Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende pembrolizumab til adjuverende behandling af højrisiko stadie II-melanom

Vers. 1.0

Bilagsoversigt

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

Den 25. maj 2023

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Til: Medicinrådet, att. Filippa Nyboe Norsker
og Camilla Vels Jensen
Dampfærgevej 21-23, 3. sal
2100 København Ø

Notat til høring om udkast til Medicinrådets anbefaling vedr. pembrolizumab til adjuverende behandling af højrisiko stadie II-melanom

MSD Danmark ønsker hermed at kvittere for muligheden for at komme med bemærkninger til Medicinrådets udkast til anbefaling vedr. pembrolizumab til adjuverende behandling af højrisiko stadie II-melanom.

Indledningsvist vil vi takke for en konstruktiv og åben dialog med sekretariatet igennem hele validerings-og vurderingsprocessen. Vi har oplevet, at sekretariatet har været meget hjælpsomt og tilgængeligt, hvilket har medvirket til en nyttig forventningsafstemning og hurtig besvarelse af spørgsmål undervejs i processen.

For så vidt angår den kliniske del af vurderingsrapporten bemærker vi, at Medicinrådet er enig i, at de inkluderede effektmål er tilstrækkelige for vurderingen og anses som standard i vurderinger af denne type behandling, idet formålet med adjuverende behandling er at nedsætte risikoen for, at patienterne får tilbagefald af deres melanom. Da Medicinrådet i 2019 anbefalede pembrolizumab til adjuverende behandling af stadie III-patienter skete det ligeledes på baggrund af data på de samme effektmål og med samme datamodenhed. Vi ønsker her igen at understrege, at prognosen er den samme eller endda dårligere for stadie II-patienter i sammenligning med stadie III-patienter.

Vi anerkender, at der endnu ikke foreligger data vedr. samlet overlevelse (OS), og glæder os over, at Medicinrådet er enig i vores vurdering af, at det i denne vurdering samlet set er sandsynligt, at en knap 40 % reduktion i risikoen for tilbagefald (DFS HR 0,61) vil betyde bedre overlevelse, og at nedsættelsen af risikoen for fjernmetastaser vil have en positiv effekt på overlevelsen.

Medicinrådet præsenterer en ICER, som er baseret på fast dosering af pembrolizumab. Vi gør opmærksom på, at pembrolizumab doseres vægtbaseret i Danmark, og vi antager således, at Rådets økonomiske vurdering baseres på den vægtbaserede dosering, som er klinisk praksis i Danmark, hvilket vil medføre en ca. 25% lavere ICER.

[redacted]

[redacted]

Med venlig hilsen,

Simon Leth
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22.05.2023

DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.06.23
Leverandør	MSD
Lægemiddel	Keytruda (pembolizumab)
Ansøgt indikation	Keytruda som monoterapi er indiceret til adjuverende behandling af voksne og unge i alderen 12 år og derover med stadie IIB-, IIC- eller III-melanom, som har fået foretaget komplet resektion.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Keytruda:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet* SAIP (DKK) April 2023	Forhandlet** SAIP (DKK)	Rabatprocent ift. AIP
Keytruda	25 mg/ml	4 ml	22.058,88	[redacted]	[redacted]	[redacted]	[redacted]

*SAIP baseret på neoadjuverende brystkræft indikationen, april 2023. ** SAIP betinget af godkendelse på denne ansøgning - adj. MM indikationen

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har haft en aftale på Keytruda siden 2015 og den nuværende aftale er en del af et fleksibelt udbud sammen med Opdivo (nivolumab) og Tecentriq (atezolizumab). Aftalen gælder til den 31.12.2023.

Keytruda omsætter årligt for ca. [redacted]

Der er igangsat en prisregulering for alle immunterapier med deadline den 26.06.2023. De nye priser vil gælde fra den 01.07.2023.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence indenfor denne indikation.

Tabel 2: Lægemiddeludgift Keytruda

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

**Vægt: 85,6 kg*

Status fra andre lande

Land	Status	Link
Sverige	Anbefalet	Link anbefaling
England	Anbefalet	Link anbefaling

Konklusion

[redacted]

Ansøgning til brug ved vurdering af pembrolizumab som adjuverende behandling af høj-risiko stadie II melanom

Indholdsfortegnelse

1. Baggrundsinformation

Kontakt information	
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Overblik over lægemidlet	
Lægemidlets navn	Keytruda
Generisk navn	Pembrolizumab
Marketingstilladelse i Danmark	MSD Danmark ApS Indikationen godkendt den 24. juni 2022
ATC code	L01XC18
Farmaceutisk gruppe	Antineoplastic agents
Aktivt stof eller stoffer	Pembrolizumab
Lægemiddelform	Koncentrat til infusionsvæske, opløsning.
Virkningsmekanisme	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.
Doseringsregime	Den anbefalede dosis af KEYTRUDA som en del af kombinationsbehandling er 400 mg hver 6. uge eller 200 mg hver 3. uge administreret som intravenøs infusion over 30 minutter.

Overblik over lægemidlet	
Terapeutisk indikation relevant for vurdering (som defineret af European Medicines Agency, EMA)	KEYTRUDA som monoterapi er indiceret til adjuverende behandling af voksne og unge i alderen 12 år og derover med stadie IIB-, IIC- eller III-melanom, som har fået foretaget komplet resektion
Andre godkendte indikationer	Melanom ▪ KEYTRUDA som monoterapi er indiceret til behandling af voksne og unge i alderen 12 år og derover med avanceret (ikke-resektabelt eller metastatisk) melanom hos voksne. Ikke-småcellet lungecancer (NSCLC) ▪ KEYTRUDA som monoterapi er indiceret til førstelinjebehandling af metastatisk ikke-småcellet lungecancer hos voksne, hvis tumorer udtrykker PD-L1 med *tumour proportion score* (TPS) ≥ 50% uden EGFR- eller ALK-positive mutationer i tumor. ▪ KEYTRUDA, i kombination med pemetrexed og platinbaseret kemoterapi, er indiceret til førstelinjebehandling af metastatisk ikke-planocellulær ikke-småcellet lungecancer hos voksne uden EGFR- eller ALK-positive mutationer i tumorer. ▪ KEYTRUDA, i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel, er indiceret til førstelinjebehandling af metastatisk planocellulær ikke-småcellet lungecancer hos voksne. ▪ KEYTRUDA som monoterapi er indiceret til behandling af lokalt avanceret eller metastatisk ikke-småcellet lungecancer hos voksne efter tidligere behandling med minimum én kemoterapi, og hvis tumorer udtrykker PD-L1 med TPS ≥ 1%. Patienter med EGFR- eller ALK-positive mutationer i tumor bør også have været i targeteret behandling inden behandling med KEYTRUDA. Klassisk Hodgkins lymfom (cHL) ▪ 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. Urotelialt karcinom ▪ KEYTRUDA som monoterapi er indiceret til behandling af lokalt avanceret eller metastatisk urotelialt karcinom hos voksne, som tidligere har fået platinbaseret kemoterapi. ▪ KEYTRUDA som monoterapi er indiceret til behandling af lokalt avanceret 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.

Planocellulært hoved-hals karcinom (HNSCC)

- KEYTRUDA som monoterapi eller i kombination med platinbaseret kemoterapi og 5-fluorouracil (5-FU) er indiceret til førstelinjebehandling af metastatisk eller ikke-resektabelt recidiverende planocellulært hoved-hals karcinom hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1.

- KEYTRUDA som monoterapi er indiceret til behandling af recidiverende eller metastatisk planocellulært hoved-hals karcinom hos voksne, hvis tumorer udtrykker PD-L1 med TPS ≥ 50% og med sygdomsprogression under eller efter platinbaseret kemoterapi.

Renalcellekarcinom (RCC)

- KEYTRUDA, i kombination med axitinib, er indiceret til førstelinjebehandling af avanceret renalcellekarcinom hos voksne.

- KEYTRUDA, i kombination med lenvatinib, er indiceret til førstelinjebehandling af avanceret renalcellekarcinom hos voksne.

- KEYTRUDA som monoterapi er indiceret til adjuverende behandling af voksne med renalcellekarcinom med øget risiko for recidiv efter nefrektomi, eller efter nefrektomi og resektion af metastatiske læsioner.

Cancertyper med høj mikrosatellitinstabilitet (MSI-H) eller *mismatch repair*-defekt (dMMR):

Kolorektal cancer (CRC)

- KEYTRUDA som monoterapi er indiceret til voksne med kolorektal cancer med MSI-H eller dMMR i følgende *settings*:
  - førstelinjebehandling af metastatisk kolorektal cancer;
  - behandling af ikke-resektabel eller metastatisk kolorektal cancer efter tidligere fluoropyrimidinbaseret kombinationsbehandling.

Ikke-kolorektal cancer

- KEYTRUDA som monoterapi er indiceret til behandling af følgende tumorer med MSI-H eller dMMR hos voksne med:
  - avanceret eller recidiverende endometriecancer med sygdomsprogression under eller efter tidligere behandling med platinbaseret terapi i enhver *setting*, og som ikke er egnet til kurativ operation eller strålebehandling;
  - ikke-resektabel eller metastatisk ventrikelkræft, tyndtarmskræft eller galdevejskræft med sygdomsprogression under eller efter mindst en forudgående behandling.

Esophagus karcinom

- KEYTRUDA, i kombination med platin- og fluoropyrimidinbaseret kemoterapi, er indiceret til førstelinjebehandling af lokalt avanceret ikke-resektabelt eller metastatisk karcinom i esophagus eller HER-2 negativ adenokarcinom i den gastroesophageale overgang, hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10.

Triple-negativ brystkræft (TNBC)

- KEYTRUDA, i kombination med kemoterapi som neoadjuverende behandling, og efterfulgt af monoterapi som post-operativ adjuverende

Overblik over lægemidlet	
	behandling, er indiceret til behandling af voksne med lokalt avanceret eller tidlig triple-negativ brystkræft med høj risiko for recidiv. ▪ KEYTRUDA, i kombination med kemoterapi, er indiceret til behandling af lokalt recidiverende ikke-resektabel eller metastatisk triple-negativ brystkræft hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10 og som ikke har fået forudgående kemoterapi for metastatisk sygdom. <u>Endometriecancer (EC)</u> ▪ KEYTRUDA, i kombination med lenvatinib, er indiceret til behandling af avanceret eller recidiverende endometriecancer hos voksne med sygdomsprogression under eller efter tidligere behandling med platinbaseret terapi i enhver *setting*, og som ikke er egnet til kurativ operation eller strålebehandling. <u>Cervixcancer</u> ▪ KEYTRUDA, i kombination med kemoterapi med eller uden bevacizumab, er indiceret til behandling af persisterende, recidiverende eller metastatisk cervixcancer hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1.
Vil udlevering være begrænset til hospitaler?	Udleveringsgruppe: BEGR
Kombinationsbehandling og/eller co-medication	N/A
Pakning – type, størrelse/antal enheder og koncentration	Styrke: 100 mg KEYTRUDA 25 mg/ml koncentrat til infusionsvæske, opløsning. Et hætteglas med 4 ml koncentrat indeholder 100 mg pembrolizumab. Hver ml koncentrat indeholder 25 mg pembrolizumab. Pakning: 1 stk. konc.t.inf.væske.
Orphan drug designation	Nej

2. Forkortelser

AIC	Akaike information criterion
AIP	Apotekernes indkøbspris
ARR	Absolut risikoreduktion
BIC	Bayesian information criterion
CHMP	Committee for Medicinal Products for Human Use
CPS	Combined Positive Score
DMSF	Distant Metastasis-Free Survival
eDMC	ekstern Data Monitorings Commitee
EMA	European Medicines Agency
HR	Hazard Ratio
IA	Interim Analyse
ICER	Incremental Cost-Effectiveness Ratio

IPD	Individual Patient Data
ITT	Intention to treat
KN	Keynote
LY	Life Years
NNT	Numbers Needed to treat
OS	Overall Survival
OWSA	One-way Sensitivity Analyses
PD-L1	Programmed Death Ligand 1
PSA	Probabilistic Sensitivity Analyses
PSM	Partitioned Survival Model
QALY	Quality-Adjusted Life Years
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RFS	Recurrence-Free Survival
RR	Relativ Risiko
ToT	Time on Treatment
WTP	Willingness to Pay

3. Tabeller og Figurer

Liste af figurer

4. Resumé

Indikation

Indikationen i denne ansøgning er pembrolizumab som monoterapi til adjuverende behandling af voksne og unge i alderen 12 år og derover med stadie IIB-, IIC- eller III-melanom, som har fået foretaget komplet resektion.

Medicinrådet anbefalede i 2018 pembrolizumab som adjuverende behandling til stadie III melanom, så denne ansøgning er rettet mod indikationsudvidelse for stadie IIB+IIC.

Ansøgningen baserer sig på resultater fra KEYNOTE-716 (KN-716), et dobbeltblindet randomiseret fase 3 studie.

Indikationen blev godkendt af European Medicine Agency (EMA) d. 24. juni 2022.

Relevant patient population

Patienter med stadie IIB og IIC melanomer grupperes i Sundhedsstyrelsens pakkeforløb for modermærkekræft sammen med patienter med stadie III melanomer som værende patienter i højrisiko for recidiv [1]. Patienterne relevante for denne ansøgning er diagnosticeret med højrisiko stadie IIB+IIC resekteret melanom i Danmark. Ansøgningen er baseret på det kliniske studie KN-716 [2]. Patientpopulationen i KN-716 er sammenlignelig med den danske patientpopulation både på alder, fordeling af køn samt fordeling mellem stadie IIB og IIC melanom, og derfor vurderer MSD, at patientpopulation i KN-716 repræsenterer den danske patientpopulation med resekteret højrisiko stadie IIB+C melanom.

Melanom diagnosticeres i alle aldersgrupper, men hyppigheden er stigende med alderen og optræder hovedsageligt i aldersgruppen 40 til 70 år [3-5]. [redacted] Vi må derfor antage, at patienter med stadie IIB og IIC melanomer, der vil takke ja til adjuverende behandling, vil være den yngre del af populationen og dermed være mere sammenlignelig med den mediane alder på patientpopulationen i KN-716 studiet, som er 60-61 år [2].

Epidemiologi

Melanom er den kræftform, der stiger mest blandt befolkningen med ca. 3-5 % stigning i antal nye tilfælde per år [8], og det er i Danmark den 4. hyppigste kræftform hos kvinder og den 6. hyppigste hos mænd [9]. I 2020 blev der registreret 4.042 nydiagnosticerede melanomer hos 3.972 patienter [3]. [redacted] hvilket også er tilfældet i patientpopulationen i KN-716, hvor der er 60% mænd [2] .

[redacted] Patienter med stadie IIB og IIC melanomer grupperes derfor i pakkeforløbet korrekt sammen med patienter med stadie III melanomer som værende patienter i højrisiko for recidiv [1]. Patienter med stadie III melanom har siden 2018 kunne tilbydes adjuverende behandling med immunterapi [10], hvilket i skrivende stund ikke er en mulighed for stadie IIB+C melanom patienter. Patienter med højrisiko stadie IIB og IIC melanomer er derfor en patientgruppe, der på lige fod med patienter med højrisiko stadie III melanomer har behov for at kunne tilbydes en adjuverende behandling, der kan mindske risikoen for recidiv.

Intervention

Interventionen i denne ansøgning er pembrolizumab, som hos voksne gives 400 mg hver 6. uge op til 9 gange eller 200 mg hver 3. uge op til 17 gange (svarende til cirka 1 år). Pembrolizumab gives som en intravenøs infusion over 30 min. Til pædiatriske patienter (12-17 år) gives pembrolizumab 2 mg/kg (200 mg max) ved IV infusion hver 3. uge op til 17 gange (svarende til cirka 1 år).

Den nuværende standardbehandling for stadie IIB og IIC er kirurgisk resektion og efterfølgende klinisk kontrol [1]. Medicinrådet anbefalede i 2018 pembrolizumab til adjuverende behandling til stadie III melanom [10], så denne anmodning er rettet mod indikationsudvidelse for stadie IIB+IIC. Pembrolizumab blev desuden anbefalet af Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) til behandling af metastaserende stadie IV melanomer i september 2015 [11].

Komparator

MSD mener, vi har valgt en klinisk relevant og hensigtsmæssig komparator i denne ansøgning. Udenfor de kliniske forsøg er der ingen farmakologisk adjuverende behandling for den aktuelle patientgrupper, og der benyttes observation (watch and wait) med kliniske og billeddiagnostiske kontroller efter komplet kirurgisk resektion jf. kliniske retningslinjer for adjuverende behandling af modermærkekræft [5] samt pakkeforløbet for modermærkekræft i huden [1]. I det kliniske studie KN-716 er komparatoren placebo, hvilket er saltvand IV infusion hver 3. uge op til 17 gange (svarende til cirka 1 år). Dette betyder, at komparatoren i KN-716 er konsistent med klinisk praksis for stadie IIB+C melanom i Danmark, og MSD anser derfor, komparatoren som relevant for denne ansøgning.

Signifikante kliniske resultater fra KN-716

<u>Data på klinisk effekt</u>

- 39% reduktion i risiko for recidiv eller død hos patienter behandlet med pembrolizumab sammenlignet med patienter behandlet med placebo
    - Hazard Ratio (HR): 0,61 (95% CI: 0,45 – 0,82), p=0,00046 efter median opfølgningstid 20,5 mdr.
- Færre fjernmetastaser som første recidiv hos patienter behandlet med pembrolizumab sammenlignet med patienter i placebo-gruppen
    - Pembrolizumab-gruppen: 45 patienter vs placebo-gruppen: 79 patienter efter median opfølgningstid 26,9 mdr.
- 36% reduktion i risiko for fjernmetastaser hos patienter behandlet med pembrolizumab sammenlignet med patienter behandlet med placebo
    - HR: 0,64, (95% CI 0,47 – 0,88), p=0.00292 efter median opfølgningstid på 26,9 mdr.
- Ved tilføjelse af farmakologisk behandling med pembrolizumab var der ingen signifikant forringelse i livskvaliteten sammenlignet placebo.
    - Livskvalitets-analyserne EORTC-QLQ-C30 og EORTC-QLQ5 fra KN-716 studiet viser en sammenlignelig livskvalitet hos patienter behandlet med pembrolizumab sammenlignet med placebo-behandlede patienter efter median opfølgningstid 20,5 mdr.

<u>Data på bivirkninger (median opfølgningstid på 20,5 mdr)</u>

- 28,2% af patienterne, der modtog pembrolizumab, oplevede grad 3-5 bivirkninger.
- 17% af patienterne, der modtog pembrolizumab, oplevede grad 3-4 behandlingsrelaterede bivirkninger.
- Der var ingen grad 5 (dødelig udgang) bivirkninger.
- Hyppigheden af bivirkninger, der førte til behandlingsophør, var 17,6%.

- Hyppigheden af endokrine bivirkninger var 22,2% i pembrolizumab-gruppen. De fleste immunrelaterede bivirkninger var af grad 1-2 og var klinisk håndterbare.

Den sundhedsøkonomiske analyse

Over en livstidshorisont forventes adjuverende pembrolizumab at tilvejebringe en betydelige sundhedsgevinst. Vores sundhedsøkonomiske analyse estimerer en gevinst på 1,16 kvalitetsjusteret leveår sammenlignet med nuværende dansk standard behandling og en favorabel ICER på 339.858 kr.

Konklusion

I pakkeforløbet ligestilles patienter med stadie IIB+C melanomer og patienter med stadie III melanomer som værende i høj risiko for recidiv [1]. I dag kan patienter med stadie III melanomer tilbydes adjuverende behandling med anti-PD-1 inhibitor, der nedsætter deres risiko for recidiv, mens patienter med stadie IIB+C patienter ikke kan tilbydes samme behandling. Formålet med adjuverende behandling er at nedsætte risikoen for at kræften vender tilbage [12], og KN-716 viser, at med adjuverende behandling med pembrolizumab af stadie IIB+C patienter reduceres patienternes risiko for recidiv med 39% og deres risiko for fjernmetastaser med 36%. De rapporterede bivirkninger i KN-716 er konsistente med de bivirkninger, der blev rapporteret i det kliniske studie KN-054, som ligger til grund for godkendelsen af adjuverende behandling med pembrolizumab til stadie III patienter [10]. Samtidig er livskvaliteten hos de pembrolizumab-behandlede patienter ikke forskellige fra livskvaliteten hos de placebo-behandlede patienter. I tillæg til de signifikante kliniske resultater, så estimerer den sundhedsøkonomiske analyse en gevinst på 1,16 kvalitetsjusteret leveår sammenlignet med nuværende dansk standard behandling og en favorabel ICER på 339.858 kr.

4.1. Kliniske og patientrelaterede overvejelser som understøtter den kliniske merværdi

MSD finder det indledningsvist relevant at forholde sig til nedenstående overvejelser ved vurdering af den kliniske merværdi for pembrolizumab som adjuverende behandling af resekterede højrisiko stadie IIB+C melanomer.

Højrisiko melanomer uden mulighed for aktiv farmakologisk behandling

I Sundhedsstyrelsens kræftpakkeforløb ligestilles patienter med stadie IIB+C melanomer og patienter med stadie III melanomer som værende i høj risiko for recidiv [1]. [redacted] I 2018 blev adjuverende behandling med pembrolizumab godkendt til stadie III patienter, hvilket betyder, at de har mulighed for at modtage en behandling, der nedsætter både deres risiko for recidiv og ikke mindst deres risiko for recidiv i form af fjernmetastaser [10]. Denne mulighed har højrisiko stadie II patienter endnu ikke.

Fra KN-716 foreligger der nu, efter 26,9 mdrs median opfølgningstid og 3 interim analyser, konklusive data på Recurrence-Free Survival (RFS) og Distant Metastasis-Free Surival (DMFS), der viser en signifikant reduktion i risikoen for recidiv samt reduktion i risikoen for fjernmetastaser efter behandling med pembrolizumab i forhold til placebo [13]. På baggrund af de 3 interim analyser i KN-716 samt erfaringer fra KN-054 antager MSD, at den effekt, der vises på RFS og DMFS, vil opretholdes over tid. I vurderingen af adjuverende behandling fokuserer vi på endepunkter for recidiv, da det endelige formål med behandlingen er at forhindre recidiv [12]. Data på overlevelse forventes ikke før om 10 år, og når overlevelsesdata er tilgængelige, vil de være forbundet med en del usikkerhed på grund af komorbiditet i forbindelse med alderdom og øvrige behandlinger i fx metastatisk regi. MSD mener derfor, at der foreligger et solidt og validt datagrundlag til brug for vurdering, og MSD mener at patienter med højrisiko stadie II melanomer bør tilbydes denne behandling på lige fod med patienter med stadie III melanomer.

RFS som primært endepunkt

RFS er et relevant primært endepunkt da:

- Relevant for patienterne, da det betyder en nedsat risiko for recidiv.
- Relevant for lægerne, da en nedsat risiko for recidiv betyder nedsat antal efterfølgende kirurgiske resektioner og kontroller.
- Data på overlevelse forventes først om ~10 år, og overlevelsesdata påvirkes ofte af andre behandlinger, som patienten gennemgår efter et recidiv, samt komorbiditet.

I KN-716 er RFS det primære endepunkt, og sammen med DMFS, de to effekt-endepunkter, som beskrives i denne ansøgning. OS er planlagt ved interim analyse 5 efter ~154 OS events, og ~120 måneder (~10 år) efter første patient blev randomiseret. Andre kliniske studier med adjuverende behandling af stadie III melanomer viser, at patienter ofte modtager anden behandling eller deltager i andet klinisk forsøg ved recidiv. Derfor kan OS både blive et mål for den adjuverende behandling samt evt. efterfølgende behandlinger og er dermed ikke et direkte mål for effekten af den adjuverende behandling [2]. Det er vist, at Hazard Ratio (HR) for RFS korrelerer med HR for OS for adjuverende behandling med interferon og checkpoint inhibitorer af stadie II + III melanomer [14, 15]. Det betyder, at en effekt af behandling på RFS også vil betyde en effekt på OS, og RFS er dermed et validt surrogat endepunkt for OS ved adjuverende behandling af stadie II + III melanomer med immunterapi. Grænsen for, hvornår RFS kan bruges som et surrogat endepunkt for OS, er en RFS HR på ≤0,77 [14, 15].

Det direkte formål med adjuverende behandling generelt er at nedsætte risikoen for recidiv [12], og RFS er dermed også et egnet mål for, om formålet med behandlingen er blevet opfyldt. RFS er derved et velegnet surrogat endepunkt for OS, men det er også et meget relevant endepunkt i sig selv. Frygten for recidiv fylder mentalt hos patienterne efter resektion, og de beskriver selv risikoen for recidiv som en psykologisk og følelsesmæssig byrde, som de gerne vil have reduceret [16, 17]. Desuden betyder en reduktion i recidiv også en reduktion i kirurgiske indgreb af lokal, regional eller lokoregional recidiv samt en reduktion i antallet af kontroller på hospitalet i årene efter. Ud fra et patientperspektiv er en reduktion i recidiv et yderst relevant mål for adjuverende behandling. Patient præference studier har således vist, at størstedelen af patienterne behandlet med adjuverende interferon-alpfa er villige til at acceptere moderat toxicitet over et år tilgengæld for en 5 års forbedring i RFS på 4% [18]. Forekomsten af recidiv har også vist sig at være forbundet med et fald i livskvalitet samt øget forekomst af depression og angst [19].

Bivirkninger vurderes acceptable

I KN-716 bliver komparatorgruppen behandlet med placebo, hvilket er en saltvandsopløsning. Derfor må det forventes, at bivirkningerne efter farmakologisk behandling med pembrolizumab er højere end ved placebo-behandling. I KN-716 var den relative forskel på antal af bivirkninger i pembrolizumab-gruppen vs. placebo-gruppen indenfor, hvad fagudvalget tidligere har vurderet som klinisk acceptabelt og håndterbart [10]. I vurdering af bivirkningsprofilen for KN-716 skal også medtages, at der ikke var rapporteret signifikant forskel på livskvaliteten mellem pembrolizumab-gruppen og placebo-gruppen, hvorfor behandlingen med pembrolizumab ikke har påvirket livskvaliteten hos patienterne negativt.

Perspektivering med KN-054- studie til grund for anbefaling af adjuverende stadie III melanom.

I ansøgningen anvendes det kliniske fase 3 studie, KN-054, som perspektiveringsgrundlag af resultaterne fra KN-716, som det også er tilfældet i EPARen [13]. I EPARen er KN-054 inkluderet som et ”supportive study”, hvilket betyder, at data fra KN-054 anvendes som et referencegrundlag og til at perspektivere data fra KN-716 i forhold til. KN-054 (NCT02362594) er et randomiseret, dobbelt-blinded fase 3 studie, der sammenlignede pembrolizumab (200 mg hver 3. uge op til 18 gange svarende til ca 1 år) med placebo som adjuverende behandling af patienter med resekteret, højrisiko stadie III melanomer og ligger til grund for anbefalingen af pembrolizumab til adjuverende behandling af resekteret stadie III melanom i Danmark. Det primære endepunkt var RFS, og sekundære endepunkter var DMFS, OS, bivirkninger samt livskvalitet. Studiestart var juli 2015 og estimeres først afsluttet juli 2026 [20]. Der er indtil nu blevet publiceret data med en median opfølgningstid på 5 år [21].

Der er mange ligheder mellem KN-054 og KN-716 i studiedesign, patientpopulation, endepunkter og resultater. Effekt- og bivirkningsdata mellem KN-054 og KN-716 er sammenlignelige, og patientpopulationerne har samme høje risiko for recidiv samt samme 5 års overlevelsesprognose [2, 20]. Data fra KN-054 kan derfor anvendes til at forstå, hvordan både effekt- og bivirkningsdata udvikler sig over tid.

I denne ansøgning anvendes data efter en median opfølgningstid på henholdsvis 20,5 mdr og 26,9 mdr, mens adjuverende behandling med pembrolizumab af stadie III melanomer blev anbefalet på baggrund af data fra KN-054 med en median opfølgningstid på 21,6 mdr [10]. For KN-054 blev der for nyligt publiceret RFS data med 5 års follow-up, hvor det ses, at forskellen i RFS-raten mellem pembrolizumab- og placebogruppen opretholdes over tid samt, at bivirkningsprofilen ikke forværres over tid [21]. Der er endnu ikke OS data tilgængelig fra KN-054. Baseret på erfaringer fra KN-054 antager vi, at data fra KN-716 vil udvikle sig på samme måde over tid, og KN-054 er derfor en vigtig reference til at forstå og perspektivere data fra KN-716.

5. Patientpopulationen, behandling og valg af komparator

5.1. Sygdommen og patientpopulationen

Patofysiologi

Modermærkekræft (melanom) udvikles i de pigmentproducerende celler (melanocyter) i huden eller i medfødte modermærker. I sjældne tilfælde kan kræften også udvikles på slimhinder eller i øjet [3]. Som respons på DNA-skade induceret af ultraviolet-lys fra solen producerer andre af hudens celler melanocyte-stimulating hormone, der binder til en receptor på melanocytterne, der dermed frigiver melanin-pigment, som beskytter mod yderligere stråling. Ved manglende eller langsom produktion af melanin-pigment er der intet skjold mod UV-stråling og dermed risiko for DNA forandringer, som over tid kan resultere i kræftformen melanom [22].

Melanom er en af de mest aggressive former for hudkræft og en af de førende årsager til kræft-relateret død pga. dens evne til at metastasere. Flere studier har vist, at spredning af melanom er forårsaget af både genetiske mutationer samt ændringer i tumormikromiljøet. Sidstnævnte er karakteriseret af overekspression af proteiner som matrix metalloproteinaser, der inducerer tumor-invasion og infiltrering i det omgivende væv [22].

Melanomer inddeles i stadier efter specifikke kriterier, som melanomets tykkelse, sårdannelse og spredning [23, 24]. Danske tal viser, at patienter med de tykkeste tumorer uden lymfeknudemetastaser (stadie IIC) har dårligere overlevelse end patienter med lymfeknudemetastaser på diagnosetidspunktet (stadie III) [3, 6]. Det tyder på, at en forøgelse af tykkelsen på melanomet samt ulcerationer forværrer prognosen, mens lymfeknudemetastaser syntes at have mindre betydning [3]. Den kliniske stadieinddeling er vist nedenfor (jf. AJCC 8th edition [23]):

- **Stadie I (A + B)**
  - Uden spredning til lymfeknude
  - Stadie IA
    - Tumortype T1a (<0,8 mm uden ulceration),
  - Stadie IB
    - T1b (<0,8 mm med ulceration eller 0,8-1,0 mm med ulceration) eller
    - T2a (>1,0 – 2,0 mm uden ulceration)
- **Stadie II (A-C)**
  - Uden spredning til lymfeknude
  - Stadie IIA
    - Tumortype T2b (>1,0 – 2,0 mm med ulceration eller
    - T3a (>2,0 – 4,0 mm uden ulceration)
  - Stadie IIB
    - T3b (>2,0 – 4,0 mm med ulceration) eller

        - T4a (>4,0 uden ulcerationer)
    - Stadie IIC
        - T4b (>4,0 med ulcerationer)
- **Stadie III (A-D)**
    - Spredning til ≥1 lymfeknude (klinisk okkult (mikroskopisk) eller klinisk detekteret (makroskopisk) eller in-transit, satellit og/eller mikrosatellit metastaser uden lymfekunde involvering)
    - Alle slags tumortyper
- **Stadie IV**
    - Metastaserende med fjernspredning
    - Alle slags tumortyper

Symptomer

Det mest almindelige symptom på melanom er, at et eksisterende eller et nyt modermærke forandrer sig [25]. Melanomer vil oftest kunne ses med det blotte øje, da de hyppigst sidder på huden og derved opdages i tidligere stadier end andre typer kræft f.eks. i indre organer. Man skal være opmærksom på, hvis et modermærke ændrer størrelse, form eller farve, eller hvis det bliver ujævnt, tykkere, får skorpedannelse eller bløder og ikke vil hele, eller hvis et modermærke klør vedvarende [25].

[redacted]

Patienter, som får foretaget komplet kirurgisk resektion af deres melanom i stadie II, er i risiko for at få recidiv og udvikle metastatisk melanom. Ved recidiv metastaserer melanomet oftest til lymfeknuder, lunger, lever og hjerne, men kan også metastasere til knogler, knoglemarv, og milt. Organmetastaser er generelt ensbetydende med en dårlig prognose [3].

Risikofaktorer for udvikling af malignt melanom

Den væsentligste årsag til udviklingen af et melanom er udsættelse for ultraviolette stråler fra sollys og solarier, men i enkelte tilfælde kan melanom være arvelig [4]. Mennesker med lysere hud og hårfarve har lavere niveau af melanin og er i højere risiko for at udvikle melanom. Desuden kan gentagne solskoldninger i barndommen hos den enkelte også øge risikoen. Risikoen øges også med antallet af modermærker på den enkeltes krop [26].

Incidens og prævalens

Incidensen af melanom er stigende verden over [27], og i Danmark er melanom den kræftform, der stiger mest blandt befolkningen med ca. 3-5 % stigning i antal nye tilfælde per år [8]. Melanom er i Danmark den 4. hyppigste kræftform hos kvinder og den 6. hyppigste hos mænd [9]. I den yngre aldersgruppe på 15-34 år i Danmark er det den hyppigste kræftform hos kvinder og den 3. hyppigste hos mænd [9].

I 2020 blev der registreret 4.042 nydiagnosticerede melanomer, hvoraf de 2.781 var invasive tumorer (med spredning) og 1.183 var in situ (uden spredning). Tumorerne blev registreret hos 3.972 patienter. Af disse var 1.172 stadie 0, 2.065 stadie I, 181 stadie IIA, 120 stadie IIB, 74 stadie IIC, 254 stadie III og 30 stadie IV, og 146 ubesvaret/uklassificeret eller uden for kategori [3].

[redacted] hvilket stemmer overens med internationale data [28]. I KN-716 er fordelingen af melanom subtyper ~65% stadie IIB melanom og 35% stadie IIC melanom [2]. Stadie IIA er ikke inkluderet i KN-716, og derfor svarer fordelingen mellem stadie IIB+IIC melanomer i KN-716 til fordelingen af stadie IIB+C melanomer blandt danske melanom patienter.

I Tabel 1 ses, at incidensen generelt ligger på omkring 2/100.000 for stadie IIB og omkring 1,25/100.000 for stadie IIC siden 2015. Dog var der i 2019 en stigning til 2,45/100.000 personer årligt for stadie IIB og til 1,45/100.000 personer årligt for stadie IIC.

Tabel 1: Incidens rate i Danmark

År	2015	2016	2017	2018	2019
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Prævalensen er opgivet samlet og inkluderer derved alle stadier af melanom. Det er ikke muligt at finde data på prævalens i de enkelte stadier. Som det ses i

Tabel 2 er prævalensen for mænd steget fra omkring 400/100.000 personer i 2015 til næsten 500/100.000 personer i 2019 [9]. For kvinder er der også sket en stigning fra 585/100.000 personer i 2015 til næsten 700/100.000 personer i 2019. I Danmark i 2018 levede 14.421 mænd og 20.415 kvinder med diagnosen (gælder personer i behandling, kontrol, og raske) [29].

Tabel 2: Prævalens rate i Danmark

År	2015	2016	2017	2018	2019
Prævalens i Danmark per 100.000 personer (alle stadier da de ikke er muligt at finde data for stadie IIB+C specifikt) [9]	**Mænd**: 401 **Kvinder:** 585	**Mænd:** 425,1 **Kvinder:** 615,2	**Mænd:** 450,1 **Kvinder:** 639,9	**Mænd:** 476,2 **Kvinder:** 670	**Mænd:** 498 **Kvinder**: 698,2

Patientpopulation

Patienterne relevante for denne ansøgning er patienter med resekteret højrisiko stadie IIB og IIC melanom. MSD vurderer, at de danske patienter med stadie IIB og IIC melanom, der vil modtage adjuverende behandling, er sammenlignelig med patientpopulationen i KN-716.

Melanom diagnosticeres i alle aldersgrupper, men hyppigheden er stigende med alderen, og melanom optræder hovedsageligt hos personer i aldersgruppen 40-70 år [3-5]. Det forekommer meget sjældent hos børn og unge [9]. Det forekommer generelt lidt hyppigere blandt kvinder end hos mænd (ratio 0,8) [3-5], [redacted] I KN-716 er der inkluderet ~60% mænd og 40% kvinder [2], og dermed er patientpopulationen i KN-716 sammenlignelig med den danske patientpopulation ifht fordeling af køn.

I KN-716 har studiepopulationen en median alder på 60-61 år [2]. [redacted] Dermed kan det forventes, at den del af stadie IIB og IIC melanom patienterne, der vil modtage adjuverende behandling, svarer til patientpopulationen i KN-716 med en median alder på omkring 60 år.

Forventet patientpopulation antal

I 2020 blev der via de plastikkirurgiske afdelinger i Danmark registreret 120 nye patienter med stadie IIB tumorer og 74 stadie IIC tumorer, hvorfor der forventes cirka **194 patienter/årligt** med højrisiko stadie IIB+C, som bør henvises til onkologerne med henblik på vurdering for adjuverende behandling med pembrolizumab [3].

[redacted] Hvis man antager, at 32% af stadie IIB+C heller ikke vil modtage behandling, vil vi forvente cirka **132 patienter** ekstra patienter årligt til adjuverende behandling i Danmark med immunterapi af stadie IIB+C melanomer (se Tabel 3).

[redacted] kan det forventes, at der vil være en større andel af stadie II patienterne, som ikke vurderes egnet til behandling, eller som ikke ønsker adjuverende behandling, og estimatet af årlige antal patienter er potentielt lavere end de 132 opgivet.

Tabel 3: Forventede antal patienter de kommende år

År	2022	2023	2024	2025	2026
Forventet antal patienter i Danmark til indikationen	132	132	132	132	132

Prognose af højrisiko stadie IIB+C melanomer

[redacted] I pakkeforløbet for modermærkekræft ligestilles stadie IIB+C melanomer derfor korrekt sammen med stadie III melanomer som værende i højrisiko for recidiv og dermed med en dårlig prognose [1].

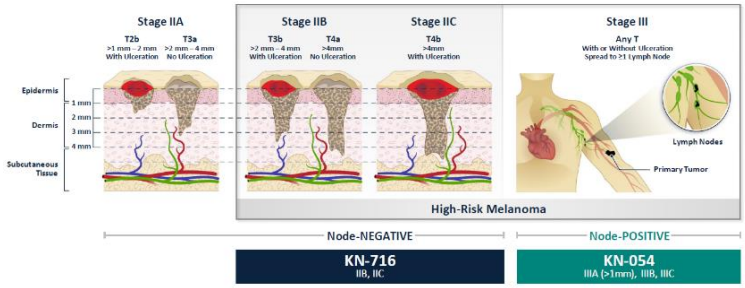
Internationale 5 års overlevelsesdata publiceret i AJCC8 angiver generelt en højere overlevelse [23, 24], end de danske data viser. MSD vurderer, at validiteten af de danske data er højest, og at 5 års overlevelsen for stadie IIB+C og III er dårligere end, hvad de internationale data viser (se nedenfor), hvilket også bakkes op af nyligt publicerede data fra Sverige og Tyskland [30, 31].

Prognose stadie IIB+C

[redacted] data publiceret i AJCC8 viser en 5 års melanom-specifik overlevelse på 94% for stadie IIA, 87% for stadie IIB og 82% for stadie IIC [23]. Nyligt publicerede data fra 2 tyske registre med henholdsvis 6.725 patienter og 10.819 patienter viser en 5 års melanom-specifik overlevelse på henholdsvis 82,8% og 86,5% for stadie IIB og henhooldsvis 70% og 76,6% for stadie IIC [30]. [redacted] Dette stemmer overens med et amerikansk studie med 738 patienter, der viste en recidiv rate (uden død) efter median opfølgningstid på 4,3 år på 32% for stadie IIB og 46% for stadie IIC. Af de patienter, der udviklede recidiv, havde henholdsvis 30% i stadie IIB og 52% i stadie IIC fjernmetastaser ved første recidiv [32]. De tyske data viser også en 5 års RFS rate (uden død) på henholdvis 61,9% og 65% for stadie IIB og 43,7% og 57,1% for stadie IIC [30]. Disse danske og internationale data viser, at en relativ høj andel af patienter med stadie IIB og IIC melanomer får recidiv, og at omkring halvdelen af disse er fjernmetastaser som første recidiv. Dermed underbygger disse data, at stadie IIB+C melanomer er i højrisiko for recidiv, hvilket også afspejles i Pakkeforløbet [1].

Recidiv er generelt forbundet med dårlig prognose, og specielt har lokalisationen af recidiv betydning for prognosen [33]. Der er efter vores bedste overbevisning ikke publiceret data, der direkte beskriver andelen af stadie IIB+C melanom patienter, der bliver sygdomsfri/kureret efter behandling af første recidiv fordelt på om første recidiv er lokoregionalt eller metastatisk. [redacted] [1]. Baseret på disse danske data vurderer MSD derfor, at det er en lille andel af stadie II patienterne, der kan anses som sygdomsfri eller kureret efter recidiv. Dvs at stadie IIB+C patienterne med høj risiko for recidiv, og hvoraf [redacted] med recidiv vil have fjernmetastaser som første recidiv, har en dårlig prognose.

Figur 1 illustrerer stadieinddelingen, hvor man kan se, at stadie IIB, IIC og III melanomer grupperes som værende højrisiko melanomer:



Figur 1: Diagram over stadieinddeling og højrisiko melanomer
Tilpasset fra Poklepovic et al 2020 [28]

Prognose stadie III

[redacted] De internationale data viser en 5 års melanom-specifik overlevelse på henholdsvis 93% for IIIA, 83% for IIIB og 69% for IIIC [23]. [redacted] Dette stemmer overens med et internationalt studie med 251 patienter, der fandt, at recidiv-raten var henholdsvis 44% for stadie IIIA patienter, 45% for stadie IIIB patienter og 74% for stadie IIIC patienter (median opfølgningstid 3,1 år) [34]. [redacted]

Tabel 4: Danske data på 5 års overlevelse (OS) og recidiv-fri overlevelse (RFS)

Stadie (AJCC8)	5 års OS – inkl død af anden årsag. Landsdækkende tal 2010-2019, data on file [6]	5 års RFS – inkl død af anden årsag. Landsdækkende tal 2010 – 2019, data on file [6]
IIA	[redacted]	[redacted]
IIB	[redacted]	[redacted]
IIC	[redacted]	[redacted]
III	[redacted]	[redacted]

Figur 2: Kaplan-Meier Overall Survival (OS) (øverst) og Recurrence-Free Survival (RFS) (nederst) kurver for stadie II og III melanomer
Baseret på data fra [6]

Danske data vs internationale data

Opgørelser med internationale data viser en 5 års melanom-specifik overlevelse på 94% for stadie IIA, 87% for stadie IIB og 82% for stadie IIC. For stadie III er 5 års overlevelsen 93% for IIIA, 83% for IIIB og 69% for IIIC [23]. Disse 5 års overlevelsesdata viser en bedre prognose end de danske data, og specielt er der forskel i data for stadie IIC [redacted] vs international 5 års OS: 82%). En forklaring kan være, at de internationale data bygger på en database med 46.986 patienter. Af disse er 18.684 patienter fra Australien [23], hvor det anbefales at lade patienter tjekke sig selv for recidiv, da evidencen for en positiv effekt af rutinemæssig follow-up hos lægen er lille, hvorved risiko for manglende opfølgning og dermed korrekt registrering går tabt [35]. En anden forklaring kan være, at de danske tal opgives i død generelt (af enhver årsag) og ikke kun melanom-specifik død, som de internationale tal. Den reelle 5 års overlevelse er derfor formentlig lavere end de internationale AJCC8 data (Gershenwald et al 2017 - [23]), hvilket også

afspejles i de danske tal, hvor 5 års OS (inkl død af enhver årsag) er så lav som 40% samt i de tyske registerdata, hvor den melanom-specifikke 5 års overlevelse er 70% [30].

Perspektivering

Stadie III patienterne har siden 2018 kunne tilbydes adjuverende behandling med immunterapi, der nedsætter risikoen for recidiv [10]. EMA har godkendt pembrolizumab som adjuverende behandling til patienter med stadie IIB+C melanomer, og MSD vurderer, at denne mulighed bør de danske patienter med stadie IIB+C melanomer også tilbydes.

[redacted]. Dette understreger igen, at stadie IIB og IIC melanomer kan kategoriseres som højrisiko melanom sammen med stadie III, og at begge melanomstadier har en dårlig prognose.

5.1.1. Patient population relevant for denne ansøgning

Den danske patientgruppe, som forventes at være kandidater til behandlingen, vil være voksne og unge ≥12 år med højrisiko stadie IIB og stadie IIC melanom, som har fået foretaget komplet resektion. Som det er tilfældet med adjuverende behandling med immunterapi til stadie III patienter, bør det være et tilbud, og den endelige beslutning om evt behandling tages mellem patient og læge.

