Medicinrådet

Bilag til Medicinrådets anbefaling vedr. pembrolizumab i kombination med kemoterapi som neoadjuverende behandling efterfulgt af pembrolizumab monoterapi som post-operativ adjuverende behandling af triple-negativ brystkræft

Patienter med lokalt fremskreden eller tidlig triple-negativ brystkræft med høj risiko for recidiv

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. pembrolizumab i kombination med kemoterapi som neoadjuverende behandling
2. Forhandlingsnotat fra Amgros vedr. pembrolizumab i kombination med kemoterapi som neoadjuverende behandling
3. Ansøgers endelige ansøgning vedr. pembrolizumab i kombination med kemoterapi som neoadjuverende behandling
4. Notat om sammenligning af adjuverende behandling i hhv. KN522-studiet og CREATE-X-studiet

DATO: 23. januar 2023

Til: Medicinrådet, att. Agla Jael Fridriksdottir og Malene Essenbæk Jakobsen, Dampfærgevej 21-23, 3. sal, 2100 København Ø

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Notat til høring om udkast til Medicinrådets anbefaling vedr. pembrolizumab i kombination med kemoterapi som (neo)adjuverende behandling af TNBC

MSD Danmark takker for muligheden for at komme med bemærkninger til Medicinrådets udkast til anbefaling vedr. pembrolizumab i kombination med kemoterapi som neoadjuverende behandling efterfulgt af pembrolizumab monoterapi som post-operativ adjuverende behandling af triple-negativ brystkræft.

Indledningsvist vil vi kvittere for en konstruktiv og åben dialog med sekretariatet igennem hele vurderingsprocessen. Vi har oplevet, at sekretariatet har været meget professionelt og tilgængeligt, hvilket har medvirket til en nyttig forventningsafstemning og hurtig afklaring af misforståelser undervejs i processen.

For så vidt angår **den kliniske del** af vurderingsrapporten bemærker vi særligt følgende:

- KN522-studiets patientpopulation svarer til den forventede patientpopulation i dansk klinisk praksis.
- Kontrolarmens pCR-rate i KN522-studiet er forventelig og sammenlignelig med historisk publicerede pCR-rater efter neoadjuverende behandling med platinbaserede regimer samt dansk klinisk praksis.
- For et samlet behandlingsforløb fra neoadjuverende behandling efterfulgt af operation og adjuverende behandling repræsenterer KN522-studiet et stærkere evidensgrundlag end den evidens, der ligger til grund for nuværende behandlingspraksis for patienter med tidlig triple-negativ brystkræft.
- EFS- og pCR-data fra KN522-studiet indikerer, at flere patienter bliver kureret ved (neo)adjuverende behandling med pembrolizumab i kombination med kemoterapi sammenlignet med nuværende dansk standard, da flere patienter opnår pCR, og færre patienter får tilbagefald i interventionsarmen under den periode, hvor patienternes risiko for tilbagefald er størst.
- Data for pCR korrelerer med en lavere risiko for recidiv og bedre overlevelse, især hos patienter med triple-negativ brystkræft.
- Der ses en halvering i både antallet af patienter, der udvikler fjernrecidiv samt antallet af patienter, der progredierer før operation i pembrolizumab-kemoterapi-armen sammenlignet med kemoterapi-armen, hvilket er hændelser, som er forbundet med en dårlig prognose.
- Data fra KN522-studiet viser, at behandling med pembrolizumab i kombination med kemoterapi hverken er forbundet med forbedring eller forværring i patienternes selvrapporterede livskvalitet sammenlignet med placebo i kombination med kemoterapi.
- Pga. studiedesignet er det ikke muligt at analysere effekten på EFS separat i den neoadjuverende og adjuverende fase i KN522, men kun i det samlede behandlingsforløb.

Desuden bemærker vi særligt følgende angående den sundhedsøkonomiske del af vurderingsrapporten:

- Vi anerkender præsentationen af resultaterne i to scenarier som et spænd, hvor omkostningseffektiviteten af pembrolizumab i kombination med kemoterapi kan befinde sig indenfor. Vi mener, det er en fornuftig fremgangsmåde i forhold til at skabe et beslutningsgrundlag, der tager højde for den usikkerhed, som uvægerligt vil forekomme ved modelleringer over en længere årrække.
- Vi noterer os, at selv med brug af konservative antagelser i den sundhedsøkonomiske model er behandlingen med pembrolizumab i kombination med kemoterapi forbundet med en betydelig QALY-gevinst og en omkostningseffektratio (ICER), der ligger på et niveau, man normalt vil betragte som omkostningseffektivt.
- I den forbindelse noterer vi os, at NICE i England foretog lignende ændringer med henblik på en konservativ estimering af ICER'en, hvilket udmøntede sig i, at NICE i november 2022 besluttede at anbefale pembrolizumab i kombination med kemoterapi som (neo)adjuverende behandling af TNBC. Anbefalingen skete bl.a. på baggrund af følgende konklusion fra ekspertgruppen (ERG) under NICE om den konservativt estimerede ICER: "*the ERG's alternative base case is below the range normally considered a cost-effective use of NHS resources*"

Vi er enige i ovenstående kliniske og sundhedsøkonomiske konklusioner fra vurderingsrapporten, der indikerer, at pembrolizumab i kombination med kemoterapi udgør et markant behandlingsfremskrift for patienterne, der gennemsnitligt er yngre og har en forværret prognose med højere risiko for tilbagefald og død sammenlignet med øvrige brystkræftpatienter, uanset stadie ved diagnose.

[redacted]

[redacted]

Med venlig hilsen,

Simon Leth
Chef for sundhedsøkonomi

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27.01.2023

DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	22.02.2023
Leverandør	MSD
Lægemiddel	Keytruda (pembolizumab)
Ansøgt indikation	Keytruda (pembrolizumab) i kombination med kemoterapi som neoadjuverende behandling efterfulgt af pembrolizumab monoterapi som post-operativ adjuverende behandling af triple-negativ brystkræft
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)	Rabatprocent ift. AIP
Keytruda	25 mg/ml	4 ml	22,624,19	[redacted]	[redacted]	[redacted]

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 udløber d. 31.12.2023.

Informationer fra forhandlingen

Keytruda omsætter i dag for ca. [redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence indenfor denne indikation.

Tabel 2: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år	Lægemiddeludgift pr. år (SAIP, DKK)
Keytruda	25 mg/ml	4 ml	2 mg/kg hver 3. uge IV	[redacted]*, **	26	[redacted]
Opdivo (nivolumab)	100 mg/ml	1	4,5 mg/kg	[redacted]	18	[redacted]

**Vægtjustere dosering. Patient vægt: 74,3 kg*
***Pakningspris med [redacted] rabat*

Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Pembrolizumab (Keytruda) - Indikasjon XXI (nyemetoder.no)
Sverige	Anbefalet		Keytruda (pembrolizumab) för neoadjuvant och adjuvant behandling av trippelnegativ bröstcancer (janusinfo.se)
England	Anbefalet		1 Recommendations | Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer | Guidance | NICE

Konklusion

Amgros vurderer, at leverandøren på nuværende tidspunkt ikke kan give en bedre pris på Keytruda før der kommer indikationsudvidelser med større patientpopulationer.

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Ansøgning om vurdering af KEYTRUDA® (pembrolizumab) i kombination med kemoterapi til neoadjuverende behandling og efterfulgt af monoterapi som post-operativ adjuverende behandling af voksne med lokalt avanceret eller tidlig triple-negativ brystkræft med høj risiko for recidiv

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Indholdsfortegnelse

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

1. Basisinformation

Contact information	
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Name	**Truc Hoang**
Title	Medical Advisor
Phone number	+45 31 61 09 11
E-mail	Truc.hoang@merck.com

Overview of the pharmaceutical	
Proprietary name	KEYTRUDA®
Generic name	Pembrolizumab
Marketing authorization holder in Denmark	MSD Danmark ApS MSD modtog d. 24. Maj 2022 European Medicines Agency (EMA) committee for Medicinal Products for Human Use (CHMP) commission decision for
ATC code	L01XC18
Pharmacotherapeutic group	Antineoplastic agents
Active substance(s)	Pembrolizumab
Pharmaceutical form(s)	Koncentrat til infusionsvæske, opløsning.

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Overview of the pharmaceutical	
Mechanism of action	KEYTRUDA® er et humaniseret monoklonalt antistof, der binder til programmed cell death-1 (PD-1)-receptoren og blokerer dets interaktion med liganderne PD-L1 og PD-L2. KEYTRUDA® aktiverer T-cellemedieret respons, herunder anti-tumorrespons, ved at blokere PD-1-bindingen til PD-L1 og PD-L2, som er udtrykt i antigenpræsenterende celler, og som kan udtrykkes af tumorer eller andre celler i tumorens mikromiljø.
Dosage regimen	Den anbefalede dosis af KEYTRUDA® som en del af kombinationsbehandling er 200 mg hver 3. uge eller 400 mg hver 6. uge administreret som intravenøs infusion over 30 minutter.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	KEYTRUDA® i kombination med kemoterapi som neoadjuverende behandling, og efterfulgt af monoterapi som post-operativ adjuverende behandling, er indiceret til behandling af voksne med lokalt avanceret eller tidlig triple-negativ brystkræft med høj risiko for recidiv

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Other approved therapeutic indications	KEYTRUDA® som monoterapi er indiceret til behandling af voksne og unge i alderen 12 år og derover med avanceret (ikke-resektabel eller metastatisk) melanom. KEYTRUDA® som monoterapi er indiceret til adjuverende behandling af voksne og unge i alderen 12 år og derover med stadie IIB-, IIC-, eller III-, som har fået foretaget komplet resektion. KEYTRUDA® som monoterapi er indiceret til førstelinjebehandling af metastatisk ikke-småcellet lungecancer hos voksne, hvis tumorer udtrykker PD-L1 med tumour proportion score (TPS) ≥ 50% uden EGFR- eller ALK-positive mutationer i tumor. KEYTRUDA®, i kombination med pemetrexed og platinbaseret kemoterapi, er indiceret til førstelinjebehandling af metastatisk ikke-planocellulær ikke-småcellet lungecancer hos voksne uden EGFR- eller ALK-positive mutationer i tumorer. KEYTRUDA®, i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel, er indiceret til førstelinjebehandling af metastatisk planocellulær ikke-småcellet lungecancer hos voksne. KEYTRUDA® som monoterapi er indiceret til behandling af lokalt 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®. KEYTRUDA® som monoterapi er indiceret til behandling af recidiverende eller refraktært klassisk Hodgkins lymfom hos voksne og pædiatriske patienter i alderen 3 år og derover, som har oplevet svigt af autolog stamcelletransplantation (ASCT), eller har oplevet svigt efter at have fået mindst 2 forudgående behandlinger, når ASCT ikke er en behandlingsmulighed. KEYTRUDA® som monoterapi er indiceret til behandling af lokalt 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. 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. 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

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

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

2. Forkortelser

1L	First-line
AE	Adverse Event
AIC	Akaike Information Criterion
ASat	as-treated
AUC	Area Under the Curve
BC	Breast Cancer
BIC	Bayesian Information Criterion
BRCA	Breast Cancer Gene
BRCAwt	BRCA wild-type
BSA	Body Surface Area
CALGB	Cancer and Leukemia Group B
CAP_{adj}	adjuverende capecitabin
CEM	Cost-Effectiveness Model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CREATE-X	Capecitabine for Residual Cancer as Adjuvant Therapy
DBCG	Dansk Bryst Cancer Gruppe
DKK	Danish Kroner
DM	Distant Metastasis
DMCG	Danske Multidisciplinære Cancer Grupper
DFS	Disease-free survival - sygdomsfrit interval
DRG	Diagnosis Related group
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EC	epirubicin + cyclophosphamid
ECOG PS	Eastern European Cooperative Group Performance Status
EF	Event Free
EFS	Event-free survival - Eventfri overlevelse
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL-five-dimension questionnaire
FA	Final analysis
HER2	Human Epidermal Growth Factor Receptor 2

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HR-QoL	Health related quality of life
HTA	Health Technology Assessment
IA	Interimsanalyse
ICERs	Incremental Cost-Effectiveness Ratios
I-O	Immuno-Oncology
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LR	Locoregional Recurrence
Lys	Life Years
NACT	Neoadjuverende kemoterapi
NICE	National Institute for Health and Care Excellence
OS	Samlet overlevelse
PBO_{adj}	ingen/placebo adjuverende behandling
$PBO+CT_{neo}$	neoadjuverende placebo + kemoterapi behandling
pCR	patologisk komplet respons
PD1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
$PEM+CT_{neo}$	neoadjuverende pembrolizumab + kemoterapi
PEM_{adj}	adjuverende pembrolizumab monoterapi
PSA	Probabilistic sensitivity analysis
Q(X)W	Every (X) week
TNBC	Triple negative brystkræft (Triple negative breast cancer)
TPs	Transition Probabilities
SEER	Surveillance, Epidemiology and End Results
$PEM+CT_{neo}$	neoadjuverende pembrolizumab + kemoterapi
TIL	Tumor infiltrerende lymfocytter
TNBC	Triple negativ brystkræft (Triple negative breast cancer)

3. Tabeller og figurer

Tabeloversigt:

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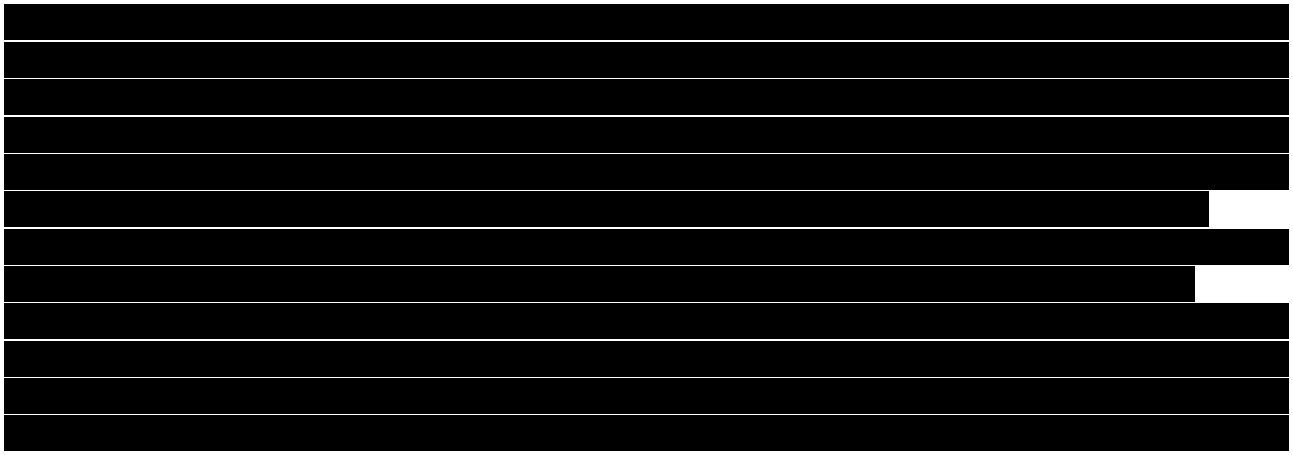
Figuroversigt:

[redacted]



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4. Resumé

Indikation og population

Den 24. maj 2022 blev pembrolizumab i kombination med kemoterapi godkendt til behandling af tidlig stadie triple negativ brystkræft (TNBC) af EMA CHMP med følgende indikation:

Pembrolizumab i kombination med kemoterapi som neoadjuverende behandling, og efterfulgt af monoterapi som adjuverende behandling efter operation, er indiceret til behandling af voksne med lokalt avanceret eller tidlig triple negativ brystkræft med høj risiko for recidiv.

EMA godkendelsen samt denne ansøgning baserer sig på de klinisk og statistisk signifikante effektdata fra KN522 (KN522), et dobbeltblindet randomiseret fase III studie, der inkluderede patienter med behandlingsnaiv ikke metastatisk lokalavanceret TNBC.

I Danmark diagnosticeres der hvert år knap 5.000 nye tilfælde af brystkræft [1]. Triple negativ brystkræft (TNBC) er en undertype af brystkræft, som udgør ca. 15 % af alle tilfælde af brystkræft og kendetegnes ved fravær og/eller lav ekspression af østrogen-, progesteron-og human epidermal vækst faktor receptor 2 (HER2), hvortil der ikke findes targeteret behandling. Sammenlignet med patientgrupper, som diagnosticeres med andre former for brystkræft, er patienter diagnosticeret med TNBC ofte yngre og har en ringere prognose med en markant forhøjet risiko for tilbagefald inkl. fjernrecidiv samt død [2, 3]. TNBC patienter med dissemineret sygdom (recidiverende eller *de novo)* har en forventet median samlet overlevelse (OS) på knapt 2 år, selv med introduktionen af PD-1/PD-L1 hæmmere til metastatisk TNBC, som trods alt demonstrerer en forlænget overlevelse sammenlignet med kemoterapi alene [4, 5].
Der er således for TNBC patientpopulationen i høj grad et fortsat behov for forbedrede behandlingsmuligheder, som kan reducere risiko for tilbagefald, udvikling af dissemineret sygdom med død til følge.

Intervention

Intervention i denne ansøgning er:

- Pembrolizumab 200 mg hver 3. uge intravenøst (i.v.), 17 serier inkl. både neoadjuverende og adjuverende fase
- Carboplatin AUC5 hver 3. uge i.v., 4 serier i cyklus 1-4 af den neoadjuverende fase
    - ELLER AUC1,5 ugentlig i.v., 12 serier i cyklus 1-4 af den neoadjuverende fase
- Paclitaxel 80 mg/m^2 ugentlig i.v., 4 serier i cyklus 1-4 af den neoadjuverende fase
- Doxorubicin 60 mg mg/m^2 hver 3. uge i.v., 4 serier i cyklus 5-8 af den neoadjuverende fase
    - ELLER Epirubicin 90 mg mg/m^2 hver 3. uge i.v., 4 serier i cyklus 5-8 af den neoadjuverende fase
- Cyclophosphamid 600 mg mg/m^2 hver 3. uge i.v., 4 serier cyklus 5-8 af den neoadjuverende fase

Pembrolizumab, som monoterapi har være anvendt som monoterapi siden 2015 og blev d. 19. oktober 2021 godkendt til behandling af inoperabel recidiverende eller metastatisk TNBC i kombination med kemoterapi. Neoadjuverende og adjuverende behandling udgør i dag behandlingsstrategien for patienter diagnosticeret med tidlig stadie TNBC og består af carboplatin, paclitaxel, doxorubicin eller epirubicin og cyclophosphamid (± capecitabine ± stråleterapi) [1]. Det neoadjuverende regime i dansk klinisk praksis afspejler kemoterapikomponenten i KN522.
Såfremt den nye intervention anbefales som standardbehandling, vil ændringen bestå i at tillægge pembrolizumab til nuværende dansk behandlingsregime og vil i så fald udgøre førstkommende mulighed for at inkorporere immunterapi til den kurativt intenderede behandling af tidlig stadie TNBC.

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Komparator

De danske kliniske retningslinjer beskriver et *dose-dense* platinholdigt regime bestående af 4 serier epirubicin og cyclophosphamide efterfulgt at 4 serier paclitaxel og carboplatin til neoadjuverende behandling af TNBC patienter.

Som komparator har vi valgt kontrolarmen i KN522, som består af:

- Carboplatin AUC5 hver 3. uge i.v., 4 serier i cyklus 1-4 af den neoadjuverende fase
    - ELLER AUC1,5 ugentlig i.v., 12 serier i cyklus 1-4 af den neoadjuverende fase
- Paclitaxel 80 mg/m^2 ugentlig i.v., 4 serier i cyklus 1-4 af den neoadjuverende fase
- Doxorubicin 60 mg mg/m^2 hver 3. uge i.v., 4 serier i cyklus 5-8 af den neoadjuverende fase
    - ELLER Epirubicin 90 mg mg/m^2 hver 3. uge i.v., 4 serier i cyklus 5-8 af den neoadjuverende fase
- Cyclophosphamid 600 mg mg/m^2 hver 3. uge i.v., 4 serier cyklus 5-8 af den neoadjuverende fase

Adjuverende capecitabin (CAP$_{adj}$) til patienter, som ikke har opnået et patologisk komplet respons var ikke standardpraksis ved initiering af KN522, hvorfor denne ikke er en del af KN522-studiet. Den direkte analyse af effekt og sikkerhed af den nye intervention på baggrund af KN522 vil derfor blive suppleret med en beskrivelse af effekt og sikkerhed af CAP$_{adj}$ baseret på det datagrundlag, som ligger til grund for de danske retningslinjer.
MSD mener således, vi har valgt en klinisk relevant og hensigtsmæssig komparator, idet ovenstående afspejler det nuværende kemoterapiregime, som udgør dansk klinisk praksis for neoadjuverende behandling for TNBC patienter. Dette sikrer desuden et statistisk robust sammenligningsgrundlag.

Klinisk relevante endepunkter for neoadjuverende og adjuverende studier

Det primære behandlingsformål med neoadjuverende og adjuverende behandling er minimering af risiko for recidiv og udvikling af metastatisk sygdom [6, 7]. Patologisk komplet respons (pCR) og *event-free survival* (EFS) er de primære kliniske endepunkter i KN522 og er relevante, da de korrelerer med det primære behandlingsformål og er associeret med langtidsoverlevelse [8]. I modsætning til mange studier i metastatisk sygdom, så er samlet overlevelse (OS) et sekundært endepunkt i KN522, da OS data først vil være modne når tilstrækkelig mange dødsfald er forekommet i studiearmene.
EFS og pCR er således de mest klinisk relevante og meningsfulde endepunkter til et studie af (neo)adjuverende behandling, da de retvisende anskueliggør effekten af den *aktuelle* (neo)adjuverende behandling til TNBC patienter og samtidigt ikke er forurenet af effekten af efterfølgende behandlingslinjer.

Vigtigste resultater fra pCR og EFS analyser i KN522

Der blev i KN522 randomiseret 784 patienter til pembrolizumab + kemoterapiarmen (PEM+CT) og 784 patienter til placebo + kemoterapi (PBO+CT). Median opfølgningstid på det seneste analyse tidspunkt (data cut-off 23. marts 2021) var 39,1 mdr. (range 30,0-48,0). For patienter i PEM+CT var der en statistisk signifikant forbedring i EFS sammenlignet med PBO+CT med en hazard ratio (HR) 0,63 (95% CI 0,48-0,82) og p-værdi <0,001. Dette er ensbetydende med en 37% risikoreduktion for progression, der udelukker operation, tilbagefald, udvikling af sekundær malignitet eller død med tillæg af pembrolizumab til kemoterapi. Den mest hyppige hændelse i begge behandlingsarme var udvikling af fjernrecidiv. Her var der i PEM+CT gruppen en halvering i incidens af fjernrecidiver med 7,7% fjernrecidiver i PEM+CT vs. 13,1% i PBO+CT gruppen. Forskellen i 3-års EFS rate var på 7,7% -point med 84,5% (95% CI 81,7-86,98) i PEM+CT vs. 76,8% (95% CI 72,2-80,7) i PBO+CT.

Den primære analyse af pCR blev udført ved første interimsanalyse (IA), data cut-off 24. september 2019 med en median opfølgningstid på 15,5 mdr. (range, 2,7 to 25,0). Her var der ligeledes en statistisk signifikant forskel i pCR rate 13,6% (5,4-21,8) til fordel for PEM+CT vs. PBO+CT, p<0,001 [9] [10].

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Resultaterne fra KN522 demonstrerer således, at neoadjuverende/adjuverende behandling med PEM+CT fører til en statistisk signifikant og klinisk relevant forbedring i både pCR og EFS og ikke mindst en halvering i fjernrecidiver, som er parametre associeret med forbedret overlevelse [11].

Bivirkninger

Bivirkninger rapporteres hos patienter, som har modtaget minimum én dosis studiemedicin (as-treated population (ASat)), som svarer til 783 patienter i PEM+CT gruppen og 389 patienter i PBO+CT gruppen.

I KN522 var median behandlingslængde sammenlignelig mellem de grupper med 13,31 mdr. (range 0,03-21,91) i PEM+CT og 13,60 mdr. (range 0,03-19,81) i PBO+CT [12].

Af patienter som fik en *all-cause* ≥grad 3 bivirkning i ASaT populationen, var der 645/783 (82,4%) i PEM+CT og 306/389 (78,7%) patienter i PBO+CT. For de behandlingsrelaterede bivirkninger, vurderet af investigator, udgjorde andelen af grad 3-5 bivirkninger 604/783 (77,1%) i PEM+CT og 285/389 (73,3 %) i PBO+CT [12]. Af de mest hyppige grad 3-5 bivirkninger (incidens ≥5%), som inkluderer neutropeni, anæmi, nedsat neutrofile leukocytal, var der kun en målbar forskel i stigning i alanin aminotransferase niveauet med 6,4% i PEM+CT og 2,8% i PBO+CT.

Den overordnede incidens af bivirkninger 'alle grader' var 99,2% i PEM+CT og 100,0% i PBO+CT. De hyppigste bivirkninger i både PEM+CT og PBO+CT var kvalme, alopecia, anæmi, neutropeni og fatigue. Disse var ensartet fordelt mellem grupperne. Den største forskel i de ovennævnte bivirkninger sås for fatigue med incidens på 46,6% i PEM+CT og 43,2% i PBO+CT.

Incidensen af alvorlige bivirkninger (SAE) var højere i PEM+CT med 43,6% sammenlignet med 28,5% i PBO+CT. Den eneste SAE, som havde en incidens på 5 % eller mere var febril neutropeni med 15,1% i PEM+CT vs. 12,1% i PBO+CT gruppen. Den største forskel i hyppighed af en SAE sås for pyreksi med 3,7% i PEM+CT vs. 0,5% i PBO+CT. Derudover var hyppighed af SAE'er sammenlignelig på tværs af behandlingsgrupperne.

Incidensen af bivirkninger, som fører til behandlingsophør (*any drug*), er *for all-grade* bivirkninger 29,9% vs. 15,4% og for SAE 12,0% vs. 3,6% i hhv. PEM+CT vs. PBO+CT gruppen [12].

Der var overordnet en højere incidens af grad 3-5 bivirkninger i PEM+CT sammenlignet med PBO+CT, og særlig i den neoadjuverende fase. Bivirkningerne er dog kendte og håndterbare.

Livskvalitet

Livskvalitets-analyserne EORTC-QLQ-C30 og EORTC QLQ-BR23 viste, at der var et fald i *health-related quality of life (HR-QoL) scores* fra baseline til uge 21, som var opfølgningstiden for den neoadjuverende behandling. Der var dog ingen signifikant i forskel mellem PEM+CT og PBO+CT. Endvidere var livskvalitet mest påvirket som følge af den neoadjuverende behandling, som forventet pga. den højere behandlingsbyrde med pembrolizumab/placebo + kemoterapi vs. adjuverende fase med pembrolizumab monoterapi/placebo [12].

På baggrund af disse analyser vurderes det, at tillæg af pembrolizumab til kemoterapi ikke fører til en forringelse i patienters livskvalitet, sammenlignet med kemoterapi alene.

Den sundhedsøkonomiske analyse

Vores sundhedsøkonomiske analyse i denne ansøgning udgøres af en cost-utility analyse, som er baseret på en Markov model. Modellen består af fire gensidigt udelukkende sundhedstilstande (event-free (EF), locoregional recurrence (LR), distant metastases (DM), og death (D)), som gør det muligt at kunne følge sygdomsforløbet, ekstrapolere udover den

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reelle opfølgningstid i studiet og i sidste ende præsentere et analyseresultat i form af en inkrementel omkostningseffektivitets-ratio (ICER). Analysen har et begrænset samfundsperspektiv og er udarbejdet med baggrund i en tidshorisont på 51,1 år (livstid). Nytteværdien til måling af den sundhedsrelaterede livskvalitet er baseret på EQ-5D-5L data tilgængelig direkte fra KN522-studiet og danske præferencevægte. De statistisk signifikante kliniske resultater på pCR og EFS understøtter estimaterne af merværdi i vores sundhedsøkonomiske model med en gevinst på 2,54 kvalitetsjusterede leveår sammenlignet med nuværende dansk standardbehandling. ICER'eren baseret på listepriser (AIP) er ligeledes favorabel for pembrolizumab med en omkostning pr. kvalitetsjusterede leveår på 35.473 kr. sammenlignet med nuværende dansk standardbehandling. Denne ICER bør ses som et udfald i et kontinuum af flere økonomiske udfald, der påvirkes af bl.a. antallet af langtidsoverlevere, som i denne analyse bygger på en parametrisk funktion, der er baseret på data fra andre adjuverende indikationer, kliniske ekspert input og observerede Kaplan-Meier kurver. ICER'en vil dermed ligge enten lidt højere eller lavere end 35.473 kr., men **resultatet understøtter, at der er et rimeligt forhold mellem effekt og omkostninger ved ibrugtagning af pembrolizumab til (neo)adjuverende behandling af TNBC patienter, da denne ligger markant lavere end tidligere Medicinrådsanbefalinger.**

Konklusion

TNBC er en aggressiv brystkræft subtype, som oftest rammer yngre kvinder <50 år. Det er en sygdom forbundet med øget risiko for recidiv og dårlig prognose til følge [2]. Neoadjuverende og adjuverende behandling er veletableret inden for brystkræft og i særdeleshed TNBC, hvor et platinbaseret regime i Denmark siden maj 2021 har udgjort standard neoadjuverende behandling i Danmark. Formålet med den neoadjuverende behandling er at maksimere pCR, da dette er en prædiktor for god prognose [1, 8, 11]. Neoadjuverende og evt. adjuverende behandling skal sammen minimere risiko for tilbagefald og progression til dissemineret sygdom [6, 7], hvor risikoen for død er markant med kun omkring 50% i live efter to år, som set i studierne for anti-PD1/anti-PDL1 hæmmere [4, 5].

Data fra KN522 viser, at pembrolizumab i kombination med et platinbaseret kemoterapiregime til neoadjuverende behandling, som afspejler dansk klinisk praksis, efterfulgt af adjuverende pembrolizumab monoterapi fører til en statistisk signifikant og klinisk relevant forbedring i både pCR og EFS. Der ses med tillæg af den aktive intervention pembrolizumab en øget frekvens i særligt de immunrelaterede bivirkninger, men ikke en forværring i de kemoterapi associerede hæmatologiske bivirkninger og der er ingen forringelse i livskvalitet sammenlignet med komparator.

Samlet set indikerer resultaterne fra KN522 en stor klinisk merværdi ved tillæg af pembrolizumab til kemoterapi vs. kemoterapi alene grundet følgende:

I. **Statistisk signifikant og klinisk relevant forbedring i pCR i PEM+CT vs. PBO+CT**
II. **Statistisk signifikant og klinisk forbedring i EFS i PEM+CT vs. PBO+CT**
III. **En klinisk relevant halvering af fjernrecidiver i PEM+CT vs. PBO+CT**
IV. **En trend mod forbedret OS i PEM+CT vs. PBO+CT (45 % af events nået for endelig analyse)**
V. **Overordnet forventet bivirkningsprofil, som er håndterbar med tillæg af pembrolizumab**
VI. **Ingen forringelse i livskvalitet i PEM+CT vs. PBO+CT**

Samtidig vurderer MSD, at omkostningerne pr. vundet leveår er rimelige set i forhold til effekten.

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5. Patientpopulationen, intervention og valg af komparatorer

5.1 Sygdommen og patientpopulationen

Triple negativ brystkræft (TNBC)

TNBC er en undertype af brystkræft, som er kendetegnet ved fravær og/eller lav ekspression af østrogen-, progesteron- og human epidermal vækst faktor receptor 2 (HER2). TNBC patienter har generelt en dårligere prognose, idet TNBC er en mere aggressiv form for brystkræft karakteriseret ved højere grad af metastasering og risiko for recidiv sammenlignet med non-TNBC sygdom [13, 14]. TNBC udgør ca. 15 % af alle brystkræft tilfælde og er primært diagnosticeret hos yngre kvinder under 50 år [3].

I Danmark bliver progesteronreceptor status hos brystkræft patienter ikke rutinemæssigt undersøgt, da udtryk af denne ikke har behandlingsmæssig eller prognostisk konsekvens. I praksis bliver denne dobbeltnegative patient population (østrogen receptor negativ og HER2 normal/negativ) anset og behandlet som TNBC sygdom [15].

For TNBC patienter betyder fraværet af receptorer på tumorcellens overflade (østrogenreceptor og HER2), at der ikke findes targeteret behandling, hvorfor kemoterapi indtil for et par år siden var eneste behandlingsmulighed. Til inoperabelt recidiverende og/eller metastatisk TNBC er der indenfor de sidste par år blevet godkendt anti-PD1/PD-L1 inhibitorer, som har givet en forbedring i median overlevelse på omkring 7 mdr. med en 2-år overlevelses rate på ca. 50% [5] [4]. Patienter med dissemineret sygdom er pr. definition inkurable. Selv med nyere behandlingsmuligheder er det kun omkring halvdelen af patienter, som lever 2 år efter deres diagnose med recidiverende eller metastatisk sygdom, hvorfor der stadig er behov for bedre behandlingsmuligheder, særligt for denne subgruppe af brystkræftpatienter.

Symptomer

Symptomerne ved TNBC er i overensstemmelse med de generelle symptomer, der observeres ved andre typer for brystkræft. Patienten præsenterer med en uforklarlig uregelmæssighed i brystet, som f.eks. en knude, indtrækning i huden, klar eller blodig væske fra brystvorten, og/eller hævede lymfeknuder i armhulen [15].

Risikofaktorer

I ca. 5-10 % af alle brystkræfttilfælde er der tale om arvelig brystkræft, hvoraf en andel af disse patienter vil være *breast cancer gene (BRCA)* positive. Dette betyder, at de har en sygdomsdisponerende mutation i et af de to gener *BRCA1* og *BRCA2,* som sammenlignet med *BRCA wild-type (BRCAwt)* giver en stærk forøget risiko for at udvikle brystkræft (inkl. gynækologiske kræftformer). Derudover er der også noget der tyder på, at bærere af *BRCA1* mutationer, som udvikler brystkræft, også er associeret med udvikling af TNBC [15, 16].
Øvrige risikofaktorer, som disponerer for brystkræft er også relevante for TNBC, hvilket inkluderer et højt alkoholindtag (→ risiko ↑), antallet af menstruationer gennem et liv (flere menstruationer→ risiko ↑), antallet af fødsler og kvindens alder på fødselstidspunkt (færre fødsler og/eller højere alder ved fødsel → risiko ↑) og amning (→ risiko ↓) [17].

Incidens og prævalens

Brystkræft er den mest hyppigt forekommende kræft, med ca. 2,3 millioner nye tilfælde af brystkræft diagnosticeret på verdensplan [18, 19]. Samtidig er prævalensen også den højeste med 7,8 millioner nulevende brystkræft patienter, som er blevet diagnosticeret indenfor de sidste 5 år [18]. I Danmark blev der i 2020 år diagnosticeret 4.752 tilfælde af

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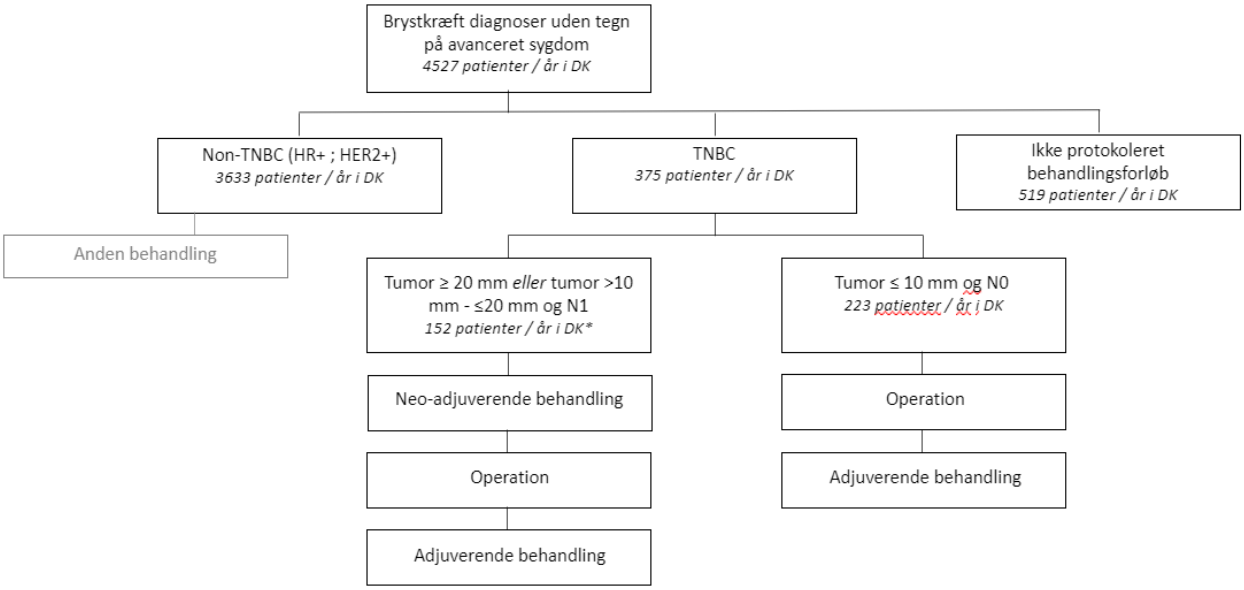
brystkræft [1], som er sammenligneligt med de epidemiologi data publiceret gennem Nordcan, hvor incidensen er n=4694, der afspejler gennemsnitsincidensen for 2012-2016 [20].

Et udtræk fra DBCG's database viser, at der i 2019 blev registreret i alt 4.527 patienter uden tegn på avanceret sygdom. Her blev 375 patienter registreret med TNBC (eller dobbeltnegativ dvs. progesteronreceptor ukendt). Der var udover de 375 patienter registreret 519, som ikke indgik i et protokolleret behandlingsforløb for operabelt brystkræft. Dette svarer til en **incidens på 904 patienter**. Derudover har vi ikke yderligere information omkring incidens eller prævalens.

Patienter, som allokeres udenfor et protokolleret behandlingsforløb, kan eksempelvis være patienter med inflammatorisk cancer, fixerede lymfeknuder i samsidig aksil eller infraclaviculære region, supraclaviculære lymfeknudemetastaser eller andet, som derfor ikke nødvendigvis følger retningslinjer omkring neoadjuverende og adjuverende behandling, hvorfor de ikke vil være kandidater til den nye intervention.

Af de 375 patienter, som indgik i protokolleret behandlingsforløb, blev **152 patienter** allokeret til neoadjuverende behandling, som derfor vil udgøre basis for patientgrundlaget til den nye intervention med pembrolizumab i kombination med kemoterapi. De resterende patienter (n=223) blev allokeret til *up-front* kirurgi eller adjuverende behandling.

Figure 1. Patient flow for patienter diagnosticeret med brystkræft uden tegn på avanceret sygdom



Kilde: DBCG

Table 1 Estimeret antal patienter, som er kandidater til behandlingen

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	38	152	152	152	152

Kilde: DBCG

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5.1.1 Forventet patientpopulation for denne ansøgning

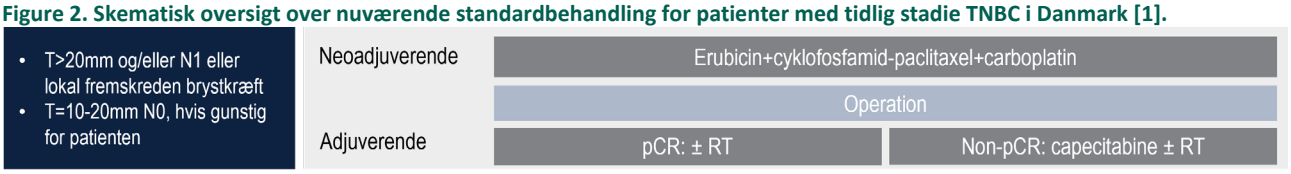
Den nye behandling forventes at være relevant for den danske patientgruppe, som er voksne diagnosticeret med lokal avanceret eller tidlig triple-negativ brystkræft med høj risiko for recidiv.

5.2 Nuværende behandlingsmuligheder og valg af komparator(er)

5.2.1 Nuværende standardbehandling i Danmark for lokal avanceret, inflammatorisk eller tidlig stadig TNBC

Danske Multidisciplinære Cancer Grupper (DMCG) og Dansk Bryst Cancer Gruppe (DBCG) har beskrevet de kliniske retningslinjer for den systemiske behandling af brystkræft, derunder TNBC (ER-negativ/HER2-normal og er illustreret i Figure 2 [21] [1].

Figure 2. Skematisk oversigt over nuværende standardbehandling for patienter med tidlig stadie TNBC i Danmark [1].



T: tumor, N: Lymfeknude, pCR: patologisk komplet respons, RT: strålebehandling

For TNBC patienter anbefales neoadjuverende kemoterapi (NACT) til patienter med tumorer > 20 mm og/eller lymfeknudeinvolvering, eller lokalt fremskreden sygdom, afhængig af evt. komorbiditet. Derudover kan NACT anvendes til patienter med tumorstørrelser >10 mm ≤ 20 mm, hvis man klinisk vurderer, at præoperativ behandling er gunstig for patienten f.eks. ved konvertering af en mastektomi til en lumpektomi. Der anbefales til den neoadjuverende behandling 4 serier epirubicin og cyclofosfamid efterfulgt af 4 serier paclitaxel og carboplatin. Til patienter, hvor carboplatin vurderes for bivirkningstungt, kan denne undlades. Til den post-neoadjuverende eller adjuverende behandling vil den anbefalede behandling være afhængig af, hvorvidt patienten opnår patologisk komplet respons (pCR), som er en "*prædiktor for en god prognose"* og korrelerer med forbedring i *event-free survival* (EFS) og *overall survival* (OS) [1] [11].

For patienter som opnår pCR (yT0/Tis N0), vil en evt. post-operativ behandling bestå af stråleterapi, som er indiceret til alle patienter, der har fået foretaget en lumpektomi eller patienter med makrometastaser i lymfeknude(r) efter en mastektomi [21]. For patienter, som ikke opnår pCR, vil den adjuverende behandling bestå af capecitabin i tillæg til evt. stråleterapi på baggrund af resultaterne fra CREATE-X studiet (Capecitabine for Residual Cancer as Adjuvant Therapy), samt en på daværende tidspunkt (af retningslinjernes udformning) upubliceret metaanalyse [22, 23].

5.2.1.1 Prognosen med nuværende behandlingsmuligheder

Prognosen for brystkræft er generelt god, idet ca. 78 % bliver diagnosticeret tidligt i deres sygdom med stadium I-II, med en forventet 3-års overlevelse mellem 95 og næsten 100 % [24]. TNBC patienter har dog uanset stadie ved diagnose en forværret prognose, med højere risiko for tilbagefald og død sammenlignet med øvrige brystkræftpatienter [25] [2].

- 5-års overlevelsen for patienter med tidlig stadie TNBC[1], som har fået neoadjuverende/adjuverende behandling er 82,5%, baseret på et dataudtræk fra DBCGs database for perioden 2016-2019 (n=1419).

[1] Ekskluderet fra analysen er patienter med primær metastatisk brystkræft, tidligere anden malign sygdom, inoperabel lokal avanceret brystkræft (mastitis carcinomatose, gennemvækst til hud eller muskler, ulcerende sygdom)

- I Cancer og Leukemia Group B (CALGB) 40603 studiet var der en 5-års OS på 74,4 % (95% CI 68,7-80,5) hos TNBC patienter behandlet med paclitaxel og carboplatin efterfulgt af et *dose-dense* regime med doxorubicin og cyclophosfamid (suppl. S4 B [26])
- Det randomiserede fase 3 studie BrighTNess viste en 4-års EFS på 79,3 % (95%CI 79,2-96,2) for patienter behandlet med NACT med carboplatin og paclitaxel efterfulgt af doxorubin og cyclophosphamid [27]
- 5-års overlevelses rate for non-pCR patienter behandlet med adjuverende capecitabin var på 78,8 %. [28].
- GEICAM/2003-11_CIBOMA/2004-01 studiet viste en 5-års DFS rate på 82,6% og en 5-års OS rate på 89,5% for TNBC patienter behandlet med anthracyklin-og taxanbaseret neoadjuverende regime efterfulgt af adjuverende capecitabin.

KN522 (KN522)'s studiedesign er opbygget således, at effekt og sikkerhed bliver vurderet samlet for både pembrolizumab i kombination med kemoterapi til neoadjuverende behandling efterfulgt af adjuverende pembrolizumab monoterapi. Man kan på baggrund af resultaterne fra KN522 derfor ikke definitivt konkludere på den relative effekt af pembrolizumab tillæg til henholdsvis den neoadjuverende og den adjuverende fase.

I overensstemmelse med den godkendte EMA indikation ansøges der derfor på baggrund af resultaterne fra KN522 studiet om ibrugtagning af både pembrolizumab + kemoterapi[2] til neoadjuverende behandling (PEM+CT_{neo}) og pembrolizumab monoterapi til adjuverende behandling (PEM_{adj}), som ét samlet behandlingsregime.

