig andel af langtidsprogressionsfri patienter, hvilket ikke afspejles i medianestimatet. Dette observeres ikke i de kliniske studier af PLD eller doxorubicin, hvilket stemmer overens med fagudvalgets kliniske erfaring med komparatorerne.

Livskvalitet

Behandling med dostarlimab

For komparatorerne findes der kun livskvalitetsdata fra ZoptEC. Her oplevede patienterne under behandling med doxorubicin en udvikling i EORTC QLQ-C30 global health scale på -11,7 [-15; -8,4]. Samtidig sås en negativ udvikling i flere funktionsparametre (særligt fysisk funktion og rollefunktion) og symptomparametre (tab af appetit, træthed og åndenød). Disse data er opnået ved behandling med doxorubicin, og fagudvalget forventer, at PLD kan medføre mindre påvirkninger af patienternes livskvalitet, da PLD ifølge fagudvalgets erfaringer generelt er mindre bivirkningstungt end doxorubicin.

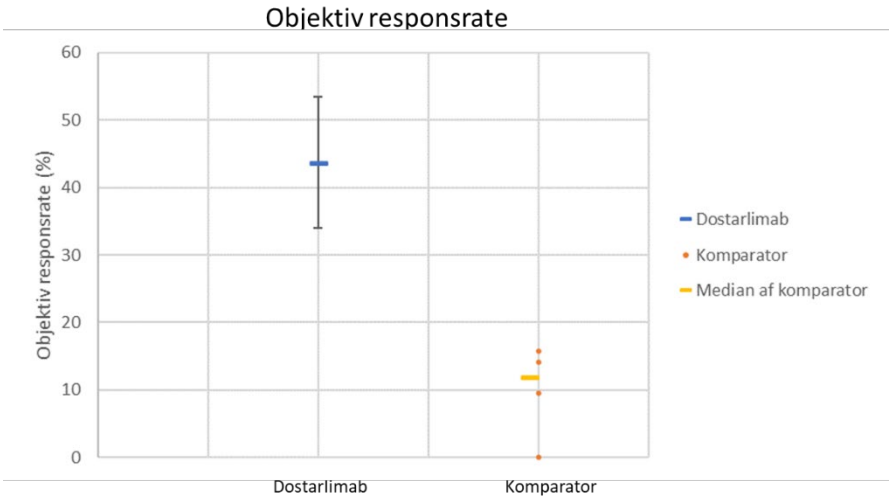
Værdien af dostarlimab overfor komparatorerne kan ikke kategoriseres ift. livskvalitet grundet manglende komparative data. Fagudvalget vurderer, at dostarlimab muligvis medfører en bedre livskvalitet, i hvert fald for en andel af patienterne under behandling. Fagudvalget fremhæver

desuden, at de nuværende data afkræfter, at behandling med dostarlimab generelt medfører fald i patienternes livskvalitet.

Komparatorerne medfører sjældent en forbedring af patienternes livskvalitet både bedømt ud fra det ene kliniske studie og fagudvalgets kliniske erfaringer. Fagudvalget er dog meget tilbageholdent med at drage konklusioner omkring livskvalitet bedømt ud fra et ikke-kontrolleret studie. Livskvalitetsdata er en subjektiv vurdering, hvor patienternes viden om at modtage aktiv behandling i sig selv kan medføre en positiv effekt.

Objektiv responsrate (ORR)
Ved dostarlimab havde 47 ud af 108 patienter (43,5 %) et objektivt respons. Af disse havde 11 patienter (10,2 %) et komplet respons og 36 patienter (33,3 %) et partielt respons. Af de resterende patienter havde 13 (12,0 %) stabil sygdom.

I den samlede komparatorgruppe havde 11,8 % (0-15,7 %) et objektivt respons. Komplette respondere var sjældne i komparatorstudierne, hvor 5 patienter (2 %) havde komplet respons i ZoptEC, mens der ikke var nogen komplette respondere i de andre studier. ORR for dostarlimab og komparatorerne er sammenlignet i Figur 5-8.



Figur 5-8: Samlede estimater for dostarlimab og komparatorerne i forhold til objektiv responsrate. De vandrette streger viser punktestimaterne, fejllinjerne viser 95 % konfidensinterval omkring estimatet for dostarlimab, og prikkerne viser estimaterne fra de enkelte studier, der indgår i komparatorgruppen.

Værdien af dostarlimab overfor komparatorerne kan ikke kategoriseres ift. ORR grundet manglende komparative data. Fagudvalget vurderer, at dostarlimab medfører en højere ORR end komparatorerne, da hele konfidensintervallet omkring punktestimatet for dostarlimab er klart afgrænset fra alle komparatorestimater. Fagudvalget kan ikke vurdere, om forskellen opnår den mindste klinisk relevante forskel på 20 %-point, men bemærker alligevel, at data indikerer, at dostarlimab er væsentlig mere effektivt end komparatorerne for dette effektmål. Det skyldes, at et respons på dostarlimab er forbundet med en meget lang responsvarighed, hvor 80 % [57; 92 %] stadig opretholder deres respons efter 18 måneder.

Bivirkninger og uønskede hændelser

Kvantitative sammenligninger
Ved dostarlimab oplevede 13,2 % minimum én uønsket hændelse af grad 3-4, der var relateret til lægemidlet (bivirkning/*adverse reaction*). Ingen af studierne af komparatorerne har opgjort dette, og fagudvalget kan derfor ikke lave en kvantitativ bedømmelse af bivirkningerne ved dostarlimab overfor komparatorerne.

Deskriptiv gennemgang
Bivirkningsprofilen for dostarlimab er beskrevet i afsnit 5.1.4.

Doxorubicin kan medføre en række bivirkninger, ofte af alvorlig grad. Hæmatologiske bivirkninger som neutropeni, anæmi og leukopeni er hyppige og ofte i alvorlig grad. Derudover er træthed, kvalme og hårtab hyppigt forekommende. Palmar-plantar erytrodysæstesi (hånd-fod-syndrom) opstår også hyppigt og kan være meget generende for patienterne og medføre dosisreduktion eller behandlingsstop. Doxorubicin kan medføre hjertesvigt, særligt ved længere tids behandling. Fagudvalget betragter samlet set doxorubicin som en meget bivirkningstung behandling.

PLD har en anderledes bivirkningsprofil end doxorubicin. Kvalme og hårtab forekommer sjældent, mens hånd-fod-syndrom, slimhindeirritation og eksem er hyppigere og ofte i mere udtalt grad. Dette kan i nogle tilfælde medføre behandlingsstop eller dosisreduktion. PLD medfører meget sjældnere alvorlig hjertetoxicitet end doxorubicin.

Samlet set kan dostarlimabs værdi ift. bivirkninger overfor PLD eller doxorubicin ikke kategoriseres. Fagudvalget vurderer, at dostarlimab er mindre bivirkningstungt end begge komparatorer, baseret på bivirkningsprofilerne for de tre stoffer og fagudvalgets kliniske erfaring med både checkpoint inhibitor-immunterapi, PLD og doxorubicin.

5.3.5 Fagudvalgets konklusion

Den samlede værdi af dostarlimab sammenlignet med pegyleret liposomalt doxorubicin eller doxorubicin til patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er er progredieret under eller efter behandling med platinbaseret kemoterapi, kan ikke kategoriseres efter Medicinrådets metoder.

Fagudvalget har sammenlignet effekten af dostarlimab med komparatorerne ved at foretage en deskriptiv sammenligning af effektestimater fra et ukontrolleret studie af dostarlimab med effektestimater fra en blanding af prospektive kliniske studier og retrospektive kohortestudier af komparatorerne. Derved er der stor usikkerhed omkring effektestimaterne, og i hvor høj grad de er sammenlignelige.

Fagudvalget bemærker, at alle tilgængelige dataestimater på nuværende tidspunkt indikerer, at dostarlimab er en mere effektiv og sikker behandling end komparatorerne. Fagudvalget lægger her særlig vægt på, at en væsentlig andel af patienterne tilsyneladende er progressionsfri i mere end 2 år efter behandling med dostarlimab, hvilket kan have en positiv effekt på den samlede overlevelse.

Fagudvalget bemærker, at det ikke-kontrollerede studie af dostarlimab (GARNET) er igangværende og forventer derfor, at yderligere data med længere opfølgningstid vil blive tilgængelige efter indsendelse til EMA i slutningen af 2022. Ydermere er fagudvalget bekendt

med, at dostarlimab undersøges i kombination med platinbaseret kemoterapi som førstelinjebehandling til dMMR-MSI-high avanceret eller recidiverende endometriecancer i et fase III-randomiseret klinisk studie. Selvom dette er en kombinationsbehandling, og patientpopulationen har en bedre prognose, forventer fagudvalget, at dette studie vil højne evidenskvaliteten for dostarlimabs effekt på sygdommen betragteligt. Data fra dette studie forventes indsendt til EMA i slutningen af 2022.

6. Andre overvejelser

Respons bedømt ved immunRecist

I Medicinrådets protokol for vurdering af dostarlimab efterspurgte fagudvalget data for objektiv responsrate bedømt ud fra immunRECIST. Immunrespons efter behandling med checkpoint inhibitor-immunterapi kan medføre pseudoprogression på scanningsbilleder, hvilket kan medføre, at den objektive responsrate underestimeres, hvis den bedømmes ud fra RECIST alene. Ansøger har indsendt data for immunRECIST (Tabel 6-1).

Tabel 6-1 Objektiv responsrate målt ved irRECIST

Immunerelateret respons (irRECIST investigator assessment)	
Ir – Objektiv reponsrate, n (%)	50 (45,5 %)
Ir - Komplet respons, n (%)	7 (6,4 %)
Ir – Partielt respons, n (%)	43 (39,1 %)
Ir – Stabil sygdom, n (%)	20 (18,2 %)
Ir – Progression, n (%)	36 (32,7 %)
Ir – Respons ikke estimeret, n (%)	4 (3,6 %)
Ir – Sygdomskontrolrate, n (%)	70 (63,6 %)
Ir – Responsvarighed, måneder	Ikke nået

Den objektive responsrate bedømt ud fra immunRECIST afviger ikke nævneværdigt fra ORR bedømt ud fra RECIST, både set ud fra den totale andel respondere, andelen af komplette og andelen af partielle respondere. Derfor er der ikke noget, der indikerer, at responsdata ved RECIST eller PFS-data har været påvirkede af pseudoprogression.

Diagnose af dMMR/MSI-H

I Medicinrådets protokol for vurdering af dostarlimab efterspurgte fagudvalget desuden ansøgers overvejelser om, hvorvidt dMMR og MSI-H-test er ligeværdige til at identificere, hvilke patienter der kan forventes at have gavn af dostarlimab. Ansøger beskriver, at patienter i GARNET var

udvalgt pba. af enten en immunhistokemisk analyse, der detekterer dMMR, eller en PCR eller NGS-test, der detekterer MSI-H. Ansøger betragter disse analyser som ligeværdige ift. at identificere patienter, der kan have gavn af dostarlimab. Fagudvalget er enig i denne betragtning, og mener, at de enkelte patologiske afdelinger kan anvende den analyse, der passer bedst ud fra lokale forhold.

Behandlingsvarighed og selektion pba. performance status
Det er ikke videnskabeligt dokumenteret, hvor længe der skal behandles med check-point inhibitor immunterapi. Fagudvalget bemærker, at behandling med check-point inhibitor immunterapi generelt bør stoppes efter 2 år, hvis ikke der er tungtvejende kliniske grunde til at fortsætte behandlingen. Dette er i tråd med de danske kliniske retningslinjer inden for behandling af metastatisk melanom med check-point inhibitor-immunterapi, hvor der stiles mod en maksimal behandlingsvarighed på 2 år, eventuelt kortere, afhængig af patientens respons på behandlingen [34].

Fagudvalget bemærker, at populationen i GARNET udelukkende indeholder patienter i performance status 0-1. Der er derfor ingen dokumentation for effekten af dostarlimab for patienter i dårligere performance status.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene og livmoderkræft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Trine Jakobi Nøttrup *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Anya Eidhammer *Ledende overlæge*	Region Nordjylland
Jacob Christian Lindegaard *Overlæge, Dr.med.*	Region Midtjylland
Trine Lembrecht Jørgensen *Afdelingslæge*	Region Syddanmark
Dejan Labudovic *Afdelingslæge*	Region Sjælland
Kristine Madsen *Afdelingslæge*	Region Hovedstaden
Trine Zeeberg Iversen *Afdelingslæge*	Dansk Selskab for Klinisk Onkologi
Henrik Horwitz *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Henrik Kjer *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Birthe Lemley *Patient/patientrepræsentant*	Danske Patienter
Dorte Blou *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	24. november 2021	Godkendt af Medicinrådet

11. Bilag

11.1 Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 11-1 Vurdering af risiko for bias McMeekin et al. 2015, IXAMPLE2, NCT00883116

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	Der er ingen information om randomiseringsprocessen, hverken i forhold til om den var skjult og/eller tilfældig. Baselinekarakteristika indikerer ikke problemer med randomiseringen.
Effekt af tildeling til intervention	**Forbehold**	Hverken patienter eller personale var blindede. Det fremgår ikke, om dette kan have medført protokolafvigelser.
Manglende data for effektmål	**Lav**	Data for effektmålene, OS, PFS og ORR er baseret på *intention-to-treat*-populationen. Data for bivirkninger er baseret på de patienter, der modtog behandlingen. 9 patienter (4 %) i kontrolgruppen modtog ikke behandlingen og indgår ikke.
Risiko for bias ved indsamlingen af data	**Høj**	Hverken patienter eller personale var blindede. ORR og PFS blev begge vurderet af investigatorerne ud fra scanningsbilleder, hvorved deres viden om patientens allokering kan have betydning for resultaterne. Bivirkningsrapportering kan være påvirket af både patienternes og investigatorernes viden om allokeringen.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Der er rapporteret data for alle angivne primære og sekundære effektmål.
Overordnet risiko for bias	**Høj**	Manglende blinding medfører høj risiko for bias i forbindelse med indsamlingen af data.

Tabel 11-2 Vurdering af risiko for bias ZoptEC, NCT01767155

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Forbehold**	Randomiseringen var centraliseret, men der er ingen information, om randomiseringsprocessen var skjult og/eller tilfældig. Baselinekarakteristika indikerer ikke problemer med randomiseringen
Effekt af tildeling til intervention	**Forbehold**	Hverken patienter eller personale var blindede. Det fremgår ikke, om dette kan have medført protokolafvigelser.
Manglende data for effektmål	**Lav**	Data for OS og ORR er rapporteret for *intention-to-treat*-populationen. Data for PFS er rapporteret ved en modificeret *intention-to-treat*-population, hvor 4 og 7 patienter mangler i hhv. interventions- og kontrolgruppen. Disse er patienter, der ikke har modtaget studiemedicinen, og det forventes ikke, at dette påvirker resultatet.
Risiko for bias ved indsamlingen af data	**Høj**	Hverken patienter eller personale var blindede. ORR og PFS blev begge vurderet af investigatorerne ud fra scanningsbilleder, hvorved deres viden om patientens allokering kan have betydning for resultaterne. Bivirkningsrapportering kan være påvirket af både patienternes og investigatorernes viden om allokeringen.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Forbehold**	Der er en afvigelse ift. studieprotokollen, hvor det var defineret, at PFS-analysen skulle foretages på *intention-to-treat*-populationen. I stedet er der publiceret data fra den modificerede population.
Overordnet risiko for bias	**Høj**	Manglende blinding medfører høj risiko for bias i forbindelse med indsamlingen af data.

11.2 Bilag 2: Beskrivelser af komparatorstudierne

Klinisk spørgsmål 1

SGSG012/GOTIC004/Intergroup study (Nagao et al. 2013 og 2015)

SGSG012/GOTIC004/Intergroup study er et retrospektivt kohortestudie udført i Japan, der undersøger behandling med platinbaseret kemoterapi i første og anden linje. Kohorten består af 262 patienter med endometriecancer eller uterine carcinosarcoma, der modtog platinbaseret kemoterapi i første linje, hvoraf 101 patienter modtog carboplatin i kombination med paclitaxel i første og anden linje. Dosis er ikke beskrevet. Studiet undersøger OS, PFS og ORR. Patienterne i studiet blev behandlet mellem januar 2005 og december 2009.

Studiet er beskrevet i to publikationer, hvor Nagao 2013 et al. analyserer betydningen af det platinfri interval efter førstelinjebehandlingen for behandlingseffektiviteten i anden linje, og Nagao et al. 2015 analyserer betydningen af valget af behandlingsregime i anden linje. Fagudvalget bruger i sin vurdering analysen fra Nagao 2015 et al., da denne analyserer data tættest på den måde, det er beskrevet i protokollen for vurderingen. I analysen fra Nagao 2015 et al. er patienter, der modtog docetaxel i kombination med carboplatin i første eller anden linje inkluderet i populationen, der modtog carboplatin i kombination med paclitaxel. Det drejer sig om 21 (17 %) patienter ud af samlet 127 patienter i analysen.

Rubinstein et al. 2019

Rubinstein et al. 2019 er et retrospektivt databasestudie, der undersøger behandling med carboplatin i kombination med paclitaxel i første og anden linje (n = 20). Patienterne i studiet modtog median 6 cykler behandling i både første og anden linje, men specifikke doser er ikke angivet. De primære effektmål i studiet var ORR, median PFS indtil genbehandling og PFS og OS efter genbehandling samt OS fra diagnosetidspunktet. Patienterne i studiet blev behandlet mellem januar 2000 og december 2014.

Miyake et al. 2011

Miyake et al. 2011 er et retrospektive kohortestudie udført i Japan, der undersøger sammenhængen mellem det behandlingsfrie interval mellem første og anden linje kemoterapi og patienternes prognose. Patienter fik carboplatin i kombination med paclitaxel med eller uden adriamycin i første linje og anden linje. Det primære effektmål i studiet var ORR. Studiet brugte ikke RECIST-kriterierne i evalueringen af respons.

Mazgani et al. 2008

Mazgani et al. 2018 er en retrospektiv analyse af 200 patienter med endometriecancer, der har fået carboplatin i kombination med paclitaxel. Formålet med analysen er at undersøge effektiviteten af genbehandling med carboplatin i kombination med paclitaxel. 52 patienter ud af de 200 blev genbehandlet med carboplatin i kombination med paclitaxel. Af dem havde 28 endometrioid histologi, og 24 havde serøs histologi. Behandlingsrespons blev målt efter RECIST-kriterierne. Patienterne i studiet blev behandlet mellem 1995 og 2007.

Vergote et al. 2015

Vergote et al. 2015 er et fase II-studie, der undersøger behandling med *granolocyte colony stimulating factor* oveni kombinationsbehandling med carboplatin og paclitaxel hos patienter med kræft i æggestokkene, livmoderhalskræft eller endometriecancer. 36 patienter havde avanceret eller recidiverende endometriecancer og modtog behandling carboplatin (AUC 2,7) i

kombination med paclitaxel (60 mg/ml) hver uge i første eller anden linje. Median tidligere behandlingslinjer var 1 (0-2). Det er ikke beskrevet, hvor mange patienter der modtog behandling i anden linje med carboplatin i kombination med paclitaxel, eller hvor langt det platinfri interval efter førstelinjebehandlingen var for disse patienter. Patienter blev rekrutteret til studiet mellem februar 2012 og marts 2013. Fagudvalget ekskluderer studiet fra vurderingen pga. den højere dosis af carboplatin.

Ueda et al. 2011

Ueda et al. 2011 er et retrospektivt studie udført i Japan, der undersøger behandling af patienter med avanceret eller recidiverende endometriecancer med platinbaseret kemoterapi i anden linje. Alle patienter (n = 40) havde modtaget kombination af taxanbaseret og platinbaseret kemoterapi i første linje. 32 patienter havde modtaget epirubicin (50mg/m^2) i første linje i kombination med carboplatin (AUC 4) og paclitaxel (150 mg/m^2) hver tredje eller fjerde uge. De resterende 8 patienter havde modtaget behandling med carboplatin (AUC 5) i kombination med paclitaxel (175 mg/m^2) hver tredje eller fjerde uge, eller carboplatin (AUC 2) i kombination med paclitaxel (80 mg/m^2) hver uge. 24 patienter modtog behandling med carboplatin i kombination med paclitaxel i anden linje efter ét af de tre ovenstående regimer. Resten modtog docetaxel i kombination med irinotecan, behandling med medroxyprogesteronacetat eller behandling med etoposid. 26 ud af de 40 patienter havde et behandlingsfrit interval længere end 6 måneder, men resultaterne af analysen er ikke opgjort efter behandlingsregimer i første eller anden linje. Det primære endepunkt i studiet var ORR. PFS og OS var sekundære effektmål. Patienterne blev behandlet mellem 2000 og 2008.

Nomura et al. 2015

Nomura et al. 2015 er et fase II-studie udført i Japan, der undersøger effekt og sikkerhed af tre forskellige kombinationer af taxaner og platinbaseret kemoterapi til patienter med avanceret eller recidiverende endometriecancer. 30 patienter i studiet blev behandlet med carboplatin (AUC 6) i kombination med paclitaxel (180 mg/ml) hver tredje uge. Ingen af patienterne havde tidligere modtaget carboplatin i kombination med paclitaxel, mens kun 4 af patienterne havde modtaget platinbaseret kemoterapi i kombination med en taxan. Fagudvalget ekskluderer studiet, da størstedelen (26 ud af 30) af patienterne, der modtog den relevante andenlinjebehandling, ikke havde modtaget samme behandling i første linje.

Klinisk spørgsmål 3

Julius et al. 2013

Julius et al. er et retrospektivt studie, der undersøger effekten og sikkerheden ved pegyleret liposomalt doxorubicin ud fra optegnelser af patienter behandlet på the University of Texas M. D. Anderson Cancer Center mellem 1996 og 2006 [30]. Patienterne var behandlet med forskellige doser liposomalt pegyleret doxorubicin (30-50 mg/m^2), og studiets formål var at sammenligne patienternes overlevelse og bivirkningerne ved behandlingen. Studiet inkluderede i alt 60 patienter, der blev behandlet for recidiverende endometriecancer, og som tidligere havde modtaget kemoterapi. Af disse modtog 42 patienter en startdosis på 40 eller 50 mg/m^2, der er de mest relevante doser i forhold til dansk klinisk praksis. Studiet opgør OS og PFS for patienterne opdelt efter dosis.

Muggia et al. 2002

Muggia et al. er et prospektivt, fase II, ikke-kontrolleret studie, hvor patienter med behandlingsresistent eller recidiverende endometriecancer blev behandlet med liposomalt pegyleret doxorubicin (50 mg/m^2). Studiet inkluderede 46 patienter, hvoraf de 40 tidligere havde modtaget kemoterapi, oftest i form af doxorubicin (32 patienter). Studiets primære effektmål var ORR og sikkerhed, men OS rapporteres også.

Makker et al. 2013

Makker et al. er et retrospektivt studie, der undersøger effekten af doxorubicin til patienter med avanceret eller recidiverende endometriecancer, der tidligere er behandlet med carboplatin i kombination med paclitaxel ved Memorial Sloan-Kettering Cancer Center mellem 1995 og 2009 [31]. Studiet inkluderede 17 patienter, der modtog 60mg/m^2 doxorubicin hver tredje uge. Studiet rapporterer data for OS, PFS, ORR og sikkerhed.

McMeekin et al. 2015

McMeekin et al. rapporterer fra IXAMPLE2, som er et prospektivt, open-label, randomiseret fase III-studie, hvor effekten af ixabepilone undersøges overfor paclitaxel (175 mg/m^2) eller doxorubicin (60 mg/m^2) i patienter med avanceret eller recidiverende endometriecancer [32]. Alle patienter var tidligere behandlet med platinbaseret kemoterapi, og inklusionskriterierne tillod desuden én behandlingslinje med kemoterapi. Patienter, der tidligere var behandlet med anthracycliner (doxorubicin, eller epirubicin) blev randomiseret til ixabepilone eller paclitaxel, mens alle andre blev randomiseret til ixabepilone eller doxorubicin. Patienterne behandlet med paclitaxel og doxorubicin er samlet til én kontrolgruppe, og der er ikke rapporteret data specifikt for patienter, der modtog doxorubicin. Størstedelen af kontrolgruppen (69 %) blev behandlet med doxorubicin. Studiets primære effektmål var OS, men der rapporteres også data for PFS, ORR og sikkerhed.

ZoptEC

ZoptEC er et prospektivt, open-label, randomiseret fase III-studie, hvor effekten og sikkerheden af zoptarelin doxorubicin (267 mg/m^2 hver tredje uge) undersøges overfor doxorubicin (60 mg/m^2 hver tredje uge). Studiet inkluderede 511 patienter, der alle havde avanceret eller recidiverende endometriecancer og var tidligere behandlet med platinbaseret kemoterapi. Patienterne var randomiseret 1:1 mellem behandlingsarmene. Resultaterne fra ZoptEC er ikke publiceret i et videnskabeligt tidsskrift. I stedet er data tilgængelige på clinicaltrials.gov [33]. Ansøger bruger desuden de individuelle deltagerdata (*Individual participant data*, IDP) fra studiets sponsor. Heri rapporteres data for OS, PFS, livskvalitet, ORR og sikkerhed.

11.3 Bilag 3: Effektestimater fra komparatorstudierne

Klinisk spørgsmål 1

Tabel 11-3 Oversigt over effektestimater fra alle studier, der indgår i besvarelsen af klinisk spørgsmål 1

Studie	Samlet overlevelse (OS)		Progressionsfri overlevelse (PFS)		Livskvalitet (EORTC QLQ-C30)	Objektiv responsrate (ORR)	Grad 3-4 bivirkninger
	Median OS	OS-rate ved 12 måneder	Median PFS	PFS-rate ved 24 måneder			
GARNET, EPAR [19]	Ikke nået [17,1 måneder; ikke nået]	69,2 % [58,6; 77,6 %]	5,5 måneder [3,3 måneder; ikke nået]	[redacted]	[redacted]	43,5 % [34,0; 53,4 %]	13,2 %
Studier af platinbaseret kemoterapi							
Mazgani et al. 2008 [21]	15 måneder [ikke angivet]	56 % [ikke angivet]	8 måneder [ikke angivet]	17 % [ikke angivet]	Ikke rapporteret	42 % [ikke angivet]	Ikke rapporteret
Rubinstein et al. 2019 [16]	27 måneder (range = 6-117 måneder)	95 % [ikke angivet]	10 måneder (range = 2-27 måneder)	6 % [ikke angivet]	Ikke rapporteret	50 % [ikke angivet]	Ikke rapporteret

Studie	Samlet overlevelse (OS)		Progressionsfri overlevelse (PFS)		Livskvalitet (EORTC QLQ-C30)	Objektiv responsrate (ORR)	Grad 3-4 bivirkninger
	Median OS	OS-rate ved 12 måneder	Median PFS	PFS-rate ved 24 måneder			
Nagao et al. 2015 [24]	48 måneder [ikke angivet]	84 % [ikke angivet]	10 måneder [ikke angivet]	20 % [ikke angivet]	Ikke rapporteret	55 % [ikke angivet]	Ikke rapporteret
Miyake et al. 2011 [22]	Ikke rapporteret	Ikke rapporteret	13 måneder [ikke angivet]	50 % [ikke angivet]	Ikke rapporteret	59 % [ikke angivet]	Ikke rapporteret
Ueda et al. 2011 [25]	13 måneder (range = 3-44 måneder)	Ikke rapporteret	5,5 måneder (range =2-20 måneder)	Ikke rapporteret	Ikke rapporteret	53 % [ikke angivet]	Ikke rapporteret
Median for platinbaseret kemoterapi	21 måneder (range = 13-48 måneder)	84 % (range = 56-95 %)	10 måneder (range = 5,5-13 måneder)	18,5 % (range = 6-50 %)	Ingen estimater	53 % (range = 42-59 %)	Ingen estimater

Klinisk spørgsmål 3

Tabel 11-4. Oversigt over effektestimater fra alle studier, der indgår i besvarelsen af klinisk spørgsmål 3

Studie	Samlet overlevelse (OS)		Progressionsfri overlevelse (PFS)		Livskvalitet (EORTC QLQ-C30)	Objektiv responsrate (ORR)	Grad 3-4 bivirkninger
	Median OS	OS-rate ved 12 måneder	Median PFS	PFS-rate ved 24 måneder			
GARNET, EPAR [19]	Ikke nået [17,1 måneder; ikke nået]	69,2 % [58,6; 77,6 %]	5,5 måneder [3,3 måneder; ikke nået]	[redacted]	[redacted]	43,5 % [34,0; 53,4 %]	13,2 %
Studier af pegyleret liposomalt doxorubicin eller doxorubicin							
Julius et al. 2013 [30]	7 måneder [ikke angivet]	28 % [ikke angivet]	7 måneder [ikke angivet]	Ikke rapporteret	Ikke rapporteret	Ikke rapporteret	Ikke rapporteret
Muggia et al. 2002 [17]	8,2 måneder [ikke angivet]	Ikke rapporteret	Ikke rapporteret	Ikke rapporteret	Ikke rapporteret	9,5 % [2,7; 22,6 %]	Ikke rapporteret
Makker et al. 2013 [31]	5,8 måneder [1,0;15,0 måneder]	48 % [ikke angivet]	2,1 måneder [0,95; 2,7 måneder]	0 % [ikke angivet]	Ikke rapporteret	0 % [ikke angivet]	0 %

Studie	Samlet overlevelse (OS)		Progressionsfri overlevelse (PFS)		Livskvalitet (EORTC QLQ-C30)	Objektiv responsrate (ORR)	Grad 3-4 bivirkninger
	Median OS	OS-rate ved 12 måneder	Median PFS	PFS-rate ved 24 måneder			
IXAMPLE2 [32]	12,3 måneder [10,7; 15,4 måneder]	53 % [ikke angivet]	4,0 måneder [2,7; 4,3 måneder]	Ikke rapporteret	Ikke rapporteret	15,7 % [11,2; 21,1 %]	Ikke rapporteret
ZoptEC [33]	10,8 måneder [9,8; 12,6 måneder]	44,6 % [38,2; 50,7 %]	4,7 måneder [4,1; 6,6 måneder]	Ikke rapporteret	-11,7 point [-15; -8,4 point]	14,1 %	Ikke rapporteret
Median for komparatorgruppen	8,2 måneder (range = 5,8-12,3 måneder)	46,3 % (range = 28-52 %)	4,4 måneder (range = 2,1-7 måneder)	0 % (kun ét estimat)	-11,7 point (kun ét estimat)	11,8 % (range = 0-15,7 %)	Ikke rapporteret

Medicinrådet

Application for the assessment of dostarlimab as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1. Basic information

Contact Information	
Name	**Birgit Andersen**
Title	Market Access Manager & Tender Manager
Area of Responsibility	Project Leader
Phone number	+ 45 2469 9153
E-mail	birgit.x.andersen@gsk.com
Navn	**Dorte Hemmingsen**
Titel	Scientific Advisor, Oncology
Area of Responsibility	Clinical/medical
Phone number	+ 45 2469 9123
E-mail	dorte.x.hemmingsen@gsk.com

Overview of the pharmaceutical	
Proprietary name	Jemperli®
Generic name	dostarlimab
Marketing authorization holder in Denmark	GlaxoSmithKline (Ireland) Limited
ATC code	L01XC40
Pharmacotherapeutic group	Anti-neoplastic agents, monoclonal antibodies
Active substance(s)	Dostarlimab.
Pharmaceutical form(s)	Solution for infusion. Clear to slightly opalescent colourless to yellow solution, free from visible particles. The solution for infusion has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

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Overview of the pharmaceutical	
Mechanism of action	Dostarlimab is a humanised mAb of the IgG4 isotype that binds to PD-1 receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway-mediated immune response results in inhibition of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti-tumour immuno responses through blockade of PD-1 binding to PD-L1 and PD-L2. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.
Dosage regimen	One vial of 10 mL solution for infusion contains 500 mg of dostarlimab. Each mL of solution for infusion contains 50 mg of dostarlimab. 500 mg (1 vial) Q3W for 4 cycles, then 1000mg (2 vials) Q6W until disease progression
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Dostarlimab is indicated as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes. BEGR
Combination therapy and/or co-medication	No.
Packaging – types, sizes/number of units, and concentrations	10 mL type I borosilicate clear glass vial, with a grey chlorobutyl elastomer stopper laminated with fluoropolymer, sealed with an aluminium flip-off cap containing 500 mg dostarlimab. Each carton contains one vial.
Orphan drug designation	No

2. Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CR	complete response
dMMR	mismatch repair deficient
DOR	duration of response
EC	endometrial cancer
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC-QLQ-C30D	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
FIGO	International Federation of Gynaecology and Obstetrics
GOG	Gynaecologic Oncology Group
HIV	human immunodeficiency virus
IA	interim analysis
ITT	intent-to-treat
MAIC	Matching adjusted indirect comparison
MMRp	mismatch repair proficient
MSI-H	microsatellite instability high
ORR	objective response rate
OS	overall survival
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcomes
QOL	quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1

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SD	stable disease
TC	carboplatin and paclitaxel
TEAE	treatment-emergent adverse event
US	United States
W	Weeks

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3. Summary

Scope of application

This technology assessment concerns Jemperli (dostarlimab), a novel and innovative immune-oncology treatment. Dostarlimab is indicated for adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC), that have progressed on or following prior treatment with a platinum-containing regimen. With no authorised standard of care treatments available following disease progression on platinum-based chemotherapy, patients in this setting are left with extremely limited and inadequate treatment options, which is supported by very limited evidence. This results in a high unmet need for a new treatment as current treatments are associated with poor median survival (<12 months), progression-free survival (PFS) (<6 months) (1), and reduced quality of life (QoL) (2).

Population and comparators

The Danish Medicines Council (DMC) protocol specifies three clinical questions concerning three sub-populations of interest where the relative efficacy and safety of dostarlimab should be determined:

- **Versus platinum-based chemotherapy** for patients with dMMR/MSI-H advanced or recurrent EC progressed approximately 6 months or more after platinum-based treatment (clinical question 1)
- **Versus placebo** for patients with dMMR/MSI-H advanced or recurrent EC progressed during or after platinum-based treatment (clinical question 2)
- **Versus pegylated liposomal doxorubicin (PLD)** for patients with dMMR/MSI-H advanced or recurrent EC progressed during or after platinum-based treatment (clinical question 3)

Results for clinical question 1:

The efficacy of dostarlimab was compared narratively to platinum-based chemotherapy in the eight comparator studies reporting mainly on the combination of carboplatin and paclitaxel. The efficacy estimate for dostarlimab is likely underestimated when compared narratively to platinum-based chemotherapy, as the factors influencing the comparability between the studies were consistently favouring the efficacy estimates of platinum-based chemotherapy (see section 5 and 6.1.3.1 for more details).

Overall, the comparison between dostarlimab and platinum-based chemotherapy strongly indicates, that patients treated with dostarlimab experience a meaningful survival benefit.

- The most important and distinctive difference noted for dostarlimab was the large proportion of patients who experience long-term disease remission.
    - This is demonstrated by the PFS and OS KM-curves, which flatten out early and form a long-tail, representing patients in long-term remission.
    - The large proportion of patients with long term response is only observed for dostarlimab, whereas patients on platinum-based chemotherapy continue to progress.
    - PFS estimates supports this claim as the PFS-rate at 24-months was [redacted] and OS-rate at 12-months was 69.2% (95% CI: 58.8-77.6) for dostarlimab, which clearly differentiate dostarlimab from platinum-based chemotherapy with the more credible comparator studies reporting a 24-months PFS of 8-25%.
    - Unfortunately, no comparator studies reported a combined proportion of patients with grade 3-4 TEAEs or HRQoL by the EORTC QLQ-C30 instrument. Results for dostarlimab on these endpoints are provided below for clinical question 3.

Acknowledging, that there is a lack of safety results reported in the comparator studies, GSK suggest that the best approach for evaluating safety would be a narrative approach, undertaken by the DMC expert committee.

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Results for clinical question 2:

The comparison requested in clinical question 2 versus placebo is not a treatment option in clinical practice, hence no placebo-controlled studies have been carried out to date. Therefore, this section is left blank in the clinical dossier. In the health economic model supporting this dossier, an option to model the cost of dostarlimab vs. placebo has been added.

Results for clinical question 3:

The efficacy of dostarlimab was compared narratively to PLD/doxorubicin in five comparator studies. Additionally, relative efficacy estimate for dostarlimab versus PLD/doxorubicin was derived from indirect comparisons (MAICs and inverse probability of treatment weighting (IPTW). The efficacy estimate for dostarlimab is likely to be underestimated when compared narratively to PLD/doxorubicin, as the factors influencing the comparability between the studies were consistently favouring the efficacy estimates of PLD/doxorubicin (see section 5 and 6.3.3.1 for details).

- Patients treated with dostarlimab experienced a notable and clinical meaningful survival benefit with 20-40% higher OS-rate at 12 months compared to PLD/doxorubicin demonstrated by 69.2% (95% CI: 58.8-77.6) of patients treated with dostarlimab were alive after 12 months compared to 28-51% of patients treated with PLD/doxorubicin (range of 3 studies reporting the outcome).
- Similarly, encouraging results were observed for median OS relative to PLD and doxorubicin, as the median OS was not reached (95% CI: 17.1-NR) after 16.3 months, whereas the comparator studies for PLD and doxorubicin reported a median OS of 5.8-12.3 months (range of 5 studies reporting the outcome).
- All indirect analysis consistently supported the narrative analysis showing a 59-71.3% lower risk of death for dostarlimab compared to PLD/doxorubicin (p< 0.001) (range of three analyses)
- At 24-month the PFS-rate results from GARNET demonstrated a clinical meaningful benefit as [redacted] of patients treated with dostarlimab remained progression-free compared to 0% for patients treated with doxorubicin
- Dostarlimab demonstrated a robust and clinically meaningful ORR of 44,7% compared to 0-15.7 % patients with PLD/doxorubicin experiencing ORR (range from 4 studies reporting this outcome).
- Dostarlimab was also shown to be well-tolerated and associated with a manageable AE profile in line with other currently licensed anti-programmed cell death ligand 1 (PD-L1) therapies.
    - Treatment emergent adverse event (TEAEs) were low grade with only 48.1% of patients reported any Grade ≥3 TEAE compared to 78.3% of patients treated with PLD/doxorubicin in the only comparator study reported this outcome. Dostarlimab is therefore associated with less grade 3-4 toxicity compared to chemotherapy, with superior results vs. doxorubicin in the ZoptEC trial
- Results strongly indicate dostarlimab stabilises and improves quality of life as measured by the EORTC QLQ-C30 instrument whereas the comparator is associated with a worsening of HRQoL.
- In GARNET, patients treated with dostarlimab reported a clinically meaningful improvement in the global QoL of [redacted] points from baseline (3) whereas for doxorubicin in the ZoptEC study demonstrated a clinically relevant worsening in their HRQoL by the change from baseline in global QoL of -11.7 (4).

Conclusion

Dostarlimab is the first anti-PD-1 immunotherapy to obtain EMA approval for patients with recurrent or advanced dMMR/MSI-H EC progressing on or after a platinum-based regimen. Although comparisons are limited by differences across trials, dostarlimab represents a targeted therapy for patients with dMMR/MSI-H EC. Dostarlimab has shown promising results for long-term survival, relatively to traditional platinum-based chemotherapy and PLD, and by that offering patients, with a poor prognosis, a highly effective treatment where no optimal treatment alternatives exist.X

4. Literature search

The DMC has requested a systematic literature review to identify evidence for dMMR/MSI-H EC patients that have progressed approximately 6 months or more following prior treatment with a platinum-based therapy (platinum sensitive patients, clinical question 1, and evidence for dMMR/MSI-H EC patients, that have progressed during or within 6 month of prior platinum-based therapy (platinum-resistant patients, clinical question 3. The evidence would allow for comparative analysis including both RCTs and observational studies. In addition, hereto the DMC requested a comparison to placebo in clinical question 2, however placebo is not a treatment option used in clinical practise and no placebo-controlled studies have been carried out to date. Therefore, this section is left blank in the clinical dossier.

The following electronic databases were searched on 07.04.2021 as by the search protocol provided by the DMC: MEDLINE and CENTRAL via PubMed and Cochrane Library. The search strategy was carried out based on the search strings provided in the protocol developed by the DMC. The inclusion and exclusion criteria were selected to be in alignment with the clinical questions, the populations, and the outcomes of interest as defined in the DMC protocol and no date limit was applied to the electronic searches. This systematic literature review (SLR) was undertaken according to the principles of systematic reviewing published in the Cochrane Handbook, the Centre for Reviews and Dissemination (CRD) (5).

Primary screening was performed by two reviewers who independently reviewed each reference (title and abstract) identified by the literature search, applied study selection criteria, and decided on whether to include or exclude the reference at that stage. Secondary screening included obtaining the full-text articles for potentially relevant studies identified by primary screening of titles and abstracts. These were independently reviewed by two reviewers against each eligibility criterion.

The systematic database searches identified 301 records in total. A de-duplication step was performed to remove studies that overlapped across the databases; 10 of the studies were identified as duplicates and excluded. The remaining 291 studies were screened based on the information reported in their titles and/or abstracts. Of these, 277 records were excluded, and 14 records were included for full-text screening. The records were further assessed for eligibility for this review by full-text screening, which resulted in exclusion of two publications and inclusion of 12 publications. Additionally, two studies were identified through the review of a clinical systematic literature review carried out by GSK global in 2019. These two studies were Vergote et al. (6) and ZoptEC (4), a trial registered on clinicaltrials.gov which has not resulted in any publications due to negative results. Finally, GSK added the clinical study report (data-on-file) (3, 7) to serve as evidence for the GARNET trial, as this provided a more recent data cut available informing the safety and efficacy of dostarlimab as compared to the publication by Oaknin et al. (8). Therefore, in accordance with DMC guidelines, the earlier data cut published in Oaknin et al is not presented in detail in this submission.

For the RCTs included in the SLR, some of the treatment arms constitute unauthorised regimens within the population of adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) EC that has progressed on or following prior treatment with a platinum-containing regimen. Therefore, some comparator arms were out of the scope of the clinical questions and were not presented in this submission as they did not inform any of the comparators in the clinical questions and could neither be used for indirect treatment comparisons.

As expected, only the single-arm GARNET study for dostarlimab reported data for the specific subgroup of patients with dMMR/MSI-H, since the chemotherapy comparator studies were conducted between 1995-2015 and routine MMR testing was not routinely available or of interest then. Therefore, no formal anchored indirect comparison can be made between dostarlimab and the comparators. Nevertheless, the importance of dMMR/MSI-H-status has previously been investigated by GSK, who conducted an SLR on the prognostic or predictive value of mismatch repair and microsatellite biomarkers in the treatment of recurrent or advanced EC. Herein it was concluded that there was no strong evidence to suggest that either dMMR or MSI-H status has a significant positive or negative prognostic value in EC patients (11

out of 13 publications reported no significant findings based on dMMR or MSI-H status) (9). The lack of information on dMMR-MSI-H status is therefore not considered to impact the comparability of study results significantly.

Figure 1. PRISMA diagram

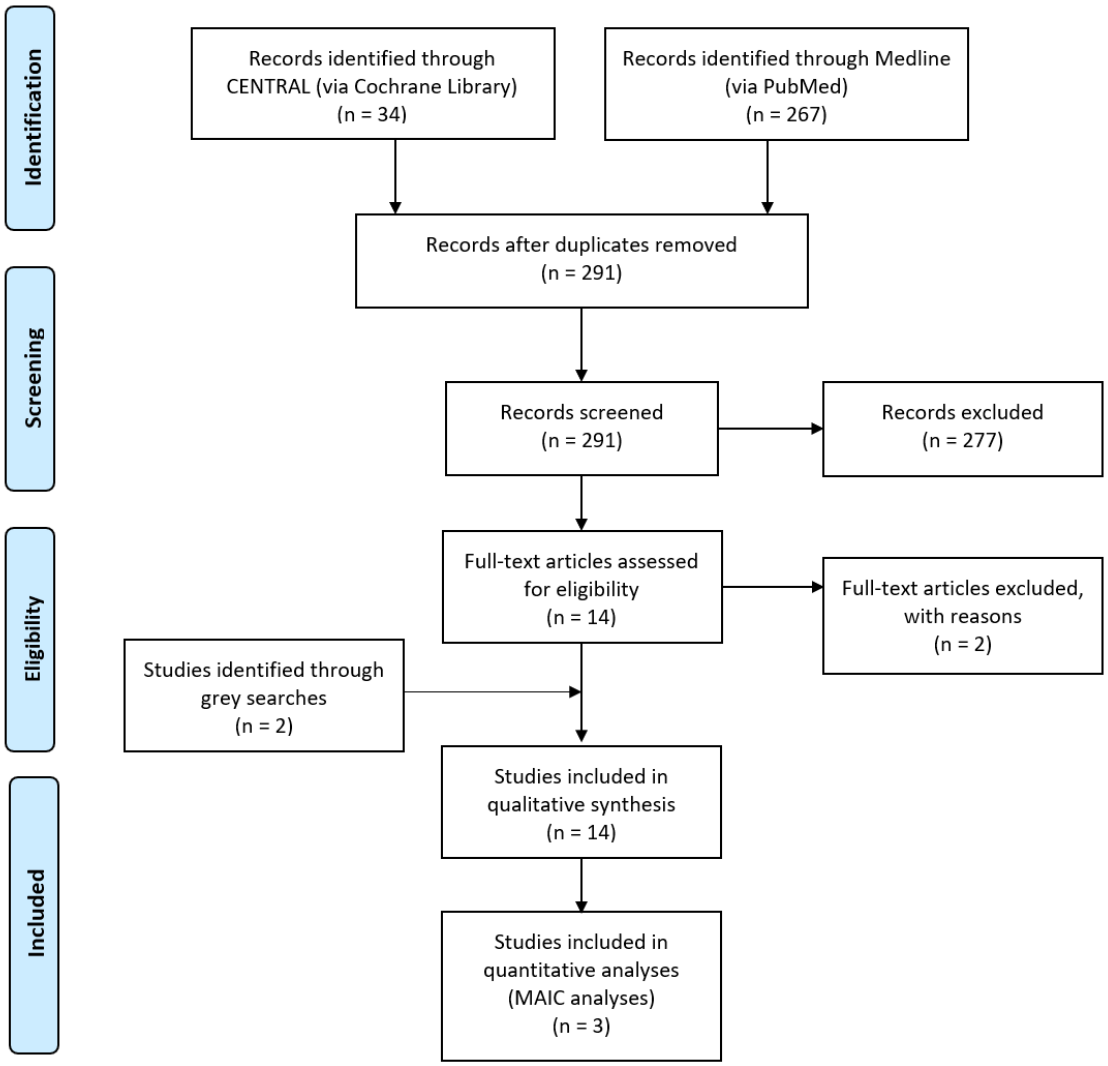

Table 1. Included studies by intervention

Trial name		
Intervention	**Non RCTs**	**RCTs**
Dostarlimab	GARNET (3, 7)	NA
Doxorubicin	Makker (10)	ZoptEC (4) McMeekin (11)
PLD	Julius (12) Muggia (13)	NA
Carboplatin and Paclitaxel	Nagao (14) Nagao (15) Rubinstein (16) Miyake (17) Mazgani (18) Vergote (6) Ueda (19)	Nomura (20)

4.1 Relevant studies

Included studies are presented in Table 1. In total, nine studies will inform clinical question 1and six studies will inform clinical question3. No studies were found that could inform clinical question 2, as no placebo-controlled trials were identified.

For clinical question 1, a high number of studies was found that investigated carboplatin and paclitaxel: one prospective interventional trial (6) , one cohort study (18) ; four retrospective studies (16) (17) (14) (15), one study was a case series (19), and one a phase II RCT (20).

For clinical question 3, the DMC protocol specified that studies describing the effects and side effects of pegylated liposomal doxorubicin (PLD) could not be found. The expert committee wished to obtain data describing the effect and side effects of doxorubicin as a proxy for PLD. Two studies informed the efficacy and safety of PLD, of which one was a retrospective study (12) and one was a prospective, phase II study (13). As evidence for PLD was limited, three studies were identified to inform the efficacy and safety of doxorubicin; two randomised controlled trials (RCTs) (4) (11), and a retrospective study (10).

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Table 1: 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
Clinical activity and safety of the anti–programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair–deficient endometrial cancer: a nonrandomized Phase 1 clinical trial Oaknin, A., Tinker, A. V., Gilbert, L., Samouëlian, V., Mathews, C., Brown, J., ... & Sabatier, R. *JAMA oncology*, *6*(11), 1766-1772. (2020).	GARNET	NCT0271 5284	The study began part 1 on March 7, 2016. The study began enrolling patients with dMMR/MSI-H on May 8, 2017. Estimated Study Completion Date: November 30, 2023	These publication results are not reported in the submission as the CSR provides a more recent data cut.
DOSTARLIMAB (TSR-042) 4010-01-001 A PHASE 1 DOSE ESCALATION AND COHORT EXPANSION STUDY OF TSR-042, AN ANTI-PD-1 MONOCLONAL ANTIBODY, IN PATIENTS WITH ADVANCED SOLID TUMOURS - PART 2B, ENDOMETRIAL CANCER (COHORTS A1 AND A2). GSK. 2020.	GARNET	NCT0271 5284	The study began part 1 on March 7, 2016. The study began enrolling patients with dMMR/MSI-H on May 8, 2017. Estimated Study Completion Date: November 30, 2023	1 and 3
Reuse of carboplatin and paclitaxel in patients with relapsed endometrial cancer—the British Columbia Cancer Agency experience. Mazgani, M., Le, N., & Hoskins, P. J. *Gynecologic oncology*, *111*(3), 474-477. (2008).	Mazgani et al.	NA	Start date: 2007 End date: 2008	1
Recurrent endometrial carcinoma: prognosis for patients with recurrence within 6 to 12 months is worse relative to those relapsing at 12 months or later. Miyake, T., Ueda, Y., Egawa-Takata, T., Matsuzaki, S., Yokoyama, T., Miyoshi, Y., ... & Kimura, T. *American journal of obstetrics and gynecology*, *204*(6), 535-e1. (2011).	Miyake et al.	NA	Start date: 2000 End date: 2009	1
Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: a retrospective study of the Memorial Sloan Kettering Cancer Center experience. Rubinstein, M., Halpenny, D., Makker, V., Grisham, R. N., Aghajanian, C., & Cadoo, K.. *Gynecologic oncology reports*, *28*, 120-123. (2019)	Rubinstein et al.	NA	Start date: January 2000 End date: December 2014	1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: the SGSG-012/GOTIC-004/Intergroup study.Nagao, S., Nishio, S., Michimae, H., Tanabe, H., Okada, S., Otsuki, T., ... & Kigawa, J *Gynecologic oncology*, *131*(3), 567-573. (2013).	Nagao et al, 2013	NA	Start date: January 2005 End date: December 2009	1
What is an appropriate second-line regimen for recurrent endometrial cancer? Ancillary analysis of the SGSG012/GOTIC004/Intergroup study. Nagao, S., Nishio, S., Okada, S., Otsuki, T., Fujiwara, K., Tanabe, H., ... & Kigawa, J. *Cancer chemotherapy and pharmacology*, *76*(2), 335-342. (2015).	Nagao et al, 2015	NA	Start date: January 2005 End date: December 2009	1
Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin. Ueda, Y., Miyake, T., Egawa-Takata, T., Miyatake, T., Matsuzaki, S., Yokoyama, T., ... & Kimura, T. *Cancer chemotherapy and pharmacology*, *67*(4), 829-835. (2011).	Ueda et al.	NA	Start date: 2000 End date: 2008	1
Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Nomura, H., Aoki, D., Takahashi, F., Katsumata, N., Watanabe, Y., Konishi, I., ... & Yaegashi, N*Annals of oncology*, *22*(3), 636-642. (2011).	Nomura et al.	NA	Start date: December 2003 End date: May 2005	1
Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: a study in 108 patients by the Belgian Gynaecological Oncology Group. Vergote, I., Debruyne, P., Kridelka, F., Berteloot, P., Amant, F., Honhon, B., ... & Laenen, A. Gynecologic oncology, 138(2), 278-284. (2015).	Vergote et al	NA	Start date: February 2012 End Date: March 2015	1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Zoptarelin doxorubicin (AEZS 108) as second line therapy for endometrial cancer (ZoptEC). ClinicalTrials.gov. [Available from: https://clinicaltrials.gov/ct2/show/NCT01767155	ZoptEC	NCT01767155.	NR	3
Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. Muggia, F. M., Blessing, J. A., Sorosky, J., & Reid, G. C. *Journal of clinical oncology*, *20*(9), 2360-2364. (2002).	Muggia et al	NA	Start date: NA End date: 2001	3
Treatment of advanced or recurrent endometrial carcinoma with doxorubicin in patients progressing after paclitaxel / carboplatin: Memorial Sloan-Kettering Cancer Center experience from 1995 to 2009. Makker, V., Hensley, ML, Zhou, Q., Iasonos, A., & Aghajanian, CA *International Journal of Gynecologic Cancer*, *23* (5). (2013).	Makker et al	NA	Start date: 1995 End date: 2009	3
Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer.McMeekin, S., Dizon, D., Barter, J., Scambia, G., Manzyuk, L., Lisyanskaya, A., ... & Vergote, I. *Gynecologic oncology*, *138*(1), 18-23. (2015).	IXAMPLE2	NCT00883116	Start date: August 2009 End date: February 2014	3
Evaluation of pegylated liposomal doxorubicin dose on the adverse drug event profile and outcomes in treatment of recurrent endometrial cancer.Julius, J. M., Tanyi, J. L., Nogueras-Gonzalez, G. M., Watkins, J. L., Coleman, R. L., Wolf, J. K., & Smith, J. A. *International Journal of Gynecologic Cancer*, *23*(2). (2013).	Julius et al	NA	From 1996 to 2006	3

4.2 Main characteristics of included studies

A summary of the main characteristics of the included studies is presented in Table 2 below. Full details are presented in Appendix 7.3.

Table 2. Summary of main characteristics of included studies.

Trial name (NCT number)	Intervention(s)*	Objective	Patients, n**	Study type and design	Primary and secondary end points	Clinical question	Used for relative efficacy and health economic model
GARNET (11) (NCT02715284)	Dostarlimab	To evaluate the anti-programmed death receptor 1 (anti-PD-1) antibody dostarlimab (also known as TSR-042) in participants with advanced solid tumours who have limited available treatment options.	IA1: 72 PP (104 ITT)*** IA2: 105 PP (129 ITT)	Multi-center, open-label, first-in-human Phase 1 study evaluating the anti-programmed death receptor 1 (anti-PD-1).	Outcomes included: Objective response rate (ORR), the Immune-related objective response rate (irORR) measured by irRECIST, Duration of Response (DOR); Disease control rate, Immune related disease control rate, Immune related duration of response, progression-free survival (PFS).	1,2 and 3	Yes
Nagao, 2013 (14)	Platinum based chemotherapies.	To evaluate the relationship between platinum-free interval and response to second-line platinum-based chemotherapy, as well as PFS and OS after second line chemotherapy.	N=262	Multicenter retrospective cohort study	The primary: overall response (RECIST 1.1). Secondary endpoints: OS, PFS, complete response (CR), partial response (PR).	1	No
Nagao, 2015 (15)	Carboplatin paclitaxel	To determine an appropriate second-line platinum-based regimen for patients with a history of receiving platinum-based first-line chemotherapy and, particularly, to evaluate whether	N=216 (enrolled); N=36, AP (first line) to TC/DC (second line); N=127	Ancillary analysis conducted using the dataset from the SGSG012/GOTIC004/Intergroup study.	Primary outcome: response rate (not specified) Secondary endpoints: PFS, CR, PR.	1	No

Trial name (NCT number)	Intervention(s)*	Objective	Patients, n**	Study type and design	Primary and secondary end points	Clinical question	Used for relative efficacy and health economic model
		alternations to second-line chemotherapy regimens are reasonable.	TC/DC (first line) to TC/DC (second line)				
Mazgani (18)	Carboplatin paclitaxel	To evaluate the efficacy of reusing carboplatin and taxol in women with relapsed EC.	N=31 (total retreated with chemotherapy in second line); N=19 (EC); N =12 (serous histology)	Retrospective study	No specification of primary/secondary Outcomes included: ORR (RECIST criteria). PFS and OS	1	Yes
Miyake (17)	Carboplatin paclitaxel	To evaluate the association of prognosis of endometrial carcinoma patients and treatment-free intervals (TFIs).	N=29 (total population); N=22 (TC)	In this retrospective study the effectiveness of second-line chemotherapy performed for patients with TFIs of 6-12 months and to patients with 12 or more months following a first line chemotherapy based on taxane (paclitaxel) and carboplatin, with or without the anthracycline (TC).	No specification of primary/secondary Outcomes included: CR, PR, PFS and OS.	1	No
Ueda (19)	Carboplatin paclitaxel	To investigate the effectiveness of second-line chemotherapy for treatment of advanced or recurrent endometrial carcinoma previously treated with a combined chemotherapy of taxane and platinum, with or without anthracycline.	N=40 (second line patients); N=24 (TC cohort)	Retrospective study	Primary endpoint: ORR Secondary endpoints: PFS, OS and treatment free interval (TFI)	1	No

Trial name (NCT number)	Intervention(s)*	Objective	Patients, n**	Study type and design	Primary and secondary end points	Clinical question	Used for relative efficacy and health economic model
Nomura (20)	Carboplatin paclitaxel, Docetaxel + cisplatin, Docetaxel + carboplatin	To assess the efficacy and safety of treatment with taxane plus platinum in combination therapies for advanced or recurrent endometrial carcinoma.	N=90 (admitted to the study), N=29 (Docetaxel + carboplatin), N=29 (Docetaxel + cisplatin), N=30 (Paclitaxel + carboplatin)	Randomised, Phase 2 study.	Primary endpoint: ORR (RECIST) Secondary endpoints: adverse events (AEs), treatment completion rate, and PFS.	1	No
Vergote (6)	Carboplatin paclitaxel	To investigate the addition of prophylactic G-CSF to each weekly paclitaxel /carboplatin patients with a recurrent platinum-resistant ovarian (OC) or recurrent or advanced endometrial (EC) or cervical carcinoma (CC).	N=108 (overall patient group); N=36 (EC cohort)	Prospective Phase II study	Primary endpoint: grade 3-4 neutropenia Secondary endpoints: grade 3–4 neutropenia per cohort, other toxicities, dose reductions and delays, PFS, ORR and OS.	1	No
Rubinstein (16)	Carboplatin paclitaxel	To examine the clinical outcomes of EC patients who received carboplatin and paclitaxel in the adjuvant setting and who were specifically re-treated with TC in the recurrent or metastatic disease setting.	N=20	Retrospective study	No specification of primary/secondary The main outcomes of interest were: ORR (RECIST), median PFS to re-treatment with TC, the PFS and OS from re-treatment with TC (cycle 1, day 1) and the OS from original diagnosis.	1	No

Trial name (NCT number)	Intervention(s)*	Objective	Patients, n**	Study type and design	Primary and secondary end points	Clinical question	Used for relative efficacy and health economic model
ZoptEC (NCT01767155) (4)	Doxorubicin		N=255	Open-label, randomised, active-controlled, two-arm Phase III study to compare the efficacy and safety of Zoptarelin Doxorubicin and doxorubicin.	Primary endpoint: OS Secondary outcomes: PFS, ORR, and clinical benefit rate (CBR) and safety.	3	No
Julius (12)	PLD	To further determine the impact of dose of PLD on the overall treatment outcomes and incidence of common adverse drug events (ADEs).	N=60	Retrospective review of medical records of patients who had received PLD as treatment of recurrent endometrial cancers between January 1, 1996, and June 30, 2006 at the University of Texas M. D. Anderson Cancer Center (UTMDACC), Gynecologic Oncology Center.	Primary endpoints: PFS Secondary endpoints: Time-to-progression (TTP)	3	Yes
IXAMPLE2 (NCT00883116) (11)	Paclitaxel/ doxorubicin	To determine whether ixabepilone resulted in improved overall survival (OS) compared with commonly used single-agent chemotherapy (doxorubicin or paclitaxel) in women with locally advanced, recurrent, or metastatic endometrial cancer with at least one failed prior platinum-based chemotherapeutic regimen.	N=248 (Doxorubicin arm)	Multicenter, open label, randomised phase III study	Primary outcome: OS Secondary endpoints included PFS (patients with measurable disease only), ORR, duration of response, time to response and toxicity.	3	No
Muggia (13)	PLD	To determine whether pegylated liposomal doxorubicin (PLD) has antitumor	N=42	Phase II trial	Primary endpoint: ORR, Secondary endpoints: AEs and DOR.	3	No

Trial name (NCT number)	Intervention(s)*	Objective	Patients, n**	Study type and design	Primary and secondary end points	Clinical question	Used for relative efficacy and health economic model
		activity in pre-treated patients with persistent or recurrent endometrial carcinoma and to define the nature and degree of toxicity of PLD.					
Makker (10)	Doxorubicin	To evaluate the efficacy of second-line doxorubicin in the treatment of advanced/recurrent endometrial carcinoma that has progressed after adjuvant paclitaxel and carboplatin TC therapy among patients treated at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1995 and 2009.	N=17	Retrospective study	Primary endpoint: PFS. Secondary endpoints: OS and AEs.	3	No

Abbreviations: AP, doxorubicin + cisplatin; AUC, area under the curve; DC, doxorubicin + carboplatin; EC, endometrial cancer; FDA, Food and Drug Administration; G-CSF, granulocyte colony stimulating factor; N, number; NR, not reported; PLD, pegylated liposomal doxorubicin; Q3W, every 3 weeks; Q6W, every 6 weeks; RCT, randomised controlled trial; TC, paclitaxel + carboplatin

*only the intervention arms fitting the scope of the protocol are listed. ** only the patient numbers for the relevant intervention arms are listed. ***The first data-readout was conducted for the IA1-population on the 8th of July 2019, with 72 patients included in the efficacy analysis (per protocol). A second data-readout was conducted on 01 March 2020 (specific date) for both the initial cohort IA1, as well as the expanded cohort IA2, which qualified for inclusion according to the prespecified criteria mentioned above. The different data-cuts and related populations are explained in more detail in section 6.1.1.1.

5. Limitations of the evidence included in the application

5.1 Study design

The single arm GARNET trial is the primary source of evidence supporting the efficacy and safety of dostarlimab in patients with dMMR/MSI-H EC. Hence, none of the comparisons can be supported by head-to-head clinical trials. Unfortunately, there are no authorised treatments available for patients with dMMR/MSI-H EC. The evidence to support the efficacy and safety of the comparators is therefore limited, as no studies were carried out with the aim to support regulatory approval for this indication. Most comparator studies identified were investigator-initiated retrospective studies with a small sample size of less than 30 patients, which greatly limits the possibility to draw robust conclusions on the efficacy and safety of the comparators included for this application.

5.2 Population

Large differences in patients' baseline characteristics were seen across comparator-studies in clinical question 1 and 3. Notably, patients in the comparator studies had less lines of prior treatment compared to patients enrolled in the GARNET trial, indicating that patients in the GARNET trial had a worse prognosis. Most studies included only Japanese patients, which is not considered transferable to Caucasian patients, due to differences in patient baseline characteristics and treatment practises. In general, less emphasis should be placed on these studies throughout the assessment.

The studies included to answer clinical question 1 reported results per platinum-free interval (PFI) defined as the interval between the date of the last platinum/treatment dose and the date of relapse detection. Most of the studies used different thresholds to report results for platinum-sensitive and platinum-resistant patients compared to the protocol received by the DMC, where a cut-off of 6 months was provided, and in general, publications tended to use a higher cut-off i.e., 12 months PFI. The higher cut-off will potentially overestimate the efficacy of platinum-based chemotherapy in platinum-sensitive patients in accordance with the DMC definition of PFI > 6 months, as patients with longer PFI respond better when reinduced with platinum-based chemotherapy.

As for clinical question 3, PFI was determined not to influence the results and conclusions for the comparison of dostarlimab vs. PLD, as split PFI results demonstrated that prior PFI does not seem to affect the efficacy of dostarlimab and PLD as described in section 6.3.3.1.

5.3 Outcomes

The quality and completeness reported in the comparator studies were low, given that these were mainly investigator-initiated retrospective studies. Most of the studies did not report quality of life and safety data, therefore, conclusions on the relative efficacy and safety of dostarlimab were limited for these outcomes. Median overall survival, median progression free survival, and response rate data were more commonly reported. When Kaplan Meier (KM) curves were included in the publications, they were used to estimate the 12-month OS/24-month PFS-estimates (visual inspection), and to add additional context to the assessment by making a complete assessment of the survival/PFS for the course of patients treated with the comparator vs. dostarlimab – specifically focusing on the probability of long-term PFS and OS.

6. Clinical questions

6.1 Clinical question one: What is the value of dostarlimab compared to platinum-based chemotherapy for patients with dMMR/MSI-H advanced or recurrent endometrial cancer progressed approximately 6 months or more after platinum-based treatment?