Da patienter med henholdsvis højrisiko stadie II og III melanomer har samme høje risiko for recidiv, mener MSD, at tilbuddet om adjuverende behandling med immunterapi skal gælde for både stadie IIB, IIC og III melanomer. Dette er i overenstemmelse med Grob et al 2018, hvor en række europæiske eksperter foreslår, at udvikle tidlig adjuverende behandlings strategier i melanom med det formål at behandle kræften før den bliver metastatisk med henblik på at øge chancen for at kurere patienten og ikke mindst for at påvirke den melanom-specifikke mortalitet [36].

5.2. Nuværende standardbehandling og valg af komparator

5.2.1. Nuværende standardbehandling i Danmark

Den nuværende standardbehandling i Danmark for melanom stadie IIB og IIC er komplet kirurgisk resektion og derefter kliniske kontroller hver 3. måned i 2 år og hver 6. måned i de efterfølgende 3 år. Der foretages FDG-PET/CT-skanning ved 6, 12, 24 og 36 måneders kontrol. Endvidere foretages ultralydsskanning af den lymfeknuderegion, hvor man har fundet positiv sentinel node. Dette foretages ved hvert ambulant fremmøde på sygehuset, såfremt der ikke foretages PET eller PET-CT skanning [1, 5].

Adjuverende behandling med pembrolizumab til patienter med stadie IIB og IIC melanomer er den første og eneste adjuverende behandling godkendt af EMA til denne patientgruppe [1, 5].

Adjuverende behandling med immunterapi til stadie III og IV er nu standardbehandling i Danmark og tilbydes relevante patienter på alle de danske afdelinger, som behandler melanom [5]. Som beskrevet tidligere grupperes stadie IIB og IIC melanomer sammen med stadie III som værende højrisiko melanomer [1], og vigtigheden af, at adjuverende behandling fremadrettet også tilbydes til patienter med stadie IIB+C melanomer, understreges af, at prognosen for patienterne med stadie IIB+C dermed er sammenlignelig med prognosen for patienter med stadie III melanomer.

5.2.2. Valg af komparator

I det kliniske studie KN-716 er komparatoren placebo, hvilket er saltvandsinfusion hver 3. uge op til 17 gange (svarende til cirka 1 år). Dette betyder, at komparatoren i KN-716 er konsistent med standard behandling for stadie II melanoma i Danmark, og MSD anser derfor komparatoren i KN-716 som relevant for denne ansøgning, da den repræsenterer dansk klinisk praksis (ingen farmakologisk behandling) [1, 5].

5.2.3. Beskrivelse af komparator

Ikke relevant da komparatoren er placebo.

5.3. Interventionen

Pembrolizumab har været anvendt i behandlingen af kræft som monoterapi siden 2015, hvor pembrolizumab blev anbefalet til behandling af metastaserende melanom [11] og siden 2018, hvor pembrolizumab blev anbefalet som adjuverende behandling til stadie III patienter [10].

- *Dosering*: Pembrolizumab 400 mg hver 6. uge i op til 9 gange eller 200 mg hver 3. uge i op til 17 serier.
- *Administrationsvej:* Pembrolizumab indgives intravenøst.
- *Behandlingslængde/Kriterier for at stoppe behandling:* I KN-716 kunne pembrolizumab administreres op til 17 serier.
- *Skal behandlingen administreres med andet medicin?* Nej
- *Nødvendige monitoreringer under administration, i behandlingsperioden og efter endt behandling:* Det anbefales at følge lokale guidelines for monitorering.
- *Behov for diagnostiske tests (f.eks. company diagnostics):* Nej, behandling med pembrolizumab som adjuverende behandling til melanom er uafhængig af PD-L1 test 22C3, som er den godkendte companion diagnostic til pembrolizumab og bruges i nogle andre indikationer ved behandling med pembrolizumab [13].

6. Litteratursøgning

6.1. Identifikation og udvælgelse af relevante studier

Der er i KN-716 studiet foretages en direkte sammenligning mellem den nye behandling (interventionen) og den relevante komparator (placebo).

Der er ikke foretaget en systematisk søgning efter dokumentation for effekt og sikkerhed, da søgningen ikke forventes at tilvejebringe yderligere relevant dokumentation for effekt og sikkerhed, da pembrolizumab er den første og eneste anti-PD-1 inhibitor, der er godkendt i denne patientpopulation.

De relevante publikationer for denne ansøgning:

- Paper: Long et al 2022. *Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial*. Lancet Oncol 2022 https://doi.org/10.1016/S1470-2045(22)00559-9
- Paper: Khattak et al 2022., *Adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma: Health-related quality of life from the randomized phase 3 KEYNOTE-716 study*, European Journal of Cancer. https://doi.org/10.1016/j.ejca.2022.08.004
- Paper: Luke et al. 2022: *Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial*, The Lancet, Volume 399, Issue 10336, 30 April–6 May 2022, Pages 1718-1729. (resultater fra interim analyse 1+2) https://doi.org/10.1016/S0140-6736(22)00562-1
- Paper: Luke et al. 2019. *KEYNOTE-716: Phase III study of adjuvant therapy with pembrolizumab versus placebo in resected high-risk stage II melanoma*. FUTURE ONCOLOGYVOL. 16, NO. 3. (clinical trial design) https://doi.org/10.2217/fon-2019-0666

Det relevante studie til denne ansøgning er:

- *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)*. NCT-nummer: NCT03553836. Studiestart den 12. September 2018 og forventet studie slutdato 12. October 2033.

For fuld liste af studiekarakteristika, se appendix B.

Data brugt til denne ansøgning er data on file (Clinical Study Report) [37], det foreløbige udkast til EPAR [13], data fra interim analyse 1+2 fra KN-716 publiceret i Luke et al 2022: *Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial*, The Lancet, Volume 399, Issue 10336, 30 April–6 May 2022, Pages 1718-1729 samt pblicerede DMFS data [38] og data på livskvalitet [39].

6.2. Liste af relevante studier

Tabel 5: Relevante studier inkluderet i denne ansøgning

Reference (titel, forfatter, journal, år)	Studienavn	NCT number	Datoer for studiet (start and forventet slutdato)	Brugt som sammenligning af*
Luke et al 2022: *Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomized, double-blind, phase 3 trial*, The Lancet, Volume 399, Issue 10336, 30 April–6 May 2022, Pages 1718-1729.	Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)	NCT03553836	Studiestart den 12. September 2018 og forventet studie slutdato 12. October 2033	Pembrolizumab vs. placebo for komplet resekteret stadie IIB+C melanomer

For detailed information about included study, refer to appendix B.

7. Effekt og sikkerhed

I KN-716 er inkluderet patienter, der er ≥12 år med nyligt diagnosticeret, komplet resekteret højrisiko (stadie IIB eller IIC) melanom uanset PD-L1 status. For baselinekarakteristika, effektdata og livskvalitetsdata præsenteres der data for *intention-to-treat* (ITT) populationen, mens sikkerhedsdata/bivirkninger rapporteres for hele *as-treated* population (minimum 1 dosis medicin i studiet).

I ansøgningen præsenteres data fra følgende populationer:

- Baselinekarakteristika for ITT-populationen.
- Recurrence-free survival (RFS) for ITT- populationen – baseret på data fra interim analyse 2 og er den endelige analyse af RFS (20,5 mdr's median opfølgningstid)
- Distant-metastasis free survival (DMFS) for ITT-populationen – baseret på data fra interim analyse 3 og er den første analyse for DMFS (26,9 mdr's median opfølgningstid)
- Bivirkninger for hele *as-treated*-populationen – baseret på interim analyse 2
- Livskvalitet for ITT-populationen – baseret på interim analyse 2

De komparative analyser er en direkte statistisk komparativ analyse af pembrolizumab sammenlignet med placebo, svarende til dansk klinisk praksis.

- 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 den inkluderede patienter, der alle modtager samme behandling i deres respektive

behandlingsarme. Den eksterne validitet er styrket af studiets design med fastsatte inklusions- og eksklusionskriterier, hvor eksklusionskriterierne inkluderer patienter med et bred aldersinterval (≥12 år) fra 16 forskellige lande og uafhængig af PD-L1 status.

7.1. Effekt og sikkerhed efter pembrolizumab-behandling sammenlignet med placebobehandling til patienter med komplet resekteret stadie IIB+C melanom

7.1.1. Relevant studie KN716

Studiedesign

KN-716 er et todelt (adjuvant and rechallenge/crossover), randomiseret, placebo-kontrolleret, parallelgruppe, multicenter, fase 3 studie af adjuverende pembrolizumab til voksne og unge ≥12 år med resekteret stadie IIB eller IIC melanom [2]. Stadie IIB og IIC melanom er defineret som T kategorier T3b, T4a og T4b (se tidligere oversigt s. 17) med negativ sentinel lymfeknudebiopsi, ingen regionale metastaser og ingen tegn på fjernmetastaser [23]. Se Figur 3 for en oversigt over studiedesignet.

Inklusionskriterier var alder ≥12 år, nyligt diagnosticeret og kirurgisk komplet resekteret høj-risiko stadie IIB eller IIC kutant melanom (AJCC-8) uden regional lymfeknude involvering (N0) bekræftet ved en sentinel lymfeknude biopsi. ECOG performance score på 0 eller 1. De inkluderede patienter måtte ikke tidligere have modtaget nogen behandling for deres melanom udover komplet resektion. Tid fra kirurgisk resektion til randomisering var max 12 uger. Der måtte ikke være tegn på metastaserende sygdom.

Eksklusionskriterierne var blandt andet uveal eller okular melanom; andre progressive cancersygdomme der krævede anti-neoplastisk behandling eller kirurgi indenfor de sidste 5 år; tidligere behandling af deres nuværende kræftsygdom; diagnose af immundefekter; langtidsbehandling med systemisk steroid eller tidligere behandling med en anti-PD-1, anti-PD-L1 eller anti-PD-L2 antistof eller andre behandlinger targeteret mod andre stimulatoriske eller co-inhibitoriske T-celle receptorer. For fuld liste af in- og eksklusionskriterier se Appendiks B.

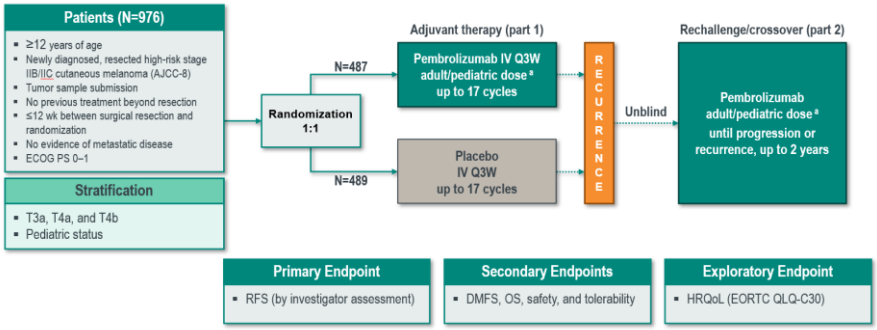
I første del af studiet blev patienterne randomiseret i en 1:1 ratio til interventionsgruppen med adjuverende behandling med pembrolizumab (voksne en dosis på 200 mg IV hver 3. uge og unge mellem 12 og 17 år en dosis på 2 mg/kg IV hver 3. uge) eller kontrolgruppen med placebo (saltvand IV hver 3. uge) begge i op til 1 år. Der blev stratificeret for T kategori 3b, 4a eller 4b og pædiatrisk status. På grund af varierende tilgængelighed af tumorbiopsi var BRAF-mutation og PD-L1-ekspression ikke en præspecificeret analyse. Desuden har data fra KN-054 vist, at effekten af adjuverende behandling af melanom med pembrolizumab er uafhængig af BRAF mutationer og PD-L1 ekspression [20].

Den anden del af studiet er en ikke-blindet crossover/rechallenge fase af studiet, hvor patienter med recidiv af deres sygdom kan modtage videre behandling med pembrolizumab, hvis de opfylder inklusionskriterierne. Denne ansøgning fokuserer udelukkende på første del af studiet, da der ikke er kommet data på anden del endnu, og de forventes ikke før om flere år.

Studiets primære endepunkt var RFS, hvilket blev vurderet af investigator. RFS er defineret som tiden fra randomisering til tidspunktet for første dokumentation af en af følgende hændelser: recidiv af melanom på et hvilket som helst sted (lokalt, in-transit eller regional lymfeknude eller fjernmetastaser) eller død (inkl død af anden årsag). Nye tilfælde af melanom eller diagnose af en anden cancer er ikke med som event i RFS opgørelsen. RFS udtrykkes i måneder. Der blev samtidig opgivet *Pattern of Recurrence*, hvilket vil sige en oversigt over, om recidiv opstår lokalt/regionalt/lokoregionalt, som fjernmetastaser eller som død.

De sekundære endepunkter var DMFS, OS og tolerability. De eksploratoriske endepunkter var *health-related quality of life* målt ved EORTC Quality of life Questionnaire Core 30 (QLQ-C30) og ED-5D-5L, farmakokinetiske endepunkter og analyse til at identificere nye biomarkører.

Effekt endepunkter blev undersøgt i ITT-populationen af alle randomiserede patienter, mens bivirkningerne (safety) blev undersøgt i *as-treated* populationen. Sygdommen blev undersøgt med CT/MRI skanning af bryst, abdomen og pelvis første gang 6 måneder efter randomisering og derefter hver 6. måned til og med det fjerde år og derefter en gang i det femte år eller som klinisk indikeret.



Figur 3: Studiedesign for KN-716

I den første del af studiet er der planlagt 5 interim analyser, som kan ses i Tabel 6. Resultaterne af interim analyserne vurderes af en ekstern Data Monitorerings Komite (eDMC), som anbefaler sponsor at fortsætte, modificere eller afslutte studiet. Alle patienterne var randomiseret før, at den første interim analyse blev foretaget. Den første interim analyse var planlagt efter ~128 events (sygdomsrecidiv eller død) og blev foretaget efter 136 events med en median opfølgningstid på 14,3 måneder.

Den anden interim analyse var planlagt ved ~179 RFS events observeret, og det var forventet, at det ville være cirka ~6 måneder efter første interimanalyse, og ~48 måneder efter den første patient blev randomiseret. Den blev foretaget efter 187 events og en median opfølgningstid på 20,5 måneder. Ved den anden interim analyse var RFS det eneste effekt endepunkt, der blev analyseret, og dette var den endelige analyse (final analysis) for RFS. Den tredje interim analyse var den første analyse for DMFS og blev foretaget efter 26,9 måneders median opfølgningstid for begge grupper.

Tabel 6: Oversigt over analyser

Interim analyse	Endepunkter	Kriterier for at foretage analysen	Estimeret tid efter første patient er blevet randomiseret	Analysens primære formål	Faktiske data cut-off	Median opfølgningstid
IA1: Interim RFS analyse	RFS	(1) inklusion er komplet og (2) ~ 128 RFS events er observeret	~33 måneder	RFS IA	4/12/2020	14,3 måneder (range 1.0 to 26.4 mdr)
IA2: Endelige RFS analyse	RFS	~179 RFS events er observeret	~48 måneder	RFS FA	21/6/2021	20,5 måneder (range 4,6 – 32,7 mdr)
IA3: Interim DMFS analyse	DMFS + eksplorativ RFS	~146 DMFS events er observeret	~60 måneder	DMFS IA	4/1/2022	26,9 måneder (range 4.6 - 39.2 mdr)
IA4: Endelige DMFS analyse	DMFS	~195 DMFS events	~108 måneder	DMFS FA		
IA5: Interim OS analyse	OS	~154 OS events	~120 måneder	OS IA		

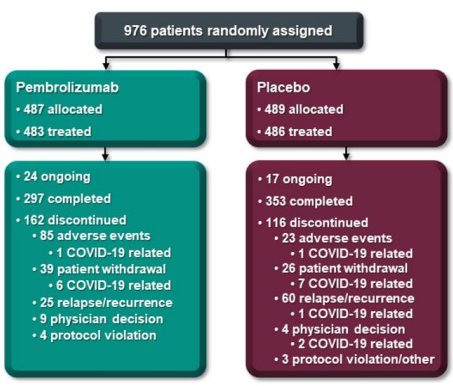
FA: Endelige OS analyse	OS	~204 OS events	~180 måneder	OS FA		

RFS = Recurrence-Free Survival; DMFS = Distant Metastatic-Free Survival; FA = Final Analysis; IA = Interim Analysis; OS = Overall Survival

Den statistiske plan havde en overordnede alfa for studiet, som var kontrolleret ved one-sided 2,5% for alle sammenligninger. Strategien for kontrol af multiple sammenligninger bliver anvendt på den primære hypotese samt de to sekundære hypoteser. Den primære hypotese tester om pembrolizumab er bedre end placebo ifht RFS. De 2 sekundære hypoteser tester om pembrolizumab er bedre end placebo med hensyn til DMFS og OS. Studiet vurderes succesfuldt, hvis RFS er statistisk signifikant på enten interim analysen eller ved den endelige analyse med kontrol for multiple testing. Den primære hypotese bliver testet først, og den følgende sekundære hypotese bliver kun testet i fald den foregående hypotese var positiv. Det er tilladt at allokere alfa videre fra en succesfuld hypotese til næste i rækken. Det vil sige, at fordi RFS var statistisk signifikant ved den første interim analyse, blev RFS ikke testet i den anden interim analyse, men derimod blev alfa allokeret til DMFS hypotesen, som blev testet ved interim analyse 3.

Studiet startede i September 2018, og i November 2020 var alle patienter inkluderet i studiet. Den anden interim analyse, som denne ansøgning hovedsageligt fokuserer på, havde data cut-off i juni 2021 efter en median opfølgningstid på 20,5 mdr. [30]. Den tredje interim analyse, hvor DMFS data er fra, havde data cut off i januar 2022 efter en median opfølgningstid på 26,9 mdr [13]. For fuld studieplan se appendix B.

976 patienter blev randomiseret til studiet og fordelt i en 1:1 ratio til en af de to grupper. Der var 487 patienter, der blev allokeret til pembrolizumab-behandling og 486 patienter allokeret til placebo-behandling. Der var 4 patienter allokeret til pembrolizumab og 3 patienter allokeret til placebo, der ikke startede behandling. Ved data cut-off til den anden interim analyse 21. juni 2021 var der i pembrolizumab-gruppen fortsat 24 patienter i behandling, 297 (61%) havde færdiggjort behandlingsregimet (færdiggjort behandling i 1 år) og 162 ophørte behandlingen før tid. Der var 85 (18%), der ophørte behandlingen pga bivirkninger, 25 (5%) pga recidiv, 39 patienter udgik eget ønske heraf 6 pga COVID-9-relaterede årsager, 9 patienter udgik grundet lægens beslutning, og 4 patienter udgik pga overtrædelser af protokollen. I placebogruppen var der 17 patienter stadig i behandling ved data cut-off, 353 (73%) havde færddiggjort behandlingsregimet (færdiggjort behandling i 1 år) og 116 ophørte behandlingen før tid. Der var 23 (5%) der havde stoppet behandling pga bivirkninger, 60 (12%) stoppede pga recidiv, 26 patienter udgik efter eget ønske heraf 7 pga COVID-19-relaterede årsager, 4 patienter udgik som følge af lægens beslutning, 1 patient udgik pga overtrædelse af protokollen, 1 patient blev mistet for opfølgning (lost to follow-up), og 1 patient udgik som følge af non-compliance study drug – se Figur 4 [2]. Protokolovertrædelser optrådte ligeligt fordelt og med lav incidence i begge grupper og er vurderet i EPARen s. 70 til ikke at have komprimeret studieudførelsen eller analyserne [13].



Figur 4: Behandlingsfordeling

Data cut-off juni 21 2021. 3 patienter er kategoriseret som "protocol violation/other" i placebogruppen. Herunder er 1 protokol violation, 1 lost to follow-up + 1 non-compliance with study drug

Baseline karakteristika for inkluderede patienter
Patientpopulationen for KN-716 er generelt ensartet fordelt på tværs af de to behandlingsgrupper med hensyn til baseline karakteristika for alle inkluderede patienter i studiet – se

Tabel **7**. Desuden er baselinekarakteristika ensartet fordelt mellem alle stratificeringsgrupper. Populationen består af ca. 60% mænd og 40% kvinder med en median alder på 60,5 år med ca. 39% (n=378) af samlede population >65 år. Desuden er knap 90% af kaukasisk oprindelse. 2 pædiatriske patienter blev inkluderet, én i hver gruppe [2]. Der var 5 patienter i pembrolizumabgruppen og 3 patienter i placebogruppen med sygdomsstadie, der falder udenfor inklusionskriterierne (stadie IIA, IIIC, IV eller missing). Dette er patienter, der efter randomisering har fået revideret deres sygdomsstadie. Der er desuden 2 patienter i pembrolizumab-gruppen og 1 patient i placebogruppen, hvor sygdomsstadiet manglede, og der er 1 patient i pembrolizumabgruppen, der havde en ECOG score på 2 og dermed også faldt udenfor inklusionskriterierne. Det vil sige at der er ialt 7 patienter i pembrolizumabgruppen og 5 patienter i placebogruppen, der efter ransomisering har vist sig at falde udenfor inklusionskriterierne, og som derfor enten er blevet randomiseret og ikke har modtaget behandling eller, som har stoppet behandling pga protokolovertrædelser. De 12 patienter (7 i pembro og 5 i placebogruppen) tæller med i intention-to-treat populationen. De 11 patienter med stadie IIA, IIIC, IV eller manglende melanomstadium tæller ikke med i T-stadie subgruppe analysen. MSD vurderer, at studiepopulationen svarer til den forventede danske population med stadie IIB+C melanom.

Tabel 7: Baseline karakteristika

Karakteristika, n (%)	Pembrolizumab (n = 487)	Placebo (n = 489)
Alder, median (range), år	60,0 (16-84)	61,0 (17-87)
12-17 år	1 (0,2)	1 (0,2)
18-64 år	302 (62)	294 (60,1)
≥65 år	184 (37,8)	194 (39,7)
Sex		
Mænd	300 (61,6)	289 (59,1)
Kvinder	187 (38,4)	200 (40,9)
Hvide	435 (89,3)	439 (89,8)
Vægt (mean, kg)	85.6	82.8
Geografiske region		
US	95 (19,5)	80 (16,4)
Ikke-US	392 (80,5)	409 (83,6)
ECOG Performance Status		
0	454 (93,2)	452 (92,4)
1	32 (6,6)	35 (7,2)
2	0 (0,0)	1 (0,2)
T kategori		
T3b	200 (41,1)	201 (41,1)
T4a	113 (23,2)	116 (23,7)
T4b	172 (35,3)	172 (35,2)
Sygdoms stadie		
IIA	1 (0,2)	0 (0,0)
IIB	309 (63,4)	316 (64,6)
IIC	171 (35,1)	169 (34,6)

IIIC	4 (0,8)	1 (0,2)
IV	0	2 (0,2)
Mangler	2 (0,4)	1 (0,2)

7.1.2. Resultater per studie

Da KN-716 foretager en direkte sammenligning mellem pembrolizumab og placebo, og at behandlingen i komparatorarmen svarer til den danske kliniske praksis, er der i denne ansøgning ikke inkluderet yderligere studier jf. afsnit 6.1 litteratursøgning.

For at beskrive den kliniske merværdi ved pembrolizumab, sammenlignet med nuværende dansk standardbehandling, gennemgås i det følgende resultater fra KN-716 studiet på RFS, DMFS samt typer af fjernmetastaser, bivirkninger og livskvalitet. Dette svarer til de effektmål, som fagudvalget tidligere har angivet som kritiske eller vigtige [10]. Overlevelsesdata (*Overall Survival, OS*) er også listet som et kritisk effektmål, men MSD vurderer, at det nuværende data-sæt fra KN-716, som præsenteres i denne ansøgning, udgør et fyldestgørende grundlag til dokumentation af pembrolizumabs kliniske merværdi sammenlignet med nuværende dansk standardbehandling. Dette med baggrund i inklusion af data på relevante endepunkter, perspektivering af data med baggrund i KN-054 og tidligere vurdering fra Medicinrådet af adjuverende behandling af stadie III melanom.

I KN-716 er RFS det primære endepunkt, og sammen med DMFS, de to effekt endepunkter vi beskriver i denne ansøgning. Den første analyse af OS er planlagt ved interim analyse 5 efter ~154 OS events og ~120 måneder (~10 år) efter, at den første patient blev randomiseret. Fra andre kliniske studier med adjuverende behandling af stadie III melanomer ved man, at patienter ofte går over til en anden behandling eller et andet klinisk forsøg efter recidiv. Det betyder, at *overall survival* dermed både bliver et mål for den adjuverende behandling samt behandlingen efter recidiv og er dermed ikke et direkte mål for effekten af den adjuverende behandling [2]. Det er vist, at HR for RFS korrelerer med HR for OS for adjuverende behandling med interferon eller checkpoint inhibitorer af stadie II + III melanomer [14, 15]. Det betyder, at en effekt af behandling på RFS også vil betyde en effekt af behandling på OS, og RFS er dermed et validt surrogat endepunkt for OS ved adjuverende behandling af stadie II + III melanomer med immunterapi. Grænsen for, hvornår RFS kan bruges som et surrogat endepunkt for OS, er en RFS HR på ≤0.77 [14, 15]. Samtidig er det direkte formål med adjuverende behandling at nedsætte risikoen for, at patienterne får recidiv [12], og RFS er dermed også et egnet mål for, om formålet med behandlingen er blevet opfyldt. Derudover er det vigtigt at huske, at RFS ikke kun er et surrogat endepunkt for OS, men også et meget relevant endepunkt i sig selv. Frygten for recidiv fylder hos patienterne efter resektion, og patienter beskriver selv risikoen for recidiv som en psykologisk og følelsesmæssig byrde, som de gerne vil have reduceret [16, 17]. Desuden betyder en reduktion i recidiv også en reduktion i kirurgiske resektioner af lokal, regional eller lokoregional recidiv samt en reduktion i antallet af kontroller, som patienterne skal igennem på hospitalet i årene efter et recidiv. Patient præference undersøgelser har også vist, at størstedelen af patienterne behandlet med adjuverende interferon-alpfa er villige til at acceptere moderat toxicitet over et år tilgengæld for en 5 års forbedring i RFS på 4% [18] og forekomsten af recidiv har vist sig at være forbundet med et fald i livskvalitet samt øget forekomst af depression og angst [19]. Ud fra et patientperspektiv er en reduktion i recidiv derfor et yderst relevant mål for adjuverende behandling.

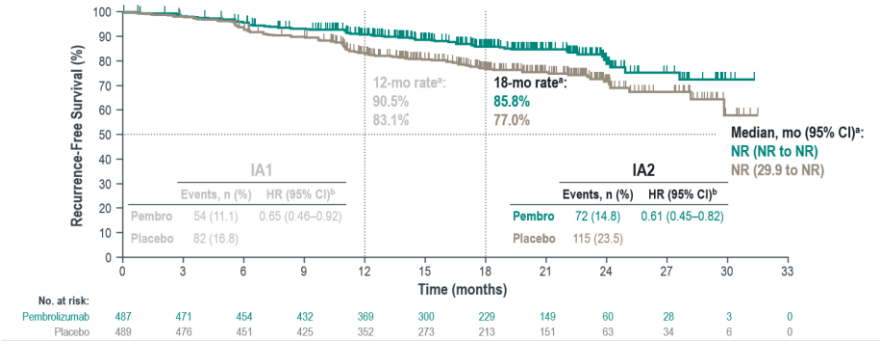
Der blev kun inkluderet 2 pædiatriske patienter mellem 12-17 år i KN-716. I vurderingen af pembrolizumab i patienter i aldersgruppen 12-17 år ekstrapoleres der derfor farmakokinetiske- og bivirkningsdata fra det kliniske studie KN-051, der inkluderer en pædiatrisk population af patienter (9 mdr – 17 år) med avanceret kræft. Resultater fra KN-051 bekræfter, at bivirkningsprofilen for pembrolizumab monoterapi hos pædiatriske patienter er konsistent med den kendte bivirkningsprofil hos voksne. Desuden anses melanom for at have den samme sygdomsbiologi hos voksne og børn, og der er derfor ikke noget biologisk rationale for, at pembrolizumab skulle virke anderledes i en pædiatrisk patient population. Denne bridging strategi er vurderet acceptabel i EPARen og reflekteret i indikationen [13].

Bivirkningsprofilen i KN-716 skal ses i forhold til, at patienter med stadie IIB og IIC melanomer er i høj risiko for recidiv af sygdom samt, at der sammenlignes en aktiv behandling som pembrolizumab med placebo.

Recurrence Free Survival (RFS)

RFS blev foretaget for ITT populationen. Data er baseret på interim analyse 2 med en median opfølgningstid på 20,5 mdr. (range 4,6 – 32,7 mdr.) og en median behandlingstid i begge grupper på 11,1 mdr. (range 0,0 – 16,4 i pembrolizumab-gruppen og range 0,0 – 15,6 mdr. i placebogruppen). Interim analyse 2 var den endelige analyse (final analysis) for RFS i den præspecificerede analyseplan og dermed den RFS analyse, ansøgningen fokuserer på. På Kaplan Meier kurven for RFS (Figur 5) ses de to behandlinger at følges ad de første 6 mdr. Af opfølgningen, hvorefter der kommer en adskillelse af kurverne med færre events i pembrolizumab-gruppen end i placebo-gruppen. Denne adskillelse af grupperne øges over tid, og ved 18 mdr. Ses der en RFS rate på 85,8% for pembrolizumab-gruppen og 77% for placebo-gruppen med en HR på 0,61 (95% CI: 0,45 – 0,82) – se Tabel 8. Det betyder en relativ reduktion i risikoen for recidiv på 39% i pembrolizumab-gruppen sammenlignet med placebo-gruppen. En risikoreduktion som ses øget fra interim analyse 1, hvor HR var 0,65 (se Figur 5) og statistisk signifikant med p=0,00658. Den mediane RFS var endnu ikke nået i hverken pembrolizumab- eller placebogruppen ved interim analyse 2 [2]. Der fandtes desuden en absolut risikoreduktion i RFS rater ved 12 og 18 mdr i pembrolizumab-gruppen sammenlignet med placebogruppen på henholdsvis 7,5% og 8,8% (

Tabel 9). [redacted] Dette korrelerer fint med placebogruppen i KN-716 på 83,1% [2].



Figur 5: Kaplan-Meier kurve for RFS for ITT populationen.

[a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with Efron's methods of tie handling with treatment as a covariate stratified by melanoma T category (T3b vs T4a vs T4b) IA1: Dec 04 2020, IA2: June 21 2021. Data cut-off var juni 21 2021, og median opfølgningstid var 20,5 mdr (range 4,6 – 32,7 mdr)

Tabel 8: RFS ved interim analyse 2

	Antal af Events (%)	Median RFS (95% CI)	Forskel i median RFS	HR for RFS (95% CI)
Pembrolizumab (n=487)	72 (14,8)	NR (NR – NR)	N/A	0,61 (0,45 – 0,82)
Placebo (n=489)	115 (23,5)	NR (29,9 – NR)		0,00046[c]

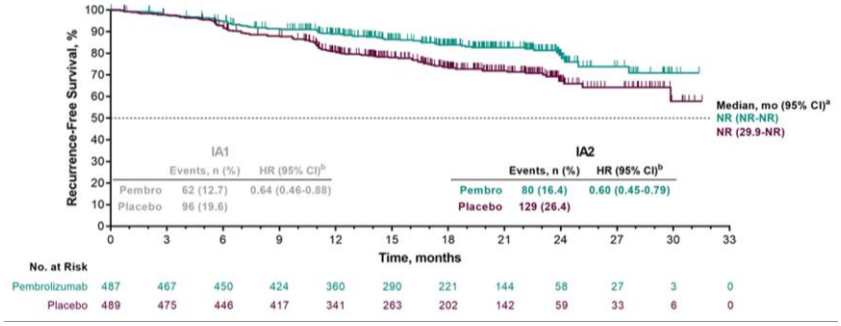
[a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b). [c]One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b). NR = Not Reached. Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first. Database Cutoff Date: 21JUN2021. Median opfølgningstid var 20,5 mdr (range 4,6 – 32,7 mdr)

Tabel 9: Forskel i 12- mdr. og 18 mdr's RFS rater ved interim analyse 2

	Forskel i RFS-rate ved 12 mdr.	Forskel i RFS-rate ved 18 mdr.
Pembrolizumab (n=487) vs. Placebo (n=489)	7,5% ARR 90,8% (95% CI 87,8 – 93,1) – 83,3% (95% CI 79,6 – 86,4)	8,8% ARR 85,8% (95% CI 82,0 – 88,9) – 77,0% (95% CI 72,6 – 80,7)

ARR = Absolut risikoreduktion. Data on file [37]. Database Cutoff Date: 21JUN2021. Median opfølgningstid var 20,5 mdr (range 4,6 – 32,7 mdr) [37]

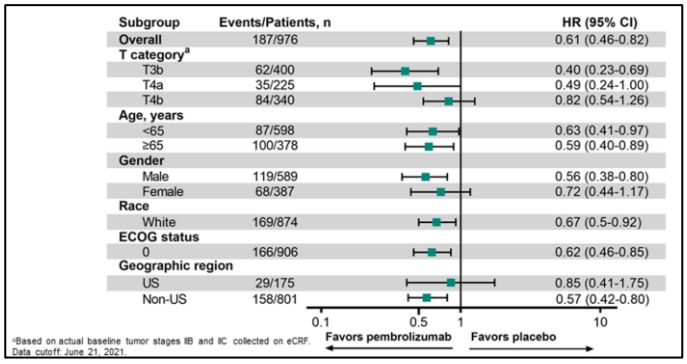
En analyse, der inkluderer nye primære melanomer, der udviklede sig samtidig med, at studiet kørte, var konsistent med den primære RFS-analyse ved interim analyse 2. Den viste, at når nye primære melanomer var inkluderet, var der stadig en reduktion i risiko for recidiv eller død på omkring 40% efter behandling med pembrolizumab sammenlignet med placebobehandling (se Figur 6).



Figur 6: RFS analyse inkl nye primære melanomer ved interim analyse 2

[a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with Efron's methods of tie handling with treatment as a covariate stratified by melanoma T category (T3b vs T4a vs T4b) IA1: Dec 04 2020, IA2: June 21 2021. Median opfølgningstid 20,5 mdr.

RFS-analysen af de præspecificerede subgrupper inddelt på baseline karakteristiska ses i Figur 7 ved interim analyse 2. Generelt er RFS til fordel for pembrolizumab-behandling på tværs af alle de testede subgrupper (Figur 7) [2].

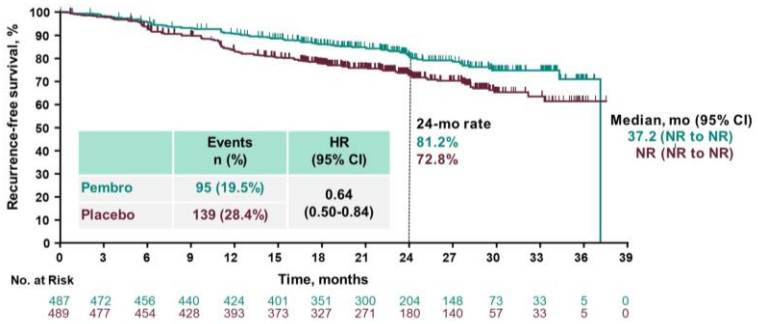


Figur 7: RFS i vigtige subgrupper ved interim analyse 2

[a]Based on actual baseline tumor stages IIB and IIC collected eCRF. Data cutoff June 21, 2021 og median opfølgningstid var 20,5 mdr.

Ved interim analyse 2 var der ialt 187 patienter, der havde udviklet recidiv, hvor 72 patienter (15%) var i pembrolizumab-gruppen, og 115 patienter (24%) var i placebogruppen. Heraf var der dobbelt så mange patienter, der udviklede fjernmetastaser som første recidiv i placebogruppen i forhold til pembrolizumab-gruppen (12,3% vs. 6,4%) [2].

Ved interim analyse 3 (data cut-off 4. jan 2022, median opfølgningstid 26,9 mdr) blev RFS rater rapporteret på baggrund af den opdaterede Kaplan-Meier kurven for RFS over tid. Fra Tabel 10 kan det ses, at forskel i RFS-raten mellem pembrolizumab-gruppen og placebo-gruppen øges fra 6 mdr. til 12 mdr. og igen til 18 mdr. Derefter forbliver forskellen i RFS-raten konstant omkring og ligger på 8.3% - 9.7% (Tabel 10) [37]. Der blev desuden rapporteret en opdateret RFS hazard ratio på 0,64 (95% CI 0,5-0,84) og dermed en fortsat reduktion i risikoen for recidic efter adjuverende behandling med pembrolizumab (Figur 8). Denne RFS analyse ved interim analyse 3 er dog eksplorativ og er ikke tildelt nogen alfa [37].



Figur 8: Kaplan-Meier kurve af RFS ved interim analyse 3
Hazard ratio for RFS med pembrolizumab versus placebo. Median opfølgningstid er 26,9 mdr. [38]

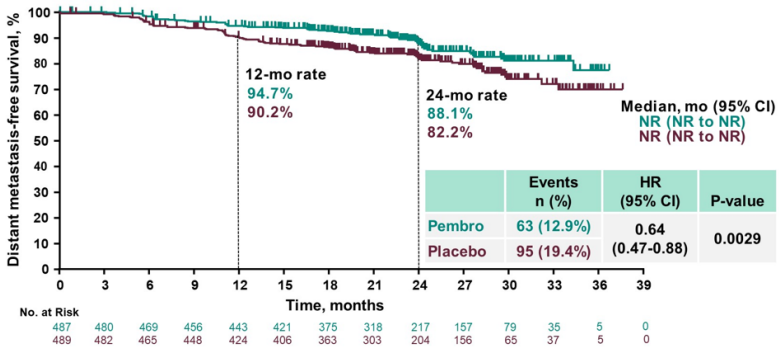
Tabel 10: RFS rater ved interim analyse 3

	Pembrolizumab (n=487) % (95% CI)[a]	Placebo (n=489) % (95% CI)[a]	Forskel i RFS rate %
RFS rate ved tidspunkt			
[redacted]			

[a]From product-limit (Kaplan-Meier) method for censored data. Recurrence-free survival is defined as time from randomization to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurs first. Database Cutoff Date: 04JAN2022. Median opfølgningstid 26,9 mdr.[37]

Distant Metastasis Free Survival (DMFS)

Som det fremgår af Tabel 6, der viser en oversigt over de præ-specificerede analyser, indeholdt interim analyse 3 den første interim analyse for DMFS. Data cutoff for interim analyse 3 var d. 4. jan 2022 efter en median opfølgningstid på 26,9 mdr. Som det ses i Figur 9 adskiller DMFS-kurverne for henholdsvis pembrolizumab og placebo sig allerede efter 6 måneder med en højere DMFS-rate for de pembrolizumab-behandlede patienter end for placebo-behandlede patienter. Forskellen i DMFS-raten mellem de 2 grupper opretholdes herefter på omkring 6-7% (Tabel 11) [37]. Generelt er DMFS til fordel for pembrolizumab-behandling på tværs af alle de testede subgrupper [38].



Figur 9: Kaplan-Meier kurve af DMFS ved interim analyse 3
Database Cutoff Date: 04JAN2022. Median opfølgningstid 26,9 mdr [38]

Tabel 11: DMFS rater ved interim analyse 3

	Pembrolizumab (N=487) % (95% CI)[a]	Placebo (N=489) % (95% CI)[a]	Forskel i DMFS rate %
DMFS rater ved tidspunkt			
[redacted]			

[a]From product-limit (Kaplan-Meier) method for censored data. Distant metastasis-free survival is defined as the time from randomization to the first diagnosis of a distant metastasis. Database Cutoff Date: 04 JAN2022. Median opfølgningstid 26,9 mdr. [37]

I Tabel 12 ses det, at ved interim analyse 3 fandtes var der ved 24 mdr. en DMFS rate på 88,1% for pembrolizumab-gruppen og 82,2% for placebo-gruppen med en HR på 0,64 (0,47 – 0,88), hvilket er statistisk signifikant. Det betyder en relativ reduktion i risikoen for fjernmetastaser på 36% i pembrolizumab-gruppen sammenlignet med placebo-gruppen (Tabel 12) [38].

Tabel 12: Distant metastasis free survival (DMFS) ved interim analyse 3

	Antal af Events (%)	Median DMFS (95% CI)	DMFS rate ved 24 mdr i % (95% CI)	Hazard Ratio[b] (95% CI)[b] p-value
Pembrolizumab (n=487)	63 (12,9)	NR (NR - NR)	88,1 (84,4 – 90,9)	0,64 (0,47 – 0,88) 0.00292[c]
Placebo (n=489)	95 (19,4)	NR (NR - NR)	82,2 (78,2 – 85,5)	

[a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T Stage (T3b vs. T4a vs. T4b). [c]One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b). NR = Not reached. Distant metastasis-free survival is defined as the time from randomization to the first diagnosis of a distant metastasis. Database Cutoff Date: 04JAN2022. Median opfølgningstid 26,9 mdr.

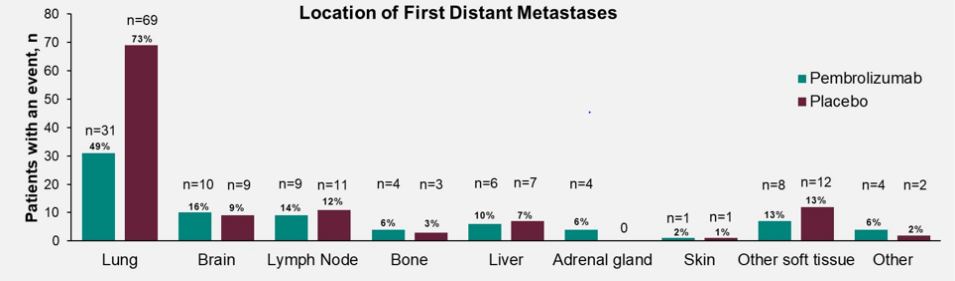
Det blev yderligere vist, at ved interim analyse 3 fik 9% af patienterne i pembrolizumab-gruppen fjernmetastase som første recidiv. I placebo-gruppen var det 16% af patienterne, der fik fjernmetastaser som første recidiv (Tabel 13). Desuden var lungerne det mest hyppige sted for første recidiv, hvilket ses i Figur 10. Her ses det, at antallet af patienter med lungemetastaser var 69 i placebo-gruppen sammenlignet med 31 i pembrolizumab-gruppen [38].

Tabel 13: Typer af fjernmetastaser ved interim analyse 3

	Pembrolizumab	Placebo

DMFS status[a]	n = 487	n = 489
Alle events, n (%)	63 (13)	95 (19)
Som første event	45 (9)	79 (16)[b]
Efter lokoregional recidiv	18 (4)	16 (3)

[a]Patienter kan have fjernmetastaser mere end et sted. [b]Inkluderer 2 patienter med stadie IV sygdom ved screening. Data cut-off 4. jan 2022. Median opfølgningstid 26,9 mdr. [38]



Figur 10: Lokation af første fjernmetastase
Data cut-off 4. jan 2022. Median opfølgningstid 26,9 mdr.[38]

Perspektivering af data for recidiv i KN-716 med KN-054

I KN-054 studiet undersøgte man effekten af adjuverende behandling med pembrolizumab til patienter med komplet resekteret stadie III melanom sammenlignet med placebo. Der blev der foretaget 5 interim analyser efter henholdsvis 1 år, 2 år, 3 år,3,5 års og 4,9 års median opfølgningstid. Her fandtes der en HR for RFS på 0,57 ved interim analyse 1, 0,56 ved interim analyse 2+3, 0,59ved interim analyse 4 og 0,61 ved interim analyse 5 – se Tabel 14. Dette betyder, at reduktionen i risiko for recidiv efter behandling med pembrolizumab i KN-054 forbliver på omkring 40% selv efter 5 års opfølgningstid [20, 21, 40, 41], og der ses ingen reduktion i effekt efter, at behandlingen er stoppet (rebound effect). HR for RFS i både KN-716 og KN-054 efter henholdsvis 12 og 18 måneder ligger på omkring 0,6 og det ses derfor, at cirka den samme reduktion i risiko for recidiv opnås med adjuverende behandling med pembrolizumab af stadie IIB+C melanomer som med adjuverende behandling af stadie III melanomer. På baggrund af data fra KN-054 kan det forventes, at effekten af pembrolizumab øges i de første 2 år og derved opretholdes over tid i KN-716.