5.2.1.2 Valg af komparator

Kontrolarmen i KN522 afspejler overordnet nuværende dansk klinisk praksis og vi vil som drøftet ved det indledende dialogmøde d. 20. januar 2022 mellem Medicinrådets sekretariat og MSD benytte kontrolarmen i KN522 som komparator i denne ansøgning. Her består behandlingen af neoadjuverende placebo + kemoterapi (paclitaxel, carboplatin, epirubicin og cyklofosfamid) (PBO+CT_{neo}) efterfulgt af ingen/placebo systemisk adjuverende behandling (PBO_{adj}).

Der er dog en række opmærksomhedspunkter, som følger:

I. Kemoterapikomponenten af PBO+CT_{neo} (og PEM+CT_{neo}) består af paclitaxel+carboplatin efterfulgt af epirubicin (eller doxorubicin)+cyclofosfamid, der også udgør kemoterapi regimet, der anbefales til neoadjuverende NACT i de danske kliniske retningslinjer.
II. I KN522 blev den neoadjuverende kemoterapi givet som 4 serier paclitaxel + carboplatin efterfulgt af 4 serier EC, hvorimod man i dansk klinisk praksis begynder med 4 serier *dose-dense* EC efterfulgt af 4 serier paclitaxel + carboplatin.
III. I KN522 blev alle patienter, uanset pCR status efter neoadjuverende behandling, behandlet med enten PEM_{adj} i interventionsarmen eller PBO_{adj} i kontrolarmen. I de danske retningslinjer, differentieres der i det post-operative behandlingsforløb efter, hvorvidt patienten har opnået pCR eller ej. Non-pCR patienter vil få adjuverende capecitabin (CAP_{adj}), baseret på en metanalyse præsenteret på San Antonia Breast Cancer Symposium (SABCS) 2019 og *Capecitabine for residual Cancer af adjuvant therapy,* CREATE-X studiet [1] [22] [23].

Sekvensen af kemoterapi vurderes af danske eksperter som ligeværdig. Et studie i HER2 negative (inkl. TNBC) patienter viste, at der ikke er forskel i klinisk effekt mellem patienter behandlet med antracyklin efterfulgt at taxan og gruppen

[2] Kemoterapi i KN522 består af paclitaxe, carboplatin, epirubicin eller doxorubicin og cyclophosphamid

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behandlet med taxan efterfulgt at antracyklin [29]. Da *dose-dense* EC er den del af det neoadjuverende regime med bedst dokumenteret klinisk effekt for TNBC patienter, vil man gerne sikre, at patienterne gennemfører dette regime forud for det mere bivirkningstunge carboplatin-holdige regime (baseret på ekspertudtalelser). Endvidere fandt man i CALGB 40603 studiet en pCR-raten på 60 % (95% CI 54-66), med et neoadjuverende regime svarende til dansk klinisk praksis og som er sammenlignelig med 54,7 % (95% CI 2,8-15,6), som rapporteret i kontrolarmen i KN522 studiet [12]. 3-års EFS i KN522 var 76,8 % vs. ca. 72% i CALGB 40603 studiet (aflæst på kurven fig. 3B i [26]. Da effektresultater af det neoadjuverende regime givet i dansk klinisk praksis er sammenlignelige med kontrolarmen i KN522, vurderes ovenstående derfor ikke at have betydning for tillæg af pembrolizumab, såfremt behandlingen anbefales som standardbehandling (baseret på ekspertudtalelser).

For brugen af adjuverende capecitabin til non-pCR patienter i dansk klinisk praksis, vil det ikke være muligt at udføre en direkte sammenligning med interventionen PEM+CT_{neo} + PEM_{adj} i KN522, da der ikke findes head-to-head studier.

Som drøftet på dialogmødet d. 20. januar, er der ydermere væsentlige forskelle mellem patientpopulationen og effektmål i hhv. KN522 og CREATE-X studiet, som vanskeliggør selv en indirekte sammenligning og derved at drage meningsfulde og valide konklusioner på baggrund af det tilgængelige datagrundlag. Disse opsummeres i det følgende [12, 28].

Patientpopulation:

- CREATE-X inkluderede HER2-negative, dvs. inkl. HR+, hvorimod KN522 udelukkende rekrutterede TNBC patienter
- CREATE-X følger udelukkende patienter efter adjuverende behandling og inkluderede kun non-pCR patienter, hvor denne gruppe udgjorde 35,2 % i KN522 studiet.
- CREATE-X var et *Japan-Korea collaborative study*, hvorfor man må forvente, at patientpopulationen primært var asiatisk, og der kan være geografiske forskelle på, hvorvidt og hvor meget patienter responderer på behandling (supplementary materials [10]). Til sammenligning udgjorde den asiatiske subgruppe i KN522 ca. 20 % [12].

Intervention:

- I KN522 vurderes effekt og sikkerhed af intervention af neoadjuverende og adjuverende behandling kombineret hos behandlingsnaive patienter, hvorimod CREATE-X udelukkende vurderer effekt og sikkerhed af adjuverende behandling til en præ-selekteret gruppe af patienter (non-pCR),

Komparator:

- I KN522 har hele studiepopulationen fået et neoadjuverende regime, som betragtes som '*standard of care*' bestående af EC +paclitaxel of cisplatin. Den neoadjuverende behandling, som patienter i CREATE-X studiet modtog forud for inklusion er mere heterogen, hvoraf størstedelen har fået et antracyklin/paclitaxel baseret regime, som er inferiørt sammenlignet med regimet ovenfor.

Outcome:

- De primære kliniske endepunkter i hhv. CREATE-X og KN522 er forskellige, idet der blev rapporteret på DFS i CREATE-X og EFS i KN522. De kliniske effektmål i de to studier kan ikke umiddelbart sammenlignes, da de måler på forskellige ting.
- DFS står for sygdomsfri overlevelse og er typisk et klinisk endepunkt, som benyttes i adjuverende studier, da det bruges til at rapportere patienternes tid til tilbagefald eller død efter operation, dvs. hvor længe de er kræftfrie og/eller i live.

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- EFS står for eventfri overlevelse, hvor events defineres som en progression, et tilbagefald eller død. EFS er typisk et effektmål, som bruges i studier, der også inkluderer en neo-adjuverende behandlingsfase. EFS gør det muligt at rapportere samlet på hhv. progression eller død i den neo-adjuverende fase og på tilbagefald og død i den adjuverende fase.
- DFS ville ikke kunne bruges i studier som KN522, da patienterne stadigvæk har en primærtumor i den neo-adjuverende fase, og de er derved per definition ikke sygdomsfrie.

Vi vil i denne ansøgning lægge vægt på den direkte sammenligning af interventionen PEM+CT_{neo} + PEM_{adj} vs. PBO+CT_{neo} + PBO_{adj}, som proxy for dansk klinisk praksis baseret på resultaterne i KN522. Denne sammenligning vil blive suppleret af en deskriptiv beskrivelse af CAP_{adj} vs. PEM+CT_{neo} + PEM_{adj} for non-PCR patienter, som baseres på:

- KN522: eksplorativ analyse for EFS i pCR vs. non-pCR patienter
- Publicerede data for CAP_{adj} til TNBC patienter i tillæg til Masuda et al. publikationen fra 2019 [23], jf. afsnit 6.

5.2.2 Beskrivelse af komparator(er)

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

Neoadjuverende kemoterapiregime: epirubicin, doxorubicin, cyclophosphamid, paclitaxel og carboplatin.

Adjuverende kemoterapiregime for non-pCR: capecitabin

Placebo
Saltvand IV hver 3. uge

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

- Carboplatin (L01XA02).
- Mode of action: Carboplatin er en uorganisk substans der hæmmer DNA-syntesen ved at frembringe tværgående forbindelser indenfor og mellem DNA-strengene.
- Pharmaceutical form: Koncentrat til infusionsvæske
- Posology: Udleveres som koncentrat til infusionsvæske, opløsning 10 mg/ml
- Method of administration: Intravenøs administration over 15 - 60 minutter
- Dosing: Area under the curve (AUC) 2 intravenøst på dag 1 og 8 hver 3. uge.
- Should the pharmaceutical be administered with other medicines? Carboplatin skal fortyndes med isotonisk natriumchlorid- eller glucose-infusionsvæske til en koncentration på mindst 0,5 mg/ml, afhængig af infusionstiden. Carboplatin kan bruges som både monoterapi og kombinationsterapi.
- Treatment duration/criteria for end of treatment: I KN355: Behandlingen med carboplatin kunne fortsætte efter lægens skøn eller indtil bekræftet sygdomsprogression, uacceptabel toksisitet eller tilbagetrækning af patientens samtykke.

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- Necessary monitoring, both during administration and during the treatment period: Carboplatin bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytotoksiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af carboplatin, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer.
- Packaging: Udleveres som 1 hætteglas, med 15 eller 45 ml koncentrat til infusionsvæske, opløsning 10 mg/ml.

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

- Paclitaxel (L01CD01)
- Mode of action: Antimitotika, som hæmmer tumorvækst ved at blokere for celledeling
- Pharmaceutical form: Pulver til infusionsvæske, dispersion
- Posology: Paclitaxel udleveres enten som koncentrat til infusionsvæske, opløsning 6mg/ml eller som pulver til infusionsvæske 60mg
- Method of administration: Intravenøs administration over 3 timer
- Dosing: I KN355: 90 mg/m^2 legemsoverflade intravenøst på dag 1, 8 og 15 hver 4. uge.
- Should the pharmaceutical be administered with other medicines? Paclitaxel som pulver skal opblandes i isotonisk natriumchlorid-infusionsvæske, Ringer-lactat eller Ringer-acetat til en slutkoncentration på 1mg/ml. Paclitaxel som koncentrat til infusionsvæske skal fortyndes med isotonisk glucose- eller natriumchlorid-infusionsvæske eller blandinger heraf til en koncentration på 0,3 – 1,2 mg/ml. Paclitaxel må ikke blandes med andre lægemidler end den anførte infusionsvæske under tilberedning. Paclitaxel kan bruges som både monoterapi og kombinationsterapi.
- Treatment duration/criteria for end of treatment: I KN355: Behandlingen med paclitaxel kunne fortsætte efter lægens skøn eller indtil bekræftet sygdomsprogression, uacceptabel toksisitet eller tilbagetrækning af patientens samtykke.
- Necessary monitoring, both during administration and during the treatment period: Paclitaxel bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytostatiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af paclitaxel, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer
- Packaging: Udleveres som 1 hætteglas med 16,7 eller 50 ml koncentrat til infusionsvæske, opløsning 6 mg/ml eller som 1 pakning med 60 mg pulver

Epirubicin er et velkendt og velafprøvet cytostatikum af kategorien anthracykliner, der findes fra flere producenter.

- Epirubicin (L01DB03)
- Mode of action: Cytostatikum, der hæmmer tumorvæksten ved at blokere for proteinsyntesen I celledelingen.
- Pharmaceutical form: Opløsning til infusionsvæske
- Posology: Epirubicin udleveres som opløsning 2mg/ml til injektions- og infusionsvæske.

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- Method of administration: Intravenøs administration over 3-20 minutter. Dosering er individuel og afhængig af kombinationsbehandling med andre cytostatika.
- Dosing: I KN522: 90 mg/m^2 legemsoverflade intravenøst på hver 3. uge i 12 uger.
- Should the pharmaceutical be administered with other medicines? Epirubicin kan fortyndes med isotonisk natriumchlorid- eller isotonisk glucose-infusionsvæske. I KN522 blev epirubicin administreret sammen med cyclophosphamid og pembrolizumab.
- Treatment duration/criteria for end of treatment: I KN522: Behandlingen med epirubicin fortsatte i 12 uger med dosering hver 3. uge. Både patienter som gennemførte de 12 ugers behandling og patienter, som afbrød behandlingen epirubicin kunne derefter blive opereret.
- Necessary monitoring, both during administration and during the treatment period: Epirubicin bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytostatiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af epirubicin, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer
- Packaging: Udleveres som 1 hætteglas med 25 ml, 50 ml eller 100 ml koncentrat til infusionsvæske, opløsning 2 mg/ml.

Doxorubicin er et velkendt og velafprøvet cytostatikum af kategorien anthracykliner, der findes fra flere producenter.

- Doxorubicin (L01DB01)
- Mode of action: Cytostatikum, der hæmmer tumorvæksten ved at nedsætte eller stoppe celledelingen gennem enzymblokering.
- Pharmaceutical form: Koncentrat til infusionsvæske
- Posology: Doxorubicin udleveres som opløsning 2mg/ml til injektions- og infusionsvæske.
- Method of administration: Intravenøs administration. Dosering er individuel og afhængig af kombinationsbehandling med andre cytostatika. Dosering bør dog aldrig overstige 550 mg/m^2 legemsoverflade.
- Dosing: I KN522: 60 mg/m^2 legemsoverflade intravenøst på hver 3. uge i 12 uger.
- Should the pharmaceutical be administered with other medicines? Doxorubicin skal fortyndes med isotonisk natriumchlorid- eller isotonisk glucose-infusionsvæske til en slutkoncentration på 0,5 mg/ml eller 0,05 mg/ml. I KN522 blev doxorubicin administreret sammen med cyclophosphamid og pembrolizumab.
- Treatment duration/criteria for end of treatment: I KN522: Behandlingen med doxorubicin fortsatte i 12 uger med dosering hver 3. uge. Både patienter som gennemførte de 12 ugers behandling og patienter, som afbrød behandlingen doxorubicin kunne derefter blive opereret.
- Necessary monitoring, both during administration and during the treatment period: Doxorubicin bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytostatiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af doxorubicin, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer

- Packaging: Udleveres som 1 hætteglas med 5 ml, 25 ml eller 100 ml koncentrat til infusionsvæske, opløsning 2 mg/ml.

Cyclophosphamid er et velkendt og velafprøvet cytotoksika, der findes fra flere producenter i forskellige formuleringer.

- Cyclophosphamid (L01AA01)
- Mode of action: Cytotoksika, der hæmmer tumorvæksten ved at blokere for proteinsyntesen I celledelingen.
- Pharmaceutical form: Pulver til injektionsvæske.
- Posology: Cyclophosphamid udleveres som pulver til injektionsvæske.
- Method of administration: Intravenøs administration. Dosering er individuel og afhængig af kombinationsbehandling med andre cytotoksika.
- Dosing: I KN522: 600 mg/m^2 legemsoverflade intravenøst på hver 3. uge i 12 uger
- Should the pharmaceutical be administered with other medicines? Cyclophosphamid skal fortyndes med isotonisk natriumchlorid- eller isotonisk glucose-infusionsvæske. I KN522 blev cyclophosphamid administreret sammen med enten epirubicin eller doxorubicin samt med pembrolizumab.
- Treatment duration/criteria for end of treatment: I KN522: Behandlingen med cyclophosphamid fortsatte i 12 uger med dosering hver 3. uge. Både patienter som gennemførte de 12 ugers behandling og patienter, som afbrød behandlingen cyclophosphamid kunne derefter blive opereret.
- Necessary monitoring, both during administration and during the treatment period: Cyclophosphamid bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytostatiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af cyclophosphamid, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer.
- Packaging: Udleveres som pulver til injektionsvæske på 200 mg, 500 mg eller 1 g vandfrit cyclophosphamid.

Capecitabin er et velkendt og velafprøvet kemoterapeutika, der findes fra flere producenter.

- Capecitabin (L01BC06)
- Mode of action: Cytotokstatika givet som pro-drug, der *in vivo* bliver konverteret af enzymer til fluorouracil (anti-metabolit), der hæmmer tumorvæksten ved at bremse for celledelingen.
- Pharmaceutical form: Filmovertrukne tabletter
- Posology: Capecitabin udleveres i tabletform i blisterpakninger.
- Method of administration: Tabletter som skal synke hele i forbindelse med et måltid eller max. 30 minutter efter et måltid.
- Dosing: I monoterapi er den anbefalede dosis for brystkræftpatienter 6-8 serier 1000 mg/m^2 legemsoverflade 2 gange dagligt i 14 dage efterfulgt af en uges pause.
- Should the pharmaceutical be administered with other medicines? Capecitabin kan administreres som monoterapi eller som kombinationsterapi.

- Treatment duration/criteria for end of treatment: 6-8 serier som adjuverende behandling
- Necessary monitoring, both during administration and during the treatment period: Capecitabin bør kun anvendes under supervision af en erfaren onkolog på afdelinger specialiseret i anvendelse af cytostatiske lægemidler. Det anbefales at følge lokale retningslinjer for monitorering af capecitabin, idet det er et velkendt og ofte anvendt lægemiddel på de danske onkologiske afdelinger.
- Need for diagnostics or other tests (i.e. companion diagnostics): Det anbefales at følge lokale retningslinjer.
- Packaging: Udleveres som blisterpakninger med 60 stk tabletter af 150 mg eller med 120 tabletter 500 mg .

5.3 Intervention

5.3.1 Rationale for behandlingseffekt PEM+CT_{neo} + PEM_{adj} hos patienter med TNBC

Pembrolizumab er et humaniseret monoklonalt antistof, der binder til overfladeproteinet programmed cell death-1 (PD-1), som bl.a. er udtrykt på immunsystemet T-lymfocytter og forhindrer binding til overpladeproteinerne programmed death-ligand 1 (PD-L1) og 2 (PD-L2). PD-L1 og PD-L2 kan være udtrykt på både tumorceller og andre celler i tumorens mikromiljø og kan også være udtrykt på kroppens normale væv. Interaktion mellem PD-1 og dets ligand PD-L1/PD-L2, hæmmer T-lymfocytters aktivitet og kan derved hæmme T-lymfocytternes respons mod kræftsygdom (reviewed i [30]). TNBC, i modsætning til brystkræft generelt, er immunologisk mere aktive tumorer med en højere grad af tumor infiltrerende lymfocytter (TILs), som korrelerer med et højere respons mod checkpoint-inhibitorer, som anti-PD1/anti-PD-L1'er. Der ses samtidig hos TNBC patienter et øget PD-L1 udtryk, som understøtter rationalet for brug af pembrolizumab i denne patientgruppe (reviewed i [31]).

Nedenfor er en kort gennemgang af udvalgte studier, som viser effekt af pembrolizumab hos TNBC patienter og danner grundlag og rationalet for KN522 studiet:

1. KEYNOTE-355 var et randomiseret fase 3 studie der undersøgte effekt og sikkerhed af pembrolizumab i kombination med kemoterapi vs. kemoterapi alene hos TNBC patienter med ikke-resektabel recidiverende eller metastatisk sygdom. Her fandt man en forbedring i median OS på 6,9 mdr. (HR 0,73, 95% CI 0,55-0,95) til fordel for pembrolizumab-armen (23,0 mdr.) vs. kemoterapi-armen (16,1 mdr.) hos patienter der er PD-L1 positive [5].
2. KEYNOTE-173 var et ikke-randomiseret fase 1b studie, som skulle undersøge sikkerhed og præliminær effekt af neoadjuverende pembrolizumab plus kemoterapi. Her fandt man overordnet en pCR rate på 60,0% (90%CI 48,6-70,7) hos 36/60 patienter. 1-års EFS var 100% for pCR patienter vs. 88% for non-pCR patienter [32].

På baggrund af bl.a. overnævnte studier samt et fortsat behov for, at forbedre behandlingen af TNBC patienter i den kurative *setting,* blev KN522 designet for at undersøge effekt af tillæg af pembrolizumab til nuværende standardbehandling bestående af carboplatin, paclitaxel, cyclophosphamid og et antracyklin. Det primære behandlingsmål for neoadjuverende/adjuverende behandling er, at opnå den højest mulige pCR-rate, længste EFS (eller DFS) og derved overlevelse [6] [33] [7]. I KN522 blev der med udgangspunkt i nuværende standardbehandling som *backbone* tillagt pembrolizumab for, at øge responset vs. respons opnået med enten kemoterapi alene eller pembrolizumab monoterapi. Derudover er der også et biologisk rationale, som bygger på, at både platin-og cyclophosphamid-baseret kemoterapi har supplerende immunmodulerende effekter. Kemoterapi kan forstærke effekten af pembrolizumab ved at bidrage til dannelsen af et immunologisk favorabelt tumormikromiljø, som i synergi med den immunaktiverende effekt af pembrolizumab forstærker anti-tumor immunresponset [34, 35].

I KN522 består interventionen af følgende:

Dosing

- Neoadjuverende. 1 cyklus = 21 dage
  - Pembrolizumab 200 mg intravenøst (i.v.) hver 3. uge, 8. serier
  - Carboplatin: AUC5 hver 3. på dag 1 i cyklus 1-4 ELLER AUC1,5 ugentligt på dag 1, 8 og 15 i cyklus 1-4
  - Paclitaxel: 80 mg/m^2, ugentlig dag 1, 8, og 15 i cyklus 1-4
  - Doxorubicin: 60 mg/m^2, hver 3. uge på dag 1 i cyklus 5-8 ELLER Epirubicin 90 mg/m^2, hver 3. uge på dag 1 1 i cyklus 5-8.
  - Cyclofosfamid: 600 mg/m^2, hver 4. uge på dag 1 i cyklus 5-8.
- Adjuverende
  - Pembrolizumab 200 mg intravenøst (i.v.) hver 2. uge, 9 serier

- Method of administration: Alle ovenstående lægermidler bliver indgivet i.v.
- Treatment duration/criteria for treatment discontinuation: Totale behandlingslængde i KN522 var foreskrevet til at være 17 serier (8 neoadjuverende + 9 adjuverende) eller indtil progression eller uacceptabel toksicitet
- Should the pharmaceutical be administered with other medicines? Ved behandling med pembrolizumab må andre lægemidler ikke administreres via samme infusionsslange
- Necessary monitoring, during administration, during the treatment period, and after the end of treatment: Det anbefales, at der følges lokale retningslinjer for monitorering.
- Need for diagnostics or other tests (i.e. companion diagnostics): n/a

Ved anbefaling i Medicinrådet vil PEM+CT_{neo} + PEM_{adj} blive en ny behandlingsmulighed for den definitive behandling for alle nydiagnosticerede TNBC patienter, som er kandidater til neoadjuverende/adjuverende behandling og bliver indplaceret i de danske behandlingsguidelines. Eftersom et sammenligneligt kemoterapiregime i forvejen bliver anvendt til denne patientpopulation, vil en ændring blot indebære en tilføjelse af pembrolizumab til nuværende behandlingsregime.

6. Litteratursøgning og identificering af effekt og sikkerhedsstudier

6.1 Identificering og selektion af relevante studier

I KN522 studiet er der foretaget en direkte sammenligning af intervention **PEM+CT_{neo} + PEM_{adj}** vs. den af MSD valgte komparator **PBO+CT_{neo} + PBO_{adj}**, som proxy for nuværende dansk klinisk praksis. Der vil for denne sammenligning derfor ikke blive udført en systematisk litteratursøgning, idet det ikke forventes at tilvejebringe yderligere relevant dokumentation.

Som nævnt i afsnit 5.2.1, beskriver de danske kliniske guidelines tillæg af CAP_{adj} for den subgruppe af TNBC patienter, som ikke opnår pCR efter neoadjuverende behandling. Denne anbefaling er baseret på *"et randomiseret studie (CREATE-X) og en ikke publiceret metanalyse, der inkluderede 12 studier"* [1]. Da studieprotokollen for KN522 blev skrevet og ved studiets initiering var CAP_{adj} til non-pCR patienter ikke en del af standard klinisk praksis, hvorfor der i KN522 studiedesign er nogle afvigelser i forhold til de danske kliniske retningslinjer.

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I KN522 differentieres adjuverende behandling ikke efter patienters pCR status og der bliver i kontrolarmen givet placebo, som adjuverende behandling.

For at imødekomme, at man i Danmark giver CAP_{adj} til non-pCR patienter, vil den direkte sammenligning af $PEM+CT_{neo}$ + PEM_{adj} vs. $PBO+CT_{neo}$ + PBO_{adj} på basis af KN522, blive suppleret med en beskrivelse af effekt og sikkerhed af CAP_{adj}. Denne beskrivelse sker med udgangspunkt i det datagrundlag, som den danske anbefaling baseres på:

I. CREATE-X [28]
II. *"ikke publiceret metanalyse, der inkluderede 12 studier" [1]* af Mackehlenberg et al. [22].

Meta-analysen er sidenhen blevet publiceret og samler sammen med en Cochrane-analyse fra 2021 den tilgængelige evidens for capecitabin i mamma-cancer [36, 37].
I de to meta-analyser er der en høj grad af heterogenitet mellem de inkluderede studier. Her indgår studier, som inkluderer forskellige patientpopulationer defineret på baggrund af receptorstatus, komparator i studierne og hvordan capecitabin indgår som intervention (tillæg vs. erstatning, (neo)adjuverende vs. metastastisk, kombination vs. monoterapi).

Fælles for de to metaanalyser er konsensus om, at capecitabin i adjuverende setting kan forbedre DFS og OS, særligt for TNBC patienter, når capecitabin bliver givet som tillæg til eksisterende behandling og ikke som erstatning. De to studier, der er relevante at fremhæve til vores formål omkring beskrivelse af adjuverende capecitabin svarende til dansk klinisk praksis, er CREATE-X studiet og GEICAM-2003-11_CIBOMA/2004-01, da disse to studier er publiceret og begge undersøger effekt og sikkerhed af adjuverende capecitabin monoterapi (ikke kombinationskemoterapi) til tidligere neoadjuverende behandlede patienter [28, 38].

- *GEICAM-2003-11_CIBOMA/2004-01* inkluderede TNBC patienter, som havde fået neoadjuverende behandling antracyklin- og/eller taxan baseret regime. Både non-pCR og pCR patienter blev inkluderet og fik CAP_{adj}.
- *CREATE-X* inkluderede HER2- patienter, som ikke havde opnået pCR efter neoadjuverende behandling.

I GEICAM-2003-11_CIBOMA/2004-01 fandt man ikke en statistisk signifikant forbedring i DFS med tillæg af capecitabin til adjuverende behandling i den overordnede gruppe af TNBC patienter [38]. Disse resultater er i modstrid med konklusionen i CREATE-X studiet, hvor der netop ses en forbedring i både OS og DFS, særligt for subgruppen af TNBC patienter [23]. Denne forskel tilskrives dog forskelle i studiepopulationen, idet der i CREATE-X studiet udelukkende inkluderede non-pCR patienter, der har en dårligere prognose sammenlignet med studiepopulationen i GEICAM-2003-11_CIBOMA/2004-01, som inkluderede både non-pCR og pCR patienter [23, 36-38].

Da det udelukkende er non-pCR patientgruppen, der i henhold til de danske kliniske retningslinjer får tilbudt adjuverende capecitabin svarende til CREATE-X studiet, vil det være effekt og sikkerhed fra dette studie, som bliver beskrevet i denne ansøgning. Dog er der, som tidligere nævnt, en række forskelle i de to studier; KN522 og CREATE-X, som ikke tillader en indirekte sammenligning (se afsnit 5.2.2)

Det er vigtigt at understrege, at det overordnede formål med KN522 var at undersøge effekt og sikkerhed af pembrolizumab i tillæg til standardbehandling (neoadjuverende kemoterapi og adjuverende placebo) for *både* den neoadjuverende og adjuverende fase af behandlingen. Med andre ord er det, med udgangspunkt i KN522-studiets statistiske analyseplan, ikke muligt at konkludere på den separate effekt af henholdsvis den neoadjuverende og adjuverende behandling på *event-free survival (EFS).*

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De publikationer, der inkluderes i denne ansøgning findes i Table 2.

Table 2 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Schmid P et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020 Feb. Schmid P et al. Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022 Feb	KN522	NCT03036488	Start: 7. marts 2017 Slut: 30. september 2025	***Direkte:*** PEM+CT_{neo} + PEM_{adj} vs. PBO+CT_{neo} + PBO_{adj} for patienter med ny-diagnosticeret tidlig stadie TNBC, som er kandidater til neoadjuverende behandling.
Masuda N et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017 Jun	CREATE-X		Start: Februar 2007 Slut: Januar 2017 https://jbcrg.jp/en/clinicaltrials/1136/	***Narrativ beskrivelse:*** Af adjuverende capecitabin til non-pCR patienter

7. Effekt og sikkerhed

Der vil i dette afsnit præsenteres effekt og sikkerhedsdata, som skal understøtte sammenligningen af PEM+CT_{neo}+ PEM_{adj} vs. CT_{neo}+ PBO_{adj} supplereret med en beskrivelse af effekt og sikkerhed af capecitabin for adjuverende behandling af non-pCR patienter på baggrund af studier, som er vist i Table 2 under afsnit 6.1.

7.1 Overvejelser omkring kliniske endepunkter efter (neo)adjuverende behandling af tidlig stadie brystkræft, herunder TNBC.

Det primære behandlingsmål med den (neo)adjuverende behandling er, at maksimere pCR-rate og minimere risiko for tilbagefald, for derved på længere sigt at reducere risikoen for brystkræftrelateret død [1] [11]. Neoadjuverende behandling er i de senere år blevet mere udbredt, særligt for brystkræftpatienter. Herved opnås mulighed for at vurdere tumorresponset af kemoterapien samtidigt med, at down-sizing af tumor og potentielt opnåelse af pCR ved neoadjuverende behandling, ikke alene reducerer risiko for tilbagefald, men også giver mulighed for at tilbyde patienten mere konservative kirurgiske procedurer, som f.eks. konvertering af potentielle mastektomier til lumpektomier [1].

I KN522 var de to primære endepunkter pCR og EFS, som begge er accepteret som relevante kliniske endepunkter for godkendelse af nye kræftlægemidler af både Food and Drug Administration (FDA) og EMA [39, 40]. Derudover er disse to kliniske endepunkter direkte associeret med det primære behandlingsmål, som er minimering af risiko for tilbagefald og død [11, 41].

Opnåelse af pCR korrelerer med en lavere risiko for recidiv samt forbedret EFS og OS, særligt for TNBC og HER2+ patienter [11, 26]. Et prospektivt databasestudie viste en forskel i 3-års overlevelsesrate på 26%-point til fordel for pCR vs. non-pCR TNBC patienter [41]. En lavere risiko for recidiv kan indirekte medføre en forbedring i livskvalitet hos

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patienten, da netop frygten for recidiv (og derved risiko for død) hos brystkræftpatienter (og andre kræftpatientgrupper) tidligere er beskrevet som en parameter, der i høj grad har indflydelse på patienternes emotionelle livskvalitet [42-44]. Målet med den neoadjuverende behandling er at maksimere pCR raten for at reducere risiko for tilbagefald, som har negativ indflydelse på langtidsoverlevelse, uden en betydelig forøgelse i bivirkningsbyrde, som kan påvirke patienters livskvalitet eller i værste fald medføre død.

EFS er i KN522 defineret som tid fra randomisering til første hændelse af én (eller flere) af følgende events: *progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause. Progression of disease, local or distant recurrence, and second primary malignancy are based on investigator determination (supplementary materials, protocol [9]).*

Her er særligt *"precludes definitive surgery"* og *"distant recurrence"* blevet fremhævet som hændelser, der medfører en betydelig forværret prognose. Progression under eller tidligt efter neoadjuverende behandling er tegn på behandlingsrefraktær sygdom og er sammen med udvikling af fjernrecidiver forbundet med en dårlig prognose, hvor patienten går fra at få behandling med kurativ sigte til en livslang behandling med varierende effekt (baseret på ekspertudtalelser). Selv med introduktion af anti-PD1/PD-L1 inhibitorer til patienter med dissemineret TNBC er den forventede 2-års overlevelse rate på omtrent 50% [4, 5]. Der er derfor fortsat et behov for forbedre behandling af patienter diagnosticeret med tidlig stadie sygdom og reducere incidens af patienter som progredierer og udvikler dissemineret sygdom.

OS er defineret som tid fra randomisering til død af alle årsager og er i KN522 et sekundært endepunkt. Forlænget overlevelse er selvsagt det ultimative mål med onkologisk behandling, men OS er ikke direkte forbundet med det primære behandlingsmål for (neo)adjuverende behandling. OS er derimod det vigtigste kliniske endepunkt i studier, der undersøger behandling af *metastatisk* kræftsygdom, da det korrelerer med det primære behandlingsmål for stadie IV patienter, som er livsforlængende behandling [45].
En forbedring i OS bliver vanskelig at vurdere i studier der undersøger neoadjuverende og/eller adjuverende behandling, da patienter, særligt behandlet med immunterapi har en længere forventet levetid og der derfor må medregnes en årelang opfølgningstid. Dette understøttes af resultaterne fra KN054-studiet, der undersøger effekt af adjuverende pembrolizumab hos patienter med resekteret højrisiko stadium III melanom og pt. repræsenterer et studie med pembrolizumab til tidlig stadie sygdom med den længste opfølgningstid. Efter en median opfølgningstid på 42,3 mdr. (IQR40,5-45,9), er det fortsat ikke muligt at evaluere på det sekundære endepunkt OS, grundet for få OS events, hvorimod en statistisk signifikant forlængelse i *distant metastasis-free survival* er blevet observeret [46].

Opsummeret kan det derfor for neoadjuverende/adjuverende studier være vanskeligt at vurdere OS effekten af interventionen pga. følgende [47]:

1. Disse studier dels vil kræve en markant længere opfølgningstid, da patienter har en længere forventet levetid sammenlignet med studier, som vurderer behandling for metastatisk sygdom.
2. Det er vanskeligt at vurdere effekten af den nye intervention, da OS også bliver påvirket af efterfølgende behandlingslinjer og *cross-over.*

Baseret på ovenstående er både pCR og EFS de mest relevante og klinisk meningsfulde endepunkter for KN522, og de vil ikke mindst kunne belyse spørgsmålet om effekt og sikkerhed af den nye intervention PEM+CT_{neo} + PEM_{adj} uden at blive påvirket af evt. efterfølgende behandlingslinjer.

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7.2 Effekt og sikkerhed af PEM+CT_{neo}+ PEM_{adj} vs. CT_{neo}+ PBO_{adj} for patienter med lokal avanceret, inflammatorisk eller tidlig stadie triple negativ brystkræft hos voksne uanset pCR status.

7.2.1 KN522

KN522 er et randomiseret fase 3, dobbeltblindet studie, som undersøger effekt og sikkerhed af neoadjuverende behandling med pembrolizumab i kombination med kemoterapi efterfulgt af post-operativ adjuverende behandling af pembrolizumab monoterapi til patienter med ny-diagnosticeret lokal avanceret tidlig stadie TNBC [48].

De komparative analyser af effekt og sikkerhed er en direkte statistisk sammenligning af intervention PEM+CT_{neo}+ PEM_{adj} vs. kontrolarmen CT_{neo}+ PBO_{adj} i KN522. Kontrolarmen i KN522 afspejler overordnet dansk klinisk praksis. Der er dog en subgruppe af danske TNBC patienter, der ikke opnår pCR med neoadjuverende behandling, som post-operativt får tilbudt CAP_{adj}, baseret på resultaterne af CREATE-X studiet og en meta-analyse af Mackelenbergh et al. ([1] [23] [22]. Se også afsnit 5.2).

Analyse af klinisk merværdi på de relevante parametre: pCR, EFS, bivirkninger samt *health related quality of life* (HR-QoL) vil blive vurderet i *intention-to-treat* (ITT) populationen, svarende til den EMA godkendte indikation og samtidig den population, som vi ansøger om ibrugtagning af PEM+CT_{neo}+ PEM_{adj} til. Parallelt vil vi, hvor klinisk relevant og tilgængeligt, beskrive tilsvarende effektresultater for capecitabin baseret på de kliniske data, som den danske anbefaling baseres på.

Der vil i det følgende afsnit blive gennemgået de vigtigste detaljer omkring studiet, og der henvises til Appendix B Inkluderede studier hovedkarakteristikafor en mere detaljeret gennemgang af de vigtigste studiekarakteristika.

7.2.1.1 Studiedesign

Patienter blev randomiseret 2:1 til hhv. PEM+CT_{neo}+ PEM_{adj} vs. komparator PBO+CT_{neo}+ PBO_{adj} og stratificeret efter lymfeknudestatus, tumor størrelse og carboplatin doseringsinterval (Figure 3, fra Schmid et al. KN522 ESMO 2021 virtual plenary [49]).

Inklusionskriterier var histologisk verificeret lokal avanceret TNBC (T1c N1-N2, T2 N0-N2, T3 N0-N2, T4a-d N0-N2 (*American Joint Committee of Cancer (AJCC) staging criteria for breast cancer).* Patienterne skulle være behandlingsnaive, være i god almen tilstand med *Eastern Cooperative Oncology Group performance status* (ECOG PS) 0 eller 1 og have vævsprøve tilgængelig til PD-L1 immunhistokemisk (IHC) analyse.
Eksklusionskriterier var bl.a. invasiv malignitet ≤5 år forud for afgivelse af informeret samtykke, med undtagelse af velbehandlet basal celle eller planocellulær hudcancer eller *in situ* cervix cancer. Patienter, som 12 måneder forud for inklusion havde været i behandling med kemoterapi, targeteret behandling eller stråleterapi blev ligeledes ekskluderet sammen med patienter, som har været i behandling med andre anti-PD-1 og anti-PD-L1 hæmmere. Der henvises til Appendix B Inkluderede studier hovedkarakteristika.

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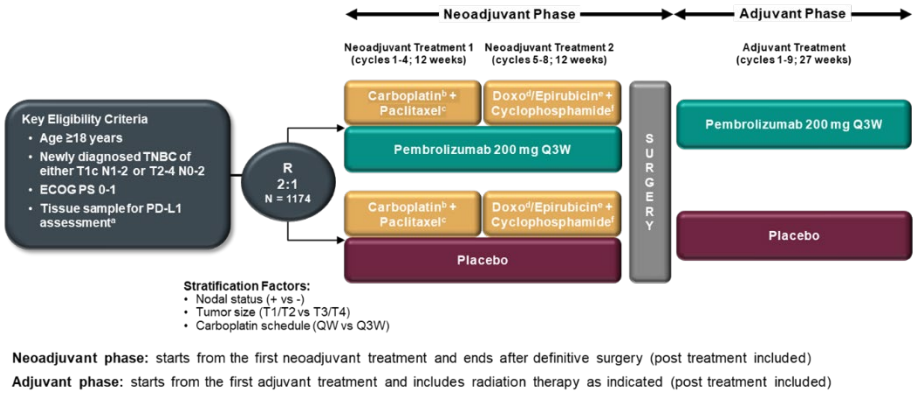

Figure 3. Skematisk oversigt over KN522's studiedesign. Tilpasset fra Schmid et al. ESMO 2021 virtual plenary .

Der var i studiet to primære endepunkter (*dual primary endpoints)* patologisk komplet respons (pCR), defineret som ypT0/Tis ypN0, og *event-free survival* (EFS) (se appendix B for nærmere beskrivelse og afsnit 7.2). Såfremt blot ét af de to primære endepunkter viste en statistisk signifikant forbedring ville studiehypotesen for KN522 være opfyldt. De sekundære endepunkter var alternativt definerede pCR rater, OS, antallet af patienter som får en bivirkning og seponerer behandling pga. en bivirkning og livskvalitet [48].

Den primære pCR analyse blev udført ved første interimsanalyse (IA1), data cutoff 24. september 2018. Såfremt der ved IA1 i PEM+CT_{neo}+ PEM_{adj} var en statistisk signifikant forbedring sammenlignet med PBO+CT_{neo}+ PBO_{adj} pCR, ville dette være den primære analyse for pCR (Figure 4). Første analyse af EFS blev udført ved anden interimsanalyse (IA2), med data cutoff d. 24. april 2019 (data ikke vist).

Der er i protokollen for KN522 planlagt 7 interimsanalyser (IA) (hvor IA4 d.d. er seneste analyse) samt en *final analysis* (FA) (side 89 i protokollen, supplementary [9]). Sidstnævnte forventes at blive foretaget ~98 måneder efter første randomiserede patient og er på nuværende tidspunkt ikke publiceret/præsenteret.

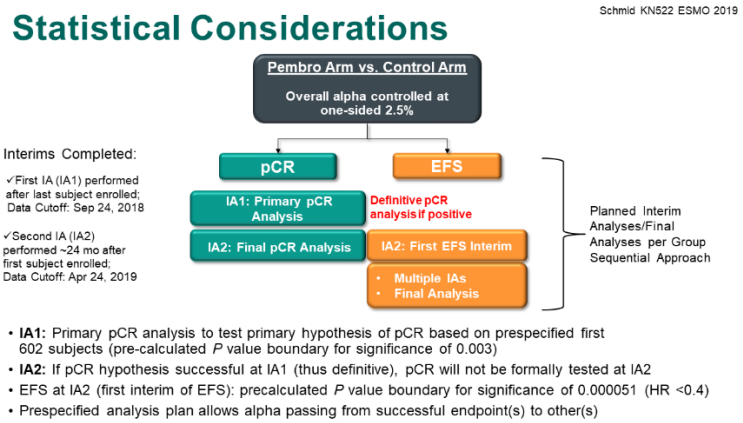

Figure 4 Skematisk oversigt over den statistiske analyseplan for KN522

Der vil i dette afsnit præsenteres følgende:

- KN522
  - Baselinekarakteristika
  - pCR fra IA1, median opfølgningstid 15,5 mdr. (range 2,7-25,0) [10]
  - pCR fra IA2 (data cutoff 24. april 2019) og IA4 (data cutoff 23. marts 2021)
  - EFS og OS fra IA4, median opfølgningstid 39,1 mdr. (range 30,0-48,0) (data cutoff 23. marts 2021) [9]
  - Bivirkninger fra IA4 [9, 50]
  - Livskvalitet fra IA4 [50]
- CREATE-X
  - DFS, data cutoff 30. september 2015, median opfølgningstid 3,6 år [23].
  - Bivirkninger fra samme analyse

7.2.1.2 Baselinekarakteristika for inkluderede patienter

Generelt set er studiepopulationen KN522 ensartet fordelt på tværs af de to behandlingsgrupper med hensyn til baseline patientkarakteristika (se appendix C).

Median alder i KN522 er henholdsvis 49 år (range 22-80) i PEM+CT_{neo}+ PEM_{adj} vs. 48 år (range 34-79) i PBO+CT_{neo}+ PBO_{adj}. ECOG score, tumorstørrelse, lymfeknudeinvolvering og sygdomsstadie var ligeledes ensartet fordelt mellem grupperne.

Det har ikke været muligt at lokalisere data for baseline karakteristika for den tilsvarende danske patientpopulation, men fra vores dialog med de danske klinikere er vurderingen, at studiepopulationen i KN522 generelt er repræsentativ for de danske patienter.

7.2.1.3 pCR i KN522

I KN522 blev der i alt inkluderet 1174 patienter, som blev randomiseret 2:1 med 784 patienter til PEM+CT_{neo}+ PEM_{adj} og 390 patienter til PBO+CT_{neo}+ PBO_{adj}. Analysen af pCR ved IA1 (Figure 5), viste at gruppen behandlet med PEM+CT_{neo} havde en pCR-rate (ypT0/Tis ypN0) på 64,8% (95% CI 59,9-69,5) sammenlignet med 51,2% (95% CI 44,1-58,3) i PBO+CT_{neo} gruppen. Dette er en statistisk signifikant difference på 13,6% (95% CI 5,4-21,8) til fordel for PEM+CT_{neo} med p<0,0005 [10]. pCR analysen ved IA1 var den primære analyse, men blev fortsat evalueret ved efterfølgende interimsanalyser, som er opsummeret i Table 3 [12].

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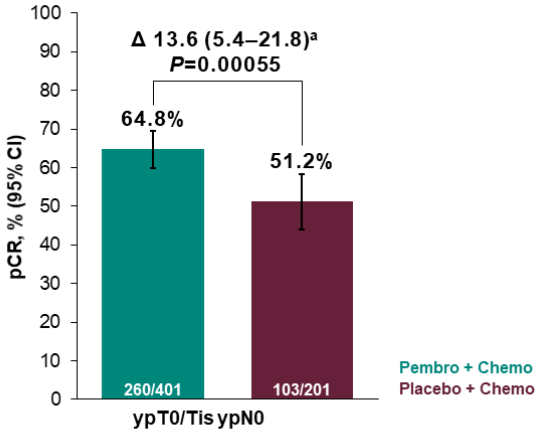

[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors.
Data cutoff date: September 24, 2018.

Figure 5. Patologisk komplet respons. Data cut-off 24. september 2018. Median opfølgningstid 15,5 mdr. [10]

Table 3. pCR rater i KN522 ved IA1, IA2 og IA4 [12]

	n	pCR rate % (95% CI)	Estimeret ΔpCR % (95% CI)	p-værdi
IA1 (data cutoff 24-09-2018)				
PEM+CT_{neo}	401	64,8 (59,9-69,5)	13,6 (5,4-21,8)	0,00055
PBO+CT_{neo}	201	51,2 (44,1-58,3)		
IA2 (date cutoff 24-04-2019)				
PEM+CT_{neo}	669	64,0 (60,2-69,6)	9,2 (2,8-15,6)	0,00221
PBO+CT_{neo}	333	54,7 (49,1-60,1)		
IA4 (data cutoff 23-03-2021)				
PEM+CT_{neo}	784	63,00 (59,5-66,4)	7,5 (1,6-13,4)	n/a
PBO+CT_{neo}	390	55,6 (50,6-60,6)		

IA1 primære pCR analyse
IA2 den endelige analyse
IA4 en understøttende analyse

Resultaterne for pCR var konsistente på tværs af alternative pCR definitioner, som var sekundære endepunkter i KN522. Ved IA1 sås absolutte forskelle på 14,5 % (95% CI 6,2-22,7) for ypT0ypN0 og 14,8 (95% CI 6,8-23,0) for ypT0Tis ypN0 til fordel for PEM+CT_{neo} vs. PBO+CT_{neo}.