6.1.1 Presentation of relevant studies

Of the 14 studies included in the SLR, nine were relevant for clinical question one. One study investigated dostarlimab (GARNET), and eight investigated platinum-based chemotherapy. The study investigating dostarlimab, GARNET (7), was a prospective interventional trial. Of the studies investigating carboplatin and paclitaxel, one was a prospective interventional trial (Vergote et al. (6)), one was a cohort study (Mazgani et al. (18)); three were retrospective studies (Rubinstein et al. (16), Miyake et al. (17), and Nagao et al, 2013 (14)); one was an ancillary analysis using a dataset from the SGSG012/ GOTIC004/ Intergroup study (Nagao et al,2015 (15)); one study was a case series (Ueda et al. (19)). Finally, Nomura et al. (20)) was a phase II-controlled trial (RCT). Nomura et al. was only included for safety outcomes, as the patient population investigated in the study was on first line treatment and therefore not comparable to the patient population included in the GARNET trial. Safety outcomes were presented from Nomura et al. because safety was assumed consistent across treatment lines.

Four trials provided evidence of treatment efficacy and safety split per duration of PFIs/TFIs. Nagao et al. 2013 (14) and Nagao et al. 2015 (15) Ueda et al. (19) and Miyake et al. (17) provided results split per TFI defined as the interval between the date of the last platinum/treatment dose and the date of relapse detection. Each of these studies have used different thresholds to report results for platinum-sensitive and platinum-resistant patients. Only the definition used by Ueda et al. for the ORR outcome matched the definition used in the DMC protocol. In Nagao et al. 2015 (15), results are reported as one value across PFIs since no breakdown per PFI duration is provided. However, only 21 (17 %) of the patients had a PFI < 6 months so the majority of the patients belongs to the population of interest for clinical question 1. A summary of the definitions used for stratifying patients based on PFI/TFI is presented in Table 3.

Table 3. Summary of definitions used to define platinum-sensitive and platinum-resistant patients

Nagao et al 2013 (14)	Nagao et al 2015 (15)	Miyake (17)	Ueda (19)
OS/PFS:	**OS/PFS:**	TFI < 6 months,	**OS/PFS:**
PFI 0-6 months	PFI <6 months;	TFI 6-12 months	TFI < 12 months
PFI 6–11 months	PFI 6≤, <12 months;	TFI ≥ 12 months	TFI ≥ 12 months
PFI 12–23 months	PFI 12≤, ≤24 months;		**ORR**:
PFI ≥24 months	And PFI 24 months≤		TFI < 6 months
	ORR:		TFI ≥ 6 months
	PFI < 12 months		
	PFI > 12 months		

Abbreviations: ORR: overall response rate; PFI: platinum-free interval, TFI: treatment-free interval,

ORR results presented in section 6.1.2.2 and 6.1.2.5 from Nagao,2013 (14) and Miyake (17) demonstrated that patients with longer PFI, respond better when reintroduced to platinum-based chemotherapy. The implications of this must be considered, as most of the comparator studies included used a higher PFI threshold for defining platinum sensitive patients, than the DMC-criteria of 6 month. The results would significantly overestimate the efficacy of platinum-based chemotherapy in accordance with the DMC definition of PFI > 6 months.

When no single stratification of PFI was available, that matched the definition of platinum-sensitive patients provided by the DMC, all subgroups on PFI were reported in the dossier.

Importantly, GARNET did not provide subgroup analyses on the efficacy of dostarlimab per TFI. Nevertheless, an exploratory analysis of ORR per TFI demonstrated, that there were no differences between platinum resistant (progression <6 months) and platinum sensitive patients (progression ≥ 6 months). The results of the GARNET trial were therefore considered appropriate to answer all three clinical questions.

Most of the comparator studies reported very limited information on the patients' baseline characteristics. The most important prognostic features are reported in Table 5. Patients included in the different studies had a median age ranging between 63-67 years. Details of the treatment history (previous lines of therapy) was reported in few studies. In the GARNET trial, 63.9% had only received one prior line of treatment, as platinum-based chemotherapy was an inclusion criterion for entry into the study. Moreover, 25.0% of patients had received second line therapy at baseline and 8.3% of patients having already been exposed to three lines of therapy at baseline. Vergote et al. (6) represent an outlier of the comparator studies as the study allowed patients to enrol if they had at least one prior line of therapy and reported patients received a median of one previous line of therapy at baseline. All other studies specifically reported results for patients strictly receiving second line chemotherapy. Overall, in comparison with patients in the comparator studies, the patients enrolled in the GARNET trial were more heavily treated, which naturally favours comparator studies. In fact, the GARNET data demonstrated that the ORR in participants with dMMR EC was higher in participants who received 1 line of prior anticancer therapy (49.2%; N=65) than in participants who received 2 or more lines of prior anticancer therapy (36.8%; N=38).

Across the studies, most patients presented with endometrioid type I histology; the exception being Rubinstein e*t al*. who enrolled predominantly serous carcinoma patients (35.0%), or those with 'other' histology (35.0%).

Most patients involved in the nine included studies had advanced disease (FIGO stage III or IV) recorded. Nevertheless, more patients enrolled in the GARNET trial had FIGO stage IV disease (68%) compared to proportions ranging from 20.7% in Nomura et al. (20) and 41.0% in Nagao et al. 2015 (15). Additionally, more patients in the GARNET trial presented an ECOG level of 1, as compared to patients enrolled in the studies investigating paclitaxel and carboplatin. In the GARNET trial, at baseline, 38.8% of patients presented an ECOG of 0 and 61.2% of patients presented an ECOG of 1. In the Nomura et al. trial (20), 82.8% had a ECOG of 0 and 17.2% and an ECOG of 1 at baseline. This suggests that patients in the GARNET study had more severe disease and poorer performance status.

Conclusion

In the comparisons versus platinum-based chemotherapies, estimates of dostarlimab's efficacy is likely to be underestimated. This is due to several differences between the studies, which consistently favour the platinum-based chemotherapy. Most importantly these differences are:

The stratification of patients based on prior PFI in the comparator studies used a higher PFI threshold (i.e. 12 months) for defining platinum sensitive patients, than in GARNET, which might overestimate the efficacy of platinum-based chemotherapy in accordance with the DMC definition of PFI > 6 months.

- Patients included in the GARNET trial were more heavily pre-treated with 36.1% of patients receiving more than one prior line of therapy, whereas the comparator-studies only studied patients receiving one prior line (Vergote et al. being the exception).
- Patients included in the GARNET trial had more severe disease (FIGO-stage) and poorer performance status (ECOG), than patients included in the comparator trials treated with platinum-based chemotherapies.

Finally, the comparison is limited by the poor quality of the comparator-studies. Many of the studies had very few patients (6 out of 8 studies had ≤ 36 relevant patients included, and 4 out of 8 studies had ≤ 3 sites (Table 4). Some studies

reported on different treatment schedules and chemotherapy combinations, that are less relevant to Danish clinical practise (DGCG) (Table 4). A summary of the included studies, relevant for clinical question one, is presented in Table 4. Additionally, a tabulated overview of patient's baseline characteristics is presented in Table 5.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 4. Summary of studies included for Clinical question one

Intervention	Dostarlimab	Paclitaxel + Carboplatin						
Trial ID	**GARNET (7)**	**Mazgani (18)**	**Rubinstein (16)**	**Vergote (6)**	**Nagao 2013 (14)/ Nagao 2015 (15)**	**Miyake (17)**	**Nomura (20)**	**Ueda (19)**
NCT #	NCT02715284	-	-	-	-	-	-	-
Study design	Phase I/IIb open-label, single-arm study	Retrospective analysis of database	Retrospective analysis	Phase II prospective interventional	Retrospective cohort study/ Ancillary analysis	Retrospective cohort study	RCT, Phase II open-label	Case series, retrospective
Locations	117 sites in 9 countries	3 sites in Canada	1 site in the USA	12 sites in Belgium and Luxembourg	30 sites in Japan	two sites in Japan	Multiple sites in Japan	2 sites in Japan
N eligible patients	Efficacy analysis set: dMMR/MSI-H, N=108 Safety analysis set (ITT): dMMR/ MSI-H, N=129	N=31 (patients treated with carboplatin + paclitaxel in second line), of which: N=19 (EC) , N= 12 (serous histology)	N=20 (endometrioid histology only)	N=108 (total) N=36 (EC cohort)	Nagao *et al.* (2013): 262 (overall group) N=147 (TC) Nagao *et al.* (2015): 216	N=22 (total population) N=12 for TFI 6–12 months N=17 for TFI ≥12 months	N=29 (Docetaxel + carboplatin), N=29 (Docetaxel + cisplatin) N= 30 (Paclitaxel + carboplatin)	N=40 (overall group) N=24 (Paclitaxel + carboplatin cohort)

Intervention	Dostarlimab	Paclitaxel + Carboplatin						
Trial ID	**GARNET (7)**	**Mazgani (18)**	**Rubinstein (16)**	**Vergote (6)**	**Nagao 2013 (14)/ Nagao 2015 (15)**	**Miyake (17)**	**Nomura (20)**	**Ueda (19)**
Intervention and dose	Dostarlimab 500mg Q3W; 1000mg Q6W	Paclitaxel (175 mg/m^2) + carboplatin (AUC 5 or 6) Q4W	Paclitaxel + carboplatin (dose NR)	Paclitaxel (60 mg/m^2) + carboplatin (AUC 2.7) weekly + GCSF (0.600 mg/mL if < 60 kg; 0.960 mg/mL if ≥ 60 kg)	Platinum based chemotherapies (dose NR) N=36, AP (first-line) to TC/DC (second line) N=127 TC/DC (first line) to TC/DC (second line)	Monthly: Paclitaxel (175 mg/m^2) + carboplatin (AUC 5) ± epirubicin (80mg/m2) Weekly: Paclitaxel (80 mg/m^2) + carboplatin (AUC 2) ± epirubicin (80mg/m^2)	- Paclitaxel 180 mg/m2 IV+ Carboplatin AUC=6 IV Q3W - Docetaxel 70 mg/m2 IV and Carboplatin AUC=6 IV Q3W - Docetaxel 70 mg/m2 IV and Cisplatin 60 mg/m2 IV	Monthly: Paclitaxel (175 mg/m^2) + carboplatin (AUC 5) ± epirubicin (80mg/m^2) Weekly: Paclitaxel (80 mg/m^2) + carboplatin (AUC 2) ± epirubicin (80mg/m^2)
Data cuts (Median duration of follow-up, months)	1st March 2020 (11.2)*	August 2007 (NR)	Patients treated between January 2000 and December 2014 (NR)	NR (NR)	Patients treated between January 2005 and December 2009 (NR)	From 2000 to 2009 (NR)	Between December 2003 and May 2005 (NR)	2000–2008 (NR)

Abbreviations: AP, doxorubicin + cisplatin; AUC, area under the curve; DC, doxorubicin + carboplatin; EC, endometrial cancer; FDA, Food and Drug Administration; G-CSF, granulocyte colony stimulating factor; N, number; NR, not reported; PLD, pegylated liposomal doxorubicin; Q3W, every 3 weeks; Q6W, every 6 weeks; RCT, randomised controlled trial; TC, paclitaxel + carboplatin

Annotation: * please see section 6.1.1.1 for additional details on data-cuts.

Table 5. Baseline characteristics of patients for studies included in clinical question one

Intervention	Dostarlimab		Paclitaxel + carboplatin										
Trial ID	**GARNET (7)**		**Mazgani (18)**	**Rubin-stein (16)**	**Vergote (6)**	**Nagao 2013(14)/ Nagao 2015 (15)**		**Miyake (17)**		**Nomura (20)**			**Ueda (19)**
No. of patients	105 (Co-hort1 IA2 cut-off)	108 (Co-hort1 IA2 cut-off, EMA)	31 (total treated with TC in second line), N= 19 (EC), N= 12 (serous histol-ogy)	20	36 (EC Co-hort)	262 [a] (ITT) 147 (TC)	214 [b] (ITT) 163 (TC/DC)	12 (TFI 6-12 months)	17 (TFI ≥12months)	30 (docetaxel + carboplatin)	30 (docetaxel + cisplatin)	30 (paclitaxel + car-boplatin	40
Age, years													
Mean (SD)	63.1 (8.72)	63.2 (8.98)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Median	64.0	64.5	NR	67	66.5	63	65	NR	NR	NR	NR	NR	NR
Range	39 - 80	NR	NR	40-83	NR	37-86	37-80	NR	NR	61	64	66	NR
<65 (%)	53 (50.5)	54 (50.0)	NR	NR	NR	NR	NR	5 [c]	8 [c]	49-74	39-74	51-73	18 [c]
≥65 (%)	52 (49.5)	43 (39.8%)	NR	NR	NR	NR	NR	7 [d]	9 [d]	NR	NR	NR	22 [d]
Previous lines of therapy, n (%)													
1	66 (62.9)	69 (63.9)	31(100)	20 (100)	NR	147 (100)	163 (100)	12 (100)	17 (100)	NR	NR	NR	40 (100)

Intervention	Dostarlimab		Paclitaxel + carboplatin										
Trial ID	GARNET (7)		Mazgani (18)	Rubin-stein (16)	Vergote (6)	Nagao 2013(14)/ Nagao 2015 (15)		Miyake (17)		Nomura (20)			Ueda (19)
2	27 (25.7)	27 (25.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
3	9 (8.6)	9 (8.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
≥4	3 (2.9)	3 (2.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Median (range previous lines of therapy)	NR	NR	NR	NR	1.0 (0-2)	NR	NR	NR	NR	NR	NR	NR	NR
Prior surgery	56 (53.3)	NR	NR	NR	NR	NR	NR	NR	NR	19 (63.3)	21 (72.4)	20 (68.9)	NR
Prior radiother-apy	95 (90.5)	98 (90.7)	NR	NR	NR	14 (5.0)	7 (6.0)	NR	NR	5 (16.7)	4 (13.8)	4 (13.8)	NR
Median PFI/TFI (months)	6.51	6.51	NR	NR	NR	9	NR	7	12	NR	NR	NR	NR
Histology [e], n (%)													
EndoType I	71 (67.6)	71 (65.7)	62 (58.86)	3 (15.0)	14 (39.4)	153 (58.0)	64 (50.0)	11 (37.9)	13 (44.8)	19 (63.3)	22 (75.9)	22 (75.9)	32 (80.0)
EndoType 2	33 (31.4)	36 (33.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Serous	4 (3.8)	5 (4.6)	49 (44.14)	7 (35.0)	NR	34 (13.0)	21 (17.0)	NR	NR	6 (20.0)	2 (6.9)	2 (6.9)	4 (10.0)
Clear cell	1 (1.0)	1 (0.9)	NR	NR	NR	17 (7.0)	7 (6.0)	NR	NR	0 (0.0)	0 (0.0)	2 (6.9)	1 (3.0)

Intervention	Dostarlimab		Paclitaxel + carboplatin										
Trial ID	GARNET (7)		Mazgani (18)	Rubin-stein (16)	Vergote (6)	Nagao 2013(14)/ Nagao 2015 (15)		Miyake (17)		Nomura (20)			Ueda (19)
Squamous Carci-noma	1 (1.0)	1 (0.9)	NR	NR	NR	NR	NR	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	NR
Undifferentiated Carcinoma	4 (3.8)	4 (3.7)	NR	NR	NR	NR	NR	NR	NR	1 (3.3)	1 (3.4)	0 (0.0)	NR
Mixed Carcinoma	4 (3.8)	6 (5.6)	NR	3 (15.0)	NR	36 (14.0)	NR	NR	NR	2 (6.7)	2 (6.9)	1 (3.4)	NR
Other/unspeci-fied	19 (18.2)	19 (17.6)	NR	7 (35.0)	NR	22 (8.0)	17 (13.0)	1 (3.4)	4 (13.8)	0 (0.0)	1 (3.4)	0 (0.0)	3 (8.0)
Unknown	1 (1.0)	1 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
FIGO stage n (%)													
I	12 (11.4)	12 (11.1)	NR	5 (25.0)[g]	NR	29 (11.0)[g]	15 (12.0)	3 (25.0)[g,h]	8 (47.1)[g,h]	NR	NR	NR	10 (25.0)[g]
II	4 (3.8)	4 (3.7)	NR	3 (15.0)	NR	23 (9.0)	11 (9.0)	NR	NR	NR	NR	NR	6 (15.0)
III	16 (15.2)	19 (17.6)	NR	7 (35.0)	NR	122 (47.0)	49 (39.0)	9 (75.0)[j]	9 (52.9)[j]	9 (30.0)	5 (17.2)	6 (20.7)	19 (48.0)
IV	71 (67.6)	71 (65.7)	NR	5 (25.0)	NR	88 (33.0)	52 (41.0)	NR	NR	9 (30.0)	13 (44.8)	6 (20.7)	5 (13.0)
ECOG n (%)													
0	42 (40.0)	42 (38.9)	NR	NR	11 (33.3)	NR	NR	NR	NR	19 (63.3)	23 (79.3)	24 (82.8)	NR

Intervention	Dostarlimab		Paclitaxel + carboplatin										
Trial ID	GARNET (7)		Mazgani (18)	Rubin-stein (16)	Vergote (6)	Nagao 2013(14)/ Nagao 2015 (15)		Miyake (17)		Nomura (20)			Ueda (19)
1	63 (60.0)	66 (61.1)	NR	NR	NR	NR	NR	NR	NR	9 (30.)	5 (17.2)	5 (17.2)	NR
2	0 (0.0)	NR	NR	NR	NR	NR	NR	NR	NR	2 (6.7)	2 (6.7)	0 (0.0)	NR
1 to 2	0 (0.0)	NR	NR	NR	22 (66.6)	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: EC: endometrial cancer, ECOG: Eastern Cooperative Oncology Group, FIGO: international Federation of Gynecology and Obstetrics. ITT: intention to treatAnnotations: *No patients had received TC within the 6 months prior to retreating, aNagao et al. (2013), bNagao et al. (2015), [c] <60 years, d>60 years, eHistology was recorded at diagnosis, fFIGO stage was most recent unless otherwise stated, [g] FIGO stage at diagnosis, [h]: FIGO stage I or II, [j]: FIGO stage III or IV

6.1.1.1 GARNET

GARNET is an ongoing Phase 1 Dose Escalation and Cohort Expansion Study of dostarlimab, in Patients with Advanced Solid Tumours (7). GARNET is a multi-centre, open-label, single-arm, first-in-human phase I study evaluating the anti-programmed death receptor 1 (anti-PD-1) antibody dostarlimab, in participants with advanced solid tumours who have limited available treatment options. The study was conducted in 2 parts:

Part 1 consisted of safety evaluation, pharmacokinetics (PK), and pharmacodynamics (PD) of escalating doses of dostarlimab. Dose escalation was based on ascending weight-based dose levels (DLs) of dostarlimab and was continued until the maximum tolerated dose (MTD) was reached, or stopped at any dose level, up to the highest dose of 20 milligrams per kilograms (mg/kg), based on emerging safety and PK/PD data.

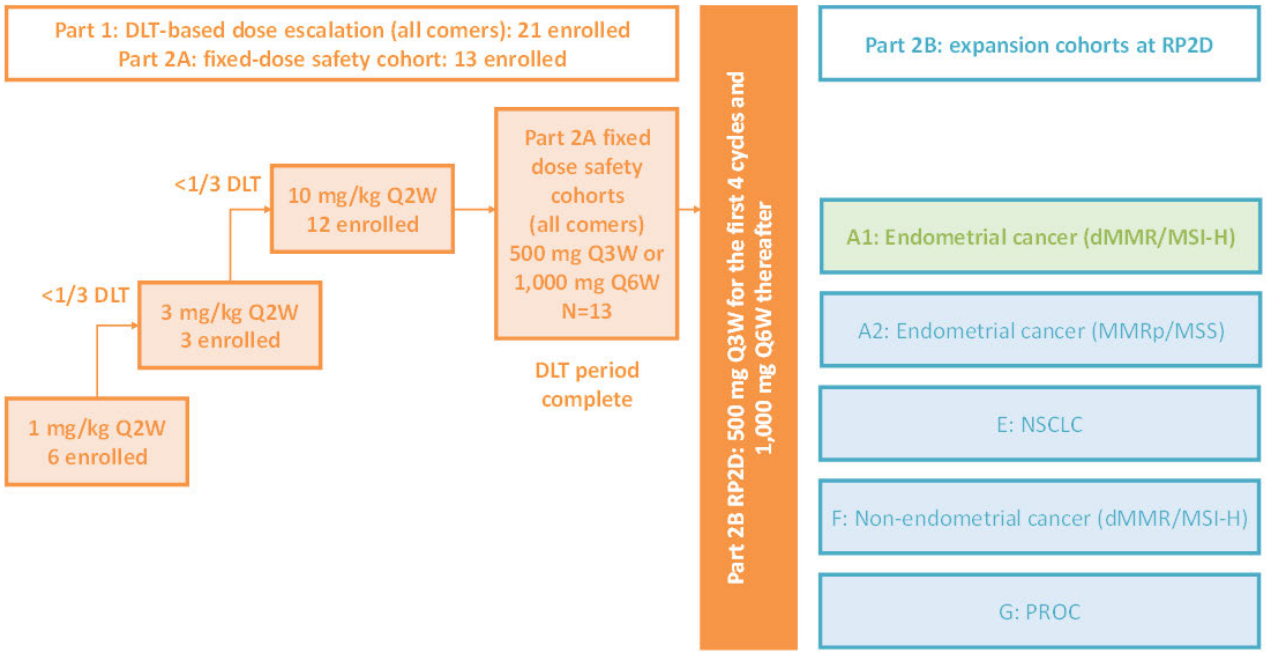
Part 2 was conducted in two subparts, Part 2A (fixed-dose safety evaluation cohorts) and Part 2B (expansion cohorts). Part 2A of the study evaluated the safety and tolerability of dostarlimab at fixed doses of 500 mg administered every 3 weeks (Q3W) and 1000 mg administered every 6 weeks (Q6W). Part 2B of the study examined the safety and clinical activity of dostarlimab in participants with specific types of advanced solid tumours. Data from Part 2B, cohort A1, and an overview of the clinical trial design is provided in Figure 2.

Part 1 of the study began on March 7, 2016 and started enrolling patients with dMMR EC on May 8, 2017. The estimated study completion date is November 30, 2023. To be included in the study, patients had to be at least 18 years of age and in addition have proven recurrent or advanced solid tumour and have disease progression after treatment with available anti-cancer therapies, or be intolerant to treatment, and finally met one of the following disease types:

- Part 1: Any histologically or cytologically proven recurrent advanced solid tumour
- Part 2A: Any histologically or cytologically proven recurrent advanced solid tumour
- Part 2B: Histologically of cytologically proven recurrent or advanced solid tumour with measurable lesion(s) per RECIST version 1.1 and meets one of the following disease types:
    - dMMR/MSI-H EC (Cohort A1)
    - MMR-proficient/MSS EC (Cohort A2)

For Part 2B, a total sample size of up to 680 participants for the expansion cohorts was estimated to provide assessment of clinical activity of dostarlimab based on ORR. In Cohort A1, which is the Cohort of interest for this submission, 129 patients with dMMR/MSI-H EC received 500 mg of dostarlimab intravenously every 3 weeks for 4 doses, followed by 1000 mg every 6 weeks until disease progression, treatment discontinuation due to toxic effect, or patient withdrawal of consent. A summary of the GARNET clinical trial design is presented in Figure 2.

Figure 2. GARNET clinical trial design



Abbreviations: DLT – dose-limiting toxicity; Q2W – every 2 weeks; Q3W – every 3 weeks; Q6W – every 6 weeks; dMMR – mismatch repair deficient; MSI-H – microsatellite instability-high; MMRp – mismatch repair proficient; MSS – microsatellite stable; NSCLC – non-small cell lung cancer; RP2D – recommended phase 2 dose; PROC – platinum-resistant ovarian cancer.

Source: adapted from clinicaltrials.gov (latest record for NCT02715284)(21), Oaknin et al. 2020(22) and GSK data on file (GARNET interim CSR report) 2019.(23)

The primary outcome of GARNET was objective response rate (ORR) and duration of response (DoR) based on independent blinded central review using RECIST version 1.1. Secondary endpoints were the Immune-related objective response rate (irORR) measured by irRECIST, disease control rate, immune related disease control rate, irDoR, PFS and OS. The median platinum-free interval was 6.51 months. An exploratory analysis of ORR based on RECIST v1.1 investigating PFI from platinum-containing prior anticancer therapy (< 6 months vs. ≥ 6 months vs. missing) was performed. The ORR in participants with dMMR EC was consistent in participants who had a PFI of ≥ 6 months or greater (46.0%; N=63) and in participants who had a PFO of < 6 months (39.5%; N=38). The results demonstrated that PFI is not a treatment modifier for dostarlimab, and results from the total population should be considered relevant to answer all clinical questions.

GARNET was planned with three interim analyses. The first interim analysis (IA-1) was performed when approximately 100 participants were enrolled using a data cut off per 08 July 2019, at which point 72 patients fulfilled the eligibility criteria for the primary efficacy, by having measurable disease at baseline and at least 24 weeks of follow-up.

The second interim analysis (IA-2) had a data cut-off of 1st of March 2020, where approximately 200 participants (including Cohort A1 and Cohort F) had measurable disease at baseline and at least 24 weeks of follow-up were enrolled. As of the cut-off date, for Cohort A1, a total of 129 participants with EC had received any amount of study drug and were included in the safety evaluation for the clinical study report.

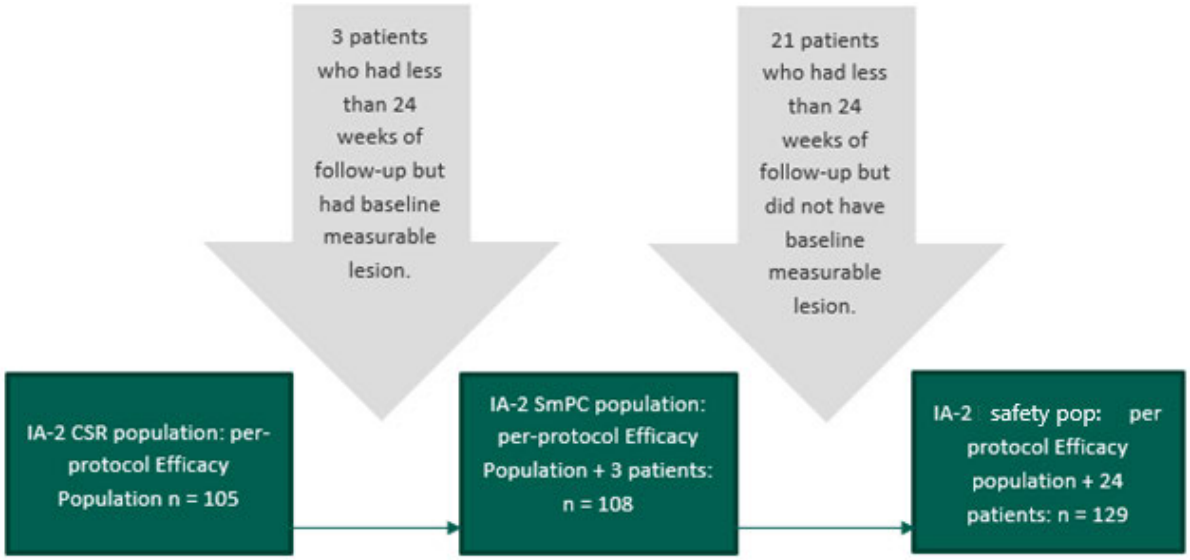
As of the second interim analysis (IA-2), a total of 105 dMMR/MSI-H EC patients fulfilled the eligibility criteria stated above. Nevertheless, as agreed with the Committee for Medicinal Products for Human use (CHMP), the efficacy population reflected in the SmPC is the per-protocol population of 105 patients, with an additional 3 patients who had measurable disease at baseline but had less than 24 weeks of follow up in the time of data cut off, and discontinued due to adverse events or disease progression, resulting in a total of 108 dMMR/MSI-H EC patients to be included in the SmPC. To be consistent with the data submitted to EMA, GSK has presented in this submission the efficacy results for the n =

108 dMMR/MSI-H EC patients presented below. It should be noted that the 72 participants with dMMR/MSI-H EC from IA-1 data cut were part of the primary efficacy analysis set of participants with dMMR/MSI-H EC (N=105) in Cohort A1 in the interim data cut-off IA-2.

The interim analysis of interest for this submission is the IA2 of March 2020 (n = 108), because of the longer follow-up and a higher number of patients included. Additionally, as mentioned above, the safety analysis set, includes all participants with dMMR/MSI-H EC (n = 129) who received dostarlimab regardless of follow-up time. Figure 3 presents the GARNET datasets and details the differences.

A subsequent analysis has been carried out in November 2020 and the results for cohort A1 have been presented at ASCO 2021. At this subsequent data cut-off, the median follow-up time was 20.4 months, and the median DOR was 34.7 months. The results of this subsequent analysis are not presented in detail in this submission as this was a partial data-cut with no relevant efficacy outcomes for the DMC protocol (24).

Figure 3. Summary of different GARNET populations within the IA-2 data cut of March 2020



The economic model uses the per protocol efficacy population n=105, where patients had sufficient follow-up of at least 24 weeks. This minor difference compared to the EMA efficacy population, is not expected to have a significant impact on the results, as patients baseline characteristics overall were extremely similar between the two patient populations. [redacted] illustrates that the number at risk remains the same for both n=105 and n=108 throughout the duration of the study. When overserving the KM-curve for PFS a complete overlap of the curves, indicating no differences should be expected between the results of the clinical dossier and the economic model.

6.1.1.2 Nagao 2013

Nagao 2013 was a multicentre retrospective cohort study including a total of 262 patients with histologically confirmed EC or uterine carcinosarcoma, who received second-line platinum-based chemotherapy between January 2005 and December 2009 (histological confirmation of recurrence was not required).

The objective of Nagao et al. 2013 (14) was to evaluate the relationship between PFI and response to second-line platinum-based chemotherapy. This was a SGSG012/GOTIC004/Intergroup study.

The primary outcome was ORR. Secondary endpoints included OS, PFS, CR and PR.

6.1.1.3 Nagao 2015

Nagao et al. 2015 (15) is an ancillary analysis conducted using the dataset from the SGSG012/GOTIC004/Intergroup study. The purpose of this study was to determine an appropriate second-line platinum-based regimen for patients with a history of receiving platinum-based chemotherapy in first line and, particularly, to evaluate whether alternations to second-line chemotherapy regimens are reasonable.

A total of 214 patients with histologically confirmed EC or uterine carcinosarcoma, who received second-line platinum-based chemotherapy between January 2005 and December 2009, were registered. All patients had received primary platinum-based chemotherapy. In this ancillary analysis, the authors extracted data of patients who received doxorubicin and cisplatin combination chemotherapy (AP therapy), paclitaxel + carboplatin (TC) therapy, or docetaxel and carboplatin combination chemotherapy (DC therapy) as first- and second-line chemotherapy regimens.

The primary outcome was ORR. Secondary endpoints included, PFS, CR and PR.

6.1.1.4 Rubinstein

Rubinstein et al. (16) is a retrospective, single-centre study that examined the clinical outcomes of EC patients who received TC in the adjuvant setting, and who were specifically re-treated with TC at the time of recurrent or metastatic disease.

Between January 2000 and December 2014, the authors identified 20 EC patients who had previously received TC and were re-treated with TC at the time of recurrence, through an institutional database at Memorial Sloan Kettering Cancer Centre. An independent radiologist blinded to patients' clinical details assessed response per RECIST 1.1 criteria.

The main outcomes of interest were ORR, the median PFS to re-treatment with TC, PFS and OS from re-treatment with TC and OS from original diagnosis.

6.1.1.5 Miyake

Miyake et al. (17) was a retrospective study which included 29 patients with EC from two sites in Japan. The purpose was to evaluate the association of prognosis of EC patients and TFI. The response to second-line chemotherapy, after failure to first-line chemotherapy (platinum and taxane with or without adriamycin) in patients with a TFI of 6-12 months was compared with those with a TFI of 12 or more months.

Patients had initial first-line adjuvant or salvage paclitaxel and carboplatin (TC) or paclitaxel and carboplatin with anthracycline (TEC). In second line, patients were offered different chemotherapy options. Of these, the ones that were retained as relevant for this submission are patients who received TEC or TC, including weekly TC.

The primary outcome was CR and secondary outcomes were PR, SD, and PFS. The study did not use RECIST criteria.

6.1.1.6 Mazgani

Mazgani et al. is a retrospective analysis of 200 high-risk patients with EC, who had been treated with TC (carboplatin AUC 5–6 and paclitaxel 175 mg/m2 over 3 h). 111 of these patients experienced a relapse during the period of 1995–2007. (18)

The objective of the study was to evaluate the efficacy of retreating with TC in women with relapsed EC. The 111 patients were subdivided into those with endometroid or papillary serous pathologies, because of their different genetic profiles and outcomes. There was no standard, mandated therapy for the patients after relapse. When carboplatin plus paclitaxel was reused, following doses were administered: carboplatin AUC 5 or 6 plus paclitaxel 175 mg/m2 over 3 h every 4 weeks until progression or unacceptable toxicity. Of the 62 women with relapses in the endometroid histology group, 28 women were retreated with chemotherapy and, of these, 19 received carboplatin–paclitaxel. In the papillary serous group of 49 relapses, 24 women were retreated with chemotherapy and of these 12 received carboplatin–paclitaxel.

Tumour measurements were abstracted from the imaging reports. Response was recorded according to the RECIST criteria based upon a CT-scan except that the best response achieved was recorded with no requirement for confirmation by repeat imaging four or more weeks later and no use was made of tumour markers.

6.1.1.7 Vergote

Vergote et al. is a phase II prospective study, and the objective of the study was to investigate the addition of G-CSF to each weekly TC treatment in patients with a recurrent platinum-resistant ovarian (OC) or recurrent or advanced EC or cervical carcinoma (CC). (6)

Eligibility criteria included being 18 years of age, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate bone marrow function.

Relevant for this assessment the study included 36 patients in the EC cohort with recurrent or advanced EC.

Patients with at least one earlier platinum treatment could be included in this cohort but they had to be platinum-refractory or platinum-resistant. Disease was measured by RECIST version 1.1 criteria. Patients were treated with weekly intravenous paclitaxel at a dose of 60 mg/m2 and carboplatin at an AUC of 2.7.

The primary endpoint of this study was the incidence of grade 3-4 neutropenia in comparison with historical controls. The secondary endpoints of the study were the occurrence of grade 3–4 neutropenia per cohort, other toxicities, dose reductions and delays, PFS, ORR and OS.

6.1.1.8 Ueda

The purpose of this retrospective study conducted at two sites in Japan, was to investigate the effectiveness of second-line chemotherapy treatment of advanced or recurrent endometrial carcinoma previously treated with a combined chemotherapy of taxane and platinum, with or without anthracycline (19).

Patients were enrolled in the study if they were treated by a second-line chemotherapy for their recurrent disease, after initial first-line adjuvant or salvage paclitaxel, epirubicin, and carboplatin (TEC) or TC therapy. In the first line setting patients received monthly TEC (TECm) treatment, paclitaxel (150 mg/m2), carboplatin (AUC = 4) and epirubicin (50 mg/m2) administered intravenously, or monthly TC regimen (TCm) therapy, paclitaxel (175 mg/m2) and carboplatin (AUC = 5) were administered. In the weekly TC regimen (TCw), paclitaxel (80 mg/m2) and carboplatin (AUC = 2) were administered on a 4-week cycle.

723 women were diagnosed with endometrial carcinomas and 40 patients required a second-line chemotherapy against a recalcitrant or recurrent disease, after having first received an adjuvant or salvage first-line chemotherapy using TECm, TCm or TCw. Of the 40 patients who received second-line chemotherapy, 24 patients received second line TEC, TCm or TCw. Despite the differences in treatment regimens and combinations data were included in the application as they were deemed relevant in accordance with the DMC's protocol.

The primary outcome of this study was ORR and secondary outcomes were PFS and OS.

6.1.1.9 Nomura

Nomura et al (20) conducted a randomised Phase 2 study comparing docetaxel plus cisplatin (DP), docetaxel plus carboplatin (DC) and TC in patients with advanced or recurrent endometrial carcinoma.

The main inclusion criteria in this study were as follows: primary lesion histologically confirmed to be EC; FIGO stage III, stage IV, or recurrent cancer. Prior chemotherapy was permitted and there was no limitation to the number of prior chemotherapy regimens. A total of 90 patients were admitted to the study, comprising 30 in each group.

Patients were randomised to docetaxel 70 mg/m2 IV on day 1 cisplatin 60 mg/m2 IV on day 1 every 21 days, docetaxel 70 mg/m2 IV on day 1 carboplatin AUC=6 IV on day 1 every 21 days or paclitaxel 180 mg/m2 IV on day 1 carboplatin AUC=6 IV on day 1 every 21 days.

The Nomura study reported several efficacy outcomes, but these are not of interest, as the patient population was mainly patients receiving first line treatment for EC, and therefore only grade 3-4 AEs reported from this trial is reported in this dossier.

6.1.2 Results per study

6.1.2.1 GARNET

Measures of mortality

Median OS

At the data cut-off of March 2020, with 16.3 months median follow-up, the was not sufficiently mature to estimate the median (median OS: NR (95% CI: (17.1, NR) (3).

OS rate at 12 months

At the IA-2 data cut-off of March 2020, with a median follow-up of 16.3 months, dostarlimab was associated with a 12-month landmark OS of 69.2% (95% CI: 58.8-77.6) .

[redacted]

Measures of disease progression

Median PFS and PFS rate at 24 months

At the data cut-off of March 2020, dostarlimab was associated with a median PFS of 5.5 months (95% CI: 3.2-NR)[redacted] Nevertheless, median PFS is an unreliable metric of the efficacy of Dostarlimab in the GARNET trial. As showed below in [redacted] Kaplan Meier median PFS-estimate is very volatile and sensitive to censoring and events, as a prolonged tail of the curve is formed right around the median, which results in a single event can shift the PFS-estimate by 6 months or more. This was observed when compared the median PFS estimate from the initial data-cut IA-1 (n = 72), which provided a median PFS of > 12 months, whereas the curve was shifted for the IA-2 population to a median PFS of 5.5 months (95% CI: 3.2-NR), due to censoring and a single event occurring (**Fejl! Henvisningskilde ikke fundet.**). The 24-month landmark PFS-estimate, presented below, is a more meaningful measure of the value of dostarlimab, as it demonstrates sustained effect and patients responding to dostarlimab experience long-term disease remission. At 24 months, it was observed that [redacted]% of patients treated with dostarlimab had not yet progressed or died, which is a very significant finding, that starkly contrast the survival observed for patients treated with platinum-based chemotherapy. This is explored further in the narrative summary provided in section 6.1.3.2.

Objective response rate

ORR was achieved by 47 patients (43.5%) [95% CI 34.0-53.4] among the 108 dMMR/MSI-H EC patients included in the analysis at the March 2020 data cut-off using RECIST 1.1 criteria. Best overall response is shown in Table 6.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 6. GARNET Best overall response, data cut IA2

Variable	N=108
Best overall response, n (%)	
CR	11 (10.2%)
PR	36 (33.3%)
SD	13 (12.0%)
PD	39 (36.1%)
Not evaluable	6 (5.6%)
Not done	3 (2.8%)
Confirmed ORR by RECIST 1.1	
n (%)	47 (43.5%)
95% CI	34.0%, 53.4%
Response on-going[a]	42 of 47 (89.4%)

[a] All responders who have not yet died or progressed (including clinical progression); denominator for percentage is number of responders.

Abbreviations: CR – complete response; ND – not done; NE – not evaluable; ORR – objective response rate; PD – progressive disease; PR – partial response; SD – stable disease.

Source: adapted from GSK data on file (data cutoff: 1 March 2020) adapted from GSK data on file (data cut off: 1 March 2020) CSR

Additionally, ORR as measured by the irRECIST assessment is presented in section 96. "Other considerations. The efficacy results in patients with dMMR EC based on the investigators' assessment using irRECIST assessments were similar to the efficacy results by BICR using RECIST v1.1 assessment.

Measure of Quality of life

EORTC QLQ-C30

In GARNET the EORTC QLQ-C30 questionnaire was collected every 3 weeks (± 7 days) for the first 12 weeks beginning on cycle 1/day 1, then every 6 weeks (± 7 days) thereafter while the patient was receiving study treatment. Once a patient discontinued treatment, PRO assessments were performed during the end of treatment (EOT) visit, safety follow-up visit, and every 90 days (±14 days) during the post-treatment follow-up period. The baseline assessment of the EORTC QLQ-C30 questionnaire was carried out in 94 out of 129 dMMR/MSI-H EC patients who received at least one dose of dostarlimab. The completion rate for the EORTC QLQ-C30 was consistent across domains, ranging from 100% at baseline to 58.5% at cycle 7.

All the scales and the single-item measures range in score from 0 to 100. For the functioning scales and global QOL, higher scores indicate better functioning; for the symptom scales, higher scores indicate a higher symptom burden. For the global health status/quality-of-life score and for the functional subscales, an increase of ≥10 points are considered a clinically relevant improvement, whereas a decrease of ≥10 points is considered a clinically relevant deterioration. For the symptom subscales, the same increase and decrease of ≥10 is considered relevant. Changes of fewer than 10 points were considered as no change, or of minor clinical relevance.(25)

The data reported in this section derives from the IA-2 data cut of March 2020. As shown in Figure 8, Figure 9, Figure 10, Figure 5. and Table 7 below, dostarlimab ensured overall stability in the patients quality of life as determined by QLQ-C30 subscales. Patients reported changes in scores ≤ 10 points across the functional scales and the symptom scales, indicating clinically relevant improvements relative to baseline in social functioning and in pain reduction and a slight worsening in dyspnoea. Figure 6. presents a summary of the number of patients who have completed the questionnaire, for each cycle.

Figure 7. Cumulative patient disposition of EORTC QLQ-C30, PRO and Safety Analysis set – Cohort 1

	Baseline	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 7 Day 1
N	94	94	94	94	94	94	94
Ongoing [n(%)]	94 (100)	91 (96.8)	87 (92.6)	82 (87.2)	73 (77.7)	61 (64.9)	55 (58.5)
Progressed [n(%)]	0	0	1 (1.1)	4 (4.3)	10 (10.6)	21 (22.3)	26 (27.7)
Died [n(%)]	0	0	0	0	0	0	0
Other [n(%)]	0	3 (3.2)	6 (6.4)	8 (8.5)	11 (11.7)	12 (12.8)	13 (13.8)

Ongoing: number of PRO questionnaire forms expected to be completed by patients. The date of treatment discontinuation is used to determine the last visit at which a patient is still expected to complete the PRO questionnaire form during the study periods.
Source: Table 1.1.1

Figure 8. Mean change in Fatigue from Baseline, Safety analysis set, Cohort A1

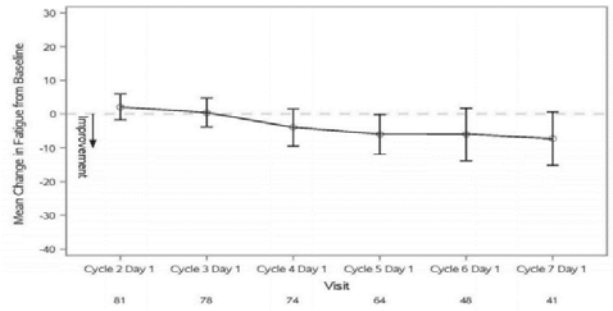


Figure 9. Mean change in Nausea and vomiting from Baseline, Safety analysis set, Cohort A1

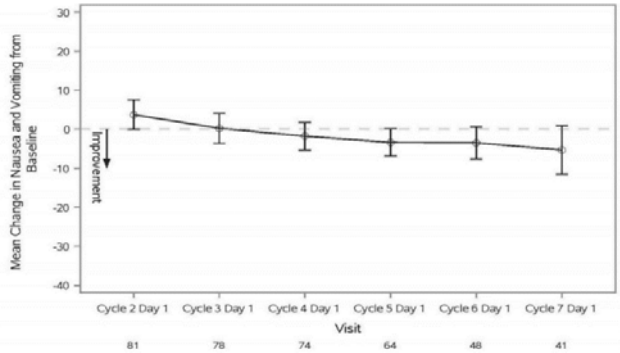


Figure 10. Mean change in Pain from Baseline, Safety analysis set / Cohort A1

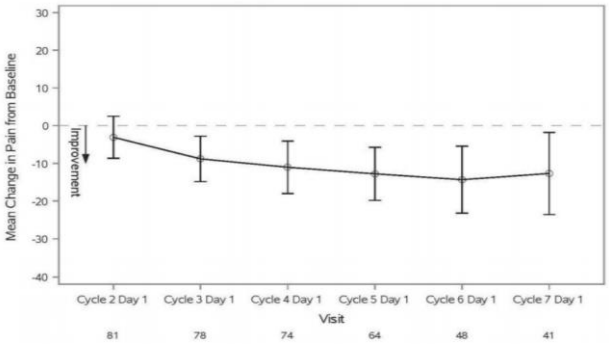


Figure 11. Mean change from Baseline in Global Health Status/ QoL, Safety analysis set – Cohort A1

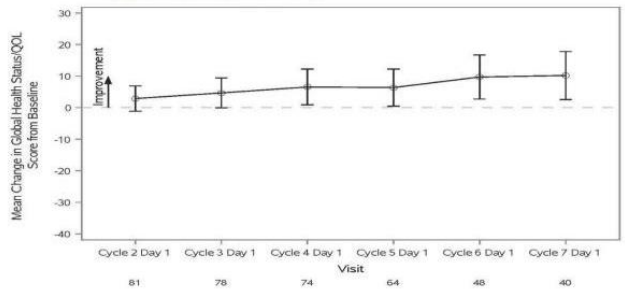


Table 7. Mean change from baseline to end of treatment in QLQ-C30 for the GARNET trial

	GARNET
Intervention	Dostarlimab
N	94
Mean (SD) CFB	
Global QoL	[redacted]
Physical Functioning	[redacted]
Role Functioning	[redacted]
Emotional Functioning	[redacted]
Cognitive Functioning	[redacted]
Social Functioning	[redacted]
Fatigue	[redacted]
Nausea and vomiting	[redacted]
Pain	[redacted]
Dyspnea	[redacted]
Insomnia	[redacted]
Appetite loss	[redacted]
Constipation	[redacted]
Diarrhoea	[redacted]
Financial difficulties	[redacted]

Abbreviations: CFB, change from baseline; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation

Adverse events

In the section below, the proportion of patients experiencing at least one adverse reaction of grade 3-4 is presented, and in addition a narrative summary of safety from the SmPC will be provided. Further details on safety are presented in Appendix 9.5.

Proportion of patients experiencing at least one adverse reaction of grade 3-4

The safety results were presented for all participants who received study treatment (safety analysis set), which included a total of 129 participants. In GARNET, at the data cut-off at March 2020, a total of 48.1% of participants experienced a grade ≥3 treatment emergent adverse event (TEAE). Full details of grade ≥3 TEAE experienced in ≥3 Participants are presented in Table 8. Discontinuation because of treatment-related AEs was low (11.6%).

Although 48.1% of participants experienced a grade ≥3 TEAE (Table 8), only 17 patients (13.2%) were reported to experience grade ≥3 TEAEs considered related to dostarlimab. Dostarlimab-related grade ≥3 TEAEs occurring in ≥2 patients were anaemia (3.9% of patients), lipase increased (2.3% of patients), alanine aminotransferase increased (1.6% of patients), diarrhoea (1.6% of patients), transaminases increased (1.6% of patients) and colitis (1.6% of patients). None of the fatal TEAEs were considered related to treatment with dostarlimab.

Table 8. Grade 3 or greater TEAEs in ≥3 Participants (Safety analysis set) data cut-off IA2

Preferred term	Number of patients (%) (n=129)
Any Grade ≥3 TEAE	62 (48.1)
Grade 3 Anaemia	19 (14.7)
Grade 3 Abdominal pain	7 (5.4)
Hyponatraemia	5 (3.9)
Grade 3	4 (3.1
Grade 4	1 (0.8)
Grade 3 Acute kidney injury	4 (3.1)
Grade 3 back pain	4 (3.1)
Pulmonary embolism	4 (3.1)
Grade 3	3 (2.3)
Grade 4	1 (0.8)
Sepsis	4 (3.1)
Grade 4	3 (2.3)
Grade 5	1 (0.8)
Grade 3 Alanine aminotransferase increased	3 (2.3)
Grade 3 Diarrhoea	3 (2.3)
Grade 3 Hypertension	3 (2.3)
Grade 3 Lipase increased	3 (2.3)
Pneumonia	3 (2.3)
Grade 3	2 (1.6)
Grade 5	1 (0.8)
Grade 3 Urinary tract infection	3 (2.3)

Abbreviations: TEAEs = treatment emergent adverse events

Narrative summary of safety

Overall safety summary:

The safety of dostarlimab has been evaluated in 515 patients with EC, or other advanced solid tumours (EMA safety pool (26)) who received dostarlimab monotherapy in the GARNET study (all Cohorts shown in Figure 2), including 129 patients with advanced or recurrent dMMR/MSI-H EC. Patients received a dose of 500 mg every 3 weeks for 4 cycles, followed by 1000 mg every 6 weeks. The safety profile for patients with dMMR/MSI-H EC in the GARNET study (N=129) did not differ from that of the overall monotherapy population presented in table 8, and therefore GSK report results of the safety profile observed in the EMA-safety pool.

Dostarlimab was most commonly associated with immune-related adverse reactions, as common for all PD-1/PD-L1 inhibitors (26). Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of dostarlimab. In the safety pool, the most common adverse reactions (> 10 %) were anemia (25.6 %), nausea (25.0 %), diarrhea (22.5 %), vomiting (18.4 %), arthralgia (13.8 %), pruritus (11.5 %), rash (11.1 %), pyrexia (10.5 %), and hypothyroidism (10.1 %). Dostarlimab was permanently discontinued due to adverse reactions in 17 (3.3 %) patients; most of them were immune-related events. Adverse reactions were serious in 8.7 % of patients; most serious adverse reactions were immune-related adverse reactions (26).

Immune-related adverse events in 129 patients with advanced or recurrent dMMR/MSI-H EC

In patients with dMMR/MSI-H EC, 47 patients (36.4%) reported irAEs. The most frequently reported irAEs (>5%) were diarrhea (8.5%) and hypothyroidism (7.0%) The median time to onset across events reported in ≥2% patients varied from 19 days (for pruritus) to 380 days (for colitis). Almost half of the patients required treatment with immune modulatory medication (IMM) to manage the irAEs and most of them were resolved at the time of the data cut-off date. (26). IrAEs reported by patients enrolled in GARNET are presented in detail in the Safety appendix, in Table 73.

Management of immune-related adverse reactions:

Immune-related adverse reactions, which may be severe or fatal, can occur in patients treated with antibodies blocking the programmed cell death protein-1 / programmed death-ligand 1 (PD-1/PD-L1) pathway, including dostarlimab. While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment.

Treatment with dostarlimab should be withheld or permanently discontinued in cases of a grade 3 or 4 immune-related adverse reaction, and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy should be administered. If not controlled by corticosteroid a systemic immunosuppressant can be considered. Treatment with dostarlimab should be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies, that are controlled with replacement hormones and unless otherwise specified in the SmPC. Detailed instructions for handling immune-related adverse reactions are provided in the SmPC including dose-modifications and treatment (26).

Early identification and management of immune-related adverse reactions are essential to ensure a safe use of PD-1/PD-L1 blocking antibodies. Patients should be monitored for symptoms and signs of immune-related adverse reactions. Blood tests, including liver tests and thyroid function tests, should be evaluated at baseline and periodically during treatment.

6.1.2.2 Nagao 2013

This study was a multicentre retrospective cohort study which included a total of 262 Japanese patients. However, the results of this study should be interpreted with caution due to the strictly Japanese baseline characteristics which are generally not considered transferable to a Danish setting. Patients included in the study received second line treatment

with platinum-based chemotherapy and were classified per duration of platinum-free interval (PFI). Results of patients with PFIs of 6–11 months, 12–23 months, and ≥24 months were reported.

Measures of mortality

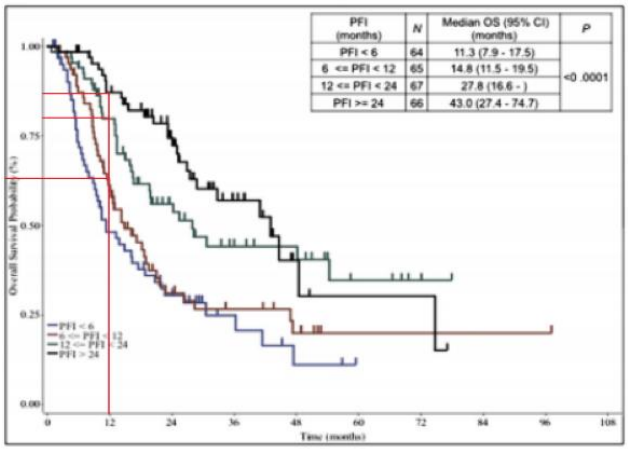
Median OS

At a median follow up of 16.9 months, the median OS was 14.8 months (11.5–19.5) for patients with PFI of 6–11 months, 27.8 months (16.6 – NA) for patients with a PFI of 12–23 months, and 40.9 months (25.3–54.2) for patients with PFI of ≥24 months (P= 0.0001,).

OS at 12 months

Based on the KM-curve in the publication, OS at 12 months was approximately 67% for patients with PFI of 6–11 months, 79% for patients with a PFI of 12–23 months and 88% for patients with a PFI of ≥24 months.

Figure 12. OS KM-curves for Nagao et al. 2013 for 2L patients by subgroups based on PFI (adapted by GSK from Nagao et al. 2013 (14))



Measures of disease progression

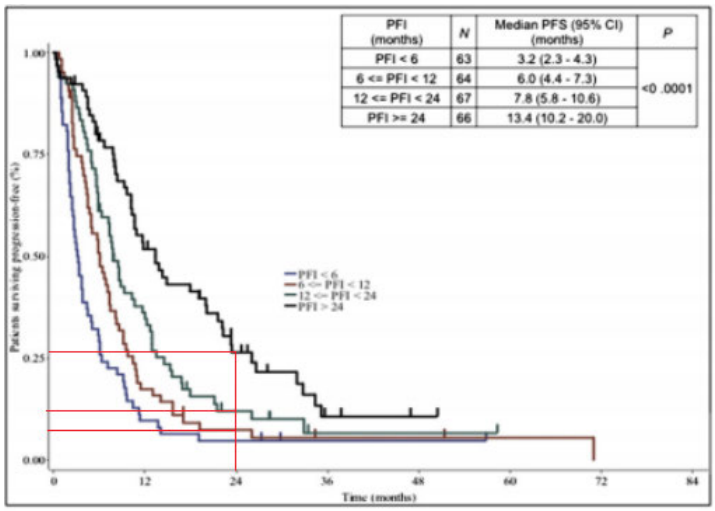
Median PFS

The median PFS was 6.0 months (4.4–7.3) for patients with PFI of 6–11 months, 7.8 months (5.8 – 10.6) for patients with a PFI of 12–23 months, and 13.4 months (10.2–20.0) for patients with PFI of ≥24 months (P= 0.0001,).

PFS at 24 months

Based on the KM-curve in the publication, the 24-month PFS-rate was approximately 8% for the patients with PFI 6-11 months, approximately 12%, for the patients with a PFI of 12–23 months and approximately 27% for the patients with PFI≥24 months.

Figure 13. PFS KM-curves for Nagao et al. 2013 for 2L patients by subgroups based on PFI (adapted by GSK from Nagao et al. 2013 (14))



Objective response rate

The response rates for patients with PFIs of, 6–11 months, 12–23 months, and ≥24 months were 38%, 61%, and 65%, respectively. The response to second-line platinum-based chemotherapy increased with a longer PFI (P < 0.0001, Cochran–Armitage trend test).

All outcomes reported in Nagao et al, 2013 are summarised in Table 9.

Table 9. DMC protocol outcomes reported for Nagao et al, 2013

	PFI of 6–11 months (n=65)	PFI of 12–23 months (n=67)	PFI of ≥24 months (n=66)
Median OS (months)	14.8 months (11.5–19.5)	27.8 months (16.6 – NA)	40.9 months (25.3–74.7)
OS at 12 months (%)	Approximately 67%	Approximately 79%	Approximately 88%
Median PFS (months)	6.0 months (4.4–7.3)	7.8 months (5.8 – 10.6)	13.4 months (10.2–20.0)
PFS at 24 months (%)	Approximately 8%	Approximately 12%	Approximately 27%
ORR (%)	38%	61%	65%
EORTC-QLQ-EN24	Non-reported	Non-reported	Non-reported
EORTC QLQ-C30	Non-reported	Non-reported	Non-reported
Adverse events of grade 3-4	Non-reported	Non-reported	Non-reported

6.1.2.3 Nagao 2015

Nagao et al. published an ancillary study to their first publication of 2013. The same limitation to the interpretability of the results due to the inclusion of only Japanese patients should be applied here. Patients treated with a second line

platinum-based chemotherapy were classified according to the first and second-line regimen and further classified by duration of PFI (<6 months; ≥6, <12 months; ≥12, ≤24 months; and ≥24 months). The 127 patients treated with paclitaxel and carboplatin (TC)/ docetaxel and carboplatin (DC) in first line and second line chemotherapy are of interest for this submission. Results are reported as one value across PFIs since no breakdown per PFI duration is provided. However, only 21 (17 %) of the 127 patients had a PFI < 6 months so the majority of the patients belongs to the population of interest for clinical question 1. ORR was reported split per PFI <12 months and >12 months.

Measures of mortality

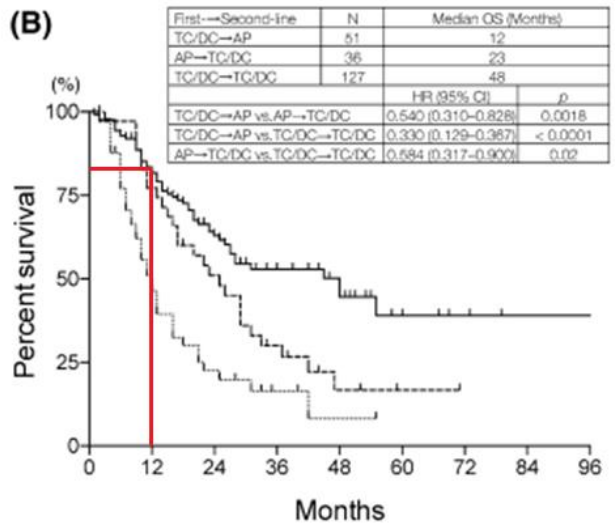
Median OS

Among the 127 patients who received paclitaxel and carboplatin / docetaxel and carboplatin (TC/DC) in first and second line, the median OS was 48 months.

OS at 12 months

Based on the KM-curve in the publication, the proportion of patients who were still alive at 12 months was estimated to be approximately 85%.

Figure 14. Estimates of OS after second-line chemotherapy in patients who received TC/DC therapy as first-line chemotherapy, and second line (15) (modified by GSK)



Measures of disease progression

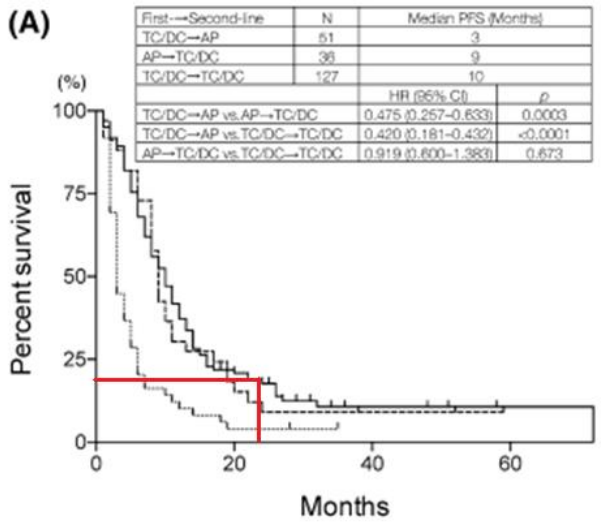
Median PFS

Among the 127 patients who received TC/DC both in first and in second line, the median PFS was 10 months.

PFS at 24 Months

Based on the KM-curve in the publication, the proportion of patients who were progression-free at 24 months was estimated to be approximately 20%.

Figure 15. Estimates of PFS after second-line chemotherapy in patients who received TC/DC therapy as first-line chemotherapy, and as second line therapy (15) (modified by GSK)



Objective response rate

Among the 127 patients who received TC/DC in both and second line and had a PFI of <12 months reported an ORR of 40%. Those patients who had a PFI >12 months reported an ORR of 67%.

Table 10. Objective response rate in Nagao et al. 2015

Platinum-free interval	< 12 months	≥12 months
First-line regimen	TC/DC	TC/DC
Second-line regimen	TC/DC	TC/DC
Complete response	9	25
Partial response	12	19
Stable disease	18	11
Progression disease	13	11
Response rate (%)	40	67

Abbreviations: AP: doxorubicin and cisplatin combination chemotherapy, TC: paclitaxel and carboplatin combination chemotherapy, DC: docetaxel and carboplatin combination chemotherapy

All outcomes reported in Nagao et al. 2015 are summarised in Table 11.

Table 11. DMC protocol outcomes reported in Nagao et al, 2015

	platinum-free intervals of >6 months
Median OS (months)	48
OS at 12 months (%)	Approximately: 84
Median PFS (months)	10
PFS at 24 months (%)	Approximately: 20
ORR (%)	See Table 10
EORTC-QLQ-EN24	Non-reported
EORTC QLQ-C30	Non-reported
Adverse events of grade 3-4	Non-reported

6.1.2.4 Rubinstein

20 EC patients who were re-treated with second line TC were retrospectively included in this study. No patients were retreated with a PFI of less than 6 months. Results should be interpreted with caution, due to the small sample size and the nature of the analysis, which was a retrospective analysis of data from the registry of a single site.

Measures of mortality

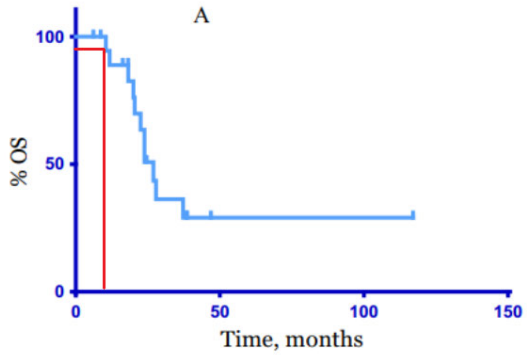
Median OS

The median OS from cycle 1 day 1 retreatment with carboplatin and paclitaxel was 27 months.

OS at 12 months

Based on the KM-curve in the publication, approximately 95% of patients treated with carboplatin and paclitaxel who were still alive at 12 months.

Figure 16. Estimates of OS at 12 months for patients retreated with carboplatin and paclitaxel. (Adapted by GSK from Rubinstein et al (16))



Measures of disease progression

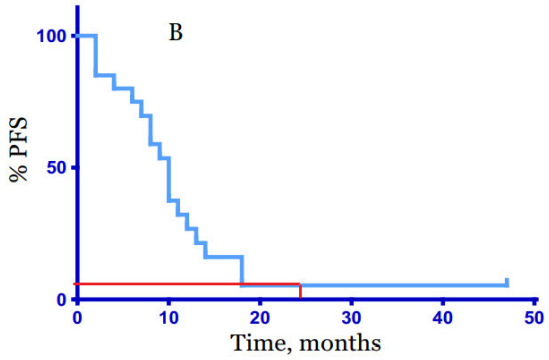
Median PFS

The median PFS from cycle 1 day 1 from retreatment with carboplatin and paclitaxel was 10 months.

PFS at 24 months

Based on the KM-curve in the publication, 6% of patients were still progression free at 24 months.

Figure 17. Estimates of PFS at 24 months for patients retreated with carboplatin and paclitaxel (Adapted by GSK from Rubinstein et al (16))



Objective response rate

At the data cut-off, there were no CR, 10 (50%) patients had PR, 3 (15%) had stable disease, 2 (10%) had progression at best response and 5 (20%) were not evaluable by RECIST. ORR was 50%. All outcomes reported in Rubinstein et al. are summarised in Table 12.

Table 12. DMC protocol outcomes reported in Rubinstein et al

	Patients retreated with carboplatin and paclitaxel n=20
Median OS (months)	27
OS at 12 months (%)	Approximately 95%
Median PFS (months)	10
PFS at 24 months (%)	Approximately 6%
ORR (%)	ORR: 50% CR: 0%, PR: 50%, SD: 15%
EORTC-QLQ-EN24	Non-reported
EORTC QLQ-C30	Non-reported
Adverse events of grade 3-4	Non-reported

6.1.2.5 Miyake

Miyake et al. retrospectively analysed data from two hospitals in Japan. Of the 29 patients included in Miyake et al. only results for 22 patients treated with TC and anthracycline combination are reported in this section. Miyake et al. results were stratified by TFI of <6 months, TFI of 6 to 12 months and TFI or more than 6 months. To answer clinical question one, the two latter ones were deemed relevant and are reported here. Results should be interpreted with caution, due

to the small sample size, the retrospective nature of the study, the restricted ethnicity of the patients, and the data collected from only two sites.

