Medicinrådet

# Bilag til Medicinrådets anbefaling vedrørende pembrolizumab til adjuverende behandling af nyrekræft med øget risiko for tilbagefald efter nefrektomi

*Vers. 1.0*

# Bilagsoversigt

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

DATO: 22. september 2023

Til: Medicinrådet, att. Cecilie Dyg Spelling og Anna Kollerup Iversen, Dampfærgevej 21-23, 3. sal, 2100 København Ø

Simon Leth, chef for sundhedsøkonomi
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# Notat til høring om udkast til Medicinrådets vurderingsrapport vedr. pembrolizumab som adjuverende behandling af nyrekræft

MSD Danmark takker for muligheden for at komme med bemærkninger til Medicinrådets udkast til vurderingsrapport vedr. pembrolizumab til adjuverende behandling af nyrekræft med øget risiko for tilbagefald efter nefrektomi.

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. Vi mener desuden, det er positivt, at Medicinrådet har valgt, at afslutningen af nærværende vurderingsproces skal foregå under den nyligt indførte fast-track proces.

Vi er enige i **hovedkonklusionen i vurderingsrapporten** om, at pembrolizumab signifikant reducerer risikoen for tilbagefald sammenlignet med nuværende dansk klinisk praksis samt, at det er rimeligt at antage, at reduktionen i risikoen for tilbagefald vil øge patienternes overlevelse.

Vi har desuden følgende bemærkninger til specifikke elementer i vurderingsrapporten:

- I vurderingsrapporten konkluderes det, at **livskvaliteten** for patienter behandlet med pembrolizumab er sammenlignelig med patienter, som modtog placebo. Dette er centralt, da det viser, at bivirkningsprofilen ved adjuverende behandling med pembrolizumab var acceptabel fra patienternes synspunkt, hvilket også har været tilfældet ved adjuverende behandling med pembrolizumab indenfor andre cancertyper, herunder bl.a. melanom. Det er således en stor styrke, at livskvaliteten ikke forværres. Til livskvalitet hører desuden også patienternes mentale helbred. Her spiller frygt for tilbagefald en væsentlig rolle, idet over halvdelen af patienter med nyrekræft, der får foretaget nefrektomi, oplever stor og vedvarende frygt for tilbagefald [1]. Den positive indvirkning på patienternes mentale helbred ved netop med pembroluzumab at kunne reducere risikoen for tilbagefald er med andre ord også væsentlig at have in mente i denne sammenhæng.

- Det anføres i vurderingsrapporten, at ***'numbers needed to treat'*** estimeres således, at 10 patienter skal behandles for at undgå ét tilbagefald indenfor de første 24 måneder. I den forbindelse skal det bemærkes, at dette estimat for '*numbers needed to treat*' (NNTT) er sammenligneligt med, hvad vi har set indenfor adjuverende behandling med pembrolizumab til øvrige cancertyper, som er blevet anbefalet som standardbehandling i Danmark af Medicinrådet. For adjuverende behandling med pembrolizumab indenfor melanomcancer er NNTT således 10,3 patienter og for (neo)adjuverende behandling med pembrolizumab indenfor triple-negativ brystcancer er NNTT 13 patienter. Ligeledes kan det antages, at NNTT for at undgå tilbagefald vil falde, når det opgøres for en længere periode end 24 måneder efter nefrektomi i takt med, at data modnes. Dette understreges af konklusionen om, at RCC-patienter har øget risiko for recidiv også mere end 5 år efter operation.

- Vedrørende **korrelationen mellem DFS og OS** anføres det i vurderingsrapporten, at det er sandsynligt, at en reduktion i risikoen for tilbagefald vil øge patienternes overlevelse, men at størrelsen af overlevelsesgevinsten er usikker. Hertil skal det bemærkes, at der til at støtte op om effekten på overlevelse i EPAR'en findes en post hoc opgørelse over PFS2 (progression på næste linje behandling efter tilbagefald). Denne opgørelse viser en klar trend mod forbedret PFS på næste påbegyndte behandling efter tilbagefald hos de patienter, der oprindeligt blev behandlet med adjuverende pembrolizumab overfor placebogruppen (HR=0,52 95% CI 0,34-0,81, nominel p=0,0018 [4]). Dette taler imod den potentielle bekymring for, at adjuverende behandling muligvis vil nedsætte effekten af efterfølgende behandling til metastatiske patienter, men indikerer derimod en langtidseffekt af den adjuverende behandling med pembrolizumb. Hertil skal tilføjes, at adjuverende pembrolizumab viste en sammenlignelig effekt på at forhindre fjernmetastatisk recidiv (DMFS, HR=0,63 95% CI 0,49-0,82) som på DFS [3]. Da langt størstedelen af tilbagefald efter nefrektomi (80-90%) [2,3] er metastatiske, er effekten på DMFS også med til at understøtte en evt. langtidseffekt på overlevelsen, da det er metastatisk nyrekræft patienterne oftest dør af.

- I **vurderingen af sikkerhed** anføres det, at den adjuverende behandling med pembrolizumab indebærer øget risiko for bivirkninger og overbehandling. I den forbindelse er det helt afgørende at have øje for selve formålet med adjuverende behandling, hvilket – som også nævnes i vurderingsrapporten – er at nedsætte risikoen for, at patienterne får tilbagefald af nyrekræft. Et tilbagefald er forbundet med 6-gange højere risiko for død og derved en betydelig forringelse af patienternes prognose, symptomer og livskvalitet. Risikoen for bivirkninger skal således vejes op mod muligheden for signifikant og klinisk betydningsfuldt at kunne nedsætte patienternes risiko for at udvikle uhelbredelig metastatisk sygdom. I forlængelse heraf er det også væsentligt at være opmærksom på, at adjuverende behandling med pembrolizumab som nævnt ovenfor også signifikant reducerer risikoen for fjernmetastaser, hvilket som oftest er det, patienterne dør af [2, 4].

- I vurderingsrapporten anføres det, at der ikke findes danske opgørelser over, hvad **recidivraten** er i gruppen af patienter med øget risiko for tilbagefald efter nefrektomi. Der henvises dog til et dansk enkelt-center studie, som viste, at 5-års recidivraten for 367 RCC-patienter (alle histologityper inkluderet dvs. clearcelle og andre) nefrektomeret med kurativt sigte i perioden 2005-2013 var 22 %. Det skal i den forbindelse bemærkes, at vi i skrivende stund i samarbejde med danske klinikere er i færd med at generere Real World Evidence med henblik på at undersøge recidivraten for en større kohorte på over 6000) af danske RCC-patienter, hvoraf mere end 1200 netop matcher KN564-studiets kriterier for patienter i øget risiko for tilbagefald. De foreløbige resultater fra dette studie, som blev præsenteret på EIKCS konferencen i Glasgow tidligere i år, viser, at recidivraterne i den danske kohorte er sammenlignelige med det, der opgøres i KN564-studiet, med en 3- og 5-års recidivrate på hhv. 30,4% og 40,1%. De endelige resultater forventes at blive publiceret i et videnskabeligt tidsskrift i slutningen af 2023 eller begyndelsen af 2024.

Vi gør desuden opmærksom på, at pembrolizumab som adjuverende behandling af nyrekræft foreløbigt er anbefalet som **standardbehandling i bl.a. følgende europæiske lande**:

1. Sverige
2. Finland
3. England
4. Holland
5. Belgien
6. Tyskland
7. Østrig
8. Italien
9. Spanien
10. Portugal
11. Skotland
12. Tjekkiet
13. Polen
14. Slovenien
15. Bulgarien

Opsummerende skal det understreges, at vi som nævnt er enige i vurderingsrapportens hovedkonklusion, der indikerer, at adjuverende behandling med pembrolizumab til nyrekræft udgør et markant behandlingsfremskrift for danske patienter, idet patienternes risiko for tilbagefald reduceres signifikant (HR=0,63). Dermed reduceres også de symptomer, forværret livskvalitet og ringere overlevelse, der følger et tilbagefald på tværs af alle subgrupper.

Med venlig hilsen,

Simon Leth
Chef for sundhedsøkonomi

**Referencer:**

1. Decat Bergerot C et al. Fear of cancer recurrence in patients with localized renal cell carcinoma. JCO Oncol Pract. 2020;16(11):1264-e1271.
2. Sundaram M, Haas NB et al. Clinical and economic burdens of recurrence following nephrectomy for intermediate high- or high-risk renal cell carcinoma: A retrospective analysis of Surveillance, Epidemiology, and End Results–Medicare data. J Manag Care Spec Pharm. 2022;28(10):1149-1160.
3. Powles T, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022;23(9):1133-44.
4. CHMP) CfMPfHU. European Public Assessment Report (EPAR): KEYNOTE-564. 2022.

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20.09.2023
CAF/DBS

# Forhandlingsnotat

| | |
|---|---|
| Dato for behandling i Medicinrådet | 25.10.2023 |
| Leverandør | MSD |
| Lægemiddel | Keytruda (pembrolizumab) |
| Ansøgt indikation | Keytruda (pembrolizumab) til adjuverende behandling af nyrekræft med øget risiko for tilbagefald efter nefrektomi. |
| Nyt lægemiddel / indikationsudvidelse | Indikationsudvidelse (fast-track proces) |

## Prisinformation

Amgros har følgende pris på Keytruda (pembrolizumab):

*Tabel 1: Aftalepris*

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

## Aftaleforhold

[redacted]

## KonkurrencesituationenX

Der er på nuværende tidspunkt ingen konkurrence indenfor denne indikation.

*Tabel 2: Lægemiddeludgift Keytruda*

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

*Vægt: 84,9 kg jf. Medicinrådet

## Status fra andre lande

Tabel 3: Status fra andre lande

| Land | Status | Link |
|---|---|---|
| Norge | Under vurdering | Link til information |
| England | Anbefalet | Link til anbefaling |
| Sverige | Anbefalet | Link til anbefaling |

## Konklusion

[redacted]

Medicinrådet

# Ansøgning om vurdering af KEYTRUDA som monoterapi indiceret til behandling af voksne med RCC med øget risiko for recidiv efter nefrektomi eller efter nefrektomi og resektion af metastatiske læsioner



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# Indholdsfortegnelse





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# 1. Basisinformation

| Kontaktoplysninger | |
|---|---|
| **Navn** | **Thomas Le Fevre** |
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| Oversigt over lægemidlet | |
|---|---|
| **Handelsnavn** | KEYTRUDA |
| **Generisk navn** | Pembrolizumab |
| **Indehaver af markedsføringstilladelse i Danmark** | MSD Danmark ApS<br>MSD modtog en CHMP positive opinion den 17. december 2021. |
| **ATC-kode** | L01XC18 |
| **Farmakoterapeutisk gruppe** | Antineoplastiske midler |
| **Aktivstof(fer)** | Pembrolizumab |
| **Farmaceutisk form(e)** | Pulver til koncentrat til infusionsvæske, opløsning.<br>Koncentrat til infusionsvæske, opløsning. |
| **Virkningsmekanisme** | KEYTRUDA er et humaniseret monoklonalt antistof, der binder til programmed cell death-1 (PD-1)-receptoren og blokerer dets interaktion med liganderne PD-L1 og PD-L2. KEYTRUDA aktiverer T-cellemedieret respons, herunder anti-tumorrespons, ved at blokere PD-1-bindingen til PD-L1 og PD-L2, som er udtrykt i antigenpræsenterende celler, og som kan udtrykkes af tumorer eller andre celler i tumorens mikromiljø. |
| **Dosering** | 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. |
| **Terapeutisk indikation, der er relevant for vurderingen (som defineret af Det Europæiske Lægemiddelagentur, EMA)** | 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 |



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| | |
|---|---|
| **Andre godkendte terapeutiske indikationer** | ▪ KEYTRUDA som monoterapi er indiceret til behandling af fremskredent (inoperabelt eller metastatisk) melanom hos voksne.<br>▪ KEYTRUDA som monoterapi er indiceret til adjuverende behandling af voksne med stadie III-melanom og lymfeknudeinvolvering, som har fået foretaget komplet resektion<br>▪ KEYTRUDA som monoterapi er indiceret til førstelinjebehandling af metastatisk NSCLC hos voksne, hvis tumorer udtrykker PD-L1 med tumor proportion score (TPS) ≥ 50% uden EGFR- eller ALK-positive mutationer i tumor.<br>▪ KEYTRUDA i kombination med pemetrexed og platinbaseret kemoterapi er indiceret til førstelinjebehandling af metastatisk ikke-planocellulær NSCLC hos voksne uden EGFR- eller ALK-positive mutationer i tumorer.<br>▪ KEYTRUDA i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel er indiceret til førstelinjebehandling af metastatisk planocellulær ikke-småcellet lungekræft hos voksne.<br>▪ KEYTRUDA som monoterapi er indiceret til behandling af lokalt fremskredent eller metastatisk NSCLC hos voksne efter tidligere behandling med minimum én kemoterapi, og hvis tumorer udtrykker PD-L1 med TPS ≥1%. Patienter med EGFR- eller ALK-positive mutationer i tumor bør også have været i targeteret behandling inden behandling med KEYTRUDA.<br>▪ KEYTRUDA som monoterapi er indiceret til behandling af recidiverende eller refraktært klassisk Hodgkins lymfom (cHL) hos voksne, som har oplevet svigt af autolog stamcelletransplantation (ASCT) og svigt af behandling med brentuximab vedotin (BVsvigt), eller som er uegnede til transplantation og har oplevet svigt af behandling med BV.<br>▪ KEYTRUDA som monoterapi er indiceret til behandling af lokalt fremskredent eller metastatisk urotelialt karcinom hos voksne, som tidligere har fået platinbaseret kemoterapi.<br>▪ KEYTRUDA som monoterapi er indiceret til behandling af lokalt fremskredent eller metastatisk urotelialt karcinom hos voksne, som er uegnede til cisplatinbaseret kemoterapi, og hvis tumorer udtrykker PD-L1 med en kombineret positiv score (CPS) ≥10.<br>▪ KEYTRUDA som monoterapi eller i kombination med platinbaseret kemoterapi og 5- fluorouracil (5-FU) er indiceret til førstelinjebehandling af metastatisk eller inoperabelt recidiverende planocellulært hoved-hals karcinom (HNSCC) hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥1<br>▪ KEYTRUDA som monoterapi er indiceret til behandling af recidiverende eller metastatisk HNSCC hos voksne, hvis tumorer udtrykker PD-L1 med TPS ≥50% og med sygdomsprogression under eller efter platinbaseret kemoterapi<br>▪ KEYTRUDA, i kombination med axitinib er indiceret til førstelinjebehandling af fremskredent renalcellekarcinom (RCC) hos voksne<br>▪ KEYTRUDA som monoterapi er indiceret til førstelinjebehandling af metastatisk kolorektal cancer med høj mikrosatellitinstabilitet (MSI-H) eller mismatch repair-defekt (dMMR) hos voksne<br>▪ KEYTRUDA, i kombination med platin- og fluoropyrimidinbaseret kemoterapi, er indiceret til førstelinjebehandling af 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<br>▪ KEYTRUDA, i kombination med kemoterapi, er indiceret til behandling af lokalt recidiverende inoperabel eller metastatisk triple-negativ brystkræft hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10 og som ikke har fået forudgående kemoterapi for metastatisk sygdom<br>▪ KEYTRUDA, i kombination med lenvatinib, er indiceret til førstelinjebehandling af fremskredent renalcellekarcinom hos voksne<br>▪ KEYTRUDA, i kombination med lenvatinib, er indiceret til behandling af fremskreden eller recidiverende endometriecancer hos voksne med sygdomsprogression under eller efter tidligere behandling med |



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| Oversigt over lægemidlet | |
|---|---|
| | platinbaseret terapi i enhver setting, og som ikke er kandidater til kurativ operation eller strålebehandling<br>▪ KEYTRUDA som monoterapi er indiceret til behandling af følgende tumorer med MSI H eller dMMR hos voksne med:<br>○ inoperabel eller metastatisk kolorektal cancer efter tidligere fluoropyrimidinbaseret kombinationsbehandling;<br>○ fremskreden eller recidiverende endometriecancer med sygdomsprogression under eller efter tidligere behandling med platinbaseret terapi i enhver setting, og som ikke er kandidat til kurativ operation eller strålebehandling;<br>○ inoperabel eller metastatisk ventrikelkræft, tyndtarmskræft eller galdevejskræft med sygdomsprogression under eller efter mindst en forudgående behandling<br>▪ KEYTRUDA, i kombination med kemoterapi med eller uden bevacizumab, er indiceret til behandling af persisterende, recidiverende eller metastatisk cervixcancer hos voksne, hvis tumorer udtrykker PD L1 med CPS ≥ 1. |
| **Vil udlevering være begrænset til hospitaler?** | Ja, udleveringsgruppe: BEGR |
| **Kombinationsbehandling og/eller co-medicinering** | Nej |
| **Emballage – typer, størrelser/antal enheder og koncentrationer** | Styrke: 100 mg<br>KEYTRUDA 25 mg/ml koncentrat til infusionsvæske, opløsning.<br>Et hætteglas med 4 ml koncentrat indeholder 100 mg pembrolizumab.<br>Hver ml koncentrat indeholder 25 mg pembrolizumab.<br>Pakning: 1 stk. konc.t.inf.væske. |
| **Orphan drug status** | Nej |

## 2. Forkortelser

| | |
|---|---|
| *AE* | *Adverse event* |
| *AEOSI* | *Adverse event of special interest* |
| *AIP* | *Apotekets indkøbspris* |
| *ARR* | *Absolut Risiko Reduktion* |
| *APaT* | *All patients as treated* |
| *BICR* | *Blinded independent central review* |
| *ccRCC* | *Clear cell renal cell carcinoma* |
| *CHMP* | *Committee for Medicinal Products for Human Use* |
| *CI* | *Confidence Interval* |
| *CPS* | *Combined Positive Score* |
| *DaRenCa* | *Dansk Renal Cancer Gruppe* |
| *DF* | *Disease-free* |
| *DFS* | *Disease-free survival* |
| *ECOG PS* | *Eastern Cooperative Oncology Group performance status* |
| *EPAR* | *European Public Assessment Report* |
| *EQ-5D* | *EuroQol-5D* |
| *EMA* | *European Medicines Agency* |
| *EORTC* | *European Organisation for Research and Treatment of Cancer* |



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| | |
|---|---|
| *FA* | *Final Analysis (endelig analyse)* |
| *HR* | *Hazard Ratio* |
| *HRQoL* | *Hazard Related Quality of Life* |
| *IA* | *Interim Analysis (Interimanalyse)* |
| *ICER* | *Inkrementel omkostningseffektivitets-ratio* |
| *IHC* | *Immunohistochemistry (immunhistokemi)* |
| *IQR* | *Interquartile range* |
| *ITT* | *Intention to treat* |
| *IV* | *Intravenøst* |
| *KM* | *Kaplan-Meier* |
| *KN564* | *KEYNOTE-564* |
| *LR* | *Locoregional recurrence* |
| *N/A* | *Not applicable* |
| *OR* | *Odds ratio* |
| *ORR* | *Objective Response Rate* |
| *OS* | *Overall Survival* |
| *PD* | *Progressive Disease* |
| *PD-L1* | *Programmed Death Ligand -1* |
| *PF* | *Progression Free* |
| *PFS* | *Progression Free Survival (Progressionsfri overlevelse)* |
| *PICO* | *Population Intervention Comparator Outcome (spørgsmål baseret på population, intervention, komparator og effektmål)* |
| *RCC* | *Renal cell carcinoma* |
| *RECIST* | *Response Evaluation Criteria in Solid Tumors* |
| *RR* | *Relative risk (relative risiko)* |
| *SAE* | *Serious adverse event (alvorlig uønsket hændelse)* |
| *TKI* | *Tyrosine kinase inhibitors (tyrosin kinase hæmmer)* |
| *TRAE* | *Treatment related adverse event* |
| *TTD* | *Time To Deterioration* |

**Markeret med gult i ansøgningen er konfidentielt**

# 3. Tabeller og figurer

### Liste over figurer





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## Liste over tabeller





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# 4. Resumé

Adjuverende behandling til clear celle renalcelle carcinom (ccRCC)-patienter efter nefrektomi er et udækket medicinsk behov. Over 30% af RCC patienter behandlet med kurativt intenderet kirurgi oplever recidiv indenfor 3 år. Recidiv leder oftest til dødelig metastatisk sygdom og medfører en 3-dobbelt forøgelse af risikoen for død, signifikant forkortet overlevelse, samt symptomer og forværret livskvalitet og potentiel tab af arbejdsevne. En behandling, der med relativt få bivirkninger kan reducere recidivraten, vil have en signifikant effekt på RCC patienters liv og prognose og generelt for behandlingen af denne sygdom i Danmark.

**Indikation og population**

Indikation i denne ansøgning er pembrolizumab som monoterapi til adjuverende behandling af voksne RCC-patienter med øget risiko for recidiv efter nefrektomi, eller efter nefrektomi og radikal resektion af syn- eller metakrone metastatiske læsioner, også kaldet M1 no evidence of disease (NED) (2) . Risikogrupperne for recidiv efter nefrektomi er defineret i Figur 3.



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## Prespecified Disease Risk Categories

| Intermediate-High Risk | | High Risk | | M1 NED |
|---|---|---|---|---|
| pT2 | pT3 | pT4 | Any pT | |
| Grade 4 or sarcomatoid | Any grade | Any grade | Any grade | NED after resection of oligometastatic sites ≤1 year from |
| N0 | N0 | N0 | N+ | |

**Figur 1 Risikogrupper der indgik i KEYNOTE-564 studiet vedr. adjuverende behandling med pembrolizumab (2)**

Ansøgningen baserer sig på resultater fra KEYNOTE-564 (herefter KN564), et dobbeltblindet randomiseret fase III studie, der er designet til at undersøge effekten af adjuverende pembrolizumab efter nefrektomi af RCC patienter i øget risiko for recidiv (2). Opfølgningen i KN564-studiet fortsætter indtil en estimeret endelig slutdato ultimo 2025. Ansøgningen til både EMA og nærværende Medicinrådsansøgning omhandler ITT-populationen baseret på ovenstående risikogrupper med øget risiko for recidiv efter nefrektomi, jf. **Error! Reference source not found.**. MSD modtog positive opinion fra CHMP 17. december 2021 og Commission Decision fra EU i januar 2022.
Hele populationen, der indgik i KN564, havde alle fået foretaget nefrektomi grundet lokaliseret, lokoregional eller lokalavanceret clearcelle renalcellekarcinom (herefter betegnet ccRCC), eller nefrektomi med metastasektomi for syn-/metakron oligometastatisk RCC med metastasektomi ≤1 år fra nefrektomi. Negative resektionsrande kræves for både primære og metastatiske læsioner og intet tegn på sygdom efter investigator-evaluering ved opstart af adjuverende pembrolizumab.

Den undersøgte population med øget risiko for recidiv efter kirurgi i KN564 er baseret på tidligere og nuværende adjuverende studier samt tilgængelig videnskabelig litteratur og kliniske ekspertudsagn (3-7). Der findes flere forskellige nomogrammer og modeller til at vurdere RCC-patienters risiko for recidiv efter nefrektomi, og det har derfor været målet i KN564 at anvende inklusionskriterier, der selekterede for patienter med øget risiko for recidiv og som derved har et reelt behov for en ny behandlingsmulighed samtidigt med at holde kriterierne simple og brede nok til ikke at fratage relevante patienter muligheden for at blive inkluderet. Det patologiske T-stadie udgør rygraden i disse inklusionskriterier, og tumorstørrelsen efter nefrektomi har også vist sig at være en af de vigtigste parametre til at forudsige recidivraten (8). En stor del af alle nefrektomerede RCC-patienter får et senere tilbagefald af sygdommen afhængigt af hvilken risikogruppe de tilhører. Når sygdommen først er manifesteret i den metastatiske fase anses den for uhelbredelig for langt størstedelen og medfører som følge heraf en kraftig reduktion i forventet levetid (6). I Danmark ved vi fra et enkeltcenterstudie, at 5-års recidivraten var 22% af alle diagnosticerede RCC-patienter (inklusive patienter med både høj og lav risiko for recidiv) (9), og i den seneste nationale danske årsrapport ligger den 3-årige recidivrate for alle RCC-patienter behandlet kirurgisk med kurativt sigte på 32% (10, 11). Disse opgørelser inkluderer både lav-, intermediær- og høj-risikopatienter og altså en bredere population med en lavere forventet recidivrate end populationen i KN564. Recidivraten i en dansk population selekteret ud fra inklusionskriterierne fra KN564 vil derfor forventes at have en højere recidivrate end de ovennævnte tal fra DaRenCas årsrapport og enkeltcenterstudiet af alle risikogrupper. Dette understøttes af et andet dansk studie, der viste at 30-50% af patienter behandlet for RCC med kurativt intenderet kirurgi senere udviklede metastaser (12, 13). **Det er således afgørende for et adjuverende studies berettigelse, at der defineres en patientgruppe med en tilstrækkelig høj risiko for recidiv. Dette er tilfældet i KN564.**

Årligt ny-diagnosticeres globalt ca. 400.000 personer med RCC, hvilket udgør ca. 2% af verdens cancertilfælde. Der ny-diagnosticeres ca. 1.000 patienter med renalcellecarcinom (RCC) årligt i Danmark, hvilket udgør 2-3% af alle ny-diagnosticerede kræfttilfælde (11). Omkring 150 patienter er metastatiske på diagnosetidspunktet (13). Der ses en



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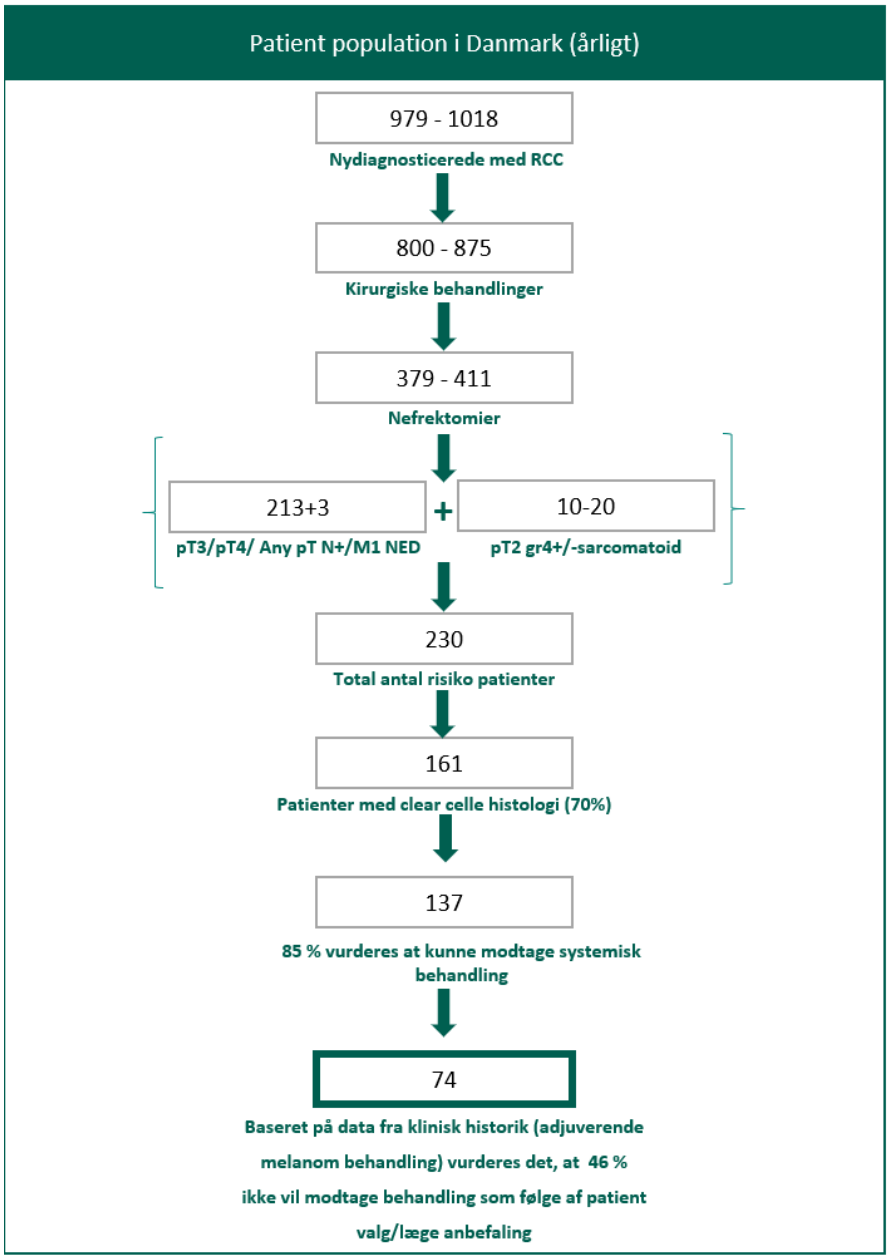
overvægt af mænd i forhold til kvinder (ratio 2:1) (11). I Danmark forventes 74 patienter årligt at være kandidater til adjuverende behandling med pembrolizumab, ud fra antagelserne i Figur 4 (se detaljeret beskrivelse i afsnit 5.2.1).