I Table 3 ses pCR resultaterne for IA2 og IA4 i tillæg til den primære analyse ved IA1, hvor ændringen i ΔpCR ændrer sig fra 13,6 % ved IA1 til 9,2 % ved IA2 og 7,5 % ved IA4. Ændringen skyldes primært en stigende andel af patienter med pCR i PBO+CT_{neo} gruppen, og er i dette tilfælde en refleksion af et højere antal inkluderede patienter sammenlignet med IA1, som giver et mere robust evidensgrundlag. Ikke desto mindre er der ved den endelige analyse IA2 fortsat en statistik signifikant forbedring i pCR til fordel for PEM+CT_{neo} vs. PBO+CT_{neo}, og er yderligere understøttet ved af analysen ved IA4. I EPAR'en beskrives non-pCR gruppen vs. pCR-gruppen med en større andel af patienter med mere avanceret sygdom (stadie III vs. stadie II og T3/T4 vs. T1/T2), postmenopausale og ældre patienter samt lavere PD-L1 ekspression (data ikke vist, men beskrevet i [12]). Dette var dog gældende for både PEM+CT_{neo} og PBO+CT_{neo} gruppen (Figure 27 og Figure 28 i appendix D samt [12]). På trods af forskellene i patientkarakteristika mellem non-pCR og pCR gruppen, er det vigtigt at understrege, at der er en klinisk relevant forbedring i pCR rate med tillæg af pembrolizumab, som er uafhængig af patienters nodal status, sygdomsstadie og PD-L1-status, (se appendix D og [12]).

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Resultaterne fra KN522, med en pCR rate på på 54,7 % (IA2, som er den endelige analyse) i kontrolarmen er forventelig og sammenlignelig med historisk publicerede pCR rater på 50-60 % efter neoadjuverende behandling med platinbaserede regimer [26, 51]. Da det neoadjuverende regime i KN522 endvidere afspejler nuværende dansk klinisk praksis, kan det med rimelighed forventes, at kontrolarmen afspejler de pCR-rater, man vil opnå med nuværende neoadjuverende behandling.

En statistik signifikant forbedring i pCR med tillægget af pembrolizumab til neoadjuverende behandling af TNBC i KN522 er klinisk relevant, da pCR, som tidligere beskrevet er:

i. En prædiktor for en god prognose [1]
ii. Korrelerer med forbedret langtids-endepunkter, såsom EFS og OS [8, 11, 33]

FDA accepterer pCR, som et acceptabelt klinisk endepunkt for accelereret godkendelse for nye lægemidler til mamma-cancer i fravær af andre endepunkter, som viser langtidsoverlevelse [39].

Som vi kan se i det næste afsnit, så er den opnåede pCR efter neoadjuverende behandling kombineret med den post-operative adjuverende behandling med pembrolizumab associeret med en statistisk signifikant forbedring i EFS.

7.2.1.4 EFS og OS i KN522

I KN522 var det andet primære endepunkt EFS, som i dette studie afspejler den kombinerede effekt af neoadjuverende og adjuverende behandling (PEM+CT_{neo}+ PEM_{adj}).

På Kaplan-Meier kurven for EFS (Figure 6), ses der en adskillelse af kurverne omkring 11 mdr. efter randomisering, med færre events (15,7%) i PEM+CT_{neo}+ PEM_{adj} sammenlignet med PBO+CT_{neo}+ PBO_{adj} (23,8%) [9]. Denne adskillelse bibeholdes over tid og kan indtil videre følges indtil 45 mdr. efter randomisering. Efter en median opfølgningstid på 39,1 mdr. var der således en signifikant forbedring i 3-års EFS rate med 84,5% (95% CI 81,7-86,9) i PEM+CT_{neo}+ PEM_{adj} vs. 76,8% (95% CI 72,2-80,7), en HR for hændelse eller død på 0,63 (95% CI 0,48-0,82) og p<0,001 [9].

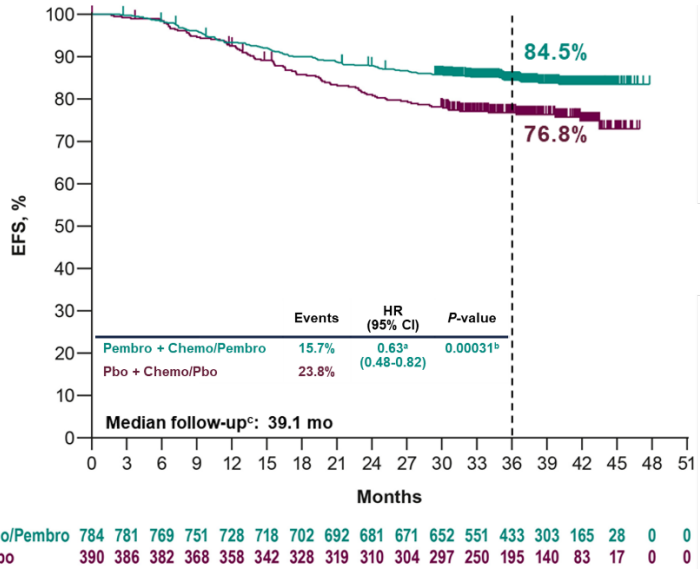

Figure 6. Kaplan-meier kurver for event-free survival. Data cutoff 23. marts 2021 og median opfølgningstid var 39,1 mdr. (range [9].

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Den mest hyppige event eller hændelse i KN522 var i begge behandlingsgrupper udvikling af fjernrecidiv og udgjorde henholdsvis 7,7% i PEM+CT_{neo}+ PEM_{adj} og 13,1% i PBO+CT_{neo}+ PBO_{adj}, svarende til næsten en fordobling af fjernrecidiver i kontrolarmen sammenlignet med interventionsarmen (Table 4**Error! Reference source not found.**). Et retrospektivt studie viste en 3-års overlevelse på 65,3% for patienter med lokal recidiv sammenlignet med en 23,4% hos patienter med fjernrecidiv [52]. Udvikling af fjernrecidiv er derfor associeret med en markant forværret prognose og overlevelse. Antallet af patienter, hvor sygdomsprogression udelukkede dem fra definitiv kirurgi, var lav, men var dobbelt så høj i PBO+CT_{neo}+ PBO_{adj} med 3,8% sammenlignet med 1,8% i PEM+CT_{neo}+ PEM_{adj} (Table 4**Error! Reference source not found.**). Dette er dels forbundet med en dårlig prognose, idet patienter som progredierer under eller kort tid efter den neoadjuverende behandling anses for at være behandlingsrefraktære. Derudover er hindring til operation også tab af et kurativt behandlingstilbud.

Table 4. Oversigt over første hændelse/*event* i EFS analysen [9]

First event, n (%)	**PEM+CT_{neo}+ PEM_{adj}, n=787**	**PBO+CT_{neo}+ PBO_{adj}, n=390**
Any first event	123 (15,7)	93 (23,8)
Progression of disease that precludes definitive surgery	14 (1,8)	15 (3,8)
*Local recurrence**	28 (3,6)	17 (4,4)
Distant recurrence	60 (7,7)	51 (13,1)
Second primary cancer	6 (0,8)	4 (1,0)
Death	15 (1.9)	6 (1,5)

Der var efterfølgende henholdsvis 13 patienter i PEM+CT_{neo}+ PEM_{adj} og 9 patienter i PBO+CT_{neo}+ PBO_{adj}, som fik fjernrecidiv.

Som diskuteret i både EPAR samt publikationen af Schmid et al. [9, 12] var forbedringen i EFS hos PEM+CT_{neo} + PEM_{adj} vs. PBO+CT_{neo} + PBO_{adj} mere eller mindre repræsentativ på tværs af subgrupper (subgruppe analysen for EFS ved IA4 er vist i Figure 29 i appendix D). For subgruppen med højt PD-L1 udtryk ses generelt en forbedring i både pCR-rater og EFS-rater. Men som drøftet ovenfor for pCR i forhold til PD-L1 subpopulationer, ses denne trend ligeledes for kontrolarmen i studiet. Da dette ses hos både interventions-og komparatorarmen og der i øvrigt også er betydelig effekt af interventionen hos patienter med lavt PD-L1 udtryk, er der ikke noget der understøtter en evt. selektion af patienter til PEM+CT_{neo} + PEM_{adj} på baggrund af PD-L1 ekspression, som afviger fra pembrolizumab (og atezolizumab) til behandling af metastatisk TNBC [4, 53].

Overall survival var i KN522 et sekundært endepunkt og data var på tidspunktet for EFS analysen (data cut-off 23. marts 2021, median opfølgningstid 39,1 mdr.) fortsat umodne med 10,2% events i PEM+CT_{neo} + PEM_{adj} sammenlignet med 14,1% event i PBO+CT_{neo} + PBO_{adj}, svarende til 45% påkrævede events for den endelige OS analyse [54]. På dette tidspunkt fandt man en 3-års overlevelse på hhv. 89,7% (95% CI 87,9-97,7) i PEM+CT_{neo} + PEM_{adj} vs. 86,9% (95% CI 83,0-89,9) i PBO+CT_{neo} + PBO_{adj} (Figure 7).

For (neo)adjuverende studier kræves en markant længere opfølgningstid for, at opsamle tilstrækkelig OS *events* for at kunne udføre en OS analyse, end det eksempelvis er tilfældet for stadie IV studier. Det er værd at bemærke, at givet at

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patienterne er yngre med en gennemsnitsalder på hhv. 49 og 48 år i PEM+CT og CT+PBO armene og at hhv. 64,8% og 51,2 % af patienterne i PEM+CT_{neo} og PBO+CT_{neo} armene opnåede et pCR, der er prognostisk for lavere recidivrater, så vil der for patienterne, forhåbentlig gå mange år inden en median OS kan registreres i studiet *[9].*

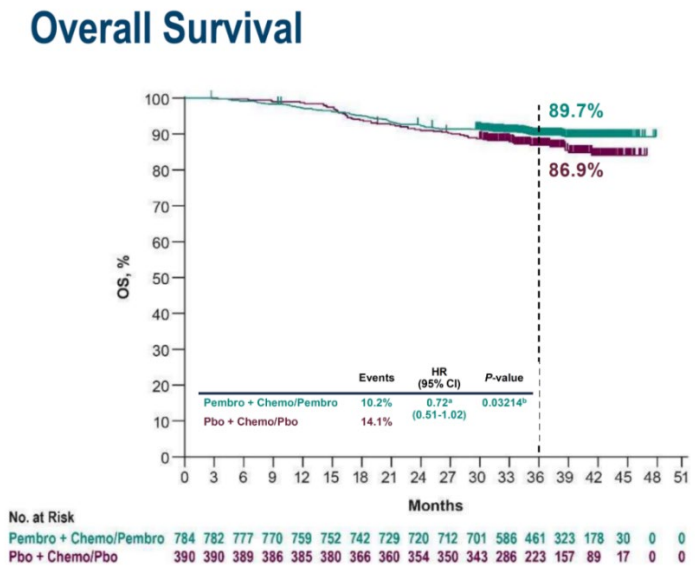

Figure 7. Kaplan-meier kurver for overall survival. Data cutoff 23. marts 2021 og median opfølgningstid 39,1 mdr. (range (modificeret fra [9, 49]).

7.2.1.5 Deskriptiv sammenligning af PEM+CT_{neo}+ PEM_{adj} vs. (tidligere neoadjuverende+) CAP_{adj} for non-pCR patienter.

For spørgsmålet vedr. klinisk merværdi af interventionen PEM+CT_{neo}+ PEM_{adj} sammenlignet med den danske non-pCR patientpopulation, som får CAP_{adj}, er det svært at drage konklusioner baseret på det tilgængelige datasæt, som består af resultaterne fra KN522 og CREATE-X studiet. Der er i de to studier væsentlige forskellige, som vanskeliggør en indirekte sammenligning og umuliggør valide og statistisk underbyggede konklusioner, jf. afsnit 5.2.1.2.

Vi vil dog på opfordring fra Medicinrådets sekretariat udføre en deskriptiv sammenligning på baggrund af eksplorative subgruppeanalyser i de to studier CREATE-X og KN522 (Figure 8):

- KN522 studiet med fokus på EFS i non-pCR subgruppen
- CREATE-X studiet med fokus på DFS i TNBC subgruppen

I CREATE-X studiet rapporteres *disease-free survival* (DFS) og ikke EFS som i KN522. De to endepunkter defineres forskelligt, som diskuteret i afsnit 5.2, hvoraf de mest væsentlige forskelle er, at progression, som udelukker operation er et *"event"* i EFS og ikke i DFS og ikke mindst, at tid fra randomisering til *"event"* er differentieret mellem EFS og DFS i de to studier, hhv. KN522 og CREATE-X (Figure 8A), som vi skal have *in mente,* når vi ser på KM-kurverne i Figure 8A og B.

En præspecificeret eksplorativ analyse blev i KN522 udført for EFS for pCR vs. non-pCR gruppen, som en ustratificeret subgruppe analyse og kan ses i Figure 8B.

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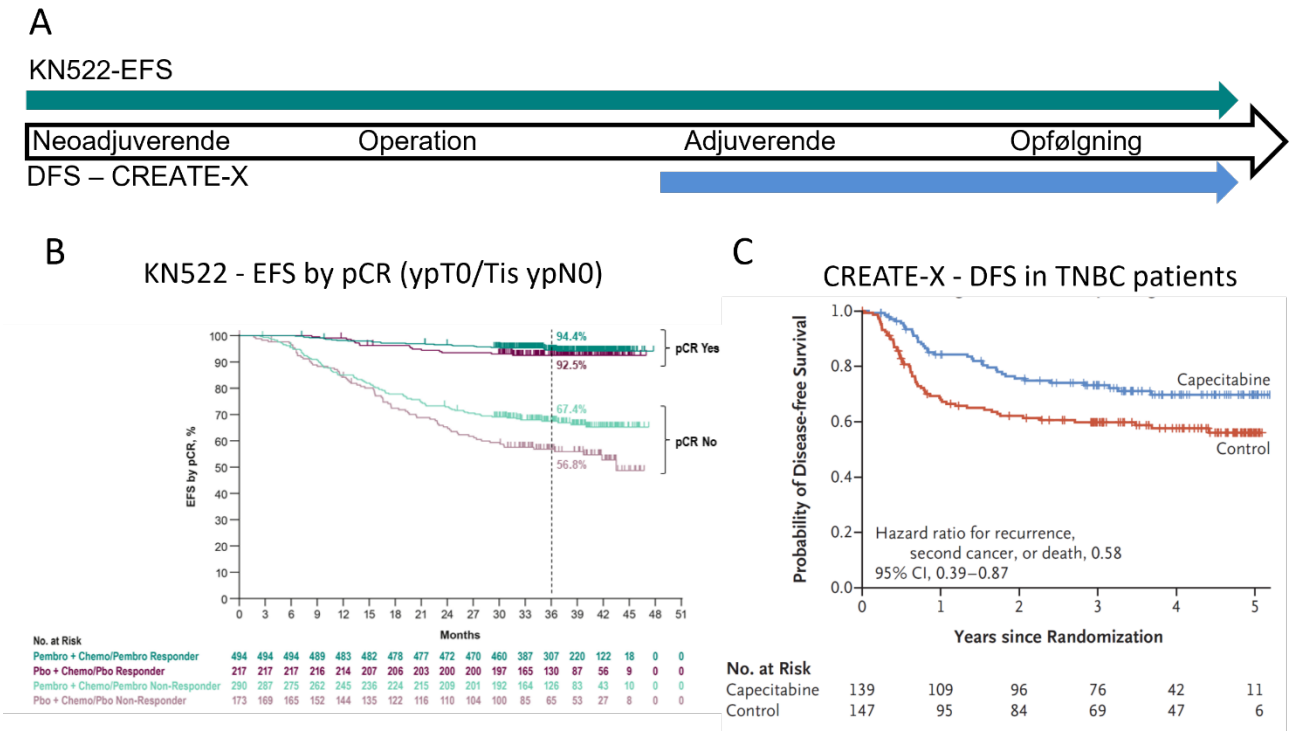

Figure 8. Event-free survival i KN522 og disease-free survival i CREATE-X. A) Tid fra randomisering vises for hhv. KN522/EFS og CREATE-X/DFS. Kaplan-Meier kurver for B) KN522 og EFS i forhold til pCR og non-pCR subgruppen, data cut-off 23. marts 2021 og C) CREATE-X og DFS for TNBC subgruppen. Modificeret fra [28, 49].

Denne analyse viser, at patienter, der opnår pCR efter neoadjuverende behandling, har en forbedret EFS sammenlignet med non-pCR patienter. Derudover ser man ved sammenligning af PEM+CT_{neo}+ PEM_{adj} vs. PBO+CT_{neo}+ PBO_{adj} en estimeret HR på 0,70 for pCR patientgruppen, som er sammenlignelig med den HR på 0,73 for en tilsvarende sammenligning hos non-pCR patientgruppen (data ikke vist, men er nævnt på s. 76 i EPAR [12]). Numerisk er forskellen mellem PEM+CT_{neo}+ PEM_{adj} vs. PBO+CT_{neo}+ PBO_{adj} mindre for pCR gruppen med estimeret forskel på 3-års EFS 1,9 %-point sammenlignet med 10,6 %-point for non-pCR gruppen (Figure 8B). Der kan dog, som der står i EPAR'en på baggrund af KN522 data ikke konkluderes på ovenstående observation [12].

I KN522 var 3-års EFS rate i non-pCR gruppen 67,4 % i PEM+CT_{neo}+ PEM_{adj} gruppen vs. 56,8 % i PBO+CT_{neo}+ PBO_{adj} (Figure 8B), som var en numerisk forbedring på på 10,6 %-point (HR: 0,70 95% CI 0,52-0,95) til fordel for PEM+CT_{neo}+ PEM_{adj} vs. PBO+CT_{neo}+ PBO_{adj} (supplementary materials [9]). Median EFS var ikke nået ved data cut-off 23. marts 2021. Til sammenligning blev der i Masuda et al. rapporteret en 3-års DFS rate på 69,8 % i capecitabin gruppen sammenlignet med 56,1 % i kontrolgruppen, som havde fået placebo, svarende til en absolut forskel på 13,7 %-point (HR:0,58 95% CI 0,39-0,87) [23].

Da patientkarakteristika ikke er opgjort særskilt for TNBC populationen i CREATE-X studiet har vi ikke mulighed for at vurdere, hvorvidt patientpopulationen er sammenlignelig med studiepopulationen i KN522.

Vi har så vidt muligt præsenteret de effektdata for CREATE-X og KN522, som tilnærmelsesvis kan sammenlignes. Der skal tages forbehold for, at non-pCR populationen med rimelighed må antages at være forskellig blot på baggrund af forudgående neoadjuverende behandling, der inkluderer pembrolizumab med en pCR rate på over 60 % i KN522,

sammenlignet med formodet 20-30 % i CREATE-X studiet [28]. Derudover er der de forskelle, som vi har været inde på tidligere omkring studiedesign og effektmål.
Det er derfor vanskeligt at konkludere på spørgsmålet omkring klinisk merværdi af PEM+CT_{neo}+ PEM_{adj} sammenlignet med non-pCR patienter, som får CAP_{adj}.

På baggrund af pCR og EFS analysen for patienter i KN522 kan det konkluderes, at:

- Der ses en statistisk signifikant og klinisk relevant forskel i pCR-rater på 13,6 % (95% CI 5,4-21,8) til fordel for PEM+CT_{neo} med p<0,0005 [10].
- Der ses en statistisk signifikant og klinisk relevant forskel i EFS med en forskel på 7,7% 3 år efter randomisering med en HR for hændelse eller død på 0,63 (95% CI 0,48-0,82) og p<0,001.
- Der var næsten en halvering i andelen af patienter, der udviklede fjernrecidiv i PEM+CT_{neo} + PEM_{adj} sammenlignet med PBO+CT_{neo} + PBO_{adj}.
- For PEM+CT_{neo} + PEM_{adj} vs CAP_{adj} hos non-pCR patienter er resultatet af den deskriptive analyse inkonklusiv.

MSD mener, at resultaterne fra KN522 indikerer en vigtig klinisk merværdi for patienter med tidlig stadie TNBC, idet der både er en statistisk signifikant og klinisk relevant forbedring i pCR rater og EFS.

7.2.1.6 Bivirkningsdata

I denne ansøgning vil bivirkningsdata som udgangspunkt blevet rapporteret for IA4 (data cut-off 23. marts 2021). Således fås et samlet billede af bivirkninger for både den neoadjuverende og adjuverende fase.
Vi vil dog hvor relevant inkludere resultater opgjort for neoadjuverende og adjuverende særskilt, for at give en indikation af bivirkningsbyrden i de forskellige behandlingsfaser med den nye intervention PEM+CT_{neo} + PEM_{adj} vs. PBO+CT_{neo} + PBO_{adj}.

I KN522 rapporteres bivirkninger hos patienter, som har modtaget minimum én dosis studiemedicin (*as-treated* (ASat) population). Dette svarer til 783 patienter i PEM+CT_{neo} + PEM_{adj} gruppen og 389 patienter i PBO+CT_{neo} + PBO_{adj} gruppen. Bivirkninger er blevet publiceret for IA1 og IA4 med en median opfølgningstid på henholdsvis 15,5 og 39,1 mdr. [9] [10, 12]. Median behandlingstid for de to grupper var ens for både den neoadjuverende og adjuverende fase (se Table 5). Her skal vi understrege, at der til sammenligning i den adjuverende fase bliver givet aktiv intervention i PEM+CT_{neo} + PEM_{adj} vs. placebo i PBO+CT_{neo} + PBO_{adj}.

Table 5 Median behandlingsvarighed

Weeks (range)	PEM+CT_{neo} + PEM_{ad}	PBO+CT_{neo} + PBO_{adj}
Neoadjuverende	22,1 (0,1-31,1)	22,1 (0,1-31,1)
Adjuverende	24,1 (0,1-37,7)	24,1 (0,1-39,7)

Table 6 *All-cause* bivirkninger

	PEM+CT_{neo} + PEM_{ad} N (%)			PBO+CT_{neo} + PBO_{adj} N (%)		
	Neo+adj N=783	Neo N=783	Adj N=588	Neo+adj n=389	Neo n=389	Adj N=331
Participants in population with						
One or more AE	777 (99,2)	777 (99,2)	542 (92,2)	389 (100,0)	389 (100,0)	294 (88,8)
Grad 3-5 AEs	645 (82,4)	627 (80,1)	316 (53,7)	306 (78,7)	295 (75,8)	38 (11,5)

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With serious AEs	341 (43,6)	315 (40,2)	41 (7,0)	111 (28,5)	101 (26,0)	14 (4,2)
With any dose modification due to AE	644 (82,2)	628 (80,2)	105 (17,9)	306 (78,7)	296 (76,1)	45 (13,6)
Who died	7 (0,9)[i]	5 (0,6)	2 (0,3)	1 (0,3)[ii]	1 (0,3)	0 (0,0)
Who discontinued any drug due to an AE	234 (29,9)	205 (26,2)	32 (5,4)	60 (15,4)	53 (13,6)	8 (2,4)

Database Cutoff Date: 23MAR2021 Grades are based on NCI CTCAE version 4.0.

Neo+adj: *Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the nonserious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events.* ***Neo:*** *Included adverse events started from the first neoadjuvant treatment including definitive surgery and prior to the first adjuvant treatment including radiation therapy or, if no adjuvant treatment, up to 30 days of the definitive surgery for the non-serious adverse events and up to 90 days of the definitive surgery for the serious adverse events or, if no surgery, up to 30 days of last neoadjuvant treatment for the non-serious adverse events and up to 90 days of last neoadjuvant treatment for the serious adverse events.* ***Adj:*** *Included adverse events started from the first adjuvant treatment including radiation therapy and up to 30 days of last adjuvant treatment including radiation therapy for the non-serious adverse events and up to 90 days of last adjuvant treatment for the serious adverse events.* [i]*4 deaths considered drug-related. 1 pneumonitis, 1 pulmonary embolism, 1 autoimmune encephalitis, 1 sepsis+multiple organ dysfunction syndrome (likely related to chemotherapy)+myocardial infarction (not considered drug-related)* [ii]*1 septic shock (considered chemotherapy-related)*

Den overordnede incidens af bivirkninger var sammenlignelig mellem de to behandlingsgrupper med 99,2% i PEM+CT_{neo} + PEM_{adj} og 100,0% i PBO+CT_{neo} + PBO_{adj} og under 5%-points forskel for incidens af grad 3-5 bivirkninger. Dødsfald i forbindelse med bivirkninger blev rapporteret i henholdsvis 7 (0,9%) i PEM+CT_{neo} + PEM_{adj} vs. 1 (0,3%) i PBO+CT_{neo} + PBO_{adj} (Table 6). Dette er lavere sammenlignet med reference datasættet, hvor der ses en incidens på 5,2% af grad 5 bivirkninger, som højst sandsynlig afspejler den yngre patientpopulation i KN522 med en bedre baseline almentilstand [12].

Der var en overhyppighed af patienter, som fik en bivirkning med behandlingsophør til følge i PEM+CT_{neo} + PEM_{adj} (29,9%) vs. PBO+CT_{neo} + PBO_{adj} (15,4%)(Table 6). Interventionsarmen PEM+CT_{neo} + PEM_{adj} repræsenter tillæg af "aktivt" pembrolizumab, hvortil man vil forvente et tillæg af bivirkninger. Denne difference i incidens afspejler den incidens af behandlingsophør af bivirkning, som der er registreret for referencedatasættet for pembrolizumab monoterapi (13,4%) [12]. De mest hyppige behandlingsrelaterede bivirkninger, som førte til behandlingsophør var med en incidens på ≥1% i PEM+CT_{neo} + PEM_{adj}, med ≥1%-point difference sammenlignet med PBO+CT_{neo} + PBO_{adj} var stigning i ALT (2,8% vs. 1,3%), stigning i AST (1,7% vs. 0,0%) og febril neutropeni (1,5% vs. 0,5%) [12]. I EPAR'en konkluderes, at man derudover ikke på baggrund af resultaterne i KN522 kan fastlægge en bivirkningsprofil, som er associeret med behandlingsophør i interventionsarmen.

Kvalitativt afspejlede bivirkningsprofilen for PEM+CT_{neo} + PEM_{adj} det, man forventer for henholdsvis pembrolizumab monoterapi og carboplatin/antracyklin baseret kemoterapiregime. De mest hyppige bivirkninger var nogenlunde ens mellem de to behandlingsgrupper, hvilket indikerer, at de kan være drevet af den fælles kemoterapi-komponent [12]. Disse var kvalme (66,7% vs. 66,1%), alopecia (60,9% vs. 58,1%), anæmi (59,1% vs 58,9%), fatique (43,2% – 46,6%), forstoppelse (41,9% vs. 38,6%) og diarré (40,6% vs. 34,2%) i henholdsvis PEM+CT_{neo} + PEM_{adj} vs. PBO+CT_{neo} + PBO_{adj} (se appendix E).

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I PEM+CT_{neo+} PEM_{adj} sås en overhyppighed af pyreksi, hypotyroidisme, diarré, udslæt og nedsat appetit sammenlignet med PBO+CT_{neo+} $PBO_{adj,}$ hvoraf størstedelen af disse var af grad 1-2 [12]. For CAP_{adj} var den hyppigste bivirkning, baseret på resultaterne fra CREATE-X studiet (n=443) hånd-og fodsyndrom (73,4%), hvoraf 11,1 % var grad 3 bivirkninger. Derudover var de mest hyppige hæmatologiske bivirkninger leukopeni (63,2%), trombocytopeni (54,9%), neutropeni (43,6%) og anæmi (39,5%). De mest almindelige ikke-hæmatologiske bivirkninger var fatigue (25,5%), kvalme (22,1%), diarré (21,9%), mukositis eller stomatitis (39,3%), samt forøgelser i alanin aminotransferase (35,6%), bilirubin (32,1%), laktat dehydrogenase (31,8%), aspartat aminotransferase (28,7%) og alkalin fosfatase (25,5%) niveauer [23]. Bivirkninger i CREATE-X studiet blev opgjort for hele populationen, dvs. HER2-negative patienter og inkluderer derfor både HR+ og TNBC og er derfor ikke nødvendigvis direkte sammenlignelige med TNBC studiepopulationen i KN522.

For de alvorlige bivirkninger rapporteret i KN522 var der en højere incidens i interventionsarmen PEM+CT_{neo+} PEM_{adj} med 43,6% vs. 28,5% i PBO+CT_{neo+} PBO_{adj}. Her var den mest hyppige alvorlige bivirkning febril neutropeni, med 15,1% vs. 12,1% for henholdsvis PEM+CT_{neo+} PEM_{adj} og PBO+CT_{neo+} PBO_{adj}. Til trods for at der kumulativt var en forskel på 15,1%-point på alvorlige bivirkninger mellem de to behandlingsgrupper, vurderes der generelt ikke at være signifikante forskelle, når man kvalitativt ser på de enkelte bivirkningstyper ved sammenligning af PEM+CT_{neo+} PEM_{adj} og PBO+CT_{neo+} PBO_{adj}. Undtagelsen var pyreksi, hvor der var en højere incidens i PEM+CT_{neo+} PEM_{adj} (3,7%) vs. PBO+CT_{neo+} PBO_{adj} (0,5%) (Table 7). I Table 7 ses de mest hyppige alvorlige bivirkninger med ≥1%, hvoraf de mest hyppige i PEM+CT_{neo+} PEM_{adj} var febril neutropeni (15,1%), pyrexia (3,7%) og anæmi ([redacted]). Til sammenligning var de mest hyppige bivirkninger i PBO+CT_{neo+} PBO_{adj} febril neutropeni (12,1%), anæmi ([redacted]) og pneumoni ([redacted]) [12, 50].

Table 7. De mest hyppige alvorlige bivirkninger ≥5 % incidens [12]

	PEM+CT_{neo} + PEM_{ad}		PBO+CT_{neo} + PBO_{adj}	
	n	%	n	%
Participants in population	783		389	
with one or more adverse event	341	43,6	111	28,5
Febrile neutropenia	118	15,1	47	12,1

Database cutoff Date: 23MAR2021

Every participant is counted a single time for each applicable specific adverse event.

Included serious adverse event started from the first treatment including definitive surgery and radiation therapy and up to 90 days of the last treatment including definitive surgery and radiation therapy.

For grad 3-5 bivirkninger var de hyppigste neutropeni (35,5 vs. 34,4%), nedsat antal neutrofile leukocytter (19,0 vs. 23,7%), anæmi (19,5 vs. 15,7%) og febril neutropeni (18,4 vs. 16,2%), i henholdsvis PEM+CT_{neo+} PEM_{adj} vs. PBO+CT_{neo+} PBO_{adj}. Disse er bivirkninger, som oftest er forbundet med kemoterapi, hvorfor de optræder i sammenlignelig hyppighed i begge behandlingsgrupper. I Table 8 ses de hyppigste (≥5%) a*ll-cause* grad 3-5 bivirkninger, som er rapporteret for de to behandlingsgrupper.

Table 8 All-cause grade 3-5 bivirkninger med incidens ≥5%

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	PEM+CT$_{neo}$ + PEM$_{adj}$		PEM+CT$_{neo}$ + PEM$_{adj}$	
	n	%	n	%
Participants in population	*789*		*389*	
With one or more advserse events	*645*	*82,4*	*306*	*78,7*
With no adverse events	*138*	*17,6*	*83*	*21,3*
Neutropenia	*276*	*35,5*	*134*	*34,4*
Neutrophil count decreased	*149*	*19,0*	*92*	*23,7*
Anaemia	*153*	*19,5*	*61*	*15,7*
Febrile neutropenia	*144*	*18,4*	*63*	*16,2*
White blood cell decreased	*61*	*7,8*	*21*	*5,4*
Alanine aminotransferase increased	*50*	*6,4*	*11*	*2,8*

Database Cutoff Date: 23MAR2021

Every participant is counted a single time for each applicable specific adverse event. A 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. Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the nonserious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. Grades are based on NCI CTCAE version 4.0.MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Generelt ses der en overensstemmelse mellem de to behandlingsgrupper for de mest hyppige *all-cause* grad 3-5 bivirkninger, trods tillægget af den aktive intervention med pembrolizumab og dets immunaktiverende mekanisme (**Table 8**). Den største forskel (≥3% point forskel) blev observeret for anæmi (19,5% vs. 15,7%) og forøgelse i alanin aminotransferase (6,4% vs. 2.8%), med en højere incidens i PEM+CT$_{neo+}$ PEM$_{adj}$ vs. PBO+CT$_{neo+}$ PBO$_{adj}$.

I den adjuverende fase af KN522 blev der generelt rapporteret en lavere frekvens af 3-5 bivirkninger. Her blev der samlet set rapporteret en incidens på [redacted] i PEM+CT$_{neo+}$ PEM$_{adj}$ og [redacted] i PBO+CT$_{neo+}$ PBO$_{adj}$. [redacted]. For CAP$_{adj}$ var de hyppigste grad 3-4 bivirkninger hånd-og fodsyndrom (11,1%), neutropeni (6,3%), diarré (2,9%), leukopeni (1,6%) og fatigue (1,1%). Til sammenligning var de mest hyppige grad 3-4 bivirkninger i kontrolarmen stigning i aspartat-og alanin aminotransferase, som begge lå på 0,4% [23]. Vi har ikke kunne lokalisere data for den overordnede incidens for grad 3-4 bivirkninger for CAP$_{adj}$ baseret på CREATE-X studiet. Den tilgængelige evidens indikerer dog, at der generelt er en højere incidens af de enkelte (f.eks. hånd-og fodsyndrom) grad 3-4 bivirkninger for CAP$_{adj}$ sammenlignet med PEM$_{adj,}$ og det er andre typer af bivirkninger, som er associeret med pembrolizumab vs. capecitabin.

Immunrelaterede bivirkninger var hyppigst forekommende i PEM+CT$_{neo+}$ PEM$_{adj}$ (43,6%) vs. PBO+CT$_{neo+}$ PBO$_{adj}$ (21,9%) med hypothyroidisme som hyppigste [redacted]), hvoraf de fleste tilfælde var grad 1 eller 2 ([redacted]) og [redacted] behandling herfor ved data cut-off [50]. Udover hypothyroidisme var de hyppigste immunrelatede bivirkninger (efter kategori), infusionsreaktioner (18,0% vs. 11,6%) og alvorlige hudreaktioner (5,7% vs. 1,0%). Der var to dødsfald (1 pneumonit og 1 autoimmun encephalit), som følge af en immunrelateret bivirkning, vurderet af investigator til at være associeret med pembrolizumab behandling [12].

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

På baggrund af gennemgangen af bivirkningsprofilerne i KN522 kan det konkluderes at:

- Bivirkningerne var håndterbare og konsistente med de allerede kendte bivirkninger af henholdsvis pembrolizumab og et antracyklin/platin baseret regime.
- Tillæg af pembrolizumab til kemoterapi ikke øger incidensen af alvorlige bivirkninger (SAE), dog med undtagelse af pyreksi, som drøftet ovenfor.
- Tillæg af pembrolizumab til kemoterapi øgede ikke incidensen af kemoterapi-inducerede toksicitet (f.eks.. hæmatologiske bivirkninger).

MSD mener, at der ved at tillægge pembrolizumab til den nuværende standardbehandling indikeres en klinisk relevant merværdi for patienter med tidlig stadie TNBC med kendte og håndterbare bivirkninger.

7.2.1.7 Livskvalitet

Resultaterne for livskvalitet i KN522 blev vurderet efter EORTC QLQ-C30, QLQ-BR23, EQ-5D for all inkluderede patienter i FAS populationen. Resultaterne, som præsenteres i denne ansøgning, er endnu ikke blevet publiceret og kan på nuværende tidspunkt findes i EPAR'en [12].

Data er opgjort særskilt for den neoadjuverende og den adjuverende fase, med en tidsramme på hhv. 21 og 24 uger, baseret på et præspecificeret krav og min. *completion rate* på 60%. C*ompliance rates*[3] lå omkring 90% ved baseline gennem hele den præspecificerede registreringsperiode, for både den neoadjuverende og adjuverende fase.

Table 9. EORTC-QLQ-C30, Least square mans ved baseline for ITT population og indtil uge 21 (neoadjuverende) og uge 24 (adjuverende)

	EORTC-QLQ-C30, LS mean fra baseline til uge 21 Neoadjuverende	**Forskel i EORTC-QLQ-C30 LS mean, uge 21 PEM+CT_{neo} vs. PBO+CT_{neo}**
PEM+CT_{neo} (baseline n=701)	-11.24 (95% CI -12,82 til -9,66)	**-1,04 point (95% CI -3.46 til 1,38) p=0.3985**
PBO+CT_{neo} (baseline n=366)	-10,20 (95% CI -12,30 til 8,10)	
	EORTC-QLQ-C30, LS mean fra baseline til uge 24 Adjuverende	**Forskel i EORTC-QLQ-C30 LS mean, uge 24 PEM+CT_{adj} vs. PBO+CT_{adj}**
PEM_{adj} (baseline n=489)	2,47 (95%CI 1,05 til 3,88)	**-0,41 point (95%CI -2,60 til 1,77)**

[3] Compliance rates, defined as the percentage of participants completing the measure among those expected to complete the measure (ie, not missing by design)

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PBO_{adj} (baseline n=283)	2,88 (95% CI 1,05 til 4,71)	**p=0,7107**

Livskvalitet blev via EORTC-QLQ-C30 målt som den gennemsnitlige ændring fra baseline (før første behandling) til henholdsvis uge 21 og 24 efter neoadjuverende og adjuverende behandling. Data er angivet som least squares (LS) means, hvilket er forskel i gruppens middelværdi efter justering for kovariater.

Der var ved baseline for både neoadjuverende og adjuverende fase ingen forskel på de to behandlingsgrupper.
Under den neoadjuverende fase var der fra baseline til uge 21 et fald i LS på -11,24 (95% CI -12,82 til -9,66) for $PEM+CT_{neo}$ og -10,20 (95% CI -12,30 til 8,10) for $PBO+CT_{neo}$. Ændringen fra baseline til uge 21, var dog sammenlignelig mellem de to behandlingsgrupper med en ikke signifikant forskel på -1,04 point (95% CI -3.46 til 1,38) (Table 9).

Dette viser, at tillæg af pembrolizumab til kemoterapi som neoadjuverende behandling ikke medfører en ændring i livskvalitet.

For den adjuverende fase var der fra baseline til uge 24 en lille stigning på 2,47 (95%CI 1,05 til 3,88) i PEM_{adj} vs. 2,88 (95% CI 1,05 til 4,71) i PBO_{adj}. Den lille forøgelse i LS mean under den adjuverende fase er sammenlignelig mellem de to behandlingsgrupper på trods af tillæg af aktiv intervention med immun-aktiverende pembrolizumab vs. placebo.

På baggrund af livskvalitetsanalysen pr. EORTC-QLQ-C30 kan det konkluderes, at der ikke var en signifikant ændring i livskvalitet hverken med tillæg af pembrolizumab til kemoterapi til neoadjuverende behandling eller pembrolizumab monoterapi til adjuverende behandling. Resultaterne fra EORTC-QLQ-C30 var i overensstemmelse med resultaterne fra både EORTC-QLQ-BR23 og EQ-5D-5L (se appendix D).

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

8. Health economic analysis

8.1 Model

The following is a description of our health economic model that is developed to demonstrate the cost effectiveness of neoadjuvant pembrolizumab + chemotherapy (carboplatin and paclitaxel, followed by doxorubicin or epirubicin and cyclophosphamide) followed by adjuvant pembrolizumab after surgery in patients with high-risk early-stage TNBC. The comparator is the chemotherapy (carboplatin and paclitaxel, followed by doxorubicin or epirubicin and cyclophosphamide) control arm of the KN522 trial.

The model takes a limited societal perspective where direct health costs and some indirect costs including relevant transportation costs and time spent for drug administration and monitoring are included [55].

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.

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8.1.1 Type of economic evaluation

This economic model estimates the expected costs and clinical effectiveness (including life years (Lys) and quality-adjusted life years (QALYs)) for each neoadjuvant and adjuvant treatment arm, as well as incremental cost-effectiveness ratios (ICERs) in terms of both incremental cost per QALY gained and incremental cost per LY gained comparing pembrolizumab + chemotherapy versus chemotherapy. Cost outcomes are reported in aggregate (total costs) as well as disaggregated by cost component. Effectiveness outcomes are also reported in aggregate as well as disaggregated by health state. All costs are reported in 2022 Danish Kroner (DKK).

The model also evaluates a budget impact analysis. Total costs (for a time horizon of 5 years) are reported for scenarios with and without pembrolizumab. The budget impact is evaluated through the difference in total costs in the two scenarios.

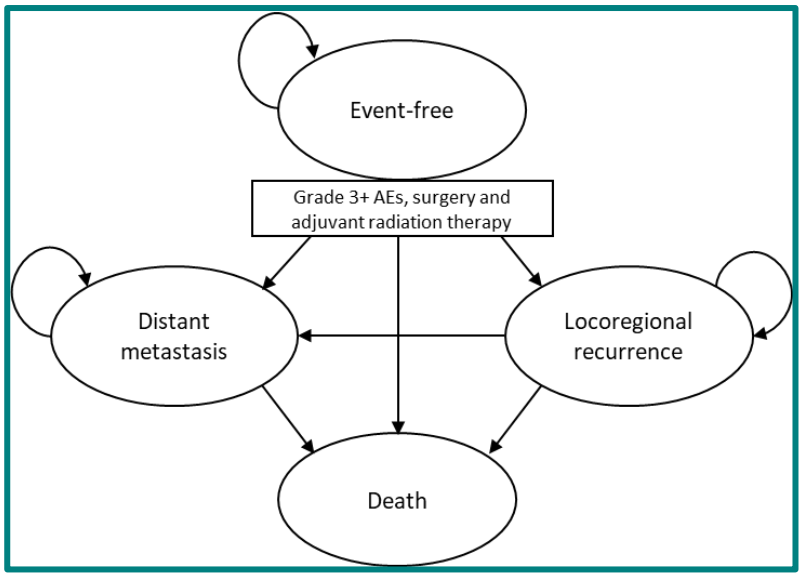
8.1.2 Model structure

The cost-effectiveness model is developed in Microsoft Excel® 2016 using a Markov cohort model. A Markov model approach is taken because it can explicitly capture disease pathway of patients with early-stage TNBC.

The model includes four mutually exclusive health states: (i) event-free (EF); (ii) locoregional recurrence (LR); (iii) distant metastasis (DM), and (iv) death, to track the disease course and survival of patients over time (Figure 9). This model differentiates health states by type of recurrence (either LR or DM) because the primary endpoint, i.e., EFS, of the KN522 trial encompasses both types of recurrence events [56]. These two types of recurrences are expected to have different implications on patients' prognosis, and therefore result in different health outcomes and costs. For each health state, specific cost and health utility are assigned to calculate the cumulative costs and cumulative QALY over the modeled time horizon.

Besides the four mutually exclusive health states, the model considers the following clinical events: Grade 3+ adverse events (AEs) from the combined neoadjuvant and adjuvant phases, the surgery following the neoadjuvant phase, and the radiation therapy in the adjuvant phase (details in section 8.2.2.3). Similarly, for each clinical event, a specific cost and utility decrement (only applicable to Grade 3+ AEs) are applied in the model.

Figure 9 Model schematic



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8.1.3 Time horizon

Based on the Danish Medicines Council guidelines, the time horizon of this model is long enough to reflect the differences in costs and outcomes between pembrolizumab and comparators [57]. For Denmark, a 51-year time horizon is used in the base case. As the mean age of the patients is 49.1 years, following them over 51 years, there will be no patients alive across all the interventions and comparators. So, the selected time horizon is long enough to capture all differences in costs and outcomes between the intervention and the comparators.

The impact of alternative time horizons is explored in the sensitivity analyses below in section 8.7.

8.1.4 Perspective

The model is conducted from a limited societal perspective based on the guidelines provided by Danish Medicines Council, where patient costs like transportation costs, patient monitoring and follow up costs are included [57].

8.1.5 Cycle length

Based on a targeted literature review, prior economic evaluations of adjuvant treatments for other cancers have generally used cycle lengths ranging from 1 week to 1 year. The present model uses a weekly cycle length to allow for precise calculation of drug acquisition and administration costs.

Treatment cycles and disease monitoring of pembrolizumab and chemotherapy can occur in 3- or 4-week cycles during the KN522 trial. Paclitaxel plus carboplatin administration occurs paclitaxel (80 mg/m^2 once weekly) plus carboplatin (area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly in the first 12 weeks). Therefore, the model employed a weekly cycle length to allow a more accurate estimation of treatment-related costs. Modelling guidelines recommend applying a within-cycle correction to reduce bias when calculating cumulative outcomes in discrete time state-transition models [58]. The model includes half-cycle correction, where trapezoidal rule is followed for the correction to reduce the bias in estimation due to time discretization. Without this correction we assume that death occurs only at the starting of the cycle. This correction is considered in the model to take care of within cycle deaths of patients, more specifically to consider the patients who died between a week.

8.1.6 Discount rate

Based on the guidelines of the Danish Ministry of Finance, both costs and effectiveness are discounted at 3.5% annually in the base-case for the cost effectiveness model [59]. In one-way deterministic sensitivity analyses, annual discount rates of 0% and 5% are tested (see section 8.7).