Measures of disease progression

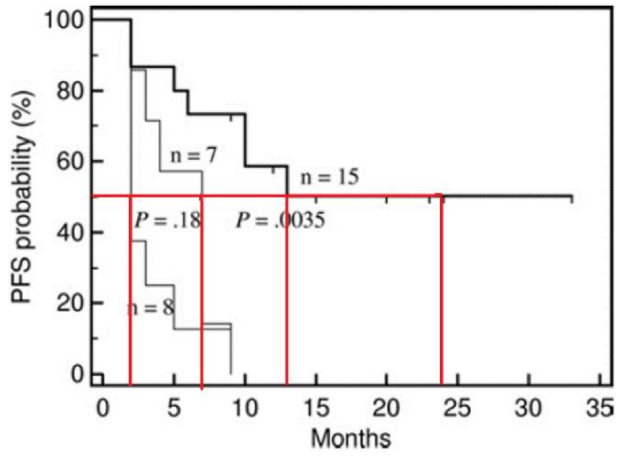
Median PFS

Based on the KM-curve in the publication, the 7 patients with a TFI of 6-12 months had a median PFS of 7,5 months and the 15 patients with a TFI of 12 or more months had a median PFS of 13 months.

PFS at 24 months

Based on the KM-curve in the publication, approximately 50% of the 15 patients with a TFI of 12 months were on PFS at 24 months and 0% of the 7 patients with a TFI of 6-12 months were progression-free at 24 months.

Figure 18: PFS KM-curves for 2L patients stratified by TFI. Note: The solid bold line indicates patients with TFI of 12 or more months. The line with n = 7 indicates patients with a TFI of 6-12 months. The line with n = 8 indicates patients with TFI less than 6 months. (Adapted by GSK from Miyake et al (17))



Objective response rate

Among the 7 patients with a TFI of 6-12 months, CR or PR was achieved in 3 patients (43%). Among the 15 patients with TFI of 12 months, CR or PR was achieved in 10 patients (68%). Response to TC-based second-line chemotherapy seemed to be better in those with a TFI of 12 or more months, than in those with a TFI of 6-12 months; however, this difference was not statistically significant (P = 0.29 by Fisher's exact test).

All outcomes reported in Miyake et al are summarised in Table 13.

Table 13. DMC protocol outcomes reported in Miyake et al

	TFI 6-12 months n = 7	TFI 12 or more months n = 15
Median OS (months)	Non-reported	Non-reported
OS at 12 months (%)	Non-reported	Non-reported
Median PFS (months)	7,5	13
PFS at 24 months (%)	0%	50%
ORR*(%)	43%	67%

EORTC-QLQ-EN24	Non-reported	Non-reported
EORTC QLQ-C30	Non-reported	Non-reported
Adverse events of grade 3-4	Non-reported	Non-reported

*Complete response or partial response

6.1.2.6 Mazgani

Mazgani et al. retrospectively analysed data of patients treated in the British Columbia Cancer agency. Out of the 200 of patients included in the study, 111 relapsed. Of the 62 women with relapses in the endometroid histology group, 28 women were retreated with chemotherapy and, of these, 19 received carboplatin–paclitaxel. In the papillary serous group of 49 relapses, 24 women were retreated with chemotherapy and of these 12 received carboplatin–paclitaxel. Results of this study should be interpreted with caution, due to the small sample size; the retrospective nature of the study, and the data having been collected at a single site.

Measures of mortality

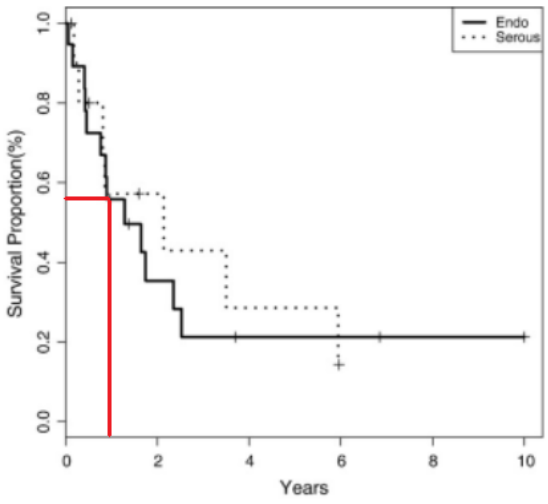
Median OS

OS from first relapse were 15 months (95% CI:9.13–30.36 months) for patients with endometroid histology and 26 months (95% CI: 9.72–71.40 months) for the papillary serous.

OS at 12 months

Based on the KM-curve in the publication, approximately 56% of patients in the endometroid group and 57% of patients in the serous histology group were alive after 12 months.

Figure 19. OS KM-curves for 2L patients stratified by histology type endometroid (filled) or serous (dotted) adapted by GSK from Mazgani et al (18).



Measures of disease progression

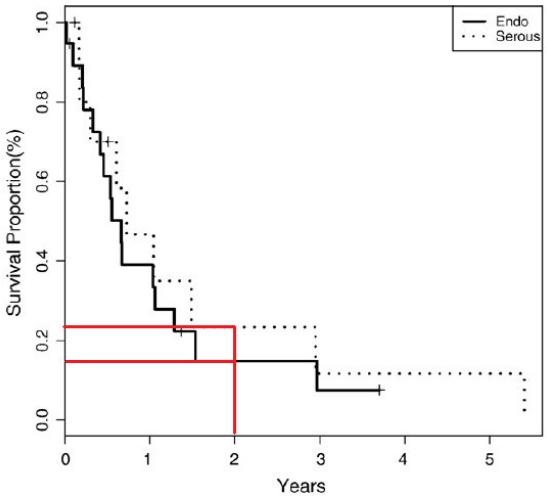
Median PFS

Median overall PFS from first relapse was 8 months (95% CI: 5.02-12.72) for those with endometroid histology and 9 months (95% CI: 3.59–35.40 months) for the papillary serous.

PFS at 24 months

Based on the KM-curve in the publication at 24 months, approximately 17% of patients in the endometroid histology group were progression-free and approximately 22% of patients in the serous histological group were progression-free.

Figure 20: PFS KM-curves for 2L patients stratified by histology type endometroid (filled) or serous (dotted) adapted by GSK from Mazgani et al (18).



Overall response rate

Of the 19 women with endometroid histology who received carboplatin–paclitaxel, eight patients (42%) had a PR or CR, and six patients (32%) had progressed. The remainder had either stable (n= 2) or unmeasurable disease, but nonprogressive (n= 3). In the papillary serous group (12 women) treated with carboplatin-paclitaxel, six patients (50%) had a PR or CR and three patients (25%) had progressed. The remainder had either stable (n= 2) or unmeasurable disease, but nonprogressive (n= 1). All outcomes reported in Mazgani et al. are summarised in Table 14.

Table 14. DMC protocol outcomes reported in Mazgani et al.

	Endometroid Histology patients n=19	Serous Histology patients n=12
Median OS (months)	15 (95% CI:9.13–30.36)	26 (95% CI: 9.72–71.40)
OS at 12 months (%)	Approximately 56%	Approximately 57%
Median PFS (months)	8 (95% CI: 5.02-12.72)	9 (95% CI: 3.59–35.40 months)
PFS at 24 months (%)	Approximately 17%	Approximately 22%
ORR (%)	CR or PR: 42% SD: 10.5% PD: 32% Not evaluable: 15.8%	CR or PR: 50% SD: 16.7% PD: 25% Not evaluable: 8.3%
EORTC-QLQ-EN24	Non-reported	Non reported
EORTC QLQ-C30	Non-reported	Non reported
Adverse events of grade 3-4	Non-reported	Non reported

6.1.2.7 Vergote

Vergote et al. carried out a Phase II prospective study evaluating TC with prophylactic G-CSF in 108 patients. Of these, 36 patients had EC, 36 had ovarian cancer, and 36 had cervical cancer. KM curves were presented for all evaluable EC patients (31 patients), which included patients who were treated in first line. The study also reported ORR, median PFS and median OS based on the number of previous lines of therapy. ORR, median PFS and median OS are hence reported for the 17 EC patients who had received one (0-2) prior lines of therapy. Survival results interpreted directly from the KM curves should be interpreted with caution, as patients who were treated in first line were included in the analysis.

Measures of mortality

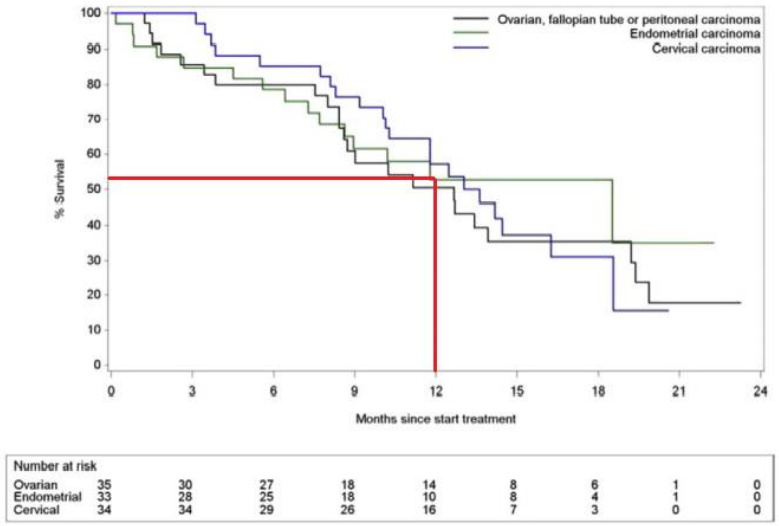
Median OS

The median OS of the 17 EC patients who had one (0-2 prior lines of therapy was 12 months (95% CI: 6 – undefined).

OS at 12 months

Based on the KM-curve in the publication approximately 52% of patients in the EC cohort were alive after 12 months.

Figure 21. OS KM-curves for 2L patients stratified by tumour type. The green line is for EC and applicable for this assessment (adapted by GSK from Vergote et al. (6))



Measures of disease progression

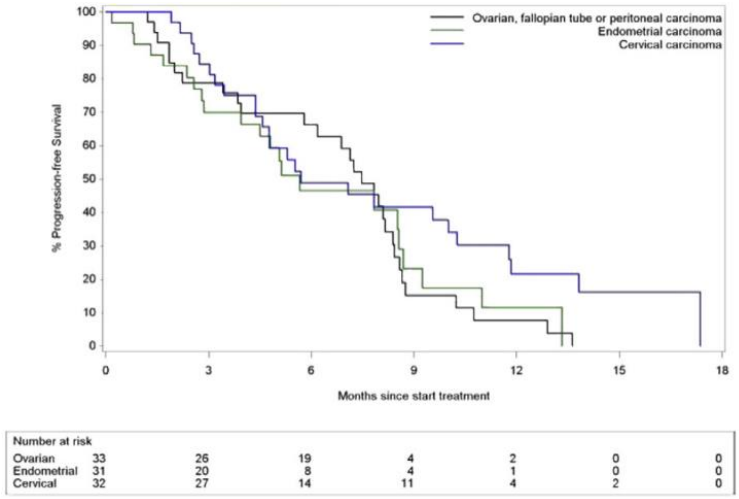
Median PFS

The median PFS of the 17 EC patients who had had one (0-2) prior lines of therapy was 5 months (95% CI: 3- 9).

PFS at 24 months

Based on the KM-curve in the publication 0% of EC patients were progression-free at 24 months.

Figure 22: PFS KM-curves for 2L patients stratified by tumour type. The green line is for EC and applicable for this assessment (adapted from Vergote et al. (6))



Objective response rate

The ORR of the 17 EC patients who had had one (0-2) prior lines of therapy was 29%.

All outcomes reported in Vergote et al. are summarised in appendix Table 15.

Table 15. DMC protocol outcomes reported in Vergote et al.

	EC patients n=17 (or 31 for OS at 12 months and PFS at 24 months)
Median OS	12
OS at 12 months	52%
Median PFS	5
PFS at 24 months	0%
ORR	29%
EORTC-QLQ-EN24	Non-reported
EORTC QLQ-C30	Non-reported
Adverse events of grade 3-4	Non-reported

6.1.2.8 Ueda

In Ueda et al. 24 patients were included, who received platinum-based chemotherapy regimens in second line. For the ORR outcome, results were split per duration of TFI, TFI <6 months and TFI ≥6 months. Hence, for this outcome, only the results for TFI ≥6 months are reported in this section. Median OS and median PFS results are provided for the overall population, not split per TFI. Results of this section should be interpreted with caution, due to the restricted (Japanese) ethnicity of the patients, and due to the data collected from only two sites.

Measures of mortality

Median OS

Of the 24 patients who received second line paclitaxel, epirubicin and carboplatin (TEC), monthly carboplatin and paclitaxel (TCm) or weekly carboplatin and paclitaxel (TCw), the median OS was 13 months (3-44).

Measures of disease progression

Median PFS

PFS was measured from the date of the last administration of chemotherapy, to the date of the radiological or pathological relapse, or to the date of the last follow-up. Of the 24 patients received second line TEC, TCm or TCw, the PFS was 5.5 months (2–20).

Objective response rate

Of the 17 patients who received second line TEC, TCm or TCw and who progressed after six months from treatment, the ORR was 53% (CR or PR)

All outcomes reported in Ueda et al. are summarised in Table 16.

Table 16. DMC protocol outcomes reported in Ueda et al.

	TFI <6 months n=7*	TFI ≥6 months n=17
Median OS (months)	13	
OS at 12 months (%)	Non reported	Non reported
Median PFS (months)	5.5	
PFS at 24 months (%)	Non reported	Non reported
ORR	Not relevant	CR or PR: 53%
EORTC-QLQ-EN24	Non-reported	Non-reported
EORTC QLQ-C30	Non-reported	Non-reported
Adverse events of grade 3-4	Non-reported	Non-reported

*the number of patients receiving paclitaxel + carboplatin was combined in the 2 subgroups for median OS and median PFS

6.1.2.9 Nomura

To be enrolled in the Nomura et al. study patients had advanced or recurrent disease and prior chemotherapy was permitted without limitation to the number of prior chemotherapy regimens. This implied that some patients may have been enrolled and treated with chemotherapy as first line. Therefore, it was considered that the efficacy results of this study were out of the scope for this submission. However, due to the lack of safety data available, it was decided to report the safety results of Nomura et al. assuming that there would be minor differences in safety between first- and second-line treatment with chemotherapy. Results were presented according to the type of platinum-based chemotherapy received at baseline: docetaxel plus cisplatin (DP), docetaxel plus carboplatin (DC), or paclitaxel plus carboplatin (TC). The results of this study should be interpreted with caution considering the ethnicity (Japanese) of the patients enrolled and the use of different chemotherapy regimens.

Adverse events

Proportion of patients experiencing at least one adverse reaction of grade 3-4

The majority of adverse events produced after treatment with the investigational products, were haematological toxic effects. Leukopenia or neutropenia was seen in nearly all patients, and adverse events of grade 3 or higher occurred at a high incidence of >80%. Febrile neutropenia was reported in four patients (13.3%) in DP and in two patients each (6.7%) in DC and TC; infection associated with grade 3–4 neutropenia was reported in two patients in DP and one patient in TC. Grade 3 motor neuropathy occurred in two patients (6.7%) in TC, and sensory neuropathy occurred in one patient (3.3%) in TC only, but in all instances, the differences were not statistically significant at the 5% level. Other grade 3 or higher adverse events that occurred at high frequency were the gastrointestinal symptoms of anorexia, diarrhea, and nausea. Details of Grade 3-4 adverse events are presented in for DP, DC, and TC patients.

Table 17. Grade 3-4 Adverse events in in patients with advanced or recurrent endometrial carcinoma treated in second line with docetaxel plus cisplatin, docetaxel plus carboplatin, or paclitaxel plus carboplatin

Grade 3-4 Adverse events	DP (docetaxel plus cisplatin) (n = 30) Grade 3–4 (%) (95% CI)	DC (docetaxel plus carboplatin) (n = 30) Grade 3–4 (%) (95% CI)	TC (paclitaxel and carboplatin) (n = 30) Grade 3–4 (%) (95% CI)
Hemoglobin	3.3 (0.1–17.2)	16.7 (5.6–34.7)	16.7 (5.6–34.7)
Leukocytes	73.3 (54.1–87.7)	86.7 (69.3–96.2)	50.0 (31.3–68.7)
Neutrophils (ANC)	83.3 (65.2–94.4)	90.0 (73.5–97.9)	76.6 (57.7–90.1)
Platelets	6.7 (0.8–22.1)	10.0 (2.1–26.5)	10.0 (2.1–26.5)
AST		3.3 (0.1–17.2)	3.3 (0.1–17.2)
ALT		3.3 (0.1–17.2)	
Allergic reaction	3.3 (0.1–17.2)	3.3 (0.1–17.2)	
Anorexia	16.7 (5.6–34.7)	10.0 (2.1–26.5)	10.0 (2.1–26.5)
Diarrhea	13.3 (3.8–30.7)	3.3 (0.1–17.2)	
Nausea	10.0 (2.1–26.5)	6.7 (0.8–22.1)	10.0 (2.1–26.5)
Motor neuropathy			6.7 (0.8–22.1)
Sensory neuropathy			3.3 (0.1–17.2)
Febrile neutropenia	10.0 (2.1–26.5)	6.7 (0.8–22.1)	3.3 (0.1–17.2)

Abbreviations: DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin; CI, confidence interval; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

6.1.3 Comparative analyses

6.1.3.1 Limitations

dMMR/MSI-H status

Dostarlimab is the only EMA approved treatment available in Denmark for patients with dMMR MSI-H EC, that has progressed on or following prior treatment with a platinum-containing regimen. For patients who progress approximately six months or more after platinum-based chemotherapy, the DMC considered that platinum-based combination therapies are the best standard of care (comparator) to which dostarlimab outcomes should be compared to.

The dMMR/MSI-H status was unknown in all the comparator studies and therefore only reported in the GARNET trial. However, as previously described, GSK has conducted an internal SLR on the prognostic or predictive value of dMMR/MSI-H status in the treatment of recurrent or advanced EC. The conclusion of the SLR, was that there was no strong evidence to suggest that either dMMR/MSI-H status has a significant positive or negative prognostic value in EC patients (11 out of 13 publications reported no significant findings based on dMMR/MSI-H status)(9). The lack of information on dMMR and MSI-H status is therefore not considered to significantly impact the comparability of the study results.

Study designs and sample size

Five out of eight of the comparator studies selected to answer clinical question 1, was non-randomised retrospective studies, that focused exclusively on Japanese patients (Nagao et al. 2013/2015, Miyake, Ueda, and Nomura), who considered to be less comparable to the Caucasian patients. Moreover, the very small sample sizes (approximately 30 patients in the groups of interest) and different platinum combinations and regimens added additional uncertainty to the comparative analysis.

Of the eight studies included to answer clinical question 1, four used data from ≤ 3 sites (Mazgani, Miyake, Ueda, Rubenstein). Enrolling participants from a reduced number of sites increases the risk of introducing a selection bias in the analysis, potentially derived from an unknown variable that causes participants enrolled at a specific site to be slightly different from the rest of the population (socio-economic status, age etc). The results of the comparison of these studies with GARNET should therefore be interpreted considering these potential biases.

Finally, six out of eight studies were retrospective with the exceptions being Nomura and Vergote et al. In addition, the comparator studies often had a broader or different objective than the scope of this application. Hence, limited data was available for the outcomes selected by the DMC, especially for safety and quality of life outcomes, where almost no study reported any details. The unavailability of data severely hampered the comparison versus dostarlimab. Furthermore, the comparator-studies reported very limited information on the patient characteristics for the population of interest, further hindering a complete assessment of the comparability of the studies. In addition, the comparator studies relied on older data, as the studies were conducted between 2000-2014, and therefore there are some uncertainties as to which extent the results are fully representative for the clinical practice today.

Treatment free-interval (TFI) / Platinum-free interval (PFI)

In general, the comparability of studies was limited by differences in TFI/PFI. First, the definition of PFI reported in the studies differed from the definition provided in the protocol by the DMC. The studies used to answer clinical question one, defined platinum sensitive disease as disease that progresses between 6-11months, between 12-23 months, and ≥24 months in Nagao et al. 2013 (14), and after 12 months for ORR, in Nagao et al. 2015 (15). The DMC defined the population of interest for clinical question one, as patients who had progressed after 6 months. Only Ueda et al. reported ORR split per platinum-sensitive, and platinum resistant patients defined as patients progressing before or after six months, respectively. Most of the comparator studies reported outcomes for patients that in general had a longer

PFI than stated in the DMC protocol, and were therefore considered to have a better prognosis, which introduces a positive bias towards platinum-based chemotherapy. The extent of this limitation should nevertheless be nuanced by the similarity of median PFIs across the three studies that reported it. In GARNET (3), the median PFI was 6.51 months (Q1, Q3: 4.4, 12.3 months) whereas in Miyake et al. (17), the median PFI was seven months for patients with a TFI of 6-12 months, and 12 months for patients with a TFI of 12 months or more. For patients enrolled in Rubinstein et al. (16), no patients were retreated with a PFI of less than six months. Additionally, the PFS and OS results for platinum-based chemotherapies reported in Nagao et al. 2015 (15) should be considered as conservative, due to the inclusion of platinum-resistant patients in the estimate, who are likely to be generally worse off than platinum-sensitive patients.

Prognosis - differences in disease severity and prior lines of therapy

Additionally, as mentioned in the introduction, patients in the GARNET trial were already more heavily pre-treated at baseline, compared to patients enrolled in the other studies. In fact, in Vergote et al. (6), patients had a median of one previous line of therapy and in Miyake et al. (17), Nagao et al. 2013 (14) and Ueda et al. (19), the analysis was conducted retrospectively, restrictively on patients receiving second line therapy, therefore all patients who have had prior lines of therapy, should have been excluded from the analyses.

Finally, differences between patients included in the studies were noted for FIGO-stage, which is used to assess the extent of the spread of EC and is an important prognostic factor. Of the patients enrolled in GARNET 68 % had FIGO stage IV, which is a higher proportion of patients than in the comparator studies ranging from 21-41 % Table 5 (15, 20).

6.1.3.1 Approach to comparative analysis

Despite the above limitations, a comparison of dostarlimab versus carboplatin and paclitaxel was carried out narratively. As mentioned previously, no head-to-head trials were available comparing dostarlimab to platinum-based chemotherapy. Evidence for the efficacy and safety of dostarlimab was provided by the single-arm GARNET trial. To estimate the comparative effectiveness of dostarlimab versus platinum-based chemotherapy, the evidence identified in the SLR was reviewed for the purpose of conducting an ITC. The cohort study carried out by Mazgani et al. (18) was selected to conduct an unanchored MAIC analysis for the main outcomes of interest (section 6.1.3.3). The study conducted by Mazgani et al. (18) was a retrospective analysis of second line treatment with carboplatin and paclitaxel in patients with relapsed EC, carried out at one centre in Vancouver, Canada. Data for 31 patients receiving carboplatin and paclitaxel combination were reported, the sample size meets the inclusion criteria for a MAIC. However, this study introduces significant bias to the MAIC as only patients who previously responded to first line carboplatin and paclitaxel were re-treated with this combination in second line. Nevertheless, this was the only publication that reported survival outcomes for a key comparator, hence, why it was included in the MAIC analysis. The remaining studies were excluded, based on three reasons: 1) The sample sizes were small (<30); 2) the publication did not present KM survival analyses, and 3) the patient populations and characteristics were significantly different to the GARNET trial (Japanese patients).

GSK has carried out an unanchored MAIC analyses to adjust for differences in the study populations by taking individual patient data from the GARNET trial and weighting it to match the aggregate data from Mazgani et al. This analysis was implemented to ensure narrative comparability of efficacy outcomes between dostarlimab and platinum-based chemotherapy. Unanchored MAIC analyses were carried out for the outcomes of OS, PFS and ORR. Results are presented in section 6.1.3.3.

Considering the limitations of the MAIC, a narrative comparison between dostarlimab, and platinum-based chemotherapy is presented in section 6.1.3.2 and summarised in 6.1.3.4.

6.1.3.2 Narrative comparison

As described in detail in section 6.1.3.1 above, the comparability of study results is limited by differences between the studies and patients' characteristics. The factors limiting the comparability of the study results was favoring the efficacy estimates of platinum-based chemotherapy notably:

- The definition of platinum-sensitiveness in the studies generally uses a cut-off of ≥ 12 months, which will provide more favourable results, than for the patients in scope of platinum-based chemotherapy as defined by the DMC by PFI of ≥ 6 months, as longer PFI is associated with an improved response and prognosis
- Patients in GARNET were generally more heavily pre-treated than patients in the comparator studies
- Patients in GARNET generally had worse prognosis due to a higher FIGO-stage, than the patients in the comparator studies

Looking beyond the limitations of comparing results across studies, a very distinctive result noted in GARNET was the large proportion of patients who experience an initial response, and who go on to experience long-term remission. This is demonstrated in the PFS- and OS-curves as a very early flattening of the KM-curves forming a long-tail representing patients in long-term remission. Comparing this response to platin-based chemotherapy in the comparator trials demonstrates, that this response is only observed for dostarlimab, whereas patients on platinum-based chemotherapy steadily continue to progress. Especially PFS-rate at 24-month for dostarlimab stand out as a meaningful result, differentiating dostarlimab from platinum-based chemotherapy. The value of dostarlimab is therefore most importantly, that a large proportion of patients will experience long-term PFS/OS, whereas this is consistently not observed for platinum-based chemotherapy in any of the comparator trials.

Median OS / OS at 12 months

In the GARNET trial (3), the median OS was not reached (95% CI: 17.1-NR) at the data cut-off of March 2020. Considering that the median follow-up time at this data cut-off was 16.3 months, and considering the plateau observed for PFS at 24 months, dostarlimab shows promising results in terms of median OS (> 16.3 months).

Studies investigating carboplatin and paclitaxel have reported similar or inferior figures. For example, Mazgani et al. (18) reported an OS of 15 months for the endometroid histology group, which was the histological group most represented in the GARNET trial. Similarly, Vergote et al. (6) reported a median OS of 12 months. Rubinstein et al. (16) reported a median OS of 27 months, but patients enrolled in this study were the least comparable to GARNET across all trials, as it included very few patient and patients in general had a different histology (serous histology), than for the patients enrolled in GARNET. In addition, patients in Rubenstein et al. had less severe disease compared to patients in GARNET, as per FIGO score, and had very long median PFI of 25 months as reported in the baseline characteristics (Table 5). In general, the results from Rubenstein et al. should be interpreted with caution due to these differences and should not hold much weight in the assessment.

According to the criteria described by the DMC in the protocol of this assessment, achieving an absolute difference in OS rate at one year of five percentage points is considered a clinically relevant result. At the data cut-off of March 2020, with a median follow-up of 16.3 months, dostarlimab was associated with a 12-month landmark OS of 69.2% (95% CI: 58.8-77.6). The reviewed literature reported paclitaxel and carboplatin OS rates at 12 months varying from approximately 56%/57% in Mazgani et al. (18) to approximately 95% in Rubinstein et al. (16). As mentioned above results from Rubinstein's should be considered of little value in the comparison, as patients were different from patients in GARNET.

Achieving a 69.2% (95% CI: 58.8-77.6) OS-rate at 12 months is therefore a clinically meaningful result for dostarlimab as compared to the most representative estimate from Mazgani et al., which will bring significant benefit to patients who currently have no treatment options approved by EMA, specifically for patients with advanced or recurrent EC who progress after a platinum-based regimen.

Finally, the MAIC analysis carried out to compare the efficacy of dostarlimab to the efficacy of paclitaxel and carboplatin demonstrated that patients receiving dostarlimab has approximately 44.1% lower risk of death compared to paclitaxel and carboplatin when adjusting for confounding factors providing the best estimate of the relative efficacy between the interventions (section 6.1.3.3).

Median PFS/ PFS at 24 months

The results indicate that patients with EC treated with dostarlimab had a median PFS of 5.5 months (95% CI: 3.2-NR). As previously described the median PFS-estimate in GARNET was not considered robust but volatile and sensitive to censoring and events, as a prolonged tail of the curve was formed right around the median, which results in a single event/censoring can shift the PFS-estimate significantly (see section 6.1.2.1). The 24-month landmark PFS-estimate provides more meaningful measures of the value of dostarlimab, as it demonstrates sustained effect and a large proportion of patients responding to the therapy becomes long-term survivors, where the 24-month PFS-estimate was [redacted] %. The median PFS estimate of dostarlimab was similar to the observed PFS for patients treated with platinum-based chemotherapies reported in Ueda et al. (19). However, when looking specifically at studies reporting results split per TFI, PFS observed in GARNET seems to be slightly lower compared to platinum-sensitive patients in Nagao et al, 2013 (14). reported a median PFS of 6 months and 7.8 months for patients with a PFI of 6-11 months and 12-23 months respectively. However, as mentioned above, it should be noted that the definition of PFI used by the authors does not match the definition from the DMC, which defines platinum-sensitive and platinum-resistant patients as participants who progress ≥ 6 months or within 6 months, respectively. Hence, results should be interpreted with caution. By using a higher cut-off of >12 months for defining platinum-sensitiveness, Nagao et al. (14) potentially reported median PFS for patients that were generally better-off, therefore introducing a positive bias towards carboplatin and paclitaxel. Furthermore, the median PFS estimate of dostarlimab seems to be also lower than Nagao et al, 2015 (15), who reported a median PFS of 10 months for a patient population that included a majority of platinum-sensitive patients (83%).

Median PFS is not an adequate measure to investigate the value of dostarlimab in patients with dMMR/MSI-H. Contrary to chemotherapy treatments, dostarlimab provides a long and sustained effect, which is not captured by observing the median PFS. PFS at 24 months is therefore considered a more appropriate measure of the value of dostarlimab. Nagao et al, 2013 (14) provided a breakdown based on three subgroups of patients-based stratification of the PFI: 1) PFI 6-11 months 2) PFI 12-23 months and 3) PFI ≥24months. For the patients with the best prognosis PFI ≥24 months, the 24-month PFS-rate was approximately 27%, for the group with PFI 12-23 months and the 24-month PFS-rate was approximately 12%, and for the PFI 6-11 months the 24-month PFS-rate was 8%. These rates are up-to 4-fold lower than the PFS-rate observed in the GARNET study. Similarly, Mazgani et al (18) reported PFS rates at 24 months of 17% and 22% for endometroid and serous histology groups, respectively. Miyake et al. (17) reported carboplatin and paclitaxel 24-month PFS rate as 50% for patients with a TFI of 12 months or more, and 0% for patients with a TFI of 6-12 months. The average 24-month PFS-rate for the combined population in Miyake et al., which would correspond to the population in scope for this clinical question, would be an estimate of approx. 25%. Finally, Rubinstein et al. (16) and Vergote et al. (6) reported very low 24-month PFS-rates for carboplatin and paclitaxel of 6% and 0% respectively.

Overall, the in-depth analysis of PFS and OS provided above, demonstrates meaningful differences in the efficacy between dostarlimab and platinum-based chemotherapy. The landmark analysis of long-term OS/PFS demonstrates, that patients responding to dostarlimab experience long-term disease remission. Specifically, the PFS-rate at 24-months, demonstrating that 39% of patients treated with dostarlimab had not yet progressed or died, is a substantial finding, that contrasts with the results observed for patients treated with platinum-based chemotherapy. These results are extremely encouraging findings, and documents, that dostarlimab will provide patients with recurrent or advanced dMMR/MSI-H EC with meaningful improvements in long-term survival.

ORR

In the GARNET trial, dostarlimab demonstrated that 43.5% of patients achieved an ORR at data cut-off of March 2020. This result is in line with ORR reported in other studies investigating similar populations. An example, in Mazgani et al. (18) an ORR of 42% was reported for patients in the histological group, and 50% for patients in the papillary serous group, and in Rubinstein et al. an ORR of 50% was observed. As described previously, results from the Rubinstein study should be interpreted with caution. Vergote et al. (6) reported an ORR of 29%. When looking at the split ORR results between platinum resistant and platinum sensitive patients, dostarlimab ORR of 43.5% is comparable to the ORR reported by Miyake et al. (17): 43% for TFI 6-12 months and Ueda et al. (19): 53% (CR or PR), for TFI ≥6 months.

Proportion of patients experiencing at least one adverse reaction of grades 3-4

Only GARNET reported detailed information on safety outcomes, as well as an overall result for the proportion of patients experiencing at least one adverse reaction of grade 3-4. Nomura et al. (20) did not report an overall for grade 3-4 AEs but the study reported a breakdown of individual grade 3-4 adverse events, that were experienced by at least one patient treated with platinum-based combinations. By comparing the two lists of adverse events reported in Table 8 and Table 17, only alanine aminotransferase and diarrhoea were commonly reported in both studies. Grade 3 or 4 Alanine aminotransferase was reported in 3.3% patients treated with platinum-based chemotherapy and in 2.3% patients treated with dostarlimab. Grade 3 or 4 diarrhoea was experienced by 16.6% of patients treated with platinum-based chemotherapies and in 2.3% patients treated with dostarlimab.

In addition, carboplatin and paclitaxel was associated with persistent and often permanent neurological adverse events, which was also observed in Nomura et al. (20) (motor neuropathy and sensory neuropathy). All platinum-based chemotherapies reported in Nomura et al. (20) reported high levels of grade 3-4 cytopenia (leukocytopenia, neutropenia, thrombocytopenia and in some cases severe febrile cytopenia (Table 17).

Despite the limited evidence available for naïve narrative comparison, dostarlimab had a favourable safety profile in comparison with platinum-based chemotherapies.

Based on the above, there is limited evidence available for the comparator in the target population as reported in the studies. Furthermore, it is reflected in the studies, that the safety profile of the comparators and that of dostarlimab are fundamentally different from each other, given that they are different therapeutic classes with different modes of actions. Therefore, the treatments are difficult to compare as events differ significantly in type, severity, and reversibility. Acknowledging, that there is a severe lack of reporting of safety in the comparator studies, based on this the best approach for evaluating safety is assumed to be a narrative approach undertaken by the DMC expert committee. In section 6.1.2.1 a summary of the safety profile of dostarlimab from the SmPC is provided, which can be used by the experts committee to compare the safety profile of the included comparators to dostarlimab.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 18. Overview of study results for narrative comparison between dostarlimab vs platinum-based chemotherapy

Study	Intervention	Median OS (months)	OS at 12 months (%)	Median PFS (months)	PFS at 24 months (%)	ORR	EORTC-QLQ-EN24	EORTC QLQ-C30	AEs grade 3-4
GARNET (3)	Dostarlimab	NR (17.1, NR)	69.2% (95% CI: 58.8-77.6)	5.5 (95% CI: 3.2-NR)	[redacted]	43.5%	NR	[redacted]	62 (48.1%)
Nagao, 2013 (14)	Platinum-based chemo-therapy	14.8 (PFI 6–11 months), 27.8 (PFI 12–23 months), and 40.9 (PFI ≥24 months)	67% (PFI 6–11 months), 79% (PFI 12–23 months), and 88% (PFI ≥24 months)	6.0 (PFI 6–11 months), 7.8 (PFI 12–23 months), and 13.4 (PFI ≥24 months)	8% (PFI 6–11 months), 12% (PFI 12–23 months), and 27% (PFI ≥24 months)	38% (PFI 6–11 months), 61% (PFI 12–23 months), and 65% (PFI ≥24 months)	NR	NR	NR
Nagao, 2015 (15)	Carboplatin paclitaxel (TC), Docetaxel carboplatin (DC), Doxorubicin cisplatin (AP)	48	84	10	20	AP to TC/DC: 71%, TC/DC to AP: 15%, TC/DC to TC/DC: 40% (PFI<12 months); AP to TC/DC: 84%, TC/DC to AP: 7%, TC/DC to TC/DC: 67% (PFI>12 months)	NR	NR	NR
Mazgani (18)	Carboplatin paclitaxel	15 (endometroid histology) 26 (papillary se-rous)	56% (endometroid histology) 57% (papillary se-rous)	8 (endometroid histology) 9 months (papil-lary serous)	17% (endometroid histology) 22% (papillary se-rous)	CR and PR: 42% SD: 10.5% PD:32%	NR	NR	NR

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						(endometroid histology) CR and PR: 50% SD: 16.7% PD:25% (papillary serous)			
Miyake	Carboplatin paclitaxel with and without anthracycline	NR	NR	7,5 (TFI 6-12 months), 13 (TFI 12 or more months)	50% (TFI 12 months or more) 0% (TFI 6-12 months)	43% (TFI 6-12 months) 67% (TFI 12 or more months)	NR	NR	NR
Ueda (19)	paclitaxel, epirubicin and carboplatin (TEC), monthly carboplatin and paclitaxel (TCm) or weekly carboplatin and paclitaxel (TCw)	13	NR	5.5	NR	CR or PR: 53% (TFI ≥6 months)	NR	NR	NR
Nomura (20)	Carboplatin paclitaxel (TC), Docetaxel cisplatin (DP), Docetaxel plus carboplatin (DC)	NR	NR	NR	NR	NR	NR	NR	See Table 17**
Vergote (6)	Carboplatin paclitaxel	12	52%	5	0%	29%	NR	NR	NR
Rubinstein (16)	Carboplatin paclitaxel	27	95%	10	6%	ORR:50% CR:0%, PR:50%, SD:15%	NR	NR	NR

*Mean (SD) change from baseline after 7 cycles of dostarlimab in the Global Health status/QoL

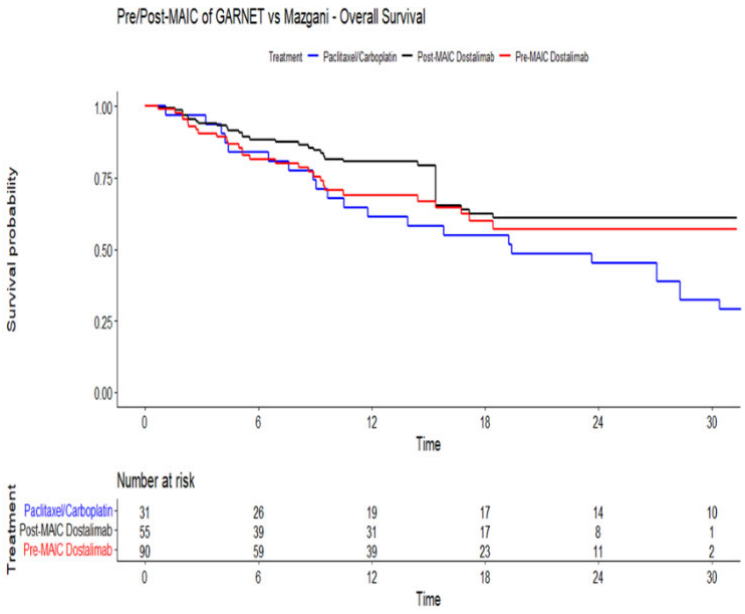
**No overall proportion for any Grade 3-4 AEs presented in the study

6.1.3.3 Indirect statistical MAIC analysis – Dostarlimab (GARNET) vs. Carboplatin in combination with paclitaxel (Mazgani)

Please refer to appendix 9.6 for individual weights with histograms and for identification and selection of baseline characteristics used as variables for the MAIC.

MAIC analysis - OS

Figure 23. GARNET vs Mazgani Kaplan-Meier of OS



Note: the number of subjects is 90 of post-MAIC Dostarlimab, but the number at risk is 55, due to the weighting used in the MAIC.

The median OS (with 95% CI) for dostarlimab pre- and post-MAIC adjustment and for paclitaxel & carboplatin are presented in Table 19.

Table 19: Summary of the number of censored and uncensored values and OS summary of the number of censored

Kaplan-Meier Analysis: Overall Survival			
	Dostarlimab (Pre-MAIC) (N=90)	**Dostarlimab (Post- MAIC) (N=90/55*)**	**Paclitaxel/Carboplatin (N=31)**
Status of OS			
Event	28	28/15#	22
Censored	62	62/40$	9
OS (in Months)			
Median (95% CI)	NR (17.1, NR)	NR (15.4, NR)	19.4 (10.5, NR)

Note: * = Number of subjects is 90 before the adjustment but after applying weighting adjustment for the MAIC, starting number of patients at risks is 55.
= Number of events is 28 on Dostarlimab (post-MAIC) but after applying weighting under MAIC, number of events is 15.
$ = Number of censored are 62 on Dostarlimab (post-MAIC) but after applying to weight under MAIC, number of censored are 40.
NR=Not Reached

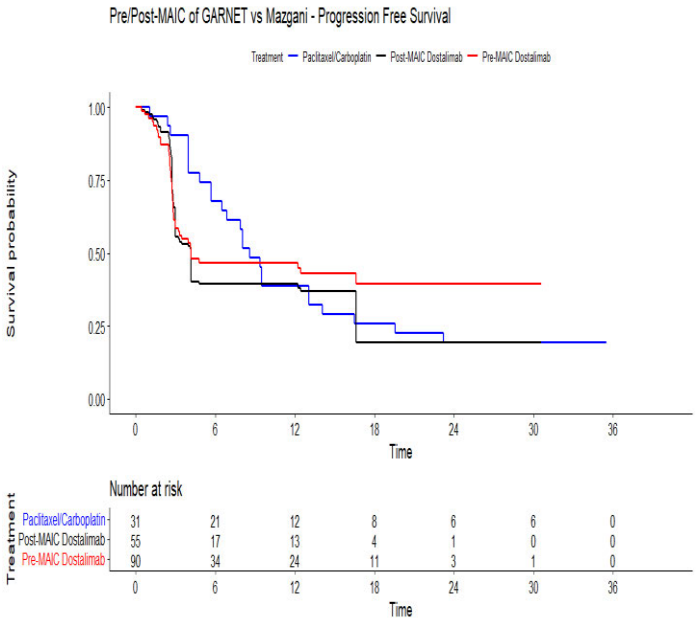
Table 20: Results of MAIC analysis for OS – GARNET vs Mazgani

	N	Hazard ratio (Dostarlimab / Paclitaxel or Carboplatin)	95% CI	Robust StdErr :log(HR)	p-value
Cox PH model	121	0.559	0.256, 1.220	0.3980	0.144
Assumption check of proportional hazard ratios					
	N	Chi-square	p-value		
Assumption check	121	0.253	0.62		

The test of the assumption of proportional hazards does not show a violation (p-value =0.62). A Cox proportional hazards model with MAIC was fitted to the data. The HR for OS was =0.559 and corresponding p-value of 0.144 indicating a numerical survival benefit for dostarlimab. The OS hazard ratio for dostarlimab (numerator of the HR) was lower than that for paclitaxel & carboplatin (in the denominator). Hence, in the above analysis dostarlimab had approximately 44.1% lower risk of death compared to paclitaxel & carboplatin.

MAIC analysis - PFS

Figure 24. GARNET vs Mazgani Kaplan-Meier of PFS



Note: The number of subjects was 90 post-MAIC Dostarlimab, and the number at risk was 55, due to the weighting used in the MAIC.

Table 21: Summary of the number of censored and uncensored

Kaplan-Meier Analysis: Progression Free Survival			
	Dostarlimab (Pre-MAIC) (N=90)	**Dostarlimab (Post- MAIC) (N=90/55*)**	**Paclitaxel/Carboplatin (N=31)**
Status of PFS			
Event	44	44/33[#]	25
Censored	46	46/22[$]	6
PFS (in Months)			
Median (95% CI)	4.17 (2.96, NR)	4.17 (2.96, 16.6)	8.56 (6.52, 16.5)

Note: * = Number of subjects are 90 but after applying weights to MAIC, the starting number at risks is 55.
= Number of events are 44 on Dostarlimab (post-MAIC) but after applying weights to MAIC, the number of events is 33.
$ = Number of censored patients are 46 on Dostarlimab (post-MAIC) but after applying to weight under MAIC, the number of censored are 22.NR=Not Reached

Table 22. Results of MAIC analysis for PFS– GARNET vs Mazgani

MAIC analysis and assumption check of proportional hazard ratios					
	N	**Chi-square**	p-value		
Assumption check	121	6.08	0.014		
Note that Cox PH model cannot be performed because assumption is violated for Cox PH model. Therefore, we use accelerated failure time (AFT) model with Weibull distribution.					
Main analysis on PFS Accelerated Failure Time (AFT) model with Weibull distribution					
	N	**Hazard ratio Dostarlimab/Paclitaxel & Carboplatin**	**95% CI**	**StdErr :log(HR)**	**p-value**
AFT model	121	1.527	0.881, 2.648	2.808	0.136

The test of the assumption of proportional hazards showed a violation (p-value =0.014). Therefore, an accelerated failure time model with Weibull distribution was fitted to the data. The HR (=1.572) and corresponding p-value (0.136) indicate a trend of a difference between the two treatments for PFS. The PFS hazard ratio for dostarlimab (numerator of the HR) is higher than that for paclitaxel & carboplatin (in the denominator). Hence, in the above analysis dostarlimab has approximately 52.7% higher risk of progression or death compared to paclitaxel & carboplatin.

Objective response rate

The ORR represents the proportion of patients who achieved a best overall response (BOR) of CR or PR. After applying the weights to the GARNET data for the MAIC, the odds ratio, relative risk, and risk reduction were calculated and are displayed in Table 22 below.

Table 23. Summary of ORR results post-MAIC: GARNET vs Mazgani

Outcome scale	Estimate	95% CI	Robust StdErr :Log(0R or RR)	p-value
Odds ratio (Dostarlimab/ Paclitaxel or Carboplatin)	**0.659**	**0.235, 1.848**	0.5266	0.4276
Relative risk (Dostarlimab/ Paclitaxel or Carboplatin)	**0.759**	**0.383, 1.503**	0.3487	0.4286
	Estimation	**95% CI**	**Ro- bust StdErr**	**p-value**
Risk difference (Dostarlimab – (Paclitaxel or Carboplatin))	-0.0934	-0.289, 0.102	0.0998	0.3495

The odds ratio (=0.659) and corresponding p-value (=0.4276) indicate a trend of a difference between the two treatments for ORR, suggesting that treatment with dostarlimab decreased the odds of ORR by 44.1% compared to the odds of ORR with paclitaxel and carboplatin

Limitations of the MAIC analyses

Although the MAIC analysis provides quantitative estimates of the relative efficacy, these MAIC analyses have some limitations, which are summarised below. The results should therefore be interpreted with caution.

- Mazgani et al. was a retrospective, observational review of treatment records from one centre in Canada, whereas GARNET was a multi-centre Phase I clinical trial: differences in design limits the comparability of these study populations.
- The clinical time periods of the studies were different - GARNET: 2017-2020, Mazgani: 1995-2007.
- As with all indirect comparisons there was a potential risk of bias of unobserved, unmeasured, and unadjusted confounding factors. Nevertheless, there was an effort made to adjust as many as possible of the identified and available prognostic factors, that could otherwise influence the results of such comparisons.
- Whilst the sample size of Mazgani (N=31) met the MAIC inclusion criteria (=>30), this was still a small sample size limiting the robustness of the comparative effective estimates.
- 8 prognostic variables were identified as relevant for the MAIC but only 1 was available in Mazgani to match on (Histology) – this limited the ability to fully match patients from GARNET and Mazgani.
- The patient population in Mazgani was markedly different to GARNET: in the Mazgani et al. patients were only retreated with paclitaxel & carboplatin if they had previously responded to 1L paclitaxel & carboplatin treatment. This likely will bias the results in favour of Mazgani. Specifically, since patients in Mazgani were more likely to respond to retreatment with paclitaxel & carboplatin in second line, given they responded to first line treatment, and because the GARNET trial included patients who had failed on or after first line platinum therapy treatment. The authors of the Mazgani publication notes this limitation: “Due to the patient selection these outcomes reported were likely to be an overstatement of what could be achieved in practice.” As a result, comparative effectiveness estimates for GARNET vs Mazgani should be viewed as biased in favour of paclitaxel & carboplatin

6.1.3.4 Conclusion

The narrative comparison and the MAIC examining the relative efficacy of dostarlimab in the pivotal GARNET trial versus patients treated with platinum-based chemotherapy in the comparator trials strongly indicates patients treated with dostarlimab experience a meaningful survival benefit.

- The most important and distinctive differences noted for dostarlimab was the large proportion of patients who experience long-term disease remission.
    - This is demonstrated by the PFS and OS KM-curves, which flatten out early and form a long-tail, representing patients in long-term remission.
    - Comparing the dostarlimab response in GARNET to the results for platinum-based chemotherapy in the comparator trials demonstrates that this response is only observed for dostarlimab, whereas patients on platinum-based chemotherapy steadily continue to progress.
    - PFS estimates supports this claim as the PFS-rate at 24-months was [redacted] and OS-rate at 12-months was 69.2% (95% CI: 58.8-77.6) for dostarlimab, which clearly differentiate dostarlimab from platinum-based chemotherapy with the more credible comparator studies reporting a 24-months PFS of 8-25%.
    - One comparator study (Mazgani et al.) was available for a MAIC analysis and was supportive of the narrative analysis demonstrating a HR for OS of 0.559 (p = 0.144) indicating a numerical survival benefit for dostarlimab.

Notably, the low comparability between GARNET and the comparator studies identified, would consistently favour the comparator in a naïve comparison, and therefore results should be considered as conservative. The major limitation of comparison between dostarlimab and platinum-based chemotherapies was the lack of a direct treatment comparison.

Although the comparisons are limited by differences across trials, dostarlimab clearly represents a promising targeted therapy for patients with recurrent or advanced dMMR/MSI-H EC offering long-term survival relative to traditional platinum-based chemotherapy.

6.2 Clinical question 2: What is the value of dostarlimab compared to placebo for patients with dMMR/MSI-H advanced or recurrent ECs progressed during or after platinum-based treatment?

6.2.1 Presentation of relevant studies

No relevant studies have been identified reporting data for second line treatment with placebo in patients with dMMR/MSI-H advanced or recurrent EC progressed during or after platinum-based treatment. Following discussion with key opinion leaders, it was confirmed, that the best supportive care treatment option that would be the most comparable to placebo in terms of efficacy would be PLD, although this would likely overestimate the true efficacy of placebo. Therefore, we kindly ask the DMC to refer to clinical question 3 to inform their assessment of clinical question 2. In terms of the HE-modelling of the placebo-comparison this is likewise made by applying PLD efficacy data and only applying monitoring costs.

6.2.2 Results per study

Not relevant

6.2.3 Comparative analyses

Not relevant

6.3 Clinical question 3: What is the value of dostarlimab compared to pegylated liposomal doxorubicin (PLD) for patients with dMMR/MSI-H advanced or recurrence ECs progressed during or after platinum-based treatment?

For clinical question 3, the DMC protocol specified, that if studies describing the efficacy and safety of PLD could not be found, the expert committee wished to obtain data describing the effect and safety of doxorubicin. Two studies were identified that described the efficacy and safety of PLD. One was a retrospective study (12) and one was a prospective, phase II study (13). Because the evidence for PLD was very limited, three studies were included concerning the efficacy and safety of doxorubicin to supplement and act as proxy data for the efficacy and safety of PLD (4, 10, 11).

6.3.1 Presentation of relevant studies

Of the 14 studies included in the SLR, six were included as relevant to answer clinical question 3. Of these, one study was the GARNET study, reporting data for dostarlimab. Of the studies presenting results for doxorubicin, one was a retrospective study (Makker et al. (10)), and two were RCTs (ZoptEC (4) and McMeekin (11)). For the two RCTs, only data on the arms of interest (doxorubicin) are presented in this application, as the other treatment arms were unauthorised regimens and could not be used to describe any indirect-treatment comparisons. Of the two studies reporting data for PLD, one was a retrospective study (Julius et al (12)) and one was a prospective study (Muggia et al. (13)). The studies included in the SLR, to answer clinical question 3, reported limited information on the patients' baseline characteristics, in particular, Julius et al. and Muggia et al. (13). However, similarly to clinical question 1, the patient population across the studies had mostly homogeneous characteristics, however, with a few important differences as described below.

Patients included in the different studies had a median age ranging between 62.5-67 years. In terms of histological classification criteria, there was consistency across the different studies with most patients presented with endometrioid type I histology and the second most common histological group serious carcinoma. As for clinical question 1, patients enrolled in the GARNET trial (3) were already heavily treated, with 36.1 % of patients receiving more than one prior line of platinum-based chemotherapy. Most patients in GARNET had received prior surgery (90.7%), and almost three-quarters had received radiotherapy (71.3%) prior to inclusion. Previous lines of therapy were generally comparable to Julius et al. (12), which reported a median of three prior lines of chemotherapy, with a range from one to five. Nevertheless, patients in Makker et al. (1), ZoptEC (4) and Muggia et al. (13) only had one previous line of chemotherapy at baseline, indicating that patients in 3 out of 4 studies generally had a better prognosis as compared to the patients enrolled in GARNET..

A larger number of patients in the GARNET trial presented an ECOG level of 1, compared to patients enrolled in studies investigating doxorubicin or PLD. In the GARNET trial, 38.9% of patients presented with an ECOG of 0 and 61.1% of patients presented with an ECOG of 1 at baseline. In the ZoptEC trial (4), 49% of patients had an ECOG score of 0 at baseline and 46.3% had a ECOG score of 1. In accordance with prior lines of treatment, this suggests that patients enrolled in the GARNET study had more severe disease and a poor performance status. Consequently, all estimates of comparative efficacy should be considered conservative estimates of dostarlimab's efficacy compared to doxorubicin or PLD.

A summary of included studies relevant for clinical question 3 is presented in Table 24. Additionally, a summary of baseline characteristics for patients included in the studies is presented in Table 25.

Table 24. Summary of studies included for clinical question 3

Intervention	Dostarlimab	Doxorubicin			PLD	
Trial ID	**GARNET (3)**	**Makker (10)**	**ZoptEC (4)**	**Mcmeekin (11)**	**Julius (12)**	**Muggia (13)**
NCT #	NCT02715284	-	NCT01767155	NCT00883116	-	
Study design	Phase I/ IIb open-label, single-arm (phase II part only of interest and 1 cohort)	Retrospective analysis	Phase III open-label RCT	Phase III open-label RCT	Retrospective review of medical records of patients	Prospective analysis
Locations	117 sites in 9 countries	1 site in the USA	multisite	90 sites in 19 countries	1 site in the USA	1 site in the USA
N eligible patients*	dMMR/MSI-H (N=108; efficacy analysis set); dMMR/MSI-H (N=129; safety analysis set)	N=17	Doxorubicin N=255	Control arm N=248 of which N=171 receiving doxorubicin and N=68 receiving paclitaxel	N=60	N=42
Intervention and dose	Dostarlimab 500mg Q3W; 1000mg Q6W	Doxorubicin 60mg/m^2	Doxorubicin or Paclitaxel	Doxorubicin 60mg/m^2 Q3W	PLD 50 mg/m2 or reduced doses of 40 mg/m^2 35mg/m^2, or 30 mg/m^2	PLD at the initial dose of 50 mg/m2 Q4W
Data cuts (Median duration of follow-up, months)	1st March 2020 (11.2)	Patients treated between 1995 and 2009 (NR)	8 th February 2012 (NR)	January 2017 (NR)	Patients treated between 1996 to 2006 (NR)	NR

* For randomized clinical trials, only patients randomized to relevant treatment arms are reported

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Table 25. Baseline characteristics of patients – studies included in clinical question 3

Intervention	Dostarlimab		Doxorubicin			PLD	
Trial ID	GARNET (7)		Makker (10)	ZoptEC (4)	McMeekin (11)	Julius (12)	Muggia 2002 (16)
No. of patients (No of randomised patients if RCT)	105 (Cohort 1 IA2 cut-off)	108 (Cohort 1 IA2 cut-off)	17	255	248	60	42
Age							
Mean (SD)	63.1 (8.72)	63.2 (8.98)	NR	63.8	NR	66.8	NR
Median	64.0	64.5	56	64	64	67	62.5
Range	39 - 80	39-80	36-78	28-87	33-88	34-87	40-79
<65	53 (50.5%)	54 (50.0%)	NR	136 (53.3%)	NR	NR	NR
≥65	52 (49.5%)	43 (39.8%)	NR	119 (46.6%)	NR	NR	NR
Previous lines of therapy, n (%)							
1	66 (62.9)	69 (63.9)	17 (100)	255 (100)	NR	NR	42 (100)
2	27 (25.7)	27 (25.0)	NR	NR	NR	NR	NR
3	9 (8.6)	9 (8.3)	NR	NR	NR	NR	NR
≥4	3 (2.9)	3 (2.8)	NR	NR	NR	NR	NR
Median (range) previous lines	NR	NR	NR	NR	NR	3 (1–5)	NR
Prior adj chemo	56 (53.3)	NR	NR	92 (36.9)	140 (57.0)	NR	40 (95.2)
Prior surgery	95 (90.5)	98 (90.7)	NR	222 (89.2)	NR	NR	NR
Prior radiotherapy	74 (70.5)	77 (71.3)	NR	138 (55.4)	NR	NR	29 (69.04)
Histology, n (%)[a]							
Endo type 1	71 (67.6)	71 (65.7%)	5 (29.4)	175 (68.9)	138 (56.0)	NR	NR

Intervention	Dostarlimab		Doxorubicin			PLD	
Trial ID	GARNET (7)		Makker (10)	ZoptEC (4)	McMeekin (11)	Julius (12)	Muggia 2002 (16)
Endo type 2	33 (31.4)	36 (33.3%)	NR	NR	NR	NR	NR
Serous	4 (3.8)	5 (4.6%)	5 (29.4)	65 (25.5)	74 (30.0)	NR	NR
Clear cell	1 (1.0)	1 (0.9%)	1 (5.9)	4 (1.6)	18 (7.0)	NR	NR
Squam Carcinoma	1 (1.0)	1 (0.9%)	NR	0 (0.0)	NR	NR	NR
Undiff Carcinoma	4 (3.8)	4 (3.7%)	2 (11.8)	NR	NR	NR	NR
Mixed Carcinoma	4 (3.8)	6 (5.6%)	4 (23.5)	NR	NR	NR	NR
Other / unspecified	19 (18.2)	19 (17.6%)	NR	22 (8.6)	17 (7.0)	NR	NR
Unknown	1 (1.0)	1 (0.9%)	NR	NR	NR	NR	NR
FIGO stage [b]							
I	12 (11.4)	12 (11.1%)	NR	NR	NR	NR	NR
II	4 (3.8)	4 (3.7%)	NR	NR	NR	NR	NR
III	16 (15.5)	19 (17.6%)	3 (17.6) [c]	NR	NR	NR	NR
IV	71 (67.6)	71 (65.7%)	14 (82.4) [c]	NR	NR	NR	NR
ECOG							
0	42 (40.0)	42 (38.9%)	8 (47.0)	125 (49.0)	NR	NR	NR
1	63 (60.0)	66 (61.1%)	7 (41.2)	118 (46.3)	NR	NR	NR
2	0 (0.0)	NR	2 (11.8)	11 (4.3)	NR	NR	NR
1 to 2	0 (0.0)	NR	NR	NR	NR	NR	NR

Abbreviations: EC: endometrial cancer, ECOG: Eastern Cooperative Oncology Group, FIGO: international Federation of Gynecology and Obstetrics. ITT: intention to treat

Annotations: *No patients had received TC within the 6 months prior to retreating, [a] Histology was recorded at diagnosis, [b] FIGO stage was most recent unless otherwise stated, [c] FIGO stage at diagnosis

6.3.1.1 GARNET

The description of the GARNET trial was detailed in section 6.1.1.1.

6.3.1.2 Julius

Julius et al. (12) conducted a retrospective review of medical records of patients who had received PLD as treatment of recurrent EC between 1996, and 2006 at the University of Texas M. D. Anderson Cancer Center (UTMDACC) and Gynecologic Oncology Center. The objective of this study was to determine the impact of PLD dosage on the overall treatment outcomes, together with the incidence of common adverse drug events (ADEs). A total of 60 recurrent EC patients were identified.

Patient demographics, PLD dose, ADEs, use of supportive care interventions, disease progression and survival were extracted. Relevant to this application the study used the Cox proportional hazards regression model to explore the effect of PLD dose on PFS and OS.

Patients included in this study had received PLD as single agent at an initial dose of 50 mg/m2 (FDA approved label dose) or reduced dose of 40 mg/m2 (standard single-agent dose in current clinical practice), 35 mg/m2, or 30 mg/m2 for the treatment of recurrent EC. All patients had received at least one chemotherapy regimen prior to being initiated on PLD regimen.

6.3.1.3 Makker

The objective of this retrospective analysis (10) was to evaluate the efficacy of second-line doxorubicin in patients with advanced/recurrent endometrial carcinoma who progressed after receiving adjuvant paclitaxel and carboplatin (TC) therapy at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1995 and 2009.

Eligible patients had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, and maximal resection of all gross intra-abdominal/pelvic disease, including macroscopically involved para-aortic and pelvic lymph nodes. From this dataset, the authors then identified the patients who had progression of disease after treatment with TC and who received doxorubicin as second-line therapy. All patients in this group were required to have measurable disease by RECIST 1.1 at the time of treatment with doxorubicin. In total, 17 patients were included in the analysis.

. In this study, the primary outcome was measured twice, following adjuvant TC and following doxorubicin upon recurrent disease. The primary outcome, PFS following TC/doxorubicin therapy, was defined as the start date of TC/doxorubicin treatment to the corresponding date of progression. OS following TC/doxorubicin chemotherapy was defined as the time elapsed from the start date of TC/doxorubicin treatment to the date of death or the date of last follow-up. For the purpose of this submission, we are only reporting the outcomes following doxorubicin in second line. The median OS and PFS time as well as the corresponding 95% CIs were estimated using the Kaplan-Meier method.

The primary outcome was PFS. Secondary outcomes included OS and adverse events.

All patients received paclitaxel (175mg/m2) and carboplatin (AUC 6) intravenously (IV) once every three weeks as adjuvant treatment following surgical management of endometrial carcinoma. At the time of measurable disease progression all 17 patients included in this study received doxorubicin (60mg/m2) IV once approximately every three weeks.

6.3.1.4 McMeekin

McMeekin et al. (11) conducted a multicenter, open label phase III study (NCT00883116), in which 496 patients were randomized in a 1:1 ratio to ixabepilone 40 mg/m2 administered as intravenous (IV) infusion every 21 days, or either paclitaxel 175 mg/m2 administered as IV infusion (or per institutional guidelines) every 21 days, or doxorubicin 60 mg/m2 given IV per institutional guidelines every 21 days, depending on prior therapy received. Patients previously

treated with an anthracycline were randomly assigned to either ixabepilone or paclitaxel, and patients who were not previously treated with an anthracycline were randomly assigned to either ixabepilone or doxorubicin.

The purpose of this study was to determine whether ixabepilone, administered to women with locally advanced, recurrent, or metastatic EC who had experienced treatment failure on prior chemotherapy that included a platinum agent, resulted in improved OS compared with commonly used single-agent chemotherapy (doxorubicin or paclitaxel).

Eligible patients included women ≥18 years of age with histologic or cytologic diagnosis of advanced, recurrent, or metastatic endometrial carcinoma, not curable by local measures, and a Karnofsky Performance Status ≥70. Patients may have received up to two prior cytotoxic chemotherapy regimens; at least one regimen had to include a platinum agent.

The primary endpoint was OS and secondary endpoints included PFS (patients with measurable disease only), ORR, duration of response, time to response and toxicity.

6.3.1.5 Muggia

The purpose of this Phase II prospective study (16) was to determine whether PLD had antitumour activity in pre-treated patients with persistent or recurrent endometrial carcinoma and to define the nature and degree of toxicity of PLD.

Eligible patients had to have histologically confirmed persistent or recurrent endometrial carcinoma and the presence of measurable disease. All epithelial cell types were eligible. The ECOG performance status had to be 0, 1, or 2. Patients had to have received one and only one prior chemotherapy regimen or to have qualified for one prior study for recurrent EC. Of 46 patients who entered the study, 42 were assessable for response, as three were declared ineligible on central pathology review and one was not assessable for response.

PLD was administered as a 1-hour infusion at the initial dose of 50 mg/m2 every 4 weeks. Premedication including dexamethasone 20 mg intravenously, together with diphenhydramine 50 mg and cimetidine 300 mg, was recommended during the first and subsequent courses.

The primary outcome was ORR and the secondary outcomes included AE and DoR.

6.3.1.6 ZoptEC

There were no statistical analyses reported for the ZoptEC study (4) as only unpublished material was identified in the SLR in the form of the Clinicaltrials.gov website page. Therefore, in order to fill the missing data gaps, IPD was obtained for the ZoptEC study from the sponsoring company, Aeterna Zentaris, in the form of tables, listings, and figures (27). It was then possible to carry out a more informed comparison.

ZoptEC (4) was an open-label, randomised, active-controlled, two-arm phase III study and the objective of the study was to compare the efficacy and safety of Zoptarelin Doxorubicin vs doxorubicin. A total of 256 patients were randomised to Zoptarelin doxorubicin 267 mg/m2 by 2-hour intravenous infusion, on Day one of 21-day (3-week) cycles for a maximum of nine cycles and 255 patients were randomised to doxorubicin / standard chemotherapy.

Eligible patients had to have advanced (FIGO stage III or IV), recurrent or metastatic disease, Measurable or non-measurable disease that has progressed since last chemotherapeutic regimen with platinum and taxane (either as adjuvant or as first line treatment).

The primary outcome was OS. The secondary outcomes were ORR, PFS, adverse events and quality of life (EORTC QLQ30 + QLQ-EN24 questionnaires).

6.3.2 Results per study

In this section, results for the outcomes of interest as defined by the DMC protocol are presented for each study. Results are then summarised and compared narratively across studies in section 6.1.3.2. Most studies did not report all the outcomes of interest. Median OS and PFS are the outcomes most often reported in the studies. Adverse events and QoL data are only reported in GARNET (7), in ZoptEC (4) and in Muggia et al. (13).