**Figur 2 Patienter der forventes at være kandidater til adjuverende behandling med pembrolizumab**

**Intervention**

Interventionen i denne ansøgning er adjuverende Pembrolizumab 200 mg givet hver 3. uge eller 400 mg. hver 6. uge ved intravenøs infusion i op til 17 serier (9 serier ved 6-ugers dosering) eller 1 år efter nefrektomi eller nefrektomi med radikal resektion af metastaser. Pembrolizumab har, i kombination med VEGF tyrosinkinasehæmmerne axitinib og lenvatinib været brugt til metastatiske RCC patienter siden hhv. 2019 og 2021 (14), og pembrolizumab som monoterapi



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har også vist effekt i metastaserende RCC patienter i KEYNOTE-427 (15) Foruden pembrolizumab findes der pt. ingen godkendte adjuverende behandlinger til nefrektomerede RCC patienter i Europa. Baseret på resultaterne fra KN564 er adjuverende pembrolizumab godkendt i bl.a. USA, EU, Brasilien og Storbritannien. Adjuverende pembrolizumab i KN564 modtog også en ESMO magnitude of clinical benefit score (MCBS) på A, som er den højest mulige score for kurative behandlinger, og adjuverende pembrolizumab er nu desuden inkluderet i de kliniske retningslinjer fra bl.a. NCCN, EAU og ESMO (16-19). Derudover er det svenske NT kommet med en anbefaling om, at RCC-patienter tilhørende de inkluderede risikogrupper fra KN564 bør behandles med adjuverende pembrolizumab (20). **Pembrolizumab er således den første mulighed for medicinsk at kunne behandle RCC patienter med henblik på klinisk betydningsfuldt at reducere risikoen for recidiv og derved uhelbredelig metastatisk sygdom.**

**Komparator**

Komparatoren i KEYNOTE-564 er placebo, og denne komparator er valgt, da der ikke findes en EMA-godkendt eller globalt accepteret adjuverende behandling til nærværende patientpopulation, og internationale guidelines har indtil udgivelsen af KN564 henvist til kirurgi og ingen medicinsk behandling til nærværende patientpopulation. De danske kliniske retningslinjer beskriver således kirurgi (radikal eller partiel nefrektomi med evt. radikal resektion af metastaser eller evt. cryoterapi/ablation ved mindre tumorer) med forskellig hyppighed i opfølgning ved scanning afhængig af patientens risiko for recidiv (hyppigere scanning ved højere risiko) (13). **Komparatoren i KN564 svarer således til dansk klinisk praksis.** (16-20)

**Baggrund for valg af DFS som primært endepunkt**

Den relative 5-års overlevelse (OS) for ny-diagnosticerede danske RCC patienter er for T2, T3 og T4 er hhv. 74%, 60% og 8% (11). Grundet det store antal medicinske onkologiske behandlingsmuligheder til metastatiske patienter, vil OS for nefrektomerede ccRCC patienter, der modtager adjuverende pembrolizumab, være et udtryk for dels effekten fra den adjuverende behandling, og dels effekten af de efterfølgende behandlinger i tilfælde af recidiv. Til gengæld repræsenterer DFS effekten af den *aktuelle* behandling. DFS har endvidere vist en god korrelation til OS ligesom patienter med recidiv har signifikant kortere OS end patienter uden recidiv (21, 22). OS som primært endepunkt er ikke anbefalet af eksempelvis FDA som primært endepunkt i adjuverende RCC kliniske trials, men derimod DFS, der også indgår som primært endepunkt i de fleste afsluttede og igangværende kliniske afprøvninger af adjuverende behandlinger til RCC (23, 24). I takt med, at antallet af behandlingslinjer, der kan tilbydes ved metastatisk sygdom stiger, vil data på overlevelse (OS) for en adjuverende behandling udvandes. Investigator-evalueret DFS blev i KN564 valgt frem for blindet centralt review (blinded independent central review; BICR) for at lægge studiets primære endepunkt tæt op ad daglig klinisk praksis. Det er af stor klinisk betydning at forebygge recidiv, da recidiv forringer prognosen markant, leder til medicinsk onkologisk behandling, medfører symptomer, bivirkninger, tab af livskvalitet, samt risiko for yderligere kirurgi og signifikant forkortet OS. Samfundsmæssigt er en reduktion af recidiv også en fordel grundet den økonomiske byrde dels af efterfølgende medicinske og kirurgiske behandlinger, men også tabt arbejdsfortjeneste og øgede sygepensioner. Hurtig sygdomsprogression og død efter tilbagefald kan forekomme hos nogle patienter, og f.eks. beskriver melanompatienter selv risikoen for tilbagefald som en vigtig følelsesmæssig og psykologisk stressfaktor efter operation (25) (26). **DFS er således det mest klinisk relevante og meningsfulde endepunkt til et studie af adjuverende behandling, da det retvisende anskueliggør effekten af den aktuelle adjuverende behandling til ccRCC patienter og samtidigt ikke er forurenet af effekten af efterfølgende behandlingslinjer.**

**Vigtigste resultater fra primære og sekundære endepunkter**

I denne ansøgning indgår data fra 2 forskellige data cutoffs: Interrim analyse 1 (IA1) med data cutoff 14/12/2020 samt en opdateret analyse efterspurgt af EMA med 6 måneders yderligere opfølgning (data cutoff 14/07/2021). Se oversigten i tabel 1. Det primære endepunkt i KN564 viser ved IA1, at adjuverende behandling med pembrolizumab medfører en



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signifikant forbedring af DFS sammenlignet med placebo (HR=0.68 [95% CI, 0,53-0,87]). 24-måneders DFS raten er 77,3% for pembrolizumab og 68,1% for placebo, udgjort af 109 events i pembrolizumab-gruppen og 151 events i placebo-gruppen (2). I den opdaterede analyse efterspurgt af EMA med 6 måneders ekstra opfølgning styrkes resultaterne yderligere for ITT-gruppen med en HR på 0,63 (95% CI 0,50-0,80),p <0,0001 (27). Her ses 114 events i Pembrolizumab-gruppen, mod 169 events i placebo-gruppen med en 24 måneders recidivrate på hhv. [redacted] og [redacted] Altså en relativ reduktion i risikoen for recidiv på hhv. 32% og 37% efter adjuverende pembrolizumab behandling efter 24 og 30 måneders opfølgning, og en absolut risikoreduktion på hhv. 9,2% og 11% ved de to tidspunkter.

Ved IA1 blev DFS-effekten vist for både M0 og M1 subpopulationerne. Således ses patienterne, der både fik foretaget nefrektomi samt radikal resektion af oligometastaser (M1 NED), og som forventes at have høj risiko for recidiv (28) også at have en betydelig effekt af adjuverende pembrolizumab (HR 0,29 [0,12-0,69]). Det er dog vigtigt at notere sig, at M1 NED kun udgjorde ca. 6% af den samlede patientpopulation i KN564 med 26 DFS events, og at M0-subgruppen behandlet med adjuverende pembrolizumab i sig selv viste en tydeligt forbedret DFS vs. placebo (HR 0,74 [0,57-0,96]) med 234 DFS events. Således udgør M0-gruppen langt de fleste events for DFS.

Ved den opdaterede EUR analyse med 6 måneders ekstra opfølgning blev en post hoc analyse foretaget, hvor DFS effekten blev opdelt for hhv. M0 intermediær/høj, M0 høj risiko samt M1 NED subpopulationerne. M1 NED havde fortsat en betydelig effekt på DFS (HR=0,28, 95% CI 0,12-0,66, n=58). M0 intermediær-høj risiko- (HR=0,68, 95% CI 0,53-0,88, n=855) og M0 høj risikogruppen (HR=0,60, 95% CI 0,33-1,1, n=76) (29) havde begge en klar effekt på DFS. Således udgør M0 intermediate-high risk gruppen 86% af hele studiepopulationen, og tallene her viser, at det ikke er én subgruppe, som trækker resultaterne for ITT-populationen, men at behandlingen derimod har effekt hos alle de undersøgte risikogrupper.

Ved både IA1 og de 6 ekstra måneders opfølgning efterspurgt af EMA (EUR) var analysen af overordnet overlevelse (OS) ikke moden. Således var hhv. 26% og 33% af de estimerede 200 OS-hændelser til den endelige OS-analyse indtruffet ved hhv. IA1 og EUR-dataskæringerne (2, 27). Trods de umodne OS-data var der en klar trend mod en effekt på overlevelse med en risikoreduktion på 46% for død (HR=0,54, 95% CI 0,30-0,96, nominel p=0.016) ved adjuverende behandling med pembrolizumab versus placebo ved IA1 (2). Dette anskueliggøres også ved næsten dobbelt så mange dødsfald i placebogruppen som pembrolizumab gruppen (33 vs. 18). Efter yderligere 6 måneders opfølgning var HR styrket yderligere til 0,52 (95% CI 0,31-0,86, nominel p=0,0048) med 10 nye dødsfald i placebogruppen mod 5 i pembrolizumab gruppen (i alt 43 vs. 23). Den endelige analyse for OS forventes i 2024-2025. Til at støtte op om en evt. effekt på overordnet overlevelse findes en post hoc opgørelse over PFS2, altså progression på næste linje behandling efter recidiv i den europæiske assessment report (EPAR (29)). Grundet dens post hoc natur og det stadig relativt lave antal hændelser, er denne analyse ligesom overlevelsesanalysen præmatur, men der ses igen en klar trend mod forbedret PFS på næste påbegyndte behandling efter recidiv hos de patienter der oprindeligt blev behandlet med adjuverende pembrolizumab overfor placebogruppen (HR=0,52 95% CI 0,34-0,81, nominel p=0,0018). Dette taler imod den potentielle bekymring for, at adjuverende behandling muligvis vil nedsætte effekten af efterfølgende behandling til metastatiske patienter og indikerer derimod en langtidseffekt af den adjuverende behandling med pembrolizumb. **Det kan derfor konkluderes, at adjuverende behandling med pembrolizumab til RCC patienter efter nefrektomi signifikant reducerede risikoen for recidiv (HR=0,63) og dermed de symptomer, forværret QoL og ringere overlevelse, der følger et recidiv på tværs af alle subgrupper. Desuden ses en klar trend mod både forbedret OS og PFS på næste påbegyndte behandling efter recidiv. En samlet oversigt over de vigtigste resultater fra de to opfølgningstidspunkter (IA1 og EUR) kan ses i tabel 1.**

**Tabel 1 Oversigt over vigtigste endepunkter fra de to data cutoffs anvendt i denne ansøgning (IA1 og EUR)**

| | Interim analyse 1 (IA1)<br>Reference: (29) | EMA efterspurgt +6 måneder (EUR).<br>Reference: (1) medmindre andet angives |
|---|---|---|



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| | | | | |
|---|---|---|---|---|
| Behandlingsgruppe | Pembrolizumab | Placebo | Pembrolizumab | Placebo |
| Median opfølgning (mdr.) | 24,1 | | 30,1 | |
| Data cutoff | 14. December 2020 | | 14. Juni 2021 | |
| DFS (95%CI) | HR=0.68 (0,53-0,87), p=0,001 | | HR=0,63 (0,50-0,80), p=0,0001 | |
| 24 mdr. DFS rate (total events) | 77,3% (109) | 68,1% (151) | [redacted] (114) Ref(30) | [redacted] (169) Ref(30) |
| DFS risikosubgrupper præsenteret | M0 vs M1 | | M0 intermediær/høj, M0 høj risiko samt M1 NED | |
| OS (95%CI) | HR=0,54, (0,30-0,96), p=0,0164[a] | | 0,52 (0,31-0,86), p=0,0048[a] | |
| 24 mdr. OS rate (total events) | 96,6% (18) | 93,5% (33) | 96,2% (23) Ref(29) | 93,8% (43) Ref(29) |
| Nye OS events siden IA1 | N/A | | 5 | 10 |
| OS modenhed ifht. final analysis | 26% (51/200 events) | | 33% (66/200 events) | |
| 24 mdr. DFS rate: lokal recurrence/DRSS1 (total events)* | 3,4% (17) | 6,6% (32) | [redacted] | [redacted] |
| 24 mdr. DFS rate: visceral recurrence/DRSS2 (total events)* | 19,8 (94) | 28,2 (134) | [redacted] | [redacted] |
| PFS2 (95% CI) | HR=0,52 (0,34-0,81), p=0,0018 | | HR=0,57 (0,39-0,85), p ikke opgivet | |
| 30 mdr. PFS2 rate | 93,1% (30) | 85,7% (56) | Ikke opgjort | Ikke opgjort |
| Gr. ≥3 TRAE** | 18,9% (92) | 1,2% (6) | Ikke opgjort | Ikke opgjort |
| Alvorlige TRAE** I % (events) | 12% (59) | <1%% (1) | 12% (59)*** | <1% (1)*** |
| AE der ledte til behandlingsstop | 20,7% (101) | 2% (10) | 21% (105) | 2% (11) |
| Behandlingsrelaterede dødsfald | 0% (0) | 0% (0) | 0% (0) | 0% (0) |
| Livskvalitet (PRO) | Opgjort | | Ikke opgjort | |

[a]Krydsede ikke den præspecificerede p-værdi på 0,000095 for OS. *HR ikke beregnet for lokal/visceral recidiv. Lokal recidiv eksluderede lokale recidiver med samtidig forekomst af fjernmetastatisk recidiv, mens fjernmetastisk recidiv inkludere samtidig lokalt recidiv (~5%). ** TRAE, treatment-related adverse events. ***, adverse events blev opgjort og præsenteret ved forekomst <90 dage efter sidste dosis, og denne periode var opnået for stort set alle patienter ved IA1, derfor som ventet ingen ændring ved 6 måneders ekstra opfølgning.

**Bivirkninger**

Bivirkninger rapporteres hos patienter, som har modtaget minimum én dosis studiemedicin (All Patients as Treated (ApaT) population), hvilket svarer til 488 patienter i pembrolizumab-gruppen og 496 patienter i placebogruppen (2). Den mediane behandlingslængde var 11,1 måned og ens for begge grupper svarende til mediant 17 modtagne doser, og det er derved lige lang tid, bivirkninger kan opstå under eksponering i de to grupper. Dette gjaldt for begge tidspunkter rapporteret (IA1 og EUR).

Overordnet gennemførte hhv. 298/488 (61%) patienter pembrolizumab-behandlingen, mens 365/496 (73,7%) patienter gennemførte placebo-behandlingen. [redacted] patienter afbrød behandling med pembrolizumab pga. en bivirkning mens 10 patienter (2,0%) afbrød placebo pga. bivirkninger. I den forbindelse skal det bemærkes, at hos bl.a. NSCLC og RCC patienter har immunrelaterede bivirkninger ved behandling med immunterapi været associeret med bedre antitumor-respons (31). Hovedparten af bivirkninger, der ledte til behandlingsafbrydelse i begge grupper, var karakteriseret som ikke alvorlige. Den mediane behandlingslængde for de [redacted] pembrolizumab patienter, der afbrød behandling, modtog gennemsnitligt 7 cykler (range, 1-16) med en median behandlingslængde på 4,4 måneder.



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Hhv. 96,3% og 91,1% af patienterne i pembrolizumab og placebo grupperne oplevede mindst én bivirkning uanset grad, mens 32,4% og 17,7% af patienterne i hhv. pembrolizumab/placebo grupperne oplevede bivirkninger af grad 3-5. De mest almindelig bivirkninger uanset grad i begge grupper var fatigue, diarré, kløe (pruritus), og artralgi. Bivirkningerne med størst risikoforskel var hypotyroidisme, hypertyroidisme, kløe (pruritus) og udslæt. Det er i den forbindelse væsentligt at bemærke, at der ikke blev registeret nogle behandlingsrelaterede dødsfald. 79,1% og 53,4% af patienterne i hhv. pembrolizumab- og placebo-grupperne oplevede behandlingsrelaterede bivirkninger af enhver grad, mens 18,9% af patienterne i pembrolizumab-gruppen, og 1,2% i placebo-gruppen oplevede en behandlingsrelateret grad 3-4 bivirkning, altså en absolut forøgelse på 17,7% for pembrolizumab versus placebo.

20,5% og 11,3% i pembrolizumab- og placebogruppen havde mindst én alvorlig bivirkning (serious adverse event; SAE), og det tilsvarende tal for alvorlige behandlingsrelaterede bivirkninger var hhv. 12,1% og 0,2%. Immunrelaterede bivirkninger (præspecificeret af MSD) af enhver grad og uden stillingtagen til sammenhæng med behandling forekom i 34,6% og 5,8% i pembrolizumab- hhv. placebo-gruppen. Immunrelaterede bivirkninger af grad 3-4 sås hos 8,6% og 0,6% i patienter behandlet med pembrolizumab vs. placebo. Der forekom ikke nogle dødsfald pga. immunmedierede bivirkninger. Steroid-brug blev opgjort fra patienterne blev randomiseret og til de udgik af studiet. 7,4% af patienter i pembrolizumab-gruppen og 0,6% i placebogruppen modtog høj-dosis corticosteroider (>40 mg pr. dag) mod immunrelaterede bivirkninger. Der var minimale forskelle på bivirkningerne rapporteret til de to tidspunkter (IA1 og EUR, se evt. Tabel 1. Ingen nye sikkerhedssignaler kom frem ved den opdaterede EUR analyse med 30,1 måneds opfølgning. **Samlet set kan det konkluderes, at den øgede mængde bivirkninger, der tilføres patienter, som ellers ikke ville være blevet medicinsk behandlet, var håndterbare og som forventet.**

**Livskvalitet**

Livskvalitetsanalyserne blev foretaget med instrumenterne FKSI-DRS og EORTC-QLQ-C30 i KN-564, og prædefinerede værdier (hhv. en forskel på 3 point FKSI-DRS og 10 for EORTC QLQ-C30 (32-34)) der bl.a. stammer fra de tidligere studier, som var med til at udvikle instrumenterne blev anvendt til at vurdere om eventuelle forskelle i patient reported outcomes (PROs) var klinisk relevante og meningsfulde. De prædefinerede endepunkter var forskel i least-squares means (LSM) fra baseline til uge 52 (behandlingsophør). Studiet viste en forskel på -1,12 (-1,53; -0,71) og -0,45 (-0,84;-0,05) LSM for hhv. pembrolizumab og placebo for FKSI-DRS, altså en lille negativ ændring for sygdomsrelaterede symptomer for begge grupper, som ansås for ikke at være klinisk meningsfuld forskellig fra hverken baseline til uge 52 eller mellem grupperne, og langt fra den kliniske meningsfulde forskel på 3 point. For EORTC QLQ-C30 Global Heath Status/QoL blev en forskel på -4,25 (-6,32; +2,19) vs. -1,68 (-3,69; 0,32) observeret i hhv. pembrolizumab- og placebogrupperne. Igen blev forskellene indenfor grupperne fra baseline til uge 52 samt forskellene mellem grupperne ikke anset for at være klinisk meningsfuld og var væsentligt under grænsen for klinisk meningsfuld forskel på 10. Overordnet set viste livskvalitetsanalyserne i mellem pembrolizumab og placebo, på trods af behandling med pembrolizumab i mediant 17 cykler/11,1 måneder, blot marginalt lavere værdier i pembrolizumab-gruppen, der ikke blev vurderet til at være af klinisk betydning for patienterne. Over 90% af alle patienter besvarede livskvalitetsskemaerne ved baseline, og 62,1%-66,5% besvarede efter 1 år. Dette må anses for en høj tilslutning, hvilket øger validiteten af data for livskvalitet. **Disse resultater viser, at bivirkningsprofilen af adjuverende pembrolizumab var acceptabel fra patienternes synspunkt, som også har været tilfældet ved adjuverende pembrolizumab behandling indenfor andre cancertyper, herunder bl.a. melanom (35). Det må anses for en stor styrke i dette studie, at livskvaliteten ikke forværres som følge af adjuverende pembrolizumab.**

**Den sundhedsøkonomiske analyse**



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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 (disease-free (DF), locoregional recurrence (LR), distant metastases (DM), og death (D)), som gør det muligt at kunne følge sygdomsforløbet, ekstrapolere udover den 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 41,1 år (livstid). Nytteværdien til måling af den sundhedsrelaterede livskvalitet er baseret på EQ-5D-5L data tilgængelig direkte fra KN564-studiet og danske præferencevægte. De statistisk signifikante kliniske resultater på DFS understøtter estimaterne af merværdi i vores sundhedsøkonomiske model med en gevinst på 1,28 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 148.798 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 148.798 kr., men **resultatet understøtter, at der er et rimeligt forhold mellem effekt og omkostninger ved ibrugtagning af pembrolizumab til adjuverende behandling af ccRCC patienter, da denne ligger markant lavere end tidligere godkendte Medicinrådsanbefalinger.**

**Kliniske og patientrelaterede overvejelser til brug for kategorisering af merværdi**

RCC er overordnet set ikke følsom overfor konventionel stråle- og kemoterapi. RCC tumorceller deler sig langsomt og for den type, som denne ansøgning omhandler, nemlig clear celle RCC, gælder, at den har en høj grad af fedtmetabolisme (navnet *clear celle* deriveres af en klar fremtoning i mikroskop grundet højt lipidindhold i RCC-celler) (36). Der er således tale om en speciel tumortype med få behandlingsprincipper. I de sidste ca. 15 år har grundstenen i medicinsk behandling af ccRCC været at modvirke angiogenese via VEGF-targeteret behandling med tyrosinkinasehæmmere (TKIere). VEGF-drevet angiogenese er central for ccRCC tumorvækst og en hæmning deraf har vist sig effektfuld i forhold til at bremse og hæmme tumorvækst i RCC (37). Metastatisk RCC anses for uhelbredelig, med en lav 5-års overlevelse på blot 13,9% fra et nyligt studie (38). I de seneste år har kombinationsbehandling med immunterapi overtaget grundstenen af systemisk medicinsk behandling til metastatisk RCC med en forbedret effekt sammenlignet med TKI monoterapi, og et deraf følgende øget antal langtidsoverlevere (39-42).

Tidligere stadier af sygdommen behandles kirurgisk eller ablativt, men med varierende risiko for tilbagefald for den enkelte patient, og der har som tidligere nævnt indtil nu ikke været en global accepteret adjuverende behandling, der kan nedsætte risikoen for recidiv efter kirurgisk behandling. Sunitinib er ganske vist godkendt i USA til adjuverende behandling efter nefrektomi på baggrund af S-TRAC studiet (43), men da sunitinib fejlede i et andet adjuverende forsøg (ASSURE), der også involverede pazopanib (44), har denne behandling ikke vundet bred tilslutning ikke mindst grundet det høje niveau af alvorlige bivirkninger (43, 44). Adjuverende sunitinib er da heller ikke EMA-godkendt (29).

Adjuverende pembrolizumab til patienter med øget risiko for recidiv har en anden virkningsmekanisme end de tidligere adjuverende studier med TKI. TKI'ere hæmmer som nævnt angiogenese og mindsker derigennem tilgangen af næringsstoffer til en voksende tumor. Dette er vigtigt for tumorer, når de når en vis størrelse, men efter nefrektomi er det primært mikrometastaser, der menes at være ansvarlige for recidiv. Mikrometastaser må forventes i mindre grad at være afhængige af angiogenese og massiv tilgang af næring til vækst grundet deres begrænsede størrelse og derved samlede energibehov.

Adjuverende pembrolizumab er immunterapi, der ved at blokere interaktionen mellem de hæmmende checkpointreceptorer PD-1 og PD-L1/L2 muliggør at immunsystemet kan starte en reaktion, der ellers ikke ville være



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startet mod RCC kræftcellerne. Immunsystem patruljerer hele kroppen effektivt og vil derfor kunne finde selv mikrometastaser bestående af få celler og helt udrydde dem, frem for blot at bremse deres vækst, som den centrale del af TKI'ernes virkningsmekanisme (37). Desuden forventes en langtidseffekt med immunterapi, hvilket bl.a. understøttes af data fra KEYNOTE-054-studiet blandt patienter med resekteret højrisikostadie III-melanom, hvortil adjuverende behandling med pembrolizumab viser en vedvarende behandlingseffekt på recidivfri overlevelse baseret på median opfølgning på 3,5 år. KEYNOTE-006 studiet, som har den længste opfølgning (median 7 år) fra et fase 3-forsøg med anti-PD-1/L1-behandling for fremskreden melanom, viste lignende resultater (45) (46).

Målet med adjuverende behandling med pembrolizumab er primært at reducere antallet af patienter med tilbagefald efter operation. Herved forlænges den sygdomsfri periode før recidiv for den behandlede population (disease-free survival [DFS]). Ud over at forlænge DFS er det også en ambition for behandling med adjuverende immunterapi at øge antallet af langtidsoverlevere. I den forbindelse er det afgørende at RCC patienter med recidiv har en signifikant dårligere overlevelse sammenlignet med patienter uden recidiv efter nefrektomi. **Opsummerende kan det således konkluderes, at Pembrolizumabs virkningsmekanisme gør det intuitivt velegnet til adjuverende behandling af RCC-patienter og desuden må forventes at have en positiv indvirkning på antallet af langtidsoverlevere.**

**Konklusion**

Patienter med RCC, der har fået foretaget radikal operation, og som har øget risiko for recidiv, har i nuværende dansk klinisk praksis ingen behandlingsmuligheder for at reducere deres risiko for recidiv. Både danske data og data fra KN564 viser, at en væsentlig del af de nefrektomerede RCC-patienter vil opleve recidiv indenfor de første 3 år efter nefrektomi. Eksempelvis er 3-års recidivraterne >30% for danske patienter behandlet med kurativt sigte og tilsvarende oplevede ca. 35% af patienterne i placebogruppen i KN564 recidiv indenfor 3 år (10, 29). Recidiv er forbundet med signifikant forkortet overlevelse, 3-gange højere risiko for død, både betydelig forringelse af patienternes prognose, symptomer og forværret livskvalitet, men også tabt arbejdsevne hos patienterne, og er ligeledes forbundet med store udgifter for sundhedsvæsenet i form af efterfølgende kirurgiske og medicinske behandlinger.

Som tidligere redegjort for, er det primære endepunkt for adjuverende behandling af RCC at signifikant reducere recidivraten. Det lykkedes i KN564-studiet. Der ses en betragtelig og klinisk afgørende risikoreduktion på 37% ved 30-måneders follow-up HR 0.63 (0.50-0.80), p<0.0001. Vi ser i studiet også en klar trend mod forbedret overlevelse, HR 0.52 (0.31-0.86), p<0.005 med 30,1 måneders opfølgning. Også PFS2-data støtter op om effekten på overlevelse, HR 0,52 (0,34-0,81), nominel p=0,0018). De to sidstnævnte HR er også efter 30 måneders follow-up, men dog fortsat præmature.

Slutteligt har behandlingen vist sig veltolereret, hvor der er et forventeligt antal patienter med bivirkninger, hvilket klinikerne i Danmark i dag har stor erfaring med at håndtere (ekspertudsagn), og centralt for studiet, så ses der ingen behandlingsrelaterede dødsfald.

I skrivende stund har flere af de større internationale faglige selskaber allerede anbefalet adjuverende pembrolizumab til nefrektomerede RCC patienter med en forhøjet risiko for recidiv, og behandlingen har yderligere fået den højeste rating (A) på ESMOs "magnitude of clinical benefit scale (MCBS)" for kurative behandlinger. I tillæg til de signifikante kliniske resultater, så estimerer den sundhedsøkonomiske analyse også en favorabel omkostning per vundet kvalitetsjusteret leveår med en ICER på 149.515 kr. sammenlignet med dansk standardbehandling, der tilmeld er markant lavere end tidligere godkendte Medicinrådsanbefalinger.

**Samlet set indikerer den signifikante og kliniske meningsfulde reduktion af risikoen for recidiv, den klare trend mod forbedret overlevelse samt de håndterbare og forventede bivirkninger en stor klinisk merværdi ved adjuverende behandling med pembrolizumab for patienter med ccRCC sammenlignet med nuværende dansk standardbehandling. Samtidig vurderer MSD, at omkostningerne pr. vundet leveår er rimelige set i forhold til effekten.**



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# 5. Patientpopulationen, interventionen og valget af komparator(er)

## 5.1 Sygdommen og patientpopulationen

### 5.1.1 Patofysiologi af nyrekræft

Nyrekræft er en malignitet, der involverer urinsystemet (47). RCC udvikler sig fra foringen af nyrernes tubuli og er den mest almindelige type af nyrekræft, der udgør ca. 90% af alle nyrekræftformer (48).

Cirka 50.000 patienter gennemgår delvis eller total nefrektomi operationer for ikke-transplantationsrelaterede indikationer i USA årligt (49). Det anslås at halvdelen af disse procedurer udføres for at fjerne nyretumorer. I Danmark nefrektomeres ca. 400 RCC patienter årligt (11).

Selvom 75% af nydiagnosticerede patienter potentielt har helbredelig lokaliseret eller lokalt avanceret sygdom[7] ligger postkirurgiske tilbagefaldsrater hos højrisikopatienter med RCC i større undersøgelser på op til 40% på grund af tilstedeværelsen af mikroskopiske tumorer i nyrerne eller mikrometastaser (50, 51), og hos højrisikopatienter med lymfeknudepositiv sygdom er recidivraten 80% (51). Målet med adjuverende behandling er at nedbringe risikoen for recidiv efter operation.