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

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

Interim results from KN522 provided efficacy, utility and safety inputs for the CUA (data cutoff date: March 23, 2021), and a total of 1,174 patients are included in the analysis.

Table 10 presents the clinical input data used in the model and how they are obtained.

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Table 10 Input data used in the model

Name of estimates*	Results from study	Input value used in the model	How is the input value obtained/estimated**
Event free survival (EFS)	KN522. Primary endpoint: To compare EFS between treatments arms. EFS is defined as time from randomization to first occurrence of one (or more) of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause. Progression of disease, local or distant recurrence, and second primary malignancy are based on investigator determination (supplementary materials, protocol [9]).	A Markov model structure is used with four mutually exclusive health states. (EF, LR, DM and death). A patient starts from the EF state and move to different health states according to different transition probabilities.	EFS curves are derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, log-normal and generalized gamma distributions) to individual patient data (IPD) from the KN522 trial. The best fitting parametric curves for EFS are used to extrapolate these efficacy outcomes beyond the trial period.
OS	KN522. Secondary endpoint: To compare OS between treatment arms. OS is defined as the time from randomization to death due to any cause.	Please see description above for EFS.	Please see description above for EFS.
Transition probabilities: EF→DM EF→LR	KN522 (Cut-off date: 23 March 2021)	Please see description above for EFS	Please refer to section 8.3
Transition probabilities: LR→DM or Death	KN522 (Cut-off date: 23 March 2021)	Please see description above for EFS	Please refer to section 8.3
Transition probabilities: DM→Death	KN522 (Cut-off date: 23 March 2021)	Please see description above for EFS	TP from DM → death is estimated based on the treatment rate, the expected mix of first line (1L) treatments in the DM state, and the efficacy of these 1L treatments in terms of mean OS. Please refer to section 8.3.4.
Adverse reaction 1 (measured in costs)		One-off AE-related costs per first-line treatment arm are applied at the beginning of the model and calculated based on the unit costs for managing each AE and the AE rate.	The unit cost of AE management per incidence is obtained based on 2022 DRG-rates from the Danish Health Data Authority [60]
Adverse reaction 2 (measured as occurrence)	AE Grade 3+ incidence rates	The AEs included in the model are all-cause grade 3-5 AEs with incidence rate ≥ 5% in at least one treatment arm. Costs associated with the management of AEs are applied as a one-time cost at model entry.	For pembrolizumab + chemotherapy and chemotherapy comparators, AE rates are obtained from the KN522 trial.
Adverse reaction 3 (measured as utility loss)		Based on utility by health state, treatment status, and AE status, the model includes the option to include the disutility associated with grade 3+ AEs.	To assess the potential disutility associated with grade 3+ AEs, the time points associated with patients experiencing grade 3+ in the EFS state are analyzed separately

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Name of estimates*	Results from study	Input value used in the model	How is the input value obtained/estimated**
			from those when patients were not experiencing those AEs.
Utility by health state, treatment status, and AE status: Base case	KN522, secondary endpoint: The EORTC-QLQ-BR23 is a 23-item questionnaire developed to assess the quality of life of breast cancer patients. Individual responses are given on a 4-point scale (1=Not at All to 4=Very Much), with a lower score indicating a better outcome. The EORTC-QLQ-BR23 score is presented for all participants and for participants with tumors expressing PD-L1.	Health state utility inputs are derived from the EuroQoL EQ-5D-5L data collected in the KN522 trial. The generic health statuses assessed from the EQ-5D questionnaires are converted to population-based utility values using Danish algorithm for the base-case analysis.	Since one patient can have multiple utility measures, linear mixed-effects models with patient-level random effects are used for this analysis to account for within-subject correlation. The linear mixed-effects models also include the presence or absence of any Grade 3+ AEs to estimate AE disutility.

* Some of these estimates will be presented in other tables in the document. This table is a summary.

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:

The Danish patient population, which is expected to be candidates for treatment, will be adults with high-risk, early-stage, TNBC (see section 5).

Patient population in the clinical documentation submitted:

The patient population in the clinical documentation is adults with high-risk, early-stage, TNBC. Based on KN522 trial (see section 5).

Patient population in the health economic analysis submitted:

The target population of the health economic analysis is adults with high-risk, early-stage, TNBC. Based on KN522 trial.

Baseline characteristics of patients in the model cohort, including starting age, body weight, and body surface area (BSA) is obtained from the KN522 trial (ITT population) (Table 12). The model assumed 100% of female.

Table 12 Characteristics of patient population

Parameter	Clinical documentation	Used in the model	Danish clinical practice
Starting age	49	49	Patient characteristics from KN522 are validated by Danish clinical expert.
Body weight (kg)(median)	67.0	67.0	
Body surface area (m^2)(mean)	1.8	1.8	
Body weight (kg)(SD)	16.3	16.3	
Body surface area (m^2)(SD)	0.2	0.2	

Source: KN522 (cutoff date: March 23, 2021)

Abbreviations: SD, standard deviation

Data from Danish clinical practice is sparse. As there is no local data to identify the characteristics of Danish TNBC patients, the inputs from KN522 have been validated by a Danish clinical expert. Based on this validation MSD considers the study population in KN522 to be representative for the Danish patient population.

8.2.2.2 Intervention

The intervention as in the clinical documentation (ITT population), as used in the health economic analysis described in Table 13 below.

Table 13 Intervention

Parameter	Clinical documentation	Used in the model	Danish clinical practice
Posology	Pembrolizumab + Chemotherapy: Neoadjuvant phase (1st phase, 1-4 cycle): • Pembrolizumab 200 mg every 3rd week (IV) OR 400 mg every 6th week (IV) • And paclitaxel 80 mg/m^2, once weekly (IV) • And carboplatin area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly (IV) Neoadjuvant phase (2nd phase, 5-8 cycle): • Pembrolizumab 200 mg every 3rd week (IV) OR 400 mg every 6th week (IV) • And cyclophosphamide 600 mg/m^2 once every 3 weeks • Or doxorubicin 60 mg/m^2 once every three weeks • Or epirubicin 90 mg/m^2 once every three weeks Surgery: definite surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase. Adjuvant phase: • Pembrolizumab 200 mg every 3rd week (IV) Or 400 mg every 6th week (IV)	Pembrolizumab + Chemotherapy: Neoadjuvant phase (1st phase, 1-4 cycle): • Pembrolizumab 2 mg/kg every 3rd week (IV) OR 4 mg/kg every 6th week (IV) • And paclitaxel 80 mg/m^2, once weekly (IV) • And carboplatin area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly (IV) Neoadjuvant phase (2nd phase, 5-8 cycle): • Pembrolizumab 2 mg/kg every 3rd week (IV) OR 4 mg/kg every 6th week (IV) • And cyclophosphamide 600 mg/m^2 once every 3 weeks • Or doxorubicin 60 mg/m^2 once every three weeks • Or epirubicin 90 mg/m^2 once every three weeks Surgery: definite surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase. Adjuvant phase: • Pembrolizumab 2 mg/kg every 3rd week (IV) Or 4 mg/kg every 6th week (IV)	Neoadjuvant phase (1st phase, 1-4 cycle): • Cyclophosphamide 600 mg/m^2 once every 3 weeks • Or doxorubicin 60 mg/m^2 once every three weeks • Or epirubicin 90 mg/m^2 once every three weeks Neoadjuvant phase (2nd phase, 5-8 cycle): • Paclitaxel 80 mg/m^2, once weekly (IV) • And carboplatin area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly (IV) Surgery: definite surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase. Adjuvant phase: • pCR patients: radiation • Non pCR patients: Capecitabine 1000 mg/m2 twice a day in 14 days and radiation
Length of treatment (time on treatment) (median)	Pembrolizumab + Chemotherapy: 22 weeks	Pembrolizumab + Chemotherapy: 22 weeks	
Criteria for discontinuation	Trial treatment is discontinued in patients with disease progression or recurrence or unacceptable toxic effects.	Trial treatment is discontinued in patients with disease progression or recurrence or unacceptable toxic effects.	
The pharmaceutical's position in Danish clinical practice			Currently not used in clinical practice for the treatment of Early TNBC prior to evaluation in the Medicines Council. Recommendation from the Danish Medicines Council will lead to the introduction of the intervention as a neo adjuvant treatment with combination with chemotherapies and as a single agent treatment as an adjuvant treatment after surgery.

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8.2.2.3 Comparators

The comparators used in the clinical documentation submitted, and in the health economic analysis is described in the Table 14 below.

Table 14 Comparator

Parameter	Clinical documentation	Used in the model	Danish clinical practice
Posology	Chemotherapy: Neoadjuvant phase (1st phase, 1-4 cycle): • Paclitaxel 80 mg/m2, once weekly (IV) • And carboplatin area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly (IV) Neoadjuvant phase (2nd phase, 5-8 cycle): • Cyclophosphamide 600 mg/m2 once every 3 weeks • Or doxorubicin 60 mg/m2 once every three weeks • Or epirubicin 90 mg/m2 once every three weeks Surgery: definite surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase. Adjuvant phase: • Radiation therapy as indicated and placebo once every 3 weeks for up to nine cycles.	Chemotherapy: Neoadjuvant phase (1st phase, 1-4 cycle): • Paclitaxel 80 mg/m2, once weekly (IV) • And carboplatin area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly (IV) Neoadjuvant phase (2nd phase, 5-8 cycle): • Cyclophosphamide 600 mg/m2 once every 3 weeks • Or doxorubicin 60 mg/m2 once every three weeks • Or epirubicin 90 mg/m2 once every three weeks Surgery: definite surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase. Adjuvant phase: • Radiation therapy as indicated and placebo once every 3 weeks for up to nine cycles.	Neoadjuvant phase (1st phase, 1-4 cycle): • Cyclophosphamide 600 mg/m^2 once every 3 weeks • Or doxorubicin 60 mg/m^2 once every three weeks • Or epirubicin 90 mg/m^2 once every three weeks Neoadjuvant phase (2nd phase, 5-8 cycle): • Paclitaxel 80 mg/m^2, once weekly (IV) • And carboplatin area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly (IV) Surgery: definite surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase. Adjuvant phase: • pCR patients: radiation • Non pCR patients: Capecitabine 1000 mg/m2 twice a day in 14 days and radiation
Length of treatment (time on treatment) (median)	Chemotherapy: 22 weeks	Chemotherapy: 22 weeks	

Although Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial demonstrated that adjuvant capecitabine for non-pCR TNBC patient prolonged survival, it was not included in the KN522 study design for the following reasons:

- KN522 was designed prior to the publication of the CREATE-X study, and at that time adjuvant capecitabine was not standard of care for non-pCR TNBC patients.
- In 2017, the NCCN guidelines were updated to include adjuvant capecitabine as an option for TNBC patients who do not achieve pCR after neoadjuvant chemotherapy, based on the results of the CREATE-X study (n=910) [23]. To avoid introducing confounding factors to the final results of KN522, and following discussions with the FDA, MSD decided not to include capecitabine in KN522.

As discussed at the dialogue meeting with the secretariat of the Danish Medicines Council on January 20th 2022, capecitabine is not included as an indirect comparator in the current analysis. The rationale is summarized as follows:

- KN522 was designed to evaluate the efficacy of 1-year administration of pembrolizumab in combination with chemotherapy as neoadjuvant treatment before surgery and continues as monotherapy as adjuvant therapy

after surgery. The study design does not allow evaluation of the individual contributions of the neoadjuvant and adjuvant phases.
    - The analysis of EFS according to pCR status was a non-randomized, exploratory analysis, and hence does not support statistical conclusions [49].
- CREATE-X and KN522 studies included two different patient populations:
    - The CREATE-X population included HER2-negative breast cancer patients whilst KN522 included only early-stage TNBC patients.
        - TNBC patients only comprised 30% of patients in CREATE-X (the rest were HR+) vs. 100% in KN522.
        - Prior neoadjuvant therapy included current standard of care combined with pembrolizumab in KN522, whereas prior neoadjuvant therapy in CREATE-X did not include pembrolizumab (or other anti-PD1/PD-L1 inhibitor) and was comprised of a heterogenous range of chemotherapeutic regimens for the individual patients in the study population.
    - CREATE-X investigated capecitabine in the adjuvant setting only, whilst KN522 evaluated a treatment regimen spanning both the neoadjuvant and adjuvant phases. Thus, there is not data to demonstrate how patients, previously treated with PEM+CT in the neoadjuvant setting, will respond to subsequent adjuvant capecitabine (non-pCR).
- The inclusion of adjuvant capecitabine in treatment guidelines is largely based on the CREATE-X study. There are critical differences between the CREATE-X and KN522 study design, that prevents a statistically valid comparison from a methodological perspective [23].
    - CREATE-X had a primary endpoint of DFS whilst KN522 has a dual primary endpoint of pCR/EFS.
    - The TNBC patients in the CREATE-X control arm had an unusually high risk of relapse that complicates comparisons between study populations.

Thus, it is not possible to include capecitabine as comparator in the current analysis, as the KN522 study and the CREATE-X study are distinct according to treatment regimen, patient population, and endpoints. Instead, the analysis is based on the results from the KN522 study with the control arm as a proxy for Danish clinical practice.

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation:
After a median follow-up time of 39.1 months a significant improvement in the 3-year EFS rate by 84.5% was evident in the pembrolizumab + chemotherapy arm in relation to 76.8% in the control arm. The HR for incident or death is 0.63 (95% CI 0.48;0.82), p<0.001 [49].

Table 15 EFS data from KN522

	Pembrolizumab + chemotherapy	Placebo + chemotherapy
	Event-free survival EFS	
Median EFS		
N	784	390
Result (CI)	NR	NR
Number of events (%)	123 (15.7)	93 (23.8)
Hazard ratio (95% CI)	0.63 (0.48;0.82)	Ref.

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p-value	<0.001	
3-year EFS rate		
N	784	209
Result (CI)	84.5% (81.7;86.9)	76.8% (72.2;80.7)
Difference	7.7	
Hazard ratio (95% CI)	0.63 (0.48-0.82)	Ref.
p-value	<0.001	

Source: KN552 **[49]**

The relative efficacy outcomes in the submitted health economic analysis:
In this economic model, the incremental effect of pembrolizumab + chemotherapy in extending EFS versus placebo + chemotherapy is determined by the parametric functions used for transitions starting from the EF state, in conjunction with background mortality rates. No waning of the treatment effect is applied in the long term. The assumption of a sustained treatment effect on EFS is in accordance with longer-term follow-up data from other adjuvant trials and KN trials in various indications, as well as the biological/clinical plausibility (see below).

A Markov model based on four health states (event-free, locoregional recurrence, distant metastases, and death) is developed. For pembrolizumab plus chemotherapy and chemotherapy arms included in KN522, parametric curves are fitted to EFS. Transition probabilities from EF → LR, EF → DM and EF → Death are from KN522 trial. In the base case, the transition probability from LR → DM is modelled using an exponential distribution. The exponential rate of LR to DM or Death is taken from KN522 trial. In each treatment arm, the transition probability from DM to death is assumed to depend on the market shares of advanced TNBC treatment regimens received in that arm.

The base-case parametric survival models are selected based on the statistical fit, visual inspection and clinical plausibility of the extrapolated model, and are summarized in section 8.3.1. Considering the uncertainty associated with the long-term extrapolation of EFS, it is important to carefully validate the EFS projections. The validation of EFS curves is conducted by 1) comparing modeled EFS vs. observed EFS in the KN522 trial, and 2) comparing the modeled EFS vs. external sources. Specifically, the modeled EFS at 3 years (pembrolizumab + chemotherapy = 84.5%, chemotherapy = 76.5%) are comparable to the observed EFS at 3 years (pembrolizumab + chemotherapy =84.5% and chemotherapy=76.8% ([redacted] and the modeled EFS curves match well with the observed EFS curves [redacted].

The modeled chemotherapy EFS is validated by relevant long-term external data [61] [8]. Thus, the base-case chemotherapy EFS is compared with the disease-free survival (DFS) following neoadjuvant chemotherapy in Walsh 2019 [61], and the EFS following neoadjuvant carboplatin-based chemotherapy in Sikov 2019 [8], respectively. As presented in [redacted] in Appendix G the modeled chemotherapy EFS curve matches well with the DFS curve from Walsh 2019 and the EFS curve from Sikov 2019, which confirms the plausibility of the EFS modelling.

As there is no clinical or real-world long-term EFS data for early-stage TNBC patients who received pembrolizumab yet, the plausibility of the projected long-term EFS of the pembrolizumab + chemotherapy arm was validated with a panel of key opinion leaders (KOLs) in this therapeutic area.

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Relevance of the documentation for Danish clinical practice:

Table 17 Summary of text regarding value

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study: Event-free survival (EFS) Overall survival (OS)	Please see [redacted] above.	Please see [redacted] above.

Table 18 Summary of text regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: Event-free survival (EFS)	The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	Due to the large number of medical oncological treatment options for metastatic patients, OS will for TNBC patients be an expression of both the effect on the neoadjuvant and adjuvant treatment and also the effect of the subsequent treatments in case of recurrence. In return, EFS presents the effect of the current treatment. Further, the use of EFS to model long-term survival in this economic evaluation is supported by a study that shows a good correlation between EFS and OS [9]. Therefore, EFS is chosen as primary endpoint in the current model, which is also accepted by FDA and EMA as relevant clinical endpoints	EFS and OS KN522 survival analysis include median survival and survival rates at different time landmarks. Again, based on recent descriptions from the Danish Medicines Council, these are relevant measurement methods. Median survival has been included in recent evaluation of clinical benefit, along with survival rates at different time landmarks [62].

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Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
		for the approval of new oncological drugs [39, 40].	
Secondary endpoint in the study: Overall survival (OS)	The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	The goal of cancer treatment is to prolong overall survival at minimal AE burden, so despite EFS being the preferred primary endpoint, OS is still a key endpoint. Also, please see above.	Please see above.

8.2.2.5 Adverse reaction outcomes

The model considers all-cause Grade 3+ AEs with an incidence of at least 5% from the combined neoadjuvant and adjuvant phases. The AE rates, and the mean duration of AEs are obtained from the KN522 trial (Table 19).

Specifically, the AE rates are considered separately for each arm. The mean durations of the included AEs are estimated based on the pooled data in the KN522 trial, and a mean duration of 12.5 weeks is applied to all AEs.

Consideration of AE-related disutility and cost are described in sections 8.4.1 and 8.5.7, respectively.

Table 19 All-cause Grades 3+ Aes with incidence ≥ 5%

Grade 3+ AE	Pembrolizumab + chemotherapy		Chemotherapy		Average duration of Aes (weeks)	
	Clinical documentation	Used in the model	Clinical documentation	Used in the model	Clinical documentation	Used in the model
Neutropenia	35.2%	35.2%	34.4%	34.4%	12.5	12.5
Neutrophil count decreased	19.0%	19.0%	23.7%	23.7%	12.5	12.5
Anemia	19.5%	19.5%	15.7%	15.7%	12.5	12.5
Febrile neutropenia	18.4%	18.4%	16.2%	16.2%	12.5	12.5
White blood cell count decreased	7.8%	7.8%	5.4%	5.4%	12.5	12.5
Alanine aminotransferase increased	6.4%	6.4%	2.8%	2.8%	12.5	12.5

Abbreviation: Aes, adverse events

The clinical documentation includes AE rates for the all subjects-as-treated population. The inclusion of specific AE types in the model is based on a combination of frequency and severity of each event. The model considers all-cause Grade 3–5 AEs that are reported in ≥5% as these are expected to have an impact on costs.

The mean durations of the included AEs and percentage of those with each AE that required hospitalization are collected from KN522 and used within the model to estimate the duration of the disutility impact and to cost associated with each AE. A mean duration of AEs of 12.5 weeks is applied to all grade 3+ AEs for chemotherapies and for IO therapies.

Duration of an AE is defined as the number of days between the start and the stop date of the AE. If the length of the AE was less than 1 day, the length in hours/minutes/seconds was converted to days. If the AE is resolving or not resolved,

the duration of an AE is defined as the number of days from the AE onset date till the censoring date of overall survival, or till the database cutoff date for AEs occurring after the censoring date of overall survival. For AEs with other outcomes for which the stop date was unknown, the AE duration is imputed as the average duration per specific adverse event term with the ceiling of the duration from the AE onset date till the censoring date of overall survival, or till the database cutoff date for AEs occurring after the censoring date of overall survival.

8.3 Extrapolation of relative efficacy

8.3.1 Transition probabilities – summarized:

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

In this economic model, the incremental effect of pembrolizumab + chemotherapy in extending EFS versus placebo + chemotherapy is determined by the parametric functions used for transitions starting from the EF state, in conjunction with background mortality rates. No waning of the treatment effect is applied in the long term. The assumption of a sustained treatment effect on EFS is in accordance with longer-term follow-up data from other adjuvant trials and KN trials in various indications, as well as the biological/clinical plausibility.

A Markov model based on four health states (event-free, locoregional recurrence, distant metastases, and death) is developed. For pembrolizumab plus chemotherapy and chemotherapy arms included in KN522, parametric curves are fitted to EFS. Transition probabilities from EF → LR, EF → DM and EF → Death are from KN522 trial. In the base case, the transition probability from LR → DM is modelled using an exponential distribution. The exponential rate of LR to DM or Death is taken from KN522 trial. In each treatment arm, the transition probability from DM to death is assumed to depend on the market shares of advanced TNBC treatment regimens received in that arm.

Table 20 presents a summary of estimation approaches and data sources for health state transitions illustrated in Figure 9. Details are provided in sections 8.3.2 through 8.3.4.

Table 20 Summary of health state transitions considered in the economic model

Transition(s)	Estimation approach	Data source(s)	Scenario or one-way sensitivity analyses performed
EF → LR EF → DM EF → Death	**Time dependent TPs are estimated based on 1) extrapolated EFS and 2) proportion of LR, DM and death as the first EFS event** • Using the patient-level data from KN522, EFS is extrapolated based on parametric functions for each arm. • No remission assumption is applied in the base-case. • No treatment waning effect is considered in the base-case. • Probability of experiencing LR, DM or death per cycle are estimated from EFS. • The probability of patients experiencing LR, DM and death as the first EFS event in Year 1 and Year 2+, respectively, are obtained from the KN522 clinical trial. • The TPs of EF → LR, EF → DM and EF → death are then calculated based on the probability of experiencing event (LR, DM or death) and the proportions of each event. • The TPs of EF → death are constrained to be at least as high as the all-cause natural mortality.	• KN522 • Life tables for Denmark [63] – *for transitions to death*	• Alternative parametric distributions
LR → DM LR → Death	**TPs starting from LR are assumed to be equivalent between arms, and constant across all cycles**	• KN522 • Life tables for Denmark [63] -	• NA

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	• The TPs of LR → DM or death are obtained from the KN522 clinical trial by pooling data from the two treatment arms. • The proportions of patients experiencing DM and death, respectively, are obtained from the KN522 clinical trial. • The TPs of LR → DM, and LR → death are calculated based on the probability of experiencing either event (DM or death) and the proportions of each event. • The TPs of LR → death are constrained to be at least as high as the all-cause natural mortality.	*for transitions to death*	
DM → Death	**TP from DM → death is estimated based on the treatment rate, the expected mix of first-line (1L) treatments in the DM state, and the efficacy of these 1L treatments in terms of mean OS** • KN355 is selected as the base-case source to estimate mean OS of all patients following distant metastases. The TPs of DM → death is derived based on assumptions and inputs related to 1) rechallenge with pembrolizumab or other immune-oncology (IO)-agent; 2) PD-L1 testing and positive rate; 3) treatment rate; 4) treatment mix for PD-L1 positives and PD-L1 negatives in the metastatic setting; and 5) mean OS of patients who received each 1L treatment and who did not receive the 1L treatments (details in section 1.3. • The TPs of DM → death are constrained to be at least as high as the all-cause natural mortality.	• KN355 • Life tables for Denmark [63] – *for transitions to death*	• Using KN522 as the source in the DM state.

Abbreviations: DM, distant metastases; EF, event-free; EFS, event-free survival; IO, 59mmune-oncology; LR, locoregional recurrence; OS, overall survival; TP, transition probability

8.3.2 Transitions from EF state

For the pembrolizumab + chemotherapy and chemotherapy arms, the TPs of EF → LR, EF → DM and EF → death are estimated based on the probability of the first EFS event, and the proportions of LR, DM and death being the first EFS event. The tables below summarize the number of events from EF to LR, DM and death.

Table 21 First EFS event, All subjects, ITT

	Pembrolizumab (N=784)	Placebo (N=390)	Total (N=1174)
Any	123	93	216
Local recurrent/PD	38	31	69
Distant recurrent/PD	70	56	126
Death	15	6	21

Table 22 EFS event, All subjects, iTT, within year 1

	Pembrolizumab (N=784)	Placebo (N=390)	Total (N=1174)
Any	52	29	81
Local recurrent/PD	19	13	32

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Distant recurrent/PD	25	15	40
Death	8	1	9

Table 23 EFS event, All subjects, ITT, after year 1

	Pembrolizumab (N=784)	Placebo (N=390)	Total (N=1174)
Any	71	64	135
Local recurrent/PD	19	18	37
Distant recurrent/PD	45	41	86
Death	7	5	12

8.3.2.1 EFS estimation approach

The EFS for pembrolizumab + chemotherapy and chemotherapy are estimated using the patient-level data from the KN522 trial (data cutoff date: March 23, 2021). As an overall modelling approach, parametric models are derived by fitting different parametric models (exponential, Weibull, lognormal, log-logistic, Gompertz, gamma and the generalized gamma) to the patient-level data from the KN522 trial to extrapolate the EFS over the modeled time horizon. The survival curve fitting is carried out in line with the NICE Decision Support Unit (DSU) guidelines [64].

The model includes the flexibility to assume patients enter remission at a specific time point. When the remission assumption is applied, the probability of EFS event for both treatment arms would be equal to zero after the specified time point. In the base-case for Denmark, no remission assumption is considered. The assumption of remission after 8 year is evaluated in scenario analysis (see section 8.7). Remission is defined as these patients are no longer at risk for events and only subject to natural mortality only; or in another word, they are “cured”.

The model also includes the flexibility to apply treatment waning to the pembrolizumab + chemotherapy arm in the model. Treatment waning is applied by setting the EFS hazard rate of the pembrolizumab + chemotherapy arm equal to the EFS hazard of the chemotherapy arm after a user-specified time-point. In the base-case for Denmark, no treatment waning effect is considered. The assumption of a sustained treatment effect on EFS is in accordance with longer-term follow-up data from other adjuvant trials and KN trials in various indications, as well as the biological/clinical plausibility. As observed in KN-522, pembrolizumab data available up to a maximum follow-up of 3 years do not indicate a treatment waning effect, i.e., the EFS curves remain separated. Longer term data from other KN clinical trials have shown a continued treatment effect post-discontinuation of pembrolizumab treatment. For example, in the KN-054 trial among patients with completely resected high-risk stage III melanoma, adjuvant pembrolizumab demonstrates a sustained treatment effect on recurrence-free survival following treatment discontinuation at 1 year based on median follow-up of 3.5 years [46]. KN-006 represents the longest follow-up (median 7 years) from a phase 3 trial of anti-PD-1/L1 therapy for advanced melanoma available to date [65]. The long-term outcomes observed in KN-006 with patients treated up to 2 years is generally consistent with those observed in the melanoma cohort of KN-001, which did not include a 2-year

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stopping rule [66, 67]. Further, the survival gap continues to increase till later years because the continued treatment effect is extrapolated based on the observed KM during the trial period.

Furthermore, from a biochemical point of view, the mechanism of action of PD-1 inhibitors like pembrolizumab enable cytotoxic CD8+ T-cells to avoid an exhausted state, thereby allowing them to keep the disease in a state of cancer-immune equilibrium, which can potentially be maintained for up to several decades even in the absence of continued therapy [68, 69]. Therefore, a sustained treatment effect post-discontinuation of adjuvant pembrolizumab in patients with TNBC is justified.

8.3.2.1.1 Joint survival models vs. separate survival models

First, the proportional hazard assumption is performed to assess two approaches for the pembrolizumab + chemotherapy and chemotherapy arms, i.e., joint survival models vs. separate survival models. When the proportional hazard assumption is valid, joint survival models is explored for both arms, where pooled data from the two arms is fitted and the same survival models is applied to both arms. When the proportional hazard assumption is violated, separate survival models is considered, where arm-specific data is fitted, and independent survival models is considered for each arm respectively.

The proportional hazard assumption is first tested using the Schoenfeld residual test, where a p-value of 1 did not suggest statistically significant violation of the proportional hazard assumption.). Hence, visual inspection of the log-cumulative hazard plots for the two arms are then performed. As the log-cumulative hazard plots of the two arms intersected, it is implausible for the proportional hazard assumption to be valid. Therefore, separate survival models are fitted for each arm to project arm-specific EFS respectively (see figures in section 1.1.1.1 in appendix G).

When fitting separate survival models for each arm, standard (one-piece) parametric models are first fitted, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalized gamma. Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection are used to select the best-fit parametric distributions.

For the pembrolizumab + chemotherapy arm, the AIC and BIC are presented in Table 24, and the EFS curve fittings are presented in [redacted]. Based on both AIC and BIC, generalized gamma is the best fit, the selection of which is further confirmed based on the visual inspection.

For the chemotherapy arm, the AIC and BIC are presented in Table 24, the EFS curve fittings are presented in [redacted] According to the AIC, generalized gamma is the best fit. According to the BIC, log-normal distribution is the best fit. Although the visual inspection suggests that generalized gamma is more plausible, neither distribution fits the observed EFS data well.

As the standard parametric models do not provide good fit to the observed data, piecewise parametric models are further explored.

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Table 24 Pembrolizumab + chemotherapy – standard parametric models – AIC and BIC

	Pembrolizumab + chemotherapy			Placebo + chematherapy		
Model	AIC	BIC	Average	AIC	BIC	Average
Exponential	1,935.793	1,940.457	1,938.125	1,377.112	1,381.078	1,379.095
Weibull	1,937.775	1,947.103	1,942.439	1,377.997	1,385.929	1,381.963
Log-normal	1,923.284	1,932.612	1,927.948	1,367.910	**1,375.842**	1,371.876
Log-logistic	1,934.894	1,944.223	1,939.558	1,374.806	1,382.738	1,378.772
Gompertz	1,931.919	1,941.248	1,936.584	1,378.184	1,386.116	1,382.150
Gamma	1,937.638	1,946.966	1,942.302	1,377.316	1,385.248	1,381.282
Generalized Gamma	**1,902.111**	**1,916.104**	1,909.108	**1,364.747**	1,376.646	1,370.696

Abbreviation: AIC: Akaike information criterion. BIC: Bayesian information criterion

[redacted]

[redacted]

8.3.2.1.2 Cutoff points of the piecewise models

The cutoff points of the piecewise models are identified according to three approaches, i.e., the hazard function, the cumulative hazard plots, and the chow tests [70]. The time points with the most pronounced changes are selected as the cut-off points: week 43, week 50, week 68, week 93 and week 109 (See Appendix G section 1.1.1.2 for figures). The piecewise parametric models are explored with each of the five cut-off points. For these piecewise models, the observed

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KM data are used directly for the period within the specific cut-off time points, and then a parametric distribution is used to estimate EFS for the remainder of the time horizon.

In the base-case model for Denmark, cut-off point of week 50 is considered. Besides plausible visual fit, a cut-off points of week 50 provides a good balance between the robust KM data to be used directly within the first 50 weeks and sufficient remaining data to fit a parametric curve after week 50. Other cut-off points are tested in the scenario analyses. The parametric estimates, AIC and BIC associated with all parametric models are presented in Appendix G Extrapolation.

8.3.2.1.3 Parametric functions from week 50 and onwards

Similarly, six parametric functions, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalized gamma, are fitted for the pembrolizumab + chemotherapy and the chemotherapy arm respectively, and the best fit is selected based on AIC, BIC, and visual inspection.

Based on both AIC and BIC for pembrolizumab + chemotherapy, generalized gamma distribution is the best fit, the selection of which is further confirmed based on the visual inspection (see more in detail in Appendix G Extrapolation).

For the chemotherapy arm, the AIC and BIC suggests gompertz as the best fit followed by log-normal. According to the visual inspection, Gompertz distribution is associated with a flat tail potentially leading to an overestimation of the long-term EFS, which suggests an implausible extrapolation. Therefore, log-normal is selected as the base-case distribution for the chemotherapy arm (see more in detail in Appendix G Extrapolation).

8.3.2.2 Summary of EFS parametric functions

The base-case parametric survival models are selected based on the statistical fit, visual inspection and clinical plausibility of the extrapolated model, and are summarized below for the pembrolizumab + chemotherapy arm, and chemotherapy arm, respectively (Table 25). The base-case modeled EFS curves and the observed KM curves are presented in [redacted]

Table 25 Summary of EFS parametric functions considered in the economic model

Treatment	Base-case parametric function	Scenario analyses performed
Pembrolizumab + chemotherapy	Piecewise model at cut-off point of week 50 - generalized gamma distribution	• Piecewise model at cut-off point of week 50 - log-normal distribution • Piecewise model at cut-off point of week 68 - log-normal distribution
Chemotherapy	Piecewise model at cut-off point of week 50 - log-normal distribution	• Piecewise model at cut-off point of week 50 - generalized gamma distribution • Piecewise model at cut-off point of week 68 - log-normal distribution

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[redacted]

Considering the uncertainty associated with the long-term extrapolation of EFS, it is important to carefully validate the EFS projections. The validation of EFS curves is conducted by 1) comparing modeled EFS vs. observed EFS in the KN522 trial, and 2) comparing the modeled EFS vs. external sources. Specifically, the modeled EFS at 3 years (pembrolizumab + chemotherapy = 84.5%, chemotherapy = 76.5%) are comparable to the observed EFS at 3 years (i.e., pembrolizumab + chemotherapy =84.5% and chemotherapy=76.8% ([redacted] and [redacted], and the modeled EFS curves match well with the observed EFS curves ([redacted] and [redacted]

When validating the modeled chemotherapy EFS by the long-term external data, a targeted literature review (see specifications in Appendix H) was first conducted to identify studies that report long-term EFS in patient with early-stage TNBC following neoadjuvant chemotherapy. Two external sources are identified, i.e., Walsh 2019 [61] and Sikov 2019 (CALGB 40603) [8]. Specifically, Walsh 2019 is a retrospective study of patients diagnosed with TNBC between January 2000 and December 2015, with a median follow-up of 30 months. Sikov 2019 (CALGB 40603) is a randomized, open-label phase II trial of 443 patients with stage II or III TNBC, which is designed to examine the impact of adding carboplatin and/or bevacizumab to the conventional neoadjuvant chemotherapy. The base-case chemotherapy EFS is compared with the disease-free survival (DFS) following neoadjuvant chemotherapy in Walsh 2019, and the EFS following neoadjuvant carboplatin-based chemotherapy in Sikov 2019 respectively. As presented in [redacted] the projected chemotherapy EFS curve matches well with the DFS curve from Walsh 2019 and the EFS curve from Sikov 2019, which confirms the plausibility of the EFS projections.

As there is no clinical or real-world long-term EFS data for early-stage TNBC patients who received pembrolizumab yet, the plausibility of the projected long-term EFS of the pembrolizumab + chemotherapy arm is validated with a panel of key opinion leaders (KOLs) in this therapeutic area.

[redacted]

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8.3.3 Transitions from the LR state

The TPs of LR → DM and LR → death are estimated based on the pooled data from the two treatment arms from the KN522 trial. Parametric models are fitted to the time from LR to DM or death, and exponential distribution is found to be the best fit. Considering the memoryless feature of the Markov cohort model structure, constant TPs from the LR state are assumed. The TPs of LR → DM, and LR → death are calculated based on the TPs of LR → DM or death, and the proportions of DM and death, respectively, which are all obtained from the KN522 trial ([redacted] Furthermore, the model constrained the TP of LR →DM or death by the all-cause natural mortality.

Therefore, the TPs of LR → DM, and LR → death are calculated as follows:

- $TP_{LR \rightarrow DM} = TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of patients progressed from LR to DM
- $TP_{LR \rightarrow death} = \max(TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of death from LR, probability of death among the general population - $TP_{LR \rightarrow DM})$

[redacted]

8.3.4 Transitions from the DM state

In the DM state, the model assumes that a proportion of patients would receive the 1L treatment for the metastatic disease, which are obtained from the KN522 trial (Table 85).

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Table 29 Proportion of patients who received 1L treatments

Parameter	Pembrolizumab + chemotherapy	Chemotherapy	Source
Proportion of patients who receive 1L	62.5%	70.3%	KN522 (Cut-off date: 23 March 2021)

Abbreviation: 1L, first-line

The model incorporates two sources to estimate TPs from DM to death and the treatment costs in the DM health state (details in section 8.5.3), i.e., KN522 and KN355. In the base-case, KN355 is considered as the data source.

When KN355 is selected, the outcomes would be derived based on the assumptions and inputs related to 1) rechallenge with pembrolizumab or other IO-agent; 2) PD-L1 testing and positive rate; 3) treatment rate; and 4) treatment mix for PD-L1 positives and PD-L1 negatives in the metastatic setting.

Specifically, the model incorporates the flexibilities of the following three scenarios for patients who received pembrolizumab + chemotherapy in the neoadjuvant phase. For Denmark, the rechallenge of pembrolizumab or use of other IO-agents are allowed.

- Pembrolizumab rechallenge: Patients are allowed to receive pembrolizumab again in the DM setting after 2 years since neoadjuvant treatment initiation.
- IO-eligibility: For patients who are ineligible for pembrolizumab rechallenge or rechallenge is not applicable, patients are allowed to use other IOs in the DM setting after 2 years since neoadjuvant treatment initiation.
- IO-ineligibility: The rest of patients would receive a mix of chemotherapies.

The treatment mix of each scenario is obtained from Danish clinical experts (Table 30). The mean OS in the DM state is estimated as a weighted average of patients who received 1L treatments and patients who did not receive the 1L treatments. The mean OS of each 1L metastatic treatment is calculated based on the predicted OS curves from the CEA of the 1L metastatic TNBC [71] (Table 31). The predicted weekly survival rate of each 1L treatment is first obtained from the model without adjusting for natural mortality or discounting effect. The area under the OS curve (i.e., restricted mean survival time within 20 years) is then estimated using the trapezoidal rule. The current model assumes capecitabine has same OS as paclitaxel when it is given in the 1L setting.

The mean OS among patients who do not receive 1L treatments were obtained from SEER Medicare [72] , and is estimated to be 21.94 weeks. The weighted mean OS of each arm is presented in [redacted] Similarly, the TPs of DM → death are estimated based on the constant hazard assumption.

Table 30 KN 355 - Market shares of 1L metastatic TNBC treatment, by neoadjuvant treatment arm and eligibility for rechallenge/IOs

Treatment mix among patients who received 1L	Pembrolizumab + chemotherapy			Chemotherapy
	Rechallenge-eligible	IO-eligible	IO-ineligible	
Pembrolizumab + paclitaxel	35%	0%	0%	0%
Pembrolizumab + nab-paclitaxel	30%	0%	0%	0%
Pembrolizumab + gemcitabine + carboplatin	10%	0%	0%	0%
Paclitaxel	0%	0%	30%	0%
Nab-paclitaxel	0%	0%	30%	0%
Gemcitabine + carboplatin	0%	5%	5%	5%

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Atezolizumab + Nab-paclitaxel	0%	70%	0%	70%
Capecitabine	25%	25%	35%	25%

Abbreviations: 1L: first-line; IO, immuno-oncology;

Table 31 KN 355 - Mean OS by 1L metastatic TNBC treatment

Treatment mix among patients who received 1L	Mean OS (weeks)
Pembrolizumab + paclitaxel	187.89
Pembrolizumab + nab-paclitaxel	230.75
Pembrolizumab + gemcitabine + carboplatin	145.86
Paclitaxel	68.37
Nab-paclitaxel	121.10
Gemcitabine + carboplatin	130.94
Atezolizumab + Nab-paclitaxel	182.56
Capecitabine	68.37

Abbreviations: 1L: first-line; OS, overall survival

[redacted]

8.3.5 Validation of OS

The predicted OS is validated against internal and external sources. Specifically, the model validated the predicted OS with the observed OS from the KN522 trial ([redacted], [redacted], and [redacted]). The modeled OS at year 3 (i.e., pembrolizumab + chemotherapy = 90.5%, chemotherapy = 89.4%) are comparable to the observed OS at year 3 (i.e., pembrolizumab + chemotherapy = 89.7% and chemotherapy = 86.9%).

When validating the modeled OS curves with external sources [8, 61], the modeled chemotherapy curve also matches well with the OS in Walsh 2019 and the OS in Sikov 2019 ([redacted] Similarly, there is no clinical or real-word long-term OS available for early-stage TNBC patients who receive pembrolizumab yet, and the plausibility of the projected long-term OS of the pembrolizumab + chemotherapy is validated with a panel of KOLs in this therapeutic area.

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[redacted]

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[redacted]

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

Utility inputs used in the base-case are derived through primary analyses of the EuroQoL-five-dimension questionnaire (EQ-5D-5L) data collected in the KN522 trial. The generic health status assessed from the EQ-5D questionnaires are converted to population-based utility values using Danish algorithm for base-case analysis [73].

The study enrollment started on March 7, 2017 (first subject first visit) and the study is ongoing. The study protocol pre-specified 7 interim analyses and a final analysis.

Overall, the compliance of EQ-5D reporting was high. The completion, compliance rates and number of missing data is provided in the table below, and a detailed table can be seen in appendix I. 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.

Table 35 Completion and compliance of EQ-5D

Treatment Visit	Category	Pembrolizumab + chemotherapy N = 762 n (%)	Placebo + chemotherapy N = 384 n (%)
Neoadjuvant	Missing by Design	0 (0.0)	1 (0.3)
Baseline	Expected to Complete Questionnaires	762 (100.0)	383 (99.7)
	Completed	707 (92.8)	369 (96.1)
	Compliance (completed per protocol)*	707 (92.8)	369 (96.3)
Neoadjuvant	Missing by Design	51 (6.7)	19 (4.5)
Week 12	Expected to Complete Questionnaires	711 (93.3)	365 (95.1)

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Treatment Visit	Category	Pembrolizumab + chemotherapy N = 762 n (%)	Placebo + chemotherapy N = 384 n (%)
	Completed	657(86.2)	336 (87.5)
	Compliance (completed per protocol)*	195 (93.3)	336 (92.1)
Neoadjuvant Week 21	Missing by Design	74 (9.7)	34 (8.9)
	Expected to Complete Questionnaires	688(90.3)	350 (91.1)
	Completed	616 (80.8)	311 (81.0)
	Compliance (completed per protocol)*	616 (89.5)	311 (88.9)
Adjuvant Baseline	Missing by Design	0 (0.0)	0 (0.0)
	Expected to Complete Questionnaires	540 (100.0)	310 (100.0)
	Completed	495 (91.7)	285 (91.9)
	Compliance (completed per protocol)*	495 (91.7)	285 (91.9)
Adjuvant Week 12	Missing by Design	12 (2.2)	6 (1.9)
	Expected to Complete Questionnaires	528 (97.8)	304 (98.1)
	Completed	485 (89.8)	274 (88.4)
	Compliance (completed per protocol)*	485 (91.9)	274 (90.1)
Adjuvant Week 24	Missing by Design	55 (10.2)	26 (8.4)
	Expected to Complete Questionnaires	485 (89.8)	284 (91.6)
	Completed	444 (82.2)	249 (80.3)
	Compliance (completed per protocol)*	444 (91.5)	249 (87.7)

*: Compliance is the proportion of subjects 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.

(Database Cutoff Date: 23MAR2021).

The model considers different options for 1) the source to model utility for each arm, 2) the utility estimation approach, and 3) the utility algorithm. Table 36 summarizes the options used in the base-case analyses. The detailed utility inputs in the base-case model are presented in Table 37. Linear mixed-effect models with fixed effects including treatment and one of the factors mentioned below:

- Health state;
- Treatment status;
- AE status;

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are 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.

Furthermore, the utility inputs of 'EF on treatment' is applied to the time to end of adjuvant treatment curve (details in section 8.5.1.2) to estimate the QALY gains when patients remain in the EF state and receive treatments, and the time to end of adjuvant treatment curve is constrained to be lower than the EFS curve. The utility inputs of 'EF off treatment' is applied to the difference between EFS and time to end of adjuvant treatment curves to estimate the QALYs gains when patients remain in the EF state and do not receive treatments, which are constrained to be no less than zero.