Tabel 14: Interim analyser ved KN-054

Interim analyse	Data cut off	Median follow-up	RFS	DMFS
IA1	Oct 2 2017	15,1 mdr	0,57	
IA2	May 2 2018	21,6 mdr	0,56	
IA3	Sep 30 2019	36,6 mdr	0,56	
IA4	April 3 2020	42,3 mdr	0,59	0,60
IA5	Januar 17 2022	4,9 år	0,61	0,62

IA = Interim Analyse. Baseret på [20, 21, 40, 41]

Numbers needed to treat (NNT)

[redacted]

- IIC: 1/(0,68 x (1-0,61)) = 4 patienter
- IIIA: 1/(0,22 x (1-0,56)) = 11 patienter
- IIIB: 1/(0,36 x (1-0,56)) = 7 patienter
- IIIC: 1/(0,65 x (1-0,56)) = 4 patienter
- IIID: 1/(0,73 x (1-0,56)) = 4 patienter
- III total: 1/(0,43 x (1-0,56)) = 6 patienter

Her ses det, at NNT for højrisiko stadie IIB+C patienter er tilsvarende NNT for stadie III melanom patienter.

Konklusion på effektdata

Formålet med adjuverende behandling er at nedsætte risikoen for, at patienterne får recidiv [12]. I interim analyse 2 i KN-716 med resekteret højrisiko stadie IIB+C melanom en relativ reduktion i risikoen for recidiv eller død på 39% efter behandling med pembrolizumab (HR 0,61), og denne effekt øges over tid. Der var en signifikant forbedret DMFS efter behandling med pembrolizumab i forhold til placebo ved interim analyse 3, og behandling med pembrolizumab resulterede i en reduktion i risikoen for fjernmetastaser på 36% i forhold til placebo (HR 0,64). Samme analyse viste, at der var færre patienter, der fik fjernmetastaser som første recidiv efter behandling med pembrolizumab i forhold til placebo (45 vs 79 patienter). Baseret på data fra KN-054 med adjuverende pembrolizumab til stadie III melanom forventes det, at reduktionen i risiko for recidiv eller død forbliver konstant, og at effekten ikke aftager over tid. Formålet med den adjuverende behandlingen er dermed opfyldt. I EPAR'en blev det desuden vurderet, at den pembrolizumab-inducerede reduktion i sygdomsrecidiv var klinisk relevant [13].

Disse resultater indikerer en stor klinisk merværdi for relevante patienter med resekteret højrisiko stadie IIB og IIC melanom efter adjuverende behandling med pembrolizumab.

Bivirkninger

Generelt var de rapporterede bivirkninger i KN-716 i overensstemmelse med, hvad der blev rapporteret i KN-054 med adjuverende pembrolizumab til stadie III melanom samt bivirkningsprofilen for KN-006 med pembrolizumab til metastaserende melanomer [42].

I KN-716 rapporteres bivirkninger hos patienter, som har modtaget minimum én dosis studiemedicin (*as-treated* populationen), hvilket var 483 patienter i pembrolizumab-gruppen og 486 patienter i placebo-gruppen. I vores ansøgning rapporteres bivirkninger fra interim analyse 2 med en median opfølgningstid på 20,5 måneder (range 4,6 – 32,7 mdr), hvilket er data publiceret i Luke et al 2022 [2]. I EPARen er rapporteret bivirkninger fra interim analyse 1, men vi har valgt at rapportere bivirkning med længere opfølgningstid. Generelt er incidencen af bivirkninger, både af enhver årsag og behandlingsrelaterede, sammenlignelig mellem første og anden interim analyse [2]. Den gennemsnitlige behandlingslængde for grupperne var ens med 11,1 måneder (range 0,0 – 16,4) for pembrolizumab og 11,1 måneder (range 0,0 – 15,6) for placebo-gruppen (IV injektion med saltvand). Den øvre grænse i intervallet for behandlingslængden overgår 12 måneder, hvilket skyldes, at den planlagte behandlingen hver tredje uge i enkelte tilfælde var forsinket, fordi patienten havde COVID-19. Herunder ses en liste med definitioner af de forskellige anvendte opgørelser af bivirkninger i ansøgningen.

- **Bivirkninger:** Enhver skadelig og utilsigtet reaktion (herunder et unormalt laboratoriefund), symptom eller sygdom, der er tidsmæssigt forbundet med brugen af en medicinsk behandling eller procedure, der kan eller måske ikke anses for at være relateret til den medicinske behandling eller procedure [43]
- **Behandlingsrelaterede bivirkninger:** Bivirkning der er vurderet af investigator til at være relateret til behandling [2]
- **Bivirkninger med særlig interesse (adverse events of special interest (AEOSI) :** Immun-medieret bivirking eller infusionsreaktioner baseret på en liste udspecificeret af sponsor. Disse er uafhængig af årsag. Listen er denne: Hypothyroidisme, Hyperthyroidisme, Colitis, Adrenal insufficiens, Hepatitis, Hypophysitis, Infusionsreaktioner,

Myastenic syndrom, Myelitis, Myocarditis, Myositis, Nefritis, Pankreatitis, Pneumonitis, Sarcoidosis, Alvorlig hudreaktion, Thyroiditis, Type 1 diabetes mellitus, Uveitis [2]

Ved den anden interim analyse var der ialt 461 (95,4%) patienter i pembrolizumab-gruppen, der oplevede en bivirkning (forårsaget af enhver årsag) sammenlignet med 444 (91,4%) i placebo-gruppen. Det er forventeligt, at der er flere i pembrolizumab-gruppen, der oplever bivirkninger i forhold til placebo-gruppen. Der var 136 patienter (28,2%) i pembrolizumab-gruppen og 93 patienter (19,1%) i placebo-gruppen, der oplevede en grad 3-4 bivirkning. Hvis man fokuserer på de behandlingsrelaterede bivirkninger, så oplevede 400 patienter (82,8%) i pembrolizumab-gruppen en sådan, mens det var 308 patienter (63,4%) i placebo-gruppen. Grad 3-4 behandlingsrelateret bivirkning blev rapporteret i 82 patienter (17%) behandlet med pembrolizumab i sammenligning med 21 patienter (4,3%) i placebo-gruppen. Der var i pembrolizumab-gruppen 79 patienter (16,4%), der stoppede behandlingen pga en behandlingsrelateret bivirkning, hvilket i placebo-gruppen var 12 patienter (2,5%). Der var ingen behandlingsrelaterede dødsfald i hverken pembrolizumab- eller placebo-gruppen (se Tabel 15).

Tabel 15: Oversigt over bivirkninger

Bivirkninger, n (%)	**Pembrolizumab (N=483)**	**Placebo (N=486)**
Alle	461 (95,4)	444 (91,4)
Grad 3-5	136 (28,1)	93 (19,1)
Behandlingsrelaterede bivirkning	400 (82,8)	308 (63,4)
Grad 3–4[a]	82 (17,0)	21 (4,3)
Førte til behandlingsophør	79 (16,4)	12 (2,5)
Førte til død	0	0

[a]Ingen grad 5 behandlingsrelateret bivirkning blev rapporteret. [2]

Relativ risiko

Når man fokuserer på grad 3-5 bivirkninger i de to grupper, som illustreret i

Tabel 16, ses det, at antallet af patienter, der oplever grad 3-5 bivirkninger (*all-causes*), er 28,2% i pembrolizumab og 19,1% i placebogruppen. Dette svarer til en forskel på 9% mellem de to grupper og en relativ risiko på 1,47 (Tabel 16).

Tabel 16: Bivirkninger af enhver årsag grad ≥3

	Gennemsnitlig behandlingslængde	**Enhver-årsag grad ≥3 bivirkninger**	**Forskel i enhver-årsag grad ≥3 bivirkninger**	**RR (95% CI)**
Pembrolizumab (n=483)	11,1 måneder (range 0.0 – 16,4)	136 (28,1%) (95% CI 24,2-32,4)	9% forskel 28,2% (95% CI 24,2-32,4) - 19,1% (95% CI 15,7-22,9)	1,47 (1,167 – 1,855)
Placebo (n=486)	11,1 måneder (range 0,0 – 15,6)	93 (19,1%) (95% CI 15,7-22,9)		

RR = Relativ Risiko

Tabel 17 viser hvor mange patienter, der stoppede behandlingen som følge af bivirkninger (alle årsager). Her ses det, at det var tilfældet for 17,6% i pembrolizumab-gruppen og for 4,7% i placebo-gruppen. Det svarer til en forskel på 12,9% mellem de to grupper og en relativ risiko på 3,71.

Tabel 17: Behandlingsophør som følge af bivirkninger af enhver årsag

	Gennemsnitlig behandlings-længde	Antal behandlingsophør som følge af bivirkninger (enhver-årsag)	Forskel i antal behandlingsophør som følge af bivirkninger (enhver-årsag)	RR (95% CI)
Pembrolizumab (n=483)	11,1 måneder (range 0,0 – 16,4)	85 (17,6%) (95% CI 14,3-21,3)	12,9% forskel 17,6% (95% CI 14,3-21,3) - 4,7% (95% CI 3,02-7,02)	3,71 (2,387 – 5,792)
Placebo (n=486)	11,1 måneder(range 0,0 – 15,6)	23 (4,7%) (95% CI 3,02-7,02)		

RR = Relativ Risiko

Kvalitativ gennemgang af bivirkninger

Tabel 18 viser de behandlingsrelaterede bivirkninger, som optræder i ≥5% af patienterne, når man kigger på alle grader af en specifik bivirkning. Her ses det, at 82,8% af de pembrolizumab-behandlede patienter oplevede en behandlingsrelateret bivirkning af enhver grad sammenlignet med 63,4% i placebo-gruppen. Det ses også, at de 3 hyppigste behandlingsrelaterede bivirkninger både i pembrolizumab-gruppen og i placebogruppen er:

- Pruritus (kløe) (pembrolizumab: 117 patienter (24,2%) vs placebo: 51 patienter (10,5%))
- fatigue (pembrolizumab: 102 patienter (21,1%) vs placebo: 88 patienter (18,1%))
- diarre (pembrolizumab: 90 patienter (18,6%) vs placebo: 54 patienter (11,1%)).

Af grad 3-4 behandlingsrelaterede bivirkninger, hvor der er størst forskel mellem pembrolizumab og placebo, er rash (7 patienter (1%) i pembrolizumab-gruppen vs 1 patient (<1%) i placebo-gruppen) og colitis (5 patienter (1%) i pembrolizumab-gruppen vs 1 patient (<1%) i placebo-gruppen). Generelt var langt de fleste af bivirkninger grad 1-2. Grad 3-4 bivirkninger udgjorde højest 1% af patienterne, hvilket også fremgår af Tabel 18. Der var ingen, der døde som følge af behandling.

Tabel 18: Bivirkninger i KN716 med hyppighed ≥5% (alle grader) af patienterne

	Pembrolizumab (N=483)		Placebo (N=486)	
Patienter, n (%)	**Alle grader**	**Grad ≥ 3**	**Alle grader**	**Grad ≥ 3**
Bivirkning forårsaget af enhver årsag	461 (95,4%)	136 (28,2%)	444 (91,4%)	93 (19,1%)
Behandlingsrelaterede bivirkning	400 (82,8%)	82 (17,0%)	308 (63,4%)	21 (4,3%)
Behandlingsrelaterede bivirkning med hyppighed (≥5%)				
Hypothyroidism	75 (15,5%)	0	12 (2%)	0
Hyperthyroidism	48 (10%)	1	3 (1%)	0
Diarrhea	90 (18,6%)	5 (1%)	54 (11,1%)	1 (<1%)
Nausea	38 (8%)	0	33 (6,8%)	0
Fatigue	102 (21,1%)	1 (<1%)	88 (18,1%)	0
Asthenia	45 (9,3%)	1 (<1%)	41 (8,4%)	0
Arthralgia	78 (16,1%)	2 (<1%)	38 (7,8%)	0
Myalgia	32 (6,6%)	2 (<1%)	16 (3,3%)	0
Increased ALT	38 (7,9%)	4 (1%)	22 (4,5%)	1 (<1%)
Increased AST	30 (6,2%)	1 (<1%)	11 (2,3%)	1 (<1%)
Pruritus	117 (24,2%)	3 (1%)	51 (10,5%)	0
Rash	76 (15,7%)	7 (1%)	34 (7%)	1 (<1%)
Rash – maculo-papular	35 (7,2%)	2	8 (2%)	0

Tabel 19 viser bivirkninger med særlig interesse, hvilket er baseret på en præspecificeret liste med immunmedierede bivirkninger eller infusionsreaktioner. Der var 182 patienter i pembrolizumab-gruppen (37,7%) vs 44 patienter (9,1%) i placebo-gruppen, der fik en immunmedieret bivirkning eller infusionsreaktion. Heraf var der 49 patienter (10,1%), hvor denne var af grad 3-4 sammenlignet med 6 patienter (1,2%) i placebogruppen. Her var hypothyroidism (83 patienter, 17,2%), hyperthyroidism (50 patienter, 10%) og colitis (18 patienter, 3,7%) de 3 hyppigste i pembrolizumabgruppen (alle grader), mens hypothyroidism (17 patienter, 3%), infusionsreaktion (7 patienter, 1,4%) og colitis (5 patienter, 1%) var de hyppigste i placebogruppen (alle grader). Generelt forekommer de immunmedierede bivirkninger oftere i pembrolizumab-gruppen end i placebogruppen, hvilket er forventeligt, da man her giver en aktiv behandling, der stimulerer immunsystemet sammenlignet med ingen aktiv behandling i placebo-gruppen (saltvandsinfusion). Som man kan se, er langt de fleste bivirkninger i både pembrolizumab- og placebogruppen af grad 1-2.

Tabel 19: Bivirkninger med særlig interesse – af enhver årsag*

	Pembrolizumab (N = 483)		Placebo (N = 486)	
Patienter, n (%)	**Alle grader**	**Grad ≥ 3**	**Alle grader**	**Grad ≥ 3**
Alle bivirkninger med særlig interesse	182 (37,7%)	49 (10,1%)	44 (9,1%)	6 (1,2%)
Hypothyroidisme	83 (17,2%)	0	17 (3,5%)	0
Hyperthyroidisme	50 (10,4%)	1 (<1%)	3 (<1%)	0
Colitis	18 (3,7%)	8 (2%)	5 (1%)	0
Adrenal insufficiens	12 (2,5%)	4 (1%)	0	0
Hepatitis	11 (2,3%)	9 (1,9%)	3 (<1%)	2 (<1%)
Hypophysitis	12 (2,5%)	3 (<1%)	0	0
Infusionsreaktioner	3 (<1%)	0	7 (1,4%)	0
Myastenic syndrom	2(<1%)	2 (<1%)	0	0
Myelitis	1 (<1%)	1 (<1%)	0	0
Myocarditis	0	0	1 (<1%)	1 (<1%)
Myositis	6 (1%)	3 (1%)	1 (<1%)	0
Nefritis	7 (1%)	3 (<1%)	0	0
Pankreatitis	2 (<1%)	2 (<1%)	0	0
Pneumonitis	10 (2,1%)	1 (<1%)	4 (<1%)	0
Sarcoidosis	5 (1%)	0	0	0
Alvorlig hudreaktion	14 (2,9%)	13 (3%)	3 (<1%)	3 (1%)
Thyroiditis	8 (1,7%)	0	2 (<1%)	0
Type 1 diabetes mellitus	2 (<1%)	2 (<1%)	0	0
Uveitis	1 (<1%)	0	0	0

*Bivirkning med særlig interesse (immunmedierede bivirkninger og infusionsreaktioner) var baseret på en liste udspecificeret af sponsor (MSD) og forårsaget af enhver årsag. [2]

Fokuseres der på de endokrine bivirkninger, som potentielt kræver hormonel behandling, som vist i Tabel 20, ses det, at 83 patienter (17,2%) fik hypothyroidisme, 8 patienter (1,7%) fik thyroiditis, 12 patienter (2,5%) fik hypophysitis, 12 patienter (2,5%) fik adrenal insufficiens og 2 patienter (0,4%) fik type-1 diabetes i pembrolizumab-gruppen. I placebo-gruppen var der 17 patienter (3,5%), der udviklede hypothyroidism, mens 2 patienter (0,4%) udviklede thyroiditis. I pembrolizumab-gruppen fik følgende patienter hormonel behandling mod deres endokring bivirkning: 73 ud af 83 patienter (87,9%) med hypothyroidism, 7 ud af 8 patienter (87,5%) med thyroiditis, 12 ud af 12 patienter (100%) med

hypophysitis, 11 ud af 12 patienter (87,5%) med adrenal insufficiens og 2 ud af 2 patienter (100%) med type 1 diabetes. I placebogruppen modtog 5 ud af 17 patienter (29,4%) med hypothyroidism og 1 ud af 2 patienter (50%) med thyroiditis hormonel behandling mod deres endokrine bivirkninger.

Tabel 20: Endokrine bivirkning som kræver hormonel behandling – af enhver årsag

Patienter, n (%)	Pembrolizumab (n=483)		Placebo (n=486)	
	Patienter[a] med event af interesse	Patienter som kræver hormonel behandling[b]	Patienter[c] med event af interesse	Patients som modtager hormonel terapi[b]
Total	107 (22,2%)	98 (20,3%)	18 (3,7%)	6 (1,2%)
Hypothyroidisme	83 (17,2%)	73 (87,9%)	17 (3,5%)	5 (29,4%)
Thyroiditis	8 (1,7%)	7 (91,6%)	2 (0,4%)	1 (50%)
Hypophysitis	12 (2,5%)	12 (100%)	0	0
Adrenal insufficiens	12 (2,5%)	11 (87,5%)	0	0
Type 1 diabetes mellitus	2 (0,4%)	2 (100%)	0	0

[a]In the pembrolizumab arm, 7 patients had both hypothyroidism and hypophysitis; 1 patient had both adrenal insufficiency and hypophysitis; 2 patients had both thyroiditis and hypothyroidism. [b]Steroid, thyroxine, or insulin. [c]In the placebo arm, 1 patient had both hypothyroidism and hypophysitis [2]

Overvejelser om, hvorvidt bivirkningerne, som følge af behandling med pembrolizumb, er midlertidige eller langvarige, er vigtige. [redacted]

Perspektivering af bivirkninger i KN-716

Som det ses af afsnittet ovenover, så er de 3 mest almindelige bivirkning i begge grupper fatigue, diarre og pruritus, hvilket er velkendte og forventelige bivirkninger. Incidens og type af behandlingsrelaterede bivirkninger var sammenlignelig mellem første og anden interim analyse, hvilket betyder, at der ikke er en forværring af bivirkningsprofilen over tid. Størstedelen af bivirkningerne var relateret til skjoldbruskkirtlen eller andre immunrelaterede bivirkninger og var konsistente med den generelle bivirkningsprofil for immunterapi i andre adjuverende studier [28].

Tabel 21: Sammenligning med KN-054

	KN-054 [20, 44]	KN-716 [2]
Andel patienter der oplever grad 3-5 bivirkninger (absolutte værdier og ikke forskel)	31%	28.1%
Andel patienter der oplever grad 3-5 behandlingsrelaterede bivirkninger (absolutte værdier og ikke forskel)	14,7%	17%
Forskel i grad 3-5 bivirkninger mellem pembrolizumab og placebo	11,9%	9%

Forskel i behandlingsophør som følge af bivirkninger mellem pembrolizumab og placebo	10,2%	12,9%

Hvis man perspektiverer til bivirkningsprofilen i KN-054, ses det, at hyppigheden af grad ≥3 bivirkninger af enhver årsag efter adjuverende behandling med pembrolizumab af stadie III melanom er lidt lavere i KN716 (28.1%) i forhold til i KN-054 (31%), mens de behandlingsrelaterede bivirkninger ≥3 er 14,7% [20] i KN-054 og 17% i KN-716 - se Tabel 15 og Tabel 21. Det skal dog bemærkes, at bivirkningsdata fra KN-054 er efter en median opfølgningstid på 15,1 måneder, mens bivirkningsdata fra KN-716 er efter en median opfølgningstid på 20,5 måneder. I KN-054 var stigningen i grad 3-5 bivirkninger i den aktive arm i fht placebo på 11,9% [10]. I KN-716 var stigningen i grad 3-5 bivirkninger mellem pembrolizumab- og placebogruppen 9% (Tabel 16 og Tabel 21). I KN-054 var stigningen i antallet af behandlingsophør som følge af bivirkninger fra placebo- til pembrolizumab på 10,2% [10], mens stigningen i KN-716 fra placebo- til pembrolizumab-gruppen var på 12,9% (Tabel 17 og Tabel 21). Desuden var der 23,4%, der fik endokrine bivirkninger i KN-054 i pembrolizumab-gruppen sammenlignet med 22,2% i pembrolizumab-gruppen i KN-716. Se Appendix E for reference-data for alle studier af pembrolizumab-behandlede patienter (n=6185). Bivirkningsprofilen i pembrolizumab-gruppen i KN-716 svarer til poolede data fra reference datasæt for pembrolizumab som monoterapi. I EPAR'en konkluderes det, at bivirkningsprofilen i KN-716 er sammenlignelig med den kendte bivirkningsprofil for pembrolizumab, og at ingen ekstra advarsler er nødvendige i SmPC [13].

Livskvalitet

Resultaterne for livskvalitet i KN-716 er målt i ITT-populationen. EuroQoL EQ-5D-5L and EORTC QLQ-C30 blev målt ved baseline (før første behandling) og derefter hver 12. uge det første år. Data er opgjort som den gennemsnitlige ændring fra baseline. I år 2 (efter behandlingen er stoppet) måles livskvalitet også hver 12. uge (uge 60, 72, 84 og 96) og derefter hver 6. måned i år 3 (måned 30 og 36 fra baseline). EORTC QLQ-C30 blev kun givet til voksne (≥18 år gamle ved baseline), da spørgeskemaet ikke er valideret i en pædiatrisk afdeling. EuroQoL EQ-5D-5L blev givet til alle patienter i studiet, da det er vurderet til at kunne bruges til personer ≥12 år. Data er angivet som Leastsquares (LS) means, hvilket er forskel i gruppens middelværdi efter justering for kovariater. Der var generelt høj compliance frem til uge 96 både for EORTC QLQ-C30 (Tabel 22) og EQ-5D-5L (Tabel 23)[39]

Tabel 22: Compliance and completion for the EORTC QlQ-C30

	Compliance *n/N* (%)		**Completion *n/N* (%)**	
Timepoint	**Pembrolizumab *n* = 483**	**Placebo *n* = 486**	**Pembrolizumab *n* = 483**	**Placebo *n* = 486**
Baseline	449/482 (93.2)	459/483 (95.0)	449/483 (93.0)	459/486 (94.4)
Week 12	409/482 (84.9)	440/486 (90.5)	409/483 (84.7)	440/486 (90.5)
Week 24	384/460 (83.5)	393/469 (83.8)	384/483 (79.5)	393/486 (80.9)
Week 36	350/439 (79.7)	366/441 (83.0)	350/483 (72.5)	366/486 (75.3)
Week 48	341/409 (83.4)	368/412 (89.3)	341/483 (70.6)	368/486 (75.7)
Week 60	267/329 (81.2)	261/318 (82.1)	267/483 (55.3)	261/486 (53.7)
Week 72	211/252 (83.7)	211/245 (86.1)	211/483 (43.7)	211/486 (43.4)
Week 84	170/192 (88.5)	155/185 (83.8)	170/483 (35.2)	155/486 (31.9)
Week 96	121/140 (86.4)	131/148 (88.5)	121/483 (25.1)	131/486 (27.0)
Month 30	21/22 (95.5)	29/29 (100)	21/483 (4.3)	29/486 (6.0)

EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30. Fra [39]

Tabel 23: Compliance and completion for the EQ-5D-5L

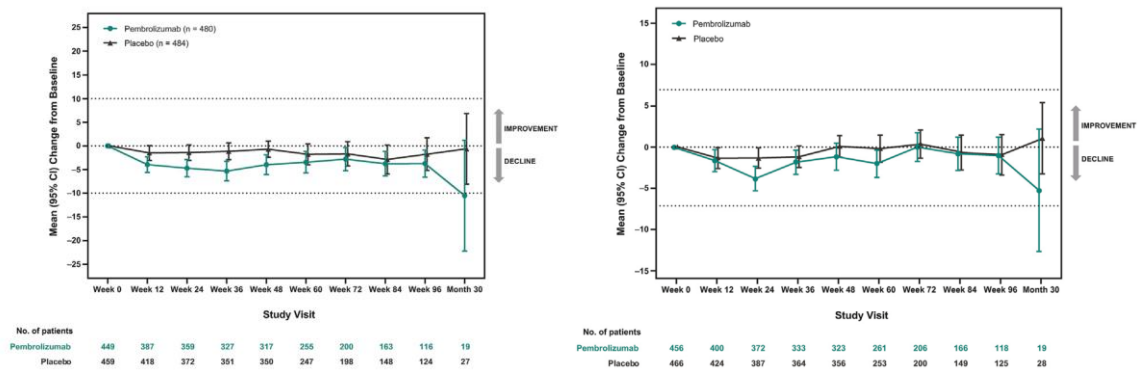
	Compliance *n/N* (%)		**Completion *n/N* (%)**	
Timepoint	**Pembrolizumab**	**Placebo**	**Pembrolizumab**	**Placebo**

	n = 483	*n* = 486	*n* = 483	*n* = 486
Baseline	456/482 (94.6)	466/483 (96.5)	456/483 (94.4)	466/486 (95.9)
Week 12	420/482 (87.1)	442/486 (90.9)	420/483 (87.0)	442/486 (90.9)
Week 24	395/460 (85.9)	404/469 (86.1)	395/483 (81.8)	404/486 (83.1)
Week 36	354/439 (80.6)	377/441 (85.5)	354/483 (73.3)	377/486 (77.6)
Week 48	344/409 (84.1)	371/412 (90.0)	344/483 (71.2)	371/486 (76.3)
Week 60	271/329 (82.4)	265/318 (83.3)	271/483 (56.1)	265/486 (54.5)
Week 72	214/252 (84.9)	211/245 (86.1)	214/483 (44.3)	211/486 (43.4)
Week 84	172/193 (89.1)	155/185 (83.8)	172/483 (35.6)	155/486 (31.9)
Week 96	122/141 (86.5)	131/148 (88.5)	122/483 (25.3)	131/486 (27.0)
Month 30	21/22 (95.5)	29/29 (100.0)	21/483 (4.3)	29/486 (6.0)

Fra [39]

Figur 11 viser livskvalitet (Health-Related Quality of Life) opgivet som EORTC QLQ-C30 og EQ-5D VAS. Her ses det, at livskvaliteten var opretholdt i patienter behandlet med pembrolizumab sammenlignet med baseline og sammenlignelig med livskvaliteten hos patienter i placebo-gruppen. Som det ses i Tabel 24 er forskellen i EORTC-QLQ-C30 LS mean mellem pembrolizumab-gruppen og placebo-gruppen på 3,67 ved 48 uger. Figur 12 viser data på pembrolizumab- og placebogruppen fordelt på de fem funktionsskalaer, tre symptomskalaer og en "global" livskvalitetsskala, som EORTC-QLQ-C30 består af. Her ses det, at pembrolizumab-gruppen er sammenlignelig med placebogruppen også i subskalaerne, og at ingen ændring fra baseline til uge 48 er højere end ≥5 point. Dette vidner om, at de bivirkninger, der påføres patienterne i pembrolizumab-gruppen ikke medfører et fald i livskvalitet, og det understreger, at bivirkningerne er klinisk håndterbare. Livskvaliteten opretholdes i pembrolizumab-gruppen trods aktiv behandling som øger risiko for bivirkninger, og er sammenlignelig med placebobehandling bestående af saltvandsindsprøjtninger. Bivirkningerne relateret til pembrolizumab påvirker derved ikke livskvaliteten hos patienterne i forhold til gruppen behandlet med placebo.

Data på livskvalitet stemmer overens med den rapporterede livskvalitet fra KN-054. Her var livskvaliteten også opretholdt helt ud til 84 uger i de pembrolizumab-behandlede patienter i fht baseline og sammenlignelig med livskvaliteten i placebogruppen [45].



Figur 11: EORTC QLQ-C30 – Global Health Status/QoL (venstre) og EQ-5D VAS (højre)

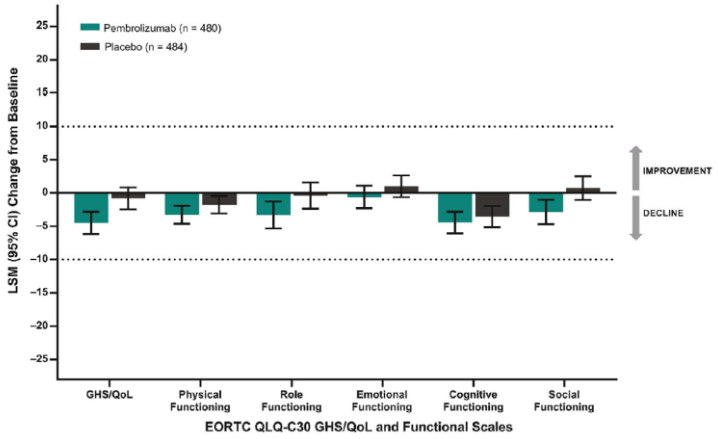
Database Cutoff Date: 21JUN2021. Median opfølgningstid 20,5 mdr. Fra [39]

Tabel 24: Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 48

	EORTC-QLQ-C30, LS mean fra baseline til uge 48	Forskel i EORTC-QLQ-C30 LS mean, uge 48
Pembrolizumab (baseline n=449)	-4,49 (95% CI -6,19 – -2,79)	-3,67 point (95% CI -5.91 - -1.44)

Placebo (baseline n=459)	-0,82 (95% CI -2,4 - 0.83)	p=0,0013

Database Cutoff Date: 21JUN2021. Median opfølgningstid 20,5 mdr. Fra [39]



Figur 12: Ændring i LS Mean fra baseline til uge 48 og 95% CI in EORTC QLQ-C30 Functional Scales/Global Health Status/Quality of Life

For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function. N is the number of subjects in the analysis population in each treatment group. Database Cutoff Date:21JUN2021. Median opfølgningstid 20,5 mdr. Fra [39]

Konklusion på bivirkninger og livskvalitet

Der var ingen pembrolizumab-relaterede dødsfald, og størstedelen af bivirkninger var af grad 1+2. Faktisk blev der kun observeret få grad 3-4 immunrelaterede bivirkninger eller infusionsreaktioner. Overvejelser omkring langtidsbivirkninger er vigtige i adjuverende kliniske studier idet, at patienterne potentielt ville have været kureret ved kirurgi alene og have levet et normalt raskt liv. At reduktionen i risiko for recidiv, som opnås ved at give adjuverende behandling, kommer med en risiko for langtidsbivirkninger skal derfor medtages i beslutningsprocessen. I dette studie blev patienter med bivirkninger af særlig interesse, så som endokrinopatier, håndteret med systemisk corticosteroidbehandling og hormonbehandling. Generalt var bivirkningerne i patienter behandlet med pembrolizumab velkendte og konsistente med tidligere rapporterede bivirkninger hos patienter behandlet med pembrolizumab både i adjuverende og metastatisk setting.

Sammenlignet med de rapporterede bivirkninger i KN-054 er bivirkningerne i KN-716 sammenlignelige og falder indenfor, hvad fagudvalget tidligere har vurderet er acceptabelt. Hvis man vurderer bivirkningerne i KN-716 efter samme kriterier som KN-054, er de derfor klinisk håndterbare og indenfor, hvad der kan vurderes acceptabelt.

Livskvaliteten blev opretholdt hos patienter i pembrolizumab-gruppen og var sammenlignelig med livskvaliteten i placebogruppen. Den aktive behandling med pembrolizumab og risiko for bivirkninger gav ikke et fald i livskvaliteten, hvorfor bivirkningerne må vurderes håndterbare for lægerne og for patienterne. Derved kommer en reduktionen i risikoen for recidiv efter adjuverende behandling med pembrolizumab ikke på bekostning af patienternes livskvalitet.

Klinisk merværdi

MSD vurderer, at der for patienter med stadie IIB+C melanomer er en stor klinisk merværdi ved adjuverende behandling med pembrolizumab. Dette skyldes, at der er en reduktion i risikoen for recidiv og specielt i forekomst af fjernmetastaser. Desuden var bivirkningerne klinisk håndterbare, og der var ingen forringelse af livskvaliteten.

8. Health economic analysis

8.1. Model

The following is a description of our economic model, that was developed to demonstrate the cost effectiveness of pembrolizumab for adjuvant treatment of resected high-risk stage II melanoma. The comparator treatment strategy included routine observation (as represented by the placebo arm of the KEYNOTE-716 trial and current Danish clinical practice[1, 5].

The model considered patients (ages 12 years or older) who have undergone surgical resection and have histologically/pathologically confirmed new diagnosis of high-risk stage IIB or IIC melanoma. This target population is consistent with the eligibility criteria in the KEYNOTE-716 trial.

The model has Denmark as the base case and takes the limited societal perspective were direct health costs and some indirect costs including relevant transportation costs and patient time spent on drug administration and monitoring are included. The following will also describe the budget impact of introducing pembrolizumab in the Danish health care budget with the help of a budget impact analysis.

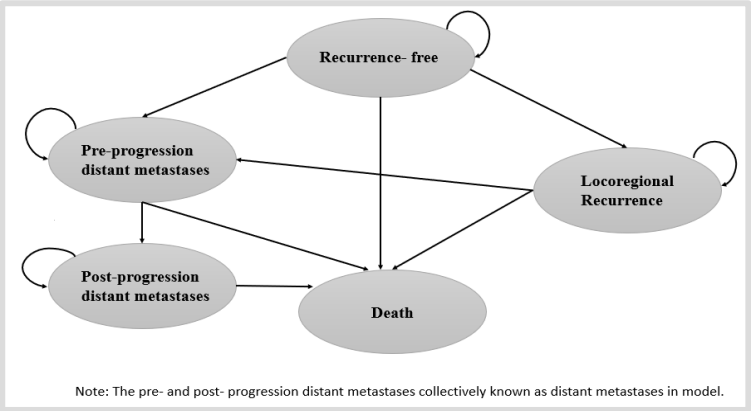
8.1.1. Model structure

The cost-effectiveness model was developed in Microsoft Excel® 2016 using a Markov cohort structure. The state transition diagram in Figur 13 illustrates the health states and allowable transitions in the Markov model. The model consists of four mutually exclusive health states (i.e., recurrence-free, locoregional recurrence, distant metastases, and death) to track the disease course and survival of patients over time.

This model structure differentiates health states by type of recurrence (either locoregional recurrence or distant metastasis) because the primary endpoint of the KEYNOTE-716 trial (i.e., RFS) encompasses both types of recurrence events. These two types of recurrence have different implications on patients' prognosis, quality of life, and disease management, and therefore result in different health outcomes and costs.

The distant metastases state incorporated two sub-states (pre- and post-progression distant metastases) in order to capture the outcomes of subsequent therapies that patients may receive upon developing advanced/metastatic melanoma. The pre-progression DM state represents patients who have a confirmed DM recurrence; all patients who transition to the DM health state enter the pre-progression sub-state and are assumed to receive first-line systemic therapy for metastatic melanoma. The post-progression DM state represents patients who have progressed on first-line therapy; a proportion of these patients are assumed to receive second-line systemic therapy for metastatic melanoma. Survival time within the distant metastases state, as well as the relative proportions of time spent in the pre- versus post-progression sub-states, depends upon the efficacy and market shares of first-line subsequent therapies. Based on these relative proportions, utility in the distant metastases state was computed as a weighted average of utilities in the pre- and post-progression sub-states. Similarly, per-cycle costs of healthcare resource use in the distant metastases state were computed as a weighted average of per-cycle costs in these two sub-states.

The health states and allowable transitions were defined such that RFS, distant metastases-free survival (DMFS, or time until distant metastases or death), and OS curves can be generated using the Markov trace. This facilitated validation of the model against observed Kaplan-Meier curves from the trial.



Figur 13: Model Schematic

8.1.2. Time horizon and cycle length

The cost-effectiveness analysis was conducted using a lifetime horizon of 40,7 years to comprehensively capture differences in costs and outcomes between Pembrolizumab and comparator arms. To approximate a lifetime horizon, the base-case model was run until the age of surviving patients in the cohort reached 100 years. The starting age of the patient cohort at model entry was based on the average age(59,3 years) in the KEYNOTE-716 trial. Based on the starting age of 59,3 years, the base case time horizon of 40,7 years must be considered appropriate to capture relevant costs and health benefits over the patient's lifetime. The impact of alternative time horizons of 20 and 30 years was explored via sensitivity analyses.

The model uses a weekly cycle length to allow for precise calculation of drug acquisition and administration costs.

Half-cycle correction was applied to costs and effectiveness for additional precision. As an exception, half-cycle correction was not applied to cost components that are incurred at the beginning of a cycle, including adjuvant drug acquisition and administration costs (costs that recur at specific time points starting from week 0) and AE-related costs (to be applied as a one-time cost at week 0). For example, in the adjuvant Pembrolizumab arm, the drug acquisition and administration cost per infusion was applied at week 0 for 100% of patients, at week 3 for the percentage remaining on therapy at week 3, and so forth.

8.1.3. Discount rates

In the base case analysis, both costs and effectiveness are discounted annually at 3.5% discount rate for year 1 to 35 and 2,5% from year 36 onwards till 70 years, consistent with the guidelines of Danish Ministry of Finance and The Danish Medicines Council methods guide for assessing new pharmaceuticals.

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

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

Interim results from KN716 study provided efficacy, utility and safety inputs for the CEA. The table below presents the clinical input data used in the model and how they are obtained.

Table 25: Summary of input used in the model and how they are estimated

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**
Recurrence-free survival **(primary endpoint)**	KN716 – primary endpoint: To compare Recurrence-free Survival (RFS) between treatment arms. RFS: Time from randomization to (1) any recurrence (local or regional [including invasive ipsilateral tumor and invasive loco-regional tumor], or distant) as assessed by the investigator, or(2) death due to any cause	RFS, distant metastases-free survival (DMFS, or time until distant metastases or death), and OS	Transitions from recurrence-free to locoregional recurrence, distant metastases, or death: Based on a parametric multistate modeling approach in which different parametric functions were fitted to each of the three individual transitions starting from RF, accounting for competing risks. Transitions from locoregional recurrence to distant metastases: Were estimated using exponential distributions separately fitted for each treatment arm of KEYNOTE-716 Transitions from distant metastases to death: Depend upon market shares and efficacy of first-line treatments for advanced/metastatic melanoma. Exponential OS distributions were estimated for each first-line treatment based on trials in advanced melanoma. For first-line Pembrolizumab, these distributions were fitted using patient-level data from KEYNOTE-006. For other first-line treatments, HRs for OS versus Pembrolizumab were obtained from an NMA of first-line drug trials in advanced melanoma. Exponential PFS distributions were similarly estimated for each first-line treatment. PFS affects the calculation of utility and disease management costs in the DM state. Expected OS following DM were calculated in each adjuvant treatment arm as a market share-weighted average of expected OS under different first-line treatments. Expected OS was then converted into a weekly hazard of DM→death. Expected PFS following DM was also estimated in a similar way for each adjuvant treatment
Distant metastasis-free survival **(Secondary endpoint)**	KN716 – secondary endpoint: To compare DMFS between treatment arms DMFS: The time from	Please see above for description under "Recurrence-free survival"	Please see above for description under "Recurrence-free survival"

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**
	randomization to appearance of a distant metastasis as assessed by the investigator. A distant metastasis refers to cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes.		
Adverse reaction 1 **(measured in costs)**		Total AE cost was calculated by multiplying cost per episode with AE incidence rate and mean number of episodes per patient with the AE (weeks).	The unit cost of AE management per incidence was obtained from DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen
Adverse reaction 2 **(measured as occurrence)**	Adverse event are reported for the all participants as treated (APat) population in the clinical documentation.	The model considered all cause grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KEYNOTE-716 trial or with a frequency of ≥5% (all grades) in the pivotal trial for any of the other comparator drugs.	Risks of the included AEs for patients treated with Pembrolizumab and observation were obtained from KEYNOTE-716
Adverse reaction 3 **(measured as utility loss)**		AE-related disutility was applied as a one-time QALY decrement in the first model cycle.	Disutility associated with AEs was calculated as a function of: treatment-specific AE risks; the mean number of episodes among patients with a given AE; the mean duration of these AEs per episode. The estimated disutility associated with an active grade 3+ AE is based on Danish specific utility algorithm of EQ-5D-5L data from the KEYNOTE-716 trial. The disutility of an active grade 3+ AE was obtained from the same regression model used to estimate the utility value for RF (without toxicity), based on the coefficient associated with the presence of any grade 3+ AE(s).
Utility by health state	KN716 exploratory endpoints:	Utility values for the recurrence-free, locoregional recurrence, and pre-progression distant metastases states	The utility values for the recurrence-free, locoregional recurrence, and pre-progression distant metastases states were derived through repeated measures regression analyses of

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**
	To characterize health utilities using the EuroQoL-5 Dimension Questionnaire(EQ-5D-5L) healthy utility scores.		patient-level EQ-5D-5L data from the KEYNOTE-716 trial using Danish utility algorithm
Transition probability 1		Calculation of transition probabilities based on cause-specific hazards For each individual transition starting from the recurrence-free state, transition probabilities in each weekly cycle were calculated within the model as a function of the cause-specific hazards for all three types of RFS failure. The following calculation steps was performed: For each cause of RFS failure k (i.e., locoregional recurrence, distant metastases, or death), the average cause-specific hazard within the cycle from week (t-1) to t were calculated as: ¯h_k (t)=H_k (t)-H_k (t-1), where H_k (.) is the cause-specific cumulative hazard of cause k (based on the parametric function selected to model cause k). The average hazard of any RFS failure within the cycle from week (t-1) to t, denoted ¯h_RFS (t), was calculated as the sum of the average cause-specific hazard for all three causes within that cycle. This hazard was converted into a probability using the formula: 1-e^(-¯h_RFS (t)) In each cycle, the relative contribution of each cause k to the overall hazard of RFS failure was derived as:	

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**
		(¯h_k (t))/(¯h_RFS (t)) This represents the probability of having had an RFS failure of type k given that an RFS failure has occurred within the cycle. [47] The relative contribution of cause k was then multiplied by the probability of any RFS failure within the cycle to obtain the transition probability corresponding to cause k. Within each cycle, the transition probability from recurrence-free → death was set equal to the maximum of the estimated probability based on parametric modeling and background mortality, given the age and gender distribution of the cohort by that cycle. All-cause mortality rates by age for men and women in the Denmark was from the Global Health Observatory data repository, WHO. [48]	

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

8.2.2.1. Patient population

The Danish patient population:
Patients with newly diagnosed, completely resected stage IIB or IIC melanoma.

Patient population in the clinical documentation submitted:
Patients aged 12 years or older with newly diagnosed, completely resected stage IIB or IIC melanoma (TNM stage T3b or T4 with a negative sentinel lymph node biopsy).

Patient population in the health economic analysis submitted:
The model considered patients aged 12 years or older with newly diagnosed, completely resected stage IIB or IIC melanoma (TNM stage T3b or T4 with a negative sentinel lymph node biopsy).

MSD believes that the target population in the health economic model is consistent with the eligibility criteria in the KEYNOTE-716 trial and with the Danish patient population. There is no data available on the size of the adolescent population in Denmark, but in DMG guidelines, the yearly number of patients below the age of 15 years is referenced as 3 per year across all stages of melanoma[46].

The age and gender distributions of the model cohort in cycle 0 were based on the reported characteristics of the KEYNOTE-716 trial population (Tabel 26). The mean and standard deviations of body surface area (BSA) was also based on the KEYNOTE-716 population (N=976). The mean weight for adults was based on the Danish Medicines Council[47]. In order to use the Danish mean weight for melanoma patients, the SD for the mean weight is calculated based on the following formula: Standard deviation for DK= Ratio of SD of weight and mean weight taken from KN716 trial (18.90 kg/84.20 kg)* country specific weight (73.0 kg)= 16.36 kg.

BSA and weight statistics were used within the model to compute the required dosage of BSA- and weight-based subsequent treatment options in the locoregional recurrence and distant metastases states. The prevalence of BRAF V600E mutation was unavailable from KEYNOTE-716 and was therefore obtained from the KEYNOTE-054 trial of Pembrolizumab as an adjuvant treatment of resected high-risk stage III melanoma[20].