### 5.1.2 Renalcellekarcinom (RCC)

RCC tegner sig for ca. 90% af nyrekræft tilfældene i de danske årsrapporter (48) svarende til ca. 2-3% af alle danske kræfttilfælde (10, 11, 13). Andre typer nyrekræft, der er mindre almindelige, omfatter transition-cellekarcinomer, Wilms-tumorer og nyresarkomer (52). RCC udviser morfologisk heterogenitet, og forskellige morfologiske undertyper af RCC er blevet karakteriseret, herunder: (52)

- Clear celle RCC, som er den mest almindelige form for RCC, udgør ca. 70% til 90% af RCC-tilfældene, og er de patienter der er inkluderet i denne ansøgning
- Non-clear celle RCC, som omfatter en samling af andre undertyper og ikke er så almindelige som clear celle RCC (indgår ikke i denne ansøgning):(53)
    - Papillær RCC, som er den næstmest almindelige form for RCC, og udgør ca. 10% af RCC-tilfældene
    - Kromofob RCC, som tegner sig for ca. 5% af alle RCC'er
    - Sjældne typer RCC, som hver udgør mindre end 1% af alle RCC'er og omfatter: samlerørs RCC, multilokular cystisk RCC, medullært karcinom, mucinøs rørformet og spindelcellekarcinom og neuroblastoma-associeret RCC

### 5.1.3 Stadieinddeling og RCC

AJCC TNM-klassifikationssystemet (8. udgave) bruges til stadieinddeling af nyrekræft, herunder RCC. Følgende er et resumé af AJCC TNM stadieinddelingerne (Tabel 2)(52, 54):

- Stadie I: tumoren er ≤7 cm på tværs og er kun i nyrerne. Der er ingen spredning til lymfeknuder eller fjerne organer
- Stadie II: tumoren er >7 cm på tværs, men er stadig kun i nyrerne. Der er ingen spredning til lymfeknuder eller fjerne organer
- Stadie III: tumoren vokser ind i en større vene (som nyrevenen eller vena cava) eller ind i væv omkring nyrerne, men den vokser ikke ind i binyrerne eller ud over Gerotas fascia. Der er ingen spredning til lymfeknuder eller fjerne organer
- Stadie IV: Primærtumor vokser ud over Gerotas fascia og kan vokse ind i binyrerne oven på nyrerne. Det kan have spredt sig til nærliggende lymfeknuder. Den har ikke spredt sig til fjerne lymfeknuder eller andre organer



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**Tabel 2 AJCC TNM stadieinddeling for nyrekræft (8. udgave) (54)**

| Stage | Stage grouping | Stage description | Included in this application (see fig. 1) |
|---|---|---|---|
| I | T1, N0, M0 | The tumor is 7 cm across or smaller and is only in the kidney (T1)<br>There is no spread to lymph nodes (N0) or distant organs (M0) | No, unless N+ or M1 NED |
| II | T2, N0, M0 | The tumor is larger than 7 cm across but is still only in the kidney (T2)<br>There is no spread to lymph nodes (N0) or distant organs (M0) | Yes (Gr. 4/ sarcomatoid, or if N+ or M1 NED). |
| III | T3, N0, M0 | The tumor is growing into a major vein (like the renal vein or the vena cava) or into tissue around the kidney, but it is not growing into the adrenal gland or beyond Gerota's fascia (T3)<br>There is no spread to lymph nodes (N0) or distant organs (M0) | Yes |
| | T1 to T3, N1, M0 | The main tumor can be any size and may be outside the kidney, but it has not spread beyond Gerota's fascia (T1 to T3)<br>The cancer has spread to nearby lymph nodes (N1) but has not spread to distant lymph nodes or other organs (M0) | Yes |
| IV | T4, Any N, M0 | The main tumor is growing beyond Gerota's fascia and may be growing into the adrenal gland on top of the kidney (T4)<br>It may or may not have spread to nearby lymph nodes (any N)<br>It has not spread to distant lymph nodes or other organs (M0) | Yes |
| | Any T, Any N, M1 | The main tumor can be any size and may have grown outside the kidney (any T)<br>It may or may not have spread to nearby lymph nodes (any N)<br>It has spread to distant lymph nodes and/or other organs (M1) | No, except M1 NED |

### 5.1.4 Kliniske symptomer

Fra DaRenCas kliniske retningslinjer for kirurgi (13):

*"Nyrecancer opdages i stigende grad tilfældigt i forbindelse med anden billeddiagnostisk udredning, da sygdommen oftest er asymptomatisk i de tidlige stadier (55). Hæmaturi ses i cirka 30% af tilfældene og er det hyppigste symptom efterfulgt at flankesmerter. Den tidligere beskrevne klassiske triade, bestående af hæmaturi, palpabel udfyldning og flankesmerter, er i dag sjælden og er ofte forbundet med fremskreden sygdom. De senere stadier er karakteriseret ved uspecifikke symptomer så som træthed, vægttab, påvirket almen tilstand, samt symptomer udløst af metastaser (oftest knogle-, hjerne- og/eller lungemetastaser) (12, 55, 56)). På grund af nyrens endokrine funktion, kan der ved nyrecancer ses en øget produktion af blandt andet en række hormoner, der kan medføre en række paraneoplastiske symptomer. Symptomerne inkluderer blandt andet hypertension, polycytæmi, anæmi, abnorm leverfunktion og neuro- eller myopati (57) og er oftest reversible efter nefrektomi (12, 57-59)." (13)*

Således ses at RCC, især i de fremskredne stadier er en meget alvorlig sygdom med en lang række symptomer og en dertilhørende dårlig prognose. Derudover er den psykologiske og emotionelle frygt for et tilbagefald af stor betydning for kræftpatienter efter kirurgisk behandling (25) (26).

### 5.1.5 Risikofaktorer for udvikling af RCC

De vigtigste veletablerede risikofaktorer for at udvikle RCC er fedme, hypertension og cigaretrygning (48, 53). I et populationsbaseret case-control studie af RCC bestående af 690 patienter i USA blev disse risikofaktorer fundet i ca. halvdelen af alle diagnosticerede tilfælde (60). I Danmark har et studie bl.a. vist at der er en association mellem overvægt i barndommen og senere udvikling af RCC (61).

Der er mange andre risikofaktorer, der kan øge risikoen for at udvikle RCC, herunder:(52)

- Eksponering for cadmium, nogle herbicider og nogle organiske opløsningsmidler



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- Familiehistorie af nyrekræft (uden en kendt arvelig tilstand)
- Eksponering for visse lægemidler, herunder phenacetin og diuretika
- Tilstedeværelse af fremskreden nyresygdom
- Mandligt køn
- Race (afroamerikanere og amerikanske indianere/indfødte i Alaska)
- Genetiske og arvelige risikofaktorer såsom: von Hippel-Lindau sygdom; Arvelig papillær RCC; CPRCC; Birt-Hogg-Dube syndrom; Familiær nyrekræft; Cowden syndrom; Tuberøs sklerose; Arveligt nyre onkocytom

### 5.1.6 Risikofaktorer for recidiv efter nefrektomi hos RCC patienter.

Flere undersøgelser er blevet udført for bedre at forstå risikoen for tilbagefald efter nefrektomi hos patienter med post-nefrektomi RCC. En række risikofaktorer for postkirurgisk recidiv er blevet identificeret. (51, 62-65) Det drejer sig bl.a. om:

- Kvinde vs. mandligt køn(62)
- Historie om delvis nefrektomi vs. ingen historie med delvis nefrektomi(62)
- Historie af laparoskopisk radikal nefrektomi vs. ingen historie med laparoskopisk radikal nefrektomi(64, 66)
- Diagnose af diabetes mellitus vs. ingen diagnose(62)
- Diagnose af hypertension vs. ingen diagnose(62)
- Højt patologisk T-trin vs. lavt T-trin(62)
- Opstaging til pT3a sygdom(65)
- ASA-score (fysisk status og evne til at tolerere kirurgi)(62)
- Clear celle histologi(62)
- BMI ≤20 versus BMI >20(63)
- Lymfeknudepositivitet(67)
- Lavt præoperativt hæmoglobin vs. højt præoperativt hæmoglobin(63)

### 5.1.7 Prognostiske faktorer post nefrektomi RCC

Mens prognostiske faktorer for metastastisk RCC er relativt veldefinerede ved de to prognostiske modeller MSKCC (Memorial Sloan Ketterting Cancer Center; udviklet hos patienter behandlet med IFN (68)) og IMDC (International Metastatic Renal Cell Carcinomar Database Consortium; udviklet med data fra patienter behandlet med VEGF-targeterede TKI'ere (69)), hvor patienter stratificeres i hhv. lav, intermediær og dårlig prognosegruppe (53), så er der større usikkerhed og faglig diskussion når det kommer til at risikostratificere RCC patienters sandsynlighed for recidiv efter nefrektomi. Blandt dem der har gennemgået en nefrektomi for RCC, er væsentlige prognostiske faktorer:

- Tumorstørrelse (≥10 cm)(70)
- Et højt patologisk tumorstadium (vs. tumorstadium pT1a)(70)
- Nuklear uddifferentieringsgrad på enten 3 eller 4 (vs. 1 eller 2)(70)
- Histologisk tumornekrose(70)
- Højt vs. lavt UCLA Integrated Staging System (71, 72)

Udviklingen af nye biomarkører er nødvendig for at forbedre og forene eksisterende prognostiske modeller og igen forbedre overensstemmelsen mellem undersøgelser, der vurderer nye adjuverende behandlinger i RCC. (71)

### 5.1.8 Prognose med nuværende behandlingsmuligheder

Overlevelsen af danske RCC-patienter samlet for alle stadier er betydeligt forbedret de seneste 15 år med en observeret 1 års overlevelse på 89% og en observeret 5 års overlevelse på 63% (samlet for begge køn fra DaRenCas årsrapport 2020). Den relative 5-års overlevelse var i Danmark i 2020 73%/74% for mænd/kvinder (11) mod 39%/44% for mænd/kvinder i perioden 1994-2003 (66). Dette skyldes dels indførelsen af nye behandlinger til metastatiske patienter, forbedret kirurgi og kortere tid mellem diagnose og behandling ved kræftpakkerne. Standardbehandling for lokaliseret og lokalavanceret RCC er i Danmark kirurgi (13), og alle nyrecancer patienters endelige behandling skal



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diskuteres på en multidiciplinær team (MDT) konference (13) (73) (74). Som udgangspunkt skal lokaliseret renalcellekarcinom fjernes kirurgisk når muligt og klinisk relevant. Se afsnit 15.3.1 og Appendiks M, DaRenCa kliniske retningslinjer for kirurgi ved renalcellecarcinom, opsummeret for yderligere information.

Efter kirurgisk fjernelse af tumorvæv ved radikal/partiel nefrektomi (eller ablation ved mindre tumorer, men disse patienter er ikke er inkluderet i KN564-indikationen fra EMA) vurderes patientens risiko for recidiv i Danmark ud fra Leibovich-scoren (som inkluderer tumorstørrelse, patologisk t-stadie, regional lymfeknude status, histologisk gradering og nekrose)(70), samt typen af kirurgisk behandling (partiel/radikal nefrektomi eller ablation), positiv/negativ resektionsrand, spredning til lymfeknuder samt tilstedeværelse af sarkomatoide/rhabdoide træk (13) (Tabel 3)

**Tabel 3 Leibovich score, venstre (50), og opfølgning efter kirurgisk behandling i Danmark ud fra patientens risikoprofil, højre (13).**

| Feature |
|---|
| Primary tumor status (pathologic T stage)[a] |
| pT1a |
| pT1b |
| pT2 |
| pT3a |
| pT3b |
| pT3c |
| pT4 |
| Regional lymph node status (N stage)[a] |
| pNx |
| pN0 |
| pN1 |
| pN2 |
| Tumor size (cm) |
| < 10 |
| ≥ 10 |
| Nuclear grade |
| 1 |
| 2 |
| 3 |
| 4 |
| Histologic tumor necrosis |
| No |
| Yes |

[a] According to the 2002 American Joint Committee on Cancer TNM staging system.[19]

***Opfølgningsprogram***

| Risikoprofil | Behandling | 6 mdr | 12 mdr | 18 mdr | 24 mdr | 30 mdr | 36 mdr | 48 mdr | 60 mdr |
|---|---|---|---|---|---|---|---|---|---|
| **Lav**<br>Leibovich 0-2 og R0 | RN/PN | - | CT | - | - | - | CT | | CT |
| **Mellem**<br>Mindst en af følgende:<br>Leibovich 3-5;<br>PN;<br>Ablation* | RN/PN/ablation* | CT | CT | - | CT | - | CT | CT | CT |
| **Høj**<br>Mindst en af følgende:<br>Leibovich >5;<br>Sarkomatoid/rhabdoid;<br>R-pos;<br>N1 | RN/PN/ablation* | CT | CT | CT | CT | CT | CT | CT | CT |
| **Alle ptt.** | | | | | | | | | CT efter 7 og 9 år |

*Ablation= cryo- og mikrobølgebehandling, og RFA*
**Ved biopsi inden ablation giver Fuhrman grad 1-2 mellem risiko, grad 3-4 høj risiko*
*CT = CT scanning thorax/abdomen; MR scanning som alternativ for CT abdomen, eller FDG PET/CT*
*PN = partiel nefrektomi*
*RN = radikal nefrektomi*
*R0 = negativ resektionsrand*
*R-pos = positiv resektionsrand*
*Leibovich score = summen af 5 histologiske parametre*

Ud fra Leibovich score samt de yderligere ovenfor nævnte faktorer risikostratificeres patienter i Danmark i hhv. lav, mellem og høj risikoprofil i forhold til sandsynligheden for at få recidiv og heraf anvises hvor tæt patienten følges med scanninger efter operation. Jo højere risiko des tættere følges patienten. Stratificeringen og opfølgningen ses i Tabel 3. I nogle tilfælde af solitære metastaser kan resektion og tæt opfølgning overvejes. Ellers er klinisk praksis medicinsk onkologisk behandling med immunterapi, TKI, eller observation.

Patienterne der er inkluderet i KN564 er karakteriseret ved en øget risiko for recidiv, men dog ikke sammenlignelige med den danske definition af høj risiko for recidiv, bl.a. fordi Leibovich score ikke indgik i KN564 (2). Der findes ingen danske studier der præcist beskriver recidivrater og overlevelse af patientpopulationen der indgår i KN564, men andre studier har vist at patienter med øget risiko for recidiv har op imod 40% risiko for at få et recidiv (50, 51). Fra et dansk enkelt-center studie ved vi at 5-års recidivrater for 367 RCC-patienter (inkl. alle histologityper dvs. clear celle og andre) nefrektomeret med kurativt sigte i perioden 2005-2013 var 12,0%, 26,6% og 52,9% for hhv. lav, mellem og høj Leibovich score (9). Recidiv blev her defineret ved både lokalrecidiv i nyren, samt i lymfeknuder og fjernmetastaser. Fra det



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oprindelige studie der udviklede Leibovich-scoren var 5-års recidivrater ca. (aflæst fra graf) 5%, 26% og 67% for lav, mellem og høj Leibovich score (70). Leibovich studiet inkluderede 1671 radikalt nefrektomerede clear-celle RCC patienter i perioden 1970-2000, og recidiv blev defineret som fremkomst af fjernmetastaser men ikke lokalrecidiv.

Af alle RCC-patienter, der gennemgår nyrekirurgi, får 20-80% et senere tilbagefald af sygdommen afhængig af deres risikofaktorer (5). I Danmark ved vi fra det også ovenfor nævnte enkelt-center studie, at ca. 22% af alle diagnosticerede RCC-patienter fik recidiv indenfor 5 år efter operation (9) og i de nationale årsrapporter ligger den 3-årige recidivrate for RCC-patienter behandlet kirurgisk med kurativt sigte på ca. 25-32% (10, 11). 22% af alle diagnosticerede RCC-patienter fik recidiv indenfor 5 år efter operation (9) og i de nationale årsrapporter ligger den 3-årige recidivrate for RCC-patienter behandlet kirurgisk med kurativt sigte på ca. 25-32% (10, 11). Det er vigtigt at understrege, at selvom hovedparten af recidiv efter nefrektomi forekommer indenfor de første 3-5 år, er der også >5 år efter nefrektomi en forøget risiko for recidiv. Dette ses eksempelvis i enkeltcenterstudiet fra Danmark hvor ca. 60% af alle recidiv forekom indenfor 3 år og derved ca. 40% af recidiv >3 år fra nefrektomi (9). Ligeledes ses i Marconi et al. med data fra RECUR databasen og med patienter, der passer til inklusionskriterierne i bl.a. KN564 og andre adjuverende immunterapi forsøg, at en vis udfladning af DFS- kurverne ses omkring 90 måneder efter nefrektomi – dog nås et plateau aldrig helt og recidiv forekommer også >10 år fra nefrektomi(6). RCC-patienter har derfor en øget risiko for recidiv i over 10 år efter nefrektomi. Disse opgørelser inkluderer både lav-, intermediær- og høj-risikopatienter. Patienter med lymfeknude-positiv sygdom har en særdeles høj recidivrate på op imod 80% (51). I KN564 var 24-måneders recidivraten i placebo-gruppen 31,9% (95% CI: 27,8%-36,5%)(29) mens den 3-årige recidivrate i placebogruppen er ca. 35% (aflæst fra graf). KN564 populationen er defineret ved en øget risiko for recidiv, og som forventet er recidivraten i placebogruppen i KN564 også højere end dem der er rapporteret for en bredere og mindre selekteret højrisikogruppe i Danmark i DaRenCas årsrapporter. Da ingen danske eller internationale studier findes med rapporterede recidivrater for nuværende klinisk praksis for den inkluderede KN564 population, må placebogruppen i KN564 anses som den bedste og mest retvisende komparator for adjuverende behandling med pembrolizumab, og det er også denne komparator som vil blive anvendt i denne ansøgning. De ovenstående data dokumenterer tilsammen at der er en stor andel af RCC patienter der efter nefrektomi får recidiv, og hvor der i dag ikke er mulighed for at forebygge det.

## 5.2 Patient populationer der er relevante for adjuverende behandling med pembrolizumab og derved denne ansøgning

### 5.2.1 Den danske patientgruppe, som forventes at være kandidater til behandlingen

I Danmark vil patienter på mindst 18 år, som er radikalt eller partielt behandlet for lokaliseret eller lokalavanceret RCC være kandidater til adjuverende behandling med pembrolizumab. Desuden kræves følgende efter nefrektomi: stadie T2 med grad 4 dedifferentiering og/eller sarcomatoid uddifferentiering. Alle stadie T3 eller T4 tumorer uafhængigt af uddifferentiering eller N- og M-stadie. Alle patienter med regionale lymfeknudemetastaser uafhængig af T-stadie, og patienter med oligometastatisk sygdom, som kan resekteres radikalt, uafhængig af T-stadie (se også **Error! Reference source not found.** (2)). For detaljerede in-/eksklusionskriterier og studieopbygning, se Appendiks B Hovedkarakteristika ved inkluderede undersøgelser.

### 5.2.2 Incidens og prævalens af RCC i Danmark

Årligt nydiagnosticeres ca. 1000 patienter med renalcellecarcinom (RCC) i Danmark, hvilket udgør 2-3% af alle danske nydiagnosticerede kræfttilfælde (11). Omkring 150 patienter er metastatiske på diagnosetidspunktet (13). Der ses en overvægt af mænd i forhold til kvinder (ratio 2:1), og antallet af tilfælde er steget fra 12,8/100.000 indbyggere i 2010-11 til 16/100.000 i 2018-19 (11), en stigning på ca. 23 patienter/år (16-12,8/(100.000 indb.x 8 år) x 5,8 mio indb). Denne incidens er på højde med den rapporteret i USA og blandt de højeste i verden (38). Størstedelen af patienterne er



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mellem 60 og 70 år (median for nydiagnosticerede danske RCC patienter = 68 år), og op imod 50% opdages tilfældigt, ofte på grund af billeddiagnostik i forbindelse med anden udredning(11).

I 2020 var incidensen af ny-diagnosticerede RCC-patienter i Danmark 979 mod 1018 året før (11), hvoraf der årligt er set ca. 800-875 kirurgiske behandlinger (gennemsnit i DaRenCas årsrapporter over de sidste 5 år = 836). Af de kirurgiske behandlinger foretoges hhv. 379 og 411 nefrektomier i 2020 og 2019 (11). Følgende forsøges at estimere hvor mange danske patienter der vil kunne tilbydes adjuverende pembrolizumab ud fra risikigrupperne anvendt i KN564: Forekomsten af pT2-tumorer med Furhman grad 4 og/eller sarcomatoid differentiering vurderes at være meget lav og kan sættes til ca. 10-20 patienter (ekspertudsagn). Alle nefrektomerede pT3 og pT4 patienter vil være kandidater, og her fandtes fra DaRenCa årsrapporten 213 pT3 patienter samt 5 pT4 patienter i 2020 i DK (11). Andelen af patienter med oligometastatisk sygdom, som kan opereres radikalt vurderes at andrage få patienter, ca. 10-20 årligt (ekspertudsagn) - disse patienter vil dog i udtalt grad være inkluderet i de ovenstående grupper og øger ikke det totale antal. Dvs. totalt vil ca. 230 RCC-patienter om året være kandidater til denne behandling, dog vurderes 15% af patientgruppen (35 patienter) ikke at kunne modtage systemisk medicinsk behandling, primært grundet komorbiditeter, alder, performance status, patientønske, eller kontraindikerende årsager (230-15%=196) (75). Til sidst kræves det for at patienter kan tilbydes adjuverende pembrolizumab at deres RCC er clear celle histologi. I DaRenCas årsrapport fra 2020 havde 69,4% af nydiagnosticerede RCC patienter clear celle histologi, og hvis det antages at disse fordeler sig jævnt ud på pTNM stadier (ekspertudsagn) vil ca. 70% af ovenstående 196 patienter kunne tilbydes adjuverende behandling med pembrolizumab, svarende til 137 patienter.

Fra indførslen af adjuverende immunterapi til melanompatienter ved vi fra DAMED-årsrapporten at ca. 54% af de patienter der er egnede til behandling ender med at modtage behandling pga. enten patientønske, lægens anbefaling mm. (76) , og vi vurderer at dette også vil gøre sig gældende for adjuverende pembrolizumab til RCC patienter med øget risiko for recidiv efter nefrektomi.

**MSD vurderer derfor at ca. 74 ccRCC patienter (54% af 137 patienter) om året vil blive behandlet med adjuverende pembrolizumab hvis denne behandling indføres.**

**Tabel 4 Incidens og prævalens af nydiagnosticerede RCC tilfælde (alle patienter og risikogrupper) i de sidste 5 år i Danmark**

| År | [2016] | [2017] | [2018] | [2019] | [2020] |
|---|---|---|---|---|---|
| Incidens i Danmark(11) | 931 | 928 | 972 | 1018 | 979 |
| Prævalens i Danmark (77) | 6657 | 7100 | 7581 | 8025 | N/A |

Data for prævalensen stammer fra Nordcan databasen (77).

**Tabel 5. Estimeret antal RCC patienter med øget risiko for recidiv der vil kunne tilbydes adjuverende pembrolizumab**

| År | [2022] | [2023] | [2024] | [2025] | [2026] |
|---|---|---|---|---|---|
| Antal patienter i Danmark, der forventes at bruge lægemidlet i de kommende år** | 10 * | 74 | 74 | 74 | 74 |

Data vedrørende incidensen i Danmark stammer fra DaRenCas årsrapport fra 2018-2020 (11).

Det estimerede antal patienter der vil kunne tilbydes adjuverende pembrolizumab er fremkommet ved at bruge den stigende tendens i incidensen af totalt antal nydiagnosticerede patienter, samt antallet af nefrektomerede patienter i de relevante TNM-stadier (ud fra KN564 inklusionskriterierne) fra DaRenCa årsrapporten 2018-2020 (11), kombineret med et lægeligt skøn over hvor stor en andel af patienterne der vil være i stand til at modtage behandling.

*Antallet af patienter estimeret til at kunne tilbydes adjuverende pembrolizumab i 2022 er sat til 10 hvilket svarer til 1-2 måneders brug og en estimeret medicinrådsafgørelse i efteråret 2022 med et årligt forventet antal på 70.

**Den stigning der er set i antallet af RCC tilfælde i Danmark har så lille en effekt på det årlige antal patienter at det vurderes en justering ikke er nødvendig pr. år.



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**Biologisk rationale for behandlingseffekt af pembrolizumab som adjuverende behandling til RCC patienter efter nefrektomi**

Da en signifikant del af RCC patienter oplever recidiv efter endt nefrektomi som allerede beskrevet i denne ansøgning, har der tidligere været lavet kliniske afprøvninger af medicinske adjuverende behandlinger til denne patientpopulation (24). Tilbage i 1990'erne blev cytokiner i form af IL-2 og interferoner forsøgt, og senere har monoterapi med tyrosinkinasehæmmere der bl.a. modvirker angiogenese været afprøvet. Kun et enkelt forsøg (S-TRAC) har vist en positiv DFS med adjuverende sunitinib versus placebo, men adjuverende sunitinib fejlede i forsøget ASSURE (43, 44), og overordnet har en efterhånden lang række forsøg indenfor adjuverende RCC ikke vist nogen effekt, samtidig med at især TKI-behandlingerne har vist sig at være behæftet med signifikante bivirkninger der ledte til en forværring af livskvalitet hos RCC patienter i de adjuverende forsøg (24).

Pembrolizumab er et humaniseret monoklonalt antistof, der binder til overfladeproteinet programmed cell death-1 (PD-1) på immunsystemets T-celler og forhindrer binding til overfladeproteinerne programmed cell death-ligand 1 (PD-L1) og 2 (PD-L2). Immunhæmning ved PD-1 binding til PD-L1/2 kaldes et immuncheckpoint, og sådanne checkpoints sørger for at vores immunsystem ikke overreagerer eller angriber vores raske væv. PD-L1/2 opreguleres naturligt ved tilstedeværelsen af interferon-gamma, der produceres ved et normalt immunrespons. Dette bevirker at immunsystemets lukkes ned igen efter nedkæmpelse af f.eks. en infektion, og er desuden også central i at beskytte fostre mod immunsystemet vha. høj PD-L1/2 ekspression i placenta. PD-L1/2 opreguleres også på tumorceller, enten ved en immunreaktion (hvor der produceres interferon-gamma) mod kræftcellerne eller pga. dysregulering af PD-L1/2 ekspression i tumoren, og PD-L1/2 "beskytter" dermed tumorcellerne fra immuneliminering. Binding mellem PD-1 og PD-L1 eller PD-L2 hæmmer således T-cellernes respons mod infektioner og også kræftceller. Pembrolizumab forhindrer den hæmmende PD-1-binding til PD-L1 og PD-L2, og kan derved genoprette T cellernes evne til at udrydde kræftcellerne. PD-L1 og PD-L2 kan være udtrykt på både tumorceller og andre celler (f.eks. immunceller) i tumorens mikromiljø.

Adjuverende immunterapi med pembrolizumab stimulerer via den ovenfor beskrevne mekanisme immunsystemet til at reagere mod, og eliminere mikrometastaser eller resttumorer hos RCC patienter efter nefrektomi, der menes at være en afgørende faktor der kan lede til recidiv (78). Et effektivt immunrespons mod resterende nyretumorceller vil eliminere alle resterende tumorceller, hvorimod behandling med TKIere er mest effektiv mod hastigt voksende større tumorer, hvor øget blod/næringstilførsel er af stor betydning. Mikrometastaser vil ikke have stort behov for vaskularisering, og denne forskel i virkningsmekanisme er derfor afgørende for effekten af adjuverende pembrolizumab modsat de tidligere TKI studier (2, 24).

## 5.3 Nuværende behandlingsmuligheder og valg af komparator(er)

### 5.3.1 Nuværende standardbehandling i Danmark af lokaliseret RCC

Vi vil i det følgende have fokus på den patientgruppe som diagnosticeres med øget risiko for recidiv efter kirurgisk fjernelse af tumor jvf. inklusionskriterierne i KN564, da det er denne patientgruppe, som vil være kandidat til adjuverende behandling med pembrolizumab.

I Danmark behandles lokaliseret/lokalavanceret RCC kirurgisk på otte urologiske afdelinger fordelt på landets 5 regioner; Rigshospitalet, Herlev Universitetshospital, Region Sjællands Sygehusvæsen, Odense Universitetshospital, Vejle Sygehus, Aalborg Universitetshospital, Hospitalsenheden Vest og Aarhus Universitetshospital. Alle afdelinger er tilknyttet multidisciplinære teams, som samarbejder om udredning og behandling, nogle på tværs af hospitalerne (11). Systemisk onkologisk behandling gives til ikke-resektable metastatiske RCC patienter på hhv. Herlev, Odense og Århus Universitetshospitalers onkologiske afdelinger. Den Danske Multisdiciplinære Cancer Gruppe (DMCG) der har beskrevet de kliniske retningslinjer for kirurgisk intervention hos RCC patienter (13) er Dansk Renal Cancer Gruppe (DaRenCa) som ligger under DUCG (Dansk Urologisk Cancer Gruppe). For patienterne der er omhandlet denne ansøgning gælder at de



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har et clear celle renalcelle carcinom (ccRCC) der kræver kirurgisk intervention ved hhv. partiel eller radikal nefrektomi, samt evt. radikal metastasektomi ved tilstedeværelse af oligometastaser (13).

