Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende pembrolizumab i kombination med kemoterapi med eller uden bevacizumab til behandling af livmoderhalskræft, hvis tumorer udtrykker PD-L1 CPS ≥ 1

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. pembrolizumab i kombination med kemoterapi med eller uden bevacizumab
2. Forhandlingsnotat fra Amgros vedr. pembrolizumab i kombination med kemoterapi med eller uden bevacizumab
3. Ansøgers endelige ansøgning vedr. pembrolizumab i kombination med kemoterapi med eller uden bevacizumab

Den 26. juni 2023

«AddressBlock»
simon.leth@merck.com
MSD Danmark ApS
Havneholmen 25, 1561 København V
msd.com

Til: Medicinrådet,
att. Natasja Gudmann og Anna Kollerup Iversen
Dampfærgevej 21-23, 3. sal
2100 København Ø

Notat til udkast til Medicinrådets anbefaling vedr. pembrolizumab i kombination med kemoterapi med eller uden bevacizumab til levetidsforlængelse af livmoderhals-kræft, hvis tumorer udtrykker PD-L1 CPS $\geq$ 1

MSD Danmark ønsker hermed at kvittere for muligheden for at komme med bemærkninger til ovennævnte udkast til anbefaling.

Allerførst vil vi sige tak til sekretariatet for dialogen i både validerings-og vurderingsprocessen. Den har været konstruktiv og åben og har hjulpet os til hurtigt at kunne svare på de stillede spørgsmål.

For så vidt angår den kliniske del af vurderingsrapporten ønsker vi at understrege vigtigheden af de opdaterede OS-data, som blev præsenteret på ASCO i juni 2023. De opdaterede data viser en statistisk og klinisk signifikant overlevelseseffekt og bekræfter dermed de data, som nærværende ansøgning er baseret på: Efter en median opfølgningstid på 39,1 måneder sås en statistisk og klinisk signifikant forskel i OS på 12,1 måneder til fordel for pembrolizumab-gruppen (28,6 mdr. vs. 16,5 mdr., HR 0.60 (0.49-0.74); P< 0.0001) (1).

Vi minder samtidig om, at kræft i livmoderhalsen forekommer hyppigst hos kvinder i alderen 30-45 år, og at 5-års overlevelsen ved metastatisk sygdom med nuværende standardbehandling er 18 %.

I forhold til den sundhedsøkonomiske analyse anerkender vi, at ekstrapolation af overlevelsesdata er behæftet med usikkerhed. Det gælder, når både vi og Medicinrådet foretager ekstrapolationerne, og i vores optik vælger Medicinrådet i denne sag en noget konservativ tilgang til ekstrapolationerne. De opdaterede data fra ASCO'23 bekræfter MSDs ekstrapolationer, hvor der i år 3 er omkring 30% og 15% i hhv. pembrolizumab- og kontrolarmen i det progressionsfri stadie, mens Medicinrådet ekstrapolerede hhv. 17% og 7%.

Omvendt vil vi gerne kvittere for, at Medicinrådet har valgt at beregne ICER'en ud fra vægtbaseret dosering af pembrolizumab. Her har vi været konservative, og baseret vores analyse på fast dosering.

[redacted]

Med udgangspunkt i den overbevisende overlevelsesgevinst på 12,1 måneder, patientpopulationen på kvinder i alderen 30-45 år med en nuværende 5-års overlevelse på 18% og en ICER, som har medført en anbefaling i de lande vi normalt sammenligner os med, mener vi, at pembrolizumab i kombination med kemoterapi udgør en oplagt standardbehandling i Danmark fremover.

Med venlig hilsen,

Simon Leth
Chef for sundhedsøkonomi, MSD Danmark

Referencer

1) Monk BJ, Colombo N, Tewari KS, Dubot C, Caceres MV, Hasegawa K, et al. Oral Abstract Session KEYNOTE-826 : Final overall survival results from a randomized , double-blind , phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy for first-line treatment of persistent , recurrent , or metastatic cervical cance. 2023;61:5500.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

28.06.2023
CAF/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.08.2023
Leverandør	MSD
Lægemiddel	Keytruda (pembrolizumab)
Ansøgt indikation	Keytruda i kombination med kemoterapi med eller uden bevacizumab, er indiceret til behandling af persisterende, recidiverende eller metastatisk cervixcancer hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Keytruda (pembrolizumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP (DKK)	Rabatprocent ift. AIP
Keytruda	25 mg/ml	4 ml.	22.058,88	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence indenfor denne indikation.

Tabel 2: Lægemiddeludgift Keytruda

Lægemiddel	Styrke	Paknings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Keytruda	25 mg/ml	4 ml	2 mg/kg hver 3. uge eller 4 mg/kg hver 6. uge IV	[redacted]	[redacted]*

*Vægt: 64,7 kg jf. Medicinrådets vurderingsrapport

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Ansøgning om vurdering af den kliniske merværdi af KEYTRUDA® (pembrolizumab) i kombination med kemoterapi med eller uden bevacizumab til behandling af patienter med persisterende, recidiverende eller metastatisk cervix cancer hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥1.

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

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Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

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

1. Basic information

Contact information	
Name	**Mette Boie Steffensen**
Title	Sundhedsøkonom
Phone number	+45 24 44 37 27
E-mail	mette.boie.steffensen@merck.com
Name	**Truc Hoang**
Title	Medical Advisor
Phone number	+45 31 61 09 11
E-mail	Truc.hoang@merck.com

Overview of the pharmaceutical	
Proprietary name	KEYTRUDA®
Generic name	Pembrolizumab
Marketing authorization holder in Denmark	MSD Danmark ApS MSD modtog d. 29. April European Medicines Agency (EMA) committee for Medicinal Products for Human Use (CHMP) commission decision.
ATC code	L01XC18
Pharmacotherapeutic group	Antineoplastic agents
Active substance(s)	Pembrolizumab
Pharmaceutical form(s)	Koncentrat til infusionsvæske, opløsning.
Mechanism of action	KEYTRUDA® er et humaniseret monoklonalt antistof, der binder til programmed cell death-1 (PD-1)-receptoren og blokerer dets interaktion med liganderne PD-L1 og PD-L2. KEYTRUDA® aktiverer T-cellemedieret respons, herunder anti-tumorrespons, ved at blokere PD-1-bindingen til PD-L1 og PD-L2, som er udtrykt på antigenpræsenterende celler, og som kan udtrykkes af tumorer eller andre celler i tumorens mikromiljø.
Dosage regimen	Den anbefalede dosis af KEYTRUDA® som en del af kombinationsbehandling er 200 mg hver 3. uge eller 400 mg hver 6. uge administreret som intravenøs infusion over 30 minutter.

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	KEYTRUDA® i kombination med kemoterapi med eller uden bevacizumab, er indiceret til behandling af persisterende, recidiverende eller metastatisk cervix cancer hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥1.

Other approved therapeutic indications	KEYTRUDA® som monoterapi er indiceret til behandling af fremskredent (inoperabelt eller metastatisk) melanom hos voksne. KEYTRUDA® som monoterapi er indiceret til adjuverende behandling af voksne med stadie III-melanom og lymfeknudeinvolvering, som har fået foretaget komplet resektion. KEYTRUDA® som monoterapi er indiceret til førstelinjebehandling af metastatisk ikke-småcellet lungecancer hos voksne, hvis tumorer udtrykker PD-L1 med tumour proportion score (TPS) ≥ 50% uden EGFR- eller ALK-positive mutationer i tumor. KEYTRUDA®, i kombination med pemetrexed og platinbaseret kemoterapi, er indiceret til førstelinjebehandling af metastatisk ikke-planocellulær ikke-småcellet lungecancer hos voksne uden EGFR- eller ALK-positive mutationer i tumorer. KEYTRUDA®, i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel, er indiceret til førstelinjebehandling af metastatisk planocellulær ikke-småcellet lungecancer hos voksne. KEYTRUDA® som monoterapi er indiceret til behandling af lokalt fremskredent eller metastatisk ikke-småcellet lungecancer hos voksne efter tidligere behandling med minimum én kemoterapi, og hvis tumorer udtrykker PD-L1 med TPS ≥ 1%. Patienter med EGFR- eller ALK-positive mutationer i tumor bør også have været i targeteret behandling inden behandling med KEYTRUDA®. KEYTRUDA® som monoterapi er indiceret til behandling af recidiverende eller refraktært klassisk Hodgkins lymfom hos voksne og pædiatriske patienter i alderen 3 år og derover, som har oplevet svigt af autolog stamcelletransplantation (ASCT), eller har oplevet svigt efter at have fået mindst 2 forudgående behandlinger, når ASCT ikke er en behandlingsmulighed. KEYTRUDA® som monoterapi er indiceret til behandling af lokalt fremskredent eller metastatisk urotelialt karcinom hos voksne, som tidligere har fået platinbaseret kemoterapi. KEYTRUDA® som monoterapi er indiceret til behandling af lokalt fremskredent eller metastatisk urotelialt karcinom hos voksne, som er uegnede til cisplatinbaseret kemoterapi, og hvis tumorer udtrykker PD-L1 med en kombineret positiv score (CPS) ≥ 10. KEYTRUDA® som monoterapi eller i kombination med platinbaseret kemoterapi og 5-fluorouracil (5-FU) er indiceret til førstelinjebehandling af metastatisk eller inoperabelt recidiverende planocellulært hoved-hals karcinom hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1. KEYTRUDA® som monoterapi er indiceret til behandling af recidiverende eller metastatisk planocellulært hoved-hals karcinom hos voksne, hvis tumorer udtrykker PD-L1 med TPS ≥ 50% og med sygdomsprogression under eller efter platinbaseret kemoterapi. KEYTRUDA® i kombination med axitinib, er indiceret til førstelinjebehandling af fremskredent renalcellekarcinom hos voksne. KEYTRUDA® i kombination med lenvatinib, er indiceret til førstelinjebehandling af fremskredent renalcellekarcinom hos voksne

Overview of the pharmaceutical	
	KEYTRUDA® som monoterapi er indiceret til adjuverende behandling af voksne med renalcellekarcinom med øget risiko for recidiv efter nefrektomi, eller efter nefrektomi og resektion af metastatiske læsioner KEYTRUDA® som monoterapi er indiceret til førstelinjebehandling af metastatisk kolorektal cancer med høj mikrosatellitinstabilitet (MSI H) eller mismatch repair-defekt (dMMR) hos voksne. KEYTRUDA® som monoterapi er indiceret til behandling af følgende tumorer med MSI-H eller dMMR hos voksne med: - ikke-resektabel eller metastatisk kolorektal cancer efter tidligere fluoropyrimidinbaseret kombinationsbehandling; - avanceret eller recidiverende endometriecancer med sygdomsprogression under eller efter tidligere behandling med platinbaseret terapi i enhver setting, og som ikke er egnet til kurativ operation eller strålebehandling; - ikke-resektabel eller metastatisk ventrikelkræft, tyndtarmskræft eller galdevejskræft med sygdomsprogression under eller efter mindst en forudgående behandling. KEYTRUDA® i kombination med platin- og fluoropyrimidinbaseret kemoterapi, er indiceret til førstelinjebehandling af patienter med lokalt fremskredent inoperabelt eller metastatisk karcinom i esophagus eller HER-2 negativ adenokarcinom i den gastroesofageale overgang hos voksne, hvis tumorer udtrykker PD L1 med CPS ≥ 10. KEYTRUDA® kombination med kemoterapi som neoadjuverende behandling, og efterfulgt af monoterapi som post-operativ adjuverende behandling, er indiceret til behandling af voksne med lokalt avanceret eller tidlig triple-negativ brystkræft med høj risiko for recidiv. KEYTRUDA® i kombination med kemoterapi, er indiceret til behandling af lokalt recidiverende inoperabel eller metastatisk triple-negativ brystkræft hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10 og som ikke har fået forudgående kemoterapi for metastatisk sygdom KEYTRUDA® i kombination med lenvatinib, er indiceret til behandling af fremskreden eller recidiverende endometriecancer hos voksne med sygdomsprogression under eller efter tidligere behandling med platinbaseret terapi i enhver setting, og som ikke er kandidater til kurativ operation eller strålebehandling.
Will dispensing be restricted to hospitals?	Udleveringsgruppe: BEGR
Combination therapy and/or co-medication	N/A

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	Styrke: 100 mg KEYTRUDA® 25 mg/ml koncentrat til infusionsvæske, opløsning. Et hætteglas med 4 ml koncentrat indeholder 100 mg pembrolizumab. Hver ml koncentrat indeholder 25 mg pembrolizumab. Pakning: 1 stk. konc.t.inf.væske.
Orphan drug designation	Nej

2. Forkortelser

AIC	*Akaike information criterion*
APat	*All participants as treated*
AUC	*Area under the curve*
BIC	*Bayesian information criterion*
CHMP	*Committee of Medicinal Products for Human Use*
CPS	*Combined positive score*
DGCG	Dansk Gynækologisk Cancer Gruppe
DMCG	Danske Multidicisplinære Cancer Grupper
DOR	*Duration of response*
ECOG PS	*Eastern Cooperative Oncology Group performance status*
EMA	*European Medicines Agency*
FA	*Final analysis*
H	Hypotese
HPV	Human Papilloma virus
HR	Hazard ratio
IA	Interimsanalyse
IHC	Immunhistokemisk
ICERs	*Incremental cost-effectiveness ratios*
ITT	*Intention-to-treat*
i.v.	intravenøst
KM	Kaplan-Meier
KN826	KEYNOTE-826
KRIS	Koordineringsrådet for ibrugtagning sygehusmedicin
LYs	*Life years*
NR	*not reached*
ORR	*Objective response rate*
OS	Samlet overlevelse
(OWSAs)	*One-way sensitivity analyses*
PBO+CT	Placebo + kemoterapi
PD-1	*Programmed Death-1*
PD-L1	*Programmed Death Ligand 1*
PEM+CT	Pembrolizumab + kemoterapi
PFS	Progressionsfri overlevelse
P/R/M	Persisterende/recidiverende/metastatisk
PrePS	*Pre-progression survival*
PPS	*Post-progression survival*

QALYs	*Quality-adjusted life years*
RECIST	*Response evaluation criteria in Solid Tumors*
SAE	Alvorlige bivirkninger
STM	*State Transition Model*
TTD	*Time to deterioration*
TTP	Time-to-progression
VAS	*Visual Analogue scale*
VEGF	*vascular endothelial growth factor*

3. Tables and Figures

Figuroversigt:

Tabeloversigt:

4. Resumé

Indikation og population

Den 29. april 2022 blev pembrolizumab i kombination med kemoterapi godkendt af EMA CHMP til behandling af patienter med persisterende, recidiverende eller metastatisk (P/R/M) cervix cancer med følgende indikation:

Pembrolizumab i kombination med kemoterapi med eller uden bevacizumab, er indiceret til behandling af persisterende, recidiverende eller metastatisk cervix cancer hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1.

EMA godkendelsen samt denne ansøgning baserer sig på de klinisk relevante og statistisk signifikante effektdata fra KEYNOTE-826 (KN826), et dobbeltblindet randomiseret fase III studie, der inkluderer patienter med ikke tidligere behandlet P/R/M cervix cancer.

Incidensen for cervix cancer har gennem den seneste årrække været faldende med gennemsnitlig 352 nye tilfælde pr. år i perioden 2015-2019 sammenlignet med 269 nye tilfælde registreret i perioden 1. juli 2020 - 30. juni 2021. juli [1, 2]. Dette er resultatet af den indsats der er blevet lagt i forebyggelse og tidlig opsporing med vaccinations-og screeningsprogrammet [2-4].

Cervix cancer er mest hyppig hos kvinder i aldersgrupperne 35-45 år og 70 år, med ca. 50% i aldersgrunden <45 år. Prognosen er generelt god med en 5-års overlevelse på 75% (95% CI 88,5-91,8) [1], da en stor del af patientgruppen bliver diagnosticeret med tidlig stadie sygdom hvortil kurativ intenderet behandling med kirurgi ± konkomittant kemostråleterapi er indiceret [2, 5]. 5-års overlevelsen falder dog markant til kun 18% for patienter diagnosticeret metastatisk sygdom [2].

Der er således for patienter med P/R/M cervix cancer fortsat et behov for nye behandlingsmuligheder, der kan forbedre overlevelsen.

Intervention

Intervention i denne ansøgning er:

- Pembrolizumab 200 mg
- Paclitaxel 175 mg/m^2
- Cisplatin 50 mg/m^2 *ELLER* carboplatin AUC 5
- ± bevacizumab 15 mg/kg

Alle behandlinger blev givet intravenøst (i.v.) hver 3. uge til progression eller uacceptabel toksicitet i op til 35 serier.

Pembrolizumab har været anvendt som monoterapi til cancerbehandling siden 2015 og er godkendt i kombination med kemoterapi til behandling af bl.a. ikke-småcellet lungekræft, hovedhalskræft og brystkræft [6], jf. afsnit 1. Eftersom kombinationen af cis-eller carboplatin, paclitaxel ± bevacizumab har været standardbehandlingen for 1. linje behandling af patienter med P/R/M cervix cancer siden 2015 [7, 8], vil ændringen være en tilføjelse af pembrolizumab til dette behandlingsregime.

Komparator

MSD mener vi har valgt den klinisk relevante og hensigtsmæssige komparator med kontrolarmen i KN826 som er en kombinationen af:

- Paclitaxel 175 mg/m^2
- Cisplatin 50 mg/m^2 *ELLER* carboplatin AUC 5
- ± bevacizumab 15 mg/kg

Ovenstående regime afspejler nuværende standardbehandling for den relevante danske patientgruppe og tillader på samme tid vurdering af klinisk merværdi af intervention på et solidt statistisk grundlag.

Vigtigste resultater fra OS og PFS analyser

KN826's studiepopulation blev inkluderet uanset PD-L1 status og den præspecificerede statistiske analyseplan tillod analyse af *overall survival* (OS) og progressionsfri overlevelse (PFS) i PD-L1 *combined positive score* (CPS) ≥1, *intention-to-treat* (ITT) og PD-L1 CPS ≥10.

Det er effektresultaterne i PD-L1 CPS ≥1 populationen, der danner grundlag for EMA godkendelsen og denne ansøgning.

Der blev i KN826 randomiseret i alt 308 patienter til pembrolizumab + kemoterapi (PEM+CT) og 309 patienter til placebo + kemoterapi (PBO+CT), hvoraf subgruppen med PD-L1 CPS ≥1 bestod af 273 patienter i PEM+CT og 275 patienter i PBO+CT. Median opfølgningstid ved data cut-off d. 3. maj 2021 var 22,0 mdr. (range 15,1-29,4).

For patienter med PD-L1 CPS ≥1 var der en statistisk signifikant forbedring i OS for PEM+CT vs. PBO+CT med en hazard ratio (HR) 0,64 (95% CI 0,50-0,81) og p<0,0001. Median OS i PEM+CT var *not reached* (NR) (95% CI 19,8-NR) vs. 16,3 mdr. (95% CI 14,5-19,4) i PBO+CT. Forskellen i 12 og 24 måneders overlevelsesrate var henholdsvis 12,2% og 11,3% til fordel for PEM+CT vs. PBO+CT.
Median PFS for PD-L1 CPS ≥1 populationen var 10,4 mdr. (95% CI 9,7-12,3) i PEM+CT vs. 8,2 mdr. (95% CI 6,3-8,5) i PBO+CT med en HR 0,62 (95% CI 0,50-0,77) og p<0,0001. Der ses efter 12 mdr. en forskel i PFS-rate på 11,4% til fordel for PEM+CT (45,5%) vs. PBO+CT (34,1%) svarende til at 33% flere patienter er progressionsfrie i PEM+CT gruppen sammenlignet med PBO+CT. Denne forskel ser ud til at øges over tid, hvor der efter 24 mdr. er en forskel i PFS-rate på 19,1% (33,1% i PEM+CT vs. 14,0% i PBO+CT), som svarer til over en fordobling af patienter i PEM+CT uden progression eller død sammenlignet med kontrolgruppen, PBO+CT [9].

Bivirkninger

Bivirkninger rapporteres hos patienter, som har modtaget minimum én dosis studiemedicin (*all participants as treated* (APat)) svarende til 307 patienter i PEM+CT og 309 patienter i PBO+CT.

Median behandlingslængde i KN826 var længere i PEM+CT gruppen med 10,0 mdr. (range 0,0-26,9 og i gennemsnit 14,0 serier) vs. 7,7 mdr. (range 0,0-27,4 og i gennemsnit 11,0 serier) i PBO+CT gruppen.

Af patienter som fik en *all-cause* ≥grad 3 bivirkning i APat-populationen, var der 251/307 (81,8%) i PEM+CT og 232/309 (75,1%) i PBO+CT. Dette er en absolut forskel på +6,7%-point i PEM+CT vs. PBO+CT, men den relative risiko var på 1,05 (95% CI 0,92-1,20), hvilket indikerer en identisk risiko for udvikling af ≥grad 3 bivirkninger for begge behandlingsgrupper.

Bivirkninger for PD-L1 CPS ≥1 populationen viser ingen betydende forskelle mellem PD-L1 CPS ≥1 og APat-populationen, hvorfor APat-populationen er vigtig som reference for sikkerhed, grundet det store patientgrundlag.

Den overordnede incidens af bivirkninger alle grader var 99,3% i PEM+CT og 99,4% i PBO+CT. De hyppigste i PEM+CT var anæmi, alopecia, kvalme, diarré og fatigue, hvoraf anæmi, alopecia og kvalme også var de hyppigste i PBO+CT, efterfulgt af forstoppelse, fatigue og opkast.

Incidensen af alvorlige bivirkninger (SAE) var højere i PEM+CT med 49,8% vs. 42,4% i PBO+CT. De SAE'er som havde en incidens på ≥5% var febril neutropeni (6,8% i PEM+CT vs. 4,2% i PBO+CT), urinvejsinfektion (5,2% i PEM+CT vs. 5,8% i PBO+CT) og anæmi (4,6% i PEM+CT vs. 3,9% i PBO+CT).

Incidensen af bivirkninger, som førte til behandlingsophør var 37,5% i PEM+CT vs. 26,5% i PBO+CT, hvoraf incidensen af behandlingsophør som følge af bivirkning i både PEM+CT og PBO+CT var højere i +bevacizumab-subgruppen (hhv. 44,9% vs. 31,6%) sammenlignet med -bevacizumab-subgruppen (hhv. 24,3% vs. 18,1%).

Der var overordnet en højere incidens af grad 3-5 bivirkninger og alvorlige bivirkninger i interventionsarmen PEM+CT vs. komparator PBO+CT. Hyppighed og profil er dog i overensstemmelse med bivirkningsprofiler for de enkelte komponenter der udgør behandlingsregimet, cisplatin, paclitaxel, bevacizumab og pembrolizumab.

Livskvalitet

Livskvalitetsanalyserne EORTC QLQ-C30 og EQ-5D-5L viste kollektivt, at der ikke var en forværring af livskvalitet hos patienter behandlet i PEM+CT-armen sammenlignet med PBO+CT til trods for tillæg af pembrolizumab til behandlingsregimet og en numerisk højere incidens af grad 3-5 og alvorlige bivirkninger. EQ-5D-5L analysen viste, at en højere andel af patienter havde forbedret eller stabil livskvalitet i forhold til baseline sammenlignet med PBO+CT og der var en forlænget *time to deterioration* (TTD).

Den sundhedsøkonomiske analyse

De signifikante kliniske resultater på overlevelse understøtter estimaterne af merværdi i vores sundhedsøkonomiske model med en gevinst på 1,407 kvalitetsjusteret leveår sammenlignet med nuværende dansk standard behandling. ICER var ligeledes favorable for PEM+CT med en estimeret omkostning pr. kvalitetsjusteret leveår på 631.276 kr. sammenlignet med kemoterapi.

Konklusion

Patienter med cervix cancer som får tilbagefald af deres sygdom eller patienter diagnosticeret med dissemineret sygdom har en dårlig prognose med en forventet median overlevelse på ca. 17 mdr. på nuværende standardbehandling. KN826 er det første randomiserede fase 3 studie, som siden

publikationen af GOG 240 studiet i 2014 har vist en signifikant overlevelsesgevinst i en population af patienter med P/R/M cervix cancer. Kontrolarmen i KN826 afspejler nuværende dansk klinisk praksis inkl. mulighed for til- eller fravalg af bevacizumab under hensyntagen til patientens individuelle risikofaktorer. Denne må derfor betragtes som den bedste komparator for interventionen, som ansøgningen omhandler.

Forbedret samlet overlevelse med mindst mulig toksicitet og forværring af livskvalitet er det optimale mål for kræftbehandling. Resultaterne fra KN826 demonstrerer en signifikant forbedring i både OS og PFS for patienter med en 37% risikoreduktion for død samt over en fordobling i 2-års PFS rate med en acceptabel numerisk øget incidens i grad 3-5 samt alvorlige bivirkninger med tillæg af pembrolizumab sammenlignet med kemoterapi alene. Dette havde dog ingen negativ indflydelse på patienters livskvalitet, hvor der derimod var en trend mod forbedret/stabil livskvalitet hos PEM+CT gruppen vs. PBO+CT samtidig med en længere tid til forværring.

Disse resultater indikerer, sammen med den estimerede QALY gevinst, en stor klinisk merværdi for patienter med P/R/M cervix cancer sammenlignet med nuværende dansk standardbehandling.

5. Patientpopulationen, intervention og valg af komparator(er)

5.1 Sygdommen og patientpopulationen

Cervix cancer

Livmoderhalskræft eller cervix cancer er kræft, som opstår i livmoderhalsens celler. Sygdommen kan ramme kvinder i alle alder, men er hyppigst hos kvinder i aldersgrupperne 35-45 år og 70 år, hvoraf omtrent halvdelen er under 45 år på diagnosetidspunktet. Prognosen er generelt god med en 5-års overlevelse på 75% (95% CI 88,5-91,8) [1], idet ca. 50 % bliver diagnosticeret med tidlig stadie sygdom (stadium I-IIA1), hvortil kurativ intenderet behandling, bestående af kirurgi ± konkomittant kemostråleterapi fortsat er muligt [2, 5]. Dette afspejles også i det høje prævalenstal, på knap 9000 set i forhold incidens tallet [1]. Prognosen bliver dog markant forværret for patienter med recidiverende og/eller dissemineret sygdom med en 5-års overlevelse på kun 18% (95% CI 11-26) med nuværende behandlingsmuligheder [2].

Histologisk er de mest udbredte former for cervix cancer, planocellulære karcinomer og adenokarcinomer, som udgør hhv. 60-65 % og 16-23 % af alle cervix cancer tilfælde, som bliver diagnosticeret i Danmark [2].

De planocellulære karcinomer er, som navnet angiver, udsprunget af pladeepitelcellerne på livmoderhalsens slimhinde, og vil derfor udvikle sig i overgangszonen mellem den indre del af cervix og den ydre del mod skeden. Derimod stammer adenokarcinomer fra de slimproducerende kirtelceller, som findes på indersiden af cervix [4]. Derudover er der en række andre, men sjældnere histologiske subtyper, hvoraf kan nævnes adenoskvamøse og neuroendocrine karcinomer.

Symptomer

Cervix cancer er i de tidligere stadier oftest asymptomatisk. De første tegn, som kan vise sig ved mere avanceret sygdom er uregelmæssig eller uforklarlig sekretion fra skeden, i form af blødning i forbindelse med eller efter samleje, vedvarende pletblødninger mellem menstruationer, blødning efter overgangsalderen, eller øget udflåd. Smerter og andre symptomer fra blære og

tarm kan også forekomme, men ofte forbundet med dissemineret sygdom, hvor kræften har bredt sig uden for cervix [4].

Risikofaktorer

Kronisk infektion med human papilloma virus (HPV), er den vigtigste årsag til celleforandringer i livmoderhalsen, som har potentiale til at udvikle sig til kræft. Derfor er risikofaktorer for udvikling af cervix cancer stærkt forbundet med de parametre, som øger risiko for eksponering for HPV. Dette er bl.a. mange seksuelle partnere og en tidlig seksuel debut. Manglende evne til at *cleare* en HPV infektion hos immunsvækkede patienter, som følge af f.eks. organtransplantation eller rygning, er derfor også associeret med et kronisk HPV forløb og risiko for udvikling af kræft [4, 10].

Incidens og prævalens

I Danmark (og andre vestlige lande) har incidensen af cervix cancer været faldende gennem den seneste årrække, som et resultat af den indsats man har lagt for både forebyggelse og tidlig opsporing i form af vaccinations-og screeningsprogrammet [2-4]. Der blev i perioden 1. juli 2020 - 30. juni 2021 diagnosticeret 269 nye tilfælde af cervix cancer i Danmark. Prævalensen for cervix cancer var ved udgangen af 2019 angivet i NORDCAN til at være 8945 patienter [1]. I nedenstående tabel har vi kun anført prævalens med udgangen af 2019, idet vi ikke har lokaliseret data fra andre år (Table 1).

Table 1 Incidens og prævalens de sidste 5 år [11]

Year	2016/2017	2017/2018	2018/2019	2019/2020	2020/2021
Incidens i Danmark	328	301	274	313	267
Prævalens i Danmark	-	-	-	8945	-

Kilder: Incidens er taget fra DGCG årsrapporter Årsrapport (dgcg.dk) [11], prævalens fra seneste NORDCAN [1]

Estimeret patientpopulation antal.

I Table 2 ses et estimat af antallet af patienter, som er kandidater til den nye intervention PEM+CT. Vi har i den seneste årsrapport fra Dansk Gynækologisk Cancer Gruppe (DGCG) identificeret data for størrelsen af patientgruppen med stadium IVB sygdom, men ikke for antallet af patienter med recidiverende/persisterende sygdom.
Der ikke findes tilgængelige data om den relevante population med persisterende, recidiverende eller metastatisk cervix cancer. Tallene i Table 2 er derfor estimeret på baggrund af en mini-MTV, som blev udarbejdet til Koordineringsrådet for ibrugtagning af sygehusmedicin (KRIS) i forbindelse med ibrugtagning af bevacizumab [8]:

- Mini-MTV udarbejdet til Koordineringsrådet for ibrugtagning af sygehusmedicin (KRIS) i forbindelse med ibrugtagning af bevacizumab, som estimerede 20 patienter egnet til bevacizumab behandling [8].
- Ikke alle patienter er egnet til at blive behandlet med bevacizumab og bevacizumab fravælges såfremt der er risiko for blødning, trombose og fistulering [7]. I KN826-studiet blev ca. 63 % af populationen behandlet med bevazicumab på baggrund af investigatorers kliniske vurdering. Antager vi, at dette også er repræsentativt for dansk klinisk praksis vil der i den danske patient population, som er egnet til platinholdig kemoterapibehandling ± bevacizumab være omtrent 32 patienter ((20 patienter/63) x 100 %)

- I KN826 var knap 90% af studiepopulation PD-L1 CPS ≥1, svarende til **28 patienter**, som således forventes at være kandidater til den nye behandling.

Table 2 Estimeret antal patienter, som vil være kandidater til behandlingen.

Year	2022	2023	2024	2025	2026
Antal patienter, som forventes at være kandidater til den nye behandling de kommende år	28	28	28	28	28

5.1.1 Forventet patientpopulation for denne ansøgning

Den nye behandling forventes at være relevante for den danske patientgruppe, som er voksne diagnosticeret med persisterende, recidiverende eller metastatisk (P/R/M) cervix cancer, hvis tumorer udtrykker PD-L1 med CPS ≥1, som ikke er kandidater til kurativ intenderet behandling.

5.2 Nuværende behandlingsmuligheder og valg af komparator(er)

5.2.1 Prognose med nuværende standardbehandling i Danmark for persisterende, recidiverende eller metastatisk cervix cancer

I Danmark behandles cervix cancer på fire afdelinger; Rigshospitalet, Odense Universitetshospital, Aarhus Universitets Hospital og Herlev Hospital. Alle afdelinger har multidisciplinære teams, der samarbejder omkring udredning og behandling.

Dansk Gynækologiske Cancer Gruppe (DGCG) har beskrevet de kliniske retningslinjer for den onkologiske behandling af ikke-kurabel persisterende/recidiverende/metastatisk (P/R/M) cervix cancer. Behandlingsstrategien for henholdsvis persisterende, recidiverende eller metastatisk cervix cancer er ens og tilsvarende gør sig gældende på tværs af de mest udbredte histologiske subtyper, planocellulært-og adenokarcinom [5, 7].

Nedenfor gennemgås overlevelse for patienter med P/R/M cervix cancer fra de relevante studier, som også ligger til baggrund for den danske anbefaling:

- I GOG 204-studiet gav platinbaseret kombinationsbehandling en median overlevelse på mellem 10,0-12,9 mdr., hvoraf kombinationen af cisplatin og paclitaxel viste en ikke signifikant forbedring med en median overlevelse på 12,9 mdr. (95% CI 10,0-16,8) vs. andre cisplatin-baserede kombinationer (+topotecan, +gemcitabine eller +vinorelbine) [12].
- GOG 204-studiet viste at tillæg af bevacizumab til cisplatin + paclitaxel eller cisplatin + topotecan førte til en median progressionsfri overlevelse på 8,2 mdr. og median overlevelse på 17,0 mdr. Median overlevelse var højest i cisplatin + paclitaxel ± bevacizumab gruppen hvor tillæg af bevacizumab gav en median overlevelse på 17,5 mdr. vs. 14,3 mdr. for cisplatin + paclitaxel alene [13].

Standardbehandling for patienter med P/R/M cervix cancer i Danmark er som tidligere nævnt cisplatin (eller carboplatin) + paclitaxel ± bevacizumab. Der er for bevacizumab behandlede patienter en øget risiko for at udvikle hypertension, fistler og perforation af hulorgan, hvorfor disse risici indgår i overvejelserne om hvorvidt bevacizumab skal lægges til dublet-behandlingen. Her vil man være særlig opmærksom på hvorvidt patienter tidligere har modtaget højdosis stråleterapi i recidivområdet [7, 13].

Med baggrund i de danske kliniske retningslinjer mener MSD, at vi har valgt den relevante komparator, som er cisplatin eller carboplatin + paclitaxel ± bevacizumab, som også udgør kontrolarmen i KEYNOTE-826 (KN826). Vi vil i det følgende omtale cisplatin eller carboplatin + paclitaxel ± bevacizumab i KN826 kontekst som kemoterapi. Det er på baggrund af de to behandlingsarme placebo + kemoterapi (PBO+CT) vs. pembrolizumab + kemoterapi (PEM+CT) i KN826, at vurdering af den kliniske merværdi af tillæg af pembrolizumab til nuværende standardbehandling vil blive vurderet. Derved sikres et statistisk robust grundlag for vurderingen.

5.2.2 Beskrivelse af komparator(er)

Nedenfor vil beskrivelse af komparatorer blive udført for de enkelte lægemidler, som benyttes i de kombinationsregimer, som er en del af dansk klinisk praksis.

Cisplatin er et velkendt og velafprøvet kemoterapeutika, som er brugt i cancerbehandling siden 1970'erne [14].

- Cisplatin (L01XA1) [15].
- Mode of action: Cisplatin er en uorganisk substans der hæmmer DNA-syntesen ved at frembringe tværgående forbindelser indenfor og mellem DNA-strengene. Protein og RNA-syntesen hæmmes i mindre grad.
- Pharmaceutical form: Koncentrat til infusionsvæske
- Posology: Cisplatin 1 mg/ml
- Method of administration: Intravenøs administration
- Dosing 50 mg/m^2 intravenøst hver 3. uge
- Should the pharmaceutical be administered with other medicines? Cisplatin skal opblandes i enten natriumchlorid-infusionsvæske eller isotonisk natriumchlorid-glucose-infusionsvæske før infusion og kan bruges både som monoterapi eller kombinationsterapi
- Treatment duration/criteria for end of treatment: Cisplatin blev administreret i op til 6 serier i KN826. Dog kunne denne forsættes efter læges skøn såfremt der forsat var gavn af behandling og ikke var nævneværdig toksicitet [16]
- Necessary monitoring, both during administration and during the treatment period: Det anbefales at følge lokale guidelines for monitorering af cisplatin, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics) Det anbefales at følge lokale guidelines
- Packaging 1 hætteglas med 10, 20, 50 eller 100 ml koncentrat til infusionsvæske, 1 mg/ml Cisplatin

Carboplatin er et velkendt og velafprøvet kemoterapeutika, der findes fra flere producenter i en række formuleringer.