Tabel 26: Patient population

Patient population **Important baseline characteristics**	**Clinical documentation / indirect comparison etc. (including source)**	**Used in the model (number/value including source)**	**Danish clinical practice (including source)**
Age, mean	59,3 (KEYNOTE-716)	59,3 (KEYNOTE-716)	
Age <18 years(%)	0,2 (KEYNOTE-716)	0,2 (KEYNOTE-716)	
Female(%)	39,7 (KEYNOTE-716)	39,7 (KEYNOTE-716)	
Weight overall population (kg), mean	84.2 (KEYNOTE-716)	73,0[47]	73,0[47]
Weight (kg), SD	16.36 kg (estimated)	16.36 kg (estimated)	
Weight (kg) among pediatric patients, mean	64,4 (KEYNOTE-716)	64,4 (KEYNOTE-716)	
Weight (kg) among pediatric patients, SD	13,0 (KEYNOTE-716)	13,0 (KEYNOTE-716)	
Body surface area (m2), mean	2,0 (KEYNOTE-716)	2,0 (KEYNOTE-716)	
Body surface area (m^2), SD	0,3 (KEYNOTE-716)	0,3 (KEYNOTE-716)	
Percent with BRAF V600E mutation	43,3% (KEYNOTE-054)		

8.2.2.2. Intervention

Intervention as expected in Danish clinical practice: Pembrolizumab 2 mg/kg (200 mg maximum) every 3 weeks or 4 mg/kg (400 mg maximum) every 6 weeks for adult patients for up to 17/9 cycles and weight-based dosing of 2 mg/kg (200 mg maximum) every 3 weeks for children for up to 17 cycles.

Intervention in the clinical documentation submitted: Pembrolizumab 200 mg (2 mg/kg up to 200 mg for pediatric patients) IV on day 1 of each 21-day cycle for up to 17 cycles

Intervention as in the health economic analysis submitted: The intervention considered in the model is Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for adult patients for up to 17/9 cycles and weight-based dosing of 2 mg/kg (200 mg maximum) every 3 weeks for children for up to 17 cycles.

The interventions are described below:

Tabel 27: Intervention

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Pembrolizumab 200 mg (2 mg/kg up to 200 mg for pediatric patients) IV on day 1 of each 21-day cycle for up to 17 cycles	Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for adult patients for up to 17/9 cycles and weight-based dosing of 2 mg/kg (200 mg maximum) every 3 weeks for children for up to 17 cycles	Pembrolizumab 2 mg/kg (200 mg maximum) every 3 weeks or 4 mg/kg (400 mg maximum) every 6 weeks for adult patients for up to 17/9 cycles and weight-based dosing of 2 mg/kg (200 mg maximum) every 3 weeks for children for up to 17 cycles
Criteria for discontinuation	Patients continue receiving adjuvant treatment until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, withdrawal of patient consent, or completing 17 cycles of therapy	Treatment with pembrolizumab was capped at 17 cycles as per the trial protocol.	Treatment of pembrolizumab is expected to be capped at 17 cycles in line with KN716
The pharmaceutical's position in Danish clinical practice			Not used in clinical practice prior to evaluation in the Medicine Council. Recommendation from the Danish Medicines Council will lead to the introduction as adjuvant treatment of high risk stage II

The Danish Medicines Council has in previous assessments of pembrolizumab indications stated that weight based dosing of pembrolizumab was a precondition for positive recommendation decision. MSD assumes the Danish

Medicines Council, also in this case, will include a precondition relating to weight based dosing, and the impact of weight based dosing of pembrolizumab was therefore explored via scenario analyses.

8.2.2.3. Comparators

The current Danish clinical practice: Observation
Comparator(s) in the clinical documentation submitted: Observation
Comparator(s) in the health economic analysis submitted: Observation

MSD believes that "Observation" must be considered as the only relevant comparator to adjuvant Pembrolizumab. This is supported by the description of patient management approach for resected high risk stage II melanoma in Sundhedsstyrelsens "Pakkeforløb for modermærkekræft i huden"[1].

The comparators are described below:

Table 28: Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	Observation (KEYNOTE-716)	Observation (KEYNOTE-716)	Observation[1]
The comparator's position in the Danish clinical practice			Observation is the current standard in Danish clinical practice

8.2.2.4. Relative efficacy outcomes

In the two tables below is the relative efficacy outcomes in KN716 on DMFS and RFS presented together with the modeled DMFS and RFS for both the Pembrolizumab arm and the placebo arm.

Table 29: Summary of DMFS in clinical documentation and in model

DMFS by year:	1	2	3	4	5	6	7	10
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table: 30 Summary of RFS in clinical documentation and in model

RFS by year:	1	2	3	4	5	6	7	10
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.2.2.5. Adverse reaction outcomes

Table 31: Adverse events

Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)
	Adverse events are reported for the all participants as treated (APat) population in the clinical documentation.	The model considered all cause grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KEYNOTE-716 trial or with a frequency of ≥5% (all grades) in the pivotal trial for any of the other comparator drugs.

The inclusion of specific adverse events (AEs) within the economic model was based on a combination of the risk and severity of each event. The model considered all cause grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KEYNOTE-716 trial or with a frequency of ≥5% (all grades) in the pivotal trial for any of the other comparator drugs. Though frequency at any grade was used to determine eligibility of inclusion for a certain type of AE, only grade 3 to 5 AEs were incorporated into the model due to their expected impact on resource utilization and quality of life.

In addition to these grade 3+ AE types, diarrhea of grades 2 or higher was also considered based on the high expected cost of managing this AE even for grade 2 events. Febrile neutropenia of any grade was selected for inclusion a priori based on similar rationale but was not observed in the trial as of the data cutoff date. Risks of the included AEs for patients treated with Pembrolizumab and observation were obtained from KEYNOTE-716 (data cutoff date: 04-Jan-2022), with an option to use all-cause AE results(base case, **Table 32**). A scenario analysis of without inclusion of adverse events was also conducted. Mean durations of each AE per episode, and mean number of episodes per patient with each AE, were collected from KEYNOTE-716 using pooled data from both treatment arms and were used within the model to estimate the duration of the disutility impact from each AE regardless of subgroup or adjuvant treatment arm.

Table 32: Risks and durations of modeled AEs

a. **Base case: All-cause AEs**

AE type	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with the AE (weeks)	Mean duration per episode (weeks)
	Pembrolizumab	Observation		
Diarrhea	7,0%	2,3%	1,16	4,33
Hyperthyroidism	0,2%	0,0%	1,00	137,00
Asthenia	0,2%	0,0%	1,00	3,71
Fatigue	0,4%	0,2%	1,00	44,43
Alanine aminotransferase increased	1,0%	0,2%	1,00	9,69
Aspartate aminotransferase increased	0,6%	0,6%	1,00	24,64
Decreased appetite	0,4%	0,0%	1,50	2,29
Hyperglycaemia	0,4%	0,2%	1,00	5,52
Arthralgia	0,4%	0,4%	1,00	9,50
Back pain	0,4%	0,0%	1,00	36,79
Myalgia	0,4%	0,0%	1,00	5,00
Pain in extremity	0,0%	0,2%	1,00	5,86
Basal cell carcinoma	0,0%	0,4%	1,50	5,62
Pruritus	0,6%	0,0%	1,00	15,94
Rash	1,4%	0,4%	1,00	33,08
Rash maculo-papular	0,4%	0,2%	1,33	4,86
Hypertension	3,3%	3,5%	1,36	26,02
Sources:	KEYNOTE-716	KEYNOTE-716	KEYNOTE-716	KEYNOTE-716

b. Scenario analysis: Drug-related AEs

AE type	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with the AE (weeks)	Mean duration per episode (weeks)
	Pembrolizumab	Observation		
Diarrhea	5,0%	1,6%	1,19	5,26
Hyperthyroidism	0,2%	0,0%	1,00	137,00
Asthenia	0,2%	0,0%	1,00	3,71
Fatigue	0,2%	0,2%	1,00	56,07
Alanine aminotransferase increased	0,8%	0,2%	1,00	10,83
Aspartate aminotransferase increased	0,2%	0,2%	1,00	17,07
Decreased appetite	0,2%	0,0%	2,00	0,64
Hyperglycemia	0,0%	0,0%	0,00	0,00
Arthralgia	0,4%	0,0%	1,00	16,93
Back pain	0,0%	0,0%	0,00	0,00
Myalgia	0,4%	0,0%	1,00	5,00

Pain in extremity	0,0%	0,0%	0,00	0,00
Basal cell carcinoma	0,0%	0,0%	0,00	0,00
Pruritus	0,6%	0,0%	1,00	15,94
Rash	1,4%	0,2%	1,00	36,79
Rash maculo-papular	0,4%	0,0%	1,50	4,81
Hypertension	0,2%	0,0%	1,00	0,29
Sources:	KEYNOTE-716	KEYNOTE-716	KEYNOTE-716	KEYNOTE-716

8.3. Extrapolation of relative efficacy

8.3.1. Time to event data – summarized:

The following is a summarization. Full description with details can be found in appendix G together with details concerning model validation; verification, external validation and cross validation.

Transition probabilities

Transition probabilities were derived based on primary analyses of patient-level data from the KEYNOTE-716 trial, a systematic literature review and NMA comparing the efficacy of Pembrolizumab in KEYNOTE-006 versus other treatments for advanced or metastatic melanoma, and a real-world retrospective database analysis. The NMA is described in appendix B, and the estimation approach for each health state transition in the Markov model is described below and in detail in appendix G. The set of allowable transitions is illustrated by the state transition diagram in (Figur 13: Model Schematic), and a summary of each of the health state transitions considered in the economic model is provided in Table 33.

The key transition probabilities driving the cost-effectiveness results are the three transitions starting from the recurrence-free state (i.e., recurrence-free to locoregional recurrence, recurrence-free to distant metastases, and recurrence-free to death). These transition probabilities were estimated using randomized controlled trial data from KEYNOTE-716 for the Pembrolizumab and observation arms. There is strong published evidence supporting that an improvement in RFS, such as that observed in KEYNOTE-716, will likely translate into an OS benefit[14, 15, 20]. In particular:

- The EORTC 18071 trial has demonstrated that the RFS and OS benefit of adjuvant treatment with an immune checkpoint inhibitor (ipilimumab) is sustained over the long term (median follow-up: 7 years) [20].
- In a recent meta-analysis of 13 clinical studies (n>5,000 patients) involving adjuvant interferon for the treatment of resected stage II-III melanoma, RFS was shown to be a good predictor and valid surrogate endpoint for OS[14].
- The findings of the above meta-analysis have since been supplemented by inclusion of data from EORTC 18071 which demonstrated that the association between RFS and OS is maintained when data specific to checkpoint inhibitors (in this case ipilimumab) in the resected stage III population are considered[15].

As of the third interim analysis of KEYNOTE-716 (data cutoff date: 04-Jan-2022), data on DMFS in each trial arm were also available for analysis, which allowed for the use of trial data to directly estimate the two transitions starting from the locoregional recurrence state (i.e., locoregional recurrence to distant metastases, and locoregional recurrence to death).

For transitions starting from the distant metastasis health state or the distant metastases health state (i.e., distant metastases to death), real-world evidence and published literature were used. The model assumes that, once patients experience a distant recurrence event, there are no ongoing benefits from the initial adjuvant Pembrolizumab course

within these health states. (In other words, the original course of adjuvant Pembrolizumab that a patient receives following resection of stage II melanoma was assumed to confer no continuing benefit after the patient's develops distant metastases. However base-case transition probabilities from distant metastases to death differed between the treatment arms due to expected differences in the distribution of subsequent treatments received in the metastatic setting.

Table 33: Summary of health state transitions considered in the economic model

Transition(s)	Estimation approach	Data source(s)	Scenario or one-way sensitivity analyses performed
RF → LR RF → DM RF → Death[1]	Based on a parametric multistate modeling approach in which different parametric functions were fitted to each of the three individual transitions starting from RF, accounting for competing risks	▪ Patient-level data from KEYNOTE-716 ▪ Life tables for Denmark - for transitions to death	▪ Alternative parametric distributions
LR → DM LR → Death[1]	Transition probabilities starting from LR were estimated using exponential distributions separately fitted for each treatment arm of KEYNOTE-716	▪ Patient-level data from KEYNOTE-716 ▪ Original data sources (included as a scenario analysis): Patient-level data from electronic health records database; and trial-based HRs of DMFS failure with adjuvant treatments for stage III melanoma vs. placebo ▪ Life tables for Denmark- for transitions to death	▪ Use original data sources for these transitions [2] ▪ Use electronic health records to model these transitions in patients who receive subsequent adjuvant treatment ▪ Exponential rates of each transition varied +/- 10%
DM → Death[1]	▪ Transition probabilities from DM→death depend upon market shares and efficacy of first-line treatments for advanced/metastatic melanoma ▪ Exponential OS distributions were estimated for each first-line treatment based on trials in advanced melanoma. For first-line Pembrolizumab, these distributions were fitted using patient-level data from KEYNOTE-006. For other first-line treatments, HRs for OS versus Pembrolizumab were obtained from an NMA of first-line drug trials in advanced melanoma ▪ Exponential PFS distributions were similarly estimated for each first-line treatment. PFS affects the calculation of utility and disease management costs in the DM state ▪ Expected OS following DM were calculated in each adjuvant treatment arm as a market share-weighted average of expected OS under different first-line treatments. Expected OS was then converted into a weekly hazard of DM→death. Expected PFS following DM was also estimated in a similar way for each adjuvant treatment	▪ Patient-level OS and PFS data from KEYNOTE-006 ▪ NMA comparing treatments for advanced melanoma in terms of OS and PFS ▪ Patient-level data from EMR or claims database ▪ Life tables for Denmark - for transitions to death	▪ Alternative assumptions about subsequent treatments for DM in each model arm ▪ Exponential rates of OS and PFS failure with treatments for metastatic melanoma varied +/- 10%

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; HR, hazard ratio; LR, locoregional recurrence; NMA, etwork meta-analysis; OS, overall survival; PFS, progression-free survival; RF, recurrence-free.

Notes:

[1] Transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from national life tables given the age and gender distribution of the cohort at each cycle.
[2] Originally, transition probabilities starting from the LR state were stratified by usage of subsequent adjuvant treatment in this state. For patients who receive no subsequent adjuvant treatment in the LR state, exponential models of LR→DM and LR→death were fitted using a real-world cohort of patients who underwent surgical resection of stage IIB/IIC melanoma, subsequent had LR, and received no adjuvant treatment for LR. For those who receive adjuvant treatment, HRs of DMFS failure vs. placebo were obtained from published trials in the stage III melanoma setting.

Below is given data on first and second events distributed for LR and DM

At time of IA3 (the most recent interim analysis), 63 and 95 patients in the pembrolizumab and placebo arms, respectively, had experienced the first DM event. At the same data cut-off, 95 patients in the pembrolizumab arm, and 139 patients in the placebo arm had experienced the first recurrence event. Within the recurrence events in patients randomized to pembrolizumab, 46, 45, and 9 events were local/regional/locoregional, distant, and death events, respectively. The corresponding figures in the placebo arm were 56, 77, and 6. The numbers are presented in Tabel 34.

[redacted]

Tabel 34: First and second events distributed in LR and DM

	Pembrolizumab	Observation
	N=487	N=489
Reccurence-free survival status		
All events (%)	95 (20)	139 (28)
Local, regional, and locoregional	46 (9)	56 (11)
Distant	45 (9)	77 (16)
Death	4 (1)	6 (1)
Distant-metastasis-free survival status		
All events (%)	63 (13)	95 (19)
As first event	45 (9)	79 (16)
After locoregional recurrence	18 (4)	16 (3)

Source: KN716 IA3

8.3.2. Transitions from recurrence-free to locoregional recurrence, distant metastases, or death

For the Pembrolizumab and observation arms, transition probabilities starting from the recurrence-free state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-716 trial, following the parametric multistate modelling approach described by Williams et al. (2017a & 2017b) [50, 51]. Parametric models were used to estimate the cause-specific hazards of each transition (i.e., recurrence-free → locoregional recurrence, recurrence-free → distant metastases, and recurrence-free → death) over time within the adjuvant Pembrolizumab and observation arms. Within each weekly cycle of the model, the probability of each of these transitions (as well as the composite probability of any RFS failure event) were calculated as a function of all three cause-specific hazards.

Validation of OS estimation of cause-specific hazard for each individual transition starting from the recurrence-free state

The cause-specific hazards of each transition in the Pembrolizumab and observation arms were estimated based on parametric models fitted to data from the Pembrolizumab and placebo arms of KEYNOTE-716. In order to fit parametric models to each of the three individual health state transitions, standard survival analysis methods were used with one modification to account for competing risks: When analyzing time to each specific type of RFS failure, the two competing failure types were treated as censoring events. For example, to model the transition from recurrence-free to distant metastases, patients who experience a locoregional recurrence or death prior to distant metastases were censored and thus treated as lost to follow-up at the time of the earlier competing event. After these additional censoring criteria were applied to the patient-level time-to-event data for each transition, parametric curve fitting was performed using the survival analysis package flexsurvreg in R software.

The following three parametric modeling approaches were tested to explore uncertainty in the estimation of transition probabilities starting from the recurrence-free state:

1. Parametric models separately fitted to each treatment arm: Under Approach #1, transition probabilities were estimated based on parametric models that were fitted individually to each treatment arm of the KEYNOTE-716 trial. Six different parametric functions were considered to model transitions from recurrence-free to locoregional recurrence and from recurrence-free to distant metastases in each treatment arm, including Exponential, Weibull, Gompertz, Log-logistic, Log-normal, and Generalized gamma distributions. Due to the small number of direct transitions from recurrence-free to death observed in KEYNOTE-716, exponential distributions were fitted for this transition in each arm.

2. Parametric proportional hazards models with a time-constant treatment effect: Under Approach #2, transition probabilities in the Pembrolizumab and observation arms were estimated based on jointly fitted proportional hazards models (i.e., Exponential, Weibull, or Gompertz) that incorporated a time-constant hazard ratio (HR) for Pembrolizumab versus placebo in KEYNOTE-716. Due to the small number of direct transitions from recurrence-free to death in the trial, an exponential model with a time-constant treatment effect was used for transitions from recurrence-free → death.

3. Parametric proportional hazards models with a time-varying treatment effect (before and after year 1): Under Approach #3, transition probabilities in the Pembrolizumab and observation arms were estimated based on jointly fitted proportional hazards models (i.e., Exponential, Weibull, or Gompertz) that incorporated a time-varying HR for Pembrolizumab versus placebo. Specifically, the models allowed the treatment effect to differ during versus after the first year following initiation of adjuvant therapy. The allowance of a differing treatment effect during the first year versus following years is based on the protocol-defined maximum treatment duration of 1 year. As in Approach #2, an exponential model with a time-constant treatment effect was used for transitions from recurrence-free → death under Approach #3, given the small number of events.

Parameter estimates associated with all parametric models under Approaches #1, 2, and 3 are reported within the Excel model.

As described below, for each of the two treatment arms, probabilities of each transition from the recurrence-free state were calculated based on all three cause-specific hazard functions. The predicted RFS curve over time in each treatment arm similarly depends upon all three cause-specific hazard functions. Therefore, in order to select base-case parametric functions, all 54 (i.e., 6×6 under approach #1 + 3×3 under approach #2 + 3×3under approach #3) possible combinations

of parametric functions for recurrence-free → locoregional recurrence and recurrence-free → distant metastases were considered (Tabel 35).

Tabel 35: Combinations of parametric models considered for transitions starting from the recurrence-free state

Overall approach	Distributions fitted to the cause-specific hazards of each transition:			# of potential combinations of distributions
	RF → LR	RF → DM	RF → Death	
Approach #1: Parametric models separately fitted to each treatment arm	Exponential Weibull Gompertz Log-normal Log-logistic Generalized gamma	Exponential Weibull Gompertz Log-normal Log-logistic Generalized gamma	Exponential*	36 (=6*6*1)
Approach #2: Proportional hazards parametric models jointly fitted to both arms with a time-constant HR	Exponential Weibull Gompertz	Exponential Weibull Gompertz	Exponential*	9 (=3*3*1)
Approach #3: Proportional hazards parametric models jointly fitted to both arms with a time-varying HR – *a*llows for different treatment effect before vs. after 1 year, based on the maximum duration of adjuvant treatment	Exponential Weibull Gompertz	Exponential Weibull Gompertz	Exponential* *(due to the small number of direct RF to death transitions)	9 (=3*3*1)
			Total:	54

Abbreviations: DM, distant metastases; LR, locoregional recurrence; RF, recurrence-free; SD, standard deviation.

Calculation of transition probabilities based on cause-specific hazards

For each individual transition starting from the recurrence-free state, transition probabilities in each weekly cycle were calculated within the model as a function of the cause-specific hazards for all three types of RFS failure. The following calculation steps was performed:

1. For each cause of RFS failure k (i.e., locoregional recurrence, distant metastases, or death), the average cause-specific hazard within the cycle from week (t-1) to t were calculated as:

   $$\overline{h}_k(\mathrm{t}) = H_k(\mathrm{t}) - H_k(\mathrm{t}-1),$$

   where $H_k(.)$ is the cause-specific cumulative hazard of cause k (based on the parametric function selected to model cause k).

2. The average hazard of any RFS failure within the cycle from week (t-1) to t, denoted $\overline{h}_{RFS}(\mathrm{t})$, was calculated as the sum of the average cause-specific hazard for all three causes within that cycle. This hazard was converted into a probability using the formula: $1 - e^{-\overline{h}_{RFS}(\mathrm{t})}$

3. In each cycle, the relative contribution of each cause k to the overall hazard of RFS failure was derived as:

   $$\frac{\overline{h}_k(\mathrm{t})}{\overline{h}_{RFS}(\mathrm{t})}$$

This represents the probability of having had an RFS failure of type k given that an RFS failure has occurred within the cycle.[52] The relative contribution of cause k was then multiplied by the probability of any RFS failure within the cycle to obtain the transition probability corresponding to cause k.

Within each cycle, the transition probability from recurrence-free → death was set equal to the maximum of the estimated probability based on parametric modeling and background mortality, given the age and gender distribution of the cohort by that cycle. All-cause mortality rates by age for men and women in the Denmark was from the Global Health Observatory data repository, WHO[53].

Selection of base-case parametric functions

As noted by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19, assessing model fit is more challenging in the context of multistate models than partitioned survival models, as the target outcomes of interest (e.g., the proportions of individuals experiencing the composite endpoint) are determined by a combination of survival models rather than by a single survival model[54].Therefore, to select base-case parametric functions, all 54 possible combinations of parametric functions for recurrence-free → locoregional recurrence, recurrence-free → distant metastases, and recurrence-free → death were considered. In accordance with recommendations in the NICE DSU TSD 14[55], base-case parametric functions were selected such that the same functional form was used to model each health state transition in both the Pembrolizumab and observation arms. The rationale for this approach was to prevent the extrapolated portion of the RFS curves from following drastically different trajectories between the two model arms. Base-case parametric functions were chosen based on the following criteria:

1. Exclusions based on clinical plausibility: Due to clinical implausibility, combinations of parametric functions that resulted in crossing RFS curves (i.e., higher long-term RFS under observation compared with Pembrolizumab) were excluded from consideration as base case. This exclusion was supported by the available data from KEYNOTE-716, as well as longer-term RFS and DMFS data from the KEYNOTE-054 trial of Pembrolizumab as an adjuvant treatment of resected high-risk stage III melanoma. Combinations were further excluded if they resulted in lower 4-year RFS and/or DMFS for either Pembrolizumab or observation than that reported for the corresponding arms of KEYNOTE-054, given the expectation of better prognosis in the stage IIB-C population.

2. Fit based on mean squared error (MSE) vs. observed RFS and DMFS: Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks[50].As extracted from Willian et al. 2017 AIC only provides information about the fit to the observed data and oftenly discounting for some measure of model complexity and not on how reasonable the extrapolation looks. Thus, when assessing model fit, it is advisable to consider several different aspects, allowing the observed fit and extrapolation to be jointly assessed. When faced with a competing risks scenario while modeling transition hazards, however, such AIC calculations are not appropriate and therefore visual assessment can be the only option. Hence MSE vs observed RFS was therefore used as an alternative diagnostic test to assess fit of the predicted RFS curve versus the observed Kaplan-Meier curve during the within-trial period in each treatment arm. Specifically, MSE was calculated based on the average of the squared difference in predicted versus observed RFS at weekly intervals across the within-trial period, with weighting by number of patients at risk in each weekly interval(Table 83 and Tabel 84).

   The secondary endpoint of DMFS was evaluated as part of the third interim analysis of KEYNOTE-716. The MSE of the predicted DMFS curve vs. the observed DMFS Kaplan-Meier curve was therefore also assessed for different combinations of parametric functions for recurrence-free → locoregional recurrence and recurrence-free → distant metastases.

In addition, the assumption of proportional hazards was assessed through formal statistical tests to evaluate the potential suitability of Approach #2 and #3. Namely, for each transition, the function cox.zph in R was used to test for independence between time and the scaled Schoenfeld residuals from a Cox proportional hazards model with a time-constant treatment covariate. The proportional hazard assumption is supported by a non-significant relationship between residuals and time.

3. Visual assessment of fit: Predictions generated by different combinations of parametric functions were also visually verified against the observed data in each treatment arm, following the approach used by William et al. (2017) [50]. Specifically, predicted versus observed cumulative incidence curves were plotted for each of the three individual transitions starting from the recurrence-free state. In base case, the resulting predictions of RFS as a composite endpoint were compared against the observed RFS and DMFS Kaplan-Meier curve in each arm.

4. External validity/ Plausibility of long-term extrapolations: Longer-term extrapolations in the observation arm were externally validated against observed data from several real-world studies (Figure 14 and Figure 15). (Of note, predicted RFS depends only on transition probabilities starting from the recurrence-free state, while predicted DMFS depends on transition probabilities starting from the recurrence-free and locoregional recurrence states. Predicted OS is a function of all transition probabilities in the model.) Survival projections in the observation arm were also validated against long-term RFS, DMFS, and OS observed in a real-world cohort study among patients with resected stage IIB or IIC melanoma using US Oncology Network electronic health records [48]. Additional sources used for external validation included three published studies that reported long-term RFS and/or OS in real-world cohorts of patients diagnosed with AJCC 8th edition stage IIB or IIC melanoma, including two different US-based cohorts[49, 56] and one European cohort[57]. Additional information on each of these studies is summarized in the Appendix L. For each of these three published sources, the following steps were performed: (1) RFS and/or OS were extracted separately for the stage IIB and IIC subgroups (using digitized Kaplan-Meier data were available); and (2) these subgroup-specific results from were then pooled as a weighted average to obtain RFS and/or OS for the combined stage IIB/IIC target population, based on the percentages of patients with stage IIB vs. IIC melanoma in KEYNOTE-716.

When applying the above criteria, Approach #1 (separately fitted models) with a log-normal function for recurrence-free → locoregional recurrence and log-normal function for recurrence-free → distant metastases appeared to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each arm. Specific considerations are summarized in Table 36 and the selection process is detailed in appendix G with a total of 54 candidate combinations, including 36 under Approach #1, 9 under Approach #2, and 9 under Approach #3. A table (**Table 94**) was also added in appendix M of this report the combination of distribution excluded in each of the steps specified in Table 36.

Table 36: Summary of selection process for base-case parametric distributions of recurrence-free → locoregional recurrence and recurrence-free → distant metastases

Step #	Description of criterion applied at each step	# Combinations of distributions that meet criterion
0	**All candidate combinations of parametric functions** ▪ Included total of 54 combinations, including 36 under Approach #1 (separately fitted), 9 under Approach #2 (jointly fitted, time-constant HR), and 9 under Approach #3 (jointly fitted, time-varying HR)	54

1	**Initial exclusions based on clinical plausibility** ▪ 12 out of 54 combinations of parametric distributions resulted in implausible crossing of the survival curves for pembrolizumab and observation, and were therefore excluded from base-case consideration ▪ 6 of these 12 combinations were also excluded based on the use of 4-year RFS and DMFS in KEYNOTE-054 (adjuvant stage III melanoma setting) as lower bounds	42
2	**Statistical fit based on MSE vs. observed RFS** ▪ MSEs relative to observed RFS and observed DMFS were ranked for all 54 combinations of distributions in each arm ▪ Because MSEs were generally lower in the pembrolizumab arm than the observation arm, statistical fit in the observation arm was prioritized. Combinations ranked among the ten worst-fitting for both RFS and DMFS in the observation arm were therefore excluded (8 combinations excluded)	34
3	**Visual assessment of fit** ▪ Most combinations of distributions produced close visual fits to observed RF → LR, RF → DM, RF → death, RFS, and DMFS in both arms; thus, no further exclusions were applied based on visual inspection alone	34
4a	**External validity of long-term extrapolations in the observation arm [48, 49]** ▪ Predicted RFS and DMFS in the observation arm up to 7 years was required to fall within +/- 5 percentage points of external RFS and DMFS data ▪ 14 combinations were retained for further consideration based on this external validity assessment. All of these combinations used either log-normal (under Approach #1) or exponential (under Approaches #1, 2, or 3) for RF → DM	14
4b	▪ The base case was selected from these 14 combinations based on MSE ranking and agreement with external RFS and DMFS data ▪ External validations of the base case against digitized external RFS and DMFS data were very encouraging and provided strong empirical support for the model's long-term survival projections in the observation arm	1
5	**Plausibility of predicted incremental benefit with pembrolizumab vs. observation** ▪ Relative to other combinations of distributions that met the external validity requirement, the selected base case predicted moderate incremental RFS and DMFS benefits with pembrolizumab vs. observation	1 **Base case:** Approach 1 / log-normal / log-normal

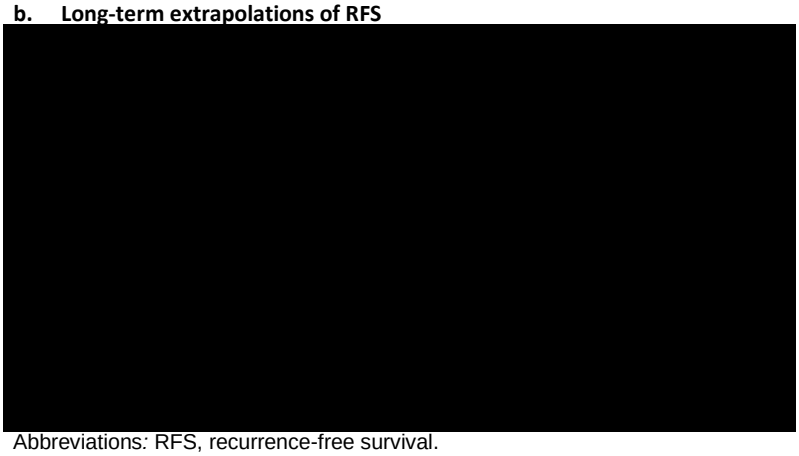
Modeled and observed RFS and DMFS

Below is presented the internal validation of the modeled and observed RFS and DMFS. For more information about the assessment and validation process, please see Appendix G.

Figure 14: Internal validations of predicted vs. observed RFS and DMFS under the base case

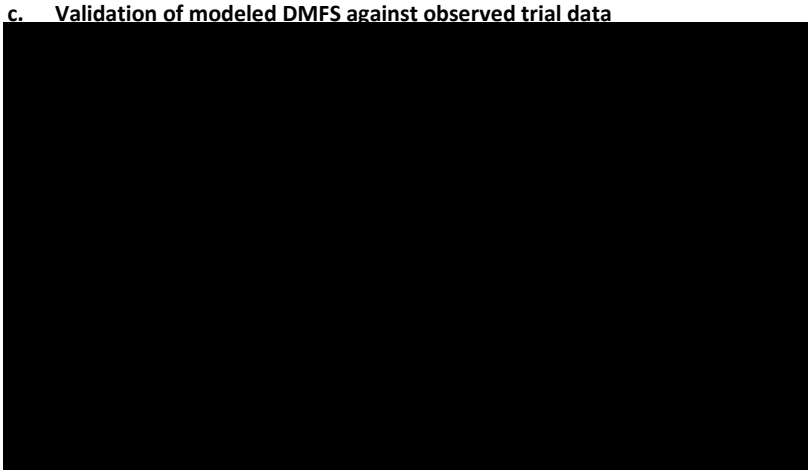
a. Validation of modeled RFS against observed trial data

b. Long-term extrapolations of RFS



Abbreviations: RFS, recurrence-free survival.

c. Validation of modeled DMFS against observed trial data



d. Long-term extrapolations of DMFS (time to distant metastases or death)

Further, the external validation of long term RFS, DMFS and OS is presented in Figure 15 and the modeled and observed RFS, DMFS and OS by year can be seen in Tabel 37, Tabel 38 and Tabel 39. Again, for more details please see Appendix G.

Figure 15: External validations of long-term base-case RFS, DMFS, and OS in the observation arm

a. External validations of RFS

Tabel 37: Modeled and observed RFS by year

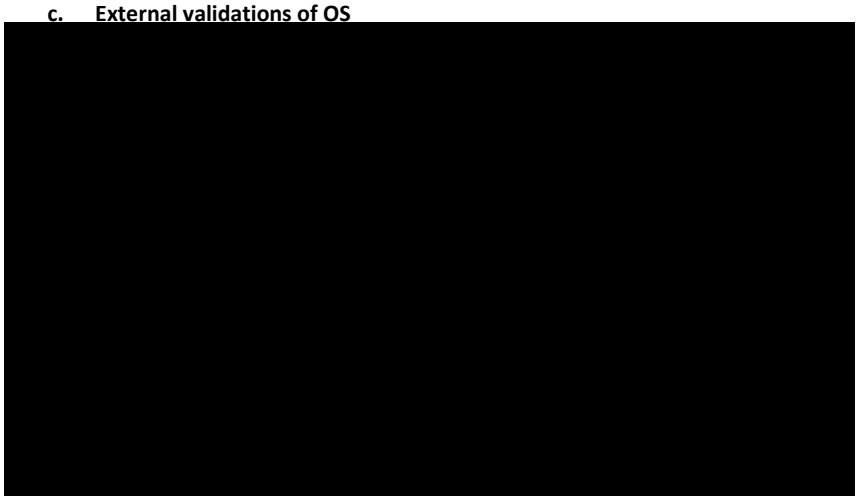
RFS by year:	1	2	3	4	5	6	7	10
Pembrolizumab, modeled RFS	90,4%	80,4%	71,8%	64,5%	58,2%	52,8%	48,0%	40,9%
Pembrolizumab, observed RFS (KEYNOTE-716)	90,8%	81,2%	71,0%	--	--	--	--	--
Observation, modeled RFS	85,5%	71,7%	60,9%	52,5%	45,8%	40,2%	35,5%	29,1%
Placebo, observed RFS (KEYNOTE-716)	83,4%	73,2%	61,3%	--	--	--	--	--
Real-world cohort, observed RFS (Bajaj et al. 2020)	87,4%	64,6%	56,7%	48,7%	44,2%	41,4%	33,6%	--
Real-world cohort, observed rwRFS (Merck)	85,6%	70,9%	58,0%	50,1%	43,2%	37,5%	35,0%	23,2%

b. External validations of DMFS

Tabel 38: Modeled and observed DMFS by year

DMFS by year:	1	2	3	4	5	6	7	10
Pembrolizumab, modeled DMFS	94,9%	86,2%	77,6%	69,8%	62,9%	56,8%	51,4%	42,3%
Pembrolizumab, observed DMFS (KEYNOTE-716)	94,5%	87,9%	76,8%	--	--	--	--	--
Observation, modeled DMFS	91,5%	80,1%	69,9%	61,2%	53,8%	47,4%	41,9%	32,5%
Placebo, observed DMFS (KEYNOTE-716)	89,8%	81,7%	68,9%	--	--	--	--	--
Real-world cohort, observed rwDMFS (Merck)	93,2%	79,5%	68,2%	61,0%	52,7%	46,4%	43,7%	29,4%

c. External validations of OS



Tabel 39: Modeled and observed OS by year

OS by year:	1	2	3	4	5	6	7	10
Pembrolizumab, modeled OS	99,1%	96,3%	92,0%	86,9%	81,3%	75,4%	69,4%	54,4%
Observation, modeled OS	98,5%	94,7%	89,2%	82,8%	76,0%	69,2%	62,6%	46,2%

Real-world cohort, observed OS (Bajaj et al. 2020)	96,4%	91,4%	86,7%	81,4%	79,8%	74,3%	74,3%	--
Real-world cohort, observed OS (Bleicher et al. 2020)	96,6%	88,5%	78,3%	72,1%	67,6%	60,3%	54,8%	52,9%
Real-world cohort, observed rwOS (Merck)	96,8%	92,1%	84,1%	79,2%	71,9%	64,1%	61,5%	42,2%
Real-world cohort, observed OS (Kanaki et al. 2019)	--	--	--	--	64,3%	--	--	43,6%

Cure Assumption

In base case analysis, the model provides the functionality to apply a cure assumption among patients who achieve long-term RFS. This analysis was conducted based on several considerations. Namely, as observed in a retrospective study by Lee et al. (2017), the 5-year cumulative incidence for physician-detected relapse was less than 10% across all substages for stage II and levelled off at three years for stage IIB and two years for stage IIC[32]. The 5-year cumulative incidence for image-detected relapse in this study was also close to the pattern of physician-detected relapse[32]. Sundhedsstyrelsens "pakkeforløb for modermærkekræft" also clearly describes that that patients with stage II melanoma are discharged beyond 5 years [1]. Furthermore, two retrospective care series studies indicate that 71.0%-90.7% of recurrences were recorded in the first 5 years of follow up for stage I/II and stage I/II+III melanoma patients and there are very few recurrences occurring beyond 10 years for patients with stage II melanoma who remain recurrence-free[58, 59]. Lastly, similar cure assumptions have been utilized in numerous past NICE and Canadian Agency for Drugs and Technologies in Health appraisals for early-stage cancers[60-64].

When the cure assumption is applied, the per-cycle risks of locoregional recurrence and distant metastases from the recurrence-free state (as estimated under the scenario with no cure assumption) is reduced by a user-specified percentage (95% by default) for patients who achieve RFS ≥ a specified time point (10 years by default).

Starting from an earlier user-modifiable time point (7 years by default), the percentage reduction in recurrence risk begins to linearly increase from 0% at 7 years to 95% by 10 years onward. The same percentage risk reduction is applied to the risk of transitions from recurrence-free to death, subject to the constraint that this risk must always be at least as high as background mortality in each cycle.

8.3.3. Transitions from locoregional recurrence to distant metastases

Following the third interim analysis of KEYNOTE-716, patient-level time-to-event data from the trial were used to estimate exponential rates and standard errors for transitions starting from locoregional recurrence (i.e., locoregional recurrence → distant metastases and locoregional recurrence → death). The exponential distribution is commonly assumed when estimating transition probabilities starting from intermediate health states in a Markov model, as the hazard rate does not depend on time since entry into the health state.

Exponential models were used to estimate the cause-specific hazards of each transition starting from the locoregional recurrence state (i.e., LR → DM and LR → death) within the adjuvant pembrolizumab and placebo arms of KEYNOTE-716 (Table 40). The analytical sample included patients in each arm who experienced LR as their first RFS failure event. Among these patients, an exponential parametric function was fitted to time (in weeks) from entry into the LR state until DM. Patients without this transition were censored at the end of follow-up. In both arms, no direct transitions from LR → death were observed; therefore, there were no censorings due to competing risk events in the sample. Because no direct transitions from LR → death were observed in the KEYNOTE-716 sample, the cause-specific hazard for this transition in both arms was approximated based on the exponential rate of RF → death in the placebo arm of KEYNOTE-

716 (i.e., the arm with the higher rate of RF → death), based on the expectation that the rate of LR → death would be at least as high.

No adjustments were performed for rechallenge or crossover regimens within the locoregional recurrence state; thus, the resulting transition probabilities incorporate any effect of crossover/rechallenge on risk of distant metastases or death. This approach was considered appropriate because, in real-world practice, patients experiencing locoregional recurrence would be eligible to receive adjuvant treatments of resected stage III melanoma (including pembrolizumab). The exponential rate of LR → DM was lower for observation than pembrolizumab, as expected given that crossover in the placebo arm of KEYNOTE-716 occurred more frequently than rechallenge in the pembrolizumab arm. (As of the 04-Jan-2022 data cutoff date, only 4 patients in the pembrolizumab arm had initiated rechallenge with pembrolizumab, while 49 patients in the placebo arm had initiated crossover with pembrolizumab.)

Table 40: Weekly exponential rates of transitions starting from locoregional recurrence based on KEYNOTE-716 data (base case)

Model arm	LR → DM		LR → Death		Source
	Exponential rate	SE	Exponential rate	SE	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; IA3, interim analysis 3; LR, locoregional recurrence; SE, standard error. Note: Within each cycle, the transition probability from locoregional recurrence → death is set equal to the maximum of the estimated probability based on parametric modeling and background mortality (Office of National Statistics, 2017-2019).

A scenario analysis with other data sources that provides the option to use e.g. original data sources for transitions from LR state can be found in Appendix G.

8.3.4. Transitions from distant metastases to death

In each model arm, the transition probability from distant metastases to death was assumed to depend on the distribution of first-line treatments for advanced melanoma received in that arm. First-line treatment options included the following: pembrolizumab, nivolumab + ipilimumab, encorafenib + binimetinib. The base-case analysis also considered the cost of second-line therapies for advanced melanoma in each adjuvant treatment arm; however, survival within the distant metastases state was assumed to depend on the choice of first-line therapy.

Estimation of mean survival by first-line treatment for advanced melanoma

For each advanced melanoma treatment option, exponential models of OS and progression-free survival (PFS) were estimated using the following approach:

- For Pembrolizumab in the advanced melanoma setting, exponential models of OS and PFS were fitted to patient-level time-to-event data from the Pembrolizumab 10 mg/kg Q3W arm of the KEYNOTE-006 trial, a multicenter, randomized, open-label phase III trial among ipilimumab-naïve unresectable or advanced melanoma patients[42]. The resulting exponential curves were plotted alongside the corresponding Kaplan-Meier curves to assess fit. (Note: The base-case analysis used OS and PFS data from the all-comers population of KEYNOTE-006, which included a mix of patients with and without prior therapy for advanced melanoma. In a scenario analysis, OS and PFS data from the previously untreated subgroup of KEYNOTE-006 were used in order to more precisely estimate the efficacy of Pembrolizumab as a first-line treatment of advanced

melanoma. Further, it does not change the effect on the OS estimates that KN006 is dosed 10 mg/kg and KN716 is using 2 mg/kg as dosing regimen. KN006 was one of the first KEYNOTE trials, and following studies have shown that a lower dosage gives the same effect. [65, 66]

- For other advanced treatment regimens consisting of Nivolumab+ Ipilimumab and Encorafenib + Binimetinib, the hazard ratios (HRs) for OS and PFS vs. Pembrolizumab were obtained from a network meta-analysis (NMA) of trials conducted in advanced melanoma(Efficacy and safety of first-line treatments for patients with advanced melanoma: systematic literature review and network meta-analysis. [Data on file]., November 30, 2021).

The exponential fit is chosen as distribution to describe PFS and OS due to the following reasons:

1. The exponential fit to the OS curve is determining the transitions. Also, the exponential fit provides a good visual fit to the OS data.
2. The exponential fit to the PFS curve is a simplifying assumption and is only used for utility and disease management costs. It is not used to inform the transition from DM-> death. Further, utility values were the same for the pre-progression and post-progression in the DM health state.
3. The OS curve was varied by 10% in the DSA with minimal impact on the results; therefore, varying the PFS by 10% would have even less of an influence on the ICER.
4. While the exponential fit may overestimate PFS from about Week 15 through Week 60, it then would underestimate PFS after Week 60 through the maximum time horizon because the PFS graph shows a clear reduction in the hazard from Week 15 onward.

Table 41 reports the exponential rates of OS and PFS failure estimated for Pembrolizumab in the advanced setting; based on these rates. Figure 16 presents modeled OS and PFS alongside the corresponding Kaplan-Meier curves from KEYNOTE-006. Table 42 summarizes the HRs of OS and PFS failure with other treatment regimens versus Pembrolizumab obtained from the NMA and resulting estimates of mean OS and PFS (in weeks) for each regimen.

Table 41: Exponential models of OS and PFS with Pembrolizumab in the advanced melanoma setting

Advanced regimen	Exponential model of OS		Exponential model of PFS		Source
	Rate	SE	Rate	SE	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival; PFS, progression-free survival; SE, standard error.

Note: For Pembrolizumab in the advanced melanoma setting, exponential models of OS and PFS were fitted to patient-level data from the Pembrolizumab arm of KEYNOTE-006 trial (all-comers population).

Table 42: HRs of OS and PFS failure with other treatment regimens vs. Pembrolizumab in the advanced melanoma setting

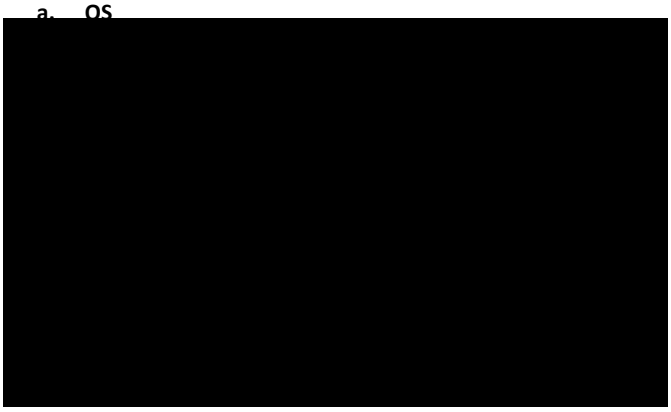
Advanced regimen	HR of death vs. Pembrolizumab		HR of progression or death vs. Pembrolizumab		Expected survival in distant metastases state (weeks)	
	HR	SE of ln(HR)	HR	SE of ln(HR)	OS	*PFS*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SE, standard error.
Note: For other advanced treatment regimens, HRs for OS and PFS vs. Pembrolizumab were each obtained from a network meta-analysis (NMA) of trials conducted in advanced melanoma. For encorafenib + binimetinib, HRs were based on NMA results for the first-line BRAF-mutant population. For other treatments not targeting BRAF, HRs were based on NMA results for the first-line BRAF all-comers population were used.