Nærmere bestemt beskriver DaRenCa gruppen at lokaliseret/lokalavanceret RCC svarende til patienterne der er inkluderet i KN564, behandles ved kirurgisk fjernelse af tumorvæv ved en nefrektomi efter billeddiagnostisk udredning (74). Partiel nefrektomi foretages når det er teknisk muligt, ellers foretages radikal nefrektomi, i begge tilfælde foretrækkes laparoskopisk nefrektomi når det er muligt. Ligeledes tilstræbes det at fjerne tumortromber i vena reanalis og vener centralt herfor når teknisk muligt. Lymfadenektomi anbefales kun ved mistanke om regionale lymfeknudemetastaser (radiologisk påvist eller peroperativt fund), og adrenalektomi foretages ved mistanke om metastase eller direkte indvækst. Solitære fjern-/oligometastaser fjernes, og der tilstræbes radikalitet, når det er teknisk muligt. Alle patienter der får foretaget partiel eller radikal nefrektomi, og som opfylder kravene til øget risiko for recidiv svarende til KN564-inklusionskriterierne (Figur 3), vil være kandidater til adjuverende pembrolizumab og er dækket af nærværende ansøgning.

Patienter med små tumorer (≤3 cm) eller som er for gamle eller dårlige til kirurgi kan tilbydes aktiv overvågning, og patienter med tumorer i tidligere stadier (cT1A) kan tilbydes ablationsbehandling, når partiel nefrektomi ikke er hensigtsmæssig. Disse patienter indgår ikke i ansøgningen da de hverken stemmer overens med definition af øget risiko for recidiv (**Error! Reference source not found.**) eller har fået foretaget nefrektomi.

I Appendiks M, DaRenCa kliniske retningslinjer for kirurgi ved renalcellecarcinom, opsummeret, ses en skematisk oversigt over den anbefalede behandling af lokaliseret/lokalavanceret RCC i DK. Det er kun patienter der har gennemgået partiel eller radikal nefrektomi med øget risiko for recidiv (se **Error! Reference source not found.**), der indgik i KEYNOTE-564 studiet (5).

#### 5.3.1.1 Efterfølgende behandling ved recidiv efter nefrektomi (og evt. adjuverende pembrolizumab behandling)

Nuværende standardbehandling for RCC patienter med recidiv efter nefrektomi afhænger af typen af recidiv. Ved lokalrecidiv, eller solitære/resektable oligometastaser, genbehandles patienten efter gennemgang på MDT konference med kirurgi eller observation. Ved ikke resektable eller multiple metastaser vil patienten blive vurderet på MDT konference til at opstarte systemisk onkologisk behandling, typisk VEGF-TKI monoterapi for patienter i god prognosegruppe samt kombinationsimmunterapi med anti-PD-1/anti-CTLA-4 for patienter i intermediær og dårlig prognosegruppe, der vurderes til at kunne tåle denne behandling (alternativt VEGF-TKI monoterapi)(13, 79).

Hvis adjuverende pembrolizumab indføres i Danmark, vil patienter med fjernmetastatisk recidiv ikke være immunterapi-naïve, som det er tilfældet for metastatiske RCC patienter i nuværende dansk praksis. Der findes ikke mange data for genbehandling med immunterapi efter immunterapi. Et fase 1b/2 enkeltarmsstudie, KEYNOTE-146, studerede 2L+ mRCC kombinationsimmunterapi med pembrolizumab og VEGF-TKIen Lenvatinib hos patienter, der havde modtaget hhv. IO/IO eller IO/TKI behandling for 1L mRCC. Den objektive responsrate (ORR) for denne kohorte af patienter var 62,5% (n=104)(80), hvilket er lidt lavere end 77,3% (KN146) samt 71% med samme kombination i fase 3 studiet for pembrolizumab og lenvatinib (1L mRCC)(42). Det viser dog også, at kombinationsimmunterapi behandling er aktiv, selv efter tidligere immunbehandling. En mulig forklaring kan findes i, at flere prækliniske studier viser, at VEGF-TKI behandling har en immunmodulerende effekt, der øger tilstrømning af bl.a. effektor CD8 T celler, og det er derfor muligt, at tilføjelse af VEGF-TKI til monoterapi med en anti-PD-1 hæmmer øger effekten af anti-PD-1 immunterapien(81-83). Det skal understreges, at tidligere immunbaseret kombinationsbehandling i KN146 blev givet i metastatisk og ikke adjuverende setting, som vil være tilfældet ved evt. introduktion af adjuverende pembrolizumab. Et retrospektivt studie



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viste, at patienter, der har afbrudt immunterapi pga. immunrelaterede bivirkninger, godt kan startes op på immunterapi igen efterfølgende (ud af 499 RCC patienter behandlet med immunterapi i første linje, havde 71% en immunrelateret bivirkning ved første behandling, men kun 45% hos patienter hvor immunterapi også indgik i 2L behandlingen. Disse data har en bias i og med, at patienter med mest alvorlige irAEer efter 1L immunterapi formentlig var underrepræsenteret i immunbehandlede 2L patienter)(81), men viser dog at det er forsvarligt at genbehandle med immunterapi. Sidst kan det nævnes, at flere studier fra melanom og lungekræft har vist god effekt af immunterapi genbehandling både med samme lægemiddel, nyt lægemiddel indenfor samme klasse (PD-(L)-1 efterfulgt af PD-(L)1 og CTLA-4 efterfulgt af CTLA-4(84).

Kort kan det altså opsummeres, at der ikke findes endegyldige data for, hvordan patienter. der får recidiv efter adjuverende pembrolizumab, skal behandles. Men det er også vist, at immunterapi genbehandling er både mulig og aktiv, og internationale eksperter har overordnet sat 3 scenarier op for genbehandling:

1) Patienter med recidiv under adjuverende pembrolizumab: Anbefales VEGF-TKI monoterapi
2) Patienter med recidiv efter adjuverende pembrolizumab:
    a. Recidiv 0-6 mdr. efter ophørt pembrolizumab: VEGF-TKI (eller IO/IO ved kontraindikation for VEGF-TKI)
    b. >6 mdr. efter ophørt pembrolizumab: IO/TKI TKI (eller IO/IO ved kontraindikation for VEGF-TKI)
3) Recidiv i patienter der afbrød adjuverende pembrolizumab pga. en bivirkning:
    a. Afbrudt pga. grad 1-2 irAE: IO/TKI eller VEGF-TKI
    b. Grad 3-4 irAE: VEGF-TKI monoterapi

For argumentation henvises til figur 1 i Berget et al. (81), men kort fortalt menes anti-PD-1 terapier som pembrolizumab ikke længere at være aktive ca. 6-12 måneder efter sidste dosis (trods en halveringstid på 12-26 dage blokerer disse antistoffer op til 40% af PD-1 receptorer i væv i over 6 måneder efter behandlingsophør). Og derfor anbefales immunkombinationsbehandling, dog anbefales IO/TKI over IO/IO, da patienten jo har fået et recidiv ved immunbaseret behandling og det tillægges derfor værdi at behandle metastaserne med 2 forskellige mekanismer frem for dobbelt immunterapi (IO/IO). Ved recidiv under adjuverende pembrolizumab behandling vurderes immunterapi ikke at være effektivt og derfor anbefales VEGF-TKI. Generelt anbefales IO/IO til patienter med recidiv med kontraindikation for VEGF-TKI, eller patientspecifikke forhold. Det kan også nævnes, at for adjuverende immunterapi hos stadie III melanompatienter, har man i Danmark besluttet at genbehandle med dobbelt immunterapi (eller CTLA-4 monoterapi), hvis et recidiv forekommer >6 måneder efterophør af anti-PD-1 adjuverende behandling (www.melanoma.sundata.dk).

## 5.4 Valg af komparator(er)

Komparatoren i KN564 studiet er placebo, og man har valgt at dobbeltblænde studiet for at minimere risikoen for bias fra hhv. behandlere og patienter. Da der ikke findes en global accepteret adjuverende behandling til RCC-patienter efter nefrektomi, og der ikke findes en godkendt adjuverende behandling til nyrekræft i Danmark, mener MSD Danmark at placebo må konkluderes at være en klinisk relevant og hensigtsmæssig komparator. Dette er også i overensstemmelse med de danske kliniske retningslinjer hvor behandlingen efter nefrektomi er opfølgning (13).

### 5.4.1 Beskrivelse af komparatoren

Da komparatoren i studiet er placebo, er dette afsnit ikke relevant. Dansk klinisk praksis efter nefrektomi er opfølgning, se Tabel 3, hvorfor placebo afspejler dansk klinisk praksis.

## 5.5 Interventionen

Pembrolizumab har været anvendt i behandlingen af cancer som monoterapi siden 2015 og indenfor RCC bl.a. kombineret med axitinib siden 2019 (85).



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- Dosering af adjuverende behandling: Pembrolizumab monoterapi 200 mg fast dosis IV på dag 1 i hver 21-dages cyklus (op til 17 cykler/1 år). Alternativt 400 mg fast dosis IV på dag 1 af 42-dages cyklus (op til 9 cykler i alt/1 år). Det skal nævnes at i de danske kliniske retningslinjer for metastastisk RCC fra DaRenCa foreslås offlabel vægtbaseret 2 mg/kg brug af pembrolizumab (Q3W) eller 4 mg/kg ved 6-ugers dosering (Q6W), og det anslås endvidere at den kliniske forskel på Q3W og Q6W samt fast og vægtbaseret dosis må anses for minimal (74).
- Administrationsmåde: Intravenøst.
- Behandlingsvarighed: Varighed er sat til et år maksimalt eller ophør ved: recidiv, bivirkninger, patientønske, behandlervurdering. Behandlingen kan genoptages efter pausering grundet bivirkninger hvis disse igen er i bero (se EPAR for detaljer)(29).
- Der er ikke behov for at administrere lægemidlet med andre lægemidler, dog er steroidbehandling op til opstart af pembrolizumab behandling ikke tilladt da de kan have en negativ effekt på den farmakodynamiske virkning. Steroidbehandling mod opståede bivirkninger efter opstart af pembrolizumab er tilladt.

### 5.5.1 Indplacering ift. nuværende behandling

På baggrund af den kliniske merværdi, som adjuverende behandling med pembrolizumab vil indebære, forventes denne behandling indplaceret som standardbehandling for alle nefrektomerede RCC-patienter i øget risiko for recidiv, samt radikalt resecerede oligometastatiske patienter med nefrektomi <1 år fra metastasektomi, der er kandidater til adjuverende behandling.

# 6. Litteratursøgning og identifikation af effektivitets- og sikkerhedsundersøgelser

## 6.1 Identifikation og udvælgelse af relevante undersøgelser

Da der i KN564 studiet er foretaget en direkte sammenligning mellem den nye behandling og den relevante komparator, er der ikke foretaget en systematisk søgning efter dokumentation for effekt og sikkerhed, da søgningen ikke forventes at tilvejebringe yderligere relevant dokumentation for effekt og sikkerhed for både intervention og komparator.

Det relevante studie der ligger til grund for denne ansøgning blev publiceret i New England Journal of Medicine og er: Chouerie TK, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma, N Engl J Med. 2021 Aug 19;385(8):683-694. doi: 10.1056/NEJMoa2106391(2). NCT-nummer: NCT03142334. Studiestart den 9. Juni 2017 og primær studie slutdato 14. december 2020. Estimeret endelig slutdato 28. december 2025. For fuld liste af studiekarakteristika, se Appendiks B Hovedkarakteristika ved inkluderede undersøgelser.

Data brugt til denne ansøgning er data on file fra ovenstående publikation (2). Desuden den fra EMA udarbejdede EPAR samt den opdaterede analyse med 6 måneders ekstra opfølgning (European updated report; EUR) og den fra KN564 udarbejdede clinical study report (CSR) (86) (29, 30).

For detaljerede oplysninger om inkluderede undersøgelser henvises til Appendiks B Hovedkarakteristika ved inkluderede undersøgelser.



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# 7. Effekt og sikkerhed

## 7.1 Effekt og sikkerhed af [intervention] sammenlignet med [komparator] for [patientpopulation]

KN564 er et dobbeltblændet randomiseret placebokontrolleret fase III studie med formålet at evaluere effekt og sikkerhed af adjuverende pembrolizumab til RCC patienter i øget risiko for recidiv efter nefrektomi. Patienter blev randomiseret 1:1 til hhv. pembrolizumab- og placebogruppen. Studiet er et multicenter internationalt studie der inkluderer 212 centre fra 21 lande. KN564 inkluderer RCC patienter med clear celle histologi der har fået foretaget nefrektomi, og som er i øget risiko for recidiv. Risikostratificeringen består af 3 overordnede grupper: intermediær-høj risiko (pT2 Furhman grad 4 og/eller sarkomatoid differentiering samt alle pT3), høj risiko (alle pT4 samt alle lymfeknudepositive RCC uanset pT-stadie) og M1 no evidence of disease (NED; oligometastatisk syn-/metakron RCC med radikal metastasektomi samtidigt med nefrektomi eller ≤1 år efter nefrektomi). Langt størstedelen af studiepopulationen er i intermediær-høj risikogruppen (855/994), mens hhv. 76 og 58 patienter var inkluderet i høj risiko samt M1 NED risikogrupperne. 5 patienter med pT2 grad ≤3 indgik også i studiet. Både EMA og FDA har godkendt adjuverende pembrolizumab til den ovenstående population. Studiet var stratificeret ud fra M1 NED (ja vs nej), samt for M0 patienter: ECOG performance status (0 vs 1) samt region (USA: ja vs. nej). PD-L1 status (CPS>1) indgik som eksplorativt endepunkt men effekten var ikke signifikant forskellig mellem patienter med PD-L1 CPS over og under 1. Patienter blev scannet hver 12. uge fra randomisering for evt. recidiv, og behandling fortsatte op til 17 cykler (1 år) eller indtil sygdoms recidiv eller opfyldelse af kriterier til at afbryde behandling. For flere detaljer se **Error! Reference source not found.** samt Appendiks B Hovedkarakteristika ved inkluderede undersøgelser. Blændet uafhængigt review (BICR) af DFS blev foretaget for at understøtte investigator evalueringen af DFS som er det primære endepunkt.

Nedenfor vises derfor data for ITT populationen, som også er grundlaget for det primære endepunkt, investigatorevalueret DFS, samt det vigtigste sekundære endepunkt, overordnet overlevelse (OS). Hvor klinisk relevant, og hvor data haves, vises data for de enkelte risikogrupper.

I ansøgningen præsenteres følgende data:

- Baselinekarakteristika for ITT populationen
- Primært endepunkt:
  - DFS for ITT populationen (Investigator evalueret).
- Vigtigste sekundære endepunkt:
  - OS for ITT populationen (vigtigste sekundære endepunkt). Foreløbig data modenhed er 33% af estimerede antal dødsfald til endelig analyse/final analysis som forventes til 2024-25.
- Andre sekundære endepunkter:
  - DFS blændet centralt review (BICR). Desuden DFS for individuelle risikogrupper
  - Lokalt / fjernt recidiv (DRSS1 og 2) for ITT (sekundært endepunkt)
  - Bivirkninger for as-treated populationen (som minimum har modtaget 1 dosis studiemedicin). Sekundært endepunkt
  - Livskvalitet for ITT populationen. Sekundært endepunkt.

Effekt og sikkerhed af pembrolizumab sammenlignet med placebo som adjuverende behandling til RCC-patienter efter nefrektomi gennemgås nedenfor. De komparative analyser er en direkte statistisk komparativ analyse af pembrolizumab sammenlignet med placebo, svarende til dansk klinisk praksis, som er baseret på interim analyse 1 (IA1)(2) samt 6 måneders yderligere opfølgning efterspurgt af EMA (30)



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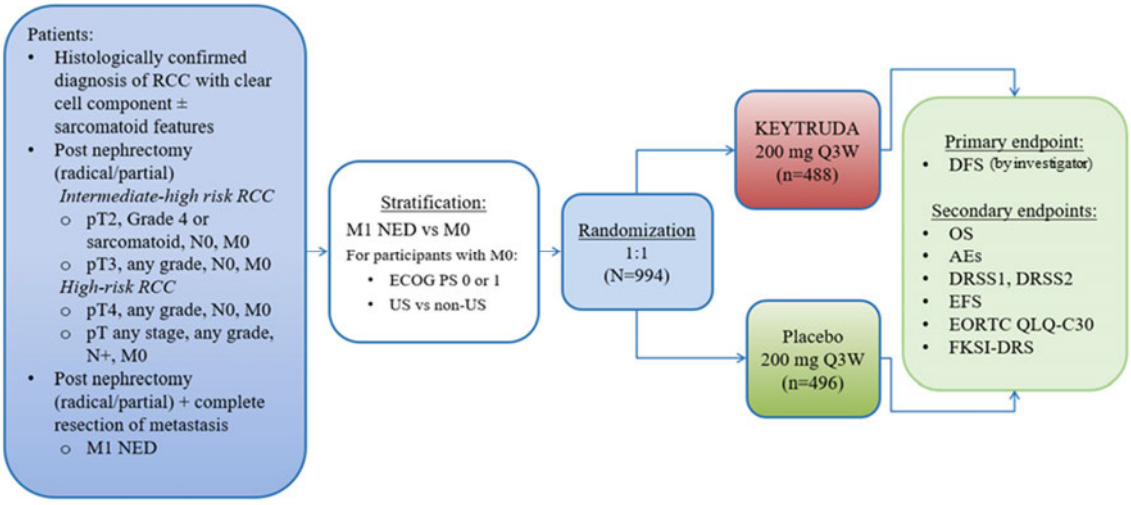
- Den interne og eksterne validitet af studiet vurderes høj. Den interne validitet styrkes af studiets design som er baseret på beregninger af studiestørrelse, er dobbeltblindet og randomiseret. Desuden er studieprotokollen nøje fastlagt, så de inkluderede patienter alle modtager samme behandling i deres respektive behandlingsarme. Den eksterne validitet er styrket af studiets design med fastsatte inklusions- og eksklusionskriterier, forskellig etnicitet (stratificeret for USA vs. andre regioner) og en intervention som er mulig for den brede patientgruppe med ccRCC.

### 7.1.1 Relevant studie (KN564)

#### 7.1.1.1 Studietype og -design

- Fase III dobbelt-blindet studie, hvor patienter blev randomiseret 1:1 til henholdsvis (Figur 3):
    - Interventionsarm (n=488): *Adjuverende:* pembrolizumab: 200 mg i.v. dag 1 af hver 3 ugers cyklus i op til 17 cykler
    - Kontrolarm (n=496): *Adjuverende:* placebo i.v. dag 1 af hver 3 ugers cyklus i op til 17 cykler




**Figur 3 KEYNOTE-564 studiedesign**

Komparatoren, placebo, svarer til dansk klinisk praksis, der består af opfølgninger med CT-scanninger i en hyppighed der modsvarer patientens risikostratificering.

#### 7.1.1.2 Stratificering

- M0 vs. M1 NED
- For M0 gælder yderligere:
    - ECOG Performance status 0 vs. 1
    - Patienter fra USA vs. patienter ikke fra USA (5, 11)

#### 7.1.1.3 Statistisk analyseplan

I den statistiske analyseplan for KN564 var hypotese 1 (H1): Der er i højere grad forbedret DFS ved adjuverende behandling med pembrolizumab end ved placebo, og H2 ligeledes at der i højere grad er forbedret OS ved adjuverende



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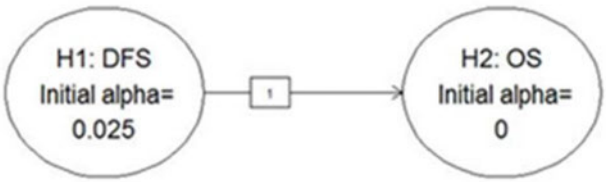
behandling med pembrolizumab end ved placebo(2). Det primære endepunkt (DFS) har allokeret 2.5% alpha (1-sidet test), og hvis H0 forkastes, kan alpha recirkuleres til OS-analysen, som er det vigtigste sekundære endepunkt. Dette betyder også, at hvis det primære endepunkt, DFS, er signifikant bedre for pembrolizumab-armen versus placebo-armen, vil det understøtte studiets overordnede hypotese og studiet vil konkluderes som et positivt studie. Studiet har 95% power til at vise en effekt på DFS på HR=0.7 med en 1-sidet alpha på 2,5%.

Andre sekundære endepunkter var antal patienter med hhv. alle bivirkninger, alvorlige bivirkninger og bivirkninger der ledte til afbrydelse af behandling. Desuden hhv. antal patienter med lokal og fjern recidiv (kaldet disease recurrence-specific survival 1 (DRSS1) og -2), event free survival (EFS) ved BICR, DFS og OS stratificeret på PD-L1 status (CPS </>1), samt QoL (gennemsnitlig ændring fra baseline ved EORTC-QLQ-C30 global sundhedsstatus og fysisk funktion samt FKSI-DRS score).

For IA1 blev der udført analyser af effekt på 'intention-to-treat' (ITT) populationen, og der blev udført analyser af sikkerhed på 'All Participants as Treated' (APaT) populationen, som omfattede alle randomiserede deltagere, der modtog mindst 1 dosis af studieintervention (2). DFS og OS blev evalueret ved at sammenligne pembrolizumab med placebo ved hjælp af en stratificeret log-rangeringstest. Estimering af hazard ratioen (HR) blev udført ved hjælp af en stratificeret Cox regressionsmodel. Event-rater over tid blev estimeret inden for hver behandlingsgruppe ved hjælp af Kaplan-Meier (KM)-metoden. Maurer- og Bretz-multiplicitetsstrategien for gruppe-sekventielt design blev anvendt til det primære slutpunkt DFS og det vigtigste sekundære endepunkt OS med henblik på at have en stærk kontrol for type I-fejl (27, 86).




**Figur 4 Statistisk analyseplan for KN564**

DFS blev testet ved efter IA1 og var præspecificeret ved ca. 265 tilfælde af recidiv svarende til 80% af det estimerede antal recidiv ved den endelig analyse (final analysis). Desuden vises DFS fra 6 måneders yderligere opfølgning efter IA1 efterspurgt af EMA i forbindelsen med processen om godkendelse herfra(27). OS-data er stadig præmature med kun 51 events (26% af de planlagte OS-events der forventes til final analysis) i den oprindelige publikation(2) samt 66 ved de ekstra 6 måneders opfølgning svarende til 33% af de 200 events der er præspecificeret ved den endelige OS analyse.

#### 7.1.1.4 In- og eksklusionskriterier

Inklusionskriterier var voksne patienter med histologisk verificeret RCC med clear celle komponent, med eller uden sarcomatoid differentiering, som har fået foretaget nefrektomi (med radikal metastasektomi for oligometastatiske patienter) med øget risiko for recidiv (se risikogruppe definitioner ovenfor eller **Error! Reference source not found.** samt Appendiks B Hovedkarakteristika ved inkluderede undersøgelser). Patienterne måtte ikke have modtaget systemisk medicinsk behandling for RCC, skulle være vurderet tumorfri af investigator, og være i ECOG performance status 0-1 og have normal organfunktion.



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Eksklusionskriterier var større operation udover nefrektomi/metastasektomi ≤12 uger før randomisering, tidligere systemisk- eller strålebehandling mod RCC, præeksisterende hjerne- eller knoglemetastaser, residual thrombus efter nefrektomi i enten vena renalis eller vena cava samt aktiv autoimmunsygdom (for fuld liste af in- og ekslusionskriterier, se Appendiks B Hovedkarakteristika ved inkluderede undersøgelser).

### 7.1.2 Sammenlignende analyser af effektivitet og sikkerhed

#### 7.1.2.1 Baseline karakteristika for inkluderede patienter i KN564.

I alt blev 1.406 deltagere screenet, den første i juni 2017 (86). Af disse blev 994 randomiseret fra juni 2017 til september 2019. Deltagerne blev tilfældigt allokeret til pembrolizmab eller placebogruppen. Af de 994 randomiserede deltagere (ITT-population) blev 984 behandlet (APaT-population; 488 i pembrolizumab-gruppen og 496 i placebogruppen). Yderligere oplysninger om deltagerdisposition findes i Appendiks B Hovedkarakteristika ved inkluderede undersøgelser & Appendiks C Baselinekarakteristika hos patienter i undersøgelser, der anvendes til sammenlignende analyse af effekt og sikkerhed.

Baseret på IA1 (Data cutoff: 14. december 2020) var baseline-patientkarakteristikaene velbalancerede mellem pembrolizumab- og placeboarmene (29, 86). Størstedelen af de indskrevne patienter var mænd (71,0%), hvide (75,4%), havde en ECOG PS på 0 (85,2%) og en median alder på 60 år. Kønsfordelingen stemmer overens med den danske patientpopulation af RCC patienter opgjort i DaRenCas seneste årsrapport fra 2020, dog er median alderen for kirurgisk behandlede patienter lidt højere i Danmark med en median alder på 66 år fra DaRenCa årsrapporten 2020 og 64 år i et enkeltcenterstudie af RCC patienter i Danmark (9, 11). Et andet studie viser en medianalder på 62 år hos systemisk behandlede metastatiske patienter hos danske patienter indsamlet fra 2006-2010 (87). Den hyppigste type operation var radikal nefrektomi (92,5%). Procentdelen af deltagere med en PD-L1-status af CPS <1 eller CPS ≥1 var henholdsvis 23,8% og 75,3%. I alt 94,2% af deltagerne havde ikke-metastatiske tumorer, og 88,6% af alle tumorer var T3 (Tabel 6). Sammenfattende er disse patienter repræsentative for den danske patientpopulation med lokaliseret eller lokalavanceret og kirurgisk behandlet RCC (ekspertudsagn).

**Tabel 6 Baseline karakteristika af patienter i KEYNOTE-564 studiet (ITT Population)**

| | KEYTRUDA (n=496) | Placebo (n=498) | Total (N=994) |
|---|---|---|---|
| **Male, n (%)** | 347 (70.0) | 359 (72.1) | 706 (71.0) |
| **Age** | | | |
| **Median (range), years** | 60.0 (27-81) | 60.0 (25-84) | 60.0 (25-84) |
| **≥65, n (%)** | 158 (31.9) | 172 (34.5) | 330 (33.2) |
| **Race** | | | |
| **White race, n (%)** | 372 (75.0) | 377 (75.7) | 749 (75.4) |
| **Asian, n (%)** | 63 (12.7) | 75 (15.1) | 138 (13.9) |
| **Region, n (%)** | | | |
| **North America** | 133 (26.8) | 125 (25.1) | 258 (26.0) |
| **European Union** | 188 (37.9) | 187 (37.6) | 375 (37.7) |
| **Rest of the world** | 175 (35.3) | 186 (37.3) | 361 (36.3) |
| **ECOG PS, n (%)** | | | |
| **0** | 421 (84.9) | 426 (85.5) | 847 (85.2) |



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| | KEYTRUDA (n=496) | Placebo (n=498) | Total (N=994) |
|---|---|---|---|
| 1 | 75 (15.1) | 72 (14.5) | 147 (14.8) |
| **Type of nephrectomy, n (%)** | | | |
| Partial | 37 (7.5) | 38 (7.6) | 75 (7.5) |
| Radical | 559 (92.5) | 460 (92.4) | 919 (92.5) |
| **PD-L1 status, n (%)** | | | |
| CPS <1 | 124 (25.0) | 113 (22.7) | 237 (23.8) |
| CPS ≥1 | 365 (73.6) | 383 (76.9) | 748 (75.3) |
| Missing | 7 (1.4) | 2 (0.4) | 9 (0.9) |
| **Primary tumor, n (%)** | | | |
| T1 | 11 (2.2) | 15 (3.0) | 26 (2.6) |
| T2 | 27 (5.4) | 33 (6.6) | 60 (6.0) |
| T3 | 444 (89.5) | 437 (87.8) | 881 (88.6) |
| T4 | 14 (2.8) | 13 (2.6) | 27 (2.7) |
| **Metastatic Staging, n (%)** | | | |
| M0 | 467 (94.2) | 469 (94.2) | 936 (94.2) |
| M1 NED | 29 (5.8) | 29 (5.8) | 58 (5.8) |
| **RCC Risk Category, n (%)** | | | |
| M0-Intermediate-High Risk | 422 (85.1) | 433 (86.9) | 855 (86.0) |
| M0-High Risk | 40 (8.1) | 36 (7.2) | 76 (7.6) |
| M0-Others | 5 (1.0) | 0 (0.0) | 5 (0.5) |
| M1 NED | 29 (5.8) | 29 (5.8) | 58 (5.8) |
| **Lymph node stage, n (%)** | | | |
| N0 | 465 (93.8) | 467 (93.8) | 932 (93.8) |
| N1 | 31 (6.3) | 31 (6.2) | 62 (6.2) |
| **Sarcomatoid Feature** | | | |
| Presence | 52 (10.5) | 59 (11.8) | 111 (11.2) |
| Absence | 417 (84.1) | 415 (83.3) | 832 (83.7) |
| Unknown | 27 (5.4) | 24 (4.8) | 51 (5.1) |

Kilde: **(86)**. Note: Participants in M0-Intermediate-high risk are pT2 (Grade 4 or sarcomatoid), N0, M0 or pT3 (Any Grade), N0, M0. Participants in M0-high risk are pT4 (Any Grade), N0, M0 or pT Any (Any Grade), N1 or greater, M0. Participants in M1 NED are participants who present not only with the primary kidney tumor but also solid, isolated, soft tissue metastases that were completely resected at the time of nephrectomy (synchronous) or <=1 year from nephrectomy (metachronous). Participants in M0-Others are T2 (grade <= 3)N0 M0 or T1 N0 M0.