- Carboplatin (L01XA02) [15].
- Mode of action: Carboplatin er en uorganisk substans der hæmmer DNA-syntesen ved at frembringe tværgående forbindelser indenfor og mellem DNA-strengene.
- Pharmaceutical form: Koncentrat til infusionsvæske
- Posology: Udleveres som koncentrat til infusionsvæske, opløsning 10 mg/ml

- Method of administration: Intravenøs administration over 15 - 60 minutter
- Dosing: Area under the curve (AUC) 5 intravenøst hver 3. uge.
- Should the pharmaceutical be administered with other medicines? Carboplatin skal fortyndes med isotonisk natriumchlorid- eller glucose-infusionsvæske til en koncentration på mindst 0,5 mg/ml, afhængig af infusionstiden. Carboplatin kan bruges som både monoterapi og kombinationsterapi.
- Treatment duration/criteria for end of treatment: Carboplatin blev administreret i op til 6 serier i KN826. Dog kunne denne forsættes efter læges skøn såfremt der forsat var gavn af behandling og ikke var nævneværdig toksicitet
- Necessary monitoring, both during administration and during the treatment period: Carboplatin bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytotoksiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af carboplatin, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer.
- Packaging: Udleveres som 1 hætteglas, med 15 eller 45 ml koncentrat til infusionsvæske, opløsning 10 mg/ml.

Paclitaxel er et velkendt og velafprøvet kemoterapeutikum og findes fra flere producenter i en række formuleringer.

- Paclitaxel (L01CD01)
- Mode of action: Anti-mitotika, som hæmmer tumorvækst ved at blokere for celledeling
- Pharmaceutical form: Pulver til infusionsvæske, dispersion
- Posology: Paclitaxel udleveres enten som koncentrat til infusionsvæske, opløsning 6 mg/ml eller som pulver til infusionsvæske 60 mg
- Method of administration: Intravenøs administration over 3 timer
- Dosing: I KN826: 175 mg/m^2 legemsoverflade intravenøst hver 3. uge.
- Should the pharmaceutical be administered with other medicines? Paclitaxel som pulver skal opblandes i isotonisk natriumchlorid-infusionsvæske, Ringer-lactat eller Ringer-acetat til en slutkoncentration på 1mg/ml. Paclitaxel som koncentrat til infusionsvæske skal fortyndes med isotonisk glucose- eller natriumchlorid-infusionsvæske eller blandinger heraf til en koncentration på 0,3 – 1,2 mg/ml. Paclitaxel må ikke blandes med andre lægemidler end den anførte infusionsvæske under tilberedning. Paclitaxel kan bruges som både monoterapi og kombinationsterapi.
- Treatment duration/criteria for end of treatment I KN826 blev paclitaxel administreret i op til 6 serier i KN826. Dog kunne denne forsættes efter læges skøn såfremt der forsat var gavn af behandling og ikke var nævneværdig toksicitet
- Necessary monitoring, both during administration and during the treatment period: Paclitaxel bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytostatiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af paclitaxel, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.

- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer
- Packaging: Udleveres som 1 hætteglas med 16,7 eller 50 ml koncentrat til infusionsvæske, opløsning 6 mg/ml eller som 1 pakning med 60 mg pulver

Bevacizumab (Aybintio) er et rekombinant humaniseret monoklonalt antistof, som fremstilles ved DNA teknologi [15, 17]

- Bevacizumab (L01FG01)
- Mode of action. Bevacizumab hæmmer tumorvækst ved at binde til endotelial vækst faktor (VEGF) og hæmme interaktionen med dets receptorer, Flt-1 (VEGFR-1) og KDR (VEGFR-2) på overfladen af endotelceller.
- Pharmaceutical form: Koncentrat til infusionsvæske, opløsning
- Posology
- Method of administration: intravenøs infusion over 90 min. Efterfølgende infusioner kan gives over 60 min og dernæst 30 min, hvis de foregående infusioner toleres godt.
- Dosing: 15mg/kg kropsvægt hver 3. uge
- Should the pharmaceutical be administered with other medicines? Bevacizumab skal opblandes i natriumchlorid (0,9%) infektionsvæske før infusion
- Treatment duration/criteria for end of treatment: behandlingen fortsættes indtil progression af den underliggende sygdom eller indtil uacceptabel toksicitet
- Necessary monitoring, both during administration and during the treatment period: Det anbefales at følge lokale guidelines for monitorering af bevacizumab, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer.
- Packaging
  - Koncentrat til infusionsvæske 100 mg/4ml
  - Koncentrat til infusionsvæske 400 mg/16ml

5.3 Interventionen

5.3.1 Rationale for behandlingseffekt af pembrolizumab + kemoterapi hos patienter med cervix cancer

Pembrolizumab er et humaniseret monoklonalt antistof, der binder til overfladeproteinet programmed cell death-1 (PD-1), som bl.a. er udtrykt på immunsystemets T-lymfocytter og forhindrer binding til overpladeproteinerne programmed death-ligand 1 (PD-L1) og 2 (PD-L2). PD-L1 og PD-L2 kan være udtrykt på både tumorceller og andre celler i tumorens mikromiljø og kan også være udtrykt på kroppens normale væv. Interaktion mellem PD-1 og dets ligand PD-L1/PD-L2, hæmmer T-lymfocytters aktivitet og kan derved hæmme T-lymfocytternes respons mod kræftsygdom [18].

Udvikling af cervix cancer er i høj grad associeret med kronisk HPV infektion. Virale infektioner inkl. HPV er forbundet med en øget ekspression of PD-L1, hvorfor man i cervix cancer væv kan måle en

opregulering af PD-L1 sammenlignet med raske celler [19, 20]. Dette understøtter det biologiske rationale bag brug af pembrolizumab til cervix cancer.

Nedenfor er en kort gennemgang af studier, som viser effekt af pembrolizumab hos cervix cancer patienter, som danner grundlag og rationale for KN826 studiet:

- KN028 var et ikke-randomiseret fase 1b studie, som undersøgte pembrolizumab monoterapi (10mg/kg hver 2. uge) i 20 forskellige PD-L1 positive solide tumortyper inkl. cervix cancer. Studiet viste et tumor svind hos 36% af patienterne og en *objective response rate* (ORR) på 17% hos cervix cancer kohorten [21].
- KN158 var et fase 2 studie, der undersøgte pembrolizumab monoterapi (200 mg hver 3. uge) hos patienter med solide tumorer inkl. cervix cancer. ORR var 12,2% (95% CI 6,5-20,4) hos alle inkluderede cervix cancer patienter, 14,6% (95% CI 7,8-24,2) hos alle PD-L1-positive patienter, 14,3% (7,4-21,4) hos tidligere behandlet PD-L1 positive patienter og 0,0 % (95% CI 0,0-21,8) hos PD-L1-negative patienter [22].

På baggrund af ovennævnte studier samt et fortsat behov for at forbedre behandlingen af patienter med P/R/M cervix cancer blev KN826 designet for at undersøge effekt af tillæg af pembrolizumab til nuværende standardbehandling bestående af cisplatin, paclitaxel ± bevacizumab til første linje behandling af patienter med P/R/M cervix cancer. Adskillige studier på tværs af tumortyper har vist, at man ved at kombinere pembrolizumab med f.eks. kemoterapi kan få et øget anti-tumorrespons og forbedret overlevelse [23, 24]. Dette bygger dels på et rationale om at udnytte den additive effekt, som kan opnås med kombinationsbehandling og dels et videnskabeligt rationale hvor kombinationen er med til at forstærke virkningen af pembrolizumab. Både platin-baseret behandling og a*nti-vascular endothelial growth factor* (anti-VEGF), såsom bevacizumab har supplerende immunmodulerende effekter, som kan bidrage til dannelsen af et immunologiske favorabelt tumormikromiljø. I samspil med den immunaktiverende effekt af pembrolizumab, kan kombinationsbehandlingen medføre en synergistisk effekt, som forstærker det kombinerede anti-tumor immunrespons [25, 26].

KN826 blev designet, så der blev inkluderet både planocellulære-og adenokarcinomer og der blev i stratificering taget højde for bevacizumab behandling, metastatisk sygdom på diagnose tidspunkt og PD-L1 status. Således består KN826's studiepopulation af patienter med de mest hyppige histologiske subtyper, der er mulighed for individuel vurdering af bevacizumab egnethed og PD-L1 status var en del af den statistiske analyseplan.

Intervention i KN826:

- Dosing: Pembrolizumab 200 mg hver 3. uge i op til 35 serier. Cisplatin 50 mg/m2 eller carboplatin AUC5 og paclitaxel 175 mg/m^2 ± bevacizumab 15 mg/kg intravenøst hver 3. uge te
- Method of administration: Alle lægemidler indgives intravenøst
- Treatment duration/criteria for treatment discontinuation I KN826 kunne der administreres op til 35 serier for Pembrolizumab, op til 6 serier for cisplatin og paclitaxel, og indtil sygdomsprogression uacceptabel toksicitet for bevacizumab.
- Should the pharmaceutical be administered with other medicines?
- Necessary monitoring, during administration, during the treatment period, and after the end of treatment Det anbefales at følge lokale guidelines for monitorering.
- Need for diagnostics or other tests (i.e. companion diagnostics) PD-L1 test 22C3 er godkendt som companion diagnostic til pembrolizumab og kan dermed anvendes som test for PD-L1 expression ved behandling med pembrolizumab

Ved en anbefaling i Medicinrådet vil PEM+CT blive en ny behandlingsmulighed for patienter i 1. linje med persisterende, recidiverende eller metastatisk cervix cancer, som udtrykker PD-L1 CPS ≥1. Eftersom cisplatin eller carboplatin, paclitaxel ± bevacizumab allerede er beskrevet som standard 1. linje behandling til denne patientgruppe, vil ændringen være tillæg af pembrolizumab til dette behandlingsregime for patienter, som udtrykker PD-L1 CPS ≥1.

6. Litteratursøgning og identificering af effekt og sikkerhedsstudier

KN826 studiet er en direkte sammenligning mellem intervention og relevant komparator og der er ikke foretaget en systematisk litteratursøgning efter dokumentation og effekt og sikkerhed, da denne ikke forventes at tilvejebringe yderligere relevant dokument for at understøtte sammenligning af intervention og komparator.

De relevante publikationer, som dokumenterer sikkerhed og effekt af tillæg af pembrolizumab til cisplatin, paclitaxel ± bevacizumab er vist i Table 3.

Table 3 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. Colombo et al. N Engl J Med 2021; 385:1856-1867 DOI: 10.1056/NEJMoa2112435	KN826	NCT03635567	Start: 25. Oktober 2019 Forventet slut: 23. November 2022
Keytruda-epar-h-c-003820-ii-0117			
Patient-Reported Outcomes from the phase 3 randomized, double-blind, KEYNOTE-826 trial of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for the first-line treatment of persistent, recurrent, or metastatic cervical cancer. Monk et al. presented at Society og Gynecologic Oncology Annual Meeting; March 18-21, 2022.			
Data on file / clinical study report			

7. Effekt og sikkerhed

Der vil i dette afsnit præsenteres effekt og sikkerhedsdata, som skal understøtte merværdi af PEM+CT vs. PBO+CT til patienter med PD-L1 CPS ≥1 P/R/M cervix cancer.

7.1 Effekt og sikkerhed af PEM+CT vs. PBO+CT for patienter med persisterende, recidiverende og metastatisk cervix cancer.

Den komparative analyse af effekt og sikkerhed er en direkte statistisk sammenligning af intervention PEM+CT vs. PBO+CT, svarende til dansk klinisk praksis, baseret på data fra KN826. Den kliniske merværdi vil bliver vurderet med baggrund i følgende relevante endepunkter:

I. Progressionsfri overlevelse (PFS) og samlet overlevelse (OS) effektdata vil blive præsenteret for PD-L1 CPS ≥ 1 populationen
II. Data for bivirkninger samt livskvalitet, *health related quality of life (*HR-QoL), vil blive præsenteret for *all participants as treated (APat)* populationen, dvs. for den population, som har modtaget minimum én dosis studiemedicin i studiet.

MSD mener disse er relevante endepunkter for vurdering af PEM+CT merværdi vs. PBO+CT, da sigtet med behandlingen er at forlænge OS for patienter med cervix cancer. Kombineret med PFS får vi samtidig belyst den direkte effekt af PEM+CT vs. PBO+CT, uden at blive forurenet af evt. efterfølgende behandlingslinjer. Endvidere er landmark analyser relevante ved analyse af klinisk merværdi for studier, der undersøger immunterapi, da disse bedre end analyser af median-værdier, afspejler det langvarige respons og den behandlingseffekt man kan opnå med immunterapi. I tillæg til effekt-relaterede endepunkter, er det væsentlig at vurdere i hvilket omfang tillæg af pembrolizumab til kemoterapi påvirker hyppighed og typer af bivirkninger og særligt hvilken indflydelse disse har på patienters livskvalitet. Derfor vil bivirkningsdata og livskvalitet blive rapportere for *all participants as treated* (APat) populationen (minimum 1 dosis medicin i studiet) for at få data på størst mulig population.

Der vil i det følgende afsnit blive gennemgået de vigtigste detaljer omkring studiet og der henvises til appendiks B for yderligere information.

7.1.1 Relevante studier(r): KEYNOTE-826

KEYNOTE-826 (KN826) er et randomiseret fase 3, placebokontrolleret dobbeltblindet studie, som undersøger effekt og sikkerhed af tillæg af pembrolizumab til første linje behandling af patienter med persisterende, recidiverende og/eller metastatisk (P/R/M) cervix cancer, som er uegnet til kurativ intenderet behandling [27].

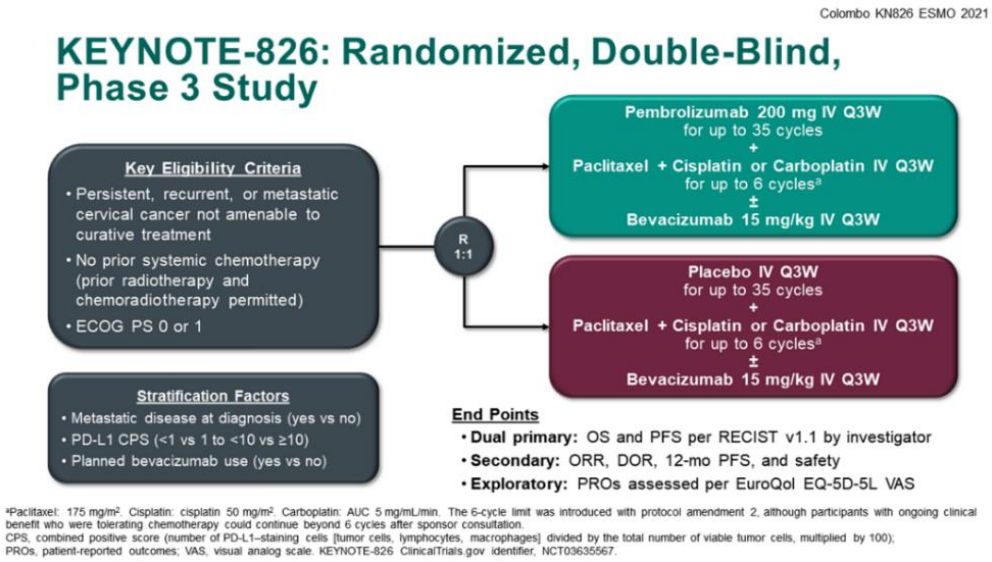

Figure 1. KEYNOTE-826 studiedesign. Fra Colombo et al. ESMO 2021.

Patienter blev randomiseret 1:1 til hhv. intervention PEM+CT og komparator PBO+CT, hvoraf komparator er sammenlignelig med nuværende dansk klinisk praksis. Patienter blev stratificeret efter metastatisk sygdom ved diagnosetidspunkt (ja eller nej), PD-L1 CPS status (<1 vs. 1 til <10 vs. ≥10) og planlagt bevacizumab brug (ja eller nej) (Figure 1).

Inklusionskriterier var behandlingsnaiv P/R/M cervix cancer, uegnet til kurativ intenderet behandling. Tidligere stråle-eller konkomittant kemostrålebehandling givet i den kurative setting var dog tilladt. Patienter skulle være i god almen tilstand med *Eastern Cooperative Oncology Group performance status* (ECOG PS) 0 eller 1 og have vævsprøve (ikke taget fra et tidligere bestrålet område) tilgængelig til PD-L1 immunhistokemisk (IHC) analyse. Patienter blev dog inkluderet uanset PD-L1 status.

Eksklusionskriterier var bl.a. anden invasiv malignitet, der var progredieret eller behandlingskrævende indenfor 3 år forud for afgivelse af informeret samtykke, med undtagelse af velbehandlet basalcelle- eller planocellulær hudcancer eller *in situ* brystkræft. Der henvises til Appendix B for en mere fyldestgørende beskrivelse af studiedesign samt in-og eksklusionskriterier.

Der var i studiet to primære endepunkter (*dual primary endpoints),* som var *overall survival* (OS) og progressionsfri overlevelse (PFS).

Såfremt blot ét af de to primære endepunkter viste en statistisk signifikant forbedring ville studiehypotesen for KN826 være opfyldt. For de primære endepunkter var den overordnede alfa for studiet, kontrolleret med en-sidet 2,5% for alle sammenligninger. Den statistiske analyseplan tillod en sekventiel analyse, hvor alfa kunne allokeres fra hypotese 1 (H1) → hypotese 2 (H2) → hypotese 3 (H3) og fra hypotese 4 (H4) → hypotese 5 (H5) → hypotese 6 (H6) (se Figure 2). Med andre ord kunne man for både PFS (H1-H3) og OS (H4-H6) evaluere effekten af tillæg af pembrolizumab til kemoterapi sekventielt i følgende subpopulationer PD-L1 CPS ≥ 1 → *intention-to-treat* (ITT) → PD-L1 CPS ≥ 10, men KUN såfremt forudgående test viste en statistisk signifikant forbedring med PEM+CT sammenlignet med PBO+CT.

De sekundære endepunkter var *objective response rate* (ORR), *duration of response* (DOR), 1-års PFS rate, frekvens af bivirkninger samt livskvalitet (se Appendiks B Inkluderede studier hovedkarakteristika [27]).

Der er i protokollen for KN826 planlagt 2 interimsanalyser (IA) efter en opfølgningstid på hhv. ~28 og ~36 måneder efter første randomiserede patient, samt én *final analysis* (FA) efter ca. 44 måneder. Data præsenteret i denne ansøgning er fra den første interimsanalyse (IA1), som d.d. er seneste analysetidspunkt med publicerede data.

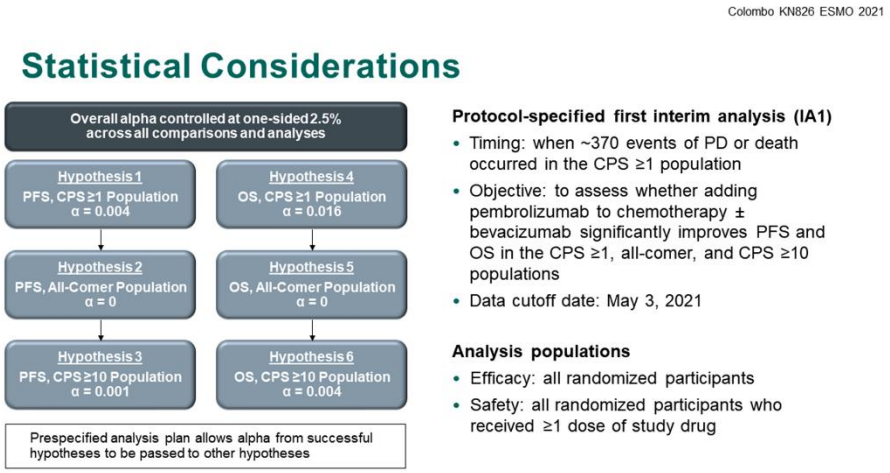

Figure 2. KEYNOTE-826 statistiske analyseplan.

7.1.2 Effekt og sikkerhed – resultater per studie

KN826 repræsenterer en direkte sammenligning af intervention PEM+CT vs. PBO+CT, hvor sidstnævnte afspejler nuværende dansk klinisk praksis. Derfor er der i denne ansøgning ikke inkluderet yderligere studier jf. afsnit 6 *Litteratursøgning og identificering af effekt og sikkerhedsstudier*. Der blev i KN826 inkluderet patienter med P/R/M cervix cancer uanset PD-L1 status og der foreligger effektresultater for både PFS og OS fra PD-L1 CPS ≥ 1, ITT og PD-L1 CPS ≥ 10, jf. den statistiske analyseplan (Figure 2). Denne ansøgning baserer sig på resultaterne fra KN826 for PD-L1 CPS ≥1, da EMA indikationen er godkendt til denne population.

Resultaterne som præsenteres i denne ansøgning og appendiks D og E vil være:

1. PFS og OS for PD-L1 CPS ≥1
2. Bivirkninger og livskvalitet i APat-populationen for at få det største datagrundlag for vurdering af disse parametre.

7.1.2.1 Baselinekarakteristika for inkluderede patienter

Patientpopulation for KN826 var generelt ensartet fordel på tværs af de to behandlingsgrupper mht. baselinekarakteristika ved inklusion i studiet. Der ses en højere prævalens af patienter med persisterende eller recidiverende sygdom med fjernmetastaser i PEM+CT vs. PBO+CT, som ikke vurderes at være til fordel for interventionsgruppe (Table 4). Der ses til gengæld en højere andel af adenokarcinomer i PBO+CT vs. PEM+CT, som overordnet kan være forbundet med en dårligere prognose [28], dog viser tal fra DGCG's årsrapport at 5-års overlevelsen er sammenlignelig for adenokarcinomer vs. planocellulære karcinomer [2]. Fordelingen mellem de forskellige histologiske subtyper i KN826 afspejler ligeledes nogenlunde fordelingen i den danske patientpopulation, hvor 65,4% havde planocellulært karcinom, 23,4% havde adenokarcinom, 1,5% havde adenoskvamøst karcinom og de resterende havde anden eller ukendt histologi [2].
Derudover var alder, ECOG PS score og stratificeringsgrupper (metastatisk, PD-L1 status og bevacizumab) ensartet fordelt mellem grupperne.

Table 4. Baseline patientkarakteristika i KN826

Karakteristika, n (%)	**PEM+CT N = 308**	**PBO+CT N = 309**
Alder, median (range), år	51 (25-82)	50 (22-79)
≥65 år	48 (15,6)	52 (16,8)
Race		
White	170 (55,2)	190 (61,5)
Non-white	138 (44,8)	119 (38,5)
Geografisk region		
Asia Pacific	63 (20,5)	42 (13,6)
EU/EMEA	103 (33,4)	108 (35,0)
Nord Amerika	39 (12,7)	43 (13,9)

Latin Amerika	103 (33,4)	116 (37,5)
ECOG Performance Status*		
0	178 (57,8)	170 (55,0)
1	128 (41,6)	139 (45,0)
Disease stage at initial diagnosis		
I	67 (21,8)	58 (18,8)
II	85 (27,6)	93 (30,1)
III	5 (1,6)	8 (2,6)
IIIA	4 (1,3)	8 (2,6)
IIIB	46 (14,9)	42 (13,6)
IVA	7 (2,3)	4 (1,3)
IVB	94 (30,5)	96 (31,1)
Disease Status at trial entry		
Metastatic	58 (18,8)	64 (20,7)
Persistent or recurrent with distant metastases	199 (64,6)	179 (57,9)
Persistent or recurrent without distant metastases	51 (16,6)	66 (21,4)
Histologisk type**		
Adenokarcinom	56 (18,2)	84 (27,2)
Adenoskvamøs karcinom	15 (4,9)	14 (4,5)
Planocellulær karcinom	235 (76,3)	211 (68,3)
PD-L1 Status combined positive score (CPS)		
<1	35 (11,4)	34 (11,0)
1 til <10	115 (37,3)	116 (37,5)
10 ≤	158 (51,3)	159 (51,5)
Tidligere behandling		
Kemostråleterapi og kirurgi	49 (15,9)	56 (18,1)
Stråleterapi og kirurgi	22 (7,1)	23 (7,4)
Kun kemostråleterapi	125 (40,6)	118 (38,2)
Kun stråleterapi	31 (10,1)	24 (7,8)
Kun kirurgi	23 (7,5)	24 (7,8)
Ingen	58 (18,8)	64 (20,7)
Kemoterapi		
Carboplatin	246	249
Cisplatin	61	59
Bevacizumab i studiet		

Ja	196 (63,6)	193 (62,5)
Nej	112 (36,4)	116 (37,5)

* I pembrolizumab-armen (PEM+CT) havde en patient (0.3%) ECOG score 2 og en patient (0.3%) havde kendt ECOG score.

**I pembrolizumab-armen, en patient (0.3%) havde tumoren karakteriseret som epidermoid carcinoma og en patient (0.3%) som ikke-differentieret carcinoma.

7.1.2.2 Overall survival hos PD-L1 CPS ≥1

Overall survival (OS) er defineret som tid fra randomisering til død uanset årsag og analysen blev foretaget efter en median opfølgningstid på 22,0 mdr. (range 15,1-29,4). Der blev for PD-L1 CPS ≥ 1 populationen randomiseret 273 og 275 patienter til hhv. PEM+CT og PBO+CT (hhv. 308 og 309 patienter i PEM+CT og PBO+CT i ITT-populationen).

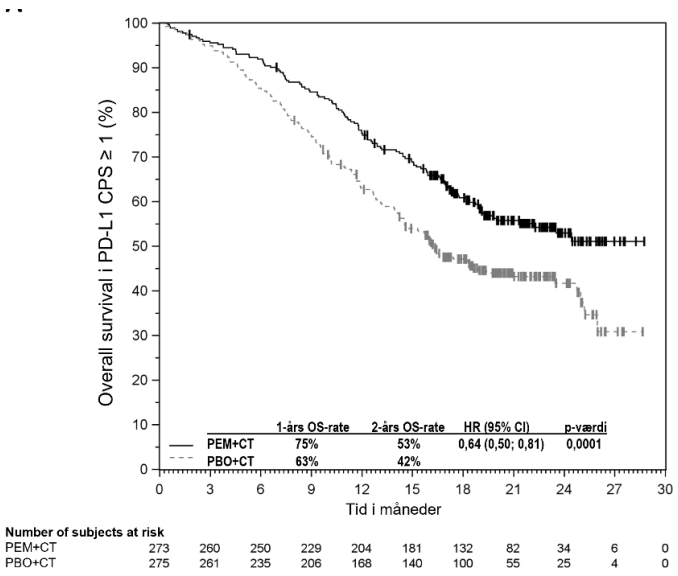

Figure 3. KM-kurve for OS i PD-L1 CPS ≥ 1 for (sort) PEM+CT og (grå) PBO+CT. Data cut-off er 3. maj 2021 med median opfølgningstid på 22,0 mdr. (range 15,1-29,4) [6].

Af Kaplan-Meier (KM) kurven i Figure 3 kan man se en begyndende adskillelse af kurverne knap 3 mdr. efter randomisering med færre OS events i PEM+CT sammenlignet med PBO+CT. Der er en vedvarende adskillelse over tid, som indtil videre kan følges indtil 2 år efter randomisering. For OS ses en absolut forskel på 12,2 % i 1-års overlevelse og 11,3 % i 2-års overlevelse til fordel for PEM+CT sammenlignet med PBO+CT (Table 5).

Table 5. Samlet overlevelse i KN826 i PD-L1 CPS ≥1 [9]

				Estimated absolute difference in effect	Estimated relative difference in effect		
Outcome	Study arm	N	Result (95%CI)	Difference	HR	95% CI	*P*- value
Median overlevelse Måneder PD-L1 CPS ≥ 1	PEM+CT	273	NR (19,8-NR)	-	0,64	0,50-0,81	0,0001
	PBO+CT	275	16,3 (14,5-19,4)				
1 års overlevelse % PD-L1 CPS ≥ 1	PEM+CT	273	75,3 (69,7-80,0)	12,2	-	-	-
	PBO+CT	275	63,1 (57,0-68,5)				

2 års overlevelse % *PD-L1 CPS ≥ 1*	PEM+CT	273	53,0 (46,0-59,4)	11,3	-	-	-
	PBO+CT	275	41,7 (34,9-48,2)				

Median OS i PEM+CT gruppen var ved IA1 med en median opfølgningstid på 22,0 mdr. (range 15,1-29,4) *not reached* (NR) (95% CI 19,8-NR), som er en statistisk signifikant forbedring sammenlignet med en median OS på 16,3 mdr. (95% CI 14,5-19,4) i PBO+CT gruppen, en HR 0,64 (95% CI 0,50-0,81) og en p<0,001 (Figure 3**Error! Reference source not found.** og Table 5).

På baggrund af OS-analysen for patienter med PD-L1 CPS ≥1 kan det konkluderes:

- Der er en klinisk relevant og signifikant forskel i overlevelse med HR 0,64 (95% CI 0,50-0,80) og en p<0,001. Forskel i median OS kan på nuværende tidspunkt ikke kvantificeres da den er NR (95% CI 19,8-NR) i PEM+CT vs. 16,3 mdr. (95% CI 14,5-19,4) i PBO+CT gruppen.
- Der ses en klinisk relevant, signifikant og vedvarende forskel i OS-raten ved 12 og 24 mdr. på henholdsvis 12,2% og 11,3% til fordel for PEM+CT, svarende til at ca. 25% flere er i live i PEM+CT efter 24 mdr. i forhold til PBO+CT i PD-L1 CPS ≥1 populationen.

MSD mener den signifikante forskel i OS med HR 0,64 (95% CI 0,50-0,80) samt en vedvarende forskel i overlevelsesraten indikerer stor klinisk merværdi for patienter med P/R/M cervix cancer med PD-L1 CPS ≥1.

7.1.2.3 Progressionsfri overlevelse i PD-L1 CPS ≥1

Progression-free survival (PFS), defineret som tid fra randomisering til død eller første dokumentation af progression per *Response Evaluation Criteria in Solid Tumors v.1.1.* (RECIST 1.1). PFS-analysen blev udført på sammen tidspunkt som OS analysen med en median opfølgningstid på 22,0 mdr. (range 15,1-29,4).

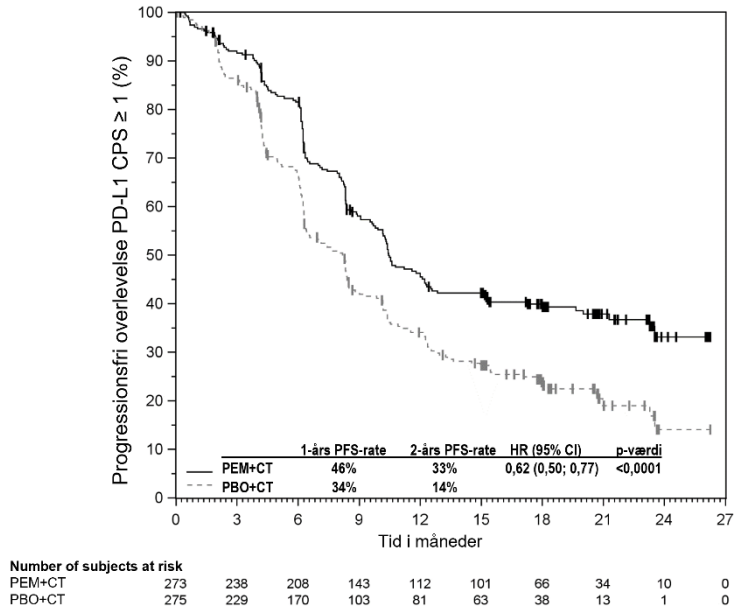

Figure 4. KM-kurve for PFS i PD-L1 CPS ≥1 for (sort) PEM+CT og (grå) PBO+CT. Data cut-off er 3. maj 2021 med median opfølgningstid på 22,0 mdr. (range 15,1-29,4).

I KN826 var der en statistisk signifikant forbedring i median PFS med en absolut forskel på 2,2 mdr. med tillæg af pembrolizumab til kemoterapi, en HR 0,62 (95% CI 0,50-0,77, *p*>0,001) (Figure 4 og

Table 6). Median PFS var for PEM+CT 10,4 mdr. (95% CI 9,7-12,3) og 8,2 mdr. (95% CI 6,3-8,5) for PBO+CT. KM-kurverne begynder at skille omkring 3 mdr. efter randomisering med en 1-års PFS rate på 45,5% (95% CI 39,2-51,5) i PEM+CT vs. 34,1 % (95% CI 28,3-40,0), svarende til ca. 40 % relativ forbedring med tillæg af pembrolizumab i PEM+CT vs. PBO+CT [9].
Denne forskel i PFS-rate bliver bibeholdt med en absolut forskel på 19,1 %-point til fordel for PEM+CT (33,1% (95%CI 25,7-40,7)) vs. PBO+CT (14,0% (95% CI 7,7-22,3). Dette svarer til, at der er mere end en fordobling i andelen af patienter som er progressionsfrie efter 2 år i PEM+CT sammenlignet med kontrolarmen. Der ses i PEM+CT en længere responsvarighed hos patienter, som responderer på PEM+CT med en median responsvarighed på 18,0 mdr. (range 1,3+ - 24,2+) i PEM+CT vs. 10,4 mdr. (range 1,5+ - 22,0+) i PBO+CT [9]. Disse resultater understøtter den mere end 2-fold forbedring i landmark analysen på 2- års PFS og i høj grad relevansen af landmark vs. median analyser, særligt i studier med immunterapi, jf. afsnit 7.1.

På baggrund af PFS-analysen for patienter med PD-L1 CPS ≥1 kan det konkluderes at:

- Der er en statistisk signifikant og kliniske relevant forbedring i median PFS på 2,2 måneder, svarende til en forbedring på ca. 25% for PEM+CT sammenlignet med PBO+CT
- Der ses en klinisk relevant forskel i PFS-raten efter et år med ca. 40% flere patienter som er progressionsfrie i PEM+CT sammenlignet med PBO+CT. Denne forskel ser ud til at blive større med tiden med over en fordobling i 2-års PFS rate i PEM+CT vs. PBO+CT.

Table 6. Progressionsfri overlevelse i PD-L1 CPS ≥1 [9]

				Estimated absolute difference in effect	Estimated relative difference in effect		
Outcome	Study arm	N	Result (95%CI)	Difference	HR	95% CI	*P*- value
Median PFS Måneder PD-L1 CPS ≥ 1	PEM+CT	273	10,4 (9,7-12,3)	2,2	0,62	0,50-0,77	<0,0001
	PBO+CT	275	8,2 (6,3-8,5)				
1 års PFS % PD-L1 CPS ≥ 1	PEM+CT	273	45,5 (39,2-51,5)	11,4	-	-	-
	PBO+CT	275	34,1 (28,3-40,0)				
2 års PFS % PD-L1 CPS ≥ 1	AT+nP	273	33,1 (25,7-40,7)	19,1	-	-	-
	PBO+nP	275	14,0 (7,7-22,3)				

MSD mener, at resultaterne fra KN826, indikerer en vigtig klinisk merværdi for patienter med PD-L1 CPS ≥1 P/R/M cervix cancer, idet der både er en statistisk signifikant og klinisk relevant forbedring i PFS, og at der er en tendens til at denne forskel bliver større med tiden til fordel for PEM+CT behandlede patienter sammenlignet med komparatorgruppen PBO+CT.

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7.1.2.6 Bivirkninger

I KN826 rapporteres bivirkninger hos patienter, som har modtaget minimum én dosis studiemedicin, *all participants as*-treated (APat) population, uanset PD-L1 status, svarende til 307 patienter i PEM+CT og 309 patienter i PBO+CT. *All-cause* bivirkninger beskrives for hele APat-populationen, da bivirkningsdata specifikt for PD-L1 CPS ≥1 populationen er sparsomme og der ikke vurderes at være betydelige forskelle i bivirkningsfrekvens eller type i forhold til patientens PD-L1 status [29]. Bivirkningsprofilen for PD-L1 CPS ≥1 redegøres derfor ved bivirkningsdatapræsentationen for APat. For at synliggøre pembrolizumabs evt. indvirkning på bivirkningsdata i kombinationsbehandlingerne, er data fra KN826 i EPAR sammenlignet med de samlede bivirkningsdata fra alle indikationer med kombinationsbehandling med pembrolizumab + kemoterapi i EU (n=2033) samt opdelt alt efter om patienten fik ± bevacizumab.