Figure 16: Exponential models of OS and PFS compared with Kaplan-Meier curve extractions for Pembrolizumab in the advanced melanoma setting (all-comers population of KEYNOTE-006)

a. OS



b. PFS

Estimation of the hazard rate of death from distant metastases by adjuvant treatment arm

In each model arm, the exponential hazard rate of distant metastases → death was assumed to depend on: the market shares of first-line treatments received for advanced melanoma (Table 43); and the expected survival associated with each advanced melanoma treatment regimen (Table 42 above). Specifically, expected OS (starting from distant metastases) was calculated in each model arm as a weighted average of expected OS associated with different first-line treatments for advanced melanoma based on the market shares of first-line advanced treatments in that arm. Expected OS in each model arm was then translated into a weekly hazard rate. Expected PFS was similarly estimated for each model arm based on the distributions of first-line treatments received, and the ratio of mean PFS to mean OS was estimated for each arm; in each model arm, this ratio was used to calculate utility values and weekly disease management costs within the distant metastases state (accounting for the proportion of time spent pre- vs. post-progression within this state.

In the base case, market shares in each model arm were estimated based on the following assumptions:

[redacted] and applied in the model as subsequent treatment for patients who transition from recurrence-free to distant metastases. For patients in the observation arm who transition from recurrence-free to distant metastases, the model applied the same subsequent treatment that were applied for the pembrolizumab arm.

[redacted] Second-line subsequent treatments in the advanced melanoma setting following progression on first line treatment was also the same for both arms.

The percentages of patients in the table below are further used to calculate the costs in section 8.2.1.

Table 43: Base case market shares of first-line regimens for advanced melanoma by adjuvant treatment arm and eligibility for rechallenge/anti-PD-1/PD-L1s

First-line regimens in advanced setting	First-line market shares, by adjuvant treatment arm and eligibility for anti-PD1/PD-L1s (%)	
	Pembrolizumab	Observation
	Anti-PD-1/PD-L1-eligible	Anti-PD-1/PD-L1-eligible
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

8.4.1. Health state utility values used in the health economic model

Health state utility inputs for the base case and scenario analyses were derived through primary analyses of EQ-5D-5L data collected from the KEYNOTE-716 (data cutoff date: 04-Jan-2022) trial specific for Denmark[67]. Patient reported outcomes were also collected regardless of recurrence/progression status/treatment completion, unless participant withdraws from this portion of the study. The trial study, the EQ-5D-5L questionnaire was administered at baseline (Cycle 1), during treatment in year 1 (at Cycle 5, 9, 13, 17), every 12 weeks during year 2 (Week 60, 72, 84, and 96 from baseline), every 6 months during year 3 (month 30 and 36 from baseline), at the treatment discontinuation visit, and at the 30-day follow-up visit.

Overall, the compliance of EQ-5D reporting was high. The completion, compliance rates and number of missing data is provided in
Tabel 44 below. Compliance is the proportion of participants who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design. Missing by design includes death,

discontinuation, translations not available, and no visit scheduled. Missing data were excluded in the analysis, which only included evaluable records. No additional analyses were completed for missing responses.

Tabel 44: Completion and compliance of EQ-5D

Treatment Visit	Category	Pembrolizumab N = 483 n (%)	Observation N = 486 n (%)
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Treatment Visit	Category	Pembrolizumab N = 483 n (%)	Observation N = 486 n (%)
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Utilities by health state

Base-case utility values for the recurrence-free, locoregional recurrence, and pre-progression distant metastases states therefore were derived through repeated measures regression analyses of patient-level EQ-5D-5L data from the KEYNOTE-716 trial using Danish utility algorithm. At each visit where health state was assessed, the corresponding EQ-5D-5L score was used to characterize utility. 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. Patient-visits with missing EQ-5D-5L responses were excluded.

A Linear mixed effects models with patient level random effects were applied to model EQ-5D scores, assuming compound symmetric structure to account for within-subject correlation due to repeated measurements of EQ-5D over time. The means of the EQ-5D scores are predicted using least square means retrieved from this model.

The KEYNOTE-716-based utility/disutility values for the model were derived from the following two regression models of utility, both of which incorporated patient-level random effects to account for correlation between repeated measurements for the same individual. The dependent variable of both models was EQ-5D-5L utility score.

1. To estimate the utility for RF (without toxicity) and disutility related to grade 3+ AEs, the first regression specification was fitted specifically to patient-visits with a utility measurement that occurred during each patient's recurrence-free period (N=967 patients, with 6.365 unique patient-visits). Independent variables included binary indicators for: the absence of any AE during the patient-visit; and the presence of any other-grade (i.e., grade less than 3) AE during the patient-visit. Utility in the RF state was expected to differ between pembrolizumab and observation only to the extent that risks of AEs differ between these two arms; therefore, pooled estimates were derived for the utility of RF (without toxicity) and AE-related disutility, and this AE-related disutility was applied to each model arm according to observed treatment-specific AE risks.

2. To estimate the utility for LR and utility for DM, a second regression specification was fitted using all patient-visits with a utility measurement (N=969 patients, with 6.512 unique patient-visits). Independent variables included binary indicators for: being in the locoregional recurrence state during the patient-visit; and being in the distant metastases state during the patient-visit. In contrast to the first specification, this specification did

not adjust for the presence/absence of AEs; the rationale was to obtain LR and DM utility estimates that incorporated any AE-related disutility associated with subsequent treatments, as the cost-effectiveness model did not separately apply AE-related disutility due to subsequent treatments within the LR and DM states.

The base case utility estimated for progressive disease among Danish respondents was extracted for use in the present model as the utility associated with post-progression distant metastases (Table 45).

Table 45: Health state utilities in the base case

Health state	Base case: Danish Utilities based on KEYNOTE-716			
	Value	SE	95% CI	Number of responses
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients with early-stage melanoma are more likely to have higher utility compared to later stages. In a 2018 systemic literature review (SLR), the mean utility for patients with stage I/II melanoma was 0.97 (95% CI 0.90-0.98) across eight studies [68]. The same SLR found that patients with stage III or III/IV melanoma had utility values of 0.77 (0.70-0.83) or 0.76 (0.76-0.77); demonstrating that patients with stage III and IV have much worse utility values compared to stage I/II patients. Thus, the utility values for the early stage melanoma patients are more likely to be close to the utility values of the general Danish population.

Disutility related to aging

Age related disutility values from The Danish Medicines Council [69] (Tabel 46) was applied within the model to account for disutility related to aging of the cohort over time. The disutility values are presented in different age brackets provided in Regression coefficients used for the estimation of age-related disutility

Tabel 46: Age related disutility value

Parameter	Utilities	Source
18 - 29	0,871	Danish Medicines Council.[69]
30 - 39	0,848	
40 - 49	0,834	
50 - 69	0,818	
70 – 79	0,813	
80 +	0,721	

In order to account for the fact that the general population's health-related quality of life, on an average, declines with age, the multiplicative method of adjusting age was considered in analysis.

For which, utilities corresponding to starting age of the model is considered as the denominator and the utilities of any other age group as numerator. e.g., if the starting age of the model is 55, then age related disutility corresponding to age 75 is:

Age-related disutility at 75 years = Utility (75 years) /Utility (55 years) = 0.813/0.818= - 0.994

Then this factor is multiplied with life years gained, to get the age adjusted QALY loss for that particular age.

Disutility related to AEs

AE-related disutility was applied as a one-time QALY decrement in the first model cycle. Disutility associated with AEs was calculated in each treatment arm as a function of: treatment-specific AE risks; the mean number of episodes among patients with a given AE; the mean duration of these AEs per episode. The estimated disutility associated with an active grade 3+ AE based on Danish specific utility algorithm of EQ-5D-5L data from the KEYNOTE-716 trial presented in Table 47.

The disutility of an active grade 3+ AE was obtained from the same regression model used to estimate the utility value for RF (without toxicity), based on the coefficient associated with the presence of any grade 3+ AE(s).

Table 47: Utility analysis in the recurrence-free state as a function of AE status, based on Danish utility algorithm on KEYNOTE-716 data

AE status at visit	Estimate	Standard error
[redacted]	[redacted]	[redacted]

Abbreviations: AE, Adverse event

8.5. Resource use and costs

Costs in the adapted model were estimated from the limited societal perspective; therefore, both direct and patient costs were included in the economic evaluation for base case. The following main cost components were considered within the model:

- Adjuvant treatment costs (including drug acquisition and administration)
- Salvage surgery and subsequent adjuvant treatment costs (including drug acquisition and administration) for locoregional recurrence
- Costs associated with disease management by health state
- Terminal care costs (for patients with melanoma-related deaths)
- Costs associated with AEs; and
- Patient costs associated with patient follow up, monitoring and transportation cost

Adjuvant drug acquisition and administration costs

Drug acquisition and administration costs per infusion or pharmacy fill of adjuvant medication were calculated in the model as a function of the list price per drug unit, defined dosing for the medication, relative dose intensity, and unit cost of drug administration. Adjuvant medication dosing schedules were based on the dosing of Pembrolizumab in the KEYNOTE-716 trial. The proportion of patients remaining on Pembrolizumab treatment over time was based on the observed Kaplan-Meier curve for time on treatment up to 17 dosages (~1 year) in KEYNOTE-716. Additional details are provided in the sub-sections below.

Unit drug cost, dosing schedule, and relative dose intensity

Pembrolizumab is available in vials of 100 mg. The list price per vial was retrieved from www.medicinpriser.dk and are presented in Table 48. The defined dosing schedule of Pembrolizumab in the adjuvant setting was a flat dose of 200 mg every 3 weeks or 400 mg every 6 weeks for adult patients and weight-based dosing of 2 mg/kg (200 mg maximum) every 3 weeks for children(Table 49). Based on inputs from a Danish clinical expert MSD assumes that, 30 % of patient will be

treated with Q3W dosing schedule while 70 % patients are on Q6W dosing in recurrence free as well as in locoregional recurrence state. For advanced melanoma setting 40 % uses Q3W while 60 % uses Q6W dosing criteria, as more patients will have a health state that requires closer follow up.

In the base case, the relative dose intensity (as reflected in the Pembrolizumab arm of KEYNOTE-716) was applied to the drug acquisition cost per infusion of adjuvant Pembrolizumab to account for any delays or interruptions in administration (e.g., due to AEs)(Table 49).

Table 48: Unit drug costs for adjuvant treatments

Drug	Strength per unit (mg or MU)	Cost per unit (DKK)
Pembrolizumab	100	23.204,61

Source: www.medicinpriser.dk (accessed December 2021)

Table 49: Dosing schedule and relative dose intensity for adjuvant treatments

Adjuvant regimen	Dosing schedule description	Relative dose intensity (%)
Pembrolizumab	200 mg IV Q3W or 400 mg IV Q6W for adults or 2 mg/kg IV (max of 200 mg) Q3W for children, up to 1 year	98,9%

Abbreviations: IV, intravenous; Q3W, once every 3 weeks.
Sources: KEYNOTE-716, EMA label

Drug administration cost

Drug administration cost per infusion of pembrolizumab was based on DRG-takster 2022[1] as can be seen in Table 50.

Table 50: Unit cost per administration of adjuvant Pembrolizumab

Route	Type of administration	Unit cost per administration or pharmacy dispensing (DKK)	Source
IV	IV infusion	2,041,00	DRG09MA98, DRG-takst 2022,[70]

Abbreviations: DRG, Diagnosis Related Group.

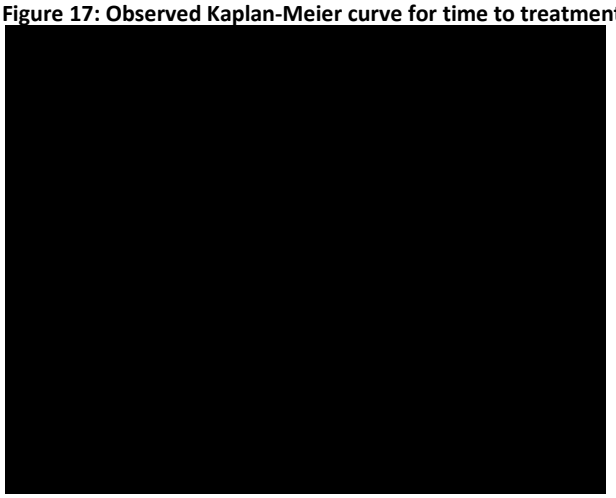
Time on treatment

The proportion of patients remaining on adjuvant Pembrolizumab at each scheduled infusion was based on the observed Kaplan-Meier curve for time to treatment discontinuation in the KEYNOTE-716 trial. In the trial, patients randomized to adjuvant Pembrolizumab received treatment for up to 1 year or until completion of 17 doses (i.e., the number of scheduled doses over 1 year). Based on this maximum duration, there were sufficient follow-up data from the trial to directly observe time on adjuvant treatment, without the need for extrapolation. From the KM data it can be seen that the percentage of patients on treatment drops to zero at the end of 60 weeks. The median actual follow-up duration is 20,5 months overall.

As illustrated in Figure 17, a small percentage of patients in the Pembrolizumab arm of KEYNOTE-716 remained on adjuvant therapy beyond 1 year, as the protocol allowed patients to complete all 17 doses past the 1-year point if there had been earlier delays in treatment. Within this model, the costs of adjuvant Pembrolizumab treatment are modelled based on a fixed interval of every 3 weeks, and so the costs of the 17th dose are applied at t = 48 weeks from baseline for the percentage of patients still on adjuvant treatment at this time point. Therefore, the model does not use the

portion of the Kaplan-Meier curve beyond the scheduled 1-year treatment period (represented by the dashed line). Below is the median time on therapy and Kaplan-Meier curves for time on treatment by arm presented. All patients discontinued or completed primary study treatment as of database cutoff for IA3 so no censoring is present in the KM curve.

Figure 17: Observed Kaplan-Meier curve for time to treatment discontinuation in both treatment arms of KEYNOTE-716



Tabel 51: Estimated Median and mean time on treatment

Treatment	N	Number of events (%)	Estimated median time in months	Estimated mean time in months	SE of estimated mean time in months	95% CI of estimated mean time in months
Pembrolizumab	483	483 (100.0)	11.072	9.253	0.172	(8.916, 9.589)
Observation	486	486 (100.0)	11.072	10.168	0.132	(9.909, 10.426)

Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method
Time on Treatment is defined as the time from the date of initial dose until the date of last dose
Number of Events is defined as number of participants who had discontinued or completed primary study treatment at the database cutoff date
Database Cutoff Date: 04JAN2022

Salvage surgery and subsequent adjuvant treatment costs for locoregional recurrence

Subsequent treatment in the locoregional recurrence state also included one-time costs of salvage surgery for a proportion of patients who enter this state. Frequencies of salvage surgery were based on observed percentages of patients with each type of surgery in the KEYNOTE-716 trial, pooling across both treatment arms. The percentages of patients with each surgery were calculated using as the denominator the number of patients in KEYNOTE-716 who experienced locoregional recurrence as their first RFS failure event. In the table below the number of patients getting each type of salvage surgery is described.

Tabel 52: No. of patients receiving salvage surgery

Salvage Surgery	No. of patients
In-transit metastases resection or other surgery	22
Lymphadenectomy	39
Skin lesion resection	23

Patients who enter the locoregional recurrence state may also receive an adjuvant treatment approved for resected high-risk stage III melanoma. Drug acquisition and administration costs for these subsequent adjuvant treatments were applied as lump-sum costs upon entry into the locoregional recurrence state and were estimated using approaches similar to those described for adjuvant pembrolizumab in the resected stage IIB/IIC melanoma setting. The mean duration of each adjuvant treatment in the stage III setting was estimated using two different approaches:

1. **Base case: Use reported time on treatment (ToT) statistics:** In the base case, observed rates of discontinuation in pivotal trials of adjuvant treatments for stage III melanoma[40, 71-74] were used to calculate the exponential rate of discontinuation for each treatment. Treatment duration was capped at the label-recommended maximum duration of each treatment.

2. **Scenario analysis:** In a scenario analysis, mean duration of each adjuvant treatment in the stage III setting was instead approximated using exponential models of RFS, up to the maximum duration of each treatment. For Pembrolizumab in the stage III adjuvant setting, an exponential rate of RFS failure (weekly rate parameter: 0,0030; standard error: 0,0002) was fitted using patient-level data from the KEYNOTE-054 trial. For other adjuvant treatments in this setting, HRs of RFS failure for each treatment vs. Pembrolizumab were obtained from a systematic literature review and NMA and were applied to the exponential rate of RFS failure for Pembrolizumab.

Table 53: Base case market shares of subsequent adjuvant treatment

Stage III adjuvant treatments in the LR state	Stage III adjuvant treatment market shares, by model arm (%)			
	Pembrolizumab	Pembrolizumab	Pembrolizumab	Observation
	Rechallenge-eligible	Anti-PD-1/PD-L1-eligible	Anti-PD-1/PD-L1-ineligible	Anti-PD-1/PD-L1-eligible
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 54: Treatment duration inputs for subsequent adjuvant treatments of resected stage III melanoma

Stage III adjuvant regimen	Drug component (same as regimen for monotherapies)	Week of initiating drug component	Max. ToT (weeks)	Based on exponential model of RFS	Based on reported ToT statistics

				HR of RFS failure vs. pembro	SE of ln(HR)	Expo. rate of discontinuation	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Expo, exponential; HR, hazard ratio; RFS, recurrence-free survival; SE, standard error; ToT, time on treatment

The unit drug administration costs associated with IV infusion was applied for intravenously administered therapies. Dabrafenib and trametinib are both orally administered and were assumed to incur no administration cost.

Subsequent drug acquisition and administration cost for distant metastases

Within the model, drug acquisition and administration costs associated with subsequent therapies were applied as a one-time cost upon entry into the distant metastases state. All patients who enter the distant metastases state were assumed to receive an active first-line treatment for advanced melanoma. In addition, a subset of these patients was assumed to receive an active second-line treatment for advanced melanoma.

The model considered first- and second-line treatment options as applied in Danish clinical practice [7].

Unit drug costs and dosing schedules

List prices of drugs used in the advanced melanoma setting were retrieved from www.medicinpriser.dk and are presented in Table 55.

Table 55: Unit drug costs for first-line and second-line therapies for advanced melanoma

Drug	Unit drug cost calculation (strength #1)		Unit drug cost calculation (strength #2)	
	Strength per unit (mg)	Cost per unit (DKK)	Strength per unit (mg)	Cost per unit (DKK)
Pembrolizumab	100	23.204,61	n/a	n/a
Ipilimumab	50	25.653,53	200	102.385,55
Nivolumab	100	9.168,23	240	22.003,74
Dabrafenib	50	257,53	75	386,00
Trametinib	0,5	453,14	2	1.610,39
Encorafenib	50	189,77	75	284,76
Binimetinib	15	255,61	n/a	n/a

Source: www.medicinpriser.dk, accessed December 2021

Dosing schedules are shown in Table 56. The dosing schedules for treatments of advanced melanoma were based on EMA labels.

For intravenous drugs with weight-based or BSA-based dosing, the model provides the option to assume that vial-sharing either is or is not allowed. For base case analysis, vial-sharing is allowed where the number of vials required per infusion were calculated based on the average body weight derived from Danish Medicines Council[47] or average BSA

of patients in the KEYNOTE-716 trial population. The assumption about vial-sharing is based on input from the coordinating lead pharmacologist at Sygehusapotek Region Sjælland.

When vial-sharing is allowed, and the number of vials required per infusion are calculated based on the average body weight or average BSA of patients. For example, number of vials for a weight-based therapy is calculated as patient weight in kg multiplied by the required dose per kg (i.e., mg/kg) divided by the strength per vial (i.e., mg/vial, based on the vial strength associated with the lowest cost per mg). When vial-sharing is not allowed, the number of vials required per infusion were estimated based on a log-normal distribution of patient weights or BSA, using the mean and standard deviation values reported for patients. This approach calculates the proportion of patients requiring different number of vials based on the estimated percentage of patients who fall into the corresponding weight or BSA interval. The prescribed BSA-based or weight-based dose for each drug was used to calculate various intervals of BSA or weight ranges. The strength of the vial is used to calculate how many vials will be needed for each BSA or weight interval. Then, using lognormal distribution, the percentages of patients requiring various amounts of the dose is calculated. The number of vials and the percentages are summed over to estimate the number of vials required when vial sharing is not allowed.

Under the scenario analysis, vial-sharing is not allowed, and the number of vials required per infusion were estimated based on a log-normal distribution of patient weight from The Danish Medicines Council, using the mean and standard deviation reported for patients in the KEYNOTE-716 trial. This approach calculates the proportion of patients requiring different number of vials based on the estimated percentage of patients who fall into the corresponding weight or BSA interval.

Table 56: Dosing schedules for first-line and second-line therapies for advanced melanoma

Regimen	Drug component (for combination therapies)	Dosing schedule description
Pembrolizumab	n/a	200 mg IV Q3W or 400 mg IV Q6W
Ipilimumab	n/a	3 mg/kg IV Q3W, up to 4 doses
Nivolumab + ipilimumab	Ipilimumab (in combination)	3 mg/kg IV Q3W, up to 4 doses
	Nivolumab (in combination)	1 mg/kg IV Q3W, up to 4 doses
	Nivolumab (maintenance)	240 mg IV Q2W or 480 mg IV Q4W, starting 3 weeks after last ipilimumab dose
Encorafenib + binimetinib	Encorafenib (in combination)	450 mg once daily, oral
	Binimetinib (in combination)	45 mg twice daily, oral

Abbreviations: IV, intravenous; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; Q6W, once every 6 weeks.
Source: NICE Pathway: Melanoma (last updated 17 March 2021)

Drug administration cost

Unit costs of intravenous drug administration were based on the DRG-takst 2022[70] (Table 57 and Table 58). In case of combination therapy such as nivolumab + ipilimumab it was considered that the administration cost of nivolumab was covered by ipilimumab administration. Oral therapies were assumed to require no administration cost in Denmark.

Table 57: Unit costs of drug administration in the advanced melanoma setting

Route	Type of administration	Unit cost per administration or pharmacy dispensing (DKK)		Source
		First	Subsequent	
IV	IV infusion	2.041,00	2.041,00	DRG09MA98, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]

Abbreviations: DRG: Diagnosis Related Group

Table 58: Drug administration costs in the advanced melanoma setting

Regimen	Drug component (for combination therapies)	Type of administration	Unit cost per administration or (DKK)
Pembrolizumab (Q3W)	n/a	IV infusion	2.041,00
Pembrolizumab (Q6W)	n/a	IV infusion	2.041,00
Ipilimumab	n/a	IV infusion	2.041,00
Nivolumab + ipilimumab	Ipilimumab (in combination)	IV infusion	2.041,00
	Nivolumab (in combination)	Assumed to be covered by ipilimumab administration	0,00
	Nivolumab Q2W (maintenance)	IV infusion	2.041,00
	Nivolumab Q4W (maintenance)	IV infusion	2.041,00
Encorafenib + binimetinib	Encorafenib (in combination)	Oral drug dispensing	0,00
	Binimetinib (in combination)	Oral drug dispensing	0,00

Time on treatment, market shares, and total regimen costs

ToT of first-line treatment regimens for advanced melanoma were approximated using the exponential rates of PFS failure to approximate treatment discontinuation rates. Mean time on treatment were assumed to be 21 weeks for all second-line regimens(As an exception, ipilimumab as monotherapy or in combination were capped at the maximum duration of 12 weeks.) The mean duration of 21 weeks is consistent with the NICE submissions for ipilimumab in previously untreated advanced melanoma (TA319)[75] and Pembrolizumab in advanced melanoma not previously treated with ipilimumab (TA366)[76], both of which assumed a fixed duration of 7 cycles at an interval of Q3W for second-line treatment. This assumption is also in line with the NICE submission for Pembrolizumab in patients previously treated with ipilimumab for advanced melanoma (TA357), which considered a mean treatment duration of 6.86 cycles (20.57 weeks) based on mean PFS in the Pembrolizumab arm of the KEYNOTE-002 trial[77].

Based on the estimated discontinuation rate and (when applicable) the maximum duration of each drug component in a regimen, the model estimated the mean total cost of each treatment regimen in the first- and second-line setting. The mean cost of first- and second-line treatment was then calculated for each adjuvant treatment arm as a weighted

average based on the first- and second-line market shares within each adjuvant treatment arm. Base-case market shares in the first-line setting are described previously in section 8.3.4, table 43 and base-case market shares in the second-line setting were estimated using similar approaches; however, the model assumed that a proportion of patients who enter the distant metastases state receive no active second-line treatment due to death or rapid progression after the first-line regimen. This proportion was approximated as 1 minus the ratio of second-line to first-line patients based on market research data (Ipsos Oncology Monitor, July 2021). The number of patients in first line is 1625 and in second line is 596 which corresponds that 63% of patients are on no active second-line treatment due to death or rapid progression after the first-line regimen.

Table 59: Maximum durations of first-line treatment regimens in the advanced melanoma setting

Regimen	Drug component (if applicable)	Maximum ToT (weeks)[1]	Exponential rate of discontinuation[2]
Pembrolizumab Q3W	n/a	No maximum	0,017
Pembrolizumab Q6W	n/a	No maximum	
Nivolumab + ipilimumab	Ipilimumab (in combination)	12	0,012
	Nivolumab (in combination)	12	
	Nivolumab (maintenance, Q2W)[3]	No maximum	
	Nivolumab (maintenance, Q4W)[3]	No maximum	
Encorafenib + binimetinib	Encorafenib	No maximum	0,009
	Binimetinib	No maximum	

Abbreviations: ToT, time on treatment.

Notes:

[1] The NICE-recommended maximum duration of each drug component in a regimen was obtained from the NICE Pathway: Melanoma.

[2] Exponential rates of discontinuation are based on the reported ToT statistics.

[3] Nivolumab maintenance therapy is assumed to begin 12 weeks after initiation of the nivolumab + ipilimumab regimen for patients remaining on treatment after the initial course of nivolumab in combination with ipilimumab.

Table 60: Time on treatment for second-line treatment regimens in the advanced melanoma setting

Regimen	Drug component (if applicable)	Mean number of infusions or pharmacy dispensing's
Pembrolizumab Q3W	n/a	7,00
Pembrolizumab Q6W	n/a	3,50
Ipilimumab	n/a	4,00
Nivolumab + ipilimumab	Ipilimumab (in combination)	4,00
Nivolumab + ipilimumab	Nivolumab (in combination)	4,00
Nivolumab + ipilimumab	Nivolumab Q2W (maintenance)	4,50

Regimen	Drug component (if applicable)	Mean number of infusions or pharmacy dispensing's
Nivolumab + ipilimumab	Nivolumab Q4W (maintenance)	2,25
Encorafenib + binimetinib	Encorafenib (in combination)	5,25
Encorafenib + binimetinib	Binimetinib (in combination)	5,25

Note: Mean time on treatment is assumed to be 21 weeks for all second-line regimens. As an exception, ipilimumab as monotherapy or in combination is capped at the maximum duration of 12 weeks.

Table 61: Market shares of second and later-line regimens for advanced melanoma by adjuvant treatment arm and eligibility for rechallenge/anti-PD-1/PD-L1s

Second-line regimens in advanced setting	Second-line market shares, by adjuvant treatment arm (%)		
	Pembrolizumab	Pembrolizumab	Observation
	Anti-PD-1/PD-L1-eligible	Anti-PD-1/PD-L1-ineligible	Anti-PD-1/PD-L1-eligible
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PD-1, programmed cell death protein; PD-L1, programmed cell-death ligand-1; SACT, Systemic Anti-cancer therapy

Notes:

[1] In both model arms, a proportion of patients was assumed to receive no active second-line treatment due to death or rapid progression after the first-line regimen. This proportion was approximated as 1 minus the ratio of second line to first-line patients based on market research data (Ipsos Oncology Monitor).

[2] In the Pembrolizumab arm, the market shares of subsequent treatments were based on observed usage of subsequent treatments among patients treated with adjuvant Pembrolizumab under clinical practice in Denmark.

[3] In the observation arm, the market shares of BRAF inhibitors were based on observed usage of these subsequent treatments among patients treated with adjuvant Pembrolizumab.

Cost of AEs

The types of AEs included in the model are those considered likely to have a significant impact in terms of either resource utilization or HRQoL. Unit costs per episode for the included AE types were obtained from the DRG-takst 2022[70]. Total AE cost was calculated by multiplying cost per episode with AE incidence rate and mean number of episodes per patient with the AE (weeks). Below is the unit cost of each AE's taken into consideration in Table 62.

Table 62: Unit costs of AE management

Adverse events	Cost per episode (DKK)	Source for cost*
Diarrhea	6.756,00	DK529B/06MA11 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Hyperthyroidism	1.845,00	DE032/10MA01 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)

Adverse events	Cost per episode (DKK)	Source for cost*
Asthenia	569,00	65TE01- Telefon- og email konsultation, samt skriftlig kommunikation ved prøvesvar (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Fatigue	4.460,00	DR539A/23MA03 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Alanine aminotransferase increased	4.460,00	DR740B/23MA03(DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Aspartate aminotransferase increased	4.460,00	DR740B/23MA03 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Decreased appetite	1.954,00	DR630/10MA98(DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Hyperglycaemia	4.460,00	DR739/23MA03(DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Arthralgia	2.015,00	DM255/08MA17 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Back pain	1.645,00	DM549/08MA98(DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Myalgia	4.460,00	DR529/23MA03 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Pain in extremity	1.909,00	DM796/08MA15(DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Basal cell carcinoma	19.518,00	DQ828W/09MA03 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Pruritus	2.041,00	DL299/09MA98(DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Rash	2.041,00	DR219/09MA98(DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Rash maculo-papular	2.041,00	DR219/09MA98 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)
Hypertension	1.318,00	DI109/05MA98 (DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen)

Source: [70]

Disease management cost by health state

Unit costs for resource use elements in the recurrence-free, locoregional recurrence, and distant metastases states were obtained from DRG Takst 2022[70]. The resource use frequencies for RF, LR and DM state are mentioned in Table 65, Table 66 and Table 67.

Disease management costs in the recurrence-free and locoregional recurrence states

Medical resource use per week in the recurrence-free states included outpatient provider visits and radiologic assessments. Resource use frequencies and resource use per week were based on the recommended schedule of surveillance for high risk resected stage IIC disease according to Danish clinical guidelines for melanoma[1]. These frequencies were time-varying to account for recommended reductions in the frequency of screening among patients who have remained recurrence-free for longer periods of time.

Disease management costs in the distant metastases state

Medical resource use in the progression-free and progressive disease states included medical oncologist, nurse, laboratory tests, and radiologic assessment(Table 67).

The distant metastases state in the present model encompasses both pre- and post-progression distant metastases. Therefore, in each adjuvant treatment arm, disease management costs per week in the distant metastases state were computed as a weighted average of resource use associated with pre- versus post-progression distant metastases, based on the estimated proportion of time spent progression-free within the distant metastases state.

Terminal care costs

Patients who transit to death were assumed to incur a one-time cost associated with palliative/terminal care if the death is melanoma related. Deaths that occurred from the distant metastases state were used as a proxy for melanoma-related deaths within the model, based on the expectation that the vast majority of deaths due to melanoma would be preceded by a metastatic disease recurrence. This assumption was also supported by the substantially higher hazards of death from the distant metastases state compared with the recurrence-free or locoregional recurrence states.

The terminal care costs were based on costs during the last 30 days before death as reported by DRG Takst 2022[70]. The cost was converted into weekly cost for further calculations. The effective terminal care cost is given in Table 63.

Table 63: Unit cost for Terminal Care

Terminal care costs	Cost (DKK)	Source
Cost incurred on assumption of 30 days care	60.330,00	DRG Takst 2022 [70]
Total terminal care costs per week	13.874,66	

Table 64: Unit costs of healthcare resources

Resource use element	Unit cost (DKK)	Sources
Salvage surgery		
In-transit metastases resection or other surgery	55.736,00	DRG09MP15, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
Lymphadenectomy	9.591,00	DRG09PR02, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
Skin lesion resection	3.698,00	DRG09PR03, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
Outpatient visits		
Medical oncologist	1.316,00	Cost per hour,[78]
Radiation oncologist	1.316,00	Cost per hour,[78]
General practitioner	143,44	Cost per hour,[78]
Plastic surgeon	1.316,00	Cost per hour,[78]
Cancer specialist nurse	554,00	Cost per hour,[78]
Laboratory tests		
Complete blood count	40,00	https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/undersoegelser-og-proever/klinisk-biokemi/blodproever/haematologiske-kvantiteter/[79]

Complete metabolic panel	79,00	NPU03577, Rigshospitalets Lab portal [80]
Lactate dehydrogenase	24,00	NPU19658, Rigshospitalets Lab portal [80]
Radiologic exams		
CT scan of abdomen/pelvis	1.979,00	DRG30PR07, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
CT scan of chest	1.979,00	DRG30PR07, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
MRI of brain	2.416,00	DRG30PR02, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
CT scan of brain	1.979,00	DRG30PR07, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
PET/CT scan	2.411,00	DRG30PR06, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
Bone scintigraphy	3.389,00	DRG36PR07, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
Echography	1.462,00	DRG30PR11, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]
Chest x-ray	1.640,00	DRG30PR18, DRG-takst 2022, "Takstvejledning. 2022." Sundhedsdatastyrelsen[70]

Abbreviations: CT, Computerized tomography; MRI, Magnetic resonance imaging; PET, positron emission tomography

Table 65: Frequencies of resource use in the recurrence-free state

Resource use element	Recurrence-free – monthly resource use up to year 3 No Adjuvant treatment		Recurrence-free – monthly resource use, up to year 3 Adjuvant treatment		Recurrence-free – monthly resource use, years 3-5 (For both treatment arms)		Recurrence-free – monthly resource use, years 5-10 (For both treatment arms)	
	% Patients	Resource use	% Patients	Resource use	% Patients	Resource use	% Patients	Resource use
Outpatient visits								
Medical oncologist	100%	0,22	100%	0,22	100%	0,17	0%	0,00
General practitioner	0%	0,00	0%	0,00	0%	0,00	100%	0,08
Cancer specialist nurse	100%	0,22	100%	0,22	100%	0,17	0%	0,00
Radiologic exams								
PET/CT scan	100%	0,14	100%	0,19	0%	0,00	0%	0,00
Total Cost (DKK):	124,80 per week		155,60 per week		35,84 per week		2,75 per week	
Sources:	Danish Health and Medicines Authority		Danish Health and Medicines Authority[1]		Danish Health and Medicines Authority		Danish Health and Medicines Authority [1]	

	[1]		[1]	

Abbreviations: CT, Computerized tomography; PET, positron emission tomography; RF, recurrence-free.

Notes:

[1] Monthly resource use frequencies were converted into costs per 1-week cycle.

[2] Resource use frequencies are based on Danish clinical guidelines[1]. The schedule of routine surveillance was assumed to be the same regardless of whether adjuvant treatment is received

Table 66: Frequencies of resource use in the locoregional recurrence state

Resource use element	LR – salvage surgery (one-time resource use upon entering health state)		LR – monthly resource use	
	% Patients	Resource use	% Patients	Resource use
Salvage surgery				
In-transit metastases resection or other surgery	21,57%	1,38	0%	0,00
Lymphadenectomy	38,24%	1,00	0%	0,00
Skin lesion resection	22,55%	1,00	0%	0,00
Outpatient visits				
Medical oncologist	0%	0,00	100%	0,22
Cancer specialist nurse	0%	0,00	100%	0,22
Radiologic exams				
PET/CT scan	0%	0,00	100%	0,17
Echography	0%	0,00	100%	0,13
Total Cost (DKK):	21.112,52 one-time cost		185,03 per week	
Sources:	Danish Health and Medicines Authority [1] and KEYNOTE-716 data; [3]		Danish Health and Medicines Authority [1] and KEYNOTE-716 data; [3]	

Abbreviations: CT, Computerized tomography; MRI, Magnetic resonance imaging; PET, positron emission tomography; LR, locoregional recurrence.

Notes:

[1] Monthly resource use frequencies were converted into costs per 1-week cycle.

[2] Resource use frequencies are based on DK clinical guidelines [1]. The schedule of routine surveillance was assumed to be the same regardless of whether adjuvant treatment is received.

[3] Frequencies of salvage surgery are based on observed percentages of patients with each type of surgery, and the average number of surgeries among patients who underwent each surgery, in KEYNOTE-716. The percentage of patients with each surgery was calculated among those who experienced locoregional recurrence as their first recurrence.

Table 67: Frequencies of resource use in the distant metastases state

Resource use element	Distant metastases (pre progression) – subsequent monthly resource use	Distant metastases (post progression) – monthly resource use

	% Patients	Resource use	% Patients	Resource use
Medical oncologist	100%	0,22	100%	0,22
Cancer specialist nurse	100%	0,22	100%	0,22
Complete blood count	100%	0,42	100%	0,42
Complete metabolic panel	100%	0,42	100%	0,42
Lactate dehydrogenase	100%	0,42	100%	0,42
PET/CT scan	100%	0,17	100%	0,17
Total Costs (DKK):	201,69 per week		201,69 per week	
Sources:	Danish Health and Medicines Authority [1]		Danish Health and Medicines Authority[1]	

Abbreviations: CT, Computerized tomography; DM, Distant metastases; MRI, Magnetic resonance imaging; PET, positron emission tomography.
Notes:
[1] Monthly resource use frequencies associated with distant metastases (pre-progression) and distant metastases (post-progression) were converted into costs per 1-week cycle.
[2] One-time resource use estimates are based on the frequencies associated with Danish Health and Medicines Authority[1]
[3] Based on the resource use frequencies while receiving first- or second-line treatment in TA319[75]
[4] Based on resource use while not receiving treatment in TA319[75]

Patient Cost

According to requirements of the Danish Medicines Council, a transportation cost of DKK 140 in travelling for IV administration, CT scan and consultation visits, was included in the model. Also, a cost of DKK 181 based on the average hourly wage (after tax) was applied to the patients for taking into account per hour infusion time and time spent at follow up visit[78].

The IV administration infusion time for several regimens are given in Table 68 below:

Table 68: IV administration infusion time according to treatment combination

Treatment	Hours spent per week	Treatment Cycles	Patient hours required for each administration
Pembrolizumab, Q3W dosing	0,17	3,00	0,50
Pembrolizumab, Q6W dosing	0,08	6,00	0,50
Nivolumab (in combination)	0,33	3,00	1,00
Ipilimumab (in combination or monotherapy)	0,50	3,00	1,50
Nivolumab (monotherapy or maintenance, Q2W dosing)	0,50	2,00	1,00
Nivolumab (monotherapy or maintenance, Q4W dosing)	0,25	4,00	1,00

The per regimen IV infusion cost is obtained as the product of hours spent per week for infusion of each regimen and per hour infusion cost. The transportation cost for each administration is calculated by dividing the transportation cost

of DKK 100 by the treatment cycles. The per infusion cost of each regimen and the transportation cost per administration is given in Table 69.

Table 69: IV infusion time cost and transportation cost according to treatment combination

Cost per patient	Per Infusion Cost (DKK)	Transportation Cost per Administration (DKK)
Pembrolizumab, Q3W dosing	29,83	33,33
Pembrolizumab, Q6W dosing	14,92	16,67
Nivolumab (in combination)	59,67	33,33
Ipilimumab (in combination or monotherapy)	89,50	33,33
Nivolumab (monotherapy or maintainence, Q2W dosing)	89,50	50,00
Nivolumab (monotherapy or maintainence, Q4W dosing)	44,75	25,00

Patient monitoring and follow-up cost

Patient monitoring and follow-up costs is calculated for all the three health states say recurrence free, locoregional recurrence and distant metastases are based on various resource used. The follow up costs are calculated by calculating the sum product of unit cost per patient follow-up with percentage of patients utilizing the resources, the average number of resources used and patient hours.

Patient Transportation Cost

A transportation cost for each of the outpatient visits, laboratory visits and radiological exams was also considered. It is calculated by calculating the sum product of unit cost for transportation, percentage of patients using the resource and average number of resources used. Lastly the monitoring and follow up costs along with transportation costs are sum totaled to get the patient costs for each health state.

Below is the

Table 70.a-c for each of the health states for patient monitoring and follow up the cost.

Table 70

a. Patient monitoring cost and follow up cost for recurrence free state

Resource Use Element	Unit Cost for patient follow-up	Unit cost for trans-portation	Patient Hours	Recurrence free-monthly resource use up to year 3 (No Adjuvant treatment)		Recurrence free-monthly resource use up to year 3 (Adjuvant treatment)		Recurrence free-monthly resource use years 3 – 5 (For both arms)		Recurrence free-monthly resource use years 5 – 10 (For both arms)	
				% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use	% Patients	Resource Use
Medical Oncologist	179	100	0,50	100%	0,22	100%	0,22	100%	0,17	0%	0,00
General Practioner	179	100	0,50	0%	0,00	0%	0,00	0%	0,00	100%	0,08

Cancer specialist Nurse	179	100	0,50	100%	0,22	100%	0,22	100%	0,17	0%	0,00
PET/ CT scan	179	100	1,00	100%	0,14	100%	0,19	100%	0,00	0%	0,00
Total patients follow up cost per 1-week cycle (DKK):				14.87 per week		17,15 per week		6,86 per week		1,72 per week	
Total transportation cost per 1-week cycle (DKK):				8.30 per week		9,58 per week		3,83 per week		1,92 per week	
Total Costs (DKK):				23.17per week		26,74 per week		10,69 per week		3,63 per week	

b. Patient monitoring cost and follow up cost for locoregional recurrence state

Resource Use Element	Unit Cost for patient follow-up	Unit cost for transportation	Patient Hours	Locoregional recurrence - salvage surgery (one-time resource use upon entering health state)		Locoregional recurrence - monthly resource use	
				% Patients	Resource Use	% Patients	Resource Use
In transit metastases resection or other surgery	179	100	0,00	21,57%	1,38	0%	0,00
Lymphadenectomy	179	100	0,00	38,24%	1,00	0%	0,00
Skin lesion resection	179	100	0,00	22,55%	1,00	0%	0,00
Medical Oncologist	179	100	0,50	0%	0,00	100%	0,22
Cancer specialist Nurse	179	100	0,50	0%	0,00	100%	0,22
PET/ CT scan	179	100	1,00	0%	0,00	100%	0,17
Echography	179	100	0,50	0%	0,00	100%	0,13
Total patients follow up cost per 1-week cycle (DKK):				0,00 per week		18,75 per week	
Total transportation cost per 1-week cycle (DKK):				0,00 per week		8,94 per week	
Total Costs (DKK):				0,00 per week		27,70 per week	

c. Patient monitoring cost and follow up cost for distant metastasis state

Resource Use Element	Unit Cost for patient follow-up	Unit cost for transportation	Patient Hours	Distant metastases (pre progression) – subsequent monthly resource use		Distant metastases (post progression) – monthly resource use	
				% Patients	Resource Use	% Patients	Resource Use
Medical Oncologist	179	100	0,50	100%	0,22	100%	0,22

Cancer specialist Nurse	179	100	0,50	100%	0,22	100%	0,22
Complete Blood Count	179	100	0,00	100%	0,42	100%	0,42
Complete Metabolic Panel	179	100	0,00	100%	0,42	100%	0,42
Lactate dehydrogenase	179	100	0,00	0%	0,42	0%	0,42
PET/ CT scan	179	100	1,00	100%	0,17	100%	0,17
Total patients follow up cost per 1-week cycle (DKK):				16,01 per week		16,01 per week	
Total transportation cost per 1-week cycle (DKK):				8,94 per week		8,94 per week	
Total Costs (DKK):				24,95 per week		24,95 per week	

8.6. Results

8.6.1. Base case overview

The model calculates expected costs, LY gained, QALYs and ICERs, including incremental cost per LY gained and incremental cost per QALY gained. The base case overview is presented in the table below:

Tabel 71: Base case overview

Comparator	Observation
Type of model	A Markov cohort model with a 1-week cycle length
Time horizon	40,7 years (life time)
Treatment line	Adjuvant treatment. Subsequent treatment lines are included.
Measurement and valuation of health effects	Utility associated with each melanoma-related health state and disutilities associated with adverse events and general aging are applied. Danish population weights were used to estimate health-state utility values
Included costs	Drug acquisition costs Drug administration costs Adverse event costs Disease management costs Terminal care costs Patient costs
Dosage of pharmaceutical	Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for adult patients for up to 17/9 cycles and weight-based dosing of 2 mg/kg (200 mg maximum) every 3 weeks for children for up to 17 cycles
RF → LR	Intervention: Log-normal

	Comparator: Log-normal
RF → DM	Intervention: Log-normal Comparator: Log-normal
RF → Death	Intervention: Exponential Comparator: Exponential

8.6.2. Base case results

Base-case results (with 3,50% discounting of costs and health benefits till 35 years and 2,50% thereafter) are presented in Tabel 72. Over a 40,7-year time horizon, total costs were DKK 1.574.156 for Pembrolizumab and DKK 1.181.356 for observation. Total QALYs over the 41-year time horizon were estimated to be 9,76 for Pembrolizumab and 8,61 for observation. Total LYs were estimated to be 10,83 and 9,57 years, respectively, for Pembrolizumab vs. observation.