CPS: Combined positive score; ECOG PS: European Cooperative Oncology Group Performance Score; ITT: Intention-to-treat; NED: No evidence of disease; PD-L1: Programmed death ligand 1; RCC: Renal cell carcinoma

### 7.1.3 Resultater pr. studie

Da KN564 foretager en direkte sammenligning af pembrolizumab vs. placebo, samt at behandlingen i komparatorarmen er svarende til dansk klinisk praksis, er der i denne ansøgning ikke inkluderet yderligere studier jf. afsnit 5.1 litteratursøgning. Resultater fra KN564 studiet er præsenteret i Appendiks D Effektivitets- og sikkerhedsresultater pr.



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undersøgelse og Appendiks E Sikkerhedsdata for intervention og komparator(er) for ITT-populationen, PD-L1 CPS >1 samt as-treated populationen hvor relevant.

For at beskrive den kliniske merværdi af pembrolizumab sammenlignet med nuværende dansk standardbehandling (placebo), gennemgås i det følgende resultater fra KN564 studiet på investigator evalueret sygdomsfri overlevelse (disease free survival/DFS; primært endepunkt) samt det vigtigste sekundære endepunkt, overordnet overlevelse (overall survival/OS). Desuden bivirkninger, Livskvalitet samt Progressionsfri Overlevelse 2 (defineret ved progression fra første behandling efter recidiv, PFS2). Dette svarer til de mest relevante kliniske endepunkter (ekspertudsagn).

Data fra ITT populationen fra både IA1(2) samt den af EMA ønskede analyse med 6 måneders yderligere opfølgning(30) danner baggrund for EMAs vurdering og godkendelse af adjuverende pembrolizumab til behandling af voksne patienter med clear celle RCC efter nefrektomi (88) og for de følgende afsnit. Hvis data fra andet end ITT-populationen vises nedenfor vil det tydeligt fremgå.

### 7.1.4 Primære endepunkt: investigator-evalueret sygdomsfri overlevelse (DFS) – IA1 (24,1 måneds opfølgning)

Adjuverende behandling med pembrolizumab viste en statistisk signifikant og klinisk relevant effekt på sygdomsfri overlevelse DFS sammenlignet med placebo i ITT-populationen (HR: 0,68 [95% CI: 0,53, 0,87]; p = 0,0010) (2). Median DFS blev ikke nået på tidspunktet for data cutoff for nogen af behandlingsgrupperne. Efter 12, 18 og 24 måneder var DFS-raterne konsekvent højere for patienter behandlet med pembrolizumab sammenlignet med placebo (Tabel 7), hvilket viser at adjuverende behandling med pembrolizumab af RCC patienter efter nefrektomi nedsætter mængden af patienter der oplever recidiv efter nefrektomi.

**Tabel 7 Resume af DFS resultaterne i KN564 Study (ITT populationen) ved IA1**

| | Pembrolizumab (n=496) | Placebo (n=498) |
|---|---|---|
| Number of events, n (%) | 109 (22.0) | 151 (30.3) |
| Disease recurrence, n (%) | 103 (20.8) | 149 (29.9) |
| Deaths, n (%) | 6 (1.2) | 2 (0.4) |
| Number of Censored (%) | 387 (78.0) | 347 (69.7) |
| Last Tumor Assessment Showing No Disease Recurrence | 375 (75.6) | 344 (69.1) |
| No Post-Baseline Disease Status Assessment | 12 (2.4) | 3 (0.6) |
| Median DFS, months (95% CI)[a] | NR (25,8, NR) | NR (13,8, NR) |
| HR (95% CI)[b] | 0.68 (0.53, 0.87); p=0.0010[c] | |
| DFS rate at 12 months, % (95% CI) | 85.7 (82.2, 88.5) | 76.2 (72.2, 79.7) |
| DFS rate at 18 months, % (95% CI) | 81.5 (77.7, 84.8) | 71.9 (67.7, 75.7) |
| DFS rate at 24 months, % (95% CI) | 77.3 (82.2, 81.1) | 68.1 (63.5, 72.2) |

Kilde: (29). Database cutoff date: December 14, 2020. CI: Confidence interval; DFS: Disease-free survival; ITT: Intention-to-treat; NR: Not reached. [a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator. [c]One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator.

KM-kurverne adskilles tidligt allerede fra omkring måned 3, hvilket understøtter effekten af adjuverende behandling med pembrolizumab. Kurverne forbliver adskilt i opfølgningsperioden (Figur 5). Forskellene i DFS-satserne mellem



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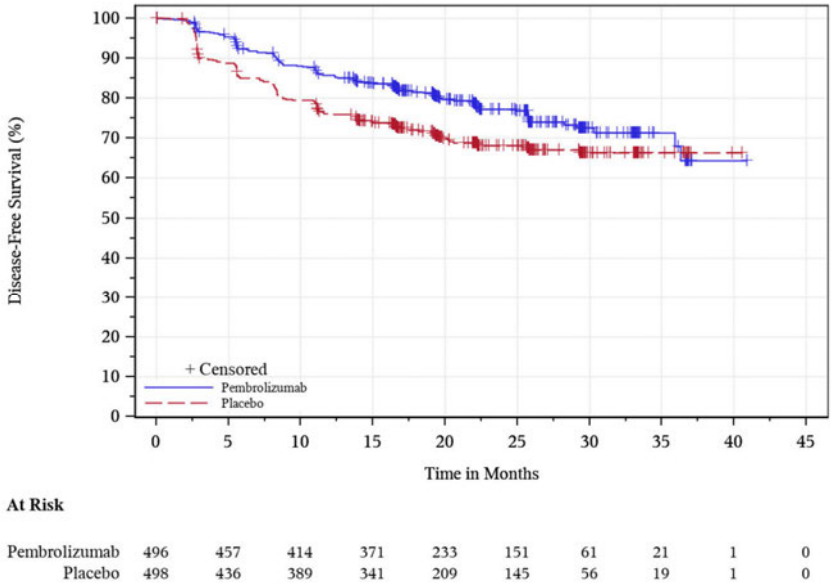
behandlingsgrupper på 12, 18 og 24 måneder var henholdsvis 9,5%, 9,6% og 9,2%, og med en HR på 0,68 reduceres sandsynligheden for at få recidiv efter nefrektomi altså med 32% ved adjuverende pembrolizumab behandling.




**Figur 5 Kaplan-Meier estimater af DFS fra KN564 (ITT-population) ved IA1**

Kilde: (86). Database cutoff date: December 14, 2020, 24.1 months of follow up .DFS: Disease-free survival; ITT: Intention-to-treat.

#### 7.1.4.1 Subgruppeanalyser af DFS

Behandlingseffekten observeret for DFS ved investigator-evaluering var konsistent på tværs af de forudspecificerede subgrupper (alder, køn, race, ECOG-præstationsskala, PD-L1-status, region, metastatisk stadie og type nefrektomi) (86). Estimater i nogle subgrupper havde brede CI'er, da antallet af DFS-hændelser var lille (partiel nefrektomi og M1 NED-status), selvom alle CI'er overlappede CI for den primære DFS HR (Figur 6). Der er altså ikke tale om en eller få subgrupper der trækker den overordnede effekt, men derimod en bred effekt i alle subgrupper.



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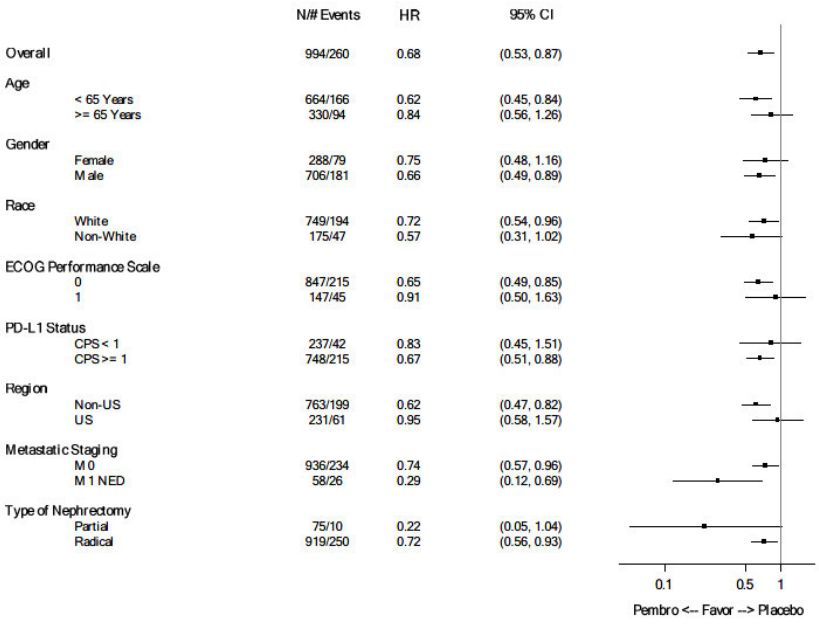
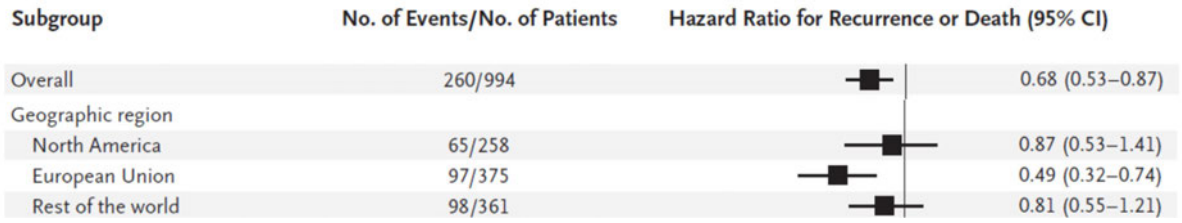



**Figur 6 Subgruppe analyse af DFS baseret på investigator evaluering fra KN564 (ITT).**




**Figur 7 Yderligere subgruppe analyse af DFS (ITT) med yderligere regionsopdeling**

Se desuden nedenfor ved den opdaterede EUR analyse med 6 måneders ekstra opfølgning for yderligere subgruppe analyser af risikogrupperne M0 intermediær-højrisiko, M0 højrisiko samt M1 NED.

### 7.1.4.2 Sygdomsfri overlevelse DFS – ekstra 6 måneders opfølgning (EMA efterspurgt).

Ved IA1 data cutoff i december 2020 var der indtruffet 260 DFS-hændelser (109 i pembrolizumab- og 151 i placebogruppen) (2). Ved de yderligere 6 måneders opfølgning af de efterspurgte EMA-data med data cutoff i juni 2021 havde der fundet 23 yderligere DFS-hændelser sted, hvilket gjorde det samlede antal DFS-hændelser til 283 (114 i pembrolizumab-gruppen og 169 i placebogruppen)(27). Pembrolizumab viste stadig en statistisk signifikant og klinisk meningsfuld forbedring i DFS sammenlignet med placebo EUR-dataafskæringen. Median DFS blev ikke nået i nogen af behandlingsgrupperne. HR var 0,63 (95% CI: 0,50, 0,80), og log-rank-testens nominelle p-værdi var <0,0001 sammenlignet med en HR på 0,68 [95% CI: 0,53, 0,87] og log-rank test p-værdi på 0,0010 ved IA1, altså en forbedret effekt af adjuverende pembrolizumab ved de ekstra 6 måneders opfølgning. KM-kurverne adskiltes fra starten til fordel for pembrolizumab, og på tidspunktet for data cut-off af EMA-data med de 6 måneders ekstra opfølgning forblev kurverne adskilt uden konvergens mellem kurvernes haler (Figur 8). Ved EMA-data cut-off var forskellen i DFS-raterne mellem behandlingsgrupper ved 12, 18 og 24 måneder mellem 9,5% til 11,0% (sammenlignet med 9,2% til 9,6% ved IA1 hhv.).



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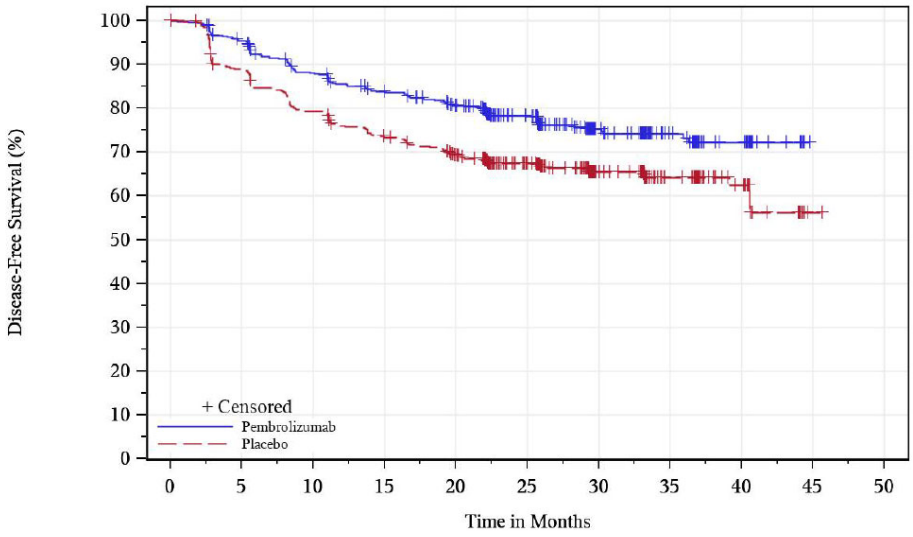
Det er desuden klinisk relevant at reduktionen i risiko for recidiv ved adjuverende pembrolizumab både gjaldt lokale og fjernmetastatiske recidiver, og dette var gældende for begge data cutoffs (IA1 og EUR). Se detaljer i afsnit 7.1.6.4 samt i tabel 1.



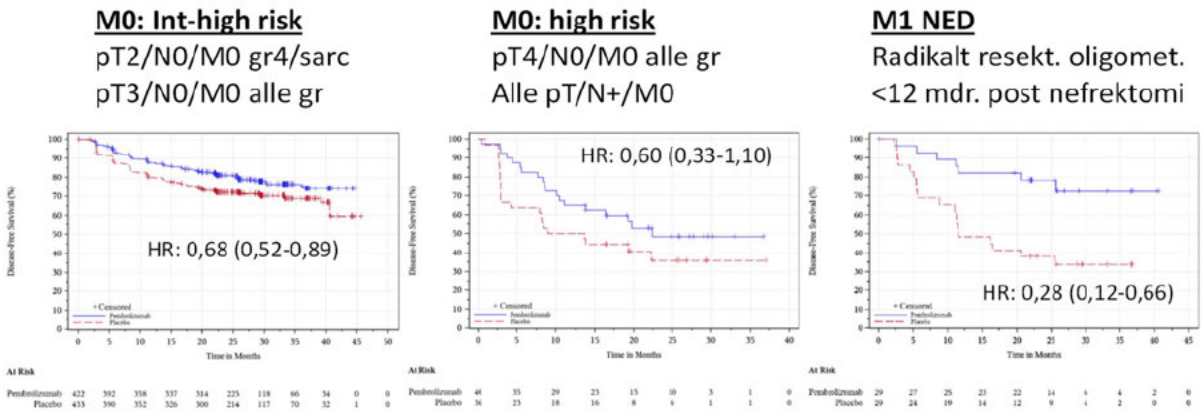

**At Risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 496 | 458 | 416 | 389 | 361 | 255 | 135 | 77 | 37 | 0 | 0 |
| Placebo | 498 | 437 | 389 | 356 | 325 | 230 | 125 | 74 | 33 | 1 | 0 |

**Figur 8 Kaplan-Meier estimater af DFS fra KN564 (ITT-population) ved 6 måneders ekstra opfølgning (EMA-data)**

[redacted]

Ved EUR data update med de 6 ekstra måneders opfølgning blev der også vist individuelle effekt resultater på DFS for de 3 hoved risikogrupper; M0 intermediær-høj risiko, M0 høj risiko samt M1 NED (Figur 9). Alle 3 risikogrupper viste en forbedring af DFS ved behandling med adjuverende pembrolizumab vs. placebo. Her er det vigtigt at huske at M1 NED kun udgør ca. 6% af den undersøgte ITT population mens M0 intermediær-høj risiko for recidiv gruppen udgør >85%. Samlet HR for M0 gruppen var 0,68 (0,53-0,88).




**Figur 9 Summary of DFS results in Baseline Disease Status Subgroups based on updated dataset June 2021**

M0: Int-high risk: pT2/N0/M0 Furhman grad 4 eller sarcomatoid dedifferentiering eller pT3/N0/M0, uanset Furhman grad. M0: high risk: pT4/N0/M0 uanset Furhman grad eller N+/M0 uanset T stadie. M1 NED: patienter med radikalt resekterede oligometastaser <12 måneder efter nefrektomi uden målbar sygdom (no evidence of disease/NED).



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Det er desuden klinisk relevant at reduktionen i risiko for recidiv ved adjuverende pembrolizumab både galdt lokale og fjernmetastatiske recidiver, og dette var gældende for begge data cutoffs (IA1 og EUR). Se detaljer i afsnit 7.1.6.3 samt i tabel 1.

#### 7.1.4.3 Følsomhedsanalyse af investigator-evalueret sygdomsfri overlevelse

For at understøtte det primære endepunkt, investigatorevalueret DFS, blev en præspecificeret følsomhedsanalyse foretaget med mere konservative censureringsregler for både dataudlæsningen ved IA1 og 6 ekstra måneders opfølgning efterspurgt af EMA. Følsomhedsanalyserne for DFS med blændet uafhængigt centralt review (BICR) viste samme konklusion som det primære endepunkt (investigatorevalueret DFS): at adjuverende pembrolizumab reducerede sandsynligheden for recidiv efter nefrektomi med meget lille afvigelse i hazard ratioerne. Dette var tilfældet både ved IA1 og EUR analyserne. Se appendix D og EPAR for yderligere detaljer.

For yderligere at vurdere robustheden af investigator-evalueret DFS blev endnu en følsomhedsanalyse udført for hændelses-fri overlevelse (event-free survival/EFS) hvor der blev stratificeret for deltagere, der hhv. blev vurderet til at have eller ikke have baseline sygdom af BICR (alle patienter var vurderet sygdomsfri af investigator ved baseline men nogle blev ved BICR vurderet til ikke at være sygdomsfri ved baseline). Definitionen af hændelsesfri overlevelse var derfor recidiv eller død for patienter der var vurderet sygdomsfri ved baseline af BICR, og progression for de patienter hvor BICR vurderede at der var målbar sygdom ved baseline. Ved dataafskæringerne IA1 og i EMA +6-måneder opfølgning var resultaterne af denne følsomhedsanalyse også i overensstemmelse med resultaterne af den primære DFS-analyse for begge analyse. En yderligere følsomhedsanalyse hvor DFS blev vurderet ved BICR blev udført, og igen var resultaterne i overensstemmelse med investigator-evalueret DFS. Overordnet var der overensstemmelse ved over 80% mellem investigator og blændet evaluering hos patienter med recidiv og over 89% overensstemmelse ved patienter uden recidiv, uden bias til større eller mindre overensstemmelse i hhv. pembrolizumab- eller placebogruppen (29)

**MSD mener, at den signifikante og klinisk relevante reduktion på hhv. 37% af recidiv opgjort ved DFS efter 30 måneders opfølgning og det faktum, at alle subgrupper viser en klar effekt på DFS, indikerer en stor klinisk merværdi af adjuverende pembrolizumab for RCC patienter med øget risiko for recidiv efter nefrektomi. Effekten understøttes af, at følsomhedsanalyserne stemmer overens med det primære endepunkt (DFS).**

### 7.1.5 Vigtigste sekundære endepunkt – overordnet overlevelse (OS)

#### 7.1.5.1 Overordnet overlevelse, OS, ved IA1 (24,1 mdr. opfølgning)

OS-dataene var umodne ved IA1 med 51 dødsfald (26% af de samlede planlagte 200 OS-hændelser ved den endelige OS analyse). For OS var HR 0,54 (95% CI: 0,30, 0,96) (p = 0,0164037), og median OS blev ikke nået i nogen af grupperne. P-værdien krydsede ikke den prædefinerede statistiske signifikans på $9{,}3\times10^{-6}$ ved IA1. Den øvre grænse på 95 % CI for OS HR var under 1,0 med næsten dobbelt så mange dødsfald i placebogruppen (33) sammenlignet med pembrolizumab-gruppen (18 dødsfald(2)). Se Figur 10(A).

#### 7.1.5.2 Overordnet overlevelse: EMA +6 måneders (EUR) opfølgning

Ved data cutoff for de 6 ekstra måneders opfølgning efterspurgt af EMA var OS-resultaterne i overensstemmelse med resultaterne fra IA1. Der var i alt indtruffet 66 dødsfald (33% af de samlede planlagte 200 OS-begivenheder ved den endelige analyse). HR var styrket i forhold til IA1 med HR=0,52 (95% CI: 0,31, 0,86) (p = 0,0047677), og median-OS blev ikke nået i nogen af grupperne. P-værdien krydsede ikke den statistiske p-værdigrænse på 0,000095 ved EUR-dataafskæringen. Den øvre grænse på 95% CI for OS HR forblev under 1,0, og der var næsten dobbelt så mange dødsfald i placebogruppen (43) sammenlignet med pembrolizumab-gruppen (23) – og ligeledes dobbelt så mange nye dødsfald i placebogruppen siden IA1 (10 vs. 5 i pembrolizumab-gruppen).



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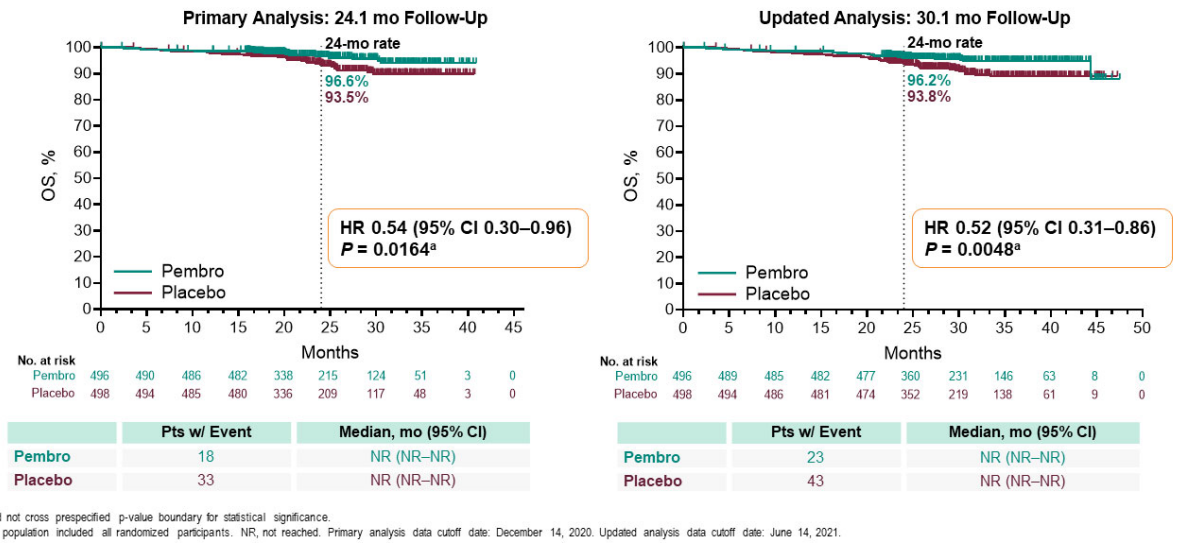


aDid not cross prespecified p-value boundary for statistical significance.
ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

**Figur 10 Kaplan-Meier estimater af OS fra KN564 (ITT-populationen) ved hhv. 24,1 (IA1) og 30,1 måneders (EUR+6 mdr.) opfølgning**

Det er vigtigt at understrege, at på trods af at OS-data er umodne, er der på 2 uafhængige data cutoffs (IA1 og EUR med hhv. 24,1 og 30,1 måneders opfølgning) vist en klar tendens til at adjuverende behandling med pembrolizumab forbedrer den overordnede overlevelse for nefrektomerede RCC patienter, med en foreløbig risikoreduktion på 48% for at dø. Det er også værd at bemærke at disse observationer er foretaget med ca. 2½ års opfølgning, og disse observationer indikerer altså en langtidseffekt på forbedret overlevelse grundet behandling med adjuverende pembrolizumab.

Der blev desuden foretaget en post hoc analyse af PFS2 baseret på investigatorevaluering. PFS2 blev defineret som tiden fra randomisering til sygdomsprogression på næste linje anticancerlægemiddelbehandling, eller død af enhver årsag, alt efter hvad der skete først. I alt 63 deltagere i pembrolizumab-gruppen og 86 deltagere i placebogruppen modtog efterfølgende kræftbehandling ved IA1, og efter yderligere 6 måneder ved EUR var tallene 67 og 99, hhv. PFS2, altså progression på første efterfølgende behandling efter recidiv i KN564, understøtter hypotesen om forbedret langtidseffekt på overlevelse, da PFS2 favoriserede pembrolizumab gruppen med en HR på hhv. 0,52 (0,34-0,81) og 0,57 (0,39-0,85) ved de to data cutoffs (IA1 og EUR ). Hvis dette ikke var tilfældet kunne man måske forvente, at en evt. effekt af adjuverende behandling med pembrolizumab kunne udlignes ved medicinsk behandling for metastatisk sygdom, der jo i høj grad beror på kombinationsbehandling med immunterapi(73). Men PFS2 data tyder altså ikke på dette, men derimod en langtidseffekt af adjuverende behandling. Se figur og detaljer afsnit 7.1.6.4

**Den tydelige trend mod en næsten halvering af risikoen for dødsfald efter behandling med adjuverende pembrolizumab til RCC patienter med øget risiko for recidiv efter nefrektomi indikerer en stor merværdi og understøttes af 2,5 års opfølgning samt, at PFS2-data understøtter en langtidseffekt af behandlingen.**

### 7.1.6 Andre sekundære endepunkter

#### 7.1.6.1 Livskvalitet - Patient-rapporterede værdier (PRO)

Livskvalitet blev evalueret ved doseringscyklus 1, 5, 9, 13 og 17 samt ved seponering, ved 30-dages opfølgning efter sidste dosis, og årligt under opfølgning efter endt behandling, indtil recidiv eller ny anticancerbehandling var indledt. De 3 præspecificerede PRO-endepunkter var: gennemsnitlig ændring (least means square) fra baseline til uge 52 i 1)



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FKSI-DRS-score, 2) EORTC-QLQC30 global sundhedsstatus / livskvalitet score og 3) EORTC-QLQ-C30 fysisk funktionsskala. Disse instrumenter blev valgt da de blandt de validerede PRO instrumenter blev vurderet til bedst at kunne fange evt. ændringer i livskvalitet forårsaget dels af nyrekræft symptomer samt bivirkninger fra pembrolizumab. Nominelle p-værdier blev beregnet for sammenligninger mellem behandlingsgrupper. Da livskvalitetsanalyserne ikke indgik som primære endepunkter i den statistiske analyseplan og der ingen formel hypotesetestning var, blev resultaterne ikke justeret for multiple sammenligninger og bør derfor fortolkes med forsigtighed. Besvarelsesraten for FKSI-DRS ved baseline til og med uge 52 var generelt høj (89,2%/92,1% ved baseline for hhv. pembrolizumab/placebo, 62,1%/66,5% i uge 52 for pembrolizumab/placebo), ligesom compliancegraden generelt var høj (90,1%/90,7% ved baseline for pembrolizumab/placebo, og 85,0% for begge grupper ved uge 52) og var sammenlignelig i begge behandlingsgrupper. Besvarelsesraten for uge 104 var hhv. 18,2%/18,5% med compliance på 77,2%/83,5% for hhv. pembrolizumab/placebo. Besvarelses- og compliancegraderne for EORTC QLQC30 og EQ-5D-5L svarede til dem der gælder for FKSI-DRS; besvarelsesrater var sammenlignelige med <4,1%-points i forskel og compliance rater var næsten identiske med <1%-point i forskel. Grundet den høje besvarelsesrate og compliance kan man overordnet sige at populationen er sammenlignelig fra baseline til uge 52 – men det er klart at der er en del patienter der udgår af studiet grundet hhv. pga. progressiv sygdom forårsaget at recidiv (når de opstarter ny behandling), og disse patienter vil formentligt være blandt dem med flest sygdoms relaterede symptomer. Da der er flest af disse patienter i placeboarmen kunne dette resultere i at livskvalitet, især til de sene tidspunkter, overestimeres især i placebogruppen.