Table 8. Oversigt over bivirkninger i APat populationen KN826 samt referencedatasæt fra alle EU population PEM+CT og pembrolizumab monoterapi. (tabel 60 i EPAR [9])

	PEM+CT (KN826) (n=307)	PBO+CT (KN826) (n=309)	Ref. datasæt Pooled Safety PEM+CT (n=2,033)	Ref. datasæt Pooled Pembrolizumab mono (n=6,185)
≥1 bivirkning (*all cause*)	305 (99,3%)	307 (99,4%)	2015 (99,1%)	5989 (96,8%)
≥ grad 3-5 bivirkning (*all cause*)	251 (81,8%)	232 (75,1%)	1583 (77,9%)	2984 (48,2%)
Alvorlig behandlingsrelateret bivirkning	93 (30,3%)	71 (23,0%)	550 (27,1%)	701 (11,3%)
Behandlingsophør som følge af bivirkning -*any drug*	115 (37,5%)	82 (26,5%)	551 (27,1)	832 (13,5)
Død grundet behandlingsrelateret bivirkning	2 (0,7%)	4 (1,3%)	43 (2,1%)	39 (0,6%)

Der var >99% af patienterne som fik ≥1 bivirkning (*all cause* + alle grader) i begge behandlingsgrupper. Af de alvorlige bivirkninger fik 30,3% en behandlingskrævende alvorlig bivirkning i PEM+CT gruppen mod 23,0% i PBO+CT. I referencesættet med 2,033 patienter som har fået PEM+CT i EU er dette tal 2,1%. Dødsfald grundet behandling er lave og korrelerer fint med referencesæt for både referencesæt for kombinationsbehandling og for pembrolizumab monoterapi.

Median behandlingslængden er længere i PEM+CT gruppen med 10,0 mdr. (range 0,0-26,9 og i gennemsnit 14,0 serier) vs. 7,7 mdr. (range 0,0-27,4 og i gennemsnit 11,0 serier) i PBO+CT gruppen (supplementary appendix [16]) og den længere behandlingsvarighed og flere serier i PEM+CT gruppen, skal være *in mente* ved gennemgang af bivirkningsdata i det følgende afsnit.

Bivirkninger grad 3-4 (*all-cause*)

For APat-populationen blev der rapporteret 251/307 (81,8%) grad 3-5 bivirkninger (*all-cause*) i PEM+CT, mest hyppig hos patientgruppen behandlet med bevacizumab (83,7%) sammenlignet med ikke bevacizumab-behandlede patienter (78,4%). I PBO+CT var andelen af patienter grad 3-5 bivirkninger (all cause) 232/309 (75,1%), svarende til en absolut forskel på +6,7% i PEM+CT vs. PBO+CT. I PBO+CT var der samme andel af grad 3-5 bivirkninger hos bevazicumab behandlede (74,6%) vs. ikke-bevacizumab behandlede (75,9%) patienter (Table 9).

Den relative risiko for bivirkninger grad 3-5 mellem PEM+CT ± bevacizumab vs. PBO+CT ± bevacizumab er 1,05 (95% 0,92-1,20), som viser en identisk risiko ≥grad 3 bivirkninger hos de to behandlingsgrupper. Den let øgede forskel i absolutte tal af *all-cause* bivirkninger, som blev rapporteret for PEM+CT gruppen vs. PBO+CT skal ses i forhold til den længere behandlingstid (+2,3 mdr. i median behandlingslængde, samt +3 behandlingsserier), samt et tillæg af aktiv intervention (pembrolizumab) i PEM+CT gruppen.

Table 9. Median behandlingslængde og *all-cause grad 3-5 bivirkninger i APat-populationen.*

	Median behandlings-længde	**All-cause grad 3-5 bivirkninger**	**Forskel i all-cause grad 3-5 bivirkninger (95% CI)**	**RR (95% CI)**
PEM+CT ± bevacizumab (n=307)	**10,0 mdr.** (range 0,0-26,9) *~ 14,0 serier*	81,8% +bevacizumab 83,7% - Bevacizumab 78,4%	**+6,7% absolute risk reduction**[1]	**1,05 (95% CI 0,92-1,20)**
PBO+CT ± bevacizumab (n=309)	**7,7 mdr.** (range 0,0-27,4 *~ 11,0 serier*	75,1% +bevazicumab (74,6%) -bevacizumab (75,9%)		

Bivirkninger grad 3-5 – Kvalitativ gennemgang

Table 10 viser de hyppigste (≥ 5% i én eller begge grupper) *all-cause* grad 3-5 bivirkninger rapporteret i de to behandlingsgrupper, hvor de hyppigste bivirkninger ses at være anæmi (30,3% vs. 26,9%), nedsat antal neutrofile celler (13,0% vs. 8,4%) og neutropeni (12,4% vs. 9,7%) i henholdsvis i PEM+CT vs. PBO+CT gruppen. Bivirkninger som oftest er forbundet med kemoterapi samt behandling med VEGF-hæmmer (bevacizumab) og optræder derfor i begge behandlingsgrupper [13, 30].

Table 10. *All-cause* grad 3-5 bivirkninger i KN826 ≥5% i én eller begge grupper (Tabel 70 s. 108 i [9]).

	PEM+CT ±bevacizumab		PBO+CT ±bevacizumab	
	n	(%)	n	(%)
Subjects in population	307		309	
with one or more adverse events	251	(81,8)	232	(75,1)
with no adverse events	56	(18,2)	77	(24,9)
Anaemia	93	(30,3)	83	(26,9)
Neutrophil count decreased	40	(13,0)	26	(8,4)
Neutropenia	38	(12,4)	30	(9,7)
Hypertension	29	(9,4)	33	(10,7)
Urinary tract infection	27	(8,8)	25	(8,1)
Thrombocytopenia	23	(7,5)	14	(4,5)
Febrile Neutropenia	22	(7,2)	14	(4,5)
Platelet count decreased	21	(6,8)	14	(4,5)

[1] 95% CI er ikke tilgængelig

White blood cell count decreased	21	(6,8)	13	(4,2)
Fatigue	11	(3,6)	14	(4,5)
Pnemonia	2	(0,7)	9	(2,9)

Der ses en let forhøjet numerisk incidens af grad 3-5 bivirkninger i PEM+CT gruppen med 81,8% mod 75,1% i PBO+CT gruppen, men den relative risiko for udvikling af en grad 3-5 bivirkning er ens de to grupper imellem (RR 1.05) og derved er der ingen signifikant forskel mellem grupperne.

Det er velkendt og accepteret, at der er en højere andel af bivirkninger med kombinationsbehandling med pembrolizumabs immunaktiverende virknings samt kemoterapis celletoksiske/statiske mekanisme sammenlignet med monoterapi behandling [6, 23, 24]. Den numerisk højere andel af bivirkninger i interventionsgruppen i KN826 er sammenlignelig med data fra det samlede datasæt for EU indikationer med kombinationen af pembrolizumab + kemoterapi (s. 138 i EPAR [9]).

Omtrent 60% af studiepopulationen i KN826 modtog bevacizumab, som del af deres behandling (PBO+CT gruppen = 196 ptt ~ 63,8% og i PBO+CT gruppen = 193 pt ~ 62,4% i). Der ses en mindre forskel i andel af grad 3-5 bivirkninger i PEM+CT gruppen alt efter om der også blev givet bevacizumab, som ikke blev observeret i PBO+CT gruppen (Table 11).

Table 11. *All-cause* grad 3-5 bivirkninger efter ± bevacizumab i de to behandlingsgrupper (Tabel 72 i EPAR [9]).

Grad 3-5 All-cause bivirkninger	PEM+CT +bevacizumab		PEM+CT -bevacizumab		PBO+CT +bevacizumab		PBO+CT -bevacizumab	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	196		111		193		116	
with one or more adverse events	164	(83,7)	87	(78,4)	144	(74,6)	88	(75,9)
with no adverse events	32	(16,3)	24	(25,4)	49	(25,4)	28	(24,1)
Anaemia	52	(26,5)	41	(36,9)	37	(19,2)	46	(39,7)
Neutrophil count decreased	29	(14,8)	11	(9,9)	20	(10,4)	6	(5,2)
Hypertension	26	(13,3)	3	(2,7)	29	(15,0)	4	(3,4)
Neutropenia	26	(13,3)	12	(10,8)	17	(8,8)	13	(11,2)
Urinary tract infection	20	(10,2)	7	(6,3)	16	(8,3)	9	(7,8)
Platelet count decreased	16	(8,2)	5	(4,5)	13	(6,7)	1	(0,9)
Febrile Neutropenia	15	(7,7)	7	(6,3)	12	(6,2)	2	(1,7)
Thrombocytopenia	12	(6,1)	11	(9,9)	6	(3,1)	8	(6,9)
White blood cell count decreased	12	(6,1)	9	(8,1)	10	(5,2)	3	(2,6)
Sepsis	10	(5,1)	1	(0,9)	4	(2,1)	0	(0,0)
Acute kidney failure	7	(3,6)	6	(5,4)	4	(2,1)	5	(4,3)
Fatigue	5	(2,6)	6	(5,4)	7	(3,6)	7	(6,0)

Ved de behandlingsrelaterede grad 3-5 bivirkninger ses der et forventeligt fald i bivirkninger i forhold til *all-cause* i begge behandlingsgrupper (Table 11 og Table 12), og det ses også at de hyppigst forekommende bivirkninger er identiske med *all-cause* bivirkningerne anæmi, nedsat antal neutrofile, hypertension samt neutropeni (Tabel 71 s. 109 i EPAR [9]).

Table 12. Behandlingsrelaterede grad 3-5 bivirkninger af efter ± bevacizumab (Tabel 73 s. 111 i EPAR [9]),

Behandlingsrelaterede grad 3-5 bivirkninger	PEM+CT +bevacizumab		PEM+CT -bevacizumab		PBO+CT +bevacizumab		PBO+CT -bevacizumab	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	196		111		193		116	
with one or more adverse events	143	(73,0)	67	(60,4)	126	(65,3)	72	(62,1)
with no adverse events	53	(27,0)	44	(39,6)	67	(34,7)	44	(37,9)

De hyppigst rapporterede ændringer i laboratoriesvar (blodbilledet) var ens mellem PEM+CT vs. PBO+CT og størstedelen blev rapporteret som grad 1-2 toksicitet (EPAR s. 120 [9]). Ændringerne i blodprøveværdierne svarede til de ændringer som også ses ved pembrolizumab monoterapi, og som skyldes den kendte suppression af de hvide og røde blodlegemer samt blodplader. Der blev ikke fundet kliniske betydningsfulde ændringer i blodbilledet grad 3-5 hos PEM+CT gruppen vs. PBO+CT og derfor vurderer EMA, at der ikke er grund til bekymring for brugen af bevacizumab sammen med PEM+CT i forhold til blodbilledet (EPAR s. 120 [9]).

Som forventet var der flere immunrelaterede bivirkninger i PEM+CT vs. PBO+CT (69,23% vs. 40,70%). Antallet svarer til referencesættet for behandling med pembrolizumab monoterapi og er angivet til: colitis (6,5% vs. 1,9%), hepatitis (1,6% vs. 0,4%), hyperthyroidisme (7,1% vs. 3,8%), hypothyroidisme (19,2% vs. 12,1%), svære hudreaktioner (5% vs. 0,4%) og pneumonitis (1,9% vs. 0,4%) (Tabel 81 s. 117 i EPAR [9]).

Bivirkninger og seponering

Analysen af bivirkninger afslørede højere grad af seponering i det eksperimentel behandlingsarm sammenlignet med kontrol (37.5% vs 26.5%) (Table 13). Bemærk, at antal af dødstilfælde var sammenlignelig mellem de to behandlingsarme (4.6% vs 4.5%). Når man ser på seponering af ethvert lægemiddel på grund af en alvorlig lægemiddelrelateret bivirkning, var antallet af patienter i pembrolizumab-armen også højere sammenlignet med kontrol; henholdsvis 39 patienter (12.7%) og 23 patienter (7.4%). Den højere seponeringsrate på grund af bivirkningerne i forsøgsarmen kan relateres til længere tid patienterne har været i studiebehandling. Samlet set var eksponeringen >12 måneder i KEYNOTE-826 længere i pembrolizumab-armen end i kontrolarmen: henholdsvis 54.6% vs. 40.9%.

[redacted]

Table 13 Antal af patienternes frafald pga. bivirkninger

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	
	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033	
with one or more adverse events	305	(99.3)	307	(99.4)	2,015	(99.1)
with no adverse event	2	(0.7)	2	(0.6)	18	(0.9)
with drug-related[a] adverse events	298	(97.1)	300	(97.1)	1,948	(95.8)
with toxicity grade 3-5 adverse events	251	(81.8)	232	(75.1)	1,583	(77.9)
with toxicity grade 3-5 drug-related adverse events	210	(68.4)	198	(64.1)	1,285	(63.2)
with serious adverse events	153	(49.8)	131	(42.4)	962	(47.3)
with serious drug-related adverse events	93	(30.3)	71	(23.0)	550	(27.1)
who died	14	(4.6)	14	(4.5)	139	(6.8)
who died due to a drug-related adverse event	2	(0.7)	4	(1.3)	43	(2.1)
discontinued any drug due to an adverse event	115	(37.5)	82	(26.5)	551	(27.1)
discontinued pembrolizumab or placebo	46	(15.0)	25	(8.1)	345	(17.0)
discontinued all drugs	18	(5.9)	15	(4.9)	125	(6.1)
discontinued any drug due to a drug-related adverse event	96	(31.3)	69	(22.3)	434	(21.3)
discontinued pembrolizumab or placebo	31	(10.1)	12	(3.9)	234	(11.5)
discontinued all drugs	10	(3.3)	6	(1.9)	76	(3.7)
discontinued any drug due to a serious adverse event	51	(16.6)	32	(10.4)	327	(16.1)
discontinued pembrolizumab or placebo	33	(10.7)	16	(5.2)	268	(13.2)
discontinued all drugs	17	(5.5)	11	(3.6)	110	(5.4)
discontinued any drug due to a serious drug-related adverse event	39	(12.7)	23	(7.4)	220	(10.8)
discontinued pembrolizumab or placebo	22	(7.2)	8	(2.6)	167	(8.2)
discontinued all drugs	10	(3.3)	4	(1.3)	63	(3.1)

Tabellen viser forekomst af bivirkninger og seponeringsrate pga. de forskellige bivirkninger i tre forskellige patient grupper; 1) KN826 Pembrolizumab+kemoterapi arm, 2) KN826 placebo+kemoterapi arm og 3) samlet datasæt for pembrolizumab+kemoterapi kombination i forskellige indikationer hvor kombinationen er godkendt i EU.

Konklusion, bivirkninger:

Det er EMA's vurdering at bivirkningsprofilen i KN826 var forventelig jf. tidligere studier med kombinationsbehandling med PEM+CT [9]. Der blev rapporteret ens risiko for udvikling af grad 3-5 bivirkninger på 81,8% i PEM+CT gruppen mod 75,1% i PBO+CT (RR 1.05).

Andelen af alvorlige bivirkninger var 30,3% vs. 23,0% for PEM+CT vs. PBO+CT. En velkendt stigning i andelen af bivirkninger hos interventionsgruppen vs. komparatorgruppen, da der tillægges pembrolizumab til behandlingen. Der blev observeret et lavt antal dødsfald i PEM+CT n=2 (0,7%) vs. PBO+CT n=4 (1,3%), begge lavere end referencesættet for alle PEM+CT behandlede i EU (2,1%).

For interventionsgruppen sås der en let øget andel af bivirkninger hos dem, som også blev behandlet med bevacizumab, der ikke blev observeret i komparatorgruppen.

Bivirkningerne i KN826 svarer til de forventede bivirkninger ved brug af pembrolizumab (fx endokrine forstyrrelser), kemoterapi (fx hårtab, anæmi, kvalme, diarre, træthed) samt bevacizumab (fx hypertension, udslet, næseblod, forhøjede værdier er leverenzymer) og det kunne

ses at antallet af bivirkninger steg med andel af behandlinger. De immunrelaterede bivirkninger i interventionsgruppen er på niveau med referencesættet for pembrolizumab monoterapi. Der blev ikke observeret eller rapporteret nye bivirkninger.

7.1.2.7 Livskvalitet

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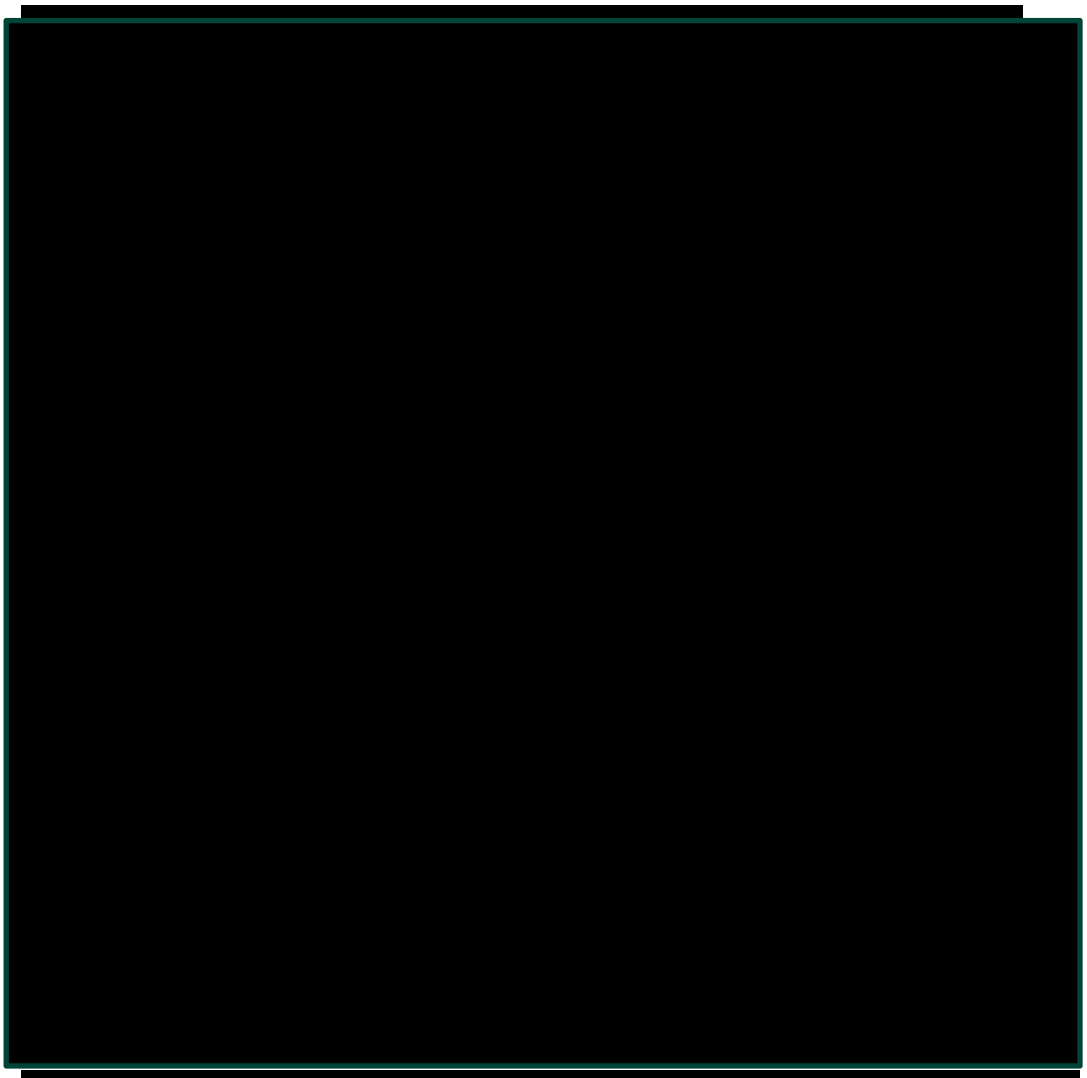

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Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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MSD vurderer, at der for patienter med P/R/M cervix cancer er en stor klinisk merværdi for tillæg af pembrolizumab til nuværende standardbehandling med god effekt på både PFS og OS, uden at livskvalitet forringes hos denne patientgruppe med ofte ringe prognose.

8. Health economic analysis

The following is a description of our economic model, that was developed to demonstrate the cost effectiveness of pembrolizumab in combination with chemotherapy ± bevacizumab as treatment for patients with persistent, recurrent or metastatic cervical cancer (PRMCC) whose tumors express PD-L1 (Combined Positive Score [CPS] ≥1) in Denmark.

8.1 Model

8.1.1 Objective

The objective of the model is to evaluate the cost effectiveness of pembrolizumab in combination with chemotherapy ± bevacizumab versus chemotherapy ± bevacizumab in a population of patients with persistent, recurrent or metastatic cervical cancer and with CPS ≥1, in line with the patients included in KN826.

The model has Denmark as the base case and takes the limited societal perspective were direct health costs and some indirect costs including relevant transportation costs and patient time spent for drug administration and monitoring are included.

8.1.2 Outcomes evaluated

During the modeled time horizon, expected costs and clinical effectiveness (including life years [LYs] and quality-adjusted life years [QALYs]) are estimated for each treatment arm. Costs are reported in aggregate as well as disaggregated by cost component (drug acquisition costs, drug administration costs, disease management costs, PD-L1 testing costs, costs for AEs, terminal care costs, costs for patients). Effectiveness outcomes are reported in aggregated as well as disaggregated style. The incremental cost-effectiveness ratios (ICERs) of pembrolizumab in combination with chemotherapy ± bevacizumab versus chemotherapy ± bevacizumab is evaluated in terms of incremental cost per QALY gained and incremental cost per LY gained. The economic model results are presented for the CPS≥1 population, in line with EMA regulatory approval.

8.1.3 Model structure

The structure adopted for this model was informed by consideration of prior economic models in this and other related disease areas (Appendix M). A semi-markov State Transition Model (STM) provides the base case for this cost-effective analysis.

In a targeted search of models previously submitted to NICE in cervical cancer, uterine cancer and ovarian cancer, there was strong precedence for using the standard three health states for oncology models (progression-free, progressed disease, and death; Appendix M). All but one appraisal used this standard model with TA59817 also including a fourth health state of subsequent progression-free survival.

The model structure involves three health states: ‘progression free’, ‘progressed disease’, and ‘death’. All patients enter the model in the ‘progression free’ health state and progress over time to the ‘death’ state (absorbing state), potentially with time spent in ‘progressed disease’ state.

8.1.3.1 A three-health state semi-Markov state transition model

Transition probabilities are calculated between each health state (progression free, progressed disease and death) based on the hazards of time-to-progression (TTP), pre-progression survival (PrePS), and post-progression survival (PPS). The transitions across the three health states occurs as illustrated in Figure 8.

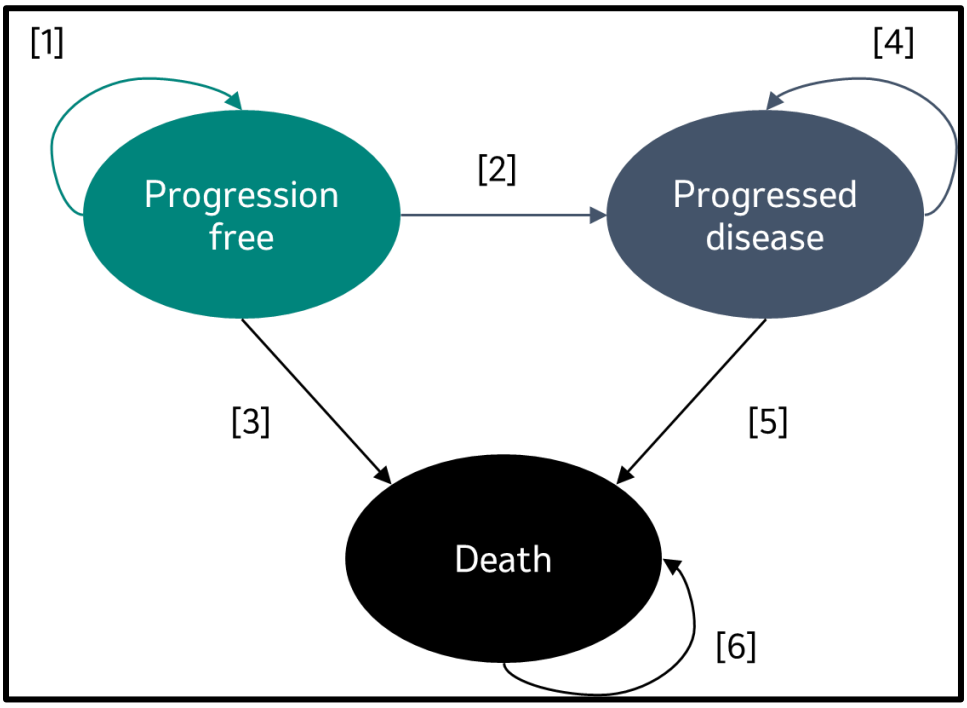


Figure 8. Three-health state semi-Markov State Transition Model

8.1.3.2 Strengths and Limitations of Semi-Markov STM structure

The STM structure uses estimates of transition probabilities based on patient-level data for time-to-progression, progression free survival and post-progression data from the KN826 trial. This is conceptually simple, reflecting the likely disease history of the patient population. Modelled outcomes adequately quantify the primary objectives of treating patients in PRMCC to improve quality of life, delay disease progression, and extend long-term survival. The state transition structure is deemed particularly reliable to assess pembrolizumab in this indication because:

- It is fundamentally important to consider the relationship between time spent in the pre-progression and post-progression health states, using a model structure where clinical events are explicitly linked, and the prognostic influence of disease progression is adequately reflected
- It is necessary to incorporate the slowing of progression event rates observed in KN826, where there is a visual plateau in the PFS/TTP data. This is likely to translate into the shape of OS beyond 39 weeks, which should be considered in decision-making
- The PPS data from KN826 are mature. As almost 90% of patients who progressed in each arm of KN826 were subsequently recorded to have a death event, the estimated probabilities associated with transitioning from the progressed disease health state to death fit the observed data very well, with minimal uncertainty in the extrapolated portion beyond the observed period
- It is arguably preferable to use a model structure that does not rely on immature overall survival data where long-term extrapolations are subject to substantial variability, such as in KN826.

The STM structure avoids some specific limitations associated with other model structures such as the standard Partitioned Survival Model structure, in the presence of immature data, such as the reliance on OS data and the associated impact of uncertainty on the results, together with assumed independence between survival endpoints. However, the STM is not devoid of its own limitations, including the complexity of handling the competing risks of progression and death from the progression-free state, and increased difficulties of validation, since OS is not directly modelled.

At the time of the first interim analysis within the PD-L1 CPS≥1 group of patients, 118 out of 273 patients in the pembrolizumab combination treatment arm (43.2%) and 154 out of 275 in the SoC arm (56.0%) had died. After the duration of follow-up, OS Kaplan-Meier (KM) estimates were 51.1% for pembrolizumab combination treatment and 30.8% for SoC.

TTP data were more mature; 132 out of 273 patients in the pembrolizumab combination treatment arm (48.4%) and 172 out of 275 in the SoC arm (62.5%) had progressed (investigator-assessed progression status). After the duration of follow-up, TTP KM estimates were 37.3% for pembrolizumab combination treatment and 16.0% for SoC.

Because the TTP data were more mature than the OS data, the extrapolation of TTP beyond the follow-up duration of the trail is less uncertain than the extrapolation of OS.

The STM structure allows fuller and more explicit use of information on prognostic intermediate endpoints (i.e., progression) to inform mortality extrapolations. In a standard three-health state transition oncology model, progression and death are explicitly related: OS is a function of TTP, pre-progression survival and PPS. On the other hand, alternative model structures, such as the PartSA approach, model OS independent of PFS.

The modelling of OS independent of PFS becomes more problematic when OS data are relatively immature, such as in KN826. In the within-trial period, all dependencies between OS and PFS are reflected in the data. However, in the post-trial period, (most of) this dependency is ignored with potentially important implications for extrapolation. Hence, in cases where OS data are relatively immature, a STM is deemed as the appropriate choice of model as it does not rely on the OS data. The reasons to prefer the STM structure may be summarised as follows:

1) The STM structure provides and allows greater assessment of the clinical and biological plausibility of extrapolations through scenario analyses
2) OS data of the KN826 trial is relatively immature compared to the TTP data. Since the STM structure is informed primarily by TTP and PPS, and does not require direct modelling of OS, the STM structure mitigates the uncertainty in results associated with reliance on immature OS data.

The NICE methods guidance recommends that the clinical and biological plausibility of extrapolations should be assessed and that alternative scenarios should be routinely considered for the extrapolation period. When decision models are underpinned by a structure reflecting biological or clinical processes (such as in the current case), it is possible to carefully consider the mechanisms underpinning extrapolations and to subject these to scrutiny and sensitivity analyses. For example, in a state transition model, the impact of assuming the same PPS for the intervention and comparator can be assessed. This scenario analysis cannot be performed in alternative model structures such as the Partitioned Survival Model.

8.1.4 Time horizon and model cycle

The model base case has a time horizon of 35 years. As the mean age in KN826 is 51 years, the base case time horizon is considered appropriate to capture relevant costs and health benefits over the patient's lifetime. The impact of alternative time horizons (20 and 50 years) was explored via scenario analyses.

8.1.5 Discount rate

In the base case analysis, both costs and effectiveness are discounted annually at 3,5% for year 1 to 35, and at 2,5% for year 36 to 70, consistent with The Danish Medicines Council methods guide for assessing new pharmaceuticals. Alternative annual discount rates were tested in sensitivity analyses.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

A three-health state semi-Markov state transition model

A semi-markov State Transition Model (STM) provides the base case for this cost-effective analysis and, transition probabilities are calculated between each health state (progression free, progressed disease and death) based on the hazards of time-to-progression (TTP), pre-progression survival (PrePS), and post-progression survival (PPS). The transitions across the three health states occurs as illustrated in Figure 8.

The transition probabilities were derived as shown in Table 17.

Table 17. Derivation of transition probabilities

Label	Name of progression	Transition probability from time t to time t+1
1	Remain progression-free	PFS(t+1, arm) / PFS(t, arm)
2	Newly progressed	1 – TTP(t+1, arm) / TTP(t, arm)
3	Pre progression death	Balancing item: = 1 – [1] – [2]
4	Remain with progressed disease	PPS(t+1, arm) / PPS(t, arm)
5	Post progression death	Balancing item: = 1 – [4]
6	Death (absorbing state)	1
Key: PFS, progression free survival; PPS, post progression survival; TTP, time to progression		

KN826 pre-progression survival data could not be used to model PrePS directly, as the number of pre-progression deaths in the trial was too small (39 events [12.7%] in the pembrolizumab + SoC arm; 42 events [13.6%] in the SoC arm). Therefore, PFS data is used to model PrePS.

Table 18. Input data used in the model

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Overall survival (OS)	KN826, Primary endpoint: To compare OS between treatment arms (OS: The time from randomization to death due to any cause)	A semi-markov State Transition Model (STM) provides the base case for this cost-effective analysis. The model structure involves three health states: 'progression free', 'progressed disease', and 'death'. All patients enter the model in the 'progression free' health state and progress over time to the 'death' state (absorbing state), potentially with time spent in 'progressed disease' state. In the model, transition probabilities are calculated between each health state (progression free, progressed disease and death) based on the hazards of time-to-progression (TTP), pre-progression survival (PrePS), and post-progression survival (PPS). The parameterization of all outcomes in the cost-effectiveness model were all informed by patient-level analysis of KN826. The outcomes included in the model are as follows: ▪ Progression-free survival ▪ Time to progression ▪ Post-progression survival ▪ Time on treatment ▪ Health-related quality of life ▪ Adverse events	The STM structure uses estimates of transition probabilities based on patient-level data for time-to-progression, progression free survival and post-progression data from the KN826 trial. The transition probabilities were derived as shown in Table 14. KN826 pre-progression survival data could not be used to model PrePS directly, as the number of pre-progression deaths in the trial was too small. Therefore, PFS data is used to model PrePS. PPS is modelled based on time since entry in the 'post-progression survival' health state. Parametric survival models were used to extrapolate outcomes beyond the trial period. Statistical testing for proportionality of hazards and visual assessment of the KM data indicated that PFS, TTP and PPS hazards for pembrolizumab and SoC were not proportional and therefore, independent survival models were fit to each arm.

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Progression-free survival (PFS)	KN826, Primary endpoint: To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms (PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first)	Please see description above for OS	Please see description above for OS
Adverse reaction 1 (measured in costs)		The unit cost of AE management per incidence was obtained from DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen	The costs associated with AEs per model cycle are calculated by multiplying the proportion of patients who receive at least one treatment in that treatment cycle with the risks for AEs per week on treatment and the unit costs per AE.
Adverse reaction 2 (measured as occurrence)	AE Grade incidence rates	The model includes grade 3-5 all cause adverse events (AEs) that occurred in at least 5% of patients in either treatment arm of KN826, CPS ≥1 population	Data on grade 3-5 all cause adverse events that occurred in at least 5% of patients in either treatment arm from KN826, CPS ≥1 population
Adverse reaction 3 (measured as utility loss)			Disutility associated with AEs were calculated by multiplying the rate of AE with dis-utilities associated with grade 3+ AE and their mean duration, as experienced in KN826

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
"Utility by progression status" approach	For patients in both arms in KN826, EQ-5D-5L data were collected at Day 1 of treatment cycles 1-14 (1 cycle=3 weeks). After cycle 14, the data were collected every other cycle, at the treatment discontinuation visit, and safety follow-up (which took place 30-day-post treatment discontinuation) . The total analysis population with a CPS≥1 consisted of 520 patients, resulting in a combined total of 6.956 EQ-5D measurements. The population comprised of patients who were randomized (n = 548), received a study treatment (n=545), and completed at least one EQ-5D-5L questionnaire (n=520).	EQ-5D-5L data collected in the KN826 trial	The EuroQol EQ-5D-5L contains five health state dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension rates on a 5-point scale from 1 (no problem) to 5 (extreme problem) was converted to Denmark-based utility valuations using the Danish algorithm based on the general Danish population to derive EQ-5D-5L utility values. The base case analysis was based on the 'utility by progression status' approach, wherein utility was linked to the patient's progression status (i.e., progression-free vs. progressive disease). Since one patient could have multiple utility measures within the same health state, mixed linear effects models with random subject intercept were used for this analysis to account for within-subject correlation. AE disutility was estimated as the difference between utility measured without a grade 3+ AE and utility measured during a grade 3+ AE. Treatment effect was evaluated to assess whether the analytic approaches capture most of the treatment effect. The utilities were also adjusted for age to account for the decrement in utilities with aging. The disutility (utility decrement) in each cycle was calculated by taking a difference of the baseline utility (0,818) and utility associated with the patient's age in each cycle.

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Transition probability-		See table 14 for details	See table 14 for details

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The Danish patient population: Patients with with persistent, recurrent or metastatic cervical cancer, that have not been treated with systemic chemotherapy and are not amenable to curative treatment.

Patient population in the clinical documentation submitted: Patients 18 years of age or older with persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma of the cervix that have not been treated with systemic chemotherapy and are not amenable to curative treatment (patients with PD-L1 CPS≥1).

Patient population in the health economic analysis submitted: Patients 18 years of age or older with persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma of the cervix that have not been treated with systemic chemotherapy and are not amenable to curative treatment (patients with PD-L1 CPS≥1).

Table 19. Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age	51 years(mean) (based on data from KN826)	51 years(mean) (based on data from KN826)	75% below the age of 60 [33]
Body surface area	1,70 M^2 (based on data from KN826)	1,70 M^2 (based on data from KN826)	Data not available
Body weight	64,70 kg (based on data from KN826)	64,70 kg (based on data from KN826)	Data not available
BMI, median	N/A	N/A	25.7 [2]

The clinical documentation and economic model are focused towards the patients whose tumors express PD-L1 with CPS ≥1 from KN826 and therefore the base line characteristic are identical. Data from Danish clinical practice is sparse. There are presently no Danish data available with regards to patient characteristics on body surface area and mean weight. However, the annual report from DGCG states that the median BMI for the patient population is 25.7. MSD does not expect great differences in the patient characteristics in the model and the Danish population.

8.2.2.2 Intervention

Intervention as in the health economic analysis submitted:

The intervention considered in the model is pembrolizumab 200 mg every 3 weeks (Q3W) for a maximum of 35 cycles (approximately 2 years) in combination with SoC chemotherapy. This is in line with the dosing regimen used in KN826 and, the EMA Summary of product characteristics (SmPC) for pembrolizumab. The approved indication allows for the option of dosing pembrolizumab as 400 mg every 6 weeks and this is included in the model as a dosing schedule option. This is an advantage from a patient and from a hospital perspective as it entails fewer IV administration compared to 3 weeks dosing.

The Danish Medicines Council has in previous evaluations of pembrolizumab indications stated that weight based dosing of pembrolizumab was a precondition for the positive recommendations decisions. The impact of weight based dosing of pembrolizumab was therefore explored via scenario analyses.

The choice to use (or not use) bevacizumab was a decision made prior to randomization in KN826. Randomization and analysis of the trial were then stratified according to bevacizumab usage. Due to selection bias, neither KN826 nor this economic model permits valid evaluation of the clinical or cost-effectiveness of adding bevacizumab.