The QALY gains in each health states are calculated as follows:

- $QALY_{EF\ on\ treatment}$ = $Utility_{EF\ on\ treatment}$ * minimum (time to end of adjuvant treatment, EFS)
- AE-related QALY decrement = one-time grade 3+ AE utility decrement
- $QALY_{EF\ off\ treatment}$ = $Utility_{EF\ off\ treatment}$ * max (EFS - time to end of adjuvant treatment, 0)
- $QALY_{LR}$ = $Utility_{LR}$ * time spent in the LR state
- $QALY_{DM}$ = $Utility_{DM}$ * time spent in the DM state

Table 36 Summary of utility inputs

Parameters	Base-case options
Source of utility value of the pembrolizumab + chemotherapy arm	• Based on KN522 pooled data
Source of utility value of the chemotherapy arm	• Based on KN522 pooled data
Utility estimation approach	• Utility by health state, treatment status (i.e., on- and off-treatment) and AE status
Utility algorithm	• Denmark 5L value set

Abbreviation: AE, adverse event

Table 37 Base-case utility inputs

Health state	Pembrolizumab + chemotherapy			Chemotherapy			Source
	Mean	Lower	Upper	Mean	Lower	Upper	
Event-free on treatment	0.865	0.851	0.880	0.865	0.865	0.880	KN522 (cutoff date: 23 March, 2021)
Grade 3+ AE utility decrement	-0.025	-	-	-0.025	-0.025	-	
Event-free off treatment	0.860	0.850	0.871	0.860	0.860	0.871	
Locoregional recurrence	0.788	0.738	0.838	0.788	0.788	0.838	
Distant metastasis	0.681	0.641	0.721	0.681	0.681	0.721	

Abbreviation: AE, adverse event

8.4.1 Disutility related to aging

AE disutilities are used in the model to account for the decrement in quality life years of a patients due to different AE's. This included in the model as a one off QALY decrement and is calculated based on the AE duration, Grade 3+ AE utility decrement and AE incidence rates. These AE disutilities values are calculated based on difference in utility values between "visits during" and "visits without" Grade 3+ AEs in each treatment arm.

The average disutility associated with the occurrence of Grade 3+ AEs was -0.025 (0.840-0.865), which is the difference in utility values between "visits during" and "visits without" Grade 3+ AEs in each treatment arm.

Age related disutility is extracted from guidelines based on Danish Medicines Council [74]. The age-wise HSUV is given in Table 38. According to the guidelines, the age adjustment values are calculated on the basis of data collected in connection with Region North Jutland study in 2017, as part of the Health and Morbidity Surveys (SUSY).

Table 38 Age-related disutility

Age brackets	Gen pop utility/Age related index
18-29	0.871
30-39	0.848
40-49	0.834
50-69	0.818
70-79	0.813
80+	0.721

Source: Medicinrådet: Age adjustment for health-related quality of life

To calculate age wise disutilities, utilities corresponding to starting age of the model is subtracted from the utilities of any other group. e.g., If the starting age of the model is 55, then age related disutility corresponding to age 75 is,

$Disutility_{75\ years} = Utility_{75\ years} – Utility_{55\ years} = 0.813\text{-}0.818 = -0.005$

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

8.5 Resource use and costs

Direct medical costs along with patient costs are included in the base-case model. Costs are estimated from a limited societal perspective in line with the guidelines from the Danish Medicines Council [55]. In this section, all costs are according to DKK 2022. The following categories of health care costs are considered:

- Neoadjuvant treatment costs
- Adjuvant treatment costs
- Distant metastatic treatment costs
- Surgery costs
- Radiation costs
- Disease management costs
- AE management costs
- Terminal care costs
- Patient costs

8.5.1 Neoadjuvant treatment costs

Neoadjuvant treatment costs are calculated based on the drug acquisition and administration costs per administration, and time on neoadjuvant treatment. In the model, neoadjuvant treatment costs are estimated precisely for each cycle, based on the respective dosing schedule. For example, patients on a once every 3 weeks (Q3W) dosing schedule would incur treatment costs in cycle 0, but would not incur treatment costs in cycle 1 or 2.

8.5.1.1 Drug acquisition costs per administration

Drug acquisition costs per administration are calculated based on unit acquisition costs, number of units (pills/vials) per administration, relative dose intensity and proportion of treatment allocation.

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Specifically, unit drug costs are estimated based on the Danish Medicines Agency [75]. When multiple vial/pill sizes were available, the vial/pill size with the lowest cost per mg is selected (Table 39). The indication for Pembrolizumab is based on a fixed dose (vials of 100 mg). The unit drug cost of the vial is obtained from Danish Medicine Agency and is DKK 23,204 [75].

The defined dosing schedule of pembrolizumab is a flat dose of either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W), consistent with the treatment protocol used in the KN522 trial. The Danish Medicines Council has in previous recommendation decisions on other pembrolizumab indications stated a preference for weight based (2 mg/kg) dosing for pembrolizumab. With that in mind, weight-based dosing is the base case in the current model, but with an option to choose a fixed dose in the model. As all patients in the KN522 received the 200 mg Q3W dosage, the base-case model considers 100% treatment allocation to 2 mg/kg Q3W.

Based on the dosage specified in the dosing schedule, the number of units (pills/vials) per administration is estimated and vial sharing is assumed. The assumption about vial sharing is based on input from the coordinating lead pharmacologist at Sygehusapotek Region Sjælland. For BSA-based drugs, the number of vials per administration is estimated based on a lognormal distribution of BSA (mean and SD specified in Table 12). Similarly, the relative dose intensity (i.e., the proportion of planned dose consumed) and the proportion of treatment allocation of each drug are obtained from the KN522 trial to account for any delays or interruptions in administration.

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.

The unit costs of administration are obtained from the 2022 DRG-rates from the Danish Health Data Authority [60] (Table 40), and the costs per administration are applied to model cycles, depending on the dosing schedule for each specific drug. The cost of IV administration is irrespective of infusion hours or whether drugs were given as a combination therapy or monotherapy. Also, there is no cost for oral drug administration in Denmark.

The detailed dosing schedule, relative dose intensity and treatment allocation are presented in Table 41.

Table 39 Unit drug acquisition cost

Drug	Mg per vial/tablet	Cost per mg (2022 DKK)	Source
Pembrolizumab	100	232.05	The Danish Medicines Agency [75]
Carboplatin	450	0.45	

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Paclitaxel	300	7.33
Doxorubicin	50	2.40
Epirubicin	200	3.33
Cyclophosphamide	50	0.18
Capecitabine	500	0.01
Gemcitabine	1200	0.26
Nab-paclitaxel	100	20.10
Atezolizumab	840	25.95

Abbreviation: PDS, powders; SOL, solution; TAB, tablet

Table 40 Unit administration costs

Administration type	Unit cost (2022 DKK)	DRG code	Source
Intravenous infusion, first hour	2,041.00	09MA98	DRG-rates from the Danish Health Data Authority[76]

Abbreviation DRG, Diagnosis Related Group

Table 41 Detailed dosing schedule, relative dose intensity and treatment allocation

Treatment arm	Component	Dosing schedule description	Relative dose intensity (%)	% Treatment allocation
Pembrolizumab + chemotherapy	Pembrolizumab (2 mg/kg Q3W)	2 mg/kg Q3W on day 1 of Cycles 1-8	95.0%	100.0%
	Pembrolizumab (4 mg/kg Q6W)	4 mg/kg Q6W on day 1 of Cycles 1-8	95.0%	0.0%
	Carboplatin (AUC 5, Q3W)	AUC 5 (max 750mg) Q3W, on Day 1 of Cycles 1-4	99.2%	42.9%
	Carboplatin (AUC 1.5, weekly)	AUC 1.5 (max 225mg) weekly, on Days 1, 8, 15 of Cycles 1-4	95.5%	57.1%
	Paclitaxel	80 mg/m2 Weekly, on Days 1, 8, 15 of Cycles 1-4	95.3%	100.0%
	Cyclophosphamide	600 mg/m2, Q3W on day 1 of Cycles 5-8	99.9%	100.0%
	Doxorubicin	60 mg/m2, Q3W on day 1 of Cycles 5-8	99.7%	67.2%
	Epirubicin	90 mg/m2, Q3W on day 1 of Cycles 5-8	99.9%	32.8%
Chemotherapy	Carboplatin (AUC 5, Q3W)	AUC 5 (max 750mg) Q3W, on Day 1 of Cycles 1-4	99.3%	43.2%
	Carboplatin (AUC 1.5, weekly)	AUC 1.5 (max 225mg) weekly, on Days 1, 8, 15 of Cycles 1-4	94.7%	56.8%
	Paclitaxel	80 mg/m2 Weekly, on Days 1, 8, 15 of Cycles 1-4	95.3%	100.0%

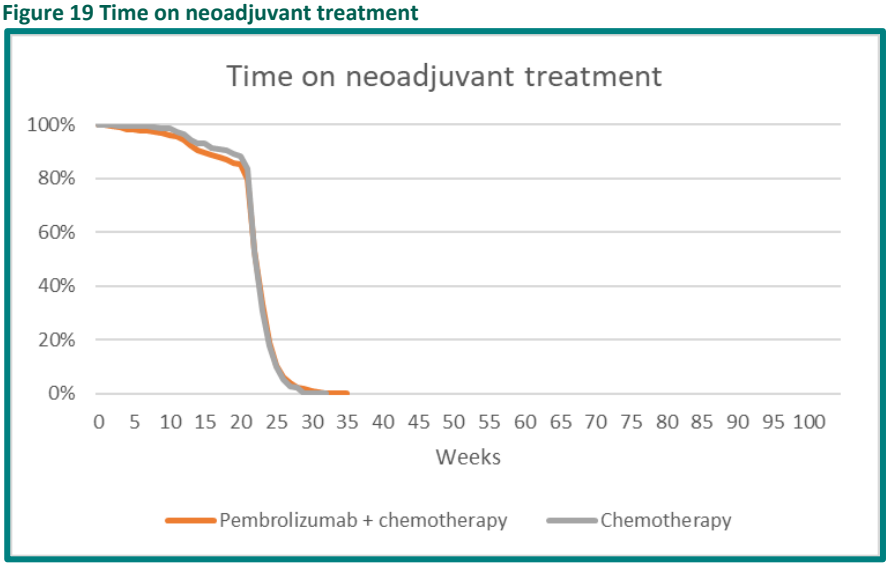
Treatment arm	Component	Dosing schedule description	Relative dose intensity (%)	% Treatment allocation
	Cyclophosphamide	600 mg/m2, Q3W on day 1 of Cycles 5-8	99.9%	100.0%
	Doxorubicin	60 mg/m2, Q3W on day 1 of Cycles 5-8	100.0%	66.9%
	Epirubicin	90 mg/m2, Q3W on day 1 of Cycles 5-8	100.0%	33.1%

Source: Dosing schedule, RDI and % treatment allocation: KN522 trial; *Abbreviations:* AUC, area under the curve; Q3W, once every 3 weeks; Q6W, once every 6 weeks

8.5.1.2 Time on neoadjuvant treatment

In the pembrolizumab + chemotherapy and chemotherapy arms, the base-case model estimates the time on neoadjuvant treatment using the observed KM curve from the KN522 trial (Figure 19). In the scenario analyses, the lower 95% CI of KM and the upper 95% CI of KM are considered.

Figure 19 Time on neoadjuvant treatment



8.5.2 Adjuvant treatment costs

Adjuvant treatment costs are calculated based on the drug acquisition and administration costs per administration, and time on adjuvant treatment. According to the KN522 trial protocol, patients who completed neoadjuvant treatment would receive definite surgery 2 to 6 weeks later followed by radiation therapy as indicated and adjuvant treatments. Therefore, not all patients will initiate adjuvant treatment at the same time. It is not feasible to calculate adjuvant treatment costs for each cycle based on the respective dosing schedule, as in the neoadjuvant treatment phase. As a result, the model first estimates the average adjuvant treatment cost per week during the planned adjuvant treatment phase (i.e., 9 cycles), and then multiplied the average weekly cost by time on adjuvant treatment.

8.5.2.1 Drug acquisition and administration cost per administration

Drug acquisition costs per administration are calculated based on unit acquisition costs, number of units (pills/vials) per administration, relative dose intensity and proportion of treatment allocation. As specified in section 8.5.1.1, unit drug acquisition costs are estimated from the Danish Medicines Agency [75] [75](Table 39). The dosing schedule of each drug in the pembrolizumab + chemotherapy and chemotherapy arms are obtained from the KN522 trial. For pembrolizumab, the base-case model considers 50% treatment allocation to the 2 mg/kg Q3W dosage and 50% to the

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4 mg/kg Q6W dosage based on input from a Danish clinical expert. In the neoadjuvant phase, patients receive chemotherapy every 3 weeks, which is why it makes sense to give them pembrolizumab Q3W, as they have to go into the hospital anyway. In the adjuvant phase, it will make sense for some patients to be able to reduce visits to the hospital by only having pembrolizumab Q6W. Danish breast oncologists estimate that it would be possible to offer it to 50% of patients. The number of units (pills/vials) per administration are estimated based on dosing schedule and vial sharing is assumed. Lastly, the relative dose intensity and the proportion of treatment allocation are obtained from the KN522 trial.

The unit costs of administration are obtained from 2022 DRG-rates from the Danish Health Data Authority [60] (Table 40), and the costs per administration are applied to model cycles, depending on the dosing schedule for each specific drug.

The detailed dosing schedule, relative dose intensity and treatment allocation are presented in Table 42.

Table 42 Detailed dosing schedule, relative dose intensity and treatment allocation in the adjuvant treatment phase

Treatment arm	Component	Dosing schedule description	Relative dose intensity (%)	% treatment allocation
Pembrolizumab + chemotherapy	Pembrolizumab (2 mg/kg Q3W)	2 mg/kg Q3W on day 1 of Cycles 1-9	99.8%	50%
	Pembrolizumab (4 mg&/kg Q6W)	4 mg/kg Q6W on day 1 of Cycles 1-9	99.8%	50%
Chemotherapy	Placebo	Not applicable	Not applicable	Not applicable

Source: Dosing schedule, RDI and % treatment allocation: KN522 trial; *Abbreviations:* Q3W, once every 3 weeks; Q6W, once every 6 weeks

8.5.2.2 Time on adjuvant treatment

The time on adjuvant treatment for pembrolizumab + chemotherapy and chemotherapy arms are estimated based on the observed KM curves from the KN522 trial. Specifically, using patient-level data, the KM curves of time to end of surgery, and the KM curves of time to end of the treatment course are first generated. Then the proportion of patients on adjuvant treatment at each point in time is calculated as the difference between the proportion of patients on treatment (based on time to end of treatment course curve) and the proportion of patients who had surgery (based on time to end of surgery curve). The observed time to end of surgery, and the observed time to end of treatment course are presented in Figure 20 and **Figure 21**, respectively. The estimated time on adjuvant treatment is presented in Figure 22.

Figure 20 Time to end of surgery

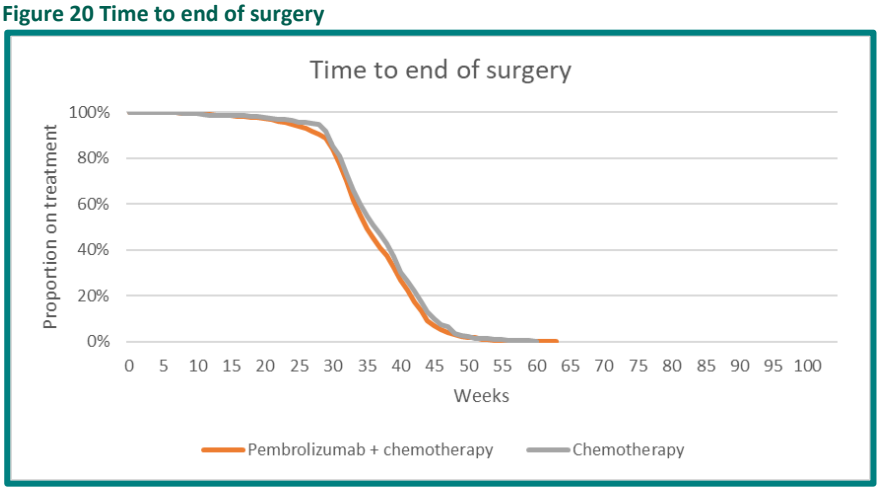

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Figure 21 Time to end of treatment course

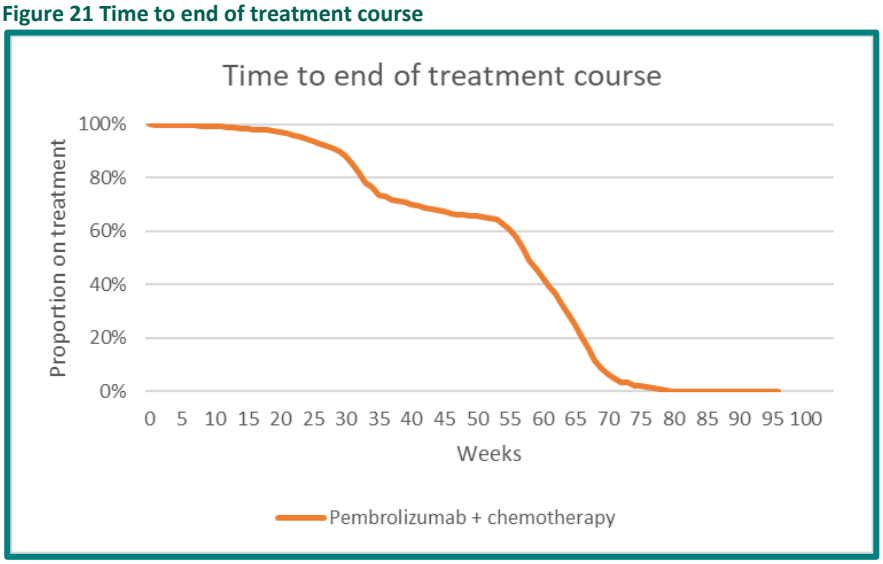
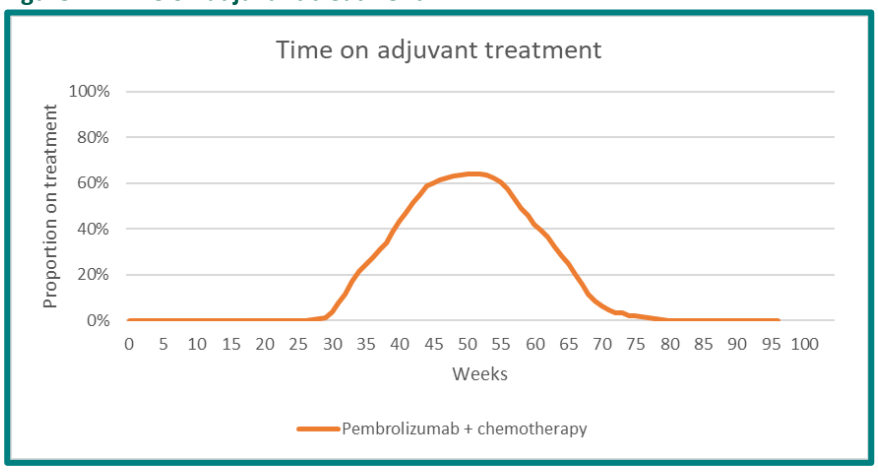


Figure 22 Time on adjuvant treatment



8.5.3 Distant metastatic treatment course

Within the model, drug acquisition and administration costs associated with metastatic TNBC therapies are applied as one-time costs upon entry into the DM state. As detailed in section 8.3.4, a proportion of patients who entered the DM state are assumed to receive an active 1L treatment for the metastatic disease. As described in section 8.3.4, two sources (i.e., KN522 and KN355) are considered to estimate the 1L treatment costs in the DM state, and KN355 is selected in the base-case. Patients who receive 1L treatments are eligible to receive subsequent lines (2L, 3L and 4L) of treatments for the metastatic disease, and the percentage of eligible patients receiving subsequent therapies of treatments for the metastatic disease are based on patients who receive 1L treatments.

The proportion of patients receiving 1L treatments are presented in Table 29, and the market shares of the treatment mix are presented in Table 30 (using KN355 as the source).

8.5.3.1 Total regimen costs by 1L metastatic treatments

The total costs for each 1L metastatic treatment regimen are calculated as a function of the weekly drug acquisition and administration costs and the mean treatment duration. Similarly, unit drug acquisition costs are obtained from the Danish Medicines Agency [75] (Table 39), and administration costs are obtained from 2022 DRG-rates from the Danish Health Data Authority [77] (Table 40).

Dosing schedule, relative dose intensity, and treatment allocation are obtained from Danish clinical experts and the CEM of 1L metastatic TNBC [71]. The mean treatment duration is estimated based on the predicted time on treatment curve (up to 20 years) from the CEM of 1L metastatic TNBC using the area under the curve approach [71]. Capecitabine is assumed to have same mean treatment duration as paclitaxel in the 1L setting. Treatment durations of atezolizumab + nab-paclitaxel is estimated based on their PFS curves due to a lack of published data for time on treatment curves. Pembrolizumab and atezolizumab-based regimens are assumed to have a maximum treatment duration of 2 years. Detailed dosing schedules, relatively dose intensity, treatment allocation and mean treatment duration for the 1L metastatic TNBC treatments in the DM state are presented in Table 43.

Besides the 1L metastatic TNBC treatments, the model considers a lump sum of subsequent lines (2L, 3L, and 4L) of treatments, following each 1L metastatic TNBC treatments. The lump sum costs for subsequent lines of treatments are also obtained from the CEM of 1L metastatic TNBC adapted for Denmark where the proportions of patients receiving each line of treatment have been considered in the total costs Table 44.

The total metastatic costs by each 1L metastatic treatment are calculated as the aggregation of 1L treatment costs and the lump sum subsequent treatment costs. (Table 45).

Table 43 Dosing schedule, dose intensity, treatment allocation and treatment duration of 1L metastatic treatment

1L metastatic TNBC treatment regimen	Component	Dosing schedule description	Relative dose intensity (%)	Treatment duration (week)	% treatment allocation
Pembrolizumab + paclitaxel	Pembrolizumab (2 mg/kg Q3W)	2 mg/kg Q3W	91.8%	49.82	100.0%
	Pembrolizumab (4 mg/kg Q6W)	4 mg/kg Q6W	91.8%	49.82	0.0%
	Paclitaxel	90 mg/m2 on days 1, 8, 15 of every 28-day cycle	81.3%	49.82	100.0%
Pembrolizumab + nab-paclitaxel	Pembrolizumab (2 mg/kg Q3W)	2 mg/kg Q3W	90.5%	46.30	100.0%
	Pembrolizumab (4 mg/kg Q6W)	4 mg/kg Q6W	90.5%	46.30	0.0%
	Nab-paclitaxel	100 mg/m^2 on days 1, 8, 15 of every 28-day cycle	85.0%	46.30	100.0%
Pembrolizumab + gemcitabine + carboplatin	Pembrolizumab (2 mg/kg Q3W)	2 mg/kg Q3W	90.7%	46.73	100.0%
	Pembrolizumab (4 mg/kg Q6W)	4 mg/kg Q6W	90.7%	46.73	0.0%
	Gemcitabine	1000 mg/m2 on days 1 and 8 of every 21-day cycle	68.3%	46.73	100.0%
	Carboplatin	AUC 2 on days 1 and 8 of every 21-day cycle	67.6%	46.73	100.0%

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Paclitaxel	Paclitaxel	90 mg/m^2 on days 1, 8, 15 of every 28-day cycle	87.1%	23.59	100.0%
Nab-paclitaxel	Nab-paclitaxel	100 mg/m^2 on days 1, 8, 15 of every 28-day cycle	91.5%	39.46	100.0%
Gemcitabine + carboplatin	Gemcitabine	1000 mg/m2 on days 1 and 8 of every 21-day cycle	75.0%	40.99	100.0%
	Carboplatin	AUC 2 on days 1 and 8 of every 21-day cycle	73.9%	40.99	100.0%
Atezolizumab + Nab-paclitaxel	Atezolizumab	840 mg Q2W	96.0%	104.00	100.0%
	Nab-paclitaxel	100 mg/m^2 on days 1, 8, 15 of every 28-day cycle	86.4%	104.00	100.0%
Capecitabine	Capecitabine	1250 mg/m2 twice daily days 1-14 of every 21-day cycle	100.0%	23.59	100.0%

Source: Dosing schedule, RDI and % treatment allocation: The CEM of 1L metastatic TNBC (Merck data on file, 2021) [71]
Abbreviations: AUC, area under the curve; TNBC, triple negative breast cancer; Q2W, the other week; Q3W, once every 3 weeks; Q6W, once every 6 weeks

Table 44 Lump sum costs for subsequent lines of treatment in metastatic TNBC, by 1L metastatic TNBC treatment

1L metastatic TNBC treatment regimen	Subsequent treatment costs (2022 DKK)
Pembrolizumab + paclitaxel	29,024.15
Pembrolizumab + nab-paclitaxel	29,024.15
Pembrolizumab + gemcitabine + carboplatin	29,024.15
Paclitaxel	27,636.54
Nab-paclitaxel	27,636.54
Gemcitabine + carboplatin	27,636.54
Atezolizumab + Nab-paclitaxel	29,024.15
Capecitabine	27,636.54

Abbreviation: TNBC, triple negative breast cancer

Table 45 Total treatment costs by 1L metastatic treatment

Treatment mix among patients who received 1L	Total 1L treatment costs (2022 DKK)	Total subsequent treatment costs (2022 DKK)	Total metastatic treatment costs (2022 DKK)
Pembrolizumab + paclitaxel	585,533.05	29,024.15	614,557.20
Pembrolizumab + nab-paclitaxel	609,575.95	29,024.15	638,600.10
Pembrolizumab + gemcitabine + carboplatin	514,570.55	29,024.15	543,594.70
Paclitaxel	54,002.66	27,636.54	81,639.20
Nab-paclitaxel	156,200.38	27,636.54	183,836.92
Gemcitabine + carboplatin	67,136.90	27,636.54	94,773.44
Atezolizumab + Nab-paclitaxel	1,485,840.61	29,024.15	1,514,864.75
Capecitabine	4,399.13	27,636.54	32,035.67

Abbreviation: TNBC, triple negative breast cancer

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8.5.3.2 Weighted average treatment costs for each neoadjuvant arm

The weighted average cost for each neoadjuvant treatment arm is calculated as a function of the proportion of patients who receive 1L treatments (Table 29) and the weighted average costs of patients who receive 1L treatments. Specifically, the weighted average costs of patients who received 1L treatments are calculated based on the total treatment costs by 1L metastatic TNBC treatment (Table 44), and the market shares of each 1L metastatic treatment (Table 30 using KN355 as the source). As a result, the weighted average costs of each arm are presented in Table 46.

Table 46 Total treatment costs in the DM setting by neoadjuvant arm

Weighted average costs	Pembrolizumab + chemotherapy			Chemotherapy
	Rechallenge-eligible	IO-eligible	IO-ineligible	
Total metastatic treatment costs (2022 DKK.)	293,152.15	670,720.57	59,746.24	754,426.50

8.5.4 Surgery costs

Surgery costs are applied as one-time costs, and are calculated based on the unit costs of initial surgery, and the proportion of patients receiving surgery in each arm. The unit costs of surgery are obtained from 2022 DRG-rates from the Danish Health Data Authority [77]. The proportion of patients receiving initial surgery is obtained from the KN522 trial for each neoadjuvant arm separately (Table 47).

Table 47 Surgery costs

Resource use	Unit cost (2022 DKK)	Number (n/N) and % patients received initial surgery						DRG code	Source
		Pembrolizumab + chemotherapy			Chemotherapy				
		n	N	%	n	N	%		
Initial surgery	25,760	768	784	98.0%	381	390	97.7%	09MP04	2022 DRG-rates from the Danish Health Data Authority[76]

Abbreviation: DRG, Diagnosis related group

8.5.5 Radiation costs

Similarly, radiation costs are applied as one-time costs, and are calculated based on the unit costs of radiation and the proportion of patients receiving radiation therapy. The unit cost of radiation is obtained from 2022 DRG-rates from the Danish Health Data Authority [60]. The proportion of patients receiving radiation in each arm is obtained from the KN522 trial (Table 48).

Table 48 Radiation costs and proportion of patients

Resource use	Unit cost (2022 DKK)	Number (n/N) and % of Patients received radiation						DRG code	Source
		Pembrolizumab + chemotherapy			Chemotherapy				
		n	N	%	n	N	%		
Radiation	4,363	583	768	75.9%	299	381	78.5%	27MP07	2022 DRG-rates from the Danish Health Data Authority [77]

Abbreviation: DRG, Diagnosis related group

8.5.6 Disease management costs

Disease management costs includes recurring disease management costs, one-off disease management costs, and terminal care costs.

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Recurring disease management costs are obtained from 2022 DRG-rates from the Danish Health Data Authority [77], and are assumed zero for patients who stayed in the EF states for more than 10 years (Table 49). The model considers the one-off disease management costs when entering LR or DM state to be zero. The cost of distant metastasis state is extracted from Denmark KN355 CE model and includes a sum of weekly costs considered in both progression free and progressed disease state in KN355 model. The details of the HCRUs used to estimate the costs are mentioned in Appendix K.

Lastly, patients who transitioned to death are assumed to incur a one-time cost associated with palliative/terminal care. In Denmark, terminal care costs are based on costs during the last 14 days before death. The cost of one day care is DKK 2,011 in Denmark. The unit terminal care cost is taken from 2022 DRG-rates from the Danish Health Data Authority (Table 50) [77].

Table 49 Recurring disease management costs

Health state	Cost per week (2022 DKK)	Source
Event-free (Year 1-3)	130	2022 DRG-rates from the Danish Health Data Authority [76]
Event-free (Year 4-5)	13	
Event-free (Year 6-10)	13	
Event-free (Year 11+)	0	
Locoregional recurrence	64	
Distant metastasis	1,533	Appendix K

Abbreviation: DRG, Diagnosis related group

Table 50 Terminal care costs

Resource	Unit cost (2022 DKK)	DRG codes	Frequency of use (number per week)	Source
One time terminal care cost	28,154	15MP01	Lump-sum cost (assumption of 14 days care)	2022 DRG-rates from the Danish Health Data Authority[76]

8.5.7 AE costs

As described in section 8.2.2.5, the model considers all cause Grade 3+ AEs that occurred at least 5% in one arm in the combined neoadjuvant and adjuvant phases. Costs associated with the management of AEs are applied as one-time costs at model entry (without a need for half-cycle correction).

The one-time AE costs for each treatment arm are calculated as a function of the AE rates, the proportion hospitalized for each AE event, and the unit costs of medical management for each AE in the inpatient or outpatient setting. Specifically, the AE rates are detailed in Table 19. The proportion of patients hospitalized per AE are obtained from the KN522 trial (Table 51).

The unit costs of medical management for each AE in the inpatient setting and the unit cost of an outpatient hospital visit for any AE are obtained from 2022 DRG-rates from the Danish Health Data Authority [77]. Unit costs are presented in Table 52 and Table 53 respectively.

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Table 51 Percent of patient hospitalized per AE

Grade 3+ AE	Pembrolizumab + chemotherapy	Chemotherapy	Source
Neutropenia	3.30%	0.80%	KN522 (Cut-off date: 23 March 2021)
Neutrophil count decreased	1.30%	0.00%	
Anemia	12.00%	13.10%	
Febrile neutropenia	80.40%	74.60%	
White blood cell count decreased	0.00%	9.50%	
Alanine aminotransferase increased	6.10%	0.00%	

Abbreviation: AEs, adverse events

Table 52 Cost per AE

Grade 3+ AE	AE Hospitalization Cost (2022 DKK)	AE outpatient Cost (2022 DKK)	Source
Neutropenia	38,408.00	3,176.00	2022 DRG-rates from the Danish Health Data Authority [77]
Neutrophil count decreased	25,419.00	3,176.00	
Anemia	41,278.00	3,176.00	
Febrile neutropenia	25,419.00	3,176.00	
White blood cell count decreased	25,419.00	3,176.00	
Alanine aminotransferase increased	4,460.00	4,460.00	

Abbreviation: AE, adverse event;

Table 53 Total AE costs by treatment arm

AE	Pembrolizumab + chemotherapy	Chemotherapy
Total AE costs (2022 DKK)	8,104.59	6,837.60

Abbreviation: AE, adverse event;

8.5.8 Patient costs

According to requirements of the Danish Medicines Council to use a limited societal perspective, a transportation cost of DKK 100, for travelling 14 km to and from the hospital on an average, is included in the model [78]. Also, a time cost of DKK 179 based on the average hourly wage (after tax) of the patients is applied to the model for taking into account per hour infusion time and time spend at follow up visit [78].

It is assumed in the model that follow up visit occurs at the time of administration (both in neo adjuvant and adjuvant treatment administration). A transportation visit cost is considered when a patient goes for administration. The IV infusion time for different treatment components is given in Table 54.

Table 54 Infusion time of different treatments

Treatment arm	In Minutes	In Hours	Source
Pembrolizumab (200 mg Q3W)	30 mins	0.50	KN522 trial
Pembrolizumab (400 mg Q6W)	30 mins	0.50	
Carboplatin (AUC 5, Q3W)	50 mins	0.83	
Carboplatin (AUC 1.5, weekly)	15 mins	0.25	
Paclitaxel	1 hr.	1.00	
Cyclophosphamide	1 hr.	1.00	
Doxorubicin	IV push	0.00	
Epirubicin	IV push	0.00	

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The hours given above is used to calculate the infusion time cost. Additionally, for patient monitoring and follow up the cost is applied according to the below Table 55.

Table 55 Patient follow up cost

	Frequency per week	Patient Hours	Total Hours per Week	Source
Consultation visit, physician	0.12	1.00	0.12	Denmark
Consultation visit, nurse	0.46	0.50	0.23	KN355 CE
CT scan	0.23	1.00	0.23	Model
Total Hours per week			**0.58**	-
Total Costs per week (2022 DKK)			**103.35**	-

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 results from the analysis are presented in an aggregated and disaggregated format and include tabular presentation of information on estimates of LY gained and QALYs. LY gained and QALYs per health state are also presented. The base case overview is presented in the Table 56.

Table 56. Base case overview

Comparator	Chemotherapy (control arm in the KN522 trial)
Type of model	Markov model
Time horizon	51 years (lifetime)
Treatment line	Neo-adjuvant, adjuvant, 1st line advanced. Subsequent treatment lines also included: 2nd, 3rd and 4th line.
Measurement and valuation of health effects	Health state utility inputs are derived from the EuroQoL EQ-5D-5L data collected in the KN522 trial. The generic health statuses assessed from the EQ-5D questionnaires are converted to population-based utility values using the Danish algorithm for the base-case analysis. Approach considered for defining health state utilities based on: Utility by health state, treatment status, and AE status Linear mixed-effect models with fixed effects are 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.
Included costs	Costs are estimated from a limited societal perspective in Denmark; therefore, direct and indirect health-related costs are included in the model. The following categories of costs are included: • Neo adjuvant drug acquisition and administration costs • Adjuvant drug acquisition and administration costs • Metastatic treatment costs • Surgery costs • Radiation costs • Disease management costs

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	• AE-related costs • Terminal care costs • Patient costs including transportation and patient monitoring and follow up the cost The costing year of the analysis is 2022.
Dosage of pharmaceutical	Pembrolizumab + Chemotherapy: Neoadjuvant phase (1st phase, 1-4 cycle): • Pembrolizumab 2 mg/kg every 3rd week (IV) • And paclitaxel 80 mg/m^2, once weekly (IV) • And carboplatin area under the curve [AUC] 5 once every 3 weeks or AUC 1.5 once weekly (IV) Neoadjuvant phase (2nd phase, 5-8 cycle): • Pembrolizumab 2 mg/kg every 3rd week (IV) • And cyclophosphamide 600 mg/m^2 once every 3 weeks • Or doxorubicin 60 mg/m^2 once every 3 weeks • Or epirubicin 90 mg/m^2 once every 3 weeks Adjuvant phase: Pembrolizumab 2 mg/kg every 3rd week (IV) (50% of the patients) and 4 mg/kg every 6th week (IV) (50% of the patients)
Average time on treatment	Intervention: Pembrolizumab + Chemotherapy: 22 weeks Comparator: Chemotherapy: 22 weeks
Parametric function for EFS	Intervention: EFS KM data followed by standard parametric curve fitting (generalized gamma) from week 50 onwards Comparator: EFS KM data followed by standard parametric curve fitting (log-normal) from week 50 onwards

8.6.2 Base case results

Over a lifetime horizon, total costs are DKK 595,549 for pembrolizumab + chemotherapy and DKK 499,116 for chemotherapy. The differences in total costs are mostly driven by drug acquisition in both the neoadjuvant and adjuvant phases. Total QALYs over the lifetime horizon are estimated to be 14.08 for pembrolizumab + chemotherapy and 11.54 for chemotherapy. Total LYs are estimated to be 16.94 and 13.99 for the pembrolizumab + chemotherapy and chemotherapy arms, respectively. The resulting ICER for pembrolizumab + chemotherapy in terms of incremental cost per QALY gained is DKK 35,473 vs. chemotherapy. The ICER in terms of incremental cost per LY gained is estimated to be DKK 30,500 vs. chemotherapy (Table 57).

Table 57. Disaggregated base-case costs and effectiveness for Pembrolizumab + Chemotherapy vs. Chemotherapy

Outcomes	Pembrolizumab + Chemotherapy (DKK)	Chemotherapy (DKK)	Pembrolizumab + chemotherapy vs. Chemotherapy (DKK)
Costs (DKK)			
Total costs (2022 DKK)	589,292	499,116	90,177

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Outcomes	Pembrolizumab + Chemotherapy (DKK)	Chemotherapy (DKK)	Pembrolizumab + chemotherapy vs. Chemotherapy (DKK)
Neoadjuvant treatment costs	266,851	46,513	220,338
Drug acquisition costs	235,585	14,731	220,854
Drug administration costs	31,266	31,782	-517
Adjuvant treatment costs	177,306	0	177,306
Drug acquisition costs	168,971	0	168,971
Drug administration costs	8,335	0	8,335
Surgery costs	25,245	25,168	77
Radiation costs	3,312	3,425	-113
Metastatic treatment costs	39,241	309,242	-270,001
Disease management costs	47,856	86,334	-38,477
Event-free	21,182	19,926	1,256
Locoregional recurrence	320	651	-331
Distant metastasis	26,354	65,756	-39,402
Terminal care costs	12,223	15,084	-2,862
Adverse event costs	8,105	6,838	1,267
Patient costs	9,155	6,513	2,642
Effectiveness			
Total QALYs	14.08	11.54	2.54
Event-free	14.20	11.14	3.06
On treatment	0.86	0.92	-0.06
AE-related QALY decrement	-0.01	-0.01	0.00
Off treatment	13.35	10.23	3.12
Locoregional recurrence	0.08	0.16	-0.08
Distant metastasis	0.23	0.57	-0.34
Age-related QALY decrement	-0.42	-0.33	-0.10
Total LYs	16.94	13.99	2.96
Event-free	16.51	12.96	3.56
Locoregional recurrence	0.10	0.20	-0.10
Distant metastasis	0.33	0.83	-0.50
ICER (2022 DKK)			
Incremental costs			90,177
Incremental QALYs			2.54
Incremental LYs			2.96
Incremental Cost per QALY Gained			35,473
Incremental Cost per LY Gained			30,500

8.7 Sensitivity analyses

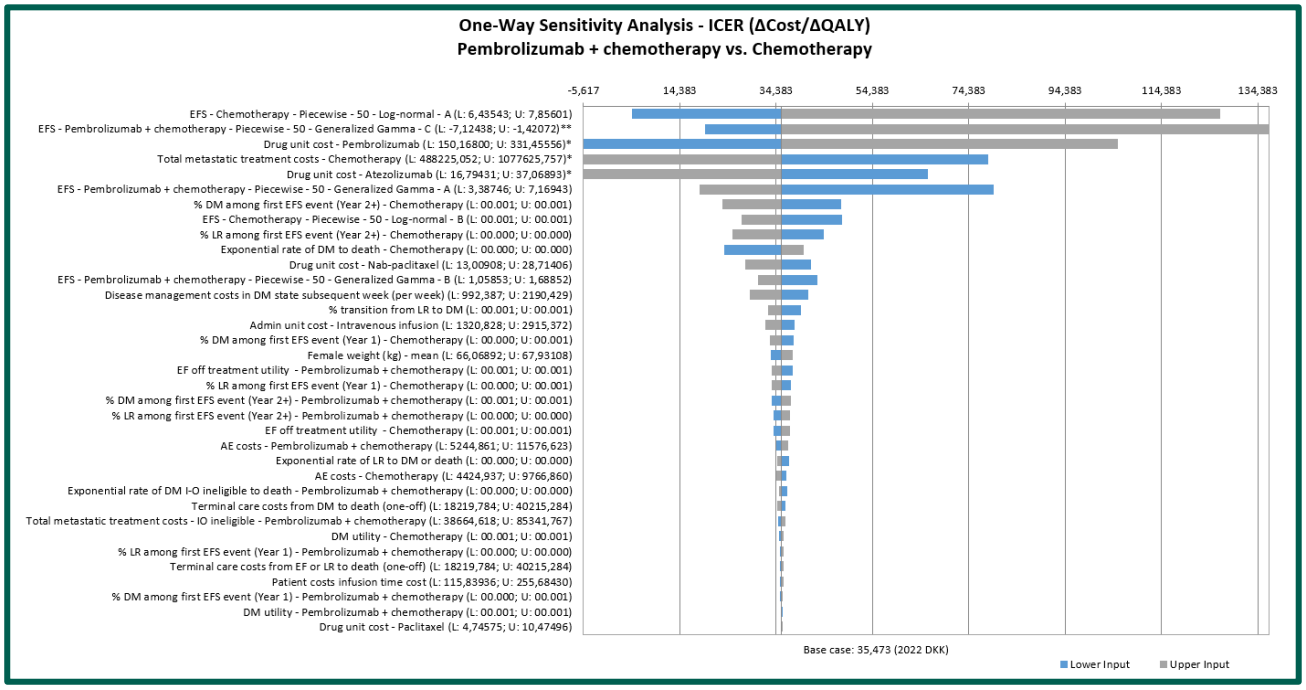
8.7.1 Deterministic sensitivity analyses

Deterministic sensitivity analyses (DSAs) are performed by varying one model input or assumption at a time in order to test the robustness of the model results. Each parameter considered in the DSA is varied by their 95% CI derived from

the standard error, Cholesky decomposition matrix, or assumptions (i.e., SE assumed to be equal to 20% of the base-case value). Results are presented in a tornado diagram, with sensitive analyses sorted from the widest to the narrowest range of ICER values to highlight parameters with a strong influence on the cost-effectiveness results.

Compared to chemotherapy, the ICERs for pembrolizumab + chemotherapy ranges from being dominant to DKK 356,015. The ICERs are most sensitive to parameters determining the pembrolizumab + chemotherapy and chemotherapy EFS extrapolations. The cost-effectiveness results are also moderately sensitive to variations in the costs of pembrolizumab, total metastatic costs and cost of atezolizumab. The 35 most influential parameters are presented in Figure 23.

Figure 23. Tornado diagram: Pembrolizumab + Chemotherapy vs. Chemotherapy



All ICERs are estimated at different prices for pembrolizumab to show the significance of the price at different levels. The table below show the AIP for pembrolizumab at different discount rates and the corresponding ICER, until the ICER becomes negative.

Table 58 AIP for pembrolizumab at different discount rates and the corresponding ICER

Pembrolizumab Cost (DKK)	Discount Rate	ICER (DKK/QALY)
23,205	0%	35,473
22,044	5%	27,311
20,884	10%	19,153
19,724	15%	10,995
18,564	20%	2,838
17,403	25%	-13,543

8.7.2 Scenario analysis results

Scenario analyses are conducted to assess uncertainty in the model related to key model assumptions and specifications:

- Alternative EFS parametric functions for pembrolizumab + chemotherapy:
  - Piecewise model at cut-off point of week 50 - log-normal distribution
  - Piecewise model at cut-off point of week 68 - log-normal distribution
  - Piecewise model at cut-off point of week 43 - log-normal distribution
- Alternative EFS parametric functions for chemotherapy:
  - Piecewise model at cut-off point of week 50 - generalized gamma distribution
  - Piecewise model at cut-off point of week 68 - log-normal distribution
  - Piecewise model at cut-off point of week 43 - log-normal distribution
- Alternative time horizon (10 years)
- Applying no half-cycle correction
- Not allowing vial-sharing
- Not applying dose intensity
- Alternative TOT measures for pembrolizumab + chemotherapy
  - KM lower 95% CI
  - KM upper 95% CI
- Alternative TOT measures for chemotherapy
  - KM lower 95% CI
  - KM upper 95% CI
- Alternative annual discount rate for costs
  - 0%
  - 5%
- Alternative annual discount rate for effectiveness
  - 0%
  - 5%
- Assuming remission after 8 years
- Using KN522 as the source for estimating DM treatment patterns
- Not considering AE costs

Compared to the base-case ICER of DKK 37,934 for pembrolizumab + chemotherapy vs. chemotherapy, the scenario analyses results in ICERs ranging from DKK 1,700 (zero discount rate for effectiveness) to DKK 366,336 (10-year time horizon) (Table 59).