6.3.2.1 GARNET

Results for the GARNET trial are presented in detail in section 6.1.2.1. As described in clinical question 1, GARNET did not provide split analysis based on TFI e.g., for patients who progress within six months of therapy and patients who progress after six months of therapy. Nevertheless, an exploratory analysis of ORR per TFI suggested no difference between platinum-resistant (progression <6 months) and platinum-sensitive patients (progression ≥ 6 months). The results are therefore considered to be applicable to answer both clinical question 1 and clinical question 3.

6.3.2.2 Julius

This retrospective study reported results from the 60 endometrial patients treated in second line with PLD doses of 30 mg/ m2 (N=7), 35 mg/m2 (N=10), and 40 mg/m2 (N=41). Results are presented in this study split per platinum sensitive and platinum resistant for the PFS outcome. However, the study did not provide an explanation of how platinum sensitive and platinum resistant disease were specifically defined. Results should be interpreted with caution due to the fact, that it was a single center study with a small sample size, different doses of PLD and data being analysed retrospectively.

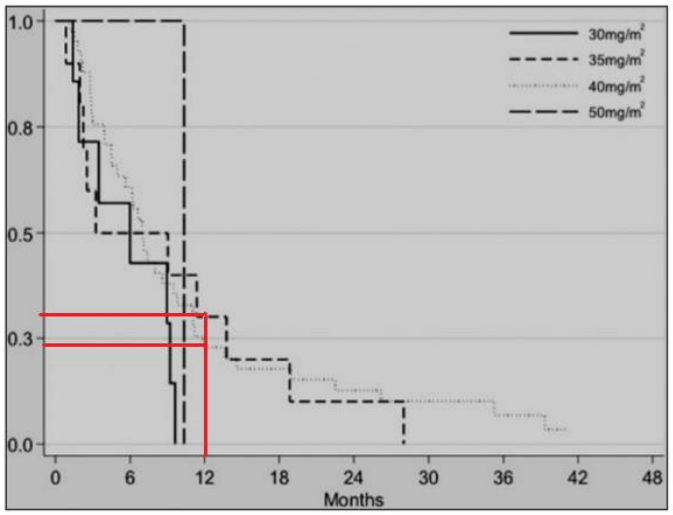
Median OS

Julius et al. (12) reported a median OS of 6.2 months in this population. Survival was not impacted by dose of PLD used on first cycle. Platinum sensitive and platinum resistant disease were not defined in the article. The median OS for platinum resistant disease was 7.1 months compared to 6.2 months in patients with platinum sensitive disease (p=0.42) and did therefore significant effect treatment efficacy. However, it is important to note that the specification of results split per platinum-sensitive and platinum-resistant is less applicable to clinical question 3 than to clinical question 1. The distinction between platinum-sensitive and platinum-resistant have been formulated to describe patients receiving platinum-based chemotherapies, not doxorubicin. It is therefore likely that the difference observed in the results of the two subgroups is insignificant.

OS at 12 months

Based on the KM-curve in the publication, the rate of patients still alive at 12 months was approximately 28% and 35% for the PLD starting doses of and 40 mg/m2 and 50mg/m2, respectively.

Figure 25. OS by PLD Starting Dose adapted by GSK from Julius et al. (12)



Median PFS

Time to progression was calculated as the interval between the date of the first cycle and the date of the last documented cycle for those patients with disease progression. The median PFS for PLD doses of 30 mg/ m2 (N=7), 35 mg/m2 (N=10), and 40 mg/m2 (N=41) was 6.0, 3.3, and 7.0 months, respectively, which was not statistically significant between groups.

All outcomes reported in Julius et al. are summarised in Table 26.

Table 26. DMC protocol outcomes reported for Julius et al (12)

	platinum-sensitive (n=NR)	platinum-resistant (n=NR)
Median OS (months)	6.2	7.1
OS at 12 months (%)	Approximately 28% (Starting dose 40mg/m2) Approximately 35% (Starting dose 50mg/m2)	
Median PFS (months)	For the PLD doses of 30 mg/ m2 (N=7), 35 mg/m2 (N=10), and 40 mg/m2 (N=41) medias PFS was 6.0, 3.3, and 7.0 months respectively.	
PFS at 24 months (%)	Non reported	Non reported
ORR (%)	Non reported	Non reported
EORTC-QLQ-EN24	Non-reported	Non-reported
EORTC QLQ-C30	Non-reported	Non-reported
Adverse events of grade 3-4	Non-reported	Non-reported

6.3.2.3 Makker

This section reports results for the 17 patients treated with doxorubicin in second line following initial paclitaxel/carboplatin adjuvant therapy. Results should be interpreted with caution due to fact, that it was a single centre study with a very small sample size and data being analysed retrospectively.

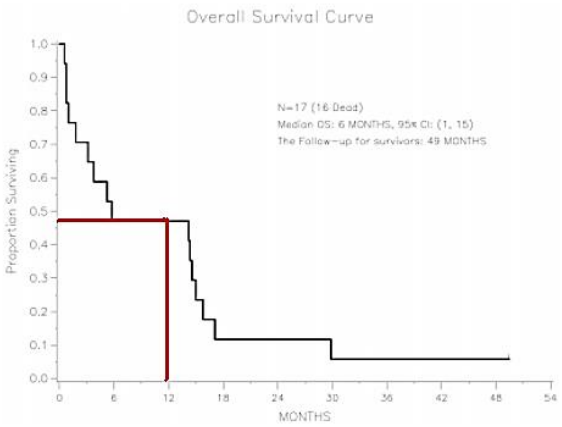
Median OS

OS following doxorubicin chemotherapy was defined as the time from the start date of doxorubicin treatment to the date of death or the date of last follow-up. The median OS reported was of 5.8 months (1.0-15.0).

OS as 12 months

Based on the KM-curve in the publication the OS rate at 12 months for the 17 patients treated with doxorubicin in second line was approximately 48%

Figure 26. OS at 12 months among advanced EC patients treated with second line doxorubicin, n=17 adapted by GSK from Makker et al. (10)



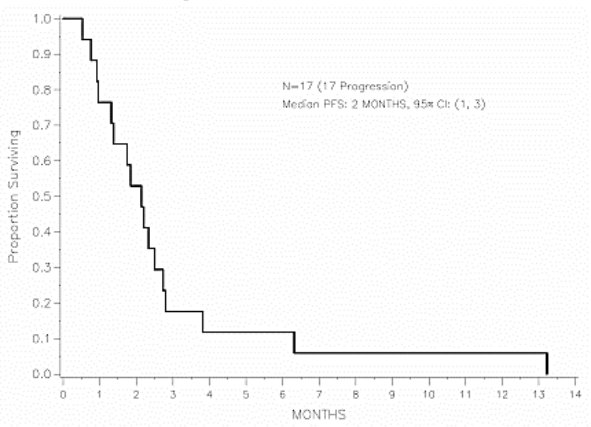
Median PFS

PFS following doxorubicin therapy was defined as the start date of doxorubicin treatment to the corresponding date of progression. The median PFS reported was of 2.1 months (0.97-2.7).

PFS at 24 months

Based on the KM-curve in the publication, 0% of the patients treated with doxorubicin in second line were progression-free after 24 months.

Figure 27. PFS among advanced EC patients treated with second-line doxorubicin (10)



ORR

ORR or disease stabilisation to doxorubicin treatment were not seen in any of the patients in this cohort.

Adverse events

Proportion of patients experiencing grade 3 or 4 adverse events.

No patients reported grade 3 or 4 toxicities.

All outcomes reported in Makker et al. are summarised in Table 27.

Table 27. DMC protocol outcomes reported for Makker et al. (1)

DMC outcomes	Patients taking doxorubicin treatment for recurrent disease (n=17)
Median OS (months)	5.8 (1.0-15.0)
OS at 12 months (%)	Approximately 48%
Median PFS (months)	2.1 (0.97-2.7)
PFS at 24 months (%)	0%
ORR (%)	0 (0%)
EORTC-QLQ-EN24	Non-reported
EORTC QLQ-C30	Non-reported
Adverse events of grade 3-4	0%

6.3.2.4 McMeekin

McMeekin et al. conducted a multicenter randomised controlled trial. Within the control arm (patients treated with paclitaxel or doxorubicin), McMeekin did not report split efficacy results for patients receiving one treatment or the other. We report here the results for the 284 patients in the overall control arm of the RCT.

Median OS

At the data cut-off of the 8th of February 2021, the median OS was 12.3 months (95% CI: 10.7–15.4) in the control chemotherapy group, which included 71 patients receiving paclitaxel and 171 patients receiving doxorubicin.

OS at 12 months

Based on the KM-curve in the publication, the rate of patients in the control arm (n=284) who were still alive at 12 months was approximately 51% (doxorubicin or paclitaxel)

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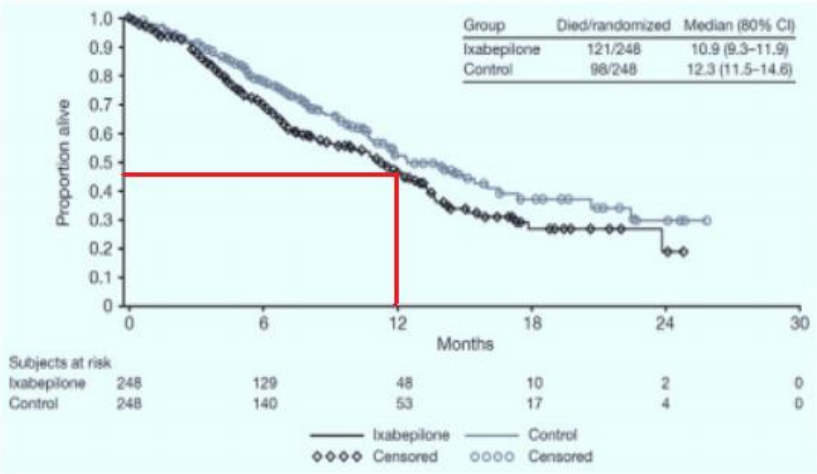
Figure 28. KM plot for OS for all randomised patients adapted by GSK from McMeekin et al (11)



Median PFS

The median PFS was 4.0 months (95% CI: 2.7–4.3) in the control chemotherapy group.

ORR

ORR were 15.7% (95% CI: 11.2-21.1) in the control group.

All outcomes reported in McMeekin et al. are summarised in Table 28.

Table 28. DMC protocol outcomes reported for McMeekin et al (11)

	Control group, 71 patients receiving paclitaxel and 171 patients receiving doxorubicin **(n=284)**
Median OS (months)	12.3 (95% CI: 10.7–15.4)
OS at 12 months (%)	Approximately 51%
Median PFS (months)	4.0 months (95% CI: 2.7–4.3)
PFS at 24 months (%)	Non reported
ORR (%)	15.7% (95% CI: 11.2-21.1)
EORTC-QLQ-EN24	Non-reported
EORTC QLQ-C30	Non-reported
Adverse events of grade 3-4	Non-reported

6.3.2.5 Muggia

Muggia et al. conducted a non-randomised prospective phase II trial including 42 patients with metastatic EC treated with PLD as second line therapy. Results should be interpreted with caution due to the small sample size.

Median OS

The median OS was 8.2 months.

ORR

Four patients (9.5%) out of 42 patients achieved a PR (95% CI: 2.7% to 22.6%).

Adverse events

The proportion of patients experiencing grade 3-4 is presented in Table 29 for each adverse event of interest.

Table 29 Number of patients experiencing a Grade 3-4 adverse event (n=43) (13)

Grade 3-4 adverse event	Number of patients experiencing a Grade 3–4 adverse event (%)
Neutropenia	7 (16.27%)
Anemia	5 (11.63%)
Mucositis	1 (2.33%)
Nausea and/or vomiting	1 (2.33%)
Other gastrointestinal	3 (6.98%)
Dermatologic	4 (9.3%)
Neurotoxicity	2 (4.65%)
Fever	1 (2.33%)
Pulmonary	1 (2.33%)
Cardiovascular	1 (2.33%)

All outcomes reported in Muggia et al. are summarised in Table 30.

Table 30. DMC protocol outcomes reported for Muggia et al. (13)

	EC patients (n=42)
Median OS (months)	8.2
OS at 12 months (%)	Non reported
Median PFS (months)	Non reported
PFS at 24 months (%)	Non reported
ORR (%)	9.5% (95% CI: 2.7% to 22.6%)
EORTC-QLQ-EN24	Non-reported
EORTC QLQ-C30	Non-reported
Adverse events of grade 3-4	See Table 29

6.3.2.6 ZoptEC

ZoptEC was a randomised controlled trial in which 255 patients with EC were randomised to receive doxorubicin.

Median OS

The median OS was 10.8 (9.8-12.6) months in the doxorubicin arm.

OS rate at 12 months

At 12 months, 106 (44.6% (95% CI: 38.2- 50.7)) of the 255 in the doxorubicin/standard chemotherapy arm had survived.

Median PFS

At the data cut-off, the median PFS was 4.7 months (4.1-6.6).

Objective response rate

At the data cut-off, 36 (14.1%) of the 255 in the doxorubicin/standard chemotherapy arm achieved ORR.

EORTC QLQ-C30

As showed in Table 31, patients enrolled in the ZoptEC trial reported a clinically relevant worsening on the physical functioning, the role functioning, and the social functioning scales as well as on their Global health status. Additionally, patients also reported a clinically relevant increase in Fatigue, dyspnoea and Appetite loss.

Table 31. Mean change from baseline to end of treatment in EORTC QLQ-C30 for the ZoptEC trial (27) (28)

Mean (SD) CFB	ZoptEC (doxorubicin arm), n = 245
Global QoL	-11.7 (26.42)
Physical Functioning	-15.3 (21.98)
Role Functioning	-22.5 (30.91)
Emotional Functioning	-2.1 (24.51)
Cognitive Functioning	-8.6 (22.79)
Social Functioning	-15.2 (31.54)
Fatigue	19.6 (27.85)
Nausea and vomiting	9.2 (22.97)
Pain	8.2 (28.50)
Dyspnoea	14.1 (29.35)
Insomnia	7.7 (31.01)
Appetite loss	19.8 (33.12)
Constipation	6.8 (31.35)
Diarrhoea	2.5 (21.33)
Financial difficulties	2.2 (29.76)

Abbreviations: CFB, change from baseline; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation

Proportion of patients experiencing at least one adverse reaction of grade 3-4

Within the safety analysis set (n=249), 195 (78.3%) of patients treated with doxorubicin experienced at least one TEAE of grade 3-4. Details are presented in Table 32.

Table 32. Grade 3 or 4 TEAEs reported in the ZoptEC trial for the doxorubicin arm (27) (28)

doxorubicin arm n=249, n (%)

Abdominal pain	4 (1.6%)
Fatigue	14 (5.6%)
Aneamia	38 (15.3%)
Neutropenia	112 (45.0%)
Nausea	13 (5.2%)
Vomiting	13 (5.2%)
Leukopenia	45 (18.1%)

All outcomes reported in the ZoptEC trial are summarised in Table 33.

Table 33. DMC protocol outcomes reported for ZoptEC (27)

	Patients receiving doxorubicin (n=255)
Median OS (months)	10.8 (9.8-12.6)
OS at 12 months (%)	44.6% (95% CI: 38.2- 50.7)
Median PFS (months)	4.7 (4.1-6.6)
PFS at 24 months (%)	Non reported
ORR (%)	14.1 (9.8-18.4)
EORTC-QLQ-EN24	Non-reported
EORTC QLQ-C30	-11.7 (26.42)
Adverse events of grade 3-4	78.3 %

6.3.3 Comparative analyses

A summary comparison of the relevant outcomes is presented in Table 43.

6.3.3.1 Limitations

For patients who progress within six months after platinum-based chemotherapy, the DMC considers PLD (or doxorubicin) as standard of care to which dostarlimab should be compared to. As mentioned previously, no head-to-head trials are available comparing dostarlimab to PLD/doxorubicin, however a total of 5 studies were identified in the SLR which served as the evidence for the comparator (PLD/doxorubicin). These studies were assessed and reviewed for the purposes of conducting an ITC. The ITCs allowed GSK to estimate the comparative effectiveness of dostarlimab versus PLD/doxorubicin.

dMMR/MSI-H status

As discussed in detail in clinical question one section 6.1.3.1 comparator studies did not report on dMMR/MSI-H status. However, the internal GSK SLR clearly suggested, that the status is unrelated to the prognosis of patients with current standard of care.

Treatment free-interval (TFI) / Platinum-free interval (PFI)

As described earlier, split results from the GARNET trial are not available for platinum-sensitive and platinum-resistant subgroups, but an exploratory analysis indicated similar ORR between PFI < 6 and PFI ≥ 6 months. Similarly, only Julius et al.(12) reported split results per platinum-sensitive/resistant, and results were similar between groups (6.2 months vs. 7.1 median OS, respectively). As described in section 5, the specification of results split per platinum- sensitive and platinum-resistant is less applicable to clinical question 3 than to clinical question 1.

6.3.3.2 Approach to comparative analysis

Indirect comparisons were carried out to provide the best possible answer to the clinical question and both a narrative and MAIC analysis is provided in the sections below.

McMeekin et al. (11) reported results from a Phase III randomised trial of second line ixabepilone versus paclitaxel or doxorubicin in women with advanced EC. The control arm of paclitaxel or doxorubicin (N=248) represents a relevant comparator for dostarlimab, unfortunately, KM data was not disaggregated for each comparator: only a combined KM OS curve was presented in the McMeekin trial. However, 171 patients included in the study did receive doxorubicin and only 68 received paclitaxel, and the results will therefore be used to approximate the efficacy of doxorubicin.

For the purposes of the MAIC analysis, dostarlimab was compared to the combined control arm of paclitaxel or doxorubicin. As McMeekin et al. (11) was a multicenter Phase III randomised trial, with a large N (=248) for the control arm, MAIC results for this study are considered the most robust.

Julius et al. (12) was a retrospective review of medical records of patients who received PLD as treatment for recurrent EC between January 1, 1996, and June 30, 2006, at one centre at The University of Texas, US. Several different doses of PLD were reported, only the 40mg/m2 dose was used for the MAIC as this dose had sufficient sample size (n=41) and because it represents standard single-agent dose in current clinical practice. Despite being a single centre retrospective review, this publication reported OS for a key comparator and was included in the MAIC analysis.

GSK have carried out unanchored MAIC analyses to adjust for differences in study populations by taking individual patient data from the GARNET trial and weighting it to match the aggregate data from the Julius et al. (12) and the McMeekin et al. (11) studies. These analyses were implemented to ensure narrative comparability of efficacy outcomes between dostarlimab and PLD or doxorubicin. Unanchored MAIC analyses were carried out for the outcomes of OS, PFS, AEs and ORR. Results are presented below.

Additionally, to facilitate a comparison of the single-arm nature of GARNET to a synthetic control utilising doxorubicin patient from the ZoptEC randomised control trial, an external control using Cox proportional hazards with inverse probability of treatment weighting (IPTW) was carried out. The results helped comparing and describe the efficacy and safety of dostarlimab against doxorubicin.

The results of the statistical analyses are presented in detail in section 0. Due to the limitations of the statistical analyses, a narrative comparison is also presented below.

6.3.3.3 Narrative Comparison

In general, there are some differences in study design and patients' characteristics between studies. Notably, patients in GARNET (3) were in general more heavily pre-treated than the patients in the comparator studies, as discussed in section 6.3.1. Furthermore, data from most of the included studies did not present data split per platinum-sensitive and platinum-resistant patients. However, data from GARNET and Julius et al. (12) indicated that PFI was not a strong treatment-modifier for either dostarlimab or PLD/doxorubicin. In addition, the non-disaggregated data presented by McMeekin et al. (11), reporting results for patients receiving doxorubicin or paclitaxel did introduce some uncertainty to the treatment comparison, because the comparison is then made versus patients that have not strictly been treated with doxorubicin. The effect that was observed in McMeekin cannot be attributed only to doxorubicin.

Looking beyond the limitations for comparing results across studies, the very distinctive result noted in GARNET was the large proportion of patients who experienced an initial response, and who continued to experience long-term disease remission. This was demonstrated by the early flattening of PFS- and OS-curves forming a long-tail representing patients in long-term remission. Comparing this response to PLD/doxorubicin demonstrated, that this response was only observed for dostarlimab, whereas patients treated with the comparator steadily continued to progress. Therefore, especially the PFS-rate at 24-month for dostarlimab stood out as a relevant result differentiating dostarlimab from PLD/doxorubicin. The value of dostarlimab is therefore most importantly, that a large proportion of patients experience long-term PFS/OS, whereas this was not observed for PLD/doxorubicin in any of the comparator trials.

Median OS/12-month OS-rate

In the GARNET trial, the median OS was not reached (95% CI: 17.1-NR) at the data cut-off of March 2020. Considering that the median follow-up time at this data cut-off was 16.3 months and considering the plateau observed for PFS at 24 months, dostarlimab showed promising results in terms of median OS . Studies investigating doxorubicin or PLD reported inferior results, despite patients had less lines of therapy at baseline compared to patients enrolled in GARNET. McMeekin et al. (11), Muggia et al. (13) and ZoptEC trial (12) reported median OS of 12.3 months, 8.2 months and 10.8 months respectively. Julius et al. reported median OS of 7.1 months for the platinum resistant patients.

According to the criteria described by the DMC in the protocol of this assessment, achieving an absolute difference in 12-month OS-rate of five percentage points is a clinically relevant difference. At the data cut-off of March 2020, with a median follow-up of 16.3 months, dostarlimab was associated with a 12-month landmark OS of 69.2% (95% CI: 58.8-77.6). The literature reports that the one-year survival for platinum resistant advanced recurrent EC is expected to be approximately 50% (13). This was confirmed by the Kaplan Meier graphs for OS presented by Makker et al. (10) and McMeekin et al. (11), which both reported that 48 and 51% of patients approximately were alive at 12 months. Additionally, this result is higher than the 12 months OS landmark reported in the ZoptEC trial (44.6% (95% CI: 38.2- 50.7) (27), despite patients enrolled in the ZoptEC trial were less heavily treated at baseline, and better than the 28% and 35% for the two initial PLD doses subgroups of patients reported by Julius et al. (12). Achieving a 69.2% (95% CI: 58.8-77.6) OS rate at 12 months is therefore a robust and clinically meaningful result for dostarlimab, which will bring significant difference to patients who currently do not have many treatment options.

Moreover, the MAIC analysis versus McMeekin et al. (11) demonstrated that dostarlimab has approximately 59.3% lower risk of death compared to paclitaxel/doxorubicin, when adjusting for confounding factors providing the best estimate of the relative efficacy between the interventions. This result is confirmed by the analysis carried out comparing GARNET patients with ZoptEC patients. The analysis demonstrated that dostarlimab is expected to result in approximately a 59.0% reduction in the risk of death compared to doxorubicin. Similarly, when looking at the results of the MAIC analysis versus Julius et al. (12), dostarlimab has approximately 71.3% lower risk of death compared to PLD (section 6.3.3.4)

Progression free survival

In the GARNET trial, patients treated with dostarlimab had a median PFS of 5.5 months (95% CI: 3.2-NR). As previously described the median PFS-estimate in GARNET is not considered robust but very volatile and sensitive to censoring and events, as a prolonged tail of the curve is formed right around the median, which results in a single event/censoring can shift the PFS-estimate significantly. This was observed when comparing the median PFS estimate from the smaller population of the initial data-cut IA-1 (n = 72), which provided a median PFS of > 12 months, whereas the curve was shifted for the IA-2 population to a median PFS of 5.5 months due to censoring and a single event (**Fejl! Henvisningskilde ikke fundet.**). Therefore, the 24-month landmark PFS-estimate provides more meaningful measures of the value of dostarlimab. In fact, contrary to chemotherapy treatments, dostarlimab provides a long and sustained effect, which is not captured by observing the median PFS. Median PFS is not an adequate measure to demonstrate sustained effect and capture the large proportion of patients responding to the therapy who become long-term survivors. In the GARNET

trial 39% of patients were progression-free at 24 months. This is a notably meaningful result when compared to the observed PFS-rate on the KM curve reported by Makker et al. (10), were the PFS-rate was 0% after 13th months.

Objective response rate

McMeekin et al. (11), Muggia et al. (13) and the ZoptEC trial reported ORR of 15.7% (95% CI: 11.2-21.1), 9.5% (95% CI: 2.7% - 22.6%), 14.1 (9.8-18.4) respectively for patients treated with doxorubicin or PLD. In comparison, the GARNET trial reported an ORRs of 43.5% for patients receiving dostarlimab. This is a remarkable difference, as patients in comparator studies had fewer prior lines of treatment and therefore had a better prognosis, compared to patients in the GARNET trial. This was confirmed with the MAIC analysis carried out versus McMeekin et al. (11), which demonstrated that treatment with paclitaxel/doxorubicin reduced the odds of ORR by 76.6% compared to the odds of ORR with dostarlimab.

Quality of life

Only two studies (GARNET and ZoptEC) reported data on quality of life investigated through the EORTC QLQ-C30. In ZoptEC (12), patients receiving doxorubicin demonstrated a mean change score for global QoL of -11.7 (26.42). They reported a clinically meaningful worsening of role functioning, physical functioning, social functioning, dyspnea and appetite loss. However, in GARNET, patients treated with dostarlimab reported an improvement in the global QoL of [redacted]. Following treatment with dostarlimab, relative to baseline, patients reported clinically meaningful improvements in social functioning and in pain reduction.

Proportion of patients experiencing grade 3 or 4 adverse events.

In regards to safety and particularly TEAEs of grade 3 or 4, the GARNET trial demonstrated better results compared to the ZoptEC trial (12) investigating doxorubicin. GARNET reported that overall, 48.1% of patients treated with dostarlimab reported at least one TEAE of grade 3 or 4 whereas in the ZoptEC trial 78.3% of patients experienced at least one TEAE of Grade 3 or 4. Makker et al. reported that no grade 3 or 4 toxicities occurred, however, Makker et al. (10) was a retrospective study, which is considered a very unreliable source for adverse events data with no formal and structured capturing of AEs. Therefore, comparing results from Makker et al. to GARNET will be biased. The safety profile observed in GARNET and ZoptEC (12) were therefore considered to be the most representative data for the overall safety profile of dostarlimab and doxorubicin/PLD, respectively.

Based on the above, results suggest dostarlimab is associated with a much lower proportion of patients experiencing grade 3-4 AEs. It is however recognised, that the safety profile of the comparators and that of dostarlimab are fundamentally different from each other given they are different therapeutical classes with different modes of actions. Therefore, the treatments are difficult to compare as events differ significantly in type, severity, and reversibility. Acknowledging, that there is a severe lack of reporting of safety in the comparator studies, GSK suggests, that the best approach for evaluating safety is a narrative approach undertaken by the DMC expert committee. In section 6.1.2.1 GSK has provided a summary of the safety profile of dostarlimab from the SmPC, which can be used by the Expert Committee to compare with the safety profile of comparators.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 34. Summary of comparison of relevant outcomes

Study	Intervention	Median OS (months)	12-month OS-rate	Median PFS (months)	24-month PFS-rate	ORR	EORTC-QLQ-EN24	Mean change from baseline in EORTC QLQ-C30	AEs grade 3-4
GARNET	Dostarlimab	NR (95% CI: 17.1-NR)	69.2% (95% CI: 58.8-77.6).	5.5 (95% CI: 3.2-NR)	[redacted]	43.5%	NR	[redacted]	62 (48.1%)
Julius (12)	PLD	6.2 months (Platinum sensitive) 7.1 months (platinum resistant)	Approximately 28% (Starting dose 40mg/m2) Approximately 35% (Starting dose 50mg/m2)	PLD doses of 30 mg/ m2 (N=7), 35 mg/m2 (N=10), and 40 mg/m2 (N=41) was 6.0, 3.3, and 7.0 months respectively	NR	NR	NR	NR	NR
Makker (10)	Doxorubicin	5.8 (95% CI: 1.0-15.0)	Approximately 48%	2.1 (95% CI: 0.97-2.7)	0%	0 (0%)	NR	NR	0%
McMeekin (11)	Doxorubicin or paclitaxel	12.3 (95% CI: 10.7–15.4)	Approximately 51%	4.0 (95% CI: 2.7–4.3)	NR	15.7% (95% CI: 11.2-21.1)	NR	NR	NR
Muggia (13)	PLD	8.2 months	NR	NR	NR	9.5% (95% CI: 2.7% - 22.6%)	NR	NR	See Table 29
ZoptEC (12)	Zoptarelin doxorubicin	10.8 (9.8-12.6)	44.6% (95% CI: 38.2-50.7)	4.7 (95% CI: 4.1-6.6)	NR	14.1% (9.8-18.4)	NR	-11.7 (26.42)	195 (78.3)

***Mean (SD) change from baseline after 7 cycles of dostarlimab in the Global Health status/QoL. NR: not reported**

6.3.3.4 Indirect statistical comparisons

Please refer to appendix 9.6 for individual weights with histograms and for identification and selection of baseline characteristics used as matching variables for the MAIC.

MAIC analysis OS- McMeekin et al.

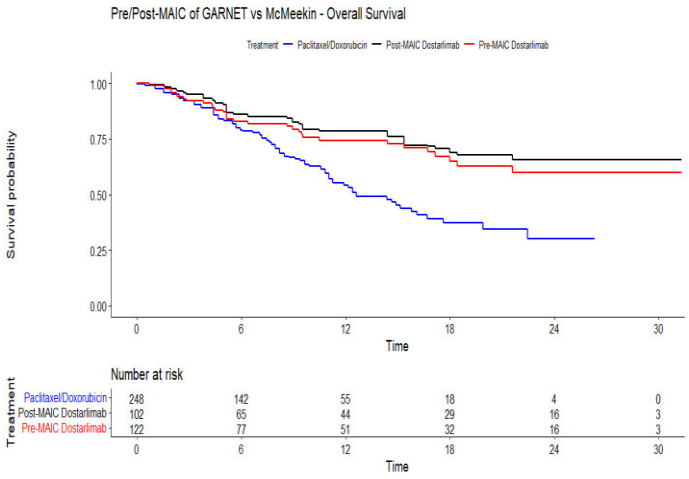
The median OS (with 95% CI) for dostarlimab pre and post MAIC adjustment and for paclitaxel/doxorubicin are presented in Table 35.

Table 35: Median OS pre and post MAIC: GARNET vs McMeekin

	Dostarlimab (Pre-MAIC)	Dostarlimab (Post- MAIC)	Paclitaxel / Doxorubicin
OS (in months)			
Median	NR	NR	12.6
(95% CI)	(21.6, NR)	(NR, NR)	(11.0, 16.7)

NR=Not Reached

Figure 29: Kaplan-Meier analysis for OS – GARNET vs McMeekin



Note: the number of subjects is 122 of pre-MAIC Dostarlimab, but the number at risk is 102, due to the weighting used in the MAIC.

These KM data indicate that dostarlimab shows better survival probabilities compared to paclitaxel/doxorubicin which is observable after approximately 3-5 months. This is expected given the mechanism of action of dostarlimab as a PD-1 inhibitor, which, relative to chemotherapy, takes longer for the immune response to be observed.

Table 36: HR for OS – GARNET vs McMeekin

	N	Hazard ratio (Dostarlimab / Paclitaxel or Doxorubicin)	95% CI	Robust StdErr :log(HR)	p-value
Cox PH model	370	0.407	0.252, 0.657	0.2448	0.0002
Assumption check of proportional hazard ratios					
	N	Chi-square		p-value	
Assumption check	370	1.16		0.28	

The test of the assumption of proportional hazards does not show a violation (p-value =0.28). A Cox proportional hazards model with MAIC was fitted to the data. The HR (=0.407) and corresponding p-value (0.0002) indicate a significant difference between the two treatments on OS. The OS hazard ratio for dostarlimab (numerator of the HR) is lower than that for paclitaxel/doxorubicin (in the denominator). Hence, in the above analysis dostarlimab has approximately 59.3% lower risk of death compared to paclitaxel/doxorubicin.

ORR / McMeekin et al

The ORR represents the proportion of patients who achieved a best overall response (BOR) of CR or PR. After applying the weights to the GARNET data for the MAIC, the odds ratio, relative risk and risk reduction were calculated and are displayed in Table 38 below.

Table 37: Summary of ORR results post-MAIC: GARNET vs McMeekin

Outcome scale	Estimate	95% CI	Robust StdErr :Log(OR or RR)	p-value
Odds ratio (Paclitaxel or Doxorubicin / Dostarlimab)	0.234	0.134, 0.409	0.285	<.0001
Relative risk (Paclitaxel or Doxorubicin / Dostarlimab)	0.354	0.241, 0.521	0.197	<.0001
	Estimation	**95% CI**	**Robust StdErr**	**p-value**
Risk difference (Paclitaxel or Doxorubicin) - Dostarlimab)	-0.286	-0.386, -0.186	0.051	<.0001

The odds ratio (=0.234) and corresponding p-value (<0.0001) indicate a trend of a difference between the two treatments for ORR, suggesting that treatment with paclitaxel/doxorubicin (numerator in OR) reduced the odds of ORR by 76.6% compared to the odds of ORR with dostarlimab (denominator in OR).

MAIC analysis OS / Julius et al

The median OS (with 95% CI) for dostarlimab pre and post MAIC adjustment and for PLD are presented in Table 39.

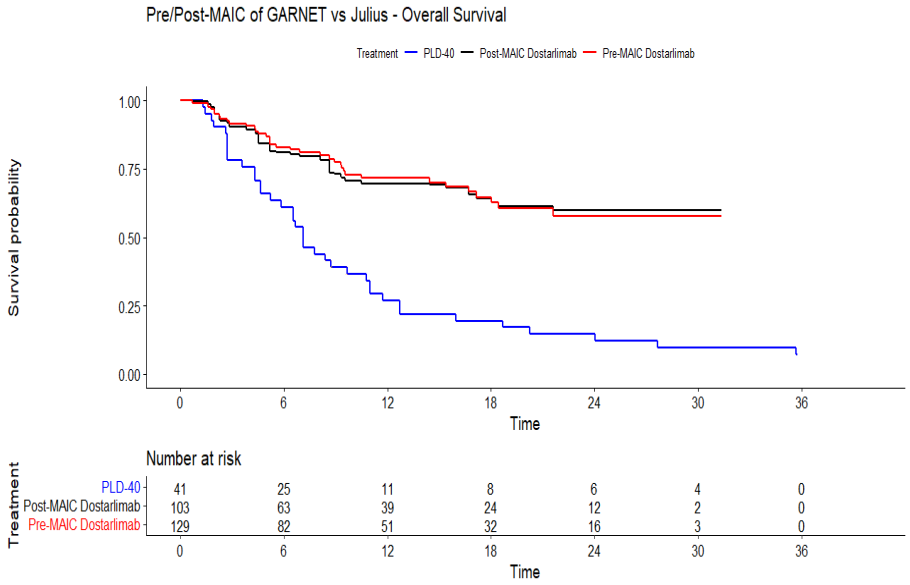
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 38: Median OS pre and post MAIC: GARNET vs Julius

	Dostarlimab (Pre-MAIC)	Dostarlimab (Post- MAIC)	PLD40 mg/m^2
OS (in Months)			
Median	NR	NR	7.1
(95% CI)	(21.62, NR)	(18.43, NR)	(5.83, 11.0)

NR=Not Reached

Figure 30: Kaplan-Meier analysis for OS – GARNET vs Julius



Note: the number of subjects in pre-MAIC Dostarlimab is 129, but the number at risk is 103, due to the weighting used in the MAIC.

Table 39: HR for OS – GARNET vs Julius

	N	Hazard ratio (Dostarlimab / PLD40 mg/m^2)	95% CI	Robust StdErr :log(HR)	p-value
Cox PH model	170	0.287	0.170, 0.486	0.2685	<0.0001
Assumption check of proportional hazard ratios					
	N	Chi-square	p-value		
Assumption check	170	1.89	0.17		

The test of the assumption of proportional hazards does not show a violation (p-value =0.17). A Cox proportional hazards model with MAIC was fitted to the data. The HR (=0.287) and corresponding p-value (<0.0001) indicate a trend of a difference between the two treatments on OS. The OS hazard ratio for dostarlimab (numerator of the HR) is lower than that for PLD (in the denominator). Hence, in the above analysis dostarlimab has approximately 71.3% lower risk of death compared to PLD.

Inverse probability of treatment weighting/ZoptEC

The main analysis was performed using a Cox proportional hazards model with stabilised-IPTW to estimate the hazard ratio for OS (dostarlimab vs doxorubicin). A proportionality test was conducted to ensure that the proportional hazards assumptions were not violated. The results of the main analysis and the proportionality test are presented in Table 40.

Table 40. Results for the main data analysis set on OS with adjusting stabilized-IPTW

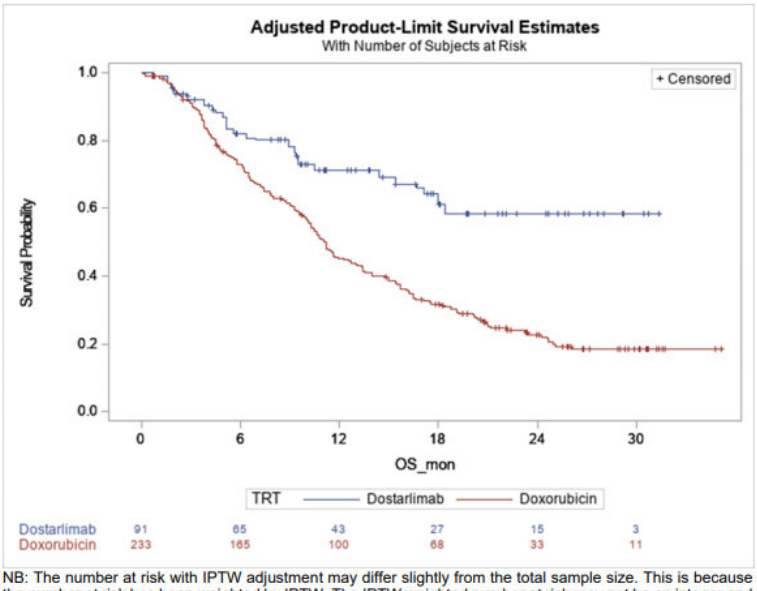
	N*	Hazard ratio (dostarlimab / doxorubicin)	95% CI	StdErr	p-value
Cox PH model	325	0.409	0.277, 0.605	0.199	<.0001
Assumption check	325	1.421	0.940, 2.150	0.211	0.0960

*(dostarlimab = 92, doxorubicin = 233)

The results from the proportionality test ensure that the proportional hazards assumptions are met, as the p-value (0.096) is greater than 0.05. As such, the adjusted analysis will utilize a Cox proportional hazards model with stabilised-IPTW. There is a statistically significant difference between the two treatments for OS (HR: 0.409, p-value < 0.0001). As such, treatment with dostarlimab is expected to result in approximately a 59.0% reduction in the risk of death compared to doxorubicin.

For reference, the Kaplan-Meier survival curves with stabilised-IPTW on OS is shown in Figure 31.

Figure 31 Kaplan Meier curves for OS with adjusting stabilised-IPTW for the main analysis data set



NB: The number at risk with IPTW adjustment may differ slightly from the total sample size. This is because the number at risk has been weighted by IPTW. The IPTW weighted number at risk may not be an integer and in the KM plots the weighted IPTW number at risk has been rounded to the nearest integer value.

Dostarlimab showed better survival probabilities throughout all survival times compared to doxorubicin except for the first 2-3 months. This is expected given the mechanism of action of dostarlimab as a PD-1 inhibitor, which, relative to chemotherapy, takes longer for the immune response to be observed. The log-rank test for homogeneity indicates a significant difference between the treatments (p<0.0001). Patients treated with dostarlimab have significantly longer OS compared to those treated with doxorubicin.

Limitations of the indirect comparisons

- Results for the control arm 'paclitaxel or doxorubicin' in Julius et al (12) and the McMeekin et al. (11) were not reported for the individual agents received, only the whole cohort. Therefore, it is not possible to assess the relative effectiveness of dostarlimab to paclitaxel or to doxorubicin as single agents.
- 8 prognostic variables were identified as relevant for the MAIC but only 4 were available in Julius et al (12) and the McMeekin et al (11) on which to match (Age, ECOG, Histology, and Race) – this limited the ability to fully match patients from GARNET.
- Julius et al (12) was a retrospective, observational review of treatment records from one centre in the US whereas GARNET was a multi-centre Phase I clinical trial: these differences in design limit comparability of these study populations.
- Whilst the sample size of Julius et al (N=41) for the PLD 40mg/m2 dose met the MAIC inclusion criteria (=>30), this was still a small sample size limiting the robustness of comparative effective estimates.
- 8 prognostic variables were identified as relevant for the MAIC but only 3 were available in Julius on which to match (Age, Race, and Number of prior chemotherapies) – this limited the ability to fully match patients from GARNET.

6.3.3.5 Conclusion

The narrative comparison and the MAIC between dostarlimab in the pivotal GARNET trial and patients treated with platinum-based chemotherapy in the comparator trials strongly indicates patients treated with dostarlimab experience superior results for all selected efficacy outcomes and most importantly a meaningful survival benefit. Notably, patients in GARNET were more heavily pre-treated than patients in the comparator-studies. This would consistently favour PLD/doxorubicin in a naïve comparison, and therefore results should be considered conservative.

- Patients treated with dostarlimab experienced a notable and clinical meaningful survival benefit compared to PLD/doxorubicin demonstrated by 69.2% (95% CI: 58.8-77.6) of patients treated with dostarlimab were alive after 12 months compared to 28-51 % of patients treated with PLD/doxorubicin (range of 3 studies reporting the outcome).
    - Dostarlimab therefore provides a approx. 20-40 % higher OS-rate at 12 months compared to PLD/doxorubicin, even though patients were more heavily pre-treated.
- Similarly, encouraging results were observed for median OS, as the median OS was not reached after 16.3 months (95% CI: 17.1-NR), whereas the comparator studies for PLD and doxorubicin reported a median OS of 5.8-12.3 months (range of 5 studies reporting the outcome).
- This was substantiated by all three indirect analyses, which demonstrated a 59%-71.3% lower risk of death for dostarlimab compared to PLD/doxorubicin.
- The progression-free survival (PFS) results from GARNET demonstrated a similar benefit in favour of dostarlimab.
    - At Month 24, [redacted] of patients treated with dostarlimab remained progression-free compared to 0% of patients receiving doxorubicin in the only study where 24-months PFS was available.
- Dostarlimab demonstrated a robust and clinically meaningful ORR of 44,7% compared to 0-15.7 % patients with PLD/doxorubicin experiencing ORR (range from 4 studies reporting this outcome).
- Dostarlimab was also shown to be well-tolerated and associated with a manageable AE profile in line with other currently licensed anti-programmed cell death ligand 1 (PD-L1) therapies. Grade ≥3 TEAE were low grade with

only 48.1% of patients experiencing an event compared to 78.3 % of patients treated with doxorubicin in the ZoptEC trial.

  - Dostarlimab is therefore associated with less grade 3-4 toxicity compared to chemotherapy, with superior results vs. doxorubicin in the ZoptEC trial

- Two studies (GARNET and ZoptEC) identified reported data on quality of life, investigated through the EORTC QLQ-C30 instrument.

  - In ZoptEC (12), patients treated with doxorubicin demonstrated a clinically relevant worsening in their quality of life measured by the change from baseline in global QoL of -11.7.

  - Contrary to the worsening observed for the comparator, in GARNET, patients treated with dostarlimab reported a clinically meaningful improvement in the global QoL of [redacted] points from baseline.

Overall, these results, strongly implies, that patients benefit from dostarlimab treatment, through a combination of enhanced therapeutic efficacy allowing for long-term OS/PFS and complemented by reduced general toxicity as measured by grade 3-4 TEAE resulting in an overall global improvement in QoL as measured by EORTC QLQ-C30.

7. Other considerations

irORR

As part of the prespecified secondary endpoints of the GARNET trial, GSK have investigated ORR by immune-related RECIST (irRECIST) classification.

Results presented in this appendix derive from the interim analysis with data cut-off on the 1st of March 2020. The population of this analysis included 103 dMMR EC patients with ≥6 months of follow-up time in the study and with ≥1 measurable lesion at baseline by BICR and 7 additional dMMR EC patients who had measurable disease at baseline by investigator assessment.

As shown in This analysis demonstrated that irORR was 45.5% in patients with dMMR EC. The efficacy results in patients with dMMR EC based on the investigators' assessment using irRECIST assessments were similar to the efficacy results by BICR using RECIST v1.1 assessments.

Table 41. ORR per irRECIST

Immune-related secondary endpoints (irRECIST by investigator assessment)	
Variable	**dMMR N=110**
irORR, n (%)	50 (45.5)
irCR	7 (6.4)
irPR	43 (39.1)
irSD	20 (18.2)
irPD	36 (32.7)
NE	4 (3.6)
irDCR,a n (%)	70 (63.6)
irDOR,b months	NR

dMMR/MSI-H diagnostic testing

As stated in SmPC the identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as IHC, PCR or NGS. In the GARNET study, IHC, PCR and NGS testing was accepted to identify eligible patients. GSK considers MMR IHC and MSI PCR tests as equal, recognizing that they each have pros and cons.

ESMO Recommendations suggest that the first method for testing is MMR IHC. IHC is a widely available laboratory test and utilises antibodies against the four MMR proteins: MLH1, MSH2, MSH6 and PMS2. ESMO also provides recommendations on MSI testing; the second method of MSI/dMMR testing is represented by polymerase chain reaction (PCR)-based assessment of microsatellite alterations using five microsatellite markers including at least BAT-25 and BAT-26 (29).

According to this, GSK considers dMMR and MSI-H test as equal in identifying patients who are expected to benefit from treatment with dostarlimab. The decision on which test to use in the clinical practice would optimally be based on local preferences.

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9. Appendices

9.1 Literature search

Table 42: Inclusion and exclusion criteria for systematic literature review

Inclusion and exclusion criteria	
Inclusion criteria	Population: advanced or recurrent dMMR/ MSI-H EC previously exposed to platinum-based therapy Intervention(s): dostarlimab Comparator(s): platinum-based chemotherapy, pegylated liposomal doxorubicin, doxorubicin Outcomes: OS, PFS, quality of life, objective response rate, adverse events Settings (if applicable): RCT and observational studies Study design: RCT and observational studies Language restrictions: English Other search limits or restrictions applied:
Exclusion criteria	Population: other than defined in protocol Intervention(s): other than defined in protocol Comparator(s): other than defined in protocol Outcomes: other than defined in protocol Settings (if applicable): NA Study design: other than defined in protocol Language restrictions: NA Other search limits or restrictions applied: other than defined in protocol

9.2 Search strings with results

The following electronic databases were searched on 07.04.2021 as by the search protocol provided by the DMC: MEDLINE and CENTRAL via Cochrane Library, and PubMed.

Table 43. Search strings Pubmed

ID	Search	Hits
#1	Endometrial Neoplasms[majr:noexp] AND drug therapy[sh]	2171
#2	(endometrial[ti] OR endometrium[ti]) AND (cancer*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti])	19435
#3	Uterine Neoplasms[majr:noexp] AND Carcinosarcoma[majr] AND drug therapy[sh]	90

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#4	uterine cancer[ti] OR uterine carcinoma*[ti] OR uterine serous carcinoma*[ti] OR uterine papillary serous carcinoma*[ti] OR uterine carcinosarcoma*[ti] OR carcinosarcoma of the uterus[ti]	2571
#5	advanced[tiab] OR incurable[tiab] OR inoperable[tiab] OR unresectable[tiab] OR unresectable[tiab] OR non-resectable[tiab] OR relaps*[tiab] OR refractory[tiab] OR metasta*[tw] OR recurren*[tw]	1804711
#6	(#1 OR #2 OR #3 OR #4) AND #5	7907
#7	radiation[ti] OR radiotherapy[ti] OR surgery[ti] OR secondary cytoreduction[ti] OR early stage[ti] OR stage I[ti] OR stage II[ti]	589129
#8	neoadjuvant[ti] OR untreated[ti] OR non-treated[ti] OR treatmentnaive[ti] OR chemo-naive[ti] OR chemotherapy-naive[ti]	27885
#9	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	6778463
#10	study[ti] OR studies[ti]	1888797
#11	#9 NOT #10	6634509
#12	#6 NOT (#7 OR #8 OR #11)	4978
#13	dostarlimab[tiab] OR TSR-042[tiab] OR TSR042[tiab] OR TSR-42[tiab] OR WBP285[tiab] OR WBP-285[tiab]	9
#14	Placebos[mh] OR placebo[tiab] OR sham[tiab] OR dummy[tiab]	329371
#15	Platinum[mh] OR Platinum Compounds[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[tiab] OR carboplatin[tiab]	129736
#16	Taxoids[mh] OR taxane*[tiab] OR paclitaxel[tw] OR docetaxel[tw] OR Taxol*[tiab]	59801
#17	#15 AND #16	14972
#18	platinum-based combination[tiab]	472
#19	liposomal doxorubicin[nm] OR Doxorubicin[mh] OR doxorubicin[tiab]	75906
#20	#13 OR #14 OR #17 OR #18 OR #19	418051
#21	#13 OR #14 OR #17 OR #18 OR #19	267

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Table 44. Search strings for CENTRAL via Cochrane Library

ID	Search	Hits
#1	(uterus next cancer or (endometrium next (cancer or carcinoma)) or carcinosarcoma):kw	989
#2	((endometrial or endometrium) near/2 (cancer* or carcinoma* or adenocarcinoma*)):ti	1135
#3	((uterine or uterus) near/2 (cancer* or carcinoma* or carcinosarcoma*)):ti	193
#4	(advanced or incurable or inoperable or un-resectable or unresectable or non-resectable or relaps* or refractory or metasta* or recurren*):ti,ab,kw	183333
#5	(#1 OR #2 OR #3) and #4	889
#6	(radiation or radiotherapy or surgery or "secondary cytoreduction" or early stage or "stage I" or "stage II"):ti	77946
#7	(neoadjuvant or untreated or non-treated or treatment-naive or chemo-naive or chemotherapy-naive):ti	9195
#8	#5 not (#6 or #7)	657
#9	(dostarlimab or TSR042 or TSR next 042 or wbp285 or wbp next 285):ti,ab,kw	20
#10	(placebo or sham or dummy):ti,ab,kw	333044
#11	(platin* or carboplatin):ti,ab,kw	13296
#12	(taxane or paclitaxel or docetaxel):ti,ab,kw	17740
#13	#11 and #12	5489
#14	(platinum-based near/2 combination):ti,ab	187
#15	doxorubicin:ti,ab,kw	7769
#16	#9 or #10 or #13 or #14 or #15	344718
#17	#8 and #16	188
#18	("conference abstract" or review):ti,pt	195421
#19	(clinicaltrials.gov or trialsearch):so	362707
#20	(meeting or conference or proceedings):so	44531
#21	#18 or #19 or #20	587390
#22	#17 not #21	86
#23	#22 not pubmed:an	34

9.3 Main characteristics of included studies

Table 45: Main study characteristics: GARNET

Main study characteristics: GARNET	
Trial name	GARNET
NCT number	NCT02715284
Objective	To evaluate the anti-programmed death receptor 1 (anti-PD-1) antibody dostarlimab (also known as TSR-042) in participants with advanced solid tumours who have limited available treatment options.
Publications – title, author, journal, year	GSK. DOSTARLIMAB (TSR-042) 4010-01-001 A PHASE 1 DOSE ESCALATION AND COHORT EXPANSION STUDY OF TSR-042, AN ANTI-PD-1 MONOCLONAL ANTIBODY, IN PATIENTS WITH ADVANCED SOLID TUMORS - PART 2B, ENDOMETRIAL CANCER (COHORTS A1 AND A2). 2020.
Study type and design	It is a multi-center, open-label, first-in-human Phase 1 study evaluating the anti-programmed death receptor 1 (anti-PD-1) antibody dostarlimab (also known as TSR-042) in participants with advanced solid tumours who have limited available treatment options. GARNET has no control arm. The study was conducted in 2 parts: Part 1 consisting of safety evaluation, pharmacokinetics (PK), and pharmacodynamics (PDy) of escalating doses of dostarlimab. Part 2 was conducted in two subparts. Part 2A of the study evaluated the safety and tolerability of dostarlimab. Part 2B of the study examined the safety and clinical activity of dostarlimab in cohorts of participants with specific types of advanced solid tumours.
Follow-up time	The data cut-off of March 2020 had a median follow-up of 16.3 months.
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** • Participant is at least 18 years of age. • Participant has proven recurrent or advanced solid tumour and has disease progression after treatment with available anticancer therapies, or is intolerant to treatment that meets the following requirements for the part of the study they will participate in: • Part 1: Any histologically or cytologically proven recurrent advanced solid tumour • Part 2A: Any histologically or cytologically proven recurrent advanced solid tumour • Part 2B: Histologically of cytologically proven recurrent or advanced solid tumour with measurable lesion(s) per RECIST version 1.1, had PD after treatment with available anticancer therapies or was intolerant

Main study characteristics: GARNET	
	to treatment and had dMMR/MSI-H endometrial cancer (COHORT A1). • Participants had archival tumour tissue available that was formalin fixed and paraffin embedded. • Female participants must have had a negative serum pregnancy test within 72 hours prior to the date of the first dose of study medication unless they were of nonchildbearing potential. • Female participants of childbearing potential must have agreed to use 1 highly effective form of contraception with their partners starting with the Screening Visit through 150 days after the last dose of study treatment. **Exclusion criteria:** • Participant had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-programmed cell death-ligand 2 agent. • Participant had known uncontrolled central nervous system metastases and/or carcinomatous meningitis. Note: Participants with previously treated brain metastases may have participated provided they were stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), had no evidence of new or enlarging brain metastases, and were clinically stable off corticosteroids for at least 7 days prior to study treatment. Carcinomatous meningitis precluded a participant from study participation, regardless of clinical stability. • Participant had a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions included basal cell carcinoma of the skin, squamous cell carcinoma of the skin that had undergone potentially curative therapy, or in situ cervical cancer. • Participant was considered a poor medical risk due to a serious, uncontrolled medical disorder; a non-malignant systemic disease; or an active infection requiring systemic therapy. Specific examples included, but were not limited to, active, non-infectious pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would have interfered with cooperation with the requirements of the study (including obtaining informed consent). • Participant had an active autoimmune disease that had required systemic treatment in the past 2 years (i.e., with the use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) was not considered a form of systemic treatment. Use of

Main study characteristics: GARNET	
	inhaled steroids, local injection of steroids, and steroid eye drops were allowed.
Intervention	Part 1: Dose escalation was based on ascending weight-based dose levels (DLs) of dostarlimab and was continued until the maximum tolerated dose (MTD) is reached or may be stopped at any dose level up to the highest dose of 20 milligrams per kilograms (mg/kg) based on emerging safety and PK/PDy data. Part 2A: Fixed doses of 500 mg were administered every 3 weeks (Q3W) and 1000 mg administered every 6 weeks (Q6W). Part 2B (Cohort A1): 129 patients received 500 mg of dostarlimab intravenously every 3 weeks for 4 doses, then 1000 mg every 6 weeks until disease progression, treatment discontinuation due to toxic effect, or patient withdrawal of consent. Part 2B (Cohort A2): MMR-proficient/MSS EC (Cohort A2)

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Main study characteristics: GARNET

Baseline characteristics

Characteristic	dMMR (N=103)	MMR-unk/ MSI-H (N=2)	Total (N=105)
Race, n (%)			
White	80 (77.7)	2 (100)	82 (78.1)
Black	2 (1.9)	0	2 (1.9)
Asian	4 (3.9)	0	4 (3.8)
American Indian or Alaska Native	3 (2.9)	0	3 (2.9)
Not reported	14 (13.6)	0	14 (13.3)
Age (years)			
n	103	2	105
Median	65.0	54.0	64.0
Min, max	39, 80	54, 54	39, 80
Characteristic	**dMMR (N=103)**	**MMR-unk/ MSI-H (N=2)**	**Total (N=105)**
Age group, n (%)			
<65 years	51 (49.5)	2 (100)	53 (50.5)
≥65 years to <75 years	41 (39.8)	0	41 (39.0)
≥75 years	11 (10.7)	0	11 (10.5)
Weight (kg)			
n	103	2	105
Median	71.00	67.10	71.00
Min, max	34.0, 141.4	51.0, 83.2	34.0, 141.4
BMI (kg/m^2)			
n	100	2	102
Median	27.97	27.88	27.97
Min, max	13.6, 53.9	21.2, 34.5	13.6, 53.9
ECOG performance status			
0	40 (38.8)	2 (100)	42 (40.0)
1	63 (61.2)	0	63 (60.0)

Primary and secondary endpoints

The primary outcomes of GARNET were ORR and Duration of Response (DOR) based on independent blinded central review using RECIST version 1.1.

Secondary endpoints were the Immune-related Objective Response Rate (irORR) measured by irRECIST, Disease control rate (DCR), Immune related disease control rate (irDCR), Immune related duration of response (irDOR), PFS and Overall OS.

Method of analysis

All efficacy analyses were intention-to treat.

DOR, irDOR, PFS, and OS analyses were performed using Kaplan-Meier (KM) methods and summarized by minimum (DOR and irDOR only), maximum (DOR and irDOR only), 25th, 50th (median), and 75th percentiles with associated 95% CIs, the number and percentage of events, number and percentage of

Main study characteristics: GARNET	
	censored observations, and median duration of follow-up (DOR and irDOR only). ORR, irORR, DCR, and irDCR analyses included summary statistics, including number of participants (n) and percentage for categorical variables and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% confidence intervals (CIs) based on the Clopper-Pearson method were provided to summarize the binomial proportion of the ORR/irORR and DCR/irDCR for both RECIST v1.1 and irRECIST assessments, where applicable.
Subgroup analyses	Subgroup analyses per PFI/TFI are not available in the GARNET trial. Nevertheless, an exploratory analysis of ORR based on RECIST v.1.1 investigating PFI from platinum-containing prior anticancer therapy (less than 6 months vs 6 months or greater vs missing) was performed.

Table 46. Main study characteristics Nagao et al, 2013 (14)

Main study characteristics: Nagao 2013	
Trial name	NA
NCT number	NA
Objective	To evaluate the relationship between platinum-free interval and response to second-line platinum-based chemotherapy, as well as PFS and OS after second line chemotherapy.
Publications – title, author, journal, year	Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: the SGSG-012/GOTIC-004/Intergroup study, Nagao, S., Nishio, S., Michimae, H., Tanabe, H., Okada, S., Otsuki, T., Tanioka, M., Fujiwara, K., Suzuki, M. & Kigawa, J., Gynecologic Oncology, 2013.
Study type and design	The study is a multicenter retrospective cohort study using data of consecutive patients with histologically confirmed endometrial cancer or uterine carcinosarcoma, who received second-line platinum-based chemotherapy between January 2005 and December 2009 (histological confirmation of recurrence was not required).
Follow-up time	The median follow-up period for OS was 16.9 months (N = 262).
Population (inclusion and exclusion criteria)	All patients had received primary platinum-based chemotherapy. Concurrent chemoradiation therapy was not regarded as a platinum-based chemotherapy even if it included a platinum agent. There was no restriction regarding

Main study characteristics: Nagao 2013	
	the type of therapy administered after completion of second-line chemotherapy. Patients were excluded if they had a uterine sarcoma or another concurrent invasive cancer.
Intervention	The platinum-free interval was defined as the period from the completion of first-line platinum-based chemotherapy to the date of diagnosis of recurrence. PFS was measured from the start date of second-line chemotherapy to the date of subsequent radiologic relapse, progression, or to the date of last contact for disease-free patients. OS was defined as the period from the start date of second-line chemotherapy to death or the date of last contact.
Baseline characteristics	A total of 279 patients from 30 centres were registered. However, 17 patients were excluded from the analysis (2 patients did not receive first-line platinum-based chemotherapy, 9 did not receive second-line platinum-based chemotherapy, 3 received second-line chemotherapy after January 2010, and the presence of residual tumour after surgery was not reported for 3 patients). Finally, data from 262 patients were analysed. The tables summarize the major characteristics of the patients and their tumours.

Main study characteristics: Nagao 2013

Patient characteristics (n = 262).

	N	%
FIGO stage at primary therapy		
I	29	11
II	23	9
III	122	47
IV	88	33
Histology		
Endometrioid	153	58
Grade 1	37	
Grade 2	62	
Grade 3	47	
Not determined	7	
Serous	34	13
Clear cell	17	7
Carcinosarcoma	36	14
Others	22	8
Radiotherapy in primary therapy		
Performed	14	5
Not performed	248	95
Site of recurrence (allowed for overlapping)		
Vaginal stump	26	10
Pelvic cavity	38	14
Abdominal cavity	74	28
Lymph nodes	68	26
Liver	24	9
Lung	78	29
Other sites	48	18
Unclear	1	0
Platinum free interval (months)		
<6 months	64	24
6 months ≤, <12 months	65	25
12 months ≤, <24 months	67	26
24 months ≤	66	25

Primary and secondary endpoints	The primary outcome was ORR. Secondary endpoints included OS, PFS, CR, PR
Method of analysis	To evaluate whether response to second-line platinum-based chemotherapy increased with longer platinum-free intervals, Cochran-Armitage test for trend was used. The PFS and OS probabilities were estimated using the Kaplan–Meier method, and log-rank trend test was used to test for a trend progression-free or OS across ordered platinum-free intervals. In addition, the probability of PFS or OS was estimated separately between groups with a platinum-free interval of <12 months and ≥12 months using the Kaplan–Meier method, and differences progression-free or OS between the two groups were evaluated by log-rank test.

Main study characteristics: Nagao 2013	
Subgroup analyses	Comparability of patient characteristics between the groups was conducted, and one-to-one matching was performed between groups to adjust one characteristic (existence or non-existence of residual tumour at primary surgery) that differed between the two groups. The probability of PFS or OS was estimated separately for each group using the Kaplan–Meier method, and differences progression-free or OS between the two groups were evaluated by log-rank test; P values < 0.05 were considered statistically significant.

Table 47. Main study characteristics, Nagao 2015 (15)

Main study characteristics: Nagao 2015	
Trial name	NA
NCT number	NA
Objective	To determine an appropriate second-line platinum-based regimen for patients with a history of receiving platinum-based first-line chemotherapy and, particularly, to evaluate whether alternations to second-line chemotherapy regimens are reasonable.
Publications – title, author, journal, year	What is an appropriate second-line regimen for recurrent endometrial cancer? Ancillary analysis of the SGSG012/GOTIC004/Intergroup study., Nagao, S., Nishio, S., Okada, S., Otsuki, T.., Fujiwara, K., Tanabe, H., Takano, M., Hasumi, Y., Takei, Y., Hasegawa, T., Matsumoto, T., Fujiwara, K., Takekuma, M., Nakamura, K., Shimada, M., Suzuki, M. & Kigawa, J., Cancer Chemotherapy and Pharmacology., 2015.
Study type and design	Ancillary analysis conducted using the dataset from the SGSG012/GOTIC004/Intergroup study.
Follow-up time	NA
Population (inclusion and exclusion criteria)	Consecutive patients with histologically confirmed EC or uterine carcinosarcoma, who received second-line platinum-based chemotherapy between January 2005 and December 2009, were registered (histological confirmation of recurrence was not required). All patients had received primary platinum-based chemotherapy. Concurrent chemoradiation therapy was not regarded as platinum-based chemotherapy, even if it included a platinum-based agent. Patients were excluded if they had uterine sarcoma or any other concurrent invasive cancer.
Intervention	214 patients received doxorubicin and cisplatin combination chemotherapy (AP therapy), paclitaxel and carboplatin (TC therapy), or docetaxel and carboplatin combination chemotherapy (DC therapy) as first- and second-line chemotherapy regimens.

Main study characteristics: Nagao 2015

Baseline characteristics

Table 3 Patient characteristics ($N = 214$)

First-line chemo-therapy	AP	TC/DC	TC/DC	
Second-line chemotherapy	TC/DC	AP	TC/DC	
	($N = 36$)	($N = 51$)	($N = 127$)	
Age (range) (years)	60 (50–69)	61 (48–78)	65 (37–80)	$p = 0.040$
FIGO stage				
I	4 (11 %)	8 (16 %)	15 (12 %)	
II	4 (11 %)	4 (8 %)	11 (9 %)	
III	20 (56 %)	23 (45 %)	49 (39 %)	
IV	8 (22 %)	16 (31 %)	52 (41 %)	$p = 0.443$
Histology				
Endometrioid	31 (86 %)	31 (61 %)	64 (50 %)	
Grade 1	9	5	19	
Grade 2	12	14	22	
Grade 3	8	10	20	
Squamous diff.	1	0	5	
Not determined	1	2	3	
Serous	1 (3 %)	6 (12 %)	21 (17 %)	
Clear cell	1 (3 %)	3 (6 %)	7 (6 %)	
Carcinosarcoma	3 (8 %)	9 (18 %)	13 (10 %)	
Others	0	2 (4 %)	17 (13 %)	$p = 0.095$
Residual tumor at primary surgery				
Yes	13 (36 %)	21 (41 %)	37 (29 %)	
No	23 (64 %)	30 (59 %)	90 (71 %)	$p = 0.356$
Radiation therapy				
Done	3 (8 %)	5 (10 %)	7 (6 %)	
Not done	33 (92 %)	46 (90 %)	120 (94 %)	$p = 0.799$
Platinum-free interval				
<6 months	8 (22 %)	31 (61 %)	21 (17 %)	
6≤, <12 months	7 (19 %)	11 (22 %)	34 (27 %)	
12≤, <24 months	10 (28 %)	7 (14 %)	38 (30 %)	
24 months≤	11 (31 %)	2 (4 %)	34 (27 %)	$p < 0.0001$

AP: doxorubicin and cisplatin combination chemotherapy, TC: paclitaxel and carboplatin combination chemotherapy, DC: docetaxel and carboplatin combination chemotherapy

Primary and secondary endpoints	The primary outcome was ORR. Secondary endpoints included, PFS, CR, PR.
Method of analysis	Background factors of patients were analysed using the one-way ANOVA with Tukey's multiple comparison test or Chi-squared test. Associations between a first- and/or second-line chemotherapy regimen and response to second-line chemotherapy, PFS, or OS after second-line chemotherapy were compared.