Pembrolizumab with or without bevacizumab is administered in combination with paclitaxel and either cisplatin or carboplatin. Accordingly, there are four regimes of chemotherapy considered in the model:

- Paclitaxel + Cisplatin (Pac + Cis)
- Paclitaxel + Carboplatin (Pac + Carbo)
- Paclitaxel + Cisplatin + Bevacizumab (Pac + Cis + Bev)
- Paclitaxel + Carboplatin + Bevacizumab (Pac + Carbo + Bev)

Distribution of patients across the four regimes used in the model, can be found in Table 20 and Table 21 below:

Table 20. Distribution of patients across treatments in the pembrolizumab arm of KN826

Pembro+Pac+Cis	Pembro+Pac+Cis+Bev	Pembro+Pac+Carbo	Pembro+Pac+Carbo+Bev
5,6%	10,1%	30,1%	54,2%

Table 21. Distribution of patients across treatments in the SoC arm of KN826

Pac+Cis	Pac+Cis+Bev	Pac+Carbo	Pac+Carbo+Bev
5,8%	9,5%	32,0%	52,6%

Pac + Cis and Pac + Carbo are considered clinically equivalent in both the trial (through its design and analysis) and the cost-effectiveness model; similarly Pac + Cis + Bev is considered clinically equivalent to Pac + Carbo + Bev. The cost-effectiveness model includes a mix of patients that either receive or do not receive bevacizumab (as per the KN826 trial). Due to selection bias, neither KN826 nor this economic model permits valid evaluation of the clinical or cost-effectiveness of adding bevacizumab.

Treatments are costed according to the duration they were received in KN826, up to a treatment cap of 35 cycles (two years) for pembrolizumab (per trial design) and up to 6 cycles for chemotherapy and bevacizumab (per trial design).

Table 22. Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Pembrolizumab 200 mg every 3 weeks (Q3W) for a maximum of 35 cycles (approximately 2 years) in combination with SoC chemotherapy(paclitaxel 175 mg/m2 intravenous (IV) + cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W))	Pembrolizumab 200 mg every 3 weeks (Q3W) for a maximum of 35 cycles (approximately 2 years) in combination with SoC chemotherapy(paclitaxel 175 mg/m2 intravenous (IV) + cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W))	Pembrolizumab 2 mg/kg every 3 weeks (Q3W) for a maximum of 35 cycles (approximately 2 years) in combination with SoC chemotherapy(paclitaxel 175 mg/m2 intravenous (IV) + cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W))
Length of treatment (time on treatment) (mean/median)	Median: 10,0 months ((APat) population)	Mean: 13,62 months (CPS ≥1 population)	
Criteria for discontinuation	Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression or a maximum of 24 months. Duration of chemotherapy treatment was capped at 6 doses	Treatment with pembrolizumab was capped at 35 cycles (2 years), and treatment with SoC (chemotherapy ± bevacizumab) was capped at 6 cycles as per the trial protocol.	Treatment of pembrolizumab is expected to be capped at 2 years in line with KN826 and all previous recommendations from The Danish Medicines Council
The pharmaceutical's position in Danish clinical practice			Not used in clinical practice prior to evaluation in the Medicine Council. Recommendation from the Danish Medicines Council will lead to the introduction of the intervention as 1L treatment

The Danish Medicines Council has in previous assessments of pembrolizumab indications stated that weight based dosing of pembrolizumab was a precondition for positive recommendation decisions. MSD assumes the Danish Medicines Council, also in this case, will include a precondition relating to weight based dosing, and the impact of weight based dosing of pembrolizumab was therefore explored via scenario analyses.

8.2.2.3 Comparators

The current Danish clinical practice is to treat with cisplatin or carboplatin, paclitaxel ± bevacizumab [5]. In the current clinical guidelines it is assumed that cisplatin and carboplatin have equivalent efficacy. The use of bevacizumab is per clinicians discretion on the basis of a balance between efficacy and safety.

Comparator(s) in the clinical documentation submitted: The comparator considered in the clinical documentation is chemotherapy ± bevacizumab, which is the SoC, as per KN826 trial: paclitaxel 175 mg/m2 intravenous (IV)+ cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W).

Comparator in the health economic analysis submitted: The comparator considered in the health economic analysis is chemotherapy ± bevacizumab, which is the SoC, as per KN826 trial: paclitaxel 175 mg/m2 intravenous (IV)+ cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W).

Chemotherapy with or without bevacizumab are both recommended in Danish clinical guidelines. The use of bevacizumab is per clinicians discretion on the basis of a balance between efficacy and safety as bevacizumab has some contraindications that are common complications of recurrent or metastatic cervical cancer. A proportion of patients cannot tolerate bevacizumab, making treatment flexibility a key need. In Denmark PRMCC patients are primarily treated with Aybintio (a bevacizumab biosimilar), and hence only its cost is considered in the cost-effectiveness analysis for chemotherapy with bevacizumab treatment combinations in both the intervention and comparator arm

MSD believes that the combination of cisplatin or carboplatin, paclitaxel ± bevacizumab is an adequate and relevant comparator in the model, as it is in line with the current Danish clinical guidelines and current clinical practice.

Table 23. Comprator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	paclitaxel 175 mg/m2 intravenous (IV)+ cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W).	paclitaxel 175 mg/m2 intravenous (IV)+ cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W).	paclitaxel 175 mg/m2 intravenous (IV)+ cisplatin 50 mg/m2 IV or carboplatin AUC 5 IV (assumed to be equal to 750 mg) ± bevacizumab 15 mg/kg IV) every 3 weeks (Q3W).
Length of treatment	Median: 7,7 months ((APat) population)	Mean: 10,24 months (CPS ≥1 population)	
The comparator's position in the Danish clinical practice		The comparator is equal to current standard treatment in Danish clinical practice as described In the clinical guidelines[5]	

8.2.2.4 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: Adverse event are reported for the all participants as treated (APat) population in the clinical documentation.

Adverse reaction outcomes in the health economic analysis submitted The economic model includes grade 3-5 all cause adverse events that occurred in at least 5% of patients in either treatment arm from KN826, PD-L1 CPS ≥1 population.

Table 24. Adverse events for the all participants as treated (APat) population in the clinical documentation.

	PEM+CT ±bevacizumab		PBO+CT ±bevacizumab	
	n	(%)	n	(%)
Anaemia	93	(30.3)	83	(26.9)
Neutrophil count decreased	40	(13.0)	26	(8.4)
Neutropenia	38	(12.4)	30	(9.7)
Hypertension	29	(9.4)	33	(10.7)
Urinary tract infection	27	(8.8)	25	(8.1)
Thrombocytopenia	23	(7.5)	14	(4.5)
Febrile Neutropenia	22	(7.2)	14	(4.5)
Platelet count decreased	21	(6.8)	14	(4.5)
White blood cell count decreased	21	(6.8)	13	(4.2)

Adverse events, grade 3-5 all cause adverse events that occurred in at least 5% of patients in either treatment arm from KN826, PD-L1 CPS ≥1 population is presented below.

Table 25. AE reporting in KN826 in the health economic analysis submitted.

Adverse event rates in KN-826 (%)	**Adverse event rates in KN-826**	
Adverse event (grade 3+)	**Incidence of all-cause grade 3+ adverse events**	
	Direct comparison	
	Pembro + SoC	**SoC**
Any AE	**81,62%**	**74,91%**
Anaemia	28,31%	25,82%
Neutrophil count decreased	13,60%	8,00%
Neutropenia	13,24%	10,18%
Hypertension	9,56%	11,27%
Thrombocytopenia	6,62%	4,00%
Febrile neutropenia	7,35%	4,36%
Platelet count decreased	7,72%	4,36%
White blood cell count decreased	6,99%	4,00%
Urinary tract infection	9,19%	8,00%

Adverse event are reported for the all participants as treated (APat) population in the clinical documentation to account for all the AE reporting in KN826 and to align with reporting in EPAR. In the health economic analysis submitted, we have only included AE reporting on KN826, CPS ≥1 population to align with approved EMA indication and scope of analysis. As is evident from Table 24 and Table 25 above there are only minimal differences.

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

The following is a summarization of the parameterisation of outcomes in the cost-effectiveness model. A more detailed describtion can be found in appendix G.

The parameterisation of all outcomes in the cost-effectiveness model were all informed by patient-level analysis of KN826. Table **26** lists the clinical outcomes included in the model.

Table 26. Clinical outcomes included in the cost-effectiveness model.

	STM structure
Progression-free survival	✓
Time to progression	✓
Post-progression survival	✓
Time on treatment	✓
Health-related quality of life	✓
Adverse events	✓

Clinical parameters for the State Transition Model (STM)

In order to model outcomes over a lifetime horizon, it was necessary to extrapolate the patient-level data of clinical outcomes beyond the trial period in KN826. Parametric analyses were conducted based on the patient-level data from KN826 following best practices for survival modelling and in line with the NICE requirements[34, 35].

For the pembrolizumab and SoC arms, PFS, TTP, and PPS curves were derived by fitting 7 different parametric models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz, Gamma and Generalized Gamma distributions) to the observed data from KN826 trial. The fitted parametric curves were used to extrapolate these outcomes beyond the trial period. Both one-piece and piecewise (Kaplan–Meier + parametric survival curve) models were fitted to the data. The survival curve fitting was carried out in line with NICE Decision Support Unit guidelines [34, 35]. Goodness-of-fit statistics based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), visual inspection (comparing fitted parametric curves to the observed Kaplan–Meier plots during the trial follow-up period), assessment of the underlying hazard functions, and clinical plausibility of the extrapolation in the longer term (versus external data were available and expert opinion by international clinicians) were used to select the best-fitted parametric curves for the base case and alternative plausible parametric survival curves to be explored in sensitivity analyses. The model base case for PFS, TTP, and PPS extrapolations were validated by clinical key international opinion leaders.

Following extrapolation, each cycle transition (or hazard) including death as an event is calculated as the maximum of the extrapolated transition (or hazard) and general population mortality based on lifetables [36]. Death is an absorbing health state, there are no transitions allowed out of this health state.

Progression-Free Survival

Parametric survival models were necessary to be able to extrapolate PFS data beyond the trial period. Statistical testing for proportionality of hazards and visual assessment of the KM data indicated that PFS hazards for pembrolizumab and SoC were not proportional and therefore, independent survival models were fit to each arm. The determination of the cut-off time points for the piecewise models include visual inspection of the one-piece fitting, combined with considerations of the patterns observed around the candidate cut-off from the chow-test plot, number of subjects remaining at the candidate cut-off time and number of events occurred post the candidate cut-off that are inferred from the KM plot. The resulting plot of the chow test statistics identified that the structural changes to the KM data were observed at week 28, 37 and

46, and hence formed the basis of the cut-off points at which two-piece models were tested (fitted). A one-piece fitting results in an underestimation of the KM data till week 28 followed by an overestimation of KM data till week 75 (week 70 for SoC). Thus, one-piece models did not provide a good visual fit to the data for pembrolizumab and SoC (particularly to the data for pembrolizumab) and were not selected for the base case parametric extrapolation. Most of the two-piece models fit at or beyond 37 weeks provide a reasonable visual fit to the data for pembrolizumab and SoC, at the cost of reduced data availability to inform the fit. Hence, when compared with one-piece fiting and two-piece models fit beyond 28 weeks, two-piece models fit at or beyond 37 weeks were chosen for the base case.

Since the log logistic distribution fulfilled all the above mentioned criteria for both the arms, and also provided a good statistical fit to the trial data, (with acceptable AIC/BIC values that lie within 5 points of the value of best fitting distribution), it was chosen as the base case parametric distribution used for extrapolations in the model. Therefore, the preferred model for both treatment arms was a two-piece model, with cut-off at 37 weeks, and a log-logistic distribution. Extrapolations for this and other distributions are presented in Appendix G.

Time-to-progression

The TTP and PFS endpoints differ in that deaths are recorded as an event for PFS, but a censoring is applied for TTP. In this way, TTP measures exactly time to progression, whereas PFS is the time to a composite endpoint of progression or death.

Parametric survival models were necessary to be able to extrapolate TTP beyond the trial period. Statistical testing for proportionality of hazards and visual assessment of the KM data indicated that TTP hazards for pembrolizumab and SoC were not proportional, therefore, independent survival models were fit to each arm.

Our findings from reviewing the model fit of various one-piece and two-piece fits of TTP were similar to those for the PFS endpoint, with one-piece fitting results in an underestimation of the KM data till week 28 followed by an overestimation of KM data till week 75 (week 70 for SoC). Thus, one-piece models did not provide a good visual fit to the data for pembrolizumab and SoC (particularly for pembrolizumab), and were not selected for the base case parametric extrapolations, in line with the findings for PFS. All (rather than some) of the two-piece models fit at or beyond 37 weeks provide a reasonable visual fit to the data for pembrolizumab and SoC. Most of the two-piece models fit beyond 46 weeks provide a good visual fit to the data for pembrolizumab; and unlike for PFS, the curves do not overshoot the last step in the KM tail. Most of the two-piece models fit beyond 46 weeks provide a good visual fit to the data for SoC, at the cost of reduced data availability to inform the curves. Since two-piece models fit at or beyond 37 provided a reasonable fit with more data to inform the curves, it was chosen for the base case analysis.

Since the log logistic distribution fulfilled all of the criteria metioned above, for both the arms, provided a good statistical fit to the trial data, (with acceptable AIC/BIC values that lie within 5 points of the value of best fitting distribution) and was in line with distribution chosen for PFS, it was also chosen as the base case parametric distribution used for extrapolations of TTP curves. The preferred model for both treatment arms as consistent with the PFS endpoint: a two-piece model, with cut-off at 37 weeks, and a log-logistic distribution. Model fit statistics and extrapolations details can be found in Appendix G.

Post-progression survival

Parametric survival models were necessary to be able to extrapolate PPS outcomes beyond the trial period. Statistical testing for proportionality of hazards and visual assessment of the KM data indicated that PPS hazards for pembrolizumab and SoC were not proportional and therefore, independent survival models were fit to each arm.

Our findings from evaluating different model fits was that one-piece models fitted the data well. Chow test conducted to detect the cut-off points of the piecewise modelsresulted in structural changes to the KM data being observed at 14 weeks. Two-piece models, (fitted at a cutt-off point of 14 weeks) did not seem to improve on one-piece fittings and hence were not used for the base case extrapolations.

Since the generalized gamma distribution fulfilled all of the criteria of clinical validity, for both the arms and provided a good statistical fit to the trial data, (with acceptable AIC/BIC values that lie within 5 points of the value of best fitting distribution) it was chosen as the base case parametric distribution for extrapolation of PPS curves. Model fit statistics and extrapolations details can be found in Appendix G.

8.4 Documentation of health-related quality of life (HRQoL)

The EuroQol EQ-5D-5L system was used to measure generic health status during KN826. The instrument contains five health state dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension rates on a 5-point scale from 1 (no problem) to 5 (extreme problem). The EQ-5D-5L data collected in the KN826 trial was converted to Denmark-based utility valuations using the Danish algorithm based on the general Danish population to derive EQ-5D-5L utility values[37]. Please also see Appendix K for further information concerning the modelling of EQ-5D health utility in the KN826 according to Danish algorithm.

For patients in both arms in KN826, EQ-5D-5L data were collected at day 1 of treatment cycles 1-14 (1 cycle=3 weeks). After cycle 14, the data were collected every other cycle, at the treatment discontinuation visit, and safety follow-up (which took place 30-day-post treatment discontinuation).

The total analysis population with a PD-L1 CPS≥1 consisted of 520 patients, resulting in a combined total of 6.956 EQ-5D measurements. The population comprised of patients who were randomized (n = 548), received a study treatment (n=545), and completed at least one EQ-5D-5L questionnaire (n=520).

Overall, the compliance of EQ-5D reporting was high. The completion, compliance rates and number of missing data is provided in Table 14. Further definitions of compliance and completion is presented in 7.1.2.7.. Missing data were excluded in the analysis, which only included evaluable records.

Statistical analysis

Based on the cost-effectiveness model development plan, the utility was analysed by two approaches: 1) by progression status 2) by time-to-death.

The base case analysis was based on the 'utility by progression status' approach, wherein utility was linked to the patient's progression status (i.e., progression-free vs. progressive disease). Since one patient could have multiple utility measures within the same health state, mixed linear effects

models with random subject intercept were used for this analysis to account for within-subject correlation. This model includes health state and presence of Grade 3+ drug-emergent AEs and mathematically represented as:

$$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \beta_2 AE_{ij} + e_i$$

The variable are described in the table below:

Table 27 Variable description

Variable (variable name)	Variable description
Intercept (β_0)	Represent progression free
Progression Status (PFINVFL (W_PD)) (β_1)	Progression-free (No_PD) vs. progressive disease (W_PD), according to RECIST, version 1.1, as based on investigator's assessment. An "Unknown" category was created for records measured with unknown progression status
AE (G35AEFL (wi Grade3+ AE)) (β_2)	Indicator for an EQ-5D-5L score measured during Grade 3+ AEs

Table **28** presents the utility estimates of the general Danish population calculated using the Danish algorithm [37].

Table 28. KN826 Utility Regression Results, based on Danish Algorithm

Fixed effects parameter	Estimate	Standard Error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

There is a limitation of the analysis based on trial-collected utility data, which is collected less frequently after progression. No further utility data were collected in the trial and therefore, the utility data for progressive disease state is limited.

The model also includes the option of evaluating utilities by the 'time-to-death' approach. Under the by 'time-to-death' approach, utilities in the cost-effectiveness model were applied based on the distribution of patients across different categorizations of time-to-death (i.e., <30, 30-90, 90-180, 180-360, ≥360 days until death). This approach to define health states based on time to death is developed by Batty et al. [38] and Hatswell et al. [39], which reflects the decline in the quality of life for patients with advanced or metastatic cancer as they approach death. It utilizes more health states and potentially offers better fit. Limitations of this approach include that the utility will only depend on overall survival, and records were labelled as "Unknown" in the analyses when measured within 360 days from OS censoring date due to uncertain time-to-death category.

For both progression-based and time-to-death approaches, AE disutility was estimated as the difference between utility measured without a grade 3+ AE and utility measured during a grade 3+ AE. Treatment effect was evaluated to assess whether the analytic approaches capture most of the treatment effect.

Analyses were conducted for the population of patients with PD-L1 CPS≥1. There were 6.956 EQ-5D measures from 520 subjects in the FAS population.

Among the twelve models evaluated, health states (progression or time-to-death category) and Grade 3+ AEs were significant predictors for quality of life. The treatment effect was not statistically significant in Model 1c-1f indicating that the pattern in quality of life due to different treatment was sufficiently captured by the health states (progression) included in each model. The models and their results are described further in Appendix K.

The preferred health state based model is model 1a, according to AIC and especially BIC statistics, and considering simplicity for implementation in the economic model, without sacrificing too much goodness-of-fit. This statistical model includes health state and presence of grade 3+ all-cause AEs. The co-efficients of the preferred model are summarised in Table **29**.

Table 29: Preferred utility regression models, CPS ≥1

Model type	Fixed effects parameter	Estimate	SE	P-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Key: CPS, combined positive score; SE, standard error				

Summary of base case assumptions.

The utility values used in the base case analysis (by progression status) using the state transition model are shown in Table **30**.

Table 30. Summary of base case utility values, by regression model and participants.

Regression model	Health state or time to death	CPS ≥1	Standard Error	95% C.I.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Key: AEs, adverse events**;** CPS, combined positive score; QALY, quality adjusted life year				

	Pembro Combo (N=256)		Control (N=264)	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
** Number of participants do not add up to the total number of participants enrolled in the arm, as a participant may be counted in more than one category.*				

In the model, estimates presented in Table 30 above were estimated as following:

[redacted]

The mean utility value for patients at baseline [redacted] for pembrolizumab and SoC treatment arms respectively, irrespective of any statistical or economic modelling. MSD does not consider the slight discrepancy in model-based utility values between the arms at baseline as a cause for concern. This derives from the TTD approach and although perhaps a little unintuitive for the first few model cycles, any potential bias would quickly disappear as treatment effect begin to

be the dominant influence on utility between the arms. Below is the development of EQ-5D-5L from baseline presented for both treatment arms.

Figure 9 Mean +/- SE of utility scores by timepoint with Danish utility weights (Participants With CPS ≥1)

These utilities were then adjusted for age to account for the decrement in utilities with aging. Table **31** lists the utilities values corresponding to the different age brackets, based on the guidelines of Danish Medicines Council [2]. According to the guidelines, the age adjustment values are calculated on the basis of data collected in connection with Region North Jutland study in 2017, as part of the Health and Morbidity Surveys (SUSY). The disutility (utility decrement) in each cycle was then calculated by taking a difference of the baseline utility [redacted] and utility associated with the patient's age in each cycle. The disutility due to AEs in KN826 trial is derived through regression model adjusting for covariates, and hence, is a conservative estimate. The disutilities from literature were derived from different sources (please see response to Ques 8 above for sources), which may not accurately reflect the KN826 trial population and may not be adjusted for covariates. Hence, it is possible for literature-based disutilities to differ from KN-826 model-based disutilities.

Table 31. Age-related utilities.

Age	General population utility	Source
18-29	0,871	Danish Medicines Council
30-39	0,848	Danish Medicines Council
40-49	0,834	Danish Medicines Council
50-69	0,818	Danish Medicines Council
70-79	0,813	Danish Medicines Council
80+	0,721	Danish Medicines Council

Source: [40]

8.5 Resource use and costs

Costs were estimated from a limited societal perspective in Denmark; therefore, direct and indirect health-related costs were included in the model. The following categories of costs were considered:

- Diagnostic testing costs
- Drug acquisition and administration costs for first-line therapy
- Drug acquisition and administration costs for subsequent therapy
- Disease management costs
- Costs for adverse events
- Terminal care costs
- Patient Costs associated with monitoring, follow up and, transportation

Diagnostic testing costs

In the evaluation of cost-effectiveness in patients whose PD-L1 is CPS ≥1, it is necessary to add the cost of implementing PD-L1 diagnostic testing. The unit cost of a test is 560 DKK (price of immunohistochemical analysis for PD-L1) which is based on The Danish Medical Council's recommendation regarding pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy for first-line treatment of locally advanced inoperable or metastatic carcinoma of the esophagus or HER2-negative adenocarcinoma in January 2022. Testing is not part of the current clinical practice in Denmark and all potential patients require a test to assess PD-L1. On the basis of the KN826 trial population, 89% of the tested patients are expected to be PD-L1 positive in the Danish population. An effective cost of 631 DKK would then be borne by each patient eligible to receive treatment with pembrolizumab.

Drug acquisition costs

As per the KN826 trial design, the model uses a 200 mg fixed dose of pembrolizumab, administered as 30-minute IV infusion every 3 weeks (Q3W). The price of a 100 mg vial of pembrolizumab is 23.205 DKK. Hence, the drug acquisition cost for pembrolizumab per administration is 46.409 DKK. The model has an option to administer a dose of 400mg every 6 weeks (Q6W) of pembrolizumab as well.

The dosing of some treatments in the model depends on the body weight or body surface area (BSA) of patients. For the base case analysis, it was assumed that patients can share vials of drugs: the minimum cost per mg across vials for each drug is multiplied by the total dose per administration to calculate the total drug acquisition cost per administration. The assumption about vial-sharing is based on input from the coordinating lead pharmacologist at Sygehusapotek Region Sjælland.

The unit drug costs and dose per unit for each treatment along with their corresponding source are summarized in Table 32. Unit drug costs were based on pharmacy purchase price (Apotekernes indkøbspris, AIP) sourced from www.medicinpriser.dk. All unit drug cost prices are presented as AIP.

Table 32. Unit costs for each treatment included in the model.

Treatment	Dose per unit	Units per pack (ml)	Cost per pack (DKK/pack)	Source
Pembrolizumab	25 mg/ml	4 ml	23.205 DKK	www.medicinpriser.dk (Febr.15, 2022)
Paclitaxel	6 mg/ml	50 ml	202 DKK	www.medicinpriser.dk (Febr.15, 2022)
Cisplatin	1 mg/ml	100 ml	200 DKK	www.medicinpriser.dk (Febr.15, 2022)
Carboplatin	10 mg/ml	45 ml	226 DKK	www.medicinpriser.dk (Febr.15, 2022)

Bevacizumab biosimilar - Aybintio	25 mg/ml	16 ml	7.708 DKK	www.medicinpriser.dk (Febr.15, 2022)
Gemcitabine	40 mg/ml	50 ml	1.200 DKK	www.medicinpriser.dk (Febr.23, 2022)

The costs per treatment administration are summarized in Table **33**. SoC chemotherapy costs in both the arms were calculated by multiplying the costs per chemotherapy by the relevant proportions of patients receiving each treatment, which were presented in Table 20 and Table 21.

Table 33. Drug acquisition costs per treatment per administration.

Treatment arm	**Drug**	**Cost per administration**	**Administration Frequency**
		Vial sharing	
Pembrolizumab + SoC	Pembrolizumab	46.409 DKK	Q3W
	Paclitaxel	200 DKK	
	Cisplatin	170 DKK	
	Carboplatin	377 DKK	
	Bevacizumab	18.701 DKK	
SoC as per KN826	Paclitaxel	200 DKK	Q3W
	Cisplatin	170 DKK	
	Carboplatin	377 DKK	
	Bevacizumab	18.701 DKK	
Key: KN826, KEYNOTE-826; Q3W, every 3 weeks; SoC, standard of care			

Finally, the drug acquisition cost is adjusted according to the ratio of actual to expected numbers of cycles of treatment received in KN826, summarized in Table 34.

Table 34. Percentage of actual vs. expected numbers of cycles, as per KN826 trial.

	Pembrolizumab +SoC		**SoC**	
	Mean	(SD)	Mean	(SD)
Pembrolizumab	91,1%	0,15	NA	NA
Cisplatin	107,4%	0,43	108,6%	0,49
Carboplatin	102,7%	0,32	105,7%	0,35
Paclitaxel	106,9%	0,33	109,7%	0,45
Bevacizumab	77,5%	0,28	83,7%	0,24
Key: SD, standard deviation; SoC, standard of care				

Drug acquisition costs for subsequent therapy

The model also considered the costs of subsequent therapies among patients who discontinued first-line treatment. The proportion of patients receiving different subsequent treatments were based on KN826 trial data, and approximately a third of the patients in both arms went on to receive subsequent treatment. The model includes subsequent treatments with at least 3% patients in either arm.

For the purpose of an accurate economic analysis, the share (percentage of patients) of the agents not included as subsequent treatments, due to threshold of at least 3% patients in either arm, have been proportionally distributed among the agents listed in Table 35, to reflect the percentage of patients receiving second-line treatment as per the KN826 trial (23.9% for pembrolizumab + SoC arm and 30.2% for the SoC arm).

Table 35. Distribution of subsequent treatments used in the model,

Second line oncologic treatment	Patients with PD-L1 CPS ≥1			
	Pembrolizumab + SoC (n=272)		SoC (n=275)	
	Number (%) received	Mean (SE) treatment duration, days	Number (%) received	Mean (SE) treatment duration, days
Bevacizumab	10 (3,8%)	247,5 (119,1)	22 (8,0%)	93,0 (19,9)
Carboplatin	36 (13,2%)	88,9 (11,8)	23 (8,5%)	93,3 (24,6)
Cisplatin	14 (5,0%)	35,9 (6,4)	17 (6,3%)	66,8 (14,2)
Gemcitabine	5 (1,9%)	26,7 (19,1)	20 (7,4%)	87,0 (24,5)
Any subsequent treatment	65 (23,9%)	117,3 (15,8)	83 (30,2%)	132,3 (12,8)

Key: CPS, combined positive score; SE, standard error; SoC, standard of care

The duration of second-line chemotherapy is based on data for both treatment arms observed in KN826. Both the drug acquisition and the drug administration costs associated with second-line treatment are included in the model. The dosing schedules, administration methods, unit costs and assumptions regarding missed doses used to calculate subsequent treatment costs are all the same as used for calculating the drug acquisition and drug administration costs of the first-line treatments included in the model.

Administration costs

Treatment administration costs are accrued for the duration of treatment in each arm of the model. All treatments included in the model are administered intravenously. Administration costs are assigned only once for combination treatments requiring multiple IV treatments on the same day. A unit cost of 1.921 DKK is implemented for administration of IV chemotherapy/immunotherapy based on DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen.

Time on treatment

Drug acquisition and drug administration costs are only applied to the proportion of patients on treatment in each treatment cycle, which is estimated from the ToT data for pembrolizumab and SoC from KN826. Treatment with pembrolizumab was capped at 35 cycles (2 years), and treatment with SoC (chemotherapy ± bevacizumab) was capped at 6 cycles as per the trial protocol.

The KM graphic for ToT for PD-L1 CPS ≥1 patients from KN826 is presented in Figure 10. Since the ToT data was mature, the Kaplan-Meier data was directly used to calculate the drug acquisition and administration cost in the base case analysis. Table 36 presents the mean time on treatment applied in the model.

Table 36. Time on treatment.

Mean treatment duration	Months
Pembrolizumab + SoC	[redacted]
SoC	[redacted]

Disease monitoring

The main source of resource utilization used in this submission is based on patient information distributed at the initiation of cervical cancer treatment at Herlev Hospital.

To capture how patient resource use changes throughout different disease stages, different disease monitoring costs are applied to the different health states in the model. This means that patients receive different costs in the 'progression free' and 'progressed disease health state'.

Disease monitoring costs are based on the frequency of certain services per week based on patient information distributed (at the initiation of cervical cancer treatment) at Herlev Hospital (for PF state) and MSD Denmark assumption (for PD state). Table 37 summarizes the frequency of each resource use and the calculated usage per week. It is assumed that disease monitoring remains the same regardless of treatment.

Table 37. Frequency of disease monitoring.

	PF State	PD State				
Resource	**Weekly frequency**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Consultation visit, physician	Every 3 weeks, alternating between physician and nurse consultation	Every 3 months	Every 6 months	Every 6 months	Once a year	Once a year
Consultation visit, nurse	Every 3 weeks, alternating between physician and nurse consultation	-	-	-	-	-
CT scan	Every 9 weeks, after every 3 series of treatment	-	-	-	-	-
Key: CT, computerised tomography; PF, progression-free; PD, progressed disease						

The unit costs for each resource were sourced from DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen and The Danish Medicines Council (Valuation of unit costs, The Danish Medicines Council)[41, 42] (see Table 32). Unit costs were multiplied by the weekly frequency of each resource to generate the total disease monitoring cost per week.

Table 38. Unit costs of disease monitoring.

Resource	Unit cost	DRG code/ reference
Consultation visit, physician	1.921 DKK	DRG 13MA98
Consultation visit, nurse	290 DKK	Danish Medicines Council; Assumption: Unit cost equals assumption that duration of nurse consultation is ½ hour
CT scan	1.979 DKK	DRG 30PR07
Key: CT, computerized tomography; Diagnosis-related groups		

Source: [41, 42]

Adverse event-related costs

The costs of all-cause Grade 3+ AEs occurring in more than 5% of the patients are considered for the PD-L1 CPS ≥1 population. The unit costs associated with managing these AEs are based on DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen. Based on a diagnose code, we have sourced the DRG codes from the simulation tool website "interaktiv DRG" (https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/gruppering-drg/interaktiv-drg). The DRG codes and diagnose codes for each unit cost estimate are presented in Table 39.

Table 39. Costs for adverse events included.

Adverse event (grade 3+)	Unit Cost	Description	Reference (DRG Code)
Anaemia	3.176 DKK	MDC16 1-day group, pat. At least 7 years; (DD648) Second anaemia	16MA98
Neutrophil count decreased	569 DKK	Telephone and email consultation	65TE01
Neutropenia	3.176 DKK	MDC16 1-day group, pat. At least 7 years; (DD709A) Neutropenia and agranulocytosis	16MA98
Hypertension	1.921 DKK	MDC13 1-day group, pat. At least 7 years; (DI109) Essential hypertension	13MA98
Thrombocytopenia	569 DKK	Telephone and email consultation	65TE01
Febrile neutropenia	2.513 DKK	MDC18 1-day group, pat. At least 7 years; (DR508B) Persistent fever of unknown cause	18MA98
Platelet count decreased	3.176 DKK	MDC16 1-day group, pat. At least 7 years; (DD696) Thrombocytopenia UNS	16MA98
White blood cell count decreased	569 DKK	Telephone and email consultation	65TE01
Urinary tract infection.	2.038 DKK	MDC11 1-day group, pat. At least 7 years	11MA98
Key: DRG, diagnosis related groups Source: [41]			

In the base case analysis, the costs associated with AEs per model cycle are calculated by multiplying the proportion of patients who receive at least one treatment in that treatment cycle with the risks for AEs per week on treatment and the unit costs per AE.

Terminal care costs

The model includes the option to apply a one-off, end-of-life cost to patients at the point of death to reflect terminal care costs. A unit cost of 2.011 DKK based on DRG rate 15MP01 was sourced from DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen. This cost was further used to estimate the cost of care during the last days before death with an assumption of 30 days' care being provided (2.011*30), resulting in a cost of 60.330 DKK per patient upon death.

Patient costs associated with IV administration.

A unit cost of 181 DKK, based on the average hourly wage rate of an employee in Denmark [42], was estimated as the per hour cost borne by the patients administered with IV treatments. This hourly cost was multiplied by the number of patients hours spent on receiving each IV administration (infusion time per treatment) to arrive at the indirect patient costs associated with IV administrations. Patient hours associated with the administration of each regimen is listed in Table 40 along with their references.

Table 40. IV infusion time per treatment

Treatment	Patient Time/ Hours Lost	Treatment Cycles	Patient hours required for each administration	Reference (for patient hours)
Pembrolizumab, Q3W dosing	0,17	3,00	0,50	"Patient-information" distributed at initiation treatment with pembrolizumab at Herlev Hospital
Pembrolizumab, Q6W dosing	0,08	6,00	-	"Patient-information" distributed at initiation treatment with pembrolizumab at Herlev Hospital
Paclitaxel	1,00	3,00	3,00	"Patient-information" distributed at initiation treatment with pembrolizumab at Herlev Hospital
Cisplatin	1,00	3,00	3,00	Chemotherapy with Cisplatin and Gemcitabine
Carboplatin	0,17	3,00	0,50	"Patient-information" distributed at initiation treatment with pembrolizumab at Herlev Hospital
Bevacizumab -first IV	1,00	3,00	1,00	"Patient-information" distributed at initiation treatment with pembrolizumab at Herlev Hospital
Bevacizumab - subsequent IV	0,17	3,00	0,50	"Patient-information" distributed at initiation treatment with pembrolizumab at Herlev Hospital
Key: IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks				

A unit cost of 140 DKK; associated with travelling 14 km to and from the hospital, is estimated as cost of transportation for each IV administration. The unit cost is divided by the number of treatment cycles of each regimen to arrive at the weekly cost of transportation borne at the time of each administration. The weekly costs of patient costs associated with IV administration (per infusion cost and transportation cost) are listed in Table 41.

Table 41. Patient costs per IV administration (weekly).

Treatments	Administration cost per week	Transportation Cost per week
Pembrolizumab, Q3W dosing	30,17 DKK	46,67 DKK
Pembrolizumab, Q6W dosing	15,08 DKK	23,33 DKK
Paclitaxel	181,00 DKK	46,67 DKK
Cisplatin	181,00 DKK	46,67 DKK
Carboplatin	30,17 DKK	46,67 DKK
Bevacizumab -first IV	181,00 DKK	-
Bevacizumab -subsequent IV	30,17 DKK	46,67 DKK
Key: IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks		

SoC IV administration costs (per infusion cost and transportation cost) were calculated by multiplying the costs per chemotherapy by the relevant proportions of patients receiving each treatment. The effective IV administration patient costs associated with the intervention and comparator are listed in Table 42.

Table 42. Patient costs per IV administration; intervention and comparator

IV administration infusion cost		
Cost Categories	**Pembrolizumab + SoC**	**SoC**
IV administration infusion cost	400,89 DKK	365,64 DKK
Transportation cost	46,67 DKK	46,67 DKK
Total	**447,56 DKK**	**412,30 DKK**
Key: IV, intravenous; SoC, standard of care		

The total cost of IV administration infusion was borne by patients remaining on treatment each cycle (ToT).

Patient Costs associated with monitoring and follow up

Patient costs associated with monitoring and follow up were calculated in a similar way as the calculation for IV administration costs (per infusion, transportation cost). The hourly patient cost (181 DKK) was multiplied by the patient hours spent on resource utilization in the PF and PD state each week, to arrive at the cost of follow up in each state. The patient hours and frequency of resource use associated with each resource is listed in Table 43 along with their references.

Table 43. Patient hours spent on follow up.