The resulting ICER in terms of incremental cost per QALY gained was DKK 339.858 for Pembrolizumab vs. observation. The ICER in terms of incremental cost per LY gained was estimated to be DKK 311.648. These results indicate that Pembrolizumab is cost-effective as an adjuvant treatment following complete resection of high-risk stage IIB/IIC melanoma.

Differences in total costs across the treatment arms were largely driven by adjuvant treatment costs and by subsequent treatment costs (the latter being lower for Pembrolizumab; Table 73). Disease management costs (excluding anti-cancer treatment) were also lower in the Pembrolizumab arm (DKK 42.192) vs. the observation arm (DKK 42.946), reflecting the lower incidence of disease recurrence achieved with Pembrolizumab, especially in later stages. This was also true for terminal care costs, which were lower for Pembrolizumab compared to observation (DKK 5.889 vs. 7.235).

Tabel 72: Base-case results

Technologies	Total costs (DKK)	Total QALYs	Total LYs	ΔCosts (DKK)	ΔQALYs	ΔLYs	ICER of Pembrolizumab vs. comparator (DKK/QALY)	ICER of Pembrolizumab vs. comparator (DKK/LY)
Pembrolizumab	1.574.156	9,76	10,83	-	-	-	-	-
Observation	1.181.356	8,61	9,57	392.799	1,16	1,26	339.858	311.648

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Table 73: Base-case disaggregated costs and effectiveness

Outcomes	Pembrolizumab	Observation
Costs (DKK)		
Total costs	**1.574.156**	**1.181.356**
Adjuvant treatment costs	655.083	0
Drug acquisition costs	636.266	0
Drug administration costs	18.817	0
Salvage surgery and subsequent adjuvant treatment costs for LR	16.019	82.357
Salvage surgery costs	3.845	4.463

Drug acquisition costs	12.174	73.696
Drug administration costs	0	4.198
Subsequent treatment costs for DM	845.662	1.039.858
Drug acquisition costs	825.462	1.015.016
Drug administration costs	20.200	24.842
Adverse event costs	824	441
Disease management costs	42.192	42.946
RF state	22.588	16.964
LR state	3.572	6.278
DM state	16.032	19.704
Terminal care costs	5.889	7.235
Patient Cost	8.486	8.519
Effectiveness		
Quality-adjusted life years	9,765	8,609
Recurrence-free	8,159	6,458
Locoregional recurrence	0,337	0,590
Distant metastases	1,272	1,563
AE-related disutility	-0,003	-0,002
Age-related disutility	10,831	9,571
Life years	8,967	7,086
Recurrence-free	0,374	0,654
Locoregional recurrence	1,490	1,831
Distant metastases	9,765	8,609

Abbreviations: DM, distant metastases; LR, locoregional recurrence; RF, recurrence-free

8.7. Sensitivity analysis

8.7.1. Results of scenario and one-way deterministic sensitivity analyses

To assess the robustness of the model results, deterministic sensitivity analyses (DSAs) and scenario analyses were conducted by varying one model input or assumption at a time. The table below Table 74 provides a complete list of the sensitivity analyses assessed and the resulting ICERs. Results from the 20 most influential sensitivity analyses are also shown graphically in tornado diagram format Figur 18 below. Sensitivity analyses in the tornado diagrams are sorted from the widest to narrowest range of ICER values to highlight parameters with the strongest influence on the cost-effectiveness results.

Across the sensitivity analyses, the incremental cost per QALY for Pembrolizumab vs. observation ranged from DKK 182.562 to DKK 479.194. The ICER was comparable to the base-case value when using a 30-year time horizon and increased in the scenario that used a short time horizon of 20 years. Because large proportions of patients in both arms were expected to survive beyond 20 and 30 years, these alternative time horizons were considered as scenario analyses only. The ICER decreased to DKK 182.562/QALY when no discounting on costs and effectiveness was considered for Pembrolizumab and observation arm. The ICER was also very sensitive to a scenario with weight based dosing of pembrolizumab with a decrease to DKK 203.353/QALY.

ICERs of Pembrolizumab vs. the observation arm were also sensitive to parameters determining transition probabilities starting from the recurrence-free state. Among the 11 scenario analyses that used alternative parametric distributions

to model transitions from the recurrence-free state, all resulted in ICERs below the DKK 1.215.921/QALY willingness-to-pay threshold. (This threshold approximately corresponds to the World Health Organization threshold of three times gross domestic product [GDP] per capita per disability-adjusted life year. GDP per capita in the Denmark was DKK 405.307 in 2020 according to the World Bank[81]. Among the 13 alternative combinations of distributions that met all criteria with respect to statistical fit, visual assessment, and external validity, the highest ICERs was measured in the scenario analysis that used separately fitted Generalized gamma/ Log-Normal distributions (DKK 479.194) to model RF → LR / RF → DM transitions; this scenario represented the upper limit of incremental effectiveness for Pembrolizumab vs. observation across these scenarios.

The ICER was not sensitive to parameters determining transition probabilities starting from the locoregional recurrence state, showing minimal changes when: varying the cause-specific hazards of LR → DM or LR → death; using EHR data alone to estimate these cause-specific hazards; or using alternative assumptions regarding market shares of subsequent adjuvant treatments for stage III melanoma in the LR state.

The ICER increased moderately when excluding the costs of second-line treatments in the distant metastases state. The ICERs was dominated in the scenario that did not apply age-related disutility and increased in the scenario using KEYNOTE-716 data to inform utility in all health states (including post-progression distant metastases). However, the ICER was not very sensitive to high/low variation in state-specific utility values. The cost-effectiveness results were also not much sensitive to the assumptions of 100% relative dose intensity for adjuvant Pembrolizumab; vial-sharing being allowed; or a 400 mg Q6W (rather than 200 mg Q3W) adjuvant Pembrolizumab dosing schedule. The results also were not sensitive to variations in drug administration costs; patient weight; state-specific medical management costs; terminal care costs; or AE-related costs and dis-utilities.

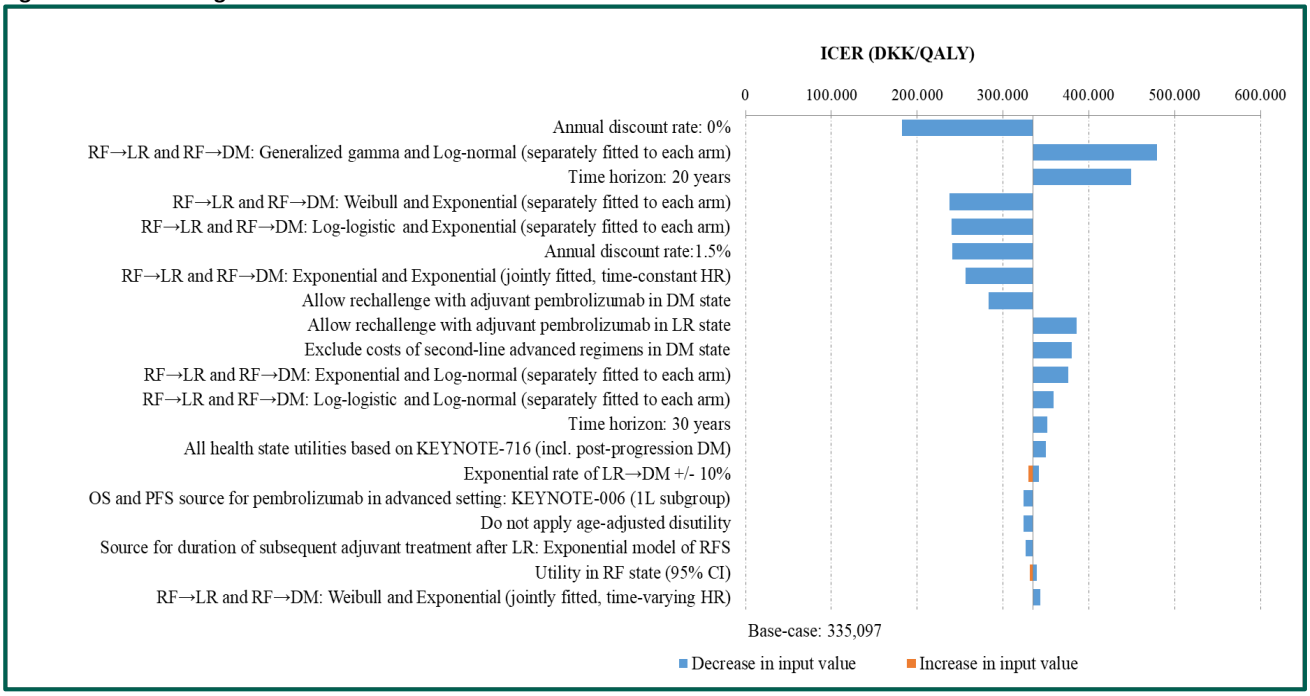
Table 74: Tabular DSA and scenario analysis results

Sensitivity analysis	ICER vs. comparator (DKK/QALY)	
	Low input value	High input value
Base case	335.097	
Weight based dosing of pembrolizumab	203.353	
Time horizon and discounting		
Time horizon: 20 years	449.557	
Time horizon: 30 years	351.374	
Annual discount rate: 0%	182.562	
Annual discount rate:1.5%	240.637	
Efficacy and transition probabilities		
RF→LR and RF→DM: Generalized gamma and Log-normal (separately fitted to each arm)	479.194	
RF→LR and RF→DM: Log-logistic and Log-normal (separately fitted to each arm)	358.729	
RF→LR and RF→DM: Gompertz and Log-normal (separately fitted to each arm)	363.223	
RF→LR and RF→DM: Weibull and Log-normal (separately fitted to each arm)	352.336	
RF→LR and RF→DM: Log-logistic and Exponential (separately fitted to each arm)	239.946	
RF→LR and RF→DM: Weibull and Exponential (separately fitted to each arm)	237.424	
RF→LR and RF→DM: Exponential and Log-normal (separately fitted to each arm)	375.693	
RF→LR and RF→DM: Exponential and Exponential (separately fitted to each arm)	256.254	
RF→LR and RF→DM: Log-normal and Exponential (separately fitted to each arm)	221.131	

RF→LR and RF→DM: Weibull and Exponential (jointly fitted, time-constant HR)	247.883	
RF→LR and RF→DM: Exponential and Exponential (jointly fitted, time-constant HR)	256.254	
RF→LR and RF→DM: Weibull and Exponential (jointly fitted, time-varying HR)	343.425	
RF→LR and RF→DM: Exponential and Exponential (jointly fitted, time-varying HR)	315.921	
LR→DM and LR→Death: Use estimates based on electronic health record data	335.097	
Exponential rate of LR→DM +/- 10%	341.798	329.483
Exponential rate of LR→Death +/- 10%	335.104	335.066
Exponential rates of OS and PFS failure with treatments for advanced melanoma +/- 10%	331.140	338.119
OS and PFS source for pembrolizumab in advanced setting: KEYNOTE-006 (1L subgroup)	324.069	
Subsequent therapies for advanced melanoma		
Source for duration of subsequent adjuvant treatment after LR: Exponential model of RFS	325.974	
Exclude costs of second-line advanced regimens in DM state	379.747	
Allow rechallenge with adjuvant pembrolizumab in LR state	385.841	
Allow rechallenge with adjuvant pembrolizumab in DM state	283.339	
Drug acquisition and administration costs		
Unit cost of simple IV drug administration +/- 10%	334.238	335.955
Mean patient weight +/- 10%	339.138	331.055
Percent receiving Q6W dose of adjuvant pembrolizumab in RF state: 30%	337.069	
Do not apply relative dose intensity to adjuvant pembrolizumab	341.144	
Do not allow vial-sharing	328.330	
Disease Management Cost		
Medical management costs in RF state (per week, up to year 3) +/- 10%	333.372	336.821
Medical management costs in RF state (per week, years 3-5) +/- 10%	335.063	335.130
Medical management costs in RF state (per week, years 5-10) +/- 10%	335.091	335.103
Salvage surgery costs upon LR state entry (one-time cost) +/- 10%	335.150	335.044
Medical management costs in LR state (per week) +/- 10%	335.323	334.871
Medical management costs in pre-progression DM state (per week) +/- 10%	335.225	334.969
Medical management costs in post-progression DM state (per week) +/- 10%	335.277	334.916
Terminal care cost (one-time cost) +/- 10%	335.213	334.980
Apply terminal care cost to: All deaths	335.753	
AE-related costs		
Cost of AEs +/- 10%	335.064	335.129
Consider drug-related AE data in the overall population	335.101	
Utilities		
Utility in RF state (95% CI)	339.481	331.023
Utility in LR state (95% CI)	332.940	337.036
Utility in pre-progression DM state (95% CI)	334.069	336.061
Utility in post-progression DM state (95% CI)	333.651	336.457
All health state utilities based on KEYNOTE-716 (incl. post-progression DM)	350.080	
Do not apply age-adjusted disutility	324.207	
Disutility from AEs (95% CI)	335.193	335.001
Do not apply AE-related disutility	334.753	

Abbreviations: AE, Adverse event; CI, confidence interval; DM, distant metastases; LR, locoregional recurrence; RF, recurrence-free

Figur 18: Tornado diagram



**Indicates sensitivity analyses in which pembrolizumab is dominated by the comparator

Note: Each blue bar represents either an alternative scenario analysis or a sensitivity analysis in which an input value was decreased to the lower limit of its plausible range. Each orange bar represents a sensitivity analysis in which an input value was increased to the upper limit of its plausible range.

To illustrate the significance of price for the ICER, the table below show the AIP for pembrolizumab at different discount rates and the corresponding ICER, until the ICER becomes negative.

Tabel 75: AIP for pembrolizumab at different discount rates and the corresponding ICER

Pembrolizumab Cost (DKK for 200 mg)	Discount Rate	ICER (DKK/QALY)
23,205	0%	340,806
20,884	10%	290,103
19,724	15%	264,752
18,564	20%	239,400
17,403	25%	214,049
16,243	30%	188,698
13,923	40%	137,995
12,763	45%	112,643
11,602	50%	87,292
10,442	55%	61,940
9,282	60%	36,589
8,122	65%	11,237
6,961	70%	-14,114

8.7.2. Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted to estimate the probability of Pembrolizumab being cost-effective relative to observation, based on different willingness-to-pay thresholds. A Monte-Carlo simulation with 1,000 iterations was conducted. In each iteration, the model inputs were randomly drawn from the distributions specified in Appendix J. The model also has an option for random seeds (any negative number) in PSA setup sheet to obtain reproducible results. If user want to reproduce same PSA results for fix number of iteration every time, then the seed value should not be changed.

Uncertainty in the transition probabilities from the recurrence-free health state for Pembrolizumab and observation was represented using multivariate normal distributions (or univariate normal for the exponential rates of recurrence-free → death), as this distribution reasonably describes the sampling distribution of the mean for many variables.

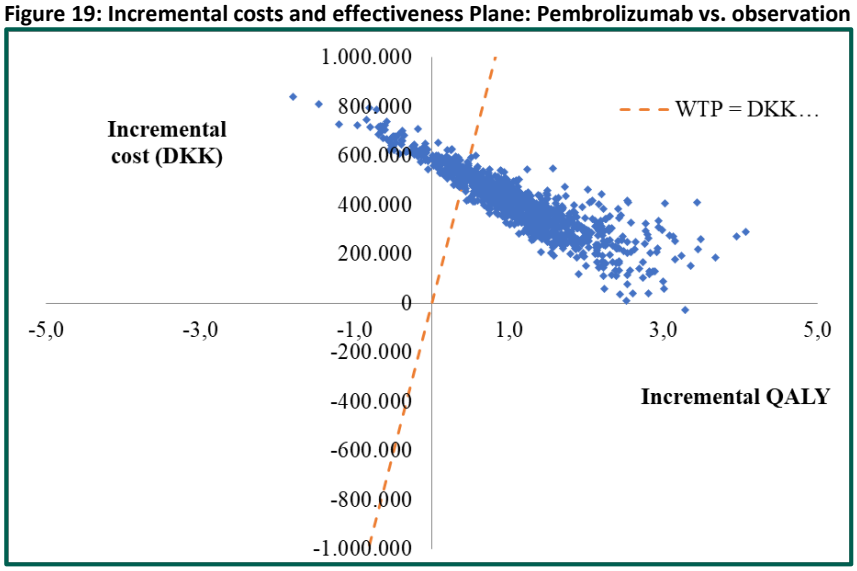
Normal distributions were used to vary exponential rates of transitions from the locoregional recurrence health state under no subsequent adjuvant treatment; and exponential rates of OS and PFS failure with Pembrolizumab in the advanced melanoma setting. Log-normal distributions were assumed for: HRs of DMFS failure with subsequent adjuvant therapies for stage III melanoma vs. no subsequent adjuvant therapy; and HRs of OS and PFS failure for other first-line treatments vs. Pembrolizumab in the advanced melanoma setting. Gamma distributions were assumed for medical management, drug administration, and adverse event cost parameters that can range between zero and infinity. Beta distributions were assumed for utilities of health states to reflect their allowable range between zero and one. For dis-utilities associated with adverse events and age and for utility associated with male gender, normal distributions were used.

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 health state cost values, the standard error for each cost parameter was assumed to be equal to 20% of the mean value.

Across the 1.000 iterations of the PSA, the average incremental cost was DKK 407.086 and the average incremental QALY gain was 1,14 for Pembrolizumab vs. observation. The resulting probabilistic ICER per QALY for Pembrolizumab vs. observation was DKK 339.858/QALY which was just DKK 16.424/QALY lower than the base case ICER of DKK 356.282/QALY.

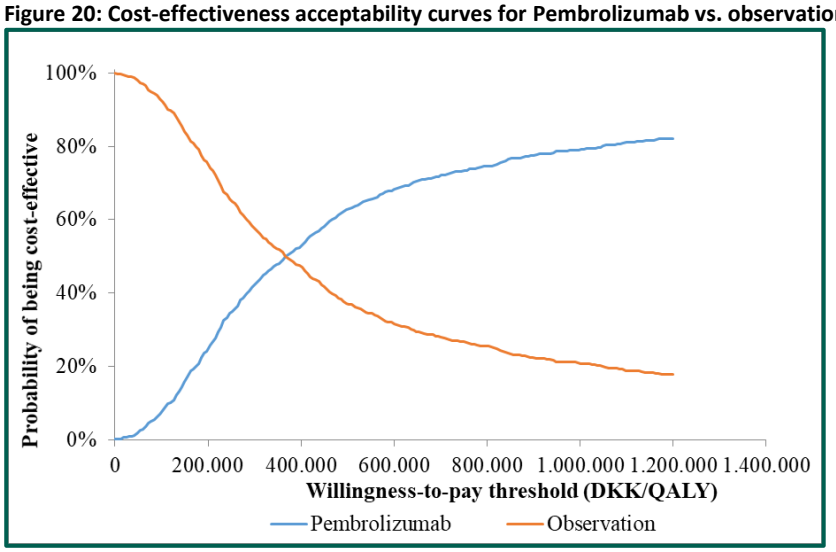
Figure 19 presents the scatterplot of simulated incremental cost and QALYs for Pembrolizumab versus observation. Cost-effectiveness acceptability curves in Figure 20**Fejl! Henvisningskilde ikke fundet.** show the probability of Pembrolizumab being cost-effective versus observation over a range of different willingness-to-pay thresholds. Based on a willingness-to-pay threshold of DKK 1.215.921 per QALY gained, Pembrolizumab had an 82,1 % probability of being cost-effective vs. observation.

Figure 19: Incremental costs and effectiveness Plane: Pembrolizumab vs. observation



Abbreviations: QALY, quality-adjusted life years; WTP, willingness to pay.

Figure 20: Cost-effectiveness acceptability curves for Pembrolizumab vs. observation



Abbreviations: QALY, quality-adjusted life years.

8.8. Budget impact analysis

A budget impact analysis is included into the model to evaluate the impact of adding pembrolizumab in drug formulary, based on the patients who were eligible for adjuvant treatment (stage IIB and IIC). The analysis is based on the same inputs as used for the CE analysis. The different components of budget impact analysis have been described in this section.

8.8.1. Budget impact analysis overview

The budget impact analysis is added in the KN716 cost effectiveness model, adapted with Danish local inputs which estimated the five-year budgetary impact for 194 annual patients who were eligible for adjuvant treatment on stage IIB and IIC. The patients are followed up in the model for 5 years. New patients entering the model in any year will incur

the year 1 cost. The patients moving from first year to second will incur the year 2 and the cycle will be followed accordingly for each year. To evaluate the impact on the budget, the model considers two scenarios:

1. Reference scenario: Observation
2. New scenario: Pembrolizumab

8.8.2. Number of patients

The model uses 194 eligible patients to receive adjuvant treatment annually based on data extraction from. The tables below shows the number of patients in each year of reference and new scenario (if pembrolizumab is recommended). A detailed description of the number of eligible patients can be found in section 5.1

Table 76: Number of patients expected to be treated over the next five-year period - if pembrolizumab is not recommended

Comparator	Year 1	Year 2	Year 3	Year 4	Year 5
Observation	194	194	194	194	194
Pembrolizumab	0	0	0	0	0
Total	194	194	194	194	194

Table 77: Number of patients expected to be treated over the next five-year period - if pembrolizumab is recommended

Comparator	Year 1	Year 2	Year 3	Year 4	Year 5
Observation	62	62	62	62	62
Pembrolizumab	132	132	132	132	132
Total	194	194	194	194	194

8.8.3. Cost calculation of budget impact analysis

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

Table 78: Costs per patient per year

Comparators	Cost Category	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Pembrolizumab	Drug acquisition costs, Stage II	636.266	0	0	0	0
	Drug administration cost, Stage II	18.817	0	0	0	0
	Disease management costs,RF	7.863	6.889	6.147	1.269	1.143
	Disease management costs,LR	253	509	560	532	476
	Disease management costs,DM	214	1.022	1.780	2.289	2.567
	Subsequent treatment cost	87.656	148.144	146.644	132.472	116.105
	AE cost, Stage II	824	0	0	0	0
	Cost per patient	**751.893**	**156.565**	**155.131**	**136.562**	**120.290**
Observation	Drug acquisition costs, Stage II	0	0	0	0	0
	Drug administration cost, Stage II	0	0	0	0	0
	Disease management costs,RF	6.166	5.076	4.291	1.056	915

	Disease management costs,LR	315	708	842	854	808
	Disease management costs,DM	400	1.580	2.462	2.956	3.163
	Subsequent treatment cost	169.331	212.216	185.254	156.964	132.533
	AE cost, Stage II	441	0	0	0	0
	Cost per patient	**176.653**	**219.579**	**192.849**	**161.830**	**137.419**

8.8.4. Budget impact analysis results

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

Table 79: Expected budget impact of recommending pembrolizumab for the current indication

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Pembrolizumab	99.189.765	119.843.724	140.308.601	158.323.862	174.192.513
Observation	-23.304.069	-52.270.995	-77.711.659	-99.060.316	-117.188.654
Total Budget Impact	**75.885.696**	**67.572.729**	**62.596.942**	**59.263.547**	**57.003.859**

9. Discussion on the submitted documentation

Klinisk og økonomisk merværdi

KN-716 demonstrerer en stor klinisk og økonomisk merværdi for patienter med stadie IIB+C melanom behandlet med pembrolizumab sammenlignet med nuværende dansk standardbehandling. Der ses ved den endelig analyse af RFS efter 20,5 mdr. median opfølgningstid en klinisk relevant og signifikant reduktion i risikoen for recidiv og død på 39% (HR=0.61 [95% CI, 0.45-0.82]; p=0.00046) efter behandling med pembrolizumab sammenlignet med placebo og en absolut forskel i RFS raten ved 18 mdr. på 8,7%. Denne forskel opretholdes og øges over tid. Ved den tredje interim analyse efter median opfølgningstid på 26,9 mdr. er der en klinisk relevant og signifikant reduktion i risikoen for fjernmetastaser på 36% (HR=0.64 [95% CI, 0.47-0.88]; p=0.00292) efter pembrolizumab-behandling og en absolut forskel i DMFS raten ved 24 mdr. på 5,9%.

Der var desuden færre patienter, der oplevede fjernmetastase som første recidiv i pembrolizumab-gruppen. Der var 28,2% i pembrolizumab-gruppen, der oplevede en grad 3-4 bivirkning. I placebo-gruppen var det 19,1%. Af disse var 17% relateret til behandlingen i pembrolizumab-gruppen sammenlignet med 4,3% i placebo-gruppen. Der var 38% i pembrolizumab-gruppen og 9% i placebogruppen, der rapporterede en immun-medieret bivirkning eller en infusionsreaktion. Af disse var de fleste grad 1-2 og vurderet som klinisk håndterbare. Overvejelser omkring langtidsbivirkninger er vigtige i adjuverende kliniske studier, og i dette studie blev patienter med bivirkninger af særlig interesse, så som endokrinopatier, håndteret med systemisk corticosteroidbehandling og hormonbehandling. Generelt var bivirkningerne hos patienter behandlet med pembrolizumab velkendte og konsistente med tidligere rapporterede bivirkninger hos patienter behandlet med pembrolizumab både i adjuverende og metastatisk setting. Den aktive behandling med pembrolizumab og risiko for bivirkninger gav ikke et fald i livskvaliteten, hvorfor bivirkningerne må vurderes håndterbare for lægerne og for patienterne. Derved kommer en reduktionen i risikoen for recidiv efter adjuverende behandling med pembrolizumab ikke på bekostning af patienternes livskvalitet.

De signifikante kliniske resultater fra KN-716 understøtter estimaterne af merværdi i vores sundhedsøkonomiske model med en gevinst på 1.04 kvalitetsjusteret leveår sammenlignet med nuværende dansk standard behandling og en favorabel ICER på 377.226 kr.

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 melanom.

Valget af placebo (IV saltvandsinfusion) svarer til dansk klinisk praksis som udelukkende er observation med kliniske og billeddiagnostiske kontroller. Placebo danner derfor grundlag for et relevant statistisk sammenligningsgrundlag.

Der ses en median opfølgningstid på 26,9 mdr. og derved rapporteres modne data på RFS, DMFS, safety og livskvalitet.

Safety/bivirkningsprofilen fra KN-716 er med bivirkninger som er velkendte og håndterbare i klinikken og svarer til bivirkningsprofiler fra andre Keynote-studier i melanom både adjuverende og metastatisk.

Patienterne i KN-716 som svarer til den danske befolkning (90% kaukasiske, median alder 60 år, 60% mænd og overtal af stadie IIB melanomer vs IIC). Med baggrund i patientkarakteristika og behandlingspraksis kan resultater fra KN-716 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. Desuden er der kun inkluderet to pædiatriske patienter i studiet: Én i hver gruppe, hvilket skyldes at melanom er yderst sjældent hos voksen og unge [9]. Som det også fremgår af EPARen ekstrapoleres der farmakokinetiske- og bivirkningsdata fra det kliniske studie keynote-051[82] og det antages at biologiske aspekter af melanom er ens på tværs af aldersgrupper. Denne bridging strategi er vurderet acceptabel i EPARen [13].

På baggrund af interim analyse 1+2 i KN-716 er RFS-og safety data blevet publiceret i en artikel [2]. Data på livskvalitet og DMFS blev præsenteret på kongressen ASCO Juni 2022 [83], [84] og er i november 2022 blevet publiceret som artikler [38, 39]. Data på overlevelse forventes først om cirka 10 år.

Styrker i vores sundhedsøkonomiske model

Vores sundhedsøkonomiske model er baseret på en Markov 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. Der er en stor grad af sikkerhed omkring modellens anvendelse af data vedrørende længde af behandling, da pembrolizumab i KN-716 er begrænset til 1 års behandling, og ToT kunne derfor estimeres meget præcist.

EQ-5D-5L data var tilgængelig direkte fra KN-716 og har således styrket modellens input vedrørende nytteværdi.

Valg af parametrisk funktion efter "transition point" er baseret på:

- Statistiske tests -"goodness of fit"

- Klinisk plausibilitet af "long-term extrapolations" af kontrolarm am er baseret på tilgængelig data og ligger meget tæt herpå
- Klinisk plausibilitet set i forhold til parametrisk funktion

Vi har således et robust ICER estimat, hvilket understreges af vores følsomheds- og scenarieanalyser. Den største følsomhed ses i scenarieanalyser hvor effekt og omkostninger ikke diskonteres, ved vægtbaseret dosering af pembrolizumab og med forskellige parametriske funktion fra "recurrence-free state". Probabilitiske følsomhedsanalyser understøtter også robustheden af base case estimater af gevinst baseret på 1.000 gentagelser.

Begrænsninger i vores sundhedsøkonomiske model

Der vil altid være et element af usikkerhed forbundet med ekstrapolation langt ud over studiets opfølgningstid. Dette gælder særligt for nye interventioner, hvor der ikke findes eksisterende langtidsdata, som kan anvendes til at validere. Derfor har vi også testet RFS med forskellige parametriske funktioner i scenarieanalysen, men alle scenarier lå under det som må antages at være en rimelig tærskelværdi for Danmark. I tillæg hertil, så bør modellens modellering af OS holdes op i mod OS data fra KN716, når det er tilgængeligt.

Der er desuden usikkerhed omkring forventning til dansk klinisk praksis vedrørende dosering af pembrolizumab, hvor Medicinrådet ved tidligere evalueringer har vurderet, at dansk klinisk praksis bør være vægtbaseret dosering fremfor fast dosis.

10. List of experts

N/A

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

Der er i KN-716 studiet foretages en direkte sammenligning mellem den nye behandling (interventionen) og den relevante komparator (placebo).

Der er ikke foretaget en systematisk søgning efter dokumentation for effekt og sikkerhed, da søgningen ikke forventes at tilvejebringe yderligere relevant dokumentation for effekt og sikkerhed, da pembrolizumab er den første og eneste anti-PD-1 inhibitor, der er godkendt i denne patientpopulation.

De relevante publikationer

- Paper: Luke et al 2022: *Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial*, The Lancet, Volume 399, Issue 10336, 30 April–6 May 2022, Pages 1718-1729. (resultater fra interim analyse 1+2) https://doi.org/10.1016/S0140-6736(22)00562-1
- Paper: Luke et al 2019. *KEYNOTE-716: Phase III study of adjuvant therapy with pembrolizumab versus placebo in resected high-risk stage II melanoma*. FUTURE ONCOLOGYVOL. 16, NO. 3. (clinical trial design) https://doi.org/10.2217/fon-2019-0666
- Abstract: Long et al 2022. *Distant Metastasis-free Survival with Pembrolizumab vs Placebo as Adjuvant Therapy in Stage IIB or IIC Melanoma: The Phase 2 KEYNOTE-716 Study*. Præsenteret på ASCO congress 2022.
- Abstract: Khattak et al 2022. *Health-related quality of life (HRQoL) with pembrolizumab (pembro) in resected high-risk stage II melanoma in the phase 3 KEYNOTE-716 study.* Præsenteret på ASCO Congress 2022.
- Abstract: Luke et al. *Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial*. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741. Præsenteret på ESMO Congress 2021.
- Abstract: Luke et al. *Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Updated results from Keynote-716*. Præsenteret på Society of Melanoma Research (SMR) Congress 2021.

Det relevante studie til denne ansøgning er: *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)*. NCT-nummer: NCT03553836. Studiestart den 12. September 2018 og forventet studie slutdato 12. October 2033.

Data brugt til denne ansøgning er data on file i Clinical Study Report[37], det foreløbige udkast til EPAR [13], data fra fra KN-716 publiceret i Luke et al 2022: *Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial*, The Lancet, Volume 399, Issue 10336, 30 April–6 May 2022, Pages 1718-1729 [2] samt data på DMFS [83] og livskvalitet [39] præsenteret på kongressen ASCO 2022.

Appendix B Main characteristics of included studies

Trial name: *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)*	**NCT number:** *NCT03553836*
Objective	*Evaluate the safety and efficacy of pembrolizumab (MK-3475) compared to placebo in participants with surgically resected high-risk Stage II melanoma.*
Publications – title, author, journal, year	*Paper: Luke et al 2022: Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial, The Lancet, Volume 399, Issue 10336, 30 April–6 May 2022, Pages 1718-1729. (resultater fra interim analyse 1+2) https://doi.org/10.1016/S0140-6736(22)00562-1* *Paper: Luke et al 2019. KEYNOTE-716: Phase III study of adjuvant therapy with pembrolizumab versus placebo in resected high-risk stage II melanoma. FUTURE ONCOLOGYVOL. 16, NO. 3. (clinical trial design) https://doi.org/10.2217/fon-2019-0666* *Abstract: Long et al 2022. Distant Metastasis-free Survival with Pembrolizumab vs Placebo as Adjuvant Therapy in Stage IIB or IIC Melanoma: The Phase 2 KEYNOTE-716 Study. Presented at ASCO congress 2022.* *Abstract: Khattak et al 2022. Health-related quality of life (HRQoL) with pembrolizumab (pembro) in resected high-risk stage II melanoma in the phase 3 KEYNOTE-716 study. Presented at ASCO Congress 2022.* *Abstract: Luke et al. Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741. Presented at ESMO Congress 2021.* *Abstract: Luke et al. Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Updated results from Keynote-716. Presented at Society of Melanoma Research Congress 2021.*
Study type and design	*KEYNOTE-716 is an international, double-blind, randomised, placebo-controlled, phase 3 study of pembrolizumab versus placebo as adjuvant therapy in patients with completely resected high-risk stage II melanoma. Patients were randomly assigned to receive adjuvant pembrolizumab or placebo in part 1 of the study (double-blind design) and after recurrence they could receive pembrolizumab as rechallenge or cross-over in part 2 (unblinded design).*
Sample size (n)	*Pembrolizumab: n=487, placebo: n=489*

Main inclusion and exclusion criteria	***Inclusion:*** • *Has surgically resected and histologically/pathologically confirmed new diagnosis of Stage IIB or IIC cutaneous melanoma per American Joint Committee on Cancer (AJCC) 8th edition guidelines* • *Has not been previously treated for melanoma beyond complete surgical resection* • *Has ≤12 weeks between final surgical resection and randomization* • *Has no evidence of metastatic disease on imaging as determined by investigator* • *Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale or Lansky Play-Performance Scale (LPS) score ≥50 for participants ≤16 years old, or a Karnofsky Performance Scale (KPS) score ≥50 for participants >16 and <18 years old* • *Has recovered adequately from toxicity and/or complications from surgery prior to study start* • *Female participants must not be pregnant or breastfeeding, and must agree to use contraception during the treatment period and for at least 120 days after the last dose of study treatment if they are a woman of childbearing potential (WOCBP)* ***Exclusion:*** • *Has a known additional malignancy that is progressing or has required active antineoplastic therapy (including hormonal) within the past 5 years with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy* • *Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment* • *Has recovered adequately from major surgery or the toxicity and/or complications from the intervention prior to starting study treatment* • *WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required* • *Has received prior therapy with an anti-Programmed Cell Death Receptor 1 (PD-1), anti-Programmed Cell Death Receptor Ligand 1 (PD-L1) or anti-Programmed Cell Death Receptor Ligand 2 (PD-L2) agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), OX-40, CD137)* • *Has received prior systemic anti-cancer therapy for melanoma including investigational agents* • *Has received a live vaccine within 30 days prior to the first dose of study treatment* • *Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment* • *Has severe hypersensitivity (≥Grade 3) to any excipients of pembrolizumab* • *Has an active autoimmune disease that has required systemic treatment in the past 2 years* • *Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis* • *Has an active infection requiring systemic therapy*

Trial name: *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)*	**NCT number:** *NCT03553836*
	• *Has a known history of human immunodeficiency virus (HIV) infection* • *Has a known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as Hepatitis C virus ribonucleic acid ((RNA)) [qualitative] is detected) infection* • *Has a history of active tuberculosis (Bacillus tuberculosis)* • *Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator* • *Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study* • *Has had an allogeneic tissue/solid organ transplant*
Intervention	*Biological: Pembrolizumab* *Administered as an intravenous (IV) infusion every 3 weeks (Q3W)* *Other Names:* • *KEYTRUDA®* • *MK-3475* *Pediatric participants receive 2 mg/kg (200 mg maximum) pembrolizumab by intravenous (IV) infusion every 3 weeks (Q3W; 21-day cycles) for up to 17 cycles (up to ~1 year) in a double-blind design in Part 1. Adult participants receive 200 mg pembrolizumab by IV infusion Q3W (21-day cycles) for up to 17 cycles (up to ~1 year) in a double-blind design in Part 1. Participants that complete 17 cycles of pembrolizumab and experience disease recurrence may be eligible to receive additional cycles of pembrolizumab in Part 2 in an open-label design. In Part 2, participants will receive up to 17 cycles (up to ~1 year) of pembrolizumab for local/distant recurrence following disease resection or up to 35 cycles (up to ~2 years) of pembrolizumab for unresectable disease recurrence. Participants with distant metastasis who undergo complete resection will receive 17 cycles (up to ~1 year) of pembrolizumab but can receive up to 35 cycles (up to ~2 years) of pembrolizumab under certain circumstances.*
Comparator(s)	*Drug: Placebo* *Administered as an IV infusion every 3 weeks (Q3W)* *Participants receive saline placebo by IV infusion Q3W (21-day cycles) for up to 17 cycles (up to ~1 year) in a double-blind design in Part 1. Participants that complete 17 cycles of placebo and experience disease recurrence may be eligible to receive pembrolizumab in Part 2 in an open-label design. In Part 2, participants will receive up to 17 cycles (up to ~1 year) of pembrolizumab for local/distant recurrence following disease resection or up to 35 cycles (up to ~2 years) of pembrolizumab for disease that cannot be resected or metastatic disease.*
Follow-up time	*Interim analysis 1: median time from randomization to date of death or database cutoff: 14.3 months (range 1.0 to 26.4 mdr)* *Interim analysis 2: median time from randomization to date of death or database cutoff: 20.5 months (range 4.6 - 32.7 mdr)* *Interim analysis 3: median time from randomization to date of death or database cutoff: 26,9 months (range 4.6 - 39.2 mdr)*

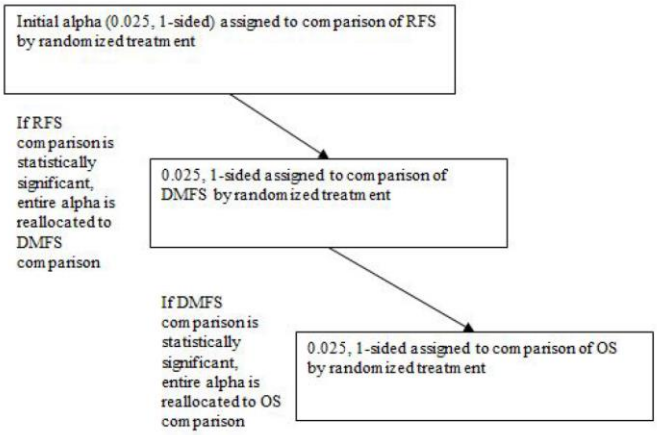
Trial name: *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)*	**NCT number:** *NCT03553836*
Is the study used in the health economic model?	*Yes*
Primary, secondary and exploratory endpoints	**Primary Outcome Measures:** 1. Recurrence-free Survival (RFS) [Time Frame: Up to 4 Years] RFS is defined as the time from randomization to any of the following events: recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) or death due to any cause. **Secondary Outcome Measures:** 2. Distant Metastasis-free Survival (DMFS) [Time Frame: Up to 9 Years] DMFS is defined as the time from randomization to the first diagnosis of a distant metastasis per RECIST 1.1. Distant metastasis refers to cancer that has spread from the original (primary) tumor and beyond local tissues and lymph nodes to distant organs or distant lymph nodes. 3. Overall Survival (OS) [Time Frame: Up to 15 Years] OS is the time from randomization to death due to any cause. 4. Incidence of Adverse Events (AEs) [Time Frame: From time of signing the informed consent form (ICF) until the end of follow-up (up to approximately 39 months)] Percentage of participants experiencing an AE defined as any unfavorable and unintended sign, symptom, disease, or worsening of preexisting condition temporally associated with study therapy and irrespective of causality to study therapy. 5. Incidence of Discontinuations [Time Frame: From time of signing the ICF until the end of study treatment (up to approximately 36 months)] Percentage of participants discontinuing study drug due to an AE. **Protocol-specified exploratory endpoints:** 6. Health-related quality of life using EORTC QLQ-C30 and ED-5D-5L 7. Pharmacokinetic endpoints 8. Analyses to identify novel biomarkers **Endpoints included in this application:** 1. Recurrence-free Survival (RFS) [Time Frame: Up to 4 Years] RFS is defined as the time from randomization to any of the following events: recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) or death due to any cause. 2. Distant Metastasis-free Survival (DMFS) [Time Frame: Up to 9 Years] DMFS is defined as the time from randomization to the first diagnosis of a distant metastasis per RECIST 1.1. Distant metastasis refers to cancer that has spread from the original (primary) tumor and beyond local tissues and lymph nodes to distant organs or distant lymph nodes. 3. Health-related quality of life using EORTC QLQ-C30 and ED-5D-5L 4. Safety/Adverse Events

Trial name: *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)*	**NCT number:** *NCT03553836*

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.



Pre-study statistical plan for test of hypothesis.

For included participants, see baseline characteristics for ITT population.

Stratification factors: T-category (T3b, T4a and T4b) and pediatric status

Subgroup analyses

RFS and DMFS analysis was conducted in the following intention-to-treat population for pembrolizumab versus placebo. The treatment difference between treatment groups was assessed using an unstratified univariate Cox proportional hazard model.

