Medicinrådet

Bilag til Medicinrådets anbefaling vedr. pembrolizumab i kombination med platin- og fluoropyrimidin-baseret kemoterapi til førstelinje-behandling af lokalt fremskredent inoperabelt eller metastatisk karci-nom i spiserøret eller HER2-nega-tiv adenokarcinom i den gastro-esofageale overgang, Siewert I, hos voksne med PD-L1 CPS ≥ 10

Vers. 1.0

Bilagsoversigt

1. Ansøgers endelige ansøgning
2. Forhandlingsnotat fra Amgros vedr. pembrolizumab (Keytruda)
3. Ansøgers notat til Rådet

Ansøgning om vurdering af den kliniske merværdi af KEYTRUDA (pembrolizumab) i kombination med platin- og fluoropyrimidine-baseret kemoterapi til førstelinjebehandling af lokal avanceret ikke-resektabel eller metastatisk spiserørskræft med PD-L1 CPS ≥ 10 hos voksne.

Version 1.0

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

Table of contents

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

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

1. Basic information

Kontaktoplysninger	
Navn	**Thomas Graham**
Titel	Sundhedsøkonom
Ansvarsområde	Health Economics
Telefonnummer	+45 2311 9491
E-mail	Thomas.graham4@merck.com
Navn	**Mette Kehlet**
Titel	Medical Advisor, Oncology
Ansvarsområde	Medical & Scientific Affairs
Telefonnummer	+45 6165 0104
E-mail	Mette.kehlet@merck.com

Overview of the pharmaceutical	
Proprietary name	Keytruda
Generic name	Pembrolizumab
Marketing authorization holder in Denmark	MSD Danmark ApS MSD modtog en CHMP positive opinion den 20. maj 2021. EC godkendt den 29. juni 2021
ATC code	L01XC18
Pharmacotherapeutic group	Antineoplastic agents
Active substance(s)	Pembrolizumab
Pharmaceutical form(s)	Pulver til koncentrat til infusionsvæske, opløsning. 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 i antigenpræsenterende celler, og som kan udtrykkes af tumorer eller andre celler i tumorens mikromiljø.

Overview of the pharmaceutical	
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.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	KEYTRUDA, i kombination med platin- og fluoropyrimidinbaseret kemoterapi, er indiceret til førstelinjebehandling af patienter med lokalt fremskredent inoperabelt eller metastatisk karcinom i esofagus eller HER-2 negativ adenokarcinom i den gastro-esofageale overgang hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10

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 (NSCLC) hos voksne, hvis tumorer udtrykker PD-L1 med tumour proportion score (TPS) ≥50% uden EGFR- eller ALK-positive mutationer i tumor KEYTRUDA som monoterapi er indiceret til behandling af lokalt fremskredent eller metastatisk NSCLC 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 i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel er indiceret til førstelinjebehandling af metastatisk planocellulær ikke-småcellet lungekræft hos voksne. KEYTRUDA, i kombination med pemetrexed og platinbaseret kemoterapi, er indiceret til førstelinjebehandling af metastatisk ikke-planocellulær NSCLC hos voksne uden EGFR- eller ALK-positive mutationer i tumorer 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 er uegnede til cisplatinbaseret kemoterapi, og hvis tumorer udtrykker PD-L1 med en kombineret positiv score (CPS) ≥ 10 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 eller i kombination med platinbaseret kemoterapi og 5- fluorouracil (5-FU) er indiceret til førstelinjebehandling af metastatisk eller inoperabelt recidiverende planocellulært hoved-hals karcinom (HNSCC) 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 (HNSCC) 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 (RCC) hos voksne KEYTRUDA som monoterapi er indiceret til førstelinjebehandling af metastatisk kolorektal cancer med høj mikrosatellitinstabilitet (MSI-H) eller mismatch repair-defekt (dMMR) hos voksne.

Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	Udleveringsgruppe: BEGR
Combination therapy and/or co-medication	N/A
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

5-FU	5-fluoropyrimidin
AIC	Akaike information criterion
AIP	Apotekernes indkøbspris
ARR	Absolut risikoreduktion
BIC	Bayesian information criterion
CPS	Combined Positive Score
DEGC	Dansk EsophagoGastrisk Cancer Gruppe
EAC	Adenokarcinom
ESCC	Planocellulær karcinom
EMA	Europoean Medicine Council
GEJ	Gastro-esophageal-junction
HR	Hazard Ratio
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
ITT	Intention to treat
KN	Keynote
LY	life years
OWSA	One-way sensitivity analyses
PD-L1	Programmed death ligand 1
PSA	Probabilistic sensitivity analyses
PSM	partitioned survival model
QALY	quality-adjusted life years
WTP	willingness to pay

[redacted]

2.1 Tables and Figures

List of tables

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

List of figures

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

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

3. Resumé

Indikation og population

Indikation i denne ansøgning er pembrolizumab i kombination med platin- og fluoropyrimidinebaseret kemoterapi til førstelinjebehandling af lokalavanceret ikke-resektabel eller metastatisk cancer i spiserøret med PD-L1 CPS ≥ 10 hos voksne.

Ansøgningen baserer sig på resultater fra KEYNOTE-590 (herefter KN-590), et dobbeltblindet randomiseret fase III studie. Ansøgningen til EMA var på ITT-populationen, men grundet effektdata på PD-L1 CPS ≥10 er EMA indikationen godkendt til denne population. MSD modtog en CHMP positive opinion den 20. maj 2021.

Definition for spiserørskræft i denne ansøgning er følgende: planocellulære og/eller HER-2 negative adenokarcinomer i esophagus + GEJ type 1 (1-5 cm over den anatomiske GEJ-linje) [1]. Denne definition afspejler inklusionskriterierne i KN-590, samt de data som præsenteres i denne ansøgning.

Niveauet for PD-L1 CPS ≥ 10 er baseret på det tidligere KN-180 studie med pembrolizumab i øvre GI-cancer, hvor resultaterne opdelt i forskellige PD-L1 CPS-scores identificerede gruppen med størst respons til PD-L1 CPS ≥10 (ca. 45% af patienterne fra ITT-populationen) med en signifikant øget ORR og signifikant øget OS. Dette cut-point blev valideret i KN-181[2].

Esophaguscancer er den 8. hyppigste kræftform med >450.000 personer diagnosticeret på verdensplan [3] og 1167 nydiagnostiserede tilfælde af esophagus, GEJ-, og ventrikelkarcinomer i Danmark i 2019 [4, 5]. Patienter med metastaserende spiserørskræft har en ringe prognose med median overlevelse ml. 6.5-11.2 måneder og en 1-års overlevelse på 34,5% alt efter anatomi, histologi samt behandlingsregimer[5] og patienterne klager ofte over synkebesvær, eventuelt opkastninger, kvalme og et betydende vægttab samt smerter[6].

Intervention

Interventionen i denne ansøgning er Pembrolizumab 200 mg hver 3. uge i op til 35 serier, Cisplatin 80 mg/m2 intravenøst hver 3. uge i op til 6 serier og 5-fluorouracil (5-fu) 800 mg/m2 intravenøst på dag 1-5 hver 3. uge i op til 35 serier.

Pembrolizumab har været anvendt i behandlingen af cancer som monoterapi siden 2015 og i kombination med cisplatin og 5-fu siden 2019, til patienter med hoved- og halskræft [7]. Mens cisplatin og 5-floururacil har været brugt i cancerbehandling siden 1950-1970'erne. Eftersom cisplatin og 5-fluorouracil allerede er beskrevet som 1. linjebehandling til patientpopulationen, vil ændringen være en tilføjelse af pembrolizumab til dette behandlingsregime.

Komparator

MSD mener, vi har valgt en klinisk relevant og hensigtsmæssig komparator med cisplatin og 5-flourouracil (cisplatin 80 mg/m2 intravenøst hver 3. uge i op til 6 serier og 5-fluorouracil 800 mg/m2 intravenøst på dag 1-5 hver 3. uge) og denne kombination kan bruges som proxy for de øvrige mulige kombinationer jf. de danske kliniske retningslinjer.

De danske kliniske retningslinjer, og fagudvalget for kræft i mavesæk og mavemund, beskriver konsensus om kombinationsbehandling til spiserørskræft med et platinholdigt kemoterapeutikum, som kan være enten cis-, oxali- eller carboplatin, samt en antimetabolit som 5-fluoropyrimidin, capecitabine eller S1, som ligeværdige behandlingsmuligheder [4, 6], da effekten er vist ens [8]. De enkelte platiner anbefalet i retningslinjerne har forskellige

typer af bivirkninger, men ikke i sværhedsgrad, og de er derfor alle rekommanderede som ligestillede behandlingsmuligheder[4].

Valget af cisplatin og 5-flourouracil danner desuden grundlag for et stærk statistisk sammenligningsgrundlag, som ikke er muligt ved de øvrige kombinationer i den relevante patientpopulation.

Vigtigste resultater fra OS og PFS analyser

Det statistiske grundlag for effekt-endepunkter er ITT-populationen, hvor der var en median opfølgningstid på 22.6 mdr. (range 19.6-27.1). I alt 373 patienter blev inkluderet i pembrolizumab +kemoterapigruppen og 376 patienter i placebo +kemoterapigruppen, heraf en PD-L1 CPS ≥ 10-population på 186 patienter i pembrolizumab +kemoterapi og 197 patienter for placebo +kemoterapi.

Data for patienter fra ITT-populationen med PD-L1 CPS ≥10 viser en median OS på 13.5 mdr. (11.1-15.6 mdr.) i pembrolizumab +kemoterapi-gruppen vs. 9.4 mdr. (8.0-10.7 mdr.) i placebo +kemoterapigruppen, og en HR 0.62 (0.49-0.78 mdr.) med en p<0.0001. Forskellen i 12 og 24 måneders overlevelsesrate er 16.7% og [redacted] for henholdsvis pembrolizumab +kemoterapi vs. placebo +kemoterapi, og er markant højere end set i tidligere studier for behandling af spiserørskræft, hvor der tidligere er rapporteret en forventet median OS mellem 8.6-11.3 mdr. for 5-FU og cisplatin-regimer i ventrikelcancer[9].

PFS for populationen med PD-L1 CPS ≥10 var 7.5 mdr. (CI 6.2-8.2 mdr.) for pembrolizumab +kemoterapigruppen vs. 5.5 mdr. (CI 4.3-6.0 mdr.) og en HR 0.51 (0.41-0.65). Desuden ses efter 12 mdr. en signifikant og klinisk betydende forskel i PFS på [redacted], som svarer til 3 gange flere patienter uden progression i pembrolizumab +kemoterapigruppen vs. placebo +kemoterapigruppen, og som efter 18 mdr. fastholdes på [redacted], hvilket svarer til 4 gange flere patienter uden progression sammenlignet med kontrolgruppen, som også er til fordel for behandlingen med pembrolizumab +kemoterapigruppen.

Bivirkninger

Bivirkninger rapporteres hos patienter, som har modtaget minimum én dosis studiemedicin (as-treated population) som svarer til 370 patienter i pembrolizumab +kemoterapigruppen og 370 patienter i placebo +kemoterapigruppen. Den gennemsnitlige behandlingslængde for grupperne er forskellig med længere behandling for pembrolizumab +kemoterapi på 7.7 mdr. (range 0.03-26.02 og i gennemsnit 11.0 cycles) vs. 5.8 mdr. (range 0.10-26.58 og i gennemsnit 8.5 cycles) for placebo +kemoterapigruppen.

Af patienter som fik en ≥grad 3 bivirkning i as-treated populationen, var der 318/370 (85.9%) i pembrolizumab +kemoterapigruppen og 308/370 (83.2%) patienter i placebo +kemoterapigruppen. Dette svarer til en absolut risiko reduktion på -2.7% (95% CI (-7.9) – (-2.4). Den relative risiko er 1.03 (95% CI 0.97-1.1), med en identisk risiko for ≥grad 3 bivirkninger hos de to behandlingsgrupper, trods den længere behandlingsvarighed (1.9 mdr.).

Bivirkninger for PD-L1 CPS ≥10 populationen viser ingen betydende forskelle mellem PD-L1 CPS ≥10 og as-treated population, hvorfor as-treated-populationen er vigtig som reference for sikkerhed, grundet det store patientgrundlag.

Den overordnede incidens af bivirkninger 'alle grader' var 100% i pembrolizumab +kemoterapigruppen og 99.5% i kemoterapigruppen. De hyppigste i pembrolizumab +kemoterapigruppen var kvalme, anæmi, nedsat appetit og fatigue, hvoraf kvalme og anæmi også var hyppige i placebo +kemoterapigruppen.

De bivirkninger, hvor der var ≥5% points forskel behandlingsgrupperne imellem, var anæmi, nedsat appetit, fatigue, nedsat antal neutrofile og nedsat antal hvide blodceller.

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

Incidensen af alvorlige bivirkninger (SAE) var ens i de to behandlingsarmen med 55.4% i pembrolizumab +kemoterapigruppen vs. 55.1% i placebo +kemoterapigruppen[10]. Den hyppigst rapporterede var pneumoni (henholdsvis [redacted] for pembrolizumab +kemoterapigruppen vs. placebo +kemoterapigruppen) [11], men ingen større forskel mellem behandlingsgrupperne blev observeret. Udover pneumoni var hyppighed af alle SAE'er <5%.

Incidensen af bivirkninger, som fører til behandlingsophør, er for alle bivirkninger 24.3% vs. 20% samt for alvorlige bivirkninger 15.7% vs. 12.7%. Da der er længere behandlingsvarighed (exposure) i pembrolizumab +kemoterapi (7.7 mdr.) vs. placebo +kemoterapi (5.8 mdr.) vurderes interventionen med tillæg af pembrolizumab ikke at øge incidensen af hverken alle eller alvorlige bivirkninger.

Livskvalitet

Livskvalitets-analyserne EORTC-QLQ-C30 og Time to deterioration fra KN-590 studiet viser uændret livskvalitet trods tilføjelse af pembrolizumab til kemoterapi-behandlingsregimet fra baseline til uge 18. Herefter ses for alle de rapporterede grupper en mindre forværring i pembrolizumab +kemoterapigruppen end for placebo +kemoterapigruppen, som kan være klinisk betydende for den enkelte patients livskvalitet

Den sundhedsøkonomiske analyse

Vores sundhedsøkonomiske analyse i denne ansøgning udgøres af en cost-utility analyse, som er baseret på en partioned survival model. Modellen har tre health states (PF, PD og død) og den er udarbejdet med det formål, at ekstrapolere udover den reelle opfølgningstid i studiet og for at kunne præsentere et analyseresultat i form af en inkrementel omkostningseffektivitets-ratio (ICER). Analysen har et begrænset samfundsperspektiv og er udarbejdet med baggrund i en tidshorisont på 30 år. Tiden i PF og PD beskrives ud fra KM kurver for PFS og OS baseret på patientdata fra KN-590 og efter et "transition point" fremskrives med en parametrisk kurve. Nytteværdien til måling af den sundhedsrelateret livskvalitet er baseret på EQ-5D-5L data tilgængelig direkte fra KN-590 og danske præferencevægte. De signifikante kliniske resultater på overlevelse understøtter estimaterne af merværdi i vores sundhedsøkonomiske model med en gevinst på 1.15 kvalitetsjusteret leveår sammenlignet med nuværende dansk standardbehandling. ICER baseret på AIP var ligeledes favorable for pembrolizumab+5FU+cisplatin med en omkostning pr kvalitetsjusteret leveår på 429.593 kr. sammenlignet med 5FU+cisplatin og 438.589 kr. sammenlignet med "blended chemo".

Konklusion

Der er begrænset evidens indenfor behandlingen af spiserørskræft, hvilket vanskeliggør vurderingen af merværdi sammenlignet med nuværende dansk standardbehandling. KN-590 er det første større fase III- studie med OS-effekt indenfor relevante population i spiserørskræft med stort behov for optimeret behandling og kontrolarmen i KN-590 må betragtes som den bedste referenceramme for prognosen med nuværende dansk standardbehandling i den specifikke patientpopulation, som ansøgningen omhandler.

Forbedret samlet overlevelse med mindst mulig toksicitet er det optimale mål for kræftbehandling. Data fra KN-590 viser, at dette mål opnås for patienter med spiserørskræft, som behandles med pembrolizumab i kombination med kemoterapi. Spiserørskræft er en livstruende sygdom og en fordobling af OS raten ved 24 mdr. og en 4-dobling af PFS raten ved 24 mdr indikerer, at der her er en meget stor klinisk merværdi for patienter med spiserørskræft sammenlignet med nuværende dansk standardbehandling. Det er ligeledes signifikant, at forbedringen i overlevelse

opnås uden at øge frekvensen af bivirkninger, selvom der tillægges kemoterapi til pembrolizumab og selvom varigheden af behandlingen med kombinationen er længere end med kemoterapi. I tillæg til de signifikante kliniske resultater, så estimerer den sundhedsøkonomiske analyse også en favorable omkostning pr. vundet kvalitetsjusteret leveår, med en ICER baseret på AIP på 429.593 kr. for pembrolizumab+5FU+cisplatin sammenlignet med 5FU+cisplatin.

3.1 Kliniske og patientrelaterede overvejelser til brug for kategorisering af merværdi

MSD finder det indledningsvist relevant at forholde sig til nedenstående overvejelser ved vurdering af den kliniske merværdi for pembrolizumab i kombination med platin- og fluoropyrimidinebaseret kemoterapi til førstelinjebehandling af lokal avanceret ikke-resektabel eller metastatisk cancer i spiserøret med PD-L1 CPS ≥ 10 hos voksne.

Definition af spiserørskræft i denne ansøgning:

I denne ansøgning anvender vi følgende definition af spiserørskræft: planocellulære og/eller HER-2 negative adenokarcinomer i esophagus + GEJ type 1 (1-5 cm over den anatomiske GEJ-linje) [1]. Denne definition afspejler inklusionskriterierne i KN-590 samt data som præsenteres i denne ansøgning.

PD-L1 CPS som biomarkør

Effekten i KN-590 er drevet af PD-L1 ekspression, hvorfor EMA har godkendt pembrolizumab i kombination med platin- og fluoropyrimidinbaseret kemoterapi til 1. linjebehandling til denne population[7].

Niveauet med PD-L1 CPS ≥ 10 er baseret på tidligere studier med pembrolizumab i øvre GI-cancer (KN-028, KN-059, KN-180, KN-181) [1]. I KN-180 blev resultaterne blandt andet opgjort efter PD-L1 CPS-scores for at identificere gruppen med størst respons[12]. Her blev fundet, at PD-L1 CPS ≥10, svarende til ca. 45% af patienterne fra ITT-populationen, var det optimale cut-point for både signifikant ORR og signifikant OS for ITT-populationen. Dette cut-point blev valideret i KN-181[2].

For at opnå yderligere respons blev KN-590 designet som et kombinationsstudie, for at targetere med både kemoterapi samt immunterapi. Kemoterapien virker direkte på tumorcellerne, men giver samtidig en stærkere aktivering af immunsystemet, så der kunne induceres et endnu mere effektivt immunrespons mod tumoren vha. immunterapi. Det biologiske rationale bygger på, at både fluoropyrimidinbaseret og platin-baseret kemoterapi har supplerende immunmodulerende effekter, som kan forstærke effekten af pembrolizumab. Kemoterapi kan dermed danne et favorabelt immunstimuleret tumormikromiljø, der virker i synergi med pembrolizumabs aktivering af T-cellerne, som herved inducerer et effektivt og forstærket immunrespons mod tumoren [1].

PD-L1 status måles ved immunohistokemi med 22C3 pharmDx assay. PD-L1 måles som CPS, som er antallet af PD-L1 positive celler (tumorceller, lymfocytter og makrofager) divideret med det totale antal tumorceller, gange med 100. Denne test er veletableret på de danske patologiske afdelinger da pembrolizumab og måling af PD-L1 har været implementeret siden 2015 [13].

Histologiske fordeling af planocellulære vs. adenokarcinomer i spiserørskræft

I Danmark er adenokarcinomer generelt hyppigere end planocellulære karcinomer i esophagus og GEJ cancer[5], men for den population, som denne ansøgning dækker *(spiserørskræft= esophagus og GEJ type 1)* er der overensstemmelse mellem histologifordelingen fra KN-590 og den i dansk klinisk praksis. For fuld gennemgang af histologiske fordeling samt stadier, se afsnit *Forventet patientpopulation Antal* side 18.

Effekt af pembrolizumab +cisplatin og 5-floururacil er uafhængig af region

KN-590 studiet var et internationalt studie med deltagelse af 26 lande. I studiet blev der stratificeret for Asian vs. non-Asian region, da den histologiske præsentation af spiserørskræft er forskellig disse regioner imellem [1].

I EMAs vurdering konkluderes det, at det er PD-L1 ekspressionen, som driver effekten, og ikke etnicitet, region eller histologi [10].

Ved gennemgang af baselinedata fra KN-590 studiet ses, at patienter med spiserørskræft i ITT populationen, at 47.5% kommer fra Non-Asian region (356 personer) og at 37% (278 personer) af ITT populationen er af kaukasisk oprindelse. Ligeledes er (15%) 114 deltagere fra EU-lande, hvorfor data fra KN-590 fint repræsenterer befolkningen med spiserørskræft i Danmark.

Begrænset evidens for behandlingen af spiserørskræft

Den begrænsede evidens indenfor behandlingen af spiserørskræft vanskeliggør vurderingen af merværdi sammenlignet med nuværende dansk standardbehandling. KN-590 er første større studie med OS-effekt indenfor relevante population i spiserørskræft med stort behov for optimeret behandling.

- Patientgruppe med dårlig prognose og høj dødelighed. Grundet begrænsede studier i den relevante patientpopulation, er prognosen for den relevante population med nuværende dansk standardbehandling derfor bedst afspejlet i komparatorarmen fra KN-590.
- Den metastatiske setting er præget af dårlig livskvalitet bl.a. grundet synkebesvær og smerter med et ofte markant vægttab til følge[6].
- Rekommandationerne for behandling af planocellulære karcinomer i spiserøret er baseret på meget begrænset antal studier og hovedsageligt ekstrapoleret fra studier indenfor adenokarcinomer [4, 14]. Derfor skal det pointeres, at der med KN-590 studiet, kommer direkte sammenlignelige data inkluderende *både* adeno- samt planocellulære karcinomer i forhold til nuværende rekommandationer og standardbehandling.

MSD mener, vi har valgt en klinisk relevant og hensigtsmæssig komparator med cisplatin og 5-flourouracil, og denne kombination kan bruges som proxy for de øvrige mulige kombinationer jf. de danske kliniske retningslinjer.

- De danske kliniske retningslinjer og fagudvalget for kræft i mavesæk og mavemund beskriver konsensus om kombinationsbehandling til spiserørskræft med et platinholdigt kemoterapeutikum, som kan være enten cis-, oxali- eller carboplatin, samt en antimetabolit som 5-fluoropyrimidin (5FU), capecitabine eller S1, som ligeværdige behandlingsmuligheder [4, 6], da effekten er vist ens [8]. De enkelte platiner anbefalet i retningslinjerne har forskellige typer af bivirkninger, men ikke i sværhedsgrad, og de er derfor alle rekommanderede som ligestillede behandlingsmuligheder[4].
- Valget af cisplatin og 5-flourouracil danner desuden grundlag for en stærk statistisk sammenligningsgrundlag, som ikke er muligt ved de øvrige kombinationer i den relevante patientpopulation.

4. Patientpopulationen, intervention og valg af komparator

4.1 Sygdommen og patientpopulationen

Inddeling af øvre GI-cancer

Den øvre gastrointestinal kanal inddeles i esophagus (spiserøret), gastroesophageale overgang (GEJ) (overgangen mellem spiserør og mavesæk) samt ventrikel (mavesæk). Den gastroesophageale overgang kan yderligere inddeles anatomisk i GEJ, Siewerts type I (distale del af esophagus), Siewerts type II (den anatomiske del af selve overgangen mellem esophagus og ventrikel) og Siewerts type III (proximale del af ventriklen) [15]

Histologisk inddeles esophaguscancer i planocellulært karcinom, oftest lokaliseret højt eller midt i esophagus samt adenokarcinom lokaliseret distalt i esophagus, men der findes også tilfælde af adenokarcinom længere oppe i esophagus [4]. GEJ cancer er primært adenokarcimoner [16]. I Danmark er andelen af adenokarcinom steget de seneste år og er nu den hyppigste histologiske subgruppe i øvre GI-cancer med ca. dobbelt så mange tilfælde som planocellulære karcinomer [4].

I Danmark er adenokarcinomer generelt hyppigere end planocellulære karcinomer i esophagus og GEJ cancer[5], men for den population, som denne ansøgning dækker *(spiserørskræft= esophagus og GEJ type 1)* er der overensstemmelse mellem histologifordelingen fra KN-590 og den i dansk klinisk praksis. For fuld gennemgang af histologiske fordeling samt stadier, se afsnit *Forventet patientpopulation Antal* side 18.

Symptomer

De første symptomer på kræft i spiserøret vil ofte være synkebesvær og eventuelt opkastninger. Der ses ofte kvalme og et betydende vægttab. Patienterne kan klage over trykken eller en brændende fornemmelse i thorax eller øvre del af abdomen. De klager ofte over træthed samt smerter, og der kan findes lav blodprocent grundet blødning fra tumoren[6, 17].

Risikofaktorer

Rygning og alkohol er de vigtigste faktorer, som øger risikoen for kræft i spiserøret af planocellulært karcinom. For adenokarcinomer er det især gastroesophageal reflux, Barret's esophagus samt høj BMI, som øger risikoen [18].

Incidens og prævalens

Esophaguscancer er den 8. hyppigste kræftform med >450.000 personer diagnosticeret på verdensplan [3]. I Danmark er det ligeledes den 8. hyppigste cancerform med et nydiagnostiseret antal i 2019 på 1167 tilfælde af esophagus, GEJ-, og ventrikelkarcinomer [4, 5].

Prævalensen for esophaguscancer (*alle stadier*) er via Kræftens Bekæmpelse angivet til at være 1156 personer ved udgangen af 2016 [19] (*ikke muligt at lokalisere nyere tal på prævalens i Danmark*), hvilket indikerer, at incidens og prævalens er nærmest identiske.

Der er en større prævalens af mænd med spiserørskræft. For adenokarcinom er mand/kvinde-ratio 4.4/1 og for planocellulært karcinom 2.7/1 [18]. Dette tilsvarer danske tal fra 2019, hvor der var 227 (24%) kvinder og 719 (76%) mænd blandt ny-diagnosticerede [5].

Gennemsnitsalder for ny-diagnosticerede med esophaguskarcinom i Danmark i årene 2016-2019 var 70 år (range 31,4-105 år) [5].

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

Forventet patientpopulation antal

Den danske patientgruppe, som forventes at være kandidater til behandlingen, vil være voksne med lokal avanceret eller metastatisk cancer i spiserøret, som tilbydes palliativ systemisk behandling i 1. linje og som har PD-L1 CPS ≥ 10.

Jf. DEGC (Dansk EsophagoGastrisk Cancer Gruppe) database rapport fra 2019 var antallet af ny-diagnosticerede esophagus og GEJ-karcinomer i Danmark 946 (alle stadier) hvoraf:

- 320 er esophaguskarcinomer (hovedsageligt planocellulære karcinomer) hvoraf ca. 100 er stadie IV [5]. Fagudvalget har tidligere vurderet, at ca. 90 patienter årligt er kandidater til 1. linje palliativ systemisk behandling af spiserørskræft af typen planocellulær karcinom [6] hvoraf data fra KN-590 viser ca. halvdelen vil have PD-L1 CPS ≥ 10, svarende til **45 patienter**.
- 626 er GEJ-karcinomer (hovedsageligt adenokarcinomer) hvoraf ca. 225 er stadie IV. Ud af disse 225 metastaserende adenokarcinomer vil ca. 25% være lokaliseret i GEJ type 1 [15], hvilket giver en patientpopulation på 56 patienter. Af dem vil ca. 75% være HER-2 negative [20] = 42 personer. Jf. data fra KN-590 vil halvdelen have PD-L1 CPS ≥ 10, svarende til **21 patienter.**

Den danske patientgruppe, som forventes at være kandidater til behandlingen **vil således være 66 patienter**.

Prognosen med nuværende behandlingsmuligheder.

Spiserørskræft diagnosticeres ofte sent i forløbet grundet dens anatomiske lokalisation, hvorved den har metastaseret og er en af de cancere, som har den dårligste prognose. Internationale studier viser at ca. halvdelen har fjernmetastaser på diagnosetidspunktet [18]. Dette medfører høj dødelighed samt begrænsede behandlingsmuligheder for operation og palliativ systemisk kemoterapi. En del patienters cancer på diagnosetidspunktet er så fremskreden, at de ikke kan tilbydes operation eller palliativ behandling, men kun Best Supportive Care [5, 16].

I DEGC databases årsrapport fra 2019, ses det at ~84% af ny-diagnostiserede esophaguscancer har så fremskreden sygdom, at de tilbydes palliativ systemisk behandling og bare ~11% af esophaguskarcinomer kan tilbydes operation med kurativ behandling i sigte [5].

Overlevelsen for patienter med cancer i spiserør, mavemund og mavesæk er, som tidligere skrevet, lav. Desuden er data på planocellulære esophaguscancer begrænsede. Nedenfor gennemgås overlevelse for patienter med cancer i esophagus, GEJ og ventrikel fra relevante studier, men de rapporterede OS data kan ikke direkte sammenlignes med KN-590 data, da der er forskel på sygdomslokalisation og stadier, men skal ses for hele gruppen af esophagus, GEJ og ventrikel cancer.

- Et Cochrane review fra 2017, som gennemgår studier med adenokarcinomer i ventrikel og GEJ, finder at en sammenligning mellem 4 studier med i alt 579 pt. at 2- vs. 3-stof behandling med 5-FU + cisplatin vs. 5-FU + cisplatin + antracyclin, OS på henholdsvis 8.6 mdr. vs. 9.9 mdr. [9].
- Samme review finder, at i 5 studier med i alt 732 pt. at 5-FU behandlingsregimer vs. capecitabine behandlingsregimer for adenokarcinomer har OS på henholdsvis 10.9 mdr. vs. 10.8 mdr. og PFS på 6.7 mdr. vs. 6.5 mdr. [9]
- Et randomiseret studie fra 2008, som undersøgte effekten af capecitabine vs. fluorouracil og cisplatin vs. oxaliplatin (REAL2 studiet) med 1002 patienter fandt ved de forskellige kombinationer median OS på mellem 9.3 mdr. - 11.2 mdr. og at stofferne og kombinationerne var ligeværdige[8].

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

- Et dansk retrospektivt databasestudie fra RegionSyd med data på 330 gastro-esophageal adenokarcinomer fra årene 2008-2009 viser at 1. linjebehandlede patienter i alle stadier (både til operation og palliativ behandling) havde en median OS på 7.8 mdr. ved 3-stof kemoterapi og 6.5 mdr. for 2-stof kemoterapi[16].
- Et randomiseret studie fra England fra 1999 viser en median OS på 8.7 mdr. med en kombination af epirubicin, cisplatin og fluorouracil til avanceret esophago-gastric cancer [21].
- Et andet internationalt multicenter randomiseret studie fra 2010 viser en median OS på 7.9 mdr. med kombination af cisplatin og fluorouracil hos patienter med avanceret gastric eller gastroesophageal adenokarcinom [22].
- En national canceropgørelse fra USA fra årene 2010-2016 viser, at 5 års overlevelsen for metastaseret esophaguscancer er 5% [23].

Grundet manglende studier i den relevante patientpopulation, er prognosen for den relevante population med nuværende dansk standardbehandling derfor bedst afspejlet i komparatorarmen fra KN-590.

4.2 Biologisk rationale for behandlingseffekt af pembrolizumab hos patienter med spiserørskræft

Pembrolizumab er et humaniseret monoklonalt antistof, der binder til overfladeproteinet programmed cell death-1 (PD-1) på immunsystemets T-celler og forhindrer binding til overfladeproteinerne programmed cell death-ligand 1 (PD-L1) og 2 (PD-L2). Binding mellem PD-1 og PD-L1 eller PD-L2, hæmmer T-cellernes respons mod kræftsygdommen. Pembrolizumab forhindrer den hæmmende PD-1-binding til PD-L1 og PD-L2. PD-L1 og PD-L2 kan være udtrykt på både tumorceller og andre celler i tumorens mikromiljø. Flere af kroppens normale væv udtrykker også PD-L1, som interagerer med PD-1 på immunceller [13]

Nedenfor er kort gennemgang af studier, som viser effekt af pembrolizumab i esophagus, GEJ og ventrikelcancer og som danner baggrund og rationale for KN-590 studiet:

- KN-028 var et fase 1, non-randomiseret, multicohorte pembrolizumab (10 mg/kg) for PD-L1 positive avanceret solide tumorer, inkl. esophagus planocellulær og adenokarcinomer samt GEJ adenokarcinomer. Alle var PD-L1 positive >1%. Studiet viste tumor svind hos 52% af patienter og en ORR på 30% (95% CI 13-53%) [24].
- KN-180 var et fase 2 open-label interventionel single arm studie med pembrolizumab monoterapi hos tidligere behandlede (>2L) med avanceret eller metastatisk esophagus adeno- eller planocellulærkarcinom eller GEJ adenokarcinom. ORR var 9.9% (95% CI 5-17%) hos alle inkluderede patienter, 13.8% (95% CI 6-25% hos PD-L1 positive og 6.3% (95% CI 2-16%) hos PD-L1 negative patienter [12]. Resultaterne blev opgjort efter PD-L1 CPS-scores for at identificere gruppen med størst respons. Her blev fundet, at PD-L1 CPS ≥10 (ca. 45% af patienterne fra ITT-populationen), var det optimale cut-point for både signifikant ORR og signifikant OS for ITT-populationen[12].
- KN-181 var et fase 3, randomiseret open label studie med pembrolizumab monoterapi vs. onkologens valg af enkeltstof behandling med docetazel, paclitaxel eller irinotecan hos avanceret/metastatisk esophagus planocellulær eller adenocarcinom eller Siewers type 1 adenokarcinom af GEJ efter 1L behandling. I planocellulær gruppe sås favorabel OS med mOS fro pembrolizumab 8.2 mdr. vs. 7.1 for SOC. Subanalyse viste mOS hos PD-L1 CPS >10 = 10.3 mdr. vs. 6.7 mdr. for SOC [2].

På baggrund af ovennævnte studier samt det fortsatte behov for at forbedre behandlingen af patienter med metastaserende spiserørskræft blev KN-590 designet for at undersøge pembrolizumab i kombination med kemoterapi, hvor studiet blev designet, så der blev inkluderet patienter med både planocellulære- og adenokarcinomer, samt PD-L1 CPS status var med i de statistiske overvejelser ved design af studiet.

Tabel 1 Incidence og prævalence de seneste 5 år

Year	2016	2017	2018	2019	2020
Spiserørskræft st. IV PD-L1 CPS ≥10 **	66	66	66	66	66
Prævalence i Danmark (alle stadier og uden biomarkørtype) **[19]**	1156	Uoplyst	Uoplyst	Uoplyst	Uoplyst

** For beregning af antal med spiserørskræft st. IV og PD-L1 CPS ≥10 se afsnit 5.1 'Forventet patientpopulation' side 18 for antagelser og tal.

Tabel 2: Forventede antal patienter i behandlingsgruppen de kommende år.

Year	2021	2022	2023	2024	2025
Forventet antal patienter i Denmark til indikationen:	33	66	66	66	66

** For beregning af forventet antal patienter i Danmark til indikationen, se afsnit 5.1 'Forventet patientpopulation' side 18. I år 2021 vil det kun være 2. halvdel af året hvor behandlingen vil være tilgængelig, derfor halvt så mange patienter som fra 2022 og frem.

4.2.1 Patientpopulation relevant for denne ansøgning

Den danske patientgruppe, som forventes at være kandidater til behandlingen, vil være voksne med lokal avanceret eller metastatisk cancer i spiserøret, som tilbydes palliativ systemisk behandling i 1. linje og som har PD-L1 CPS ≥ 10.

4.3 Nuværende standardbehandling og valg af komparator

4.3.1 Nuværende standardbehandling i Danmark for lokal avanceret eller metastatisk spiserørskræft

I Danmark behandles spiserørskræft på fire afdelinger; Rigshospitalet, Odense Universitetshospital, Aalborg Universitetshospital og Aarhus Universitetshospital. Alle afdelinger har multidisciplinære teams, som samarbejder om udredning og behandling.

Danske Multidisciplinære Cancer Grupper (DMCG) har beskrevet de kliniske retningslinjer for den onkologiske behandling af non-kurabel cancer i esophagus, GEJ og ventrikel [4]. Retningslinjerne beskriver i al væsentlighed ens behandlingsstrategier og muligheder for både planocellulært- og adenokarcinom. Studierne som ligger til grund for retningslinjerne, baserer sig overvejende på undersøgelser af patienter med adenokarcinomer og datagrundlaget for behandling af planocellulær spiserørskræft er sparsomt [4].

Retningslinjerne beskriver at ikke-resektabel eller metastatisk sygdom bør tilbydes kombinationsbehandling, enten med to-stof (fluoropyrimidin og platin) eller tre-stof (fluoropyrimidin, platin og taxan), afhængig af behandlingsmål, bivirkningsprofil samt patientønske. Desuden bør patienter, hvis tumor er HER2 positiv, desuden tilbydes behandling med trastuzumab.

Fagudvalget for kræft i mavesæk og mavemund beskriver generel konsensus om palliativ kemoterapi til tidligere behandlingsnaive patienter, eller patienter med recidiverende uhelbredelig kræft i spiserøret, som består af en kombination af et platinholdigt kemoterapeutikum, som kan være enten cis-, oxali- eller carboplatin, samt en

antimetabolit som 5-fluoropyrimidin (5FU), capecitabine eller S1 [6], men der er ikke konsensus om det bedste behandlingsregime, hvorfor den behandlende onkologiske afdeling kan vælge kombination ud fra ovenstående valg jf. patientpræferencer og risiko for bivirkninger. Dertil kan eventuelt tillægges et taxan hvis patienten tåler dette[4].

Muligheden for afdelings/onkolog præference mellem kombinationerne stammer bla. fra REAL-2 studiet fra 2008 med 1002 patienter med ikke-tidligere behandlet avanceret esophagastisk cancer. Her blev det evalueret i et 2*2 design om capecitabine (oral fluoropyrimidine) og oxaliplatin (platin) er alternativer til flourouracil og cisplatin og konklusionen var, at behandlingerne var ens for effektdata for både flourouracil vs. capecitabine og for oxaliplatin vs. cisplatin. Der var ligeledes ens bivirkningsprofil af capecitabine og fluorouracil mens der for oxaliplatin vs. cisplatin var forskelle i bivirkninger med en lavere incidens af grad 3-4 neutropeni, alopeci, nyrepåvirkning og thromboemboli ved oxiliplatin, men højere incidens af grad 3-4 diarre og neuropati [8]. Da bivirkningsprofilerne er forskellige af type, men ens i sværhedsgrad og de er ligestillet i danske kliniske retningslinjer, er det i de kliniske retningslinjer specificeret, at der skal tages højde for patientpræference i forhold til valg af behandling i samråd med behandlende onkolog[4].

4.3.2 Valg af komparator

MSD mener, vi har valgt en klinisk relevant og hensigtsmæssig komparator med cisplatin og 5-flourouracil og denne kombination kan bruges som proxy for de øvrige mulige kombinationer jf. de danske kliniske retningslinjer.

De danske kliniske retningslinjer og fagudvalget for kræft i mavesæk og mavemund beskriver konsensus om kombinationsbehandling til spiserørskræft med et platinholdigt kemoterapeutikum, som kan være enten cis-, oxali- eller carboplatin, samt en antimetabolit som 5-fluoropyrimidin (5FU), capecitabine eller S1, som ligeværdige behandlingsmuligheder [4, 6], da effekten er vist ens [8]. De enkelte platiner anbefalet i retningslinjerne har forskellige typer af bivirkninger, men ikke i sværhedsgrad, og de er derfor alle rekommanderede som ligestillede behandlingsmuligheder.

Valget af cisplatin og 5-flourouracil danner desuden grundlag for en stærk statistisk sammenligningsgrundlag, som ikke er muligt ved de øvrige kombinationer i den relevante patientpopulation.

4.3.3 Beskrivelse af komparator

Cisplatin er et velkendt og velafprøvet kemoterapeutika, som er brugt i cancerbehandling siden 1960'erne og 1970'erne [25].