Frequency per health state - PF				
Resource	**Patient time/ hours lost**	**Frequency (per week)**	**Patient Hours**	**Reference (for patient hours)**
Consultation visit, physician	0,083	0,167	0,5	MSD assumption
Consultation visit, nurse	0,083	0,167	0,5	MSD assumption
CT scan	0,111	0,111	1	MSD assumption
Frequency per health state - PD				
Consultation visit, physician	0,019	0,038	0,5	MSD assumption
Key: CT, computerized tomography; PD, progressed disease; PF, progression free				

The transportation cost (140 DKK) was multiplied with the weekly frequency of resource utilization in the PF and PD state to arrive at the transportation cost associated with follow up in each state (each cycle). The total patient follow up and monitoring costs (including transportation costs) borne by patient in the PF and PD state each cycle are listed in Table 44.

Table 44. Patient costs associated with follow up in each cycle.

Monitoring and follow up Costs		
Cost Categories	**Pembrolizumab + SoC**	**SoC**
PF state		
Patient Monitoring and follow up Costs	50,28 DKK	50,28 DKK
Transportation Costs	62,22 DKK	62,22 DKK
Total	**112,50 DKK**	**112,50 DKK**
PD state		
Patient Monitoring and follow up Costs	3,48 DKK	3,48 DKK
Transportation Costs	5,38 DKK	5,38 DKK
Total	**8,87 DKK**	**8,87 DKK**
Key: PD, progressed disease; PF, progression free; SoC, standard of care		

The total patient follow up and monitoring costs (including transportation costs) associated with PF and PD state were borne by patients residing in each of the health states (health state occupancy).

8.6 Results

8.6.1 Base case overview

The key assumptions of the economic analysis are described Table 45.

As per the reference case, effectiveness is estimated in QALYs, the economic perspective is limited societal (with indirect patient costs), and a 3,5% annual discount rate is used for LYs, QALYs and costs. The cost categories considered in the base case analysis are PD-L1 testing costs, drug acquisition costs, drug administration costs, adverse event (AE) costs, other resource use costs, patient costs, subsequent treatment costs (acquisition and administration costs of subsequent treatments), and end-of-life costs.

The cost-effectiveness model has a cycle length of 1 week and allows accurate estimation of the drug acquisition and drug administration costs of treatments with different dosing schedules.

Table 45. Summary of model assumptions

Topic	Assumption	Note
Model structure	STM	
Patient population	Patients whose tumors express PD-L1 with CPS ≥1	In line with EMA approved indication
Perspective and discounting	Limited societal perspective with costs, LYs and QALYs discounted by 3,5% annually (applied annually from year 1 and onward).	
Time horizon	Equal to 35 years.	35 years was deemed sufficiently long to reflect lifetime.
Half-cycle correction	Not applied.	The model cycle is sufficiently short (one week) that a half-cycle correction was not deemed necessary.
Progression-free survival	Two-piece with cut-off at 37 weeks, log-logistic distribution	See appendix G
Time to progression	Two-piece with cut-off at 37 weeks, log-logistic distribution	See appendix G
Post-progression survival	One piece, generalized gamma distribution, treatment arm specific	See appendix G
Time on treatment	KM data	
Subsequent treatments	As observed in the trial (agents used by at least 3% of patients in either arm)	
Utilities	Denmark EQ-5D-5L value set utility by progression status, regression based.	

Source of costs	Resource use: Patient information at Herlev hospital and MSD assumption Unit costs: Danish Medicines Council and Danish Health and Medicines Authority	
Use of bevacizumab biosimilars	100% market share to Aybintio	
Key: CPS, combined positive score; EMA, European Medicines Agency; LYs, life years; QALYs, quality adjusted life years; STM, state transition model; ToT, time on treatment		

8.6.2 Base case results

Health outcomes

Pembrolizumab + SoC was associated with 3,986 LYs as compared with 2,211 LYs with the SoC, a difference of 1,775 greater LYs for pembrolizumab + SoC. The additional LYs were accumulated primarily in the pre-progression health state (Table 46).

Table 46. Disaggregated life years by health state and treatment arm.

Health state	SoC	Pembrolizumab + SoC	Incremental
Pre-progression	1,457	3,197	1,740
Post-progression	0,754	0,789	0,035
Total LYs	**2,211**	**3,986**	**1,775**
Key: LYs, life years; SoC, standard of care.			

Pembrolizumab + SoC was associated with 3,100 QALYs as compared with 1,693 QALYs with the SoC, a difference of 1,407 greater QALYs for pembrolizumab + SoC. The additional QALYs were accumulated primarily in the pre-progression health state (). Additionally, a loss of 0,008 QALYs, due to the disutility associated with the incidence of all-cause AEs, was observed for pembrolizumab + SoC as compared to a loss of 0,006 QALYs for SoC; resulting in a higher QALY loss (0,002) for pembrolizumab + SoC as compared to SoC (Table 47).

Table 47. Disaggregated QALYs by health state and treatment arm, base case

Category	SoC	Pembrolizumab +SoC	Incremental
Pre-progression	1,164	2,548	1,384
Post-progression	0,535	0,560	0,025
QALY loss AEs	-0,006	-0,008	-0,002
Total QALYs	**1,693**	**3,100**	**1,407**
Key: AEs, adverse events; QALY, quality adjusted life year; SoC, standard of care.			

Costs

The cost of SoC was 189.578 DKK, comprising predominantly the acquisition cost of bevacizumab (52.140 DKK) and terminal care costs (56.678 DKK). In contrast, pembrolizumab + SoC cost 1.077.795 DKK in totality, comprising predominantly the acquisition cost of pembrolizumab (801.037 DKK) and resource use cost (101.183 DKK). The pembrolizumab + SoC regimen therefore costs 888.218 DKK more than SoC, attributable primarily to the difference in drug acquisition costs (798.148 DKK), followed by a difference in resource use costs (53.542 DKK). A full breakdown is provided in Table 48.

Table 48. Disaggregated costs by treatment arm, base case.

Category	SoC	Pembrolizumab +SoC	Incremental
Drug acquisition	55.204 DKK	853.352 DKK	798.148 DKK
Pembrolizumab	0 DKK	801.037 DKK	801.037 DKK
Paclitaxel	1.151 DKK	1.111 DKK	-40 DKK
Cisplatin	143 DKK	149 DKK	6,6 DKK
Carboplatin	1.769 DKK	1.662 DKK	-108 DKK
Bevacizumab	52.140 DKK	49.393 DKK	-2.747 DKK
Administration	10.291 DKK	36.403 DKK	26.112 DKK
Adverse events	1.862 DKK	2.275 DKK	413 DKK
Diagnostic testing	0 DKK	631 DKK	631 DKK
Subsequent treatments	8.339 DKK	7.399 DKK	-940 DKK
Resource Use	47.641 DKK	101.183 DKK	53.542 DKK
Terminal care	56.678 DKK	52.400 DKK	-4.278 DKK
Patient Costs	9.562 DKK	24.152 DKK	14.590 DKK
Total costs	**189.578 DKK**	**1.077.795 DKK**	**888.218 DKK**
Key: SoC, standard of care.			

Cost effectiveness

Table 49 presents the full base case cost-effectiveness results for pembrolizumab + SoC versus SoC alone. In patients with PRMCC in Denmark, treatment with pembrolizumab, in addition to SoC, results in an average increase in LYs of 1,775 (+80%) and an average increase in QALYs of 1,407 (+83%) compared with SoC alone. The base case incremental cost effectiveness ratio (ICER) of pembrolizumab + SoC versus SoC in terms of QALYs gained is 631.276 DKK.

Table 49. Cost effectiveness of Pembrolizumab + SoC versus SoC.

Treatment	Totals per treatment arm			Incremental results			ICER (DKK/QALY)	NMB (DKK)
	LYs	QALYs	Costs (DKK)	LYs	QALYs	Costs (DKK)		
SoC	2,211	1,693	189.578	1,775	1,407	888.218	631.276	862.011
Pembrolizumab +SoC	3,986	3,100	1.077.795					
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; NMB, net monetary benefit (at a willingness to pay of 1.243.926 DKK per QALY); SoC, standard of care								

To illustrate the significance of price for the ICER, the table below show the AIP for pembrolizumab at different discount rates and the corresponding ICER, until the ICER becomes negative. Please note that even with the price of pembrolizumab being zero, ICER is still positive, as the administration cost and resource use cost are keeping the incremental cost for pembrolizumab positive.

Table 50 AIP for pembrolizumab at different discount rates and the corresponding ICER

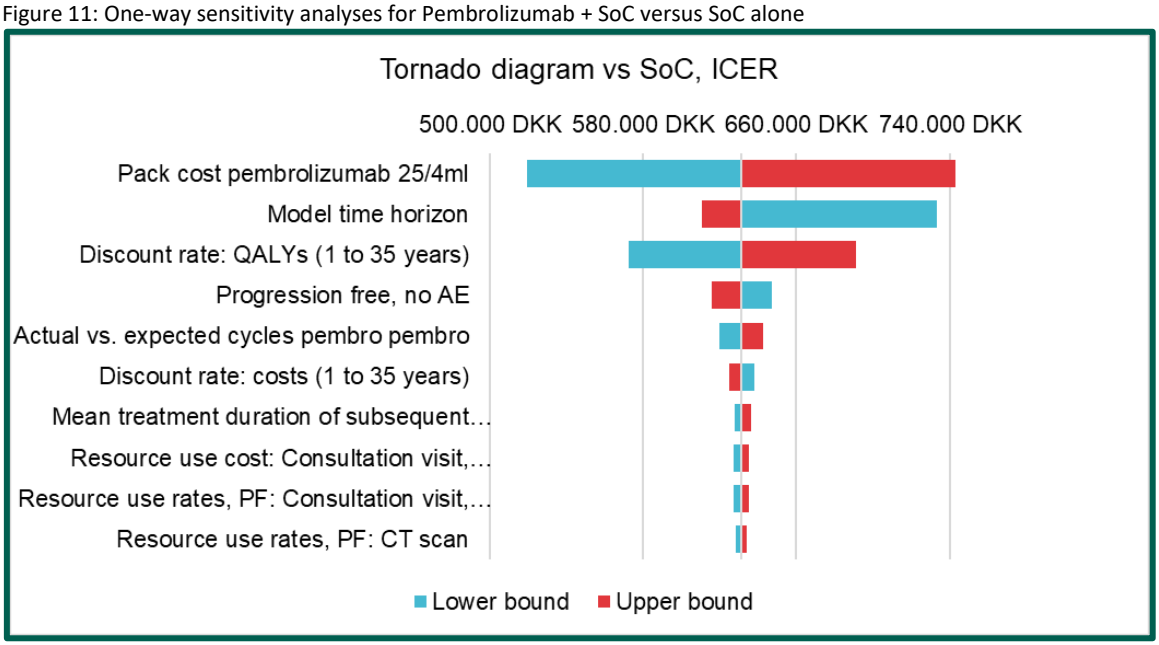
Pembrolizumab Cost (DKK for 200 mg)	Discount Rate	ICER (DKK/QALY)
23,204.61	0%	631,275.80
22,044.38	5%	602,810.05
20,884.15	10%	574,344.31
19,723.92	15%	545,878.57
18,563.69	20%	517,412.82
17,403.46	25%	488,947.08
16,243.23	30%	460,481.33
15,083.00	35%	432,015.59
13,922.77	40%	403,549.85
12,762.54	45%	375,084.10
11,602.31	50%	346,618.36
10,442.07	55%	318,152.62
9,281.84	60%	289,686.87
8,121.61	65%	261,221.13
6,961.38	70%	232,755.39
5,801.15	75%	204,289.64
4,640.92	80%	175,823.90
3,480.69	85%	147,358.16
2,320.46	90%	118,892.41
1,160.23	95%	90,426.67
0.00	100%	61,960.93

8.7 Sensitivity analyses

A series of one-way sensitivity analyses (OWSAs) were performed to evaluate the sensitivity of the model results to individual inputs, holding all else constant, according to their precision as indicated by SEs or 95% CIs where available. When such information was not available, the upper and lower bounds were assumed to be within ± 10% of the base case value, except for time horizon and discount rates (for each LY, QALY and cost), which were varied at 20 and 50 years, and 2,5% and 4,5% respectively (please see , all parameters is presented in appendix J.

for more information). The most sensitive parameters is provided in the tornado plot below (Figure 11), all parameters is presented in appendix J.

Figure 11: One-way sensitivity analyses for Pembrolizumab + SoC versus SoC alone



Key: AE, adverse event; CT, computerized tomography; ICER, incremental cost-effectiveness ratio; PF, progression free; QALY, quality-adjusted life-year; SoC, standard of care.

Results from the OWSA show that the ICER was most influenced by the pack cost of pembrolizumab followed by discounting on QALYs.

The detailed results of OWSA are presented in Table 51. The difference in the values of upper and lower bound of the ICERs ranged from 5.561 DKK to 231.179 DKK.

Table 51. Summary of Influential Parameters; Pembrolizumab + SoC v/s SoC (ICER).

Parameter Name	Lower Bound	Upper Bound	Absolute Difference
Pack cost pembrolizumab 25/4ml	519.692 DKK	742.859 DKK	223.167 DKK
Discount rate QALYs	572.323 DKK	691.216 DKK	118.893 DKK
Model time horizon	733.269 DKK	610.628 DKK	122.641 DKK
Utility in progression free state, with no AEs	647.464 DKK	615.878 DKK	31.586 DKK
Actual vs, expected cycles - pembrolizumab, in pembrolizumab (arm)	620.136 DKK	642.416 DKK	22.280 DKK
Discount rate: costs	638.095 DKK	625.276 DKK	12.819 DKK
Mean treatment duration of subsequent treatment in pembrolizumab arm (%) - Bevacizumab	628.100 DKK	636.379 DKK	8.279 DKK
Resource use cost: Consultation visit, physician	627.208 DKK	635.343 DKK	8.135 DKK
Resource use rates in PF state: Consultation visit, physician	627.227 DKK	635.324 DKK	8.097 DKK
Resource use rates in PF state: CT scan	628.495 DKK	634.056 DKK	5.561 DKK

Key: AE, adverse event; CT, computerized tomography; ICER, incremental cost-effectiveness ratio;PF, progression free; QALYs, quality adjusted life years; SoC, standard of care.

Scenario analyses

To assess the robustness of the model results, scenario analyses were conducted by varying one model input or assumption at a time. Table 52 provides a complete list of the scenario analyses assessed and the resulting ICERs.

Varying the parametric survival models (used to extrapolate clinical data) had a substantial impact on the ICER, with the highest ICER (1.071.745 DKK/QALY) for pembrolizumab + chemotherapy v/s chemotherapy observed for the scenario where the PFS and TTP curves were extrapolated using a gamma distribution (two-piece fitting with data cut-off at 37 weeks), while the PPS curves were extrapolated using a log logistic distribution (one-piece fitting), compared to the base case setting (TTP and PFS: 37 weeks, log logistic; PPS: one-piece, generalized gamma) with an ICER of 631.276 DKK/QALY.

On the other hand, at lower ICER (527.859 DKK/QALY) compared to the base case setting was observed for the scenario where the PFS and TTP curves were extrapolated using a generalized gamma distribution (two-piece fitting with data cut-off at 46 weeks) while the PPS curves were extrapolated using a generalized gamma distribution (one-piece fitting), compared to the base case setting.

The lowest ICER (430.107 DKK/QALY) was observed for the scenario of weight based dosing of pembrolzimab.

Additionally, it can be noted that not accounting for subsequent treatments costs and age adjusted dis-utilities lead to small change in the base case ICER (631.276 DKK/QALY), with an ICER of 631.276 DKK/QALY and 627.562 DKK/QALY observed for each of the scenario respectively.

Appendix L lists the additional scenarios evaluated for the Danish Medicines Council as a part of the validation process.

Table 52: Results of scenario analyses for Pembrolizumab + SoC versus SoC alone

Scenario label	Base case setting	Scenario analysis setting	Pembrolizumab		SoC		Incremental		
			Total QALYs	Total costs	Total QALYs	Total costs	QALYs	Costs	ICER (DKK/QALY)
Base Case Results			**3,10**	**1.081.255 DKK**	**1,69**	**191.127 DKK**	**1,41**	**890.128 DKK**	**631.276**
Weight based dosing, 3QW			3,10	794.746 kr.	1,69	189.578 kr.	1,41	**605.169 kr.**	**430.107**
Subsequent treatment cost	Included	Not included	3,10	1.070.396,09 kr.	1,69	181.238,71 kr.	1,41	889.157,37 kr.	**631.944**
Age correction for utilities	Applied	Not applied	3,11	1.077.795,27 kr.	1,69	189.577,71 kr.	1,42	888.217,57 kr.	**627.562**
Utility analysis	Based on health state	Based on time to death	3,21	1.091.048,52 kr.	1,73	189.577,71 kr.	1,48	901.470,81 kr.	**599.835**
Model structure	State transition	TTP and PFS: 37 weeks, Weibull; PPS: one-piece, log-logistic	2,38	1.060.369,10 kr.	1,49	189.577,71 kr.	0,88	870.791,39 kr.	**985.330**
		TTP and PFS: 37 weeks, log-logistic; PPS: one-piece, log-logistic	3,10	1.097.855,70 kr.	1,79	199.081,56 kr.	1,32	898.774,15 kr.	**674.888**
		TTP and PFS: 37 weeks, gamma; PPS: one-piece, log-logistic	2,34	1.077.612,91 kr.	1,53	189.613,85 kr.	0,81	887.999,06 kr.	**1.071.745**
		TTP and PFS: 37 weeks, log-normal; PPS: one-piece, log-logistic	3,25	1.193.915,36 kr.	1,85	315.906,87 kr.	1,40	878.008,48 kr.	**637.914**
		TTP and PFS: 46 weeks, Weibull; PPS: one-piece, log-logistic	3,13	1.077.795,27 kr.	1,49	189.577,71 kr.	1,64	888.217,57 kr.	**549.227**
		TTP and PFS: 46 weeks, gamma; PPS: one-piece, log-logistic	2,93	1.077.795,27 kr.	1,51	189.577,71 kr.	1,42	888.217,57 kr.	**629.743**
		TTP and PFS: 46 weeks, generalized gamma; PPS:	3,33	1.075.520,11 kr.	1,62	187.715,47 kr.	1,71	887.804,63 kr.	**527.859**

		one-piece, log-logistic							
		TTP and PFS: 37 weeks, Weibull; PPS: one-piece, log-normal	2,35	1.170.266,70 kr.	1,45	199.523,18 kr.	0,90	970.743,51 kr.	**970.622**
		TTP and PFS: 37 weeks, log-logistic; PPS: one-piece, log-normal	3,08	1.089.028,18 kr.	1,75	201.288,65 kr.	1,33	887.739,53 kr.	**667.801**
		TTP and PFS: 37 weeks, gamma; PPS: one-piece, log-normal	2,31	1.025.394,96 kr.	1,49	132.899,33 kr.	0,82	892.495,63 kr.	**1.054.574**
		TTP and PFS: 37 weeks, log-normal; PPS: one-piece, log-normal	3,22	1.076.294,62 kr.	1,81	187.191,57 kr.	1,41	889.103,05 kr.	**631.576**
		TTP and PFS: 46 weeks, Weibull; PPS: one-piece, log-normal	3,10	1.077.164,64 kr.	1,45	189.577,71 kr.	1,66	887.586,94 kr.	**544.116**
		TTP and PFS: 46 weeks, gamma; PPS: one-piece, log-normal	2,90	1.077.795,27 kr.	1,47	189.577,71 kr.	1,43	888.217,57 kr.	**623.181**
		TTP and PFS: 46 weeks, generalized gamma; PPS: one-piece, log-normal	3,30	1.047.140,92 kr.	1,58	177.602,06 kr.	1,72	869.538,85 kr.	**524.397**
		TTP and PFS: 37 weeks, Weibull; PPS: one-piece, generalized gamma	2,37	1.077.798,54 kr.	1,40	189.845,89 kr.	0,98	887.952,65 kr.	**891.953**
		TTP and PFS: 37 weeks, log-logistic; PPS: one-piece, generalized gamma	3,10	1.045.541,62 kr.	1,69	179.080,50 kr.	1,41	866.461,13 kr.	**631.276**
		TTP and PFS: 37 weeks, gamma; PPS: one-piece, generalized gamma	2,33	1.083.829,66 kr.	1,43	192.415,92 kr.	0,90	891.413,75 kr.	**962.094**

		TTP and PFS: 37 weeks, log-normal; PPS: one-piece, generalized gamma	3,24	1.079.007,75 kr.	1,75	177.348,98 kr.	1,49	901.658,77 kr.	**599.198**
		TTP and PFS: 46 weeks, Weibull; PPS: one-piece, generalized gamma	3,13	1.070.381,36 kr.	1,39	178.218,83 kr.	1,74	892.162,54 kr.	**519.735**
		TTP and PFS: 46 weeks, gamma; PPS: one-piece, generalized gamma	2,92	1.086.929,04 kr.	1,41	183.848,54 kr.	1,51	903.080,50 kr.	**590.950**
		TTP and PFS: 46 weeks, generalized gamma; PPS: one-piece, generalized gamma	3,33	1.047.060,53 kr.	1,53	177.493,75 kr.	1,80	869.566,78 kr.	**502.929**
Key: PFS, progression free survival; PPS, post progression survival; QALYs, quality adjusted life years; SoC, standard of care; TTP, time to progression									

8.7.1 Probabilistic sensitivity analyses

Please see appendix J for the probabilistic analysis.

8.8 Budget impact analysis

A budget impact analysis is included into the model to evaluate the impact of adding pembrolizumab in drug formulary, based on the patients with persistent, recurrent or metastatic cervical cancer and with CPS ≥1, in line with the patients included in KN826. The analysis is based on the same inputs as used for the CE analysis. The different components of budget impact analysis have been described in this section.

8.8.1 Budget impact analysis overview

The budget impact analysis is added in the KN826 cost effectiveness model, adapted with Danish local inputs which estimated the five-year budgetary impact for 28 annual patients with persistent, recurrent or metastatic cervical cancer and with CPS ≥1. The patients are followed up in the model for 5 years. New patients entering the model in any year will incur the year 1 cost. The patients moving from first year to second will incur the year 2 and the cycle will be followed accordingly for each year. To evaluate the impact on the budget, the model considers two scenarios:

1. Reference scenario: SoC
2. New scenario: Pembrolizumab + SoC

8.8.2 Number of patients

The model uses 28 eligible patients to receive treatment annually. The tables below shows the number of patients in each year of reference and new scenario (if pembrolizumab is recommended).

Table 53. Number of patients expected to be treated over the next five-year period - if pembrolizumab +SoC is not recommended.

Scenario were pembrolizumab is not recommended					
Regimen	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Pembrolizumab + SoC	0	0	0	0	0
SoC as per KN826	28	28	28	28	28
Total	28	28	28	28	28

Table 54. Number of patients expected to be treated over the next five-year period - if pembrolizumab +SoC is recommended.

Scenario were pembrolizumab is recommended					
Regimen	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Pembrolizumab + SoC	28	28	28	28	28
SoC as per KN826	0	0	0	0	0
Total	28	28	28	28	28

8.8.3 Expenditure per patient

As mentioned all the costs are obtained from the cost effectiveness model, the costs of different treatments according to the year is given in the table below. These costs are then used for further analysis.

Table 55. Costs per patient per year.

Cost Category	Cost Category	Year 1	Year 2	Year 3	Year 4	Year 5
Pembrolizumab + SoC	Drug acquisition	588.571 DKK	274.048 DKK	0 DKK	0 DKK	0 DKK
	Administration	24.372 DKK	12.452 DKK	0 DKK	0 DKK	0 DKK
	Adverse event	2.275 DKK	0 DKK	0 DKK	0 DKK	0 DKK
	Testing	631 DKK	0 DKK	0 DKK	0 DKK	0 DKK
	Subsequent trt	4.651 DKK	1.544 DKK	719 DKK	438 DKK	218 DKK
	Resource use	24.082 DKK	12.924 DKK	9.366 DKK	7.465 DKK	6.265 DKK
	End of life	12.099 DKK	17.498 DKK	8.964 DKK	4.939 DKK	3.058 DKK
	Cost per patient	**656.680 DKK**	**318.467 DKK**	**19.049 DKK**	**12.843 DKK**	**9.541 DKK**
SoC as per KN826	Drug acquisition	55.204 DKK	0 DKK	0 DKK	0 DKK	0 DKK
	Administration	10.291 DKK	0 DKK	0 DKK	0 DKK	0 DKK
	Adverse event	1.862 DKK	0 DKK	0 DKK	0 DKK	0 DKK
	Testing	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK
	Subsequent trt	5.982 DKK	1.648 DKK	610 DKK	217 DKK	0 DKK
	Resource use	20.970 DKK	8.126 DKK	4.561 DKK	3.021 DKK	2.208 DKK
	End of life	19.815 DKK	19.353 DKK	9.065 DKK	4.392 DKK	2.337 DKK
	Cost per patient	**114.124 DKK**	**29.127 DKK**	**14.236 DKK**	**7.630 DKK**	**4.545 DKK**

8.8.4 Budget impact

The table below represents the total 5-year budget impact for Denmark.

Table 56. Expected budget impact of recommending the pharmaceutical for the current indication.

Total budget impact					
Regimen	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Pembrolizumab + SoC	18.660.223 DKK	27.709.767 DKK	28.251.061 DKK	28.616.001 DKK	28.887.131 DKK
SoC as per KN826	-3.242.951 DKK	-4.070.630 DKK	-4.475.172 DKK	-4.691.974 DKK	-4.821.124 DKK
Total budget impact	**15.417.272 DKK**	**23.639.137 DKK**	**23.775.889 DKK**	**23.924.027 DKK**	**24.066.008 DKK**

10. Discussion on the submitted documentation

Klinisk og økonomisk merværdi

KN826 demonstrerer en vigtig klinisk og økonomisk merværdi for patienter med P/R/M PD-L1 CPS ≥1 cervix cancer sammenlignet med nuværende dansk standardbehandling. Der ses en klinisk relevant og statistisk signifikant forbedring i median OS med HR 0,64 (95% CI 0,50-0,81) og p=0,0001. Efter en median opfølgningstid på 22,0 mdr. (range 15,1-29,4) er forskel i median OS

ikke kvantificerbar, da median OS i PEM+CT er NR (95% CI 19,8-NR) vs. 16,3 mdr. (95% CI 14,5-19,4) i PBO+CT. Der ses en vedvarende forskel i OS rate ved 12 og 24 mdr. på henholdsvis 12,1% og 11,3 %. Risikoen for progression og død reduceres med 38% i PEM+CT vs. PBO+CT og der ses efter et 24 mdr. over en fordobling i antallet af patienter uden progression eller død i PEM+CT vs. PBO+CT. Tillæg af pembrolizumab til nuværende anvendte kombinationskemoterapi regime er forbundet med en mindre numerisk stigning i andelen af grad 3-5 bivirkninger i PEM+CT vs. PBO+CT, der skal sættes i perspektiv relativt til en længere behandlingsvarighed samt tillægget af den aktive intervention pembrolizumab. Der er på trods af den øgede incidens af grad 3-5 bivirkninger i PEM+CT vs. PBO+CT ingen negativ påvirkning af livskvalitet. Der ses endda for livskvalitet målt ved EQ-5D-5L en større andel med forbedret eller stabil livskvalitetsscore og en længere tid til forværring hos PEM+CT gruppen sammenlignet med PBO+CT gruppen.

De signifikante kliniske resultater på overlevelse understøtter estimaterne af merværdi i vores sundhedsøkonomiske model med en gevinst på 1,407 kvalitetsjusteret leveår sammenlignet med nuværende dansk standard behandling. ICER var ligeledes favorable for pembrolizumab + kemoterapi med en omkostning pr kvalitetsjusteret leveår på 632.634 kr. sammenlignet med kemoterapi.

Styrker i vores kliniske dokumentation

Den kliniske dokumentation styrkes af studiets design, som er baseret på beregninger af studiestørrelse, er dobbeltblindet og randomiseret. Studieprotokollen er nøje fastlagt før studiets påbegyndelse, således at alle inkluderede patienter modtager den sammen behandling i de respektive behandlingsarme.

De fastlagte in-og eksklusionskriterier muliggjorde en bedst muligt repræsentation af *real-world* patientpopulation med P/R/M cervix cancer ved at inkluderer de histologiske subtyper, som er mest hyppige for cervix cancer populationen (adeno-og planocellulære karcinomer) og tillader også inklusion af patienter uanset egnethed for bevacizumab behandling. Triplet-behandling af cisplatin, paclitaxel og bevacizumab, som udgør kontrolarmen i KN826, repræsenterer nuværende standardpraksis, da dette regime indtil nu har givet den længste overlevelsesgevinst. Ikke alene er den korrekte komparator inkluderet i KN826, men der er også mulighed for tilpasse behandling med ± bevacizumab i henhold til individuelle risikofaktorer forbundet med bevacizumab behandling.

Ovenstående danner grundlag for et solidt statistisk sammenligningsgrundlag, der samtidig afspejler dansk klinisk praksis.

Der ses en median opfølgningstid på 22,0 mdr. (range 15,1-29,4) og der rapporteres derved modne resultater på OS, PFS, sikkerhed og livskvalitet.

Bivirkningsdata fra KN826 repræsenterer en hyppighed og profil, som svarer til bivirkningsprofiler fra andre KEYNOTE-studier med kombinationsbehandling og med bivirkninger som er velkendte og håndterbare i klinikken.

Begrænsninger i klinisk dokumentation

Trods stratificeringer og in-/eksklusionkriterier, er det svært helt at undgå selektionsbias ved randomiserede forsøg, da patienter skal have en hvis forventet levetid for at indgå i studiet. Derfor findes der ikke data på de patienter som i en dansk klinisk hverdag vil være 'outliers' på enten performance status, alder etc.

Da der ikke findes offentlig tilgængelig data på den danske patientpopulation kan det være vanskeligt på et databaseret grundlag at foretage en vurdering om i hvor høj grad studiepopulationen i KN826 repræsenterer den danske patientpopulation.

Vi kan dog på baggrund af opgørelser i DGCG årsrapport konkludere, at KN826's studiepopulation repræsenterer den danske population mht. histologisk subtype. I KN826 udgøres af de planocellulære-, adeno-og adenoskvamøse karcinomer, som tilsammen udgør ca. 90% af de danske patienter som diagnosticeres med cervix cancer.

Styrker i vores sundhedsøkonomiske model

Vores sundhedsøkonomiske model er baseret på en semi-markov State Transition Model, hvilket er en veletableret tilgang og meget anvendt model til sundhedsøkonomisk evaluering af onkologiske lægemidler.

Data på sundhedseffekter og længde af behandling er i modellen baseret på patient data fra KN826. Med baggrund i antal events, så må data anses for at være modne, hvilket styrker den langsigtede ekstrapolation af studiedata. Der er en stor grad af sikkerhed omkring modellens anvendelse af data vedrørende længde af behandling, således har den relative lange opfølgningstid betydet, at KM-data har kunnet anvendes direkte. Ydermere, så er pembrolizumab i KN826 begrænset til 35 doser, svarende til 2 års behandling.

EQ-5D-5L data var tilgængelig fra KN826 og har således styrket modellens input vedrørende nytteværdi.

Vores model har inddraget de relevante behandlingsomkostninger baseret på danske markedspriser. Vi har således også robust ICER estimat, hvilket understreges af vores følsomheds- og scenarieanalyser. Den største følsomhed ses i scenarieanalyser med vægtbaseret dosering, samt i scenarier med forskellige parametriske funktion. Probalitiske følsomhedsanalyser understøtter også robustheden af base case estimater af gevinster baseret på 1.000 gentagelser.

Det må forventes at vægtbaseret dosering af pembrolizumab bliver dansk klinisk praksis, jf. alle tidligere anbefalinger fra Medicinrådet. Vores følsomhedsanalyse af dette scenarie viste, at vægtbaseret dosering af pembrolizumab resulterede i den laveste ICER af alle scenarier. Den ICER som præsenteres i hovedanalysen må derfor også anses for at være et meget konservativt estimat.

Begrænsninger i vores sundhedsøkonomiske model

Valg af parametrisk funktion efter er baseret på:

- Vurdering af grafisk præsentation – tilpasning til Kaplan–Meier data
- Klinisk plausibilitet af "long-term extrapolations"
- Klinisk plausibilitet set i forhold til parametrisk funktion
- Statistiske tests - "goodness of fit"

Der vil dog altid være et element af usikkerhed forbundet med ekstrapolation langt ud over studiets opfølgningstid. Dette gælder særligt for nye interventioner som PEM+CT , hvor der ikke findes eksisterende langtidsdata, som kan anvendes til at validere.

En anden begrænsning er usikkerhed omkring forventning til dansk klinisk praksis vedrørende dosering af pembrolizumab, hvor Medicinrådet ved tidligere evalueringer har vurderet at dansk klinisk praksis er vægtbaseret dosering fremfor fast dosis.

11. List of experts

N/A

12. References

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

Appendix A Literature search for efficacy and safety of intervention and comparator(s)

Da der i KN826 studiet er foretaget en direkte sammenligning mellem den nye behandling og den relevante komparator, er der ikke foretaget en systematisk søgning efter dokumentation for effekt og sikkerhed, da denne ikke forventes at frembringe yderligere relevant dokumentation for effekt og sikkerhed for intervention vs. komparator.

Relevante data, som er brugt til denne ansøgning er med udgangspunkt i det randomiserede, dobbeltblindede studie KN826, som sammenligner intervention og komparator og er opsummeret i Table 3 Litteratursøgning og identificering af effekt og sikkerhedsstudier under afsnit 6.

Appendiks B Inkluderede studier hovedkarakteristika

Table 57. KN826 studiets hovedkarakteristika.