Main study characteristics: Nagao 2015	
	PFS and OS curves were constructed using the Kaplan–Meier method and evaluated for statistical significance using the log-rank test. For survival analysis, TC therapy and DC therapy were integrated into taxane and carboplatin combination therapy (TC/DC therapy) because those had similarities in some characteristics including less toxic and convenient. In the primary analysis, a threshold of the platinum sensitivity as 12 months was set. The Cox proportional hazards model was used to investigate the significance of first- and second-line chemotherapy on outcome, controlling for all other parameters found significant in univariate analysis. The two-tailed test was applied in all statistical analysis, and a p value <0.05 was considered statistically significant.
Subgroup analyses	NA.

Table 48. Main study characteristics, Rubinstein et al (16)

Main study characteristics: Rubinstein	
Trial name	NA
NCT number	NA
Objective	To examine the clinical outcomes of EC patients who received TC in the adjuvant setting and who were specifically re-treated with TC in the recurrent or metastatic disease setting.
Publications – title, author, journal, year	Retreatment with carboplatin and paclitaxel for recurrent EC: a retrospective study of the Memorial Sloan Kettering Cancer Center experience., Rubinstein, M., Halpenny, D., Makker, V., Grisham, R. N., Aghajanian, C., & Cadoo, K., Gynecologic oncology reports 28., 2019.
Study type and design	Retrospective study using data from 2000-2014 identified through an institutional database at Memorial Sloan Kettering Cancer Center.
Follow-up time	NA.
Population (inclusion and exclusion criteria)	EC patients who received TC in adjuvant setting and specifically re-treated with TC in the recurrent or metastatic disease setting.
Intervention	20 EC patients who previously received TC in the adjuvant setting and specifically were re-treated with TC in the recurrent or metastatic disease setting.

Main study characteristics: Rubinstein	
Baseline characteristics	**Table 1** Patient and tumor characteristics at diagnosis. *N* = 20 Median age (range) 67 (40–83) Median BMI 30 (23–44) Comorbidities: N (%) Diabetes 2 (10) Hypertension 12 (60) Hyperlipidemia 8 (40) Coronary artery disease 3 (15) FIGO stage (2009): N (%) I 5 (25) II 3 (15) III 7 (35) IV 5 (25) Histology: N (%) Endometrioid 3 (15) Serous 7 (35) Carcinosarcoma 7 (35) Mixed endometrioid/serous 3 (15)
Primary and secondary endpoints	The main outcomes of interest were ORR, the median PFS to re-treatment with PC, the PFS and the OS from re-treatment with TC (cycle 1, day 1) and the OS from original diagnosis. An IRB approved retrospective analysis of patient, tumour and treatment characteristics was performed. An independent radiologist, blinded to patients' clinical details assessed response per RECIST 1.1 criteria.
Method of analysis	The Kaplan Meier method was used to estimate the median progression free survival (PFS) to re-treatment with PC, the PFS and OS(OS) from re-treatment with TC (cycle 1, day 1) and the OS from original diagnosis. Statistical reporting was descriptive.
Subgroup analyses	NA.

Table 49. Main study characteristics, Miyake et al (17)

Main study characteristics: Miyake	
Trial name	NA
NCT number	NA

Objective	To evaluate the association of prognosis of endometrial carcinoma patients and treatment-free intervals (TFIs).
Publications – title, author, journal, year	Recurrent endometrial carcinoma: prognosis for patients with recurrence within 6 to 12 months is worse relative to those relapsing at 12 months or later. Miyake, T., Ueda, Y., Egawa-Takata, T., Matsuzaki, S., Yokoyama, T., Miyoshi, Y., Kimura, T., Yoshino, K., Fujita, M., Yamasaki, M., Enomoto, T. & Kimura, T. American journal of obstetrics and gynecology. 2011.
Study type and design	The study is retrospective study using data from Departments of Obstetrics and Gynecology of the Osaka University and the Osaka Rosai Hospitals of Osaka in Japan. Treatment-free intervals (TFIs) was defined as the period between the last administration of first-line chemotherapy and the initiation of the second-line chemotherapy.
Follow-up time	NA
Population (inclusion and exclusion criteria)	Patients were recruited if they were treated by a second-line chemotherapy for their recurrent disease, after first having an initial first-line adjuvant or salvage paclitaxel and carboplatin (TC) or paclitaxel and carboplatin with anthracycline (TEC). All the patients had measurable disease equal to or larger than 10 mm by a computerized tomography (CT) scan. The diseases were observed in the abdominal cavity in 24 cases (83%), retroperitoneal lymph nodes in 16 cases (55%), and other distant tissues including lung and supraclavicular and inguinal lymph nodes in 10 cases (34%).
Intervention	A total of 29 patients were treated in the study. In the first-line TEC treatment, paclitaxel (150 mg/m2), carboplatin (area under the curve [AUC], and epirubicin (50 mg/m2) were administered intravenously every 3-4 weeks. The dose of chemotherapy drugs appropriate for the population was determined in phase I/II studies which previously has been conducted (and submitted). In the monthly TC therapy, paclitaxel (175 mg/m2) and carboplatin (AUC 5) were administered intravenously every 3-4 weeks, based on published protocols. In the weekly TC regimen, paclitaxel (80 mg/m2) and carboplatin (AUC 2) were administered intravenously on days 1, 8, and 15 on a 4 week cycle. As second-line chemotherapy, some patients received TEC or TC, including weekly TC, and others were given docetaxel (30 mg/m2) and CPT-11 (60 mg/m2 , irinotecan) (docetaxel plus CPT-11) on days 1 and 8, on a 3-4 week cycle, or daily oral medroxyprogesterone acetate (MPA) (400-600 mg/day).

Baseline characteristics

TABLE 1
Clinical characteristics of the patients

Characteristic	TFI 6–12 mo	TFI ≥12 mo	*P* value
Number	12	17	—
Age, y			1.0
<60	5	8	
≥60	7	9	
Histology			.37
Endometrioid	11	13	
Nonendometrioid	1	4	
Initial stage			.27
I/II	3	8	
III/IV	9	9	
Second-line chemotherapy			.092
TEC/TC	7	15	
Others[a]	5	2	

All patients received a first-line chemotherapy using TC/TEC.
MPA, medroxyprogesterone acetate; *TC*, anthracycline; *TEC*, epirubicin; *TFI*, treatment-free interval.
[a] MPA, oral etoposide, and a combination therapy of docetaxel and CPT-11 (irinotecan). The *P* value was calculated by Fisher's exact test.
Miyake. Prognosis for recurrent endometrial cancer. Am J Obstet Gynecol 2011.

Primary and secondary endpoints

Primary endpoints:

- CR, defined as the disappearance of all known disease, determined by 2 observations not less than 4 weeks apart.
- PR was defined as a 50% or more reduction in the summed products of the 2 largest perpendicular dimensions of bi-dimensionally measurable lesions, for at least 4 weeks.
- SD was defined as a less than 50% decrease, or a less than 25% increase, of tumour size, with no new detectable lesions.
- PD was defined as a greater than 25% increase in tumour size or the appearance of new lesions.

Secondary endpoints:

- PFS was measured from the date of the last administration of chemotherapy to the date of the radiologic or pathologic relapse or to the date of the last follow-up.
- OS was defined as the period from the start of chemotherapy to the patient's disease-specific death or the date of the last follow-up, as previously described.

Method of analysis

The association between sensitivity to second-line chemotherapy and TFI was analysed

	by Fisher's exact test. PFS and OS curves determined by a TFI were constructed using the Kaplan-Meier method and were evaluated for statistical significance by the log-rank test. The multivariate Cox proportional hazards model was used to calculate the significant factors contributing to OS after second-line chemotherapy. Results were considered to be significant when the $p<0.05$.
Subgroup analyses	NA.

Table 50. Min study characteristics, Mazgani et al (18)

Main study characteristics: Mazgani	
Trial name	NA
NCT number	NA
Objective	To evaluate the efficacy of reusing carboplatin and taxol in women with relapsed EC.
Publications – title, author, journal, year	Reuse of carboplatin and paclitaxel in patients with relapsed EC — the British Columbia Cancer Agency experience. Mazgani, M., Le, N., & Hoskins, P. J. Gynecologic oncology. 2008.
Study type and design	Retrospective study using data of high-risk patients with EC treated as per institutional policy at the British Columbia Cancer Agency centers using the GOENDCAT protocol (Gynecologic Oncology ENDometrial Carboplatin Taxol).
Follow-up time	NA.
Population (inclusion and exclusion criteria)	Newly diagnosed high-risk patients with EC treated with carboplatin–paclitaxel at diagnosis, with subsequent relapse for the period of 1995–2007.
Intervention	200 patients received carboplatin plus paclitaxel was reused with following doses: carboplatin AUC 5 or 6 plus paclitaxel 175 mg/m2 over 3 h every 4 weeks until progression or unacceptable toxicity.
Baseline characteristics	NA.
Primary and secondary endpoints	**Endpoints:** • CR was the disappearance of all disease. • PR was a 30% or greater decrease in the sum of the longest dimension of all measurable lesions with no progression of any pre-existing lesion or development of any new lesion. • Progressive disease (PD) was a 20% or more increase in the sum of the longest dimensions or development of new lesions or

Main study characteristics: Mazgani	
	symptomatic deterioration leading to treatment discontinuation in the absence of imaging confirmation of progressive disease. • Stable disease (SD) was any state not meeting the above criteria in patients with measurable disease. If the patient had evaluable, but not measurable disease, the patients were coded as NED (no evaluable disease) unless progression occurred on treatment. • PFS recorded from the date of relapse. • OS recorded from the date of relapse.
Method of analysis	Tumour measurements were abstracted from the imaging reports. Response was recorded according to the RECIST criteria based upon CT scanning except that the best response achieved was recorded with no requirement for confirmation by repeat imaging four or more weeks later and no use was made of tumour markers. PFS and OS were recorded from the date of relapse. Survival curves were obtained using the Kaplan and Meier method. Log-rank test was used to compare differences between those either not retreated with any chemotherapy or not retreated with carboplatin–paclitaxel.
Subgroup analyses	NA.

Table 51. Main study characteristics, Vergote et al (6)

Main study characteristics: Vergote	
Trial name	NA
NCT number	NA
Objective	To investigate the addition of prophylactic G-CSF to each weekly paclitaxel/carboplatin course in patients with recurrent platinum-resistant ovarian (OC), or recurrent or advanced endometrial (EC) or cervical carcinoma (CC).
Publications – title, author, journal, year	Vergote, I., Debruyne, P., Kridelka, F., Berteloot, P., Amant, F., Honhon, B., ... & Laenen, A. (2015). Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: a study in 108 patients by the Belgian Gynaecological Oncology Group. Gynecologic oncology, 138(2), 278-284.
Study type and design	Prospective phase 2 study. Patients (p=108) with histologically confirmed recurrent ovarian, endometrial and cervical cancer (each cohort 36 patients) were enrolled at 12 Belgian and Luxemburg Gynecological Oncology Group (BGOG) centers between February 20, 2012 and March 14, 2013. A total of 6

Main study characteristics: Vergote	
	patients were excluded from the analysis due to a lack of data or scarce data resulting in 102 patients eligible for toxicity and survival evaluation.
Follow-up time	NA
Population (inclusion and exclusion criteria)*	Inclusion criteria: • > 18 years of age • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 • Adequate bone marrow function, represented by an absolute neutrophil count (ANC) ≥1.5 × 10^9 /L, hemoglobin ≥9 g/dL (5.6 mmol/L) and platelets ≥ 100 × 10^9 /L. • Adequate renal function, in accordance with a calculated creatinine clearance (Cockroft) ≥30 mL/min. • Adequate hepatic function, as evidenced by total bilirubin concentrations ≤1.5 × the upper normal limit and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper normal limit. • Disease should be measurable by RECIST version 1.1 criteria. • All patients must sign an informed consent prior to performance of study specific procedures or assessments and must be willing to comply with treatment and follow-up. • Patients with recurrent or advanced EC could be included in the EC cohort. Exclusion criteria: • Earlier weekly or dose-dense regimens with paclitaxel and carboplatin were not allowed in the EC cohort.
Intervention	A total of 102 patients received on day 1 of each 7-day cycle, with a maximum of 18 cycles, intravenous paclitaxel at a dose of 60 mg/m^2 and carboplatin at an AUC of 2.7 with dose calculated according to the Cockroft formula. The regimen was given on an outpatient basis. Premedication with oral antihistamines (10 mg of cetirizine hydrochloride) and oral steroids (10 mg of dexamethasone) and H2 antagonist (or equivalent) was given 12 h and 3 h prior to paclitaxel infusion. Paclitaxel (60 mg/m^2) was given as a 1 hour intravenous infusion in 250 mL NaCl 0.9% followed by carboplatin, dissolved in 500 ml glucose 5% (adjusted to NaCl 0.9% when needed) was given intravenously over 60 min

Main study characteristics: Vergote	
	following the administration of paclitaxel. Filgrastim (Neupogen®) 30 Mio U (0.600 mg/mL) was given to all patients on day 5 of each course in patients weighing less than 60 kg and filgrastim (Neupogen®), 48 Mio 0.5 mL (0.960 mg/mL) to patients of 60 kg or more. The courses were repeated 18 times weekly, except for course 10, which was given 2 weeks after course 9. Imaging (CT) was performed during week 10. The mean dosage per week, taking reductions and delays into account, was for paclitaxel 52 mg/m^2 and for carboplatin 2.3 AUC. Dose adjustments and delayed administration were based on bone marrow toxicity. The full dose of carboplatin and paclitaxel was given without delay when on day 8 the absolute neutrophil count (ANC) was 0.5 × 10^9 /L or more and the platelet count was 50 × 10^9 /L or more. When ANC was lower than 0.5 × 10^9 /L on day 8 without a history of fever, the dose was delayed until ANC was 0.5 × 10^9 /L or more and paclitaxel and carboplatin are given in the same dose with filgrastim on days 5 and 6. When ANC was lower than 0.5 × 10^9 /L on day 8 without a history of fever but with former course with filgrastim on days 5 and 6, the dose was delayed until ANC was 0.5 × 10^9 /L or more. Then a reduced dose of paclitaxel 40 mg/m2 and carboplatin AUC 2.0 was given with filgrastim on days 5 and 6. Chemotherapy was not re-escalated. When there was a history of neutropenic fever during the study (STEP A), also a reduced dose of paclitaxel 40 mg/m^2 and carboplatin AUC 2.0 was given together with filgrastim on days 5 and 6. When there was a history of neutropenic fever during the study after STE.P A, the study is terminated. When platelet count was lower than 50 × 109 /L (STEP B) on day 8 and the number of neutrophils was sufficient, the dose was delayed until platelet count was 50 × 10^9/L or more and paclitaxel 60 mg/m2 and carboplatin AUC 2.0 were administered. The study was terminated when the patient was not recovered after 21 days. The study was also stopped when a patient experienced peripheral neuropathy grade 3. Erythropoietin and intravenous iron therapy were started according to the discretion of the investigator.
Baseline characteristics	The median age of the evaluable patients was 61 years (range 51–70 years). The median number of prior chemotherapy lines was 3 for ovarian, 1 for endometrial and 1 for cervical cancer. The majority of patients had ECOG performance score 1 or 2 (63.7%). In total, 32 patients (31.4%) had serous histological subtype, 20 patients (19.6%) had adenocarcinoma and another 20 patients (19.6%) had squamous histological subtype. For patients with ovarian cancer, 91.4% had platinum-resistant disease and 8.6% had platinum-refractory disease. Baseline characteristics of the patients included for analyses:

Main study characteristics: Vergote

Variable	Diagnosis age median (IQR)	Prior lines median (IQR)	ECOG 0 n/N (%)	ECOG 1–2 n/N (%)	Main histological subtype at initial diagnosis
Ovarium	63.0 (54.9–71.3)	3.0 (2.0–4.0)	7/35 (20%)	28/35 (80%)	Serous 65.7%
Endometrium	66.5 (62.1–75.6)	1.0 (0.0–2.0)	11/33 (33.3%)	22/33 (66.6%)	Endometroid 39.4%
Cervix	49.3 (44.5–56.9)	1.0 (0.0–1.0)	19/34 (55.9%)	15/34 (44.1%)	Squamous 55.9%
Total	60.9 (51.3–70.4)	1.0 (0.0–3.0)	37/102 (36.3%)	65/102 (63.7%)	Serous 31.4%

Primary and secondary endpoints	The primary endpoint of the study was the occurrence of grade 3–4 neutropenia. The incidence resulting from this study was compared with historical data. The secondary endpoints of the study were the occurrence of grade 3–4 neutropenia per cohort, other toxicities, dose reductions and delays, PFS, ORR and OS.
Method of analysis	The tumour response rate (CR + PR) was presented with a 95% confidence interval (95% CI). If response was confirmed by a following assessment of response while on the regimen or in the follow-up period, the term "confirmed" was added to the obtained result. 1-year and 5-year PFS and OS rates were calculated, and survival curves were generated using the Kaplan–Meier methodology. All analyses are complete case analyses and were performed using SAS software version 9.3 (SAS Institute Inc, Cary, NC, USA). PFS was defined as the time between the start of treatment and assessment of PD or death. Patients without any of both events were censored at the date of the last scan. OS was defined as the time between the start of treatment and death. Patients alive were censored at the last follow-up date. Follow-up procedures consisting of general and gynecological examination were performed every 3 months in the first 2 years after termination of treatment and every 6 months in year 3 to 5. Toxicity grading for the entire patient population and per cohort, the proportion of patients with grade 3–4 neutropenia was calculated, and a 95% CI was constructed based on Wilson's method. The occurrence of grade 3–4 neutropenia during weekly paclitaxel/carboplatin without prophylactic G-CSF for the treatment of ovarian, endometrial and cervical cancer has been reported in previous studies to be 84%. If the upper 95% CI limit is lower than 84%, we can conclude that the occurrence of grade 3–4 neutropenia is lower compared to historical data. The binomial test was used for comparing proportions to historical data.
Subgroup analyses	NA.

*The first cohort included patients with histologically confirmed diagnosis of invasive epithelial ovarian, fallopian tube, or peritoneal carcinoma. Patients with at least one earlier platinum treatment could be included in this cohort but they had to be platinum-refractory or platinum-resistant. Patients experiencing progression within 28 days after the last dose of platinum were defined as platinum-refractory. Patients experiencing progression within 6 months after the last dose of platinum were defined as platinum resistant. Earlier weekly or dose-dense regimens with paclitaxel

and carboplatin were not allowed in this cohort while consolidation after the last platinum dose with non-platinum containing chemotherapy or molecular targeted drugs was allowed. Disease should be measurable by Evaluation Criteria In Solid Tumours (RECIST) version 1.1 criteria [19] or serum cancer antigen 125 (CA125) measurements of progression using the Gynecological Cancer Intergroup (GCIG) criteria. Patients with recurrent or advanced cervical carcinoma could be included in the cervical cancer cohort. Earlier platinum therapy was allowed in cervical cancer cohort but earlier weekly or dose-dense regimens with paclitaxel and carboplatin were not allowed.

Table 52. Main study characteristics, Ueda et al (19)

Main study characteristics: Ueda	
Trial name	NA
NCT number	NA
Objective	To investigate the effectiveness of second-line chemotherapy for treatment of advanced or recurrent endometrial carcinoma previously treated with a combined chemotherapy of taxane and platinum, with or without anthracycline.
Publications – title, author, journal, year	Ueda, Y., Miyake, T., Egawa-Takata, T., Miyatake, T., Matsuzaki, S., Yokoyama, T., ... & Kimura, T. (2011). Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin. Cancer chemotherapy and pharmacology, 67(4), 829-835.
Study type and design	The study is a respective study including 723 patients with diagnosed EC at the Departments of Obstetrics and Gynecology of the Osaka University and the Osaka Rosai Hospitals, Osaka, Japan from 2000-2008. The subset of these cases that eventually required treatment by second-line chemotherapy was retrospectively analysed. The histological diagnoses were made by authorized pathologists from the Department of Pathology of the Osaka University and the Osaka Rosai Hospitals.
Follow-up time	NA.
Population (inclusion and exclusion criteria)	Patients were enrolled in the present study, after obtaining their written informed consent, if they were treated by a second-line chemotherapy for their recurrent disease, after first having an initial first-line adjuvant or salvage TEC or TC therapy.
Intervention	Patients (n=40) enrolled in the present study, were treated by a second-line chemotherapy for their recurrent disease, after first having an initial first-line adjuvant or salvage TEC or TC therapy. In the initial first-line monthly TEC (TECm) treatment, paclitaxel (150 mg/m^2), carboplatin (AUC = 4) and epirubicin (50 mg/m^2) were administered intravenously every 3–4 weeks. In the monthly TC (TCm) therapy, paclitaxel (175 mg/m^2) and carboplatin (AUC = 5) were also administered intravenously every 3–4 weeks. In the weekly TC regimen (TCw), paclitaxel (80 mg/m^2) and carboplatin (AUC = 2) were administered intravenously on days 1, 8 and 15 on a 4-week cycle. X

Main study characteristics: Ueda	
	Some patients received TECm or TCw (as described above) as second-line chemotherapy. Others were given docetaxel (30 mg/m^2) and CPT-11 (60 mg/m^2) (docetaxel + CPT) on days 1 and 8, on a 3–4-week cycles, or daily oral medroxyprogesterone acetate (MPA) (400–600 mg/day). Among the 40 patients, 24 patients received second-line TECm, TCm or TCw, 3 received docetaxel+CPT, 7 received oral MPA therapy, and 6 received oral Etoposide therapy. Eighty percent (32 out of 40 cases) of the patients received first-line TECm therapy; the other eight cases underwent either monthly or weekly TC (TCm or TCw) therapy, prior to the second-line chemotherapy.
Baseline characteristics	The clinicopathological characteristics of the sudy cases are shown in table 1.

Characteristics	Patients ($n = 40$)	
	Number	%
Age (years)		
<60	18	45
≥60	22	55
Histology		
Endometrioid	32	80
Serous	4	10
Clear cell	1	3
Others	3	8
Initial stage		
I	10	25
II	6	15
III	19	48
IV	5	13
First-line chemotherapy		
TEC	32	80
TC	7	18
Weekly TC	1	3

All patients received first-line chemotherapy using taxane and carboplatin (with or without epirubicin, TC/TEC)

TECm monthly administration of taxane (paclitaxel), epirubicin and carboplatin, *TCm* monthly administration of paclitaxel and carboplatin, *TCw* weekly administration of paclitaxel and carboplatin

Primary and secondary endpoints	The primary outcome of this study was ORR. A CR was defined as the disappearance of all known disease, determined by two observations not less than 4 weeks apart. PR was defined as a 50% or more reduction in the summed products of the two largest perpendicular dimensions of bi-dimensionally measurable lesions, for at least 4 weeks. The secondary endpoints included: Stable disease (SD was defined as a less than 50% decrease, or a less than 25% increase, of tumour size, with no new detectable lesions); progressive disease (PD was defined as a greater than 25% increase in tumour size or as the appearance of new lesions); PFS (PFS was measured from the date of the last administration of chemotherapy to

Main study characteristics: Ueda	
	the date of the radiological or pathological relapse or to the date of the last follow-up); OS(OS was defined as the period from the start of chemotherapy to the patient's disease-specific death or to the date of the last follow-up); TFI was defined as the period between the last administration of first-line chemotherapy and the initiation of the second-line chemotherapy.)
Method of analysis	The association between sensitivity to second-line chemotherapy and sensitivity to a TFI was analysed by Fisher's exact test. PFS curves determined by a TFI were constructed using the Kaplan–Meier method and were evaluated for statistical significance by the log-rank test. The multivariate Cox proportional hazards model was used to calculate the significant factors contributing to PFS after second-line chemotherapy.
Subgroup analyses	NR.

Table 53. Main study characteristics, Nomura et al (20)

Main study characteristics: Nomura	
Trial name	NA
NCT number	NA
Objective	To compare docetaxel plus cisplatin, docetaxel plus carboplatin and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma, with the objective of evaluating the appropriate arms for a proposed phase III study
Publications – title, author, journal, year	Nomura, H., Aoki, D., Takahashi, F., Katsumata, N., Watanabe, Y., Konishi, I., ... & Yaegashi, N. (2011). Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Annals of oncology, 22(3), 636-642.
Study type and design	Randomized phase 2 study. The stratified factors used to adjust allocation to treatment were prior chemotherapy with taxanes and presence of a measurable lesion in the previously irradiated region. Patients were randomly allocated to three groups at a rate of 30 per group by the minimization method. The study treatments were to be given until disease progression or adverse events prohibited further therapy.
Follow-up time	NR.

Main study characteristics: Nomura	
Population (inclusion and exclusion criteria)	Inclusion criteria: • Primary lesion histologically confirmed to be endometrial carcinoma. • International Federation of Gynecology and Obstetrics (FIGO) stage III, stage IV, or recurrent cancer • Maximum measurable diameter at computed tomography (CT) or magnetic resonance imaging at least 20 mm; or a maximum measurable diameter at helical CT of at least 10 mm. • Eastern Cooperative Oncology Group performance status 0–2, at least 6 months since last treatment with other chemotherapeutic agents, at least 4 weeks since prior radiotherapy, at least 2 weeks since prior treatment with antimetabolic drugs, hormone therapy, or immunotherapy • Age ‡20 and <75 years • Adequate hematologic and major organ function preserved, with an absolute granulocyte count ‡2000/mm^3, platelet count ‡100 000/mm^3, hemoglobin ‡9.0 g/dl, aspartate aminotransferase £100 U/l, alanine aminotransferase £100 U/l, bilirubin £1.5 mg/dl, serum creatinine £1.2 mg/dl, creatinine clearance ‡60 ml/min, normal electrocardiogram • Provision of written consent to participate in this study Exclusion criteria: • Presence of sarcomatous components • Apparent infection • Serious complications • Active multiple cancers • Apparent interstitial pneumonia or pulmonary fibrosis • Pleural effusion or ascites requiring continuous drainage • Grade 2 or higher peripheral neuropathy or grade 2 or higher edema • A history of hypersensitivity to preparations containing polysorbate 80, polyoxyethylene castor oil, or hardened castor oil • Patients judged by the investigator to be ineligible for other reasons.
Intervention	Patients were randomized to DP (n=30) (docetaxel 70 mg/m^2 + cisplatin 60 mg/m^2 , day 1, every 3 weeks), DC (n=30) (docetaxel 60 mg/m^2 + carboplatin area under the curve (AUC) 6 mg/mlmin, day 1, every 3 weeks), or TC (n=30) (paclitaxel 180 mg/m^2 + carboplatin AUC 6 mg/mlmin, day 1, every 3 weeks), each regimen to be given until disease progression or adverse events prohibited further therapy

Main study characteristics: Nomura

Baseline characteristics

Characteristics	DP (n = 29)	DC (n = 29)	TC (n = 30)	Total (n = 88)	P value
Prior chemotherapy with taxane					0.9161
No	26	26	26	78	
Yes	3	3	4	10	
Measurable lesion in the previously irradiated region					0.7590
No	28	27	29	84	
Yes	1	2	1	4	
Disease status					0.2919
Stage III	9	6	5	20	
Stage IV	9	6	13	28	
Recurrent	11	17	12	40	
ECOG performance status					0.3717
0	23	24	19	66	
1	5	5	9	19	
2	1	0	2	3	
Histology					0.5705
Adenocarcinoma	1	2	1	4	
Endometrioid adenocarcinoma	18	19	14	51	
Endometrioid adenocarcinoma with squamous differentiation	4	3	5	12	
Serous adenocarcinoma	2	2	6	10	
Clear cell adenocarcinoma	0	2	0	2	
Mucinous adenocarcinoma	0	0	1	1	
Squamous cell carcinoma	0	0	0	0	
Mixed carcinoma	2	1	2	5	
Undifferentiated carcinoma	1	0	1	2	
Others	1	0	0	1	

Main study characteristics: Nomura

Age (years)					
Median (range)	64.0 (39–74)	66.0 (51–73)	61.0 (49–74)	62.5 (39–74)	
Prior surgery					0.7510
No	8	9	11	28	
Yes	21	20	19	60	
Prior radiotherapy					0.9372
No	25	25	25	75	
Yes	4	4	5	13	
Prior chemotherapy					0.0714
No	24	16	19	59	
Yes	5	13	11	29	
Regimens of prior chemotherapy					
Taxane/platinum	2	3	4	9	
Anthracyclin/platinum	2	9	8	18	
Taxane/anthracyclin/platinum	1	0	1	2	
Platinum	0	2	0	2	
Hormone	0	0	1	1	
Others	0	1	0	1	

DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin; ECOG, Eastern Cooperative Oncology Group.

Primary and secondary endpoints	The primary end point was the tumour response rate, and the secondary endpoints were the frequency of adverse events, the treatment completion rate, and PFS. Objective tumour assessments were evaluated every two cycles in accordance with the RECIST guidelines, and CR and PR were confirmed at least 4 weeks after the initial responses. The response rate was defined as a total of CR and PR. Adverse events were classified and evaluated by grade in accordance with the National Cancer Institute– Common Toxicity Criteria. Treatment completion was defined as being able to appropriately commence treatment and administer at least three cycles.
Method of analysis	All efficacy analyses were intention-to-treat. Kaplan–Meier method was used to estimate rates of PFS and OS.
Subgroup analyses	NR.

Table 54. Main study characteristics, McMeekin et al (11)

Main study characteristics: McMeekin	
Trial name	IXAMPLE2
NCT number	NCT00883116
Objective	The purpose of this multicenter, open label, randomized phase III study was to determine whether ixabepilone resulted in improved OS compared with commonly used single-agent chemotherapy (doxorubicin or paclitaxel) in women with locally advanced, recurrent, or metastatic EC with at least one failed prior platinum-based chemotherapeutic regimen.
Publications – title, author, journal, year	Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced EC.McMeekin, S., Dizon, D., Barter, J., Scambia, G., Manzyuk, L., Lisyanskaya, A., ... & Vergote, I. *Gynecologic oncology*, *138*(1), 18-23. (2015).
Study type and design	This was a multicenter, open label phase III study (NCT00883116), in which eligible patients were randomized in a 1:1 ratio to ixabepilone 40 mg/m2 administered as a 3-hour intravenous (IV) infusion every 21 days, or either paclitaxel 175 mg/m2 administered as a 3-hour IV infusion (or per institutional guidelines) every 21 days, or doxorubicin 60 mg/m2 given IV per institutional guidelines every 21 days, depending on prior therapy received. Patients previously treated with an anthracycline were randomly assigned to either ixabepilone or paclitaxel, and patients who were not previously treated with an anthracyline were randomly assigned to either ixabepilone or doxorubicin. Randomization was stratified by the presence or absence of measurable disease, prior anthracycline therapy, papillary serous or clear cell carcinoma, and investigator site. Treatment was continued until disease progression, unacceptable toxicity, withdrawal from the study, or for patients receiving doxorubicin, upon reaching the maximum allowed cumulative dose of 500 mg/m2 of doxorubicin.
Follow-up time	29.6 month
Population (inclusion and exclusion criteria)	Eligible patients included women ≥18 years of age with histologic or cytologic diagnosis of advanced, recurrent or metastatic endometrial carcinoma, not curable by local measures, and a Karnofsky Performance Status ≥70. Measurable or non-measurable disease progression was required since the last treatment, along with one failed prior platinumbased chemotherapeutic regimen for EC, regardless of setting or disease stage. Patients may have received up to two prior cytotoxic chemotherapy regimens; at least one regimen must have included a platinum agent. Any number of prior non-cytotoxic regimens was permitted such as monoclonal antibodies, cytokines, signal transduction inhibitors, or hormonal therapy; previous radiation therapy was allowed. All therapy directed at EC must have been discontinued 21 days prior to the start of treatment, except for hormonal therapy which must have been

Main study characteristics: McMeekin	
	discontinued at least 1 week prior to the beginning of therapy. Concurrent administration of hormone replacement therapy was permitted. Key exclusion criteria included: known brain metastases; prior treatment with ixabepilone; a left ventricular ejection fraction of b50% as measured by multi-gated radionuclide angiography or echocardiography for patients whose prior therapy did not include an anthracycline (e.g. doxorubicin); history of prior malignancy within the last 5 years except non-melanoma skin cancer, carcinoma in situ of the cervix, or carcinoma in situ of the breast not treated with chemotherapy; absolute neutrophil count b1500/mm3 ; platelets b100,000/mm3 ; hemoglobin b9 g/dL; total bilirubin N1.5 × upper limit of normal [ULN]; aspartate aminotransferase or alanine aminotransferase N2.5 × ULN; serum creatinine N1.5 × ULN; Common Terminology Criteria of Adverse Events (CTCAE) grade ≥ II sensory or motor neuropathy; and continued treatment with potent inhibitors of CYP3A4. This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization, and local and national regulatory requirements. The protocol was approved by the Institutional Review Board/Independent Ethics Committee of each participating institution and all patients provided written informed consent (NCT00883116).
Intervention	Patients were randomized in a 1:1 ratio to ixabepilone 40 mg/m2 administered as a 3-hour intravenous (IV) infusion every 21 days, or either paclitaxel 175 mg/m2 administered as a 3-hour IV infusion (or per institutional guidelines) every 21 days, or doxorubicin 60 mg/m2 given IV per institutional guidelines every 21 days, depending on prior therapy received.

Main study characteristics: McMeekin

Baseline characteristics

Baseline demographics and treatment exposure.

	Ixabepilone	Control	Total
	n = 248	n = 248	n = 496
Race, n (%)			
White	215 (87)	213 (86)	428 (86)
Black	12 (5)	18 (7)	30 (6)
Asian	6 (2)	5 (2.0)	11 (2)
Other	15 (6.0)	12 (5)	27 (6)
Age (years)			
Median	64.0	64.0	64.0
Min–max	39.0–86.0	33.0–88.0	33.0–88.0
Karnofsky Performance Status, n (%)			
100	86 (35)	86 (35)	172 (35)
90	95 (38)	79 (32)	174 (35)
80	48 (19)	64 (26)	112 (23)
70	19 (8)	16 (6)	35 (7)
70	0	2 (1)	2 (0.4)
Not reported	0	1 (0.4)	1 (0.2)
Disease diagnosis histology, n (%)			
Endometrioid	153 (62)	138 (56)	291 (59)
Papillary serous	68 (27)	74 (30)	142 (27)
Clear cell	14 (6)	18 (7)	32 (7)
Other	13 (5)	17 (7)	30 (7)
Number of patients who received prior chemotherapy in neoadjuvant/adjuvant setting (%)	135 (54)	140 (57)	275 (55)
Number of patients who received metastatic chemotherapy (%)	140 (57)	123 (50)	263 (53)
Prior systemic therapy >5%, n (%)			
Carboplatin	199 (80)	201 (81)	400 (81)
Paclitaxel	193 (78)	195 (79)	388 (78)
Cisplatin	57 (23)	50 (20)	107 (22)
Doxorubicin	52 (21)	47 (19)	99 (20)
Cyclophosphamide	23 (9)	15 (6)	38 (8)
Epirubicin	13 (5)	13 (5)	26 (5)
Investigational antineoplastic	14 (6)	7 (3)	21 (4)
Median number of courses of ixabepilone (min–max)	4.0 (1.0–26.0)	–	–
Median number of courses of paclitaxel (min–max)	–	5.0 (1.0–23.0)	–
Median number of courses of doxorubicin (min–max)	–	4.0 (1.0–10.0)	–

Primary and secondary endpoints	The primary endpoint was to compare OS in women treated with ixabepilone versus control chemotherapy (paclitaxel or doxorubicin). Secondary endpoints included PFS (patients with measurable disease only), ORR, duration of response, time to response and toxicity.
Method of analysis	For OS, 441 deaths were required to detect a hazard ratio (HR) of 0.74 between the two treatment arms using a two-sided, log-rank test at an alpha level of 0.05 with 84% power. A HR of 0.74 corresponds to a 2.8 month increase in median OS for patients randomized to ixabepilone over control (10.8 versus 8 months). The power calculations were adjusted for a planned interim analysis of futility using a Gamma (1.8) spending function. Kaplan–Meier curves of OS and PFS were presented for each treatment arm. The treatment arms were compared using a stratified log rank test; the HR along with a two-sided 95% confidence interval (CI) was calculated using a stratified Cox proportional

Main study characteristics: McMeekin	
	hazard model. Response rate and a two-sided 95% CI, descriptive statistics for time to response, and Kaplan–Meier median and two-sided 95% CI for duration of response, were calculated for each randomized arm. An interim analysis was conducted after 176 deaths had been observed or 300 patients had been randomized and followed for 6 months, whichever came earlier. If the follow-up on 300 patients occurred first, a minimum number of 160 deaths were required before conducting the futility analysis. The futility boundary to reject the alternative hypothesis was set at a HR of 0.9, but the exact boundary was calculated at the time of the analysis.
Subgroup analyses	NR

Table 55. Main study characteristics , ZoptEC (27) (4)

Main study characteristics: ZoptEC	
Trial name	ZoptEC
NCT number	NCT01767155
Objective	To investigate whether administration of ixabepilone results in superior outcome as assessed by OS compared with that achieved with standard chemotherapy (paclitaxel or doxorubicin) in women with advanced EC that has progressed following first-line chemotherapy.
Publications – title, author, journal, year	NR
Study type and design	Open-label, randomized, active-controlled, two-arm Phase III study to compare the efficacy and safety of AEZS-108 and doxorubicin.
Follow-up time	NR
Population (inclusion and exclusion criteria)	**Inclusion Criteria:** 1. Women ≥ 18 years of age 2. Histologically confirmed EC 3. Advanced (FIGO stage III or IV), recurrent or metastatic disease. 4. Measurable or non-measurable disease that has progressed since last treatment.

Main study characteristics: ZoptEC

5. 5. Patients with advanced, recurrent or metastatic EC who have received one chemotherapeutic regimen with platinum and taxane (either as adjuvant or as first line treatment) and who have progressed.
6. Availability of fresh or archival FFPE (formalin-fixed and paraffin-embedded) tumour specimens for analysis of LHRH (luteinizing hormone releasing hormone) receptor expression.

Exclusion Criteria:

1. ECOG (Eastern Cooperative Oncology Group) performance status > 2.
2. Inadequate hematologic, hepatic or renal function
3. Red blood cell transfusion within 2 weeks prior to anticipated start of study treatment.
4. History of myocardial infarction, acute inflammatory heart disease, unstable angina, or uncontrolled arrhythmia within the past 6 months.
5. Impaired cardiac function defined as left ventricular ejection fraction (LVEF) < 50 % (or below the study site's lower limit of normal) as measured by MUGA (multigated radionuclide angiography) or ECHO (echocardiography).
6. Concomitant use of prohibited therapy (specified in protocol)
7. Chemo-, immune-, or hormone-therapy within 5 elimination half life times or 4 weeks prior to randomization, whichever is the shorter. Radiotherapy (including pre- or post-operative brachytherapy) within 4 weeks prior to randomization.
8. Previous anthracycline-based chemotherapy (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone and valrubicin), in any formulation.
9. Anticipated ongoing concomitant anticancer therapy during the study.
10. History of serious co-morbidity or uncontrolled illness that would preclude study therapy, such as active tuberculosis or any other active infection.
11. Brain metastasis, leptomeningeal disease.
12. Pregnant or lactating female or female of child-bearing potential not employing adequate contraception.
13. Subjects with known hypersensitivity to peptide drugs, including LHRH agonists.
14. Receipt of 2 or more prior cytotoxic chemotherapy regimens for advanced, recurrent, or metastatic EC.
15. Prior treatment with AEZS-108.
16. Use of LHRH agonist or antagonist treatment within 6 months prior to randomization.
17. Malignancy within last 5 years except non-melanoma skin cancer.
18. Any concomitant disease or condition which would interfere with the subjects' proper completion of the protocol assignment.
19. Concomitant or recent treatment with other investigational drug (within 4 weeks or 5 elimination half life times prior to anticipated start of study treatment).
20. Lack of ability or willingness to give informed consent.

Main study characteristics: ZoptEC	
	21. Anticipated non-availability for study visits/procedures.
Intervention	Patients were randomized to: - Drug: AEZS-108 / zoptarelin doxorubicin 267 mg/m^2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles for a maximum of 9 cycles - Drug: doxorubicin 60 mg/m^2 by intravenous bolus injection or 1-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles
Baseline characteristics	

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Main study characteristics: ZoptEC

No. of patients	255
Age, years	
Mean (SD)	63.8 (8.8)
Median	64
IQ Range	28-87
<65 (%)	136 (53.3)
≥65 (%)	119 (46.7)
BMI (Kg/m^2)	
Mean (SD)	NR
Median	NR
IQ Range	NR
Treatment history, n (%)	
1 prior Tx	NR
2 prior Txs	NR
3 prior Txs	NR
≥4 prior Txs	NR
Prior adjuvant chemotherapy	92 (36.9)
Prior surgery	222 (89.2)
Prior radiotherapy	138 (55.4)
Histology, n (%)	
Endometrioid Type I	164 (64.3)
Serous carcinoma	65 (25.5)
Clear cell carcinoma	4 (1.6)
Squamous cell carcinoma	0 (0.0)
Undifferentiated carcinoma	NR
Mixed carcinoma	NR
Other/Unspecified	22 (8.6)
Unknown	NR
FIGO stage most recent	
I	NR
II	NR
III	NR
IV	NR
Unknown	NR
Advanced (Stage III or IV)	94 (36.9)
Metastatic	90 (35.3)
Recurrent	71 (27.8)
ECOG	
0	125 (49.0)
1	118 (46.3)
2	11 (4.3)
Race, n (%)	
White	240 (94.1)
Black	7 (2.7)
Asian	5 (2.0)
American Indian/Alaska Native	1 (0.4)
Other	2 (0.8)
Unknown	NR
NR	NR
Ethnicity, n (%)	
Hispanic or Latino	14 (5.5)
Non-Hispanic/Latino	238 (93.3)
Unknown	NR
Not reported	3 (1.2)

Primary and secondary endpoints	The primary endpoint was the OS of Patients Treated With AEZS-108 to the OS of Patients Treated With Doxorubicin. [Time Frame: From randomization to death from any cause. During ongoing treatment: response evaluation every 3 cycles. For patients gone of treatment: re-assessment every 12 weeks.] Secondary endpoints were: - Objective Response Rate (ORR). [Time Frame: 3 years]

Main study characteristics: ZoptEC	
	- Progression-free Survival (PFS). [Time Frame: During ongoing treatment: response evaluation every 3 cycles. For patients gone of treatment: re-assessment every 12 weeks. - Clinical Benefit Rate (CBR). [Time Frame: 3 years]
Method of analysis	The primary efficacy variable will be OS. The primary analysis of the primary efficacy variable will be based on the ITT population. The final OS analysis, which is event-based, will be conducted after approximately 384 randomized patients have died. In the primary analysis, a log-rank test with an overall two-sided Type I error rate of 0.05 after taking the interim analyses into account will be used to compare OS between the two treatment arms via a SAS lifetest procedure. Kaplan-Meier estimates will be used to calculate median OS and the 95% confidence interval of the median OS. The proportion of patients alive at six and 12 months (from randomization date) and the 95% confidence intervals for these estimated proportions, if appropriate, will be presented. Approximately 384 events of deaths will be required to achieve 80 % power to detect a treatment difference at the two-sided 0.05 significance level. It is expected that approximately 500 patients will be enrolled during an estimated 24-month recruitment period and will then be followed for 12 months to observe a total of approximately 384 death events. In the sample size calculation, it is assumed that the median OS is 12 months for AEZS-108 and 9 months for doxorubicin. The sample size calculation has taken two planned interim looks into account, the first being a futility analysis only. Population pharmacokinetic methodology will be applied to analyze results derived from sparse PK sampling and from the PK sub-study.
Subgroup analyses	NR

Table 56. Main study characteristics, Makker et al (10)

Main study characteristics Makker	
Trial name	Makker et al
NCT number	NR
Objective	To investigate the activity of doxorubicin in the second-line setting in patients who progressed after paclitaxel/ carboplatin adjuvant treatment.
Publications – title, author, journal, year	Retreatment with carboplatin and paclitaxel for recurrent EC: a retrospective study of the Memorial Sloan Kettering Cancer Center experience. Rubinstein,

Main study characteristics Makker	
	M., Halpenny, D., Makker, V., Grisham, R. N., Aghajanian, C., & Cadoo, K.. *Gynecologic oncology reports*, *28*, 120-123. (2019).
Study type and design	Retrospective analysis
Follow-up time	NR
Population (inclusion and exclusion criteria)	Following Institutional Review Board approval, patients with stage I-IV endometrial carcinoma who had received adjuvant TC at MSKCC between 1995 and 2009 were identified. MSKCC electronic medical records were reviewed for patient age, diagnosis date, type of primary surgery, residual disease at completion of primary surgery, stage, treatment (chemotherapy and radiation therapy), dates of progression and death, site(s) of first recurrence, and toxic side effects. Patients had to have undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, and maximal resection of all gross intraabdominal/pelvic disease, including macroscopically involved para-aortic and pelvic lymph nodes. Peritoneal cytology and lymph node dissection were optional if there were no intraoperative clinical manifestations of residual intra-abdominal disease. All patients had to have histologic confirmation of endometrial carcinoma at MSKCC. Patients were allowed to have received intravaginal radiation therapy (IVRT)/pelvic RT as part of their adjuvant treatment. Patients with carcinosarcoma were not included. From this dataset, we then identified the patients who had progression of disease after treatment with TC and who received doxorubicin as second-line therapy. All patients in this group were required to have measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST 1.1) (13) at the time of treatment with doxorubicin. Toxicity was determined by review of clinical documentation. Toxicity was assessed by the treating physician at each visit and graded using version 4.0 of Common Terminology Criteria for Adverse Events (CTCAE).
Intervention	All patients received paclitaxel (175mg/m2) and carboplatin (AUC 6) intravenously (IV) once every 3 weeks as adjuvant treatment following surgical management of endometrial carcinoma. One patient with stage IIIB, high-grade serous carcinoma received IVRT for 2100 cGy in 3 fractions in conjunction with adjuvant TC.

Main study characteristics Makker

Baseline characteristics

Patient Characteristics

Patient Demographics	N (= 17)	%
Vital Status		
Alive	1	5.9
Dead	16	94.1
Progressed	17	100
Age at Diagnosis, years		
Median	57.0	
Range	36-78	
FIGO Stage		
IIIA	1 (serous histology)	5.9
IIIB	1 (serous histology)	5.9
IIIC	1 (serous histology)	5.9
IVB	14	82.4
Histologic sub-type		
Endometrioid	5	29.4
Grade 1	1	5.9
Grade 2	0	
Grade 3	4	23.5
Serous	5	29.4
Mixed Cell Type	4	23.5
Undifferentiated	2	11.8
Clear Cell	1	5.9
Race		
White	16	94.1
Black	1	5.9
ECOG Performance Status		
0	8	47.0
1	7	41.2
2	2	11.8
CA-125		
< 35 U/ml	13	76.5
> 35 U/ml	4	23.5

FIGO, International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group

Primary and secondary endpoints	Median PFS, median OS. No indication on the primary and secondary split.
Method of analysis	As no early-stage patients were identified, patients were analysed as one group: advanced endometrial carcinoma treated with TC adjuvant chemotherapy, followed by second-line doxorubicin chemotherapy for recurrent, measurable disease. Sites of first recurrence after TC therapy and sites of progression after doxorubicin therapy were classified as vaginal, pelvic, liver abdomen,

Main study characteristics Makker	
	lung, peritoneal carcinomatosis, inguinal lymph nodes, para-aortic lymph nodes, and retroperitoneal lymph nodes. Patients with multiple sites of first recurrence were counted separately for each site. PFS following TC/doxorubicin therapy was defined as the start date of TC/doxorubicin treatment to the corresponding date of progression. OS following TC/doxorubicin chemotherapy was defined as the time elapsed from the start date of TC/doxorubicin treatment to the date of death or the date of last follow-up. The median OS and PFS time as well as the corresponding 95% CIs were estimated using the Kaplan-Meier method. The analyses were performed using SAS 9.1.
Subgroup analyses	NR

Table 57. Main study characteristics, Julius et al (12)

Main study characteristics: Julius	
Trial name	Julius et al
NCT number	NR
Objective	To determine factors which may increase the likelihood of adverse drug events (ADEs) in recurrent EC patients treated with pegylated liposomal doxorubicin (PLD) as well as this agent's impact on clinical outcomes.
Publications – title, author, journal, year	Evaluation of pegylated liposomal doxorubicin dose on the adverse drug event profile and outcomes in treatment of recurrent EC.Julius, J. M., Tanyi, J. L., Nogueras-Gonzalez, G. M., Watkins, J. L., Coleman, R. L., Wolf, J. K., & Smith, J. A. *International Journal of Gynecologic Cancer*, *23*(2). (2013).
Study type and design	Retrospective review
Follow-up time	NR
Population (inclusion and exclusion criteria)	Patients were included who had received PLD as treatment of recurrent ECs between January 1, 1996, and June 30, 2006 at The University of Texas M. D. Anderson Cancer Center (UTMDACC), Gynecologic
Intervention	Patients had received PLD as single agent at initial doses of 50 mg/m2 (FDA approved label dose) or reduced doses of 40 mg/m2 (standard single-agent dose in current clinical practice), 35 mg/m2 , or 30 mg/m2 for the treatment of recurrent EC.

Main study characteristics: Julius

Baseline characteristics

Patient Demographics

Characteristic	Mean (SD)	Median (range)
Age (years)	66.8 (9.6)	67.0 (34–87)
BMI	29.8 (8.2)	28.2 (19.8–49.6)
Number of prior chemotherapy regimens	2 (2)	3 (1–5)
CA-125 response		
Cycle 1	922.4 (2782.0)	140.8 (3.5–18,356.0)
Cycle 2	1048.1 (2848.1)	191.7 (8.4–16954.0)
Cycle 3	656.9 (1365.8)	159.3 (7.0–6960.0)
Cycle 4	420.9 (499.1)	233.7 (11.4–1742.8)
Cycle 5	250.6 (270.3)	198.5 (10.6–980.0)
Cycle 6	390.6 (528.2)	203.8 (9.6–1959.0)
Cycles of PLD	4.72 (4.23)	3.0 (1–25)
Mean Dose per cycle (mg)	63 (5.3)	64 (50–75)
Mean cumulative dose (mg)	306 (277.7)	225 (55 – 1627)

Characteristic	Number (%)
Ethnicity	
White	44 (73.3%)
Hispanic	6 (10.0%)
African American	10 (16.7%)
Comorbidities	
Diabetes	9 (15%)
Hypertension	36 (60%)
Other Cardiovascular	16 (26.6%)
Cycle 1 PLD dose	
30 mg/m^2	7 (11.7%)
35 mg/m^2	10 (16.7%)
40 mg/m^2	42 (70.0%)
50 mg/m^2	1 (1.7%)
Reason PLD discontinued	
Disease progression	45 (75.0%)
Toxicity	5 (8.3%)
Lost to follow-up	4 (6.7%)
Not reported	2 (3.3%)
End of treatment planned	2 (3.3%)
High cumulative dose	1 (1.7%)
Chemotherapy break	1 (1.7%)

Abbreviations: SD, standard deviation; BMI, body mass index; PLD, pegylated liposomal doxorubicin. Data are number (%) of patients, unless otherwise indicated.

Primary and secondary endpoints	Progression free survival (PFS) and OSwere outcomes of interest. No specification of primary/secondary was included.
Method of analysis	The Cox proportional hazards regression model was employed to explore the effect of PLD dose on progression free survival (PFS). Time to progression was calculated as the interval between the date of the first cycle and the date of the last documented cycle for those patients with disease progression. In addition to the PFS analysis, a time-to-progression (TTP) analysis was also performed. The secondary objectives of this study included: 1) explore the impact of PLD dose on response, 2) explore the impact of PLD dose on the incidence of PPE, and 3) to explore the impact of using cooling mechanisms on the incidence and grade of PPE. The Pearson's chi square or Fisher's exact test were used to evaluate the association between PLD dose and the incidence of disease

Main study characteristics: Julius	
	progression. These were also used to evaluate the relationship between the incidence of PPE and PLD dose and between the incidence of PPE and the use of cooling mechanisms. Finally, the Pearson's chi-square or Fisher's exact test were also used to explore the relationship between PPE and platinum sensitivity; each of 8 toxicities, or pre-existing co-morbidities, independently. To explore the relationship between PLD dose and each of 8 toxicities evaluated a test for trend across ordered groups was completed. Summary statistics were used to describe CA125 response in the first 6 cycles, first cycle dose, and the reported reasons for dose reduction.
Subgroup analyses	NR

Table 58. Main study characteristics, Muggia et al (13)

Main study characteristics: Muggia	
Trial name	Muggia et al
NCT number	NR
Objective	The objective of this study was to determine whether pegylated liposomal doxorubicin (PLD) has antitumour activity in pre-treated patients with persistent or recurrent endometrial carcinoma and to define the nature and degree of toxicity of PLD.
Publications – title, author, journal, year	Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic EC: a Gynecologic Oncology Group study. Muggia, F. M., Blessing, J. A., Sorosky, J., & Reid, G. C. *Journal of clinical oncology*, *20*(9), 2360-2364. (2002).
Study type and design	Phase II Trial of the Pegylated Liposomal Doxorubicin
Follow-up time	
Population (inclusion and exclusion criteria)	Eligible patients had to have histologically confirmed persistent or recurrent endometrial carcinoma and the presence of measurable disease. All epithelial cell types were eligible. The GOG performance status was to be 0, 1, or 2. At least 3 weeks had to elapse from prior therapy, and recovery had to take place from any recent treatment. Patients were required to have adequate organ function as evidenced by WBC count ≥ 3,000/µL, granulocyte count ≥ 1,500/µL, platelet count ≥ 100,000/µL, creatinine level ≤ 2.0 mg/100 mL, bilirubin level ≤ 1.5 times the institutional normal, and AST and alkaline phosphatase ≤ three times the institutional normal. A normal left ventricular ejection fraction by radionuclide multiple-gated acquisition (MUGA) scan was required. Patients had to have received one and only one prior chemotherapy regimen or to have qualified for one prior study for recurrent EC. Prior treatment with doxorubicin was allowed if the cumulative dose level was ≤ 350 mg/m2. Therefore, patients who entered and completed GOG Protocol 163 (doxorubicin/cisplatin versus doxorubicin/paclitaxel) were eligible to enter this study. Of 46 patients who entered the study, 42 were assessable for response, as three were declared ineligible on central pathology review and one was not assessable for response.

Main study characteristics: Muggia	
Intervention	PLD was administered as a 1-hour infusion at the initial dose of 50 mg/m2 every 4 weeks. Premedication including dexamethasone 20 mg intravenously, together with diphenhydramine 50 mg and cimetidine 300 mg, was recommended during the first and subsequent courses. Subsequent courses of PLD were not administered until the granulocyte count was greater than 1,500/mL, the platelet count was greater than 100,000/mL, and the patient had recovered fully from any nonhematologic toxicity. Dose modification by 25% was based on nadir grade 4 platelets or neutrophils, or any grade 3 or greater nonhematologic toxicity (expected to be primarily skin or mucosal toxicities).
Baseline characteristics	**Table 1. Patient Characteristics (n = 42)**

Characteristic		No. of Patients
Age, years		
Median	62.5	
Range	40-79	
Ethnicity		
White		34
Black		6
Other		2
GOG performance status		
0		19
1		17
2		6
Grade		
1		7
2		17
3		18
Prior radiotherapy		29
Prior chemotherapy		40
Prior hormonal therapy		11
Courses, n		
Median	2.5	
Range	1-14	

Primary and secondary endpoints	ORR, adverse events. No specification primary/secondary
Method of analysis	Patients were assessable for response after receiving PLD and being observed for at least 4 weeks. Objective responses were defined by standard GOG criteria
Subgroup analyses	NR

9.4 Results per study

Table 59: Results of GARNET study

Results of study GARNET, NCT02715284 **(3)**											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS	Dostarlimab	108	NR (17.1, NR)	NA	NA	NA	NA	NA	NA	The median OS are based on the Kaplan–Meier estimator per RECIST 1.1.	EPAR (26)
OS- rate at 12 months	Dostarlimab	108	69.2 % (58.8-77.6)	NA	NA	NA	NA	NA	NA	*At the data cut-off in March 2020. The OS rate at 12 months are based on the Kaplan–Meier estimator per RECIST 1.1	EPAR (26)
Median PFS	Dostarlimab	108	5.5 months (3.2 – NR)	NA	NA	NA	NA	NA	NA	The median PFS are based on the Kaplan–Meier estimator per RECIST 1.1.	EPAR (26)
PFS at 24 months	Dostarlimab	108	[redacted]	NA	NA	NA	NA	NA	NA	The PFS at 24 months are based on the Kaplan–Meier estimator per RECIST 1.1.	EPAR (26)
ORR		108		NA	NA	NA	NA	NA	NA		EPAR (26)

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Results of study GARNET, NCT02715284 **(3)**											
	Dostarlimab		43.5% (34.0-53.4%)*							*At the data cut-off in March 2020. Two-sided exact 95% confidence intervals (CIs) based on the Clopper-Pearson method were provided to summarize the binomial proportion of the ORR using RECIST v1.1.	
≥3 TEAE	Dostarlimab	129	48.1 %*	NA	NA	NA	NA	NA	NA	The safety results are presented for all participants who received any amount of study treatment (safety analysis set), which included a total of 129 participants	
EORTC QLQ-C30	Dostarlimab	94	[redacted]	NA	NA	NA	NA	NA	NA	*Mean change from baseline (SD = 23.77).	Data on file.