- Cisplatin 'Ebewe' ATC-code: L01XA1 [26]
- 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 1mg/ml
- Method of administration: Intravenøs administration
- Dosing 80 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 KN-590
- 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

Fluorouracil er et velkendt og ofte anvendt kemoterapeutika, som er brugt i cancerbehandling siden 1950'erne og 1960'erne[25]

- Fluorouracil 'Pfizer' ATC-code: L01BC02 [27]
- Mode of action: 5-Fluorouracil er en pyrimidianalog substans, der virker som en antimetabolit til uracil. Det aktive 5-flour-deoxyuridinmonophosphat virker ved at hæmme enzymet thymidylat syntetase. Hermed nedsættes dannelse af thymidin som dermed påvirker DNA-syntesen, 5-fluorouracil kan også påvirke RNA. 5-fluorouracil interfererer via førnævnte mekanismer mod celledeling og vækst.
- Pharmaceutical form: Injektionsvæske, opløsning
- Posology: Fluorouracil 50 mg/ml
- Method of administration: Intravenøs administration
- Dosing: 800 mg/m2 intravenøst på dag 1-5 hver 3 uge
- Should the pharmaceutical be administered with other medicines? 5-fluorouracal skal opblandes i enten natriumchlorid-infusionsvæske eller isotonisk natriumchlorid-glucose-infusionsvæske før infusion og kan gives både som monoterapi og i kombination med andre lægemidler
- Treatment duration/criteria for end of treatment: 5-flourouracil blev administreret i op til 35 serier i KN-590
- Necessary monitoring, both during administration and during the treatment period: Det anbefales at følge lokale guidelines for monitorering af 5-fluorouracil idet det er et velkendt og ofte anvendt lægemiddel
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale guidelines
- Packaging: 1 hætteglas med 10, 50 eller 100 ml injektionsvæske, 50 mg/ml

4.4 Interventionen

Pembrolizumab har været anvendt i behandlingen af cancer som monoterapi siden 2015 og i kombination med cisplatin og 5-fu siden 2019 til patienter med hoved- og halskræft [7].

- Dosing: Pembrolizumab 200 mg hver 3. uge i op til 35 serier, Cisplatin 80 mg/m2 intravenøst hver 3. uge i op til 6 serier og 5-fluorouracil 800 mg/m2 intravenøst på dag 1-5 hver 3. uge i op til 35 serier
- Method of administration Pembrolizumab indgives intravenøst, det samme gælder for cisplatin og 5-fluorouracil
- Treatment duration/criteria for treatment discontinuation I KN-590 kunne der administreres op til 35 serier for Pembrolizumab og 5-fluorouracil mens der kunne gives cisplatin i op til 6 serier
- 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 anbefaling i Medicinrådet vil Pembrolizumab i kombination med cisplatin og 5-fluorouracil vil blive en ny behandlingsmulighed i 1. linje for patienter med spiserørskræft og PD-L1 CPS ≥10 og vil blive indplaceret i de danske behandlingsguidelines. Eftersom cisplatin og 5-fluorouracil allerede er beskrevet som 1. linjebehandling vil ændringen være en tilføjelse af pembrolizumab til dette behandlingsregime.

5. Litteratursøgning

5.1 Identifikation og udvælgelse af relevante studier

Da der i KN-590 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 søgningen ikke forventes at tilvejebringe yderligere relevant dokumentation for effekt og sikkerhed for både intervention og komparator, som også drøftet med Medicinrådets sekretariat ved indledende dialogmøde af 25. marts 2021.

Det relevante og endnu ikke selvstændigt publicerede studie til denne ansøgning er: Kato, K et al. Pembrolizumab Plus Chemotherapy Versus Chemotherapy as First-Line Therapy in Patients With Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study. NCT-nummer: NCT03189719. Studiestart den 25. Juli 2017 og studie slutdato 2. juli 2020. For fuld liste af studiekarakteristika, se appendix B.

Data brugt til denne ansøgning er data on file (Clinical Study Report)[11], det foreløbige udkast til EPAR [10] samt data fra orale præsentationer med tilhørende abstracts fra de onkologiske konferencer ESMO 2020 og ESMO-GI 2021 [28, 29].

6. Effekt og sikkerhed

Studiedesignet i KN-590 er foretaget med inklusion af patienter med lokal avanceret eller metastatisk spiserørskræft uanset PD-L1 status, mens denne ansøgning gælder for populationen med spiserørskræft og PD-L1 CPS ≥ 10, jf. EMAs godkendelse, præsenteres nedenfor data for ITT populationen, hvor dette er klinisk relevant, samt for PD-L1 CPS ≥ 10 populationen, hvor dette er tilgængeligt samt klinisk relevant.

For baselinekarakteristika rapporteres for ITT population, men i udkast til EPAR er baselinekarakteristika beskrevet at være tilsvarende ITT-populationen for de stratificerede grupper (fx Asian vs. non-Asian). Bivirkninger samt livskvalitet rapporteres hovedsageligt fra ITT-populationen, der er dog foretaget analyser for PD-L1 populationen som understøtter data fra ITT, hvorfor disse rapporteres når muligt.

I ansøgningen præsenteres der data fra følgende populationer:

- Baselinekarakteristika for ITT-populationen.
- OS for PD-L1 CPS ≥ 10 populationen.
- PFS for PD-L1 CPS ≥ 10 populationen.
- Bivirkninger for hele *as-treated*-populationen samt for PD-L1 CPS ≥ 10 hvor muligt.
- Livskvalitet for ITT-populationen samt for PD-L1 CPS ≥ 10 hvor muligt.

Effekt og sikkerhed af pembrolizumab plus platin- og fluoropyrimidinebaseret kemoterapi sammenlignet med placebo +platin- og fluoropyrimidinebaseret kemoterapi til patienter med spiserørskræft med PD-L1 CPS ≥ 10 gennemgås nedenfor.

De komparative analyser er en direkte statistisk komparativ analyse af pembrolizumab +kemoterapi sammenlignet med kemoterapi, svarende til dansk klinisk praksis, som er baseret på data fra final-analyse fra KEYNOTE-590.

For sikkerhedsdata/bivirkninger er disse foretaget for *as*-treated populationen (minimum 1 dosis medicin i studiet) for alle patienter fra studiet og samt for patienter med PD-L1 CPS ≥ 10 hvor muligt. Da det ikke vurderes, at der er korrelation mellem PD-L1 status og bivirkningsprofil ved brug af pembrolizumab (i kombination med kemoterapi) [30], kan der ved gennemgang af bivirkninger med fordel bruges alle patienter i as-treated populationen for at få data på størst mulig population. Det samme gør sig gældende for analyserne for livskvalitet.

- Den interne og eksterne validitet af studiet vurderes høj. Den interne validitet styrkes af studiets design som er baseret på beregninger af studiestørrelse, er dobbeltblindet og randomiseret. Desuden er studieprotokollen nøje fastlagt, så de inkluderede patienter alle modtager samme behandling i deres respektive behandlingsarme. Den eksterne validitet er styrket af studiets design med fastsatte inklusions- og eksklusionskriterier, hvor inklusionskriterierne er bredere end i andre tilsvarende studier (inkluderet både planocellulære og adenokarcinomer), forskellig etnicitet (stratificeret for Asian vs. non-Asian) samt uafhængig af biomarkører (PD-L1 status) og en intervention som er mulig for den brede patientgruppe med spiserørskræft.

6.1 Patientpopulation: Voksne med spiserørskræft og PD-L1 CPS ≥10

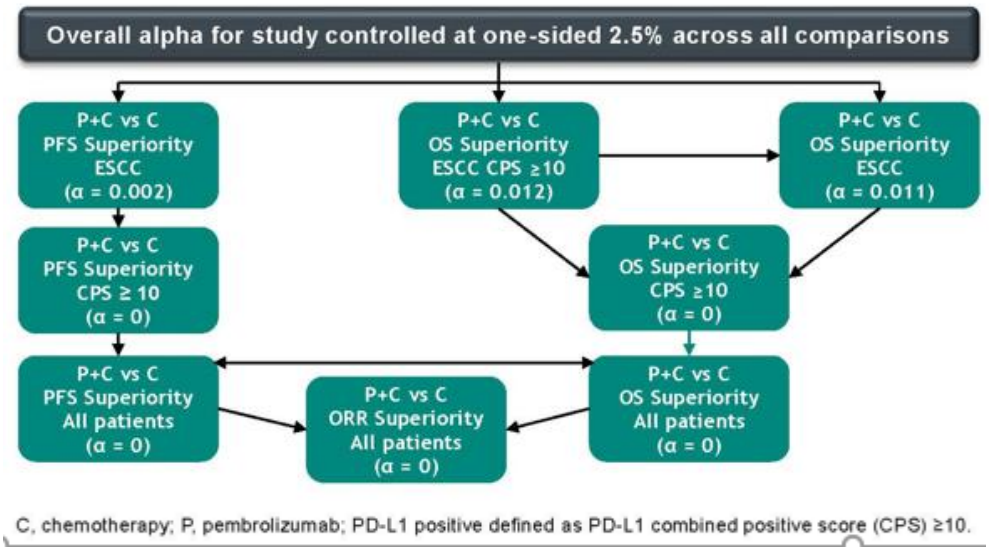
6.1.1 Relevant studie KEYNOTE-590

6.1.2 Studiedesign

KEYNOTE-590 er et randomiseret, dobbelt-blindet studie med to arme, som har undersøgt effect og sikkerhed af pembrolizumab i kombination med kemoterapi (cisplatin + 5-fluorouracil) versus placebo og kemoterapi (cisplatin + 5-fluorouracil), svarende til dansk klinisk praksis, hos patienter med ikke tidligere behandlet lokalavanceret eller metastatisk spiserørskræft.

Dosis:
Pembrolizumab: 200 mg iv hver 3. uge i op til 35 serier.
Cisplatin: 80 mg/m^2 iv hver 3. uge i op til 6 serier.
5-fluorouracil: 800 mg/m^2 iv på dag 1-5 hver 3. uge i op til 35 serier.

Der blev stratificeret for Asia vs. ikke-Asia region, planocellulær vs. adenokarcinom samt ECOG Performance Status 0 vs. 1. Den statistiske plan havde en overordnede alfa for studiet, som var kontrolleret ved one-sided 2.5% for alle sammenligninger. De 3 primære hypoteser blev testet først og parallelt, og de følgende hypoteser blev kun testet i fald de foregående hypoteser var positive. Det var tilladt at allokere alfa videre fra succesfuld hypotese til næste i rækken (figur 1).



Figur 1: Statistikplan for test af hypoteser i KN-590

Inklusionskriterier var histologisk eller cytologisk verificeret lokal avanceret, ikke-resektabel eller metastatisk planocellulær eller adenokarcinom i esophagus eller adenokarcinom i GEJ (Siewert type 1), alle med tilgængelig vævsprøve til PD-L1 til immunohistokemisk analyse. Patienterne skulle være behandlingsnaive, ECOG performance status 0 eller 1 samt have målbar sygdom jf. RECIST v1.1.

Eksklusionskriterier var tidligere behandling for deres cancersygdom, resektabel sygdom, aktive CNS metastaser eller karcinogen meningitis samt aktiv autoimmunsygdom (for fuld liste af in- og eksklusionskriterier se appendiks B.

Studiet var designet med to primære endepunkter (dual primary-endpoints) hvoraf studiehypotesen var opfyldt hvis pembrolizumab + kemoterapi var superior til placebo + kemoterapi for ét af de primære endepunkter. De primære endepunkter i studiet var Overall Survival, OS for de 4 grupper:

- Planocellulære karcinomer med PD-L1 CPS ≥10
- Planocellulære karcinomer
- PD-L1 CPS ≥10
- ITT-populationen

Samt Progressions Free Survival, PFS for de 3 grupper:

- Planocellulære karcinomer
- PD-D1 CPS ≥10
- ITT-population

Sekundære endepunkter var Overall Response Rate, ORR (pr. RECIST v1.1) og Duration of Response, DOR hos ITT-populationen, samt antal bivirkninger stop af behandling grundet bivirkninger hos as-treated populationen og Qality of Life (for fuld liste af sekundære endepunkter se appendix B).

Der var planlagt én interimanalyse efter minimum 13 måneders follow-up (35 mdr. efter randomisering) med planlagt final PFS-analyse.

Endelig analyse (final OS-analyse) var med data cut-off dato d. 2. juli 2020, og er disse data som præsenteres i denne ansøgning

For fuld studieplan se appendix B.

6.1.3 Baselinekarakteristika for inkluderede patienter

Patientpopulationen for KN-590 er generelt ensartet fordelt på tværs af de to behandlingsgrupper med hensyn til baseline-karakteristika for alle inkluderede patienter i studiet. Der ses en højere prævalens af ≥65 år i pembrolizumab +kemoterapigruppen vs. placebo + kemoterapigruppen, som ikke vurderes at være en fordel for interventionsgruppen. Histologisk subtype, etnicitet, PD-L1 status og ECOG score er ensartet fordelt mellem grupperne. Desuden er baselinekarakteristika ensartet fordelt mellem alle stratificeringsgrupper[10].

Table 3: Demografi og baselinekarakteristik ITT populationen fordelt i behandlingsarme fra KN-590.

Karakteristika, n (%)	Pembrolizumab + kemoterapi N = 373	kemoterapi N = 376
Alder, median (range), år	64.0 (28-94)	62.0 (27-89)
≥65 år	172 (46.1)	150 (39.9)
Mænd	306 (82.0)	319 (84.8)
Asia Region†	196 (52.5)	197 (52.4)
Race		
Asian	201 (53.9)	199 (52.9)
White	139 (37.3)	139 (37.0)

Missing	14 (3.8)	15 (4.0)
American Indian	9 (2.4)	12 (3.2)
African American	5 (1.3)	2 (0.5)
Other	5 (1.3)	6 (1.6)
ECOG Performance Status		
0	149 (39.9)	150 (39.9)
1	223 (59.8)	225 (59.8)
2	1 (0.3)	1 (0.3)
Primary Diagnosis		
Planocellulær	274 (73.5)	274 (72.9)
Adenokarcinom	99 (26.5)	102 (27.1)
EAC	58 (15.5)	52 (13.8)
Siewert type 1 GEJ adenocarcinoma	41 (11.0)	50 (13.3)
Disease Status		
Metastatic	344 (92.2)	339 (90.2)
Unresectable-locally advanced	29 (7.8)	37 (9.8)
PD-L1 Status		
CPS ≥10	186 (49.9)	197 (52.4)
ESCC	143 (38.3)	143 (38.0)
Adenocarcinoma	43 (11.5)	54 (14.3)
CPS <10	175 (46.9)	172 (45.7)
ESCC	121 (32.4)	126 (33.5)
Adenocarcinoma	54 (14.4)	46 (12.2)
Not evaluable/missing	12 (3.2)	7 (1.9)

*Data er for intention-to-treat populationen. Other includes patients with multiple ethnicities. †Countries in Asia region include China, Hong Kong, Japan, Korea, and Taiwan. Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction.

Baselinedata for subpopulationen med PD-L1 CPS ≥10 er ikke tilgængelig. For baselinekarakteristika på EU vs. Ex-EU populationen i ITT populationen se desuden appendix C.

6.1.4 Resultater pr. studie

Da KN-590 foretager en direkte sammenligning af pembrolizumab +kemoterapi vs. placebo +kemoterapi, samt at behandlingen i komparatorarmen er svarende til dansk klinisk praksis, er der i denne ansøgning ikke inkluderet yderligere studier jf. afsnit 6.1 litteratursøgning. Resultater fra KN-590 studiet er præsenteret i appendix D og E for ITT-populationen, PD-L1 CPS ≥10 samt as-treated populationen hvor relevant.

For at beskrive den kliniske merværdi der er ved pembrolizumab +kemoterapi, sammenlignet med nuværende dansk standardbehandling, gennemgås i det følgende resultater fra KN-590 studiet på Overall Survival OS, Bivirkninger, Livskvalitet samt Progressionsfri Overlevelse, PFS. Dette svarer også til de, af fagudvalget for kræft i mavesæk og mavemund, kritiske og vigtige effektmål for spiserørskræft [6].

Data fra ITT-populationen danner baggrund for EMA's vurdering og godkendelse af pembrolizumab +kemoterapi til 1L behandling af patienter med lokalt avanceret inoperabelt eller metastatisk karcinom i esophagus eller HER-2 negativ adenokarcinom i den gastro-esophageale overgang hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10.

6.1.5 Overall Survival, OS

Nedenfor gennemgås KN-590 OS-data for de inkluderede patienter med PD-L1 CPS ≥10 fra ITT-populationen.

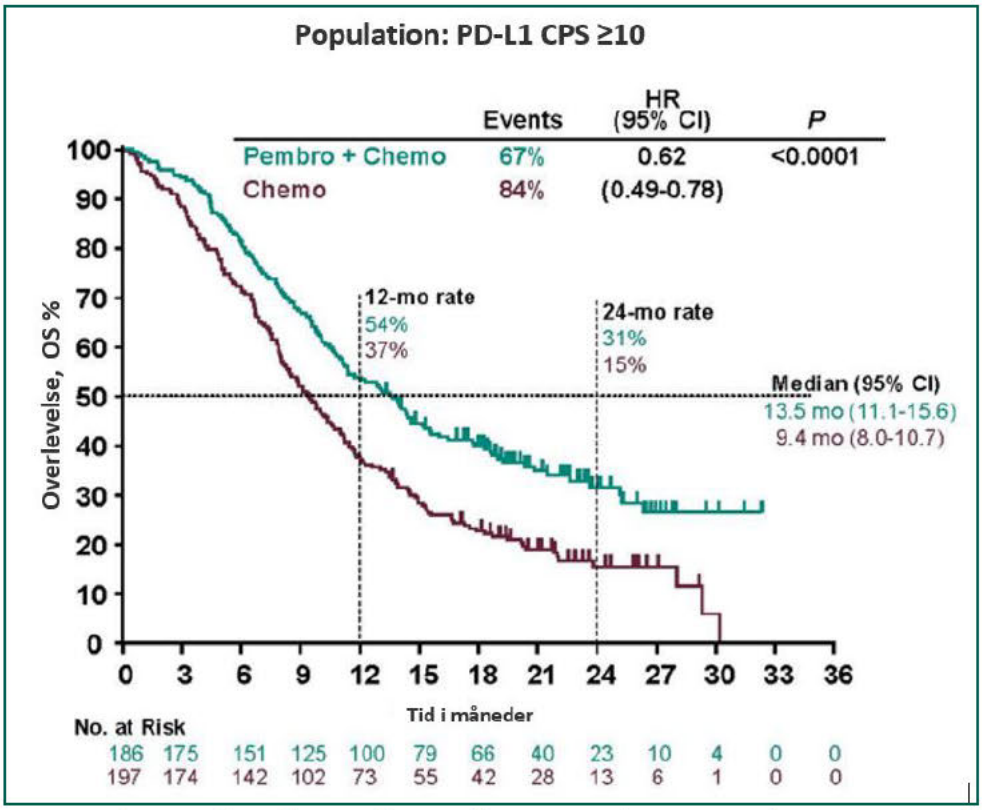
6.1.6 Overall Survival, OS, for PD-L1 CPS ≥10

OS-analysen blev foretaget for ITT-populationen med en median opfølgningstid på 22.6 mdr. (range 19.6-27.1) og i alt 373 patienter blev randomiseret til pembrolizumab +kemoterapi-gruppen og 376 patienter blev randomiseret til placebo +kemoterapigruppen for alle inkluderede patienter, svarende til 186 patienter med PD-L1 CPS ≥ 10 for pembrolizumab +kemoterapi og 197 patienter med PD-L1 CPS ≥ 10 for placebo +kemoterapi

På Kaplan-Meier kurven for OS for patienter med PD-L1 CPS ≥10 (figur 2), ses der efter 2-3 måneders behandling en adskillelse af kurverne, med færre events i pembrolizumab +kemoterapi-gruppen end i placebo +kemoterapi-gruppen. Denne adskillelse øges over tid og kan indtil videre følges indtil 24 mdr. efter behandlingsstart. Der er en median OS på 13.5 mdr. (11.1-15.6 mdr.) i pembrolizumab +kemoterapi-gruppen vs. 9.4 mdr. (8.0-10.7) i placebo +kemoterapi-gruppen, og en HR 0.62 (0.49-0.78 mdr.) med en p<0.0001.

I DEGCs årsrapport fra 2019 ses andelen af patienter i live 1 år efter første systemiske behandling (onkologisk palliativt forløb) på landsplan i Danmark at være 34.5% (uselekteret patientmateriale) [5] hvilket korrelerer fint med komparatorarmen i KN-590 på 37% (figur 2).

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



Figur 2: Kaplan-Meier kurve for Overall Survival for PD-L1 CPS ≥ 10 i ITT-populationen. Data cut-off 2. juli 2020 og median opfølgningstid var 22.6 mdr. (range 19.6-27.1)

Table 4: Median OS i KEYNOTE-590 for patienter med PD-L1 CPS ≥ 10 i ITT-populationen [10, 28].

	Median OS (95% CI)	Forskel i median OS	HR for OS (95% CI)
Pembrolizumab +kemoterapi (n=186)	13.5 mdr. (95% CI 11.1-15.6)	**4.1 mdr.**	**0.62 (95% CI 0.49-0.78)** P<0.0001
Placebo +kemoterapi (n=197)	9.4 mdr. (95% CI 8.0-10.7)		

Table 5 Overlevelsesrater i KEYNOTE-590 for patienter med PD-L1 CPS ≥ 10 i ITT-populationen[10] [11]

	Forskel i OS-rate ved 12 mdr.	Forskel i OS-rate ved 24 mdr.
Pembrolizumab +kemoterapi (n=186) vs. Placebo +kemoterapi (n=197)	16.7% ARR 53.8% (95% CI 46.3-60.6) vs. 37.1% (95% CI 30.3-43.8))	[redacted] ARR [redacted] vs. [redacted]

Andelen af patienter i live i interventionsarmen for patienter med PD-L1 CPS ≥ 10 efter 12 og 24 måneder (16.7% vs. [redacted]) er markant højere end set i tidligere studier for behandling af spiserørskræft, hvor der tidligere er rapporteret en forventet median OS mellem 8.6-11.3 mdr. for 5-FU og cisplatin-regimer i ventrikelcancer[9].

I EPAR gennemgås OS for subgruppen EU-populationen separat (*n=114*) hvor det konkluderes, at det gælder for EU-populationen som for hele ITT-populationen, at det er PD-L1 ekspressionen, som driver effekten, og ikke etnicitet, region eller histologi[10]. For hele EU-populationen findes der en mOS på 11.4 mdr. (95% CI 8.0-17.2 vs 11.0 mdr. (95% CI 8.0-13.3) i interventions vs. kontrolgruppen, med en HR 0.72 (95% CI 0.47-1.10) samt en OS rate ved 12 mdr. 49.2% (95% CI 36.2-60.9) vs. 47.2% (95% CI 33.4-59.8). For EU-populationen med PD-L1 CPS ≥10, ses en signifikant forskel i mOS mellem intervention (11.4 mdr.) og kontrolgruppe (8.6 mdr.) (HR 0.60 CI N/A), ligesom der ses en forskel i OS-rate ved 12 mdr. på 14% som stiger til 21% efter 24 mdr. til fordel for pembrolizumab +kemoterapigruppen, hvorfor det i EPAR konkluderes, at det er PD-L1 ekspressionen som driver effekten , også i denne subgruppe (EU-populationen)[10].

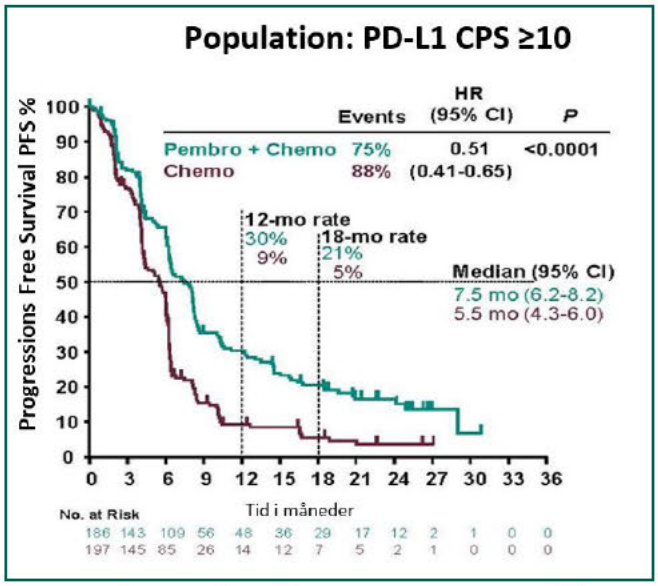
På baggrund af OS-analysen for patienter med PD-L1 CPS ≥10 kan det konkluderes:

- Der ses en klinisk relevant og signifikant forskel i mediane OS på 4.1 mdr. med en HR 0.62 (95% CI 0.49-0.78) til fordel for pembrolizumab +kemoterapi i ITT populationen.
- Der ses en klinisk relevant, signifikant og vedvarende forskel i OS-raten ved 12 og 24 mdr. på henholdsvis 16.7% og [redacted] til fordel for pembrolizumab +kemoterapi, svarende til at dobbelt så mange er i live i pembrolizumab +kemoterapigruppen efter 24 mdr. i forhold til placebo +kemoterapigruppen for ITT populationen, og for EU-populationen er disse henholdsvis 14% og 21%.

MSD mener den signifikante forskel i mOS med HR 0.62 (0.49-0.78) samt fordoblingen i overlevelsesraten efter 24 mdr. indikerer stor klinisk merværdi for patienter med spiserørskræft og PD-L1 CPS ≥10.

6.1.7 Progression Free Survival – PFS for inkluderede patienter med PD-L1 CPS ≥10

PFS er defineret som tiden fra behandlingsstart til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 eller dødsfald. PFS blev foretaget for ITT-populationen med en median opfølgningstid på 22.6 mdr. (range 19.6-27.1 mdr.) og i alt 373 patienter blev randomiseret til pembrolizumab +kemoterapigruppen og 376 patienter blev randomiseret til placebo +kemoterapigruppen for alle inkluderede patienter, svarende til 186 patienter med PD-L1 CPS ≥ 10 for pembrolizumab +kemoterapi og 197 patienter med PD-L1 CPS ≥ 10 for placebo +kemoterapi.



Figur 3: Kaplan-Meier kurve for Progression Free Survival for PD-L1 CPS ≥ 10 i ITT-populationen. Data cut-off 2. juli 2020 og median opfølgningstid var 22.6 mdr. (range 19.6-27.1 mdr.) [10, 28]

Tabel 6: Median PFS i KEYNOTE-590 for patienter med PD-L1 CPS ≥ 10 i ITT-populationen [10, 28].

	Median PFS (95% CI)	Forskel i median PFS	HR for PFS (95% CI)
Pembrolizumab +kemoterapi (n=186)	7.5 mdr. (95% CI 6.2-8.2)	**2 mdr.**	**0.51 (95% CI 0.41-0.65)** P<0.0001
Placebo +kemoterapi (n=197)	5.5 mdr. (95% CI 4.3-6.0)		

Tabel 7: Progressions Free Survival-rater i KEYNOTE-590 for patienter med PD-L1 CPS ≥ 10 i ITT-populationen] [11].

	Forskel i PFS-rate ved 12 mdr.	Forskel i PFS-rate ved 18 mdr.
Pembrolizumab +kemoterapi (n=186) vs. Placebo +kemoterapi (n=197)	[redacted]% ARR [redacted] vs. [redacted]	[redacted]% ARR [redacted] vs. [redacted]

På Kaplan-Meier kurven for PFS for patienter med PD-L1 CPS ≥10 (figur 3), ses der færre events i pembrolizumab +kemoterapigruppen i forhold til placebo +kemoterapigruppen de første 3-4 mdr. Herefter ses en adskillelse af kurverne, som øges over tid, med signifikant færre events i pembrolizumab +kemoterapigruppen end i placebo +kemoterapigruppen. Der ses en median PFS på 7.5 mdr. (CI 6.2-8.2 mdr.) for pembrolizumab +kemoterapigruppen vs. 5.5 mdr. (CI 4.3-6.0 mdr.) og en HR 0.51 (0.41-0.65). Desuden ses efter 12 mdr. en signifikant og klinisk betydende forskel i PFS på [redacted] og som efter 18 mdr. fastholdes på [redacted] også til fordel for behandlingen med pembrolizumab +kemoterapigruppen.

EMA har gennemgået PFS for EU sub-populationen og finder, at der observeres en fordel i PFS for alle EU-patienterne (HR 0.55 95% CI NA), som øges ved PD-L1 CPS ≥10 (PFS HR 0.48 95% CI NA) [10].

På baggrund af PFS-analysen for patienter med PD-L1 CPS ≥10 kan det konkluderes:

- Der ses en klinisk relevant forskel i PFS-raten efter 12 mdr. med 3 gange flere patienter uden progression i pembrolizumab +kemoterapigruppen vs. placebo +kemoterapigruppen og denne forskel øges til 4 gange flere patienter uden progression ved 18 mdr. sammenlignet med kontrolgruppen.
- Behandlingseffekten af pembrolizumab i kombination med kemoterapi, viser en signifikant bedre PFS end behandling med kemoterapi efterfulgt af 2L anti-PD-1/PD-L1 behandling jf. KN-181 studiet [2].

Den absolutte forskel med >3 gange så mange PFS ved 12 mdr. og >4 gange flere PFS ved 18 mdr. i pembrolizumab +kemoterapigruppen indikerer en til stor klinisk merværdi for patienterne med spiserørskræft og PD-L1 CPS ≥10.

6.1.8 Bivirkninger grad 3-4

I KN-590 rapporteres bivirkninger hos patienter, som har modtaget minimum én dosis studiemedicin (as-treated population). Dette svarer til 370 patienter i pembrolizumab +kemoterapi-gruppen og 370 patienter i placebo +kemoterapi-gruppen. Den mediane opfølgningstid var 22.6 mdr. (range 19.6-27.1) ved rapportering af bivirkninger, mens den gennemsnitlige behandlingslængde for grupperne er forskellig med længere behandling for pembrolizumab +kemoterapi med 7.7 mdr. (range 0.03-26.02 og i gennemsnit 11.0 cycles) vs. 5.8 mdr. (range 0.10-26.58 og i gennemsnit 8.5 cycles) for placebo +kemoterapigruppen.

All-cause bivirkninger beskrives for hele as-treated populationen, da separate data på populationen med PD-L1 CPS ≥10 er sparsomme, dog gennemgås de data, som er til rådighed nedenfor. Der vurderes ikke at være betydende forskelle i bivirkninger i forhold til PD-L1 status [30], hvorfor bivirkningsdata for ITT-populationen dermed også redegør for subpopulationen med PD-L1 CPS ≥10.

Bivirkningsprofilen af capecitabine og fluorouracil er ens, mens der for oxaliplatin vs. cisplatin er forskelle i bivirkninger med en lavere incidens af grad 3-4 neutropeni, alopeci, nyrepåvirkning og thromboemboli ved oxiliplatin, men højere incidens af grad 3-4 diarre og neuropati [8]. Da bivirkningsprofilerne er forskellige af type, men ens i sværhedsgrad og de er ligestillet i de danske kliniske retningslinjer, er det i de kliniske retningslinjer specificeret, at der skal tages højde for patientpræference i forhold til valg af behandling i samråd med behandlende onkolog [4].

I denne ansøgning rapporteres bivirkninger fra kombinationsbehandling med cisplatin, da det som tidligere beskrevet er den korrekte komparator til denne ansøgning, dog vil der grundet forskelligheden i bivirkningsprofilerne mellem cisplatin og oxiliplatin være risiko for at der både overrapporteres og underrapporteres bivirkninger tilknyttet cisplatin i forhold til de øvrige platiner.

Table 8: All-cause grad 3-4 bivirkninger i KN-590 i 'as-treated-population' [10]

	Gennemsnitlig behandlings-længde	All-cause grad 3-4 bivirkninger	Forskel i all-cause grad 3-4 bivirkninger (95% CI)	RR (95% CI)
Pembrolizumab +kemoterapi (n=370)	7.7 måneder (SD 6.48)	85.9%	**-2.7% absolute risk reduction (95%CI (-7.9) – (2.4))**	**1.03 (95% CI 0.97-1.1)**
Kemoterapi (n=370)	5.8 måneder (SD 4.76)	83.2%		

Af patienter som har fået ≥grad 3 bivirkning, er der rapporteret 318/370 (85.9%) i pembrolizumab +kemoterapigruppen og 308/370 (83.2%) patienter i placebo +kemoterapigruppen. Dette svarer til en absolut risiko reduktion på -2.7% (95% CI (-7.9) – (2.4). Den relative risiko er 1.03 (95% CI 0.97-1.1) som viser en identisk risiko for ≥grad 3 bivirkninger hos de to behandlingsgrupper. Den ens relative risiko skal ses i forhold til den gennemsnitlige behandlingsvarighed i pembrolizumab-gruppen var 7.7 måneder (range 0.03-26.02) mod 5.8 måneder (range 0.10-26.58) i placebo +kemoterapigruppen[10], så trods en længere behandlingsvarighed (1.9 mdr.) samt tillæg af aktiv intervention (pembrolizumab) i pembrolizumab +kemoterapigruppen, ses der fortsat uændret antal ≥grad 3 bivirkninger.

6.1.9 Bivirkninger grad 3-4 – kvalitativ gennemgang

I tabel 10 ses de hyppigste (≥5%) all-cause grad 3-5 bivirkninger rapporteret i de to behandlingsgrupper, hvor de hyppigste bivirkninger er nedsat antal neutrofile leukocytter (24.1% vs. 17.3%) samt anæmi (17.0% vs. 21.9%) og neutropeni (14.6% vs. 16.5%), i henholdsvis pembrolizumab +kemoterapi vs. placebo +kemoterapigruppen. Bivirkninger som alle oftest er forbundet med kemoterapi[10] og derfor optræder i begge behandlingsgrupper.

Table 9 All-cause grad 3-5 bivirkninger i KN-590 med hyppighed (≥5%) [10]

	Pembrolizumab +kemoterapi		Placebo +kemoterapi	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	318	(85.9)	308	(83.2)
with no adverse events	52	(14.1)	62	(16.8)
Neutrophil count decreased	89	(24.1)	64	(17.3)
Anaemia	63	(17.0)	81	(21.9)
Neutropenia	54	(14.6)	61	(16.5)
Hyponatraemia	45	(12.2)	41	(11.1)
Pneumonia	35	(9.5)	35	(9.5)
White blood cell count decreased	34	(9.2)	18	(4.9)
Dysphagia	29	(7.8)	26	(7.0)
Fatigue	29	(7.8)	25	(6.8)
Nausea	27	(7.3)	26	(7.0)
Vomiting	27	(7.3)	20	(5.4)

Hypokalaemia	24	(6.5)	32	(8.6)
Stomatitis	21	(5.7)	14	(3.8)
Decreased appetite	15	(4.1)	20	(5.4)
Weight decreased	11	(3.0)	19	(5.1)
Platelet count decreased	7	(1.9)	20	(5.4)

Generelt ses der overensstemmelse mellem andelen i de to behandlingsgrupper for all-cause grad 3-5 bivirkninger, trods forskellene mellem pembrolizumabs immunaktiverende virkningsmekanisme og kemoterapis cytotoxiske/cytostatiske virkningsmekanisme. Dog ses der en højere andel med nedsat antal hvide blodlegemer (9.2% vs. 4.9%) samt stomatit (5.7% vs. 3.8%) for henholdsvis pembrolizumab +kemoterapi vs. placebo +kemoterapigruppen.

Table 10: All cause bivirkninger PD-L1 CPS ≥10 populationen [11]

AEs (Grades 3+)	Pembrolizumab + 5-FU + cisplatin	5-FU + cisplatin
Safety population	185	193
Anemia	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

Key: 5-FU, fluorouracil; AE, adverse event; CPS, combined positive score; PD-L1, programmed death-ligand 1.

Source: KEYNOTE-590 (data cut-off date: July 2, 2020).

Der er også beskrevet bivirkninger for PD-L1 CPS ≥10 populationen (tabel 10) hvor det ses, at der ikke er betydende forskelle mellem PD-L1 CPS ≥10 og as-treated population, hvorfor as-treated-populationen er vigtig som reference for sikkerhed, grundet det store patientgrundlag.

6.1.10 Bivirkninger alle grader – kvalitativ gennemgang

Bivirkninger rapporteres i KN-590 for as-treated population, dvs. deltagere som har modtaget minimum én behandling i studiet. Den gennemsnitlige behandlingslængde for pembrolizumab +kemoterapigruppen var 7.7 mdr. vs. 5.8 mdr. i placebo +kemoterapigruppen. Der var en overordnet incidens af bivirkninger alle grader på 100% i pembrolizumab +kemoterapigruppen og 99.5% i kemoterapigruppen. De hyppigste i pembrolizumab +kemoterapigruppen var kvalme, anæmi, nedsat appetit og fatigue, hvoraf kvalme og anæmi også var hyppige i placebo +kemoterapigruppen.

De bivirkninger, hvor der var ≥5% points forskel behandlingsgrupperne imellem, var anæmi, nedsat appetit, fatigue, nedsat antal neutrofile og nedsat antal hvide blodceller. Ved sammenligning med reference-data for alle studier af pembrolizumab + kemoterapibehandlede patienter (n=1437), ses der i KN-590 en højere andel af kvalme, nedsat appetit, opkast samt forstoppelse i begge behandlingsarme i forhold til referencedata konsistent med den anatomiske lokation af canceren[10].

Nedenfor ses tabel 11 med gennemgang af alle bivirkninger ≥10% i enten pembrolizumab +kemoterapi eller placebo +kemoterapigruppen i KN-590.

Tabel 11: Bivirkninger alle grader ≥10% i KN-590 for as-treated populationen[10]

	KN-590 Pembrolizumab +kemoterapi		KN-590 Placebo +kemoterapi		Pembrolizumab +kemoterapi Rerefencesæt
	n	(%)	n	(%)	n (%)
Subjects in population	370		370		1437
with one or more adverse events	370	(100.0)	368	(99.5)	
with no adverse events	0	(0.0)	2	(0.5)	
Nausea	249	(67.3)	232	(62.7)	789 (54.9)
Anaemia	187	(50.5)	208	(56.2)	735 (51.1)
Decreased appetite	164	(44.3)	141	(38.1)	483 (33.6)
Fatigue	149	(40.3)	126	(34.1)	562 (39.1)
Constipation	148	(40.0)	149	(40.3)	527 (36.7)
Neutrophil count decreased	139	(37.6)	111	(30.0)	-
Diarrhoea	135	(36.5)	123	(33.2)	476 (33.1)
Vomiting	126	(34.1)	117	(31.6)	405 (28.2)
Stomatitis	100	(27.0)	95	(25.7)	-
Neutropenia	97	(26.2)	90	(24.3)	420 (29.2)
White blood cell count decreased	97	(26.2)	69	(18.6)	-
Weight decreased	87	(23.5)	90	(24.3)	-
Blood creatinine increased	79	(21.4)	78	(21.1)	220 (15.3)
Hyponatraemia	68	(18.4)	77	(20.8)	151 (10.5)
Hypokalaemia	67	(18.1)	71	(19.2)	187 (13.0)
Platelet count decreased	62	(16.8)	62	(16.8)	-
Asthenia	60	(16.2)	45	(12.2)	260 (18.1)
Dysphagia	60	(16.2)	63	(17.0)	-
Cough	59	(15.9)	56	(15.1)	300 (20.9)
Mucosal inflammation	59	(15.9)	68	(18.4)	-
Hiccups	56	(15.1)	53	(14.3)	-
Alopecia	55	(14.9)	39	(10.5)	248 (17.3)
Pyrexia	55	(14.9)	44	(11.9)	245 (17.0)
Pneumonia	54	(14.6)	52	(14.1)	193 (13.4)

Insomnia	49	(13.2)	44	(11.9)	158 (11.0)
Malaise	48	(13.0)	43	(11.6)	-
Rash	44	(11.9)	26	(7.0)	299 (20.8)
Hypothyroidism	40	(10.8)	24	(6.5)	165 (11.5)
Dysgeusia	38	(10.3)	32	(8.6)	131 (9.1)
Neuropathy peripheral	37	(10.0)	37	(10.0)	154 (10.7)
Hypoalbuminaemia	35	(9.5)	49	(13.2)	
Thrombocytopenia	28	(7.6)	37	(10.0)	279 (19.4)
Every subject is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.					

Incidensen af alvorlige bivirkninger (SAE) var ens i de to behandlingsarmen med 55.4% i pembrolizumab +kemoterapigruppen vs. 55.1% i placebo +kemoterapi-gruppen[10]. Den hyppigst rapporterede af de mest alvorlige bivirkninger var pneumoni (henholdsvis [redacted] [11], men ingen større forskel mellem behandlingsgrupperne blev observeret. Udover pneumoni var hyppighed af alle SAE'er <5%. Den største forskel blev observeret for pneumonitis med [redacted]% vs [redacted]% for pembrolizumab +kemoterapigruppen vs. placebo +kemoterapigruppen.