Trial name: KEYNOTE-826 [27]	**NCT number: 03635567**
Objective	*The purpose of this study is to evaluate the efficacy and safety of pembrolizumab (MK-3475) plus chemotherapy vs placebo plus chemotherapy in women with persistent, recurrent, or metastatic cervical cancer*
Publications – title, author, journal, year	• *Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, Gümüş M, Olivera Hurtado de Mendoza M, Samouëlian V, Castonguay V, Arkhipov A, Toker S, Li K, Keefe SM, Monk BJ; KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med. 2021 Nov 11;385(20):1856-1867. doi: 10.1056/NEJMoa2112435. Epub 2021 Sep 18. PMID: 34534429.Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators.* ***Pembrolizumab for Early Triple-Negative Breast Cancer****. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.* • *Presented at Society of Gynecologic Oncology Annual Meeting on Women's Cancer (SGO) 2022. B.J. Monk, K.S. Tewari, C. Dubot, M.V. Caceres K. Hasegawa, R. Shapira-Frommer, P. Salman, E. Yañez, M. Gümüş, M. Olivera Hurtado de Mendoza, V. Samouëlian, V. Castonguay, A. Arkhipov, C. Tekin, K. Li, A. Martin Nguyen, M.J. Monberg, N. Colombo, D. Lorusso. Patient-Reported Outcomes From the Phase 3 Randomized, Double-Blind, KEYNOTE-826 Trial of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer* • *EPAR-Keytruda-h-c-003820-ii-0117* • *Data on file: MSD KN826 clinical study report*
Study type and design	*Double-blinded randomized placebo-controlled phase 3 study.* *Enrolled patients were randomly assigned 1:1 with the use of a central interactive voice-response system with an integrated Web-response system. No cross-over was allowed between the phases. Triple masking of participant, investigator, and sponsor. Patients were stratified before randomization according to metastatic disease at diagnosis (yes vs. no), planned bevacizumab use (yes vs. no), and PD-L1 CPS (<1 vs. 1 to <10 vs. ≥10).* *Status: Active, not recruiting (as of latest update on November 13, 2020)* *Actual Study Start Date: October 25, 2022* *Estimated Primary Completion Date: November 23, 2022* *Estimated Study Completion Date: November 23, 2022*
Sample size (n)	*N=617*

Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Has persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which has not been treated with systemic chemotherapy and is not amenable to curative treatment (such as with surgery and/or radiation)* • *Not pregnant or breastfeeding, and at least one of the following conditions applies: a.) Not a woman of childbearing potential (WOCBP), b.) A WOCBP must agree to use effective contraception during the treatment period and for at least 120 days after the last dose of pembrolizumab/placebo and 210 days after the last dose of chemotherapy/bevacizumab* • *Has measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology* • *Has provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated for prospective determination of Programmed Cell Death-Ligand 1 (PD-L1) status prior to randomization* • *Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 within 14 days prior to randomization* • *Has adequate organ function* *Exclusion Criteria:* ▪ *A women of child bearing potential who has a positive urine pregnancy test within 72 hours prior to randomization* ▪ *Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with known brain metastases may participate provided that the brain metastases have been previously treated (except with chemotherapy) and are radiographically stable.* ▪ *Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, transitional cell carcinoma of urothelial cancer, or carcinoma in situ (e.g. breast cancer) that have undergone potentially curative therapy are not excluded.* ▪ *Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization* ▪ *Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with 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) is not considered a form of systemic treatment and is allowed* ▪ *Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis* ▪ *Has an active infection requiring systemic therapy* ▪ *Has a known history of human immunodeficiency virus (HIV) infection* ▪ *Has a known history of Hepatitis B or known active Hepatitis C virus infection*

Trial name: KEYNOTE-826 [27]	NCT number: 03635567

- *Has a known history of active tuberculosis (TB; Bacillus tuberculosis)*
- *Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX 40, CD137)*
- *Has received prior systemic chemotherapy for treatment of cervical cancer.*
- *Has not recovered adequately from toxicity and/or complications from major surgery prior to randomization*
- *Has received prior radiotherapy within 2 weeks prior to randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.*
- *Has received a live vaccine within 30 days prior to randomization*
- *Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.*
- *Has a contraindication or hypersensitivity to any component of cisplatin, carboplatin, paclitaxel, or bevacizumab*
- *Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization*
- *Is pregnant or breastfeeding or expecting to conceive within the projected duration of the study, starting with the screening visit through 120 days following last dose of pembrolizumab/placebo and 210 days following last dose of chemotherapy/bevacizumab*
- *Has had an allogeneic tissue/solid organ transplant*

Trial name: KEYNOTE-826 [27]	NCT number: 03635567
Intervention	*N=308* *Pembrolizumab + Chemotherapy* *Biological: Pembrolizumab* *200 mg administered IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles* *Other Names: MK-3475, KEYTRUDA®* *Drug: Paclitaxel* *175 mg/m^2 on Days 1 of a 21-day cycle, up to 6 cycles (patient with ongoing clinical benefit can continue if no unacceptable side effects), IV infusion.* *Other Name: TAXOL®* *Drug: Cisplatin (choice between cisplatin or carboplatin)* *50 mg/m^2 on Days 1 of a 21-day cycle, up to 6 cycles (patient with ongoing clinical benefit can continue if no unacceptable side effects), IV infusion.* *Other Name: PLATINOL®* *Drug: Carboplatin (choice between cisplatin or carboplatin)* *AUC5 on Day 1 of a 21-day cycle, up to 6 cycles (patient with ongoing clinical benefit can continue if no unacceptable side effects), IV infusion.* *Other Name: PARAPLATIN®* *Drug: ± bevazizumab* *15 mg/kg on Day 1 of a 21-day cycle until progression or toxicity, IV infusion.* *Other Name: Avastin®*

Trial name: KEYNOTE-826 [27]	NCT number: 03635567
Comparator(s)	*N=309* *Placebo + Chemotherapy* *Placebo* *Normal saline or dextrose solution administered IV on Day 1 of each 3-week cycle (Q3W) for up to 35 cycles* *Drug: Paclitaxel* *175 mg/m^2 on Days 1 of a 21-day cycle, up to 6 cycles (patient with ongoing clinical benefit can continue if no unacceptable side effects), IV infusion.* *Other Name: TAXOL®* *Drug: Cisplatin (choice between cisplatin or carboplatin)* *50 mg/m^2 on Days 1 of a 21-day cycle, up to 6 cycles (patient with ongoing clinical benefit can continue if no unacceptable side effects), IV infusion.* *Other Name: PLATINOL®* *Drug: Carboplatin (choice between cisplatin or carboplatin)* *AUC5 on Day 1 of a 21-day cycle, up to 6 cycles (patient with ongoing clinical benefit can continue if no unacceptable side effects), IV infusion.* *Other Name: PARAPLATIN®* *Drug: ± Bevazizumab* *15 mg/kg on Day 1 of a 21-day cycle until progression or toxicity, IV infusion.* *Other Name: Avastin®*
Follow-up time	*IA1 median follow-up 22.0 months (range 15.1-29.1), defined as time from randomization to data cutoff May 3rd 2021.*
Is the study used in the health economic model?	*Yes*

Trial name: KEYNOTE-826 [27]	NCT number: 03635567

Primary, secondary and exploratory endpoints

Primary endpoints

1. *Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Investigator [Time Frame: Up to approximately 2 years]*
2. *Overall Survival (OS) [Time Frame: Up to approximately 2 years]*

Secondary endpoints

1. *Objective Response Rate (ORR) Per RECIST 1.1 as Assessed by Investigator [Time Frame: Up to approximately 2 years]*
2. *Duration of Response (DOR) Per RECIST 1.1 as Assessed by Investigator [Time Frame: Up to approximately 2 years]*
3. *Month 12 PFS Rate Per RECIST 1.1 as Assessed by Investigator [Time Frame: Month 12]*
4. *PFS per RECIST 1.1 as Assessed by Blinded Independent Central Review (BICR) [Time Frame: Up to approximately 2 years]*
5. *Number of Participants Who Experience an Adverse Event (AE) [Time Frame: From randomization through 30 days after last dose of study treatment (Up to approximately 25 months)]*
6. *Number of Participants Who Experience a Serious AE (SAE) [Time Frame: From randomization through 90 days after last dose of study treatment (Up to approximately 27 months)]*
7. *Number of Participants Who Experience an Immune-related AE (irAE) [Time Frame: From randomization through 90 days after last dose of study treatment for serious irAEs (Up to approximately 27 months); From randomization through 30 days after last dose of study treatment for nonserious irAEs (Up to approximately 25 months)]*
8. *Number of Participants Who Discontinue Study Treatment Due to an AE [Time Frame: Up to approximately 2 years]*
9. *Number of Participants with a 10-point Change from Baseline in Quality of Life (QoL) Based on the European Organisation for the Research & Treatment of Cancer (EORTC) QoL Questionnaire-30 (QLQ-C30) Global Score [Time Frame: Baseline (Cycle 1 Day 1: Predose) and up to 30 days after last dose of study treatment (Up to approximately 25 months)]*

Trial name: KEYNOTE-826 [27]	NCT number: 03635567

Method of analysis

Efficacy was assess in the intention-to-treat population, which included all randomized patients.

Safety was assessed in the all participants as treated population, which included all patients who had undergone randomization and received at least one dose of pembrolizumab or placebo

The Kaplan-Meier (KM) method was used to estimate rates of overall survival, progression-free survival, and duration of response. Between-group differences in overall-and progression-free survival were analyzed with the stratified log-rank test with the magnitude of the difference assessed with the use of the stratified Cox proportional-hazards model and Efron's method of handling ties to assess the magnitude of treatment difference. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. Median PFS and its 95% CIs was updated post the second interim analysis; however, no formal statistical test was performed. For OS, participants without documented death at the time of analysis were censored at the date of last known contact.

For PRO, the magnitude of the between-group treatment difference in time to deterioration was assessed using the stratified Cox proportional hazards model stratified by the randomization stratification factors and Efron's method of tie handling. CI calculations were based on Miettinen & Nurminen method with population-based weighting stratified by strata. To evaluate the treatment effect on the health-related QoL outcomes at prespecified time points, a constrained longitudinal data analysis (cLDA) model was applied with the PRO score as the response variable and the treatment by time interaction and stratification factors (Metastatic at diagnosis, Bevacizumab use & PD-L1 status) as covariates. Least square mean (ls mean) change from baseline was summarized. Group-wise comparisons were performed and model-based ls mean score was provided by treatment group and study visit. Use of covariates was chosen based on the commonly held view that these features adjust for imbalance in the trial design (stratification factors) and correlate with study treatment outcome (time on treatment). Covariates were validated during designing the trial.

The graphical method of Maurer and Bretz was used to control the familywise type 1 error rate at a one-sided alpha level of 0.025 across six primary hypotheses, two interim analyses and a final analysis.

Subgroup analyses

- *Stratification factors*
  - *Metastatic at diagnosis (yes vs. no)*
  - *Bevacizumab use (yes vs. no)*
  - *PD-L1 status (CPS<1 vs. CPS 1 to <10 vs. CPS≥10)*
- *Age group (<65 years vs. ≥ 65 years)*
- *Race (white, non-white)*
- *ECOG performance status (0,1)*

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Other relevant information

Timeline for collection of HRQoL data (Study Protocol Section 8.2.3)

Study Period	Screening	Treatment						End of Treatment	Post-Treatment			Comments
Treatment Cycle	Screening	C1	C2	C3	C4	C5	C6-C35	EOT	Safety Follow-up	Follow-up	Survival Follow-up	
Scheduled Days	-28 to -1		±3	±3	±3	±3	±3	At time of discon-tinuation	30 days from last dose[a] (+7d)	Q9W or Q12W[b] (±7d)	Q12W (±7d)	
Health Related Quality of Life (HRQoL)												
ePROs (perform in this order) 1) EuroQoL EQ-5D-5L 2) EORTC QLQ-C30 3) EORTC QLQ-CX24		X	X	X	X	X	X	X	X			Perform on Day 1 of Cycles 1 to 14, every other cycle thereafter, EOT, and Safety Follow-up. If the participant does not complete the HRQoL survey(s), the MISS_MODE form must be completed to capture the reason the assessment(s) was not performed.
Study Drug Administration												
MK-3475 or placebo + Chemotherapy		X	X	X	X	X	X					Order of study intervention administration: 1) pembrolizumab or placebo, 2) paclitaxel, 3) cisplatin or carboplatin, 4) bevacizumab

a. If the End of Treatment Visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required. All procedures for both visits will be performed at the End of Treatment Visit.
b. Follow-Up visits to be scheduled to coincide with Follow-Up imaging.
c. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR, and confirmed by the site per iRECIST when clinically appropriate (for participants treated with pembrolizumab/placebo), initiating a new anti-cancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy or death.

Appendix C Baseline patientkarakteristika fra de kliniske studier, der inkluderes i den sammenlignende analyse af effekt og sikkerhed

Table 58. Baseline patientkarakteristika.

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety		
No. (%), unless stated otherwise	PEM+CT N=308	PBO+CT N=309
Age, year		
Median (range)	51 (25-82)	50 (22-79)
≥65	48 (15,6)	52 (16,8)
Race		
White	170 (55,2)	190 (61,5)
Non-white	138 (44,8)	119 (38,5)
ECOG PS		
0	178 (57,8)	170 (55,0)
1	128 (41,6)	139 (45,0)
Disease status at initial diagnosis		
I	67 (21,8)	58 (18,8)
II	85 (27,6)	93 (30,1)
III	5 (1,6)	8 (2,6)
IIIA	4 (1,3)	8 (2,6)
IIIB	46 (14,9)	42 (13,6)
IVA	7 (2,3)	4 (1,3)
IVB	94 (30,5)	96 (31,1)
Disease status at trial entry		
Metastatic	58 (18,8)	64 (20,7)
Persistent or recurrent with distant metastases	199 (64,6)	179 (57,9)
Persistent or recurrent without distant metastases	54 (16,6)	66 (21,4)
Histology type		
Adenocarcinoma	56 (18,2)	84 (27,2)
Adenosquamous carcinoma	15 (4,9)	14 (4,5)
Squamous-cell carcinoma	235 (76,3)	211 (68,3)
PD-L1 combined positive score		
<1	35 (11,4)	34 (11,0)
1 to <10	115 (37,3)	116 (37,5)
≥10	158 (51,3)	159 (51,5)
Previous therapy		
Chemoradiotherapy and surgery	49 (15,9)	56 (18,1)

Radiotherapy and surgery	22 (7,1)	23 (7,4)
Chemoradiotherapy only	125 (40,6)	118 (38,2)
Radiotherapy only	31 (10,1)	24 (7,8)
Surgery only	23 (7,5)	24 (7,8)
None	58 (18,8)	64 (20,7)
Bevacizumab use during the trial		
Yes	196 (63,6)	193 (62,5)
No	112 (36,4)	116 (37,5)

Baseline patientkarakteristika for PD-L1 CPS ≥1 populationen var generelt i overensstemmelse med ITT-populationen [9].

Comparability of patients across studies

N/A

Comparability of the study populations with Danish patients eligible for treatment

KN826 studiet er et internationalt studie med deltagelse fra 19 lande. I KN826 er der ud af ITT-populationen ca. 60 % af kaukasisk oprindelse og ca. 1/3 kommer fra et EU land, hvilket fint repræsenterer den danske patientpopulation. Der findes ikke, så vidt vi er orienteret, ikke danske data specifikt for den patientpopulation med persisterende, recidiverende eller metastatisk cervix cancer, svarende til den population, som blev inkluderet i KN826.

Følgende datasæt er dog identificeret, som tilnærmelsesvis kan udgøre et sammenligningsgrundlag for danske patienter vs. studiepopulationen i KN826:

- DGCG årsrapporten indeholder i appendiks 3 patientkarakteristika for hele 2020/2021 cervix cancer kohorten, hvor data er opgjort samlet for både metastatiske og ikke-metastatiske patienter [2]. Rapporten inkluderer ikke patienter med persisterende eller recidiverende sygdom.
- En publikation af Taarnhøj et al. opgør data fra 80 identificerede patienter fra en samlet kohorte på 1523 patienter, som alle blev diagnosticeret med tidlig stadie (op til stadium IB) cervix cancer i perioden 2005-2013 [43].

Stadie ved diagnosetidspunkter kan ikke sammenlignes, idet man i KN826, specifikt har selekteret for patienter med P/R/M (inklusiv *de novo* metastatisk) sygdom, og patienters sygdomsstadie ved initial diagnose spænder fra stadium I-IVB. Derimod er kohorten i publikation af Taarnhøj et al. udelukkende patienter med recidiverende sygdom og sygdomsstadie ved initial diagnose er udelukkende på til stadium IB.

Ikke desto mindre viser tilgængelig data, at 22,7% er ≥ 60 år [43] sammenlignet med KN826, hvor ca. 16-17 % lå i aldersgruppen ≥65 år [16]. De planocellulære carcinomer udgør størstedelen af alle cervix cancer tilfælde. I både årsrapporten fra DGCG og i Taarnhøj et al. publikationen, repræsenterede denne gruppe omtrent 60-65 %, som er i nogenlunde overensstemmelse med de 68-75% planocellulære carcinomer, som man fandt i KN826.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 59. Definition of included outcomes

Outcome measure	Definition	Validity	Clinical relevance
PFS	*PFS is defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. PFS is assessed by the investigator per RECIST 1.1. [Time Frame: Up to approximately 2 years].*		*Progression-free survival has been used as an acceptable primary endpoint in randomized Phase III trials to support regulatory approval for new treatments in advanced solid tumors in both the first-line setting and in participants who have failed prior treatments. Therefore, PFS is included as a primary endpoint for the study.* *The primary analysis of PFS will be based on BICR in order to limit bias. In order to avoid PD being determined prematurely by the investigator, participants with suspected radiologic progression first identified at the site will have all scans submitted for BICR verification of PD. The results of central PD verification will be communicated to the site promptly (KN826 protocol, supplementary [16].*
OS	*OS is defined as the time from randomization to death due to any cause. The OS will be presented. [Time Frame: Up to approximately 2 years]*		*Overall survival is the ultimate gold standard endpoint to demonstrate superiority of anti -cancer therapy (KN826 protocol, supplementary [16].*
Safety, Adverse Events	*An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and*		*Safety parameters commonly used for evaluating investigational systemic anti-cancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0. (KN826 protocol, supplementary [16].*

Outcome measure	Definition	Validity	Clinical relevance
	unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE. The number of participants that experience an AE will be reported for each arm.		
Quality of life, EORTC QLQ – C30	*The EORTC QLQ-C30 is a 30-item questionnaire developed to assess the QoL of cancer patients. It incorporates 5 functional scales (physical, role, cognitive, emotional & social), 3 symptom scales (fatigue, pain, & nausea & vomiting), a global health status/QoL scale, & single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation & diarrhoea) & perceived financial impact of the disease. All of the scales & single-item measures range in score from 0 to 100. A 10-point change in the EORTC QLQ-C30 score is perceived to be clinically meaningful. Participant post-baseline EORTC QLQ-C30 scores will be classified as "improvement", "stable", or "deterioration" according to a 10-point or*	*The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument.* *This instrument has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. (KN826 protocol, supplementary [16]*	

Outcome measure	Definition	Validity	Clinical relevance
	greater change for EORTC QLQ-C30 global score. [Time Frame: Baseline (Cycle 1 Day 1: Predose) and up to 30 days after last dose of study treatment (Up to approximately 25 months)]		
Quality of life EuroQoL EQ-5D-5L	*The 5 health state dimensions in the EuroQoL EQ-5D-5L include the following: mobility, self care, usual activities, pain/discomfort, and anxiety/depression.* *Each dimension is rated on a 5 point scale from 1 (no problem) to 5 (unable to/extreme problems). The EuroQoL EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment.*	*The EuroQoL EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [44]* *This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [45]*	
[redacted]			

Results per study

Resultaterne i nedenstående tabel er for PD-L1 CPS ≥ 1 populationen medmindre andet er angivet.

Table 60. Results in KN826

Table A3a Results of [KEYNOTE-826 (NCT03635567)]											
				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, months	PEM+CT	273	10.4 (9.7–12.3)	2.2	-	-	HR: 0.62	0.50-0.77	p<0.001	*The median PFS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	[9, 16]
	PBO+CT	275	8.2 (6.3-8.5)								
1-year PFS, %	PEM+CT	273	45.5 (39.2-51.5)	11.4	2.9-19.9	-	-	-	-	*The progression free survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	
	PBO+CT	275	34.1 (28.3–40.0)								
Median OS, months	PEM+CT	273	Not reached (19.8-NR)	-			HR: 0.64	0.50-0.81	p<0.001	*The median OS is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model*	
	PBO+CT	275	16.3 (14.5-19.4)								

Table A3a Results of [KEYNOTE-826 (NCT03635567)]							
							with adjustment for stratification, and study arm.
2-year OS	PEM+CT	273	53.0% (46.0-59.4)	11.3%	-	-	*The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*
	PBO+CT	275	41.7% (34.9-48.2)				
All-cause all grade AEs in APat, %	PEM+CT	307	99.3	-0,1	-1.27-1.26		*An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants who experience an AE will be presented*
	PBO+CT	309	99.4				
All-cause grade 3-5 AEs in APat, %	PEM+CT	307	81.8	+6.7	0.2-13.15		
	PBO+CT	309	75.1				
All-cause SAEs in APat, %	PEM+CT	307	49.8	+7.4	-0.41-15.29		An SAE is defined as any untoward medical occurrence that, at any dose: a.) Results in death; b.) Is life-threatening; c.) Requires inpatient hospitalization or prolongation of existing

Table A3a Results of [KEYNOTE-826 (NCT03635567)]							
	PBO+CT	309	42.4				hospitalization; d.) Results in persistent or significant disability/incapacity; e.) Is a congenital anomaly/birth defect; f.) Other important medical events; h.) Is a new cancer (that is not a condition of the study) or i.) Is associated with an overdose. The number of participants who experience an SAE will be presented.
AEs leading to treatment discontinuation in APat, %	PEM+CT	307	37.5	+11.0	3.6-18.24		*The number of participants who discontinue study treatment due to an AE will be presented.*
	PBO+CT	309	26.5				
EORTC QLQ-C30 *Baseline – week 30* *ITT-population*	PEM+CT	307	[redacted]	[redacted]	[redacted]	[redacted]	*The EuroQoL EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-CX24 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EuroQoL EQ-5D-5L first, then EORTC QLQ-C30, and then EORTC QLQ-CX24. The questionnaires should be administered prior to dosing*
	PBO+CT	309	[redacted]				

Table A3a Results of [KEYNOTE-826 (NCT03635567)]	
	on Day 1 of Cycles 1 to 14, every other cycle thereafter, EOT, and Safety Follow-up.

Appendix E Safety data for intervention and comparator(s)

Se venligst afsnit 7.1.2.4

Appendix F Comparative analysis of efficacy and safety

N/A – der er ikke blevet lavet en meta-analyse

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Appendix G Extrapolation

Overview

The parameterisation of all outcomes in the cost-effectiveness model were all informed by patient-level analysis of KN826. Table 61 lists the clinical outcomes included in the model.

Table 61. Clinical outcomes included in the cost-effectiveness model

	STM structure
Progression-free survival	✓
Time to progression	✓
Post-progression survival	✓
Time on treatment	✓
Health-related quality of life	✓
Adverse events	✓

Clinical parameters for the State Transition Model (STM)

In order to model outcomes over a lifetime horizon it was necessary to extrapolate the patient-level data of clinical outcomes beyond the trial period in KN826. Parametric analyses were conducted based on the patient-level data from KN826 following best practices for survival modelling and in line with the NICE requirements[34, 35].

For the Pembrolizumab and SoC arms, PFS, TTP, and PPS curves were derived by fitting 7 different parametric models (Exponential, Weibull, Log-normal, Log-logistic, Gompertz, Gamma and Generalized Gamma distributions) to the observed data from KN826 trial. The fitted parametric curves were used to extrapolate these outcomes beyond the trial period. Both one-piece and piecewise (Kaplan–Meier + parametric survival curve) models were fitted to the data. The survival curve fitting was carried out in line with NICE Decision Support Unit guidelines[34, 35]. Goodness-of-fit statistics based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), visual inspection (comparing fitted parametric curves to the observed Kaplan–Meier plots during the trial follow-up period), assessment of the underlying hazard functions, and clinical plausibility of the extrapolation in the longer term (versus external data were available and expert opinion by international clinicians) were used to select the best-fitted parametric curves for the base case and alternative plausible parametric survival curves to be explored in sensitivity analyses. The model base case for PFS, TTP, and PPS extrapolations were validated by clinical key international opinion leaders.

Following extrapolation, each cycle transition (or hazard) including death as an event is calculated as the maximum of the extrapolated transition (or hazard) and general population mortality based on lifetables[36]. Death is an absorbing health state, there are no transitions allowed out of this health state. The selection and validation of the models for PFS, TTP and PPS are discussed in below.

Progression-Free Survival

KM analyses for PFS in patients with CPS ≥1 are presented in **Figure 12**. This illustrates that PFS data was fairly mature. Nevertheless, parametric survival models were necessary to be able to extrapolate outcomes beyond the trial period. Statistical testing for proportionality of hazards and

visual assessment of the KM data indicated that PFS hazards for pembrolizumab and SoC were not proportional (**Figure 12**, **Figure 13** and Figure 14), and therefore, independent survival models were fit to each arm.

Key: CPS, combined positive score; INV, Investigator assessed; KM, Kaplan–Meier; PFS, progression-free survival .

Key: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; PFS, progression-free survival

Key: CPS, combined positive score; PFS, progression-free survival

Our findings from reviewing the model fit of various one piece and two-piece fits were as follows:

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A one-piece fitting results in an underestimation of the KM data till week 28 followed by an overestimation of KM data till week 75 (week 70 for SoC) as observed in Figure 15. Thus, one-piece models did not provide a good visual fit to the data for pembrolizumab and SoC (particularly to the data for pembrolizumab) and were not selected for the base case parametric extrapolation.

(a) Pembrolizumab arm

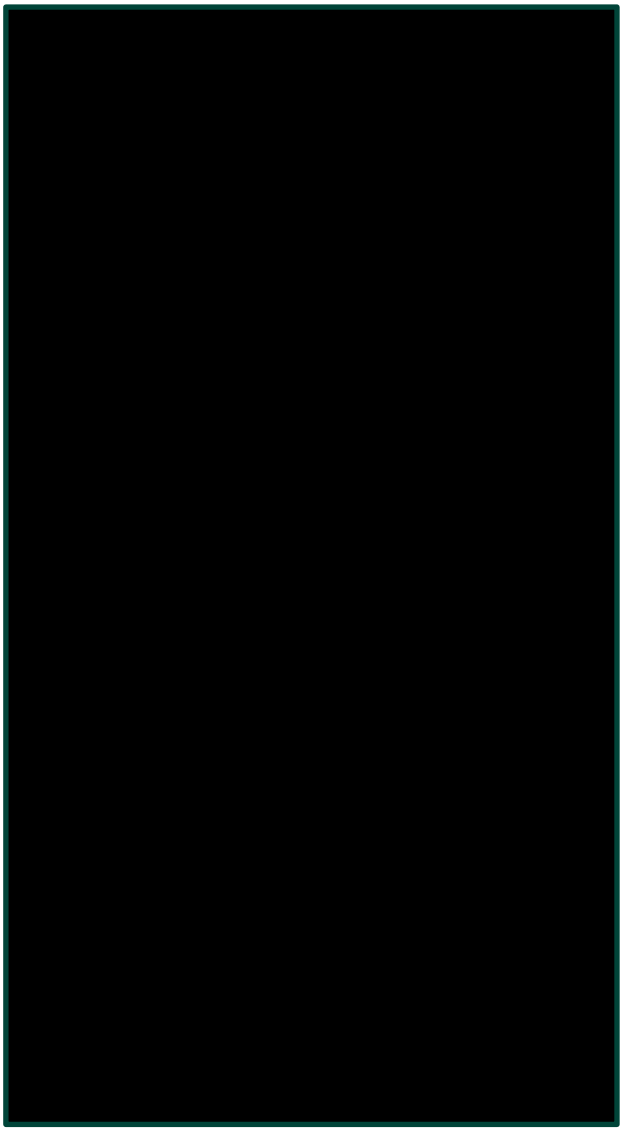
(b) SoC arm

Key: CPS, combined positive score; INV, Investigator assessed; PFS, progression-free survival

The determination of the cut-off time points for the piecewise models include visual inspection of the one-piece fitting, combined with considerations of the patterns observed around the candidate cut-off from the chow-test plot, number of subjects remaining at the candidate cut-off time and number of events occurred post the candidate cut-off that are inferred from the KM plot and survival summary table. The resulting plot of the chow test statistics is displayed in Figure 16. Based on Figure 15 and Figure 16, it is identified that the structural changes to the KM data were observed at week 28, 37 and 46, and hence formed the basis of the cut-off points at which two-piece models were tested (fitted).

a) Pembrolizumab arm

b) SoC



Key: SoC, Standard of care

Two-piece models fit beyond 28 weeks do not provide a good visual fit to the data for pembrolizumab (Figure 17). One model provided a reasonable visual fit to the data (Gompertz), but resulted in a clinically implausible long-term extrapolation Figure 18 shows a constant PFS after 104 weeks, which is clinically implausible as patients in the PF state are likely to decrease with time). Many of the two-piece models fit beyond 28 weeks did provide a good visual fit to the data for SoC Figure 17.

(a) Pembrolizumab arm

(b) SoC arm

Key: CPS, combined positive score; INV, Investigator assessed; PFS, progression-free survival

Key: CPS, combined positive score; PFS, progression free survival

Most of the two-piece models fit at or beyond 37 weeks provide a reasonable visual fit to the data for pembrolizumab and SoC, at the cost of reduced data availability to inform the fit Figure 19. Hence, when compared with one-piece fiting and two-piece models fit beyond 28 weeks, two-piece models fit at or beyond 37 weeks were chosen for the base case.

a) Pembrolizumab arm

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Key: CPS, combined positive score; INV, Investigator assessed; PFS, progression-free survival

Further, clinical validation was performed to assess the parametric distribution to be used for performing the cost-effectiveness analyses. The distribution was selected on the following criteria which were considered for the pembrolizumab + SoC arm and the SoC arm separately:

- Visual fit to the KM data, where the nature of fit and magnitude of deviations is visually assessed for different parametric functions
- Clinical plausibility of long-term extrapolations, wherein the outcomes at 50 years (modelled) are checked for overestimation. External validation is also conducted to ensure the alignment among the modelled outcomes at 4 years and the 4 year survival observed in GOG 240 trial[46]
- Plausibility of hazard functions and assumptions, assessed based on the shape of the hazard function
- Statistical fit to the data, where the AIC and BIC values for the parametric fit are within 5 points of the lowest (and best fitting) function

After weighing the different parametric distributions based on these criteria, it was observed that:

- The exponential distribution showed large deviations from the KM data for the intervention arm (also visible in Figure 19, where the said distribution is farthest from the KM curve), and hence did not fulfil the visual fit criteria. On the other hand, all the parametric distributions provided a good visual fit to the KM data for the SoC arm (Figure 19).
- The generalized gamma and gompertz distribution predicted a 50 year PFS (10,35% and 33,38% respectively) that was outside the plausible range of the expected PFS (where the expected PFS rate should be less than or equal to 5%) for the intervention arm and hence did not fulfil the criteria of long term clinical plausibility. For the comparator arm, the log normal distribution predicted a 4 year PFS that showed a deviation (beyond the accepted 3% deviation) from the PFS evaluted in the GOG 240 trial[46] and hence did not qualify as a favourable distribution.
- Additionally, the goodness of fit of parametric estimates (for long term extrapolations) can also be visually assessed by fitting the smooth spline estimates to hazard functions.
- 19 (a) displays the various estimates of hazards over time for the intervention arm (and (b) for comparator arm). The parametric estimates are made by assuming that the underlying true hazards follow different parametric distributions (similar to the ones used for long term survival extrapolations). The figure also displays the smooth spline estimate; that serves as a benchmark since it does not require any parametric assumptions other than assuming the underlying true hazard being smooth over time. The shaded area represents the 95% confidence region estimated using this smooth spline approach. A

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quick glance at Figure 20(a) and (b) showed that the exponential, weibull and gamma distributions resulted in clinically implausbile shape of the hazard functions over time (for both the arms), with the distributions displaying a relatively flatter PFS after 37 weeks (instead of a falling PFS evident from the smooth spline estimate curve). Furthermore, the distributions did not fit the spline estimates well (with the said distributions being farthest from the smooth spline estimate curve) and hence were not considered as favourable distributions for long term extrapolations. Generalized gamma additionally resulted in implausible hazard functions for the SoC arm (Figure 20(b).

Since the log logistic distribution fulfilled all the above mentioned criteria for both the arms, and also provided a good statistical fit to the trial data, (with acceptable AIC/BIC values that lie within 5 points of the value of best fitting distribution), it was chosen as the base case parametric distribution used for extrapolations in the model.

Table 63 Parmetric model fit statistics for SoC arm, PFS, 37-week cut-off, CPS≥1

Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	542,4617	1	545,1252	1
Weibull	544,3950	4	549,7219	4
Log-normal	545,5338	6	550,8607	6
Log-logistic	543,4249	2	548,7518	2
Gompertz	544,0319	3	549,3588	3
Gamma	544,4426	5	549,7694	5
Generalized Gamma	545,6457	7	553,6360	7

Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; PFS, progression free survival

Model fit statistics are provided in Table 62 and Table 63. The preferred model for both treatment arms was a two-piece model, with cut-off at 37 weeks, and a log-logistic distribution. Extrapolations for this and other distributions are given in Figure 19 along with the base case distribution (extrapolation) in Figure 20.

Table 62 Parmetric model fit statistics for pembrolizumab arm, PFS, 37-week cut-off, CPS≥1

Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	599,4448	7	602,4420	7
Weibull	594,8391	5	600,8335	5
Log-normal	588,0119	3	594,0063	2
Log-logistic	591,8106	4	597,8050	4
Gompertz	587,1819	1	593,1764	1
Gamma	596,0964	6	602,0908	6
Generalized Gamma	587,8652	2	596,8568	3

Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; PFS, progression free survival

Table 63 Parmetric model fit statistics for SoC arm, PFS, 37-week cut-off, CPS≥1

Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	542,4617	1	545,1252	1

Weibull	544,3950	4	549,7219	4
Log-normal	545,5338	6	550,8607	6
Log-logistic	543,4249	2	548,7518	2
Gompertz	544,0319	3	549,3588	3
Gamma	544,4426	5	549,7694	5
Generalized Gamma	545,6457	7	553,6360	7
Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; PFS, progression free survival				

a) Pembrolizumab arm

b) SoC arm

Key: PFS, progression free survival; SoC, Standard of care

a) Pembrolizumab arm (log hazard estimates)

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Key: INV, Investigator assessed; PFS, progression free survival

b) Pembrolizumab arm (hazard estimates) cut off 28 weeks

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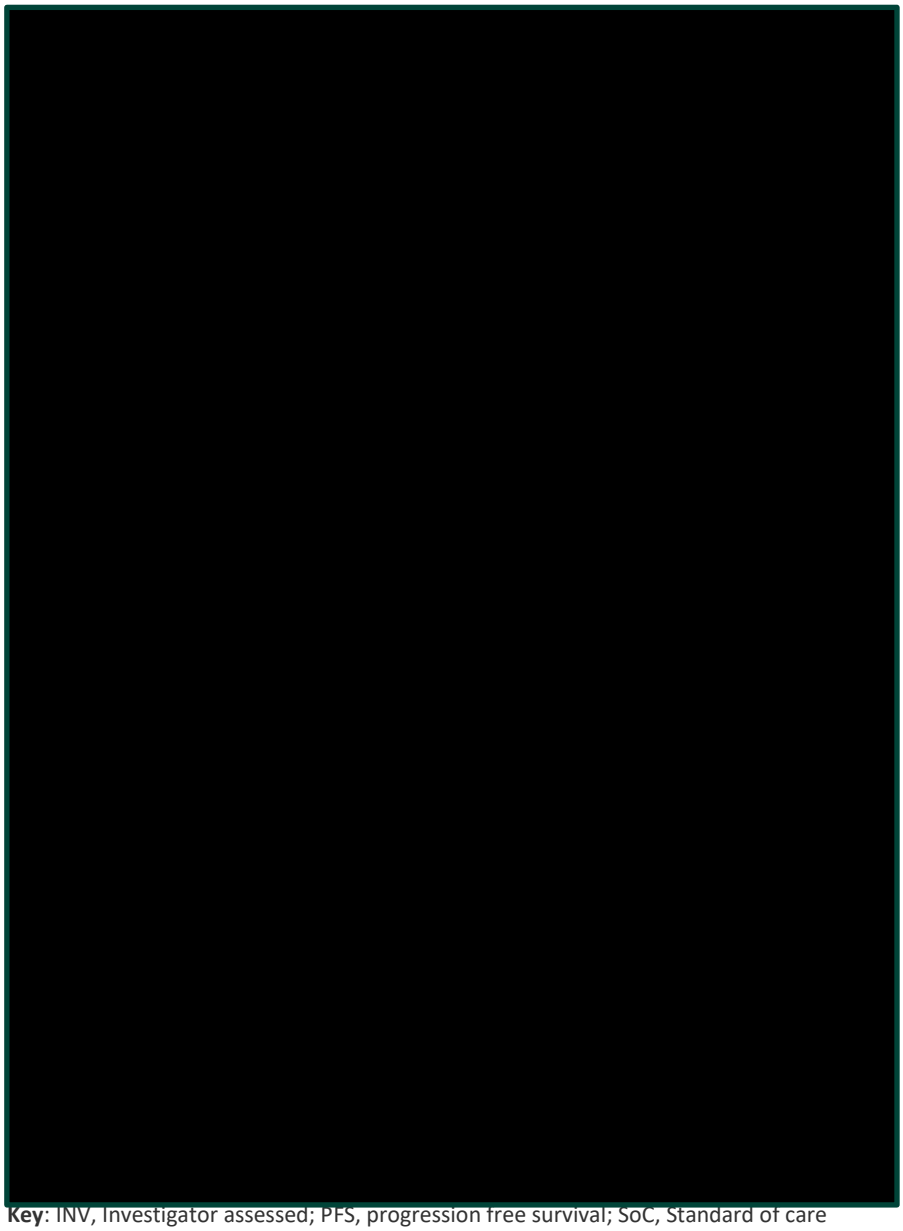

Key: INV, Investigator assessed; PFS, progression free survival; SoC, Standard of care

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Time-to-progression

The TTP and PFS endpoints differ in that deaths are recorded as an event for PFS, but a censoring is applied for TTP. In this way, TTP measures exactly time to progression, whereas PFS is the time to a composite endpoint of progression or death.

KM analyses for TTP in patients with CPS≥1 are presented in Figure **22**. This illustrates that TTP data was not fully mature. Parametric survival models were necessary to be able to extrapolate outcomes beyond the trial period. Statistical testing for proportionality of hazards and visual assessment of the KM data indicated that TTP hazards for pembrolizumab and SoC were not proportional (Figure **22**, **Figure 23** and **Figure 24**), therefore, independent survival models were fit to each arm.

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Our findings from reviewing the model fit of various one piece and two-piece fits of TTP were similar to those for the PFS endpoint:

A one-piece fitting results in an underestimation of the KM data till week 28 followed by an overestimation of KM data till week 75 (week 70 for SoC) as observed in **Figure 25**. Thus, one-piece models did not provide a good visual fit to the data for pembrolizumab and SoC (particularly for pembrolizumab), and were not selected for the base case parametric extrapolations, in line with the findings for PFS.