- ***T category***
  - *T3b*
  - *T4a*
  - *T4b*
- ***Age, years***
  - *<65*
  - *≥65*
- ***Sex***
  - *Male*
  - *Female*
- ***Race***
  - *White*
  - *Not white*
  - *Missing*
- ***ECOG status***
  - *0*
  - *1*
- ***Geographical region***
  - *USA*
  - *Not USA*

Other relevant information

Oversigt over referencestudier

Trial name: [redacted]	NCT number: NA
Objective	[redacted]
Publications – title, author, journal, year	[redacted]
Study type and design	[redacted]
Sample size (n)	[redacted]
Main inclusion and exclusion criteria	[redacted]
Intervention	[redacted]
Comparator(s)	[redacted]
Follow-up time	[redacted]
Is the study used in the health economic model?	[redacted]

Trial name: [redacted]	NCT number: NA
Primary, s exploratory endpoints	[redacted]
Method of analysis	[redacted]

Trial name: [redacted]	NCT number: NA
Subgroup analyses	[redacted]
Other relevant information	

Trial name: Study of Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (MK-3475-054/1325-MG/KEYNOTE-054)	NCT number: NCT02362594
Objective	*To evaluate pembrolizumab as adjuvant therapy in patients with resected, high-risk stage III melanoma*
Publications – title, author, journal, year	*Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma, Eggermont et al, The New England Journal of Medicine, 2018* *Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial, Eggermont et al 2020, J Clin Oncol* *Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind,randomised, controlled, phase 3 trial, Eggermont et al, 2021, Lancet Oncology* *Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325 MG/KEYNOTE-054): health-related quality-of-life results from a double-blind, randomised, controlled, phase 3 trial. Bottomley et al., Lancet Oncol, 2021* *Five-Year Analysis of Adjuvant Pembrolizumab or Placebo in Stage III Melanoma, Eggermont et al, 2022, NEJM Evidence*
Study type and design	*KEYNOTE-054 is an international, double-blind, randomised, placebo-controlled, phase 3 study of pembrolizumab versus placebo as adjuvant therapy in patients with completely resected stage III melanoma. Patients were randomly assigned to receive adjuvant pembrolizumab or placebo in part 1 of the study (double-blind design) and after recurrence they could receive pembrolizumab as rechallenge or cross-over in part 2 (unblinded design).*

Trial name: Study of Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (MK-3475-054/1325-MG/KEYNOTE-054)	NCT number: NCT02362594
Sample size (n)	*Patients with completely resected stage III melanoma were randomly assigned (with stratification according to cancer stage and geographic region) to receive 200 mg of pembrolizumab (514 patients) or placebo (505 patients) intravenously every 3 weeks for a total of 18 doses (approximately 1 year) or until disease recurrence or unacceptable toxic effects occurred.*
Main inclusion and exclusion criteria	*Main inclusion criteria:* *Patients who were 18 years of age or older and had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes. The patients had to have either stage IIIA melanoma (patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer 2009 classification, 7th edition.14 A complete regional lymphadenectomy was required to have been performed within 13 weeks before the start of treatment.* *Main exclusion criteria:* *Eastern Cooperative Oncology Group (ECOG) performance status score of more than 1 (scores range from 0 to 5, with higher numbers indicating greater disability), autoimmune disease, uncontrolled infections, use of systemic glucocorticoids, and previous systemic therapy for melanoma.*
Intervention	*Biological: Pembrolizumab* *Administered as an intravenous (IV) infusion every 3 weeks (Q3W)* *Other Names:* *• KEYTRUDA®* *• MK-3475* *Adult participants receive 200 mg pembrolizumab by IV infusion Q3W (21-day cycles) for up to 17 cycles (up to ~1 year) in a double-blind design in Part 1. Participants that complete 17 cycles of pembrolizumab and experience disease recurrence may be eligible to receive additional cycles of pembrolizumab in Part 2 in an open-label design. In Part 2, participants will receive up to 17 cycles (up to ~1 year) of pembrolizumab for local/distant recurrence following disease resection or up to 35 cycles (up to ~2 years) of pembrolizumab for unresectable disease recurrence. Participants with distant metastasis who undergo complete resection will receive 17 cycles (up to ~1 year) of pembrolizumab but can receive up to 35 cycles (up to ~2 years) of pembrolizumab under certain circumstances.*
Comparator(s)	*Drug: Placebo* *Administered as an IV infusion every 3 weeks (Q3W)* *Participants receive saline placebo by IV infusion Q3W (21-day cycles) for up to 17 cycles (up to ~1 year) in a double-blind design in Part 1. Participants that complete 17 cycles of placebo and experience disease recurrence may be eligible to receive pembrolizumab in Part 2 in an open-label design. In Part 2, participants will receive up to 17 cycles (up to ~1 year) of pembrolizumab for local/distant recurrence following disease resection or up to 35 cycles (up to ~2 years) of pembrolizumab for disease that cannot be resected or metastatic disease.*

Trial name: Study of Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (MK-3475-054/1325-MG/KEYNOTE-054)	NCT number: NCT02362594
Follow-up time	*Median follow-up time up to 4,9 years*
Is the study used in the health economic model?	*Nej det er ikke anvendt i den økonmiske model.* *Studiet er relevant da det udgør et vigtigt referencegrundlag og supportere data fra keynote-716. Studierne har næsten identisk studiedesign, samt inkluderer begge en patientpopulation med samme risikoprofil hvorfor data fra keynote-054 kan bruges til at kontekstualisere data fra keynote-716. Dette for at skabe en forståelse for den generelle effekt af adjuverende behandling med pembrolizumab af høj-risiko melanomer, uden at der foretages en direkte sammenligning. Keynote-054 længere opfølgningstid og mere modne data kan bruges til at forstå, hvordan data fra keynote-716 vil udvikle sig over tid. Derfor er data fra keynote-054 ikke medtaget som argument for behandlingens effekt i stadie II men som udgangspunkt til at vurdere data fra keynote-716.*
Primary, secondary and exploratory endpoints	***The primary end point*** - *Recurrence-free survival in the overall intention-to-treat population* - *Recurrence-free survival in the subgroup of patients with PD-L1–positive tumors* ***Secondary end points*** - *Distant metastasis-free survival* - *Overall survival* - *Safety measures* - *Measures of health-related quality of life.*
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*
Subgroup analyses	- *Tumor PD-L1 expression* - *Sex* - *Age* - *AJCC 2009 melanoma classification* - *No. of positive lymph nodes* - *Type of positive lymph nodes* - *Ulceration* - *Lymph-node and ulceration status* - *BRAF mutation status*
Other relevant information	

Trial name: Study to Evaluate the Safety and Efficacy of Two Different Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Participants With Advanced Melanoma (MK-3475-006/KEYNOTE-006)	NCT number: NCT01866319
Objective	*To evaluate the safety and efficacy of 2 different dosing schedules of pembrolizumab (MK-3475), every 2 weeks (Q2W) and every 3 weeks (Q3W), and compare the 2 schedules to treatment with ipilimumab in ipilimumab-naïve participants with unresectable or metastatic melanoma.*
Publications – title, author, journal, year	*Pembrolizumab versus Ipilimumab in Advanced Melanoma, Roberts et al, 2015. The New England Journal of Medicine* *Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006), Schachter et al 2017, Lancet* *Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study, Roberts et al, 2019, Lancet Oncology* *Patient-reported outcomes in KEYNOTE-006, a randomised study of pembrolizumab versus ipilimumab in patients with advanced melanoma, Petrella et al, 2017, Eur J Cancer*
Study type and design	*Open-label, multicentre, randomised, controlled, phase 3 study done at 87 academic institutions, hospitals, and cancer centres in 16 countries that compared pembrolizumab with ipilimumab in ipilimumab-naive patients with histologically confirmedunresectable stage III or IV melanoma* *Patients were randomly assigned in a 1:1:1 ratio to receive pembrolizumab at a dose of 10 mg per kilogram of body weight either every 2 weeks or every 3 weeks or four cycles of ipilimumab at a dose of 3 mg per kilogram every 3 weeks.*
Sample size (n)	*Pembrolizumab every 2 weeks n=279, pembrolizumab every 3 weeks n= 277 + ipilimumab n=278*
Main inclusion and exclusion criteria	*Main inclusion criteria* *Patients who were 18 years of age or older were eligible for enrollment if they had histologically confirmed, unresectable stage III or IV melanoma and had received no more than one previous systemic therapy for advanced disease. Known BRAF V600 mutational status was required; previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels and no clinically significant tumor-related symptoms or evidence of rapidly progressive disease. Other key eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability) and provision of a tumor sample adequate for assessing PD-L1 expression.* *Main exclusions criteria:* *Patients who had received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors and those who had ocular melanoma, active brain metastases, or a history of serious autoimmune disease*

Trial name: Study to Evaluate the Safety and Efficacy of Two Different Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Participants With Advanced Melanoma (MK-3475-006/KEYNOTE-006)	NCT number: NCT01866319
Intervention	*Patients were randomly assigned in a 1:1:1 ratio to receive pembrolizumab at a dose of 10 mg per kilogram of body weight either every 2 weeks or every 3 weeks or four cycles of ipilimumab at a dose of 3 mg per kilogram every 3 weeks.* *Pembrolizumab was administered intravenously during a 30-minute period and continued until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, withdrawal of patient consent, or 24 months of therapy. Patients with confirmed complete response who received pembrolizumab for at least 6 months could discontinue therapy after receiving at least two doses beyond the determination of complete response.* *Biological: Pembrolizumab* *10 mg/kg IV, administered Q2W or Q3W based upon randomization.* *Other Name: MK-3475 or Keytruda®*
Comparator(s)	*Biological: Ipilimumab 3 mg/kg IV Q3W.* *Ipilimumab was administered intravenously during a 90-minute period and continued for four cycles or until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, or withdrawal of patient consent.*
Follow-up time	*Median follow-up time up to 5 years*
Is the study used in the health economic model?	*Ja*
Primary, secondary and exploratory endpoints	***Primary end points*** - *Progression-free survival (defined as the time from randomization to documented disease progression according to RECIST or death from any cause)* - *Overall survival (defined as the time from randomization to death from any cause).* ***Secondary end points**:* - *Objective response rate (defined as the percentage of patients with complete or partial response according to RECIST), the duration of response (defined as the time from the first documented response to radiologic progression according to RECIST)* - *Safety.*

Trial name: Study to Evaluate the Safety and Efficacy of Two Different Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Participants With Advanced Melanoma (MK-3475-006/KEYNOTE-006)	NCT number: NCT01866319
Method of analysis	*Efficacy was analysed in the intention-to-treat population (all randomly assigned patients) and safety was analysed in all randomly assigned patients who received at least one dose of study treatment. Efficacy and safety data from the two pembrolizumab dosing schedules (10 mg/kg every 2 weeks and every 3 weeks) were combined, however, combination of these data was not prespecified in the protocol. Median progression-free survival and median overall survival of the two pembrolizumab dosing schedules were compared using the stratified log-rank test, and two-sided p values were calculated. Progression-free survival, overall survival, and duration of response were estimated using the Kaplan-Meier method. Data for patients who did not have disease progression or who were lost to follow-up were censored at the time of last tumour assessment for progression-free survival. Overall survival was assessed up to 5 years, whereas progression-free survival was not assessed up to 5 years because imaging was performed per protocol and therefore imaging scans were not available for all patients up to 5 years. Treatment differences for survival were assessed using the stratified log-rank test. Hazard ratios (HRs) and associated 95% Cis were assessed by a stratified Cox proportional hazards model with Efron's method of handling ties.*
Subgroup analyses	- *Line of therapy* - *BRAFV600 status* - *Exposure to previous BRAF or MEK inhibitors for those patients with BRAFV600E-mutant or BRAFV600K-mutant disease*
Other relevant information	

Trial name: Systematic literature review and network meta-analysis for patients not previously treated with non-targeted therapy for advanced melanoma (NMA)	
[redacted]	[redacted]
[redacted]	[redacted]

Trial name: Systematic literature review and network meta-analysis for patients not previously treated with non-targeted therapy for advanced melanoma (NMA)	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

List of included studies

Trial ID	Trial Number	Principal publication	Principle Publication Title	Associated publications
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial ID	Trial Number	Principal publication	Principle Publication Title	Associated publications
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety		
Karakteristika, n (%)	**Pembrolizumab (n = 487)**	**Placebo (n = 489)**
Alder, median (range), år	60,0 (16-84)	61,0 (17-87)
12-17 år	1 (0,2)	1 (0,2)
18-64 år	302 (62,0)	294 (60,1)
≥65 år	184 (3,8)	194 (39,7)
Sex		
Mænd	300 (61,6)	289 (59,1)
Kvinder	187 (38,4)	200 (40,9)
Hvide	435 (89,3)	439 (89,8)
Geografiske region		
US	95 (19,5)	80 (16,4)
Ikke-US	392 (80,5)	409 (83,6)
ECOG Performance Status		
0	454 (93,2)	452 (92,4)
1	32 (6,6)	35 (7,2)
2	0 (0,0)	1 (0,2)
T kategori		
T3b	200 (41,1)	201 (41,1)
T4a	113 (23,2)	116 (23,7)
T4b	172 (35,3)	172 (35,2)
Sygdoms stadie		
IIA	1 (0,2)	0 (0,0)
IIB	309 (63,4)	316 (64,6)
IIC	171 (35,1)	169 (34,6)
IIIC	4 (0,8)	1 (0,2)
IV	0	2 (0,2)
Mangler	2 (0,4)	1 (0,2)

11.1. Comparability of patients across studies

N/A

11.2. Comparability of the study populations with Danish patients eligible for treatment

Patienterne relevante for denne ansøgning er patienter med resekteret højrisiko stadie IIB og IIC melanom. MSD vurderer, at de danske patienter med stadie IIB og IIC melanom, der vil modtage adjuverende behandling, er sammenlignelig med patientpopulationen i KN-716.

Melanom diagnosticeres i alle aldersgrupper, men hyppigheden er stigende med alderen, og melanom optræder hovedsageligt hos personer i aldersgruppen 40 til 70 år. Det forekommer generelt lidt hyppigere blandt kvinder end hos mænd (ratio 0,8) [3-5], [redacted]. I KN-716 er der inkluderet ~60% mænd og 40% kvinder [30], og dermed er patientpopulationen i KN-716 sammenlignelig med den danske patientpopulation ifht fordeling af køn.

I KN-716 har studiepopulationen en median alder på 60-61 år [30]. [redacted] Det må derfor også formodes, at det vil være den yngre del af stadie IIB+C populationen, som vil blive tilbudt og takke ja til behandling med adjuverende pembrolizumab. Dermed kan det forventes, at den del af stadie IIB og IIC melanom patienterne, der vil modtage adjuverende behandling, svarer til patientpopulationen i KN-716 med en median alder på omkring 60 år.

Appendix D Efficacy and safety results per study

11.3. Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition
Recurrence Free Survival	RFS is defined as the time from randomization to any of the following events: recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) or death due to any cause.
Distant Metastasis-Free Survival	DMFS is defined as the time from randomization to the first diagnosis of a distant metastasis per RECIST 1.1. Distant metastasis refers to cancer that has spread from the original (primary) tumor and beyond local tissues and lymph nodes to distant organs or distant lymph nodes.
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.
Life Quality, EQ-5D-5L	The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability

11.4. Results per study

Table A3a Results of *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716) (NCT03553836)*

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
RFS rate 12 months (data cutoff 21/6/2021)	*Pembrolizumab*	*487*	90,8% (87,8 – 93,1)	7,5% ARR	N/A	N/A	HR: 0,65	0,46-0,92	p=0,00658	*The recurrence 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.*	[37], [2]
	Placebo	489	83,3% (79,6 – 86,4)								
RFS rate 18 months (data cutoff 21/6/2021)	Pembrolizumab	487	85,8% (82,0 – 88,9)	8,8% ARR	N/A	N/A	HR: 0,61	0,45-0,82	0,00046	*The recurrence 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.*	
	Placebo	489	77,0% (72,6 – 80,7)								
DMFS rate 18 months (data cutoff 4/1/2022)	Pembrolizumab	487	92,7% (89,9 – 94,7)	4,5% ARR	N/A	N/A				*The distant metastasis free survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for*	[38], [37], [13]
	Placebo	489	86,5% (83,1 – 89,3)								

Table A3a Results of *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716) (NCT03553836)*

										stratification, and study arm.	
DMFS rate 24 months (data cutoff 4/1/2022)	Pembrolizumab	487	88,1% (84,4 - 90,9)	5,9% ARR	N/A	N/A	HR: 0,64	(0.47 – 0.88)	P=0,0029	*The distant metastasis 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.*	[38], [37]
	Placebo	489	82,2% (78,2 - 85,5)								
All cause safety grade 3-4 *as-treated population*	Pembrolizumab	487	28,2% (24,2-32,4)	9,1% ARR			RR = 1,47	1,167 – 1,855		*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. Data on adverse events were collected throughout the study through self-report by patient or reported by caregivers and reviewed by investigators during screening and then every 3 weeks from randomisation, and up to 30 days (90 days for serious adverse events) after treatment discontinuation and graded*	[2] Table S6
	Placebo	489	19,1% (15,7-22,9)								

Table A3a Results of *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716) (NCT03553836)*

								according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.	
Treatment discontinuation due to adverse events	Pembrolizumab	487	17,6% (14,3-21,3)	12,9% ARR		RR = 3,71	2,387 – 5,792	*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. Data on adverse events were collected throughout the study through self-report by patient or reported by caregivers and reviewed by investigators during screening and then every 3 weeks from randomisation, and up to 30 days (90 days for serious adverse events) after treatment discontinuation and graded according to the National Cancer Institute Common Terminology Criteria for Adverse*	[2] Figure 1 i Ref 2
	Placebo	489	4,7% (3,02-7,02)						

Table A3a Results of *Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716) (NCT03553836)*

							Events, version 4.0.	
EORTC QLQ-C30 *Baseline – week 48* *ITT-population*	Pembrolizumab	449	-4,49 (-6,19 to -2,79)	-3,74 points	-5,91 to -1,44	P=0,013	*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*	[39], [37]
	Placebo	459	-0,82 (-2,4 to 0,83)					

Appendix E Safety data for intervention and comparator(s)

Se venligst afsnittene:

7.1.8 Bivirkninger

7.1.9 Kvalitativ gennemgang af bivirkninger

7.1.10 Perspektivering af bivirkninger

	KN716 Data for Pembrolizumab[k]		KN716 Data for Placebo[l]		KN054 Data for Pembrolizumab[m]		EU Reference Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		486		509		6,185	
with one or more adverse events	449	(93.0)	433	(89.1)	480	(94.3)	5,989	(96.8)
with no adverse events	34	(7.0)	53	(10.9)	29	(5.7)	196	(3.2)
Fatigue	138	(28.6)	119	(24.5)	170	(33.4)	1,967	(31.8)
Diarrhoea	129	(26.7)	89	(18.3)	139	(27.3)	1,295	(20.9)
Pruritus	125	(25.9)	59	(12.1)	103	(20.2)	1,111	(18.0)
Arthralgia	102	(21.1)	79	(16.3)	90	(17.7)	1,149	(18.6)
Rash	87	(18.0)	37	(7.6)	67	(13.2)	936	(15.1)
Hypothyroidism	75	(15.5)	16	(3.3)	76	(14.9)	699	(11.3)
Headache	73	(15.1)	54	(11.1)	95	(18.7)	747	(12.1)
Nausea	64	(13.3)	52	(10.7)	89	(17.5)	1,282	(20.7)
Cough	56	(11.6)	51	(10.5)	71	(13.9)	1,200	(19.4)
Asthenia	51	(10.6)	53	(10.9)	55	(10.8)	692	(11.2)
Alanine aminotransferase increased	50	(10.4)	25	(5.1)	38	(7.5)	429	(6.9)
Hyperthyroidism	50	(10.4)	3	(0.6)	53	(10.4)	261	(4.2)
Constipation	37	(7.7)	38	(7.8)	34	(6.7)	1,032	(16.7)
Hypertension	37	(7.7)	41	(8.4)	76	(14.9)	318	(5.1)
Back pain	36	(7.5)	34	(7.0)	36	(7.1)	709	(11.5)
Vomiting	30	(6.2)	15	(3.1)	40	(7.9)	784	(12.7)
Decreased appetite	26	(5.4)	9	(1.9)	36	(7.1)	1,181	(19.1)
Pyrexia	26	(5.4)	24	(4.9)	24	(4.7)	802	(13.0)
Dyspnoea	20	(4.1)	23	(4.7)	45	(8.8)	1,020	(16.5)
Anaemia	15	(3.1)	11	(2.3)	7	(1.4)	872	(14.1)
Weight decreased	12	(2.5)	5	(1.0)	56	(11.0)	574	(9.3)
Influenza like illness	10	(2.1)	11	(2.3)	56	(11.0)	245	(4.0)
Weight increased	3	(0.6)	6	(1.2)	65	(12.8)	209	(3.4)

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[k] Includes all participants who received at least one dose of Pembrolizumab in KN716.

[l] Includes all participants who received at least one dose of Placebo in KN716.

[m] Includes all participants who received at least one dose of Pembrolizumab in KN054.

[n] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN0177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 04DEC2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN177: 19FEB2020)

Appendix F Comparative analysis of efficacy and safety

N/A for meta analysis

Appendix G – Extrapolation

11.5. Is defined as the Transition probabilities

11.5.1. Transitions from recurrence-free state

The selection process of base case parametric functions for transitions from recurrence-free state

The selection process detailed below started with a total of 54 candidate combinations, including 36 under Approach #1, 9 under Approach #2, and 9 under Approach #3. Tabel 84a-c and Tabel 85a-c list all candidate combinations of parametric functions in each treatment arm, including the rankings in terms of MSE in each model arm and long-term predictions of RFS, DMFS, and OS. (Note: These long-term RFS, DMFS, and OS predictions under each combination of functions reflect the base-case cure assumption, i.e., risk reduction that linearly increases from 0% at 7 years to 95% at 10 years onward for patients who remain recurrence-free.)

Initial exclusions based on clinical plausibility

Of the 54 combinations of parametric distributions under consideration, 12 were excluded due to implausible crossing of the survival curves for pembrolizumab and observation (i.e., higher long-term RFS under observation than pembrolizumab). Six of these 12 parametric distribution combinations were also excluded when applying 4-year RFS and DMFS in KEYNOTE-054 (trial of Pembrolizumab vs. placebo as adjuvant treatment of resected high-risk stage III melanoma) as lower bounds for 4-year RFS and DMFS predictions in each arm. (These exclusions are illustrated through color-coding in Tabel 84a-c and Tabel 85a-cAs shown in Table 80a below, observed RFS and DMFS at 1,2 and 3 years was higher for Pembrolizumab and placebo in KEYNOTE-716 than in the corresponding arms of KEYNOTE-054, supporting the expectation of better survival in the stage IIB-C population. Table 80b presents observed DMFS for each arm of KEYNOTE-054.

Table 80: Observed survival endpoints in the Pembrolizumab and placebo arms of KEYNOTE-716 and KEYNOTE-054

a. RFS in each arm of KEYNOTE-716 and KEYNOTE-054

RFS by year:	1	2	3	4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. DMFS in each arm of KEYNOTE-716 and KEYNOTE-054

DMFS by year:	1	2	3	4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Fit statistics:

As shown in Tabel 84a-c and Tabel 85a-c, the ranking of statistical fit was similar whether based on MSE relative to observed RFS or MSE relative to observed DMFS. (In other words, combinations of distributions that demonstrated good statistical fit with RFS generally also showed good fit with DMFS.) However, there were few combinations of distributions that had poor ranking of statistical fit in both the pembrolizumab and observation arms. Because MSEs were generally higher for observation than pembrolizumab, the selection of base-case parametric functions prioritized fit in the observation arm. Combinations of distributions were therefore excluded if they ranked among the ten worst-fitting combinations in terms of both RFS and DMFS in the observation arm, regardless of their ranking in the pembrolizumab arm. This criterion led to the exclusion of 8 combinations in total (Weibull/Weibull, Weibull/Gompertz, Exponential/Weibull, and Exponential/Gompertz under Approaches #2 and #3).

The proportional hazards assumption could not be rejected for either RF → LR (p=0.844) or RF → DM (p=0.224) based on statistical tests. Thus, no exclusions were made based on proportional hazards testing, and combinations of distributions under Approaches #2 and #3 were retained for further consideration as base-case or scenario analyses.

Visual assessment of fit

For each of the following outcomes, graphs were generated to compare observed curves with predicted curves from all 54 different combinations of parametric functions: cumulative incidences of RF → LR (Figure 21), RF → DM (Figure 22), and RF → death (Figure 23); RFS (

Figure **24**); and DMFS (Figure 25). In each graph, solid lines are based on parametric distributions separately fitted to each treatment arm (i.e., Approach #1), dashed lines are based on proportional hazards parametric models jointly fitted to both arms with a time-constant HR (i.e., Approach #2), and dotted lines are based on proportional hazards parametric models jointly fitted to both arms with a time-varying HR (i.e., Approach #3). In the figures for RF → LR, each color family represents one of the different distributions fitted to the cause-specific hazards of RF → LR, while the different shades within a color family represent different distributions fitted to the cause-specific hazards of RF → DM. In the figures for RF → DM, RF → Death, RFS, and DMFS, each color family represents one of the different distributions fitted to the cause-specific hazards of RF → DM, while the different shades within a color family represent different distributions fitted to the cause-specific hazards of RF → LR.

The interpretation of each figure is summarized below in Table 81:

Table 81: Summary of findings from visual inspection of fit between predicted vs. observed RF → LR, RF → DM, RF → death, RFS, and DMFS

Figure	Interpretation
Figure 21: Predicted vs. observed cumulative incidence of transitions	▪ All combinations of parametric functions produced a close visual fit to the observed cumulative incidence of RF → LR.

from recurrence-free to locoregional recurrence in each arm	
Figure 22: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases in each arm: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases in each arm	▪ In both arms, combinations using log-normal for the cause-specific hazards of RF → DM demonstrated good visual fit to the cumulative incidence of RF → DM. ▪ In the pembrolizumab arm, combinations using exponential for RF → DM yielded worse visual fit under Approaches #1 and #2, but good visual fit under Approach #3, In the observation arm, combinations using exponential for RF → DM under all approaches demonstrated the best visual fit during the second year of follow-up. Combinations using exponential for RF → DM were thus retained for further consideration.
Figure 23: Predicted vs. observed cumulative incidence of transitions from recurrence-free to death in each arm	▪ During the trial period, fit was indistinguishable between different combinations of parametric functions due to the very small number of observed RF → Death events in KEYNOTE-716. (Note: The predicted curves for RF → Death in the pembrolizumab were higher than the observed curve because background mortality immediately exceeded the parametrically estimated rates of RF → death in this arm.) ▪ The large divergence seen in the long-term is due to the interplay between competing risks and background mortality: Under combinations of distributions that yield low risks of LR and DM, more patients are estimated to die directly from RF (rather than from LR or DM) once patients reach ages at which background mortality is high.
Figure **24**: Predicted vs. observed cumulative incidence of transitions from recurrence-free to death in each arm Figure 25: Predicted vs. observed distant metastases-free survival in each arm	▪ All combinations of parametric distributions produced close visual fits with the composite endpoints RFS and DMFS in each arm.

Based on the above findings, no exclusions were made based on visual fit alone.
Under the final selected base case (i.e., log-normal/log-normal under Approach #1),

Figure 26 illustrates the close visual alignment between predicted versus observed cumulative incidences of all three individual transitions starting from the recurrence-free state. Figur 27 presents the alignment between predicted versus observed RFS and DMFS in each arm.

External validations of predicted RFS, DMFS, and OS for observation:

Predicted RFS in the observation arm was validated against long-term RFS data from two external studies. Across the Bajaj et al. (2020) study and the US Oncology Network study conducted by Merck [48] RFS for observation ranged narrowly over a 7-year period (e.g., RFS at 7 years ranged from 33.6% to 35.0%; simple average: 34.3%); 10-year RFS for observation was only available from the US Oncology Network study, at 23.2%. Predicted DMFS in the observation arm was validated against observed DMFS from the US Oncology Network study, as DMFS was not reported in Bajaj et al. (2020).

To better ensure externally valid extrapolations in the observation arm, further exclusions were applied based on the requirements that: predicted RFS for observation must fall within the range of these studies +/- 5 percentage points of the simple average of these two studies through 7 years; and predicted DMFS for

observation must fall within the range of the US Oncology Network study +/- 5 percentage points through 7 years. Fourteen combinations of distributions (listed in Table 82) met these external validity requirements. As shown, all but one of these 14 combinations were also within +/- 5 percentage points of RFS and/or DMFS in the US Oncology Network study at 10 years.

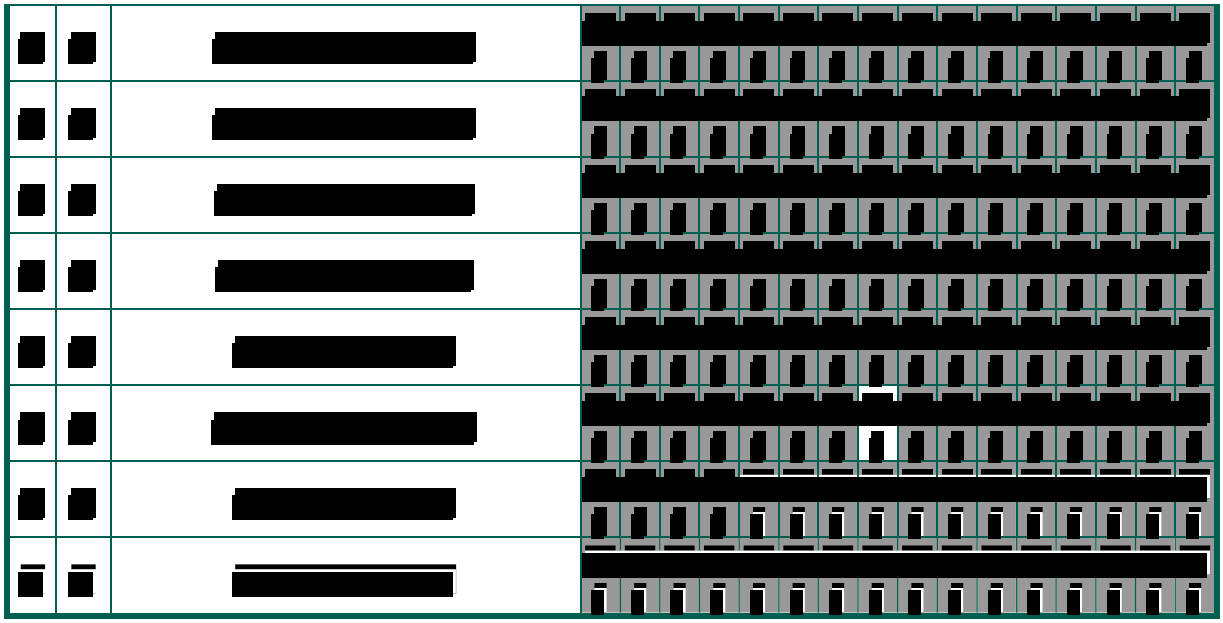
Description of the external studies:

- Based on Bajaj et al. (2020) patients with primary cutaneous melanoma and enrolled within 2 months of initial diagnosis or 6 months within first recurrence or metastasis are considered.
- Based on US Oncology study, patients with stage IIB or IIC cutaneous melanoma that was completely resected within the 10-year period from 1 January 2008 to 31 December 2017 (index period) were eligible for this retrospective study if they were ≥18 years old at the time of diagnosis and had at least two visits recorded within The US Oncology Network (The Network) after their diagnosis.
- All the three studies deals with cutaneous melanoma. The similarities between KEYNOTE-716 and US oncology study is that both of them deals with adult patients with stage IIB and IIC resected cutaneous melanoma with T staging subgroup (T3b,T4b,T4a etc.). In all the three studies the pathological staging is done based on AJCC 8 guidelines.

Table 82: Summary: External validations of predicted RFS for observation

[redacted] Predicted RFS or DMFS is within +/- 5 percentage points of external data

Rank by RFS MSE	Rank by DMFS MSE	Approach # / RF → LR / RF → DM	RFS by year								DMFS by year							
			1	2	3	4	5	6	7	10	1	2	3	4	5	6	7	10
External validation sources for RFS and DMFS																		
[redacted]																		
Modeled RFS and DMFS in the observation arm under selected combinations of distributions (approach # / RF → LR / RF → DM)																		
[redacted]																		



Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LR, locoregional recurrence; RF, recurrence-free; RFS, recurrence-free survival.

Figur 27 and Figure 28 visually illustrate the exclusion of combinations of distributions based on the external validity of RFS and DMFS predictions, respectively.

Of these 14 finalist combinations, one was chosen as base case and the remaining 13 were considered in scenario analyses. Approach #1 / log-normal / log-normal was selected as the base-case combination based on its high MSE ranking with respect to both RFS (9th best-fitting out of 54 combinations) and DMFS (17th best-fitting out of 54) in the observation arm. In terms of statistical fit, this combination was outperformed by only two of the 14 finalist combinations (i.e., Approach #1/generalized gamma/log-normal and Approach #1/Gompertz/log-normal), both of which deviated further from external validation sources in an overestimated direction. Additionally, Approach #1/log-normal/log-normal yielded moderate predictions of incremental RFS and DMFS benefit for pembrolizumab vs. observation (see discussion below).

Figure 15a plots base-case RFS predictions for observation against external RFS data from Bajaj et al. (2020) study and the US Oncology Network study, as well as the RFS Kaplan-Meier curve from KEYNOTE-716 (data cutoff date: January 04, 2022). Figure 15b plots base-case DMFS predictions for observation against the DMFS Kaplan-Meier curve from the US Oncology Network study, and Figure 15c plots base-case OS predictions for observation against OS data from the US Oncology Network study and the three published external studies [49, 56, 57].

Plausibility of predicted RFS, DMFS, and OS for Pembrolizumab:

Table 83 summarizes the incremental RFS and DMFS benefit of pembrolizumab relative to observation under the 14 aforementioned combinations of parametric distributions, and when taking the average of these 14 combinations. As shown, incremental RFS and DMFS benefits predicted by the selected base case (Approach #1/log-normal/log-normal) were close to the average of the 14 finalist combinations of distributions at each time point and were slightly below the average from year 4 onward.

Table 83: Summary: Incremental RFS benefit of pembrolizumab vs. observation under the 14 finalist combinations of distributions

Approach # / RF → LR / RF → DM	Predicted difference in RFS (pembrolizumab vs. observation)								Predicted difference in DMFS (pembrolizumab vs. observation)							
	1 yrs	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	10 yrs	1 yrs	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	10 yrs
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Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LR, locoregional recurrence; RF, recurrence-free; RFS, recurrence-free survival.

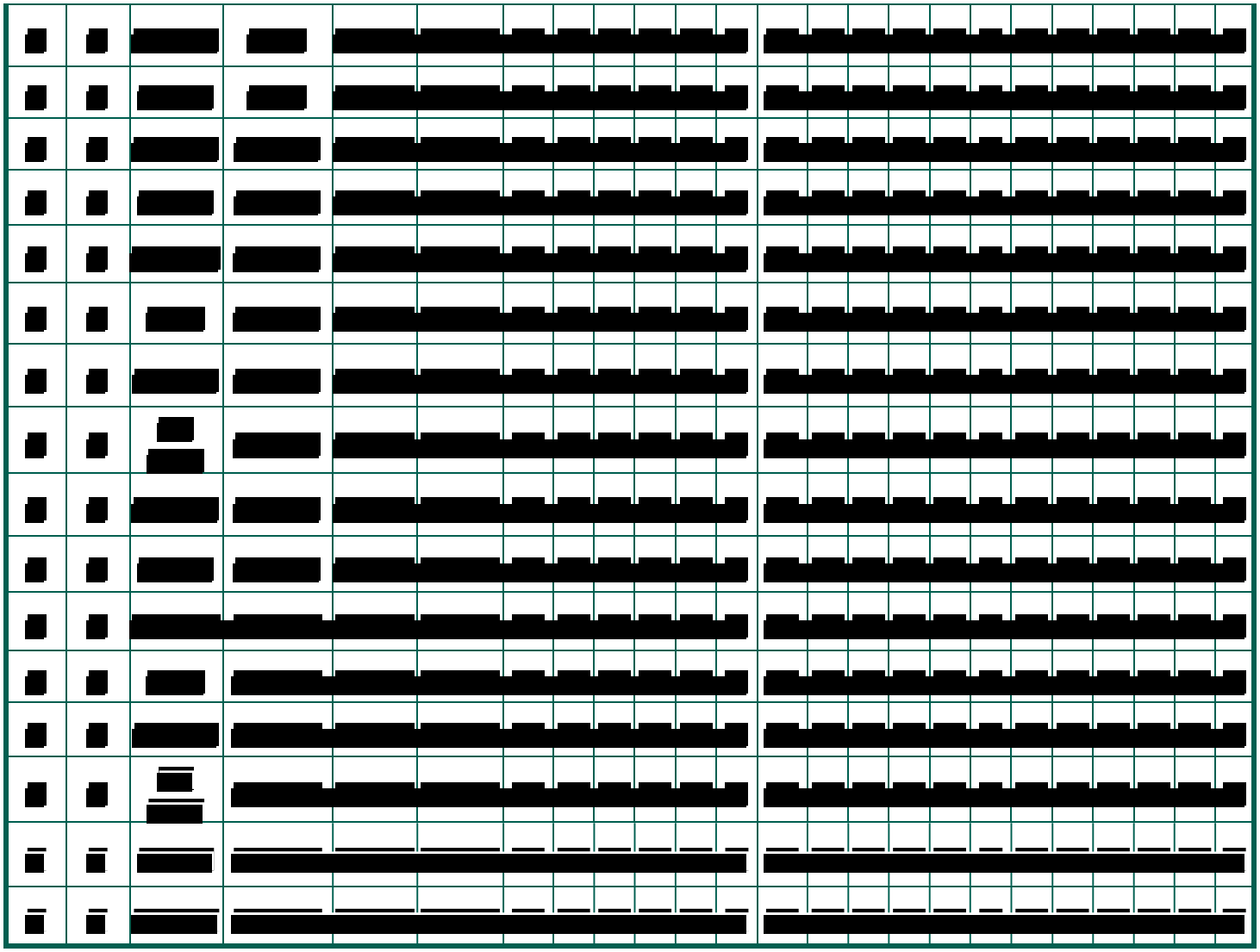
Tabel 84: Comparison of different parametric functions used to model RFS in the pembrolizumab arm: Fit with observed data and long-term extrapolations

Color key:

	Predicted survival curve is lower than for observation when using the same distributions for observation (excluded from consideration as base case)
	Predicted 4-year RFS or DMFS for pembrolizumab is below that observed in pembrolizumab arm of KEYNOTE-054 (excluded from consideration as base case)
~~MSE~~	Ranked among ten worst-fitting combinations in terms of both RFS and DMFS in the observation arm (excluded from consideration as base case)

a. **Approach #1: Parametric models separately fitted to each treatment arm: Pembrolizumab**

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE vs. observed RFS	MSE vs. observed DMFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
		RF → LR	RF → DM			4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
[redacted]																							



b. Approach #2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect: Pembrolizumab

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE vs. observed RFS	MSE vs. observed DMFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
		RF → LR	RF → DM			4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
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c. Approach #3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect: Pembrolizumab

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE vs, observed RFS	MSE vs, observed DMFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
		RF → LR	RF → DM			4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LR, locoregional recurrence; MSE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.

Tabel 85: Comparison of different parametric functions used to model RFS in the observation arm: Fit with observed data and long-term extrapolations

Color key:

Predicted survival curve is lower than for observation when using the same distributions for observation (excluded from consideration as base case)

Predicted 4-year RFS or DMFS for pembrolizumab is below that observed in pembrolizumab arm of KEYNOTE-054 (excluded from consideration as base case)

~~MS~~ Ranked among ten worst-fitting combinations in terms of both RFS and DMFS in the observation arm (excluded from consideration as base case)

a. Approach #1: Parametric models separately fitted to each treatment arm: Observation

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE vs. observed RFS	MSE vs. observed DMFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
		RF → LR	RF → DM			4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
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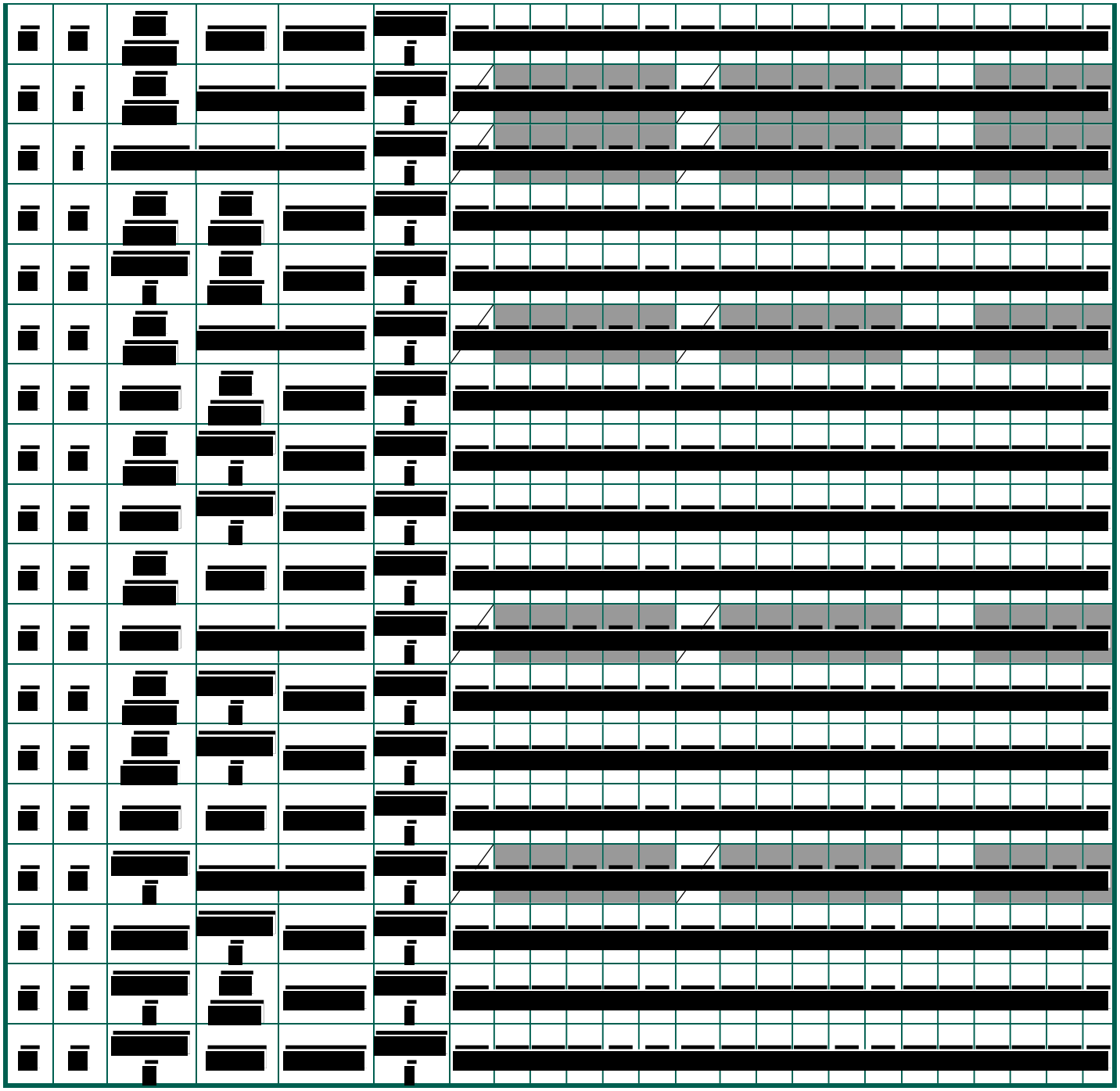
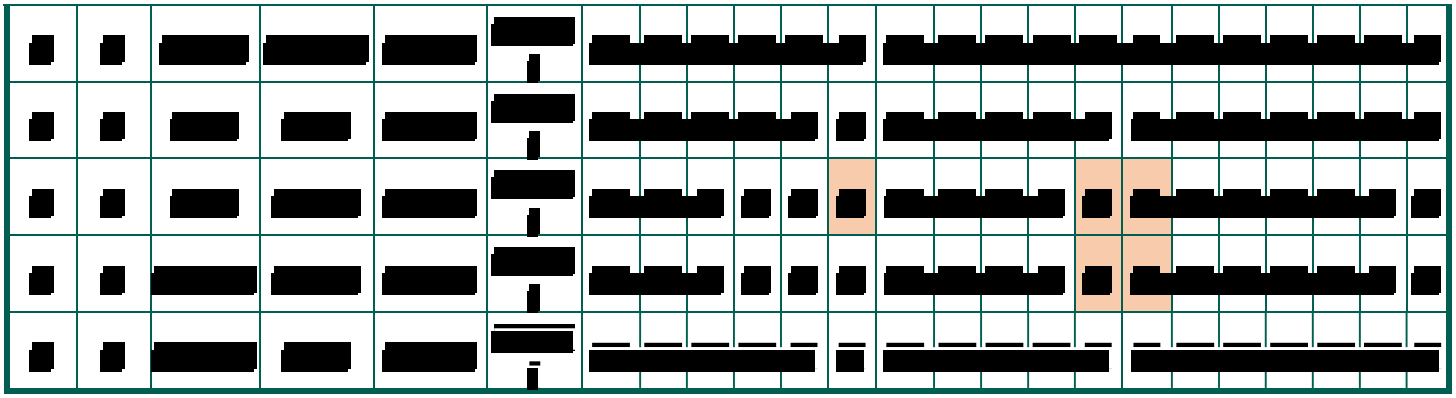


b. Approach #2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect: Observation

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE vs. observed RFS	MSE vs. observed DMFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
		RF → LR	RF → DM			4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs



c. Approach #3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect: Observation

Rank by RFS MSE	Rank by DMFS MSE	Parametric functions		MSE vs. observed RFS	MSE vs. observed DMFS	Predicted RFS (%)						Predicted DMFS (%)						Predicted OS (%)					
		RF → LR	RF → DM			4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
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Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LR, locoregional recurrence; MSE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.