#### 7.1.6.2 Vigtige PRO-slutpunkter: Ændring fra baseline i FKSI-DRS og EORTC QLQ-C30 Global Health Status / Livskvalitet

En ændring i FKSI-DRS-score på ≥3 og en ændring i EORTC QLQ-C30-score på ≥10 blev anset for at være klinisk meningsfuld ud fra bl.a. tidligere studier der inkluderer de studier der var med til at udvikle de anvendte PROredskaber (32-34)). For både FKSI-DRS og EORTC QLQ-C30 global sundhedsstatus / QoL-score sås der en marginal reduktion fra baseline til uge 52 i både pembrolizumab- og placebogrupperne der ikke ansås for at være klinisk betydende for patienterne (Tabel 9, Tabel 10, Figur 11 og Figur 12).

**Tabel 9 Ændring fra baseline i EORTC QLQ-C30 Global Health Status/QoL til uge 52 (PRO fulde analyse set (FAS) Population)**

| | Baseline | | Week 52 | | Change from Baseline to Week 52 | |
|---|---|---|---|---|---|---|
| Treatment | N | Mean (SD) | N | Mean (SD) | N | LS Mean (95% CI)[a] |
| Pembrolizumab | 438 | 79.22 (18.46) | 301 | 74.92 (18.26) | 484 | -4.25 (-6.32, -2.19) |
| Placebo | 450 | 77.04 (17.61) | 325 | 76.82 (19.56) | 492 | -1.68 (-3.69, 0.32) |
| Pairwise Comparison | | | | | Difference in LS Means[a] (95% CI) | p-Value[a] |
| Pembrolizumab vs. Placebo | | | | | -2.57 (-5.22, 0.08) | 0.0571 |

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.
For baseline and Week 52, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 14DEC2020



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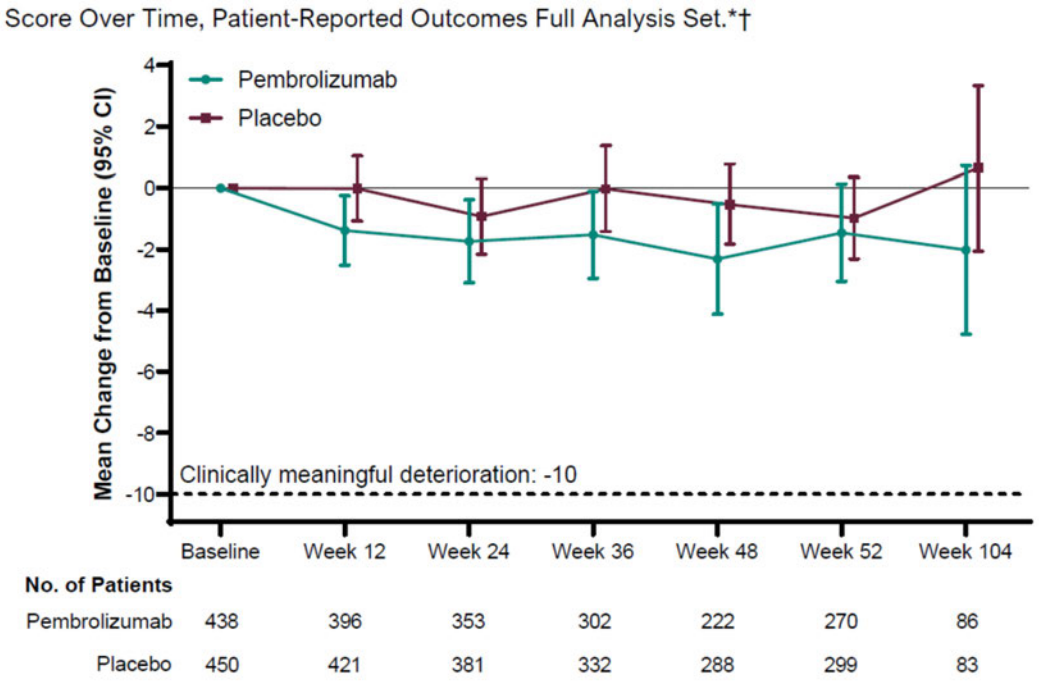


**Figur 11 Empirisk ændring fra baseline i EORTC QLQ-C30 Global Health Status/QoL til uge 52 (PRO FAS Population)**

***Patientrapporterede outcomes blev analyseret hos alle randomiserede patienter, der fik mindst 1 dosis af studiebehandling og gennemført mindst 1 patientrapporteret resultatvurdering. †Klinisk meningsfuld ændring defineret som gennemsnitlig ændring på ≥10 point(34).**

**Tabel 10 Ændring fra baseline i FKSI-DRS-score til uge 52 (PRO FAS-population)**

| Treatment | Baseline | | Week 52 | | Change from Baseline to Week 52 | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | N | LS Mean (95% CI)[a] |
| Pembrolizumab | 435 | 32.86 (3.50) | 300 | 31.85 (4.69) | 483 | -1.12 (-1.53, -0.71) |
| Placebo | 447 | 32.79 (3.53) | 328 | 32.51 (4.13) | 492 | -0.45 (-0.84, -0.05) |
| Pairwise Comparison | | | | | Difference in LS Means[a] (95% CI) | p-Value[a] |
| Pembrolizumab vs. Placebo | | | | | -0.67 (-1.23, -0.12) | 0.0170 |

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.
For baseline and Week 52, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
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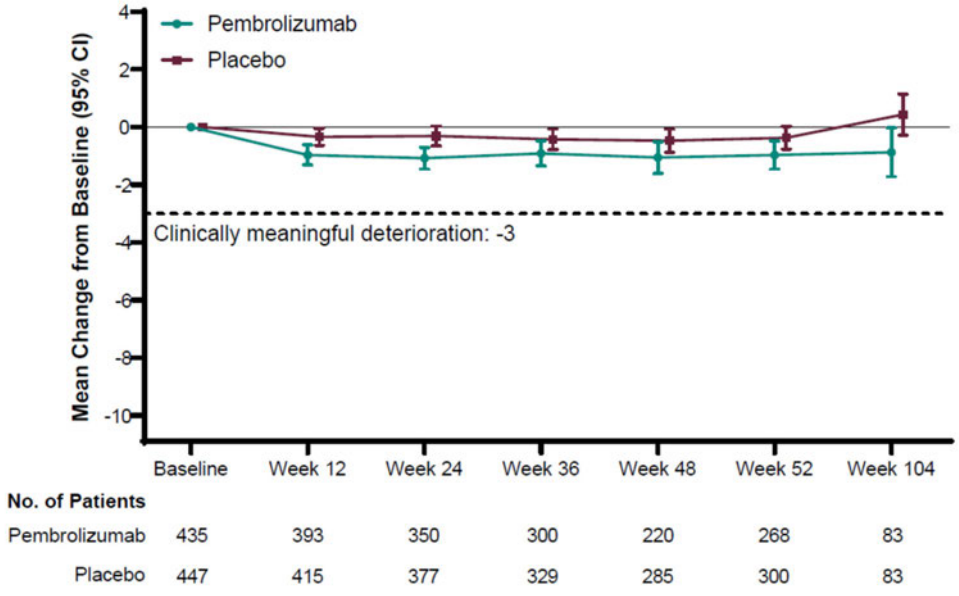


**Figur 12 Ændring fra baseline i FKSI-DRS-score til uge 52 (PRO FAS-population)**

Ved livskvalitetsundersøgelser er det vigtigt at overveje, hvilke bias der kan introduceres under dataindsamlingen. Generelt kan man sige at instrumenterne, der blev anvendt ikke specifikt er udviklet til adjuverende behandling, men snarere symptomatisk metastatisk RCC (FKSI-DRS) og desuden blev EORTC-QLQ-C30 udviklet under en æra, hvor kemoterapi og strålebehandling var fremtrædende og før introduktionen af immunterapi. Derfor er disse instrumenter ikke nødvendigvis optimale til at evaluere livskvalitet hos KN564 patientpopulationen, men når det er sagt er de begge grundigt validerede, og anerkendte til at påvise større forskelle i livskvalitet for cancerpatienter. De er desuden udvalgt i samarbejde med regulatorer og klinikere og vurderet til at være de bedst egnede instrumenter.
Mht. tidspunkt for dataindsamlingen blev dette foretaget jævnt hen over det år, patienter var i behandling, 30 dage efter sidste visit samt årligt for både at opfange evt. signaler/ændringer for livskvalitet under og efter behandling. Da mange bivirkninger opstår indenfor de første 2-4 måneder, dækker tidspunkterne efter 1., 5. og 9. cykel denne periode.
Missing data blev behandlet efter manualerne til livskvalitetsinstrumenternes anbefalinger, og det var på forhånd defineret, at "mean change from baseline" analyserne skulle udføres ved det seneste tidspunkt hvor ≥60% af PRO-FAS populationen besvarede spørgeskemaerne (CR-T), og hvor compliance samtidigt var ≥80% (CR-E).
Til at understøtte validiteten af livskvalitetsmålingerne anvendtes 2 parametre: Fuldførelsesgrad (completion rate of treated patients; CR-T): antallet af patienter der udfyldte mindst ét item af et spørgeskema divideret med antallet af patienter i PRO FAS-populationen (alle der på et tidspunkt minimum har besvaret ét livskvalitetsspørgeskema/instrument og modtaget én dosis studiemedicin) ved det givne tidspunkt. Formlen er:

$$\text{CR-T} = \frac{\textit{Number of treated participants who complete at least one item}}{\textit{Number of treated participants in the PRO analysis population}}$$

Da fuldførelsesgraden forventes at svinde undervejs i studiet pga. patienter der udgår, anvendtes "compliance rate af eligible patienter" (CR-E), defineret ved antallet af patienter, der udfyldte mindst et item af et livskvalitetsspørgeskema divideret med antallet af patienter, der forventes at besvare på det givne tidspunkt, dvs. PRO-FAS populationen fratrukket patienter der var "missing by design" som bl.a kunne forårsages af flg: opstartet næste linje behandling, afbrudt behandling grundet bivirkninger eller recidiv, tilbagetrukket samtykke, klinikers eller patients beslutning om at afslutte behandlingen, tabt til opfølgning, eller non-adherence til protokollen). Kort sagt hvor mange af de tilbageværende i PRO-populationen, der svarede. Formlen er:



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$$\text{CR-E} = \frac{Number\ of\ treated\ participants\ who\ complete\ at\ least\ one\ item}{Number\ of\ eligible\ participants\ who\ are\ expected\ to\ complete}$$

Effektmålet for livskvalitetsanalyserne, "mean change from baseline", var i den statistiske plan på forhånd bestemt til at skulle opgøres til det seneste tidspunkt, hvor CR-T ≥ 60% og CR-E ≥ 80% og uge 52 blev valgt på baggrund af blindet review forud for databaselock for alle PRO-analyserne.

Beslutningen om at vælge uge 52 blev foretaget på blindet grundlag inden data-unblinding. Der var generelt en høj svarrate og compliance, der var meget sammenlignelig i begge grupper, og der er ikke umiddelbart nogen systematisk bias tilknyttet indsamlingen af PRO. Den bias, der måtte forekomme, skulle være ved, at PRO besvarelser indhentedes indtil ophør af behandling – og her var der flere patienter i pembrolizumab gruppen, der ophørte behandling pga. bivirkninger, mens der var flere patienter, der ophørte behandling i placebogruppen pga. recidiv. Begge årsager må forventes overordnet set potentielt at forværre patienternes livskvalitet i form af sygdomssymptomer og bivirkninger. Ligeledes modtog flere patienter i placebogruppen efterfølgende behandling, hvorved PRO stoppes, og her undervurderes altså den potentielt negative livskvalitetsværdi af efterfølgende behandlinger. Opsummerende kan det altså siges, at der er mulighed for at introducere bias i PRO datasættet, men at disse findes både hos placebo og pembrolizumab behandlede patienter og kan antages at udjævne hinanden.

Der blev ikke foretaget en opdateret analyse af livskvalitet til den af EMA efterspurgte analyse med 6 måneders ekstra opfølgning. Overordnet sås en klinisk meningsfuld og statistisk signifikant forbedring af DFS efter adjuverende behandling med pembrolizumab, uden at dette forringede de behandlede patienters livskvalitet sammenlignet med placebo, som er dansk klinisk praksis.

**MSD anser det for afgørende, at adjuverende behandling med pembrolizumab er tolerabelt set fra patienternes syn, og altså signifikant reducerer risikoen for recidiv efter nefrektomi uden at forringe patienternes livskvalitet.**



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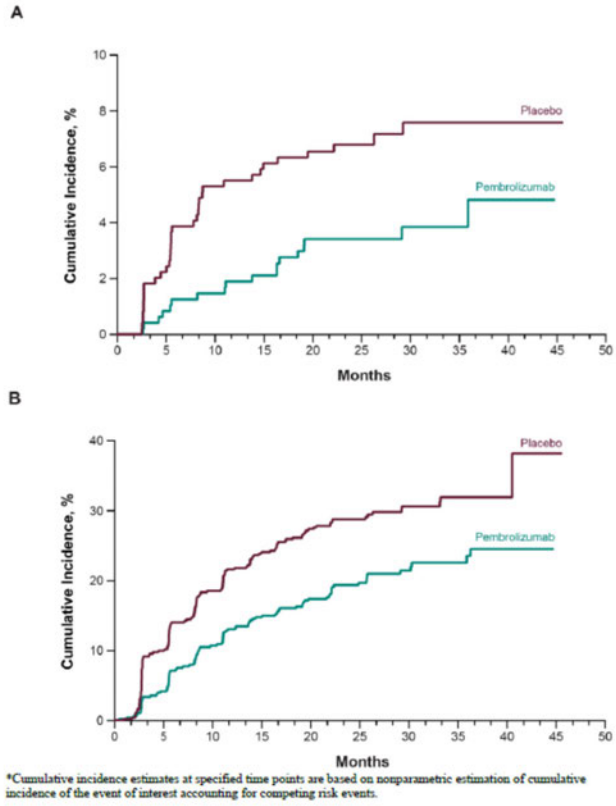
### 7.1.6.3 Lokal og fjernrecidiv

Det er kliniske relevant at opdele RCC patienter med recidiv efter nefrektomi i hhv. lokal (i samme nyre, kaldet disease-recurrence-specific survival 1/DRSS1)) og fjern (recidiv med viscerale metastaser med eller uden localrecidiv, DRSS2) recidiv, da behandlingsmodaliteten for lokalt recidiv oftest vil være kirurgi, mens fjern recidiv med viscerale metastaser oftest behandles med systemiske medicinske modaliteter (13, 73). Lokal recidiv omfattede renal fossa, nyreseng/perinefritiske rum, eller lokale lymfeknuder. Fjern recidiv omfattede binyrerne, fjerne lymfeknuder, kontralateral nyre eller ethvert andet organ, væv eller rum. Bekræftelse af recidiv via biopsi eller cytologi blev foretaget når muligt. Resultaterne for lokalt (DRSS1) og fjernt (DRSS2) recidiv for både IA1 og EMA-data med 6 måneders yderligere opfølgning viste at både lokale og fjerne recidiver for pembrolizumab-gruppen konsekvent var lavere sammenlignet med placebogruppen. Således havde 17 (3,4%) og 32 (6,6% af patienterne fået lokalrecidiv ved IA1 i hhv. Pembrolizumab og placeboarmen, og tilsvarende havde 94 (19,8%) og 134 (28,2%) af patienterne fået fjernmetastatisk recidiv I pembrolizumab/placeboarmen (IA1). Ved EUR analysen med de 6 ekstra måneders opfølgning havde 108/496 patienter (21,8 %) I pembrolizumab armen fået et recidiv fordelt på 18 (3,4%) lokalrecidiv og 100 (19,3%) fjernrecidiv. I placeboarmen var antallet af recidiv 166/498 patienter (33,3 %) fordelt på 35 (6,8%) lokale og 149 (28,7%) fjernmetastatiske recidiv.




**Figur 13 Kumulativ incidens af (A) lokal (DRSS1) samt (B) fjernmetastatisk (DRSS2) recidiv fra KN564, med 30,1 måneders opfølgning(1)-suppl.**

KN564 studiet viste desuden, at ca. 80% af tilbagefald sker i form af et fjernmetastatisk recidiv, som er korreleret med højere dødelighed (1, 67). Den store andel fjernmetastatisk recidiv stemmer overens med data fra en nyligt publiceret restrospektiv analyse der inkluderede 269 Medicare RCC-patienter diagnosticeret mellem 2007-2016 i de KN564 definerede intermediær-høj (95,9 %) og høj (4,1 %) risikogruppe fra den amerikanske SEER database. Af patienter med et recidiv efter nefrektomi viste dette studie at 10,8 % havde fået et lokalrecidiv og 89,2 % havde fået et fjernrecidiv(89). I Tabel 1 i indledningen ses antal events for lokal-/fjernrecidiv fra både IA1 og EUR data cutoffs, og på Figur 13 ses akkumuleret lokal samt fjernmetastisk recidiv fra det sene data (EUR) cutoff med 30,1 måneders opfølgning. Data viser, at pembrolizumab reducerer risikoen for både lokalt og fjernmetastatisk recidiv efter nefrektomi.

### 7.1.6.4 PFS2

Desuden er et vigtigt endepunkt i adjuverende forsøg PFS2 – altså progression på efterfølgende linjer af behandling efter recidiv (her defineret som medicinsk behandling, altså fraset kirurgi og stråling). Grundet PFS2 analysens post hoc natur og det stadig relativt lave antal hændelser er denne analyse ligesom overlevelsesanalysen præmatur, men der ses igen en klar trend af bedre progressionsfri overlevelse på påbegyndt behandling efter recidiv hos de patienter der



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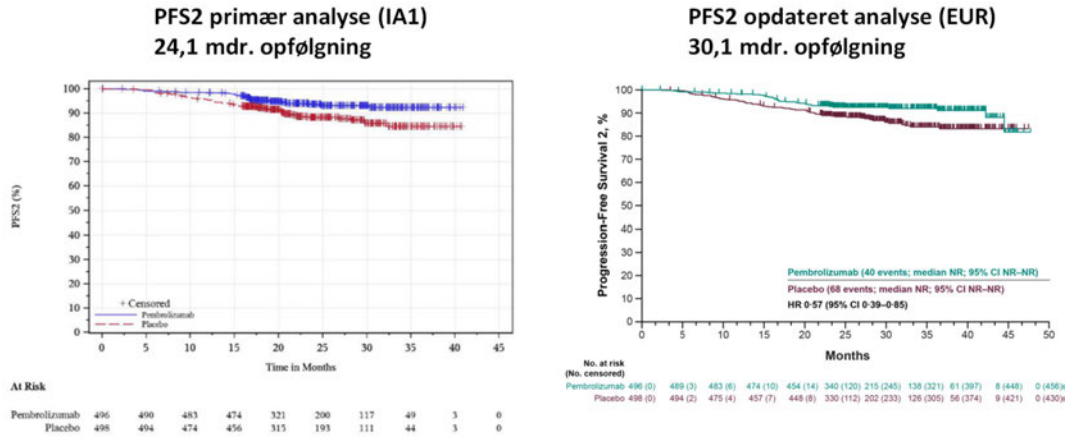
oprindeligt blev behandlet med adjuverende pembrolizumab. Dette modsiger bekymringen for at adjuverende behandling muligvis vil nedsætte effekten af efterfølgende behandling til metastatiske patienter. Ved IA1 var HR=0,52 (95% CI 0,34-0,81, nominel p=0,0018). Således er det interessant og relevant at ud af de 63 patienter med recidiv i pembrolizumab gruppen der fik efterfølgende medicinsk behandling var der 30 (47,6%) der progredierede eller døde på næste linje behandling, mens der ud af de 86 patienter med recidiv i placebogruppen der modtog efterfølgende medicinsk behandling var 56 (=65,1%) af patienterne der progredierede eller døde på næste linje behandling. Ved yderligere 6 måneders opfølgning (EUR data cutoff med 30,1 mdr. opfølgning) var HR=0,57 (0,39-0,85) med hhv. 40 og 68 events I pembrolizumab/placebogruppen, og stadig en større andel der progredierede på PFS2 analysen i placeboarmen. Med andre ord er der større risiko for at progrediere på næste linje behandling, hvis man fik et recidiv efter at have modtaget placebo frem for pembrolizumab, og dette til trods for, at en højere andel af patienter med medicinsk behandling efter recidiv i placeboarmen (59/99 eller 60%) end i pembrolizumab armen (16/67 eller 24%) fik immunbaseret behandling.




**Figur 14 PFS2 ved de to data cutoffs med hhv. 24,1 (IA1 (29)) og 30,1 (EUR (1)) måneders opfølgning. PFS2 defineres ved progression på første efterfølgende behandling**

**Disse data understøtter en langtidseffekt af adjuverende pembrolizumab, der ikke udlignes ved næste linje behandling og den generelle store kliniske merværdi.**

### 7.1.6.5 Bivirkninger

Bivirkninger rapporteres hos patienter, som har modtaget minimum én dosis studiemedicin (All Patients as Treated (ApaT) population) som svarer til 488 patienter i pembrolizumab-gruppen og 496 patienter i placebogruppen. Den mediane behandlingslængde for grupperne var for begge grupper 11,1 mdr. (range 0,0-14,3 mdr. for pembrolizumab- og 0,0-15,4 mdr. i placebogruppen) svarende til mediant 17 modtagne doser i begge grupper. Det er vigtigt at have for øje at der her er tale om en aktiv behandling (adjuverende pembrolizumab) overfor placebo, der svarer til dansk klinisk praksis (opfølgning efter nefrektomi), både fordi det forventes at en aktiv behandling vil medføre flere bivirkninger end placebo, men også fordi at hovedparten af bivirkningerne i placebo-armen må antages at stamme fra komorbiditeter og alders-specifik tilstand hos patienterne – og at der er signifikante adverse events (bedre beskrivende ord end bivirkning i dette tilfælde) ved patienterne selv i placebo armen.

Den samlede incidens af bivirkninger var sammenlignelig i de 2 behandlingsgrupper. Andelen af deltagere, der havde ”all-cause” og behandlingsrelaterede grad 3 til 5 bivirkgninger, alvorlige bivirkninger og bivirkninger der førte til



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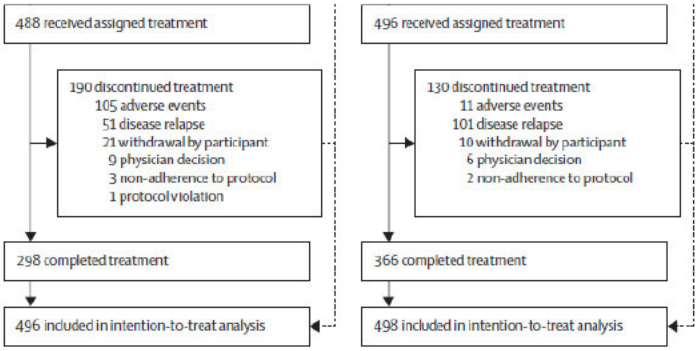
behandlingsophør var højere i pembrolizumab-gruppen sammenlignet med placebogruppen ved IA1 [Tabel 11], som forventet i sammenligningen af en aktiv behandling (pembrolizumab) versus placebo. To dødsfald på grund af AE'er i pembrolizumab-gruppen (lungebetændelse og multipelt organdysfunktionssyndrom) og 1 død på grund af AE'er i placebogruppen (intrakraniel blødning) blev rapporteret. Ingen af dødsfaldene blev vurderet behandlingsrelaterede af investigatorerne. Der blev ikke observeret nye typer af immunmedierede bivirkninger ifht. tidligere pembrolizumab studier. Der blev ikke rapporteret om ændringer I type, art, resultater og styring af bivirkninger af særlig interesse. Der blev ikke identificeret nogen klinisk meningsfulde forskelle mellem individuelle demografiske subpopulationer og den samlede mængde bivirkninger.




**Figur 15 Oversigt over antal patienter og årsager til behandlingsophør. Modificeret fra (1)**

Data med længst mulig opfølgning (EUR, 30,1 måneders opfølgning) viste at hhv. 298/488 (61%) patienter gennemførte pembrolizumab behandlingen mens 366/496 (73,7%) patienter gennemførte placebo behandlingen. Ved de ekstra 6 måneders opfølgning var der 105 (21,5%) patienter der afbrød behandling med pembrolizumab pga. en bivirkning mens 11 patienter (2,2%) afbrød placebo pga. bivirkninger, hvoraf hovedparten ikke var alvorlige (Figur 15). Altså yderligere 4 patienter i pembrolizumab armen og 1 patient i placebo armen siden opgørelsen ved IA1. Den hyppigst forekommende årsag til at afbryde behandling udover bivirkninger var i begge grupper recidiv. Den mediane behandlingslængde for de 105 pembrolizumab patienter der afbrød behandling modtog gennemsnitligt 7 cykler (range, 1-16) med en median behandlingslængde på 4,4 måneder (range, 0,03-11,1) ved IA1. Mht. De 11 patienter i placebo gruppen, der afbrød behandling pga. en bivirkning, inkluderede disse: forhøjet blodkreatinin, artralgi, ataxia, choroid melanom, colon neoplasma, alkoholisk hepatitis, hapatotoksisitet, multiple skader, ikke-hjerte relateret brystsmerter, nethindeløsning og død. Generelt kan det siges for studiets patientpopulation, at den er karakteriseret ved relativt høj alder, og ~15% havde en ECOG performance status på 1, hvilket indikerer betydende underliggende comorbiditeter udover deres nyrecancer. Da studiet er dobbeltblindet, er det ikke overraskende, at der for en vis andel af patienter - selv under placebo behandling - vil opstå kliniske udfordringer, der kræver behandlingsophør, selvom det næppe er relateret til placebo-behandlingen. Igen er den engelske term, adverse events, bedre beskrivende end det danske bivirkning, da sidstnævnte indikerer en kausal sammenhæng med (i dette tilfælde) placebo. Hhv. 96,3% og 91,1% af patienterne i pembrolizumab og placebo grupperne oplevede mindst én bivirkning uanset grad, mens 32,4% og 17,7% af patienterne i hhv. pembrolizumab/placebo grupperne oplevede bivirkninger af grad 3-5. De mest almindelig bivirkninger uanset grad i begge grupper var fatigue, diarré, kløe (pruritus), og artralgi i de to grupper. Bivirkningerne med størst forskel var hypotyroidisme, hypertyroidisme, kløe (pruritus) og udslæt. Disse er kendte bivirkninger for pembrolizumab og ingen nye sikkerhedssignaler blev fundet. 79,1% og 53,4% af patienterne i hhv pembrolizumab- og placebo-grupperne oplevede behandlingsrelaterede bivirkninger af enhver grad, mens 18,9% af patienterne i pembrolizumab-gruppen, og 1,2% i placebo-gruppen oplevede en behandlingsrelateret grad 3-4 bivirkning.



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**Tabel 11 Bivirkningstabel, IA1**

| | Pembrolizumab | | Placebo | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | |
| with one or more adverse events | 470 | (96.3) | 452 | (91.1) |
| with no adverse event | 18 | (3.7) | 44 | (8.9) |
| with drug-related[a] adverse events | 386 | (79.1) | 265 | (53.4) |
| with toxicity grade 3-5 adverse events | 158 | (32.4) | 88 | (17.7) |
| with toxicity grade 3-5 drug-related adverse events | 92 | (18.9) | 6 | (1.2) |
| with serious adverse events | 100 | (20.5) | 56 | (11.3) |
| with serious drug-related adverse events | 59 | (12.1) | 1 | (0.2) |
| who died | 2 | (0.4) | 1 | (0.2) |
| who died due to a drug-related adverse event | 0 | (0.0) | 0 | (0.0) |
| discontinued drug due to an adverse event | 101 | (20.7) | 10 | (2.0) |
| discontinued drug due to a drug-related adverse event | 86 | (17.6) | 3 | (0.6) |
| discontinued drug due to a serious adverse event | 49 | (10.0) | 5 | (1.0) |
| discontinued drug due to a serious drug-related adverse event | 37 | (7.6) | 0 | (0.0) |

[a] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 14DEC2020.

20,5% og 11,3% i pembrolizumab- og placebogruppen havde mindst én alvorlig bivirkning (serious adverse event; SAE), og det tilsvarende tal for alvorlige behandlingsrelaterede bivirkninger var hhv. 12,1% og 0,2%. Immunrelaterede bivirkninger (præspecificeret af MSD) af enhver grad og uden stillingtagen til sammenhæng med behandling forekom i 34,6% og 5,8% i pembrolizumab- hhv. placebo-gruppen. Immunrelaterede bivirkninger af grad 3-4 sås hos 8,6% og 0,6% i patienter behandlet med pembrolizumab vs. placebo. Der forekom ikke nogen dødsfald pga. immunmedierede bivirkninger. Steroid-brug blev opgjort fra patienter blev randomiseret og til de de udgik af studiet. 7,4% af patienter i pembrolizumab-gruppen og 0,6% i placebogruppen modtog høj-dosis corticosteroider (>40 mg pr. dag) mod immunrelaterede bivirkninger. for yderligere tabeller om bivirkninger se Appendiks E Sikkerhedsdata for intervention og komparator(er).