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A chow test was conducted to detect the cut-off points of the piecewise models, combined wiith visual inspection of the one-piece fitting, number of subjects remaining at the candidate cut-off time and number of events occurred post the candidate cut-off that are inferred from the KM plot and survival summary table. The resulting plot of the chow test statistics is displayed in Figure **26**. Structural changes to the KM data were observed at 28, 37 and 46 weeks in **Figure 25** and **Figure 26** and hence formed the basis of the cut-off points at which two-piece models were tested (fitted).This is in line with the findings for PFS.

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Two-piece models fit beyond 28 weeks do not provide a good visual fit to the data for pembrolizumab (Figure **27**). A model that provides the most reasonable visual fit to the data (gompertz), resulted in a clinically implausible long-term extrapolation (**Figure 28** shows a constant TTP after 104 weeks, which is clinically implausible as TTP curve is likely to decrease with time). Many of the two-piece models fit beyond 28 weeks do provide a good visual fit to the data for SoC. This is in line with the findings for PFS .

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All (rather than some) of the two-piece models fit at or beyond 37 weeks provide a reasonable visual fit to the data for pembrolizumab and SoC (**Figure 29**). Most of the two-piece models fit beyond 46 weeks provide a good visual fit to the data for pembrolizumab; and unlike for PFS, the curves do not overshoot the last step in the KM tail. Most of the two-piece models fit beyond 46 weeks provide a good visual fit to the data for SoC, at the cost of reduced data availability to inform the curves. Since two-piece models fit at or beyond 37 provided a reasonable fit with more data to inform the curves, it was chosen for the base case analysis.

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Further, clinical validation was performed to assess the parametric distribution to be used for performing the cost-effectiveness analyses. The distribution was selected on the basis of same 4 criteria as for PFS. After weighing the different parametric distributions based on these crietria, it was observed that:

- The exponential distribution showed large deviations from the KM data for the intervention arm (also visible in **Figure 29**, where the said distribution is farthest from the KM curve), and hence did not fulfil the visual fit criteria. On the other hand, all the parametric distributions provided a good visual fit to the KM data for the SoC arm (**Figure 29**).
- The generalized gamma and gompertz distribution predicted a 50 year TTP (13,14% and 38,03% respectively), that was outside the plausible range of the expected TTP (where the TTP is expected to be less than or equal to 5%) of the intervention arm and hence did not

fulfil the criteria of long term clinical plausibility. For the comparator arm, the exponential, weibull and gamma distributions predicted a 4 year OS that showed a deviation (greater than the accepted 5% deviation) from the OS evaluted in the GOG 240 trial[46]and hence did not qualify as favourable distributions (since TTP is not published for GOG 240 trial, the validation was based on OS extrapolations).

- Additionally, the goodness of fit of parametric estimates (for long term extrapolations) can also be visually assessed by fitting the smooth spline estimates to hazard functions. **Figure 30**(a) displays the various estimates of hazards over time for the intervention arm (and (b) for comparator arm). A quick glance at **Figure 30**(a) showed that the exponential distribution resulted in a clinically implausible shape of the hazard function over time for the intervention arm with the distribution displaying a flat TTP after 37 weeks (instead of a falling TTP evident from the smooth spline estimate curve). Furthermore, the distribution did not fit the spline estimates well (with the said distribution being farthest from the smooth spline estimate curve) and hence was not considered as favourable distribution for long term extrapolations. For similar reasons, it could be concluded that exponential, gamma and weibull disributions resulted in implausible hazard functions for SoC arm as depicted in **Figure 30**(b).

Since the log logistic distribution fulfilled all of the criteria metioned above, for both the arms, provided a good statistical fit to the trial data, (with acceptable AIC/BIC values that lie within 5 points of the value of best fitting distribution) and was in line with distribution chosen for PFS, it was also chosen as the base case parametric distribution used for extrapolations of TTP curves (**Figure 30**).

The preferred model for both treatment arms as consistent with the PFS endpoint: a two-piece model, with cut-off at 37 weeks, and a log-logistic distribution. Model fit statistics are provided in Table 64 and Table 65, and extrapolations are illustrated in **Figure 29** along with the base case extrapolation in

Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	516,4504	1	519,1044	1
Weibull	518,4037	4	523,7116	4
Log-normal	520,2723	7	525,5802	6
Log-logistic	517,9499	2	523,2579	2
Gompertz	518,2404	3	523,5483	3
Gamma	518,4325	5	523,7404	5
Generalized Gamma	520,0143	6	527,9762	7

Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; TTP, time to progression

Figure 30.

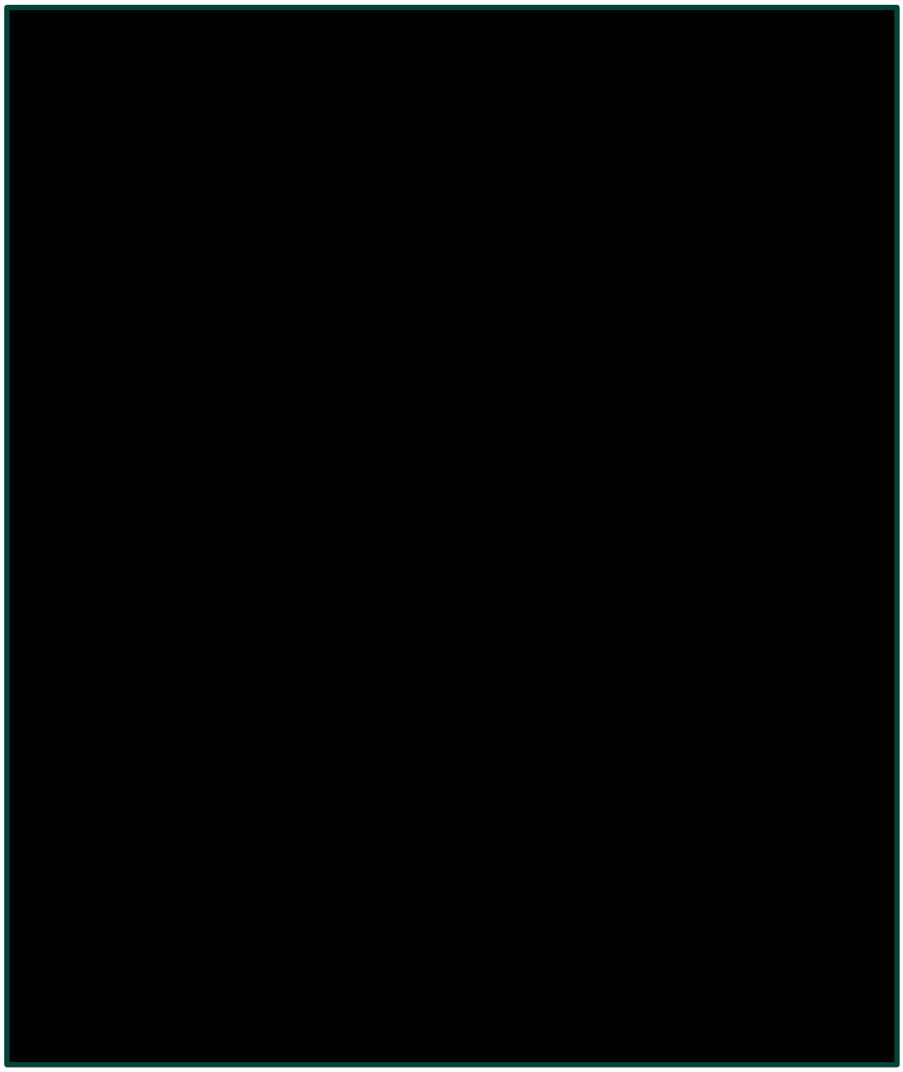
Table 64. Parametric model fit statistics for pembrolizumab arm, TTP, 37-week cut-off, CPS≥1

Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	571,0483	7	574,0387	7

Weibull	566,0523	5	572,0332	5
Log-normal	559,6297	3	565,6105	2
Log-logistic	563,3405	4	569,3214	4
Gompertz	558,6989	1	564,6798	1
Gamma	567,2593	6	573,2401	6
Generalized Gamma	559,4039	2	568,3752	3
Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; TTP, time to progression				

Table 65 Parametric model fit statistics for SoC arm, TTP, 37-week cut-off, CPS≥1

Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	516,4504	1	519,1044	1
Weibull	518,4037	4	523,7116	4
Log-normal	520,2723	7	525,5802	6
Log-logistic	517,9499	2	523,2579	2
Gompertz	518,2404	3	523,5483	3
Gamma	518,4325	5	523,7404	5
Generalized Gamma	520,0143	6	527,9762	7
Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; TTP, time to progression				



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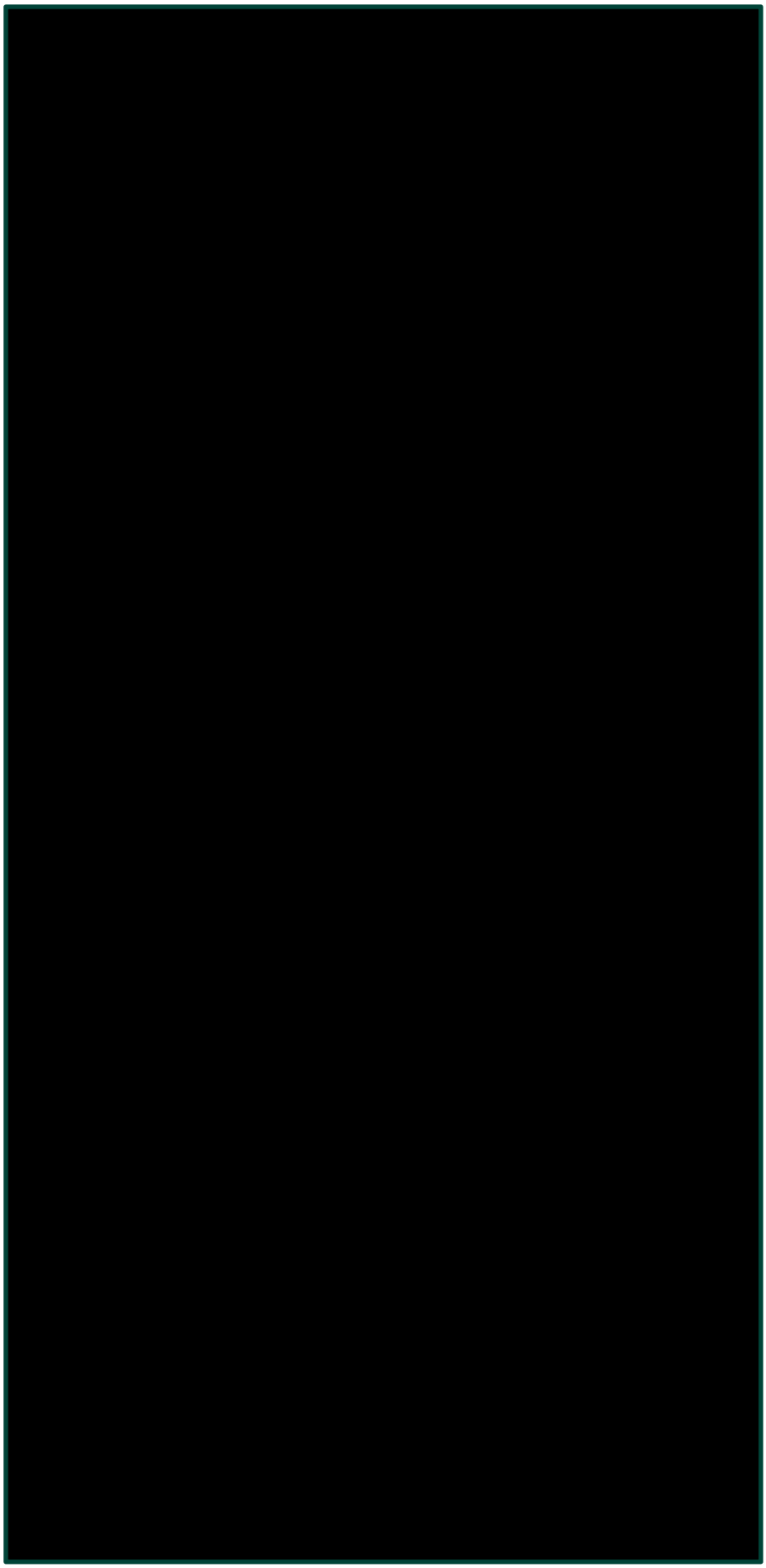

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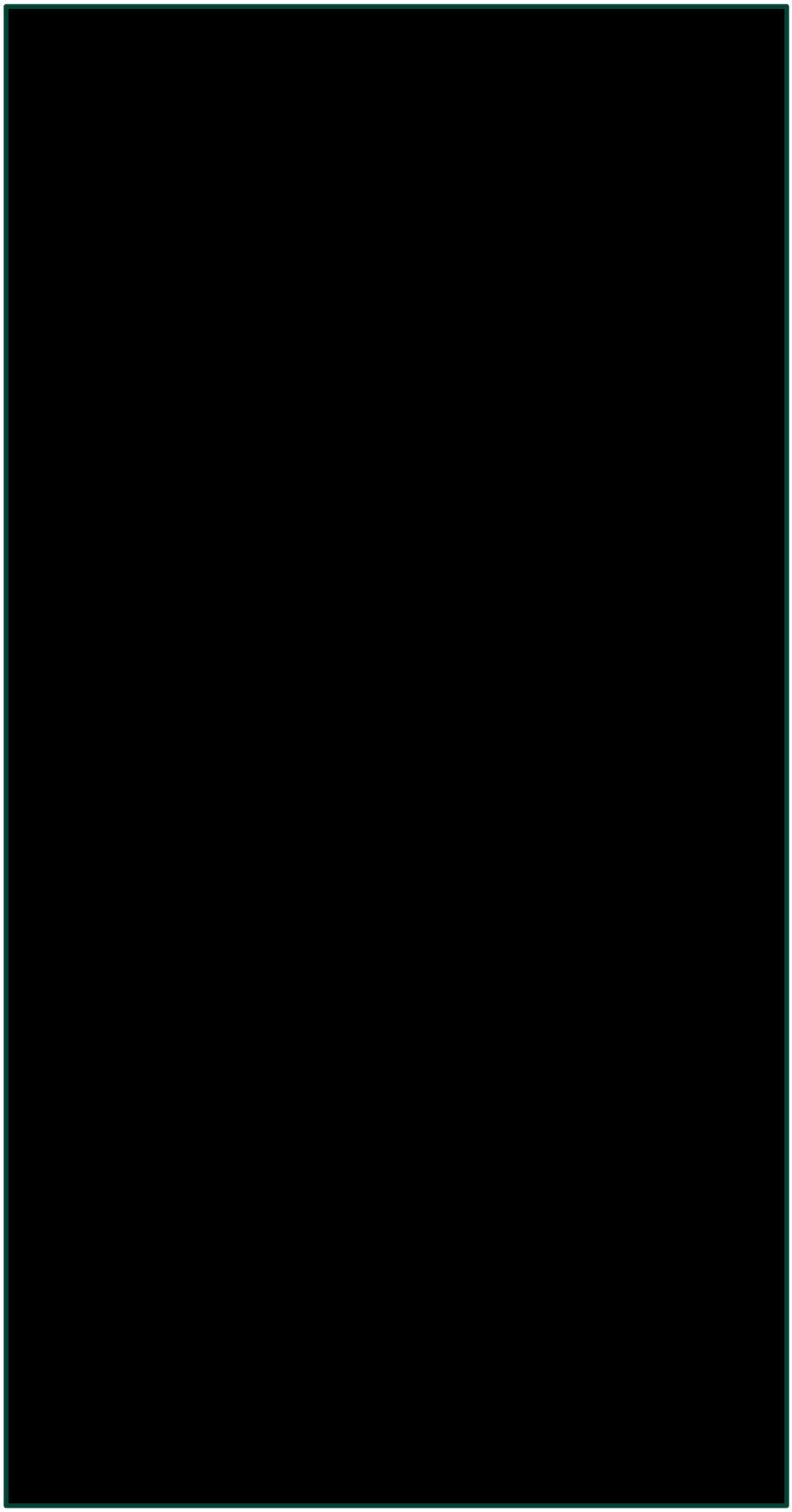

Post-progression survival

KM analyses for PPS in patients with CPS ≥1 are presented in Figure **32**. This illustrates that PPS data was fairly mature. Nevertheless, parametric survival models were necessary to be able to extrapolate outcomes beyond the trial period. Statistical testing for proportionality of hazards and visual assessment of the KM data indicated that PPS hazards for pembrolizumab and SoC were not

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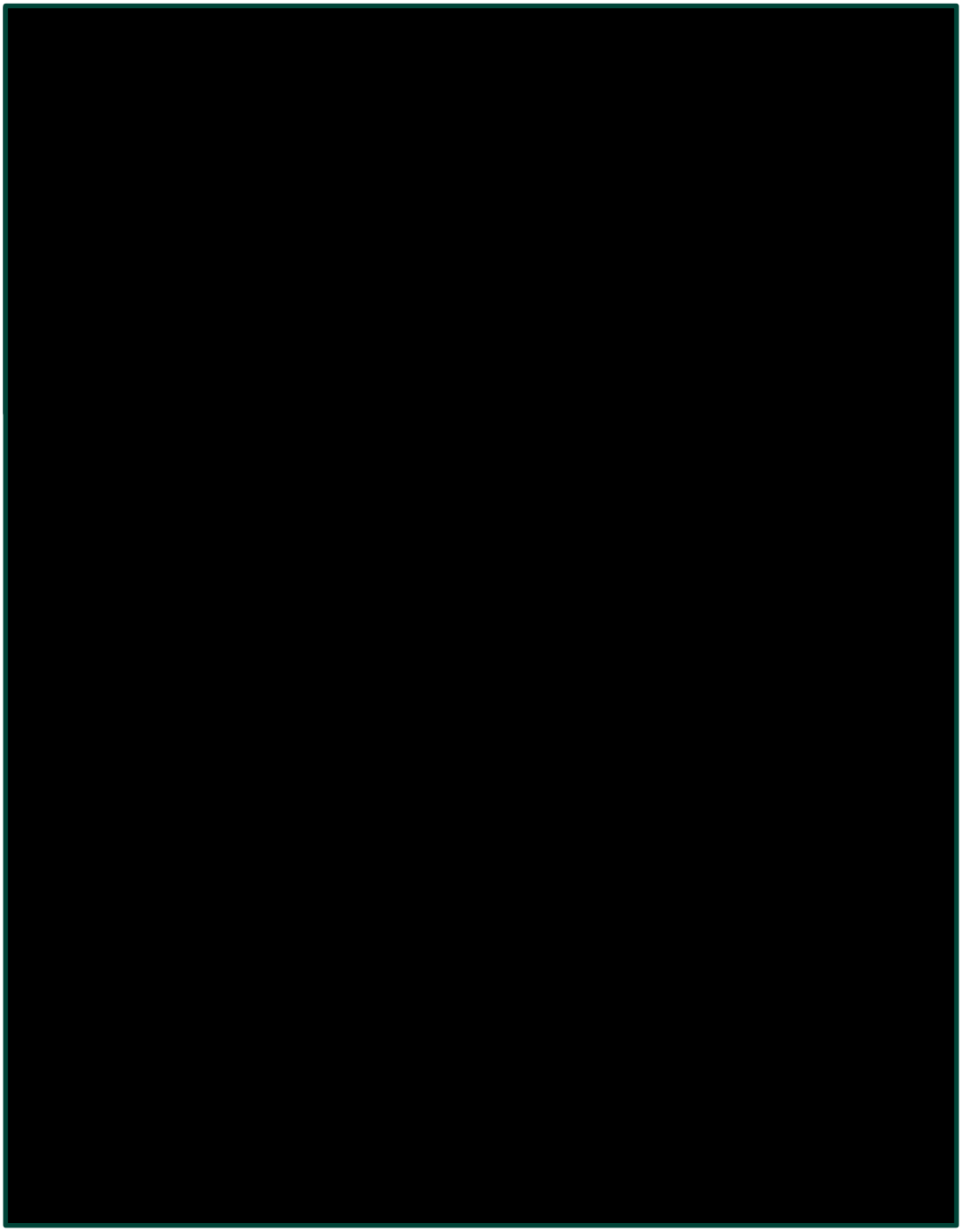
proportional (Figure **32**, **Figure 33** and **Figure 34**), and therefore, independent survival models were fit to each arm. Given the close KM curves, the model evaluated a scenario in which PPS is pooled across both treatment arms.



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Our findings from evaluating different model fits was that one-piece models fitted the data well (**Figure 35**,**Figure 36**). Chow test conducted to detect the cut-off points of the piecewise models (**Figure 37**) resulted in structural changes to the KM data being observed at 14 weeks. Two-piece models, (fitted at a cutt-off point of 14 weeks) did not seem to improve on one-piece fittings **Figure 37**) and hence were not used for the base case extrapolations. As part of clinical validity in addition to model fit it was observed that:

- The exponential distribution showed large deviations from the KM data for the intervention arm (also visible in **Figure 35**, where the said distribution is farthest from the KM curve), and hence did not fulfil the visual fit criteria. On the other hand, all the parametric distributions provided a good visual fit to the KM data for the SoC arm (Figure **35**).
- All parametric distributions predicted a 50 year PPS that lied well within the plausabile range of the expected PPS (less than or equal to 5%) for the intervention arm. For the comparator arm, exponential, weibull, gompertz and gamma distributions predicted a 3 year PPS that showed a deviation (beyond the accepted 3% deviation) from the PPS evaluted in the GOG 240 trial[46] and hence did not qualify as favourable distributions.
- In line with the reasons described in the PFS and TTP it can be concluded that weibull, gompertz and gamma distributions resulted in a clinically implausible shape of the hazard function over time for the intervention arm Figure **39** (a) (where the said distributions do not fit spline estimates and consequently do not show a similar trend as the smooth spline estimate curve) and hence were not considered as favourable distributions for long term extrapolations. On the other hand, all the distributions except generalized gamma and exponential distribution resulted in clinically implausible hazard functions for SoC arm (**Figure 39**(b)).

Since the generalized gamma distribution fulfilled all of the criteria of clinical validity, for both the arms and provided a good statistical fit to the trial data, (with acceptable AIC/BIC values that lie within 5 points of the value of best fitting distribution) it was chosen as the base case parametric distribution for extrapolation of PPS curves.

Table 66. Parametric model fit statistics for pembrolizumab arm, PPS, one piece, CPS≥1

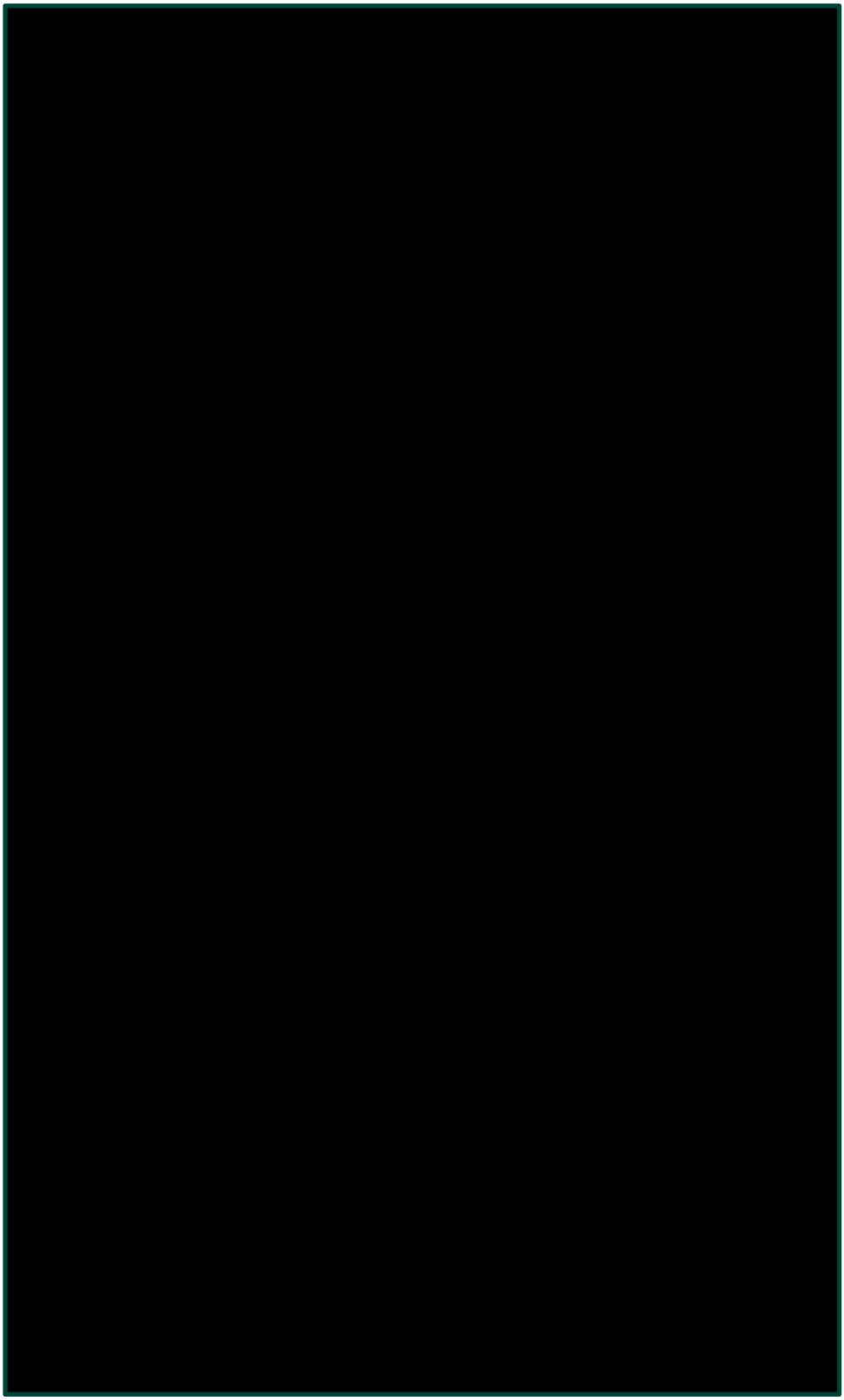
Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	841,1253	7	844,0232	7
Weibull	820,5607	5	826,3564	5
Log-normal	812,9600	1	818,7557	1
Log-logistic	815,2542	3	821,0498	2
Gompertz	831,6882	6	837,4839	6
Gamma	817,0312	4	822,8269	3
Generalized Gamma	814,8095	2	823,5030	4

Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; PPS, post progression survival

Table 67 Parametric model fit statistics for SoC arm, PPS, one piece, CPS≥1

Statistical Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	1107,558	7	1110,728	6
Weibull	1102,064	5	1108,405	4
Log-normal	1097,905	1	1104,246	1
Log-logistic	1098,509	2	1104,850	2
Gompertz	1107,392	6	1113,733	7
Gamma	1100,233	4	1106,574	3
Generalized Gamma	1099,189	3	1108,701	5

Key: AIC, Akaike's information criteria; BIC, Bayesian Information Criteria; CPS, combined positive score; PPS, post progression survival



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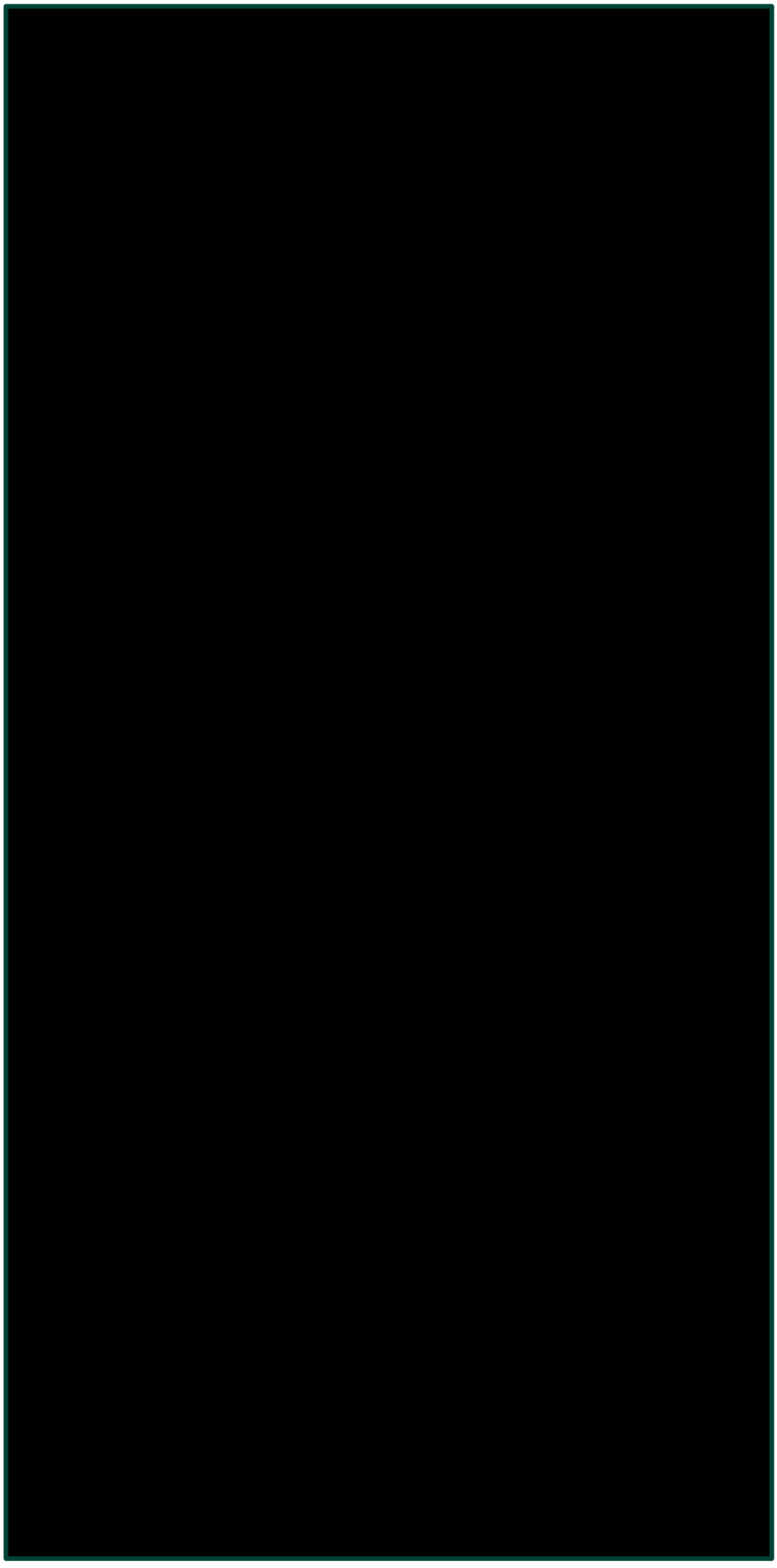

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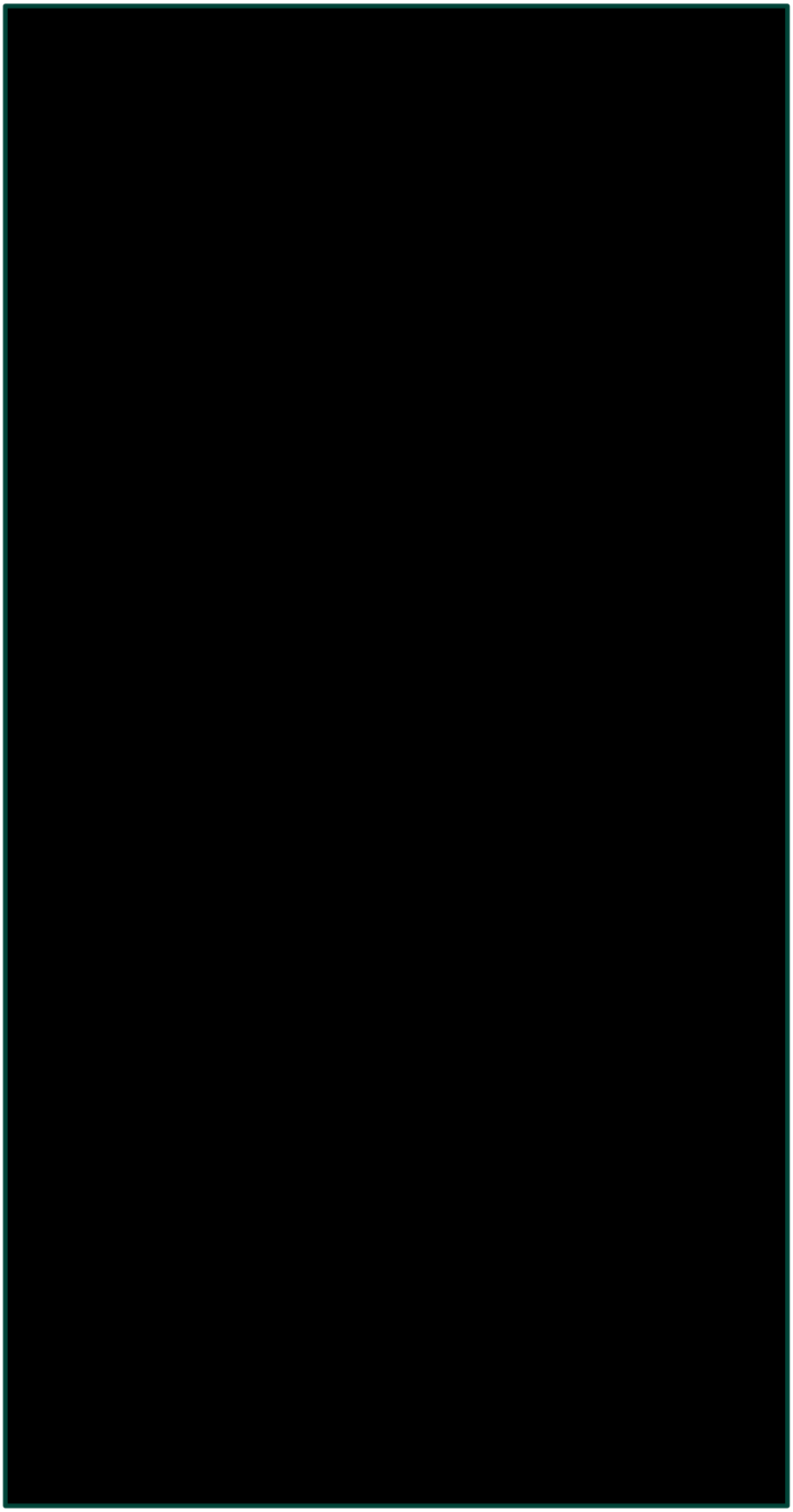

Economic model implementation

A Visual Basic® for Applications (VBA) macro was used to ensure that patients in the 'progressed disease' health state are assigned the correct probabilities for transition to the 'death' health state irrespective of in which cycle they enter the 'progressed disease' health state. The VBA macro

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implements the usual calculations for tunnel states but is computationally more efficient than programming these into front-end Excel®.

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Appendix H – Literature search for HRQoL data

N/A da HRQoL er indsamlet i KN826.

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Appendix I Mapping of HRQoL data

N/A

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Appendix J Sensitivity analyses

In this appendix we have also included some background information relating our one-way sensitivity analysis. The most sensitive parameters in the OWSA is provided in section 8.7 and all parameters are presented below.