Figure 21: Predicted vs. observed cumulative incidence of transitions from recurrence-free to locoregional recurrence in each arm

a. Pembrolizumab arm, for Trial period

b. Pembrolizumab arm, for long term period separating the combination of distributions in 6 different panels for each approach

c. Observation arm, trial period

d. Observation arm, trial period separating the combination of distributions in 6 different panels for each approach

Figure 22: Predicted vs. observed cumulative incidence of transitions from recurrence-free to distant metastases in each arm

a. Pembrolizumab, trial period

b. Pembrolizumab, long term period separating the combination of distributions in 6 different panels for each approach

c. Observation, trial period

d. Observation, long term period separating the combination of distributions in 6 different panels for each approach

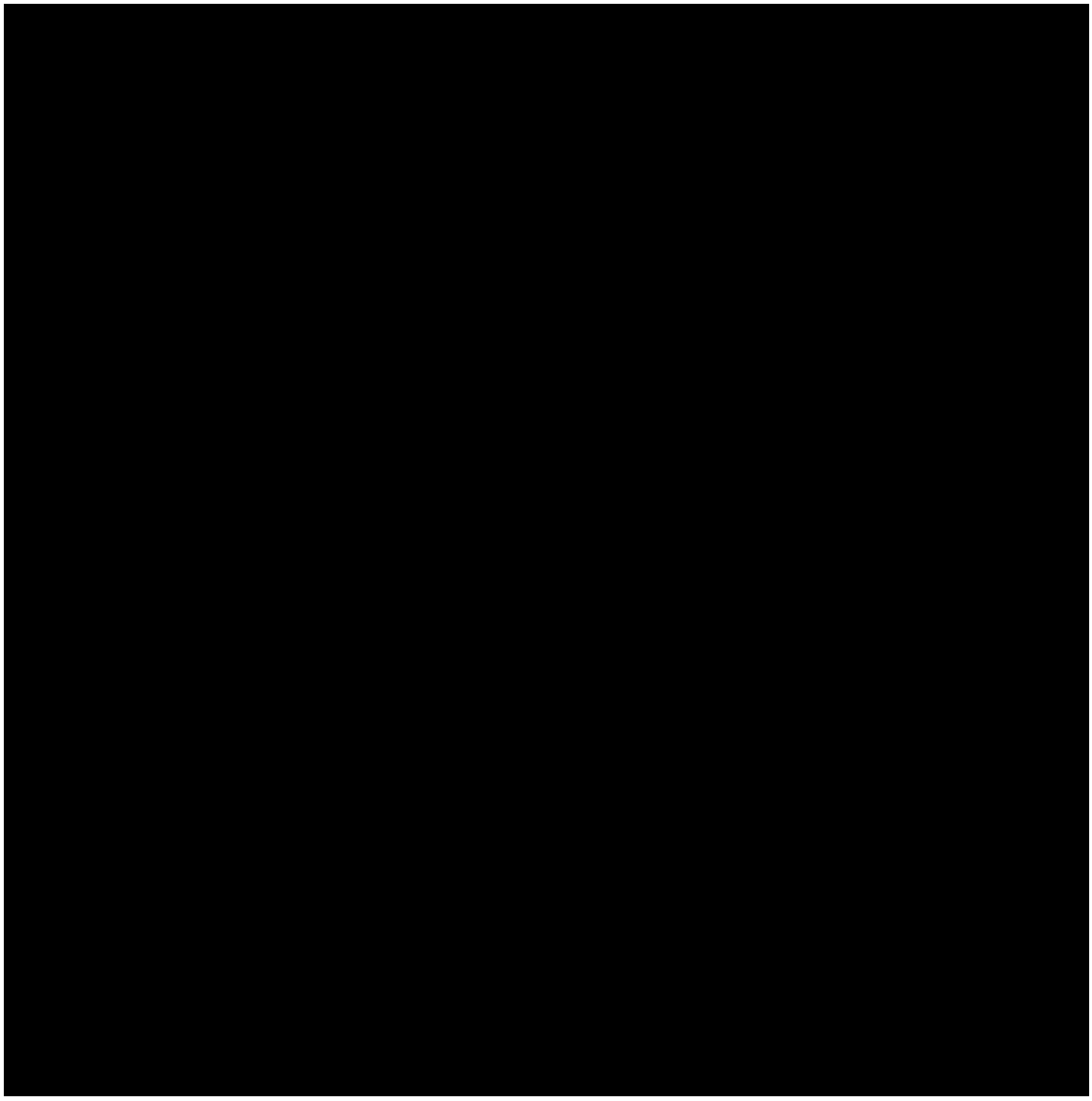


Figure 23: Predicted vs. observed cumulative incidence of transitions from recurrence-free to death in each arm

a. Pembrolizumab, for trial period

b. Pembrolizumab, for long term period separating the combination of distributions in 6 different panels for each approach

c. Observation, for trial period

d. Observation, for long term period separating the combination of distributions in 6 different panels for each approach

Figure 24: Predicted vs. observed recurrence-free survival in each

a. Pembrolizumab, for trial period

b. Pembrolizumab, for long term period

c. Observation, for long term period

d. Observation, for long term period

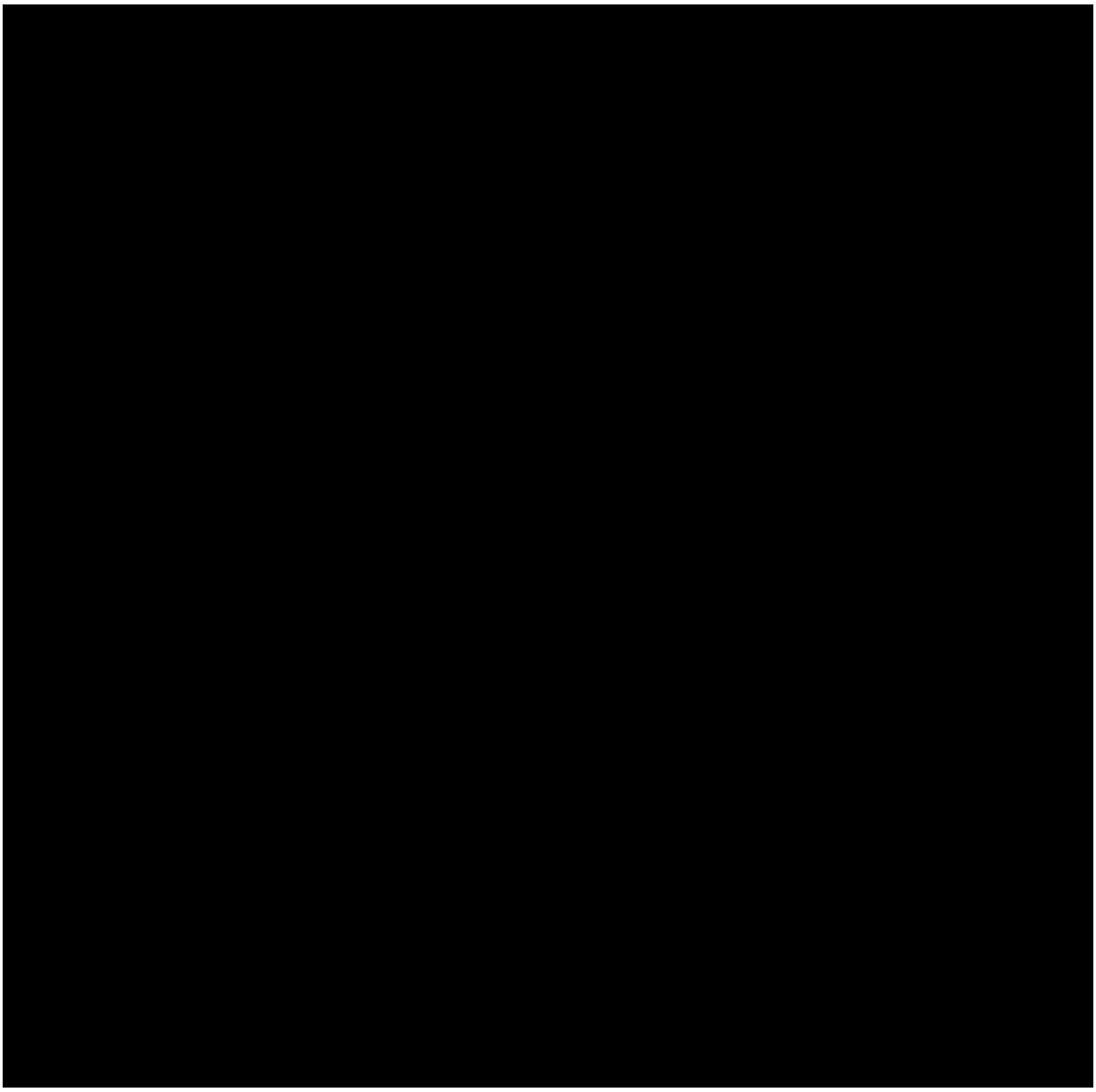
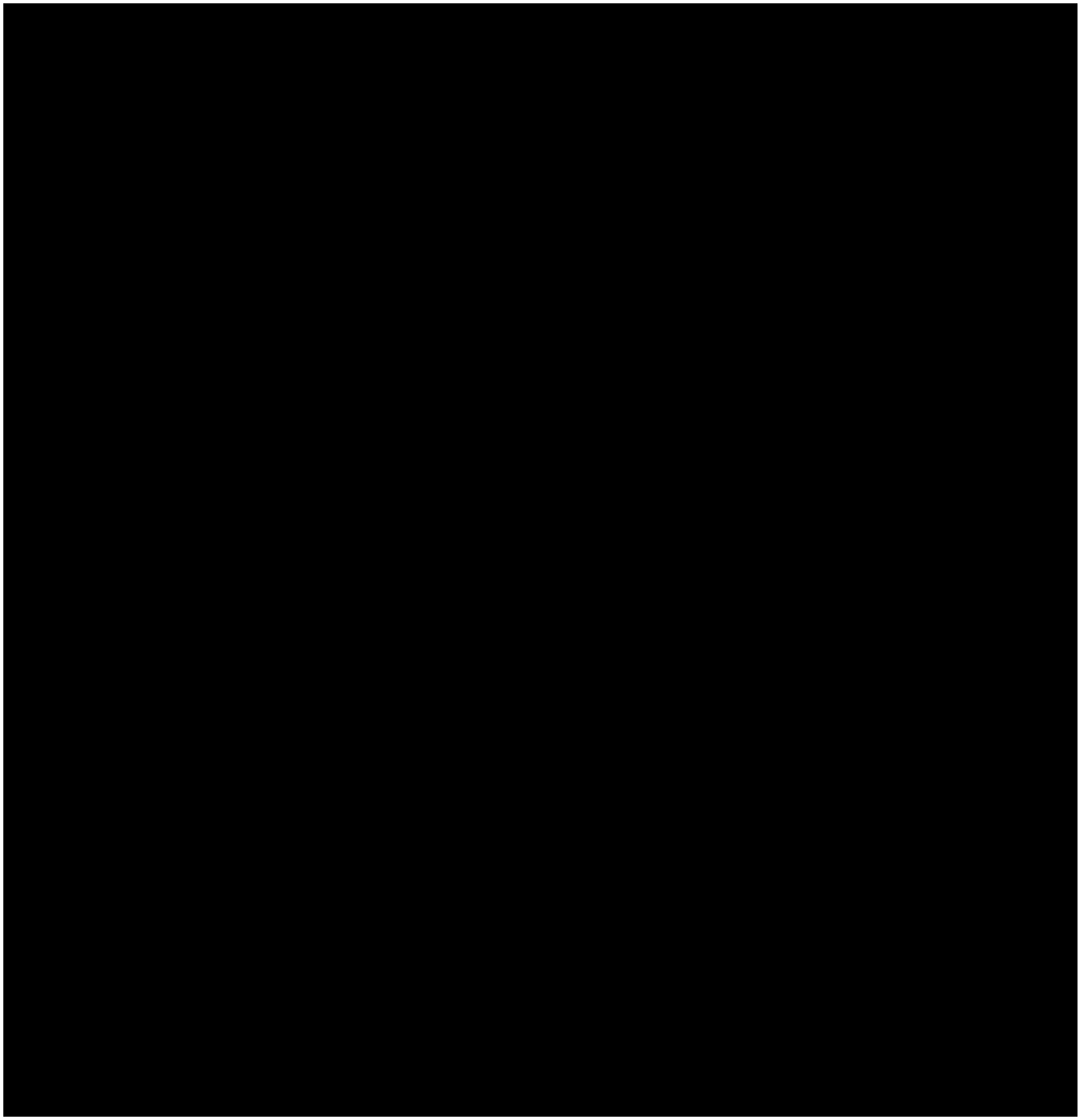


Figure 25: Predicted vs. observed distant metastases-free survival in each arm

a. Pembrolizumab, for trial period

b. Pembrolizumab, for long term period



c. Observation, for trial period

d. **Observation, for long term period**

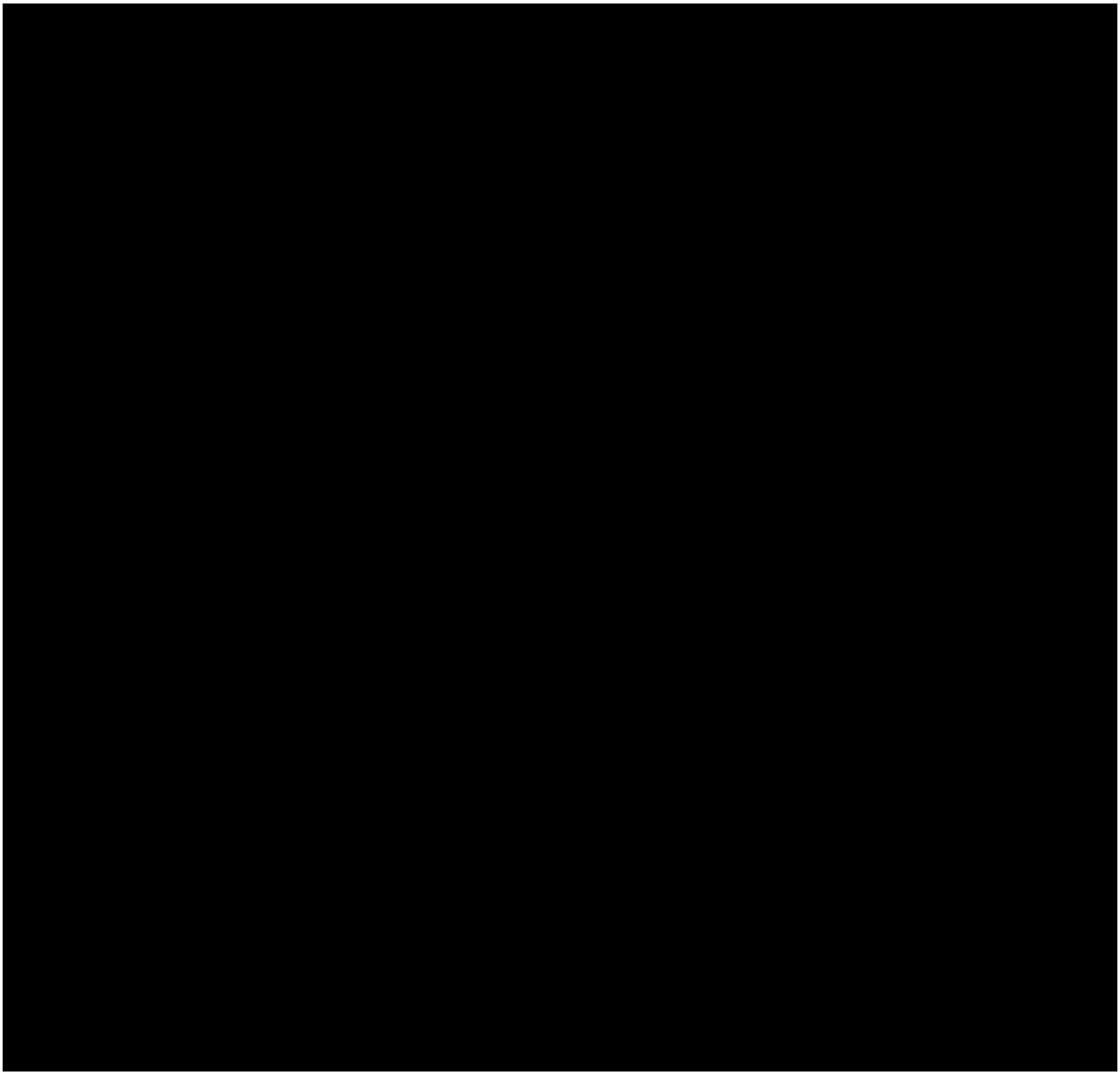


Figure 26: Internal validations of predicted vs. observed cumulative incidences of transitions from the recurrence-free state under the base case

Abbreviations: DM, distant metastases; LR, locoregional recurrence; RF, recurrence-free.

Figur 27: External validation of predicted RFS in the observation arm vs. observed RFS in the real-world USON and Bajaj et al. (2020) studies

a. All 54 combinations of distributions

b. After excluding combinations based on external validity requirements

Figure 28: External validation of predicted DMFS in the observation arm vs. observed DMFS in the real-world USON study

e. All 54 combinations of distributions

f. After excluding combinations based on external validity requirements

11.5.1.1. Alternative parametric modeling approaches

In scenario analyses, alternative parametric distributions were tested for the cause-specific hazards of recurrence-free → locoregional recurrence and recurrence-free → distant metastases in the Pembrolizumab and observation arms, as described in Table 86 below.

Table 86: Alternative parametric distributions tested in scenario analyses

Distributions used for RF→LR and RF→DM in scenario analyses	Rationale for scenario
Gen. gamma / log-normal under Approach #1 (separately fitted)	▪ This combination represented the lower bound of incremental RFS benefit for pembrolizumab vs. observation, among the 14 combinations of distributions that met all criteria with respect to statistical fit, visual assessment, and external validity ▪ This deviates from externally observed RFS and DMFS data for observation to a larger extent than the base case (in an overestimated direction)
Log-normal / exponential under Approach #1 (separately fitted)	▪ This combination represented the upper bound of incremental RFS benefit for pembrolizumab vs. observation, among the 14 combinations of distributions that met all criteria with respect to statistical fit, visual assessment, and external validity
Exponential / exponential under Approach #1 (separately fitted) Exponential / exponential under Approach #2 (jointly fitted, time-constant hazard ratio) Exponential / exponential under Approach #3 (jointly fitted, time-varying hazard ratio)	▪ Among the 14 combinations that met all criteria with respect to visual assessment, statistical fit, and external validity, these combinations most closely matched external data on RFS and DMFS at 10 years ▪ Similar to the base-case combination, Approach #3/exponential/exponential predicted moderate incremental RFS and DMFS benefits for pembrolizumab vs. observation

Gompertz / log-normal under Approach #1 Log-logistic / log-normal under Approach #1 Weibull / log-normal under Approach #1 Exponential / log-normal under Approach #1 Log-logistic / exponential under Approach #1 Weibull / exponential under Approach #1 Weibull / exponential under Approach #2 Weibull / exponential under Approach #3	▪ Other combinations that met all criteria with respect to visual assessment, statistical fit, and external validity

Abbreviations: RF, recurrence-free; RFS, recurrence-free survival; DM, distant metastases; LR, locoregional recurrence.

11.5.1.2. Cure Assumption

In base case analysis, the model provides the functionality to apply a cure assumption among patients who achieve long-term RFS. This analysis was conducted based on several considerations. Namely, as observed in a retrospective study by Lee et al. (2017), the 5-year cumulative incidence for physician-detected relapse was less than 10% across all substages for stage II and levelled off at three years for stage IIB and two years for stage IIC[32]. The 5-year cumulative incidence for image-detected relapse in this study was also close to the pattern of physician-detected relapse[32]. Sundhedsstyrelsens "pakkeforløb for modermærkekræft" also clearly describes that that patients with stage II melanoma are discharged beyond 5 years[1]. Furthermore, two retrospective care series studies indicate that 71.0%-90.7% of recurrences were recorded in the first 5 years of follow up for stage I/II and stage I/II+III melanoma patients and there are very few recurrences occurring beyond 10 years for patients with stage II melanoma who remain recurrence-free[58, 59]. Lastly, similar cure assumptions have been utilized in numerous past NICE and Canadian Agency for Drugs and Technologies in Health appraisals for early-stage cancers[60-64].

When the cure assumption is applied, the per-cycle risks of locoregional recurrence and distant metastases from the recurrence-free state (as estimated under the scenario with no cure assumption) is reduced by a user-specified percentage (95% by default) for patients who achieve RFS ≥ a specified time point (10 years by default).

Starting from an earlier user-modifiable time point (7 years by default), the percentage reduction in recurrence risk begins to linearly increase from 0% at 7 years to 95% by 10 years onward. The same percentage risk reduction is applied to the risk of transitions from recurrence-free to death, subject to the constraint that this risk must always be at least as high as background mortality in each cycle.

11.5.2. Transitions from locoregional recurrence to distant metastases

Scenario analysis using other data sources for transitions from LR state

As scenario analyses, the model also provides the option to use the original data sources for transitions from the LR state. Patients were considered to have resectable stage III melanoma upon entry into the LR state. Thus, the cause-specific hazards of LR→DM and LR→death were originally modeled to depend upon the market shares and relative efficacy of subsequent treatments that patients may receive in the LR state. Potential management strategies in the LR state in Denmark could include treatment with an adjuvant treatment indicated for resected stage III melanoma (specifically, pembrolizumab, nivolumab, dabrafenib + trametinib) or no adjuvant treatment (i.e., observation alone).

For patients who receive no adjuvant therapy in the LR state, cause-specific hazards of LR→DM and LR→death transitions were fitted using a real-world electronic medical records database. Specifically, an observational study was conducted using the US Oncology Network's iKnowMed (iKM) and electronic health record (EHR) database as well as Limited Access Death Master File (LADMF). The analytical sample included patients who underwent surgical resection of stage II melanoma and were subsequently identified as having a locoregional recurrence. Among these patients, exponential parametric functions were fitted to observed data on time to distant metastases and time to death from the time of entry into the locoregional state, accounting for competing risks (Table 87). When modeling each of these transitions, patients were censored at the end of follow-up or upon the occurrence of the competing transition type. Within the LR state, patients may receive treatment consisting of salvage surgery followed by routine observation alone or with an adjuvant treatment approved for resected stage III melanoma.

For patients who receive a subsequent adjuvant treatment in the LR state, the model considered two different approaches to estimate transition probabilities from the LR state:

a. **Scenario analysis: Use trial-based HRs of DMFS failure:** Under the base-case approach, transition probabilities were estimated using trial-based HRs of DMFS failure for each adjuvant treatment vs. placebo, as reported in randomized controlled trials conducted in the stage III melanoma setting. These HRs are applied to the exponential rates of each transition (LR→DM and LR→death) among patients who receive no adjuvant treatment in this setting (Table 88a).

b. **Scenario analysis: Using estimates based on EHR data:** Under this alternative scenario, exponential rates of these transitions are estimated through analyses of real-world electronic health record data. Under this approach, transition probabilities are not differentiated by specific adjuvant treatment received for stage III melanoma (Table 88b).

Table 87: Weekly exponential rates of transitions starting from locoregional recurrence among patients who receive no subsequent adjuvant treatment (used in scenario analyses only)

Adjuvant regimen in LR state	LR → DM		LR → Death		Source
	Exponential rate	SE	Exponential rate	SE	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; LR, locoregional recurrence; SE, standard error.

Table 88: Weekly exponential rates of transitions starting from locoregional recurrence among patients who receive subsequent adjuvant treatment

a. Scenario analysis: Using trial-based HRs of DMFS failure

Adjuvant regimen in LR state	HR of DMFS failure vs. no adjuvant treatment			Weekly exponential rate	
	HR	SE of ln(HR)	Source	LR → DM	LR → Death
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. Scenario analysis: Using estimates based on electronic health records data

Adjuvant regimen in LR state	LR → DM		LR → Death		Source
	Exponential rate	SE	Exponential rate	SE	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; HR, hazard ratio; LR, locoregional recurrence; SE, standard error; US, United States.

Note:
In the CheckMate 238 trial of nivolumab as an adjuvant treatment of resected stage III or IV melanoma, the comparator arm was an adjuvant ipilimumab regimen that differed from the ipilimumab regimen evaluated in the EORTC 18071 trial (i.e., the maximum duration of ipilimumab was 1 year in CheckMate 238 vs. 3 years in EORTC 18071). The HR of DMFS failure for nivolumab vs. no adjuvant treatment therefore could not be estimated directly or indirectly using results from CheckMate 238.

In each model arm, the exponential rates of LR→DM and LR→death were each calculated as a weighted average based on: the exponential rates of these transitions for each subsequent adjuvant treatment regimen (Table 87 and Table 88) and the market shares of subsequent adjuvant treatments by model arm

11.5.3. Transitions from distant metastases to death

Estimation of the hazard rate of death from distant metastases by adjuvant treatment arm

Table 89: Hazards of death from distant metastases by model arm under base-case market shares of first-line treatments for advanced melanoma

Adjuvant regimen	Eligibility for rechallenge / anti-PD-1/PD-L1s in the advanced melanoma setting	Expected survival in distant metastases state (weeks): Weighted average based on first-line advanced treatment market shares			Distant metastases → death: Exponential hazard rate based on expected OS
		OS	PFS	Ratio of PFS to OS	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

11.6. Model Validation - Verification

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken by the model developer team to ensure that the mathematical calculations are performed correctly and are consistent with the model's specifications. The model was also independently reviewed by two external health economists, who evaluated the model from an overall health economics perspective.

The internal validity of the model was also assessed by comparing modelled efficacy outcomes against the original sources that informed the efficacy inputs. For example, the RFS and DMFS curves predicted for the two arms of KEYNOTE-716 were plotted alongside the observed Kaplan-Meier curves for RFS and DMFS to ensure that the curves are well-aligned during the trial period.

Validation has also been performed according to the Danish Medicines Council check and the detailed steps are described in appendix N.

11.7. Model Validation - External validation

Model predictions were compared against observed data from three published external studies that reported long-term RFS and/or OS in real-world cohorts of patients diagnosed with AJCC 8th edition stage IIB or IIC melanoma [49, 56, 57]. These three external studies were conducted in distinct patient cohorts, including two US-based cohorts [49, 56] and one European cohort[57]. Survival projections in the observation arm were also validated against long-term RFS, DMFS, and OS observed in a real-world study using US Oncology Network electronic health records [48]. Additionally, international clinical experts were consulted to validate the efficacy inputs (e.g., the plausibility of long-term RFS, DMFS, and OS) and other key model decisions (e.g., assumptions about post-recurrence treatments) from a clinical perspective.

11.8. Model Validation - Cross-validation

A targeted search for HTA submissions in adjuvant oncology settings did not identify any prior submissions for adjuvant treatments for high-risk stage II melanoma. Consequently, it was not possible to cross-validate the current model results against other, independently developed economic evaluations in the same indication. However, prior HTAs and published cost-effectiveness studies in other adjuvant oncology indications provided support and precedence for the assumptions used in the current model.

Appendix H – Literature search for HRQoL data

NA

Appendix I - Mapping of HRQoL data

NA

Appendix J – PSA inputs

Table 90: PSA inputs

Input parameter		Distribution	Mean	SE	Note
Parameter estimates for RF→LR	Parameter A, observation	Multivariate normal	7,29	-	Uncertainty in the cause-specific hazards of transitioning from recurrence-free to locoregional recurrence, distant metastases, and death is represented by the variance-covariance matrix or standard errors of the parameter estimates.
	Parameter B, observation	Multivariate normal	2,280	-	
	Parameter A, Pembrolizumab	Multivariate normal	7,92	-	
	Parameter B, Pembrolizumab	Multivariate normal	2,533	-	
Parameter estimates for RF→DM	Parameter A, observation	Multivariate normal	5,97	-	
	Parameter B, observation	Multivariate normal	1,38	-	
	Parameter A, Pembrolizumab	Multivariate normal	6,42	-	
	Parameter B, Pembrolizumab	Multivariate normal	1,362	-	
Parameter estimates for RF→Death	Parameter A, observation	Normal	0,0001	-	
	Parameter A, Pembrolizumab	Normal	0,0001	-	
Exponential rates of LR→DM	Pembrolizumab	Normal	0,0085	0,0011	SEs are based on the original source for these exponential rates, i.e., US Oncology Network electronic health records.
	Observation	Normal	0,0053	0,0014	
Exponential rates of LR→Death	Pembrolizumab	Normal	0,0001	0,0005	
	Observation	Normal	0,0001	0,0006	
HR of DMFS failure vs. no adjuvant treatment	Pembrolizumab, HR of DMFS vs. no adjuvant treatment	Log-normal	0,60	0,102	HRs for adjuvant regimens vs. no adjuvant treatment in the stage III melanoma setting were obtained from randomized controlled trials in this setting.
	Nivolumab, HR of DMFS vs. no adjuvant treatment	Log-normal	0,60	0,102	
	Ipilimumab, HR of DMFS vs. no adjuvant treatment	Log-normal	0,76	0,093	
	Dabrafenib + trametinib, HR of DMFS vs. no adjuvant treatment	Log-normal	0,55	0,118	
Exponential rates of OS and PFS failure with different treatments in the advanced melanoma setting	Pembrolizumab, OS	Normal	0,01	0,001	Exponential rates and corresponding standard errors for Pembrolizumab were estimated based on long-term results from the KEYNOTE-006 trial; HRs for other advanced regimens vs. Pembrolizumab were obtained from a network meta-analysis of trials in the advanced melanoma setting. Percentile matching is used for each OS/PFS pair to preserve the rank of these two outcomes for each treatment regimen.
	Pembrolizumab, PFS	Normal	0,02	0,001	
	Ipilimumab, HR of OS vs. Pembrolizumab	Log-normal	1,47	0,117	
	Ipilimumab, HR of PFS vs. Pembrolizumab	Log-normal	1,82	0,111	
	Nivolumab, HR of OS vs. Pembrolizumab	Log-normal	0,80	0,152	
	Nivolumab, HR of PFS vs. Pembrolizumab	Log-normal	0,75	0,141	
	Nivolumab + ipilimumab, HR of OS vs. Pembrolizumab	Log-normal	1,36	0,260	
	Nivolumab + ipilimumab, HR of PFS vs. Pembrolizumab	Log-normal	0,77	0,261	
	Dabrafenib + trametinib, HR of OS vs. Pembrolizumab	Log-normal	1,09	0,232	
	Dabrafenib + trametinib, HR of PFS vs. Pembrolizumab	Log-normal	0,56	0,231	
	Encorafenib + binimetinib, HR of OS vs. Pembrolizumab	Log-normal	1,00	0,231	
	Encorafenib + binimetinib, HR of PFS vs. Pembrolizumab	Log-normal	0,53	0,231	
Medical management costs by health state	Medical management costs in RF state (per week, up to year 3)	Gamma	155,60	6,22	SE assumed to be equal to 20% of the base-case value.
	Medical management costs in RF state (per week, years 3-5)	Gamma	35,84	1,43	
	Medical management costs in RF state (per week, years 5-10)	Gamma	2,75	0,11	

	Salvage surgery costs upon LR state entry (one-time cost)	Gamma	21112,52	844,50	
	Medical management costs in LR state (per week)	Gamma	185,03	7,40	
	Medical management costs in pre-progression DM state (per week)	Gamma	201,69	8,07	
	Medical management costs in post-progression DM state (per week)	Gamma	201,69	8,07	
	Terminal care cost (one-time cost)	Gamma	13874,66	554,99	
Drug administration costs	Unit cost of simple IV drug administration	Gamma	2041,00	408,20	SE assumed to be equal to 20% of the base-case value.
		Gamma	2041,00	408,20	
Cost of AEs	Pembrolizumab	Gamma	824,18	164,84	SE assumed to be equal to 20% of the base-case value.
	Observation	Gamma	441,33	88,27	
Utilities and disutilities	Utility of RF (without toxicity)	Beta	0,93	0,004	SEs are based on the original sources for the utility inputs, i.e., KEYNOTE-716 and Beusterien et al. 2009. (Note: If utility values from Middleton et al. 2017 are used, SEs are assumed to be equal to 20% of the mean.) Percentile matching is used to preserve rank of utility values from best to worst health state.
	Utility of LR	Beta	0,90	0,01	
	Utility of pre-progression DM	Beta	0,86	0,01	
	Utility of post-progression DM	Beta	0,86	0,01	
	Disutility from AEs	Normal	-0,05	0,01	
	Utility associated with age (18-29)	Beta	0,87	0,17	SE assumed to be equal to 20% of the absolute value of the mean.
	Utility associated with age (30-39)	Beta	0,85	0,17	
	Utility associated with age (40-49)	Beta	0,83	0,17	
	Utility associated with age (50-69)	Beta	0,82	0,16	
	Utility associated with age (70-79)	Beta	0,81	0,16	
	Utility associated with age (80+)	Beta	0,72	0,1442	

Abbreviations: AE, Adverse event; DM, distant metastases; DMFS, Distant metastases-free survival; IV, intravenous; LR, locoregional recurrence; OS, overall survival; PFS, progression-free survival; RF, recurrence-free; SE, standard error.

Appendix K – Additional scenarios

Appendix L lists the additional scenarios evaluated for the Danish Medicines Council as a part of the validation process. The detailed steps involved for performing various scenarios are described in Tabel 91.

Tabel 91: Denmark Scenario Analysis

S/N	Tasks	Steps involved	ICER (DKK/QALY)	% Change in ICER
1.	Set the patient number to zero	• Set the value of cell H20 in both Trace_AdjReg1 and Trace_AdjReg2 to zero • Set the values of column C of Raw_ToT KM curves to zero	0	100%
2.	Set the patient number to one	The model calculations are based on one patient	240.448	No change
3.	Set efficacy, administration, monitoring, AEs and patient costs to be to be the same for both intervention and comparator	Efficacy is already set same in the model and unit monitoring, AE, administration, and patient costs are same.	240.448	No change
4.	Set the mortality rate to 100 %	Set AG and AV column of Life Tables sheet to 1 starting from row 22	662.266.003	Huge Increase in ICER
5.	Reduce Mortality Rate to 0%	Set the column AG and AV to zero from row 22	210.726	44,13% decrease in ICER
6.	Set all unit costs for administration and monitoring to double level	• Multiplied the Unit cost of Recurrence Free State, Locoregional sate (Cell H74:R74) and Distant Metastasis (Cell J114:L114) disease management cost with 2 in HCRU sheet • Multiplied the Unit cost of administration cost (Cell H138:K139) with 2 in Drug & Admin Cost sheet.	385.775	2,26% increase in ICER
7.	Set all unit costs for administration and monitoring to zero	• Updated the Unit cost of monitoring (Cell G15:G46) into 0 in HCRU sheet • Updated the Unit cost of administration cost (Cell H138) to 0 in Drug & Admin Cost sheet	368.676	2,26% decrease in ICER
8.	Set the costs of AEs to zero	Selected “consider AE cost” and “ AE related disutility” as No in Model Specifications sheet. This will set the cost of AEs to zero.	376.419	ICER decreases by 0,21%

9.	Raise the time horizon	Updated the starting age (I6) to 30 in Raw – Demographics sheet	186.120	50,66% decrease in ICER
10.	Reduce the time horizon	Updated the starting age (I5) to 70 in Raw – Demographics sheet	779.421	107% increase in ICER
11.	Raise the discount rate to 100%	Updated the discount rate for cost and effectiveness in specifications sheet	27.496.239	Big change in Cost and QALY's, ICER increases 73 times from the base case
12.	Reduce the discount rate to 0%	Updated the discount rate for cost and effectiveness in specifications sheet	210.995	44,06% decrease in ICER
13.	For subsequent treatments: adjust the percentages for the different treatments	Changed some of the cells like D7(60), D9(20), D12(20) in Raw – Market shares sheet	411.840	9,17% increase in ICER

Appendix L - Overview of sources used for external validation

Model predictions were compared against observed data from three published external studies that reported long-term RFS and/or OS in real-world cohorts of patients diagnosed with AJCC 8th edition stage IIB or IIC cutaneous melanoma[49, 56, 57].

Attributes of the three external studies are summarized below in Table 83. RFS and OS data from Bajaj et al. (2020) were used to validate modeled RFS and OS in the observation arm up to ~7 years. OS data from Bleicher et al. (2020) and Kanaki et al. (2019) were used to validate modeled OS in the observation arm up to ~10 years. Of note, Bleicher et al. also reported RFS for patients with stage IIA and IIB melanoma up to ~10 years; however, 2-year RFS reported by Bleicher et al. (IIB: 90,5%; IIC: 81,7%; pooled IIB/IIC, using stage distribution from KEYNOTE-716: 87,4%) was ~16 percentage-points higher than 2-year RFS observed in the placebo arm of KEYNOTE-716 (71,7%) and ~7 percentage-points higher than that observed in the Pembrolizumab arm (80,5%). The large difference in observed RFS between Bleicher et al. and KEYNOTE-716, despite the apparent comparability of the study populations, suggested potential inconsistencies in the definition or measurements of RFS that could not be determined from the information provided in the publication. Nevertheless, this source was retained for use in the external validation of OS, as the OS curves for stage IIA and IIB in Bleicher et al. were within the range of OS data from the other included external validation sources.

In addition to these three studies, survival projections in the observation arm were also validated against long-term (up to 10-year) RFS, DMFS, and OS observed in a real-world study using US Oncology Network electronic health records (data on file).

Several other published real-world cohort studies[23, 134] and clinical trials[41, 74] among patients with stage II melanoma were also reviewed, but were found to be unsuitable as external validation sources due to differences in the patient characteristics, outcome definitions, and/or treatment protocols. Specific reasons for the exclusion of each source are summarized in Table 92.

Table 92: Characteristics of published real-world studies included in external validity assessments

Attribute	Bajaj et al. (2020)	Bleicher et al. (2020)	Kanaki et al. (2019)
Data source / setting	NYU Langone Health Interdisciplinary Melanoma Cooperative Group prospective cohort database (2010-2016)	Electronic health records from the University of Utah Huntsman Cancer Institute (2000-2017)	Retrospective cohort within the tumour registries of the Department of Dermatology Essen, Germany (2003-2018)
Age of study population	Mean: 58,6 years[1]	Median: 62 years[2]	Median: 60 years[3]
Median follow-up	2,9 years[1]	4,9 years[2]	3,3 years[3]
Sample sizes in IIB/IIC	IIB: N=63 IIC: N=27	IIB: N=220 IIC: N=80	IIB: N=290 IIC: N=126
Availability of RFS	Kaplan-Meier RFS curves presented up to ~7 years for IIB and IIC	Kaplan-Meier RFS curves presented up to ~10 years for IIB and IIC	Not reported
Availability of DMFS	Not reported	Not reported	Not reported
Availability of OS	Kaplan-Meier OS curves presented up to ~7 years for IIB and IIC	Kaplan-Meier OS curves presented up to ~10 years for IIB and IIC	5-year and 10-year OS reported for IIB and IIC

Notes:

[1] Mean age and median follow-up in Bajaj et al. is reported across stages I-III.

[2] Median age and follow-up in Bleicher et al. is reported across stages IIA-IIC.

[3] Median age and follow-up in Kanaki et al. is reported across stage I-IV.

Tabel 93: Additional studies excluded from external validity assessments

Study	Reason for exclusion
Leiter et al. (2012)	RFS was reported only for a combined stage IIA-IIC melanoma cohort. The inclusion of patients with stage IIA (comprising 55% of the IIA-IIC cohort) would prevent an interpretable comparison with modeled RFS in the stage IIB-IIC target population.
Gershenwald et al. (2017)	This study within the International Melanoma Database and Discovery Platform cohort only reported melanoma-specific survival (MSS), which is not directly comparable to OS. Moreover, several subsequent studies have reported substantially lower MSS relative to that reported for the IMDDP cohort (for example, see discussion in Kanaki et al. 2019).
Eggermont et al. (2020) [EORTC 18081 trial]	This trial was excluded due to the focus on patients with ulcerated melanoma and under-recruitment of patients.
Hansson et al. (2011) [Nordic IFN trial]	This trial was excluded due to the use of an outdated tumor staging system and limited use of sentinel node biopsy (discussed in the study publication).

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer.

Appendix M - Summary of all the possible combination of distribution that meets criterion for each of the steps

Different parametric distribution combination involved in different steps for selecting base case parametric distribution.

Table 94: Parametric distributions considered to model transitions starting from recurrence-free

Step 0: Total of 54 potential combinations of parametric distributions, each resulting in a different RFS curve

Overall approach	Distribution considered for each transition			# Potential combination of distribution
	RF → LR	RF → DM	RF → Death	
Approach 1: Parametric models separately fitted to each treatment arm	Exponential	Exponential	Exponential*	6*6*1=36
	Gompertz	Gompertz		
	Weibull	Weibull		
	Generalized gamma	Generalized gamma		
	Log-logistic	Log-logistic		
	Log-normal	Log-normal		
Approach 2: Proportional hazards parametric models jointly fitted to both treatment arms with a time-constant treatment effect	Exponential	Exponential	Exponential*	3*3*1=9
	Gompertz	Gompertz		
	Weibull	Weibull		
Approach 3: Proportional hazards parametric models jointly fitted to both treatment arms with a time-varying treatment effect	Exponential	Exponential	Exponential*	3*3*1=9
	Gompertz	Gompertz		
	Weibull	Weibull		

*(due to small number of direct transitions from DM to death)

Step 1: Initial exclusions based on clinical plausibility: KEYNOTE-054 RFS and DMFS as lower bounds (combinations of parametric distributions were excluded if they resulted in lower 4-year RFS and/or DMFS for either pembrolizumab or observation than that reported for the corresponding arms of KEYNOTE-054 (adjuvant stage III melanoma), given the expectation of better prognosis in the stage IIB-C population).

Rank by RFS MSE (Out of all 54 combinations under approaches 1-3)	Rank by DMFS MSE (Out of all 54 combinations under approaches 1-3)	Parametric distribution considered for each transition	
		RF → LR	RF → DM
1	4	Log-normal	Generalized gamma
2	5	Generalized gamma	Generalized gamma

3	3	Log-logistic	Generalized gamma
4	2	Weibull	Generalized gamma
5	6	Gompertz	Generalized gamma
6	1	Exponential	Generalized gamma
17	8	Generalized gamma	Gompertz
22	9	Log-normal	Gompertz
23	7	Gompertz	Gompertz
28	10	Log-logistic	Gompertz
34	11	Weibull	Gompertz
41	12	Exponential	Gompertz

Step 2: Statistical fit based on mean squared error (MSE). (Combinations ranked among the ten worst-fitting for both RFS and DMFS in the observation arm were therefore excluded (8 combinations excluded)).

Rank by MSE (Out of all 54 combinations under approaches 1-3)	Rank by MSE (Out of all 54 combinations under approaches 1-3)	Parametric distribution considered for each transition	
		RF → LR	RF → DM
46	50	Weibull	Weibull
47	45	Weibull	Gompertz
51	47	Exponential	Gompertz
53	52	Exponential	Weibull
49	46	Weibull	Gompertz
50	53	Weibull	Weibull
52	48	Exponential	Gompertz
54	54	Exponential	Weibull

Step 3: Visual assessment of fit (no exclusion was performed on the basis of visual fit only).

Rank by MSE (Out of all 54 combinations under approaches 1-3)	Rank by MSE (Out of all 54 combinations under approaches 1-3)	Parametric distribution considered for each transition	
		RF → LR	RF → DM
46	50	Weibull	Weibull
47	45	Weibull	Gompertz
51	47	Exponential	Gompertz
53	52	Exponential	Weibull
49	46	Weibull	Gompertz
50	53	Weibull	Weibull
52	48	Exponential	Gompertz

54	54	Exponential	Weibull

Step 4: External validations / clinical plausibility of predicted RFS, DMFS, and OS (combinations of parametric distributions were excluded if their predicted RFS and DMFS in the observation arm up to 7 years will not fall within +/- 5 percentage points of external RFS and DMFS data)

Rank by MSE (Out of all 54 combinations under approaches 1-3)	Rank by MSE (Out of all 54 combinations under approaches 1-3)	Parametric distribution considered for each transition	
		RF → LR	RF → DM
10	30	Generalized gamma	Log-logistic
12	28	Gompertz	Log-logistic
14	32	Log-normal	Log-logistic
15	38	Generalized gamma	Weibull
16	37	Gompertz	Weibull
21	39	Log-normal	Weibull
24	34	Log-logistic	Log-logistic
29	35	Weibull	Log-logistic
37	40	Log-logistic	Weibull
40	27	Generalized gamma	Exponential
39	41	Weibull	Weibull
43	31	Gompertz	Exponential
44	36	Exponential	Log-logistic
48	44	Exponential	Weibull
27	49	Gompertz	Weibull
35	43	Gompertz	Gompertz
42	29	Gompertz	Exponential
25	51	Gompertz	Weibull
30	42	Gompertz	Gompertz
45	33	Gompertz	Exponential

Step 5: Plausibility of predicted incremental benefit with pembrolizumab vs. observation (combinations for which RFS and DMFS benefits with pembrolizumab vs. observation is relatively low was excluded).

Rank by MSE (Out of all 54 combinations under approaches 1-3)	Rank by MSE (Out of all 54 combinations under approaches 1-3)	Parametric distribution considered for each transition	
		RF → LR	RF → DM
7	15	Generalized gamma	Log-normal
8	13	Log-logistic	Log-normal

8	36	Gompertz	Log-normal
13	14	Weibull	Log-normal
18	19	Exponential	Exponential
26	18	Exponential	Lognormal
31	24	Log-logistic	Exponential
32	22	Weibull	Exponential
19	20	Exponential	Exponential
36	25	Weibull	Exponential
20	21	Exponential	Exponential
33	23	Weibull	Exponential
38	26	Log-normal	Exponential

For base case analysis, log normal/log normal was used and the rest thirteen were used in scenario analyses.