Table 60. Results of study Nagao 2013 (14)

Results of study Nagao 2013 (14)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		Nagao et al. 2013
Median OS	PFI 6-11 months	129	14.8%	NA	NA	NA	NA	NA	<.0001	The median OS were estimated using the Kaplan–Meier method, and log-rank trend test was used to test for a trend in OS across ordered platinum-free intervals.	
	PFI 12-23 months	129	27.8%								
	PFI more than 24 months	129	40.9%								
Median PFS	PFI 6-11 months	129	6.0%	NA	NA	NA	NA	NA	<.0001	The median PFS were estimated using the Kaplan–Meier method, and log-rank trend test was used to test for a trend progression-free across ordered platinum-free intervals.	Nagao et al. 2013
	PFI 12-23 months	129	7.8%								

Results of study Nagao 2013 (14)										
	PFI more than 24 months	129	13.4%							
ORR	PFI 6-11 months		38%	NA	NA	NA	NA	NA	<0.0001	The ORR is estimated using Cochran-Armitage trend test.	Nagao et al. 2013
	PFI 12-23 months		61%							
	PFI more than 24 months		65							

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Table 61. Results of study Nagao 2015 (15)

Results of study Nagao 2015 (15)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		Nagao et al. (2015) **(15)**
Median OS*	Second line TC/DC therapy, PFI <12 months	42	10 months	NA	NA	NA	HR: 3.179	1.835-5.507	<0.0001	The median OS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model. *For patients with PFI ≥12 months OS of neither regimen had been reached yet at the time of the paper.	Nagao et al. (2015) **(15)**
	Second line AP therapy, PFI <12 months	55	23 months								
Median PFS	Second line TC/DC therapy, PFI <12 months	42	7 months	NA	NA	NA	3.255	1.908-5.555	<0.0001	The median PFS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model.	Nagao et al. (2015) **(15)**
	Second line AP therapy,	55	3 months								

Results of study Nagao 2015 (15)										
	PFI <12 months									Nagao et al. (2015) **(15)**
	Second line TC/DC therapy, PFI ≥12 months	9	12 months	NA	NA	NA	1.441	0.609-3.410	0.406	
	Second line AP therapy, PFI ≥12 months	72	11 months							
ORR	AP to TC/DC (PFI <12 months)	NA	71%	NA	NA	NA	NA	NA	NA	Nagao et al. (2015) **(15)**
	TC/DC to AP (PFI <12 months)	NA	15 %							
	AP to TC/DC	NA	84%	NA	NA	NA	NA	NA	NA	

Results of study Nagao 2015 (15)			
	(PFI ≥12 months)		
	TC to AP (PFI ≥12 months)	NA	7%

Table 62. T Results of study Rubinstein (16)

Results of study Rubinstein (16)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS	Patients re-treated with carboplatin and paclitaxel	20	27 (6-117) months	NA	NA	NA	NA	NA	NA	The median OS is based on the Kaplan–Meier estimator.	Rubinstein et al. 2018 **(16)**

Results of study Rubinstein (16)											
Median PFS	Patients re-treated with car-boplatin and paclitaxel	20	10 months (2-47)	NA	NA	NA	NA	NA	NA	The median PFS is based on the Kaplan–Meier estimator.	Rubinstein et al. 2018 **(16)**
ORR	Patients re-treated with car-boplatin and paclitaxel	20	50%*	NA	NA	NA	NA	NA	NA	*At the data cut-off, there were no CR, 10 (50%) patients had PR, 3 (15%) had stable disease, 2 (10%) had progression at best response and 5 (20%) were not evaluable by RECIST.	Rubinstein et al. 2018 **(16)**

Table 63. Results of study Miyake (17)

Results of study Miyake (17)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS*										The median PFS is based on the Kaplan–Meier estimator.	Miyake et al. 2011 **(17)**

Results of study Miyake (17)											
	TFI 6-12 months	7	7.5 months	NA	NA	NA	3.780	1.046- 13.802	0.0035	The HR is based on a log-rank test. *HR is only for the study arms TFI 6-12 months and TFI≥12 months.	
	TFI≥12 months	15	13 months								
Median OS**	TFI 6-12 months	NR*	NR*	NA	NA	NA	4.081	1.124 14.816	0.0086	The median OS is based on the Kaplan–Meier estimator. The HR is based on a log-rank test. *Not reported in the study. **HR is only for the study arms TFI 6-12 months and TFI≥12 months.	Miyake et al. 2011 **(17)**
	TFI≥12 months	NR*	NR*								
ORR*				NA	NA	NA	NA	NA	NA		

Results of study Miyake (17)											
	TFI 6-12 months	7	43%							The association between sensitivity to second-line chemotherapy and TFI was analysed by Fisher's exact test. *Complete response or partia response	Miyake et al. 2011 **(17)**
	TFI≥12 months	15	68%								

Table 64. Results of study Mazgani (18)

Results of study Mazgani (18)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS	Endometroid histology patients	19	15 (9.13–30.36) months	NA	NA	NA	NA	NA	NA	Survival curves were obtained using the Kaplan and Meier method. Log-rank test was	Mazgani et al. 2008 **(18)**

Results of study Mazgani (18)											
	Serous Histology patients	12	26 (9.72–71.40) months							used to compare differences between those either not retreated with any chemotherapy or not retreated with carboplatin–paclitaxel.	
Median PFS	Endometroid histology patients	19	8 (5.02-12.72) months	NA	NA	NA	NA	NA	NA	Survival curves were obtained using the Kaplan and Meier method. Log-rank test was used to compare differences between those either not retreated with any chemotherapy or not retreated with carboplatin–paclitaxel.	Mazgani et al. 2008 **(18)**
	Serous Histology patients	12	9 (3.59–35.40) months								
ORR	Endometroid histology patients	19	CR+PR:42%; SD:10.5%; PD:32%; NE*: 15.8%	NA	NA	NA	NA	NA	NA	*Not evaluable.	Mazgani et al. 2008 **(18)**
	Serous Histology patients	12	CR+PR:50%; SD:16.7%; PD:25%; NE*: 8.3%								

Table 65. Results of study Vergote (6)

Results of study Vergote (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS	EC patients (1-4 prior lines of therapy)	17	12 months (95% CI: 6 – undefined)	NA	NA	NA	NA	NA	NA	OS were calculated using the Kaplan–Meier methodology	**(6)**
Median PFS	EC patients (1-4 prior lines of therapy)	17	5 months (95% CI: 3- 9).	NA	NA	NA	NA	NA	NA	PFS were calculated using the Kaplan–Meier methodology	**(6)**
ORR	EC patients (1-4 prior lines of therapy)	17	29%	NA	NA	NA	NA	NA	NA	Tumour response to therapy was evaluated with clinical examination, on imaging (CT/MRI abdomen and pelvis (and if	**(6)**

Results of study Vergote (6)										
									applicable CT thorax)) and by CA125. Response evaluation was assessed according to the Evaluation Criteria In Solid Tumours (RECIST) criteria [19] and Gynecological Cancer Intergroup (GCIG) criteria [20,21]. Scans for response assessment to therapy were evaluated at visit 10, at the end of treatment and every 3 months until progression thereafter	

Table 66. Results of study Ueda (19)

Results of study Ueda (19)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS	TFI≥6 months, TEC/weekly	7	13	NA	1.79–8.01	0.002	HR: 0.70	0.55–0.90	0.005	log-rank test	**(19)**

Results of study Ueda (19)										
	TFI<6 months, TEC/weekly	17								
Median PFS	TFI≥6 months, TEC/weekly	7	5.5	NA	NA	NA	NA	NA	NA	Multivariate Cox proportional hazards analysis were used for effectiveness of second-line chemotherapy on PFS.	**(19)**
	TFI<6 months, TEC/weekly	17								
ORR	TFI≥6 months, TEC/weekly	17	CR or PR: 53%	NA	NA	NA	NA	NA	NA		**(19)**

Table 67. Results of study Nomura

Results of study Nomura (20)	
Adverse events of ≥ Grade 3	

Toxic effects	DP (n = 30)				DC (n = 30)				TC (n = 30)			
	Grade			Grade 3–4 (%) (95% CI)	Grade			Grade 3–4 (%) (95% CI)	Grade			Grade 3–4 (%) (95% CI)
	2	3	4		2	3	4		2	3	4	
Hemoglobin	15		1	3.3 (0.1–17.2)	13	5	1	16.7 (5.6–34.7)	14	3	2	16.7 (5.6–34.7)
Leukocytes	7	15	7	73.3 (54.1–87.7)	3	21	5	86.7 (69.3–96.2)	8	13	2	50.0 (31.3–68.7)
Neutrophils (ANC)	4	9	16	83.3 (65.2–94.4)	2	8	19	90.0 (73.5–97.9)	3	11	12	76.6 (57.7–90.1)
Platelets	1	2		6.7 (0.8–22.1)	4	3		10.0 (2.1–26.5)	2	3		10.0 (2.1–26.5)
AST	1				2	1		3.3 (0.1–17.2)		1		3.3 (0.1–17.2)
ALT					3	1		3.3 (0.1–17.2)	3			
Allergic reaction	1		1	3.3 (0.1–17.2)	1	1		3.3 (0.1–17.2)				
Anorexia	10	5		16.7 (5.6–34.7)	7	3		10.0 (2.1–26.5)	6	3		10.0 (2.1–26.5)
Diarrhea	6	3	1	13.3 (3.8–30.7)	1	1		3.3 (0.1–17.2)	2			
Nausea	12	3		10.0 (2.1–26.5)	12	2		6.7 (0.8–22.1)	5	3		10.0 (2.1–26.5)
Motor neuropathy					1					2		6.7 (0.8–22.1)
Sensory neuropathy									3	1		3.3 (0.1–17.2)
Febrile neutropenia		2	1	10.0 (2.1–26.5)		2		6.7 (0.8–22.1)		1		3.3 (0.1–17.2)

DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin; CI, confidence interval; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 68. Results of study McMeekin (11)

Results of study IXAMPLE2 (McMeekin, NCT00883116 (11))											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS	Doxorubicin	284	12.3 (10.7–15.4)	NR	NR	NR	NR	NR	NR	Kaplan Meier curve	McMeekin et al **(11)**
OS at 12 months	Doxorubicin	284	approximately 51%	NR	NR	NR	NR	NR	NR	Kaplan Meier curve	McMeekin et al **(11)**
Median PFS	Doxorubicin	284	4.0 (2.7–4.3)	NR	NR	NR	NR	NR	NR	Kaplan Meier curve	McMeekin et al **(11)**
ORR	Doxorubicin	284	15.7% (11.2-21.1)	NR	NR	NR	NR	NR	NR	Response and disease progression were evaluated using RECIST v1.1	McMeekin et al **(11)**

Table 69. Results of study ZoptEC (27)

Results of study ZoptEC, NCT01767155 (27)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Out-come	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS	Doxorubicin	255	10.8 (9.8-12.6)	NR	NR	NR	NR	NR	NR	Kaplan Meier estimates	ZoptEC (27)
OS rate at 12 months	Doxorubicin	255	44.6% (38.2- 50.7)	NR	NR	NR	NR	NR	NR	Kaplan Meier estimates	ZoptEC (27)
Median PFS	Doxorubicin	255	4.7 (4.1-6.6).	NR	NR	NR	NR	NR	NR	Kaplan Meier estimates	ZoptEC (27) ZoptEC (27)
ORR	Doxorubicin	255	14.1% (9.8-18.4)	NR	NR	NR	NR	NR	NR	The ORR was defined as the sum of the CR and PR per RECIST v1.1	ZoptEC (27)
EORTC QLQ-C30	Doxorubicin	245									ZoptEC (27)

Results of study ZoptEC, NCT01767155 (27)

Global QoL	-11.7 (26.42)
Physical Functioning	-15.3 (21.98)
Role Functioning	-22.5 (30.91)
Emotional Functioning	-2.1 (24.51)
Cognitive Functioning	-8.6 (22.79)
Social Functioning	-15.2 (31.54)
Fatigue	19.6 (27.85)
Nausea and vomiting	9.2 (22.97)
Pain	8.2 (28.50)
Dyspnoea	14.1 (29.35)
Insomnia	7.7 (31.01)
Appetite loss	19.8 (33.12)
Constipation	6.8 (31.35)
Diarrhoea	2.5 (21.33)
Financial difficulties	2.2 (29.76)

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Table 70. Results of study Julius (12)

Results of study Julius (12)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS	PLD platinum sensitive	NR	6.2	NR	NR	NR	NR	NR	NR	KM curve	**Julius (12)**
	PLD platinum resistant	NR	7.1								
OS at 12 months	PLD Starting dose 40mg/m2	41	Approximately 28%	NR	NR	NR	NR	NR	NR	KM curve	**Julius (12)**
	PLD Starting dose 50mg/m2	NR	Approximately 35%								
Median PFS	PLD Starting dose 30mg/m2	7	6,0	NR	NR	NR	NR	NR	NR	KM curve	**Julius (12)**
	PLD Starting dose 35mg/m2	10	3,3								

Results of study Julius (12)												
	PLD Starting dose 40mg/m2	41	7,0									

Table 71. Results of study Muggia (13)

Results of study Muggia (13)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS	PLD	43	8.2	NR	NR	NR	NR	NR	NR	NR	Muggia et al 10)
ORR	PLD	43	9.5% (2.7% - 22.6%)	NR	NR	NR	NR	NR	NR	NR	Muggia et al 10)
AEs	PLD	43								NR	Muggia et al 10)

Results of study Muggia (13)

Table 3. Adverse Effects (n = 43)

Adverse Effect	Grade 1	2	3	4
Neutropenia	3	6	5	2
Thrombocytopenia	9	0	0	0
Anemia	6	11	4	1
Mucositis*	6	7	0	1
Anorexia	2	3	0	0
Nausea and/or vomiting	4	8	1	0
Other gastrointestinal†	6	3	3	0
Dermatologic	9	4	4	0
Neurotoxicity	4	0	2	0
Infusion reaction	1	1	0	0
Alopecia	2	4	0	0
Fever	2	2	1	0
Pulmonary	1	1	1	0
Cardiovascular‡	0	3	1	0

*Includes stomatitis, esophagitis, bronchitis, vaginitis, nasal soreness, and rectal bleeding.

†Includes two events beyond grade 1 for diarrhea and weight loss, and one each of constipation, dehydration, and indigestion.

‡Refers to three patients who had decreased left ventricular ejection fraction (see text).

Table 72. Results of study Makker (10)

Results of study Makker (10)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS	Doxorubicin	17	5.8 (1.0-15.0)	NR	NR	NR	NR	NR	NR	Kaplan-Meier method	Makker et al (10)
OS at 12 months	Doxorubicin	17	Approximately 48%	NR	NR	NR	NR	NR	NR	Kaplan-Meier method	Makker et al (10)
Median PFS	Doxorubicin	17	2.1 (0.97-2.7)	NR	NR	NR	NR	NR	NR	Kaplan-Meier method	Makker et al (10)
PFS at 24 months	Doxorubicin	17	0%	NR	NR	NR	NR	NR	NR	Kaplan-Meier method	Makker et al (10)
ORR	Doxorubicin	17	0%	NR	NR	NR	NR	NR	NR	RECIST 1.1	Makker et al (10)
AEs	Doxorubicin	17	0%	NR	NR	NR	NR	NR	NR	NR	Makker et al (10)

9.5 Adverse events

The main Result per study sections of this application only reported TEAEs of grade ≥ 3 adverse events, as this was the outcome of interest described in the protocol. Additionally, in line with the DMC protocol, this appendix contains all information on safety and adverse events reported by the study included in this application. This includes all TEAEs of grade ≥ 3 as well as any other information on the safety profile reported by the studies. Please note that some of the studies like Vergote et al reported safety results for a broader population as compared to the population of interest for this application, hence they have not been included in the main results sections.

9.5.1 Studies included in clinical question one

GARNET

Figure 32. Overall Summary of TEAEs in Participants with dMMR/MSI-H EC (Safety Analysis Set) reported by dostarlimab in GARNET

TEAE Category, n (%)	dMMR (N=126)	MMR-unk/ MSI-H (N=3)	Total (N=129)
Any TEAEs	120 (95.2)	3 (100)	123 (95.3)
Any Grade ≥3 TEAEs	61 (48.4)	1 (33.3)	62 (48.1)
Any treatment-related TEAEs	80 (63.5)	2 (66.7)	82 (63.6)
Any Grade ≥3 treatment-related TEAEs	17 (13.5)	0	17 (13.2)
Any TEAE with outcome of death	5 (4.0)	0	5 (3.9)
Any SAEs	43 (34.1)	1 (33.3)	44 (34.1)
Any treatment-related SAEs	12 (9.5)	0	12 (9.3)
Any TEAEs leading to discontinuation of study treatment	15 (11.9)	0	15 (11.6)
Any treatment-related TEAEs leading to discontinuation of study treatment	5 (4.0)	0	5 (3.9)
Any treatment-related TEAE leading to death	0	0	0
Any TEAE leading to study treatment infusion interruption	1 (0.8)	0	1 (0.8)
Any TEAE leading to study treatment interruption	31 (24.6)	0	31 (24.0)
Any irAE	44 (34.9)	1 (33.3)	45 (34.9)
Any treatment-related irAE	27 (21.4)	1 (33.3)	28 (21.7)

Source: Table 14.3.1.1a

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for [redacted] dMMR=mismatch repair-deficient; EC=endometrial cancer; EOT=End-of-Treatment; irAE=immune-related adverse event; MMR-unk=unknown mismatch repair tumor status; MSI-H=microsatellite instability high; NCI=National Cancer Institute; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: For each category, participants were included only once, even if they experienced multiple events in that category. TEAEs are new AEs that began, or any preexisting condition that worsened in severity, after at least 1 dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anticancer therapy, whichever occurred earlier). AE severity was graded using NCI CTCAE v4.03.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00
medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 33. TEAEs Experienced by ≥5% of Participants with dMMR/MSI-H EC by PT (Safety Analysis Set) in GARNET

PT, n (%)	dMMR (N=126)	MMR-unk/ MSI-H (N=3)	Total (N=129)
Any TEAEs	120 (95.2)	3 (100)	123 (95.3)
Nausea	40 (31.7)	2 (66.7)	42 (32.6)
Diarrhoea	35 (27.8)	1 (33.3)	36 (27.9)
Anaemia	35 (27.8)	0	35 (27.1)
Fatigue	31 (24.6)	1 (33.3)	32 (24.8)
Asthenia	28 (22.2)	0	28 (21.7)
Constipation	25 (19.8)	0	25 (19.4)
Vomiting	24 (19.0)	0	24 (18.6)
Abdominal pain	21 (16.7)	0	21 (16.3)
Cough	19 (15.1)	2 (66.7)	21 (16.3)
Arthralgia	18 (14.3)	2 (66.7)	20 (15.5)
Urinary tract infection	19 (15.1)	1 (33.3)	20 (15.5)
Back pain	19 (15.1)	0	19 (14.7)
Pruritus	18 (14.3)	0	18 (14.0)
Decreased appetite	16 (12.7)	0	16 (12.4)
Myalgia	13 (10.3)	1 (33.3)	14 (10.9)
Pyrexia	13 (10.3)	1 (33.3)	14 (10.9)
Oedema peripheral	11 (8.7)	2 (66.7)	13 (10.1)
Rash	13 (10.3)	0	13 (10.1)
Headache	12 (9.5)	0	12 (9.3)
Hypomagnesaemia	10 (7.9)	0	10 (7.8)
Hypothyroidism	9 (7.1)	1 (33.3)	10 (7.8)
Upper respiratory tract infection	9 (7.1)	1 (33.3)	10 (7.8)
Abdominal distension	9 (7.1)	0	9 (7.0)
Alanine aminotransferase increased	9 (7.1)	0	9 (7.0)
Aspartate aminotransferase increased	9 (7.1)	0	9 (7.0)
Blood creatinine increased	9 (7.1)	0	9 (7.0)
Dizziness	9 (7.1)	0	9 (7.0)
Dyspnoea	8 (6.3)	1 (33.3)	9 (7.0)
Muscular weakness	9 (7.1)	0	9 (7.0)
Productive cough	9 (7.1)	0	9 (7.0)
Weight decreased	9 (7.1)	0	9 (7.0)
Hypokalaemia	8 (6.3)	0	8 (6.2)
Insomnia	8 (6.3)	0	8 (6.2)
Pain in extremity	8 (6.3)	0	8 (6.2)
Hypertension	5 (4.0)	2 (66.7)	7 (5.4)
Hyponatraemia	6 (4.8)	1 (33.3)	7 (5.4)
Pelvic pain	7 (5.6)	0	7 (5.4)

Source: Table 14.3.1.2a and Table 14.3.1.3a

Abbreviations: AE=adverse event; dMMR=mismatch repair-deficient; EC=endometrial cancer; EOT=End-of-Treatment; MedDRA=Medical Dictionary for Regulatory Activities; MMR-unk=unknown mismatch repair tumor status; MSI-H=microsatellite instability high; PT=preferred term; TEAE=treatment-emergent adverse event.

Note: AEs were coded using MedDRA version 23.0. For each PT, a participant was included only once, even if they experienced multiple events in that PT. TEAEs are new AEs that began, or any preexisting condition that worsened in severity, after at least 1 dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anticancer therapy, whichever occurred earlier).

Figure 34. Treatment-Related TEAEs Experienced by ≥5% of Participants with dMMR/MSI-H EC by PT (Safety Analysis Set) in GARNET

PT, n (%)	dMMR (N=126)	MMR-unk/ MSI-H (N=3)	Total (N=129)
Any treatment-related TEAEs	80 (63.5)	2 (66.7)	82 (63.6)
Diarrhoea	20 (15.9)	1 (33.3)	21 (16.3)
Asthenia	18 (14.3)	0	18 (14.0)
Fatigue	17 (13.5)	0	17 (13.2)
Nausea	16 (12.7)	0	16 (12.4)
Arthralgia	11 (8.7)	0	11 (8.5)
Pruritus	11 (8.7)	0	11 (8.5)
Anaemia	9 (7.1)	0	9 (7.0)
Hypothyroidism	8 (6.3)	1 (33.3)	9 (7.0)
Rash	7 (5.6)	0	7 (5.4)

Source: Table 14.3.1.6a and Table 14.3.1.7a

Abbreviations: AE=adverse event; dMMR=mismatch repair-deficient; EC=endometrial cancer; EOT=End-of-Treatment; MedDRA=Medical Dictionary for Regulatory Activities; MMR-unk=unknown mismatch repair tumor status; MSI-H=microsatellite instability high; PT=preferred term; TEAE=treatment-emergent adverse event.

Note: AEs were coded using MedDRA version 23.0. Only TEAEs were summarized. For each PT, a participant was included only once, even if they experienced multiple events in that PT. TEAEs are new AEs that began, or any preexisting condition that worsened in severity, after at least 1 dose of study treatment was administered and throughout the treatment period until 90 days after the EOT Visit (or until the start of alternate anticancer therapy, whichever occurred earlier). Treatment-related AEs refer to any TEAE assessed by the Investigator as related to study treatment ("Related," "Possibly Related," or missing).

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Table 73. irAE by Category and Preferred Term (≥2% Patients) (Safety Analysis Set - Patients with dMMR/MSI-H EC)(DCO 1 March 2020)

			Treated with IMM**			Not treated with IMM**		
Category Preferred Term, n(%)	Overall (N=129) n(%)	Median time to on-set (days)	n(%)	Resolved n(%)	Median time to resolution (days) 95% CI	n(%)	Resolved n(%)	Median time toresolution (days) 95% CI
Any immune-related TEAE	47 (36.4)							
Immune-mediated Gastrointestinal	13 (10.1)							
Diarrhoea	11 (8.5)	70.0	0	0		11 (100.0)	10 (90.9)	6.0 (1.0,26.0)
Colitis	3 (2.3)	380.0	2 (66.7)	2 (100.0)	35.0 (24.0, NE)	1 (33.3)	0	NE (NE, NE)
Immune-mediated endo-crinopathies	12 (9.3)							
Hypothyroidism	9 (7.0)	168.0	9 (100.0)	2 (22.2)	NE (63.0, NE)	0	0	
Hyperthyroidism	4 (3.1)	53.5	2 (50.0)	2 (100.0)	42.0 (41.0, NE)	2 (50.0)	2 (100.0)	42.0 (20.0, NE)
Immune-mediated musculoskel-etal	7 (5.4)							
Arthralgia	6 (4.7)	52.0	1 (16.7)	0	NE (NE, NE)	5 (83.3)	3 (60.0)	366.0 (23.0, NE)
Immune-mediated hepatic	6 (4.7)							

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Alanine aminotransferase increased	4 (3.1)	112.5	2 (50.0)	2 (100.0)	6.5 (5.0, NE)	2 (50.0)	2 (100.0)	11.0 (8.0, NE)
Aspartate aminotransferase increased	3 (2.3)	33.0	3 (100.0)	2 (66.7)	5.0 (3.0, NE)	0	0	
Transaminases increased	3 (2.3)	176.0	2 (66.7)	2 (100.0)	11.0 (7.0, NE)	1 (33.3)	1 (100.0)	14.0 (NE, NE)
Immune-mediated pancreatitis	6 (4.7)							
Lipase increased	4 (3.1)	108.5	0	0		4 (100.0)	4 (100.0)	42.5 (7.0, NE)
Amylase increased	3 (2.3)	130.0	1 (33.3)	1 (100.0)	14.0 (NE, NE)	2 (66.7)	1 (50.0)	NE (16.0, NE)
Immune-mediated skin adverse reactions	6 (4.7)							
Pruritus	4 (3.1)	19.0	0	0		4 (100.0)	3 (75.0)	82.0 (7.0, NE)
Immune-mediated renal	4 (3.1)							
Blood creatinine increased	4 (3.1)	53.5	1 (25.0)	1 (100.0)	1.0 (NE, NE)	3 (75.0)	2 (66.7)	13.5 (8.0, NE)

Abbreviations: AE=adverse event; CI=confidence interval; IMM=immune-modulatory medication; irAE=immune-related adverse event; NE=not evaluable.

Source: Table 14.3.1.25.a

Note: AEs are coded using MedDRA version 23.0. irAEs are identified as any Grade ≥2 AEs based on prespecified preferred terms.

** If a patient experienced the same event multiple times, the highest grade was taken. If a patient experienced the same event with the same grade more than once, the one that was treated with IMM was taken. If a patient experienced the same event with the same grade more than once and treated with the same IMM or no treatment, the longer duration to recovery will be taken.

Percentages are calculated using 'No. of patients with irAE' as denominator. IMM with or without Resolved columns % are calculated using n(%).

Vergote

The adverse events reported in Vergote et al were reported for a wider group of patients than the population of interest for scope for this submission.

Figure 35. Incidence of grade ¾ neutropenia in Vergote et al (6)

Neutropenia grade 3–4	n/N	Incidence (95% CI)	*P*-value*
Ovarium	10/35	29% (16–45%)	<0.0001
Endometrium	12/33	36% (22–53%)	<0.0001
Cervix	13/24	38% (24–55%)	<0.0001
Total	35/102	34% (26–44%)	<0.0001

* *P*-value for a comparison with historical data (84%) using a Binomial test; the occurrence of grade 3–4 neutropenia is lower than 84% in all cohorts.

Figure 36. Incidence of other toxicities by grade in Vergote et al (6)

Event	Grade 1		Grade 2		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
Anemia	4	3.9	43	42.2	36	35.3	4	3.9
Neutropenia	7	6.9	17	16.7	20	19.6	15	14.7
Febrile neutropenia	0	0.0	0	0.0	0	0.0	1	1.0
Thrombocytopenia	10	9.8	12	11.8	29	28.4	13	12.7
Peripheral neuropathy	22	21.5	14	13.7	3	2.9	0	0.0
Sepsis unconfirmed	–	–	–	–	–	–	8	7.8
Sepsis confirmed	–	–	–	–	–	–	5	4.9

Nomura

Figure 37. Adverse events observed by three cycles reported in Nomura et al. (20)

Toxic effects	DP ($n = 30$)				DC ($n = 30$)				TC ($n = 30$)			
	Grade			Grade 3–4 (%)	Grade			Grade 3–4 (%)	Grade			Grade 3–4 (%)
	2	3	4	(95% CI)	2	3	4	(95% CI)	2	3	4	(95% CI)
Hemoglobin	15		1	3.3 (0.1–17.2)	13	5	1	16.7 (5.6–34.7)	14	3	2	16.7 (5.6–34.7)
Leukocytes	7	15	7	73.3 (54.1–87.7)	3	21	5	86.7 (69.3–96.2)	8	13	2	50.0 (31.3–68.7)
Neutrophils (ANC)	4	9	16	83.3 (65.2–94.4)	2	8	19	90.0 (73.5–97.9)	3	11	12	76.6 (57.7–90.1)
Platelets	1	2		6.7 (0.8–22.1)	4	3		10.0 (2.1–26.5)	2	3		10.0 (2.1–26.5)
AST	1				2	1		3.3 (0.1–17.2)		1		3.3 (0.1–17.2)
ALT					3	1		3.3 (0.1–17.2)	3			
Allergic reaction	1		1	3.3 (0.1–17.2)	1	1		3.3 (0.1–17.2)				
Anorexia	10	5		16.7 (5.6–34.7)	7	3		10.0 (2.1–26.5)	6	3		10.0 (2.1–26.5)
Diarrhea	6	3	1	13.3 (3.8–30.7)	1	1		3.3 (0.1–17.2)	2			
Nausea	12	3		10.0 (2.1–26.5)	12	2		6.7 (0.8–22.1)	5	3		10.0 (2.1–26.5)
Motor neuropathy					1					2		6.7 (0.8–22.1)
Sensory neuropathy									3	1		3.3 (0.1–17.2)
Febrile neutropenia		2	1	10.0 (2.1–26.5)		2		6.7 (0.8–22.1)		1		3.3 (0.1–17.2)

DP, docetaxel plus cisplatin; DC, docetaxel plus carboplatin; TC, paclitaxel plus carboplatin; CI, confidence interval; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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9.5.2 Studies included in clinical question three

Julius

Figure 38. Adverse events by PLD starting dose in Julius et al (12)

	No. of patients by cycle 1 PLD dose (%)				
Toxicity	**30 mg/m²**	**35 mg/m²**	**40 mg/m²**	**50 mg/m²**	***P***
Disease progression	3 (42.9)	3 (30.0)	8 (19.0	1 (100.0)	0.555
Nausea	3 (42.9)	4 (40.0)	15 (35.7)	1 (100.0)	0.879
Vomiting	1 (14.3)	0 (0.0)	7 (16.7)	0 (0.0)	0.640
Mucositis	1 (14.3)	1 (10.0)	11 (26.2)	0 (0.0)	0.465
Neutropenia	0 (0.0)	0 (0.0)	7 (16.7)	1 (100.0)	0.013
Myocardial toxicity	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0.400
Muscle weakness	2 (28.6)	3 (30.0)	10 (23.8)	0 (0.0)	0.555
Muscle pain	1 (14.3)	0 (0.0)	5 (11.9)	1 (100.0)	0.174
Peripheral neuropathy	1 (14.3)	3 (30.0)	7 (16.7)	1 (100.0)	0.551
PPE	1 (14.3)	4 (40.0)	14 (33.3)	1 (100.0)	0.318

Abbreviation: PPE, palmar-plantar erythrodysesthesia. [redacted]ere similar across the doses observed with the exception of neutropenia which was more common at higher dose levels.

Makker

Figure 39. Toxicities from Doxorubicin Treatment in Makker et al (10)

Toxicity	**Grade**		**%**
	1	**2**	
Anorexia	2	0	6.3
Constipation	2	2	23.5
Diarrhea	2	0	11.7
Fatigue	5	3	47.1
HSN	0	0	0
Musculoskeletal	1	1	11.8
Nausea/Vomiting	3	4	41.2
Neutropenia	0	2	11.7
Peripheral Neuropathy	1	1	11.7
Pulmonary	0	0	0
Renal	0	0	0

HSN, hypersensitivity reaction

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Muggia

Figure 40. Adverse effects n=43 in Muggia et al (13)

Adverse Effect	Grade 1	2	3	4
Neutropenia	3	6	5	2
Thrombocytopenia	9	0	0	0
Anemia	6	11	4	1
Mucositis*	6	7	0	1
Anorexia	2	3	0	0
Nausea and/or vomiting	4	8	1	0
Other gastrointestinal†	6	3	3	0
Dermatologic	9	4	4	0
Neurotoxicity	4	0	2	0
Infusion reaction	1	1	0	0
Alopecia	2	4	0	0
Fever	2	2	1	0
Pulmonary	1	1	1	0
Cardiovascular‡	0	3	1	0

*Includes stomatitis, esophagitis, bronchitis, vaginitis, nasal soreness, and rectal bleeding.

†Includes two events beyond grade 1 for diarrhea and weight loss, and one each of constipation, dehydration, and indigestion.

‡Refers to three patients who had decreased left ventricular ejection fraction (see text).

McMeekin

Figure 41. Most frequent AEs (≥20% frequency) in McMeekin et al. (11)

AE, n (%)	Ixabepilone	Control		
	n = 248	n = 239		
		Doxorubicin	Paclitaxel	Total
		n = 171	n = 68	n = 239
Fatigue	125 (50)	88 (52)	21 (31)	109 (46)
Nausea	119 (48)	104 (61)	17 (25)	121 (51)
Alopecia	102 (41)	63 (37)	36 (53)	99 (41)
Decreased appetite	83 (34)	45 (26)	12 (18)	57 (24)
Constipation	79 (32)	51 (30)	7 (10)	58 (24)
Diarrhea	79 (32)	48 (28)	8 (12)	56 (23)
Peripheral sensory neuropathy	79 (32)	10 (6)	29 (43)	39 (16)
Vomiting	74 (30)	50 (29)	8 (12)	58 (24)
Anemia	66 (27)	48 (28)	16 (24)	64 (27)
Neutropenia	62 (25)	72 (42)	11 (16)	83 (35)
Arthralgia	46 (19)	9 (5)	23 (34)	32 (13)
Dyspnea	37 (15)	36 (21)	8 (12)	44 (18)
Myalgia	32 (13)	4 (2)	17 (25)	21 (9)

AE, adverse event.

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ZoptEC

Table 74. Treatment related adverse events (TRAEs) Grade ≥3

	Doxorubicin (N=249)
Abdominal pain	N = 1 (0.4%)
Fatigue	N = 4 (4.4%)
Anaemia	N = 36 (14.5%)
Neutropenia	N = 111 (44.6%)
Nausea	N = 8 (3.2%)
Vomiting	N = 7 (2.8%)
Leukopenia	N = 44 (17.7%)

Table 75. TEAEs leading to withdrawal with ANY frequency in either arm using the Safety Analysis Set in ZoptEC trial (28)

	Doxorubicin(N=249)
TEAE leading to withdrawal	**N=38**
Anaemia	N=1 (0.40%)
Ascites	N=1 (0.40%)
Atrial flutter	N=1 (0.40%)
Blood creatinine increased	N=1 (0.40%)
Blood lactate dehydrogenase increased	N=1 (0.40%)
Candidiasis	N=1 (0.40%)
Cardiotoxicity	N=2 (0.80%)
Cholecystitis acute	N=1 (0.40%)
Dermatitis	N=1 (0.40%)
Dizziness	N=1 (0.40%)
Drug intolerance	N=1 (0.40%)
Dyspnoea	N=2 (0.80%)
Ejection fraction decreased	N=12 (4.82%)
Electrocardiogram QT prolonged	N=1 (0.40%)
Fatigue	N=3 (1.20%)
Febrile neutropenia	N=1 (0.40%)
Haematemesis	N=1 (0.40%)

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	Doxorubicin(N=249)
TEAE leading to withdrawal	**N=38**
Hydronephrosis	N=1 (0.40%)
Leukaemia	N=1 (0.40%)
Lymphangitis	N=1 (0.40%)
Nausea	N=1 (0.40%)
Neutropenia	N=1 (0.40%)
Oedema	N=1 (0.40%)
Oedema peripheral	N=1 (0.40%)
Oral candidiasis	N=1 (0.40%)
Pain	N=1 (0.40%)
Pain in extremity	N=1 (0.40%)
Pleural effusion	N=2 (0.80%)
Postoperative wound infection	N=1 (0.40%)
Pulmonary embolism	N=2 (0.80%)
Rhabdomyolysis	N=1 (0.40%)
Sepsis	N=2 (0.80%)
Septic shock	N=1 (0.40%)
Stomatitis	N=2 (0.80%)
Tachyarrhythmia	N=1 (0.40%)
Thrombocytopenia	N=1 (0.40%)
Tumour necrosis	N=1 (0.40%)
Vomiting	N=1 (0.40%)

Table 76. CTCAE of grade 3or higher occurring with ANY frequency in either arm using the Safety Analysis Set in ZoptEC trial

	Doxorubicin(N=249)
CTCAE of grade 3or higher	**N=195**
Abdominal pain	N=4 (1.61%)
Abdominal pain lower	N=2 (0.80%)
Abdominal pain upper	N=1 (0.40%)
Activated partial thromboplastin time prolonged	N=1 (0.40%)

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	Doxorubicin(N=249)
CTCAE of grade 3or higher	**N=195**
Alopecia	N=2 (0.80%)
Anaemia	N=38 (15.26%)
Anxiety	N=1 (0.40%)
Arthralgia	N=1 (0.40%)
Ascites	N=2 (0.80%)
Aspartate aminotransferase increased	N=1 (0.40%)
Asthenia	N=6 (2.41%)
Atrial fibrillation	N=1 (0.40%)
Atrial flutter	N=1 (0.40%)
Back pain	N=4 (1.61%)
Balance disorder	N=1 (0.40%)
Blood calcium decreased	N=1 (0.40%)
Blood creatinine increased	N=2 (0.80%)
Blood lactate dehydrogenase increased	N=1 (0.40%)
Blood magnesium decreased	N=1 (0.40%)
Blood uric acid increased	N=1 (0.40%)
Cardiac arrest	N=1 (0.40%)
Cardio-respiratory arrest	N=1 (0.40%)
Catheter site pain	N=1 (0.40%)
Cholecystitis acute	N=1 (0.40%)
Condition aggravated	N=1 (0.40%)
Decreased appetite	N=1 (0.40%)
Deep vein thrombosis	N=1 (0.40%)
Dehydration	N=3 (1.20%)
Diarrhoea	N=4 (1.61%)
Dizziness	N=3 (1.20%)
Dysgeusia	N=1 (0.40%)
Dyspnoea	N=4 (1.61%)
Eastern Cooperative Oncology Group performance	N=1 (0.40%)
Ejection fraction	N=1 (0.40%)
Ejection fraction decreased	N=5 (2.01%)

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Embolism	N=3 (1.20%)
Enterocutaneous fistula	N=1 (0.40%)
Fatigue	N=14 (5.62%)
Febrile neutropenia	N=9 (3.61%)
Female genital tract fistula	N=2 (0.80%)
Gamma-glutamyltransferase increased	N=5 (2.01%)
General physical health deterioration	N=1 (0.40%)
Haematemesis	N=1 (0.40%)
Headache	N=2 (0.80%)
Herpes zoster	N=1 (0.40%)
Hip fracture	N=1 (0.40%)
Hydronephrosis	N=3 (1.20%)
Hyperglycaemia	N=1 (0.40%)
Hyperkalaemia	N=1 (0.40%)
Hypertensive crisis	N=1 (0.40%)
Hypoalbuminaemia	N=1 (0.40%)
Hypocalcaemia	N=3 (1.20%)
Hypokalaemia	N=10 (4.02%)
Hypomagnesaemia	N=1 (0.40%)
Hyponatraemia	N=4 (1.61%)
Hypophosphataemia	N=3 (1.20%)
Hypotension	N=1 (0.40%)
Ileal stenosis	N=1 (0.40%)
Ileus	N=1 (0.40%)
Ileus paralytic	N=1 (0.40%)
Infection	N=1 (0.40%)
Intestinal obstruction	N=1 (0.40%)
Intracardiac thrombus	N=1 (0.40%)
Joint swelling	N=1 (0.40%)
Left ventricular dysfunction	N=2 (0.80%)
Lethargy	N=2 (0.80%)
Leukaemia	N=1 (0.40%)
Leukocytosis	N=1 (0.40%)

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9.6 MAIC

1) Baseline characteristics

A targeted literature review was conducted in May 2020 to identify a range of prognostic variables typically associated with survival in endometrial cancer. These were subsequently validated with a panel of oncologists in Germany, UK, and Canada through advisory boards and/ or telephone interviews.

Of note, clinicians could not identify any treatment effect modifiers based on the comparators of interest - no oncologist provided clinical reasoning to expect any and there is a paucity of data to identify them (they cannot be identified from single arm studies). Clinicians thought that if any existed, they would be a subset of prognostic variables. It is not necessary to identify such treatment effect modifiers if this latter condition holds to make a comparison between two studies because the unanchored MAIC algorithm would apply the same technique in both instances. However, if treatment effect modifiers exist, the results from this comparison only apply to the population of the study being matched to. This is discussed further in the limitations section.

Of note, clinicians could not identify any treatment effect modifiers based on the comparators of interest - no oncologist provided clinical reasoning to expect any and there is a paucity of data to identify them (they cannot be identified from single arm studies). Clinicians thought that if any existed, they would be a subset of prognostic variables. It is not necessary to identify such treatment effect modifiers if this latter condition holds to make a comparison between two studies because the unanchored MAIC algorithm would apply the same technique in both instances. However, if treatment effect modifiers exist, the results from this comparison only apply to the population of the study being matched to. This is discussed further in the limitations section.

The prespecified longer list after consultation being:

- Age
- Race
- Number of prior anticancer treatments
- Histology (Endometrioid vs. non-endometrioid)
- MMR (mismatch repair) / MSI (microsatellite instability) molecular profile type
- Whether undergone prior surgery for study indication
- ECOG score before comparator treatment start date
- Most recent FIGO Stage score before comparator treatment start date
- Grade of disease at diagnosis

The prespecified shorter list holding:

- Number of prior anticancer treatments
- Histology (Endometrioid vs. non-endometrioid)
- ECOG score before comparator treatment start date

Shown in Table 77 are the breakdown of the available prognostic information by each study to be data analysed. This table shows that no study other than GARNET provided data on:

- Number of prior anticancer treatments
- Whether undergone prior surgery for study indication
- MMR (mismatch repair) / MSI (microsatellite instability) molecular profile type

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Table 77: Available prognostic information by each study

Pathological Factor and grouping	Author (Year)			
	GARNET, 2020 [11]	Mazgani, 2008 [16]	McMeekin, 2015 [17]	Julius, 2013 [18]
Race	Yes	NR	Yes	Yes
Increased age	Yes	NR	NR. Median only	NR. Median and Mean only
ECOG status	No. No patients had an ECOG of 2	NR	Yes[a]	NR
Histology by Endometrioid *vs*. nonendometrioid	Yes	Yes	Yes	NR
Most recent FIGO stage	Yes	NR	NR	NR
BMI	Yes	NR	NR	Yes
Grade of disease at diagnosis	Yes	NR	NR	NR
Number of prior anticancer regimens	Yes	NR	NR	NR
Proportion of trial patients received prior surgery for study indication	Yes	NR	NR	NR
Other Important Prognostic Factors:[b] MMR/ MSI (Molecular profiles)	Yes	NR	NR	NR

2) Weights

GARNET vs McMeekin

Prognostic balance

Table 78: GARNET prognostic balance table pre and post MAIC adjustment for OS compared to McMeekin2015

	Dostarlimab Unweighted	Paclitaxel or Doxorubicin	Dostarlimab Weighted
Age	63.11	64.00	64.00
ECOG = 1 not 0	0.557	0.332	0.332
Endometrioid Type 1	0.656	0.556	0.556
Race = White	0.754	0.859	0.859
All values represent proportions except Age (mean)			

Effective Sample size and weights distribution

Signorovitch *et al.* suggest that the effective sample size (ESS) of the pseudo-population formed by weighting the population is approximated by individual level population;

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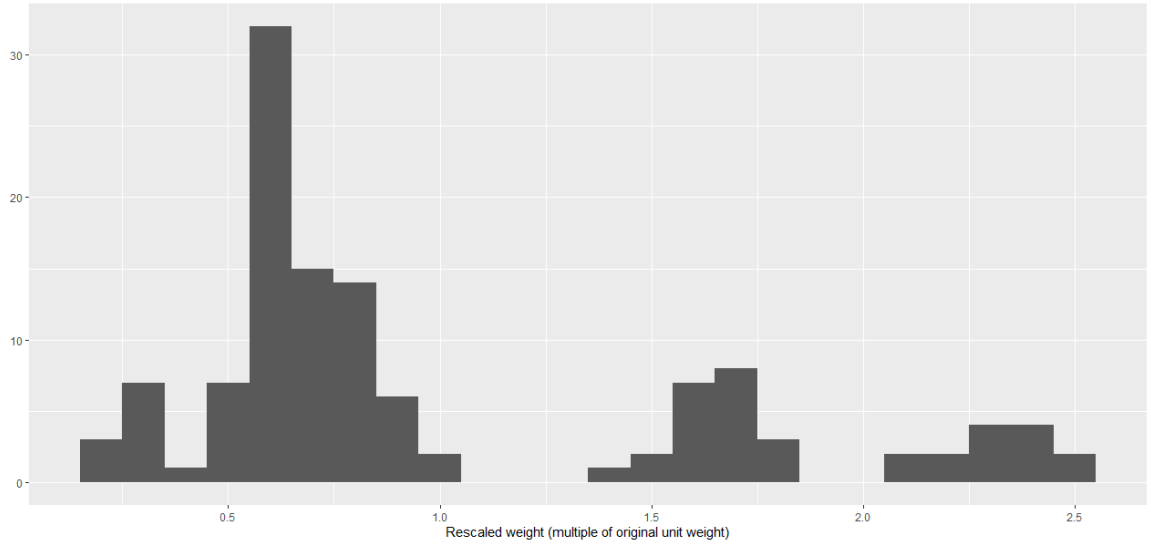
$$ESS=\frac{\left(\sum_{i=1}^{n} WT_i\right)^2}{\sum_{i=1}^{n}\left(WT_i^2\right)}$$

Figure 43: GARNET vs McMeekin Effective Sample Size



GARNET vs Mazgani

Table 79. GARNET prognostic balance table pre and post MAIC adjustment for OS compared to Mazgani 2008:

	Dostarlimab Unweighted	Paclitaxel/Carboplatin	Dostarlimab Weighted
Endometrioid Type 1	0.9444	0.6129	0.6129

Effective Sample size and weights distribution

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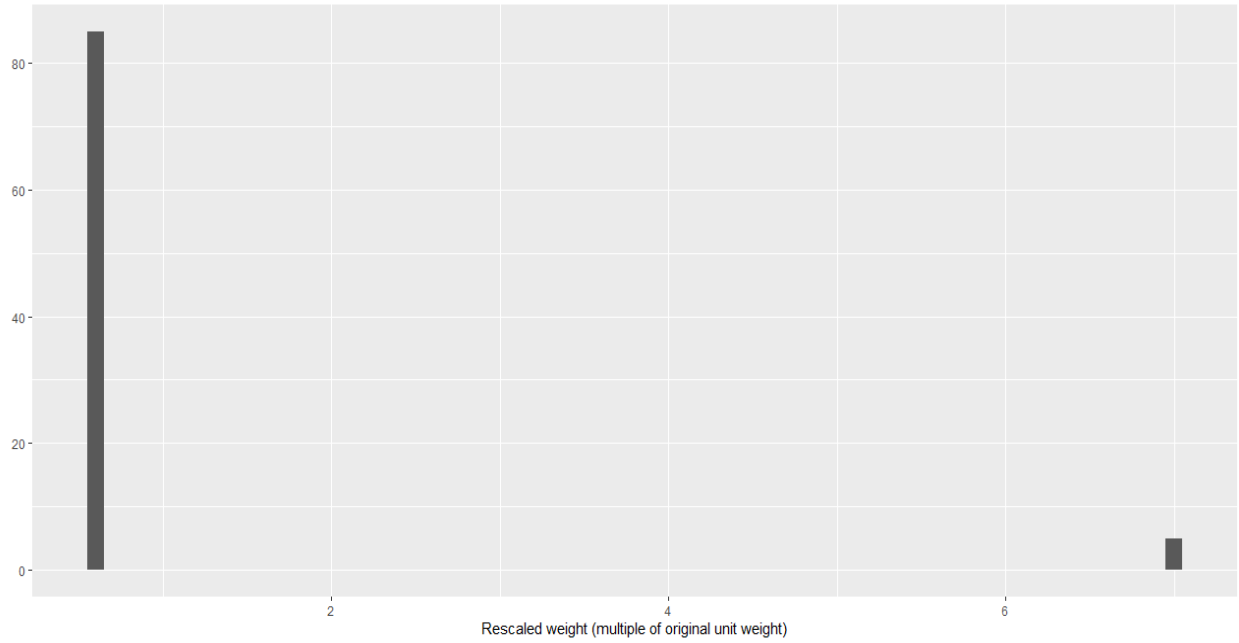
Figure 44: GARNET vs. Mazgani Effective Sample Size



GARNET vs Julius Prognostic value

Table 80: GARNET prognostic balance table pre and post MAIC adjustment for OS compared to Julius2013: PLD 40 mg/m^2

	Dostarlimab Un-weighted	PLD 40 mg/m^2	Dostarlimab Weighted
Age	63.095	66.800	66.800
Race=White	0.754	0.733	0.733
Number of Prior chemo-therapy	1.516	2	2
Race represents proportions.			

Effect sample size and weights distribution

Signorovitch *et al.* suggest that the effective sample size (ESS) of the pseudo-population formed by weighting the population is approximated by individual level population;

$$\text{ESS}=\frac{\left(\sum_{i=1}^{n} WT_i\right)^2}{\sum_{i=1}^{n}\left(WT_i^2\right)}$$

This approximate ESS is only accurate if the weights are fixed and known, or if they are uncorrelated with out-come – neither of which is true here; as such, this approximation is likely to be an underestimate of the true ESS (NICE DSU Technical Support Document 18: section 2.2.1).

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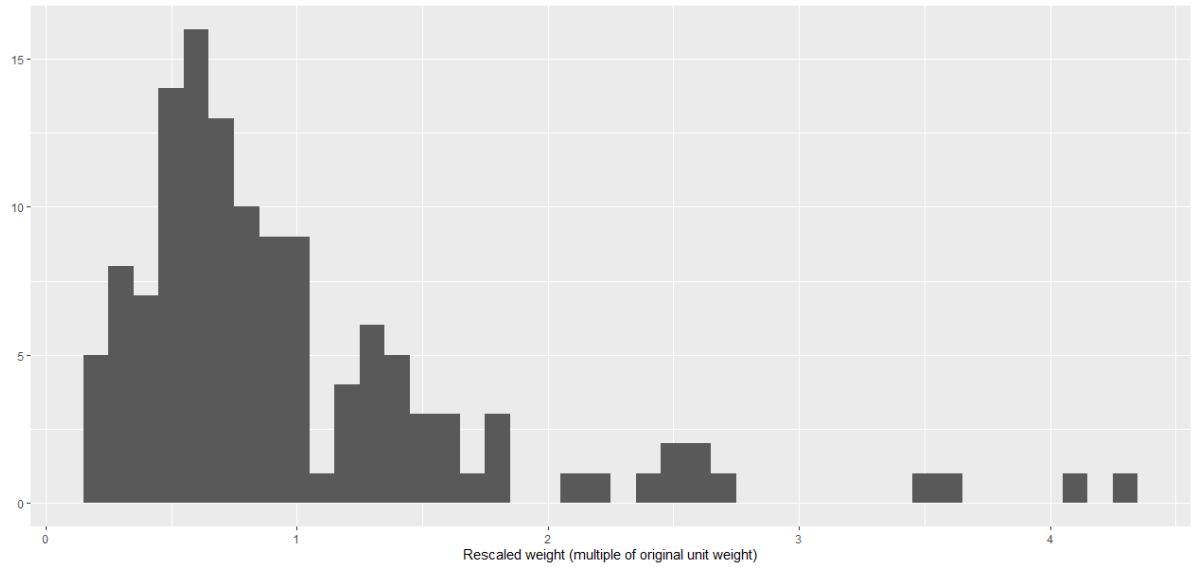
Figure 45: GARNET vs. Julius Effective Sample Size



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Cost and budget impact analysis of Jemperli (dostarlimab) for treatment of dMMR/MSI-high endometrial cancer

Technical document
Application to the Danish Medicine Council

Contact person:

Nikoline Vestergaard Dich

Corporate Affairs and Market Access Manager

Tel. direct: +45 24699127

Mail: nikoline.x.vestergaarddich@gsk.com

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Executive summary

Background

This report provides a technical summary of a cost-effectiveness model developed to demonstrate the cost-effectiveness of dostarlimab, an anti-Programmed cell death ligand-1 (PD-L1) therapy developed by GlaxoSmithKline (GSK), relative to existing comparator therapies in patients with advanced or recurrent microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) endometrial cancer who have progressed on or after treatment with platinum-based chemotherapy and are PD-L1 naive. The model adopts a Danish reference case.

Model overview

The main data source for dostarlimab is cohort A1 of the phase I/II open-label, single-arm GARNET study, comprising adult patients with dMMR or MSI-H endometrial cancer. Comparisons are made against several existing mono- and combination therapies, as defined in the DMC protocol: carboplatin + paclitaxel, doxorubicin, pegylated liposomal doxorubicin (PLD), doxorubicin *or* PLD (weighted basket). In the absence of head-to-head data, comparator effectiveness is modelled using hazard ratios derived from a series of matching-adjusted indirect comparisons (MAICs) and/or independent parameterisations of comparator endpoints (standard of care arm only). The model adopts a societal perspective and applies a cycle length of 21 days in keeping with the dosing schedule for dostarlimab and key chemotherapy comparators.

Model assumptions

Based on statistical and visual fit, clinical input and GSK guidance, a generalised gamma distribution was applied to GARNET overall survival and progression-free survival data in the model base case, with additional scenarios to explore sensitivity to alternative distributional assumptions. Time on treatment for dostarlimab was parameterised independently of disease progression, and no stopping rule was applied. Chemotherapy comparators are assumed to be received for a maximum of 8 model cycles (24 weeks).

Results

Pairwise estimates suggested dostarlimab to be both more costly and more effective than standard chemotherapy comparators, with incremental cost estimates ranging from DKK 700,758 (*versus* PLD) to DKK 764,563(*versus* placebo). Scenario analyses suggest the choice of parametric distribution applied to progression and survival endpoints, stopping rule assumptions, and uncertainties around hazard ratios to be key drivers of relative cost-effectiveness.

	Total costs	Total life years	Incremental costs	Incremental life years
Dostarlimab	DKK 788,322	4.6	-	-
Carboplatin + paclitaxel	DKK 84,537	2.2	DKK 703,785	2.3
Placebo	DKK 23,759	0.9	DKK 764,563	3.6
Pegylated liposomal doxorubicin (PLD)	DKK 87,564	0.9	DKK 700,758	3.6

Results Budget Impact

The estimated budget impact of recommending dostarlimab as a possible standard treatment for the population defined in clinical question 1 was DKK 3.0 mil. in year 5. The estimated budget impact of recommending dostarlimab as a possible standard treatment for the population defined in clinical question 2 was DKK 0 mil. in year 5. The estimated budget impact of recommending dostarlimab as a possible standard treatment for the population defined in clinical question 3 was DKK 8.7 mil. in year 5.

1. Background

Uterine cancer is the fifth most common cancer among women in Denmark, and the most frequent form of gynaecological cancer (1). Around 800 women are diagnosed with uterine cancer each year, with the most common form (> 90%) is cancer of the lining of the uterus (endometrial cancer) (1, 2). The disease typically affects older women (median age 63 years) (3) and almost 11,000 patients live with the disease in Denmark (2).

Patients with endometrial cancer (EC) are at risk of recurrence; patients with advanced or recurrent endometrial cancer represent a small, well-defined subset of the total population. Advanced or recurrent disease is life-threatening and incurable, with a 5-year survival rate of ~20% (4); for those who relapse on or after first-line platinum-based therapy, median life expectancy is less than 1 year (4) (1). In Denmark, there are approximately 100 patients per year with newly diagnosed advanced EC (1) and approximately 30 patients with recurrent EC (1). About half of these patients experience progression after first-line treatment and still be in a general condition to receive second-line treatment.

There are currently no treatments approved by the EMA specifically for patients with advanced or recurrent EC who progress on or after a platinum-based regimen. There is an urgent need for a new treatment in post-platinum advanced/recurrent EC, since current treatments are associated with poor median survival (<12 months), progression-free survival (PFS) (<6 months) (4), and reduced quality of life (QoL) (5).

Dostarlimab is an anti-programmed death receptor-1 (PD-1) monoclonal antibody that binds with high affinity to the PD-1 receptor and effectively blocks interaction with PD-1 ligands (programmed death ligand-1 [PD-L1] and ligand-2 [PD-L2]), restoring cytotoxic T-cell activity and freeing the T-cell to kill the tumour cell (6). The expected european marketing authorisation indication for dostarlimab is monotherapy treatment for adult patients with advanced (stage ≥IIIB) or recurrent EC who have progressed on or after a platinum-based regimen and whose tumours are dMMR/MSI-H positive.

The GARNET study (6) of dostarlimab was at the time, the largest prospective evaluation of an anti-PD-1/L1 agent as monotherapy in patients with advanced or recurrent EC who had progressed on or after prior platinum-based therapy.

Dostarlimab demonstrated a durable response in the dMMR/MSI-H cohort (Part 2B, Cohort A1), with an objective response rate (ORR) of 43.5% (median duration of response [DOR] was not reached). Dostarlimab was generally well tolerated with a manageable adverse events profile; the most common treatment-emergent adverse events (TEAEs) observed in GARNET were diarrhoea, asthenia, fatigue and nausea, and the occurrence of serious TEAEs (≥Grade 3) was low (13.2%) (ITT population; data cutoff: 1 March 2020) with a low discontinuation rate (5%). No deaths were associated with dostarlimab. Treatment with dostarlimab preserves patient-reported health-related quality of life compared to baseline.

A key limitation of the evidence base was that no randomised clinical trial evidence was available for dostarlimab with which to compare efficacy and safety to relevant comparators, with the single-arm GARNET trial representing the primary source of evidence for dostarlimab in patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) EC. No clinical trial or observational evidence was available that allowed for the formal indirect comparisons, hence

naïve narrative comparisons were applied. To reduce the bias of the naïve comparisons of dostarlimab versus the carbotaxel and pegylated liposomal doxorubicin, MAIC analyses were carried out.

Dostarlimab was the first anti-PD-1 immunotherapy option to be available in Denmark and would fulfil an unmet need for a highly effective, targeted treatment for patients with recurrent or advanced dMMR/MSI-H EC following a platinum-based regimen.

1.1 Objectives

The economic model was developed to estimate the incremental costs per patient as well as the budget impact of dostarlimab as treatment for patients with advanced or recurrent dMMR/ MSI-H EC who have progressed on or after treatment with platinum-based chemotherapy and are PD-L1 naive as defined by the clinical questions in the protocol (7). The model will utilize a restricted societal perspective, thereby including patient costs and transportation costs as defined by the method guidelines of the DMC(8).

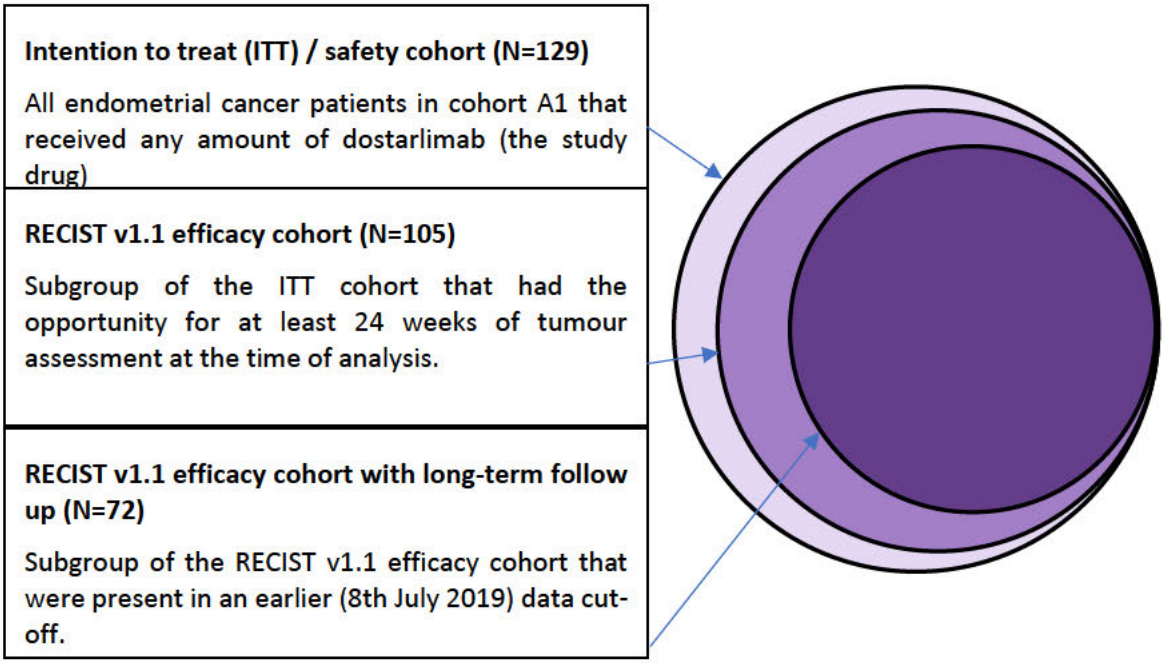
2. Model Overview

2.1 Population

The economic model population is adult patients with advanced or recurrent EC that have been previously treated with platinum-based chemotherapy and are PD-(L)1 naïve. The main data source for the economic model is cohort A1 of the GARNET study (March 2020 data cut-off). Cohort A1 includes patients with EC that have tumours with dMMR (confirmed by immunohistochemistry (IHC) testing) or MSI-H (polymerase chain reaction (PCR), or next-generation sequencing (NGS)) and have progressed on or after platinum doublet therapy. Patients in the cohort have received no more than two lines of anti-cancer therapy for recurrent or advanced (Stage ≥IIIB) disease.

Within cohort A1 of the GARNET study, three population groups of interest were identified (Figure 1).

Figure 1 Overview of GARNET cohort A1 subgroup definitions



Analyses of key endpoints (overall survival, progression-free survival and time on treatment) were conducted separately for each of the three cohort groups, with functionality in the model to select which cohort is used as the basis of estimates for each endpoint.

Results described in the body of this technical report correspond to the efficacy cohort (N=105), with corresponding estimates for efficacy subgroups reported in the appendices. Broadly, the three cohort groups were found to be comparable in terms of baseline patient characteristics (Table 1) and survival functions as represented by Kaplan-Meier (KM) curves (Figure 1).

Table 1: GARNET patient baseline characteristics

N	**129**	**105**	**72**
Age mean, SD (years)	63.1 (8.72)	63.3 (8.88)	63.1 (8.74)
Age median (years)	64	64	64
Height mean, SD (cm)	159.8 (6.93)*	159.81 (6.60)**	159.80 (7.04)***
Height median (cm)	160*	160**	160***
Weight mean, SD (kilo)	75.8 (21.7)	74.1 (21.0)	76.4 (21.8)
Weight median (kilo)	72.4	71.0	71.7
BMI (mean) (kg/m^2)	29.7 (8.08)*	29.0 (7.77)**	29.9 (7.96)***
BMI (median) (kg/m^2)	29.0	28.0	28.8
ECOG performance status status (n, %)			
0	55 (42.6%)	42 (40.0%)	25 (34.7%)
1	74 (57.4%)	63 (60.0%)	47 (65.3%)
Histology at diagnosis			
Adenocarcinoma	1 (0.8%)	1 (1%)	0 (0%)
Adenosquamous	1 (0.8%)	0 (0%)	0 (0%)
Clear Cell Carcinoma	1 (0.8%)	1 (1%)	0 (0%)
Endometrial Adenocarcinoma	1 (0.8%)	1 (1%)	1 (1.4%)
Endometrial Carcinoma Type II	17 (13.2%)	14 (13.3%)	9 (12.5%)
Endometrioid Adenocarcinoma	2 (1.6%)	2 (1.9%)	1 (1.4%)
Endometrioid Carcinoma Type I	85 (65.9%)	71 (67.6%)	50 (69.4%)
Mixed Carcinoma	7 (5.4%)	4 (3.8%)	2 (2.8%)
Moderately Differentiated Endometrial	1 (0.8%)	0 (0%)	0 (0%)
Serous Carcinoma	5 (3.9%)	4 (3.8%)	4 (5.6%)
Squamous Carcinoma	1 (0.8%)	1 (1%)	1 (1.4%)
Undifferentiated Clear Cell Carcinoma	1 (0.8%)	1 (1%)	1 (1.4%)
Undifferentiated Carcinoma	5 (3.9%)	4 (3.8%)	2 (2.8%)
Unknown	1 (0.8%)	1 (1%)	1 (1.4%)

MSI/MMR status			
MSI-H/dMMR	126	103	70
MSI-H/MMR unknown	3	2	2

**N=126; **N=102; ***N=70*
Abbreviations: NR, not reported
Source: Data on file – GARNET CSR

2.2 Intervention

The intervention is dostarlimab 500 mg administered via IV infusion every 3 weeks (Q3W) (Day 1 of each 21-day cycle) for the first 4 cycles. This is followed by dostarlimab 1,000 mg administered via IV infusion every 6 weeks (Q6W) (Day 1 of each 42-day cycle) for all subsequent cycles till treatment discontinuation.

2.3 Comparators

The model included the following three comparator therapies, as outlined in the DMC protocol(7):

Carboplatin + paclitaxel

Placebo

Pegylated liposomal doxorubicin (PLD)

2.4 Outcomes

The model generates the following outcomes:

- Total and disaggregated costs per patient
- Survival
    - Total life-years (LYs) per patient
- Incremental results (pairwise and fully incremental)
    - Incremental costs
    - Incremental life years

2.5 Discounting

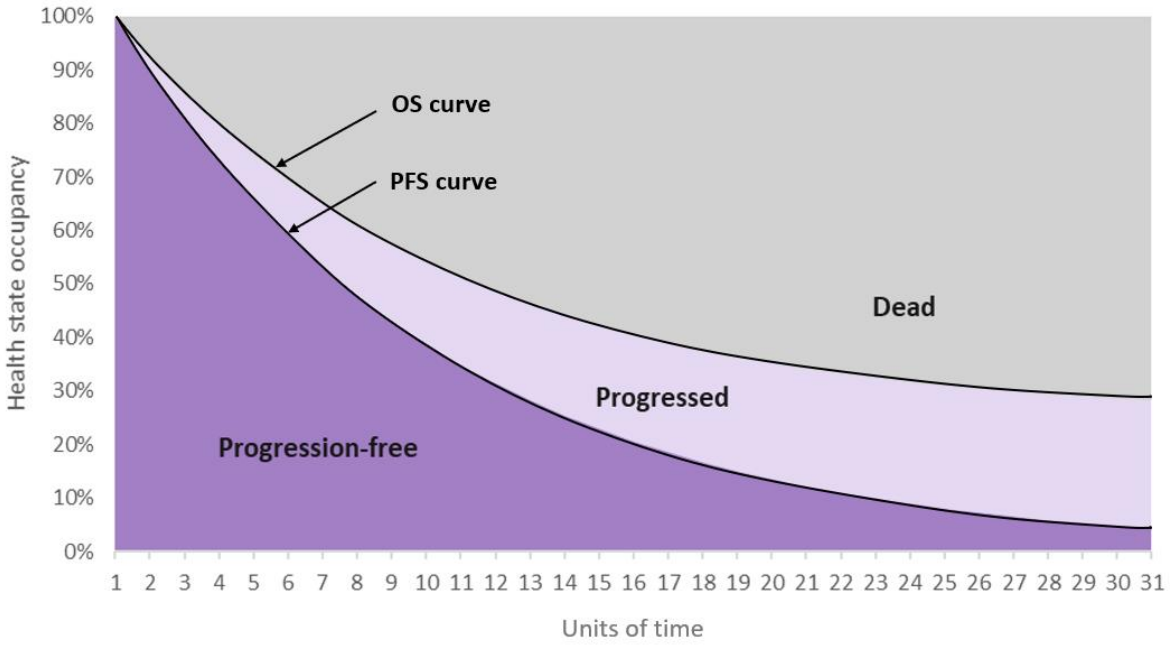
In the base-case, the annual discount rate for future costs was 3.5% for model year ≤35 and 2.5% for model year 35 to 70 in alignment with DMC's guidelines(8, 9). Discounting in the model is performed after the first year on a yearly basis.

3. Model Structure

3.1 Model framework

The economic model has been developed in Microsoft Excel and using a three-state PartSM structure, with health states (progression-free, progressive disease, dead) defined according to progression and survival estimates as illustrated in Figure 2.

Figure 2: Illustration of the partitioned survival model structure used in the model



All patients enter the model in the progression-free survival (PFS) health state, indicating no disease progression since first exposure to post-platinum therapy at model baseline. At subsequent time points, the proportion of patients remaining progression-free is defined according to the PFS curve, and the proportion of patients with progressive disease are defined as overall survival (OS) *minus* PFS. For some patients, treatment may discontinue prior to progression (due for instance to adverse events) or may continue beyond progression (where an ongoing treatment benefit is expected). To incorporate this assumption, a time on treatment endpoint is parameterised independently of disease progression.

Using a standard PartSM structure (Figure 2), parametric survival curves are fitted to study endpoints - typically including OS and PFS – to approximate survival rates based on observed data and provide extrapolations over later time periods. Relative numbers of patients in different health states (progression-free, progressed or dead, where OS and PFS are considered) are estimated according to the relative positioning of these curves.(10) The validity of alternative parameterisations are assessed based on statistical and visual fit to observed data and the clinical validity of extrapolations. Estimates of relative effectiveness for comparator therapies may be applied as hazard ratios (relative hazard of an event occurring at a given time point), as time ratios (relative time to an event occurring) or independent time-to-event parameterisations.

Survival estimates for the dostarlimab arm are calculated in the *R* software package using GARNET study individual patient data (IPD) as described in section 4. Estimates of progression and survival rates for individual mono/combination comparator chemotherapies are estimated using hazard ratios

relative to the dostarlimab arm. For the standard of care arm, for which pseudo-IPD was available, functionality is also provided to base comparator progression and survival estimates independently of GARNET estimates on a naïve (unadjusted) basis.

The PartSM structure was identified as an appropriate approach for several reasons. Firstly, the approach is commonly used and widely accepted by HTA bodies as an appropriate method in oncology indications.

Secondly, the approach is aligned with (and easily validated against) secondary endpoints of the GARNET study, avoiding data needs required by transition-based approaches. While an advantage to the Markov structure is that a structural link between progression and mortality events is modelled directly, the derivation of transition probabilities requires substantially more data. IPD is typically required for both the study treatment and for comparators to estimate differences between arms in the probabilities of transition between health states.

Thirdly, the PartSM structure provides flexibility in scenario testing to account for uncertainty around the relative clinical plausibility of alternative approaches to parameterising and extrapolating disease progression and survival estimates, as outlined in the DMC guidelines(11). A range of parametric and flexible (spline) models fitted to non-parametric Kaplan-Meier (KM) trial data can be explored to evaluate cost-effectiveness results according to divergent assumptions around progression and survival rates beyond the time horizon captured directly by trial data. This may be of importance in circumstances where OS data are immature, and reference to database studies identified in the SLR or expert clinical input is required to inform and/ or validate survival extrapolations.

3.2 Perspective

The perspective of the economic model is a restricted societal perspective, which includes costs related to drug acquisition, drug administration, monitoring, adverse events, routine care, patient time, and transportation. Indirect costs are not included following the DMC's guidelines(8).