Table 68: Inputs Varied in OWSA

	Parameter Name	Mean	SE	Distribution	Lower	Upper	Variation in OWSA
1	Model time horizon	35,00	-	-	20,00	50,00	-
2	Discount rate: life years	3,5%	-	-	0,025	0,045	-
3	Discount rate QALYs	3,5%	-	-	0,025	0,045	-
4	Discount rate: costs	3,5%	-	-	0,025	0,045	-
5	Pack cost paclitaxel 6/50ml	201,50	20,15	Normal	162,01	240,99	Within 95% CI
6	Pack cost cisplatin 1/100ml	200,00	20,00	Normal	160,80	239,20	Within 95% CI
7	Pack cost carboplatin 10/45ml	226,39	22,64	Normal	182,02	270,76	Within 95% CI
8	Pack cost bevacizumab bio sim aybintio 25/16ml	7.707,76	770,78	Normal	6.197,07	9.218,45	Within 95% CI
9	Pack cost pembrolizumab 25/4ml	23.204,61	2.320,46	Normal	18.656,59	27.752,63	Within 95% CI
10	Pack cost gemcitabine 200mg/vial	1.200,00	120,00	Normal	964,80	1.435,20	Within 95% CI
11	Administration cost: IV chemotherapy	1.921,00	192,10	Normal	1.544,49	2.297,51	Within 95% CI
12	Actual vs, expected cycles - pembrolizumab, in pembrolizumab (arm)	0,91	0,01	Normal	0,89	0,93	Within 95% CI
13	Actual vs, expected cycles - cisplatin, in pembrolizumab (arm)	1,07	0,06	Normal	0,96	1,19	Within 95% CI
14	Actual vs, expected cycles -carboplatin, in pembrolizumab (arm)	1,03	0,02	Normal	0,99	1,07	Within 95% CI
15	Actual vs, expected cycles -paclitaxel, in pembrolizumab (arm)	1,07	0,02	Normal	1,03	1,11	Within 95% CI
16	Actual vs, expected cycles – bevacizumab, in pembrolizumab (arm)	0,78	0,02	Normal	0,73	0,82	Within 95% CI
17	Actual vs, expected cycles – cisplatin, in SoC (arm)	1,09	0,07	Normal	0,95	1,23	Within 95% CI
18	Actual vs, expected cycles -carboplatin, in SoC (arm)	1,06	0,02	Normal	1,01	1,10	Within 95% CI
19	Actual vs, expected cycles- paclitaxel, in SoC (arm)	1,10	0,03	Normal	1,04	1,15	Within 95% CI
20	Actual vs, expected cycles -bevacizumab, in SoC (arm)	0,84	0,02	Normal	0,80	0,87	Within 95% CI
21	Proportion of patients testing positive for PD-L1	0,89	0,089	Beta	0,673	0,992	Within 95% CI
22	Cost of testing for PD-L1	560,00	56,000	Normal	450,24	669,76	Within 95% CI
23	Distribution of subsequent treatments in pembrolizumab arm - Observed in KN-826 (%) - Bevacizumab	3,8%	0,00	Normal	0,03	0,045	Within 95% CI
24	Distribution of subsequent treatments in pembrolizumab arm - Observed in KN-826 (%) - Carboplatin	13,2%	0,01	Normal	0,11	0,158	Within 95% CI

25	Distribution of subsequent treatments in pembrolizumab arm- Observed in KN-826 (%) - Cisplatin	5,0%	0,01	Normal	0,04	0,060	Within 95% CI
26	Distribution of subsequent treatments in pembrolizumab arm - Observed in KN-826 (%) - Gemcitabine	1,9%	0,00	Normal	0,02	0,023	Within 95% CI
27	Distribution of subsequent treatments in SoC arm -Observed in KN-826 (%) - Bevacizumab	8,0%	0,01	Normal	0,06	0,095	Within 95% CI
28	Distribution of subsequent treatments in SoC arm- Observed in KN-826 (%) - Carboplatin	8,5%	0,01	Normal	0,07	0,102	Within 95% CI
29	Distribution of subsequent treatments in SoC arm- Observed in KN-826 (%) - Cisplatin	6,3%	0,01	Normal	0,05	0,075	Within 95% CI
30	Distribution of subsequent treatments in SoC arm - Observed in KN-826 (%) - Gemcitabine	7,4%	0,01	Normal	0,06	0,089	Within 95% CI
31	Mean treatment duration of subsequent treatment in pembrolizumab arm (%) - Bevacizumab	247,5	119,10	Gamma	71,873	529,734	Within 95% CI
32	Mean treatment duration of subsequent treatment in pembrolizumab arm (%) - Carboplatin	88,9	11,80	Gamma	67,290	113,474	Within 95% CI
33	Mean treatment duration of subsequent treatment in pembrolizumab arm (%) - Cisplatin	35,9	6,40	Gamma	24,469	49,487	Within 95% CI
34	Mean treatment duration of subsequent treatment in pembrolizumab arm (%) - Gemcitabine	26,7	19,10	Gamma	3,116	75,037	Within 95% CI
35	Mean treatment duration of subsequent treatment in SoC arm (%) - Bevacizumab	93,0	19,90	Gamma	58,172	135,868	Within 95% CI
36	Mean treatment duration of subsequent treatment in SoC arm (%) - Carboplatin	93,3	24,60	Gamma	51,487	147,337	Within 95% CI
37	Mean treatment duration of subsequent treatment in SoC arm (%) - Cisplatin	66,8	14,20	Gamma	41,927	97,372	Within 95% CI
38	Mean treatment duration of subsequent treatment in SoC arm (%) - Gemcitabine	87,0	24,50	Gamma	45,806	141,187	Within 95% CI
39	AE rates in Pembrolizumab + SoC arm - Anaemia	0,28	0,03	Normal	0,228	0,339	Within 95% CI
40	AE rates in Pembrolizumab + SoC arm - Neutrophil count decreased	0,14	0,01	Normal	0,109	0,163	Within 95% CI
41	AE rates in Pembrolizumab + SoC arm - Neutropenia	0,13	0,01	Normal	0,106	0,158	Within 95% CI
42	AE rates in Pembrolizumab + SoC arm - Hypertension	0,10	0,01	Normal	0,077	0,114	Within 95% CI
43	AE rates in Pembrolizumab + SoC arm - Thrombocytopenia	0,07	0,01	Normal	0,053	0,079	Within 95% CI

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44	AE rates in Pembrolizumab + SoC arm - Febrile neutropenia	0,07	0,01	Normal	0,059	0,088	Within 95% CI
45	AE rates in Pembrolizumab + SoC arm - Platelet count decreased	0,08	0,01	Normal	0,062	0,092	Within 95% CI
46	AE rates in Pembrolizumab + SoC arm - White blood cell count decreased	0,07	0,01	Normal	0,056	0,084	Within 95% CI
47	AE rates in Pembrolizumab + SoC arm- Urinary tract infection	0,09	0,01	Normal	0,074	0,110	Within 95% CI
48	AE rates in SoC arm-Anaemia	0,26	0,03	Normal	0,208	0,309	Within 95% CI
49	AE rates in SoC arm - Neutrophil count decreased	0,08	0,01	Normal	0,064	0,096	Within 95% CI
50	AE rates in SoC arm - Neutropenia	0,10	0,01	Normal	0,082	0,122	Within 95% CI
51	AE rates in SoC arm - Hypertension	0,11	0,01	Normal	0,091	0,135	Within 95% CI
52	AE rates in SoC arm - Thrombocytopenia	0,04	0,00	Normal	0,032	0,048	Within 95% CI
53	AE rates in SoC arm - Febrile neutropenia	0,04	0,00	Normal	0,035	0,052	Within 95% CI
54	AE rates in SoC arm - Platelet count decreased	0,04	0,00	Normal	0,035	0,052	Within 95% CI
55	AE rates in SoC arm - White blood cell count decreased	0,04	0,00	Normal	0,032	0,048	Within 95% CI
56	AE rates in SoC arm - Urinary tract infection	0,08	0,01	Normal	0,064	0,096	Within 95% CI
57	AE duration in Pembrolizumab + SoC arm-Anaemia	142,60	9,99	Gamma	123,687	162,839	Within 95% CI
58	AE duration in Pembrolizumab + SoC arm - Neutrophil count decreased	14,43	0,98	Gamma	12,580	16,405	Within 95% CI
59	AE duration in Pembrolizumab + SoC arm - Neutropenia	13,38	0,92	Gamma	11,634	15,246	Within 95% CI
60	AE duration in Pembrolizumab + SoC arm - Hypertension	190,51	13,58	Gamma	164,818	218,035	Within 95% CI
61	AE duration in Pembrolizumab + SoC arm - Thrombocytopenia	77,13	6,94	Gamma	64,124	91,319	Within 95% CI
62	AE duration in Pembrolizumab + SoC arm - Febrile neutropenia	8,54	0,37	Gamma	7,830	9,280	Within 95% CI
63	AE duration in Pembrolizumab + SoC arm - Platelet count decreased	43,56	3,21	Gamma	37,500	50,067	Within 95% CI
64	AE duration in Pembrolizumab + SoC arm - White blood cell count decreased	41,79	5,20	Gamma	32,220	52,585	Within 95% CI
65	AE duration in Pembrolizumab + SoC arm - Urinary tract infection	62,11	8,35	Gamma	46,833	79,510	Within 95% CI
66	AE duration in SoC arm - Anaemia	123,80	8,57	Gamma	107,574	141,149	Within 95% CI
67	AE duration in SoC arm - Neutrophil count decreased	17,27	1,83	Gamma	13,875	21,031	Within 95% CI
68	AE duration in SoC arm - Neutropenia	25,83	2,53	Gamma	21,105	31,025	Within 95% CI
69	AE duration in SoC arm - Hypertension	139,84	10,44	Gamma	120,129	161,026	Within 95% CI
70	AE duration in SoC arm - Thrombocytopenia	98,00	9,68	Gamma	79,951	117,858	Within 95% CI
71	AE duration in SoC arm - Febrile neutropenia	9,85	0,31	Gamma	9,256	10,462	Within 95% CI

72	AE duration in SoC arm - Platelet count decreased	60,50	5,02	Gamma	51,066	70,721	Within 95% CI
73	AE duration in SoC arm - White blood cell count decreased	48,67	5,98	Gamma	37,667	61,061	Within 95% CI
74	AE duration in SoC arm - Urinary tract infection	37,19	4,82	Gamma	28,351	47,210	Within 95% CI
75	AE disutility- Anaemia	0,09	0,17	Beta	0,000	0,537	Within 95% CI
76	AE disutility- Neutrophil count decreased	0,28	0,03	Beta	0,227	0,336	Within 95% CI
77	AE disutility-Neutropenia	0,28	0,03	Beta	0,227	0,336	Within 95% CI
78	AE disutility-Hypertension	0,28	0,03	Beta	0,227	0,336	Within 95% CI
79	AE disutility-Thrombocytopenia	0,11	0,01	Beta	0,089	0,132	Within 95% CI
80	AE disutility- Febrile neutropenia	0,09	0,05	Beta	0,023	0,196	Within 95% CI
81	AE disutility- Platelet count decreased	0,11	0,01	Beta	0,089	0,132	Within 95% CI
82	AE disutility- White blood cell count decreased	0,28	0,03	Beta	0,227	0,336	Within 95% CI
83	AE disutility- Urinary tract infection	0,19	0,02	Beta	0,154	0,228	Within 95% CI
84	AE cost - Anaemia	3.176,00	317,60	Normal	2.553,52	3.798,48	Within 95% CI
85	AE cost - Neutrophil count decreased	569,00	56,90	Normal	457,48	680,52	Within 95% CI
86	AE cost - Neutropenia	3.176,00	317,60	Normal	2.553,52	3.798,48	Within 95% CI
87	AE cost - Hypertension	1.921,00	192,10	Normal	1.544,49	2.297,51	Within 95% CI
88	AE cost - Thrombocytopenia	569,00	56,90	Normal	457,48	680,52	Within 95% CI
89	AE cost - Febrile neutropenia	2.513,00	251,30	Normal	2.020,46	3.005,54	Within 95% CI
90	AE cost - Platelet count decreased	3.176,00	317,60	Normal	2.553,52	3.798,48	Within 95% CI
91	AE cost - White blood cell count decreased	569,00	56,90	Normal	457,48	680,52	Within 95% CI
92	AE cost - Urinary tract infection	2.038,00	203,80	Normal	1.638,56	2.437,44	Within 95% CI
93	Resource use rates in PF state: Consultation visit, physician	0,17	0,02	Normal	0,13	0,20	Within 95% CI
94	Resource use rates in PF state: Consultation visit, nurse	0,17	0,02	Normal	0,13	0,20	Within 95% CI
95	Resource use rates in PF state: CT scan	0,11	0,01	Normal	0,09	0,13	Within 95% CI
96	Resource use rates in PD state: Consultation visit, physician	0,04	0,00	Normal	0,03	0,05	Within 95% CI
97	Resource use rates in PD state: Consultation visit, nurse	0,00	0,00	Normal	0,00	0,00	Within 95% CI
98	Resource use rates in PD state: CT scan	0,00	0,00	Normal	0,00	0,00	Within 95% CI
99	Resource use cost: Consultation visit, physician	1.921,00	192,10	Normal	1.544,49	2.297,51	Within 95% CI
100	Resource use cost: Consultation visit, nurse	289,74	28,97	Normal	232,95	346,53	Within 95% CI
101	Resource use cost: CT scan	1.979,00	197,90	Normal	1.591,12	2.366,88	Within 95% CI
102	Utility in progression free state, with no AEs	0,80	0,010	-	0,78	0,82	Within 95% CI
103	Utility in progressed state	0,71	0,007	-	0,70	0,72	Within 95% CI
104	Grade 3+ AE (disutility)	-0,04	0,006	-	-0,05	-0,02	Within 95% CI

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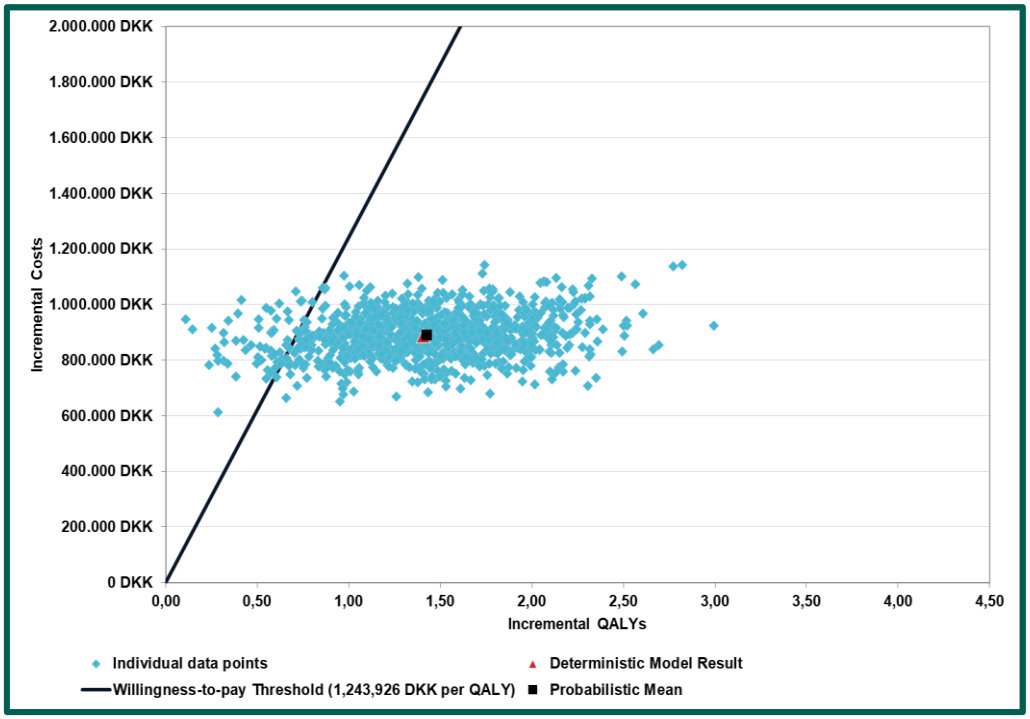
Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to estimate the probability of pembrolizumab being cost-effective relative to SoC based on different willingness-to-pay thresholds. All inputs were varied simultaneously over 1.000 iterations, based on reported uncertainty values and appropriate distributional information. Where uncertainty data (that is, standard errors (SEs), confidence intervals, etc) were not reported, it was assumed that the SE was 10% of the mean value. Table 69 shows the outcomes generated by PSA performed for pembrolizumab + SoC vs. SoC alone. Based on the PSA results, it can be observed that when all the inputs values are varied simultaneously the incremental effectiveness is 0,57% higher than the increment in effectivesness in the base case. Similarly, varying all the input parameters result in incremental costs that are 0,34% higher than the base case and an ICER that is 0,23% lower than the base case. It can thus be concluded that the uncertainty associated with the incremental effectiveness (of QALYs), costs and cost effectiveness of pembrolizumab is relatively less when compared to the base case, since varying the input parameters leads to minor variation in the base case results (**Figure 40**).

Table 69. Probabilistic Results (Pembrolizumab + SoC v/s SoC)

Treatment	Totals per treatment arm			Incremental results			ICER (DKK/QALY)	NMB (DKK)
	LYs	QALYs	Costs (DKK)	LYs	QALYs	Costs (DKK)		
SoC	2,272	1,737	190.835 DKK	1,803	1,426	890.093 DKK	624.371 DKK	883.227 DKK
Pembrolizumab +SoC	4,075	3,163	1.080.928 DKK					

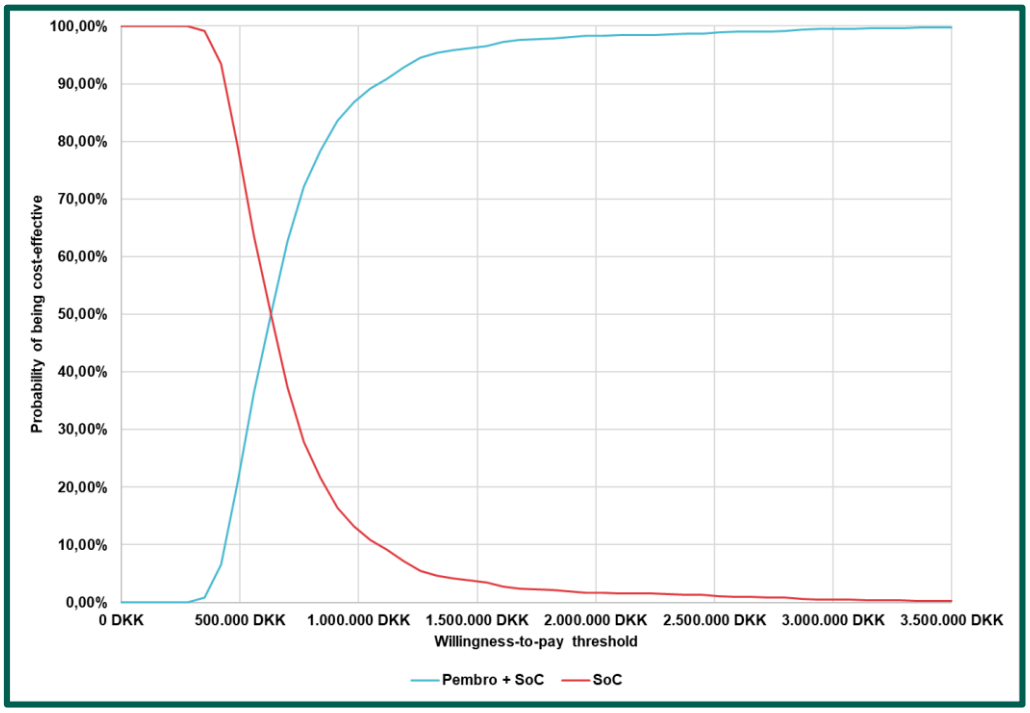
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; NMB, net monetary benefit



Key: QALYs, quality-adjusted life years; SoC, standard of care

Figure 40. Cost-Effectiveness plane for Pembrolizumab + SoC versus SoC

The cost effectiveness acceptability curve (CEAC) presented in Figure 41 projects that at a willingness to pay threshold (WTP) of 1.243.926 DKK (3 times GDP per capita) pembrolizumab + SoC has approximately 93% probability of being cost effective as compared to SoC.



Key: CEAC, cost effectiveness acceptability curve; Pembro, pembrolizumab; SoC, standard of care

Figure 41. CEAC For Pembrolizumab + SoC v/s SoC

Appendix K.

This appendix provides further information concerning the modelling of EQ-5D health utility in the KN826 according to Danish algorithm.

Table 71 provides a description of the variables contained in the dataset used in this analysis.

Table 71. Variables contained in the dataset

Variable (variable name)	Variable description
Utility	EQ-5D-5L utility based on EQ-5D-5L data.
Progression Status (PFINVFL)	Progression-free (No_PD) vs. progressive disease (W_PD), according to RECIST, version 1.1, as based on investigator's assessment. An "Unknown" category was created for records measured with unknown progression status.
Treatment (TRT01P)	Pembrolizumab+ chemotherapy vs. placebo + chemotherapy allocated at randomization
AE (G35AEFL (wi Grade3+ AE))	Indicator for an EQ-5D-5L score measured during grade 3+ AEs
Time-to-death (T2DTHCAT)	<30, 30-90, 90-180, 180-360, ≥360 days until death. An "Unknown" category was created for records measured within 360 days from OS censoring date due to uncertain time-to-death category.

Six statistical models based around progression status were evaluated, and six models based around time-to-death categories, as listed in Table 72.

Table 72. Specification of statistical models

Model	Specification
Model 1a	$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \beta_2 AE_{ij} + e_i$
Model 1b	$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \beta_2 Age_i + \beta_3 AE_{ij} + e_i$
Model 1c	$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + e_i$
Model 1d	$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \beta_2 Treatment_i + \beta_3 Age_i + \beta_4 AE_{ij} + e_i$
Model 1e	$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + \beta_4 Progression\ Status_{ij} * Treatment_i + e_i$
Model 1f	$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + \beta_4 Age_i + \beta_5 Progression\ Status_{ij} * Treatment_i + e_i$
Model 2a	$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 AE_{ij} + e_i$
Model 2b	$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Age_i + \beta_3 AE_{ij} + e_i$
Model 2c	$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Treatment_i + \beta_2 AE_{ij} + e_i$
Model 2d	$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Treatment_i + \beta_3 Age_i + \beta_4 AE_{ij} + e_i$
Model 2e	$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + \beta_4 Time\ to\ death_{ij} * Treatment_i + e_i$
Model 2f	$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Treatment_i + \beta_3 AE_{ij} + \beta_4 Age_i + \beta_5 Time\ to\ death_{ij} * Treatment_i + e_i$

Note: i denotes individual and j denotes time when the EQ-5D-5L measures was taken.

This section provides results of the utility regression modelling performed for target population with CPS≥1, using the Danish utility weights and value set as described in section 8.4.2. All analyses in this section involved a dataset of 520 patients and 6.956 EQ-5D records.

Health state-based models (models 1a-1f)

Model 1a is the simplest health state-based model considered.

Table 73. Utility regression results for model 1a

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

Model 1b suggests that, although there is a random patient intercept in the statistical model, adding an age coefficient may improve model fit.

Table 74. Utility regression results for model 1b

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

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The treatment effect (TRT01P Pembrolizumab + Chemotherapy) was not statistically significant (P= 0,761) according to model 1c. The pattern in utility due to different treatment was sufficiently captured by the health states defined using progression status.

Table 75. Utility regression results for model 1c

Fixed effects parameter	Estimate	Standard Error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

The treatment effect (TRT01P Pembrolizumab + Chemotherapy) was not statistically significant (P= 0,741) in model 1d either, which is an extension of model 1b.

Table 76. Utility regression results for model 1d

Fixed effects parameter	Estimate	Standard Error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

In model 1e, neither the treatment effect (TRT01P Pembrolizumab + Chemotherapy) nor the interaction term (PFINVFL * TRT01P) were statistically significant (P= 0,791 and P= 0,690 respectively).

Table 77. Utility regression results for model 1e

Fixed effects parameter	Estimate	Standard Error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Similarly in model 1f, neither the treatment effect (TRT01P Pembrolizumab + Chemotherapy) nor the interaction term (PFINVFL * TRT01P) were not statistically significant (P= 0,773 and P= 0,671 respectively).

Table 78. Utility regression results for model 1f

Fixed effects parameter	Estimate	Standard Error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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

Model fit statistics for the health state based utility models are summarized in Table 79. Model 1a was highest ranking for BIC and second highest for AIC; model 1b was highest ranking for AIC and second highest ranking for BIC.

Table 79: Model fit statistics (AIC and BIC) for health state based models, all-comers

Model	Number of fixed parameters	AIC	AIC rank	BIC	BIC rank
1a	3	-4633,138	2	-4599,397	1
1b	4	-4633,924	1	-4593,435	2
1c	4	-4625,260	4	-4584,771	3
1d	5	-4626,035	3	-4578,798	4
1e	5	-4616,626	6	-4569,389	5
1f	6	-4617,422	5	-4563,436	6
Key: AIC, Akaike's information criteria; BIC, Bayesian information criteria.					

Time-to-death models (models 2a-2c)

Model 2a is the simplest time-to-death based regression model considered: $Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 AE_{ij} + e_i$

Table 80 Utility regression results for Model 2a

Fixed effects parameter	Estimate	Standard error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Model 2b suggests that adding age may help with model fit, although there is a patient random intercept already included in the statistical model: $Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Age_i + \beta_3 AE_{ij} + e_i$

Table 81 Utility regression results for Model 2b

Fixed effects parameter	Estimate	Standard error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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

Model 2c suggests that the treatment effect (TRT01PPembrolizumab + Chemotherapy) was not statistically significant (P=0.3530). The pattern in utility due to different treatment was sufficiently captured by the health states defined using time-to-death categories: $Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Treatment_i + \beta_2 AE_{ij} + e_i$

Table 82 Utility regression results for Model 2c

Fixed effects parameter	Estimate	Standard error	P-value
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Appendix L

Table 83 lists the additional scenarios evaluated for the Danish Medicines Council as a part of the validation process.

Table 83. Additional scenario analysis

S/N	Scenario	Steps Involved	Direction of ICER change	ICER (DKK/QALY) % Change in ICER
1	Set the patient number to zero	• Setting patient number equal to 0 would imply no patient receives treatment, experience adverse events and transition across the three health states (PF, PD, Death). The following steps should be taken to set patient number equal to 0 • Set the following columns on sheet 'STM - ToT - KM Data' equal to 0. ○ BZ15:BZ150 ○ CD15:CD124 ○ CH15:CH47 ○ CL15:CL107 ○ CP15:CP111 ○ CT15:CT128 ○ CX15:CX47 ○ DB15:DB116 ○ DF15:DF115 • Set the following cells on sheet 'STM – ToT' equal to 0. ○ S249 ○ AH249 ○ AW249 ○ BL249 ○ CA249 ○ CQ249 ○ DF249 ○ DU249	As expected, the total costs and QALYs for both the comparator and intervention arm turn 0. ICER in such a case is not evaluated.	-

		○ EJ249 • No transitions across health states (since there are 0 patients) eliminates the dependence on extrapolated survival curves, and hence the following columns on 'PF - STM - Pembro arm' sheet is set to 0. ○ Q29:Q3161 ○ S29:S3161 ○ W29:W3161 ○ On the same sheet set U29 and AF29 equal to 0, indicating that no patients reside in the PF state in cycle 0 • For similar reasons the following columns on sheet 'PF - STM - SoC arm' are set to 0 ○ P29:P3161 ○ R29:R3161 ○ V29:V3161 ○ Set T29 and AE29 equal to 0. ○ Change the formula in cell Z30 from '=1-(P30/P29)' to '=IFERROR(1-(P30/P29),0)' and drag down the formula across the entire column. • Run macro named 'HSO_PD' to update the health state occupancy in PD state (for both the arms). • Since no patients receive treatment, no patients are likely to have experienced any adverse events for any days, and hence the following cells on sheet 'AE Data' are set to 0. ○ D32:E40 ○ N31:N32 ○ U32:X40 • On sheet 'AEs' change the formula in cell D46 from '=D29/D$17' to '=IFERROR(D29/D$17,0)' ○ A similar change is to be performed for cells D46:E54 and D62:E70 • Since no patients would be tested for PD-L1, cell F15 is set to 100% (implying 100% of the 0 patients are tested).		
2	Set the patient number to 1	Since the base case analysis is also performed for a single patient, no change would be made to the existing model settings.	ICER remains unchanged	645.606 DKK/QALY (0%)
3	Set efficacy, administration, monitoring, AEs and patient costs to be to be the same for both intervention and comparator	Same efficacy for both the arms would imply that the same number of patients would remain on treatment in both arms (ToT), patients would follow a similar transition (TTP, PFS, PPS), have similar incidence of AEs, and similar subsequent distribution of patients. With the following steps the efficacy of SoC will be set equal to efficacy of pembrolizumab + SoC • On the 'STM – ToT' sheet set ○ CQ249:CQ3380 = AH249:AH3380 ○ DF249:DF3380 = AW249:AW3380 ○ DU249:DU3380 = BL249:BL3380	The QALYs for both the intervention and comparator arm would be same. However, the intervention (pembrolizumab + SoC) would have a positive incremental cost over the comparator (SoC) because of a positive acquisition, administration, testing and patient costs. Even if the administration of	-

		○ EJ249:EJ3380 = CA249:CA3380 • On the 'STM – TTP' sheet set ○ AU89:AU3219= Y89:Y3219 • On the 'STM – PFS' sheet set ○ AU91:AU3221= Y91:Y3221 • On the 'STM – PPS' sheet set ○ AO89:AU3220= S89:S3220 • Run macro named 'HSO_PD' to update the health state occupancy in PD state • On 'Subsequent Trt Costs' set ○ E49:E52 = E31:E34 ○ Change the formula of C67:C70 from "=p_subsTx_duration_soc" to "=p_subsTx_duration_pembro" • On sheet 'AE Data' set ○ E32:E40 = D32:D40 ○ N32 = N31 ○ O32 = O31 ○ W32:W40 = U32:U40 ○ X32:X40 = V32:V40 • On sheet 'Drug Costs' set ○ F69 = "RDI_pembro_cis" ○ F70 = "RDI_pembro_carbo" ○ F71 = "RDI_pembro_pac" ○ F72 = "RDI_pembro_bev" ○ G69:G72 = D69:D72 ○ H69:H72 = E69:E72 • On 'Controls' sheet set ○ F198:G198 = "con_Cis.Use_Pem" ○ F199:G199 = "con_Carbo.Use_Pem" ○ F200:G200 = "con_Bev.Use_Pem"	pembrolizumab is capped at 6 cycles (J126=6 on 'Controls' sheet), the reliance on ToT data for pembrolizumab for calculating administration costs would result in a difference between the administration and hence patient costs of the intervention and comparator. The monitoring cost would be identical for both the arms With 0 incremental QALYs and a positive incremental cost, the ICER cannot be determined.	
4	Set the mortality rate to 100 %	• The model currently calculates the mortality rate based on the probability of death. However, since the mortality rate is to be set to 100%, cells J36:J135 of sheet 'Lookup tables' is to set to 100%. • Since mortality is set to 100%, no patient is likely to receive treatment as well, hence, the following cells are to be set 0 in sheet 'STM - ToT - KM Data' ○ BZ15:BZ150 ○ CD15:CD150 ○ CH15:CD47 ○ CL15:CL107 ○ CP15:CP111 ○ CT15:CT128 ○ CX15:CX47 ○ DB15:DB116 ○ DF15:DF115 • Run macro named 'HSO_PD' to update the health state occupancy in PD state (for both the arms	Owing to a higher QALY loss due to AEs, the intervention is no longer more effective than the comparator, resulting in negative incremental QALYs. The incremental costs also decrease. As pembrolizumab has lower QALYs and higher cost for this scenario, pembrolizumab + SoC is dominated by SoC alone	-26.149.437 DKK/QALY (substantial decrease)

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5	Reduce Mortality Rate to 0%	• The model currently calculates the mortality rate based on the probability of death. However, since the mortality rate is to be set to 0%, cells J36:J135 of sheet 'Lookup tables' is to set to 0%. • Run macro named 'HSO_PD' to update the health state occupancy in PD state (for both the arms	The incremental costs decrease while the incremental QALYs increase resulting in a fall in the ICER	642.328 DKK/QALY (decrease of 0,51%)
6	Set all unit costs for administration and monitoring to double level	• To double the administration cost multiply cell D118 on the 'Drug Costs' by 2. • To double the monitoring cost multiply cells D39:D41 on sheet 'Other Costs' by 2	The incremental costs increase while the incremental QALYs do not change, resulting in an increase in the ICER.	701.963 DKK/QALY (increase of 8,73%)
7	Set all unit costs for administration and monitoring to zero	Setting the administration and monitoring to 0 would imply not incurring any costs for administration and monitoring. The effect of this scenario can be seen by changing the dropdown in cells J146 AND J148 on 'Controls' sheet to 'No'	The incremental costs decrease while the incremental QALYs do not change, resulting in a fall in the ICER	588.600 DKK/QALY (decrease of 8,83%)
8	Set the costs of AEs to zero	Setting the AEs cost to 0 would imply not incurring any costs for the AEs experienced. The effect of this scenario can be seen by changing the dropdown in cell J147 on 'Controls' sheet to 'No'	The incremental costs decrease while the incremental QALYs do not change, resulting in a fall in the ICER	645.302 DKK/QALY (decrease of 0,05%)
9	Raise the time horizon	Set cell J14 on the 'Controls' sheet to 50 (from 35)	Both total and incremental cost & QALYs increase, but the increment in QALYs is higher than increment in cost, reducing the ICER	644.633 DKK/QALY (decrease of 0,15%)
10	Reduce the time horizon	Set cell J14 on the 'Controls' sheet to 20 (from 35)	Both total and incremental cost & QALYs decrease, but the decrement in QALYs is higher than the decrement in cost, increasing the ICER	748.341 DKK/QALY (increase of 15,91%)
11	Raise the discount rate to 100%	Set cells J23:J25 in 'Controls' sheet to 100%	As expected, there is a huge drop in the total costs and QALYs (for both intervention and comparator), however the reduction QALYs is higher than the reduction in costs thus increasing the ICER	6.057.225 DKK/QALY (substantial increase)
12	Reduce the discount rate to 0%	Set cells J23:J25 in 'Controls' sheet to 0%	There is an increase in the total costs and QALYs (for both intervention and comparator), however the increase in the incremental QALYs is higher than the increase in the incremental costs thus reducing the ICER	453.690 DKK/QALY (decrease of 29,73%)
13	For subsequent treatments: adjust the percentages for	The distribution of subsequent treatments among patients is adjusted by changing the formula in the following cells of 'Subsequent Trt Costs' sheet	The total costs for both the intervention and comparator increase, while the QALYs do not change,	648.592 DKK/QALY (increase of 0,46%)

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	the different treatments	• Set E31: E33 to "=(10/(6+21+8+3))*E30" (6.3%) • Set E34 to "=(8/(6+21+8+3))*E30" (5.0%) • Set E50:E51 to "=(14/(14+15+11+13))*E48" (8.0%) • Set E52 to "=(11/(14+15+11+13))*E48" (6.3%)	thus increasing the incremental costs and ICER	

Key: AEs, adverse events; ICER, incremental cost effectiveness ratio; KM, Kaplan Meier; KN-826, KEYNOTE 826; PF, progression free; PD, progressed disease; PPS, post progression survival; QALYs, quality adjusted life years; SoC, standard of care; TOT, time on treatment; TTP, time to progression

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Appendix M

Overview of modelling approaches used in previous NICE submissions

Table 84 provides a summary of modelling approaches used in previous NICE submissions. There have been eight submissions in cervical, ovarian and uterine cancers. Of these, 7 adopted modelling with three states whereas one adopted modelling with four states (TA598). At least 5 of the 8 were PartSA structures, the remainder likely being semi-markov STMs.

Table 84. Summary of modelling approaches used in previous NICE submissions in cervical, ovarian and uterine cancers

Appraisal (technology)	Disease area	Treatment line	Model structure	Time horizon	Comparators	Utility approach	Subgroups
Cervical Cancer							
TA183 (Topotecan + Cisplatin)	Cervical cancer	Second line	Three-state partitioned survival model	36 months	Cisplatin Paclitaxel + Cisplatin	Health state based	Persistent, Recurrent and Stage IVb Trial data also included a subgroup of cisplatin-naïve patients
Other Cancers							
TA620 (Olaparib)	Ovarian cancer	Second line	Three-state partitioned survival model	50 years	Placebo	Health state based	Relapsed platinum sensitive cancers Participants with BRCA mutation
TA611 (Rucaparib)	Ovarian cancer	Second line	Three-state partitioned survival model	50 years	Routine surveillance	Health state based	Relapsed platinum sensitive
TA598 (Olaparib)	Ovarian cancer	Second line	Four-state partitioned survival model	50 years	Routine surveillance	Health state based	Participants with BRCA mutation
TA528 (Niraparib)	Ovarian cancer	Second line	Three-state partitioned survival model	~40 years (lifetime)	Placebo	Health state based	Relapsed platinum sensitive
TA389 [Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine]	Ovarian cancer	Second line	Three state model, model type not reported	15 years	Pegylated liposomal doxorubicin hydrochloride alone	Health state based	Relapsed platinum sensitive
TA285 (Bevacizumab + gemcitabine + carboplatin)	Ovarian cancer	Second line	Three state Semi-Markov (state transition) model	10 years	Placebo + gemcitabine + carboplatin	Health state based	Relapsed platinum sensitive

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Appraisal (technology)	Disease area	Treatment line	Model structure	Time horizon	Comparators	Utility approach	Subgroups
TA284 (Bevacizumab + Paclitaxel + carboplatin)	Ovarian cancer	First line	Three state Semi-Markov (state transition) model	10 years	Placebo + carboplatin + paclitaxel	Health state based	Advanced cancer

Key: BRCA, breast cancer gene; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

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