Dødsfald i forbindelse med bivirkninger blev rapporteret i henholdsvis pembrolizumab +kemoterapigruppen vs. placebo +kemoterapigruppen hos 28 vs. 38 patienter 7.6% vs 10.3% [10].

Bivirkningsprofilen mellem intervention og kontrolgruppe er overordnet ens og svarer også til poolede data fra reference datasæt for kombinationsbehandling med pebrolizumab og kemoterapi (tabel 11) .

Incidensen af bivirkninger, som fører til behandlingsophør er for alle bivirkninger 24.3% vs. 20% samt for alvorlige bivirkninger 15.7% vs. 12.7% Da der er længere behandlingsvarighed (exposure) i pembrolizumab +kemoterapi (7.7 mdr.) vs. placebo +kemoterapi (5.8 mdr.) vurderes interventionen med tillæg af pembrolizumab ikke at øge incidensen af hverken alle eller alvorlige bivirkninger.

Immunrelaterede bivirkninger var hyppigst forekommende i pembrolizumab +kemoterapigruppen med hypothyrodisme som hyppigste (10.3%), hvoraf alle tilfælde var grad 1 eller 2 og kun 1 patient modtog kortikosteroid behandling herfor ved data cut-off. Desuden var der 6.2% som fik pneumonitis i pembrolizumab +kemoterapigruppen, hvoraf 5.9% blev vurderet relateret til behandlingen og 0.8% var grad 1, 3% var grad 2 og 1.9% var grad 3 og 0.5% grad 5. Størstedelen af patienterne blev behandlet med kortikosteroider og 21.7% var ikke færdigbehandlet ved data cut-off [10].

EMA vurderer, at der ikke er nye safety issues fra de rapporterede laboratorieprøver på blodprøver taget under KN-590 [10]. Desuden findes ingen relevante forskelle i bivirkningsprofiler baseret på region (EU vs. Ex-EU). Langt størstedelen af toksicitet kunne tilskrives kemoterapien samt sygdommen, og incidensen af bivirkninger blev ikke øget væsentligt ved tillæg af pembrolizumab[10].

De danske onkologiske afdelinger har behandlet patienter med pembrolizumab siden 2015 og langt de fleste af de immunrelaterede bivirkninger er håndterbare i klinikken, når patienterne, som anbefalet, følges tæt med samtaler og blodprøvekontroller for at detektere bivirkninger i opløbet[31].

På baggrund af gennemgang af bivirkningens profilerne i KN-590 kan det konkluderes at:

- Bivirkningerne var håndterbare og konsistente med de allerede kendte bivirkninger af henholdsvis pembrolizumab, 5-flourouracil og cisplatin.
- Tillæg af pembrolizumab til kemoterapi ikke øger incidensen af alvorlige bivirkninger (SAE), som ikke kan håndteres i klinikken.
- Tillæg af pembrolizumab til kemoterapi øgede ikke incidensen af kemoterapi-inducerede toksicitet (f.eks.. hæmatologiske bivirkninger).
- Bivirkningsprofil for cisplatin og oxiliplatin er forskellig i type men ikke i grader og er ligestillet i de danske kliniske retningslinjer. Vigtigt med god dialog mellem onkolog og patient for præferencer.

MSD mener, at der ved at tillægges pembrolizumab til den nuværende standardbehandling, uden at øge alvorlige bivirkninger eller død indikerer en klinisk relevant merværdi for patienter med spiserørskræft og PD-L1 CPS ≥10.

6.1.11 Livskvalitet EORTC QLQ

Resultaterne for livskvalitet i KN-590 er målt i ITT-populationen og er fremlagt ved oral præsentation på ESMO-GI kongres 2021 og fra MSD Clinical Study Report[11, 29]. Der foreligger endnu ikke en publikation.

Data er opgjort, som den gennemsnitlige ændring fra baseline (*før første behandling*) til uge 18 og derefter hver 9. uge indtil 1 år eller død i KN-590 i EORTC QLQ-C30 Global Health Status/Quality of Life-scoren for de to behandlingsgrupper. Da opfølgningen mellem behandlingsgrupperne fortsætter længere end til det præ-specificerede målepunkt ved uge 18, er ligeledes indsat ændringen fra baseline til uge 60, som er længste opfølgningstid dokumenteret. Data er angivet som leastsquares (LS) means, hvilket er forskel i gruppens middelværdi efter justering for kovariater.

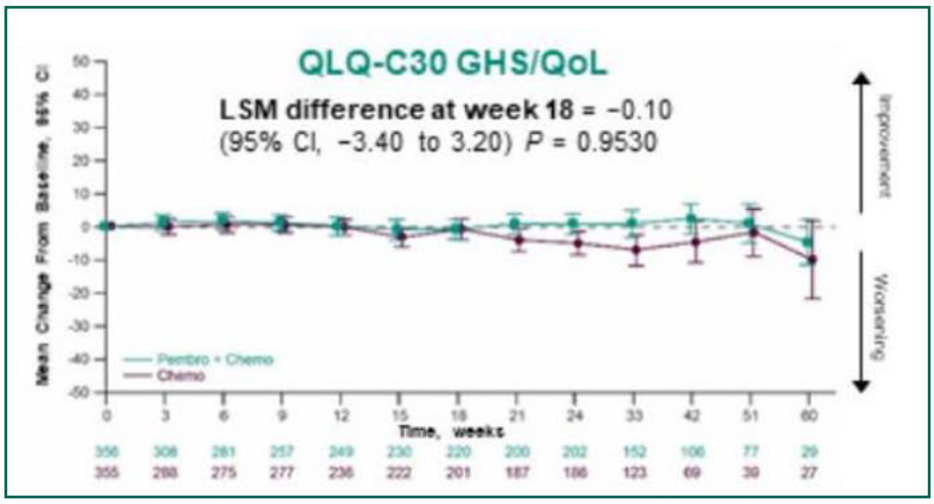
Compliance var ≥ 90% ved baseline og uge 18 for forventede svar.

Table 12: EORTC-C30, Least Square Means ved baseline for ITT-populationen og efter 18 og 60 uger[11] [29]

	EORTC-QLQ-C30, LS mean fra baseline til uge 18	Forskel i EORTC-QLQ-C30 LS mean, uge 18
Pembrolizumab +kemoterapi (baseline n=356)	[redacted]	**-0.10 point (95% CI -3.40 til 3.20) p=0.9530**
Placebo +kemoterapi (baseline n=355)	[redacted]	
	EORTC-QLQ-C30, LS mean fra baseline til uge 60 (aflæst figur 4)	**Forskel i EORTC-QLQ-C30 LS mean, uge 60**

Pembrolizumab +kemoterapi (baseline n=356)	-5.0 (95% CI NA)	**5 point (95% CI N/A) p=N/A**
Placebo +kemoterapi (baseline n=353)	-10 (95% CI NA)	

Ved uge 18 i KN-590 ligger EORTC-QLQ-C30 LS mean omkring samme niveau som ved baseline [redacted] og forskellen ved uge 18 er -0.10 (95% CI -3.40 til 3-20) p=0.9530 [11] [29]. Kurverne for de to behandlingsarme følges indtil uge 18. Herefter kommer der en mindre separation kurverne imellem og ved uge 60 er der en forskel på 5 point, med -5 LSM fra baseline for pembrolizumab +kemoterapigruppen og -10 LSM for placebo +kemoterapigruppen (des højere minus tal, des mere forværring) hvorfor forskellen ved 60 uger på 5 point er til fordel for pembrolizumab +kemoterapigruppen (aflæst figur 4).

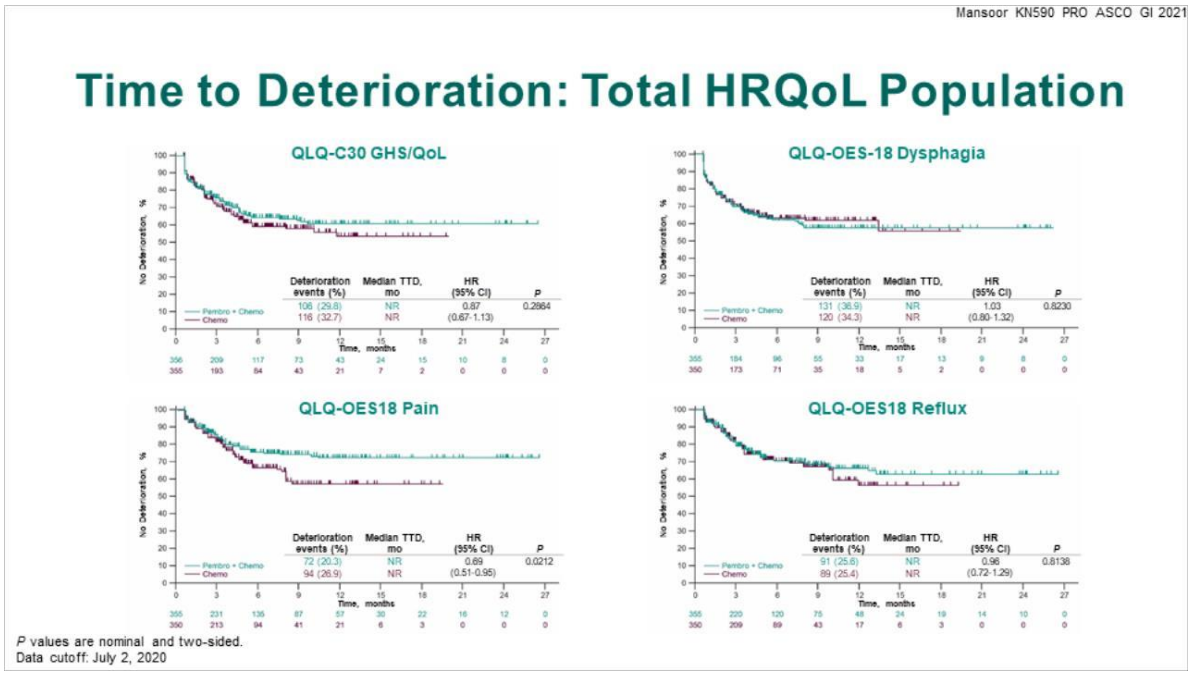


Figur 4: Mean Change fra baseline til og med uge 60 for EORTC QLQ-C30 Global Health Status/QoL over time for ITT-population[29].

I besvarelsen af QLQ-C30 blev fordelingen af patienter, som blev kategoriseret til 'improved," "stable," eller "deteriorated" fundet ens behandlingsgrupperne imellem. Deltagere som var 'improved' og forblev 'stable' var [redacted] pembrolizumab +kemoterapigruppen og [redacted] i placebo +kemoterapigruppen [11].

Ved præsentation på ESMO-GI 2021 blev også rapporteret EORTC-QLQ-C30 for subgruppen med PD-L1 CPS ≥ 10 og her ses samme resultat efter 18 uger med en LSM forskel på -1.77 (95% CI -6.7 til 3.17) p=0.4810 og en forskel kurverne imellem efter 60 uger aflæst på ca. 5-7 point[29].

Ud over EORTC QLQ-C30 er der også rapporteret tid til forværring 'Time to deterioration' i ITT-populationen (figur 5). Her ses kurverne for dysphagi at følges fra baseline til uge 18 med en HR 1.03 (95% CI 0.80-1-32). For QLQ-OES18 for smerte ses ved uge 18 signifikant færre smerter i pembrolizumab +kemoterapigruppen vs. kemoterapigruppen med en HR 0.69 (95% CI 0.51-0.95) p=0.0212. QLQ-OES18 for reflux viser ligeledes færre gener fra reflux hos pembrolizumab +kemoterapigruppen vs. kemoterapigruppen med en HR 1.03 (95% CI 0.80-1.32).

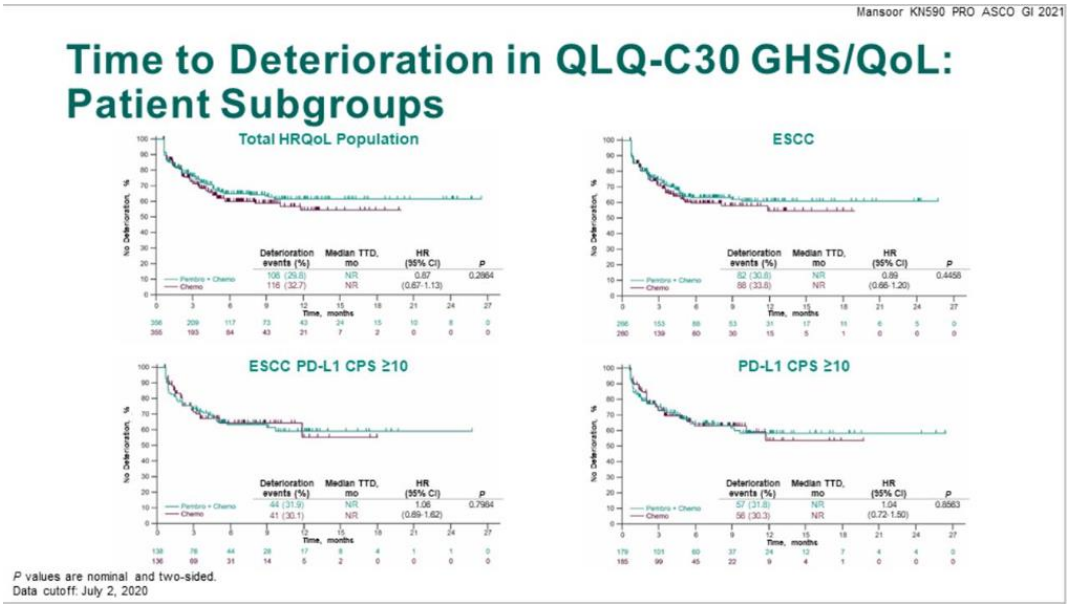


Figur 5: Time to Deterioration i ITT-populationen [29]

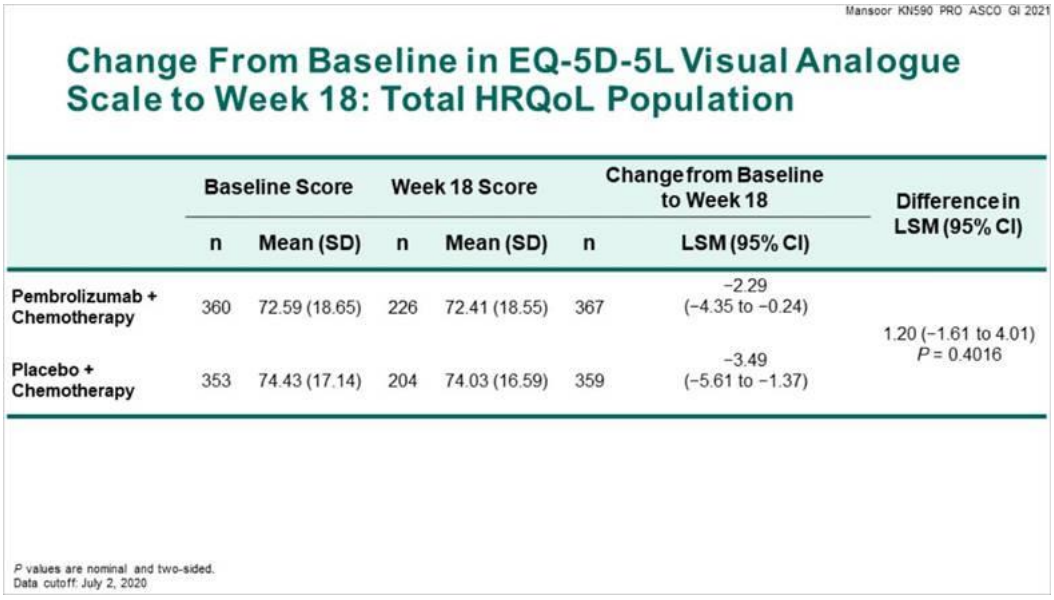
Både EORTC-QLQ-C30 (ITT og PD-L1 CPS ≥ 10-populationerne) samt 'Time to deterioration' (ITT-populationen) viser at tilføjelsen af pembrolizumab til kemoterapi-regimet ikke forværrer livskvaliteten hos disse patienter, og at der observeres færre smerter i ITT-populationen i interventionsgruppen end i kontrolgruppen (figur 5).

Ændringen fra baseline til uge 18 for EQ-5D-5L visual analog skala (evaluerer 5 helbredsdimensioner: mobilitet, self-care, vanlig aktivitet, smerte/ubehag, angst/depression) som viser en forskel målt som least-square means hos interventionsgruppen på -2.29 (95% CI -4.35 til -0.24) og i kontrolgruppen på -3.49 (95% CI 5.61 til 1.37) Dette svarer til en forskel de to grupper imellem på least square means 1.20 til interventionsgruppens fordel (95% CI -1.61 til 4.01) P=0.4016 [29].

På figurer fra ASCO-GI præsentationen ses der ved 'Time to deterioration' for både den totale HRQoL population (figur 5) samt for QLQ-C30 GHS/QoL patient subgrupper (ESCC, ESCC PD-L1 CPS ≥10, PD-L1 CPS ≥10) (figur 5a) en konsistent bedre performance for interventionsgruppen end for kontrolgruppen (ikke signifikant) trods interventionsgruppen behandles med standardbehandling + immunterapi.



Figur 5a: QLQ-C30 GHS/QoL patient subgrupper: ESCC, ESCC PD-L1 CPS ≥10, PD-L1 CPS ≥10 [29]



	Baseline Score		Week 18 Score		Change from Baseline to Week 18		Difference in LSM (95% CI)
	n	Mean (SD)	n	Mean (SD)	n	LSM (95% CI)	
Pembrolizumab + Chemotherapy	360	72.59 (18.65)	226	72.41 (18.55)	367	−2.29 (−4.35 to −0.24)	1.20 (−1.61 to 4.01) *P* = 0.4016
Placebo + Chemotherapy	353	74.43 (17.14)	204	74.03 (16.59)	359	−3.49 (−5.61 to −1.37)	

Figur 5b:Change from baseline in EQ-5D-5L visual analogue scale to week 18, ITT population [29]

Et valideringsstudie fra 1998 rapporterede ændringer i livskvalitet under kemoterapi-behandling hos 246 patienter med brystcancer og 80 patienter med småcellet lungekræft [32] og fastsatte her tærskelværdier for forskel i LSM på 5-10 som en mindre ændring i livskvalitet, 10-20 som moderat ændring og >20 som stor ændring. Det er dog uvist om disse tærskelværdier kan ekstrapoleres til andre kræftformer eller andre systemiske behandlinger, især da den kliniske betydning for de enkelte patientgrupper ikke er undersøgt nærmere, dog viser et studie indenfor kolorektal cancer, at den minimale vigtige forskel for de fleste skalaer i C30 ligger mellem 5-10 point i absolutte værdier for at have klinisk betydning for patienterne[33].

På baggrund af livskvalitets-analyserne EORTC-QLQ-C30 og Time to deterioration kan det konkluderes:

- Der ses ikke en forværring af livskvalitet ved tilføjelse af pembrolizumab til kemoterapi-behandlingsregimet.
- Efter ens forløb af kurver fra baseline til uge 18, ses der herefter for alle de rapporterede grupper en mindre forværring i pembrolizumab +kemoterapigruppen end for placebo +kemoterapigruppen, som kan være klinisk betydende for den enkelte patients livskvalitet.
- Der ses en signifikant forbedring i smerter for pembrolizumab +kemoterapigruppen.

MSD vurderer, at der for patienter med spiserørskræft er en stor klinisk merværdi, ved at tillægge pembrolizumab til den nuværende kombinations-kemobehandling med god effekt, uden at livskvaliteten forringes hos denne patientgruppe med stor sygdomsburde og ofte ringe prognose.

7. Health economic analysis

7.1 Model

The following is a description of our economic model, that was developed to demonstrate the cost effectiveness of pembrolizumab + 5-FU + cisplatin as a first-line treatment for locally advanced unresectable or metastatic esophageal cancer expressing PD-L1 (CPS ≥10) in Denmark.

7.1.1 Objective

The objective of the model is to evaluate the cost effectiveness of pembrolizumab + 5-FU + cisplatin versus 5-FU + cisplatin (trial comparator in KN-590) and relevant non-trial comparators in the first-line treatment of locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative EGJ adenocarcinoma in adults whose tumors express PD-L1 (CPS ≥10).

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 time spent for drug administration and monitoring are included.

7.1.2 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 + 5-FU + cisplatin versus each comparator are evaluated in terms of incremental cost per QALY gained and incremental cost per LY gained.

Outcome evaluated will be presented for the following:

- pembrolizumab + 5-FU + cisplatin,
- 5-FU + cisplatin and
- blended chemotherapy

Outcomes are evaluated for “blended chemotherapy” to account for the numerous possible combinations that the current Danish guideline includes and is only included in the model to explore the impact on cost as we assume equivalent efficacy between the non-trial chemotherapy comparators and the trial chemotherapy comparator; 5-FU + cisplatin.

7.1.3 Model structure

The model was developed in Microsoft Excel® using a three health state (progression-free, progressive disease and death) partitioned survival model (PSM) structure (see Figure 6) based on OS and PFS, which are key clinical outcomes assessed in KN-590. PSM is a common approach in modeling metastatic cancers [34].

The PSM directly applies OS and PFS to estimate proportions of patients in progression-free, progressive disease and death states over time. Specifically, based on OS and PFS curves, the proportion of patients in each of these three health states is calculated as PFS, OS–PFS, and 1–OS, respectively.

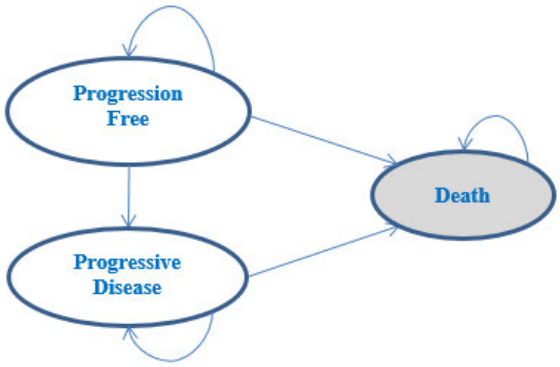


Figure 6: Model structure

Our model has the following cell keys:

Model input (user-modifiable)	
Model input (user-modifiable drop-down menu)	
Model input (fixed, do not change)	
Calculations (do not change)	

Please see the Excel file "MSD.SØmodel.13juni2021" for more details.

7.1.4 Time horizon and model cycle

The model base case has a time horizon of 30 years. As the mean age of all PD-L1+ patients in KN-590 is 61.9 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 (15 and 40 years) was explored via scenario analyses.

The model has a weekly cycle length which allows for precise calculation of drug acquisition and administration costs. For example, if a particular first-line treatment is administered on a schedule of once Q3W, the cost of that treatment is applied in the model at 3-week intervals starting from Week 1.

The model provides options to choose half-cycle correction. For the model base case, half-cycle correction is not applied.

7.1.5 Discount rate

In the base case analysis, both costs and effectiveness are discounted annually at 3.5%, consistent with The Danish Medicines Council methods guide for assessing new pharmaceuticals. Alternative annual discount rates (0%, 7.0%) were tested in sensitivity analyses.

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

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

Table 13: 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)	KN-590, Primary endpoint: To compare OS between treatment arms	The partitioned survival model (PSM) structure is based on OS and PFS. The PSM directly applies OS and PFS to estimate proportions of patients in progression-free, progressive disease and death states over time. Specifically, based on OS and PFS curves, the proportion of patients in each of these three health states is calculated as PFS, OS–PFS, and 1–OS, respectively.	OS and PFS curves were derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, log-normal and generalized gamma distributions) to individual patient data (IPD) from the KN-590 trial. The best fitting parametric curves for PFS and OS were used to extrapolate these efficacy outcomes beyond the trial period.
Progression-free survival (PFS)	KN- 590, Primary endpoint: To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms	Please see description above for OS	Please see description above for OS
Adverse reaction 1* (measured in costs)		One-off AE-related costs per first-line treatment arm were applied at the beginning of the model and were calculated based on the unit costs for managing each AE and the AE rate	The unit cost of AE management per incidence was obtained from DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
Adverse reaction 2* (measured as occurrence)	AE Grade 3+ incidence rates	AE Grade 3+ incidence rates after applying 5% cut-off	Data on file from KN 590

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**
Adverse reaction 3* (measured as utility loss)		AE-related disutility was applied as a one-time QALY decrement in the first model cycle (i.e. Week 0).	Disutility associated with AEs per patient was calculated in each treatment arm as a function of the rates of included AEs in the treatment arm, the mean duration of AEs and the estimated disutility associated with Grade 3+ AE
Utility by time to deaths: base case	KN- 590, Other secondary endpoints: To evaluate changes from baseline in HRQoL using the EORTC QLQ-C30 and EORTC QLQ-OES18 KN- 590, Exploratory endpoints: To characterize PRO utilities using EQ-5D-5L questionnaire	The utility inputs used in the base case and scenario analysis were based on linear mixed-effects models fitted with EQ-5D-5L data collected in the KN-590 trial. Danish tariff for EQ-5D-5L was applied to derive EQ-5D-5L utility values. For patients in both arms in KN-590, the EuroQol EQ-5D-5L data were collected at Day 1 of treatment cycles 1-9 (1 cycle=3 weeks). After cycle 9 (Week 24), the data were collected every three cycles (i.e., Week 33, 42, 51 and so on). The EQ-5D-5L data were collected for up to one year or end of treatment, whichever comes first. The EQ-5D-5L data were also collected at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit.	Since one patient could have multiple utility measures, linear mixed-effects models with patient-level random effects were used for this analysis to account for within-subject correlation. The linear mixed-effects models also included the presence or absence of any Grade 3+ AEs to estimate AE disutility. In the model, utilities were applied based on the distribution of patients across different categorizations of time to death in each weekly cycle. In a given weekly cycle, the proportion of patients within each time to death category was estimated based on the modeled OS within each treatment arm.

7.2.1.1 Patient population

The Danish patient population:
Locally advanced unresectable or metastatic carcinoma of the esophagus or EGJ adenocarcinoma carcinoma

Patient population in the clinical documentation submitted:
Locally advanced or metastatic esophageal or HER2-negative EGJ adenocarcinoma carcinoma (tumors with epicenter 1 to 5 centimeters above the GEJ) whose tumors express PD-L1+ (CPS ≥10).

Patient population in the health economic analysis submitted:
Locally advanced or metastatic esophageal or HER2-negative EGJ adenocarcinoma carcinoma (tumors with epicenter 1 to 5 centimeters above the GEJ) whose tumors express PD-L1+ (CPS ≥10).

Model target population
For this economic evaluation, the target population is adult patients (aged 18 years and older) for the first-line treatment of locally advanced or metastatic esophageal or HER2-negative EGJ adenocarcinoma carcinoma (tumors with epicenter 1 to 5 centimeters above the GEJ) whose tumors express PD-L1+ (CPS ≥10). This base case population is represented by the patients whose tumors express PD-L1+ (CPS ≥10) in the KN-590 trial.

The mean age, gender distribution, body weight and body surface area (BSA) of the base case population are based on PD-L1+ (CPS ≥10) patients in KN-590(see Table 14).

Table 14: Model cohort characteristics.

Characteristics	PD-L1+ (CPS ≥10)
Starting age (years), mean	61.9
Male (%)	81.7%
Weight (kg) – mean	62.56
Weight (kg) – standard deviation	14.25
Body surface area (m^2)	1.70
Body surface area (m^2) – standard deviation	0.22
Key: CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive. Source: KN-590 (data cut-off date: July 2, 2020) [11]	

Table 15: Patient population [5, 10, 11]

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, mean	62,4 years	61,9 years	71
Proportion of male	83,4	81,7%	65,6%
Weight (kg) - mean	63,08	62,56 kg	
Body surface area (m^2)	1,7	1,70 m^2	
CPS ≥10	51,1%		
Asia/EU	52,5%		

The data on patient characteristics in the clinical documentation is based on data on the ITT population from KN-590, while the model input is based on individual patient level data from PD-L1+ (CPS ≥10) population.

Data from Danish clinical practice is sparse. The data from Danish clinical practice on age and sex is based on all stages of newly diagnosed patients with esophageal cancer while the data used in the model is based on locally advanced unresectable or metastatic cancer.

A difference between the clinical documentation/model input and Danish clinical practice can be observed with regards to geographic region, with approximately half the patients in KN-590 being enrolled in the Asia region. KN-590 also demonstrated treatment effect in patients from the EU region, so the difference compared to Danish clinical practice is not expected to have clinical implications. This is also supported by conclusions in the EPAR highlighting that PD-L1 expression is the driver of treatment effect[10].

7.2.1.2 Intervention

Intervention as expected in Danish clinical practice:

Pembrolizumab + 5-FU + cisplatin is the intervention and is represented by the intervention arm in KN-590:

- Pembrolizumab: 200 mg IV on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 2 years)
- 5-FU: 800 mg/m2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4,000 mg/m2 per 3-week cycle) for up to 35 cycles
- Cisplatin: 80 mg/m2, IV on Day 1 of every 21-day cycle for up to six cycles

The Danish Medicines Council has in previous recommendation decisions on other pembrolizumab indications stated a preference for weight based(2 mg/kg) dosing for pembrolizumab.

Intervention in the clinical documentation submitted:

Pembrolizumab + 5-FU + cisplatin is the intervention and is represented by the intervention arm in KN-590:

- Pembrolizumab: 200 mg IV on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 2 years)
- 5-FU: 800 mg/m2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4,000 mg/m2 per 3-week cycle) for up to 35 cycles
- Cisplatin: 80 mg/m2, IV on Day 1 of every 21-day cycle for up to six cycles

Intervention as in the health economic analysis submitted:

Pembrolizumab + 5-FU + cisplatin is the intervention and is represented by the intervention arm in KN-590:

- Pembrolizumab: 200 mg IV on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 2 years)
- 5-FU: 800 mg/m2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4,000 mg/m2 per 3-week cycle) for up to 35 cycles
- Cisplatin: 80 mg/m2, IV on Day 1 of every 21-day cycle for up to six cycles

Intervention in the clinical documentation submitted and, in the health, economic analysis submitted are identical.

The model has the option for alternative pembrolizumab dose of 400 mg, IV on Day 1 of every 42-day (6-week) cycle for up to 18 administrations (up to approximately 2 years). In the model base case, all patients receive pembrolizumab at a flat dose of 200 mg.

Table 16: Intervention [10, 11]

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Pembrolizumab + 5-FU + cisplatin: - Pembrolizumab: 200 mg IV on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 2 years) - 5-FU: 800 mg/m2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4000 mg/m2 per 3-week cycle) for up to 35 cycles - Cisplatin: 80 mg/m2, IV on day 1 of every 21-day cycle for up to 6 cycles	Pembrolizumab + 5-FU + cisplatin: - Pembrolizumab: 200 mg IV on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 2 years) - 5-FU: 800 mg/m2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4000 mg/m2 per 3-week cycle) for up to 35 cycles - Cisplatin: 80 mg/m2, IV on day 1 of every 21-day cycle for up to 6 cycles Pembrolizumab: 25mg/ml 5-FU: 50 mg/ml Cisplatin 1 mg/ml	Pembrolizumab + 5-FU + cisplatin: - Pembrolizumab: 2 mg/kg IV on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 2 years) - 5-FU: 800 mg/m2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4000 mg/m2 per 3-week cycle) for up to 35 cycles - Cisplatin: 80 mg/m2, IV on day 1 of every 21-day cycle for up to 6 cycles Pembrolizumab: 25mg/ml 5-FU: 50 mg/ml Cisplatin 1 mg/ml
Length of treatment (time on treatment) (mean/median)	Pembrolizumab:7,7 months	Pembrolizumab: 8,5 months Cisplatin: 3,0 months 5-FU: 6,3 months	
Criteria for discontinuation	Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression or a maximum of 24 months. Duration of cisplatin treatment was capped at 6 doses	Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression or a maximum of 24 months. Duration of cisplatin treatment was capped at 6 doses	Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression or a maximum of 24 months. Duration of cisplatin treatment capped at 6 doses
The pharmaceutical's position in Danish clinical practice			Not used in clinical practice for the treatment of esophageal cancer 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 recommendation decisions on other pembrolizumab indications stated a preference for weight based(2 mg/kg) dosing for pembrolizumab.

The time on treatment data in the clinical documentation is based on the ITT population and the model input is based on the PD-L1+ CPS>10 population. The longer time on treatment in the PD-L1+ CPS>10 population reflect that pembrolizumab appears to be associated with PD-L1 expression.

7.2.1.3 Comparators

The current Danish clinical practice:

The guidelines from June 2020 describes 1L treatment of non-curable esophageal cancer as chemotherapy combination of platinum and fluoropyrimidine or a chemotherapy combination of platinum, fluoropyrimidine and taxane. The specific platinum or taxane to be used is not described [4].

Comparator in the clinical documentation submitted:

- 5-FU + cisplatin (KN-590 trial comparator)
  - 5-FU: 800 mg/m^2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4,000 mg/m^2 per 3-week cycle) for up to 35 cycles
  - Cisplatin: 80 mg/m^2, IV on Day 1 of every 21-day cycle for up to six cycles

Comparator(s) in the health economic analysis submitted:

Model comparators include:

- 5-FU + cisplatin (KN-590 trial comparator)
  - 5-FU: 800 mg/m^2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4,000 mg/m^2 per 3-week cycle) for up to 35 cycles
  - Cisplatin: 80 mg/m^2, IV on Day 1 of every 21-day cycle for up to six cycles
- Blended chemotherapy, which consists of treatment options listed as equivalent to 5-FU + cisplatin (KN-590 trial comparator) in Danish clinical guideline[4].
  - 5-FU + cisplatin
  - 5-FU + oxaliplatin + leucovorin
  - Capecitabine + cisplatin
  - Capecitabine + oxaliplatin
  - 5-FU + cisplatin + epirubicin
  - 5-FU + oxaliplatin + epirubicin
  - Capecitabine + cisplatin + epirubicin
  - Capecitabine + oxaliplatin + epirubicin

The comparators position in the Danish clinical practice

MSD believe that Cisplatin+5-FU is an adequate comparator in the model as it is in line with the current Danish clinical guidelines[4]. Based on the Danish guidelines it is plausible to assume equivalent efficacy between the non-trial chemotherapy comparators and the trial chemotherapy comparator 5-FU + cisplatin. The “blended chemo” model comparator is only included in the model to explore the impact on cost.

The guidelines from June 2020 on treatment of non-curable esophageal cancer describes 1L treatments as chemotherapy combination of platinum and fluoropyrimidine or a chemotherapy combination of platinum, fluoropyrimidine and taxane. This has also been confirmed recently in the Medicines Council protocol used for the evaluation of nivolumab for the treatment of 2L esophageal cancer[6]. In this protocol, it is also referenced that the 1 year survival rate with the present standard of care in Denmark is 34%. In the KN-590 trial, the 1 year survival rate 37%, so the control arm of 5-FU+cisplatin from the study, performs very much like what you what expect to see with present standard of care in Denmark.

There is very little evidence available regarding treatment of esophageal cancer and guideline formulation is to a large extent based on extrapolation from gastric cancer. The choice of treatment among the alternatives, 5-FU + cisplatin KN-590 trial comparator included, is based on each individual patients preference and adverse events considerations. The specific platinum or taxane to be used is not described in the Danish guidelines and the guideline states that there is not a consensus as to which of the combinations to use. There are not data available on the distribution of treatments between the alternatives in Denmark. Based on the lack of consensus it is difficult to present precise picture of which treatments are being used in clinical practice but the following is MSDs estimation based on the informal information we have been able to gather:

Table 17: Distribution of treatments in the blended chemotherapy arm

Blended chemo treatments	**MSD assumption on Danish clinical practice**
5-FU + cisplatin	34.0%
5-FU + oxaliplatin + leucovorin	0.0%
Capecitabine + cisplatin	0.0%
Capecitabine + oxaliplatin	33.0%
5-FU + cisplatin + epirubicin	0.0%
5-FU + oxaliplatin + epirubicin	0.0%
Capecitabine + cisplatin + epirubicin	0.0%
Capecitabine + oxaliplatin + epirubicin	33.0%
Key: 5-FU, fluorouracil; chemo, chemotherapy.	

The distribution in table 17 is used for the “Blended chemo” model comparator.

Result will be presented for the following:

- pembrolizumab + 5-FU + cisplatin,
- 5-FU + cisplatin and
- blended chemotherapy

Based on the Danish guidelines it is plausible to assume equivalent efficacy between the non-trial chemotherapy comparators and the trial chemotherapy comparator 5-FU + cisplatin[4, 8]. Therefore, the OS and PFS of the blended chemotherapy comparator are assumed to be the same as that of the trial comparator 5-FU + cisplatin in our model. The ToT of individual drugs in the blended chemotherapy comparator arm is assumed to be the same as either the 5-FU ToT or cisplatin ToT in the 5-FU + cisplatin arm and detailed assumptions are presented in Table 40.

Detailed dosing and market share of the regimens included in the blended chemotherapy are described in Section 7.5.

The model comparators have not previously been evaluated and recommended by the Danish Medicines Council but as they are:

- established standard Danish treatment practice over a longer period
- low cost comparator

we will refrain from health economic analysis to assess, if the model comparators reasonably can be assumed to be cost-effective. This has been discussed with the Danish Medicines Council Secretariat at a meeting in March 2021.

Table 18: Comparator [10, 11]

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration	**1)** Cisplatin+5-FU (100%) Cisplatin 80 mg/m2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m2 IV per day on Day 1 to Day 5 of each three-week cycle B) Blended chemo 1) Cisplatin+5-FU (34%) Cisplatin 80 mg/m2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m2 IV per day on Day 1 to Day 5 of each three-week cycle **2)** Oxaliplatin+Capecitabine (33%) Oxaliplatin 130mg/m2 Q3W IV on Day 1 of each three-week cycle and Capecitabine 1.000mg/m^2 bid, Q3W, Day 1-14 each three-week cycle **3)** Oxaliplatin+Capecitabine +epirubicin(33%) **Oxaliplatin** 130mg/m^2 Q3W IV on Day 1 of each three-week cycle, **Capecitabine** 625mg/m^2 bid, Q3W, Day 1-	1) Cisplatin+5-FU (34%) Cisplatin 80 mg/m2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m2 IV per day on Day 1 to Day 5 of each three-week cycle **2)** Oxaliplatin+Capecitabine (33%) Oxaliplatin 130mg/m2 Q3W IV on Day 1 of each three-week cycle and Capecitabine 1.000mg/m^2 bid, Q3W, Day 1-14 each three-week cycle. **3)** Oxaliplatin+Capecitabine +epirubicin(33%) **Oxaliplatin** 130mg/m^2 Q3W IV on Day 1 of each three-week cycle, **Capecitabine** 625mg/m^2 bid, Q3W, Day 1-21 each three-week cycle and **epirubicin** 50mg/m^2 Q3W IV on Day 1 of each three-week cycle

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
		21 each three-week cycle and **epirubicin** 50mg/m^2 Q3W IV on Day 1 of each three-week cycle	
Length of treatment	5.8 months	a) Cisplatin+5-FU: Cisplatin: 3,0 months 5-FU: 5,0 months B) Blended chemo The ToT of individual drugs in the blended chemotherapy comparator arm is assumed to be the same as either the 5-FU ToT or cisplatin ToT in the 5-FU + cisplatin arm	

The time on treatment data in the clinical documentation is based on the ITT population and the model input is based on the PD-L1+ CPS>10 population.

7.2.1.4 Efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation:

Table 19: Median OS, KN-590 PD-L1 CPS ≥ 10[10, 28].

	Median OS (95% CI)	Median OS/delta	HR for OS (95% CI)
Pembrolizumab+ 5FU+cisplatin (n=186)	13.5 months (95% CI 11.1-15.6)	**4.1 months**	**0.62 (95% CI 0.49-0.78)** P<0.0001
5FU+cisplatin (n=197)	9.4 months (95% CI 8.0-10.7)		

Table 20: Landmark survival rates, KN-590 PD-L1 CPS ≥ 10 [10][11]

	OS-rate delta at 12 months	OS-rate delta at 24 months
Pembrolizumab+ 5FU+cisplatin (n=186) vs. 5FU+cisplatin (n=197)	16.7% ARR 53.8% (95% CI 46.3-60.6) vs. 37.1% (95% CI 30.3-43.8))	[redacted] ARR [redacted] vs. [redacted]

Table 21: Median PFS, KN-590 PD-L1 CPS ≥ 10[10, 28].

	Median PFS (95% CI)	Median PFS/delta	HR for PFS (95% CI)
Pembrolizumab+ 5FU+cisplatin (n=186)	7.5 months (95% CI 6.2-8.2)	**2 months**	**0.51 (95% CI 0.41-0.65)** P<0.0001
5FU+cisplatin (n=197)	5.5 months (95% CI 4.3-6.0)		

Table 22: Landmark PFS rates, KN-590 PD-L1 CPS ≥ 10[10].