Baseret på pembrolizumab reference sikkerhedsdata (RSD) fra 5884 (hovedsageligt metastatiske) patienter, der har indgået i KEYNOTE studier, ved vi, at hovedparten af bivirkninger fra pembrolizumab er reversible og kan behandles med enten pausering/ophør af pembrolizumab, steroider eller best supportive care. Afgørende for behandling af bivirkninger og deres alvorlighed/varighed er tidlig opsporing og erfaring med multidisciplinær involvering af håndtering. De danske nyrekræftafdelinger har flere års håndtering med dette. Det er dog vigtigt at anføre, at bivirkninger, især de immunrelaterede, ved pembrolizumab (og immunterapi generelt) kan være irreversible. Årsagen hertil er, at pembrolizumab øger immunsystemets aktivitet ved at blokere en negativ regulator af immunsystemets aktivitet (PD-1 receptoren). Dette kan ændre på tolerance af autoreaktive immunceller, f.eks. T celler, og derved forårsage bivirkninger, der har karakter af autoimmune sygdomme. Denne balance forskydes ikke nødvendigvis tilbage ved pausering eller ophør af behandling. Det er vigtigt at bemærke forskellen på bivirkninger ved anti CTLA-4 (som ipilimumab), anti-PD-1 (som pembrolizumab) og dobbeltimmunterapi som nivolumab-ipilimumab. Et studie opgjorde irAEs gr.≥3 ved ca. 6%, 24% og 55% for hhv. anti-PD-(L)1, anti-CTLA-4 og kombinationen af de to (90). Her beskrives også, at de fleste irAEs opstarter indenfor de første 12 uger af behandling med anti-PD-(L)1, og generelt afsluttet indenfor 6-8 uger(90). Irreversible bivirkninger kan være endokrine, hvor immunsystemet f.eks. angriber hormon-producerende celler i en kirtel - her kan f.eks. nævnes diabetes og hyper/hypothyroidisme som et eksempler. I nærværende studie var der opgjort 9/488 (1,8%) patienter i APaT populationen med grad 3 Type 1 diabetes melitus, og 5/488 (1%) patienter i pembrolizumab armen, der fik grad ≥3 diabetisk ketoacidose. I vores reference sikkerhedsdatasæt fra 5884 patienter, primært metastatiske patienter med forskellige tumorer, er der tilsvarende 0,3% med T1DM og 0,2%



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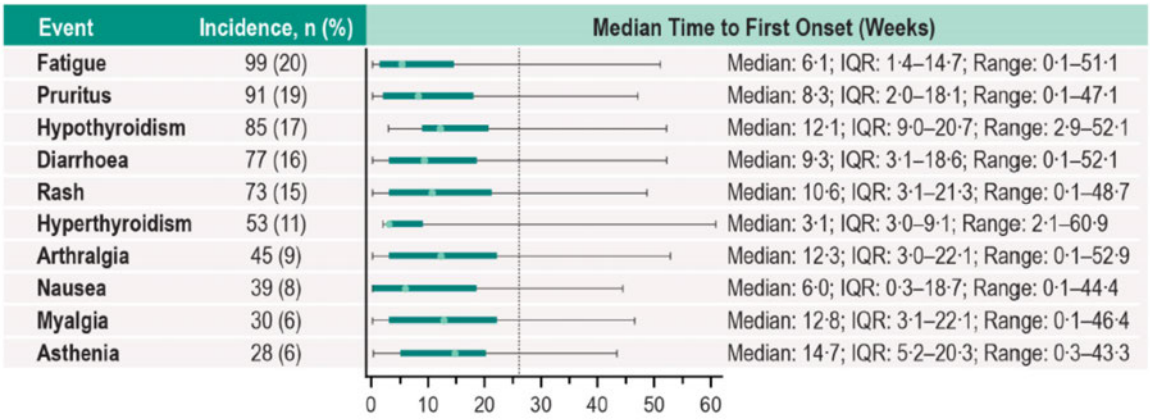
med diabetisk ketoacidose. Hyper- og hypothyroidisme samt binyreinsufficiens er også kendte endokrine bivirkninger, men her var alle registrerede tilfælde af thyroidisme grad 1-2 udover een patient hver med grad 3 hyper- og hypothyroidisme, og 6 patienter med grad 3-4 binyreinsuffiens. Hovedparten af disse blev behandlet med hormon-erstatning. Hovedparten af alle, samt immunrelaterede bivirkninger, begynder mediant 1-4 måneder fra behandlingsstart (Figur 16), og den mediane varighed af immunrelaterede bivirkninger (de af MSD på forhånd definerede bivirkninger af særlig interesse (AEOSI)) var 101 dage, mens bivirkninger hos 42,2% af patienter med en eller flere AEOSI ikke var afsluttet ved de 24,1 måneders opfølgning (IA1). Disse data er ikke opgjort for EUR data cutoff med 30,1 måneders opfølgning .(1, 91).




**Figur 16 Tid (uger) til første hændelse af alle grader behandlingsrelaterede bivirkninger (incidens ≥6% in pembrolizumab armen(1)**

På baggrund af gennemgang af bivirkningens profilerne i KN564 kan det konkluderes at:

- Bivirkningerne var håndterbare og konsistente med de allerede kendte bivirkninger for pembrolizumab
- Tillæg af pembrolizumab ikke øger incidensen af alvorlige bivirkninger (SAE), som ikke kan håndteres i klinikken (ekspertudsagn).
- Bivirkningsprofil ved immunterapi kan principielt forekomme overalt i kroppen. Vigtigt med god dialog mellem onkolog og patient for tidlig behandling og udredning af bivirkninger

Overordnet kan det konkluderes at adjuverende behandling med pembrolizumab til RCC patienter efter nefrektomi signifikant reducerede risikoen for recidiv mens den øgede mængde bivirkninger der tilføres patienter der ellers ikke ville være blevet medicinsk behandlet var håndterbar og som forventet.

**MSD mener, at den håndterbare og forventede øgning af bivirkninger ved adjuverende pembrolizumab kombineret med den kliniske effekt indikerer en vigtig klinisk relevant merværdi for patienter med ccRCC efter nefrektomi.**

# 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 pembrolizumab for adjuvant treatment of patients with renal cell carcinoma (RCC) who have undergone nephrectomy. The following will also describe the budget impact of introducing pembrolizumab in the Danish health care budget with the help of a budget impact analysis.

### 8.1.1 Brief summary of relevant economic modeling literature

No economic model evaluating the cost-effectiveness of pembrolizumab as an adjuvant treatment RCC has been published. A targeted literature review was previously conducted in February 2018 to identify published cost-effectiveness studies of adjuvant therapies for melanoma, (93-96)or other adjuvant oncology indications (97-99). A subsequent update of this targeted literature review in January 2020 identified several newly published cost-effectiveness studies of adjuvant therapies(100-102) (103, 104) as well as an older adjuvant cost-effectiveness publication that used a multi-state modeling approach(105). However, no published economic evaluations were identified for adjuvant treatments of RCC.

A targeted review was conducted in October 2019 to identify and examine prior HTAs of novel adjuvant or neoadjuvant treatments in oncology indications, including appraisals by the National Institute of Health and Care Excellence (NICE) in the UK, the pan-Canadian Oncology Drug Review (pCODR) in Canada, the Scottish Medicine Consortium (SMC) in Scotland, and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. Overall, 19 appraisals are identified for (neo)adjuvant treatments of melanoma and breast cancer and are referenced in the development of this model. No completed appraisals of adjuvant treatments for RCC are identified. The NICE appraisal in development for sunitinib as an adjuvant treatment of RCC was suspended in December 2018.(106)

### 8.1.2 Objective

The objective of the model is to evaluate the cost-effectiveness and budget impact of introducing adjuvant pembrolizumab compared with relevant alternative strategies to manage RCC patients who have undergone nephrectomy and have increased risk of recurrence. The comparator treatment strategy includes routine surveillance (i.e., as represented by the placebo arm of the KN-564 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.

### 8.1.3 Type of economic evaluation and outcomes evaluated

This economic model estimates the expected costs and clinical effectiveness for each adjuvant treatment arm. Costs are reported in total and disaggregated by component, and included costs associated with drug acquisition and administration, adverse events (AEs), disease management, terminal care, and patient cost. Effectiveness outcomes include QALYs and life years and are reported in aggregate as well as disaggregated by health state. The ICER of pembrolizumab versus routine surveillance is evaluated in terms of incremental cost per QALY gained and incremental cost per life year gained.

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.

### 8.1.4 Model structure

This cost-effectiveness model and budget impact analysis is developed in Microsoft Excel® 2016 (Microsoft Corporation, Redmond, Washington) using a Markov cohort structure. The state transition diagram in Figure 17 illustrates the health states and allowable transitions in the Markov model. The model consists of four mutually exclusive health states (disease-free, locoregional recurrence, distant metastases, and death) to track the disease course and survival of patients over time.



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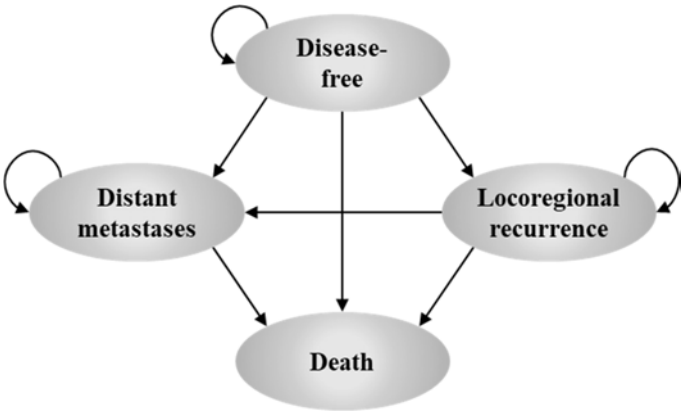
This model structure differentiates health states by type of recurrence (either locoregional recurrence or distant metastasis) because the primary endpoint of the KN-564 trial (i.e., DFS) encompasses both types of recurrence events. These two types of recurrence are expected to have different implications on patients' prognosis, health-related quality of life, and disease management, and therefore result in different health outcomes and costs.

The health states and allowable transitions are defined such that DFS and OS curves can be generated using the Markov trace. This facilitates validations of the model against observed Kaplan-Meier curves from the trial and external data sources. The detailed estimation of the DFS and OS curves are mentioned in section 8.3.

**Figure 17 Model schematic**




### 8.1.5 Model comparator

Routine surveillance is considered as a comparator to adjuvant pembrolizumab for patients who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 NED RCC, as there is no recommended adjuvant treatments for this population in Denmark (13) (13).

### 8.1.6 Time horizon

The cost-effectiveness analysis is conducted using a lifetime horizon to comprehensively capture differences in costs and outcomes between pembrolizumab and comparator arms (107). In this model we use a 41.1 years' time horizon. As the average age of the patients is 58.9 years, following them over 41.1 years, it can be observed that there will be less than 0.25% 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 comparator. The starting age of the patient cohort at model entry is based on the average age of the European population in the KN-564 trial.

The impact of alternative time horizons is explored via sensitivity analyses in the section 8.6.

### 8.1.7 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. In the present model we use a weekly cycle length to allow for precise calculation of drug acquisition and administration costs.



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Half-cycle correction is applied to costs and effectiveness. As an exception, half-cycle correction is not applied to cost and utility components that are incurred at the beginning of a cycle, including adjuvant drug acquisition and administration costs (recurring costs starting from week 0) and AE-related costs and disutility (applied as a one-time cost at week 0).

### 8.1.8 Discount rate

In the base case analysis, both costs and effectiveness are discounted annually at 3,5%, consistent with The Danish Medicines Council methods guide for assessing new pharmaceuticals (2). Alternative annual discount rates of 0% and 1.5% are tested in the sensitivity analysis in the section 8.6.

## 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

**Table 12 Input data used in the model**

| Name of estimates* | Results from study or indirect treatment comparison (ITC) (clarify if ITT, per-protocol (PP), safety population) | Input value used in the model | How is the input value obtained/estimated |
|---|---|---|---|
| **Disease free survival (DFS)** | KN-564, primary endpoint: To compare DFS between treatment arms.<br><br>DFS is defined as time from randomization until disease recurrence (i.e., local recurrence of RCC, occurrence of distant metastasis, or occurrence of a secondary systemic malignancy) or death. | A Markov model structure is used with four mutually exclusive health states. (EF, LR, DM and death). A patient starts from the DF state and move to different health states according to different transition probabilities. | DFS curves were derived by fitting different parametric models (Weibull, exponential, Gompertz, log-logistic, log-normal and generalized gamma distributions) to individual patient data (IPD) from the KN-564 trial. |
| **Overall survival (OS)** | KN564, secondary endpoint: To compare OS between treatment arms.<br><br>OS is defined as the time from randomization to death due to any cause. | Please see description above for DFS. | In this model OS curves are not directly derived by fitting parametric models to KN564 OS data, given the OS data are immature. OS prediction was a combined results of all transition probabilities in the Markov model. |



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| Name of estimates* | Results from study or indirect treatment comparison (ITC) (clarify if ITT, per-protocol (PP), safety population) | Input value used in the model | How is the input value obtained/estimated |
|---|---|---|---|
| **Transition probabilities:**<br>DF→LR<br>DF→DM<br>DF→ Death | KN-564 | Please see description above for DFS. | Transition probabilities starting from the disease-free state are estimated based on survival analyses of individual patient-level data from the KN-564 trial, following a parametric multistate modelling approach.<br>Transition probabilities from DF → death are estimated based on survival analyses of individual patient-level data from the KEYNOTE-564 trial. Due to the small number of events, these transitions are modeled using an exponential distribution (and, under efficacy estimation approach used in the base case model, a time-constant hazard ratio is applied for pembrolizumab vs. routine surveillance). Within each cycle, the transition probability from DF → death is set equal to the maximum of the trial-based estimate for this probability and background mortality.<br>Please see appendix G for extended description. |
| **Transition probabilities:**<br>LR→DM or Death | SEER-Medicare data | Please see description above for DFS | The cause-specific hazards of LR → DM are estimated using patient-level data from the SEER-Medicare database. Due to the small size of the SEER-Medicare cohort, the cause-specific hazards of LR → death is set equal to the exponential rate of the DF → death transition in the routine surveillance arm (as estimated from KN-564 trial data). Within each cycle, the transition probability from LR → death is set equal to the maximum of the estimated probability based on parametric modeling and background mortality.<br>Please see appendix G for extended description. |
| **Transition probabilities:**<br>DM→Death | | Please see description above for DFS | In each adjuvant treatment arm, the exponential hazard rate of DM → death is assumed to depend on: the market shares of first-line treatments received for advanced RCC and the expected survival associated with each advanced RCC treatment regimen.<br>Please see appendix G for extended description. |



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| Name of estimates* | Results from study or indirect treatment comparison (ITC) (clarify if ITT, per-protocol (PP), safety population) | Input value used in the model | How is the input value obtained/estimated |
|---|---|---|---|
| **Adverse reaction 1 (measured as costs)** | | One-off AE-related costs per first-line treatment arm were 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 from DRG-takster 2022, "Takstvejledning, 2022", Sundhedsdatastyrelsen. |
| **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. | Data is obtained from the KN564 trial. |
| **Adverse reaction 3 (measured as utility loss)** | | Based on utility by progression status, the model includes the option to include the disutility associated with grade 3+ AEs. | Disutility associated with AEs per patient was calculated in each treatment arm as a function of the rates of included AEs in the treatment arm, the mean duration of AEs and the estimated disutility associated with Grade 3+ AE. |
| **Utility by time to deaths: base case** | KN-564, secondary endpoint:<br>To evaluate changes in health-related quality-of-life (QoL) using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer–Specific Quality of Life Questionnaire (EORTC QLQ-BR23).<br><br>KN564, exploratory endpoint:<br>To characterize utilities using EuroQol-5 Dimension Questionnaire (EQ-5D™). | The utility inputs are derived through primary analyses of EQ-5D-5L data collected from the KN-564 trials and additional evidence from literature. 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. | At each visit the health state of each patient was assessed from the EQ-5D questionnaires. Then the EQ-5D scores was subsequently converted into a single summary number (index value), which reflects how good or bad a health state is according to the preferences of the general population Denmark, thus reflecting the utility associated with a health state.<br>Since one patient can have multiple utility measures, linear mixed-effects models with patient-level random effects were used for this analysis to account for within-subject correlation. The linear mixed-effects models also included the presence or absence of any Grade 3+ AEs to estimate AE disutility.<br><br>In the model, utilities were applied based on the distribution of patients across different categorizations of time to death in each weekly cycle. In a given weekly cycle, the proportion of patients within each time to death category was estimated based on the modeled OS within each treatment arm. |

* 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, is adult RCC patients (aged 18 years or older) who have undergone nephrectomy and have increased risk of recurrence (see section 5.2.1).

**Patient population in the clinical documentation submitted:**
Adult ccRCC patients (aged 18 years or older) who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 NED RCC (see section 7.1).

**Patient population in the health economic analysis submitted:**
The patient population of the health economic analysis is adult ccRCC patients (aged 18 years or older) who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 NED RCC.

Baseline characteristics of patients in the model cohort, including age, gender distribution, and bodyweight at model entry are based on reported characteristics of the KN-564 trial population (see Table 13 below).

**Table 13 Patient population (2, 11)**

| Patientpopulation<br>Vigtige baseline egenskaber | Clinical documentation<br><br>(ITT population) | Used in the model<br>(European subset) | Danish clinical practice |
|---|---|---|---|
| Starting age, median | 60 years | 58.9 years | 66 years |
| Proportion of female | 29% | 26.7% | 28.6% |
| Weight (kg) – mean | 83.9 | 84.9 | |
| Weight (kg) - median | | 82.0 | |
| Geographic region = Europe | 37,7% | | |

The data on patient characteristics in the clinical documentation is based on data on the ITT population from KN-564, while the model inputs is based on the individual patient level data from the European subset.

Data from Danish clinical practice is sparse. Data from Danish clinical practice is based on data from the Danish Urological Cancer Group (DaRenCa). The data on age and sex is based on surgically treated RCC patients while the data used in the model is based on ccRCC patients who have undergone nephrectomy and have increased risk of RCC. MSD does not consider the differences between patient characteristics in the KN-564 trial and the Danish RCC population to impact the interpretation of results significantly.

#### 8.2.2.2 Intervention

The intervention as in the clinical documentation (ITT population), as used in the health economic analysis, and as expected in Danish clinical practice are identical (see Table 14 below).

The indication for Pembrolizumab is based on a fixed dose (200 mg (IV) every 3rd week for up to 17 administrations (one year)). 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 base case in the current model, hence there is an opportunity to choose a fixed dose in the model. Further, the health economic model provides the flexibility to modify the maximum treatment duration for all drugs.



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Table 14 Intervention (2, 74)

| Intervention | Clinical documentation (ITT population) | Used in the model | Expected Danish clinical practice |
|---|---|---|---|
| **Posology** | Pembrolizumab:<br>◦ 200 mg (IV) every 3rd week for up to 17 series of administration (approx. one year) OR 400 mg (IV) every 6th week for up to 9 series of administration (approx. one year). | Pembrolizumab:<br>◦ 2 mg/kg (IV) every 3rd week for up to 17 series of administration (approx. one year) OR 4 mg/kg (IV) every 6th week for up to 9 series of administration (approx. one year). | Pembrolizumab:<br>◦ 2 mg/kg (IV) every 3rd week for up to 17 series of administration (approx. one year) OR 4 mg/kg (IV) every 6th week for up to 9 series of administration (approx. one year) (74). |
| **Length of treatment (time on treatment) (median)** | Pembrolizumab : 11.1 months/17 cycles (range 0.0-14.3) | Pembrolizumab : 11.1 months/17 cycles | |
| **Criteria for discontinuation** | In KN-564, treatment could be continued for up to 12 months or stopped if the patient experienced recurrence or adverse events, wished to stop, or if the clinician stopped the treatment. | In KN-564, treatment could be continued for up to 12 months or stopped if the patient experienced recurrence or adverse events, wished to stop, or if the clinician stopped the treatment. | Treatment with pembrolizumab will presumably continue until recurrence, adverse events or a maximum of 12 months. |
| **The pharmaceutical's position in Danish clinical practice** | | | Currently not used in clinical practice for adjuvant treatment of RCC patients prior to evaluation in the Danish Medicines Council. However, pembrolizumab is standard clinical practice in a range of other indications. Recommendation from the Danish Medicines Council will lead to the introduction of the intervention as adjuvant treatment. |

#### 8.2.2.3 Comparator

The comparator in KN-564 is placebo. It is chosen because there do not exists any EMA recommended or globally accepted adjuvant treatment for the current patient population. This is the same case in Denmark. The Danish clinical guideline for treatment after nephrectomy is routine surveillance (13). Thus, the comparator treatment strategy includes routine surveillance (represented by the placebo arm of the KN-564 trial).

Table 15 Comparator

| Intervention | Clinical documentation (ITT population) | Used in the model | Expected Danish clinical practice |
|---|---|---|---|
| **Posology** | Routine surveillance (represented by the placebo arm of the KN-564 trial). | Routine surveillance | |
| **Length of treatment (time on treatment) (median)** | 11.1 months/17 cycles (range 0.0-15.4) | 11.1 months/17 cycles | |



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#### 8.2.2.4 Relative efficacy outcomes

**The relative efficacy outcomes in the submitted clinical documentation:**
In the updated analysis with 6 months additional follow-up, the HR for the ITT group is 0.63 (95% CI 0.50-0.80), p <0.0001. Here, 114 events are seen in the Pembrolizumab group, compared to 169 events in the placebo group (27).

**Table 16 DFS and OS data from KN564**

| | Pembrolizumab N= 496 | Routine surveillance N= 498 |
|---|---|---|
| **Disease-free state (DFS)** | | |
| Number of events (%) | 114 (23.0) | 169 (33.9) |
| Death | 6 (1.2) | 3 (0.6) |
| Disease recurrence | 108 (21.8) | 166 (33.3) |
| Hazard ratio (95% CI) | 0.63 (0.50, 0.80) | Ref. |
| p-value | <0.0001 | |
| DFS rate at 12 months (%) (95% CI) | 85.5 (82.0, 88.4) | 76.0 (72.0, 79.5) |
| DFS rate at 18 months (%) (95% CI) | 82.1 (78.3, 85.3) | 71.3 (67.0, 75.1) |
| DFS rate at 24 months (%) (95% CI) | 78.3 (74.3, 81.8) | 67.3 (62.9, 71.3) |
| **Overall survival** | | |
| Number of events (%) | 23 (4.6) | 43 (8.6) |
| Hazard ratio (95% CI) | 0.52 (0.31, 0.86) | Ref. |
| p-value | 0.0047677 | |
| OS rate at 12 months (95% CI) | 98.6 (97.0, 99.3) | 98.0 (96.3, 98.9) |
| OS rate at 18 months (95% CI) | 97.8 (96.0, 98.8) | 96.8 (94.8, 98.0) |
| OS rate at 24 months (95% CI) | 96.2 (94.1, 97.6) | 93.8 (91.3, 95.6) |

*Source*: KEYNOTE-564 (data cutoff date: June 14, 2021)

**The relative efficacy outcomes in the submitted health economic analysis:**
In this economic model, the incremental effect of pembrolizumab in extending DFS versus routine surveillance is determined by the parametric functions used for transitions starting from the DF state, in conjunction with background mortality rates. No alteration or waning of the treatment effect is applied in the long term. The assumption of a sustained treatment effect on DFS 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.

The long-term extrapolation of DFS and OS for routine surveillance is externally validated against observed Kaplan-Meier curves from the placebo arms of prior trials such as the S-TRAC trial of sunitinib versus placebo; the ASSURE trial of sunitinib and sorafenib versus placebo (focusing specifically on the clear-cell, high-risk subgroup results); the PROTECT trial of pazopanib versus placebo; and the ATLAS trial of axitinib versus placebo. On the other hand, the plausibility of long-term DFS and OS extrapolations in the pembrolizumab arm are assessed based on clinical expert opinion and data from another adjuvant indication, which do indicate long term treatment effect post discontinuation of pembrolizumab (45, 46).



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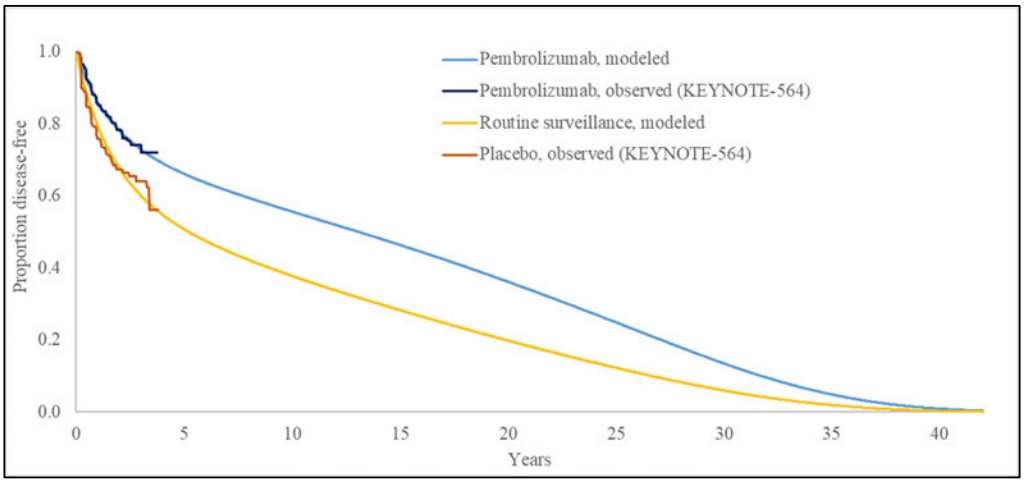
A Markov model based on four health states (disease-free, locoregional recurrence, distant metastases, and death) is developed. For pembrolizumab and routine surveillance arms included in KN-564, parametric curves are fitted to DFS (for transition from DF → LR and DF → DM). Due to the small number of events, transitions from DF → death are modeled using an exponential distribution. In the base case, the transition probability from LR → DM is assumed to be equivalent between the two adjuvant arms. The cause-specific hazards of LR → DM are estimated using patient-level data from the SEER-Medicare database. Due to the small size of the SEER-Medicare cohort, the cause-specific hazards of LR → death is set equal to the exponential rate of the DF → death transition in the routine surveillance arm (as estimated from KN-564 trial data). In each adjuvant treatment arm, the transition probability from DM to death is assumed to depend on the market shares of advanced RCC treatment regimens received in that arm.

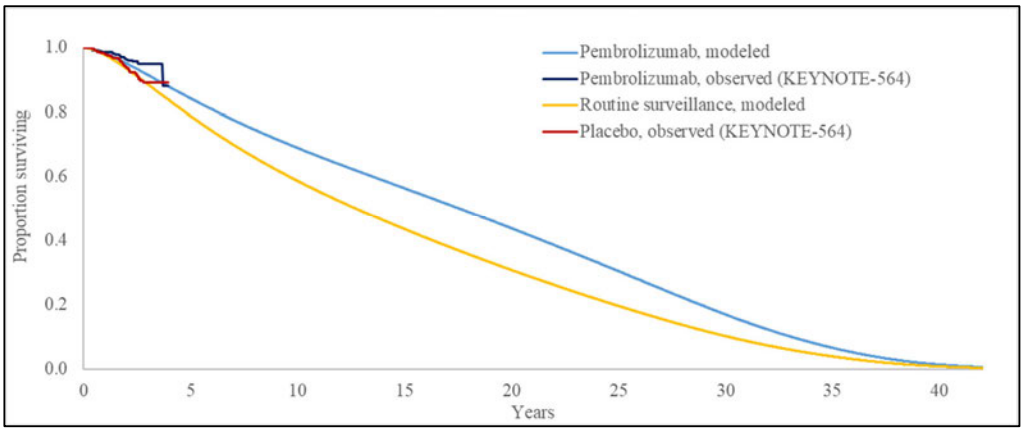
Transition probabilities are derived based on primary analyses of patient-level data from the KN-564 trial, a systematic literature review and NMA comparing the efficacy of first-line treatments for advanced or metastatic RCC, a real-world retrospective database analysis, and a targeted review of published literature to identify relevant clinical inputs not estimable using trial data (108). The sections 8.3.2 through 8.3.4 summarize the specific estimation approach used for each health state transition in the Markov model, and Appendiks G – Ekstrapolering describe the calculation and validation in depth. Below is the observed and modeled long term data for respectively DFS and OS presented.

**Figure 18 Base-case DFS and OS over the modeled time horizon**

a. DFS




b. OS




*Note:* OS is not modeled directly in this economic evaluation. The predicted OS curves shown above in (b) are the combined result of all transition probabilities in the Markov model. DFS data from KN-564 (data cutoff date: June 14, 2021) are used to estimate transition probabilities starting from the DF state. Although post-recurrence data from KN-564 are not used in the transition probability estimation, the above graph presents the overlay of observed OS curves from KN-564 with predicted OS curves in both model arms.

Further, it is worth to note that the number of patients from month 35 (approx. year 3) of the observed OS data is very limited.