Table 59. Scenario analysis results for Pembrolizumab + Chemotherapy vs. Chemotherapy

Scenarios	ICER (ΔCost/ΔQALY)	% Change vs. Base case
EFS		
EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - Log-normal	99,928	181.7%
EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 68 - Log-normal	52,140	47.0%
EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 43 - Log-normal	73,100	106.1%
EFS function - Chemotherapy - Piecewise - Week 50 - Generalized Gamma	42,946	21.1%
EFS function - Chemotherapy - Piecewise - Week 68 - Log-normal	43,487	22.6%
EFS function - Chemotherapy - Piecewise - Week 43 - Log-normal	13,760	-61.2%
TOT		
TOT measure - Pembrolizumab + chemotherapy - KM lower 95% CI	30,617	-13.7%
TOT measure - Pembrolizumab + chemotherapy - KM upper 95% CI	40,757	14.9%
TOT measure - Chemotherapy - KM lower 95% CI	35,721	0.7%

TOT measure - Chemotherapy - KM upper 95% CI	35,234	-0.7%
Costs		
DM treatment patterns based on KN522	118,725	234.7%
No AE costs	34,975	-1.4%
Model specifications		
Time horizon (10 years)	356,015	903.6%
No half-cycle correction	34,877	-1.7%
Do not allow vial-sharing	34,877	-1.7%
Do not apply relative dose intensity	35,473	0.0%
Annual discount rate - costs (0%)	Dominant	-
Annual discount rate - costs (5%)	45,488	28.2%
Annual discount rate - effectiveness (0%)	17,402	-50.9%
Annual discount rate - effectiveness (5%)	46,182	30.2%
Remission after 8 years	88,184	148.6%

8.7.3 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) is performed to characterize uncertainty in the model results. The PSA is generated by simultaneously varying key model parameters based on specified distributional assumptions over a number of iterations (i.e., 1,000 iterations). The normal distribution is assumed for weight, body surface area, and age-adjusted disutility. Uncertainty in the parametric estimates of EFS are explored using multivariate normal analysis. The beta distribution is assumed for the proportion transitioning from LR to DM, the proportion receiving surgery, the proportion receiving radiation, and utility inputs. The gamma distribution is assumed for costs (Table 60).

Table 60 PSA Inputs

Parameter	PSA distribution	Notes
Female weight (kg) - mean	Normal	Source for weight values and SE: KN522
Body surface area (m2) - mean	Normal	Source for weight values and SE: KN522
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - A	Multivariate normal	PSA inputs based on Cholesky decomposition matrix
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - B	Multivariate normal	PSA inputs based on Cholesky decomposition matrix
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - C	Multivariate normal	PSA inputs based on Cholesky decomposition matrix
EFS - Chemotherapy - Piecewise - 50 - Log-normal - A	Multivariate normal	PSA inputs based on Cholesky decomposition matrix
EFS - Chemotherapy - Piecewise - 50 - Log-normal - B	Multivariate normal	PSA inputs based on Cholesky decomposition matrix
Exponential rate of LR to DM or death	Normal	PSA inputs based on Cholesky decomposition matrix
% Transition from LR to DM	Beta	PSA inputs based on Cholesky decomposition
Exponential rate of DM I-O ineligible to death - Pembrolizumab + chemotherapy	Normal	Source: KN522
Exponential rate of DM to death - Chemotherapy	Normal	SE assumed to be equal to 20% of the base-case value
% LR among first EFS event (Year 1) - Pembrolizumab + chemotherapy	Beta	Source: KN522

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Parameter	PSA distribution	Notes
% LR among first EFS event (Year 1) - Chemotherapy	Beta	Source: KN522
% DM among first EFS event (Year 1) - Pembrolizumab + chemotherapy	Beta	Source: KN522
% DM among first EFS event (Year 1) - Chemotherapy	Beta	Source: KN522
% LR among first EFS event (Year 2+) - Pembrolizumab + chemotherapy	Beta	Source: KN522
% LR among first EFS event (Year 2+) - Chemotherapy	Beta	Source: KN522
% DM among first EFS event (Year 2+) - Pembrolizumab + chemotherapy	Beta	Source: KN522
% DM among first EFS event (Year 2+) - Chemotherapy	Beta	Source: KN522
% Received initial surgery - Pembrolizumab + chemotherapy	Beta	Source: KN522
% Received initial surgery - Chemotherapy	Beta	Source: KN522
% Received radiation - Pembrolizumab + chemotherapy	Beta	Source: KN522
% Received radiation - Chemotherapy	Beta	Source: KN522
EF on treatment utility - Pembrolizumab + chemotherapy	Beta	Source: KN522
EF on treatment utility - Chemotherapy	Beta	Source: KN522
EF off treatment utility - Pembrolizumab + chemotherapy	Beta	Source: KN522
EF off treatment utility - Chemotherapy	Beta	Source: KN522
LR utility - Pembrolizumab + chemotherapy	Beta	Source: KN522
LR utility - Chemotherapy	Beta	Source: KN522
DM utility - Pembrolizumab + chemotherapy	Beta	Source: KN522
DM utility - Chemotherapy	Beta	Source: KN522
Grade 3+ AE utility decrement - Pembrolizumab + chemotherapy	Beta	Source: KN522
Grade 3+ AE utility decrement - Chemotherapy	Beta	Source: KN522
Drug unit cost - Pembrolizumab	Gamma	Source: KN522
Drug unit cost - Carboplatin	Gamma	Source for utility values and SE: KN522
Drug unit cost - Doxorubicin	Gamma	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Epirubicin	Gamma	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Cyclophosphamide	Gamma	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Capecitabine	Gamma	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Gemcitabine	Gamma	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Nab-paclitaxel	Gamma	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Atezolizumab	Gamma	SE assumed to be equal to 20% of the base-case value
Admin unit cost - Intravenous infusion	Gamma	SE assumed to be equal to 20% of the base-case value
Total metastatic treatment costs - rechallenge - Pembrolizumab + chemotherapy	Gamma	SE assumed to be equal to 20% of the base-case value
Total metastatic treatment costs - IO eligible - Pembrolizumab + chemotherapy	Gamma	SE assumed to be equal to 20% of the base-case value
Total metastatic treatment costs - IO ineligible - Pembrolizumab + chemotherapy	Gamma	SE assumed to be equal to 20% of the base-case value

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Parameter	PSA distribution	Notes
Total metastatic treatment costs - Chemotherapy	Gamma	SE assumed to be equal to 20% of the base-case value
Surgery cost	Gamma	SE assumed to be equal to 20% of the base-case value
Radiation cost	Gamma	SE assumed to be equal to 20% of the base-case value
Disease management costs in EF state (per week, year 1-3)	Gamma	SE assumed to be equal to 20% of the base-case value
Disease management costs in EF state (per week, year 4-5)	Gamma	SE assumed to be equal to 20% of the base-case value
Disease management costs in EF state (per week, year 6-10)	Gamma	SE assumed to be equal to 20% of the base-case value
Disease management costs in LR state subsequent week (per week)	Gamma	SE assumed to be equal to 20% of the base-case value
Disease management costs in DM state subsequent week (per week)	Gamma	SE assumed to be equal to 20% of the base-case value
Terminal care costs from EF or LR to death (one-off)	Gamma	SE assumed to be equal to 20% of the base-case value
Terminal care costs from DM to death (one-off)	Gamma	SE assumed to be equal to 20% of the base-case value
AE costs - Pembrolizumab + chemotherapy	Gamma	SE assumed to be equal to 20% of the base-case value
AE costs - Chemotherapy	Gamma	SE assumed to be equal to 20% of the base-case value
Patient costs transportation	Gamma	SE assumed to be equal to 20% of the base-case value
Patient costs infusion time cost	Gamma	SE assumed to be equal to 20% of the base-case value

Across the 1,000 iterations of the PSA, the average incremental costs and QALY gains for pembrolizumab + chemotherapy vs chemotherapy are consistent with results from the base-case analysis. The probabilistic ICER for pembrolizumab + chemotherapy vs. chemotherapy is DKK 38,477 (**Table 61**).

Figure 24 presents the scatterplot of simulated incremental cost and QALY pairs for pembrolizumab + chemotherapy vs chemotherapy and a willingness-to-pay threshold of DKK 1,205,732 per QALY gained. The cost-effectiveness acceptability curve in Figure 25 shows the probability that pembrolizumab + chemotherapy is cost-effective compared to chemotherapy at different willingness-to-pay thresholds. At a willingness-to-pay threshold of DKK 1,205,732 per QALY gained (WTP is based on the literature recommendation of up to three times GDP per capita of Denmark [79]. This threshold is only for presentation purpose), the probability of pembrolizumab + chemotherapy being the most cost-effective therapy is 98.9%.

Table 61. PSA Results for Pembrolizumab + Chemotherapy vs. Chemotherapy

	Total Costs (DKK)	Total QALYs	Incremental Costs (DKK)	Incremental QALYs	ICER (DKK) versus baseline (QALYs)
Pembrolizumab + chemotherapy	588,231	13.91			
Chemotherapy	502,291	11.51	85,940	2.40	35,805

Figure 24. Incremental Cost and Effectiveness Plane: Pembrolizumab + Chemotherapy vs. Chemotherapy

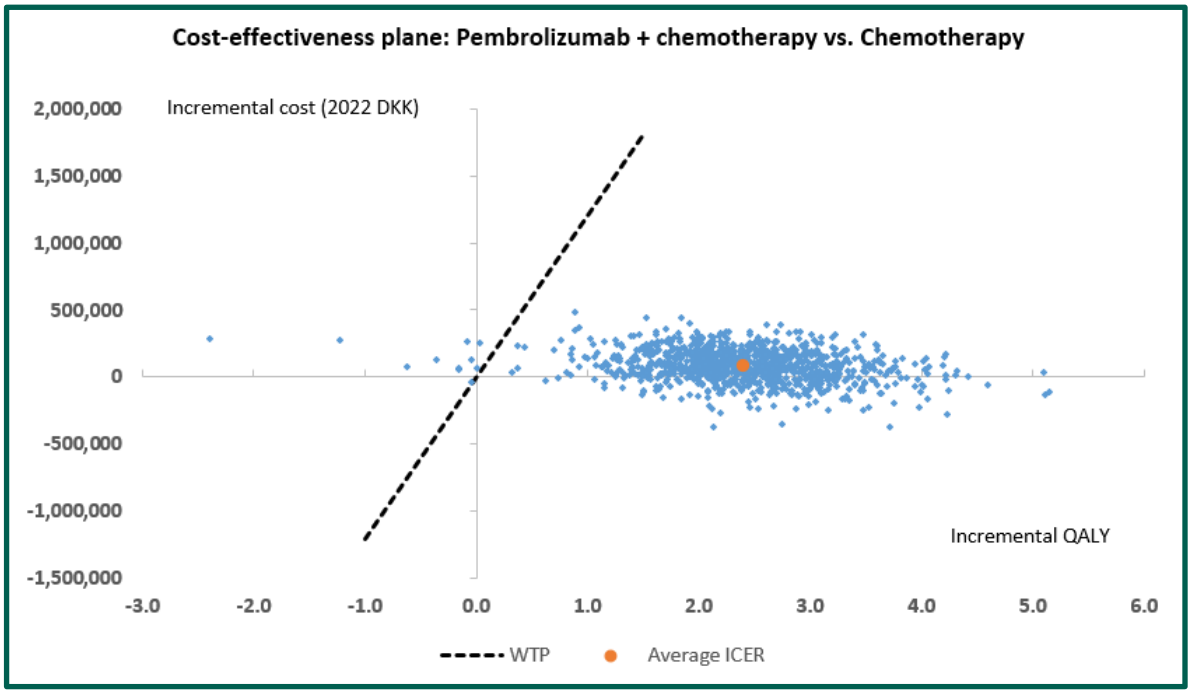
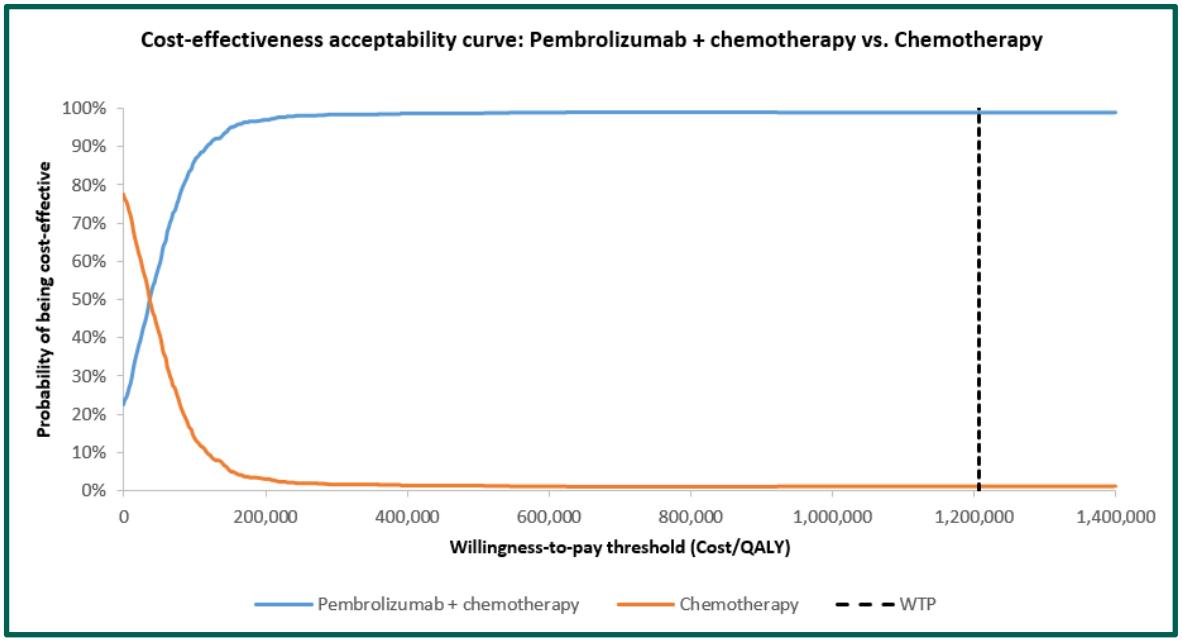


Figure 25. Cost-Effectiveness Acceptability Curve: Pembrolizumab + Chemotherapy vs. Chemotherapy



9. Budget impact analysis

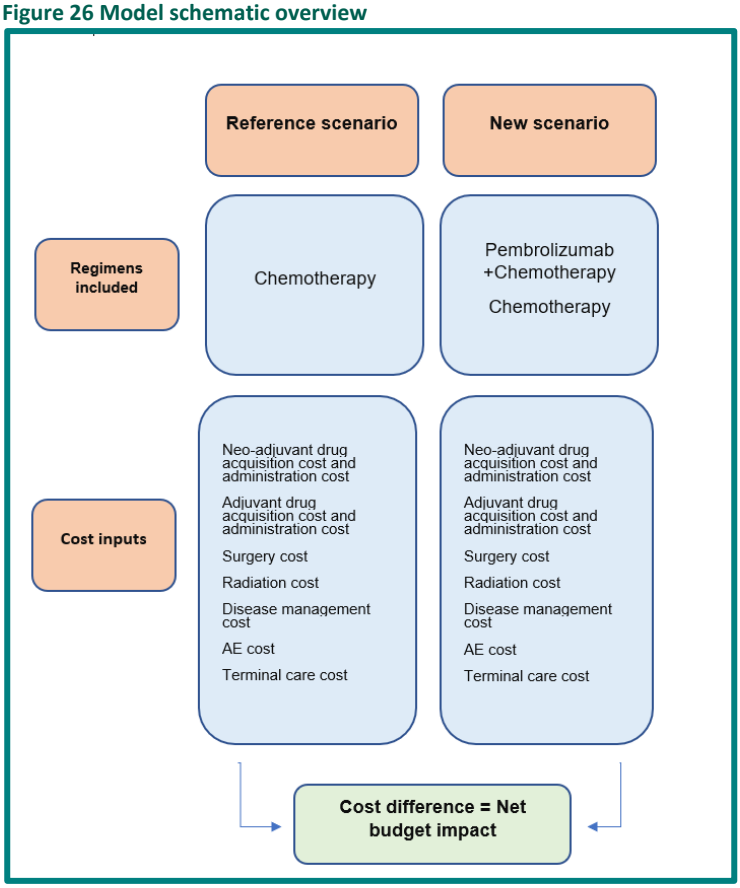
As per the requirements of the Danish Medicines Council a budget impact analysis is included into the model to evaluate the impact of adding pembrolizumab + chemotherapy in drug formulary, based on the patients who were eligible for a neo-adjuvant treatment (high-risk early-stage TNBC patients). The 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.

9.1 Budget impact analysis overview

The budget impact analysis is added in the KN522 cost effectiveness model, adapted with Danish local inputs which estimated the five-year budgetary impact for 152 annual patients who were eligible for early stage TNBC treatment. 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: Pembrolizumab + chemotherapy is not available as neoadjuvant and as a single agent as adjuvant treatment for high risk, early stage TNBC patients.
2. New scenario: Pembrolizumab + chemotherapy is available as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery along with other treatment options for high risk, early stage TNBC patients.

Figure 26 Model schematic overview



9.2 Calculations of the Budget impact analysis

The expected number of patients entering the target population is calculated according to the patient population (refer to section 9.3) for each year during the five years. To calculate the number of patients assigned to each treatment in each year in reference and new scenario, the market share of each regimen is multiplied by the target population size in each year under each scenario (Table 62).

For the first year, the total budget calculations include the costs incurred by patients eligible to receive treatment in the first year. In all subsequent years, the total budget calculations include costs incurred by the new patients entering each year and costs incurred by the alive patients who entered in the previous years and continue to receive treatment till the current year.

The total budget per year is calculated under the scenarios with and without pembrolizumab + chemotherapy. Specifically, the cost in each category (neo adjuvant drug acquisition and administration costs, adjuvant drug acquisition and administration costs, surgery cost, radiation cost, disease management costs, AE-related costs and terminal care costs) are calculated for different years from the cost effectiveness model (Table 55). Treatment costs are multiplied by the number of patients initiating the treatment and summed to derive the total cost for each year under the scenario with and without pembrolizumab + chemotherapy.

9.3 Patient population

The model uses 152 eligible patients to receive neo-adjuvant early stage TNBC treatment annually based on data extraction from the DBCG database.

Table 62 shows the number of patients in each year of reference and new scenario.

Table 62. Number of patients in each scenario

Comparator	Year 1	Year 2	Year 3	Year 4	Year 5
Reference scenario					
Pembrolizumab + chemotherapy	0	0	0	0	0
Chemotherapy	152	152	152	152	152
Total	152	152	152	152	152
New scenario					
Pembrolizumab + chemotherapy	38	76	76	114	114
Chemotherapy	114	76	76	38	38
Total	152	152	152	152	152

9.4 Market share

Market share inputs describe the percentage of patients on each treatment regimen within the healthcare plan in the target population with and without the inclusion of pembrolizumab + chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. Market share values were based on expert opinion in Denmark as well as market research data on other pembrolizumab indications and the amount of data available to support the added value of pembrolizumab + chemotherapy.

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The current and projected market shares are shown in Table 63.

Table 63. Market share of reference and new scenario

Market share	Year 1	Year 2	Year 3	Year 4	Year 5
Reference scenario					
Pembrolizumab + chemotherapy	0%	0%	0%	0%	0%
Chemotherapy	100%	100%	100%	100%	100%
New scenario					
Pembrolizumab + chemotherapy	25%	50%	50%	75%	75%
Chemotherapy	75%	50%	50%	25%	25%

9.5 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 Table 64. These costs are then used for further analysis.

Table 64. Cost of different treatments according to different years

Treatment	Year 1 (2022 DKK)	Year 2 (2022 DKK)	Year 3 (2022 DKK)	Year 4 (2022 DKK)	Year 5 (2022 DKK)
Reference Scenario					
Pembrolizumab + Chemotherapy	0	0	0	0	0
Chemotherapy	13,668,348	15,631,332	17,870,140	19,368,533	20,738,731
Total	13,668,348	15,631,332	17,870,140	19,368,533	20,738,731
New scenario					
Pembrolizumab + Chemotherapy	15,736,876	34,802,256	38,528,507	54,841,663	58,506,295
Chemotherapy	10,251,261	8,306,412	9,494,772	6,641,778	6,804,082
Total	25,988,137	43,108,668	48,023,279	61,483,441	65,310,378

9.6 Budget impact analysis results

Table 65 represents the total 5- year budget impact for Denmark.

Table 65. Annual Budget Impact

	Year 1 (2022 DKK)	Year 2 (2022 DKK)	Year 3 (2022 DKK)	Year 4 (2022 DKK)	Year 5 (2022 DKK)	Total	Yearly Average
Reference Scenario	13,668,348	15,631,332	17,870,140	19,368,533	20,738,731	87,277,083	17,455,417

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(Without Pembrolizumab)							
New Scenario (With Pembrolizumab)	25,988,137	43,108,668	48,023,279	61,483,441	65,310,378	243,913,902	48,782,780
Budget Impact	**12,319,789**	**27,477,337**	**30,153,139**	**42,114,908**	**44,571,646**	**156,636,819**	**31,327,364**

10. Discussion on the submitted documentation

10.1 Results summary

Based on the KN522 trial, this analysis considers the neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab after surgery in patients with high-risk early-stage TNBC. The comparator is the chemotherapy control arm of the KN522 trial. Over the modelled lifetime horizon, the addition of pembrolizumab yields improvements in QALYs relative to treatment with chemotherapy alone.

Results suggest that compared to chemotherapy, pembrolizumab + chemotherapy is associated with incremental total costs of DKK 96,433 annually which is driven mostly by the drug acquisition cost in the neoadjuvant and drug acquisition and administration costs of adjuvant phases, and offset by metastatic treatment costs, disease management costs, and terminal care costs. The incremental QALYs over the lifetime horizon are estimated to be 2.54, and incremental LYs over the lifetime horizon are estimated to be 2.96. Therefore, the ICER per QALY gained and ICER per LY gained are estimated to be DKK 37,934 and DKK 32,617 comparing pembrolizumab + chemotherapy vs. chemotherapy.

Results from the DSA and scenario analyses support the base-case findings, with the ICER most sensitive to the extrapolation of EFS and time horizon. Probabilistic ICERs across 1,000 iterations are consistent with deterministic base-case ICERs. Results from the DSA and PSA confirm the robustness of the base-case outcomes.

The impact of introducing pembrolizumab as neoadjuvant treatment (for 152 patients) will lead to an average annual increase of DKK 31,327,364 in the budget. The budget increase is driven largely by the projection that more patients will be receiving pembrolizumab regimens and also due to higher per patient cost in pembrolizumab arm.

Market share values for each scenario in the model are derived from projections based on market research in Denmark, so the magnitude and sign of the budget impact for a payer will depend on their plan specific market share inputs.

10.2 Strengths of the economic evaluation

Markov cohort model is a well-established modeling approach and has been commonly used in prior HTA submissions for treatments of breast cancer and other oncology indications.

The major strength of this analysis is the reliance upon direct, head-to-head comparative data from the phase III KN522 trial to inform the economic evaluation of pembrolizumab+ chemotherapy vs. chemotherapy, representing the current standard of care for the neoadjuvant and adjuvant treatment of TNBC. This data facilitates the extrapolations of EFS beyond the trial period which was carried out in line with the NICE DSU guidelines [64]. The proportional hazards assumption is verified to assess whether independent survival models were to be explored in each treatment arm. The

predicted EFS and OS are validated using two external sources which evaluated efficacy outcomes in patients with early-stage TNBC.

Utility and AE-related disutility inputs are directly estimated from the KN522 trial, and are measured using the EQ-5D, i.e., the utility measure preferred by the Danish Medicines Council. The QALY decrement associated with AEs is considered in each treatment arm, accounting for the mean duration of AEs in both arms and the treatment-specific AE rates. In the base-case, the same utilities are applied for both treatment arms based on the pooled data from KN522.

The economic evaluation appropriately accounted for 1L and/or subsequent lines of therapies for metastatic TNBC by incorporation drug acquisition costs, administration costs, and estimated market share for each regimen.

10.3 Limitations of the economic evaluation

As with any pharmacoeconomic evaluation, this model is subject to some limitations. One limitation of the model is the uncertainty around long-term extrapolation of EFS based on the immature data from KN522. Multiple scenario analyses have been undertaken to evaluate alternative extrapolation approaches for EFS. Parameter uncertainty associated with the base case EFS extrapolation is also tested in the PSA. Another limitation of the model is that it did not include Capecitabine as a comparator as explained in section 8.2.2.3 of the report.

Results from the sensitivity analyses supports the robustness of the base-case ICER. A further validation step is also conducted to address this uncertainty. Specifically, EFS curves from the published literature are digitized and fitted into the model so that the predicted EFS at specific time points could be compared against external data.

10.4 Conclusion

This economic evaluation is conducted from a Danish limited societal perspective. Based on the model results, pembrolizumab in combination with chemotherapy is highly cost-effective relative to chemotherapy, at a willingness-to-pay threshold of DKK 1,205,732 /QALY. The base-case analysis estimates that the incremental costs per QALY gained of pembrolizumab + chemotherapy vs. chemotherapy was DKK 37,934. The results are further confirmed by testing assumptions in scenario and sensitivity analyses (deterministic and probabilistic) where results support the robustness of the base-case ICER.

In the budget impact analysis, the introduction of pembrolizumab plus chemotherapy as a neoadjuvant treatment and then as a single agent as an adjuvant treatment after surgery for early stage TNBC patients will lead to increase in current health expenditure of Danish third-party healthcare payers. The budget increase is mainly driven by the expansion of immunotherapy market upon the entry of pembrolizumab.

11. Liste over eksperter

- Ann Søegaard Knoop, overlæge, Rigshospitalet
- Malgorzata Tuxen, overlæge, Herlev Hospital
- Dorte Hjorthenborg, koordinerende ledende farmakonom på Region Sjællands Sygehusapotek

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Appendix A Litteratursøgning for effekt og sikkerhed af intervention og komparator

KN522 er en direkte sammenligning af intervention og komparator. Der er ikke blevet udført en systematisk litteratursøgning, da det ikke forventes at tilvejebringe yderligere data, som kan understøtte sammenligning, jf. afsnit 6.

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Appendix B Inkluderede studier hovedkarakteristika

Table 66. Appendix B, inkluderede studier hovedkarakteristika

Trial name: KN522	NCT number: 03036488
Objective	*The purpose of this study is to evaluate the efficacy and safety of pembrolizumab (MK-3475) plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy in participants who have early triple negative breast cancer (TNBC)*
Publications – title, author, journal, year	• *Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Untch M, Fasching PA, Cardoso F, Andersen J, Patt D, Danso M, Ferreira M, Mouret-Reynier MA, Im SA, Ahn JH, Gion M, Baron-Hay S, Boileau JF, Ding Y, Tryfonidis K, Aktan G, Karantza V, O'Shaughnessy J; KN522 Investigators.* ***Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer****. N Engl J Med. 2022 Feb 10;386(6):556-567. doi: 10.1056/NEJMoa2112651. PMID: 35139274.* • *Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KN522 Investigators.* ***Pembrolizumab for Early Triple-Negative Breast Cancer****. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.*
Study type and design	*Double-blinded randomized placebo-controlled phase 3 study. Enrolled patients were randomly assigned 2:1 with the use of a central interactive voice-response system with an integrated Web-response system. No cross-over was allowed between the phases. Quadruple masking of participant, care provider, investigator, and outcomes assessor. Patients were stratified before randomization according to nodal status (positive or negative), tumor size (T1 to T2 or T3 to T4), and schedule of carboplatin administration (once weekly or every 3 weeks).* *Status: Active, not recruiting (as of latest update on March 18, 2020)* *Actual Study Start Date: March 7, 2017* *Estimated Primary Completion Date: September 30, 2025* *Estimated Study Completion Date: September 30, 2025*
Sample size (n)	*N=1174*

Main inclusion and exclusion criteria	*Inclusion Criteria:* ▪ *Has newly diagnosed, locally advanced, centrally confirmed TNBC, as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines.* ▪ *Has previously untreated locally advanced non-metastatic (M0) TNBC defined as the following combined primary tumor (T) and regional lymph node (N) staging per current American Joint Committee of Cancer (AJCC) staging criteria for breast cancer as assessed by the investigator based on radiological and/or clinical assessment:* ○ *T1c, N1-N2* ○ *T2, N0-N2* ○ *T3, N0-N2* ○ *T4a-d, N0-N2* ▪ *Provides a core needle biopsy consisting of at least 2 separate tumor cores from the primary tumor at screening to the central laboratory.* ▪ *Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 performed within 10 days of treatment initiation.* ▪ *Demonstrates adequate organ function.* ▪ *Males and female participants of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 12 months after the last dose of study treatment for participants who have received cyclophosphamide, and 6 months after the last dose of study treatment for participants who did not.* *Exclusion Criteria:* *Has a history of invasive malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.* *Has received prior chemotherapy, targeted therapy, and radiation therapy within the past 12 months.* *Has received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-programmed death - ligand 1 (anti-PD-L1), or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4], OX-40, CD137 [tumor necrosis factor receptor superfamily member 9 (TNFRSF9)]) or has previously participated in a pembrolizumab (MK-3475) clinical study.* *Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 4 weeks of the first dose of treatment in this current study.* *Has received a live vaccine within 30 days of the first dose of study treatment.* *Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).* *Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (i.e., dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.* *Has a known history of Human Immunodeficiency Virus (HIV).* *Has known active Hepatitis B or Hepatitis C.* *Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.*

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Trial name: KN522	NCT number: 03036488
	Has an active infection requiring systemic therapy. *Has significant cardiovascular disease, such as: history of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months OR congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF NYHA Class III or IV.* *Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 12 months after the last dose of study treatment for participants who have received cyclophosphamide, and for 6 months after the last dose of study treatment for participants who have not.* *Has a known hypersensitivity to the components of the study treatment or its analogs.* *Has a known history of active tuberculosis (TB, Bacillus Tuberculosis).*

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Trial name: KN522	NCT number: 03036488
Intervention	*N=784* *Pembrolizumab + Chemotherapy* *Biological: Pembrolizumab* *200 mg administered IV on Day 1 of each 3-week cycle (Q3W) for a total of 17 cycles* *Other Names: MK-3475, KEYTRUDA®* *Drug: Carboplatin* *AUC5 on Day 1 of Cycles 1-4 of the neoadjuvant phase of the study OR AUC 1.5 on Days 1, 8, 15 of Cycles 1-4 of the neoadjuvant phase of the study; IV infusion.* *Other Name: PARAPLATIN®* *Drug: Paclitaxel* *80 mg/m^2 on Days 1, 8 and 15 of Cycles 1-4 in the neoadjuvant phase of the study; IV infusion.* *Other Name: TAXOL®* *Drug: Doxorubicin* *60 mg/m^2 on Day 1 of Cycles 5-8 of the neoadjuvant phase of the study; IV injection.* *Other Name: ADRIAMYCIN®* *Drug: Epirubicin* *90 mg/m^2 On Day 1 of Cycles 5-8 of the neoadjuvant phase of the study; IV injection.* *Other Name: ELLENCE®* *Drug: Cyclophosphamide* *600 mg/m^2 On Day 1 of Cycles 5-8 of the neoadjuvant phase of the study; IV infusion.* *Other Name: CYTOXAN®*

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Trial name: KN522	NCT number: 03036488
Comparator(s)	*N=390* *Placebo + Chemotherapy* *Placebo* *Normal saline administered IV on Day 1 of each 3-week cycle (Q3W) for a total of 17 cycles* *Drug: Carboplatin* *AUC5 on Day 1 of Cycles 1-4 of the neoadjuvant phase of the study OR AUC 1.5 on Days 1, 8, 15 of Cycles 1-4 of the neoadjuvant phase of the study; IV infusion.* *Other Name: PARAPLATIN®* *Drug: Paclitaxel* *80 mg/m^2 on Days 1, 8 and 15 of Cycles 1-4 in the neoadjuvant phase of the study; IV infusion.* *Other Name: TAXOL®* *Drug: Doxorubicin* *60 mg/m^2 on Day 1 of Cycles 5-8 of the neoadjuvant phase of the study; IV injection.* *Other Name: ADRIAMYCIN®* *Drug: Epirubicin* *90 mg/m^2 On Day 1 of Cycles 5-8 of the neoadjuvant phase of the study; IV injection.* *Other Name: ELLENCE®* *Drug: Cyclophosphamide* *600 mg/m^2 On Day 1 of Cycles 5-8 of the neoadjuvant phase of the study; IV infusion.* *Other Name: CYTOXAN®*
Follow-up time	*IA1 median follow-up 15.5 months, data cutoff April 24 2019 → pCR analysis.* *IA4 median follow-up 39.1 months, data cutoff March 23 2021 → EFS analysis.*
Is the study used in the health economic model?	*Yes*

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Trial name: KN522	NCT number: 03036488
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** *Primary endpoints* 1. *Pathological complete response (pCR) rate using the definition of ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; noninvasive breast residuals allowed) at the time of definitive.* 2. *Event-free Survival (EFS) as assessed by Investigator* *Secondary endpoints* 3. *Percentage of participants who experience an adverse event (AE)* 4. *Percentage of participants who discontinue study treatment due to an AE [Time Frame: Up to approximately 57 weeks]* 5. *Health-related quality of life (HRQoL) as reported in EORTC-QLQ-C30 and EORTC-QLQ-BR23* **Other endpoints:** 1. *pCR rate using an alternative definition, ypT0 ypN0 (i.e., no invasive or noninvasive residual in breast or nodes) at the time of definitive surgery* 2. *pCR rate using the definition of ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; noninvasive breast residuals allowed) at the time of definitive surgery* 3. *EFS in participants with tumors expressing PD-L1* 4. *pCR rate using an alternative definition, ypT0/Tis (i.e., absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement) at the time of definitive surgery* 5. *Overall survival (OS) (because data is not yet mature)*
Method of analysis	*Efficacy was assessed in the intention-to-treat population, which included all randomized patients.* *The stratified method of Miettinen and Nurminen with weights proportional to the stratum size, was used to compared between-group difference in the percentages of patients with pCR (defined as ypT0/Tis for the co-primary endpoint).* *The Kaplan-Meier (KM) method was used to estimate rates of event-free survival, and a stratified log-rank test for treatment comparisons. Hazard ratios and associated 95% confidence intervals (CI) were analyzed with the use of a stratified Cox proportional-hazards model and Efron's method of handling ties to assess the magnitude of treatment difference.* *Safety was assessed in the as-treated population, which included all patients who had undergone randomization and received at least one trial drug, underwent surgery, or both.*

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Trial name: KN522		NCT number: 03036488
Subgroup analyses	▪ *Nodal status: Positive vs. Negative* ▪ *Tumor size: T1/T2 vs. T3/T4* ▪ *Choice of Carboplatin (Cb): Q3W vs. Weekly* ▪ *Tumor PD-L1 status applies to all subjects with locally advanced TNBC (positive vs.* ▪ *negative)* ▪ *Menopausal status (for females only; pre- vs. post-menopausal)* ▪ *Age (<65 years vs. ≥65 years)* ▪ *Geographic region (Europe/Israel/North America/Australia vs Asia vs. Rest of World)* ▪ *Ethnic origin (Hispanic vs. Non-Hispanic)* ▪ *ECOG performance status (0 vs. 1)* ▪ *HER2 status (1+ by IHC vs. 0 by IHC)* ▪ *LDH (≥2.0 x Upper Limit of Normal [ULN] vs. <2.0 x ULN)*	
Other relevant information	*N/A*	

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

Table 67. Appendix C. Baseline patientkarakteristika

	KN522 [10]	
No. (%), unless stated otherwise	PEM+CT	PBO+CT
Age, year		
Median (range)	49 (22-80)	48 (24-79)
<65	701 (89,4)	342 (87,7)
Menopausal status		
Premenopausal	438 (55,9)	221 (56,7)
postmenopausal	345 (44,0)	169 (43,3)
PD-L1 status		
Positive	656 (8,7)	317 (81,3)
Negative	127 (16,2)	69 (17,7)
ECOG PS		
0	678 (86,5)	341 (87,4)
1	106 (13,5)	49 (12,6)
LDH level		
≤ULN	631 (80,5)	309 (79,2)
>ULN	149 (19,0)	80 (20,5)
Administration of carboplatin		
Q3W	335 (42,7)	167 (42,8)
Q1W	449 (57,3)	223 (57,2)
Primary tumor classification		
T1 to T2	580 (74,0)	290 (74,4)
T3 to T4	204 (26,0)	100 (25,6)
Nodal involvement		
Positive	405 (51,7)	200 (51,3)
Negative	379 (48,3)	190 (48,7)
Overall disease stage		
Stage II	590 (75,3)	291 (74,6)

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Stage III	194 (24,7)	98 (25,1)
HER2 status score		
0-1	595 (75,9)	286 (73,3)
2+	188 (24,0)	104 (26,7)

Comparability of patients across studies

n/a, da vi kun inkluderer ét studie i sammenligningen

12.1 Comparability of the study populations with Danish patients eligible for treatment

Det har desværre ikke været muligt for os at identificere patientkarakteristika for danske TNBC patienter. Baseret på de tilbagemeldinger, vi har fået fra de danske klinikere, er det vores forståelse, at studiepopulationen i KN522 overordnet er repræsentativ for den danske patientpopulation. Median alderen <50 år er et af kendetegnene ved TNBC, idet denne patientgruppe oftest er yngre en den generelle brystkræftpopulation. I supplerende appendix til *"Event-free survival with Pembrolizumab in Early Triple-Negative Breast Cancer",* har Schmid et al. i tabel S2 også udtalt, at studiepopulationen er som forventet med hensyn til køn og alder. Desuden er størstedelen af studiepopulationen fra Europa (48,4%) og Nordamerika (48,4%), med 64,3% af kaukasisk oprindelse, hvilket vi også mener kan repræsentere en dansk patient population (Supplementary appendix [9]).

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Appendix D Effekt og sikkerhed pr. studie

Definition, validity and clinical relevance of included outcome measures

Table 68. Appendix D. Definition, validitet og klinisk relevans af inkluderede effektmål

Outcome measure	Definition	Validity	Clinical relevance
pCR	*pCR defined as ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; noninvasive breast residuals allowed) at the time of definitive surgery.* *pCR rate (ypT0/Tis ypN0) is defined as the percentage of participants without residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by current American Joint Committee on Cancer (AJCC) staging criteria assessed by the local pathologist at the time of definitive surgery.*	*pCR er et accepteret endepunkt for godkendelse af nye kræftlægemidler af EMA og FDA [39] [40]* *En metanalyse af 52 publikationer fandt at pCR hos TNBC patienter var forbundet med en forbedret EFS (HR=0,18; 95% PI 0,10-0,31) og OS (HR=0,22; 95% PI 0,15-0,30) [11]* *Et prospektivt database studie viste en forskel i 3-års overlevelsesrate på 26%-point til fordel for pCR vs. non-pCR TNBC patienter [41]* *pCR er associeret med forbedret EFS og OS [26]*	*I de danske kliniske retningslinjer står der følgende: "Ved NACT er der mulighed for at opnå pCR, som er en prædiktor for en god prognose. pCR defineret som ypT0 eller ypT0 er ypN0 forbundet med forbedre overlevelse" [21].* *Ved down-sizing af tumor og potentielt opnåelse af pCR ved neoadjuverende behandling, reducerer man risiko for tilbagefald og kan give mulighed for at tilbyde patienten mere konservative kirurgiske procedurer, som f.eks. konvertering af potentielle mastektomier til lumpektomier, som er en væsentlig kosmetisk forbedring af betydning for patienter [21].*
EFS	*EFS is defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence, second primary*	*EFS er et accepteret endepunkt for godkendelse af nye kræftlægemidler af EMA og FDA [39] [40]*	*Foruden død, inkluderer EFS flere hændelser som har klinisk relevans.* *Patienter, som progredierer under eller tidligt efter neoadjuverende behandling og ikke kan bliver opereret har en dårlig prognose og indikerer at sygdommen er behandlingsrefraktær.*

Outcome measure	Definition	Validity	Clinical relevance
	malignancy (breast or other cancers) or death due to any cause. As assessed by the investigator		*Patienter som udvikler fjernrecidiv bliver ikke længere behandlet med kurativ sigte, men i stedet for pallierende får uhelbredelig sygdom.*
AE/Safety	*i. Percentage of participants who experience an adverse event* *ii. Percentage of participants who discontinue study treatment due to an AE* *An AE is defined as any untoward medical occurrence in a participant administered study treatment which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment or protocol-specified procedure, whether or not considered related to study treatment or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that is temporally*	*n/a*	*n/a*

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Outcome measure	Definition	Validity	Clinical relevance
	associated with the use of study treatment, is also an AE.		
EORTC QlQ-C30	*The EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the quality of life of cancer patients. Individual responses are given on a 4-point scale (1=Not at All to 4=Very Much), with a lower score indicating a better outcome. The EORTC-QLQ-C30 score will be presented for all participants*	*n/a*	*n/a*
EORTC-QLQ-BR23	*The EORTC-QLQ-BR23 is a 23-item questionnaire developed to assess the quality of life of breast cancer patients. Individual responses are given on a 4-point scale (1=Not at All to 4=Very Much), with a lower score indicating a better outcome. The EORTC-QLQ-BR23 score will be presented for all participants*	*n/a*	*n/a*

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Results per study

Table 69. Appendix D. Resultater i KN522

Results of [KN522 (NCT03036488)]											
				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**		
pCR rate	*PEM+CT$_{neo}$ +PEM$_{adj}$*	401	64,8 (59,9-69,5) %	13,6	5,4-21,8	<0,001				*The stratified method of Miettinen and Nurminen with weights proportionalto the stratum size, was used to compare between group differences in the percentages of patients with a pathological complete response. Patients for whom no results with respect to pathological complete response were available because of discontinuation of trial treatment or missing data were considered not to have had a response*	[10] [12]
	PBO+CT$_{neo}$ +PBO$_{adj}$	201	51,2 (44,1-58,3) %								
Median EFS	*PEM+CT$_{neo}$ +PEM$_{adj}$*	784	NR				HR: 0,63	0.48-0,82	<0,001	*The Kaplan–Meier method was used to estimate event-free survival. The treatment*	[9] [12]

Results of [KN522 (NCT03036488)]									
	PBO+CT$_{neo}$ +PBO$_{adj}$	390	NR					*difference in event-free survival was assessed with the use of the stratified log-rank test for all patients and patients with PD-L1–positive tumors; hazard ratios and associated 95% confidence intervals were analyzed with the use of a stratified Cox proportional-hazards model and Efron's method of handling ties to assess the magnitude of the treatment difference..*	
3-year EFS rate	*PEM+CT$_{neo}$ +PEM$_{adj}$*	784	84,5% (81,7-86,9)	7,7		HR: 0,63	0.48-0,82	<0,001	*The 95% confidence intervals associated with the between-group differences in the percentages of event-free survival were not adjusted for multiple comparisons and hence cannot be used to infer effects The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	[10] [12]
	PBO+CT$_{neo}$ +PBO$_{adj}$	390	76,8% (72,2-80,7)							
	PEM+CT$_{neo}$	783	82,4%							

Results of [KN522 (NCT03036488)]								
All-cause safety grade 3-5	*+PEM$_{adj}$* *PBO+CT$_{neo}$* *+PBO$_{adj}$*	389	78,7%	-3,7 absolute risk reduction			*The 95% confidence intervals associated with the between-group differences in the percentages of event-free survival were not adjusted for multiple comparisons and hence cannot be used to infer effects The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	[50]
Neoadjuvant *EORTC QLQ-C30* *Baseline – week 21*	*PEM+CT$_{neo}$*	701	-11,24 LS Mean (-12,82 to -9,66)	-1,04 difference in LS means	-3,46 to 1,38	0,3985	Patient Reported Outcomes (PRO) EORTC QLQ-C30, EORTC QLQBR23, and EQ-5D™ questionnaires will be administered for Neoadjuvant Treatment Phase on Day 1 of Cycle 1 of Treatment 1, On Day 1 of Cycles 1 and 4 of Treatment 2	[50]
	PBO+CT$_{neo}$	366	-10.20 LS mean (-12.30, -8.10)					
Adjuvant *EORTC QLQ-C30* *Baseline – week 24*	*PEM+CT$_{neo}$* *+PEM$_{adj}$*	489	2.47 LS mean (1,05 to 3,88)	-0.41 difference in LS means	-2,60 to 1,77	0.7107	Patient Reported Outcomes (PROs) EORTC QLQ-C30, EORTC QLQBR23, and EQ-5D™ questionnaires will be administered for adjuvant Treatment Phase on Day 1 of	[50]
	PBO+CT$_{neo}$	283	2.88 LS mean (1,05 to 4,71)					

Results of [KN522 (NCT03036488)]			
	+PBO$_{adj}$		Cycles 1, 5, and 9, At the Early Discontinuation Visit, Long-term Follow up Visits (After the Adjuvant Treatment Phase, PROs will occur every 12 months for 2 years or until PD, whichever is earlier).