	PFS-rate delta at 12 months	PFS-rate delta at 24 months
Pembrolizumab+ 5FU+cisplatin (n=186) vs. 5FU+cisplatin (n=197)	[redacted]% ARR vs. [redacted]	[redacted]% ARR vs. [redacted]

Relevance of the documentation for Danish clinical practice:
OS and PFS has recently been described by the Medicines Council as relevant outcomes to evaluate clinical benefit in gastro-oesophageal cancer with emphasis on OS as this is a disease with short life expectancy. OS after first systemic palliative treatment is also an indicator that is monitored in the yearly report from Dansk EsophagGastrisk Cancer gruppe[5].

OS and PFS KN-590 survival analysis include median survival and survival rates at different time landmarks. Again, based on recent descriptions from the Medicines Council, these are relevant measurement methods. Median survival has been included in recent evaluation of clinical benefit, along with survival rates at different time landmarks. 12 months survival is also included and monitored in the from Dansk EsophagGastrisk Cancer gruppe[5, 6].

The relative efficacy outcomes in the submitted health economic analysis:
Overall survival and progression-free survival:
For each treatment arm, the PSM estimated the amount of time spent in the progression-free, progressive disease and death states based on the areas under the PFS and OS curves.

For the pembrolizumab + 5-FU + cisplatin and the 5-FU + cisplatin arms, OS and PFS curves were derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, log-normal and generalized gamma distributions) to individual patient data (IPD) from the KN-590 trial. The fitted parametric curves for PFS and OS were used to extrapolate these efficacy outcomes beyond the trial period. Both one-piece and piecewise (Kaplan–Meier + parametric survival curve) models were fitted to the data. Given the availability of IPD and the different mechanisms of action of pembrolizumab and chemotherapy, parametric survival models were fitted separately to each treatment

arm, as this approach required fewer assumptions than jointly fitted models(see section 8.3 and appendix G for more details)

Table 23 summarizes the base case choice of OS and PFS for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms for the PD-L1+ (CPS ≥10) population

	Treatment arm	Base case choice
Overall survival	Pembrolizumab + 5-FU + cisplatin	Piecewise log-normal, cut-off at Week 40
	5-FU + cisplatin	Piecewise log-normal, cut-off at Week 40
Progression-free survival	Pembrolizumab + 5-FU + cisplatin	Piecewise log-logistic, cut-off at Week 10
	5-FU + cisplatin	Piecewise log-logistic, cut-off at Week 10
Key: 5-FU, fluorouracil; CPS, combined positive score; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.		

[redacted]

[redacted]

[redacted]

Table 25: Summary of text regarding value

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study:		[redacted]
Overall survival (OS)	Please see table 19-22 above	
Progression-free survival (PFS)		

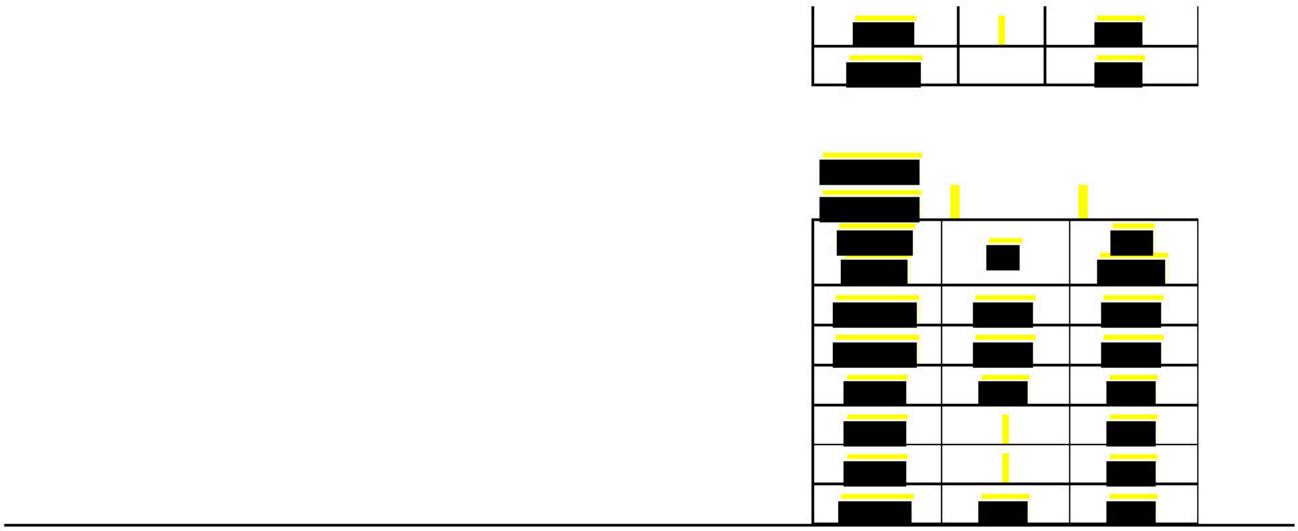


Table 26: Summary of text regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: Overall survival (OS) Progression-free survival (PFS)	OS and PFS KN-590 survival analysis include median survival and survival rates at different time landmarks	OS and PFS has recently been described by the Medicine Council as relevant outcomes to evaluate clinical benefit in gastro-oesophageal cancer with emphasis on OS as this is a disease with short life expectancy. OS after first systemic palliative treatment is also an indicator that is monitored in the yearly report from Dansk EsophagGastrisk Cancer gruppe	OS and PFS KN-590 survival analysis include median survival and survival rates at different time landmarks. Again, based on recent descriptions from the Medicine Council, these are relevant measurement methods. Median survival has been included in recent evaluation of clinical benefit, along with survival rates at different time landmarks. 12 months survival is also included and monitored in the from Dansk EsophagGastrisk Cancer gruppe

7.2.1.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted:

AE Grade 3+ incidence rates in ITT population and PD-L1+ (CPS≥10) population

Adverse reaction outcomes in the health economic analysis submitted:

AE risks associated with the pembrolizumab + 5-FU + cisplatin arm and the 5-FU + cisplatin arm were obtained from the KEYNOTE-590 trial. The inclusion of specific AE types in the model was based on a combination of frequency and severity of each event. The model considered both all-cause and treatment-related Grade 3–5 AEs that were reported

in ≥5% of patients in any treatment arm the PD-L1+ (CPS≥10) population (see AE rates in Table 27 and Table 28). The model base case applied all-cause AEs; treatment-related AEs were explored in scenario analysis.

Blended chemotherapy comparator AE rates are assumed to be the same as the 5-FU + cisplatin arm. The use of AE rates for the blended chemotherapy arm based on literature was explored in scenario analysis [35-37] (see Table 29). The unit costs and disutilities associated with AEs were applied in each treatment arm at the beginning of the first model cycle. Details on AE unit costs and disutilities are provided in Sections 7.5 and 7.4, respectively.

Table 27: All-cause AE Grade 3+ incidence rates reported in ≥5% patients in any treatment arm

	PD-L1+ (CPS ≥10)	
AEs (Grades 3+)	**Pembrolizumab + 5-FU + cisplatin**	**5-FU + cisplatin**
Safety population	**185**	**193**
Anemia	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

Key: 5-FU, fluorouracil; AE, adverse event; CPS, combined positive score; PD-L1, programmed death-ligand 1.

Source: KN-590 (data cut-off date: July 2, 2020).

Table 28: Treatment-related AE Grade 3+ incidence rates reported in ≥5% patients in any treatment arm

	PD-L1+ (CPS ≥10)	
AEs (Grades 3+)	**Pembrolizumab + 5-FU + cisplatin**	**5-FU + cisplatin**
Safety population	**185**	**193**
Anemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]

Nausea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

Key: 5-FU, fluorouracil; AE, adverse event; CPS, combined positive score; PD-L1, programmed death-ligand 1.

Source: KN-590 (data cut-off date: July 2, 2020).

Table 29: Literature-based adverse event rates for blended chemotherapy arm

AEs (Grades 3+)	Yoon 2016 [37]	Cleary 2019 [36]	Waddell 2013[35]
Anemia	0.0%	0.0%	5.6%
Dysphagia	4.8%	0.0%	0.0%
Fatigue	4.8%	15.0%	0.0%
Hypokalemia	0.0%	2.5%	6.0%
Nausea	4.8%	2.5%	0.0%
Neutropenia	19.1%	36.3%	27.8%
Neutrophil count decreased	4.8%	0.0%	0.0%
Platelet count decreased	0.0%	2.5%	4.1%
Vomiting	0.0%	0.0%	8.7%
Weight decreased	0.0%	1.3%	0.0%

Mean durations of the AEs were based on KN-590 and were used together with AE rates and AE disutility to estimate the QALY decrements of each modeled arm due to AEs. AE durations are assumed to be the same for all modeled arms but are differentiated by all-cause and treatment-related AEs (see table 30).

Table 30: Duration of Grade 3+ AEs in KN-590

	Mean duration (weeks)	SD	N
All cause AEs	8.24	15.8	2,246
Treatment related AEs	8.05	15.4	1364

Key: AE, adverse event; SD, standard deviation; N, number.

Source: KN-590 (data cut-off date: July 2, 2020).

Table 31: Adverse reaction outcomes

Adverse reaction outcome	Clinical documentation		Used in the model (numerical value)	
	Pembrolizumab + 5-FU + cisplatin	Cisplatin+5-FU/Blended chemo	Pembrolizumab + 5-FU + cisplatin	Cisplatin+5-FU/Blended chemo
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]

The clinical documentation includes AE rates for both the ITT population and the PD-L1+ (CPS≥10) population. The inclusion of specific AE types in the model was based on a combination of frequency and severity of each event. The model considered all-cause Grade 3–5 AEs that were reported in ≥5% as these were expected to have an impact on costs. The all-cause Grade 3–5 AEs rates used in the model was based on the PD-L1+ (CPS≥10) population to align with the use of IPD in the base case population of PD-L1+ (CPS≥10).

7.3 Extrapolation of relative efficacy

7.3.1 Time to event data-summarized:

For full method used and results, please see Appendix G.

Overall survival and progression-free survival

For each treatment arm, the PSM estimated the amount of time spent in the progression-free, progressive disease and death states based on the areas under the PFS and OS curves.

For the pembrolizumab + 5-FU + cisplatin and the 5-FU + cisplatin arms, OS and PFS curves were derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, log-normal and generalized gamma distributions) to individual patient data (IPD) from the KN-590 trial. The fitted parametric curves for PFS and OS were used to extrapolate these efficacy outcomes beyond the trial period. Both one-piece and piecewise (Kaplan–Meier + parametric survival curve) models were fitted to the data. Given the availability of IPD and the different mechanisms of action of pembrolizumab and chemotherapy, parametric survival models were fitted separately to each treatment arm, as this approach required fewer assumptions than jointly fitted models

For OS, within each cycle of the model the probability of death was constrained to be at least as high as the age and gender-matched general population mortality. Age and gender-specific general population mortality for Denmark were obtained from the World Health Organization[38].

A systematic literature review was conducted to identify randomized clinical trials in locally advanced or metastatic esophageal cancer. Only two trials evaluating the efficacy and safety of chemotherapy in this setting were identified as meeting the inclusion criteria. There were key differences in patient population and eligibility criteria between KN-590 and the two trials identified for chemotherapy[39, 40]. While KN-590 was carried out in multiple centers internationally, both trials identified for chemotherapy were conducted at the same single center in South Korea. Only ESCC patients were included in the two chemotherapy trials; but patients with ESCC, esophageal adenocarcinoma and EGJ adenocarcinoma were all permitted to enroll in KN-590. Due to the heterogeneity and small degree of overlap between the patient characteristics of KN-590 and the two external trials, a matching-adjusted indirect comparison was not deemed appropriate in the context of this study. Furthermore, Danish guideline and Cunningham et al. 2008 [4, 8] support the assumption of equivalent efficacy between the non-trial chemotherapy comparators and the trial chemotherapy comparator 5-FU + cisplatin. Therefore, the OS and PFS of the blended chemotherapy comparator are assumed to be the same as that of the trial comparator 5-FU + cisplatin.

The survival curve fitting was carried out in line with NICE Decision Support Unit guidelines[41]. 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) and clinical plausibility of the extrapolation in the longer term (versus external data were available and/or international expert opinion by clinicians) were used to select the best-fitted parametric survival curves for the base case and alternative plausible parametric survival curves to be explored in sensitivity analyses. The model base case for OS and PFS extrapolations were validated by clinical key international opinion leaders.

Summary of base case

Table 32 summarizes the base case choice of OS and PFS for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms for the PD-L1+ (CPS ≥10) population.

Table 32: Base case choice of OS and PFS for pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin, PD-L1+ (CPS ≥10)

	Treatment arm	Base case choice
Overall survival	Pembrolizumab + 5-FU + cisplatin	Piecewise log-normal, cut-off at Week 40
	5-FU + cisplatin	Piecewise log-normal, cut-off at Week 40
Progression-free survival	Pembrolizumab + 5-FU + cisplatin	Piecewise log-logistic, cut-off at Week 10
	5-FU + cisplatin	Piecewise log-logistic, cut-off at Week 10

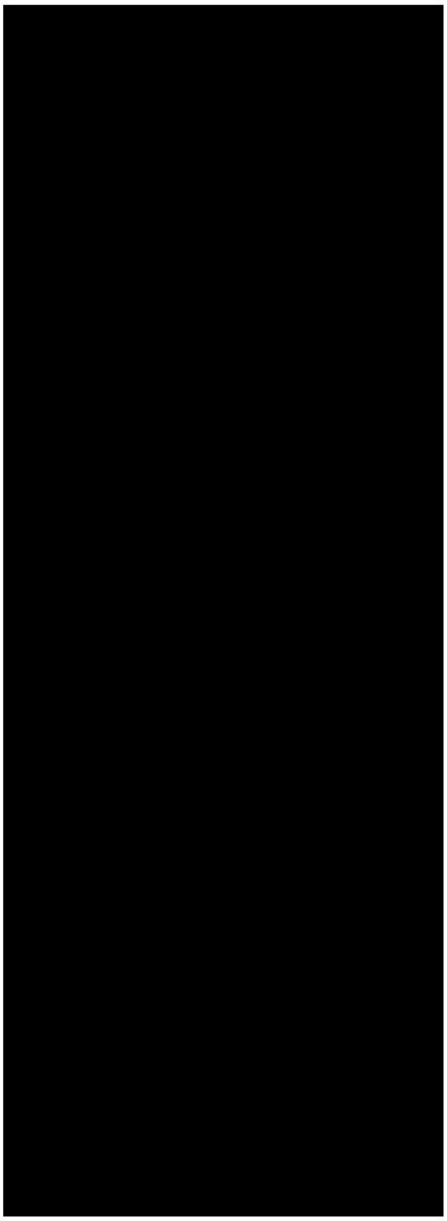
Key: 5-FU, fluorouracil; CPS, combined positive score; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.

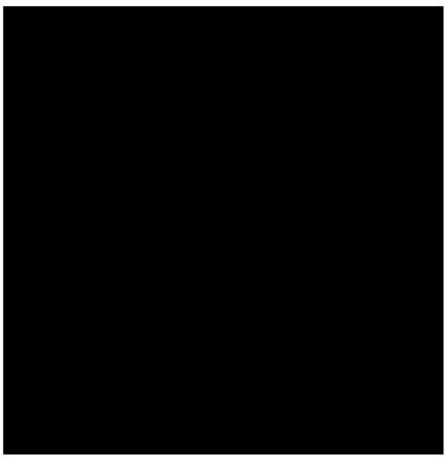
Figure 7 and Figure 8 summarize the base case OS and PFS extrapolations and observed Kaplan–Meier data for pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms for the PD-L1+ (CPS ≥10) population.

Key: 5-FU, fluorouracil; Cis, cisplatin; CPS, combined positive score; KM, Kaplan–Meier; Lnormal, log-normal; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; Pem, pembrolizumab.

Key: 5-FU, fluorouracil; Cis, cisplatin; CPS, combined positive score; KM, Kaplan–Meier; Llogistic, log-logistic; PD-L1+, programmed death-ligand 1-positive; Pem, pembrolizumab; FS, progression-free survival.

[redacted]





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

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

Health-related quality of life

The utility inputs used in the base case and scenario analysis were based on linear mixed-effects models fitted with EQ-5D-5L data collected in the KN-590 trial. A linear mixed effect model considers varying intercept which captures difference in repeated measures of one patient. It takes into account the random effect between patients and the unbalance of the number of records between patients. Test were performed for the linear mixed regression model and the random intercept effect were not ignorable, thus linear mixed regression model is appropriate to analyze the utility data. The rand() function in the package "lmerTest" was used to test random effect, and we used unspecified correlation structure for the models we fitted.

An EQ-5D summary index is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). The collection of index values (weights) for all possible EQ-5D health states is called a value set (or preference weights) . Most EQ-5D value sets have been obtained from a standardized valuation exercise, in which a representative sample of the general population in a country/region is asked to place a value on EQ-5D health states. The Danish Medicines Council methods guide for assessing new pharmaceuticals states that the preference weights based on the general Danish population must be applied to calculate health-related quality of life and thus, Danish tariff for EQ-5D-5L was applied to derive EQ-5D-5L utility values [42]. Since one patient could have multiple utility measures, linear mixed-effects models with patient-level random effects were used for this analysis to account for within-subject correlation. The linear mixed-effects models also included the presence or absence of any Grade 3+ AEs to estimate AE disutility.

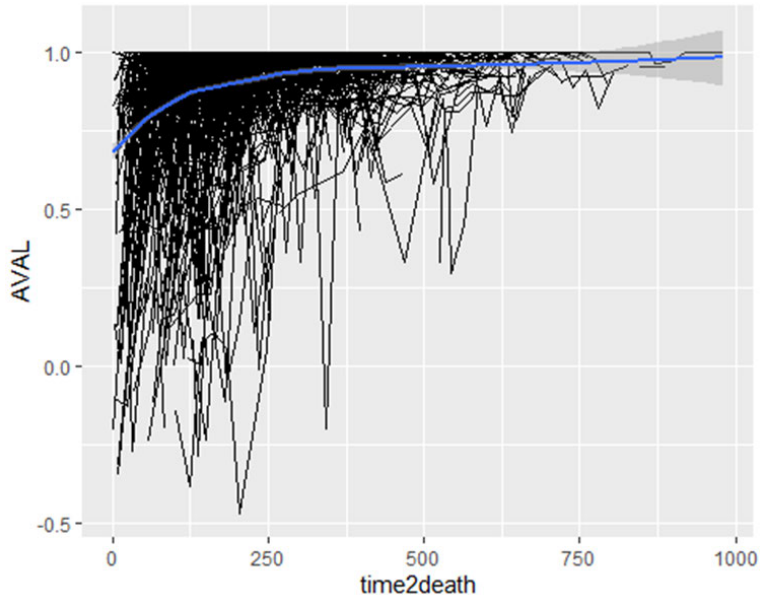
7.4.1 Health state utility values used in the health economic model

Utility by time to deaths: base case

Under the base case utility approach, utility was linked to different categories of time to death. This approach to define health state utilities based on time to death was developed by Batty et al. 2011 [43] and Hatswell et al. 2014 [44] and reflects the decline in quality of life for patients with advanced or metastatic cancer as they approach death.

The utility by time to death approach is preferred over the utility by progression status approach because it more finely and completely captures declines in health-related quality of life over time (see Figure 9) relative to use of utilities by progression status. For instance, deteriorations in quality of life over time within progression-free and progressive disease states typically occurs as a patient approaches their death date, and these declines are reflected in

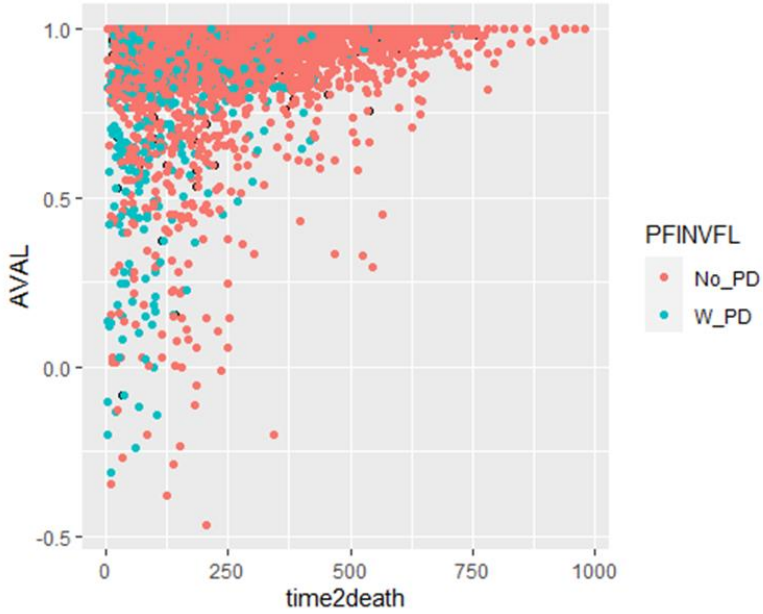
the time to death approach. As shown in Figure 10, estimating the utility only by progression status does not fully capture the trend over time within the progression-free and progressive disease health states.



Key: LOESS, locally weighted smoothing

Note: Y-axis: utility value. X-axis: time to death as a continuous variable. Measures for the same patient are connected in the line plot. The blue curve is the non-parametric loess smooth curve with the confidence interval shown as gray shaded area. Records measured within 360 days from overall survival censoring date are excluded due to uncertain time to death category.

Figure 9: LOESS plot of utility by time to death



Key: No_PD, no progressive disease; W_PD, with progressive disease.

Note: Y-axis: utility value. X-axis: time to death as a continuous variable. Records measured within 360 days from overall survival censoring date are excluded due to uncertain time to death category. Records measured with unknown progression status are also excluded.

Figure 10: Scatter plot of utility by time to death and progression status

In addition, the EQ-5D-5L data were collected for up to 1 year or end of treatment, whichever came first. EQ-5D-5L data were also collected at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit. This limit, to the earlier portion of the progressive disease state, the time horizon over which health utilities were assessed in patients with progressive disease who discontinued treatment.

Furthermore, one important limitation of the utility by time to death approach is that the records measured within 360 days of the OS censoring date cannot be assigned to a time to death category due to the death date being unknown. However, for KN-590, by the data cut-off date of July 2, 2020, 571 of 749 patients (76.2%) in the intention-to-treat population had a known death date. Among all 5,744 EQ-5D-5L measures, only 318 (5.54%) had an unknown time to death category. For this analysis, the uncertainty in the utility by time to death approach due to unknown death dates is relatively low.

The time to death utility approach was accepted and deemed appropriate in multiple metastatic cancer HTA submissions to NICE, and in a number of other pembrolizumab submissions to NICE in other metastatic cancer settings (e.g. TA531, originally TA447).

In this analysis, the linear mixed-effects regression model included indicators for time to death (i.e. 0–29, 30–89, 90–179, 180–359, or ≥360 days until death) and the presence or absence of any Grade 3+ AEs, as well as patient-level random effects to account for correlation between repeated measurements of the same patient. In the model, utilities were applied based on the distribution of patients across different categorizations of time to death in each weekly cycle. In a given weekly cycle, the proportion of patients within each time to death category was estimated based on the modeled OS within each treatment arm.

Table 34 reports the time to death utilities based on the linear mixed-effects model for the PD-L1+ (CPS ≥10) population. The same utilities were applied to all treatment arms in the model.

Table 34: Time to death utilities in KN-590 based on linear mixed-effects model, PD-L1+ (CPS ≥10) population

Time to death	Pooled pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin
≥360	[redacted]
[180–360)	[redacted]
[90–180)	[redacted]
[30–90)	[redacted]
<30	[redacted]
Disutility for Grade 3+ AE	[redacted]

Key: 5-FU, fluorouracil; AE, adverse events; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive.

Source: KN-590 (data cut-off date: July 2, 2020).

Utility by health state: scenario analysis

In scenario analyses, utility based on each patient's progression status (i.e., progression-free versus progressive disease) was used in the model. Utility in both the progression-free and the progressive disease states were estimated by the linear mixed-effects model. The model included indicators for progression-based health states (progression-free versus progressive disease) and the presence or absence of any Grade 3+ AEs. The same utilities were applied to all treatment arms in the model.

Table 35: Progression-based utilities in KN-590 based on linear mixed-effects model, PD-L1+ (CPS ≥10) population

	Pooled pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin
Progression-free	[redacted]
Progressive disease	[redacted]
Disutility for Grade 3+ AE	[redacted]

Key: 5-FU, fluorouracil; AE, adverse event; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive.
Source: KN-590 (data cut-off date: July 2, 2020).

Disutility related to adverse events

AE-related disutility was applied as a one-time QALY decrement in the first model cycle (i.e. Week 0). Disutility associated with AEs per patient was calculated in each treatment arm as a function of the rates of included AEs in the treatment arm (see Table 27 and Table 28), the mean duration of AEs (see Table 30) and the estimated disutility associated with Grade 3+ AE (see Table 34 and Table 35).

Table 36 presents the estimated one-off QALY decrements due to Grade 3+ AE by treatment arm based on the base case time to death approach. The blended chemotherapy comparator was assumed to have the same QALY decrement as the 5-FU + cisplatin arm.

Table 36: One-off QALY decrements due to Grade 3+ AEs by treatment arm

	Pembrolizumab + 5-FU + cisplatin	5-FU + cisplatin
Average disutility per patient due to Grade 3+ AEs	[redacted]	[redacted]

Key: 5-FU, fluorouracil; AE, adverse event; QALY, quality-adjusted life year.

Disutility related to age

The model's base case considered additional age-related utility decrements as the modeled population ages over the modeled time horizon. The age decrements were calculated as the relative change of the general population utility at the modeled age compared with the general population utility at the starting age (see table 14) The calculated age adjustments were then applied to the estimated time to deaths or progression-based utility values in the model. The Danish age-related general population utility was derived from the literature (see Table 37) [45].

Table 37: General population utility/Age related index in Denmark [45]

Age	General population utility/age related index
18–29	0.871
30–39	0.848

40–49	0.834
50–69	0.818
70–79	0.813
80+	0.721

7.5 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:

- Drug acquisition and administration costs for first-line therapy
- Drug acquisition and administration costs for subsequent therapy
- Disease management costs
- AE-related costs
- Terminal care costs
- Testing costs (PD-L1)
- Transportation cost and time spend by patients

The costing year of the analysis is 2021

Drug acquisition costs

Drug acquisition cost per cycle for pembrolizumab + 5-FU + cisplatin and comparators were calculated in the model as a function of the unit drug cost, dosing schedule, relative dose intensity (i.e. proportion of actual dose over expected dose) and proportion of patients on treatments.

Unit drug costs were based on pharmacy purchase price(Apotekernes indkøbspris, AIP) sourced from www.medicinpriser.dk and are presented in Table 38. All unit drug cost prices are presented as AIP. For the blended chemotherapy comparator, the drug acquisition and administration costs were estimated as the weighted average by individual chemotherapy treatment (weights are shown in Table 39).

Table 38: Drug acquisition unit costs of first-line treatment

Drug	Administration route	Vial/package size (mg)	Drug costs (kr., 2021 price)	Cost per mg (kr., 2021 price)
Pembrolizumab	IV infusion	100	24.409,84	244,10
Fluorouracil "Pfizer"	IV infusion	2.500	160,00	0,0640
	IV infusion	5.000	300,00	0,0600
Cisplatin "Ebewe"	IV infusion	50	109,00	2,1800
	IV infusion	100	218,00	2,1800
Oxaliplatin "Fresenius Kabi"	IV infusion	100	68,80	0,69
	IV infusion	200	127,82	0,64
	IV infusion	50	41,18	0,82.
Calciumfolinat Fresenius Kabi	IV infusion	10.000	3.300,00	0,33
Capecitabine "Accord"	Tablet (oral)	9.000	196,00	0,0218
	Tablet (oral)	60.000	250,00	0,0042

Drug	Administration route	Vial/package size (mg)	Drug costs (kr., 2021 price)	Cost per mg (kr., 2021 price)
Epirubicin "Accord"	IV infusion	100	980,00	9,80
	IV infusion	200	666,00	3,33
	IV infusion	50	180,00	3,60
Key: 5-FU, fluorouracil; IV, intravenous.				

Table 39: Distribution of treatments in the blended chemotherapy arm

Blended chemo treatments	MSD assumption on Danish clinical practice
5-FU + cisplatin	34.0%
5-FU + oxaliplatin + leucovorin	0.0%
Capecitabine + cisplatin	0.0%
Capecitabine + oxaliplatin	33.0%
5-FU + cisplatin + epirubicin	0.0%
5-FU + oxaliplatin + epirubicin	0.0%
Capecitabine + cisplatin + epirubicin	0.0%
Capecitabine + oxaliplatin + epirubicin	33.0%
Key: 5-FU, fluorouracil; chemo, chemotherapy.	

The dosing schedule is presented in Table 40. In the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms, the dosing schedule was based on the KN-590 trial protocol. In the blended chemotherapy comparator arm, the dosing schedule was based on the Summary of Product Characteristics of each therapy and the literature.

For IV drugs with BSA-based dosing, such as 5-FU and cisplatin, vial-sharing (i.e. no drug wastage) was assumed in the model base case. Under the vial sharing assumption, the number of vials required per infusion can be a fraction of the vial size, and the per infusion cost was calculated based on the average BSA (see table 14) and cost per mg (the lowest cost per mg if there are multiple vial sizes). The assumption that vial-sharing is not allowed (i.e. full vial has to be used by a patient, so drug wastage would occur) was evaluated in a scenario analysis, were the calculation is based on the log-normal distribution of BSA and the cost of a full vial (for simplicity, only the vial size with the lowest cost per mg was considered for the no vial-sharing scenario).

The mean relative dose intensity was based on the KN-590 trial for drugs in the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms, and on assumptions for drugs in the blended chemotherapy comparator arm (see Table 40). Relative dose intensities account for the fact that patients may not take the full planned dosage due to dose interruption or reduction associated with AEs or non-compliance.

Table 40: Dosing schedules and relative dose intensity for first-line treatments

Regimen	Component	Dose schedule	Treatment cycle (weeks)	Relative dose intensity	Source/assumption
Treatment arms in KN-590 trial					
Pembrolizumab	Pembrolizumab	200 mg Q3W	3	[redacted]	Source: KN-590

+ 5-FU	5-FU	800 mg/m² Q3W, Day 1-5	3	[redacted]	
+ cisplatin	Cisplatin	80 mg/m² Q3W	3	[redacted]	
5-FU	5-FU	800 mg/m² Q3W, Day 1-5	3	[redacted]	
+ cisplatin	Cisplatin	80 mg/m² Q3W	3	[redacted]	
Treatment regimen in the blended chemotherapy arm (apart from 5-FU + cisplatin)					
5-FU	5-FU	2,600 mg/m² 24-hour IV, Q2W	2	[redacted]	5-FU, leucovorin, capecitabine, epirubicin are assumed to have same ToT, maximum treatment cycles and dose intensity as 5-FU in the 5-FU + cisplatin arm in KN-590 Cisplatin and oxaliplatin are assumed to have the same ToT, maximum treatment cycles and dose intensity as cisplatin in the 5-FU + cisplatin arm in KN-590
+ oxaliplatin	Oxaliplatin	85 mg/m² Q2W	2	[redacted]	
+ leucovorin	Leucovorin	200 mg/m² Q2W	2	[redacted]	
Capecitabine	Capecitabine	1,000 mg/m² bid, Q3W, Day 1–14	3	[redacted]	
+ cisplatin	Cisplatin	80 mg/m² Q3W	3	[redacted]	
Capecitabine	Capecitabine	2,000 mg/m², Q3W, Day 1–14	3	[redacted]	
+ oxaliplatin	Oxaliplatin	130 mg/m² Q3W	3	[redacted]	
5-FU	5-FU	200 mg/m², Q3W, Day 1–21	3	[redacted]	
+ cisplatin	Cisplatin	60 mg/m² Q3W	3	[redacted]	
+ epirubicin	Epirubicin	50 mg/m² Q3W	3	[redacted]	
5-FU	5-FU	200 mg/m², Q3W, Day 1–21	3	[redacted]	
+ oxaliplatin	Oxaliplatin	130 mg/m² Q3W	3	[redacted]	
+ epirubicin	Epirubicin	50 mg/m² Q3W	3	[redacted]	
Capecitabine	Capecitabine	625 mg/m² bid, Q3W, Day 1–21	3	[redacted]	
+ cisplatin	Cisplatin	60 mg/m² Q3W	3	[redacted]	
+ epirubicin	Epirubicin	50 mg/m² Q3W	3	[redacted]	
Capecitabine	Capecitabine	625 mg/m² bid, Q3W, Day 1–21	3	[redacted]	
+ oxaliplatin	Oxaliplatin	130 mg/m² Q3W	3	[redacted]	
+ epirubicin	Epirubicin	50 mg/m² Q3W	3	[redacted]	

Key: 5-FU, fluorouracil; Q2W, once every 2 weeks; Q3W, once every 3 weeks; ToT, time on treatment.
Source: KN-590 (data cut-off date: July 2, 2020).

Drug administration costs

Unit costs of IV drug administration were based on DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen (see Table 41). Table 42 presents the drug administration costs per treatment cycle and the assumptions for all modeled treatment arms. It was assumed oral drugs have no drug administration costs.

Table 41: Drug administration unit costs for intravenous drugs

Description	Unit cost (kr., 2021 price)	Notes
Chemotherapy IV drug DRG06MA98	2.277,00	DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
5-FU one-off cost relating to port-a-cath placement; DRG70OP02	7.658,00	DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen.
Oral drug	0,00	Assume no administration cost for oral drug
Key: DRG, diagnosis-related group; IV, intravenous; kr, Danish krone.		

Table 42: Drug administration unit costs by first-line regimen

Regimens	Component	Administration cost per treatment cycle or one-off cost (for 5-FU only) (kr., 2021 price)	Notes/assumption
Pembrolizumab + 5-FU + cisplatin	Pembrolizumab	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
	5-FU	7.658,00 kr.	One-off cost relating to port-a-cath placement; DRG70OP02, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen. Administration cost included in DRG for pembrolizumab
	Cisplatin	-	Included in DRG for pembrolizumab
5-FU + cisplatin	5-FU	7.658,00 kr.	One-off cost relating to port-a-cath placement; DRG70OP02, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen. Administration cost included in DRG for cisplatin
	Cisplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
Blended chemo			
5-FU + oxaliplatin + leucovorin	5-FU	7.658,00 kr.	One-off cost relating to port-a-cath placement; DRG70OP02, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen. Administration cost included in DRG for oxaliplatin
	Oxaliplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
	Leucovorin	-	Administration cost included in DRG for Oxaliplatin
Capecitabine	Capecitabine	0.00 kr.	Assume no administration cost for oral drug

Regimens	Component	Administration cost per treatment cycle or one-off cost (for 5-FU only) (kr., 2021 price)	Notes/assumption
+ cisplatin	Cisplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
Capecitabine + oxaliplatin	Capecitabine	0.00 kr.	Assume no administration cost for oral drug
	Oxaliplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
5-FU + cisplatin + epirubicin	5-FU	7.658,00 kr.	One-off cost relating to port-a-cath placement; DRG70OP02, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen. Administration cost included in DRG for cisplatin
	Cisplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
	Epirubicin	-	Included in DRG for cisplatin
5-FU + oxaliplatin + epirubicin	5-FU	7.658,00 kr.	One-off cost relating to port-a-cath placement; DRG70OP02, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen. Administration cost included in DRG for cisplatin
	Oxaliplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
	Epirubicin	-	Included in DRG for oxaliplatin
Capecitabine + cisplatin + epirubicin	Capecitabine	-	Assume no administration cost for oral drug
	Cisplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
	Epirubicin	-	Included in DRG for cisplatin
Capecitabine + oxaliplatin + epirubicin	Capecitabine	-	Assume no administration cost for oral drug
	Oxaliplatin	2.277,00 kr.	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
	Epirubicin	-	Included in DRG for oxaliplatin

Key: 5-FU, fluorouracil; DRG, diagnosis-related group; kr, Danish krone.

Time on treatment

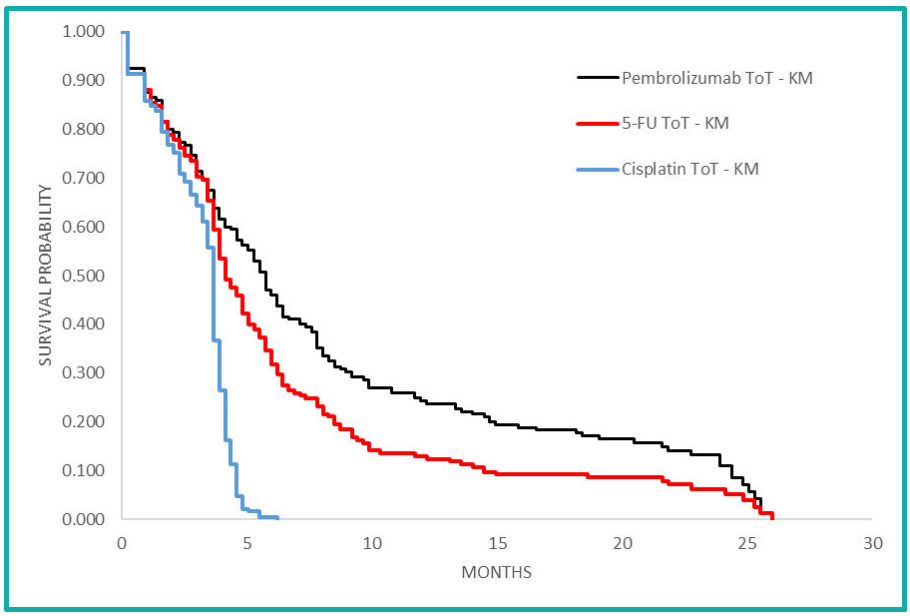
ToT survival curves for modeled first-line treatments were used to estimate the proportion of patients on each drug treatment over time. ToT Kaplan–Meier data for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms in KN-590 are mature (at 0% within the trial period); therefore, the model base case applied observed ToT Kaplan–Meier data directly. In scenario analysis, one-piece parametric survival models were fitted to IPD from KN-590 for the ToT of pembrolizumab and 5-FU in the pembrolizumab + 5-FU + cisplatin arm, and ToT of 5-FU in the 5-FU + cisplatin arm. The best-fitting curve, based on AIC/BIC and visual inspection, was used in the scenario analysis. Parametric survival curves

for cisplatin in both arms were not explored as cisplatin has a maximum treatment duration of six cycles (18 weeks), based on the KN-590 trial protocol, and all of the standard parametric survival models had poor visual fit with the observed cisplatin Kaplan–Meier data.

Figure 11 and Figure 12 present the observed ToT Kaplan–Meier data used in the model base case for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms, respectively, for the PD-L1+ (CPS ≥10) population.

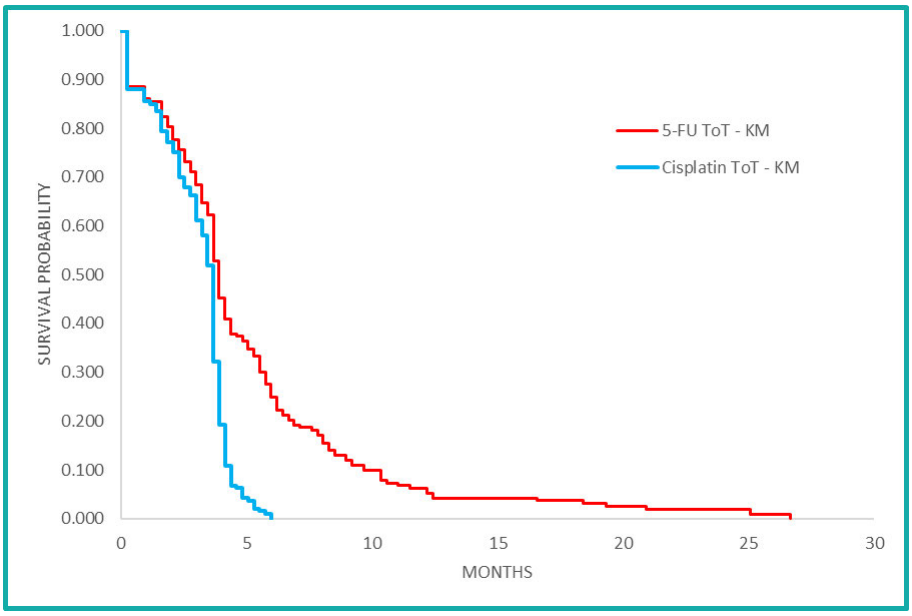
To align with the KN-590 trial protocol, for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms, a maximum treatment duration of 35 cycles (105 weeks) was applied to pembrolizumab and 5-FU, and a maximum treatment duration of six cycles (18 weeks) was applied to cisplatin.