3.3 Cycle length

The model adopts a cycle length of 21 days, reflecting the dosing schedule of dostarlimab and key comparators. Treatment acquisition, administration and monitoring costs for items delivered at asynchronous time points are applied as 21-day averages.

By default, a half-cycle correction is applied to the model in order to account for mid-cycle transitions. Optionally, half-cycle correction may be disabled to estimate cost results based on start-of-cycle rather than mid-cycle populations.

3.4 Time horizon

The time horizon for estimating costs should be sufficiently long to reflect any differences in costs between the technologies that are being compared. Given the nature of the condition and the importance of overall survival as a key endpoint, a life-time time horizon is considered appropriate. This is approximated using a time horizon of 40 years in the base case (to age 103 based on GARNET baseline characteristics), by which point mortality events have occurred in >99% of the patient population under base case assumptions. Functionality is included to estimate cost-effectiveness over shorter time horizons (20 or 30 years) as scenarios.

4. GARNET Time to event analysis

Dostarlimab is applied as the reference therapy in the model. On this basis, key endpoints (overall survival, progression-free survival and time on treatment) for dostarlimab patients are estimated using patient-level GARNET data. The relative efficacy of (mono- or combination) comparator therapies are applied using hazard ratios derived from off-model naïve comparisons, matching-adjusted indirect comparisons or meta-analyses. For the standard of care arm – comprising a basket of current therapy options – estimates may be applied as hazard ratios relative to the GARNET arm, as for other comparators, or on the basis of independently-parameterised KM data (described in more detail in section 4.4).

4.1 Time-to-event endpoints

Time-to-event analyses of GARNET patient-level data were conducted independently for four distinct endpoints:

Overall survival (OS), defined as the time from the date of the first dose of study medication to the date of death from any cause.(12) Cases are considered censored if alive at data cut-off.

Progression-free survival (PFS), defined as the time from the first dose of study medication to the first documented disease progression based on blinded independent central review (BICR) assessment using RECIST v1.1 (or to death, if earlier).(12) Cases are considered censored if alive and progression-free at data cut-off.

Time on treatment (ToT), defined as the time between first and last exposure to treatment. Cases are considered censored if alive and on treatment at data cut-off.

OS and PFS analyses were based on patient-level event times and corresponding censoring flags reported in the GARNET time-to-event (*ADTTE)* dataset. The ToT endpoint was defined using values reported in the subject-level (*ADSL*) study dataset, such that:

$$ToT\ (days)\ =\ (TRTEDT - TRTSDT) + 1$$

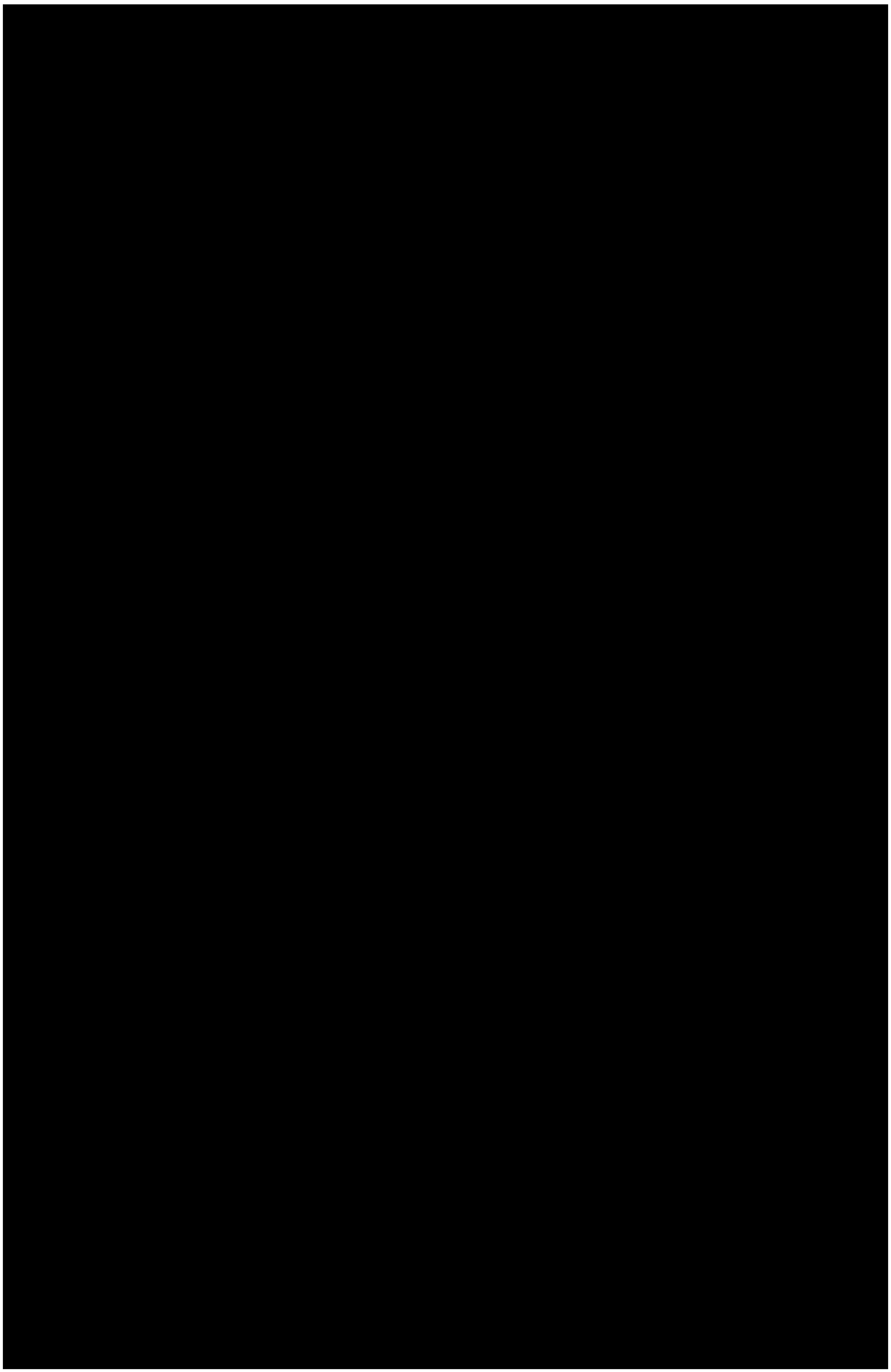
Where *TRTSDT was* the date of first exposure to treatment and *TRTEDT* was the date of last exposure to treatment. Censoring flags for ToT estimates were derived based on end-of-treatment status (*EOTSTT)* such that patients with an 'ongoing' treatment status at data cut-off were considered censored and those coded as 'discontinued' (due either to death or cessation of treatment) were considered uncensored.

Pairwise comparisons of patient progression and end-of-treatment dates showed close alignment between ToT and PFS (Figure 3). Notably, however, several outliers were identified suggesting that some patients remained on treatment several months following, or discontinued treatment prior to, disease progression.

It should be noted that the derivation of estimated ToT differs from the duration of treatment estimates summarised in GARNET Table 14.1.14a, which applies to the above definition plus 21 days ("*if the last cycle of treatment is <= 4 cycles and death has not occurred during that period) or the above plus 42 days (if the last cycle of treatment is >= 5 cycles and death has not occurred during that period*").

This distinction has been made since, from the perspective of the economic model, ToT is used solely to determine the proportion of patients incurring treatment costs at a given time period.

Kaplan-Meier curves for OS, PFS and ToT in the GARNET ITT cohort (N=105) are illustrated in Figure 4 below, with corresponding cumulative hazard curves shown in Figure 5.



4.2 Parameterisation of endpoints

Parametric survival models were fitted to the GARNET time-to-event data using the *Flexsurv* package in *R* version 4.0.0, using a standard range of parametric distributions (generalised gamma, Weibull, gamma, exponential, log-logistic, lognormal and Gompertz distributions) as recommended by the NICE Decision Support Unit(13) and summarised in Table 2.

Table 2: Overview of standard parametric functions

Parametric distribution	Survival function	Notation	Main hazard characteristics	Model type
Exponential	$S(t) = \exp(-\lambda t)$	λ rate t time	Constant hazard 1 parameter	PH
Weibull	$S(t) = \exp\left(-\left(\frac{t}{\lambda}\right)^{p}\right)$	λ scale parameter p shape parameter	Either increase or decrease monotonically 2 parameters	AFT
Gompertz	$S(t) = \exp\left(\left(\frac{\lambda}{p}\right)(1-e^{pt})\right)$	λ scale parameter p shape parameter	Either increase or decrease monotonically 2 parameters	PH
Lognormal	$S(t) = 1 - \Phi\left(\frac{\ln(t) - \mu}{\sigma}\right)$	Φ standard normal function μ meanlog σ sdlog	Hazard increases initially to a maximum, before decreasing as t increases 2 parameters	AFT
Log-logistic	$S(t) = \frac{1}{1+\left(\frac{t}{\lambda}\right)^{p}}$	λ scale parameter p shape parameter	Can be non-monotonic with respect to time. 2 parameters	AFT
Gamma	$S(t) = 1 - \frac{\gamma(k,\lambda t)}{\Gamma(k)}$ $\gamma(k,x) = \int_0^x \lambda^{k-1}e^{-x}dx$	λ rate parameter k shape parameter $\gamma(k,x)$ lower incomplete gamma function	Either increase or decrease monotonically 2 parameters	AFT
Generalized gamma	$S(t) = 1 - \frac{\gamma(k,(t/\lambda)^{\alpha})}{\Gamma(k)}$ $\gamma(k,x) = \int_0^x \lambda^{k-1}e^{-x}dx$	α shape λ scale parameter k shape parameter $\gamma(k,x)$ lower incomplete gamma function	Includes Weibull, gamma and log-normal as cases 3 parameters When $\alpha = 1$, the distribution collapses to a gamma When k = 1, the distribution collapses to a Weibull When k = 1 & $\alpha = 1$, the distribution collapses to an exponential	AFT

As outlined in NICE Technical Support Document (TSD) 21, standard parametric distributions may not be suitable for approximating more complex hazard function shapes.(14) This may be of particular importance in immunotherapies, such as dostarlimab, where delayed responses to treatment and the potential existence of long-term survivors are greater than for standard chemotherapies.(14) To

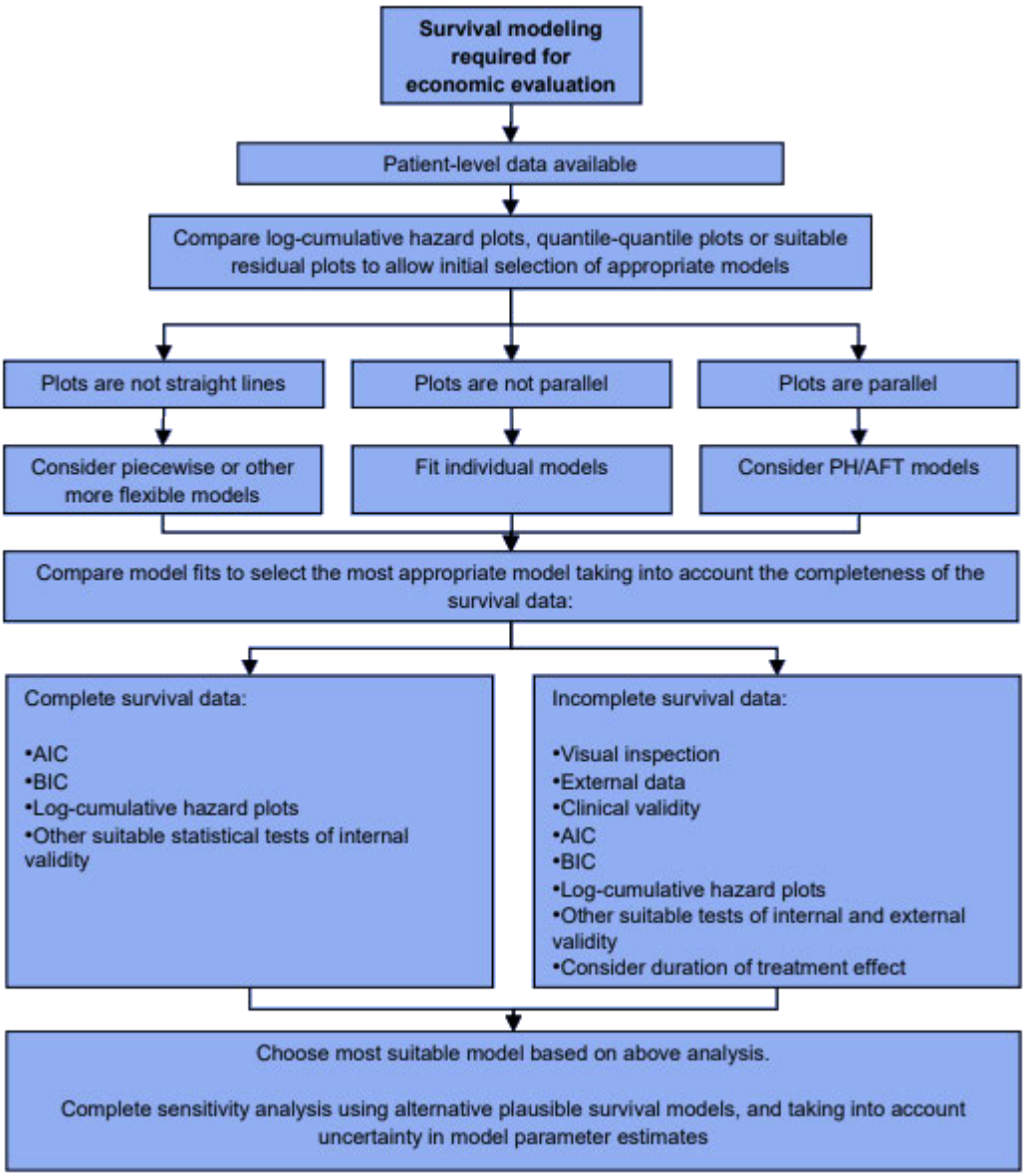
explore the potential benefits of a more flexible approach, a series of Royston and Parmar spline models(15) were specified using R's *flexsurvspline* function. Spline-based models fit polynomial functions between boundary and interior 'knots' placed at specific time points. Functionality is provided in the model to apply 1- and 2-knot splines for all endpoints, with exploratory analyses assessing additional specifications discussed below.

4.3 Assessment of parametric fit

Optimal model choice was assessed based on several considerations, as recommended by NICE TSD 14(13):

- Statistical goodness of fit based on relative Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. AIC and BIC provide a comparative measure of how well a model fits the observed data, while penalising for the number of parameters included (to minimise the likelihood of overfitting). Within each set of models, lower AIC and BIC values suggest a more optimal fit. AIC and BIC figures are not directly comparable between alternative sets of endpoints and/or cohorts.
- Visual fit to Kaplan-Meier curves.
- Clinical plausibility, with reference to clinical expert opinion collected during advisory board meetings and clinician interviews conducted over the course of the study.

Figure 6: Survival model selection process algorithm



Source: NICE TSD 14(13)

4.4 Endpoint selection in the economic model

Within the Excel model, functionality is provided to either (a) apply parametric distributions from model baseline, or (b) apply Kaplan-Meier curves for a specified period, with parametric distributions applied thereafter. Where parametric distributions are not applied from baseline, Kaplan-Meier curves can be applied directly for 6, 12, 18 or 24 months, or until the final time point at which the Kaplan-Meier curve crosses the selected parametric distribution. Where the latter option is selected, survival estimates beyond the selected Kaplan-Meier period are aligned with parameterisations applied from model baseline.

Due to the immaturity of the GARNET data and increasing uncertainty associated with survival estimates in the tails of the distributions, extrapolations were derived from parametric curves fitted across all timepoints (i.e. from baseline) in all scenarios.

4.5 Progression-free survival (PFS)

4.5.1 Blinded independent central review (BICR)

Goodness-of-fit statistics for the parametric models fitted to the GARNET PFS BICR data are shown in Table 3. Figure 7 depicts the corresponding curves extrapolated to time periods of 5 years and 20 years.

In terms of statistical fit (AIC and BIC), the single-knot spline curve provided the best fit to the GARNET data for PFS. This aligns with the assessment based on visual fit to the GARNET Kaplan-Meier curve: none of the standard parametric functions appeared to capture the relatively steep rate of progression implied by Kaplan-Meier curves during the initial 6 months from baseline. Exploratory analysis showed that an 11-knot spline (a very clear case of overfitting) would be required to achieve a minimal AIC (378.4).

Given the immaturity of GARNET data, the divergence of parametric functions extrapolated over longer time periods, and limited informativeness of AIC/BIC measures, clinical plausibility is crucial to consider an appropriate base case. Due to the lack of observational evidence around IOs in the current treatment landscape, uncertainty exists around expected progression and survival rates over longer time periods. However, it has been noted that clinicians included in a clinical advisory board undertaken during the present study estimated (on average) that approximately 24% of dostarlimab patients may be expected to be progression-free at 10 years, and 10% at 20 years, based on inspection of GARNET KM curves.(16)

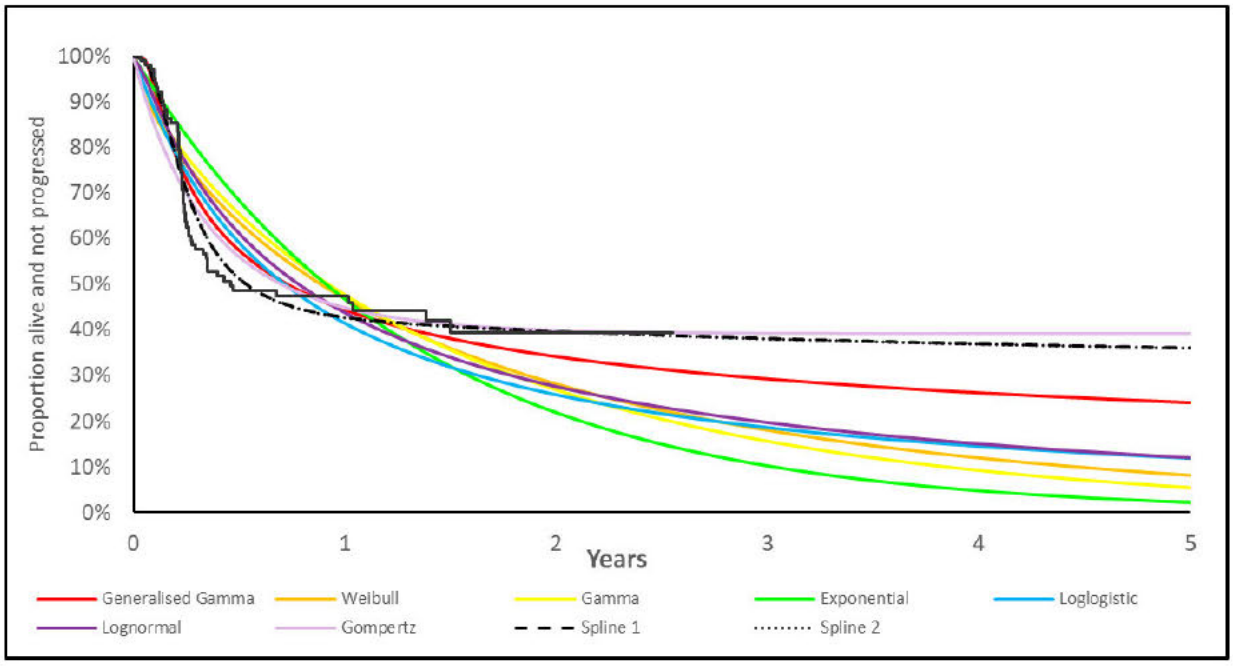
While the flexibility afforded by spline modelling provides a superior fit to Kaplan-Meier curves relative to the standard parametric options, extrapolations of 1- and 2-knot spline curves appear to exceed expected levels of progression-free survival according to clinicians' longer-term estimates. Extrapolations of both spline options yield estimates of 32% of patients remaining progression-free at 10 years, and 29% at 20 years. The Gompertz curve also yields a 20-year PFS extrapolation that substantially exceeds clinicians' estimates.

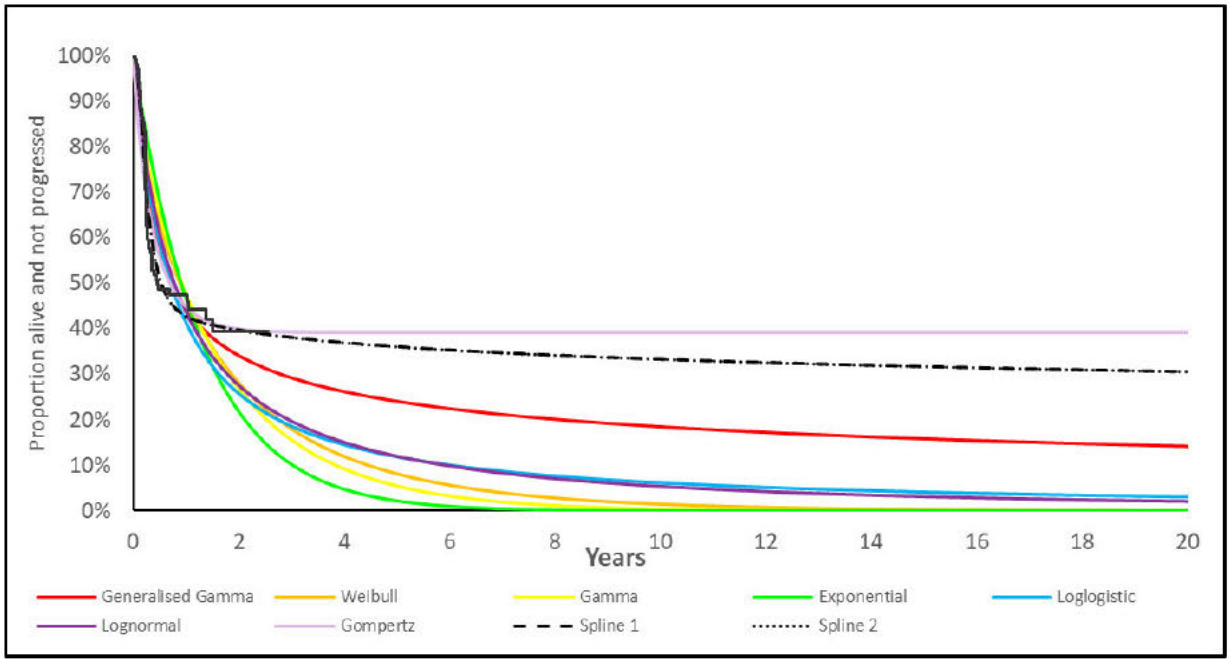
Since standard parametric functions provide a limited fit to the GARNET PFS data during the first 6 month period, and spline curves did not appear clinically valid when extrapolated, a potential base case option is to apply the KM data directly in the initial months (up to one year, or the point at which curves cross) and a parametric function (generalised gamma or lognormal, as advised by clinical opinion) thereafter. This is considered preferable to the alternative approach of transitioning from a spline-based extrapolation to a standard parametric function: application of the KM curve directly would (by definition) provide a more accurate representation of study data than a spline curve of any complexity, while being methodologically less complex and achieving similar results. Therefore, for the base case, KM data have been directly applied till the 6-month point, where a log-normal function have been applied for the following extrapolation. The log-normal function provides a more clinically plausible long-term extrapolation than the generalised gamma function, and is therefore just in the base-case. The impact of the alternative extrapolation options are explored in scenario analyses.

Table 3: Goodness of fit (AIC, BIC) – GARNET PFS BICR (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	387.6	3	395.6	3
Weibull	424.6	7	429.9	7
Gamma	428.2	8	433.5	8
Exponential	430.8	9	433.5	8
Log-logistic	412.0	6	417.3	6
Lognormal	406.8	5	412.1	5
Gompertz	400.5	4	405.8	4
Spline 1 knots	373.2	1	381.1	1
Spline 2 knots	375.2	2	385.8	2

Figure 7: Parametric survival curves – GARNET PFS BICR (N=105)





4.5.2 Investigator review (IR)

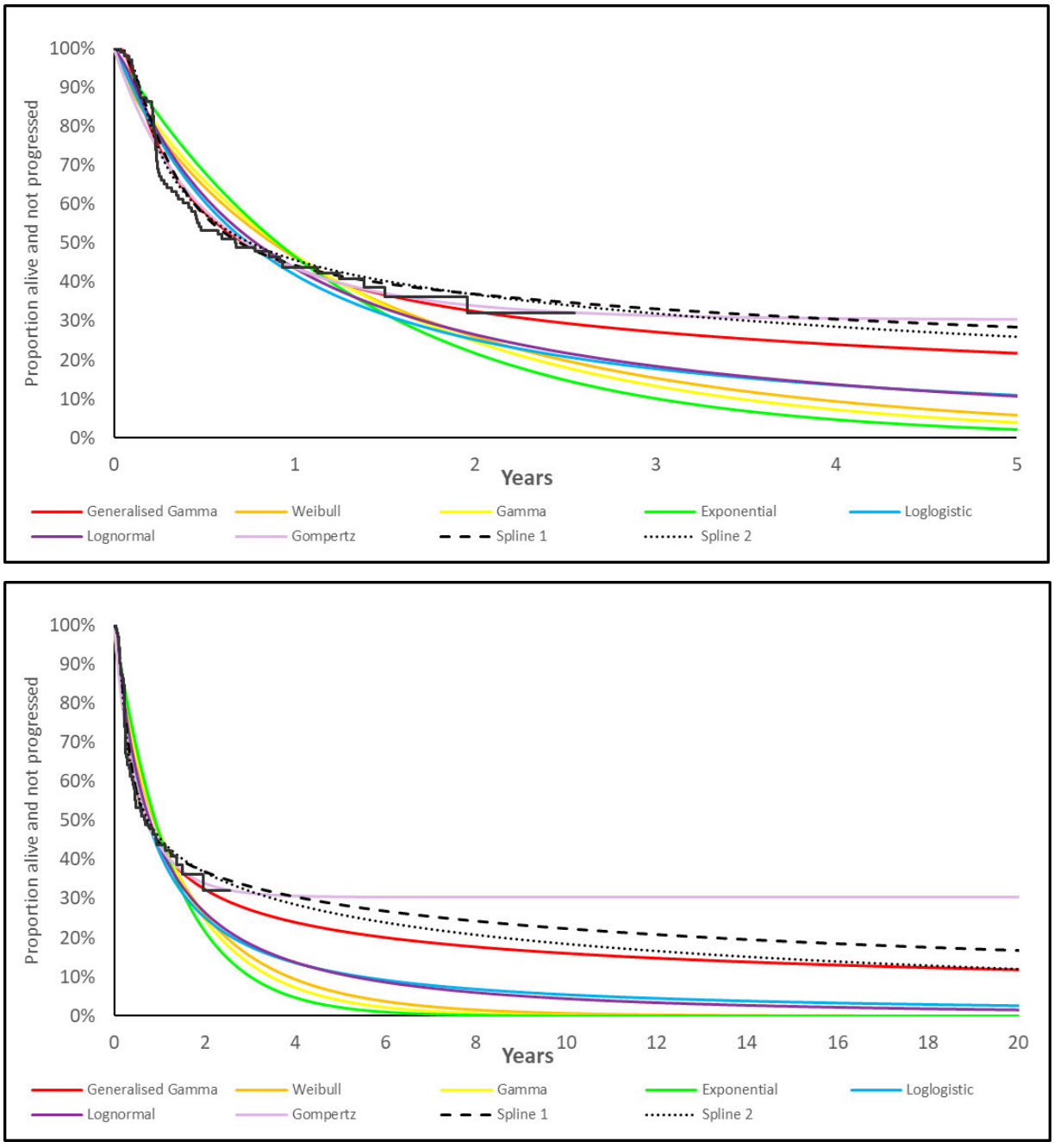
Goodness-of-fit statistics for the parametric models fitted to the GARNET PFS based on investigator assessment are detailed in Table 4. Corresponding curves extrapolated to time periods of 5 and 20 years are illustrated in Figure 8.

In keeping with PFS estimates based on BICR assessment, spline curve models provide the best fit to the observed data based on AIC and BIC, although visual inspection (and the relative scoring of AIC and BIC measures) suggests little improvement relative to parametric curves. The use of investigator review data has not been used in the base case analysis.

Table 4: Goodness of fit (AIC, BIC) – GARNET PFS IR (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	432.9	3	440.9	2
Weibull	458.3	7	463.6	8
Gamma	460.4	8	465.7	9
Exponential	460.5	9	463.1	7
Log-logistic	447.9	6	453.2	6
Lognormal	443.3	4	448.6	4
Gompertz	445.3	5	450.6	5
Spline 1 knots	430.2	1	438.2	1
Spline 2 knots	430.7	2	441.3	3

Figure 8: Parametric survival curves – GARNET PFS IR (N=105)



4.6 Overall Survival (OS)

Goodness-of-fit statistics for the parametric models fitted to the GARNET OS endpoint are detailed in Table 5, with corresponding curves extrapolated to time periods of 5 years and 20 years illustrated in Figure 9.

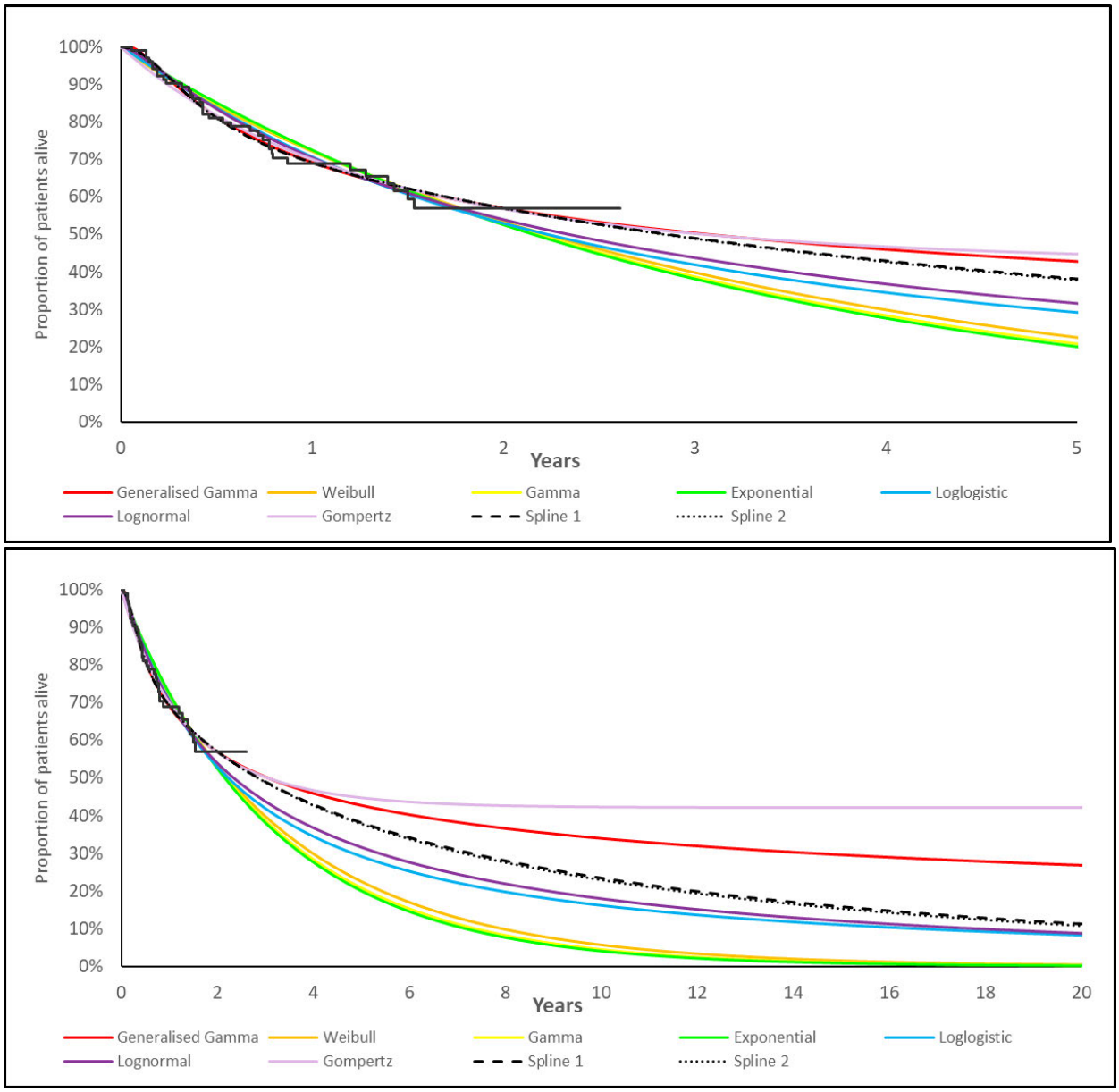
In contrast to PFS estimates, standard parametric functions appear (based on visual assessment) to provide a reasonable fit to Kaplan-Meier curves over the study period. On the basis of AIC, the generalised gamma distribution provides the best statistical fit, although both the lognormal and exponential are ranked at similar levels based on AIC and/or BIC.

Based on visual inspection of the above curves, the generalised gamma was understood to be the preferred extrapolation of clinicians engaged in the advisory board.(16) However, it is notable that landmark survival estimates associated with the lognormal (8.8% at 20 years) aligns well with the estimate (9%) provided by clinicians in the advisory board and based on inspection of Kaplan-Meier curves(16). Therefore, it appears that the lognormal function provides clinically plausible long-term extrapolations for OS. A a lognormal distribution has therefore been chosen for the extrapolation of OS from the GARNET trial.

Table 5: Goodness of fit (AIC, BIC) – GARNET OS (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	321.4	1	329.4	3
Weibull	327.2	8	332.5	7
Gamma	327.3	9	332.7	8
Exponential	325.4	7	328.0	2
Log-logistic	324.9	6	330.2	5
Lognormal	322.2	2	327.5	1
Gompertz	324.6	5	329.9	4
Spline 1 knots	322.3	3	330.3	6
Spline 2 knots	324.3	4	334.9	9

Figure 9: Parametric survival curves – GARNET OS (N=105)



4.7 Time on treatment (ToT)

Goodness-of-fit statistics for the parametric models fitted to the GARNET TOT are detailed in Table 6, with corresponding curves extrapolated to 5 years illustrated in Figure 10. The 2-knot spline curve provides the best statistical fit in terms of AIC, though visual inspection suggests no clear advantage over standard parametric distributions in relation to the trial data, as the generalised gamma distribution appears to provide a near-identical fit as the 2-knot spline function. Therefore, for the base case, a generalised gamma function has been chosen for the extrapolation of the GARNET TOT data.

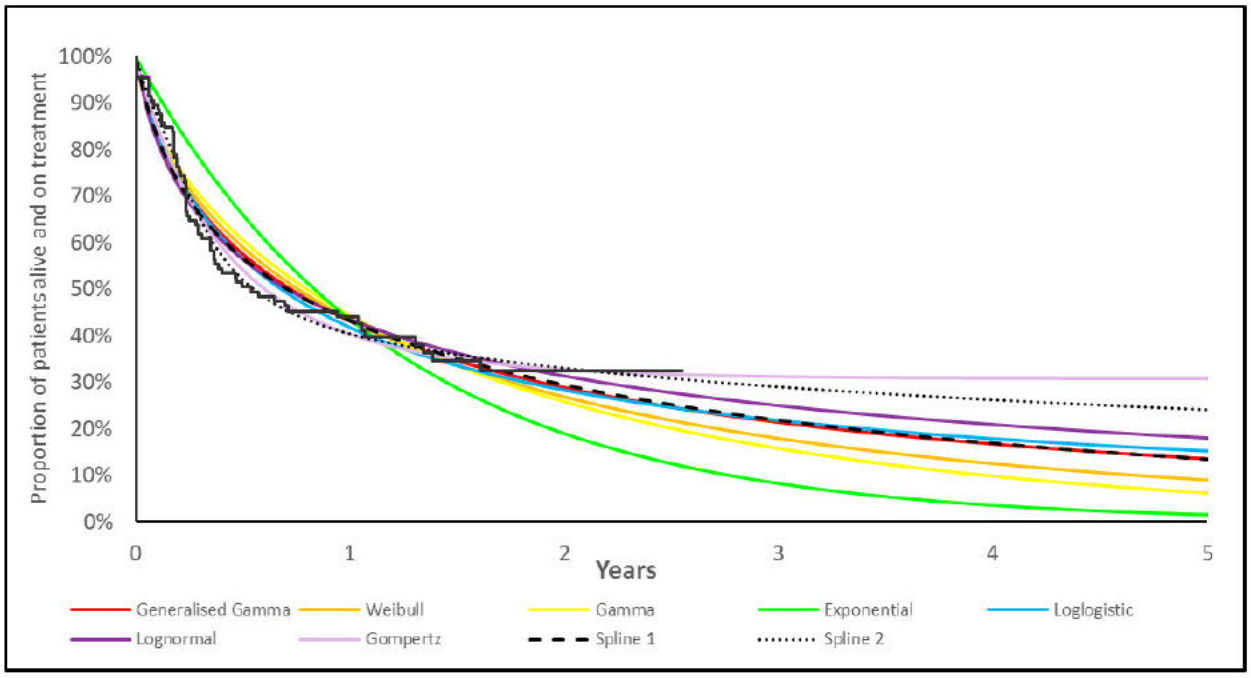
As discussed above, landmark estimates are a central consideration in assessing the plausibility of alternative extrapolation methods used for OS and PFS estimation. Extrapolations of time on treatment assumptions are less easily assessed on this basis, as longer-term extrapolations are likely to be overridden by the stopping rules (illustrated in Section 4.8.3) or maximum treatment duration assumptions applied to a majority of therapies included.

To reflect an assumption that patients are largely treated to disease progression, a scenario option is available within the economic model to apply ToT estimates based on PFS, rather than apply parameterisations of the derived ToT measure.

Table 6: Goodness of fit (AIC, BIC) – GARNET ToT (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	463.1	5	471.1	6
Weibull	463.3	7	468.7	5
Gamma	465.9	8	471.2	7
Exponential	479.4	9	482.1	9
Log-logistic	458.8	3	464.1	3
Lognormal	462.7	4	468.0	4
Gompertz	455.8	2	461.1	1
Spline 1 knots	463.2	6	471.2	7
Spline 2 knots	451.4	1	462.0	2

Figure 10: Parametric survival curves – GARNET ToT (N=105)



4.8 Adjustment of modelled time to event estimates

4.8.1 OS adjustment according to general population survival/mortality

Several options are provided for capping predicted survival relative to general population estimates, using background mortality data obtained from Danish life table 2019:2020 (HISB8) published by

Statistics Denmark(17). In the base case, the OS was capped by the mortality observed in the general population.

Functionality for the other options is provided in the model dashboard to:

A) Apply no adjustment (extrapolated OS is allowed to exceed that of the general population)

B) Cap OS according to age-specific survival rates in the general population

C) Cap OS according to age-specific mortality rates in the general population (base case)

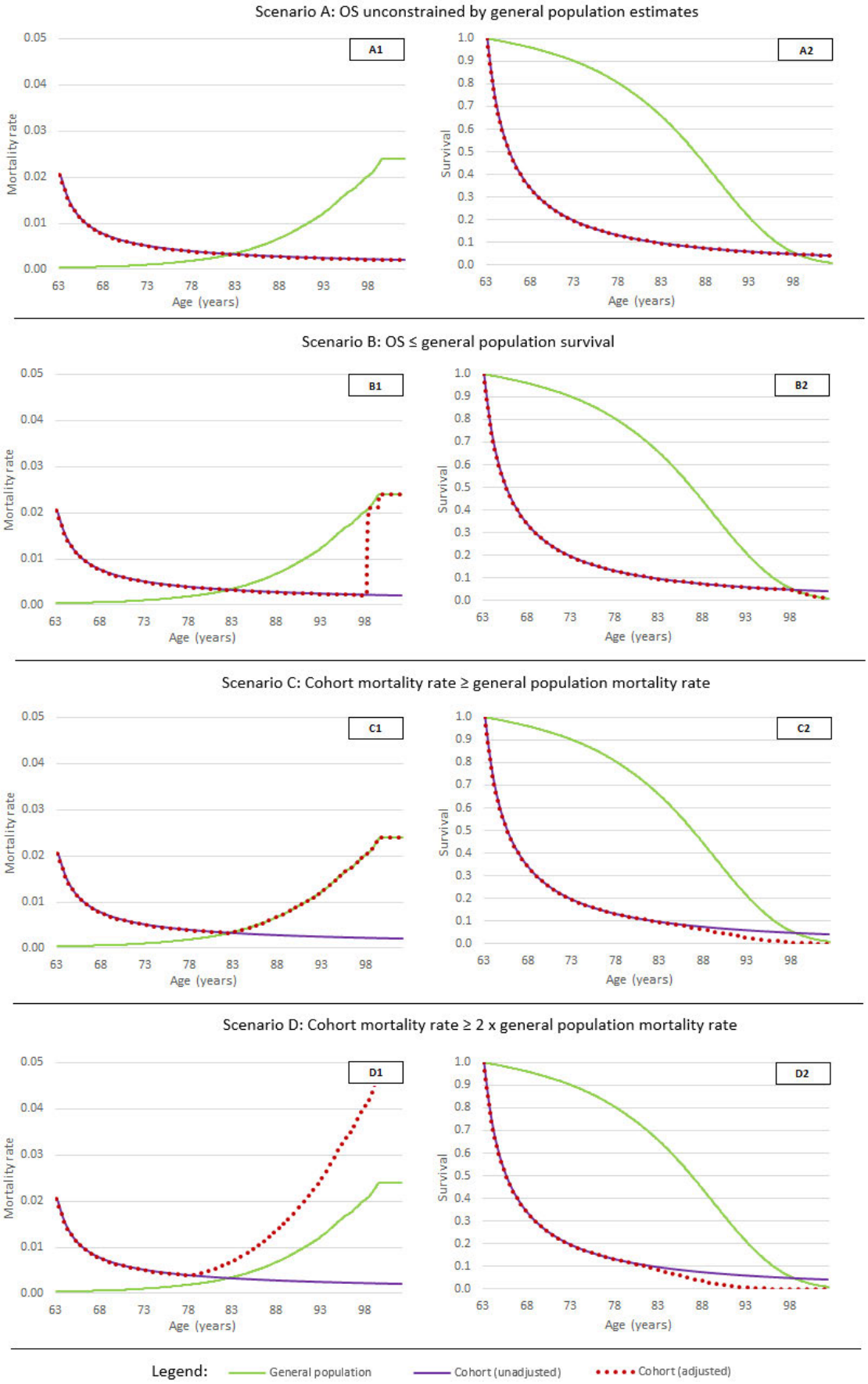
D) Cap OS according to age-specific mortality rates in the general population with a multiplier. Under this scenario, it is assumed that age-specific mortality will always be higher in the patient population than the general population.

Figure 11 demonstrates how each of these alternative adjustments affects mortality rates (A1, B1, C1, D1) and survival rates (A2, B2, C2, D2) within the model. In each figure, mortality/survival rates shaded in green reflect general population estimates, those in purple reflect rates in the patient population (dostarlimab arm) without adjustment, and those in red reflect rates in the patient population with adjustment.

4.8.2 Adjustment of progression-free survival according to overall survival

In all scenarios, progression-free survival is capped such that progression-free survival rates cannot exceed overall survival at any time point.

Figure 11: Illustration of OS general population mortality/survival adjustment methods



4.8.3 Stopping rules

Patients enrolled in the GARNET study were treated for up to two years, subject to neither unacceptable toxicities nor disease progression occurring, with the option for continued treatment beyond this period were considered beneficial by the treating physician and sponsor(18). Similarly, a stopping rule of 2 years has been recommended for other immunotherapies (pembrolizumab) in Denmark by the DMC(19). Therefore, in the base case, a stopping rule is applied to the dostarlimab arm at two years.

For chemotherapy comparators, a maximum treatment duration of 9 cycles (27 weeks) have been reported in the DMC protocol for this assessment. Therefore, a maximum treatment duration of 8 cycles (24 weeks) is applied in the base case, with functionality to increase maximum treatment up to 9 cycles (27 weeks).

4.8.4 Treatment waning assumptions

In the base case, long-term outcomes associated with dostarlimab are derived from parametric curves fitted to GARNET data. By extrapolating survival distributions over a lifetime (subject to the adjustments outlined above), an underlying assumption is that the progression and survival rates associated with dostarlimab continue over the lifetime horizon captured by the model.

A key uncertainty – particularly where longer-term evidence is unavailable, is whether the assumption of a continued treatment benefit is reasonable. To reflect this uncertainty, the model includes functionality to "wane" treatment effects such that, once a user-specified time point is reached, dostarlimab progression and survival rates align with the hazards associated with a (user-specified) comparator. Waning assumptions may be estimated separately for OS and PFS.

Treatment waning assumptions are applied by specifying in the model dashboard the comparator used as the referent for progression/survival following treatment waning. Separate user inputs are used to select the time point at which waning begins to take effect, and the length of time taken for waning to reach full effect. Hazard ratios applicable at intervening time points are interpolated on a logarithmic time scale. No treatment waning has been applied for the base case.

5. Comparator therapies

As outlined in Section 2.3, the model is structured to supports the three comparator therapies described in the DMC protocol.

Carboplatin + paclitaxel (up to 8 cycles)

Placebo

Pegylated liposomal doxorubicin (PLD) (up to 8 cycles)

For all comparators, relative efficacy is estimated using hazard ratios only. As no data is available for placebo, the efficacy of PLD is applied as a proxy for placebo, and as no treatment is given, no treatment costs are applied for this model arm. Therefore, for this arm, only monitoring costs are modelled, and therefore no costing will be reported for the placebo arm in the following sections.

5.1 Chemotherapy comparators

Estimates of relative efficacy relative to dostarlimab for PLD and carboplatin + paclitaxel was estimated using hazard ratios.

Statistical analyses, summarised in a separate report, considered a range of studies across divergent treatments. Data availability observed in the SLR (see SLR in clinical application) determined the number of studies from which estimates could be obtained. The availability was found to vary between comparators and endpoints (PFS estimates, for instance, was only available in the Mazgani et al. study, which investigated the efficacy of carboplatin + paclitaxel).

Hazard ratios included in the model are derived via unanchored matching adjusted indirect comparisons (MAICs), whereby the GARNET sample is reweighted to approximate the inclusion criteria and cohort characteristics of comparator studies.

To allow for alternative proxies of efficacy to be explored fully considering data limitations, the model allows for hazard ratios to be applied for each comparator using any of the studies explored, without requiring the study therapy to be consistent with the model arm. Therefore, the progression-free survival hazard ratio of dostarlimab versus carboplatin + paclitaxel derived from the MAIC analysis with the Mazgani et al. (20) study was applied to estimate the relative efficacy in PFS of dostarlimab versus PLD.

Hazard ratios available within the model for OS and PFS are provided in Table 7 and Table 8. Hazard ratios (exponentiated) are expressed relative to dostarlimab, such that a hazard ratio >1 favour dostarlimab (lower hazard). Hazard ratios for dostarlimab relative to comparators may be estimated as the reciprocal of this figure (1/HR).

For all comparators, hazard ratios selected for PFS were also applied to ToT as well. The maximum number of treatment cycles applied in the model is 8. The impact of alternative maximum cycles is explored in the scenario analysis.

Table 7: Overall survival hazard ratios derived from MAICs

Method	Study therapy	Study description	Log HR (dostarlimab as active) *	SE	HR vs dostarlimab **	Lower	Upper
MAIC	Paclitaxel or doxorubicin	McMeekin	-0.899	0.245	2.46	1.52	3.97
MAIC	Pegylated liposomal doxorubicin	Julius	-1.248	0.269	3.48	2.06	5.90
MAIC	Carboplatin + Paclitaxel	Mazgani	-0.582	0.398	1.79	0.82	3.90

*Log HR <0 implies dostarlimab superior to comparator
** HR >1 implies dostarlimab superior to comparator

Table 8: Progression-free survival hazard ratios derived from MAICs

Method	Therapy	Studies	Log HR (dostarlimab as active) *	SE	HR vs dostarlimab **	Lower	Upper
MAIC	Carboplatin + paclitaxel	Mazgani	0.245	0.260	0.78	0.47	1.30

*Log HR <0 implies dostarlimab superior to comparator
** HR >1 implies dostarlimab superior to comparator

The MAIC analyses were conducted to facilitate the comparison of the single-arm nature of GARNET to relevant comparator data from the published literature. A summary of the selected studies is presented below in Table *9*.

Table 9: Summary of trials/studies included in the MAIC analysis

Author (Year)	Region	Study design	Intervention/ Comparator	Study Type	Available endpoint(s)	Sample Size for MAIC
GSK, March 2020(21)	Global	Non-randomised prospective interventional	Dostarlimab	Non-RCT; SAD		129
McMeekin, 2015(22)	Global	Open-label, randomised, active-controlled	Ixabepilone/ Paclitaxel or doxorubicin	RCT	OS ORR SAEs	248*
Julius, 2013(23)	USA	Retrospective review of medical records of patients	PLD	Non-RCT; CHT	OS	41**
Mazgani, 2008(20)	Canada	Retrospective study	Carboplatin + paclitaxel	Non-RCT; CHT	OS PFS ORR	31

Abbreviations: BICR, blinded independent central review; CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, partial response; RCT, randomised controlled trial; TTP, time to progression; SAD, single-arm clinical trial; CHT, retrospective chart or registry study
***248 sample relates to the comparator arm of interest = Paclitaxel or doxorubicin**
****Only the 40mg/m² dose (standard clinical) of PLD has been used from Julius 2013: other doses do not represent standard care**

Three studies met MAIC inclusion criteria from the literature: McMeekin et al. (22), Julius et al. (23) and Mazgani et al. (20). Each MAIC was conducted separately and involved first removing patients from GARNET that did not meet inclusion/exclusion criteria for each comparator study and then weighting the remaining patients based on prognostic factors identified.

The MAIC analysis versus the Julius paper had some important limitations due to a low sample size (n=41) and because Julius et al. was a retrospective review of medical records at one centre in the US. Results should be interpreted with some caution but indicate a trend of a difference between the two treatments on OS; dostarlimab has approximately 71.3% lower risk of death compared to PLD.

The MAIC analysis versus the McMeekin paper was considered the most robust because McMeekin et al. had a large sample size (n=248) and because McMeekin et al. was a Phase III RCT. Doxorubicin was considered to be an adequate proxy of the efficacy of PLD, in line with the DMC's opinion presented

in the protocol. Nevertheless, McMeekin et al. investigated the efficacy of doxorubicin and paclitaxel and no disaggregated results were provided for each agent. It was therefore not possible to assess the relative effectiveness of dostarlimab to paclitaxel or doxorubicin as single agents. Despite these limitations, the results for OS indicated a trend of a difference between the two treatments; dostarlimab has approximately 59.3% lower risk of death compared to paclitaxel/doxorubicin.

The MAIC analysis versus the Mazgani paper had multiple important limitations that severely limit the interpretation of results. The Mazgani paper had a low sample size (n=31), was a retrospective review of medical records at one centre in Canada, only one prognostic factor could be utilized in the match, and selection bias was identified that could favour treatment with carboplatin + paclitaxel in comparative analyses. For these reasons, the results from this MAIC are severely limited and interpretation should be viewed with caution.

Despite these limitations, across these MAICs, an expected OS improvement of dostarlimab as compared to all relevant comparators identified was observed. These OS estimates are expected to be of significant value when assessing the overall value of dostarlimab for the treatment of advanced and/or recurrent EC.

6. Adverse events

Treatment-related adverse events of Grade 3 or more were included in the model, where reported in 5% or more of the GARNET population or any comparator study. Notably, little evidence around rates of individual adverse events was available for comparator therapies: only four out of thirteen unique studies identified in a clinical SLR conducted to support model development (24) presented safety and tolerability profiles of treatments, and of these studies, most only provided values aggregated across event types and/or severity grades. However, IPD data (25) was available for one trial on doxorubicin in patients with endometrial cancer (26), where both treatment-related AEs and treatment-emergent AEs of Grade 3 or more were reported. Therefore, in lack of more evidence, the adverse events rates of doxorubicin have been applied as a proxy for the included chemotherapy comparators.

Within the model, adverse events are applied in the first model cycle, to reflect the assumption that events of high severity are most likely to be experienced during the initial phases of treatment. Costs associated with adverse events are sourced from the Danish DRG tariff lists as detailed in sections 7.5. Where adverse events are experienced, cost are applied across comparator arms.

Table 10 reports grade 3+ treatment-related adverse event rates as applied in the model, alongside equivalent rates for treatment-emergent adverse events (those that occur or worsen during treatment but are not necessarily linked causally to treatment).

Table 10: Grade 3+ adverse event rates reported in GARNET and ZoptEC studies (TRAEs and TEAEs reported in at least 5% of either study population)

	Treatment-related AEs grade 3+				Treatment-emergent AEs grade 3+			
Study	**GARNET[a]**		**ZoptEC (dox)[b]**		**GARNET[c]**		**ZoptEC (dox)[d]**	
N	**129**		**249**		**129**		**249**	
Abdominal pain	0	0.0%	1	0.4%	7	5.4%	4	1.6%
Fatigue	0	0.0%	11	4.4%	1	0.8%	14	5.6%
Anaemia	5	3.9%	36	14.5%	19	14.7%	38	15.3%
Neutropenia	1	0.8%	111	44.6%	2	1.6%	112	45.0%
Nausea	0	0.0%	8	3.2%	0	0.0%	13	5.2%
Vomiting	0	0.0%	7	2.8%	0	0.0%	13	5.2%
Leukopenia	1	0.8%	44	17.7%	2	1.6%	45	18.1%

Source: a) GARNET T14.3.1.9a; b) ZoptEC T14.3.1.18; c) GARNET T14.3.1.4a; d) ZoptEC T14.3.1.4

7. Resource use and costs

7.1 Screening costs

In cohort A1 of the GARNET trial, MMR/MSI tumour status was tested using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS), with eligibility determined according to MMR IHC results.(27)

To determine the unit cost of the screening, the Department of Pathology at Rigshospitalet[1] was contacted. The department informed us that the unit cost of an IHC test was DKK 616, when ordered separately. Therefore, a one-off cost of DKK 616 has been applied at model baseline for all dostarlimab patients.

Table 11: Screening costs

	Value	Source
IHC test		
Cost	DKK 616	By telephone contact with the Department of Pathology at Rigshospitalet on the 1st of June 2021

7.2 Treatment costs

Drug acquisition costs applied to dostarlimab and comparator therapies are summarised in Table 13. Recommended dosages are based on the DMC protocol or the relevant SmPCs and corresponding unit costs from Medicinpriser.dk(28). Where dosage guidance varies according to disease category, and

[1] Patologisk afdeling på Rigshospitalet (celle- og vævsbaseret diagnostik) – 32 45 86 15, contacted June 1st, 2021

guidance specific to endometrial cancer is not available, proxy conditions used to inform dosage assumptions are detailed in the table footnotes.

Cost assumptions applied in the model are based on baseline patient characteristics reported in the GARNET trial (Table 12). Unit costs for treatment typically vary according to vial/caplet size and intensity, meaning that optimal acquisition costs for IV therapies may include a combination of vial sizes: Table 13 details the lowest available acquisition cost (based on Medicinpriser.dk) for each vial/package size available. Costs associated with the model are based on the combination of vial/packages that minimises wastage in monetary terms (rather than by volume) based on baseline GARNET cohort characteristics. Drug wastage is assumed in the base case, with functionality to assume vial sharing (no wastage), or partial vial sharing (whereby it is assumed that only a portion of surplus vial contents is wasted) as scenarios.

Table 12: GARNET baseline patient characteristics (N=105)

Measure	Value	SD
Height at baseline (cm)	159.8	6.6
Weight at baseline (kg)	74.1	21.0
BMI at baseline (kg/m^2)	29.0	7.77
Body surface area at baseline (m^2)	1.8	1.8

In the base case, administration costs (DKK 1,636[2] per IV administration estimated using the Danish DRG grouper, Interaktiv DRG) was included.

Table 13: Acquisition costs, dosage guidelines and dosing schedules for dostarlimab and comparators

Mode of administration	Dosage	Dosing schedule (frequency - days)	Vial/pack size	Vial/pack cost (DKK)	Supplier	Description	Source
Dostarlimab (cycles 1-4)							
IV	500mg	21	500mg/10ml	DKK 42,313.85	-	Dostarlimab (500 mg, 50 mg/mL)	GSK
Dostarlimab (cycles 5+)							
IV	1000mg	42	500mg/10ml	DKK 42,313.85	-	Dostarlimab (500 mg, 50 mg/mL)	GSK
Paclitaxel							
IV	175 mg/m^2	21	300mg/50ml	DKK 201.50	Fresenius Kabi	Paclitaxel 6mg/50ml concentrate for solution for infusion vials	Medicinpriser.dk
IV	175 mg/m^2	21	100mg/16.7 ml	DKK 110.50	Fresenius Kabi	Paclitaxel 6mg/16.7ml concentrate for solution for infusion vials	Medicinpriser.dk

[2]DRG 2021, 13MA98 MDC13 1-dagsgruppe, pat. mindst 7år Diagnosis: DC549: Livmoderkræft Procedure: BWAA62: Medicingivning ved intravenøs infusion

Mode of administration	Dosage	Dosing schedule (frequency - days)	Vial/pack size	Vial/pack cost (DKK)	Supplier	Description	Source
Carboplatin*							
IV	400mg/m²	28	150mg/15ml	DKK 84.00	Accord Healthcare BV	Carboplatin 150mg/15ml concentrate for solution for infusion vials	Medicinpriser.dk
IV	400mg/m²	28	450mg/45ml	DKK 203.00	Accord Healthcare BV	Carboplatin 450mg/45ml concentrate for solution for infusion vials	Medicinpriser.dk
PLD**							
IV	50mg/m²	28	20mg/10ml	DKK 2,551.09	Janssen-Cilag Ltd	Caelyx pegylated liposomal 20mg/10ml concentrate for solution for infusion vials	Medicinpriser.dk

*Based on standard dose (assuming healthy kidney function - insufficient patient data to apply calvert formula whereby Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

**Dosage based on DMC protocol(7)

7.3 Disease management and monitoring

Resource use estimates for patients on dostarlimab and comparator therapies are derived from clinical expert opinion, gathered through a resource use interview, conducted to support the application. The clinician, however, requested to be anonymous. The clinician involved in this exercise were asked to estimate the frequency of use of primary and secondary care according to patients' progression status (pre-progression or post-progression), treatment status (on or off treatment), and study arm (dostarlimab or comparators).

Overall, the clinician suggested that levels of resource use would differ according to patients' progression (pre-/post-progression) and treatment (on/off treatment) status, but that resource use could otherwise be considered equivalent between dostarlimab and comparator therapies. Expected levels of primary- and secondary-care contacts per model cycle was applied in the model, based on clinician interview, summarised in Table 14.

Table 14: Estimated frequency of resource use according to progression and treatment status

	Pre-progression (on treatment)	Pre-progression (off treatment)	Post-progression (off treatment)
Outpatient Visit (Consultant Oncologist)	1	0.3	1
Blood test (FBC)	1	0.3	0.3
CT scan	0.3	0.3	0.3

Costs associated with routine care and monitoring resources are summarised in Table 15.

Table 15: Unit costs of routine care and monitoring resources

Element	Unit cost (DKK)	Source

Outpatient Visit (Consultant Oncologist)	DKK 1,636	DRG 2021, 13MA98 MDC13 1-dagsgruppe, pat. mindst 7år Diagnosis: DC549: Livmoderkræft Procedure: BKUA1C: Planlagt konsultation ved obstetriker
Blood test (FBC)	DKK 31	B-Hæmoglobin; https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2403
CT scan	DKK 2,433	DRG 2021, 36PR07: Klinisk fysiologi/nuklearmedicin grp. G Diagnosis: DC549: Livmoderkræft Procedure: WDTCPXYXX: CT-scanning, PET/CT, uspecificeret isotop

7.4 Patient and transportation cost

Patient costs are included in the model in line with the DMC method guidelines(8, 29). The unit cost per hour is assumed to be DKK 179 in line with the DMC guidelines(8, 29). All treatment regimens included in the model are IV, and therefore a hospital visit is required for each treatment administration. The relevant SmPCs (30-32) or pro.medicin.dk(33) have been consulted to estimate the duration of each administration, please see Table 16 for the duration and patient cost of the administration of each treatment regimen.

Table 16: Patient cost associated with administration of treatment regimens

Element	Time usage (hours)	Admin frequency per 3-week cycle	Patient cost per cycle (DKK)	Notes
Dostarlimab	0.5	1	89.50	IV infusion time of 1 hour
Carboplatin + Paclitaxel	4	1	134.25	Carboplatin IV infusion time is 1 hour, and Paclitaxel IV infusion time is 3 hours
Pegylated liposomal doxorubicin	1	0.75	716.00	IV infusion time of 1 hour

Patient cost associated with disease monitoring has been estimated using the frequency of resource use presented in Table 14 and the time usage presented in Table 17.

Table 17: Time usage of disease monitoring

	Time usage (hours)
Outpatient Visit (Consultant Oncologist)	1
Blood test (FBC)	0.5
CT scan	1

Table 18: Patient cost associated with disease monitoring

Patient cost per 3-week cycle	Pre-progression (on treatment) (DKK)	Pre-progression (off treatment) (DKK)	Post-progression (on treatment) (DKK)	Post-progression (off treatment) (DKK)
Outpatient Visit (Consultant Oncologist)	179.00	53.70	53.70	53.70
Blood test (FBC)	89.50	26.85	26.85	26.85
CT scan	53.70	53.70	53.70	53.70
Total cost per cycle (DKK)	**420.76**	**232.81**	**232.81**	**232.81**

Transportation costs was included in the model in line with DMC guidelines(8, 29) and was applied together with the patient cost at every occurrence of a visit to the hospital in the model. An average rate of DKK 98.56 per visit was applied in the model in line with the DMC guidelines(8, 29). Please consult Table 19 for the transportation cost per visit applied in the model.

Table 19: Transportation cost applied in the model

Element	Unit cost (DKK)	Source
Transportation cost per visit	98.54	DMC – "Estimating unit costs"(29)

7.5 Adverse event costs

One-off costs associated with adverse events (summarised Table 20) were obtained using the Danish DRG grouper, Interaktiv DRG, for 2021(34) or through microcosting based on KOL consultation and the DMC unit cost list(29). Adverse event costs were applied in the first model cycle on the assumption that events would largely be concentrated in initial treatment cycles.

Table 20: Estimated costs associated with adverse events

Adverse event	Estimate	Source
Abdominal pain	DKK 5,130	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR100: Akutte mavesmerter
Anaemia	DKK 3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel
Fatigue	DKK 3,987	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Nausea	DKK 359.6	Based on KOL consultation: 15 min consultation with physician + prescription of domperidon (Motilium, 10 mg, 30 pc)
Neutropenia	DKK 3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
Thrombocytopenia	DKK 3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD696: Trombocytopeni UNS

Vomiting	DKK 5,130	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR119C: Opkastning
Leukopenia	DKK 3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728H: Leukopeni

7.6 Terminal care

No end of life costs was included in the model.

8. Scenario analyses

The exploration of the robustness of cost-model for potential sources of uncertainty is done using scenario analyses.

Scenario analyses consider alternative plausible scenarios around model perspective (including time horizon and discounting assumptions), data sources (such as choice of patient cohort and relative efficacy estimates), and the generalisability of observed data to clinical practice and long-term time horizons (including choice of parametric distribution applied to TTE endpoints, and stopping rules). The SCENARIOS sheet of the model automates the exploration of individual scenarios by cycling singularly through all scenario options available in the model dashboard, outputting incremental cost estimates relative to a user-specified comparator. More complex scenarios that combe assumptions outside the model base case may be explored by manually selecting a chosen combination of assumptions in the model dashboard.

9. Model Evaluations

9.1 Base-case Scenario

A list of the key parameters in the base case economic model evaluation is presented in Table 21.

Table 21: Summary of key base case parameter values and rationale.

Adverse event	Base Case Value	Rationale
Treatment comparators	Carboplatin + paclitaxel, placebo (no treatment), Pegylated liposomal doxorubicin	Alignment with DMC protocol
Reference treatment	Dostarlimab	Study treatment
Time horizon	40 years	Suitable to capture lifetime (<1% patients alive at 40 years)
Discount rate (costs and outcomes)	3.5% till year 35, then 2.5%	As per DMC method guidelines
Perspective	Restrictive societal perspective	Aligns with DMC method guidelines
Cycle length	3 weeks	Aligns with common treatment cycles
Half-cycle correction	Yes	Reduce bias

OS evidence	Efficacy cohort, N=105	Alignment with clinical application
OS survival function	Log-normal	AIC/BIC, visual fit, clinical opinion, clinical plausibility of long-term extrapolation
PFS evidence	Efficacy cohort, N=105	Alignment with clinical application
PFS survival function	KM to 6, month then parametric curve log-normal	Clinical plausibility AIC/BIC, visual fit, clinical opinion, clinical plausibility of long-term extrapolation
TOT evidence	Efficacy cohort, N=105	Alignment with clinical application
TOT survival function	Generalised gamma	AIC/BIC, visual fit, clinical opinion
Adverse event probabilities	GARNET TLFs (dostarlimab), ZoptEC	Chemo AE rates proxied by ZoptEC (doxorubicin) due to unavailability of equivalent data for other chemo comparators
Vial sharing	Not assumed	Drug wastage assumed
Dostarlimab stopping rule	2 years	Aligns with study protocol and Danish clinical practice with PD-L1-inhibitors

9.2 Alternative scenarios

A list of key scenarios conducted is presented in Table 22.