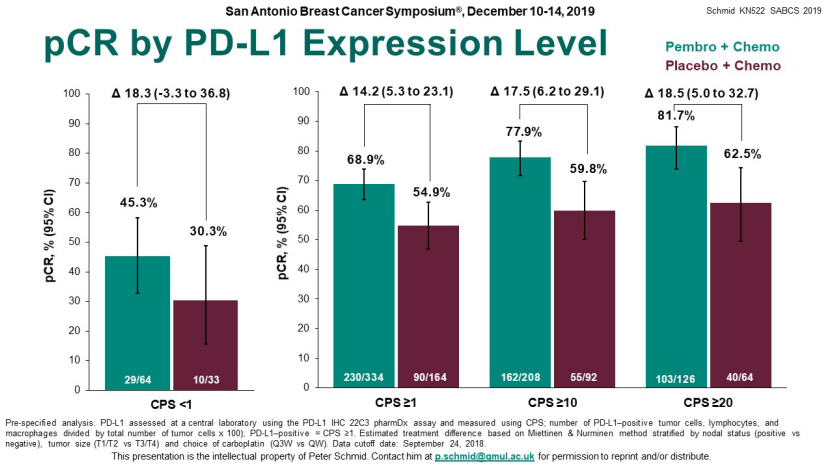

Figure 27. Histogram over pCR efter PD-L1 ekspression. Schmid et al. SABCS 2019

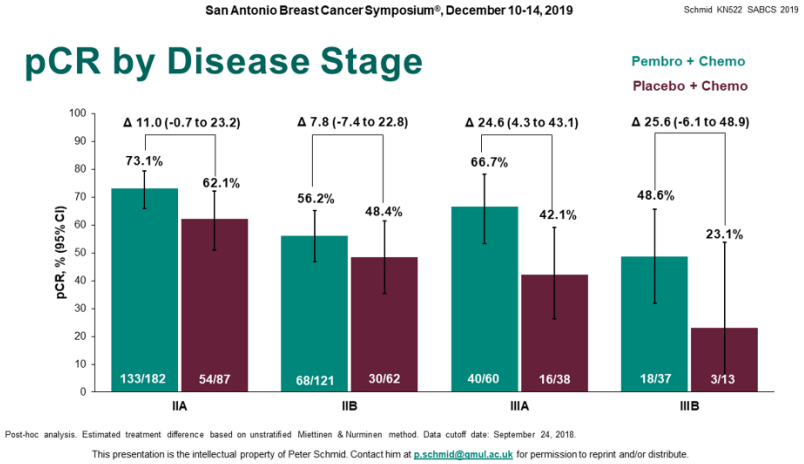

Figure 28. pCR efter sygdomsstadie, Schmid et al. SABCS 2019

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Subgroup analysis for EFS (IA4)

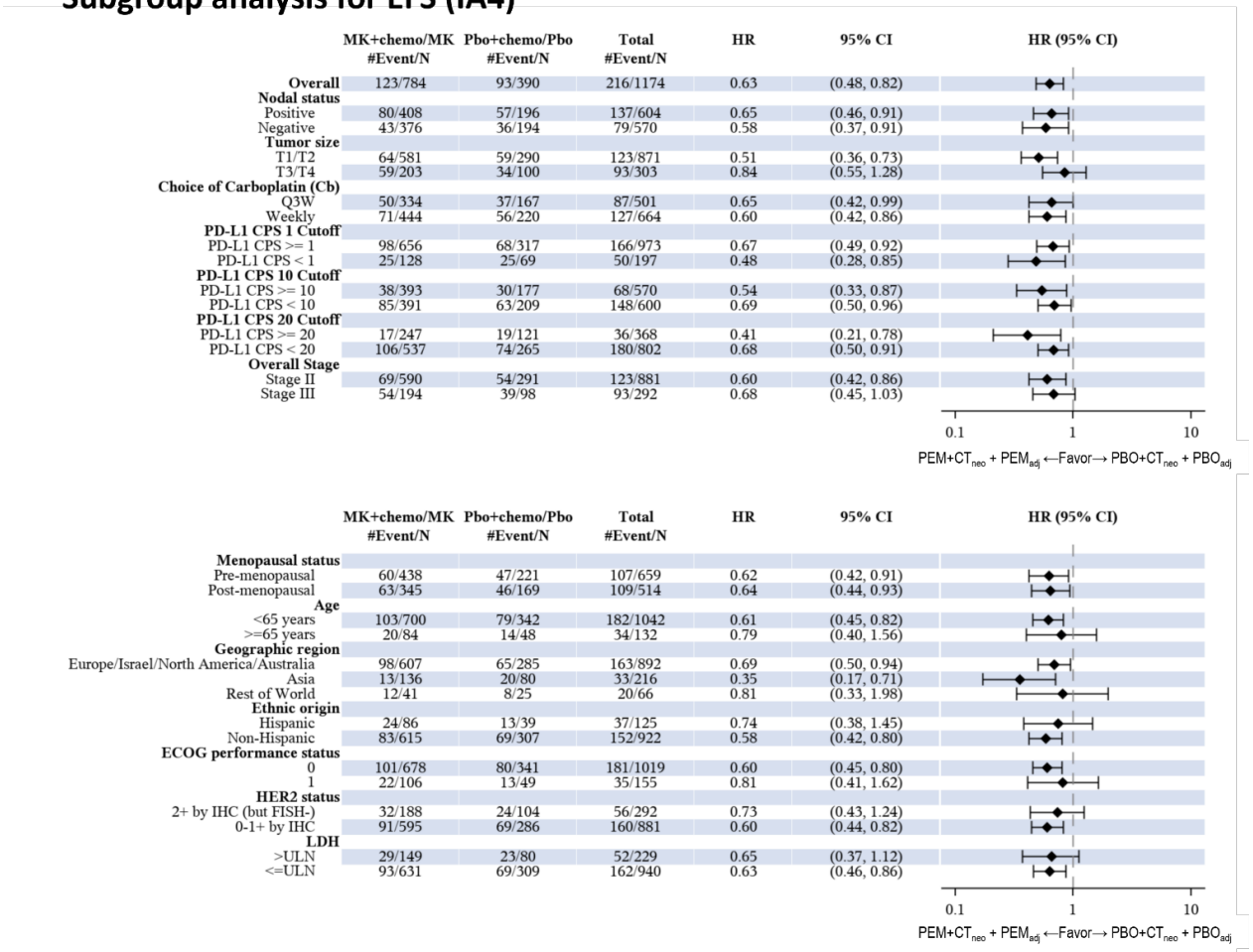

Figure 29. Forest plot, som viser subgruppe analyser ved IAI, data cut-off 23. marts 2021 median opfølgningstid på 39,1 mdr. [12]

Livskvalitet

Table 70 Change in LS Means for EORTC-QLQ-BR23

	EORTC-QLQ-BR23, LS mean fra baseline til uge 21 Neoadjuverende	Forskel i EORTC-QLQ-BR23 LS mean, uge 21 PEM+CT_{neo} vs. PBO+CT_{neo}
PEM+CT_{neo} (baseline n=695)	[redacted]	[redacted]
PBO+CT_{neo} (baseline n=361)	[redacted]	
	EORTC-QLQ-BR23, LS mean fra baseline til uge 24 Adjuverende	**Forskel i EORTC-QLQ-BR23 LS mean, uge 24 PEM+CT_{adj} vs. PBO_{adj}**
PEM_{adj} (baseline n=356)	[redacted]	[redacted]
PBO_{adj} (baseline n=353)	[redacted]	

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Table 71. Change in LS Means for EQ-5D

	EQ-5D LS mean fra baseline til uge 21 Neoadjuverende	Forskel i EQ-5D LS mean, uge 21 PEM+CT_{neo} vs. PBO+CT_{neo}
PEM+CT_{neo} (baseline n=707)	[redacted]	[redacted]
PBO+CT_{neo} (baseline n=369)	[redacted]	
	EQ-5D LS mean fra baseline til uge 24 Adjuverende	Forskel i EQ-5D LS mean, uge 24 PEM+CT_{adj} vs. PBO_{adj}
PEM_{adj} (baseline n=495)	[redacted]	[redacted]
PBO_{adj} (baseline n=285)	[redacted]	

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Appendix E Bivirkningsdata for intervention og komparator(er)

Table 72. All-cause bivirkninger med en incidens ≥10%

	PEM+CT_{neo} + PEM_{ad} N (%)	PBO+CT_{neo} + PBO_{adj} N (%)	TNBC Pembrolizumab N (%)
	Neo+adj N=783	Neo+adj n=389	Monotherapy n=595
Participants in population with			
One or more AE	777 (99,2)	389 (100,0)	559 (93,9)
Grad 3-5 AEs			
Nausea	522 (66,7)	257 (66,1)	113 (19,0)
Alopecia	477 (60,9)	226 (58,1)	8 (1,3)
Anaemia	463 (59,1)	229 (58,9)	62 (10,4)
Neutropenia	376 (48,0)	190 (48,8)	6 (1,0)
Fatigue	365 (46,6)	168 (43,2)	152 (25,5)
Constipation	328 (41,9)	150 (38,6)	98 (16,5)
Diarrhoea	318 (40,6)	133 (34,2)	75 (12,6)
Vomiting	244 (31,2)	108 (27,8)	57 (9,6)
Headache	234 (29,9)	113 (29,0)	74 (12,4)
Alanine aminotransferase increased	238 (30,4)	77 (19,8)	39 (6,6)
Neuropathy peripheral	163 (20,8)	90 (23,1)	14 (2,4)
Decreased appetite	178 (22,7)	65 (16,7)	72 (12,1)
Insomnia	178 (22,7)	74 (19,0)	22 (3,7)
Peripheral sensory neuropathy	156 (19,9)	72 (18,5)	7 (1,2)

Myalgia	153 (19,5)	73 (18,8)	42 (7,1)
Febrile neutropenia	151 (19,3)	66 (17,0)	2 (0,3)
Pruritus	147 (18,8)	66 (17,0)	66 (11,1)
Stomatitis	141 (18,0)	58 (14,9)	13 (2,2)
Radiation skin injury	114 (14,6)	73 (18,8)	3 (0,5)
Hot flush	117 (14,9)	69 (17,7)	21 (3,5)
Urinary tract infection	123 (15,7)	62 (15,9)	27 (4,5)
Epistaxis	117 (14,9)	63 (16,2)	5 (0,8)
Dizziness	118 (15,1)	60 (15,4)	36 (6,1)
Thrombocytopenia	110 (14,0)	68 (17,5)	10 (1,7)
Dysgeusia	128 (16,3)	49 (12,6)	11 (1,8)
White blood cell count decreased	113 (14,4)	56 (14,4)	6 (1,0)
Dyspepsia	111 (14,2)	56 (14,4)	13 (2,2)
Abdominal pain	112 (14,3)	49 (12,6)	36 (6,1)
Mucosal inflammation	112 (14,3)	49 (12,6)	9 (1,5)
Back pain	97 (12,4)	63 (16,2)	60 (10,1)
Upper respiratory tract infection	106 (13,5)	47 (12,1)	23 (3,9)
Dyspnoea	99 (12,6)	50 (12,9)	91 (15,3)
Leukopenia	98 (12,5)	51 (13,1)	6 (1,0)
Hypothyroidism	118 (15,1)	22 (5,7)	53 (8,9)
Pain in extremity	91 (11,6)	49 (12,6)	42 (7,1)
Erythema	81 (10,3)	36 (9,3)	16 (2,7)
Nasopharyngitis	65 (8,3)	52 (13,4)	28 (4,7)

Platelet count decreased	78 (10,0)	37 (9,5)	7 (1,2)
Abdominal pain upper	80 (10,2)	34 (8,7)	22 (3,7)
Hypokaelaemia	88 (11,2)	24 (6,2)	12 (2,0)
Bone pain	70 (8,9)	39 (10,0)	13 (2,2)
Breast pain	64 (8,2)	43 (11,1)	17 (2,9)
Infusion related reaction	79 (10,1)	27 (6,9)	3 (0,5)
Gastrooesohageal reflux disease	57 (7,3)	43 (11,1)	8 (1,3)

Database Cutoff Date: 23MAR2021

Neo+adj: Every participant is counted a single time for each applicable specific adverse event. Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the nonserious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events

Table 73. Immunrelaterede bivirkninger, *adverse events of special interest (AEOSI)*, incidens ≥1% (table 12-15 s. 186 I EPAR)

	PEM+CT_{neo} + PEM_{ad} N (%)			**PBO+CT_{neo} + PBO_{adj} N (%)**		
	Neo+adj N=783	Neo N=783	Adj N=588	Neo+adj n=389	Neo n=389	Adj N=331
Participants in population with						
One or more AE	341 (43,6)		60 (10,2)	389 (100,0)		20 (6,0)
Grad 3-5 AEs	117 (14,9)		17 (2,9)	306 (78,7)		1 (0,3)
Hypothyroidism	118 (15,1)		17 (2,9)	22 (5,7)		12 (3,6)
Infusion related reaction	79 (10,1)		2 (0,3)	27 (6,9)		2 (0,6)
Hypersensitivity	40 (5,1)		6 (1,0)	10 (2,6)		1 (0,3)

Hyperthyroidism	41 (5,2)	5 (0,9)	7 (1,8)	2 (0,6)
Drug hypersensitivity	20 (2,6)	3 (0,5)	8 (2,1)	1 (0,3)
Pneumonitis	16 (2,0)	6 (1,0)	6 (1,5)	2 (0,6)
Adrenal insufficiency	20 (2,6)	3 (0,5)	0 (0,0)	0 (0,0)
Rash	14 (1,8)	5 (0,9)	1 (0,3)	0 (0,0)
Rash maculo-papular	15 (1,9)	n/a	0 (0,0)	n/a
Colitis	8 (1,0)	2 (0,3)	3 (0,8)	0 (0,0)
Thyroiditis	8 (1,0)	0 (0,0)	5 (1,3)	1 (0,3)
Autoimmune thyroiditis	8 (1,0)	n/a	(2 (0,5)	n/a
Hepatitis	11 (1,4)	n/a	3 (0,8)	n/a
Hypophysitis	15 (1,9)	n/a	(1 (0,3)	n/a

Database Cutoff Date: 23MAR2021

Neo+adj: *Every participant is counted a single time for each applicable specific adverse event. "Infusion related reaction" includes infusion related reactions due to pembrolizumab and chemotherapy, for example, Paclitaxel. Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the nonserious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events.* ***Adj:*** *Included adverse events started from the first adjuvant treatment including radiation therapy and up to 30 days of last adjuvant treatment including radiation therapy for the non-serious adverse events and up to 90 days of last adjuvant treatment for the serious adverse events.*

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Table 73. De mest hyppige alvorlige bivirkninger ≥1 % incidens [12]

	PEM+CT (N = 783)	PBO+CT (N = 389)	Difference in % vs. PBO+CT Estimate (95% CI)*
Participants in population			
with One or more AEs	341 (43,6)	111 (28,5)	15,0 (9,2 ; 20,6)
With no AEs	442 (56,4)	278 (71,5)	-15,0 (-20,6; -9,2)
Blood and lymphatic system disorders	**154 (19,7)**	**58 (14,9)**	**4,8 (0,1; 9,1)**
Anemia	20 (2,6)	9 (2,3)	0,2 (-2,0; 2,0)
Febrile neutropenia	118 (15,1)	47 (12,1)	3,0 (-1,3; 6,9)
Neutropenia	12 (1,5)	1 (0,3)	1,3 (0,0; 2,4)
Pancytopenia	11 (1,4)	4 (1,0)	0,4 (-1,3; 1,7)
Cardiac disorders	**13 (1,7)**	**3 (0,8)**	**0,9 (-0,7; 2,2)**
Endocrine disorders	**24 (3,1)**	**0 (0,0)**	**3,1 (2,1; 4,5)**
Adrenal insufficiency	8 (1,0)	0 (0,0)	1,0 (0,0; 2,0)
Hypophysitis	8 (1,0)	0 (0,0)	1,0 (0,0; 2,0)
Gastrointestinal disorders	**37 (4,7)**	**9 (2,3)**	**2,4 (0,1; 4,5)**
General disorders and administration site conditions	**42 (5,4)**	**9 (2,3)**	**3,1 (0,7; 5,2)**
Pyrexia	29 (3,7)	2 (0,5)	3,2 (1,6; 4,8)
Hepatobiliary disorders	**17 (2,2)**	**1 (0,3)**	**1,9 (0,6; 3,2)**
Immune system disorders	**11 (1,4)**	**1 (0,3)**	**1,1 (-0,1; 2,3)**
Infections and infestations	**86 (11,0)**	**31 (8,0)**	**3,0 (-0,7; 6,4)**
Pneumonia	7 (0,9)	8 (2,1)	-1,2 (-3,2; 0,2)

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Postoperative wound infection	3 (0,4)	5 (1,3)	-0,9 (-2,6; 0,1)
Sepsis	9 (1,1)	4 (1,0)	0,1 (-1,5; 1,3)
Injury, poisoning and procedural complications	**23 (2,9)**	**4 (1,0)**	**1,9 (0,1; 3,5)**
Investigations	**16 (2,0)**	**3 (0,8)**	**1,3 (-0,3; 2,7)**
Metabolism and nutrition disorders	**14 (1,8)**	**3 (0,8)**	**1,3 (-0,3; 2,7)**
Nervous system disorders	**16 (2,0)**	**5 (1,3)**	**1,0 (-0,6; 2,3)**
Renal and urinary disorders	**17 (2,2)**	**4 (1,0)**	**1,1 (-0,6; 2,6)**
Acute kidney injury	8 (1,0)	1 (0,3)	0,8 (-0,5; 1,8)
Respiratory, thoracic, and mediastinal disorders	**23 (2,9)**	**9 (2,3)**	**0,6 (-1,6; 2,5)**
Pneumonitis	9 (1,1)	4 (1,0)	0,1 (-1,5; 1,3)
Pulmonary embolism	12 (1,5)	2 (0,5)	1,0 (-0,4; 2,2)
Skin and subcutaneous tissue disorders	**12 (1,5)**	**1 (0,3)**	**1,3 (0,0; 2,4)**
Vascular disorders	**11 (1,4)**	**3 (0,8)**	**0,6 (-0,9; 1,9)**

** Based on Miettinen & Nurminen method; since 95% CIs are provided without adjustment for multiplicity, they should be regarded as a helpful descriptive measure, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences.*

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. Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan. Included serious adverse events started from the first treatment including definitive surgery and radiation therapy and up to 90 days of the last treatment including definitive surgery and radiation therapy.

Appendix F Comparative analysis of efficacy and safety

Ikke relevant.

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Appendix G Extrapolation

Transition probabilities

Table 74 presents a summary of estimation approaches and data sources for health state transitions illustrated in Figure 9.

Table 74. Summary of health state transitions considered in the economic model

Transition(s)	Estimation approach	Data source(s)	Scenario or one-way sensitivity analyses performed
EF → LR EF → DM EF → Death	**Time dependent TPs are estimated based on 1) extrapolated EFS and 2) proportion of LR, DM and death as the first EFS event** • Using the patient-level data from KN522, EFS is extrapolated based on parametric functions for each arm. • No remission assumption is applied in the base-case. • No treatment waning effect is considered in the base-case. • Probability of experiencing LR, DM or death per cycle are estimated from EFS. • The probability of patients experiencing LR, DM and death as the first EFS event in Year 1 and Year 2+, respectively, are obtained from the KN522 clinical trial. • The TPs of EF → LR, EF → DM and EF → death are then calculated based on the probability of experiencing event (LR, DM or death) and the proportions of each event. • The TPs of EF → death are constrained to be at least as high as the all-cause natural mortality.	• KN522 • Life tables for Denmark[63] - *for transitions to death*	• Alternative parametric distributions
LR → DM LR → Death	**TPs starting from LR are assumed to be equivalent between arms, and constant across all cycles** • The TPs of LR → DM or death are obtained from the KN522 clinical trial by pooling data from the two treatment arms. • The proportions of patients experiencing DM and death, respectively, are obtained from the KN522 clinical trial. • The TPs of LR → DM, and LR → death are calculated based on the probability of experiencing either event (DM or death) and the proportions of each event. • The TPs of LR → death are constrained to be at least as high as the all-cause natural mortality.	• KN522 • Life tables for Denmark[63] - *for transitions to death*	• NA

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DM → Death	**TP from DM → death is estimated based on the treatment rate, the expected mix of first-line (1L) treatments in the DM state, and the efficacy of these 1L treatments in terms of mean OS** • KN355 is selected as the base-case source to estimate mean OS of all patients following distant metastases. The TPs of DM → death is derived based on assumptions and inputs related to 1) rechallenge with pembrolizumab or other immune-oncology (IO)-agent; 2) PD-L1 testing and positive rate; 3) treatment rate; 4) treatment mix for PD-L1 positives and PD-L1 negatives in the metastatic setting; and 5) mean OS of patients who received each 1L treatment and who did not receive the 1L treatments (details in section 1.3. • The TPs of DM → death are constrained to be at least as high as the all-cause natural mortality.	• KN355 • Life tables for Denmark [63] *- for transitions to death*	• Using KN522 as the source in the DM state.

Abbreviations: DM, distant metastases; EF, event-free; EFS, event-free survival; IO, immuno-oncology; LR, locoregional recurrence; OS, overall survival; TP, transition probability

1.1 Transitions from the EF state

For the pembrolizumab + chemotherapy and chemotherapy arms, the TPs of EF → LR, EF → DM and EF → death are estimated based on the probability of the first EFS event, and the proportions of LR, DM and death being the first EFS event. Section 1.1.1 describes the methodology to select the base-case EFS parametric functions, estimate the probability of these three events, and validate the projected EFS curves.

1.1.1 EFS estimation approach

The EFS for pembrolizumab + chemotherapy and chemotherapy are estimated using the patient-level data from the KN522 trial (data cutoff date: March 23, 2021). As an overall modelling approach, parametric models are derived by fitting different parametric models (exponential, Weibull, lognormal, log-logistic, Gompertz, gamma and the generalized gamma) to the patient-level data from the KN522 trial to extrapolate the EFS over the modeled time horizon. The survival curve fitting is carried out in line with the NICE Decision Support Unit (DSU) guidelines [80].

1.1.1.1 Joint survival models vs. separate survival models

First, the proportional hazard assumption is performed to assess two approaches for the pembrolizumab + chemotherapy and chemotherapy arms, i.e., joint survival models vs. separate survival models. When the proportional hazard assumption is valid, joint survival models would be explored for both arms, where pooled data from the two arms would be fitted and the same survival models would be applied to both arms. When the proportional hazard assumption is violated, separate survival models would be considered, where arm-specific data would be fitted, and independent survival models would be considered for each arm respectively.

The proportional hazard assumption is first tested using the Schoenfeld residual test, where a p-value of 1 did not suggest statistically significant violation of the proportional hazard assumption (in the graph the red line is the baseline denoting zero value of the residual, the black clustered point at the lower and upper part of the graph are the Schoenfeld residuals and the blue line is a smoothing spline fit to the plot.) (Figure 30). Hence, visual inspection of the log-cumulative hazard plots for the two arms are then performed (Figure 31). As the log-cumulative hazard plots of the two arms intersected, it is implausible for the proportional hazard assumption to be valid. Therefore, separate survival models are fitted for each arm to project arm-specific EFS respectively.

Figure 30. Schoenfeld residual plot for EFS from the KN522 trial

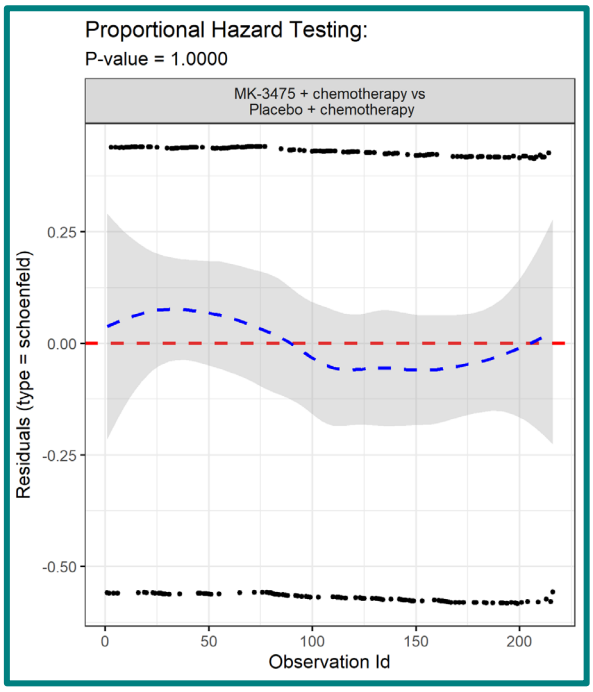
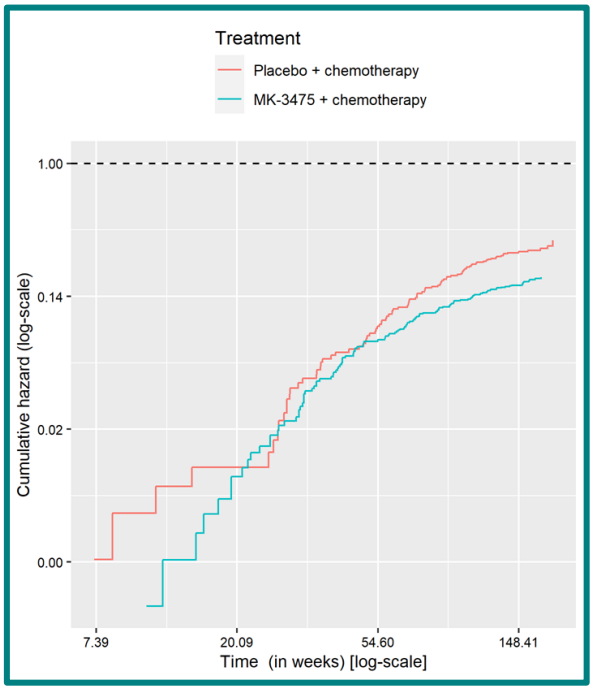


Figure 31. Log-cumulative hazard plot for EFS from the KN522 trial



When fitting separate survival models for each arm, standard (one-piece) parametric models are first fitted, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalized gamma. Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection are used to select the best-fit parametric distributions.

For the pembrolizumab + chemotherapy arm, the AIC and BIC are presented in Table 75, and the EFS curve fittings are presented in Figure 32. Pembrolizumab + chemotherapy - EFS standard parametric curve fitting. Based on both AIC and BIC, generalized gamma is the best fit, the selection of which is further confirmed based on the visual inspection.

For the chemotherapy arm, the AIC and BIC are presented in Table 76 the EFS curve fittings are presented in Figure 33. According to the AIC, generalized gamma is the best fit. According to the BIC, log-normal distribution is the best fit. Although the visual inspection suggests that generalized gamma is more plausible, neither distribution fits the observed EFS data well.

As the standard parametric models do not provide good fit to the observed data, piecewise parametric models are further explored.

Table 75. Pembrolizumab + chemotherapy - standard parametric models - AIC and BIC

Model	AIC	BIC	Average
Exponential	1,935.793	1,940.457	1,938.125
Weibull	1,937.775	1,947.103	1,942.439
Log-normal	1,923.284	1,932.612	1,927.948
Log-logistic	1,934.894	1,944.223	1,939.558
Gompertz	1,931.919	1,941.248	1,936.584
Gamma	1,937.638	1,946.966	1,942.302
Generalized Gamma	**1,902.111**	**1,916.104**	1,909.108

Abbreviation: AIC: Akaike information criterion. BIC: Bayesian information criterion

Figure 32. Pembrolizumab + chemotherapy - EFS standard parametric curve fitting

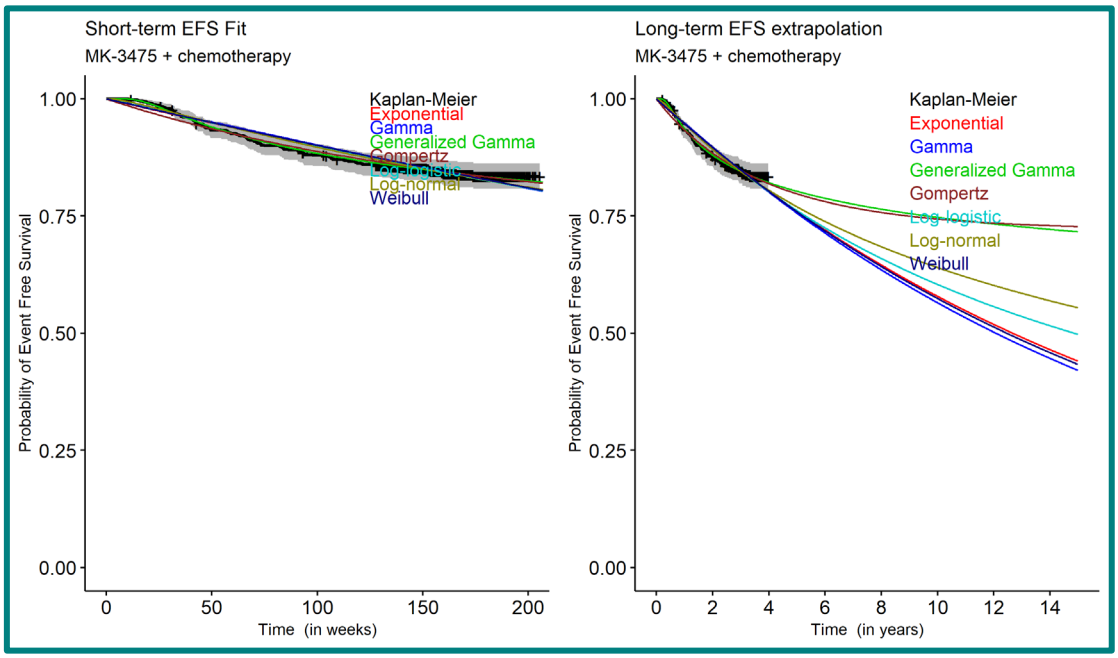
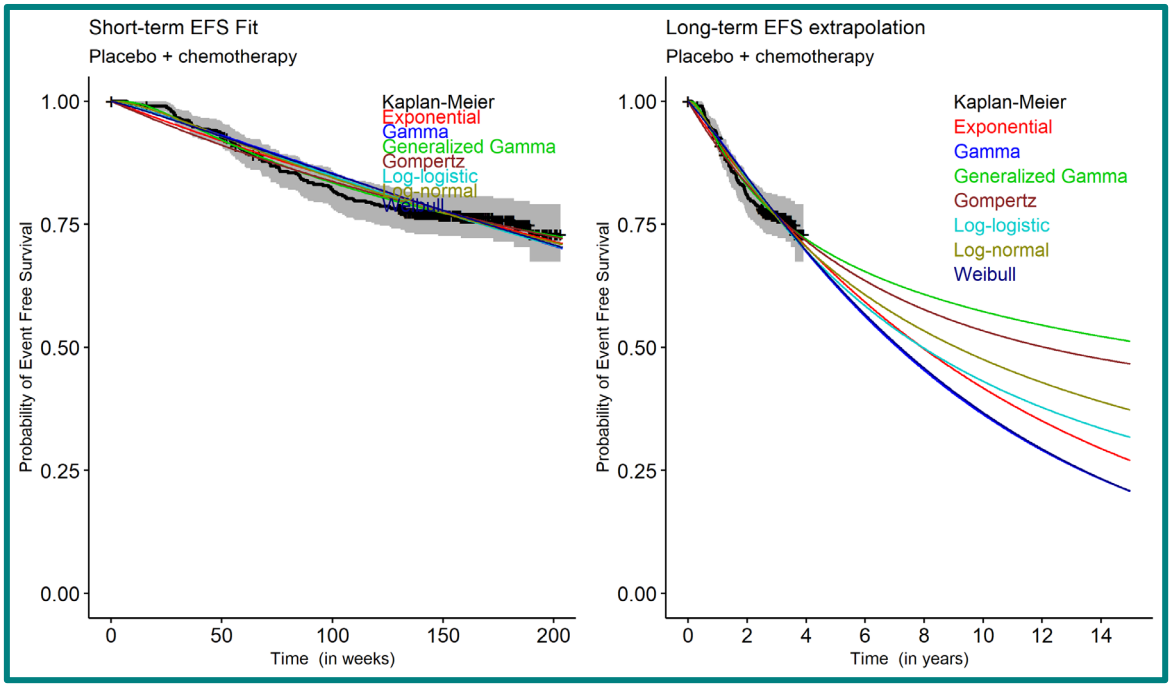


Table 76. Chemotherapy - standard parametric models - AIC and BIC

Model	AIC	BIC	Average
Exponential	1,377.112	1,381.078	1,379.095
Weibull	1,377.997	1,385.929	1,381.963
Log-normal	1,367.910	**1,375.842**	1,371.876
Log-logistic	1,374.806	1,382.738	1,378.772
Gompertz	1,378.184	1,386.116	1,382.150
Gamma	1,377.316	1,385.248	1,381.282
Generalized Gamma	**1,364.747**	1,376.646	1,370.696

Abbreviation: AIC: Akaike information criterion. BIC: Bayesian information criterion

Figure 33. Chemotherapy - EFS standard parametric curve fitting



1.1.1.2 Cutoff points of the piecewise models

The cutoff points of the piecewise models are identified according to three approaches, i.e., the hazard function, the cumulative hazard plots, and the chow tests [70]. The time points with the most pronounced changes are selected as the cut-off points. The hazard plots of both arms are presented in Figure 34 and cut-off points of week 43 and week 68 were selected because these are turning points for hazard functions. Similarly, the cumulative hazard plots in Figure 35 suggest that week 50 is another turning point, and therefore it was selected as the cut-off point. Chow tests [70] are performed to estimate structural changes to the Kaplan-Meier (KM) curve. Based on the Chow tests, week 93 and week 109 suggest potential structural changes to the slope of the cumulative hazard curve (i.e., the hazard rate) and are selected as the cut-off points.

In summary, piecewise parametric models are explored with each of the five cut-off points: week 43, week 50, week 68, week 93 and week 109. For these piecewise models, the observed KM data are used directly for the period within the specific cut-off time points, and then a parametric distribution is used to estimate EFS for the remainder of the time horizon.

In the base-case model for Denmark, cut-off point of week 50 is considered. Besides plausible visual fit, a cut-off points of week 50 provides a good balance between the robust KM data to be used directly within the first 50 weeks and sufficient remaining data to fit a parametric curve after week 50. Other cut-off points are tested in the scenario analyses. The parametric estimates, AIC and BIC associated with all parametric models are presented in section 0 below.

Figure 34. Hazard plot of EFS for both arms in the KN522 trial

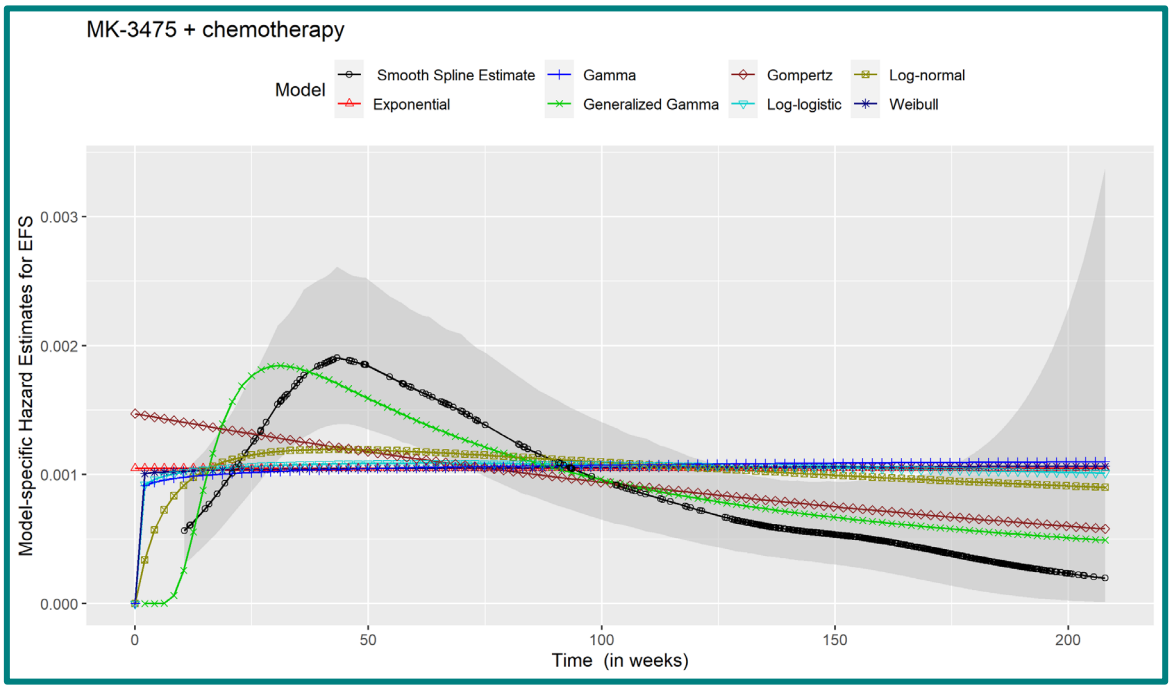


Figure 35. Cumulative hazard plot of EFS for both arms in the KN522 trial

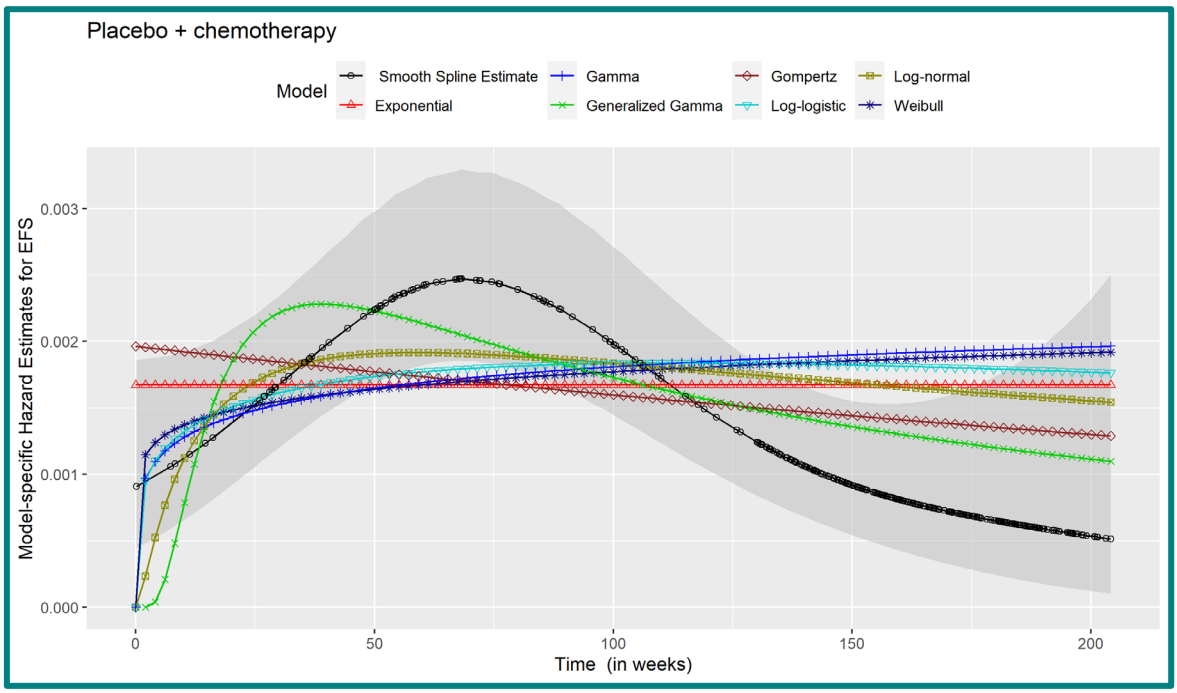
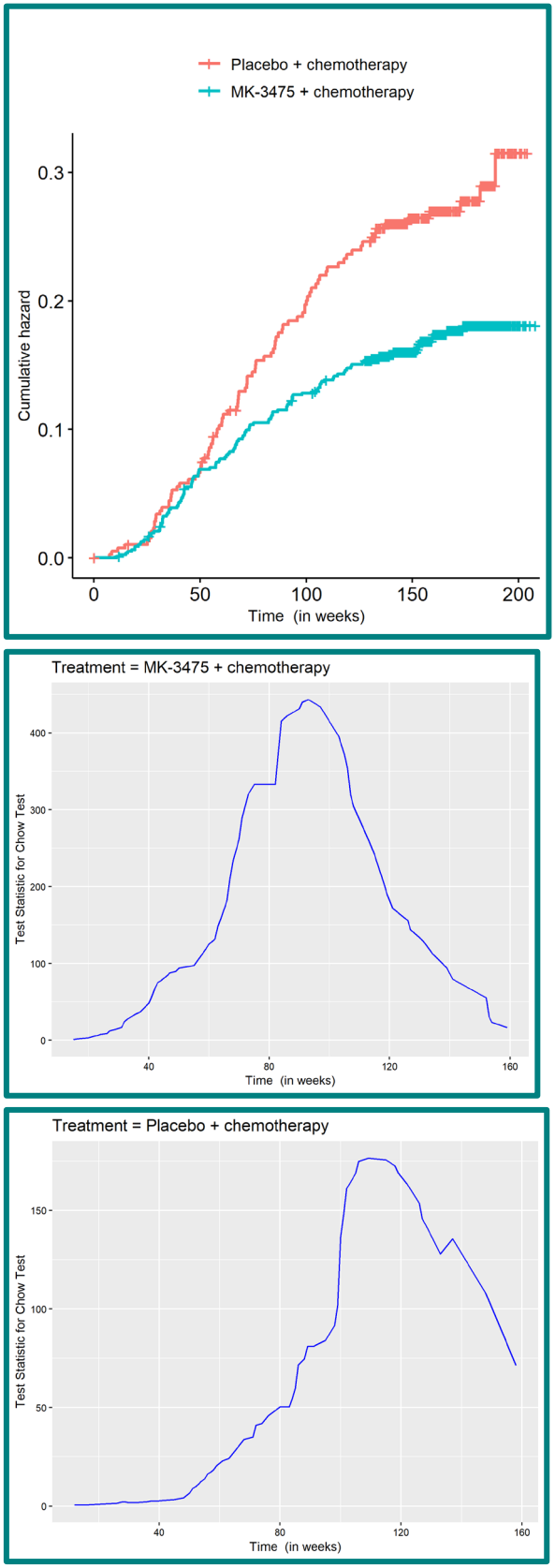


Figure 36. Chow Test results for both arms in the KN522 trial



1.1.1.3 Parametric functions from week 50 onwards

Similarly, six parametric functions, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalized gamma, are fitted for the pembrolizumab + chemotherapy and the chemotherapy arm respectively, and the best fit is selected based on AIC, BIC, and visual inspection.

For pembrolizumab + chemotherapy, the AIC and BIC are presented in Table 77, and the EFS curve fittings are presented in [redacted] Based on both AIC and BIC, generalized gamma distribution is the best fit, the selection of which is further confirmed based on the visual inspection.

For the chemotherapy arm, the AIC and BIC are presented in Table 78 and the EFS curve fittings are presented in [redacted] Based on AIC and BIC, Gompertz is the best fit followed by log-normal. According to the visual inspection, Gompertz distribution is associated with a flat tail potentially leading to an overestimation of the long-term EFS, which suggests an implausible extrapolation. Therefore, log-normal is selected as the base-case distribution for the chemotherapy arm.

Table 77. Pembrolizumab + chemotherapy - piecewise parametric models after week 50 - AIC and BIC

Model	AIC	BIC	Average
Exponential	1,140.244	1,144.835	1,142.540
Weibull	1,140.708	1,149.889	1,145.299
Log-normal	1,134.584	1,143.764	1,139.174
Log-logistic	1,139.909	1,149.090	1,144.500
Gompertz	1,134.875	1,144.056	1,139.466
Gamma	1,140.950	1,150.130	1,145.540
Generalized Gamma	**1,127.351**	**1,141.121**	**1,134.236**

Abbreviation: AIC: Akaike information criterion. BIC: Bayesian information criterion

[redacted]

Table 78. Chemotherapy - piecewise parametric models after week 50 - AIC and BIC

Model	AIC	BIC	Average
Exponential	980.8536	984.7452	982.7994
Weibull	972.6106	980.3939	976.5022

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Log-normal	**969.9094**	**977.6927**	**973.8010**
Log-logistic	971.6983	979.4816	975.5900
Gompertz	968.4863	976.2696	972.3779
Gamma	973.1538	980.9371	977.0455
Generalized Gamma	971.8675	983.5424	977.7050

Abbreviation: AIC: Akaike information criterion. BIC: Bayesian information criterion

[redacted]

[redacted]

1.1.1.4 Summary of EFS parametric functions

The base-case parametric survival models are selected based on the statistical fit, visual inspection and clinical plausibility of the extrapolated model, and are summarized below for the pembrolizumab + chemotherapy arm, and chemotherapy arm, respectively (Table 79). The base-case modeled EFS curves and the observed KM curves are presented in [redacted]

Table 79. Summary of EFS parametric functions considered in the economic model

Treatment	Base-case parametric function	Scenario analyses performed
Pembrolizumab + chemotherapy	Piecewise model at cut-off point of week 50 - generalized gamma distribution	• Piecewise model at cut-off point of week 50 - log-normal distribution • Piecewise model at cut-off point of week 68 - log-normal distribution
Chemotherapy	Piecewise model at cut-off point of week 50 - log-normal distribution	• Piecewise model at cut-off point of week 50 - generalized gamma distribution • Piecewise model at cut-off point of week 68 - log-normal distribution

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[redacted]

1.1.1.5 Validation of the EFS curves

Considering the uncertainty associated with the long-term extrapolation of EFS, it is important to carefully validate the EFS projections. The validation of EFS curves is conducted by 1) comparing modeled EFS vs. observed EFS in the KN522 trial, and 2) comparing the modeled EFS vs. external sources.

Specifically, the modeled EFS at 3 years (i.e., pembrolizumab + chemotherapy = 84.5%, chemotherapy = 76.5%) are comparable to the observed EFS at 3 years (i.e., pembrolizumab + chemotherapy =84.5% and chemotherapy=76.8% ([redacted] and [redacted]), and the modeled EFS curves match well with the observed EFS curves ([redacted] and [redacted]

When validating the modeled chemotherapy EFS by the long-term external data, a targeted literature review was first conducted to identify studies that report long-term EFS in patient with early-stage TNBC following neoadjuvant chemotherapy. Two external sources are identified, i.e., Walsh 2019 [61] and Sikov 2019 (CALGB 40603) [8]. Specifically, Walsh 2019[61] is a retrospective study of patients diagnosed with TNBC between January 2000 and December 2015, with a median follow-up of 30 months. Sikov 2019 (CALGB 40603) is a randomized, open-label phase II trial of 443 patients with stage II or III TNBC, which is designed to examine the impact of adding carboplatin and/or bevacizumab to the conventional neoadjuvant chemotherapy.