The ToT of individual drugs in the blended chemotherapy comparator arm is assumed to be the same as either the 5-FU ToT or cisplatin ToT in the 5-FU + cisplatin arm and detailed assumptions are presented in Table 40.



Key: 5-FU, fluorouracil; CPS, combined positive score; KM, Kaplan–Meier; PD-L1+, programmed death-ligand 1-positive; ToT, time on treatment.

Figure 11: ToT KM: pembrolizumab + 5-FU + cisplatin arm, PD-L1+ (CPS ≥10) population



Key: 5-FU, fluorouracil; CPS, combined positive score; KM, Kaplan–Meier; ToT, time on treatment.

Figure 12: ToT KM: 5-FU + cisplatin arm, PD-L1+ (CPS ≥10) population

Drug acquisition and administration costs of subsequent therapy

The model also considered the costs of subsequent therapies among patients who discontinued first-line treatment. The proportion of patients receiving different these subsequent treatments were based on KN-590 trial data. Approximately half the patients in both arms went on to receive subsequent treatment.

The list of subsequent treatment after discontinuation for the pembrolizumab + 5-FU + cisplatin was based on description of current Danish 2L treatment in the Danish Medicines Council protocol used for the evaluation of nivolumab for the treatment of 2L esophageal cancer[6]. It is assumed that the ongoing evaluation by The Danish Medicines Council of nivolumab for 2L esophagus cancers will lead to a recommendation as standard treatment. It is furthermore assumed that nivolumab is not used as a subsequent treatment for the pembrolizumab + 5-FU + cisplatin arm and is the only subsequent treatment for 5-FU + cisplatin arm(see Table 43).

Table 43: Proportion of patients who receive each subsequent treatment

	Pembrolizumab + 5-FU + cisplatin	5-FU + cisplatin
Docetaxel "Accord"	12.1%	
Irinotecan "Accord"	7.1%	
Paclitaxel "Fresenius Kabi"	33.6%	
Nivolumab		52.3%

Key: 5-FU, fluorouracil.

Source: KN-590 (data cut-off date: July 2, 2020); Medicinrådets protokol for vurdering af nivolumab til behandling af planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi, version 1.1, 14 januar 2021

Table 44 presents the unit drug acquisition cost, dosing schedule and drug administration per treatment cycle of each subsequent treatment option. Table 45 presents the mean duration of treatment of each subsequent treatment based on the KN-590 trial for chemotherapy treatments and OPDIVO assessment report (Procedure No.

EMEA/H/C/003985/II/0080) for nivolumab. For simplicity, relative dose intensity was not considered and vial sharing (i.e. no wastage) was assumed for subsequent treatments.

Table 44: Dosing schedules, drug acquisition and administration unit costs by subsequent regimens

Drug	Admini-stration route	Recommended dosing per infusion	Dosage frequency	Number of doses per cycle	Vial/package size (mg)	Drug costs (kr., 2021 price)	Cost per mg (kr., 2021 price)	Drug cost per week (kr., 2021 price)	Administration cost per week (kr., 2021 price)
Docetaxel "Accord"	IV	75 mg/m2	Q3W	1	160	309,00	1,93	82,08	759,00
Irinotecan "Accord"	IV	180 mg/m2	Q2W	1	500	200,00	0,40	61,20	1.138,50
Paclitaxel "Fresenius Kabi"	IV	90 mg/m2	Days 1, 8, 15 of 28 day	3	300	201,50	0,67	77,07	569,25
Nivolumab	IV	240 mg	Q2W	1	240	22.567,94	94,03	11.283,97	1.138,50

Key: 5-FU, fluorouracil; Q#W, every # week(s); IV, intravenous; kr, Danish krone.
Source for drug acquisition cost: www medicinpriser.dk
Source for drug administration cost: DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen.

Table 45: Mean treatment duration (weeks) for subsequent treatments

	PD-L1+ (CPS ≥10)	
	Pembrolizumab + 5-FU + cisplatin	**5-FU + cisplatin**
Docetaxel (Docetaxel "Accord")	6.7	
Irinotecan hydrochloride (Irinotecan "Accord")	4.4	
Paclitaxel (Paclitaxel "Fresenius Kabi")	10.0	
Nivolumab		21.3

Key: 5-FU, fluorouracil; CPS, combined positive score; PD-L1, programmed death-ligand 1.
Source: KN-590 (data cut-off date: July 2, 2020); Opdivo assessment report, Procedure No. EMEA/H/C/003985/II/0080

The weighted average (based on distribution in Table 43) one-off subsequent treatment costs for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms for the PD-L1+ (CPS ≥10) population, broken down by drug acquisition and drug administration costs, are presented in Table 46. The blended chemotherapy comparator arm was assumed to have the same one-off subsequent treatment cost as the 5-FU + cisplatin arm.

Table 46: One-off subsequent treatment costs

	PD-L1+ (CPS ≥10)	
	Pembrolizumab + 5-FU + cisplatin	**5-FU + cisplatin**
Drug acquisition cost	344,98 kr.	125.479,81 kr.
Drug administration cost	2.887,84 kr.	12.660,33 kr.
Total cost	3.232,82 kr.	138.140,14 kr.

Key: 5-FU, fluorouracil; CPS, combined positive score; PD-L1, programmed death-ligand 1.

Disease management costs

Healthcare resource use model inputs for the disease management of patients in progression-free and progressive disease health states are presented in Table 47. The resource use items, and frequencies of resource use, are estimations based on information from Danish patient guidedance at hospitals in Region Hovedstaden, Midtjylland and Nordjylland made available to patients at start of treatment of combination chemotherapy. The various patient guidance are not completely aligned but we have included the most conservative input. Unit costs for resource use elements were obtained from "Takstvejledning. 2021." Sundhedsdatastyrelsen.

Table 47: Disease management costs

Resource	Unit cost (kr., 2021 price)	Frequency (per week)		References (unit cost)
		Pre-progression	Post-progression	
CT scan	1.835,00	0.12	0.04	DRG30PR07, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
Consultation visit, nurse	272,00	0.46		Average hourly cost for nurses is 544 kr. per hour with reference to "værdisætning af enhedsomkostninger Version 1.4, Medicinrådet 31. January 2020". We assume that duration of nurse consultation is ½ hour
Consultation visit, physician	2.277,00	0.23	0.04	DRG06MA98, DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
Total cost (weekly)		**869,03 kr.**	**164,48 kr.**	
Key: CT, computerized tomography; DRG, diagnosis-related group; kr., Danish krone.				

Terminal care costs

Patients who transition to death were assumed to incur a one-off cost associated with palliative or terminal care (see Table 48). Terminal care costs were based on the DRG15MPO1 cost with an assumption of 30 days' care being provided.

Table 48: One-off terminal care costs

Description	Cost (kr., 2021 price)	Source for terminal care cost
Terminal care	78.570,00	DRG-takst 2021, "Takstvejledning. 2021." Sundhedsdatastyrelsen
Key: kr, Danish krone.		

Adverse event-related costs

The unit cost of AE management per incidence is based on DRG-takst 2021, "Takstvejledning. 2021." 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 49.

Table 49: Adverse event management unit costs

	Unit cost (kr., 2021 price)	Code
Anemia	40.604,00	DRG16MA05/(DD559)Anæmi forårsaget af enzymatisk forstyrrelse UNS
Dysphagia	5.130,00	DRG03MA98/(DR139)Synkebesvær UNS
Fatigue	3.987,00	DRG23MA03/(DR539A)Udmattelse
Hypokalemia	1.518,00	DRG10MA98/(DE876)Hypokaliæmi
Hyponatremia	24.306,00	DRG10MA06/(DE871A)Hyponatriæmi
Nausea	5.130,00	DRG06MA11/(DR119)Kvalme og opkastning
Neutropenia	3.114,00	DRG16MA98/(DD709A)Neutropeni og agranulocytose forårsaget af lægemiddel
Neutrophil count decreased	2.155,00	65TE01- Telefon- og email konsultation, samt skriftlig kommunikation ved prøvesvar
Platelet count decreased	35.483,00	DRG16MA03/(DD696)Trombocytopeni UNS
Pneumonia	36.514,00	DRG04MA13/(DJ189)Pneumoni UNS
Stomatitis	1.862,00	DRG06MA98/(DK120)Aftøs mundbetændelse
Vomiting	5.130,00	DRG06MA11/(DR119)Kvalme og opkastning
Weight decreased	5.130,00	DRG06MA11/(DK909)Malabsorption UNS
White blood cell count decreased	2.155,00	65TE01- Telefon- og email konsultation, samt skriftlig kommunikation ved prøvesvar
Key: DRG, diagnosis-related group; kr, Danish krone.		

One-off AE-related costs per first-line treatment arm were applied at the beginning of the model and were calculated based on the unit costs for managing each AE (see Table 49) and the AE rate (see table 27 and table 28). Table 50 summarizes the one-off AE costs for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms for the PD-L1+ (CPS ≥10) population.

The blended chemotherapy comparator was assumed to have the same one-off AE costs as the 5-FU + cisplatin arm.

Table 50: One-off adverse event management costs

	PD-L1+ (CPS ≥10)	
	Pembrolizumab + 5-FU + cisplatin	**5-FU + cisplatin**
One-off AE costs	17.688 kr.	19.437 kr.
Key: 5-FU, fluorouracil; AE, adverse event; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive.		

PD-L1 testing costs

PD-L1 testing costs were included in the pembrolizumab + 5-FU + cisplatin arm. The number of patients needed to take the PD-L1 test to get one PD-L1+ patient is calculated as one divided by the PD-L1+ rate. Therefore, effective PD-L1 testing costs were calculated in the model as unit PD-L1 testing cost per patient divided by the proportion of PD-L1+ patients (see table 51). The PD-L1 testing costs were assumed to be incurred at the beginning of the model.

Table 51: PD-L1 testing costs

Description	Values	Source
Unit PD-L1 testing cost (2021 price)	1.150,00 kr.	MSD estimate based on input from pathologist who do not wish to be named
% PD-L1 positive (CPS ≥10)	51.1%	KN-590
Overall PD-L1 testing cost (2021 price)	2.248,96 kr.	
Key: CPS, combined positive score; PD-L1, programmed death-ligand 1.		

Transport cost and time spend by patients

The model base case includes indirect costs from a limited societal perspective.

Societal costs were separated into three categories:

- costs for time spent for monitoring and follow-up,
- time spent for IV infusion
- transportation costs.

Unit cost for an hour was 179 kr. based on average salary in Denmark and unit cost for transportation was 100 kr. It was assumed monitoring and follow-up visits occur at the same time as some IV infusion visits, therefore, transportation costs are only applied to IV infusion to avoid double counting. All societal costs are assumed to occur during active first-line treatments.

Time spend by patients: monitoring and follow up

It was estimated that the frequencies of for consultation visit (physician), consultation visit (nurse) and computerized tomography scan were 0.12, 0.46, and 0.23 per week and for each monitoring and follow-up patients spend 1.00, 0.50, and 1.00 hours, respectively (see 52.). These result in a total of 0.58 hours per week for patient monitoring and follow up(see table 54).

Table 52: Patient monitoring and follow up hours per week

	Frequency of use per week	Patient hours per use
Consultation visit, physician	0.12	1.00
Consultation visit, nurse	0.46	0.50
CT scan	0.23	1.00
Key: CT, computerized tomography. Source: Danish patient guidedance at hospitals in Region Hovedstaden, Midtjylland and Nordjylland made available to patients at start of treatment of combination chemotherapy .		

Time spend by patients: IV infusion

IV infusion frequency and hours per infusion for each treatment were presented in table 53. These result in 15.00, 14.83 and 5.65 (weighted average based on distribution of individual chemotherapy treatments in the blended chemotherapy comparator) total infusion hours per week for pembrolizumab + 5-FU + cisplatin, 5-FU + cisplatin, and blended chemotherapy comparator, respectively(see table 54). It is assumed that 5-FU infusion is carried out at home and every hour of 5-FU infusion equals to 20 min for the purpose of calculating indirect costs. This is to account for some degree of patient cost, even though the infusion takes place at home.

Table 53: IV administration infusion hours per week

	Drug	Hours for each IV infusion	Infusion frequency (every # weeks)	Total infusion hours per week
Pembrolizumab + 5-FU + cisplatin	Pembrolizumab	0.5	3.0	14.83
	Cisplatin	4.0		
	5-FU	40.0		
5-FU + cisplatin	Cisplatin	4.0	3.0	14.67
	5-FU	40.0		
5-FU + oxaliplatin + leucovorin	Oxaliplatin	2.5	2.0	21.50
	Leucovorin	0.5		
	5-FU	40.0		
Capecitabine + cisplatin	Capecitabine	-	3.0	1.33
	Cisplatin	4.0		
Capecitabine + oxaliplatin	Capecitabine	-	3.0	0.83
	Oxaliplatin	2.5		
5-FU + cisplatin + epirubicin	Epirubicin	0.5	3.0	14.83
	Cisplatin	4.0		
	5-FU	40.0		
5-FU + oxaliplatin + epirubicin	Epirubicin	0.5	3.0	14.33
	Oxaliplatin	2.5		
	5-FU	40.0		
Capecitabine + cisplatin + epirubicin	Epirubicin	0.5	3.0	1.50
	Cisplatin	4.0		
	Capecitabine	-		
Capecitabine + oxaliplatin + epirubicin	Epirubicin	0.5	3.0	1.00
	Oxaliplatin	2.5		
	Capecitabine	-		

Key: 5-FU, fluorouracil; IV, intravenous.

Source: Infusion time for pembrolizumab and 5-FU is based on KN 590, all other based Danish patient guidedance at hospitals in Region Hovedstaden, Midtjylland and Nordjylland made available to patients at start of treatment of combination chemotherapy .

Transportation cost

Transportation costs were applied to each IV infusion based on IV infusion frequency presented in Table 53.

Summary of Transport cost and time spend by patients

Table 54 presents a summary of modeled transport cost and time spend by patients costs across the different treatments options. The final total societal costs are 2.822 kr., 2.792 kr. and 1.148 kr. per week for the pembrolizumab + 5-FU + cisplatin, 5-FU + cisplatin and blended chemotherapy arms respectively. These costs are then applied to the ToT curves for each treatment arm.

Table 54: Transport cost and time spend by patients summary

	Hours per week			Cost per week (kr., 2021 price)		
	Pembrolizumab + 5-FU + cisplatin	5-FU + cisplatin	Blended chemo	Pembrolizumab + 5-FU + cisplatin	5-FU + cisplatin	Blended chemo
Total	15.41	15.24	6.17	2.792	2.762	1.138
IV administration infusion time	14.83	14.67	5.59	2.655	2.625	1.001
Patient monitoring and follow-up	0.58	0.58	0.58	103	103	103
Transportation cost	-	-	-	33	33	33
Key: 5-FU, fluorouracil; chemo, chemotherapy; IV, intravenous; kr, Danish krone.						

7.6 Results

7.6.1 Base case overview

The KN-590 trial demonstrates superior OS and PFS with pembrolizumab + 5-FU + cisplatin versus 5-FU + cisplatin as a first-line treatment for patients with advanced and metastatic esophageal cancer. Over a lifetime model horizon, first-line treatment with pembrolizumab + 5-FU + cisplatin is expected to yield improvements in QALYs by 1.15 years and LYs by 1.27 years, relative to relevant comparators in patients with advanced or metastatic esophageal carcinoma. The base case ICERs for pembrolizumab + 5-FU + cisplatin compared with 5-FU + cisplatin and blended chemotherapy were 427.968 kr. per QALY and 436.778 kr. per QALY, respectively.

This cost-effectiveness analysis shows that pembrolizumab + 5-FU + cisplatin offers benefits to patients with advanced and metastatic esophageal cancer in terms of LY and QALY gains, in comparison with relevant comparators. The incremental drug acquisition cost of pembrolizumab is partially offset by the savings in subsequent treatment costs, terminal care costs and AE costs when compared with chemotherapy comparators. With a normal range of willingness-to-pay (WTP) thresholds of around 800.000 kr./QALY to 1.200.000 kr./QALY (around 2-3 times GDP per capita) that normally used for assessing cost-effectiveness of new health technologies, pembrolizumab + 5-FU + cisplatin is a cost-effectiveness treatment option compared with relevant comparators for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative EGJ adenocarcinoma in adults whose tumors express PD-L1 (CPS ≥10).

Results from the OWSA and scenario analyses supported the base case findings, with the biggest uncertainty observed in scenario analyses; the largest driver of uncertainty was the choice of parametric survival models of OS. In addition, the model was also sensitive to the time horizon and the approach for modeling utility.

Probabilistic results across 5,000 iterations were consistent with the deterministic base case results.

Table 55: Base case overview

Comparator	Cisplatin+5-FU Outcomes are also evaluated for "blended chemotherapy" to account for the numerous possible combinations that the current Danish guideline includes and is only included in the model to explore the impact on cost as we assume equivalent efficacy between the non-trial chemotherapy comparators and the trial chemotherapy comparator; 5-FU + cisplatin.
Type of model	Partitioned survival model (PSM)
Time horizon	30 years (life time) Mean age of all PD-L1+ patients in KN-590 is 61.9 years
Treatment line	1st line. 1 subsequent treatment line included.
Measurement and valuation of health effects	The utility inputs used in the base case and scenario analysis were based on linear mixed-effects models fitted with EQ-5D-5L data collected in the KN-590 trial. Danish tariff for EQ-5D-5L was applied to derive EQ-5D-5L utility values. Since one patient could have multiple utility measures, linear mixed-effects models with patient-level random effects were used for this analysis to account for within-subject correlation. The linear mixed-effects models also included the presence or absence of any Grade 3+ AEs to estimate AE disutility.
Included 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 included: ▪ Drug acquisition and administration costs for first-line therapy ▪ Drug acquisition and administration costs for subsequent therapy ▪ Disease management costs ▪ AE-related costs ▪ Terminal care costs ▪ Testing costs (PD-L1) ▪ Transportation cost and time spend by patients The costing year of the analysis is 2021
Dosage of pharmaceutical	Pembrolizumab + 5-FU + cisplatin:

	- Pembrolizumab: 200 mg IV on Day 1 of every 21-day (3-week) cycle for up to 35 administrations (up to approximately 2 years) - 5-FU: 800 mg/m2/day, IV on each of Days 1 to 5 every 21-day cycle (total of 4000 mg/m2 per 3-week cycle) for up to 35 cycles - Cisplatin: 80 mg/m2, IV on day 1 of every 21-day cycle for up to 6 cycles
Average time on treatment	Intervention: Pembrolizumab: 8,5 months Cisplatin: 3,0 months 5-FU: 6,3 months Comparator: Cisplatin: 3,0 months 5-FU: 5,0 months
Parametric function for PFS	Intervention: Piecewise log-logistic, cut-off at Week 10 Comparator: Piecewise log-logistic, cut-off at Week 10
Parametric function for OS	Intervention: Piecewise log-normal, cut-off at Week 40 Comparator: Piecewise log-normal, cut-off at Week 40

7.6.2 Base case results

Table 56 presents the base case deterministic results (with 3.5% annual discounting for costs and health benefits) using the AIP for pembrolizumab and other drugs. Over the modeled time horizon, total costs were 808.026 kr.; 307.166 kr. and 296.855 kr. for pembrolizumab + 5-FU + cisplatin, 5-FU + cisplatin and blended chemotherapy, respectively; total QALYs over the same timeframe were estimated to be 2.32, 1.15 and 1.15, respectively, and total LYs were estimated to be 2.65, 1.35 and 1.35 years, respectively. The resulting ICER for pembrolizumab + 5-FU + cisplatin in terms of incremental cost per QALY gained was 427.968 kr. versus 5-FU + cisplatin and 436.778 kr. versus blended chemotherapy; the ICER in terms of incremental cost per LY gained was 387.658 kr. versus 5-FU + cisplatin and 395.638 kr. versus blended chemotherapy.

Table 56: Cost-effectiveness base case results (pairwise), PD-L1+ (CPS ≥10)

Treatment arm	Costs (kr.)	LYs	QALYs	Δ Costs (kr.)	ΔLYs	ΔQALYs	ICER (kr./LY)	ICER (kr./ QALY)
Pembrolizumab + 5-FU + cisplatin	808.026	2.65	2.32					
5-FU + cisplatin	307.166	1.35	1.15	500.860	1.29	1.17	387.658	427.968
Blended chemo	296.855	1.35	1.15	511.171	1.29	1.17	395.638	436.778

Key: 5-FU, fluorouracil; chemo, chemotherapy; kr, Danish krone; LY, life year; PD-L1+, programmed death-ligand 1-positive; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Table 57 presents disaggregated base case results of LYs, based on progression status and time to death health states.

Table 58 reports disaggregated base case results of costs. Differences in total costs between pembrolizumab + 5-FU + cisplatin and comparators were largely driven by the drug acquisition costs, which were significantly lower in the comparator arms versus the intervention arm. For pembrolizumab + 5-FU + cisplatin, drug acquisition and administration costs in the first line were the primary driver for the total costs (82.0%).

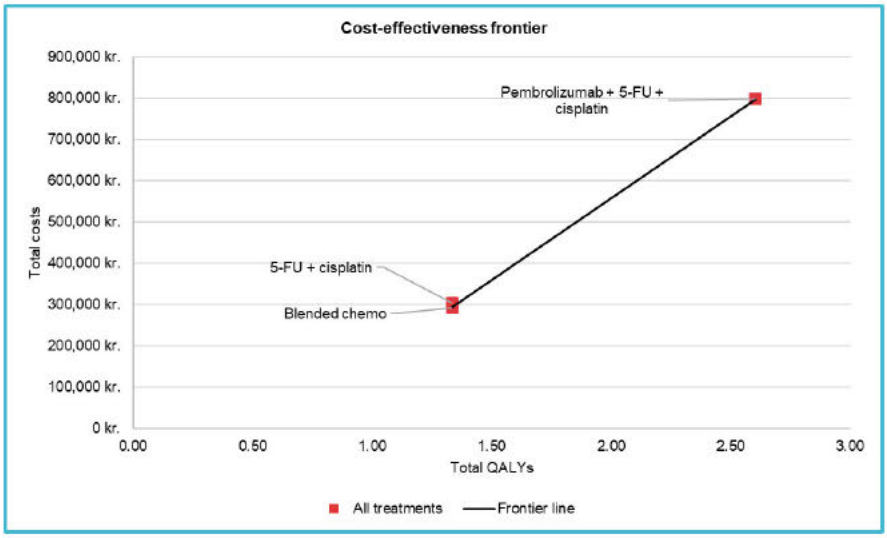
Table 57: Life years disaggregated base case results, PD-L1+ (CPS ≥10) population

	Pembrolizumab + 5-FU + cisplatin	5-FU + cisplatin	Blended chemo
Based on progression status			
Pre-progression	1.15	0.54	0.54
Post-progression	1.50	0.81	0.81
Total	2.65	1.35	1.35
Based on time to death health states			
>360	1.92	0.68	0.68
[180, 360)	0.31	0.27	0.27
[90, 180)	0.21	0.20	0.20
[30, 90)	0.14	0.14	0.14
<30	0.07	0.07	0.07
Total	2.65	1.35	1.35
Key: 5-FU, fluorouracil; chemo, chemotherapy; PD-L1, programmed death-ligand 1.			

Table 58: Cost disaggregated base case results, PD-L1+ (CPS ≥10) population

	Pembrolizumab + 5-FU + cisplatin (kr.)	5-FU + cisplatin (kr.)	Blended chemo (kr.)
Total	808.026	307.166	296.855
Patient costs	772.972	286.178	280.526
Drug acquisition cost	576.109	3.282	2.685
Drug administration cost	36.248	18.239	13.185
Disease management cost, progression-free	52.136	24.511	24.511
Disease management cost, progressive disease	12.838	6.978	6.978
Subsequent treatment cost	3.152	137.536	137.536
Terminal care cost	72.553	76.195	76.195
AE management cost	17.688	19.437	19.437
PD-L1 testing cost	2.249	0	0
Societal cost	35.054	20.988	16.328
Key: 5-FU, fluorouracil; AE, adverse event; chemo, chemotherapy; kr, Danish krone; PD-L1+, programmed death-ligand 1-positive.			

Figure 13 presents the cost-effectiveness frontier for all treatment arms modeled



Key: 5-FU, fluorouracil; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive; QALY, quality-adjusted life year

Figure 13: Cost-effectiveness frontier, PD-L1+ (CPS ≥10)

7.7 Sensitivity analyses

7.7.1 Deterministic sensitivity analyses

One-way sensitivity analyses results

To assess the parameter uncertainty, a one-way sensitivity analysis (OWSA) was conducted on key model parameters by varying one model input parameter at a time. Base case inputs were varied by the lower and upper bounds of the 95% CI, if such information was reported or could be derived from the original source. If such information was not available, it was assumed the standard error was 10% of the mean for the input, and the 95% CI was calculated based on the mean and assumed standard error and the assumed distribution for the input (the distribution is also used for probabilistic sensitivity analysis [PSA]). Table 59 presents the list of parameters assessed in OWSA.

Table 59: One-way sensitivity analysis inputs: model parameters

Parameters	Base case	OWSA input
Discount rate		
Discount rate: Costs	3.5%	0% and 7%
Discount rate: Health outcomes	3.5%	0% and 7%
Patient demographics and characteristics		
Patient starting age	61.90	95% CI: 61.0; 62.8
Proportion of male	81.7%	95% CI: 77.7%; 85.4%
Average patient weight (kg)	62.56	95% CI: 61.1, 64.0
Average patient body surface area (m2)	1.70	95% CI: 1.68, 1.72
Efficacy		
Pembrolizumab + 5-FU + cisplatin, PD-L1+: OS - Lnormal intercept	[redacted]	

Parameters	Base case	OWSA input
Pembrolizumab + 5-FU + cisplatin, PD-L1+: OS - Llnormal log(scale)	[redacted]	2.5% and 97.5% percentile of each coefficient based on multivariate normal distribution using variance–covariance matrix of the parameters
5-FU + cisplatin, PD-L1+: OS - Lnormal intercept	[redacted]	2.5% and 97.5% percentile of each coefficient based on multivariate normal distribution using variance–covariance matrix of the parameters
5-FU + cisplatin, PD-L1+: OS - Lnormal log(scale)	[redacted]	
Pembrolizumab + 5-FU + cisplatin, PD-L1+: PFS - Llogistic intercept	[redacted]	2.5% and 97.5% percentile of each coefficient based on multivariate normal distribution using variance–covariance matrix of the parameters
Pembrolizumab + 5-FU + cisplatin, PD-L1+: PFS - Llogistic log(scale)	[redacted]	
5-FU + cisplatin, PD-L1+: PFS - Llogistic intercept	[redacted]	2.5% and 97.5% percentile of each coefficient based on multivariate normal distribution using variance–covariance matrix of the parameters
5-FU + cisplatin, PD-L1+: PFS - Llogistic log(scale)	[redacted]	
Pembrolizumab + 5-FU + cisplatin, PD-L1+: Pembrolizumab, ToT	KM	HR = 1.1 and 0.9 applying to the KM
Pembrolizumab + 5-FU + cisplatin, PD-L1+: 5-FU, ToT	KM	HR = 1.1 and 0.9 applying to the KM
5-FU + cisplatin, PD-L1+: 5-FU, ToT	KM	HR = 1.1 and 0.9 applying to the KM
Utilities		
Duration of Grade 3+ AEs (weeks)	[redacted]	95% CI: 7.59, 8.89
Utility by time to death: intercept	[redacted]	2.5% and 97.5% percentile of each coefficient based on multivariate normal distribution using variance–covariance matrix of the parameters
Utility by time to death: Coefficient for AEs	[redacted]	
Utility by time to death: Coefficient for TTD >=360 days	[redacted]	
Utility by time to death: Coefficient for TTD 180-360 days	[redacted]	
Utility by time to death: Coefficient for TTD 90-180 days	[redacted]	
Utility by time to death: Coefficient for TTD 30-90 days	[redacted]	
Utility by time to death: Coefficient for TTD <30 days	[redacted]	
Drug administration unit cost		
Chemo IV drug admin cost DRG06MA98	2.277,00 kr.	10% mean as SE, gamma distribution
5-FU one-off cost relating to port-a-cath placement; DRG70OP02	7.658,00 kr.	10% mean as SE, gamma distribution
Oral drug admin cost	0.00 kr.	
Drug relative dose intensity		
Pembrolizumab + 5-FU + cisplatin RDI: pembrolizumab	[redacted]	10% mean as SE, beta distribution

Parameters	Base case	OWSA input
Pembrolizumab + 5-FU + cisplatin RDI: 5-FU	[redacted]	10% mean as SE, beta distribution
Pembrolizumab + 5-FU + cisplatin RDI: cisplatin	[redacted]	10% mean as SE, beta distribution
5-FU + cisplatin RDI: 5-FU	[redacted]	10% mean as SE, beta distribution
5-FU + cisplatin RDI: cisplatin	[redacted]	10% mean as SE, beta distribution
Subsequent therapy drug cost		
Pembrolizumab + 5-FU + cisplatin	3.232,82 kr.	10% mean as SE, gamma distribution
5-FU + cisplatin	138.140,14 kr.	10% mean as SE, gamma distribution
Blended chemo	138.140,14 kr.	10% mean as SE, gamma distribution
Disease management cost		
Weekly cost in progression-free state	869,03 kr.	10% mean as SE, gamma distribution
Weekly cost in progressive disease state	164,48 kr.	10% mean as SE, gamma distribution
AE-related costs		
Pembrolizumab + 5-FU + cisplatin: one-off AE costs	17.688 kr.	10% mean as SE, gamma distribution
5-FU + cisplatin: one-off AE costs	19.437 kr.	10% mean as SE, gamma distribution
Blended chemo: one-off AE costs	19.437 kr.	10% mean as SE, gamma distribution
PD-L1 testing cost		
Unit PD-L1 testing cost	1.150,00 kr.	10% mean as SE, gamma distribution
Terminal care cost		
Cost of terminal care (one-off cost)	78.570,00 kr.	10% mean as SE, gamma distribution
Societal costs		
Hourly salary	179,00 kr.	10% mean as SE, gamma distribution
Transportation cost	100,00 kr.	10% mean as SE, gamma distribution

Key: 5-FU, fluorouracil; AE, adverse event; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; kr, Danish krone; OWSA, one-way sensitivity analysis; OS, overall survival; PD-L1, programmed death-ligand 1; RDI, relative dose intensity; SE, standard error; ToT, time on treatment; TTD, time to death.

The Top 10 most influential model parameters in the OWSA for pembrolizumab + 5-FU + cisplatin versus 5-FU + cisplatin and versus blended chemotherapy are presented in Table 60 and Table 61 and shown as tornado diagrams in Figure 14 and Figure 15, respectively. The OWSA results show that the model parameters with the greatest impact on the ICER versus both 5-FU + cisplatin and the blended chemotherapy was coefficients of the base case OS parametric curve for extrapolation.

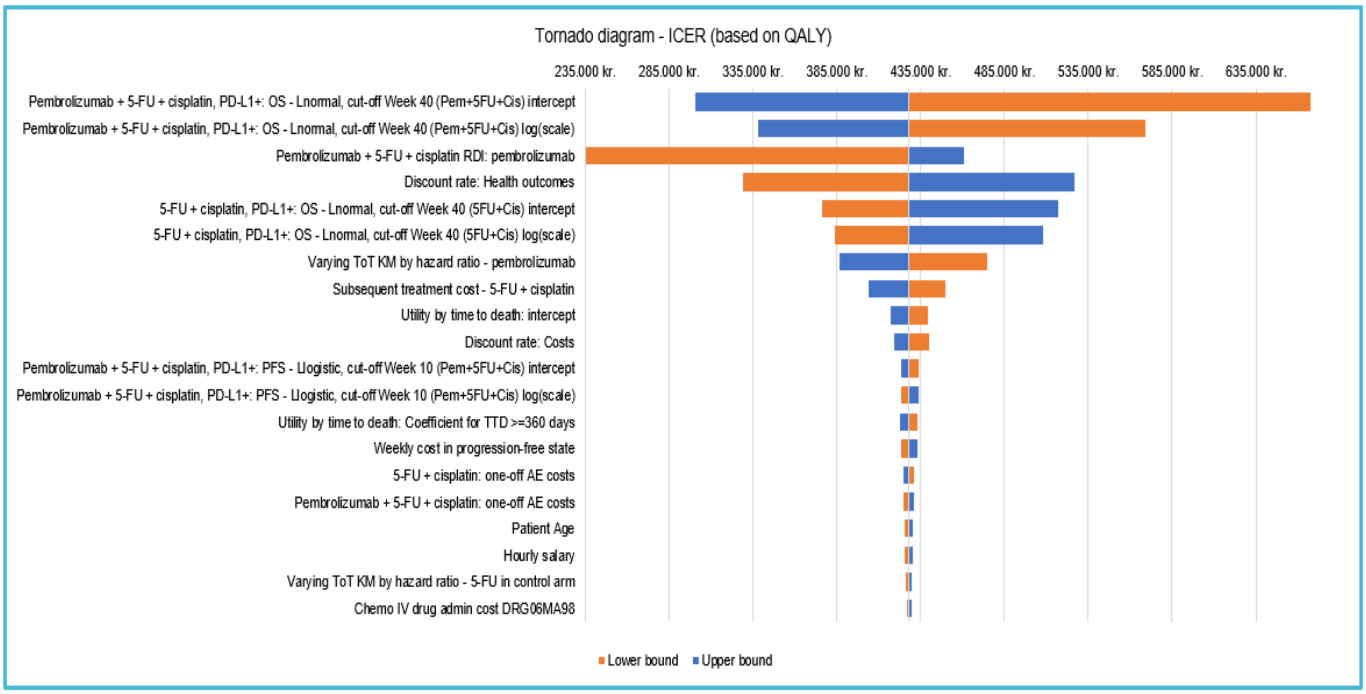
Table 60: Top 10 parameters by impact on ICER (versus 5-FU + cisplatin), PD-L1+ (CPS ≥10)

Model parameter	ICER: lower bound (kr.)	ICER: upper bound (kr.)

Base case	427.968	
Pembrolizumab + 5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 intercept	667.472 (56%)	300.583 (-30%)
Pembrolizumab + 5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 log(scale)	569.138 (33%)	338.003 (-21%)
Pembrolizumab + 5-FU + cisplatin RDI: pembrolizumab	235.5803 (-45%)	461.163 (8%)
Discount rate: Health outcomes	329.064 (-23%)	526.988 (23%)
5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 intercept	376.445 (-12%)	517.313 (21%)
5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 log(scale)	383.783 (-10%)	507.745 (19%)
Varying ToT KM by hazard ratio – pembrolizumab	474.681 (11%)	386.990 (-10%)
Subsequent treatment cost - 5-FU + cisplatin	449.869 (5%)	403.842 (-6%)
Utility by time to death: intercept	439.046 (3%)	417.435 (-2%)
Discount rate: Costs	440.307 (3%)	418.946 (-2%)
Key: 5-FU, fluorouracil; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; kr, Danish krone; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death.		

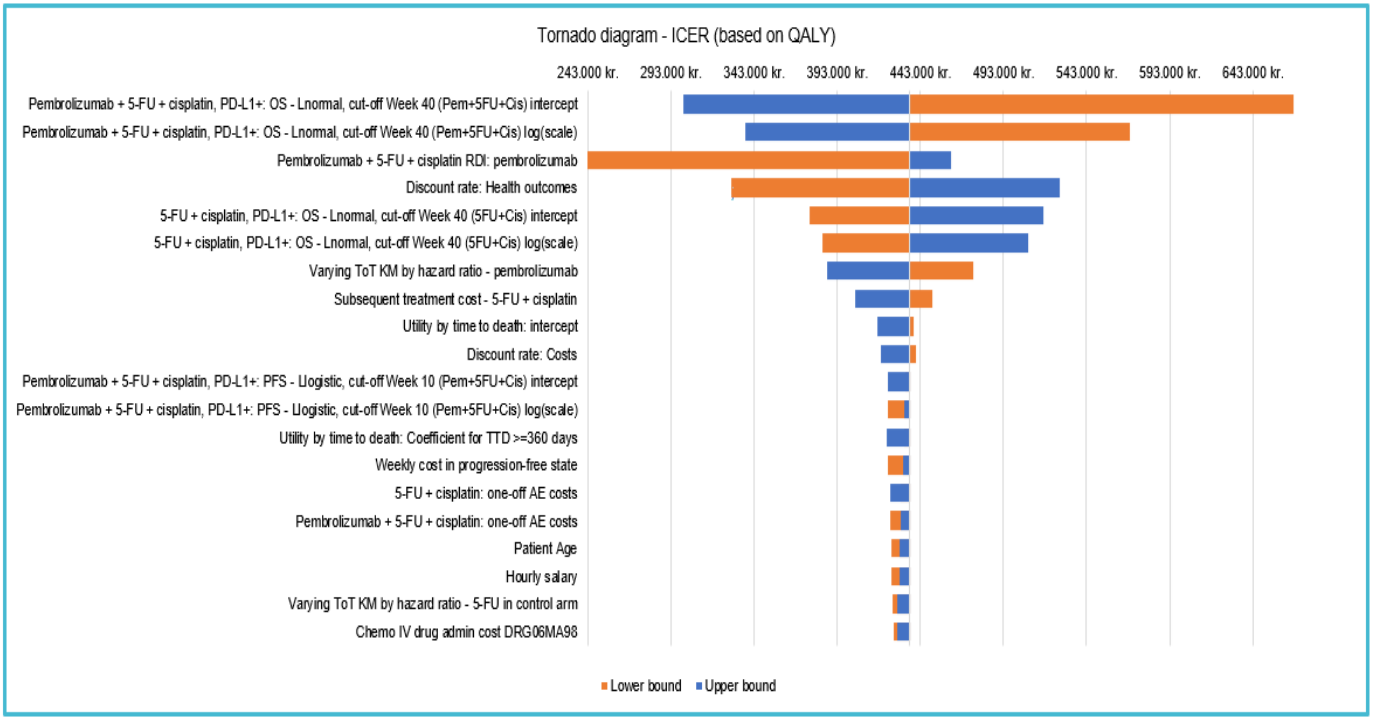
Table 61: Top 10 parameters by impact on ICER (vs blended chemotherapy), PD-L1+ (CPS ≥10)

Model parameter	ICER: lower bound (kr.)	ICER: upper bound (kr.)
Base case	436.778	
Pembrolizumab + 5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 intercept	681.285 (56%)	306.732 (-30%)
Pembrolizumab + 5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 log(scale)	580.897 (33%)	344.934 (-21%)
Pembrolizumab + 5-FU + cisplatin RDI: pembrolizumab	244.391 (-44%)	469.974 (8%)
Discount rate: Health outcomes	335.838 (-23%)	537.836 (23%)
5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 intercept	384.179 (-12%)	527.989 (21%)
5-FU + cisplatin, PD-L1+: OS - Lnormal, cut-off Week 40 log(scale)	391.670 (-10%)	518.222 (19%)
Varying ToT KM by hazard ratio - pembrolizumab	483.492 (11%)	395.801 (-9%)
Subsequent treatment cost - Blended chemo	458.679 (5%)	412.652 (-6%)
Utility by time to death: intercept	448.084 (3%)	426.028 (-2%)
Discount rate: Costs	449.136 (3%)	427.739 (-2%)
Key: 5-FU, fluorouracil; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; kr, Danish krone; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death.		



Key: 5-FU, fluorouracil; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; PD-L1+, programmed death-ligand 1-positive; OS, overall survival; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death; QALY, quality-adjusted life year.

Figure 14: Tornado diagram of Top 10 parameters by impact on ICER (versus 5-FU + cisplatin), PD-L1+ (CPS ≥10)



Key: 5-FU, fluorouracil; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death; QALY, quality-adjusted life year.

Figure 15: Tornado diagram of top 10 parameters by impact on ICER (vs blended chemotherapy), PD-L1+ (CPS ≥10)

Scenario analysis results

A range of scenario analyses were performed to explore the uncertainty of key model assumptions and alternative model choices. Table 62 describes the scenario analyses performed and presents the impact on ICERs for pembrolizumab + 5-FU + cisplatin versus 5-FU + cisplatin versus blended chemotherapy.

The scenario analysis includes other plausible parametric survival models. For OS, the second, third and fourth best-fitting piecewise models with cut-off at Week 40, as well as best-fitting piecewise models with cut-off at Week 32 and best-fitting one-piece model were tested (which were both log-logistics). For PFS, the second, third and fourth best-fitting piecewise models with cut-off at Week 10, as well as best-fitting piecewise model with cut-off at Week 37 (exponential) were tested. For ToT, the best-fitting one-piece models for the pembrolizumab (Weibull) and 5-FU (exponential) were tested. For safety, alternative AE type (i.e. treatment-related AE) and alternative source of AE rates for blended chemotherapy comparator were tested. For health utility, alternative progression-based utility, the option to exclude AE disutility was tested. For costs, 100% relative dose intensity, excluding subsequent treatment cost, and assuming no vial sharing were explored. Other general model settings explored in scenario analysis include alternative time horizon (15 and 40 years) and without half-cycle correction.