Table 22: Summary of key scenarios and rationale.

Adverse event	Scenarios Case Value	Rationale
Time horizon	20,30 years	Explore sensitivity excluding longer time horizons where greater uncertainty exists
Half-cycle correction	No	Sensitivity check
OS survival function	Exponential, Weibull, gamma, lognormal, log-logistic, Gompertz, spline (1 knot), spline (2 knots)	Uncertainty around optimal fit based on AIC/BIC, visual fit, clinical opinion
PFS Parameterisation approach	Parametric curve from baseline, KM to 6, 12, 18 and 24 months, then parametric curve	Test impact of various options of parameterisation
PFS survival function	Exponential, Weibull, gamma, lognormal, log-logistic, Gompertz, spline (1 knot), spline (2 knots)	Uncertainty around optimal fit based on AIC/BIC, visual fit, clinical opinion
TOT Choice of KM curve	PFS	Test impact of TOT based on PFS
TOT survival function	Exponential, Weibull, gamma, lognormal, log-logistic, Gompertz, spline (1 knot), spline (2 knots)	Uncertainty around optimal fit based on AIC/BIC, visual fit, clinical opinion

Chemotherapy – max treatment cycles	6, 7, 8, 9 cycles	Test impact of different max treatment cycles
Apply MMR screening costs (dostarlimab)	No	Explore impact of screening cost
Vial sharing	100% vial sharing assumed	Exploration of cost reductions associated with vial sharing assumptions

10. Results

Central deterministic results summarised in Table 23 and Table 24 below correspond to the base assumptions specified in the dashboard of the current model version.

10.1 Pairwise comparisons

Results show dostarlimab to be more costly than the comparators included in the model.

Notably, total costs are substantially higher for dostarlimab than any of the comparators included in the model, with discounted incremental costs ranging from DKK 700,758 to DKK 764,563 over a lifetime perspective. Cost differences are driven mainly by acquisition costs, dostarlimab commanding a higher price than any of the chemotherapy comparators. Due to the low toxicity profile of IOs and expectations around prolonged clinical benefit relative to chemotherapies (which have treatment caps of 8 cycles), treatment cost are also incurred over a comparatively longer period, increasing the total expected cost associated with routine on-treatment monitoring as well as direct drug costs.

In regard with efficacy, dostarlimab demonstrated to offer patients an increment of 2.3 life years in comparison with carboplatin + paclitaxel and an increment of 3.6 in comparison with PLD.

Table 23: Summary of results (discounted)

	Total costs	Total life years	Incremental costs	Incremental life years
Dostarlimab	DKK 788,322	4.6	-	-
Carboplatin + paclitaxel	DKK 84,537	2.2	DKK 703,785	2.3
Placebo	DKK 23,759	0.9	DKK 764,563	3.6
Pegylated liposomal doxorubicin (PLD)	DKK 87,564	0.9	DKK 700,758	3.6

All the comparator efficacy assumptions applied in the model base case are favourable to dostarlimab in terms of life year gains.

Table 24: Summary of deterministic baseline results (disaggregated, discounted)

	Dostarlimab	Carboplatin + paclitaxel	Placebo	Pegylated liposomal doxorubicin

Screening costs	DKK 616	DKK 0	DKK 0	DKK 0
Study treatment costs	DKK 633,900	DKK 4,247	DKK 0	DKK 44,610
Administration costs	DKK 15,055	DKK 10,172	DKK 0	DKK 7,629
Patients and transportation costs – administration	DKK 1,731	DKK 5,065	DKK 0	DKK 1,448
PFS on treatment – monitoring costs	DKK 33,403	DKK 13,704	DKK 0	DKK 13,704
PFS off treatment – monitoring costs	DKK 18,716	DKK 36,489	DKK 19,851	DKK 12,818
PD - monitoring costs	DKK 61,736	DKK 3,969	DKK 127	DKK 127
Patients and transportation costs – PFS monitoring	DKK 14,759	DKK 7,265	DKK 3,757	DKK 4,113
Patients and transportation costs – PD monitoring	DKK 8,222	DKK 529	DKK 24	DKK 17
End of life costs	DKK 0	DKK 0	DKK 0	DKK 0
Adverse events costs	DKK 185	DKK 3,097	DKK 0	DKK 3,097
Total costs	**DKK 788,322**	**DKK 84,537**	**DKK 23,759**	**DKK 87,564**

10.2 Scenario analyses

Scenario analyses corresponding to dostarlimab relative to standard of care are summarised in Table 25 below. Notably, approaches exploring the direct application of Kaplan-Meier data during the initial months for which study data were observed showed relatively little impact on incremental costs. By contrast, incremental costs results were sensitive to the choice of parametric distribution used to approximate and extrapolate survival estimates. Applied from model baseline, incremental costs result versus carboplatin + paclitaxel using alternative OS distributions ranged from DKK 659,728 (Exponential) to DKK 762,308 (Gompertz), whereas incremental costs versus PLD varied from DKK 674,820 (Exponential) to DKK 725,597 (Gompertz). Incremental costs versus PLD results using alternative PFS distributions were similarly varied, ranging from DKK 666,732(Exponential) to DKK 739,571 (Gompertz). Incremental costs versus carboplatin + paclitaxel obtained by varying PFS distributions were also similarly varied, ranging from DKK 663,705 (Exponential) to DKK 736,544 (Gompertz).

Further expected drivers of incremental costs such as the time horizon and the maximum number of treatment cycles were varied. All these elements resulted in very minor variation in the incremental costs versus carboplatin + paclitaxel, versus placebo and versus PLD.

A summary of all the scenario analyses is presented in Table 25.

Table 25: Scenario analysis: dostarlimab relative to standard of care

PARAMETER	SCENARIO	INCREM. costs versus carboplatin + paclitaxel	INCREM. costs versus placebo	INCREM costs versus PLD
All	Central	DKK 700,758	DKK 764,563	DKK 703,785
Time horizon (years)	20	DKK 693,285	DKK 757,090	DKK 697,263
Time horizon (years)	30	DKK 699,896	DKK 763,700	DKK 703,022
Half-cycle correction	Off	DKK 700,658	DKK 765,140	DKK 703,714
OS Parametric function	Weibull	DKK 748,883	DKK 811,883	DKK 725,346
OS Parametric function	Gamma	DKK 664,671	DKK 728,437	DKK 678,169
OS Parametric function	Exponential	DKK 661,083	DKK 724,953	DKK 675,726
OS Parametric function	Loglogistic	DKK 659,728	DKK 723,599	DKK 674,820
OS Parametric function	Lognormal	DKK 695,746	DKK 759,571	DKK 701,093
OS Parametric function	Gompertz	DKK 762,308	DKK 823,575	DKK 725,597
OS Parametric function	Spline1	DKK 716,083	DKK 779,415	DKK 711,294
OS Parametric function	Spline2	DKK 714,261	DKK 777,536	DKK 710,245
PFS Parameterisation approach	Parametric curve from baseline	DKK 809,291	DKK 874,123	DKK 812,156
PFS Parameterisation approach	KM to 12 months, then parametric curve	DKK 723,957	DKK 787,761	DKK 726,984
PFS Parameterisation approach	KM to 18 months, then parametric curve	DKK 725,529	DKK 789,333	DKK 728,556
PFS Parameterisation approach	KM to 24 months, then parametric curve	DKK 726,938	DKK 790,743	DKK 729,965
PFS Parametric function	Weibull	DKK 732,235	DKK 796,040	DKK 735,262
PFS Parametric function	Gamma	DKK 705,967	DKK 769,772	DKK 708,994
PFS Parametric function	Exponential	DKK 697,009	DKK 760,813	DKK 700,035
PFS Parametric function	Loglogistic	DKK 663,705	DKK 727,510	DKK 666,732
PFS Parametric function	Lognormal	DKK 694,459	DKK 758,263	DKK 697,486
PFS Parametric function	Gompertz	DKK 736,544	DKK 800,349	DKK 739,571
PFS Parametric function	Spline1	DKK 735,861	DKK 799,666	DKK 738,888
PFS Parametric function	Spline2	DKK 735,697	DKK 799,502	DKK 738,724
ToT Choice of KM curve	PFS	DKK 708,784	DKK 773,963	DKK 712,322
ToT Parameterisation approach	KM to 6 months, then parametric curve	DKK 707,550	DKK 772,665	DKK 711,138
ToT Parameterisation approach	KM to 12 months, then parametric curve	DKK 706,836	DKK 771,952	DKK 710,425

ToT Parameterisation approach	KM to 18 months, then parametric curve	DKK 703,862	DKK 768,977	DKK 707,450
ToT Parameterisation approach	KM to 24 months, then parametric curve	DKK 703,604	DKK 768,719	DKK 707,192
ToT Parameterisation approach	KM to final crossover, then parametric curve	DKK 703,022	DKK 768,137	DKK 706,610
ToT Parametric function	Weibull	DKK 700,100	DKK 763,965	DKK 703,160
ToT Parametric function	Gamma	DKK 696,848	DKK 760,901	DKK 700,011
ToT Parametric function	Exponential	DKK 662,250	DKK 727,396	DKK 665,651
ToT Parametric function	Loglogistic	DKK 701,147	DKK 765,090	DKK 704,250
ToT Parametric function	Lognormal	DKK 699,098	DKK 762,555	DKK 701,935
ToT Parametric function	Gompertz	DKK 700,359	DKK 764,537	DKK 703,590
ToT Parametric function	Spline1	DKK 700,475	DKK 764,205	DKK 703,461
ToT Parametric function	Spline2	DKK 697,966	DKK 762,639	DKK 701,468
Maximum treatment cycles	6	DKK 713,110	DKK 764,563	DKK 709,381
Maximum treatment cycles	7	DKK 706,755	DKK 764,563	DKK 706,502
Maximum treatment cycles	9	DKK 695,097	DKK 764,563	DKK 701,151
Apply MMR screening costs (dostarlimab)	No	DKK 700,142	DKK 763,947	DKK 703,169
Vial options	Vial sharing	DKK 705,827	DKK 764,563	DKK 704,347

11. Duration spent in each health state

The model calculates the mean duration in the health states, on-treatment state, pre-progression state (defined by PFS) and post-progression state (PPS). The estimated mean durations in the health states are reported in Table 26.

Table 26: Summary of mean duration spent in health states

	Time on treatment (months)	Time in PFS (months)	Time in PPS (months)	Total time alive (months)
Dostarlimab	*9.61*	20.11	34.63	**54.74**
Carboplatin + paclitaxel	*3.94*	24.41	2.23	**26.64**
Placebo	*0.00*	11.13	0.07	**11.21**
Pegylated liposomal doxorubicin (PLD)	*3.94*	11.13	0.07	**11.21**

12. Budget impact analysis

12.1 Methods

The budget impact model was developed to estimate the expected budget impact of recommending dostarlimab as a possible standard treatment in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of dostarlimab in Denmark.

The cost per patient model was partially nested within the budget impact model, and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient model.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where dostarlimab is recommended as standard treatment and the scenario where dostarlimab is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios. Three budget impact analyses have been included in the cost model, one for each clinical question.

12.1.1 Incidence of patients each year

20 patients with dMMR/MSI-H status endometrial cancer are expected each year as described in the DMC protocol. Each year, 5 patients are expected to receive carboplatin + paclitaxel, 15 patients are expected to receive pegylated liposomal doxorubicin and 0 patients will receive placebo.

Therefore, a yearly incidence of 5 patients have been applied for clinical question 1, a yearly incidence of 0 patients have been applied for clinical question 2 and a yearly incidence of 15 patients have been applied for clinical question 3. Please see Table 27 for the total number of patients and yearly incidence.

Table 27: Total number of patients and yearly incidence applied in the budget impact model

	Year 1	Year 2	Year 3	Year 4	Year 5
Yearly incidence Clinical question 1	5	5	5	5	5
Yearly incidence Clinical question 2	0	0	0	0	0
Yearly incidence Clinical question 3	15	15	15	15	15
Total yearly incidence	**20**	**20**	**20**	**20**	**20**
Total number of patients	**20**	**40**	**60**	**80**	**100**

12.1.2 Market Share

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Regardless, the estimates will be associated with uncertainty, and therefore different scenarios were tested in the model.

The expected market shares were estimated for each clinical question based on the current use and expected projections.

The market shares used in the budget impact analyses are presented in Table 28, Table 29 and Table 30.

Table 28: Market shares, clinical question 1

	No recommendation for dostarlimab					Recommendation for dostarlimab				
Treatment	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Dostarlimab	0%	0%	0%	0%	0%	80%	90%	90%	90%	90%
Carboplatin + paclitaxel	100%	100%	100%	100%	100%	20%	10%	10%	10%	10%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Table 29: Market shares, clinical question 2

	No recommendation for dostarlimab					Recommendation for dostarlimab				
Treatment	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Dostarlimab	0%	0%	0%	0%	0%	80%	80%	80%	80%	80%
Placebo	100%	100%	100%	100%	100%	20%	20%	20%	20%	20%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Table 30: Market shares, clinical question 3

	No recommendation for dostarlimab					Recommendation for dostarlimab				
Treatment	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Dostarlimab	0%	0%	0%	0%	0%	80%	90%	90%	90%	90%
Pegylated lyposomal doxorubicin	100%	100%	100%	100%	100%	20%	10%	10%	10%	10%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

12.1.3 Costs

Included costs in the budget impact model were drug acquisition costs, administration costs, monitoring costs, adverse event costs, and screening cost. Patient- and transportation costs were not included as these are not part of the regional budgets. Discounting was not used in the budget impact model in line with DMC's methods guidelines(8). The undiscounted cost output of the cost per patient model was used directly to inform the cost per year per patient in the budget impact model for dostarlimab, placebo, carboplatin + paclitaxel, and pegylated liposomal doxorubicin.

12.2 Results

12.2.1 Base case results

Based on the base case assumptions, the estimated budget impact of recommending dostarlimab as a possible standard treatment for the population defined in clinical question 1 was DKK 3.0 mil. in year 5 as shown in Table 31.

Based on the base case assumptions, the estimated budget impact of recommending dostarlimab as a possible standard treatment for the population defined in clinical question 2 was DKK 0 mil. in year 5 as shown in Table 32.

Based on the base case assumptions, the estimated budget impact of recommending dostarlimab as a possible standard treatment for the population defined in clinical question 3 was DKK 8.7 mil. in year 5 as shown in Table 33.

Table 31: Budget impact for clinical question 1

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	DKK 202,451	DKK 245,890	DKK 276,056	DKK 296,268	DKK 311,492
Recommended	DKK 1,937,591	DKK 3,081,628	DKK 3,240,874	DKK 3,280,589	DKK 3,314,248
Total budget impact	**DKK 1,735,141**	**DKK 2,835,737**	**DKK 2,964,818**	**DKK 2,984,321**	**DKK 3,002,756**

Table 32: Budget impact for clinical question 2

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Recommended	DKK 0	DKK 0	DKK 0	DKK 0	DKK 0
Total budget impact	**DKK 0**	**DKK 0**	**DKK 0**	**DKK 0**	**DKK 0**

Table 33: Budget impact for clinical question 3

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	DKK 1,119,588	DKK 1,177,219	DKK 1,203,916	DKK 1,216,781	DKK 1,224,176
Recommended	DKK 5,915,221	DKK 9,281,569	DKK 9,753,817	DKK 9,869,789	DKK 9,967,885
Total budget impact	**DKK 4,795,634**	**DKK 8,104,349**	**DKK 8,549,902**	**DKK 8,653,008**	**DKK 8,743,710**

13. Discussion

As a novel immunotherapy, a key area of uncertainty is the expected long-term efficacy of dostarlimab relative to conventional chemotherapies, for which longer-term evidence is available. Clinician

feedback obtained during the current study was optimistic about the longer-term impact on progression and survival rates; however, clinical estimates around landmark survival rates were reliant mainly on visual extrapolations of the (relatively short-term) GARNET data rather than direct experience of long-term outcomes.

A further limitation to the analysis is the reliance upon single-arm data. In the absence of a head-to-head study, relative estimates of key outcomes are reliant upon indirect treatment comparisons that are not subject to the randomisation methods and consistency of approach available from a randomised controlled trial. As far as possible, the bias associated with such comparisons has been mitigated with the use of MAICs, whereby GARNET data are reweighted to approximate the inclusion criteria and patient profiles of comparator studies. However, it is notable that unobserved differences between studies (including the MMR/MSI status of patients in comparator populations) may not be adequately accounted for. Further constraints arise from the relative dearth of data available for endometrial cancer patients in the post-platinum setting: comparator trials typically involved small patient samples, hence increased uncertainty around relative estimates, and study data suitable for conducting comparative analyses were not available for all combinations of therapies and endpoints explored in the economic model.

Additional points of uncertainty arise from the validity of proportional hazard assumptions assumed in the application of hazard ratios to progression and survival estimates within the model. While results obtained from the comparator MAIC analyses for OS estimates indicated that proportionality could reasonably be assumed on the basis of visual and statistical (log-log/ Schoenfeld residual) tests, further adaptation would be required to explore the impact of alternative modelling approaches to account for potential violation of proportional hazards assumptions associated with PFS relative to comparator therapies. Notably, due to the discrepancy between hazard ratios applied for OS (favourable to dostarlimab) and PFS, where available, (favourable to comparators), base estimates assume comparators to have lower rates of disease progression but higher rates of mortality than dostarlimab, resulting in small numbers progressing prior to death in comparator arms over longer time periods.

14. Conclusion

The positive safety profile and promising results demonstrated in the GARNET trial suggest that dostarlimab is an effective treatment for adults with advanced or recurrent endometrial cancer that have been previously treated with platinum-based chemotherapy and are PD-(L)1 naïve. Using available data for comparator studies, the cost model results suggests dostarlimab to be more costly than conventional chemotherapy options like carboplatin + paclitaxel and PLD and placebo.

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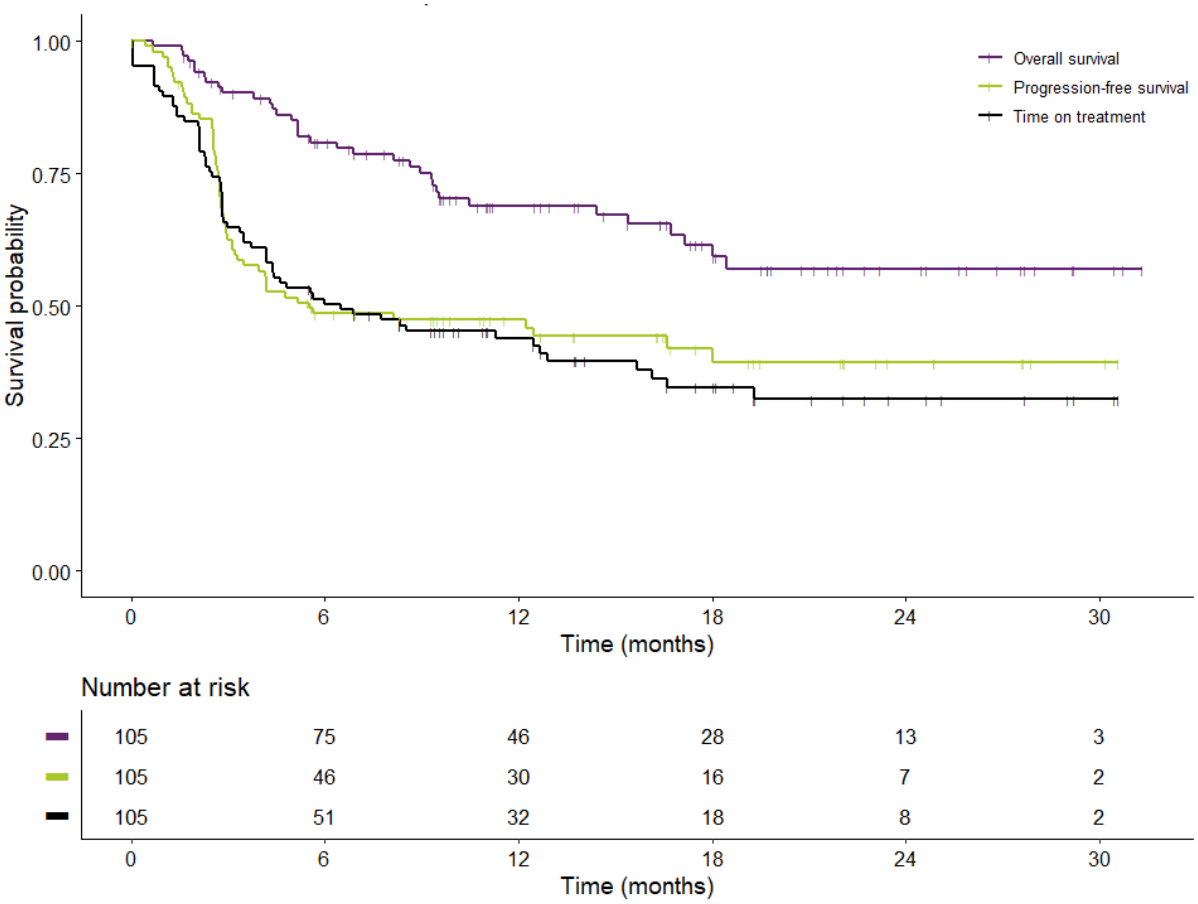
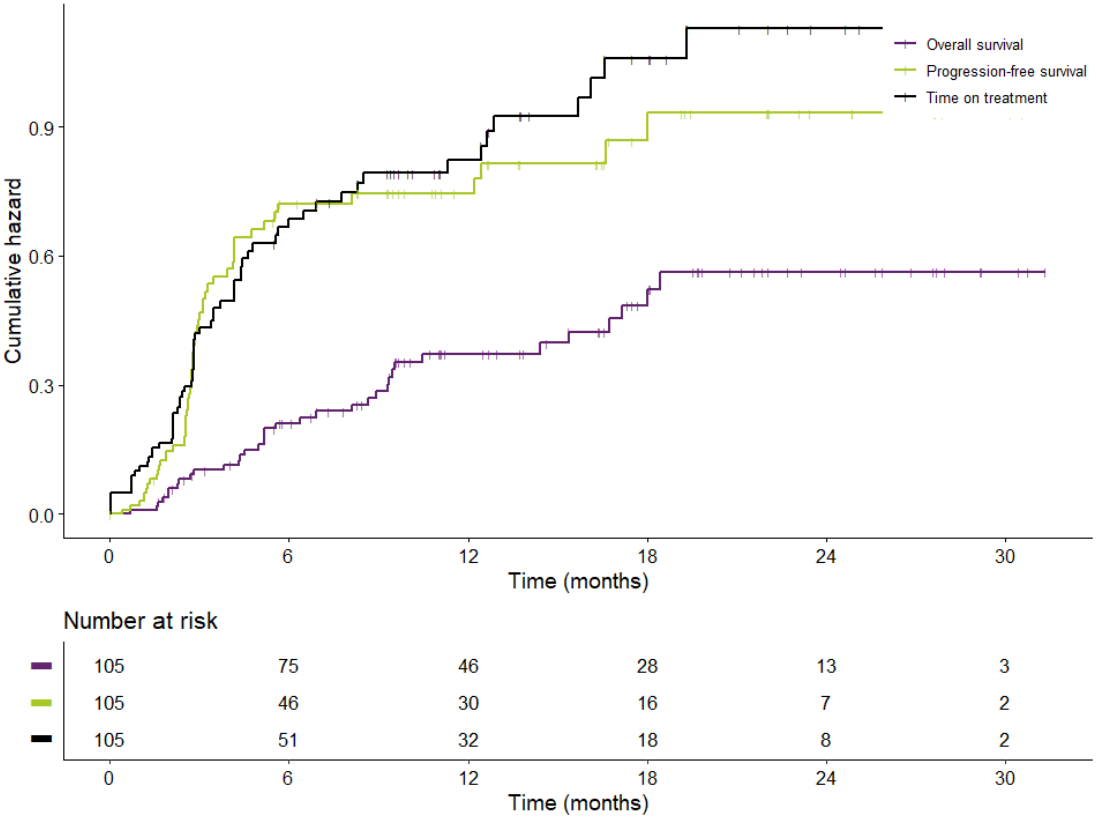
Appendices

Appendix I: Time-to-event estimates (GARNET efficacy cohort N=105)

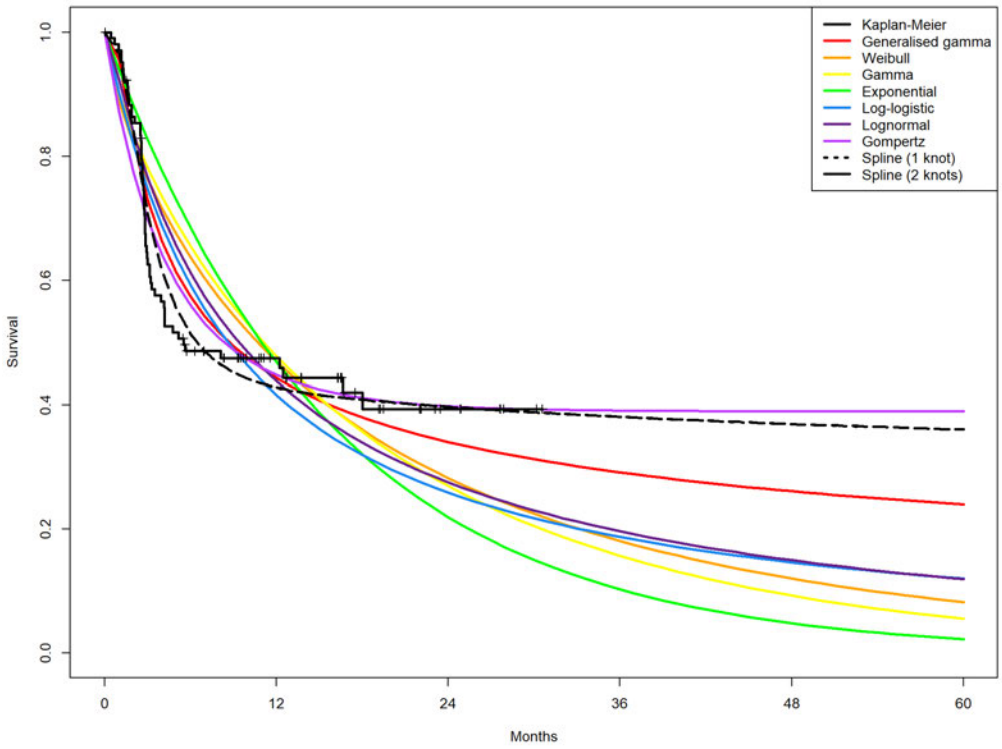
GARNET Kaplan-Meier curves: Overall survival, progression-free survival, time on treatment (March 2020 data cut – Efficacy cohort (N=105)



GARNET cumulative hazard curves: Overall survival, progression-free survival, time on treatment (March 2020 data cut – Efficacy cohort (N=105)



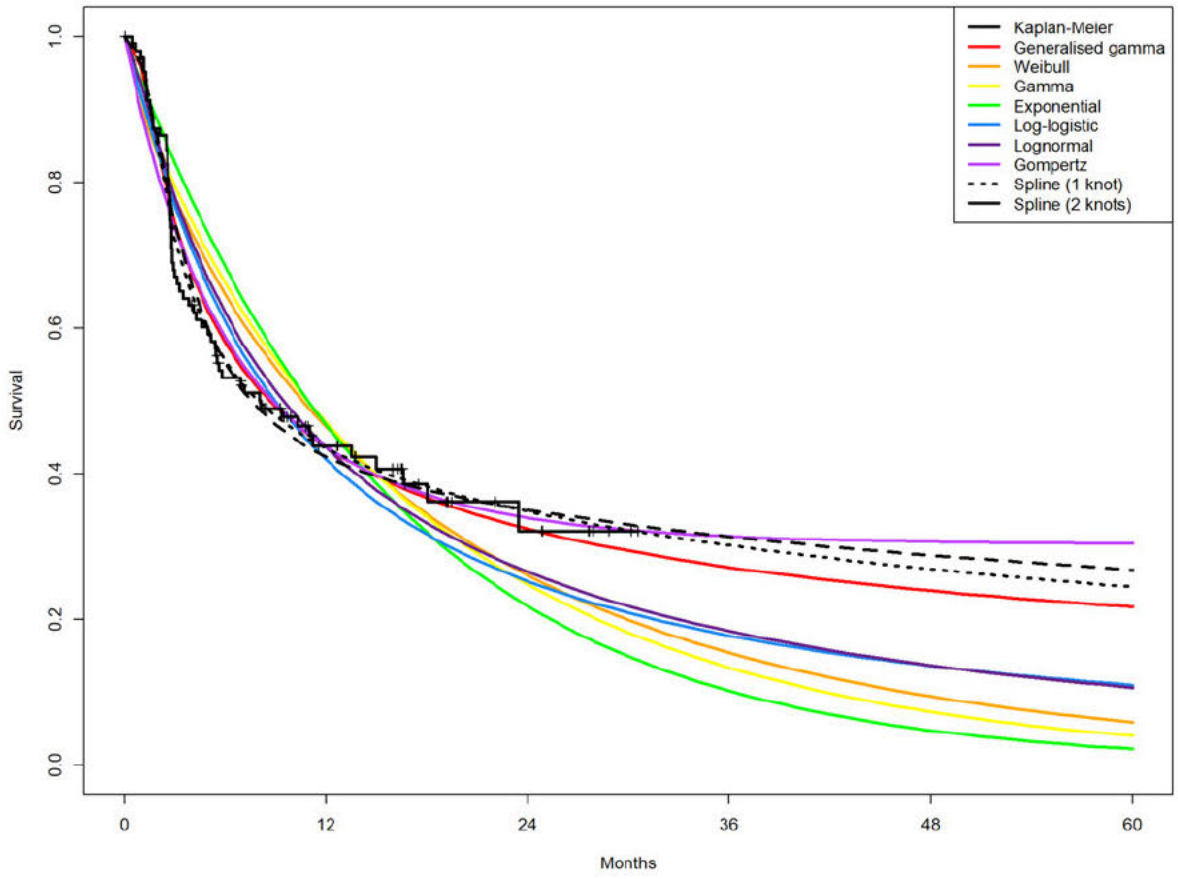
Parametric survival curves – GARNET PFS BICR (N=105)



Goodness of fit (AIC, BIC) – PFS BICR (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	387.6	3	395.6	3
Weibull	424.6	7	429.9	7
Gamma	428.2	8	433.5	8
Exponential	430.8	9	433.5	8
Log-logistic	412.0	6	417.3	6
Lognormal	406.8	5	412.1	5
Gompertz	400.5	4	405.8	4
Spline 1 knots	373.2	1	381.1	1
Spline 2 knots	375.2	2	385.8	2

Parametric survival curves – PFSIR (N=105)

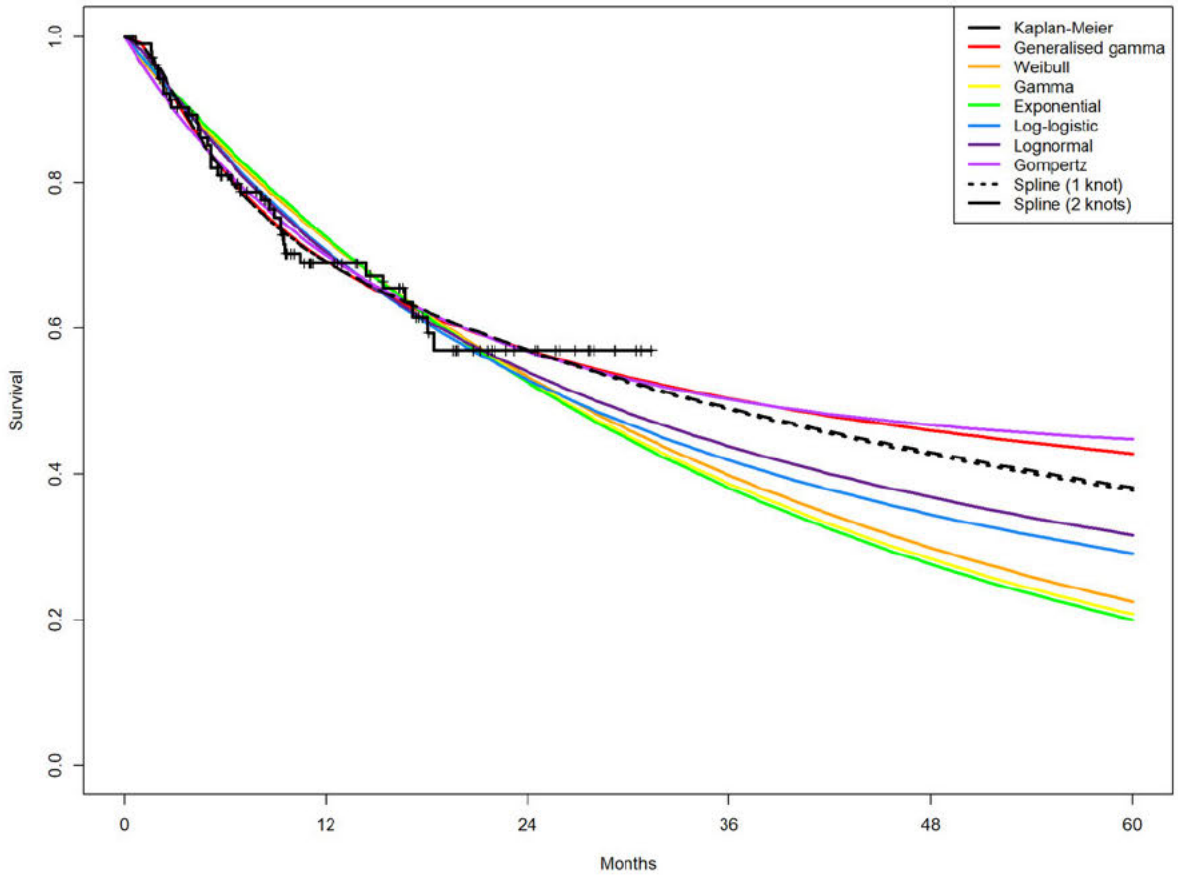


Goodness of fit (AIC, BIC) – PFSIR (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	432.9	3	440.9	2

Weibull	458.3	7	463.6	8
Gamma	460.4	8	465.7	9
Exponential	460.5	9	463.1	7
Log-logistic	447.9	6	453.2	6
Lognormal	443.3	4	448.6	4
Gompertz	445.3	5	450.6	5
Spline 1 knots	430.2	1	438.2	1
Spline 2 knots	430.7	2	441.3	3

Parametric survival curves – OS (N=105)

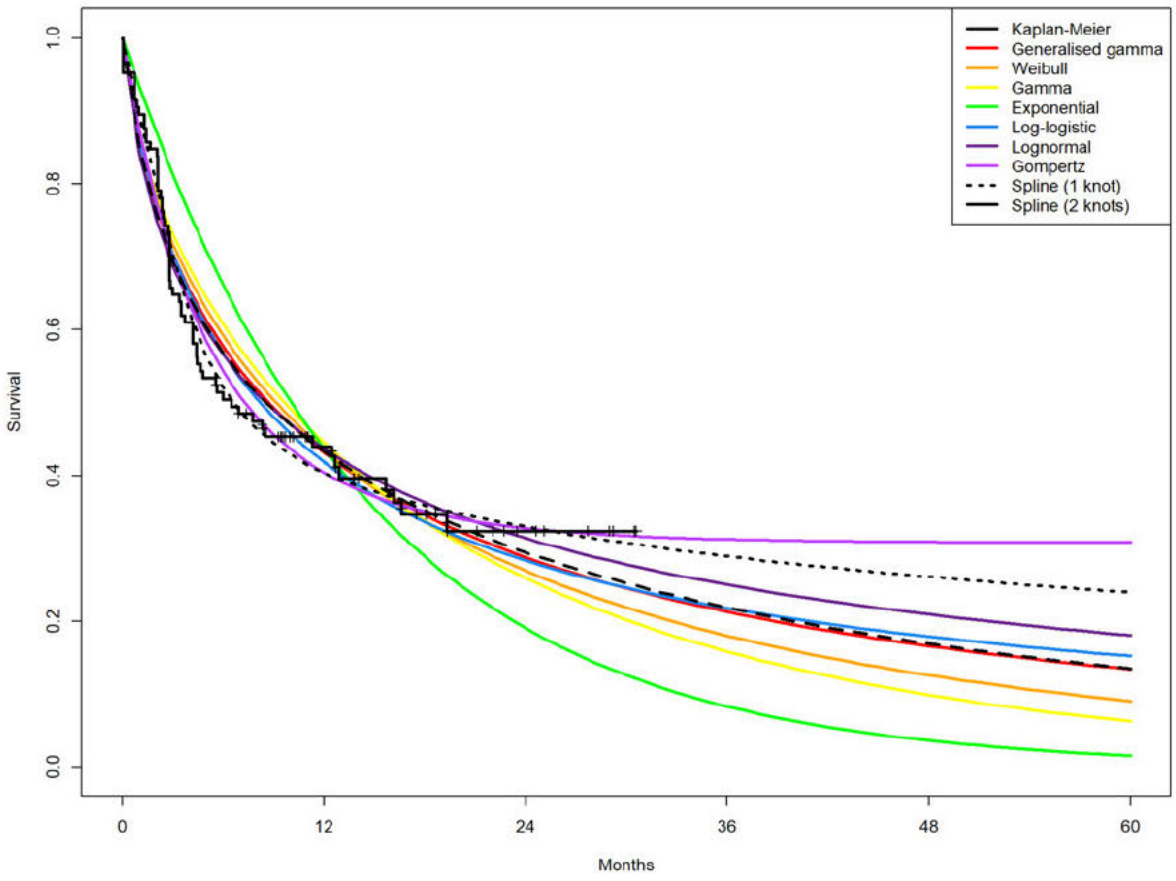


Goodness of fit (AIC, BIC) – OS (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	321.4	1	329.4	3
Weibull	327.2	8	332.5	7
Gamma	327.3	9	332.7	8
Exponential	325.4	7	328.0	2

Log-logistic	324.9	6	330.2	5
Lognormal	322.2	2	327.5	1
Gompertz	324.6	5	329.9	4
Spline 1 knots	322.3	3	330.3	6
Spline 2 knots	324.3	4	334.9	9

Parametric survival curves – ToT (N=105)



Goodness of fit (AIC, BIC) – ToT (N=105)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	463.1	5	471.1	6
Weibull	463.3	7	468.7	5
Gamma	465.9	8	471.2	7
Exponential	479.4	9	482.1	9
Log-logistic	458.8	3	464.1	3
Lognormal	462.7	4	468.0	4
Gompertz	455.8	2	461.1	1

Spline 1 knots	463.2	6	471.2	7
Spline 2 knots	451.4	1	462.0	2

Medicinrådet

Medicinrådets protokol for vurdering vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden

Version 1.0

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 protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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 den ansøgende virksomhed få besked.

Dokumentoplysninger	
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1. Begreber og forkortelser

AUC 5	5 x arealet under kurven for koncentration i forhold til tid *(Area under the curve)*
CR	Komplet respons (*complete response*)
dMMR:	Defekt mismatch repair (*mismatch repair deficient)*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency*)
EORTC-QLQ-C30	Spørgeskema til vurdering af livskvalitet (*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*)
EORTC-QLQ-EN24:	Spørgeskema til vurdering af livskvalitet (*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire- Endometrial Cancer Module 24*)
ESGO:	*European Society of Gynaecological Oncology*
EUnetHTA:	*European Network for Health Technology Assessment*
FDA:	*The Food and Drug Administration*
FINOSE:	Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HTA:	Medicinsk teknologivurdering (*Health Technology Assessment)*
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
ITT:	*Intention to treat*
MKRF:	Mindste klinisk relevante forskel
MSI-H:	Høj mikrosatellit-ustabilitet (*microsatellite instability-high)*
NICE:	*The National Institute for Health and Care Excellence*
ORR:	Objektiv responsrate
OS:	Samlet overlevelse (*Overall survival*)
PFS:	Progressionsfri overlevelse (*progression free survival*)
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*
PD:	Receptor (*Programmed death*)
PD-L:	Ligand (*Programmed death ligand*)
PP:	*Per Protocol*

PR: Partielt respons

RECIST: *Response Evaluation Criteria in Solid Tumors*

RR: Relativ risiko

SMD: *Standardized Mean Difference*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra GSK, som ønsker, at Medicinrådet vurderer dostarlimab (Jemperli) til avanceret eller recidiverende endometriecancer med defekt mismatch repair (dMMR)/høj mikrosatellit ustabilitet (MSI-H) ved progression under eller efter behandling med platinbaseret kemoterapi (dMMR/MSI-H). Medicinrådet modtog den foreløbige ansøgning den 21. december 2020. GSK fik positive opinion i EMA den 25. februar 2021.

2.1 Livmoderkræft

Livmoderkræft er den 5. hyppigste kræftform blandt kvinder i Danmark, og den hyppigste form for gynækologisk kræft [1]. Omkring 800 kvinder får hvert år konstateret livmoderkræft, hvor den hyppigste form (> 90 %) er kræft i livmoderslimhinden (endometriecancer) [1,2]. Sygdommen rammer typisk ældre kvinder (median alder 63 år) [3], og knap 11.000 patienter lever med sygdommen i Danmark [2].

Endometriecancer diagnosticeres i ca. 80 % af tilfældene tidligt, i stadie I, pga. tydelige symptomer [4]. Konstateres sygdommen i et tidligt stadie, betragtes den som kirurgisk helbredelig med en 5-års overlevelse på omkring 80-85 % [2,4]. Lokaltavanceret eller metastatisk endometriecancer (samlet benævnt avanceret endometriecancer) betragtes som uhelbredelig, og prognosen for overlevelse er væsentlig lavere med en median overlevelse på ca. 4 år for stadie III og 2 år for stadie IV [4].

Nogle patienter vil opleve tilbagefald af sygdommen inden for få år efter endt primærbehandling. Dette karakteriseres som oftest som uhelbredelig endometriecancer med en median overlevelse på omkring 12 måneder [5]. I Danmark er der ca. 100 patienter om året med nydiagnosticeret avanceret endometriecancer [1] samt ca. 30 patienter med recidiverende endometriecancer [1,6]. Omkring halvdelen af disse patienter vil opleve progression efter førstelinjebehandling og stadig være i en almen tilstand til at kunne modtage andenlinjebehandling. Resten af patienterne tilbydes palliativ behandling.

Mismatch repair (MMR)-systemet er et cellulært system, der bl.a. reparerer fejl i DNA-strengene [7]. En arvelig eller somatisk mutation i et af generne MLH1, MSH2, MSH6 eller PMS2 kan medføre dMMR. I væv med dMMR ophobes mutationer. Dette sker særligt i de såkaldte mikrosatellitregioner af DNA, hvorved dMMR ofte kan identificeres ved en høj grad af ustabilitet i disse DNA-regioner (MSI-H/*Microsatelite instability-High*) [7]. Funktionelle defekter i MMR-systemet i tumorvæv medfører en ophobning af såkaldt mutations-associerede neoantigener, som kan genkendes af immunsystemet [8]. Neoantigener er tumorspecifikke og dermed også patientspecifikke. Derved spiller et aktivt immunrespons en vigtig rolle i at bekæmpe dMMR/MSI-H-tumorer, hvilket giver et rationale for immunterapi til patienter med disse tumorer. dMMR/MSI-H skyldes oftest somatiske forandringer men kan også være arvelige (Lynch syndrom).

Ca. 22-30 % af tilfældene med endometriecancer har ifølge litteraturen dMMR/MSI-H, uanset sygdomsstadie [9,10]. Fagudvalget vurderer dog, at andelen er noget lavere hos patienter med avanceret eller recidiverende endometriecancer, men der findes ikke studier, der belyser dette. Fagudvalget vurderer, at der vil være ca. 20 nye patienter med dMMR/MSI-H pr. år, der er kandidater til andenlinjebehandling.

2.2 Dostarlimab

Dostarlimab (Jemperli) er et monoklonalt antistof, der binder til receptoren, *programmed death-1* (PD-1) og derved hæmmer dets binding til liganderne *programmed death-ligand-1 og -2* (PD-L1 og -2). PD-1-receptoren er til stede på overfladen af immunceller, og når receptoren aktiveres via PD-L1-binding medfører det et negativt feedback respons, der hæmmer T-celle-medieret celledød [11]. PD-L1 er overudtrykt på mange tumorceller, hvilket beskytter tumorcellerne fra immunsystemets reaktion. Ved at bryde PD-L1/PD-1-interaktionen i tumorceller kan dostarlimab modvirke denne beskyttelse [10], hvilket øger T-cellemedieret celledød i tumorer med mange mutations-associerede neoantigener.

Den forventede EMA-indikation er:

- monoterapi til behandling af voksne patienter med recidiverende eller avanceret endometriecancer med dMMR/MSI-high, som er progredieret under eller efter platinbaseret behandling.

Dostarlimab administreres som intravenøst over 30 minutter. Forventet dosis er 500 mg hver tredje uge over 4 cyklusser og derefter 1000 mg hver 6. uge indtil sygdomsprogression.

2.3 Nuværende behandling

Behandlingen af endometriecancer er beskrevet i kliniske retningslinjer fra Dansk Gynækologisk Cancer Grupper (DGCG) [5,12]. Størstedelen af patienter med endometriecancer i de tidlige stadier behandles med operation med kurativt (helbredende) sigte [1,12]. Avanceret og recidiverende endometriecancer behandles ligeledes med operation hvis muligt, hvor fjernelse af al synligt kræftvæv (makroradikal operation) har stor betydning for overlevelsen [5]. Efter operation behandles med carboplatin og paclitaxel i 6 serier. Formålet med denne behandling er at forlænge overlevelsen ved at begrænse yderligere sygdomsprogression. Herved opnås medianoverlevelse fra 15 måneder til over 3 år [13,14]. Patienter, der progredierer ca. 6 måneder eller mere efter afsluttet platinbehandling, betragtes som platinsensitive og kan efter progression genbehandles med platinbaseret kemoterapi [3][15].

Ved progression under eller op til et halvt år efter behandling med carboplatin og paclitaxel gives som standard pegyleret liposomalt doxorubicin. Denne behandling er ikke godkendt af EMA til indikationen, hvorfor brugen kan betragtes som off-label. I Danmark anses behandlingen med pegyleret liposomalt doxorubicin som standard i

dansk klinisk praksis [5]. Klinikerne i Danmark har flere års erfaring med brugen af pegyleret liposomalt doxorubicin til disse patienter. Anvendelsen af pegyleret liposomalt doxorubicin er også beskrevet som behandling til denne patientpopulation i de danske kliniske retningslinjer (DGCG) [5]. Den kliniske effekt af denne behandling er begrænset, og fagudvalget vurderer, at patienter, der modtager behandling med pegyleret liposomalt doxorubicin, har en median overlevelse på ca. 12 måneder [16].

Fordi patienter behandles forskelligt, alt efter om de forventes at respondere på genbehandling med platin-baseret kemoterapi, har fagudvalget valgt at dele patienterne op i to underpopulationer i de kliniske spørgsmål. Fagudvalget har derudover valgt to kliniske spørgsmål til populationen af patienter, der progredierer under eller efter platin-baseret kemoterapi, fordi nuværende standardbehandling ikke er godkendt af EMA. Da der ikke findes et godkendt lægemiddel til behandling af voksne patienter med recidiverende eller avanceret endometriecancer med dMMR/MSI-high, som er progredieret under eller efter platinbaseret behandling, vil Medicinrådets vurdering af den kliniske merværdi og dermed endelige anbefaling for denne population bero på sammenligning med placebo (klinisk spørgsmål 2).

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

Da der ikke findes en godkendt behandling til patienter med avanceret eller recidiverende endometriecancer, som er progredieret under eller inden for 6 måneder efter platin-baseret behandling. Derfor vil dostarlimab blive sammenlignet med placebo, og Medicinrådets anbefaling vil tage udgangspunkt i denne sammenligning. Medicinrådets fagudvalg vil derudover foretage en vurdering af værdien af dostarlimab sammenlignet med dansk standardbehandling, uanfægtet om denne er off-label. Denne vurdering vil dog ikke danne grundlag for Medicinrådets anbefaling.

3.1 Klinisk spørgsmål 1

Hvilken værdi har dostarlimab sammenlignet med platinbaseret kemoterapi for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling?

Population
Voksne med avanceret eller recidiverende dMMR/MSI-H endometriecancer, der er progredieret ca. 6 måneder eller mere efter platinbaseret behandling.

Intervention
Dostarlimab, som beskrevet i afsnit 2.2.

Komparator
Platinbaseret kemoterapi. Fx carboplatin AUC5 (5 x arealet under kurven for koncentration i forhold til tid) og paclitaxel 175 mg/m^2 hver tredje uge i op til 6-9 serier.

Effektmål
De valgte effektmål fremgår af Tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har dostarlimab sammenlignet med placebo for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?

Population
Voksne med avanceret eller recidiverende dMMR/MSI-H endometriecancer, der er progredieret under eller efter platinbaseret behandling.

Intervention
Dostarlimab, som beskrevet i afsnit 2.2.

Komparator
Placebo.

Effektmål
De valgte effektmål fremgår af Tabel 1.

3.3 Klinisk spørgsmål 3

Hvilken værdi har dostarlimab sammenlignet med pegyleret liposomalt doxorubicin for patienter med dMMR/MSI-high avanceret eller recidiverende endometriecancer, der er progredieret under eller efter platinbaseret behandling?

Population
Voksne med avanceret eller recidiverende dMMR/MSI-H endometriecancer, der er progredieret under eller efter platinbaseret behandling.

Intervention
Dostarlimab, som beskrevet i afsnit 2.2.

Komparator
40-50 mg/m^2 pegyleret liposomalt doxorubicin i.v. hver 4. uge i op til 6-8 serier. Denne behandling er ikke godkendt af EMA til indikationen men anses som standard i dansk klinisk praksis [5]. Hvis der ikke kan findes studier, der beskriver effekt og bivirkninger af pegyleret liposomalt doxorubicin, ønsker fagudvalget at få data, der beskriver effekt og bivirkning af doxorubicin.

Effektmål
De valgte effektmål fremgår af Tabel 1.

3.4 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i Tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1 Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Overlevelse (OS)	Kritisk	Dødelighed	Median OS	3 måneder
			OS-rate ved 12 måneder	5 procentpoint
Progressionsfri overlevelse	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Median PFS	3 måneder
			PFS-rate ved 24 måneder	10 procentpoint
Livskvalitet	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	EORTC-QLQ-EN24 i tillæg til EORTC-QLQ-C-30 Gennemsnitlig ændring i post-basislinje relativt til basislinjen	10 point
Objektiv responsrate	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel, der opnår komplet eller partielt respons	20 procentpoint
Bivirkninger / uønskede hændelser	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienter, der oplever mindst en bivirkning af grad 3-4	10 procentpoint
			Kvalitativ gennemgang af uønskede hændelser og bivirkninger	

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

3.4.1 Kritiske effektmål

Samlet overlevelse
Forbedret samlet overlevelse (OS) med mindst mulig toksicitet er det optimale mål for kræftbehandling. OS defineres som tiden fra randomisering eller behandlingsstart til død uanset årsag. For OS anvendes to mål til at vurdere den absolutte effekt: median OS og OS-rate. De to mål supplerer hinanden.

Avanceret eller recidiverende endometriecancer er en livstruende sygdom med dårlig prognose, og fagudvalget betragter derfor OS som et kritisk effektmål. For patienter med avanceret eller recidiverende endometriecancer er 1-årsoverlevelsen ca. 50 % med median OS på mindre end 12 måneder for platinresistente patienter [16][17]. Det er fagudvalgets erfaring, at for patienter, der er kandidater til platinbaseret kemoterapi i anden linje er 1-årsoverlevelsen ca. 60 % og median OS ca. 18-20 måneder [15]. Fagudvalget vurderer derfor, at en absolut forskel i OS-rate ved 1 år på 5 procentpoint og en absolut forskel for median OS på 3 måneder mellem intervention og komparator er klinisk relevant.

Progressionsfri overlevelse
Progressionsfri overlevelse (PFS) defineres som tiden fra randomisering eller behandlingsstart til første dokumentation af progression i henhold *til Response Evaluation Criteria i Solid Tumors* (RECIST)-kriterierne [18] eller død.

PFS anvendes som mål for sygdomsbyrde i vurderingen af dostarlimab til avanceret eller recidiverende endometriecancer. Fagudvalget vurderer, at det er et mål i sig selv at forsinke progressionen, fordi behandling med PFS også vil afspejle varigheden af effekten, hvilket fagudvalget vurderer, er et vigtigt potentiale ved immunterapeutisk behandling.

Fagudvalget vurderer derfor, at PFS er et kritisk effektmål. For patienter med platinresistent avanceret eller recidiverende endometriecancer er det fagudvalgets vurdering, at median PFS er mellem 3 og 6 måneder. Patienter, der er kandidater til platinbaseret kemoterapi i anden linje, vurderer fagudvalget, har en median PFS mellem 6-10 måneder [15]. Fagudvalget vurderer derfor, at en absolut forskel i PFS-rate ved 24 måneder på 10 procentpoint og en forskel i median PFS på 3 måneder mellem intervention og komparator er klinisk relevant.

3.4.2 Vigtige effektmål

Livskvalitet
Livskvalitet er et afgørende mål for den enkelte patient. Hos kræftpatienter kan livskvalitet måles med forskellige instrumenter, som omfatter både sygdomsspecifikke og generiske værktøjer. I dette tilfælde ønsker fagudvalget at vurdere livskvaliteten ved brug af European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Endometrial Cancer Module 24 (EORTC QLQ-EN24) [19] i tillæg til European Organisation for Research and Treatment of Cancer Quality-of-life questionnaire Core 30 (EORTC QLQ-C30) [20]. Redskaberne undersøger patienternes påvirkning af funktion, symptombyrde samt patienternes selvvurderede helbred. Der anvendes en scoringsskala fra 0-100. Den mindste klinisk relevante forskel baserer sig på en lille ændring, defineret som 10 point på tværs af domæner [21]. Ved opgørelsen ønsker fagudvalget at se, hvorledes livskvaliteten ændres igennem behandlingsforløbet, og den endelige værdi skal opgives som gennemsnittet af alle post-baseline-målinger fratrukket den gennemsnitlige baseline-måling.

Objektiv responsrate
Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons og afspejler interventionens antineoplastiske potentiale. Ved vurdering af ORR kategoriserer man ændringer af tumors størrelse efter påbegyndt behandling, jf. standardiserede guidelines (*Response Evaluation Criteria in Solid Tumors* (RECIST), version 1.1) [18]. Fagudvalget vurderer, at et væsentligt tumorsvind ofte vil mindske patientens sygdomsbyrde.

ORR underinddeles i følgende kategorier:

- Komplet respons (CR): Radiologisk kræftfri. Alle tumorlæsioner er væk, og ingen nye er fremkommet.
- Partielt respons (PR): Mindst 30 %-reduktion af tumorlæsioner sammenlignet med baseline.

Objektivt respons opnås for en patient, hvis vedkommende er klassificeret som CR eller PR, og objektiv responsrate defineres som CR + PR delt med det samlede patientantal. Fagudvalget vil vurdere den samlede andel af patienter, som opnår objektivt respons, samt andelene af patienter med CR eller PR.

Fagudvalget vurderer, at patienter med platinresistent avanceret eller recidiverende endometriecancer kan opnå en ORR på omkring 10 % ved nuværende behandling. Fagudvalget vurderer, at patienter, der er kandidater til platinbaseret kemoterapi i anden linje, har en ORR mellem 20 og 50 % [15]. Desuden vurderer fagudvalget, at en forskel på 20 procentpoint mellem intervention og komparator er klinisk relevant. Den høje grænse afspejler, at det er svært at overføre ORR til et direkte patientrelevant effektmål.

Bivirkninger / uønskede hændelser
Forekomst af bivirkninger grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [22]. På den baggrund vurderer fagudvalget, at bivirkninger er et vigtigt effektmål.

Fagudvalget ønsker data på nedenstående måleenheder:

- Andelen af patienter, der oplever mindst en bivirkning af grad 3 eller 4.

Fagudvalget mener, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere bivirkninger af grad 3 eller 4, er relevant for vurderingen. Uønskede hændelser af grad 3-4 er defineret i henhold til *National Cancer Institute* CTCAE, version 4.03 [22]. Fagudvalget vurderer, at en forskel på 10 procentpoint er klinisk relevant.

- Kvalitativ gennemgang af bivirkninger og uønskede hændelser.

Ansøger skal indsende en opgørelse over frekvensen af alle uønskede hændelser og bivirkninger. Fagudvalget vil gennemgå alle uønskede hændelser og bivirkninger, der opstår ved behandling med dostarlimab versus komparator med henblik på at vurdere hændelsernes type, håndterbarhed og reversibilitet, samt i hvor høj grad uønskede hændelser og bivirkninger medfører behandlingsstop. Eftersom virkningsmekanismerne og dermed bivirkningsprofilerne mellem intervention og komparator i de kliniske spørgsmål er forskellige, vil fagudvalget lægge stor vægt på den kvalitative gennemgang i sin vurdering af dostarlimab.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Anvendelse af upublicerede data sker ift. Medicinrådets princippapir [1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets princippapir.

Medicinrådet er i ansøgers foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor dostarlimab er sammenlignet direkte med placebo/doxorubicin/liposomalt doxorubicin/platinbaseret kemoterapi. Derfor skal ansøger søge efter studier til en indirekte sammenligning.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparatorer.

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Fagudvalget er dog opmærksomme på, at det vil være svært at finde studier omhandlende komparator, hvor MMR/MSI-status er kendt. Betydningen af MMR/MSI-status for sygdomsprognosen er uklar, da der ikke findes en entydig konklusion mellem studier, der har undersøgt betydningen af dMMR/MSI-H for sygdomsprognosen [10]. Fagudvalget kan derfor ikke udtale sig om betydningen af dMMR/MSI for sygdomsprognosen og ønsker at se data for relevant komparator uanset MMR/MSI-status.

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, fx i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

[1] For yderligere detaljer se Medicinrådets principper for anvendelse af upublicerede data

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.

- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Særlige forhold i denne protokol

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Medicinrådet 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.

Diagnostik
Der testes ikke rutinemæssigt for dMMR/MSI-H ved endometriecancer. Fagudvalget oplyser, at det er hensigten, at patienter med avanceret eller recidiverende endometriecancer skal testes på diagnosetidspunktet. I fælles guidelines fra ESMO-ESGO anbefales det at undersøge betydningen af MSI-H ved avanceret endometriecancer i fremtidige kliniske studier [3]. dMMR/MSI-test er klinisk praksis inden for kolorektalkræft, hvorved metoderne er tilgængelige og kendte [23,24]. Fagudvalget ønsker ansøgers overvejelser om, hvorvidt dMMR og MSI-H test er ligeværdige til at identificere, hvilke patienter der kan forventes at have gavn af dostarlimab.

irORR
Fagudvalget ønsker at se data for effektmålet immunrelateret ORR (irORR). Fagudvalget vurderer, at dette vil give et mere komplet billede af effekten/responset af dostarlimab, men vil ikke bruge effektmålet i kategoriseringen af lægemidlets værdi.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i æggestokkene og livmoderkræft

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Trine Jakobi Nøttrup *Overlæge*	Lægevidenskabelige Selskaber og Dansk Selskab for Klinisk Onkologi
Medlemmer	**Udpeget af**
Anya Eidhammer *Ledende overlæge*	Region Nordjylland
Jacob Christian Lindegaard *Overlæge*	Region Midtjylland
Trine Lembrecht Jørgensen *Afdelingslæge*	Region Syddanmark
Dejan Labudovic *Afdelingslæge*	Region Sjælland
Kristine Madsen *Afdelingslæge*	Region Hovedstaden
Trine Zeeberg Iversen *Afdelingslæge*	Dansk Selskab for Klinisk Onkologi
Henrik Horwitz *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi
Henrik Kjer *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Birthe Lemley *Patient/patientrepræsentant*	Danske Patienter
Dorte Blou *Patient/patientrepræsentant*	Danske Patienter
Tidligere medlemmer, der har bidraget til arbejdet med protokollen	**Udpeget af**

Sammensætning af fagudvalg	
Bente Lund *Overlæge*	Region Nordjylland

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	24. marts 2021	Godkendt af Medicinrådet

12. Bilag

Bilag 1: Søgestrenge

Søgestreng til PubMed: https://pubmed.ncbi.nlm.nih.gov/advanced/

#	Søgestreng	Kommentar
#1	Endometrial Neoplasms[majr:noexp] AND drug therapy[sh]	Søgetermer for population
#2	(endometrial[ti] OR endometrium[ti]) AND (cancer*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti])	
#3	Uterine Neoplasms[majr:noexp] AND Carcinosarcoma[majr] AND drug therapy[sh]	
#4	uterine cancer[ti] OR uterine carcinoma*[ti] OR uterine serous carcinoma*[ti] OR uterine papillary serous carcinoma*[ti] OR uterine carcinosarcoma*[ti] OR carcinosarcoma of the uterus[ti]	
#5	advanced[tiab] OR incurable[tiab] OR inoperable[tiab] OR un-resectable[tiab] OR unresectable[tiab] OR non-resectable[tiab] OR relaps*[tiab] OR refractory[tiab] OR metasta*[tw] OR recurren*[tw]	
#6	(#1 OR #2 OR #3 OR #4) AND #5	
#7	radiation[ti] OR radiotherapy[ti] OR surgery[ti] OR secondary cytoreduction[ti] OR early stage[ti] OR stage I[ti] OR stage II[ti]	Eksklusion af irrelevante publikationstyper og behandlinger/stadier
#8	neoadjuvant[ti] OR untreated[ti] OR non-treated[ti] OR treatment-naive[ti] OR chemo-naive[ti] OR chemotherapy-naive[ti]	
#9	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	
#10	study[ti] OR studies[ti]	
#11	#9 NOT #10	
#12	#6 NOT (#7 OR #8 OR #11)	
#13	dostarlimab[tiab] OR TSR-042[tiab] OR TSR042[tiab] OR TSR-42[tiab] OR WBP285[tiab] OR WBP-285[tiab]	Søgetermer for intervention og kompartorer
#14	Placebos[mh] OR placebo[tiab] OR sham[tiab] OR dummy[tiab]	
#15	Platinum[mh] OR Platinum Compounds[mh] OR Organoplatinum Compounds[mh] OR Carboplatin[mh] OR platin*[tiab] OR carboplatin[tiab]	

#16	Taxoids[mh] OR taxane*[tiab] OR paclitaxel[tw] OR docetaxel[tw] OR Taxol*[tiab]	
#17	#15 AND #16	
#18	platinum-based combination[tiab]	
#19	liposomal doxorubicin[nm] OR Doxorubicin[mh] OR doxorubicin[tiab]	
#20	#13 OR #14 OR #17 OR #18 OR #19	
#21	#12 AND #20 AND english[la]	Endelig søgning

Feltkoder
ti: titel
tiab: titel, abstract, forfatter-keywords
majr: major mesh term
nm: supplementary concept/substance
sh: subheadings
tw: feltkode for enkeltord, der optræder i titel, abstract, forfatter-keyword, mesh term m.fl.
pt: publikationstype
la: sprog

Søgestreng til CENTRAL: https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgestreng	Kommentar
#1	(uterus next cancer or (endometrium next (cancer or carcinoma)) or carcinosarcoma):kw	Søgetermer for population
#2	((endometrial or endometrium) near/2 (cancer* or carcinoma* or adenocarcinoma*)):ti	
#3	((uterine or uterus) near/2 (cancer* or carcinoma* or carcinosarcoma*)):ti	
#4	(advanced or incurable or inoperable or un-resectable or unresectable or non-resectable or relaps* or refractory or metasta* or recurren*):ti,ab,kw	
#5	(#1 OR #2 OR #3) and #4	
#6	(radiation or radiotherapy or surgery or "secondary cytoreduction" or early stage or "stage I" or "stage II"):ti	
#7	(neoadjuvant or untreated or non-treated or treatment-naive or chemo-naive or chemotherapy-naive):ti	
#8	#5 not (#6 or #7)	
#9	(dostarlimab or TSR042 or TSR next 042 or wbp285 or wbp next 285):ti,ab,kw	Søgetermer for intervention og komparatorer
#10	(placebo or sham or dummy):ti,ab,kw	
#11	(platin* or carboplatin):ti,ab,kw	
#12	(taxane or paclitaxel or docetaxel):ti,ab,kw	
#13	#11 and #12	
#14	(platinum-based near/2 combination):ti,ab	
#15	doxorubicin:ti,ab,kw	
#16	#9 or #10 or #13 or #14 or #15	
#17	#8 and #16	
#18	("conference abstract" or review):ti,pt	Eksklusion af irrelevante publikationstyper
	(clinicaltrials.gov or trialsearch):so	
	(meeting or conference or proceedings):so	
	#18 or #19 or #20	

	#17 not #21	
	#22 not pubmed:an	Endelig søgning, fratrukket referencer fra Pubmed. Afgrænses til Trials

Feltkoder
ti: titel
ab: abstract
kw: indekserede termer fra MeSH/Medline eller Emtree/Embase
so: source
pt: publikationstype