The base-case chemotherapy EFS is compared with the disease-free survival (DFS) following neoadjuvant chemotherapy in Walsh 2019, and the EFS following neoadjuvant carboplatin-based chemotherapy in Sikov 2019, respectively. As presented in [redacted] the projected chemotherapy EFS curve matches well with the DFS curve from Walsh 2019 and the EFS curve from Sikov 2019, which confirms the plausibility of the EFS projections.

As there is no clinical or real-world long-term EFS data for early-stage TNBC patients who received pembrolizumab yet, the plausibility of the projected long-term EFS of the pembrolizumab + chemotherapy arm was validated with a panel of key opinion leaders (KOLs) in this therapeutic area.

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1.1.2 Consideration of the remission assumption

The model includes the flexibility to assume patients enter remission at a specific time point. When the remission assumption is applied, the probability of EFS event for both treatment arms would be equal to zero after the specified time point. In the base-case for Denmark, no remission assumption is considered. The assumption of remission after 8 year is evaluated in scenario analysis.

1.1.3 Consideration of the treatment waning effect

The model also includes the flexibility to apply treatment waning to the pembrolizumab + chemotherapy arm in the model. Treatment waning is applied by setting the EFS hazard rate of the pembrolizumab + chemotherapy arm equal to the EFS hazard of the chemotherapy arm after a user-specified time-point. In the base-case for Denmark, no treatment waning effect is considered.

1.1.4 Estimation of TPs from EF→LR, EF → DM, and EF →death

Within each cycle, the cause-specific probability of each transition (i.e., EF → LR, EF → DM, and EF → death) is calculated based on the estimated probability of an EFS event, and the probability that the EFS event being LR, DM or death (

Table 81). Specifically, the estimated probability of an EFS event is detailed in section 1.1.1.1. The probability of the EFS event being LR, DM or DM is estimated using the KN522 trial, where the time to LR, time to DM, and time to death are analyzed using the Gray's method considering competing risks [81].

The probability of the EFS event is constrained by the all-cause natural mortality. Therefore, the TPs of EF → LR, EF → DM, and EF → death are calculated as follows:

- $TP_{EF \rightarrow LR} = TP_{EFS\ event}$ * probability of the first EFS event being LR
- $TP_{EF \rightarrow DM} = TP_{EFS\ event}$ * probability of the first EFS event being DM
- $TP_{EF \rightarrow death}$ = max ($TP_{EFS\ event}$ * probability of the first EFS event being death, probability of death among the general population – $TP_{EF \rightarrow LR}$ – $TP_{EF \rightarrow DM}$)

Table 81. Probability of the first EFS event

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Treatment arm	Year 1			Year 2+		
	% LR	% DM	% Death	% LR	% DM	% Death
Pembrolizumab + chemotherapy	36.5%	48.1%	15.4%	26.8%	63.4%	9.9%
Chemotherapy	44.8%	51.7%	3.4%	28.1%	64.1%	7.8%

Abbreviations: DM, distant metastasis; LR, locoregional recurrence

1.1.5 Validation of cumulative incidence of EF → LR, EF → DM, and EF → death

The predicted cumulative incidence of EF → LR, EF → DM and EF → death is validated with the observed cumulative incidence from the KN522 trial. [redacted] and [redacted] and [redacted] and [redacted] illustrate that the modeled cumulative incidence rates are comparable to the observed data.

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

1.2 Transitions from the LR state

The TPs of LR → DM and LR → death are estimated based on the pooled data from the two treatment arms from the KN522 trial. Parametric models are fitted to the time from LR to DM or death, and exponential distribution is found to be the best fit. Considering the memoryless feature of the Markov cohort model structure, constant TPs from the LR state are assumed. The TPs of LR → DM, and LR → death are calculated based on the TPs of LR → DM or death, and the proportions of DM and death, respectively, which are all obtained from the KN522 trial ([redacted] Furthermore, the model constrained the TP of LR →DM or death by the all-cause natural mortality.

Therefore, the TPs of LR → DM, and LR → death are calculated as follows:

- $TP_{LR \rightarrow DM} = TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of patients progressed from LR to DM
- $TP_{LR \rightarrow death} = \max(TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of death from LR, probability of death among the general population - $TP_{LR \rightarrow DM})$

[redacted]

1.3 Transitions from the DM state

In the DM state, the model assumes that a proportion of patients would receive the 1L treatment for the metastatic disease, which are obtained from the KN522 trial (Table 85).

Table 85. Proportion of patients who received 1L treatments

Parameter	Pembrolizumab + chemotherapy	Chemotherapy	Source
Proportion of patients who receive 1L	62.5%	70.3%	KN522 (Cut-off date: 23 March 2021)

Abbreviation: 1L, first-line

The model incorporates two sources to estimate TPs from DM to death and the treatment costs in the DM health state (details in section 8.5.3), i.e., KN522 and KN355. In the base-case, KN355 is considered as the data source.

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When KN355 is selected, the outcomes would be derived based on the assumptions and inputs related to 1) rechallenge with pembrolizumab or other IO-agent; 2) PD-L1 testing and positive rate; 3) treatment rate; and 4) treatment mix for PD-L1 positives and PD-L1 negatives in the metastatic setting.

Specifically, the model incorporates the flexibilities of the following three scenarios for patients who received pembrolizumab + chemotherapy in the neoadjuvant phase. For Denmark, the rechallenge of pembrolizumab or use of other IO-agents are allowed.

- Pembrolizumab rechallenge: Patients are allowed to receive pembrolizumab again in the DM setting after 2 years since neoadjuvant treatment initiation.
- IO-eligibility: For patients who are ineligible for pembrolizumab rechallenge or rechallenge is not applicable, patients are allowed to use other IOs in the DM setting after 2 years since neoadjuvant treatment initiation.
- IO-ineligibility: The rest of patients would receive a mix of chemotherapies.

The treatment mix of each scenario is obtained from Danish clinical experts (Table 86). The mean OS in the DM state is estimated as a weighted average of patients who received 1L treatments and patients who did not receive the 1L treatments. The mean OS of each 1L metastatic treatment is calculated based on the predicted OS curves from the CEM of the 1L metastatic TNBC [71] (Table 87). The predicted weekly survival rate of each 1L treatment is first obtained from the model without adjusting for natural mortality or discounting effect. The area under the OS curve (i.e., restricted mean survival time within 20 years) is then estimated using the trapezoidal rule. The current model assumes capecitabine has same OS as paclitaxel when it is given in the 1L setting.

The mean OS among patients who do not receive 1L treatments were obtained from SEER Medicare [72], and is estimated to be 21.94 weeks. The weighted mean OS of each arm is presented in Table 88. Similarly, the TPs of DM → death are estimated based on the constant hazard assumption.

Table 86: KN355 - Market shares of 1L metastatic TNBC treatment, by neoadjuvant treatment arm and eligibility for rechallenge/IOs

Treatment mix among patients who received 1L	Pembrolizumab + chemotherapy			Chemotherapy
	Rechallenge-eligible	IO-eligible	IO-ineligible	
Pembrolizumab + paclitaxel	35%	0%	0%	0%
Pembrolizumab + nab-paclitaxel	30%	0%	0%	0%
Pembrolizumab + gemcitabine + carboplatin	10%	0%	0%	0%
Paclitaxel	0%	0%	30%	0%
Nab-paclitaxel	0%	0%	30%	0%
Gemcitabine + carboplatin	0%	5%	5%	5%
Atezolizumab + Nab-paclitaxel	0%	70%	0%	70%
Capecitabine	25%	25%	35%	25%

Abbreviations: 1L: first-line; IO, immuno-oncology;

Table 87. KN355 - Mean OS by 1L metastatic TNBC treatment

Treatment mix among patients who received 1L	Mean OS (weeks)
Pembrolizumab + paclitaxel	187.89

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Pembrolizumab + nab-paclitaxel	230.75
Pembrolizumab + gemcitabine + carboplatin	145.86
Paclitaxel	68.37
Nab-paclitaxel	121.10
Gemcitabine + carboplatin	130.94
Atezolizumab + Nab-paclitaxel	182.56
Capecitabine	68.37

Abbreviations: 1L: first-line; OS, overall survival

Table 88. KN355 - TPs of DM → death for the pembrolizumab + chemotherapy and chemotherapy arms

Treatment arm	Eligibility for IOs in the DM state	Weighted mean OS (weeks)	DM → death: Exponential rate (weekly) based on weighted mean OS
Pembrolizumab + chemotherapy	Rechallenge-eligible	112.4	0.0089
Pembrolizumab + chemotherapy	IO-eligible	102.9	0.0097
Pembrolizumab + chemotherapy	IO ineligible	62.8	0.0159
Chemotherapy	-	113.0	0.0089

Abbreviations: DM, distant metastasis; IO, immuno-oncology; OS, overall survival

1.4 Validation of OS

The predicted OS is validated against internal and external sources. Specifically, the model validated the predicted OS with the observed OS from the KN522 trial ([redacted] Table 90 and Table 89). The modeled OS at year 3 (i.e., pembrolizumab + chemotherapy = 90.5%, chemotherapy = 89.4%) are comparable to the observed OS at year 3 (i.e., pembrolizumab + chemotherapy = 89.7% and chemotherapy = 86.9%).

hen validating the modeled OS curves with external sources (i.e., Walsh 2019 and Sikov 2019 [61] [8]), the modeled chemotherapy curve also matches well with the OS in Walsh 2019 and the OS in Sikov 2019 ([redacted]**).** Similarly, there is no clinical or real-word long-term OS available for early-stage TNBC patients who receive pembrolizumab yet, and the plausibility of the projected long-term OS of the pembrolizumab + chemoherapy is validated with a panel of KOLs in this therapeutic area.

[redacted]

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[redacted]

[redacted]

Table 90. Validation of modeled OS vs. observed OS for the pembrolizumab + chemotherapy arm

Pembrolizumab + chemotherapy	0.5-year	1.0-year	1.5-year	2.0-year	3.0-year	5.0-year	8.0-year	10.0-year	20.0-year
Modeled OS	99.6%	98.1%	96.3%	94.2%	90.5%	85.7%	81.3%	79.5%	72.4%
Observed OS (KM estimate)	99.2%	97.3%	95.1%	92.6%	89.7%	#N/A	#N/A	#N/A	#N/A
Observed OS (KM lower 95% CI)	98.6%	96.2%	93.6%	90.8%	87.6%	#N/A	#N/A	#N/A	#N/A
Observed OS (KM upper 95% CI)	98.6%	96.2%	93.6%	90.8%	87.6%	#N/A	#N/A	#N/A	#N/A

Abbreviations: CI, confidential interval; KM, Kaplan-Meier; OS, overall survival

Table 89 Validation of modeled OS vs. observed OS for the chemotherapy arm

Chemotherapy	0.5-year	1.0-year	1.5-year	2.0-year	3.0-year	5.0-year	8.0-year	10.0-year	20.0-year
Modeled OS	99.8%	99.0%	97.0%	94.6%	89.4%	79.9%	69.6%	64.8%	52.0%
Observed OS (KM estimate)	99.7%	98.7%	93.8%	91.3%	86.9%	#N/A	#N/A	#N/A	#N/A
Observed OS (KM lower 95% CI)	99.2%	97.6%	91.5%	88.5%	83.5%	#N/A	#N/A	#N/A	#N/A
Observed OS (KM upper 95% CI)	100.0%	99.8%	96.3%	94.1%	90.4%	#N/A	#N/A	#N/A	#N/A

Abbreviations: CI, confidential interval; KM, Kaplan-Meier; OS, overall survival

[redacted]

[redacted]

Abbreviation: OS, overall survival

Table 90 Parametric estimates of EFS for pembrolizumab + chemotherapy and chemotherapy

Functional form	Parameter A	Parameter B	Parameter C
Exponential	Log(rate)	-	-
Weibull	log(scale)	log(shape)	-
Log-logistic	log(scale)	log(shape)	-
log-normal	meanlog	log(sdlog)	-
Gompertz	shape	log(rate)	-
Gamma	log(shape)	log(rate)	-
Generalized Gamma	mu	log(sigma)	Q

Table 91 One-piece models

	Pembrolizumab + chemotherapy						Chemotherapy					
Functional Form	A	B	C	AIC	BIC	Average	A	B	C	AIC	BIC	Average
Exponential	-6.861	-	-	1935.8	1940.5	1938.1	-6.393	-	-	1377.1	1381.1	1379.1
Weibull	6.840	0.012	-	1937.8	1947.1	1942.4	6.257	0.106	-	1378.0	1385.9	1382.0
Log-logistic	6.654	0.065	-	1934.9	1944.2	1939.6	6.029	0.190	-	1374.8	1382.7	1378.8
Log-normal	6.912	0.601	-	1923.3	1932.6	1927.9	6.164	0.429	-	1367.9	1375.8	1371.9
Gompertz	-0.004	-6.521	-	1931.9	1941.2	1936.6	-0.002	-6.233	-	1378.2	1386.1	1382.1
Gamma	0.044	-6.751	-	1937.6	1947.0	1942.3	0.165	-6.058	-	1377.3	1385.2	1381.3
Generalized Gamma	4.847	0.884	-3.934	1902.1	1916.1	1909.1	5.520	0.727	-1.487	1364.7	1376.6	1370.7

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 92 Piecewise models with cutoff of week 43

	Pembrolizumab + chemotherapy						Chemotherapy					
Functional Form	A	B	C	AIC	BIC	Average	A	B	C	AIC	BIC	Average
Exponential	-6.935	-	-	1303.3	1307.9	1305.6	-6.314	-	-	1040.6	1044.5	1042.6
Weibull	7.622	-0.277	-	1298.0	1307.2	1302.6	6.682	-0.212	-	1038.9	1046.7	1042.8
Log-logistic	7.433	-0.239	-	1297.4	1306.6	1302.0	6.421	-0.148	-	1037.2	1045.1	1041.1
Log-normal	8.166	1.015	-	1294.8	1304.1	1299.4	6.695	0.803	-	1032.3	1040.1	1036.2
Gompertz	-0.011	-6.359	-	1293.1	1302.3	1297.7	-0.011	-5.728	-	1031.5	1039.3	1035.4
Gamma	-0.289	-7.823	-	1298.4	1307.6	1303.0	-0.220	-6.852	-	1039.5	1047.3	1043.4
Generalized Gamma	8.221	1.184	-0.334	1296.6	1310.5	1303.5	5.768	1.156	-1.620	1030.5	1042.2	1036.3

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 93 Piecewise models with cutoff of week 50

	Pembrolizumab + chemotherapy	Chemotherapy

Functional Form	A	B	C	AIC	BIC	Average	A	B	C	AIC	BIC	Average
Exponential	-7.016	-	-	1140.2	1144.8	1142.5	-6.305	-	-	980.9	984.7	982.8
Weibull	7.359	-0.140	-	1140.7	1149.9	1145.3	6.986	-0.353	-	972.6	980.4	976.5
Log-logistic	7.215	-0.109	-	1139.9	1149.1	1144.5	6.704	-0.295	-	971.7	979.5	975.6
Log-normal	7.790	0.861	-	1134.6	1143.8	1139.2	7.146	0.994	-	969.9	977.7	973.8
Gompertz	-0.009	-6.525	-	1134.9	1144.1	1139.5	-0.014	-5.627	-	968.5	976.3	972.4
Gamma	-0.137	-7.431	-	1140.9	1150.1	1145.5	-0.380	-7.297	-	973.2	980.9	977.0
Generalized Gamma	5.278	1.374	-4.273	1127.4	1141.1	1134.2	7.123	1.075	-0.175	971.9	983.5	977.7

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 96 Piecewise models with cutoff of week 68

	Pembrolizumab + chemotherapy						Chemotherapy					
Functional Form	A	B	C	AIC	BIC	Average	A	B	C	AIC	BIC	Average
Exponential	-7.091	-	-	892.1	896.6	894.3	-6.472	-	-	704.3	708.1	706.2
Weibull	8.009	-0.310	-	887.9	897.0	892.4	7.122	-0.293	-	701.6	709.2	705.4
Log-logistic	7.888	-0.291	-	887.7	896.8	892.3	6.919	-0.253	-	701.0	708.7	704.9
Log-normal	8.970	1.128	-	887.2	896.4	891.8	7.478	0.986	-	699.5	707.2	703.3
Gompertz	-0.012	-6.550	-	886.9	896.0	891.5	-0.014	-5.873	-	698.6	706.2	702.4
Gamma	-0.314	-8.181	-	888.0	897.1	892.6	-0.304	-7.333	-	701.8	709.5	705.6
Generalized Gamma	8.731	0.945	0.260	889.2	902.9	896.0	7.480	1.092	-0.221	701.4	712.9	707.2

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 94 Piecewise models with cutoff of week 93

	Pembrolizumab + chemotherapy						Chemotherapy					
Functional Form	A	B	C	AIC	BIC	Average	A	B	C	AIC	BIC	Average
Exponential	-7.265	-	-	564.0	568.5	566.3	-6.676	-	-	431.9	435.6	433.7
Weibull	8.555	-0.361	-	560.7	569.7	565.2	7.340	-0.247	-	431.9	439.4	435.6
Log-logistic	8.465	-0.348	-	560.7	569.8	565.2	7.199	-0.221	-	431.6	439.2	435.4
Log-normal	10.220	1.281	-	561.8	570.9	566.4	7.899	0.987	-	429.6	437.2	433.4
Gompertz	-0.013	-6.803	-	562.7	571.8	567.3	-0.016	-6.135	-	430.1	437.6	433.9
Gamma	-0.366	-8.743	-	560.7	569.7	565.2	-0.246	-7.471	-	432.0	439.5	435.7
Generalized Gamma	NA	NA	NA	NA	NA	NA	4.605	1.486	-5.068	427.6	438.9	433.2

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 95 Piecewise models with cutoff of week 109

	Pembrolizumab + chemotherapy						Chemotherapy					
Functional Form	**A**	**B**	**C**	**AIC**	**BIC**	**Average**	**A**	**B**	**C**	**AIC**	**BIC**	**Average**
Exponential	-7.445	-	-	373.6	378.1	375.8	-6.920	-	-	271.3	275.0	273.1
Weibull	7.695	-0.072	-	375.5	384.5	380.0	7.822	-0.277	-	271.7	279.2	275.4
Log-logistic	7.668	-0.069	-	375.4	384.4	379.9	7.735	-0.263	-	271.7	279.2	275.5
Log-normal	8.892	0.972	-	374.3	383.4	378.9	9.143	1.163	-	272.1	279.5	275.8
Gompertz	-0.009	-7.171	-	374.8	383.8	379.3	-0.009	-6.646	-	272.7	280.1	276.4
Gamma	-0.063	-7.693	-	375.5	384.5	380.0	-0.288	-8.006	-	271.7	279.2	275.4
Generalized Gamma	NA	NA	NA	NA	NA	NA	7.637	0.075	1.226	273.7	284.9	279.3

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion

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Appendix H – Literature search for HRQoL data

Ikke relevant fsva. HRQoL.

Literature search to identify validation studies

A targeted literature review of English publications was conducted through MEDLINE, EMBASE and Cochrane CENTRAL in December 2021. The searches include keywords related to “breast cancer”, “neoadjuvant treatment”, and “survival”. Publications that include EFS or OS curves for early-stage TNBC patients with follow-up longer than 5 years were considered to use as validation studies for this model. The literature search resulted in two eligible studies: Walsh 2019 and Sikov 2019.

Appendix I Mapping of HRQoL data

Table 96 Completion and compliance of EQ-5D by visit and by treatment

Table 14.2-61
Completion and Compliance of EQ-5D by Visit and by Treatment
All Participants
Neoadjuvant Phase
(FAS Population)

Treatment Visit	Category	MK-3475 + chemotherapy N = 762 n (%)	Placebo + chemotherapy N = 384 n (%)
Neoadjuvant Baseline	Missing by Design	0 (0.0)	1 (0.3)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to relapse/recurrence	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by parent/guardian	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	0 (0.0)	0 (0.0)
	Expected to Complete Questionnaires	762 (100.0)	383 (99.7)
	Not Complete	55 (7.2)	14 (3.6)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	15 (2.0)	5 (1.3)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	1 (0.1)	0 (0.0)
	Other	11 (1.4)	5 (1.3)
	With visit, no record	28 (3.7)	4 (1.0)
	Completed	707 (92.8)	369 (96.1)
	Compliance (completed per protocol)[a]	707 (92.8)	369 (96.3)
Neoadjuvant Week 12	Missing by Design	51 (6.7)	19 (4.9)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)

Completion and Compliance of EQ-5D by Visit and by Treatment
All Participants
Neoadjuvant Phase
(FAS Population)

Treatment Visit	Category	MK-3475 + chemotherapy N = 762 n (%)	Placebo + chemotherapy N = 384 n (%)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to relapse/recurrence	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by parent/guardian	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	1 (0.3)
	Subject died	1 (0.1)	0 (0.0)
	No visit scheduled	50 (6.6)	18 (4.7)
	Expected to Complete Questionnaires	711 (93.3)	365 (95.1)
	Not Complete	54 (7.1)	29 (7.6)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Not completed due to site staff error	17 (2.2)	8 (2.1)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	2 (0.3)	1 (0.3)
	Subject lost to follow-up/unable to contact	1 (0.1)	0 (0.0)
	Subject did not complete due to side effect of treatment	2 (0.3)	0 (0.0)
	Subject refused for other reasons	1 (0.1)	4 (1.0)
	Other	14 (1.8)	6 (1.6)
	With visit, no record	16 (2.1)	10 (2.6)
	Completed	657 (86.2)	336 (87.5)
	Compliance (completed per protocol)[a]	657 (92.4)	336 (92.1)
Neoadjuvant Week 21	Missing by Design	74 (9.7)	34 (8.9)
	Discontinued due to adverse event	6 (0.8)	2 (0.5)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	2 (0.3)	0 (0.0)
	Discontinued due to progressive disease	1 (0.1)	1 (0.3)
	Discontinued due to relapse/recurrence	0 (0.0)	0 (0.0)

Completion and Compliance of EQ-5D by Visit and by Treatment
All Participants
Neoadjuvant Phase
(FAS Population)

Treatment Visit	Category	MK-3475 + chemotherapy N = 762 n (%)	Placebo + chemotherapy N = 384 n (%)
	Discontinued due to clinical progression	0 (0.0)	2 (0.5)
	Discontinued due to withdrawal by subject	2 (0.3)	0 (0.0)
	Discontinued due to withdrawal by parent/guardian	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	3 (0.4)	0 (0.0)
	No visit scheduled	60 (7.9)	29 (7.6)
	Expected to Complete Questionnaires	688 (90.3)	350 (91.1)
	Not Complete	72 (9.4)	39 (10.2)
	Subject did not complete due to disease under study	1 (0.1)	0 (0.0)
	Not completed due to site staff error	26 (3.4)	17 (4.4)
	Subject in hospital or hospice	1 (0.1)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject lost to follow-up/unable to contact	0 (0.0)	1 (0.3)
	Subject did not complete due to side effect of treatment	2 (0.3)	1 (0.3)
	Subject refused for other reasons	8 (1.0)	3 (0.8)
	Other	25 (3.3)	10 (2.6)
	With visit, no record	9 (1.2)	6 (1.6)
	Completed	616 (80.8)	311 (81.0)
	Compliance (completed per protocol)[a]	616 (89.5)	311 (88.9)

[a] 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.

Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adpldan; adpron]

Table 14.2-67
Completion and Compliance of EQ-5D by Visit and by Treatment
All Participants
Adjuvant Phase
(FAS Population)

Treatment Visit	Category	MK-3475 N = 540 n (%)	Placebo N = 310 n (%)
Adjuvant Baseline	Missing by Design	0 (0.0)	0 (0.0)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to relapse/recurrence	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by parent/guardian	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	0 (0.0)	0 (0.0)
	Expected to Complete Questionnaires	540 (100.0)	310 (100.0)
	Not Complete	45 (8.3)	25 (8.1)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	21 (3.9)	10 (3.2)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	1 (0.3)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (0.4)	1 (0.3)
	Other	4 (0.7)	6 (1.9)
	With visit, no record	18 (3.3)	7 (2.3)
	Completed	495 (91.7)	285 (91.9)
	Compliance (completed per protocol)[a]	495 (91.7)	285 (91.9)
Adjuvant Week 12	Missing by Design	12 (2.2)	6 (1.9)
	Discontinued due to adverse event	0 (0.0)	0 (0.0)
	Discontinued due to death	0 (0.0)	0 (0.0)

Completion and Compliance of EQ-5D by Visit and by Treatment
All Participants
Adjuvant Phase
(FAS Population)

Treatment Visit	Category	MK-3475 N = 540 n (%)	Placebo N = 310 n (%)
	Discontinued due to physician decision	0 (0.0)	0 (0.0)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to relapse/recurrence	0 (0.0)	0 (0.0)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by parent/guardian	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	0 (0.0)	0 (0.0)
	No visit scheduled	12 (2.2)	6 (1.9)
	Expected to Complete Questionnaires	528 (97.8)	304 (98.1)
	Not Complete	43 (8.0)	30 (9.7)
	Subject did not complete due to disease under study	0 (0.0)	2 (0.6)
	Not completed due to site staff error	26 (4.8)	12 (3.9)
	Subject in hospital or hospice	1 (0.2)	0 (0.0)
	Subject was physically unable to complete	1 (0.2)	1 (0.3)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	6 (1.1)	1 (0.3)
	Other	6 (1.1)	10 (3.2)
	With visit, no record	3 (0.6)	4 (1.3)
	Completed	485 (89.8)	274 (88.4)
	Compliance (completed per protocol)[a]	485 (91.9)	274 (90.1)
Adjuvant Week 24	Missing by Design	55 (10.2)	26 (8.4)
	Discontinued due to adverse event	17 (3.1)	2 (0.6)
	Discontinued due to death	0 (0.0)	0 (0.0)
	Discontinued due to physician decision	7 (1.3)	1 (0.3)
	Discontinued due to progressive disease	0 (0.0)	0 (0.0)
	Discontinued due to relapse/recurrence	9 (1.7)	7 (2.3)

Completion and Compliance of EQ-5D by Visit and by Treatment
All Participants
Adjuvant Phase
(FAS Population)

Treatment Visit	Category	MK-3475 N = 540 n (%)	Placebo N = 310 n (%)
	Discontinued due to clinical progression	0 (0.0)	0 (0.0)
	Discontinued due to withdrawal by subject	9 (1.7)	8 (2.6)
	Discontinued due to withdrawal by parent/guardian	0 (0.0)	0 (0.0)
	Discontinued due to other	0 (0.0)	0 (0.0)
	Translation not available in subjects language	0 (0.0)	0 (0.0)
	Subject died	1 (0.2)	0 (0.0)
	No visit scheduled	12 (2.2)	8 (2.6)
	Expected to Complete Questionnaires	485 (89.8)	284 (91.6)
	Not Complete	41 (7.6)	35 (11.3)
	Subject did not complete due to disease under study	0 (0.0)	0 (0.0)
	Not completed due to site staff error	17 (3.1)	13 (4.2)
	Subject in hospital or hospice	0 (0.0)	0 (0.0)
	Subject was physically unable to complete	0 (0.0)	0 (0.0)
	Subject lost to follow-up/unable to contact	0 (0.0)	0 (0.0)
	Subject did not complete due to side effect of treatment	0 (0.0)	0 (0.0)
	Subject refused for other reasons	2 (0.4)	5 (1.6)
	Other	11 (2.0)	9 (2.9)
	With visit, no record	11 (2.0)	8 (2.6)
	Completed	444 (82.2)	249 (80.3)
	Compliance (completed per protocol)[a]	444 (91.5)	249 (87.7)

[a] 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.
Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adpldaa; adproa]

Appendix J Probabilistic sensitivity analyses

Table 97 1Parameters and distributional assumptions considered in the probalistic analysis are copied from the model sheet PSA parameters.

Table 97 1Parameters and distributional assumptions considered in the probalistic analysis

Parameter	PSA distribution	Base-case Mean	SE	Alpha	Beta	Notes for SE
Female weight (kg) - mean	Normal	67.00	0.48	67.00	0.48	-
Body surface area (m2) - mean	Normal	1.76	0.01	1.76	0.01	-
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - A	Multivariate normal	5.28	NA	NA	NA	Not applicable; PSA inputs based on Cholesky decomposition matrix
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - B	Multivariate normal	1.37	NA	NA	NA	Not applicable; PSA inputs based on Cholesky decomposition matrix
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - C	Multivariate normal	-4.27	NA	NA	NA	Not applicable; PSA inputs based on Cholesky decomposition matrix
EFS - Chemotherapy - Piecewise - 50 - Log-normal - A	Multivariate normal	7.15	NA	NA	NA	Not applicable; PSA inputs based on Cholesky decomposition matrix
EFS - Chemotherapy - Piecewise - 50 - Log-normal - B	Multivariate normal	0.9945	NA	NA	NA	Not applicable; PSA inputs based on Cholesky decomposition matrix
Exponential rate of LR to DM or death	Normal	0.0133	0.0021	0.0133	0.0021	-
% transition from LR to DM	Beta	0.9000	NA	36.0000	4.0000	-
Exponential rate of DM I-O ineligible to death - Pembrolizumab + chemotherapy	Normal	0.0159	0.0032	0.0159	0.0032	SE assumed to be equal to 20% of the base-case value
Exponential rate of DM to death - Chemotherapy	Normal	0.0089	0.0018	0.0089	0.0018	SE assumed to be equal to 20% of the base-case value
% LR among first EFS event (Year 1) - Pembrolizumab + chemotherapy	Beta	0.3654	NA	36.5385	63.4615	-
% LR among first EFS event (Year 1) - Chemotherapy	Beta	0.4483	NA	44.8276	55.1724	-
% DM among first EFS event (Year 1) - Pembrolizumab + chemotherapy	Beta	0.4808	NA	48.0769	51.9231	-
% DM among first EFS event (Year 1) - Chemotherapy	Beta	0.5172	NA	51.7241	48.2759	-
% LR among first EFS event (Year 2+) - Pembrolizumab + chemotherapy	Beta	0.2676	NA	26.7606	73.2394	-
% LR among first EFS event (Year 2+) - Chemotherapy	Beta	0.2813	NA	28.1250	71.8750	-
% DM among first EFS event (Year 2+) - Pembrolizumab + chemotherapy	Beta	0.6338	NA	63.3803	36.6197	-
% DM among first EFS event (Year 2+) - Chemotherapy	Beta	0.6406	NA	64.0625	35.9375	-
% received initial surgery - Pembrolizumab + chemotherapy	Beta	0.9800	NA	768.0000	16.0000	-
% received initial surgery - Chemotherapy	Beta	0.9770	NA	381.0000	9.0000	-
% received radiation - Pembrolizumab + chemotherapy	Beta	0.7590	NA	583.0000	185.0000	-
% received radiation - Chemotherapy	Beta	0.7850	NA	299.0000	82.0000	-
EF on treatment utility - Pembrolizumab + chemotherapy	Beta	0.8650	0.0050	4039.5500	630.4500	-
EF on treatment utility - Chemotherapy	Beta	0.8650	0.0050	4039.5500	630.4500	-
EF off treatment utility - Pembrolizumab + chemotherapy	Beta	0.8600	0.0050	4140.9000	674.1000	-
EF off treatment utility - Chemotherapy	Beta	0.8600	0.0050	4140.9000	674.1000	-
LR utility - Pembrolizumab + chemotherapy	Beta	0.7880	0.0250	209.8362	56.4534	-
LR utility - Chemotherapy	Beta	0.7880	0.0250	209.8362	56.4534	-
DM utility - Pembrolizumab + chemotherapy	Beta	0.6810	0.0200	369.1684	172.9291	-
DM utility - Chemotherapy	Beta	0.6810	0.0200	369.1684	172.9291	-
Grade 3+ AE utility decrement - Pembrolizumab + chemotherapy	Beta	0.0250	0.0208	1.3797	53.8089	-
Grade 3+ AE utility decrement - Chemotherapy	Beta	0.0250	0.0208	1.3797	53.8089	-

Drug unit cost - Pembrolizumab	Gamma	232.05	46.41	25.00	9.28	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Carboplatin	Gamma	0.4511	0.0902	25.0000	0.0180	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Paclitaxel	Gamma	7.33	1.47	25.00	0.29	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Doxorubicin	Gamma	2.40	0.48	25.00	0.10	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Epirubicin	Gamma	3.33	0.67	25.00	0.13	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Cyclophosphamide	Gamma	0.1813	0.0363	25.0000	0.0073	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Capecitabine	Gamma	0.0091	0.0018	25.0000	0.0004	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Gemcitabine	Gamma	0.2583	0.0517	25.0000	0.0103	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Nab-paclitaxel	Gamma	20.10	4.02	25.00	0.80	SE assumed to be equal to 20% of the base-case value
Drug unit cost - Atezolizumab	Gamma	25.95	5.19	25.00	1.04	SE assumed to be equal to 20% of the base-case value
Admin unit cost - Intravenous infusion	Gamma	2,041	408	25	82	SE assumed to be equal to 20% of the base-case value
Total metastatic treatment costs - rechallenge - Pembrolizumab + chemotherapy	Gamma	346,781	69,356	25	13,871	SE assumed to be equal to 20% of the base-case value
Total metastatic treatment costs - IO eligible - Pembrolizumab + chemotherapy	Gamma	670,721	134,144	25	26,829	SE assumed to be equal to 20% of the base-case value
Total metastatic treatment costs - IO ineligible - Pembrolizumab + chemotherapy	Gamma	59,746	11,949	25	2,390	SE assumed to be equal to 20% of the base-case value
Total metastatic treatment costs - Chemotherapy	Gamma	754,426	150,885	25	30,177	SE assumed to be equal to 20% of the base-case value
Surgery cost	Gamma	25,760	5,152	25	1,030	SE assumed to be equal to 20% of the base-case value
Radiation cost	Gamma	4,363	873	25	175	SE assumed to be equal to 20% of the base-case value
Disease management costs in EF state (per week, year 1-3)	Gamma	130.47	26.09	25.00	5.22	SE assumed to be equal to 20% of the base-case value
Disease management costs in EF state (per week, year 4-5)	Gamma	13.44	2.69	25.00	0.54	SE assumed to be equal to 20% of the base-case value
Disease management costs in EF state (per week, year 6-10)	Gamma	13.44	2.69	25.00	0.54	SE assumed to be equal to 20% of the base-case value
Disease management costs in LR state subsequent week (per week)	Gamma	64.29	12.86	25.00	2.57	SE assumed to be equal to 20% of the base-case value
Disease management costs in DM state subsequent week (per week)	Gamma	1,533	307	25	61	SE assumed to be equal to 20% of the base-case value
Terminal care costs from EF or LR to death (one-off)	Gamma	28,154	5,631	25	1,126	SE assumed to be equal to 20% of the base-case value
Terminal care costs from DM to death (one-off)	Gamma	28,154	5,631	25	1,126	SE assumed to be equal to 20% of the base-case value
AE costs - Pembrolizumab + chemotherapy	Gamma	8,105	1,621	25	324	SE assumed to be equal to 20% of the base-case value
AE costs - Chemotherapy	Gamma	6,838	1,368	25	274	SE assumed to be equal to 20% of the base-case value
Patient costs transportation	Gamma	100.00	20.00	25.00	4.00	SE assumed to be equal to 20% of the base-case value
Patient costs infusion time cost	Gamma	179.00	35.80	25.00	7.16	SE assumed to be equal to 20% of the base-case value

Appendix K Disease management cost for DM state

The unit costs of disease management for DM state were estimated based on 2022 DRG-rates from the Danish Health Data Authority [77]. Cost elements included CT scan, consultation visit, blood sample and metabolism test and MR scan.

A weekly disease management cost for in DM (PF & PD) health states were given in Table 100.

Table 100 Disease management costs For DM state

Resource	Unit cost (2022)	DRG codes	Frequency of use (number per week)	Source for unit cost (including codes if available)	Source for frequency of use
For PF state					
CT-scan	DKK 1,979.00	30PR07	0.08	DRG-rates from the Danish Health Data Authority	An information leaflet regarding treatment with Atezolizumab and Nab-paclitaxel for patients with breast cancer who have spread [82]
Consultation visit	DKK 2,041.00	MDC09/09 MA98	0.25		
Blood sample and metabolism test	DKK 1,515.00	23MA04	0.25		
Total pre-progression cost per week (2022 DKK)					DKK 1,047
For PD state					
CT-scan	DKK 1,979.00	30PR07	0.08	DRG-rates from the Danish Health Data Authority	Based on expert Input from the oncology department at Rigshospitalet
MR-scan	DKK 2,057.00	30PR03	0.08		
Consultation visit	DKK 2,041.00	MDC09/09 MA98	0.08		
Total post-progression cost per week (2022 DKK.)					DKK 486

Source: KN355 CE model

Notat om sammenligning af adjuverende behandling i hhv. KN522-studiet og CREATE-X-studiet

Studiedesignet i KN522

Keynote-522 (KN522) studiet blev designet som et "single-study trial design", som inkluderede både neoadjuverende og adjuverende behandling med en statistisk analyse plan, der muliggjorde statistisk valide konklusioner på både patologisk komplet respons (pCR) samt langtidseffektmålet "event-free survival". Denne studiemodel, som kombinerer både neoadjuverende og adjuverende behandling, giver en væsentlig kortere tidshorisont sammenlignet med en tilsvarende multistudie model, hvor separate studier skal planlægges og udføres med dertilhørende opfølgningstid. At kunne nå en konklusion tidligt på langtidseffektmål er særlig relevant for en patientpopulation med triple negativ brystkræft (TNBC), som har en markant dårligere prognose sammenlignet med øvrige brystkræftpatientpopulationer og hvor der i høj grad er behov for nye og bedre behandlingsmuligheder.

Baggrund for introduktion af capecitabin som adjuverende behandling

Da capecitabin for ca. 4 år siden blev inkluderet som et adjuverende behandlingstilbud i de danske nationale retningslinjer til non-pCR patienter [1], var det med afsæt i CREATE-X studiet samt en meta-analyse af Mackelenbergh et al. [2], der samlede studier, som beskrev effekten af capecitabin enten som mono- eller kombinationsbehandling til enten neoadjuverende eller adjuverende behandling af patienter med brystkræft. CREATE-X studiet indgik også som et studie i Mackelenbergh et al. analysen. Mackelenberg et al. konkluderede, at CREATE-X studiet er det eneste adjuverende studie, ud af de inkluderede studier, hvor man på enkelt-studie-niveau kunne påvise en forbedring i disease-free survival (DFS) med tilføjelse af capecitabin som monoterapi. F.eks. sås ingen forbedring i DFS i GEICAM/2003-11_CIBONA/2004-01 studiet, hvor capecitabin blev tilføjet i forlængelse af standard antracyklin-baseret neoadjuverende eller adjuverende kemoterapi [3]. I CREATE-X studiet fandt man dog en forbedring i DFS med en HR på 0,70 (95% CI 0,53-0,92) for DFS (recidiv, sekundær cancer eller død), som var mere udtalt for subgruppen af TNBC-patienter. Til trods for, at denne konklusion var draget på en mindre subpatientpopulation (n=139 capecitabin, b=147 i kontrolgruppen) og at dette ikke førte til en EMA-godkendt indikationsudvidelse af capecitabin, blev det et behandlingstilbud til danske patienter, idet der var og fortsat er et behov for forbedring af behandlingsmulighederne for særligt undergruppen af brystkræftpatienter med TNBC.

Sammenligning af adjuverende behandling i hhv. KN522-studiet og CREATE-X-studiet

Metodisk er det ikke muligt at udføre en statistisk indirekte sammenligning af pembrolizumab vs. capecitabin til adjuverende behandling af TNBC-patienter, idet de to studier, KN522 og CREATE-X, adskiller sig markant på væsentlige parametre (se afsnit 5.2.1.2 i vores Medicinrådsansøgning).

Ved overvejelser omkring, hvorvidt pembrolizumab eller capecitabin skal tilbydes som adjuverende behandling til non-pCR patienter, har vi i vores Medicinrådsansøgning på baggrund af CREATE-X- og KN522-studiet udført en deskriptiv analyse med fokus på hhv. TNBC-subgruppen i CREATE-X og den eksplorative analyse af EFS i non-pCR patienter i KN522. I den forbindelse rejses yderligere spørgsmål, som ikke kan besvares ud fra det tilgængelige datagrundlag:

1. Studiepopulationen i CREATE-X havde forud for inklusion i studiet modtaget suboptimal neoadjuverende behandling sammenlignet med nuværende praksis, som har inkluderet platin ± pembrolizumab. Spørgsmålet er der derfor, om der i CREATE-X-studiet var flere patienter, som var kemoterapi-sensitive og derved kunne forventes at have et højere respons på efterfølgende adjuverende capecitabin?
2. Hvad er effekten af adjuverende capecitabin, forudgået af neoadjuverende platin- og pembrolizumab-baseret behandling, som i KN522-studiet?
3. Hvad er effekten af adjuverende capecitabin hos en dansk patientpopulation, idet CREATE-X-studiet var baseret på centre i Asien, hvorfor studiepopulationen udelukkende bestod af asiatiske patienter?
4. Derudover er dosering af capecitabin i CREATE-X studiet 1250 mg/m² 2 gange dagligt højere end dosering af capecitabin i dansk klinisk praksis, som er 1000 mg/m² 2 gange dagligt. Denne dosisreduktion er givet for at mindske hyppigheden af bivirkninger. Vi er ikke bekendt med studier, som beskriver effekt og sikkerhed af dette doseringsregime med capecitabin.
5. Slutteligt kompliceres sammenligningen af den adjuverende del i hhv. KN522-studiet og CREATE-X-studiet yderligere af, at pCR i sidstnævnte vurderes i henhold til 'Japanese Response criteria', som afviger fra definitionen af pCR i KN522. Dette er endnu en medvirkende faktor til, at non-pCR-grupperne i de to studier er forskellige, og at EFS-resultaterne for disse grupper dermed ikke kan sammenlignes.

Ved en sammenligning af resultater for hhv. EFS i KN522 og DFS i CREATE-X noteres følgende:

- I KN522 var 3-års EFS-raten i non-pCR-gruppen 67,4 % i PEM+CT_{neo}+ PEM_{adj} gruppen vs. 56,8 % i PBO+CT_{neo}+ PBO_{adj}, som var en numerisk forbedring på 10,6 %-point (HR: 0,70 95% CI 0,52-0,95) til fordel for PEM+CT_{neo}+ PEM_{adj} vs. PBO+CT_{neo}+ PBO_{adj} [4].

Hvis man ser helt ukritisk på de numeriske værdier, er forbedring i EFS med adjuverende pembrolizumab i KN522-studiet sammenlignelig med forbedring i DFS med adjuverende capecitabin i CREATE-X-studiet.

Udover de ovenfornævnte tvivlsspørgsmål er de følgende faktorer desuden helt afgørende at have for øje i den sammenhæng, idet de nuancerer billedet betydeligt:

- I KN522-studiet dækker behandlingen over både neoadjuverende og adjuverende fase, hvorfor der i EFS også inkluderes "events" som finder sted før påbegyndelsen af den adjuverende behandling. Forudgående events bliver derimod ikke inkluderet i DFS for CREATE-X, idet studiet kun beskriver den adjuverende del.
- Samlet set er evidensgrundlaget i KN522 mere robust, idet der i hele studiet blev randomiseret 1197 TNBC-patienter (n=463 i non-pCR subgruppen) vs. blot 286 patienter i TNBC-subgruppen i CREATE-X-studiet.
- KN522 er til dato det studie, der har det mest robuste evidensgrundlag, hvorved en intervention har påvist en klinisk forbedring i EFS.

- Den kliniske merværdi af pembrolizumab i kombination med kemoterapi som neoadjuverende behandling efterfulgt af adjuverende pembrolizumab monoterapi er desuden understøttet af, at KN522 er blevet anbefalet i alle større internationale guidelines (ASCO, ESMO og NCCN). Hos det europæiske onkologiske selskab (ESMO) modtog KN522 den højest mulige evidensbedømmelse: A.
- Slutteligt skal det bemærkes, at der i KN522-studiet deltager 434 patienter fra europæiske centre, mens der ikke er en eneste europæisk patient i CREATE-X studiet.

Konklusion

Grundet de væsentlige forskelle mellem KN522-studiet og CREATE-X-studiet, er det ikke muligt at lave en indirekte statistisk sammenligning. Det står dog klart, at KN522-studiet udgør et væsentligt mere robust evidensgrundlag end CREATE-X-studiet, hvilket også afspejles ved, at KN522 er anbefalet i alle større internationale guidelines og i de vesteuropæiske lande, som indtil videre har vurderet KN522, herunder Norge og Sverige samt NICE i UK. En afledt effekt af ikke at anbefale pembrolizumab som adjuverende behandling til danske TNBC-patienter vil således være, at Danmarks forskningsmæssige muligheder for at indgå i internationale studier svækkes, idet Danmark ikke vil være 'on par' med standardbehandlingen i de lande, vi normalt sammenligner os med. På baggrund af disse faktorer kan det konkluderes, at pembrolizumab bør være det primære valg til adjuverende behandling af TNBC-patienter.

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