The scenarios with the greatest impact on the ICER were alternative parametric function choices for modeling OS, for the comparison versus both 5-FU + cisplatin and blended chemotherapy.

Table 62: Summary of scenario analysis and impact on pairwise ICER

Parameters	Base case	Scenario analysis setting	ICER (vs 5-FU + cisplatin, kr./QALY)	ICER (vs blended chemotherapy, kr./QALY)
Base case ICER			427.968	436.778
Time horizon	30 years	15 years	493.332	503.573
		40 years	425.495	434.246
Half cycle correction	Without half cycle correction	With half cycle correction	428.456	437.270
OS parametric survival model for pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin	Piecewise cut-off at Week 40 – log- normal	Piecewise cut-off Week 40 – Weibull	752.392	768.022
		Piecewise cut-off Week 40 – log-logistic	475.827	485.637
		Piecewise cut-off Week 40 – Gompertz	220.167	224.638
		One-piece log-logistic	872.151	890.241
		Piecewise cut-off Week 32 – log-logistic	595.068	607.370
PFS parametric survival model for pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin	Piecewise cut-off at Week 10 – log-logistic	Piecewise cut-off Week 10 – exponential	421.692	430.502
		Piecewise cut-off Week 10 – log-normal	427.797	436.607
		Piecewise cut-off Week 10 – generalized gamma	423.756	432.566
		Piecewise cut-off Week 37 – exponential	423.168	431.978

Parameters	Base case	Scenario analysis setting	ICER (vs 5-FU + cisplatin, kr./QALY)	ICER (vs blended chemotherapy, kr./QALY)
AE type	All-cause AE	Treatment-related AE	430.107	438.919
AE rate for blended chemotherapy	Assume same as trial comparator	Literature based: Yoon 2016	427.968	453.994
		Literature based: Cleary 2019	427.968	452.317
		Literature based: Waddell 2013	427.968	450.491
Utility approach	Time-to-death	Progression-based	484.580	494.555
AE related disutility	Include	Exclude	427.866	436.674
ToT approach for pembrolizumab	KM	One-piece – Weibull	412.230	421.040
ToT approach for 5-FU in pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms	KM	One-piece – exponential	427.234	436.140
Relative dose intensity for first line drugs	Applied	Not applied (i.e. 100%)	462.945	471.971
Subsequent treatment costs	Include	Exclude	542.794	551.604
Vial sharing assumption	With vial sharing	Without vial sharing	428.842	440.565
Pembrolizumab dosing schedule: % of 400mg Q6W	0%	50%	433.004	441.814

Key: 5-FU, fluorouracil; AE, adverse event; CI, confidence interval; ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; OWSA, one-way sensitivity analysis; PD-L1, programmed death-ligand 1; PFS, progression-free survival, SE, standard error; ToT, time on treatment; QALY, quality-adjusted life year.

In addition, different pembrolizumab prices (kr., 100 mg vial) were explored to test its impact on ICER between the intervention arm vs. 5-FU + cisplatin arm (see Figure 16) and vs. blended chemotherapy arm (see Figure 17).

[redacted]

Key: 5-FU, fluorouracil; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[redacted]

Key: 5-FU, fluorouracil; chemo, chemotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

7.7.2 Probabilistic sensitivity analyses

Table with assumptions that form the basis of the probability distributions used in the probabilistic analysis can be found in appendix J.

PSA was conducted to estimate the probability of pembrolizumab + 5-FU + cisplatin being cost effective relative to comparators, based on different WTP thresholds. A Monte Carlo simulation with 5,000 iterations was conducted. In each iteration, the model inputs were randomly drawn from the specified distributions:

- Multivariate normal distributions based on variance–covariance matrix were applied to:
  - Parameters of parametric survival models for OS, PFS and ToT
  - Coefficients for linear mixed-effects models for estimating health utilities and disutilities
- Beta distributions were assumed for some parameters with value ranges between 0 and 1, including:
  - Proportion of males
  - AE incidence rates for the pembrolizumab + 5-FU + cisplatin arm
  - AE incidence rates for the 5-FU + cisplatin arm
  - AE incidence rates for blended chemotherapy
  - Relative dose intensity
- Normal distributions were used for starting age, duration of Grade 3+ AE
- Log-normal distributions were used for HRs and patient body surface area
- Gamma distributions were assumed for all model costing inputs

Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around mean inputs, the standard errors for these parameters were assumed to be equal to 10% of the base case mean inputs.

Table 63 shows that the average incremental costs and QALY gains and ICER for pembrolizumab + 5-FU + cisplatin versus 5-FU + cisplatin and versus blended chemotherapy were consistent between the PSA results (based on 5.000 iterations) and the base case deterministic results. Probabilistic ICERs were 427.069 kr. per QALY and 435.836 kr. per QALY (versus

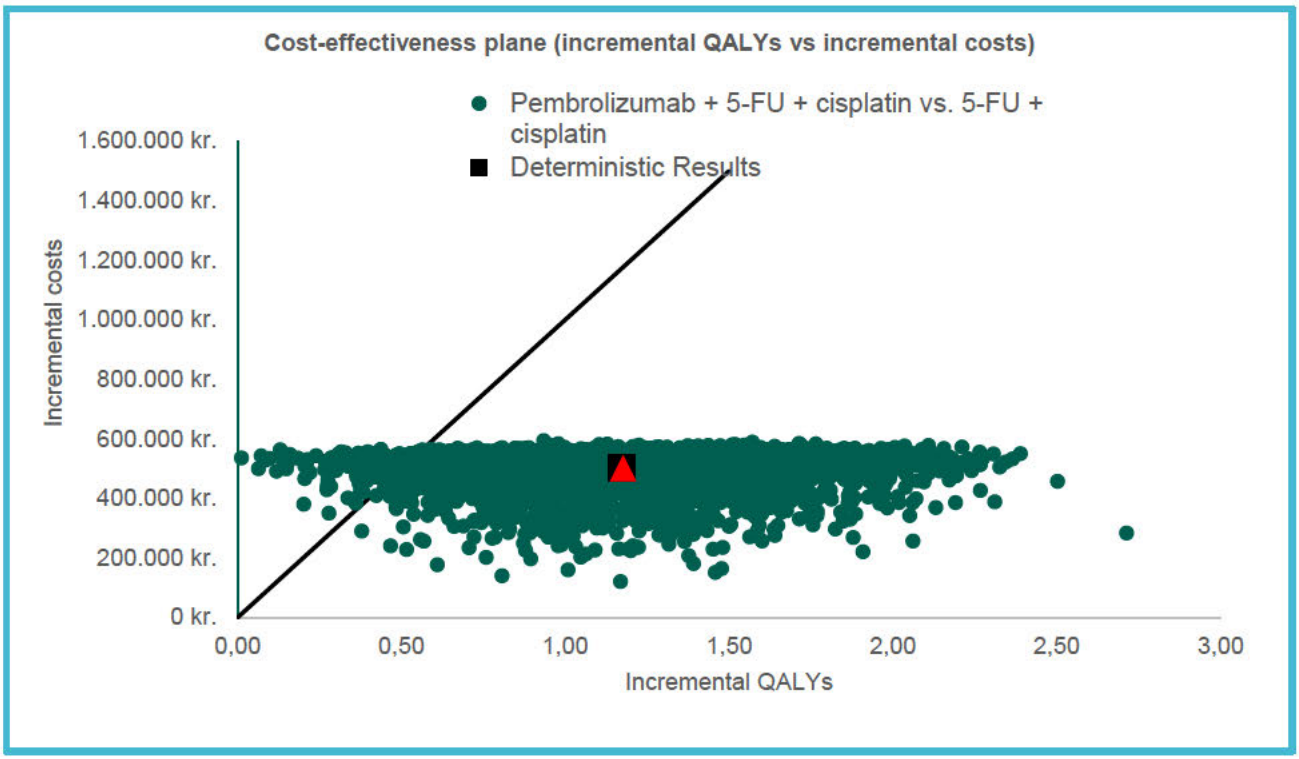
427.968 kr. and 436.778 kr. based on deterministic results) for pembrolizumab + 5-FU + cisplatin versus -FU + cisplatin and versus blended chemotherapy, respectively.

Figure 17 and Figure 18 present scatterplots of simulated incremental cost and QALY for pembrolizumab + 5-FU + cisplatin versus 5-FU + cisplatin and versus blended chemotherapy, respectively. The cost-effectiveness acceptability curve in Figure 19 shows the probability of pembrolizumab + 5-FU + cisplatin or 5-FU + cisplatin being most cost effective over a range of willingness-to-pay (WTP) thresholds. Pembrolizumab + 5-FU + cisplatin is the most cost effective treatment option above a 430.000 kr. threshold which is below the normal range of WTP thresholds of around 800.000 kr./QALY to 1.200.000 kr./QALY (around 2-3 times gross domestic product [GDP] per capita) that normally used for assessing cost-effectiveness of new health technologies. The probability of pembrolizumab + 5-FU + cisplatin being more cost effective versus 5-FU + cisplatin are 92.9% to 98.2% at WTP thresholds of 800.000 kr./QALY and 1.200.000 kr./QALY.

Table 63: Probabilistic cost-effectiveness and incremental cost-effectiveness results: 5.000 iterations, PD-L1+ (CPS ≥10)

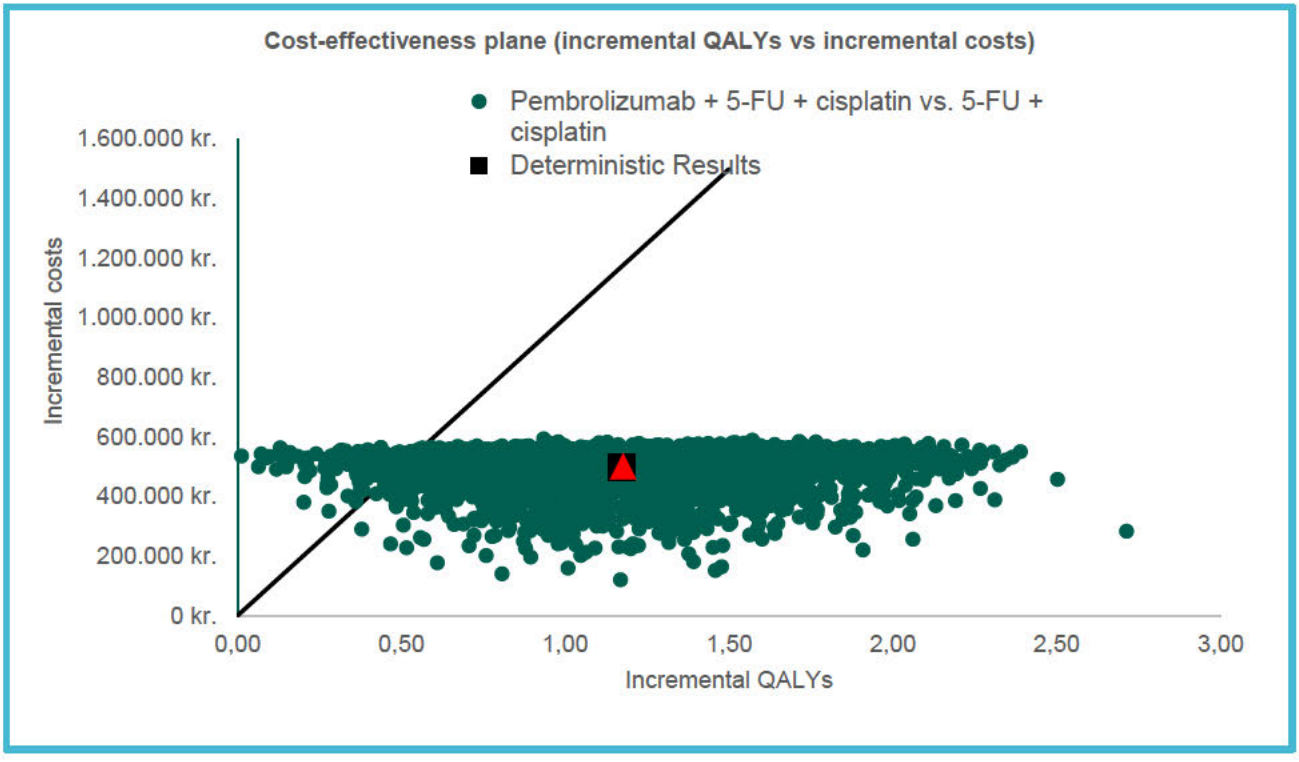
	Incremental costs (kr.)	Incremental QALYs	Incremental LYs	ICER (kr./QALY)	ICER (kr./LY)
Versus 5-FU + cisplatin					
Deterministic results	500.860	1.17	1.29	427.968	387.658
PSA results – mean	501.963	1.18	1.30	427.069	386.708
PSA results - CI (LB, UB)	(334.988,561.223)	(0.47, 1.94)	(0.52, 2.15)	(236.672,1.034.269	(214.175,933.923
Versus blended chemo					
Deterministic results	511.171	1.17	1.29	436.778	395.638
PSA results – mean	512.268	1.18	1.30	435.836	394.647
PSA results - CI (LB, UB)	(343.227,573.159)	(0.47, 1.94)	(0.52, 2.15)	(241.240,1.060.766)	(218.888,970.745

Key: 5-FU, fluorouracil; chemo, chemotherapy; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; LY, life year; PD-L1+, programmed death-ligand 1-positive; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.



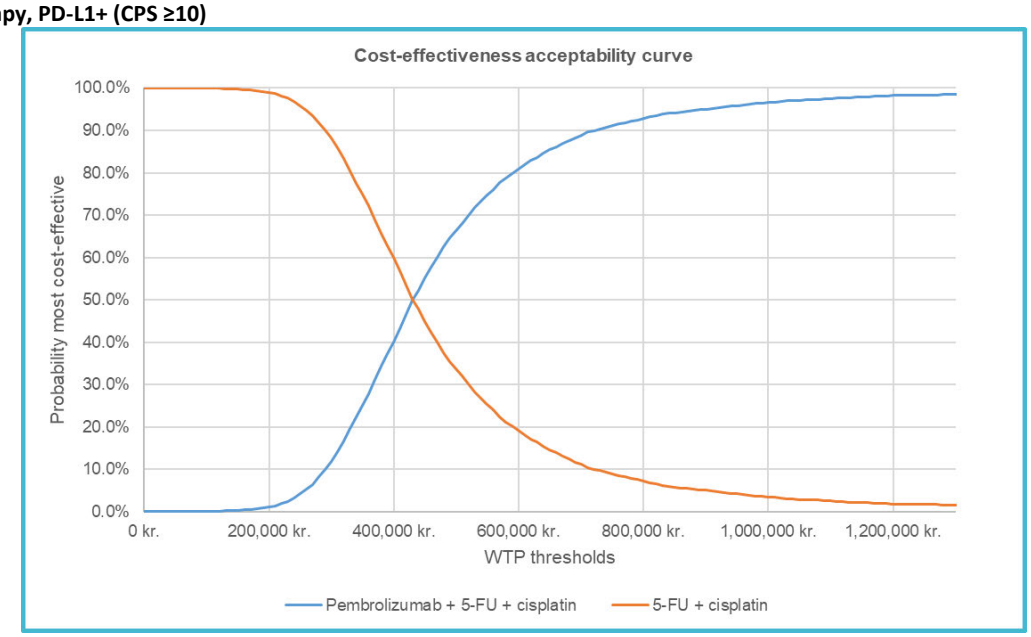
Key: 5-FU, fluorouracil; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 18: Scatterplot of incremental cost and incremental effectiveness: pembrolizumab + 5-FU + cisplatin versus 5-FU + cisplatin, PD-L1+ (CPS ≥10)



Key: 5-FU, fluorouracil; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 19: Scatterplot of incremental cost and incremental effectiveness: pembrolizumab + 5-FU + cisplatin versus blended chemotherapy, PD-L1+ (CPS ≥10)



Key: 5-FU, fluorouracil; chemo, chemotherapy; CPS, combined positive score; PD-L1, programmed death-ligand 1.

Figure 20: Cost-effectiveness acceptability curve: pembrolizumab + 5-FU + cisplatin vs 5-FU + cisplatin, PD-L1+ (CPS ≥10)

8. Budget impact analysis

The budget impact analysis is based on the following assumptions:

- We assume that 66 patients per year will be treated with pembrolizumab + 5-FU + cisplatin if recommended
- If pembrolizumab + 5-FU + cisplatin is not recommended, we assume that no patients will be treated with this intervention
- The cost per patient are undiscounted
- The cost per patient does not include cost for patients related to transportation and time spend on infusion and follow up

Number of patients

The assumption that 66 patients per year will be treated with pembrolizumab + 5-FU + cisplatin if recommended is based on the following:

- In the Danish Medicines Council protocol used for the evaluation of nivolumab for the treatment of 2L esophageal cancer it is estimated that there are approximately 90 metastatic esophageal cancer that are eligible for 1L treatment. Based on the incidence of 50 %PD-L1 CPS ≥ 10 in KN 590 we estimate that 45 patients with esophageal cancer are candidates for treatment with pembrolizumab + 5-FU + cisplatin .
- Of the 626 EGJ adenocarcinoma diagnosed in Denmark, 225 have stage IV disease. We estimate that 25% or 56 of the patients with stage IV disease are GEJ type 1(tumors with epicenter 1 to 5 centimeters above the

GEJ), and approximately 75% or 42 patients are HER-2 negative . Based on the incidence of 50 %PD-L1 CPS ≥ 10 in KN 590 we estimate that 21 patients with GEJ type 1 are candidates for treatment with pembrolizumab + 5-FU + cisplatin .

Table 64: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is recommended by the Danish Medicines Council

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended					
Pembrolizumab + 5-FU + cisplatin	23	66	66	66	66
5-FU + cisplatin	23	0	0	0	0

Table 65: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is not recommended by the Danish Medicines Council

Not recommended	Year 1	Year 2	Year 3	Year 4	Year 5
Pembrolizumab + 5-FU + cisplatin	0	0	0	0	0
5-FU + cisplatin	66	66	66	66	66

Table 66: Cost per patient per year

		Year 1	Year 2	Year 3	Year 4	Year 5
Pembrolizumab + 5-FU + cisplatir						
	Drug acquisition costs	440.642	140.208	0	0	0
	Drug administration cost	29.505	6.979	0	0	0
	Disease management costs, PF	28.544	9.036	4.391	2.699	1.904
	Disease management costs, PD	1.466	1.743	1.473	1.250	1.094
	Subsequent treatment cost	2.211	601	182	81	44
	Terminal cost	35.863	17.752	6.698	3.785	2.524
	PD-L1 testing cost	2.249				
	AE cost	17.688				
	Cost per patient	**558.167**	**176.318**	**12.744**	**7.815**	**5.566**
5-FU + cisplatin						
	Drug acquisition costs	3.121	167	0	0	0
	Drug administration cost	18.239	0	0	0	0
	Disease management costs, PF	21.442	1.926	554	258	150
	Disease management costs, PD	1.987	1.699	950	626	457
	Subsequent treatment cost	125.017	10.445	1.593	507	224
	Terminal cost	48.348	17.566	5.103	2.409	1.396
	AE cost	19.437				
	Cost per patient	**237.592**	**31.804**	**8.198**	**3.800**	**2.228**
Blended chemo						
	Drug acquisition costs	2.543	147	0	0	0
	Drug administration cost	13.185	0	0	0	0
	Disease management costs, PF	21.442	1.926	554	258	150
	Disease management costs, PD	1.987	1.699	950	626	457
	Subsequent treatment cost	125.017	10.445	1.593	507	224
	Terminal cost	48.348	17.566	5.103	2.409	1.396
	AE cost	19.437				
	Cost per patient	**231.960**	**31.784**	**8.198**	**3.800**	**2.228**

Budget impact

The budget impact is the difference between a scenario were pembrolizumab + 5-FU + cisplatin is recommended and a scenario were pembrolizumab + 5-FU + cisplatin is not recommended. The budget impact analysis is based on pharmacy purchase price(AIP) unit drug cost.

Table 67: Expected budget impact of recommending pembrolizumab + 5-FU + cisplatin – base case

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	15.681.081	17.780.127	18.321.217	18.571.993	18.719.039
Recommended	18.419.525	42.657.554	48.896.612	49.575.064	50.016.636
Budget impact	**2.738.444**	**24.877.428**	**30.575.395**	**31.003.072**	**31.297.597**

Table 68: Expected budget impact of recommending pembrolizumab + 5-FU + cisplatin – blended chemo

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	15.309.370	17.407.088	17.948.179	18.198.954	18.346.001
Recommended	18.419.525	42.657.554	48.896.612	49.575.064	50.016.636
Budget impact	**3.110.155**	**25.250.466**	**30.948.433**	**31.376.110**	**31.670.635**

The expected budget impact in the base case is presented in table 67. The budget impact the first year is approximately 2.7 mio. kr. and 31.3 mio. kr. in year 5. The expected budget impact in the comparison with blended chemotherapy is presented in table 68. The budget impact the first year is approximately 3.1 mio. kr. and 31.7 mio. kr. in year 5.

10. Discussion on the submitted documentation

Klinisk og økonomisk merværdi

KN-590 demonstrerer en stor klinisk og økonomisk merværdi for patienter med spiserørskræft og PD-L1 CPS ≥10 sammenlignet med nuværende dansk standardbehandling. Der ses en klinisk relevant og signifikant forskel i mediane OS på 4.1 mdr. med HR 0.62 (0.49-0.78) og en vedvarende forskel i OS-raten ved 12 og 24 mdr. på henholdsvis 16.7% og 16%. Overlevelsesraten efter 24 mdr. er således fordoblet. Risikoen for progression og død reduceres med 49% og der ses en klinisk relevant og signifikant forskel i PFS-raten efter 12 mdr. med 3 gange flere patienter uden progression i pembrolizumab +kemoterapigruppen vs. placebo +kemoterapigruppen og denne forskel øges til 4 gange flere patienter uden progression ved 18 mdr. sammenlignet med kontrolgruppen. Den øgede overlevelse opnås uden at der sker forværringer i bivirkningsraten eller i patienternes livskvalitet. De signifikante kliniske resultater på overlevelse understøtter estimaterne af merværdi i vores sundhedsøkonomiske model med en gevinst på 1.15 kvalitetsjusteret leveår sammenlignet med nuværende dansk standard behandling. ICER var ligeledes favorable for pembrolizumab+5FU+cisplatin med en omkostning pr kvalitetsjusteret leveår på 427.968 kr. sammenlignet med 5FU+cisplatin og 436.778 kr. sammenlignet med ”blended chemo”.

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 påbegyndelse, så de inkluderede patienter alle modtager samme behandling i de respektive behandlingsarme.

Desuden er der fastsatte inklusions- og eksklusionskriterier, hvor inklusionskriterierne er bredere end i andre tilsvarende studier (inkluderer både planocellulære og adenokarcinomer), forskellig etnicitet (stratificeret for Asian vs.

non-Asian) samt uafhængig af biomarkører (PD-L1 status) og en intervention som er mulig for den brede patientgruppe med spiserørskræft.

Valget af cisplatin og 5-flourouracil som komparator danner grundlag for en stærk statistisk sammenligningsgrundlag, som ikke er muligt ved de øvrige kombinationer i den relevante patientpopulation.

Nuværende behandlingsvejledninger baseres hovedsageligt på studier med adenokarcinomer, og det er en styrke at der nu også kommer studiedata på planocellulære karcinomer så vel som adenokarcinomer.

Der ses en median opfølgningstid på 22.6 mdr. (range 19.6-27.1 mdr.) og derved rapporteres modne data på OS, PFS, safety og livskvalitet.

Safety/bivirkningsprofilen fra KN-590 er med bivirkninger som er velkendte og håndterbare i klinikken og svarer til bivirkningsprofiler fra andre Keynote-studier med kombinationsbehandling.

Stor andel patienter i KN-590 som svarer til den danske befolkning (47.5% non-Asia region og 37.3% kaukasisk oprindelse)

Med baggrund i patientkarakteristika og behandlingspraksis kan resultater fra KN-590 overføres til danske patienter.

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.

Der er endnu ikke publiceret en peer-reviewed artikel med data fra KN-590, men resultatdata baseres på udkast til EPAR.

Den kliniske dokumentation kunne være styrket, hvis der i KN-590 havde været mulighed for onkologens valg af de ligestillede behandlingsmuligheder for kemoterapi. Dette ville dog stille endnu større krav til patientantal og studiedesign.

Styrker i vores sundhedsøkonomiske model
Vores sundhedsøkonomiske model er baseret på en partioned survival analyse/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 KN-590. Med baggrund i antal events, så må det konkluderes, at det er modne data, som styrker den langsigtet ekstrapolation af studiedata. Der er en stor grad af sikkerhed omkring modellens anvendelse af data vedrørende længde af behandling. Pembrolizumab er i KN-590 begrænset til 35 doser, svarende til 2 år behandling og ved data cut off var der meget tæt på 0% i behandling.

EQ-5D-5L data var tilgængelig fra KN-590 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 forskellige parametriske funktion. Desuden er modellen også følsom i forhold til pris på

pembrolizumab, tidshorisont og tilgang til nytteværdi(time to death vs. Progression-based). Probalitiske følsomhedsanalyser understøtter også robustheden af base case estimater af gevinster baseret på 5.000 gentagelser

Begrænsninger i vores sundhedsøkonomiske model
Valg af parametrisk funktion efter "transition point" 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"

men der vil altid være et element af usikkerhed forbundet med ekstrapolation langt ud over studiets opfølgningstid. Dette gælder særligt for nye interventioner som pembrolizumab+5FU+cisplatin, hvor der ikke findes eksisterende langtidsdata, som kan anvendes til at validere.

En anden begrænsning er, at der ikke findes en direkte sammenligning af pembrolizumab+5FU+cisplatin med modellens "non trial comparators". Med baggrund i manglende data på sundhedseffekter af "non trial comparators" i den population som ansøgningen omhandler, så antages det i modellen , at sundhedseffekter for "blended chemo" er de samme som for 5FU+cisplatin. Denne tilgang understøttes af dansk klinisk guideline.

En tredje 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

1. Kato K, Shah MA, Enzinger P, Bennouna J, Shen L, Adenis A, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol. 2019;15(10):1057-66.
2. Kojima T, Shah MA, Muro K, Francois E, Adenis A, Hsu CH, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. J Clin Oncol. 2020;38(35):4138-48.
3. Janmaat VT, Steyerberg EW, van der Gaast A, Mathijssen RH, Bruno MJ, Peppelenbosch MP, et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev. 2017;11:CD004063.
4. DECG DMCG-. Onkologisk behandling af non-kurabel cancer i esophagus, GEJ og ventrikel. Klinisk Retningslinje.; 2020 6. juni 2020.
5. (DECG) DECGd. Årsrapport 2019. 2019 August 2020.
6. Medicinrådet. Medicinrådets protokol for vurdering af nivolumab til behandling af planocellulært karcinom i spiserøret med avanceret sygdom efter tidligere behandling med kemoterapi. 2021 14. jan 2021.
7. Agency EM. Summary of opinion, Keytruda Pembrolizumab. 2021.

8. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358(1):36-46.
9. Wagner AD, Syn NL, Moehler M, Grothe W, Yong WP, Tai BC, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2017;8:CD004064.
10. Agency EM. EPAR (assessment report Procedure No. EMEA/H/C/003820/II/0097) 20 May 2021 (https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0097-epar-assessment-report-variation_en.pdf)11. Merck Sharp & Dohme Corp M. Clinical Study Report, Esophageal carcinoma (Confidential). 2021.
12. Shah MA, Kojima T, Hochhauser D, Enzinger P, Raimbourg J, Hollebecque A, et al. Efficacy and Safety of Pembrolizumab for Heavily Pretreated Patients With Advanced, Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus: The Phase 2 KEYNOTE-180 Study. JAMA Oncol. 2019;5(4):546-50.
13. Gruppe DM. Onkologisk behandling af inoperabel metastatisk melanom. 2020.
14. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50-v7.
15. Siewert JR, Stein HJ, Feith M. Adenocarcinoma of the esophago-gastric junction. Scand J Surg. 2006;95(4):260-9.
16. Schonnemann KR, Mortensen MB, Bjerregaard JK, Fristrup C, Pfeiffer P. Characteristics, therapy and outcome in an unselected and prospectively registered cohort of patients with gastro-oesophageal cancer. Acta Oncol. 2014;53(3):385-91.
17. Harris C, Croce B, Munkholm-Larsen S. Esophageal cancer. Ann Cardiothorac Surg. 2017;6(2):190.
18. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381(9864):400-12.
19. Bekæmpelse K. Statistik om spiserørskræft 2019 [Available from: https://www.cancer.dk/spiseroerskraeft-oesofaguscancer/statistik-om-spiserorskraeft/.
20. Zhao D, Klempner SJ, Chao J. Progress and challenges in HER2-positive gastroesophageal adenocarcinoma. J Hematol Oncol. 2019;12(1):50.
21. Waters JS, Norman A, Cunningham D, Scarffe JH, Webb A, Harper P, et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer. 1999;80(1-2):269-72.
22. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28(9):1547-53.
23. Society AC. Survival Rates for Esophageal Cancer 2021 [Available from: https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staging/survival-rates.html.
24. Chung HC, Piha-Paul SA, Lopez-Martin J, Schellens JHM, Kao S, Miller WH, Jr., et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J Thorac Oncol. 2020;15(4):618-27.
25. DeVita VT, Jr., Chu E. A history of cancer chemotherapy. Cancer Res. 2008;68(21):8643-53.
26. promedicin.dk. Cisplatin 'Ebewe' 2021 [Available from: https://pro.medicin.dk/Medicin/Praeparater/4099.
27. Promedicin.dk. Fluorouracil 'Pfizer' 2021 [Available from: https://pro.medicin.dk/Medicin/Praeparater/1469.
28. Kato K. Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study. ESMO2020.
29. Mansoor W. Health-related quality of life (HRQoL) of pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase III KEYNOTE-590 study. 2021.
30. Medicinrådet. Medicinrådets vurdering af klinisk merværdi for pembrolizumab i kombination med kemoterapi til behandling af ikke-planocellulær ikke-småcellet lungekræft. 2019 20.01.2019.
31. Svane IM. Vurdering og håndtering af bivirkninger relateret til immunterapi med checkpoint hæmmere. 2018.
32. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139-44.

33. Musoro JZ, Sodergren SC, Coens C, Pochesci A, Terada M, King MT, et al. Minimally important differences for interpreting the EORTC QLQ-C30 in patients with advanced colorectal cancer treated with chemotherapy. Colorectal Dis. 2020.
34. Woods B SE, Palmer S, et al. . NICE DSU TECHNICAL SUPPORT DOCUMENT 19: PARTITIONED SURVIVAL ANALYSIS FOR DECISION MODELLING IN HEALTH CARE: A CRITICAL REVIEW. 2017. 2017 [Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf.
35. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14(6):481-9.
36. Cleary JM, Horick NK, McCleary NJ, Abrams TA, Yurgelun MB, Azzoli CG, et al. FOLFOX plus ziv-aflibercept or placebo in first-line metastatic esophagogastric adenocarcinoma: A double-blind, randomized, multicenter phase 2 trial. Cancer. 2019;125(13):2213-21.
37. Yoon HH, Bendell JC, Braiteh FS, Firdaus I, Philip PA, Cohn AL, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. Ann Oncol. 2016;27(12):2196-203.
38. Organization WH. Global Health Observatory data repository, Life tables by country, Denmark. 2019 2019 [Available from: https://apps.who.int/gho/data/view.main.60450.
39. Lee J, Im YH, Cho EY, Hong YS, Lee HR, Kim HS, et al. A phase II study of capecitabine and cisplatin (XP) as first-line chemotherapy in patients with advanced esophageal squamous cell carcinoma. Cancer Chemother Pharmacol. 2008;62(1):77-84.
40. Lee SJ, Kim S, Kim M, Lee J, Park YH, Im YH, et al. Capecitabine in combination with either cisplatin or weekly paclitaxel as a first-line treatment for metastatic esophageal squamous cell carcinoma: a randomized phase II study. BMC Cancer. 2015;15:693.
41. N. L. NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA. University of Sheffield, 2013 2013 [Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf.
42. Elgaard Jensen K. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy. 2021.
43. Batty AJ, Fisher D, Winn B, Wang Q, Tolley K, Rowen D. PCN148 Estimating Quality of Life in Advanced Melanoma; A Comparison of Standard Gamble, SF-36 Mapped, and Eortc QLQ-C30 Mapped Utilities. Value in Health. 2011;14(7):A461-A2.
44. Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health Qual Life Outcomes. 2014;12:140.
45. Medicinrådet. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet 2021 [Available from: https://medicinraadet.dk/media/mbtgpjjl/efter-1-januar-2021_appendiks-til-medicinr%C3%A5dets-metodevejledning-aldersjustering_adlegacy.pdf.
46. Cancer.Net. Esophageal cancer: statistics. 2020 2020 [Available from: https://www.cancer.net/cancer-types/esophageal-cancer/statistics#:~:text=The%205%2Dyear%20survival%20rate%20of%20people%20with%20cancer%20located,the%20survival%20rate%20is%205%25.
47. Gavin AT, Francisci S, Foschi R, Donnelly DW, Lemmens V, Brenner H, et al. Oesophageal cancer survival in Europe: a EUROCARE-4 study. Cancer Epidemiol. 2012;36(6):505-12.
48. Society AC. Survival Rates for Esophageal Cancer. 2020 2020 [Available from: https://www.cancer.org/content/cancer/en/cancer/esophagus-cancer/detection-diagnosis-staging/survival-rates/.
49. Wu SG, Zhang WW, He ZY, Sun JY, Chen YX, Guo L. Sites of metastasis and overall survival in esophageal cancer: a population-based study. Cancer Manag Res. 2017;9:781-8.
50. Wu SG, Xie WH, Zhang ZQ, Sun JY, Li FY, Lin HX, et al. Surgery Combined with Radiotherapy Improved Survival in Metastatic Esophageal Cancer in a Surveillance Epidemiology and End Results Population-based Study. Sci Rep. 2016;6:28280.
51. Tanaka T, Fujita H, Matono S, Nagano T, Nishimura K, Murata K, et al. Outcomes of multimodality therapy for stage IVB esophageal cancer with distant organ metastasis (M1-Org). Dis Esophagus. 2010;23(8):646-51.

Medicinrådet Dampfærgevej 27-29, 3. th. 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 KN-590 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 søgningen ikke forventes at tilvejebringe yderligere relevant dokumentation for effekt og sikkerhed for både intervention og komparator, som også drøftet med Medicinrådets sekretariat ved indledende dialogmøde af 25. marts 2021.

Det relevante og endnu ikke selvstændigt publicerede studie til denne ansøgning er: Kato, K et al. Pembrolizumab Plus Chemotherapy Versus Chemotherapy as First-Line Therapy in Patients With Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study. NCT-nummer: NCT03189719. Studiestart den 25. Juli 2017 og studie slutdato 2. juli 2020. For fuld liste af studiekarakteristika, se appendix B].

Data brugt til denne ansøgning er data on file (Clinical Study Report)[11], det foreløbige udkast til EPAR [10] samt data fra orale præsentationer med tilhørende abstracts fra de onkologiske konferencer ESMO 2020 og ESMO-GI 2021 [28, 29].

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

Appendix B Main characteristics of included studies

[Complete the table for each included study. Comply with section 3 of the guideline.]

Trial name:	**NCT number: NCT03189719**
First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590)	
Objective	*The purpose of this trial is to evaluate efficacy and safety of pembrolizumab plus cisplatin and 5-fluorouracil (5-FU) chemotherapy versus placebo plus cisplatin and 5-FU chemotherapy as first-line treatment in participants with locally advanced or metastatic esophageal carcinoma.*
Publications – title, author, journal, year	*(Description of study background):)Kato K, Shah MA, Enzinger P, Bennouna J, Shen L, Adenis A, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol. 2019;15(10):1057-66.* *(Oral presentation and abstract at ESMO 2020) Kato K. Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study. ESMO2020.* *(Oral presentation and abstract at ESMO-GI 2020) Mansoor W. Health-related quality of life (HRQoL) of pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase III KEYNOTE-590 study. 2021.*
Study type and design	*The KEYNOTE-590 study is a rRandomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial. is a randomized, double-blind, placebo-controlled Phase III study (Figure 1). Eligible patients will be randomly assigned in a 1:1 ratio to receive pembrolizumab 200 mg or placebo (normal saline) by intravenous (iv.) infusion every 3 weeks (Q3W) in combination with chemotherapy. The chemotherapy regimen for both arms will consist of cisplatin 80 mg/m2 iv. Q3W (maximum six doses) plus 5-fluorouracil 800 mg/m2 continuous iv. infusion on days 1–5 Q3W. No crossover was allowed* *Actual Primary Completion Date : July 2, 2020*
Sample size (n)	*749 participants*

Main inclusion and exclusion criteria	***Inclusion Criteria**:* *Has histologically- or cytologically-confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction (EGJ)* *Has measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment* *Eastern Cooperative Group (ECOG) performance status of 0 to 1* *Can provide either a newly obtained or archival tissue sample for PD-L1 by immunohistochemistry analysis* *Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to randomization and be willing to use an adequate method of contraception (e.g. abstinence, intrauterine device, diaphragm with spermicide, etc.) for the course of the study through 120 days after the last dose of study treatment and up to 180 days after last dose of cisplatin* *Male participants of childbearing potential must agree to use an adequate method of contraception (e.g. abstinence, vasectomy, male condom, etc.) starting with the first dose of study treatment through 120 days after the last dose of study treatment and up to 180 days after last dose of cisplatin, and refrain from donating sperm during this period* *Has adequate organ function* ***Exclusion Criteria:*** *Has locally advanced esophageal carcinoma that is resectable or potentially curable with radiation therapy (as determined by local investigator)* *Has had previous therapy for advanced/metastatic adenocarcinoma or squamous cell cancer of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ* *Has had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment* *Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early-stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, in situ breast cancer that has undergone potentially curative therapy, and in situ or intramucosal pharyngeal cancer* *Has known active central nervous system metastases and/or carcinomatous meningitis.* *Has an active autoimmune disease that has required systemic treatment in past 2 years* *Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment, or has a history of organ transplant, including allogeneic stem cell transplant* *Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis, or has an active infection requiring systemic therapy* *Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study medication and up to 180 days after last dose of cisplatin*

Trial name:	NCT number: NCT03189719
First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590)	
	Has received prior therapy with an anti-programmed cell death protein-1 (anti-PD-1), anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor or has previously participated in a pembrolizumab (MK-3475) clinical trial *Has severe hypersensitivity (≥ Grade 3) to any study treatment (pembrolizumab, cisplatin, or 5-FU) and/or any of its excipients* *Has a known history of active tuberculosis (TB; Mycobacterium tuberculosis) or human immunodeficiency virus (HIV) infection* *Has known history of or is positive for hepatitis B or hepatitis C* *Has received a live vaccine within 30 days prior to the first dose of study treatment* *Has had radiotherapy within 14 days of randomization. Participants who received radiotherapy >14 days prior to randomization must have completely recovered from any radiotherapy-related AEs/toxicities*
Intervention	*373 patients were randomized to the intervention and 370 received at least 1 dose.* *Experimental: Pembrolizumab + Cisplatin + 5-FU* *Participants receive pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W), cisplatin 80 mg/m^2 IV Q3W, and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours). All treatments will be administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.* --- *Biological: Pembrolizumab* *200 mg administered IV Q3W on Day 1 of each 3-week cycle, up to 35 administrations.* *Other Name: MK-3475* *Drug: Cisplatin* *80 mg/m^2 administered IV Q3W on Day 1 of each 3-week cycle. Duration of cisplatin treatment will be capped at 6 doses.* *Drug: 5-FU* *800 mg/m^2/day (4000 mg/m^2 total per cycle) administered as continuous IV infusion on Days 1 to 5 (120 hours) of each 3-week cycle, or per local standard for 5-FU administration, up to 35 administrations.*

Trial name:	NCT number: NCT03189719
First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590)	
Comparator(s)	*376 patients were randomized to the comparator and 370 received at least 1 dose.* *Placebo Comparator: Placebo + Cisplatin + 5-FU* *Participants receive placebo to pembrolizumab (saline) IV Q3W, cisplatin 80 mg/m^2 IV Q3W, and 5-FU 800 mg/m^2/day continuous IV infusion on Days 1 to 5 (120 hours). All treatments will be administered on an outpatient basis beginning on Day 1 of each 3-week dosing cycle.* --- *Drug: Placebo* *Placebo to pembrolizumab (saline) administered IV Q3W on Day 1 of each 3-week cycle, up to 35 administrations.* *Drug: Cisplatin* *80 mg/m^2 administered IV Q3W on Day 1 of each 3-week cycle. Duration of cisplatin treatment will be capped at 6 doses.* *Drug: 5-FU* *800 mg/m^2/day (4000 mg/m^2 total per cycle) administered as continuous IV infusion on Days 1 to 5 (120 hours) of each 3-week cycle, or per local standard for 5-FU administration, up to 35 administrations.*
Follow-up time	*Median follow-up of 22.6 months. (range 19.6-27.1)*
Is the study used in the health economic model?	*Yes*

Primary, secondary and exploratory endpoints

Primary Endpoints

1. *Overall Survival (OS) in Participants With Esophageal Squamous Cell Carcinoma (ESCC) Whose Tumors Are Programmed Cell Death-Ligand 1 (PD-L1) Biomarker-Positive (Combined Positive Score [CPS] ≥10) [Time Frame: Up to approximately 2 years]*
2. *OS in Participants With ESCC [Time Frame: Up to approximately 2 years]*
3. *OS in Participants Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Up to approximately 2 years]*
4. *OS in All Participants [Time Frame: Up to approximately 2 years]*
5. *Progression-free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) As Assessed By Investigator in Participants With ESCC [Time Frame: Up to approximately 2 years]*
6. *PFS Per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Up to approximately 2 years]*
7. *PFS Per RECIST 1.1 As Assessed By Investigator in All Participants [Time Frame: Up to approximately 2 years]*

Secondary Endpoints

1. *Objective Response Rate (ORR) Per RECIST 1.1 As Assessed By Investigator in All Participants [Time Frame: Up to approximately 2 years]*
2. *ORR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC Whose Tumors Are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Up to approximately 2 years]*
3. *ORR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC [Time Frame: Up to approximately 2 years]*
4. *ORR per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Up to approximately 2 years]*
5. *Duration of Response (DOR) per RECIST 1.1 As Assessed By Investigator in All Participants [Time Frame: Up to approximately 2 years]*
6. *DOR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Up to approximately 2 years]*
7. *DOR per RECIST 1.1 As Assessed By Investigator in Participants With ESCC [Time Frame: Up to approximately 2 years]*
8. *DOR per RECIST 1.1 As Assessed By Investigator in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Up to approximately 2 years]*
9. *Number of Participants With an Adverse Event (AE) [Time Frame: Up to approximately 27 months]*
10. *Number of Participants Discontinuing Study Treatment Due to an AE [Time Frame: Up to 2 approximately years]*
11. *Change from Baseline in the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) Score in All Participants [Time Frame: Baseline, approximately 1 year]*
12. *Change from Baseline in the EORTC QLQ-C30 Score in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Baseline, approximately 1 year]*

Trial name:	NCT number: NCT03189719
First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590)	

13. *Change from Baseline in the EORTC QLQ-C30 Score in Participants With ESCC [Time Frame: Baseline, approximately 1 year]*
14. *Change from Baseline in the EORTC QLQ-C30 Score in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Baseline, approximately 1 year]*
15. *Change from Baseline in the EORTC Quality Of Life Questionnaire Oesophageal Module (QLQ-OES18) Score in All Participants [Time Frame: Baseline, approximately 1 year]*
16. *Change from Baseline in the QLQ-OES18 Score in Participants With ESCC Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Baseline, approximately 1 year]*
17. *Change from Baseline in the QLQ-OES18 Score in Participants With ESCC [Time Frame: Baseline, approximately 1 year]*
18. *Change from Baseline in the QLQ-OES18 Score in Participants Whose Tumors are PD-L1 Biomarker-Positive (CPS ≥10) [Time Frame: Baseline, approximately 1 year]*

Endpoints included in this application:

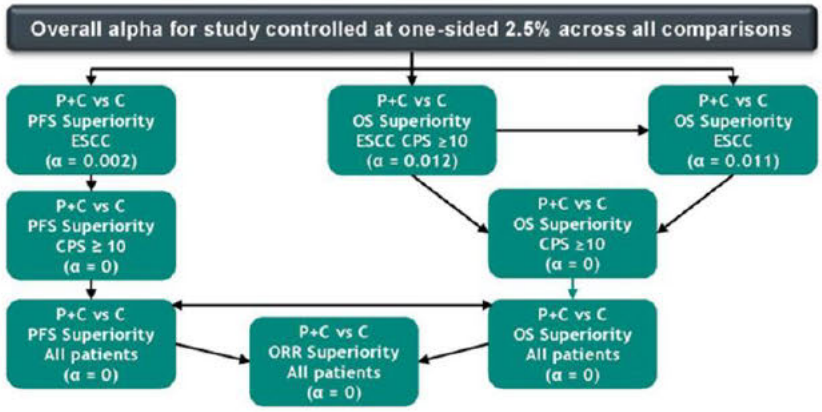
The primary endpoints in this application:

1. *Overall Survival, OS, as defined as the time from randomization to death due to any cause. For this analysis, OS will be assessed in participants whose tumors are PD-L1 biomarker-positive (CPS ≥10).*
2. *Progression-free Survival, PFS, as defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by investigator, or death due to any cause, whichever occurs first..*
3. *Safety/Adverse Events*
4. *Health-related quality of life (HRQoL) as assessed by QLQ-C30.*

Method of analysis	*Efficacy will be assessed in the intent-to-treat population (all randomly assigned patients) and analyzed by randomized treatment group. Safety will be assessed in all randomly assigned patients who received at least one dose of study drug and will be analyzed by treatment received* *Kaplan–Meier method is used to estimate rates of progression-free survival and overall survival.*

Trial name:	NCT number: NCT03189719
First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590)	

Subgroup analyses



C, chemotherapy; P, pembrolizumab; PD-L1 positive defined as PD-L1 combined positive score (CPS) ≥10.

Pre-study statistical plan for test of hypothesis.

For included participants, see baseline characteristics for ITT population.

Stratification factors: Stratified according to geographic region (Asia vs rest of world), histology (adenocarcinoma vs SCC), and Eastern Cooperative Oncology Group (ECOG), performance status (0 or 1)

Other relevant information

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Below the table, provide a description of the comparability of the baseline characteristics across the studies and how well the study populations align with patients treated in Danish clinical practice.]

Baseline characteristics of ITT-population in Keynote-590 included for the comparative analysis of efficacy and safety		
Karakteristika, n (%)	**Pembrolizumab + kemoterapi N = 373**	**kemoterapi N = 376**
Alder, median (range), år	64.0 (28-94)	62.0 (27-89)
≥65 år	172 (46.1)	150 (39.9)
Mænd	306 (82.0)	319 (84.8)
Asia Region[†]	196 (52.5)	197 (52.4)
Race		
Asian	201 (53.9)	199 (52.9)
White	139 (37.3)	139 (37.0)
Missing	14 (3.8)	15 (4.0)
American Indian	9 (2.4)	12 (3.2)
African American	5 (1.3)	2 (0.5)
Other	5 (1.3)	6 (1.6)
ECOG Performance Status		
0	149 (39.9)	150 (39.9)
1	223 (59.8)	225 (59.8)
2	1 (0.3)	1 (0.3)
Primary Diagnosis		
Planocellulær	274 (73.5)	274 (72.9)
Adenocarcinom	99 (26.5)	102 (27.1)
EAC	58 (15.5)	52 (13.8)
Siewert type 1 GEJ adenocarcinoma	41 (11.0)	50 (13.3)

Disease Status		
Metastatic	344 (92.2)	339 (90.2)
Unresectable-locally advanced	29 (7.8)	37 (9.8)
PD-L1 Status		
CPS ≥10	186 (49.9)	197 (52.4)
ESCC	143 (38.3)	143 (38.0)
Adenocarcinoma	43 (11.5)	54 (14.3)
CPS <10	175 (46.9)	172 (45.7)
ESCC	121 (32.4)	126 (33.5)
Adenocarcinoma	54 (14.4)	46 (12.2)
Not evaluable/missing	12 (3.2)	7 (1.9)

Baseline characteristics of EU vs. Ex-EU-population in Keynote-590 included for the comparative analysis of efficacy and safety

	EU		Ex-EU		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	114		635		749	
Gender						
Male	92	(80.7)	533	(83.9)	625	(83.4)
Female	22	(19.3)	102	(16.1)	124	(16.6)
Age (Years)						
< 65	68	(59.6)	359	(56.5)	427	(57.0)
>= 65	46	(40.4)	276	(43.5)	322	(43.0)
Mean	61.4		62.6		62.4	
SD	9.3		9.5		9.5	
Median	61.0		63.0		63.0	
Range	27 to 79		30 to 94		27 to 94	
Race						
American Indian Or Alaska Native	0	(0.0)	21	(3.3)	21	(2.8)
Asian	3	(2.6)	397	(62.5)	400	(53.4)
Black Or African American	0	(0.0)	7	(1.1)	7	(0.9)
Multiple	0	(0.0)	14	(2.2)	14	(1.9)
American Indian Or Alaska Native, White	0	(0.0)	9	(1.4)	9	(1.2)
Black Or African American, White	0	(0.0)	5	(0.8)	5	(0.7)
White	82	(71.9)	196	(30.9)	278	(37.1)
Missing	29	(25.4)	0	(0.0)	29	(3.9)

Ethnicity						
Hispanic Or Latino	3	(2.6)	96	(15.1)	99	(13.2)
Not Hispanic Or Latino	79	(69.3)	532	(83.8)	611	(81.6)
Not Reported	2	(1.8)	1	(0.2)	3	(0.4)
Unknown	26	(22.8)	6	(0.9)	32	(4.3)
Missing	4	(3.5)	0	(0.0)	4	(0.5)
Region						
Asia	0	(0.0)	393	(61.9)	393	(52.5)
Rest of World	114	(100.0)	242	(38.1)	356	(47.5)
Primary Diagnosis						
Squamous Cell Carcinoma of the Esophagus	66	(57.9)	482	(75.9)	548	(73.2)
Adenocarcinoma of the Esophagus	27	(23.7)	83	(13.1)	110	(14.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	21	(18.4)	70	(11.0)	91	(12.1)
Metastatic Staging						
M0	11	(9.6)	55	(8.7)	66	(8.8)
M1	103	(90.4)	580	(91.3)	683	(91.2)
Brain Metastasis						
Yes	0	(0.0)	3	(0.5)	3	(0.4)
No	114	(100.0)	632	(99.5)	746	(99.6)
Current Disease Stage						
IB	0	(0.0)	1	(0.2)	1	(0.1)
IIB	0	(0.0)	1	(0.2)	1	(0.1)
III	2	(1.8)	8	(1.3)	10	(1.3)
IIIA	0	(0.0)	9	(1.4)	9	(1.2)
IIIB	5	(4.4)	15	(2.4)	20	(2.7)
IIIC	4	(3.5)	21	(3.3)	25	(3.3)
IV	84	(73.7)	473	(74.5)	557	(74.4)
IVA	5	(4.4)	11	(1.7)	16	(2.1)
IVB	11	(9.6)	95	(15.0)	106	(14.2)
IVC	1	(0.9)	1	(0.2)	2	(0.3)
IVE	2	(1.8)	0	(0.0)	2	(0.3)
ECOG Performance Scale						
0	52	(45.6)	247	(38.9)	299	(39.9)
1	62	(54.4)	386	(60.8)	448	(59.8)
2	0	(0.0)	2	(0.3)	2	(0.3)
Histology						
Adenocarcinoma	48	(42.1)	153	(24.1)	201	(26.8)
Squamous Cell Carcinoma	66	(57.9)	482	(75.9)	548	(73.2)
Disease Status						
Metastatic	103	(90.4)	580	(91.3)	683	(91.2)
Unresectable - Locally Advanced	11	(9.6)	55	(8.7)	66	(8.8)

Comparability of patients across studies

N/A

Comparability of the study populations with Danish patients eligible for treatment

KN-590 studiet var et internationalt studie med deltagelse af 26 lande. Ved gennemgang af baselinedata fra KN-590 studiet ses at patienter med spiserørskræft i ITT populationen, at 47.5% kommer fra Non-Asian region (356 personer) og at 37% (278 personer) af ITT populationen er af kaukasisk oprindelse. Ligeledes er (15%) 114 deltagere fra EU-lande, hvorfor data fra KN-590 fint repræsenterer befolkningen med spiserørskræft i Danmark bortset fra aldersgennemsnit i KN-590 er 63 år (range 27-94) og jf. DEGCs årsrapport 2019 er den i DK 70 år (range 31,4-105 år) på ny-diagnostiserede, som ikke er direkte sammenlignelige med KN-590 patienter.

I Danmark er adenokarcinomer generelt hyppigere end planocellulære karcinomer i esophagus og GEJ cancer, men for den population, som denne ansøgning dækker *(spiserørskræft= esophagus og GEJ type 1)* er der overensstemmelse mellem histologifordelingen fra KN-590 og den i dansk klinisk praksis.

Appendix D Efficacy and safety results per study

Definition of included outcome measures

Outcome measure	Definition
Overall Survival	OS is defined as the time from randomization to death due to any cause. For this analysis, OS will be assessed in participants whose tumors are PD-L1 biomarker-positive (CPS ≥10).
Progression Free Survival	PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by investigator, or death due to any cause, whichever occurs first. For this analysis, PFS will be assessed in participants whose tumors are PD-L1 biomarker-positive (CPS ≥10).
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 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.
Life Quality, EORTC QLQ	The EORTC QLQ-C30 was developed to assess the quality of life of patients with cancer. It contains 30 questions (items), 24 of which aggregate into nine multi-item scales representing various aspects, or dimensions, of quality of life (QOL): one global scale, five functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain), and six additional single-symptom items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. Individual items are scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Raw scores for each scale are standardized into a range of 0 to 100 by linear transformation; a higher score on the global and functional scales represents a higher ("better") level of functioning, and a higher score on the symptom scale represents a higher ("worse") level of symptoms.

Results per study

Table A3a Results of First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590) NCT03189719

				Estimated difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**HR & 95% CI**	***P* value**		
Median overall survival *PD-L1 CPS ≥ 10*	Intervention	186	13.5 (11.1-15.6) months	4.1 months	HR 0.62 (CI 0.49-0.78)	P<0.0001	*The median survival is based on the Kaplan–Meier estimator. Hazard ratios will be estimated using a stratified Cox proportional hazards regression model using the same factors for randomization*	[10, 28]
	Comparator	197	9.4 (8.0–10.7) months					
Median Overall Survival EU-population	Intervention	61	11.4 (8.0-17.2) months	0.4 months	HR 0.72 (CI 0.47-1.10)	P=0.0619		[10]
	Comparator	53	11.0 (8.0-13.3) months					
Median Overall Survival *EU-pop PD-L1 CPS ≥ 10*	Intervention	31	11.4 months (CI NA)	2.8 months	HR 0.60 (CI NA)	P=NA		[10]
	Comparator	26	8.6 months (CI NA)					

Table A3a Results of First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590) NCT03189719								
1-year survival *PD-L1 CPS ≥ 10*	Intervention	186	[redacted]	[redacted]	N/A	N/A	*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.*	[11]
	Comparator	197	[redacted]					
2-year survival *PD-L1 CPS ≥ 10*	Intervention	186	[redacted]	[redacted]	N/A	N/A	*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.*	[11]
	Comparator	197	[redacted]					
Median PFS *PD-L1 CPS ≥ 10*	Intervention	186	7.5 months	2 months	HR 0.51 (CI 0.41-0.65)	P<0.0001	*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*	[10, 28]
	Comparator	197	5.5 months					
1-year PFS rates *PD-L1 CPS ≥ 10*	Intervention	186	[redacted]	[redacted]	N/A	N/A	*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*	[11]
	Comparator	197	[redacted]					
2-year PFS rates *PD-L1 CPS ≥ 10*	Intervention	186	[redacted]	[redacted]	N/A	N/A	*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*	[11]
	Comparator	197	[redacted]					

Table A3a Results of First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590) NCT03189719								
All cause safety grade 3-4 *as-treated population*	Intervention	370	85.9%	-2.7 absolute risk reduction	-7.9 to 2.4	RR=1.03 (0.97-1.1)	*Safety will be assessed in all randomly assigned patients who received at least one dose of study drug and will be analyzed by treatment received. Safety will be monitored throughout the study and for 30 days after the end of treatment (90 days for serious adverse events). Safety analysis will include the incidence, causality and outcome of adverse events; changes in vital signs; and changes in laboratory values. Adverse events will be graded and recorded throughout the trial and follow-up period per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4*	[10]
	Comparator	370	83.2%					
EORTC QLQ-C30 *Baseline – week 18* *ITT-population*	Intervention	356	-1.74 (-4.24 to 0.75)	-0.10 points	-3.40 to 3.20	P=0.9530	*Patient-reported outcome assessments (EORTC QLQ-C30, EORTC QLQ-OES18 and EQ-5D-5L) will be administered electronically on day 1 (before drug administration, adverse event evaluation and disease status notification) of each cycle during cycles 1–9, every three cycles thereafter for up to 1 year, at the time of treatment discontinuation and at 30 days after treatment discontinuation*	[11]
	Comparator	355	-1.64 (-4.21 to 0.92)					
EORTC QLQ-C30	Intervention	356	-5.0				*Patient-reported outcome assessments (EORTC QLQ-C30, EORTC QLQ-OES18 and EQ-5D-5L) will be administered*	

Table A3a Results of First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590) NCT03189719							
Baseline – week 60 *ITT-population*	Comparator	355	-10	5 points	N/A	N/A	*electronically on day 1 (before drug administration, adverse event evaluation and disease status notification) of each cycle during cycles 1–9, every three cycles thereafter for up to 1 year, at the time of treatment discontinuation and at 30 days after treatment discontinuation [11]*

Appendix E Safety data for intervention and comparator(s)

Se venligst afsnittene:

7.1.8 Bivirkninger grad 3-4
7.1.9 Bivirkninger grad 3-4, kvalitativ gennemgang
7.1.10 Bivirkninger alle grader – kvalitativ gennemgang

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

Appendix F Comparative analysis of efficacy and safety

N/A for meta-analyse

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

Appendix G – Extrapolation

Overall survival and progression-free survival

For each treatment arm, the PSM estimated the amount of time spent in the progression-free, progressive disease and death states based on the areas under the PFS and OS curves.

For the pembrolizumab + 5-FU + cisplatin and the 5-FU + cisplatin arms, OS and PFS curves were derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, log-normal and generalized gamma distributions) to individual patient data (IPD) from the KN-590 trial. The fitted parametric curves for PFS and OS were used to extrapolate these efficacy outcomes beyond the trial period. Both one-piece and piecewise (Kaplan–Meier + parametric survival curve) models were fitted to the data. Given the availability of IPD and the different mechanisms of action of pembrolizumab and chemotherapy, parametric survival models were fitted separately to each treatment arm, as this approach required fewer assumptions than jointly fitted models

For OS, within each cycle of the model the probability of death was constrained to be at least as high as the age and gender-matched general population mortality. Age and gender-specific general population mortality for Denmark were obtained from the World Health Organization[38].

A systematic literature review was conducted to identify randomized clinical trials in locally advanced or metastatic esophageal cancer. Only two trials evaluating the efficacy and safety of chemotherapy in this setting were identified as meeting the inclusion criteria. There were key differences in patient population and eligibility criteria between KN-590 and the two trials identified for chemotherapy[39, 40]. While KN-590 was carried out in multiple centers internationally, both trials identified for chemotherapy were conducted at the same single center in South Korea. Only ESCC patients were included in the two chemotherapy trials; but patients with ESCC, esophageal adenocarcinoma and EGJ adenocarcinoma were all permitted to enroll in KN-590. Due to the heterogeneity and small degree of overlap between the patient characteristics of KN-590 and the two external trials, a matching-adjusted indirect comparison was not deemed appropriate in the context of this study. Furthermore, Danish guideline and Cunningham 2008 [4, 8] support the assumption of equivalent efficacy between the non-trial chemotherapy comparators and the trial chemotherapy comparator 5-FU + cisplatin. Therefore, the OS and PFS of the blended chemotherapy comparator are assumed to be the same as that of the trial comparator 5-FU + cisplatin.

The survival curve fitting was carried out in line with NICE Decision Support Unit guidelines[41]. 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) and clinical plausibility of the extrapolation in the longer term (versus external data were available and/or international expert opinion by clinicians) were used to select the best-fitted parametric survival curves for the base case and alternative plausible parametric survival curves to be explored in sensitivity analyses. The model base case for OS and PFS extrapolations were validated by international clinical opinion leaders.

Parametric survival model parameters by functional form are described in Table 69.

Table 69: Parametric survival model parameters by functional form

Functional form	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized gamma
Parameter A	Rate parameter (λ)	Scale parameter	Log mean parameter	Scale parameter	Shape parameter	Location parameter

Parameter B	-	Shape parameter	Log standard deviation parameter	Shape parameter	Rate parameter	Scale parameter
Parameter C	-	-	-	-	-	Shape parameter

Overall survival

One-piece and piecewise models with cut-off at Week 32 and Week 40 were fitted for OS for the pembrolizumab + 5-FU + cisplatin and the 5-FU + cisplatin arms, based on IPD for patients with PD-L1+ (CPS ≥10) from KN-590. The cut-off points were selected based on the structural changes suggested by the Chow tests on observed Kaplan–Meier data and the non-parametric smoothed hazard plot.

Figures 21 -28 illustrates fitted OS curves vs KM using 6 one-piece models, 6 piecewise models with cut-off at Week 40, base case piecewise model (log-normal) for the pembrolizumab in combination with cisplatin and 5-FU arm and the cisplatin and 5-FU arm, respectively and comparison between base case piecewise model and one-piece model.

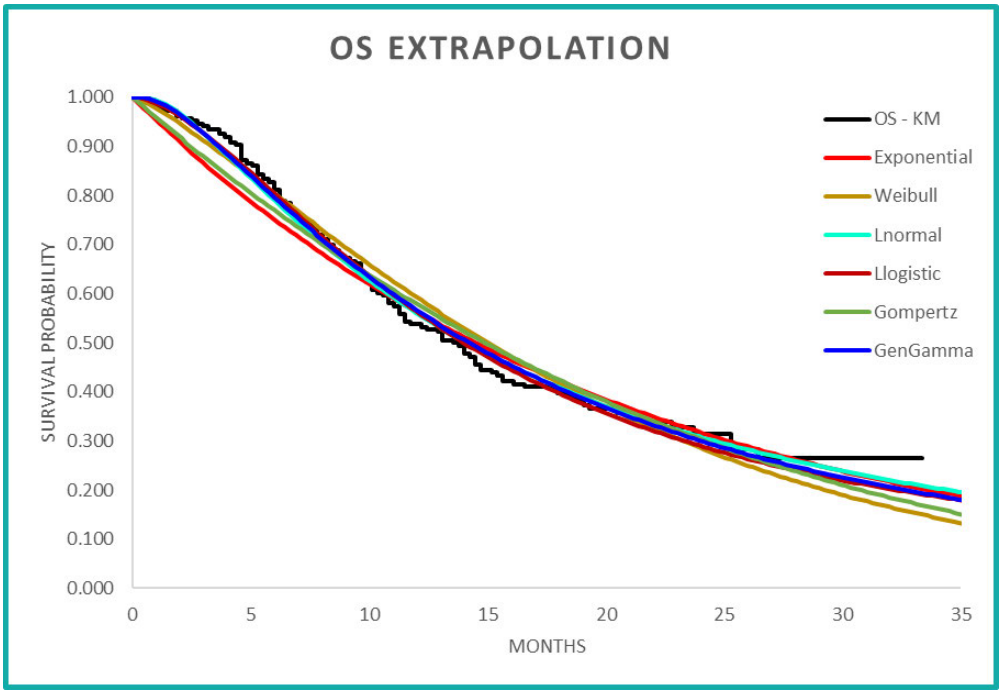


Figure 21: One piece, pembrolizumab + 5-FU + cisplatin

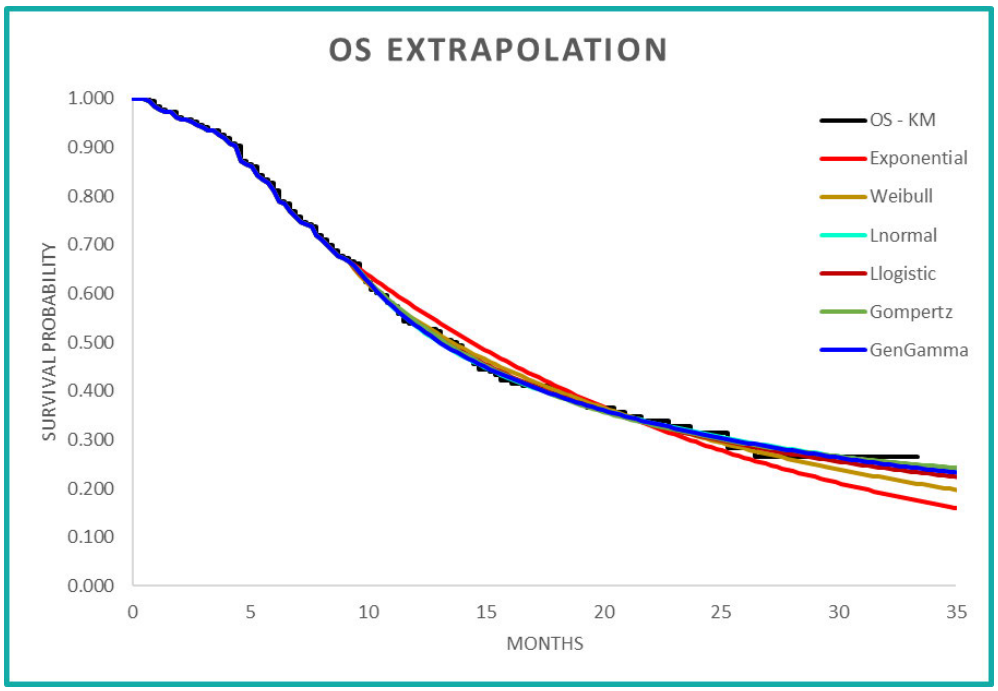


Figure 22: 6 piecewise models with cut-off at Week 40, pembrolizumab + 5-FU + cisplatin

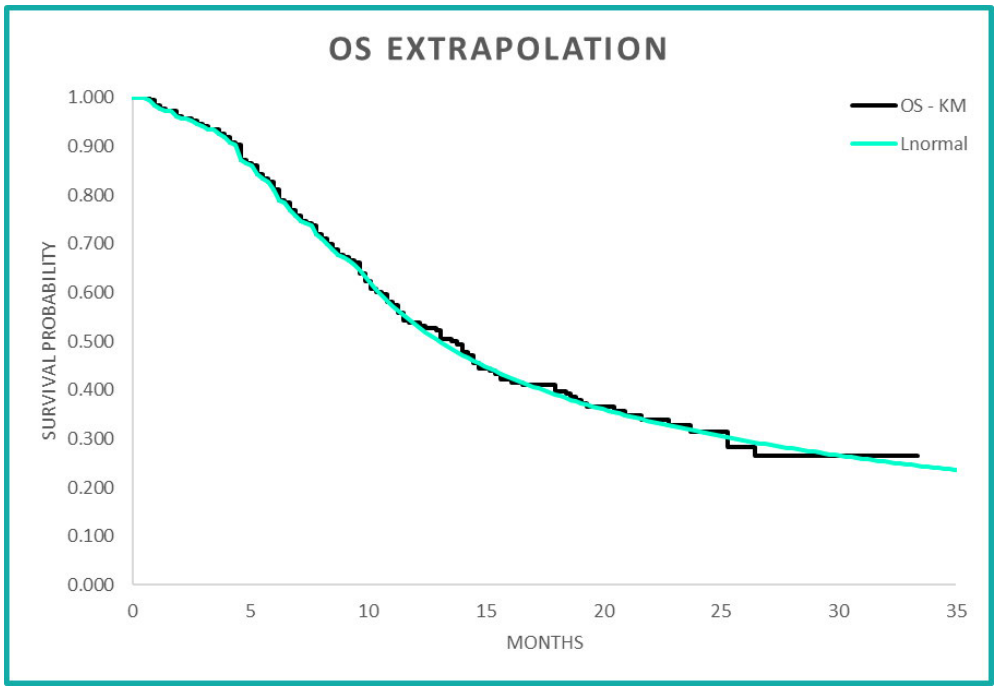


Figure 23: base case piecewise model (log-normal), pembrolizumab + 5-FU + cisplatin

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

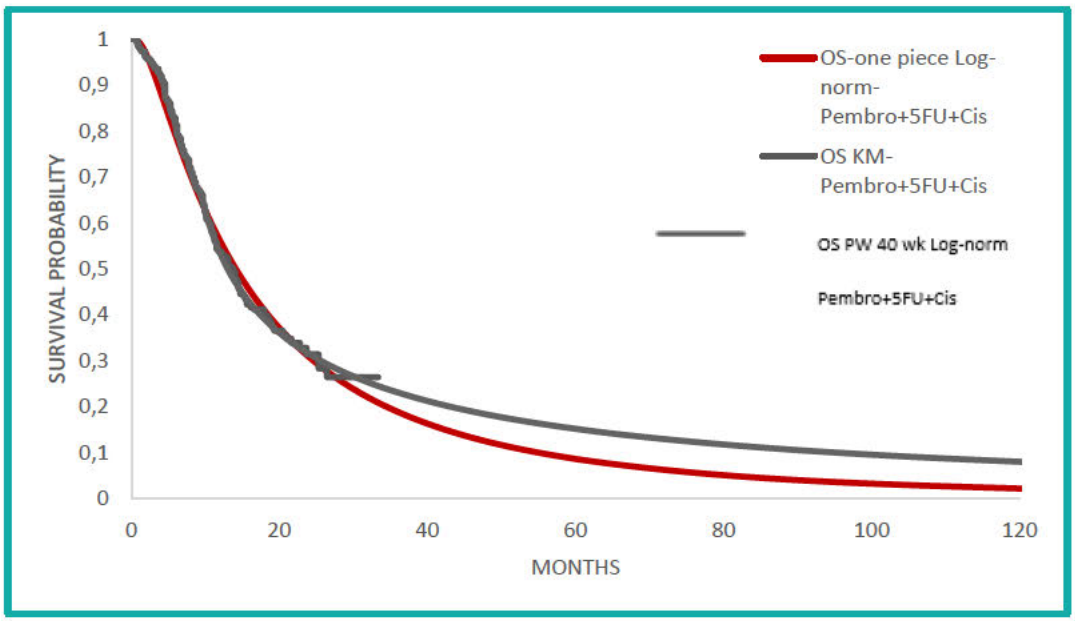


Figure 24: comparison between base case piecewise model and one-piece model, pembrolizumab + 5-FU + cisplatin.

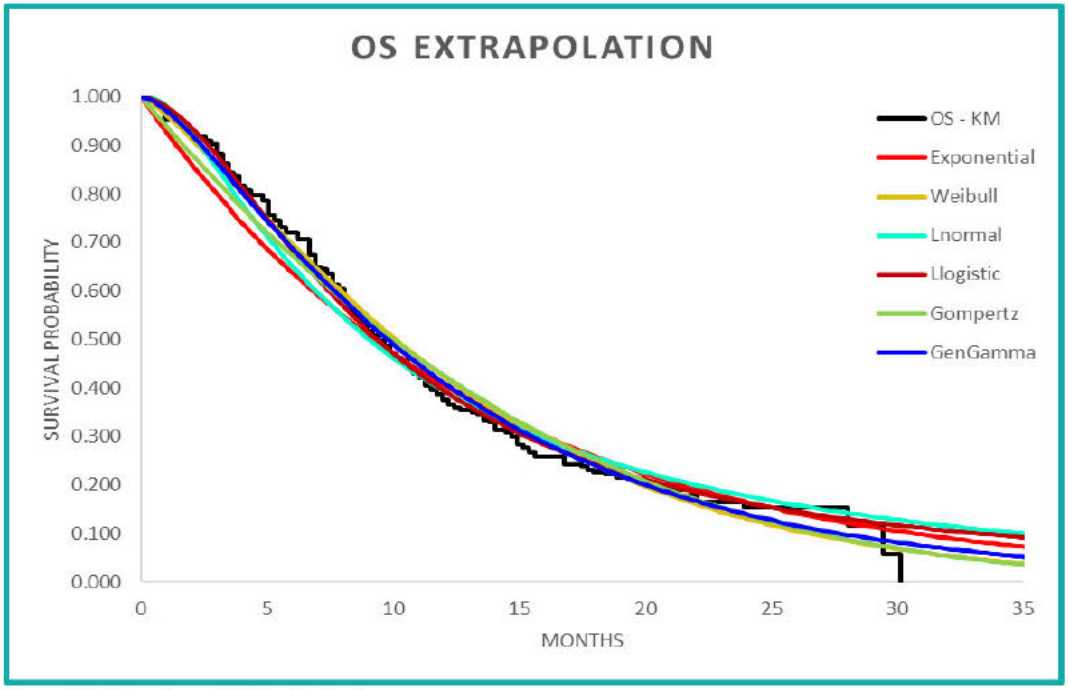


Figure 25: One piece, 5-FU + cisplatin

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

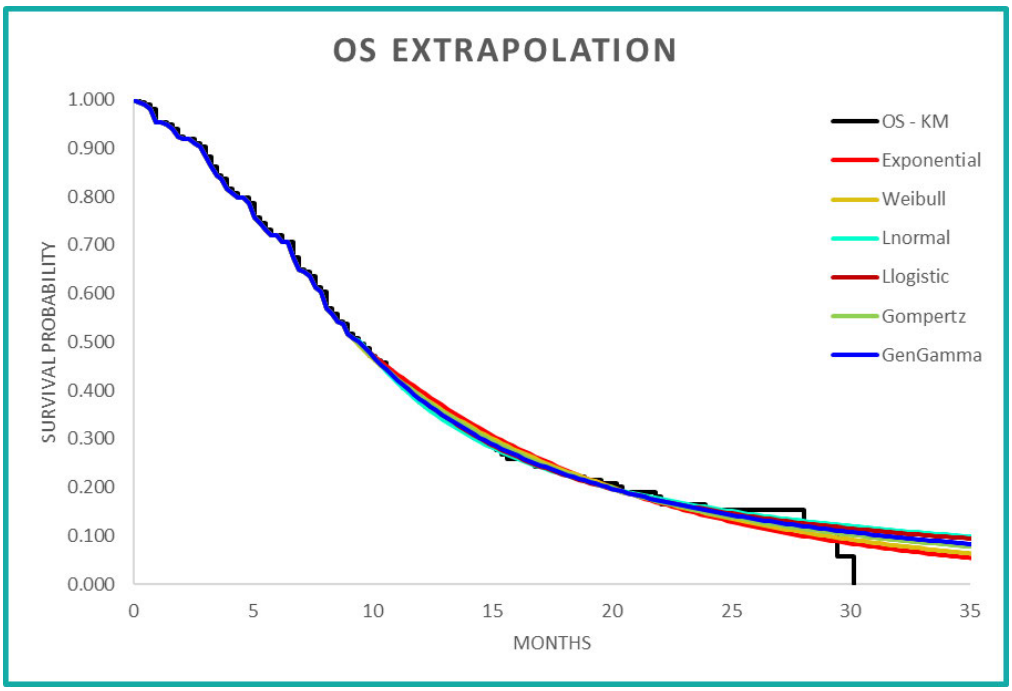


Figure 26: 6 piecewise models with cut-off at Week 40, 5-FU + cisplatin

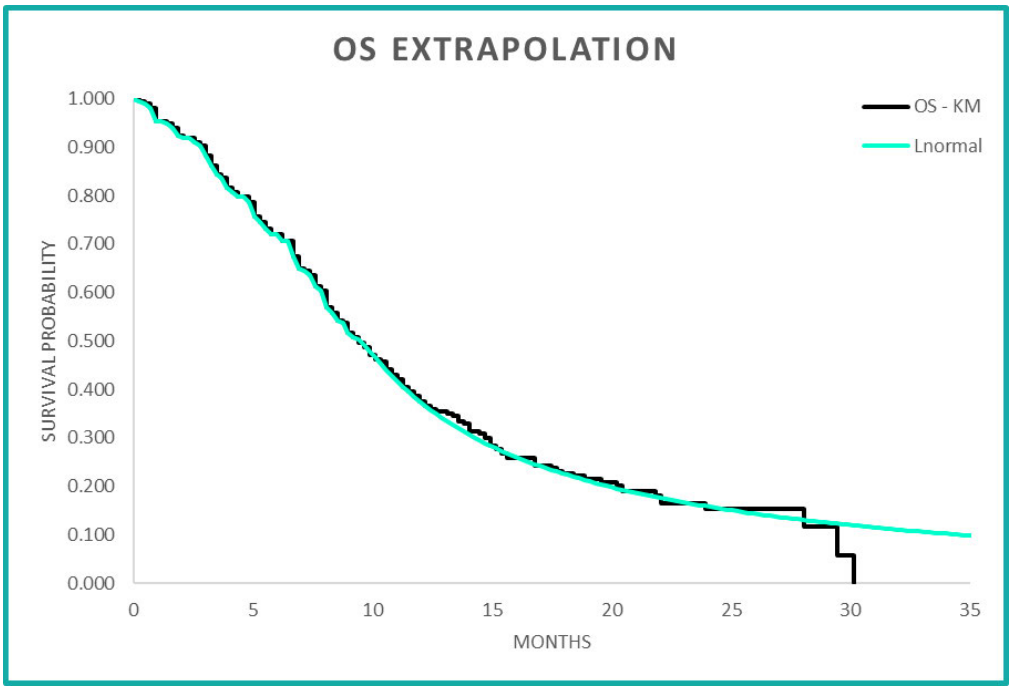


Figure 27: base case piecewise model (log-normal), 5-FU + cisplatin

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

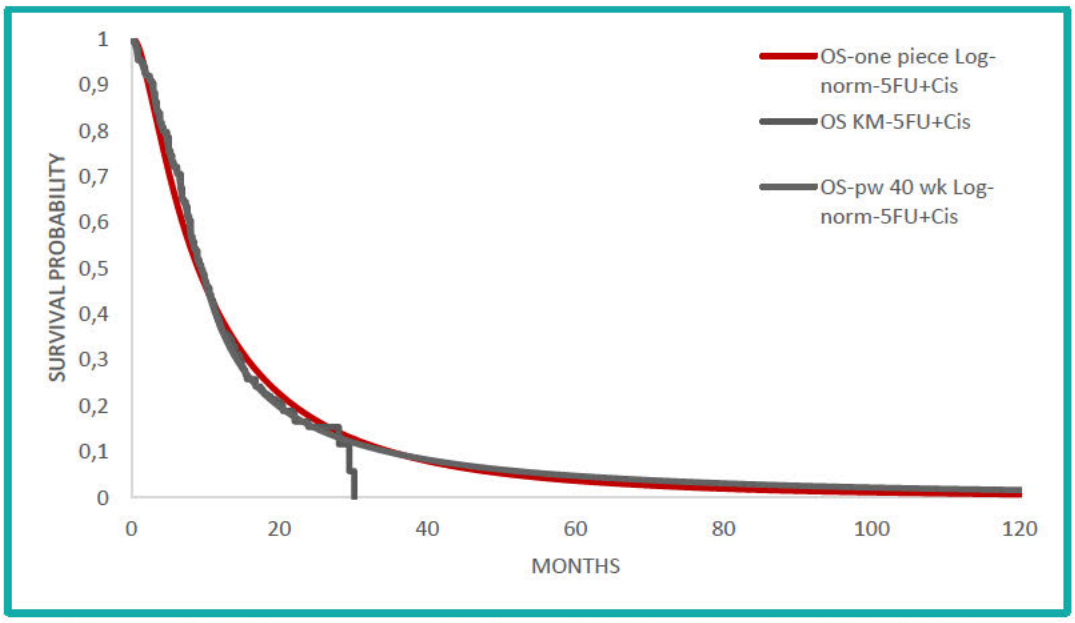
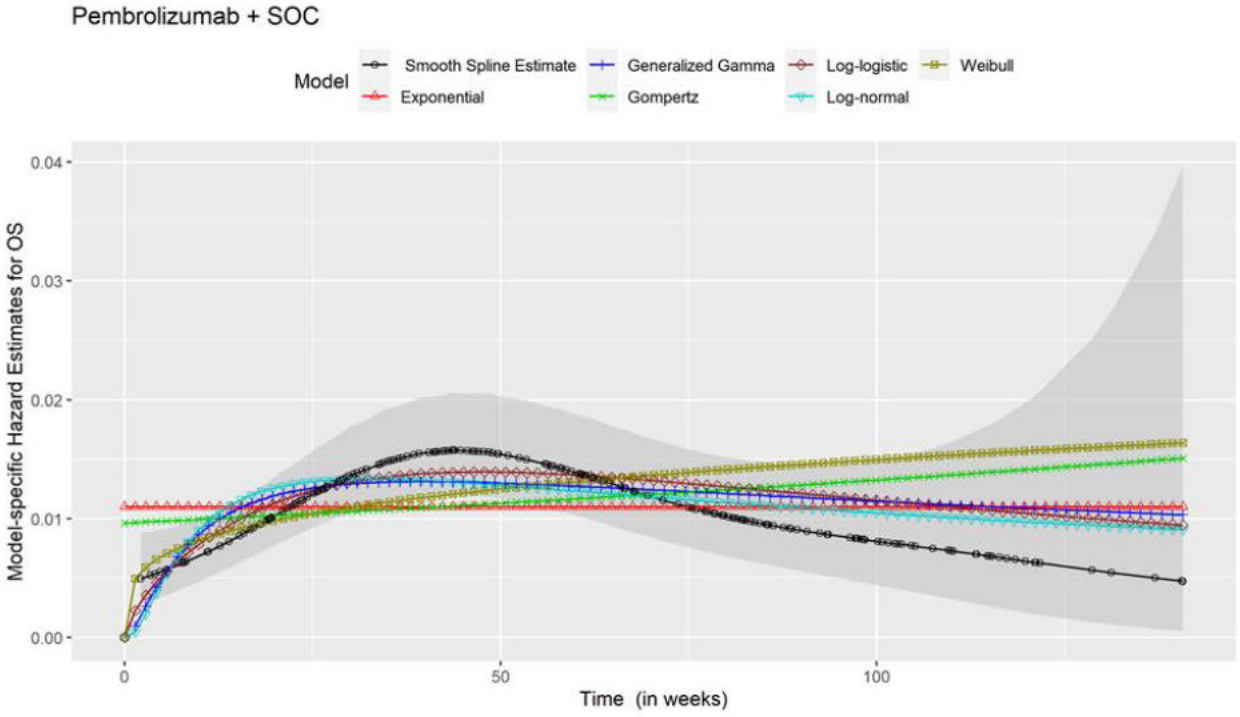


Figure 28: comparison between base case piecewise model and one-piece model, 5-FU + cisplatin.

One-piece models have poor visual fit versus piecewise models. All fitted one-piece models, including the statistically best-fitting log-logistic curve based on AIC/BIC, underestimated the observed OS Kaplan–Meier in the first 8 months for both arms. Literature suggested that 5-year OS for Stage IV esophageal cancer before immunotherapy becomes available is approximately 5% [46]. The best-fitting one-piece log-logistic distribution underestimated 5-year survival for the trial comparator arm, and also likely underestimated the 5-year survival rate for the intervention arm, which is expected to be above 10% based on international clinical experts' opinion. In addition, all fitted one-piece models poorly described the trend in hazard of death and overestimated the hazard after Week 75 (see Figure 29).



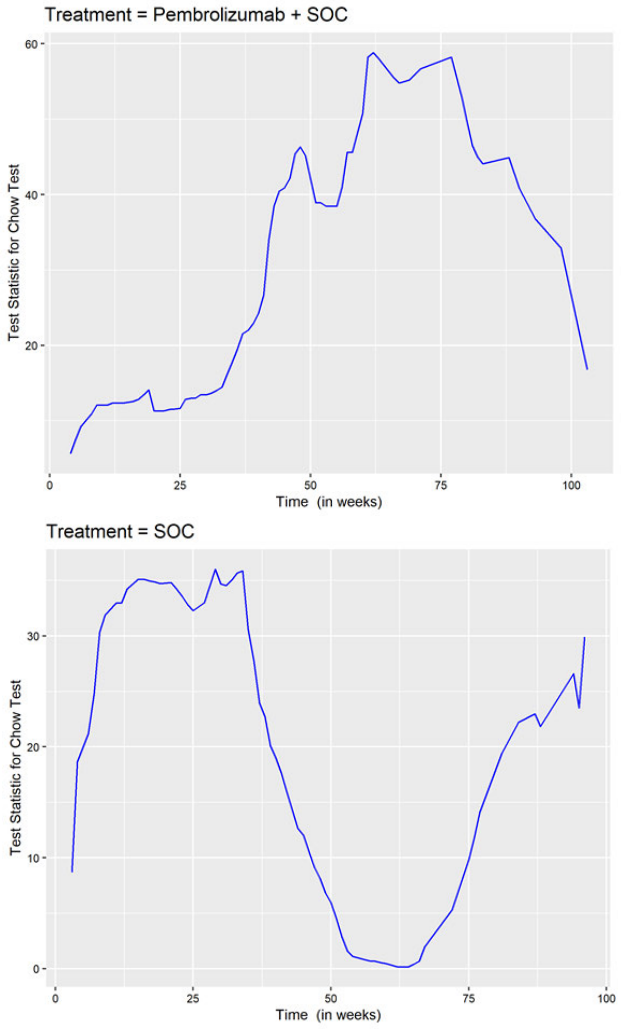
Key: CI, confidence interval; CPS, combined positive score; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; SOC, standard of care.

Note: The shaded area refers to 95% CIs for the smooth spline estimates.

Figure 29: Plot of hazard function of OS assuming smooth spline or one-piece parametric distributions used for long-term extrapolation for pembrolizumab + SOC, PD-L1+ (CPS ≥10) population.

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

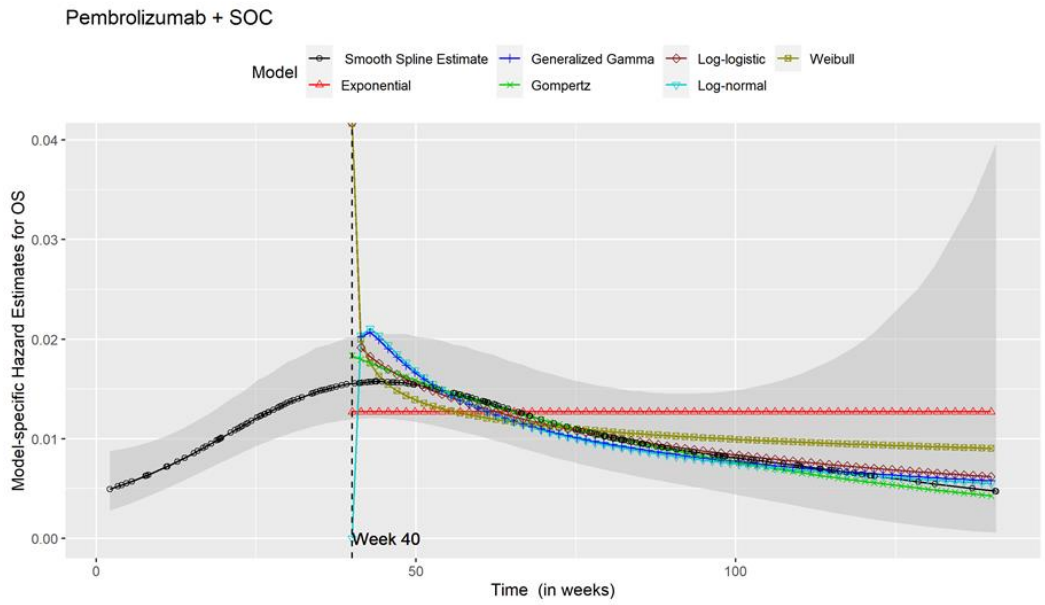
The two cut-offs at Week 32 and Week 40 for the piecewise models were identified based on structural changes observed by the Chow tests for OS for the pembrolizumab + 5-FU + cisplatin arm and 5-FU + cisplatin arm in the PD-L1+ (CPS ≥10) population in KN-590 (see Figure 30), with higher Chow test statistics indicating a higher likelihood of structural change. The peak for the Chow test statistics was observed to be approximately Week 60 and Week 40 for the pembrolizumab + 5-FU + cisplatin arm and 5-FU + cisplatin arm, respectively. The structural change in hazard around 40 weeks was also evident for the pembrolizumab + 5-FU + cisplatin arm based on the non-parametric smoothed hazard plot(see Figure 31). One practice constraint and disadvantage for selecting a later cut-off for the piecewise model is that fewer patients at risk are left beyond cut-off to fit the parametric survival curves, which will increase the uncertainty of the fitted parametric curves. Therefore, considering all factors we selected Week 40 as the base case. The Week 32 cut-off and one-piece models were explored in the scenario analysis.



Key: 5-FU, fluorouracil; CPS, combined positive score; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; SOC, standard of care.

Figure 30: Plot of multiple Chow test statistics for OS in KN-590: pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin, PD-L1+ (CPS ≥10) population

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



Key: CI, confidence interval; OS, overall survival; SOC, standard of care.

Note: The shaded area refers to 95% CIs for the smooth spline estimates.

Figure 31: Plot of hazard function of OS assuming smooth spline or piecewise parametric distributions with cut-off at Week 40 used for long-term extrapolation for pembrolizumab + SOC

Parametric survival model parameters and goodness-of-fit statistics for the piecewise model with cut-off at Week 40 are presented in Table 70 for the pembrolizumab + 5-FU + cisplatin arm and in Table 71 for the 5-FU + cisplatin arm. Parametric survival extrapolations and the observed Kaplan–Meier data within the trial period are presented in Figure 32 for the pembrolizumab + 5-FU + cisplatin arm and Figure 33 for the 5-FU + cisplatin arm.

In the base case, the piecewise log-normal model with cut-off at Week 40 was used to model OS for both the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms. For both the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms, the log-normal model has the best AIC and BIC and good visual fit within the trial period when compared with the observed Kaplan–Meier data. Furthermore, the log-normal model was shown as the best-fitting curve to describe the trend in hazard of death as shown in Figure 31.

More importantly, the log-normal curve with a cut-off at 40 weeks provides the most clinically plausible prediction for a 5-year survival rate of 4.7% for the standard of care 5-FU + cisplatin arm compared with available external data. The long-term extrapolation for the pembrolizumab + 5-FU + cisplatin arm (5-year OS of 15.2%) was also considered as clinically plausible by international experts, based on the mechanism of action for immunotherapy where a subset of patients is expected to receive long-term survival benefit.

Table 70: Parametric models fitted to OS in KN-590: pembrolizumab + 5-FU + cisplatin, cut-off at Week 40, PD-L1+ (CPS ≥10)

Functional form	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized gamma
A	-4.3655	4.4758	4.0362	4.0118	-0.0146	4.0858
B		-0.2059	0.6002	-0.0327	-3.9985	0.5744
C						0.0908
AIC	667.32	665.75	663.35	664.31	664.46	665.33

BIC	670.14	671.39	668.99	669.95	670.10	673.79

Key: 5-FU, fluorouracil; AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; OS, overall survival; PD-L1+, programmed death-ligand 1-positive.

Note: see Table 69 for specifications for parameters A, B and C.

Source: KN-590 (data cut-off date: July 2, 2020).

Key: 5-FU, fluorouracil; CPS, combined positive score; KM, Kaplan–Meier; OS, overall survival; PD-L1+, programmed death-ligand 1-positive.

Source: KN-590 (data cut-off date: July 2, 2020).

Table 71: Parametric models fitted to OS in KN-590: 5-FU + cisplatin, cut-off at Week 40, PD-L1+ (CPS ≥10) population

Functional form	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized gamma
A	-3.9191	3.9292	3.4372	3.4569	-0.0061	3.6606
B		-0.0804	0.3960	0.1581	-3.7684	0.2870
C						0.4173
AIC	670.99	672.38	671.80	671.93	672.08	672.97
BIC	673.60	677.59	677.01	677.14	677.29	680.79

Key: 5-FU, fluorouracil; AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; OS, overall survival; PD-L1+, programmed death-ligand 1-positive.

Note: See Table 69 for specifications for parameters A, B and C.

Source: KN-590 (data cut-off date: July 2, 2020).

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

Key: 5-FU, fluorouracil; CPS, combined positive score; KM, Kaplan–Meier; OS, overall survival; PD-L1+, programmed death-ligand 1-positive.
Source: KN-590 (data cut-off date: July 2, 2020).

[redacted]

External validation

To help with the selection and validation of base case parametric survival models for extrapolation, a targeted literature search was conducted to identify studies reporting long-term OS for advanced and metastatic esophageal cancer.

A pan-European study based on esophageal patients diagnosed between 1995 and 1999, and followed up to 2003, in 66 cancer registries across 24 European countries, including Denmark, reported a 5-year survival rate of 3.8% for patients with distant stage esophageal cancer [47].

A 5-year survival rate of 5% for distant esophageal cancer was reported by the American Cancer Society based on the US Surveillance, Epidemiology, and End Results (SEER) database for people diagnosed with esophageal cancer between 2009 and 2015 [23, 48]. Similar estimates were reported by other publications using Stage IV esophageal patients in the SEER database between 2010 and 2014 [49]. Based on patients with metastatic esophageal cancer in the database between 1988 and 2012, Wu et al. reported 5-year and 10-year survival rates of 5.4% and 3.5% [50]. In a small, single-site retrospective study of 80 patients with ESCC and distant organ metastasis in Japan, a 5-year survival rate of less than 5% was reported [51]. These external studies reporting long-term OS for patients with advanced/distant and metastatic esophageal cancer support the use of our chosen base case log-normal piecewise model, with a cut-off of Week 40 that estimates a 5-year and 10-year OS of 4.7% and 1.7%, respectively, for the 5-FU + cisplatin arm.

Progression-free survival

Piecewise models with cut-off at Week 10 and Week 37 were fitted for PFS for the pembrolizumab + 5-FU + cisplatin and the 5-FU + cisplatin arms using IPD from KN-590. Based on the KN-590 trial protocol, the first scheduled tumor imaging assessment was performed at Week 9 (± 1 week); visual inspection of PFS Kaplan–Meier data revealed a steep drop between randomization and Week 10 in both arms. Therefore, piecewise models with cut-offs of Week 10 were selected for the model base case as they align with the first scheduled tumor imaging assessment in the trial and have plausible long-term extrapolations based on validation by clinical

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

experts. The PFS is not a key driver for model results based on the sensitivity and scenario analyses performed.

Parametric survival model parameters and goodness-of-fit statistics for the piecewise model, with a cut-off at Week 10, are presented in Table 72 for the pembrolizumab + 5-FU + cisplatin arm; Table 73 presents the 5-FU + cisplatin arm. Parametric survival extrapolations and the observed Kaplan–Meier data within the trial period are presented in Figure 34 for pembrolizumab + 5-FU + cisplatin arm and Figure 35 for 5-FU + cisplatin arm.

In the base case, the log-logistic model was used to model PFS for both the pembrolizumab + 5 FU + cisplatin and 5-FU + cisplatin arms. For the pembrolizumab + 5-FU + cisplatin arm, the log-logistic model has the best AIC and BIC and good visual fit within the trial period when compared with the observed Kaplan–Meier data. International clinical experts also deemed the longer-term extrapolation of 3.5% at Year 5 clinically plausible. For the 5-FU + cisplatin arm, the log-logistic model also has the best AIC and BIC and good visual fit. The longer-term extrapolation of 0.4% at Year 5 was deemed plausible by the international experts. The use of a log-logistic model for the 5-FU + cisplatin arm also maintains consistency with the choice for the pembrolizumab + 5-FU + cisplatin arm.

Table 72: Parametric models fitted to PFS in KN-590: pembrolizumab + 5-FU + cisplatin, cut-off at Week 10, PD-L1+ (CPS ≥10) population

Functional form	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized gamma
A	-3.8504	3.8505	3.3617	3.3539	-0.0065	3.5570
B		0.0010	0.2306	0.3700	-3.6614	0.1389
C						0.3884
AIC	1,098.20	1,100.20	1,097.03	1,088.92	1,097.25	1,095.64
BIC	1,101.20	1,106.19	1,103.02	1,094.91	1,103.24	1,104.63

Key: 5-FU, fluorouracil; AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.
Note: See Table 69 for specifications for parameters A, B and C.
Source: KN-590 (data cut-off date: July 2, 2020).

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

Key: 5-FU, fluorouracil; CPS, combined positive score; KM, Kaplan–Meier; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.

Source: KN-590 (data cut-off date: July 2, 2020).

[redacted]

Table 73: Parametric models fitted to PFS in KN-590: 5-FU + cisplatin, cut-off at Week 10, PD-L1+ (CPS ≥10) population

Functional form	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized gamma
A	-3.1434	3.1804	2.7589	2.7513	-0.0044	2.8639
B		0.1539	-0.0758	0.7260	-3.0617	-0.1126
C						0.2472
AIC	1104.16	1,100.79	1,084.40	1,067.45	1,105.16	1,083.66
BIC	1107.17	1,106.82	1,090.43	1,073.49	1,111.20	1,092.71

Key: 5-FU, fluorouracil; AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.

Note: See Table 69 for specifications for parameters A, B and C.

Source: KN-590 (data cut-off date: July 2, 2020).

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

Key: 5-FU, fluorouracil; CPS, combined positive score; KM, Kaplan–Meier; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.
Source: KN-590 (data cut-off date: July 2, 2020).

Summary of base case

Table 74 summarizes the base case choice of OS and PFS for the pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms for the PD-L1+ (CPS ≥10) population.

Table 74: Base case choice of OS and PFS for pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin, PD-L1+ (CPS ≥10)

	Treatment arm	Base case choice
Overall survival	Pembrolizumab + 5-FU + cisplatin	Piecewise log-normal, cut-off at Week 40
	5-FU + cisplatin	Piecewise log-normal, cut-off at Week 40
Progression-free survival	Pembrolizumab + 5-FU + cisplatin	Piecewise log-logistic, cut-off at Week 10
	5-FU + cisplatin	Piecewise log-logistic, cut-off at Week 10
Key: 5-FU, fluorouracil; CPS, combined positive score; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival.		

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

Figure 36 and Figure 37 summarize the base case OS and PFS extrapolations and observed Kaplan–Meier data for pembrolizumab + 5-FU + cisplatin and 5-FU + cisplatin arms for the PD-L1+ (CPS ≥10) population.

Key: 5-FU, fluorouracil; Cis, cisplatin; CPS, combined positive score; KM, Kaplan–Meier; Lnormal, log-normal; OS, overall survival; PD-L1+, programmed death-ligand 1-positive; Pem, pembrolizumab.

[redacted]

Key: 5-FU, fluorouracil; Cis, cisplatin; CPS, combined positive score; KM, Kaplan–Meier; Llogistic, log-logistic; PD-L1+, programmed death-ligand 1-positive; Pem, pembrolizumab; FS, progression-free survival.

[redacted]

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

Appendix H – Literature search for HRQoL data

[Follow sections 3 and 7.1.2 of the guideline.]
Describe how the literature search for the health-related quality of life data was performed.
Explain the selection of search criteria and terms, inclusion and exclusion criteria.
Objective of literature search: [What questions is the literature search expected to answer?]
Databases: [Describe briefly which databases, registers and any conference material used in the literature search, either in text or table.]

Example of table: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm. yyyy
Specific health economics databases[1]			dd.mm. yyyy
			dd.mm. yyyy

Abbreviations:
Table: [Registers included in the search]
Table: [Conference material included in the search]
List: [Supplementary manual searches]
[Enter which other sources have been manually searched (e.g. web pages, EPAR/HTA institutes, journal issues, reference lists, etc.).]

Search strategy

[Describe the development of the search strategy and search string. Enter the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time frame, etc.)
The search must be documented for each database or resource incl. terms and syntax used, number of results retrieved, and date searched/accessed, either in text or table.
Describe which criteria have been used to reject irrelevant studies (for example of a table to record exclusions, see table 5 in NICE DSU Technical Support Document 9) and how the final selection has been made. Use PRISMA charts if appropriate (see example here).]

Literature search results included in the model/analysis:
[Insert results in a table]

Quality assessment and generalizibility of estimates

[Provide a complete quality assessment for each relevant study identified. When non-Danish estimates are used, generalizability must be addressed.]

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

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

Unpublished data

[The quality of any unpublished data must be specifically addressed. Submission of a publication plan for unpublished data is encouraged.]

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

Appendix I Mapping of HRQoL data

[Describe the method used for mapping according to section 7 (and 7.1.1) of the guidelines. Always include details of the methodology used, how the method was validated and whether it has been published. Present the results.]

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

Appendix J Probabilistic sensitivity analyses

Appendix J Probabilistic sensitivity analyses

Table 75: Assumptions that form the basis of the probability distributions used in the probabilistic analysis is copied from the model sheet "Parameters"

Parameters	Mean	N	SD	SE	Lower	Upper	Distribution used in PSA	α	β	Random number	PSA value	Active Value	Notes
Patient Information													
Patient Age	63,00	383	9,40	0,48	61,0	62,0	Normal			0,04	62,38	63,00	
Proportion male	81,7%	383			77,7%	85,6%	Beta	383,00	70,00	0,61		81,7%	
Average patient weight (kg)	62,56	383	14,25	0,73	61,1	64,0	Lognormal			0,69	62,91	62,56	
Average patient body surface area (m2)	1,70	383	0,22	0,01	1,68	1,72	Lognormal			0,65	1,70	1,70	
Efficacy inputs - OS, PFS, and TOT survival curves													
OS parametric curve fitting - Pem+5FU+Cis													
Pembrolizumab + 5-FU + cisplatin, PD-L1+ OS - Lnormal, cut-off Week 40 (Pem+5FU+Cis) intercept							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ OS - Lnormal, cut-off Week 40 (Pem+5FU+Cis) log(scale)							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ OS - Lnormal, cut-off Week 40 (Pem+5FU+Cis) shape							Multivariate Normal						Varied on TTE_Inputs Sheet
OS parametric curve fitting - 5FU+Cis													
5-FU + cisplatin, PD-L1+ OS - Lnormal, cut-off Week 40 (5FU+Cis) intercept							Multivariate Normal						Varied on TTE_Inputs Sheet
5-FU + cisplatin, PD-L1+ OS - Lnormal, cut-off Week 40 (5FU+Cis) log(scale)							Multivariate Normal						Varied on TTE_Inputs Sheet
5-FU + cisplatin, PD-L1+ OS - Lnormal, cut-off Week 40 (5FU+Cis) shape							Multivariate Normal						Varied on TTE_Inputs Sheet
PFS parametric curve fitting - Pem+5FU+Cis													
Pembrolizumab + 5-FU + cisplatin, PD-L1+ PFS - Llogistic, cut-off Week 10 (Pem+5FU+Cis) intercept							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ PFS - Llogistic, cut-off Week 10 (Pem+5FU+Cis) log(scale)							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ PFS - Llogistic, cut-off Week 10 (Pem+5FU+Cis) shape							Multivariate Normal						Varied on TTE_Inputs Sheet
PFS parametric curve fitting - 5FU+Cis													
5-FU + cisplatin, PD-L1+ PFS - Llogistic, cut-off Week 10 (5FU+Cis) intercept							Multivariate Normal						Varied on TTE_Inputs Sheet
5-FU + cisplatin, PD-L1+ PFS - Llogistic, cut-off Week 10 (5FU+Cis) log(scale)							Multivariate Normal						Varied on TTE_Inputs Sheet
5-FU + cisplatin, PD-L1+ PFS - Llogistic, cut-off Week 10 (5FU+Cis) shape							Multivariate Normal						Varied on TTE_Inputs Sheet
ToT parametric curve fitting - Pem+5FU+Cis - Pem													
Pembrolizumab + 5-FU + cisplatin, PD-L1+ Pembrolizumab, ToT - KM intercept							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ Pembrolizumab, ToT - KM log(scale)							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ Pembrolizumab, ToT - KM shape							Multivariate Normal						Varied on TTE_Inputs Sheet
ToT parametric curve fitting - Pem+5FU+Cis - 5FU													
Pembrolizumab + 5-FU + cisplatin, PD-L1+ 5-FU, ToT - KM intercept							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ 5-FU, ToT - KM log(scale)							Multivariate Normal						Varied on TTE_Inputs Sheet
Pembrolizumab + 5-FU + cisplatin, PD-L1+ 5-FU, ToT - KM shape							Multivariate Normal						Varied on TTE_Inputs Sheet
ToT parametric curve fitting - 5FU+Cis - 5FU													
5-FU + cisplatin, PD-L1+ 5-FU, ToT - KM intercept							Multivariate Normal						Varied on TTE_Inputs Sheet
5-FU + cisplatin, PD-L1+ 5-FU, ToT - KM log(scale)							Multivariate Normal						Varied on TTE_Inputs Sheet
5-FU + cisplatin, PD-L1+ 5-FU, ToT - KM shape							Multivariate Normal						Varied on TTE_Inputs Sheet

Parameters	Mean	N	SD	SE	Lower	Upper	Distribution used in PSA	α	β	Random number	PSA value	Active Value	Notes
Varying ToT KM by hazard ratio													
Varying ToT KM by hazard ratio - pembrolizumab	1,00				0,90	1,10	User defined					1,00	Assume HRs 0.9 and 1.1 as lower and upper bound
Varying ToT KM by hazard ratio - 5-FU in intervention arm	1,00				0,90	1,10	User defined					1,00	Assume HRs 0.9 and 1.1 as lower and upper bound
Varying ToT KM by hazard ratio - cisplatin in intervention arm	1,00				0,90	1,10	User defined					1,00	Assume HRs 0.9 and 1.1 as lower and upper bound
Varying ToT KM by hazard ratio - 5-FU in control arm	1,00				0,90	1,10	User defined					1,00	Assume HRs 0.9 and 1.1 as lower and upper bound
Varying ToT KM by hazard ratio - cisplatin in control arm	1,00				0,90	1,10	User defined					1,00	Assume HRs 0.9 and 1.1 as lower and upper bound
Utility Inputs													
Duration of Grade 3+ AEs (weeks)	8,24			0,33	7,59	8,89	Normal			0,23	8,00	8,24	
Utility by progression status (mixed effects model)													
Utility by progression: intercept							Multivariate Normal						Varied on Utility Sheet
Utility by progression: Coefficient for AE+							Multivariate Normal						Varied on Utility Sheet
Utility by progression: Coefficient for progression (PFSNYLN)							Multivariate Normal						Varied on Utility Sheet
Utility by progression: Coefficient for progression (PFSNYLY)							Multivariate Normal						Varied on Utility Sheet
Utility by time to death (mixed effects model)													
Utility by time to death: intercept							Multivariate Normal						Varied on Utility Sheet
Utility by time to death: Coefficient for AEs							Multivariate Normal						Varied on Utility Sheet
Utility by time to death: Coefficient for TTD 180-360 days							Multivariate Normal						Varied on Utility Sheet
Utility by time to death: Coefficient for TTD 30-90 days							Multivariate Normal						Varied on Utility Sheet
Utility by time to death: Coefficient for TTD 90-180 days							Multivariate Normal						Varied on Utility Sheet
Utility by time to death: Coefficient for TTD <30 days							Multivariate Normal						Varied on Utility Sheet
Utility by time to death: Coefficient for TTD >=360 days							Multivariate Normal						Varied on Utility Sheet
Administration cost for IV													
Chemo IV drug admin cost DRG98MA98	2.277,00 kr.			227,70 kr.	1.952,88 kr.	2.744,44 kr.	Gamma	100,00	22,77	0,43	2.227,11 kr.	2.277,00 kr.	
5-FU one off cost relating to port-a-cath placement; DRG70OP02	7.858,00 kr.			785,80 kr.	6.230,85 kr.	9.230,11 kr.	Gamma	100,00	78,58	0,93	8.789,88 kr.	7.858,00 kr.	
Relative dose intensity													
Pembrolizumab - 5-FU + cisplatin RDI pembrolizumab	93,4%			9,3%	86,7%	99,7%	Beta	5,67	0,40	0,90	100,0%	93,4%	
Pembrolizumab - 5-FU + cisplatin RDI 5-FU	71,8%			7,2%	56,8%	84,7%	Beta	27,48	10,79	0,82	78,6%	71,8%	
Pembrolizumab - 5-FU + cisplatin RDI cisplatin	58,2%			5,8%	46,6%	69,4%	Beta	41,22	29,60	0,86	64,8%	58,2%	
5-FU + cisplatin RDI 5-FU	76,9%			7,7%	60,0%	90,0%	Beta	22,33	6,71	0,40	77,1%	76,9%	
5-FU + cisplatin RDI cisplatin	65,2%			6,5%	50,9%	77,4%	Beta	34,15	18,23	0,02	55,0%	65,2%	
Subsequent treatment costs													
Subsequent treatment cost - Pembrolizumab - 5-FU - cisplatin	3.232,82 kr.			323,28 kr.	2.630,35 kr.	3.896,48 kr.	Gamma	100,00	32,33	0,28	3.036,69 kr.	3.232,82 kr.	
Subsequent treatment cost - 5-FU - cisplatin	138.140,14 kr.			13.814,01 kr.	112.396,33 kr.	166.498,86 kr.	Gamma	100,00	1381,40	0,18	126.264,79 kr.	138.140,14 kr.	
Subsequent treatment cost - Blended chemo	138.140,14 kr.			13.814,01 kr.	112.396,33 kr.	166.498,86 kr.	Gamma	100,00	1381,40	0,47	126.740,59 kr.	138.140,14 kr.	
Disease Management Costs													
Weekly cost in progression-free state	869,03 kr.			86,90 kr.	707,09 kr.	1.047,43 kr.	Gamma	100,00	8,69	0,56	879,74 kr.	869,03 kr.	
Weekly cost in progressive disease state	164,40 kr.			16,45 kr.	133,83 kr.	198,25 kr.	Gamma	100,00	1,64	0,95	193,14 kr.	164,40 kr.	
Cost of terminal care (one-off cost)	78.570,00 kr.			7.857,00 kr.	63.927,69 kr.	94.699,59 kr.	Gamma	100,00	785,70	0,42	76.647,72 kr.	78.570,00 kr.	
PD-L1 testing costs													

Parameters	Mean	N	SD	SE	Lower	Upper	Distribution used in PSA	α	β	Random number	PSA value	Active Value	Notes
AE costs (one-off)													
Pembrolizumab + 5-FU + cisplatin: one-off AE costs	17.595,19 kr.			1.759,52 kr.	14.242,91 kr.	21.098,81 kr.	Gamma	100,00	175,95	0,03	14.252,47 kr.	17.595,19 kr.	
5-FU + cisplatin: one-off AE costs	19.450,80 kr.			1.945,08 kr.	15.825,95 kr.	23.443,05 kr.	Gamma	100,00	194,51	0,07	16.887,12 kr.	19.450,80 kr.	
Blended chemo: one-off AE costs	19.450,80 kr.			1.945,08 kr.	15.825,95 kr.	23.443,05 kr.	Gamma	100,00	194,51	0,37	18.758,17 kr.	19.450,80 kr.	
Societal costs													
Hourly salary	171,00 kr.			17,10 kr.	145,64 kr.	215,75 kr.	Gamma	100,00	1,71	0,43	175,26 kr.	171,00 kr.	
Transportation cost	100,00 kr.			10,00 kr.	81,96 kr.	120,53 kr.	Gamma	100,00	1,00	0,82	109,32 kr.	100,00 kr.	

Appendices K, L ... etc. Company-specific appendices

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

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.01.2022
Leverandør	MSD
Lægemiddel	Pembrolizumab (Keytruda)
Ansøgt indikation	1. linjebehandling af lokalt avanceret eller metastatisk spiserørskræft eller HER2-negativ kræft i overgangen mellem spiserør og mavesæk

Forhandlingsresultat

Amgros har følgende pris på pembrolizumab:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Pembrolizumab	25 mg/ml	4 ml	24.409,85	[redacted]	[redacted]

Amgros har haft en aftale på pembrolizumab siden 2015 og den nuværende aftale er en del af et fleksibelt udbud sammen med nivolumab og atezolizumab.

I udbuddet er der mulighed for prisregulering og Amgros har planer om at igangsætte denne for alle immunterapierne så snart vurderingen af cemiplimab og atezolizumab til lungekræft er færdigbehandlet af Medicinrådet. Det er planen at give leverandører til avelumab, durvalumab, nivolumab, pembrolizumab,

cemiplimab og atezolizumab mulighed for en prisjustering og efterfølgende vil disse aftalepriser blive implementeret i regionerne.

Forventningerne fra Amgros side er at Medicinrådet i januar godkender det kliniske sammenligningsgrundlag og omkostningsanalyse indenfor lungekræft. Herefter er det muligt for Amgros at igangsætte prisreguleringsmekanismen hvorefter leverandøren har to måneder til at give en ny pris. De nye aftaler skal derfor gerne træde i kraft d. 1/4-2022.

Konkurrencesituationen

Der er på nuværende tidspunkt inden konkurrence på denne indikation.
[redacted]

Status fra andre lande

Norge: Under evaluering[1].

England: Pembrolizumab er godkendt til denne indikation i september 2021.

Konklusion

Prisen på pembrolizumab bliver ikke bedre på nuværende tidspunkt, da patientpopulationen på denne indikation ikke er større. Som beskrevet ovenfor vil det være muligt at justere prisen når prisreguleringsmekanismen igangsættes efter Medicinrådet har godkendt det kliniske sammenligningsgrundlag og omkostningsanalysen for lungekræft. X
[redacted]

[1] Pembrolizumab (Keytruda) - Indikasjon XVIII (nyemetoder.no)

Notat

I henhold til Medicinrådets procesvejledning for vurdering af nye lægemidler, har MSD udarbejdet dette notat, som en tilbagemelding på udkastet til vurdering af pembrolizumab i kombination med platin- og fluoropyrimidinbaseret kemoterapi til førstelinjebehandling af lokalt fremskredent inoperabelt eller metastatisk karcinom i spiserøret eller HER2-negativ adenokarcinom i den gastro-esofageale overgang hos voksne med PD-L1 CPS ≥ 10, som MSD modtog den 21. december 2021.

Vi anerkender, at denne vurdering er én af de første, som følger Medicinrådets nye metodevejledning og at vurderingsrapporten derfor vil afspejle dette, men derfor føler vi også, at det er uhyre vigtigt, at gøre Rådet opmærksom på, at udkastet til vurdering ikke udgør et fyldestgørende beslutningsgrundlag. Der mangler således to helt essentielle elementer i forhold til et fyldestgørende beslutningsgrundlag:

1) **En perspektivering fra fagudvalget** af hvad de kliniske data, som viser en fordobling af OS raten ved 24 mdr. og en 4-dobling af PFS raten ved 24 mdr. uden at øge frekvensen af bivirkninger, betyder for danske patienter og for mulighederne for at forbedre overlevelsen i Danmark.
2) **Et kontinuum af relevante sundhedsøkonomiske scenarier**. NICE i England har i september 2021 godkendt pembrolizumab i kombination med kemoterapi til den samme indikation som Medicinrådet vurderer, men Medicinrådet har i den sundhedsøkonomiske analyse forkastet relevante forudsætninger, som har ført til godkendelse i NICE

Fraværende fagudvalgs-perspektivering af klinisk data

MSD vil gerne understrege den altafgørende vigtighed af fagudvalget i en Medicinrådsproces. Den inkrementelle omkostningseffektivitetsratio bør udelukkende benyttes som beslutningsstøtte og der bør fortsat lægges stor vægt på kliniske effekter. Vurderinger fra fagfolk, bør altid indgå i og fremgå af beslutningsgrundlaget.

I Medicinrådets diskussion af MSD's ansøgning, står estimatet af den inkrementelle omkostningseffektivitetsratio fra Medicinrådets sundhedsøkonomiske analyse meget alene. De sundhedsøkonomiske estimater er netop estimater og ikke et resultat, der kan slås to streger under. Det er derfor helt essentielt, at der i beslutningsgrundlaget indgår en perspektivering af de kliniske data fra fagudvalget. Spiserørskræft diagnosticeres ofte sent og er én af de kræftformer, som har den dårligste prognose og med høj dødelighed. Patienter med metastatisk spiserørskræft er præget af dårlig livskvalitet, bl.a grundet synkebesvær og smerter, ofte med markant vægttab til følge.
Data fra KEYNOTE-590 viser en fordobling af OS raten ved 24 mdr. og en 4-dobling af PFS raten ved 24 mdr., hvilket indikerer, at der her er en meget stor klinisk merværdi for patienter med spiserørskræft sammenlignet med nuværende dansk standardbehandling. Det er ligeledes signifikant, at forbedringen i overlevelse opnås uden at øge frekvensen af bivirkninger, selvom der tillægges kemoterapi til pembrolizumab og selvom varigheden af behandlingen med kombinationen er længere end med kemoterapi. Hvis udkastet til vurdering skal være et fyldestgørende beslutningsgrundlag, så bør det suppleres med en perspektivering fra fagudvalget af, hvad ovenstående data betyder for patienter med spiserørskræft i forhold til at forbedre overlevelsen i Danmark.

Et kontinuum af relevante sundhedsøkonomiske scenarier, herunder relevante antagelser anvendt i NICE

Medicinrådets har i udkastet til vurdering afvist muligheden for langtidsoverlevere og har på den baggrund forkastet de forudsætninger i MSD´s sundhedsøkonomiske model, som har været medvirkende til, at NICE i september 2021 besluttede at anbefale pembrolizumab i kombination med kemoterapi. NICE har på samme måde som Medicinrådet vurderet parametriske funktioner til ekstrapolation af data i MSD's model og hvor Medicinrådet konkluderer følgende: *" Der var flere af de standardparametriske ekstrapolationsmodeller, som Medicinrådet kunne forkaste, da de ekstrapolerede kurver ikke var klinisk plausible. Medicinrådet vurderer dog, at der er stor usikkerhed i forhold til, om parametrisk ekstrapolering med en Weibull eller en eksponentiel fordeling er mest*

retvisende.", så drager NICE den helt modsatrettet konklusion: *"The clinical experts agreed that a small proportion of people receiving pembrolizumab could be cured or enter long-term remission"* og *"In addition, it is implausible to consider that the exponential and Weibull models would be appropriate to estimate the hazard profile of the pembrolizumab plus chemotherapy trajectory"* [1].

Medicinrådet har ændret den parametriske funktion fra fremskrivning med log -normal- fordeling til en fremskrivning med Weibull og i forlængelse heraf, valgt ikke at præsentere estimaterne fra MSD's sundhedsøkonomiske analyse, hverken i afsnittene med opsummering/diskussion og ej heller som led i følsomhedsanalyse. Medicinrådets ændring af den parametriske funktion indebærer, at den inkrementelle QALY gevinst halveres. Det er således en ændring, som har meget stor betydning og der bør være fuld transparens omkring dette, så derfor præsenteres estimaterne nedenfor, så Rådet også har disse informationer:

Behandling	**QALYs(MSD)**	**Inkrementelle QALYs (MSD)**	**Inkrementelle QALYs (Medicinrådet)**
Pembrolizumab + kemoterapi	2.32	1.17	0.66
komparator	1.15		

Medicinrådet begrunder ændringen af parametrisk funktion med, at MSD's model antager, at en mindre del af patienterne er i live efter 10 år (8%) og Medicinrådet anser ikke dette for realistisk. Medicinrådet antager således, at alle patienter behandlet med pembrolizumab i kombination med kemoterapi er døde efter 10 år. Der er dog en stadig større mængde data, blandt andre cancerformer med ringe prognose, som fx lungekræft og malignt melanom, hvor patienter behandlet med pembrolizumab, nu bliver langtidsoverlevere og det er en rimelig antagelse, at dette også vil være gældende for en andel af patienter med spiserørskræft.

Et fyldestgørende beslutningsgrundlag bør derfor også inkludere et scenarie, hvor en andel af patienterne bliver langtidsoverlevere , således at Medicinrådets sundhedsøkonomiske analyse har mulighed for at præsentere et kontinuum, hvor den inkrementelle QALY gevinst sandsynligvis ligger i et spænd mellem 0,66 til 1,17.

Pembrolizumab i kombination med kemoterapi som standardbehandling til patienter med spiserørskræft

Spiserørskræft er en livstruende sygdom og data fra KN-590 viser en fordobling af OS raten ved 24 mdr. og en 4-dobling af PFS raten ved 24 mdr. Denne forbedring i overlevelse opnås uden at øge frekvensen af bivirkninger, selvom der tillægges kemoterapi til pembrolizumab og selvom varigheden af behandlingen med kombinationen er længere end med kemoterapi. I tillæg til de signifikante kliniske resultater, så estimerer den sundhedsøkonomiske analyse også en favorable omkostning pr. vundet kvalitetsjusteret leveår, hvilket allerede har ført til en anbefaling i NICE. Samlet set bør de dokumenterede kliniske effekter og den favorable omkostning pr. vundet kvalitetsjusteret leveår føre til at pembrolizumab i kombination med kemoterapi anbefales som standardbehandling til patienter med spiserørskræft med PD-L1 CPS ≥ 10.

[1] - Final appraisal document – pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer, Issue date: September 2021