**Table 18 Summary of text regarding value**

| Clinical efficacy outcome | Clinical documentation | Used in the model (value) |
|---|---|---|
| **Primary endpoint in the study:**<br>Disease-free survival (DFS)<br>Overall survival (OS) | Please see Table 16 above. | Please see Table 16 above. |



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**Table 19 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:**<br><br>Disease-free survival (DFS) | DFS 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 median 5-year survival for newly diagnosed RCC patients is for T2, T3, and T4, respectively 74%, 60% and 8% (11). Due to the large number of medical oncological treatment options for metastatic patients, OS will be an expression of both the effect on the adjuvant treatment and the effect of the subsequent treatments in case of recurrence. In return, DFS presents the effect of the current treatment.<br><br>Further, the use of DFS to model long-term survival in this economic evaluation is supported by a real-world, retrospective analysis that examined the strength of DFS as a predictor for OS in RCC following initial nephrectomy (21, 22).<br><br>Therefore, DFS is chosen as primary endpoint in the current model, which is also the recommendation from FDA in adjuvant RCC clinical trials and the primary endpoint in several ended and ongoing clinical trials of adjuvant treatment of RCC (23, 24). | OS and PFS KN364 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 (109). |
| **Secondary endpoint in the study:**<br><br>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 DFS being the preferred primary endpoint OS is still a key endpoint.<br><br>Also, please see above. | |

#### 8.2.2.5 Adverse reaction outcomes

The inclusion of specific AEs within the economic model is based on a combination of the risk and severity of each event. The model considers AEs occurring in the adjuvant setting (AEs associated with subsequent treatments in the metastatic setting are not considered due to their small expected impact on the incremental cost-effectiveness of adjuvant pembrolizumab versus comparators). In the adjuvant setting, the model considers all cause grade 3+ AEs that occurred with a frequency of ≥5% (all grades) in either the pembrolizumab or placebo arm of the KN-564 trial. Risk at any grade is used to determine the set of AEs included in the model, but risks of grade 3 to 5 AEs are incorporated into the model due to their expected impact on resource utilization and quality of life. Grades 3 to 5 AEs occurring with 0% frequency are not included in the model.



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**Adverse reaction outcomes in the clinical documentation submitted:**

AE Grade 3+ incidence rates in ITT population.

**Adverse reaction outcomes in the health economic analysis submitted:**

All-cause grade 3+ AEs with an incidence ≥ 5% in at least one treatment arm are included in the model. For pembrolizumab and the comparator, AE rates are obtained from the KN-564 trial (2).

Table 20 provides a summary of all-cause grade 3+ AE rates included in the model.

**Table 20 All-cause AE Grade 3+ incidence rates reported in ≥5% patients in any treatment arm**

| Adverse reaction outcome | Clinical documentation | | | Used in the model | | |
|---|---|---|---|---|---|---|
| | Pembrolizumab | Placebo | Mean duration (weeks)[1] | Pembrolizumab | Routine surveillance | Mean duration (weeks) |
| Abdominal pain | 0,4% | 0,2% | 4,9 | 0,4% | 0,2% | 4,9 |
| Alanine aminotransferase increased | 2,3% | 0,2% | 18,6 | 2,3% | 0,2% | 18,6 |
| Arthralgia | 0,4% | 0,4% | 10,1 | 0,4% | 0,4% | 10,1 |
| Aspartate aminotransferase increased | 1,6% | 0,2% | 5,6 | 1,6% | 0,2% | 5,6 |
| Asthenia | 0,2% | 0,2% | 66,1 | 0,2% | 0,2% | 66,1 |
| Back pain | 0,2% | 0,2% | 13,7 | 0,2% | 0,2% | 13,7 |
| Blood creatinine increased | 0,2% | 0,0% | 3,6 | 0,2% | 0,0% | 3,6 |
| Constipation | 0,0% | 0,2% | 4,9 | 0,0% | 0,2% | 4,9 |
| Decreased appetite | 0,2% | 0,0% | 19,3 | 0,2% | 0,0% | 19,3 |
| Diarrhoea | 1,8% | 0,2% | 9,3 | 1,8% | 0,2% | 9,3 |
| Dizziness | 0,2% | 0,0% | 4,0 | 0,2% | 0,0% | 4,0 |
| Dry mouth | 0,2% | 0,0% | 81,0 | 0,2% | 0,0% | 81,0 |
| Dyspnoea | 0,2% | 0,0% | 0,3 | 0,2% | 0,0% | 0,3 |
| Fatigue | 1,0% | 0,0% | 46,9 | 1,0% | 0,0% | 46,9 |
| Hyperglycaemia | 1,4% | 0,6% | 22,7 | 1,4% | 0,6% | 22,7 |
| Hypertension | 2,9% | 2,6% | 35,0 | 2,9% | 2,6% | 35,0 |
| Hyperthyroidism | 0,2% | 0,0% | 5,0 | 0,2% | 0,0% | 5,0 |
| Hypothyroidism | 0,2% | 0,0% | 171,9 | 0,2% | 0,0% | 171,9 |
| Influenza-like illness | 0,2% | 0,2% | 0,7 | 0,2% | 0,2% | 0,7 |
| Myalgia | 0,2% | 0,0% | 168,3 | 0,2% | 0,0% | 168,3 |
| Nausea | 0,4% | 0,0% | 1,8 | 0,4% | 0,0% | 1,8 |

[1] Mean duration of each grade 3-5 AE type is obtained from KEYNOTE-564 and reflects the average weeks per unique all-cause event multiplied by the mean number of unique all-cause events per patient who had a particular AE type.



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| Adverse reaction outcome | Clinical documentation | | | Used in the model | | |
|---|---|---|---|---|---|---|
| | Pembrolizumab | Placebo | Mean duration (weeks)[1] | Pembrolizumab | Routine surveillance | Mean duration (weeks) |
| Pain in extremity | 0,4% | 0,0% | 55,4 | 0,4% | 0,0% | 55,4 |
| Pruritus | 0,2% | 0,0% | 10,9 | 0,2% | 0,0% | 10,9 |
| Pyrexia | 0,2% | 0,0% | 0,4 | 0,2% | 0,0% | 0,4 |
| Rash | 0,8% | 0,4% | 38,0 | 0,8% | 0,4% | 38,0 |
| Upper respiratory tract infection | 0,2% | 0,0% | 3,1 | 0,2% | 0,0% | 3,1 |
| Urinary tract infection | 0,2% | 0,6% | 1,1 | 0,2% | 0,6% | 1,1 |
| Vomiting | 0,6% | 0,0% | 0,4 | 0,6% | 0,0% | 0,4 |

Risks of the included AEs for patients treated with pembrolizumab and placebo are obtained from KN-564, based on the proportions of patients with AEs reported for the all-subjects-as-treated population (
Table 20).

Mean durations of the included AEs are collected from KN-564 and are used within the model to estimate the duration of the disutility impact from each AE regardless of adjuvant treatment arm. Consideration of AE-related disutility and cost is described in sections 8.4.3 and 8.5.3, respectively.

## 8.3 Extrapolation of relative efficacy

### 8.3.1 Transition probabilities – summarized:

For full method used and results, please see Appendiks G – Ekstrapolering.

Transition probabilities are derived based on primary analyses of patient-level data from the KN-564 trial, a systematic literature review and NMA comparing the efficacy of first-line treatments for advanced or metastatic RCC, a real-world retrospective database analysis, and a targeted review of published literature to identify relevant clinical inputs not estimable using trial data (108). The sections 8.3.2 through 8.3.4 describe the specific estimation approach used for each health state transition in the Markov model. The set of allowable transitions and corresponding data sources are summarized in Table 21. An in-depth description of the calculations is provided in Appendiks G – Ekstrapolering.

The key transition probabilities driving the cost-effectiveness results are the three transitions starting from the disease-free state (i.e., disease-free to locoregional recurrence, disease-free to distant metastases, and disease-free to death). These transition probabilities are estimated using randomized controlled trial data from KN-564 for the pembrolizumab and placebo arms. The use of DFS to model long-term survival in this economic evaluation is supported by a real-world, retrospective analysis that examined the strength of DFS as a predictor for OS in RCC following initial nephrectomy (110). The study used the Surveillance, Epidemiology and End Results (SEER)-Medicare database (2007-2016) to identify a cohort of 643 patients with non-metastatic intermediate-high or high risk RCC who underwent nephrectomy. In the baseline-adjusted multivariable regression analysis, each additional year of DFS is associated with 0.73 additional years of OS post-nephrectomy (95% confidence interval [CI]: 0.40, 1.05; p<0.001). Among patients with recurrence, those with longer time to recurrence demonstrated significantly longer OS. When adjusting for age at recurrence instead of age at nephrectomy, the incremental OS increases from 0.73 years to 0.85 years per one additional year of DFS (95% CI: 0.52, 1.18 years; p<0.001), which reflected a negative indirect effect from time to recurrence to post-recurrence survival mediated through age. Additional details on this study are provided in Appendix K.



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For transitions starting from the locoregional recurrence health state or the distant metastases health state, real-world evidence, patient-level data from KN-564, life tables for Denmark and published literature are used. The model conservatively assumed that, once patients experience a recurrence event, there will be no ongoing benefit from adjuvant pembrolizumab from these health states, as the available follow-up in KN-564 was too limited to establish ongoing efficacy of adjuvant pembrolizumab after recurrence. Transition probabilities from distant metastases to death could differ between the model arms when the subsequent treatments received in the advanced RCC setting differs.

In the base-case analysis the market shares of first and subsequent treatments for advanced RCC are equivalent between the two arms for IO eligible patients. For IO ineligible patients in pembrolizumab arms, market shares of first and subsequent treatments are redistributed among non-immunotherapies according to the share of non-immunotherapies in IO eligible patients, as described in section 8.3.4.

**Table 21 Summary of health state transitions considered in the economic model**

| Transition(s) | Estimation approach | Data source(s) | Scenario or one-way sensitivity analyses performed |
|---|---|---|---|
| **DF → LR**<br>**DF → DM**<br>**DF → Death**[1] | • Based on a parametric multistate modeling approach in which different parametric functions are fitted to each of the three individual transitions starting from DF, accounting for competing risks. | • Patient-level data from KN-564.<br>• Life tables for Denmark - *for transitions to death.* | • Alternative parametric distributions. |
| **LR → DM**<br>**LR → Death**[1] | • An exponential model of LR→DM is fitted using a real-world database (SEER-Medicare), accounting for competing risks. The survival analysis is conducted in a cohort of patients with RCC who underwent nephrectomy and are identified as having a subsequent locoregional recurrence.<br>• Due to the small number of events in the SEER-Medicare cohort, the exponential rate of LR→death is assumed equal to DF→death in the placebo arm of KN-564.<br>• The model conservatively assumes no ongoing efficacy of adjuvant treatment after recurrence. Therefore, the same exponential rates of LR→DM and LR→death are used for each model arm. | • Patient-level analysis of SEER-Medicare database<br>• Patient-level data from KN-564.<br>• Life tables for Denmark - *for transitions to death.* | • Exponential rates of each transition varied +/- 20%. |
| **DM → Death**[1] | • OS depends on all transition probabilities in the model.<br>• Transition probabilities from DM→death depend upon market shares of first-line treatments for metastatic RCC and the efficacy of those first-line treatments with respect to OS.<br>• Exponential OS distributions are estimated for each first-line treatment based on trials in metastatic RCC. For first-line sunitinib, this distribution is estimated based on results from the KN-426 trial. For other first-line treatments, HRs for OS versus sunitinib are obtained from an NMA of first-line drug trials in metastatic RCC.<br>• Exponential PFS distributions are similarly estimated for each first-line treatment. PFS enters into the calculation of utility and disease management costs in the DM state. | • OS and PFS results from KN-426.<br>• NMA comparing treatments for advanced RCC in terms of OS and PFS.<br>• Patient-level analysis of SEER-Medicare database.<br>• Life tables for Denmark - *for transitions to death.* | • Alternative assumptions about subsequent treatments in each model arm.<br>• Exponential rates of OS and PFS failure with treatments for advanced RCC varied +/- 20%. |



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| Transition(s) | Estimation approach | Data source(s) | Scenario or one-way sensitivity analyses performed |
|---|---|---|---|
| | • The model provides an option to assume that a proportion of patients receive no first-line treatment for metastatic RCC. PFS and OS for these patients are estimated using SEER-Medicare data.<br>• Expected OS following DM are calculated in each model arm as a market share-weighted average of expected OS under different first-line treatments. Expected OS is then converted into a weekly hazard of DM→death. Expected PFS following DM was similarly estimated for each model arm. | | |

Abbreviations: DF, disease-free; DM, distant metastases; LR, locoregional recurrence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; SEER, Surveillance, Epidemiology and End Results.

Notes:

[1] Transition probabilities to death are constrained to be at least as high as all-cause mortality, as estimated from national life tables given the age and gender distribution of the cohort at each cycle.

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

Transition probabilities starting from the disease-free state are estimated based on survival analyses of individual patient-level data from the KN-564 trial, following the parametric multistate modelling approach described by Williams et al. (2017a & 2017b) (111, 112). Parametric models are used to estimate the cause-specific hazards of each transition (i.e., DF → LR, DF → DM, and DF → death) over time within the adjuvant pembrolizumab and placebo arms of the trial. Within each weekly cycle of the model, the probability of each of these transitions (as well as the composite probability of any DFS failure event) are calculated as a function of all three cause-specific hazards.

#### 8.3.2.1 Estimation of cause-specific hazards for each individual transition starting from the disease-free state

In the base case, cause-specific hazards of each transition in the pembrolizumab and routine surveillance arms are estimated based on parametric models that are separately fitted to data from the pembrolizumab and placebo arms of KN-564. In order to fit parametric models to each of the three individual health state transitions, standard survival analysis methods are used with one modification to account for competing risks: When analyzing time to each specific type of DFS failure, the two competing failure types are treated as censoring events (113, 114). For example, to model the transition from disease-free to distant metastases, patients who experience a locoregional recurrence or death prior to distant metastases are censored and thus treated as lost to follow-up at the time of the earlier competing event. After these additional censoring criteria are applied to the patient-level time-to-event data for each transition, parametric curve fitting are performed using the survival analysis package *flexsurvreg* in R software (115), similar to the process for fitting parametric functions for a partitioned survival model.

The following three parametric modeling approaches are tested to explore uncertainty in the estimation of transition probabilities starting from the DF state:

1. Parametric models separately fitted to each treatment arm: Under Approach #1, transition probabilities are estimated based on parametric models that are fitted individually to each treatment arm of the KN-564 trial. Six different parametric functions are considered to model transitions from DF to LR and from DF to DM in each treatment arm, including exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions. Due to the small number of direct transitions (9 out of 994 patients) from DF to death observed in KN-564, exponential distributions are fitted for this transition in each arm.



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2. Parametric proportional hazards models with a time-constant treatment effect: Under Approach #2, transition probabilities in the pembrolizumab and routine surveillance arms are estimated based on jointly fitted proportional hazards models (i.e., exponential, Weibull, or Gompertz) that incorporates a time-constant hazard ratio (HR) for pembrolizumab versus placebo in KN-564. Due to the small number of direct transitions from DF to death in the trial, an exponential model with a time-constant treatment effect is used for transitions from DF → death.
3. Parametric proportional hazards models with a time-varying treatment effect (before and after year 1): Under Approach #3, transition probabilities in the pembrolizumab and routine surveillance arms are estimated based on jointly fitted proportional hazards models (i.e., exponential, Weibull, or Gompertz) that incorporates a time-varying HR for pembrolizumab versus placebo. Specifically, the models allow the treatment effect to differ during versus after the first year following initiation of adjuvant therapy. The allowance of a differing treatment effect during the first year versus following years is based on the protocol-defined maximum treatment duration of 1 year. As in Approach #2, an exponential model with a time-constant treatment effect is used for transitions from DF → death under approach 3, given the small number of events.

As described in Appendiks G – Ekstrapolering, for each of the two model arms, probabilities of each transition from the DF state are calculated based on all three cause-specific hazard functions. The predicted DFS curve over time in each treatment arm similarly depend upon all three cause-specific hazard functions. Therefore, in order to select base-case parametric functions, all possible combinations of parametric functions for DF → LR and DF → DM are considered (as noted above, the cause-specific hazard of DF → death is based on a constant exponential rate in each arm given the small number of events.) Criteria for the selection of base-case parametric functions are described below.

#### 8.3.2.2 Selection of base-case parametric functions

As noted by the NICE Decision Support Unit (DSU) Technical Support Document (TSD), assessing model fit is more challenging in the context of multistate models than partitioned survival models, as the target outcomes of interest (e.g., the proportions of individuals experiencing the composite endpoint) are determined by a combination of survival models rather than by a single survival model (113).

Therefore, to select base-case parametric functions, all possible combinations of parametric functions for DF → LR, DF → DM, and DF → death are considered. In accordance with recommendations from the Danish medicines council (107), base-case parametric functions are selected such that the same functional form is used to model each health state transition in both the pembrolizumab and routine surveillance arms. The rationale for this approach is to prevent the extrapolated portion of the DFS curves from following drastically different trajectories between the two model arms.

Base-case parametric functions were chosen based on the following criteria:

- Visual assessment of fit vs. observed DFS: Predictions generated by different combinations of parametric functions are also visually verified against the observed data in each trial arm, following the approach used by William et al. (2017)(111). Specifically, predicted versus observed cumulative incidence curves are plotted for each of the three individual transitions starting from the DF state (Figure 19 and [redacted] In addition, the assumption of proportional hazards is assessed through visual inspection of the log-cumulative hazard plots for each transition ([redacted] Lastly, the resulting predictions of DFS as a composite endpoint are compared against the observed DFS Kaplan-Meier curve in each arm (Figure 21).



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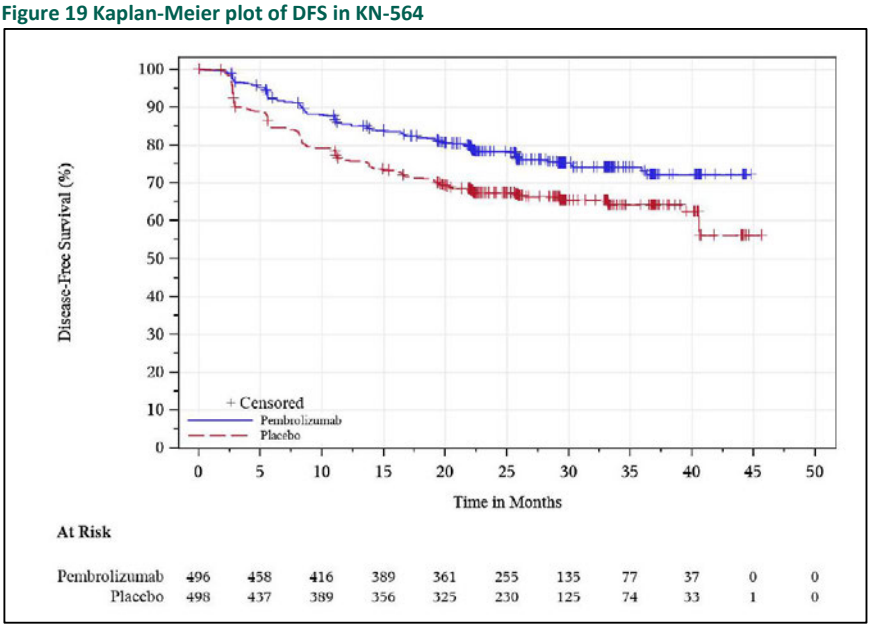
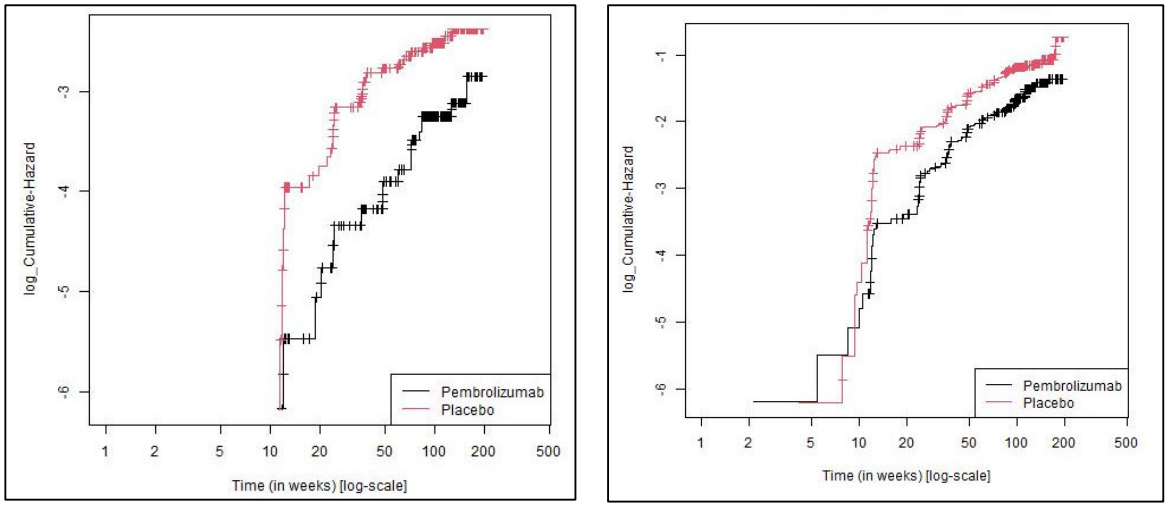
**Figure 19 Kaplan-Meier plot of DFS in KN-564**




*Source:* KEYNOTE-564 (data cutoff date: June 14, 2021)

**Figure 20 Log-cumulative hazards plots of transitions from the disease-free state in KN-564**

*Disease-free → locoregional recurrence* *Disease-free → distant metastases*




- Fit based on mean squared error (MSE) vs. observed DFS: Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks (111). MSE is therefore used as an alternative diagnostic test to assess fit of the predicted DFS curve versus the observed Kaplan-Meier curve during the within-trial period in each treatment arm ([redacted] and [redacted]
- External validity/clinical plausibility of long-term extrapolations: Due to clinical implausibility, parametric functions that resulted in crossing DFS curves (i.e., higher long-term DFS under routine surveillance compared with pembrolizumab) are excluded from consideration as base case. This exclusion is supported by feedback



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from clinical experts and the available data from KN-564. The Kaplan-Meier curves for DFS separates from the outset in favor of pembrolizumab, and at the time of the June 14, 2021 data cutoff, the curves remain separated, with no convergence of the tails of the curves.

Longer-term extrapolations of DFS and OS for routine surveillance (Figure 18) are externally validated against observed Kaplan-Meier curves from the placebo arms of prior trials of TKI inhibitors as adjuvant therapy for RCC ( [redacted] and [redacted] ). (Of note, predicted DFS depends only on transition probabilities starting from the DF state, while predicted OS is a function of all transition probabilities in the model). Based on comparability with the KN-564 trial population, published Kaplan-Meier curves for DFS and OS (when available) from the following trials are compared with DFS and OS predictions for routine surveillance: the S-TRAC trial of sunitinib versus placebo(116, 117); the ASSURE trial of sunitinib and sorafenib versus placebo (focusing specifically on the clear-cell, high-risk subgroup results)(118, 119); the PROTECT trial of pazopanib versus placebo(120, 121); and the ATLAS trial of axitinib versus placebo(122). The SORCE trial of sorafenib versus placebo(123, 124). Attributes of these trials are summarized in appendix L. The SORCE trial of sorafenib versus placebo(123, 124) and the intention-to-treat analysis of the ASSURE trial are not used as external validation sources due to the large representation of patients with low risk and non-clear cell RCC in these trials.

Because external data sources were unavailable for pembrolizumab as adjuvant treatment of RCC, the plausibility of long-term DFS and OS extrapolations in the pembrolizumab arm (Figure 18) are assessed based on clinical expert opinion, data from another adjuvant indication, and the correlation between DFS and OS observed in real-world study. Details are provided in appendix G.

When applying the above criteria, Approach #3 (jointly fitted models with a time-varying treatment effect) with an exponential function for DF → LR and Gompertz function for DF → DM appears to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each arm. Specific considerations are summarized in Table 22 and the exhaustive list of the distribution considered under each approach and step is presented in Appendiks G – Ekstrapolering.

**Table 22 Summary of selection process for base-case parametric distributions of DF → LR and DF → DM**

| Step # | Description of criterion applied at each step | # combinations of distributions that meet criterion |
|---|---|---|
| 0 | **All candidate combinations of parametric functions**<br>Includes total of 54 combinations, including 36 under Approach #1 (separately fitted), 9 under Approach #2 (jointly fitted, time-constant HR), and 9 under Approach #3 (jointly fitted, time-varying HR) | 54 |
| 1 | **Initial exclusions based on clinical plausibility**<br>Excludes 2 combinations of distributions under Approach #1 that yielded crossing DFS curves in the long term | 52 |
| 2 | **Visual assessment of fit vs. observed DFS data**<br>▪ Visual inspection of predicted vs. observed cumulative incidence curves for transitions from DF strongly favored combinations of distributions that uses Gompertz or generalized gamma (under Approach #1) or Gompertz (under Approaches #2 and #3) for DF→DM<br>Log-cumulative hazards plots show minimal deviations from parallel lines beyond week 12. These findings support the consideration of proportional hazards models (particularly Approach #3, which allows for a different treatment effect after year 1). | 16 |



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| Step # | Description of criterion applied at each step | # combinations of distributions that meet criterion |
|---|---|---|
| 3 | <u>Statistical fit based on MSE vs. observed DFS</u><br><br>MSE statistics aligns with findings from visual assessment, with all 16 remaining combinations ranking within the top 50% of all candidate distributions based on fit vs. observed DFS | 16 |
| 4a | <u>External validations of DFS and OS under routine surveillance</u><br><br>Excludes 10 combinations of distributions that predicted 5-year DFS outside a plausible range of 51% ± 2.5 percentage points, based on three separate adjuvant trials reporting ~51% DFS with placebo at year 5 | 6 |
| 4b | ▪ Of the remaining 6 combinations of distributions, the selected base-case combination achieves the closest fit of predicted DFS compared to external reported DFS across different time points.<br><br>External validation of OS under routine surveillance also supports the selected base case. | 1 |
| 5 | <u>Clinical plausibility of long-term DFS and OS benefit for pembrolizumab</u><br><br>▪ Predicted DFS benefit of pembrolizumab vs. placebo is compared to data from adjuvant sunitinib in S-TRAC and validated based on clinical expert opinion.<br><br>Predicted correlation between DFS and OS is validated with the observed real-world study. | 1<br><br>Base case: Exponential/Gompertz under Approach #3 |

A list of all candidate combinations of parametric functions in each treatment arm, including the rankings in terms of MSE in each model arm and long-term predictions of DFS and OS, the assessment of visual fit, including the observed cumulative incidence of transitions from DF → LR in the pembrolizumab and routine surveillance arms, respectively, alongside the predicted cumulative incidence from different combinations of parametric functions, and the external validations of predicted DFS and OS for routine surveillance can be seen in Appendiks G – Ekstrapolering.

<u>Clinical plausibility of long-term DFS and OS benefit for pembrolizumab</u>: S-TRAC is the only randomized controlled trial demonstrating a significant DFS benefit of a TKI (sunitinib) vs. placebo in the adjuvant RCC setting (HR: 0.76, 95% CI, 0.59 to 0.98, by blinded independent central review), although this treatment benefit conflict with the results of its own investigator assessment and ASSURE trial. The observed treatment effect size on DFS is larger in magnitude for pembrolizumab vs. placebo in KN-564 (HR: 0.63, 95% CI, 0.50 to 0.80) than for sunitinib vs. placebo in S-TRAC, which supports a larger modeled DFS benefit of pembrolizumab relative to that observed for sunitinib in S-TRAC. [redacted] summarizes the predicted incremental DFS benefit with pembrolizumab vs. placebo under the 6 aforementioned combinations of distributions, alongside the observed incremental DFS benefit with sunitinib vs. placebo in the S-TRAC trial. As shown, the base-case predicted DFS benefit of pembrolizumab is aligned with the clinical expectation. Under two of the combinations (Exponential/Generalized gamma and Exponential/Gompertz under Approach #1), the incremental DFS benefit with pembrolizumab at 7 years (11.0-11.2%) is similar to that observed for sunitinib in S-TRAC at this time point (10.5%). These two combinations of distributions are considered highly conservative, and therefore included in the scenario analyses to show the lower bound of incremental effectiveness with pembrolizumab vs. routine surveillance.

In this economic model, the incremental effect of pembrolizumab in extending DFS versus routine surveillance is determined by the parametric functions used for transitions starting from the DF state, in conjunction with background mortality rates. No alteration or waning of the treatment effect is applied in the long term. The assumption of a



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sustained treatment effect on DFS 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-564, pembrolizumab data available up to a maximum follow-up of 4 years do not indicate a treatment waning effect, i.e., the DFS curves remained separated, and the log cumulative hazard plots show no evidence of converging. In the S-TRAC trial, sunitinib with 1-year administration shows a continued separation of DFS curves with a rate difference ranging from 4.4% at 2 years to 10.5% at 7 years (116). 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 (45). 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 (125). 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 stopping rule (126, 127). 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. For the approach 3, proportional hazard is assumed so the treatment effect from DF to LR and DF to DM continues post year 1, which is why it is expected to see an accumulated reduction of recurrences over time.

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(128, 129). Therefore, a sustained treatment effect post-discontinuation of adjuvant pembrolizumab in patients with RCC is justified.

Under the base-case parametric distributions, adjuvant pembrolizumab is expected to confer incremental gains of 4.57 DF life-years and 2.53 overall life-years relative to routine surveillance (before the application of 3.5% annual discounting). These results imply a 0.55-year increase in OS per 1-year increase in DFS with pembrolizumab, a ratio that is plausible and conservative relative the ratio of 0.73 years of additional OS per 1 year of additional DFS that is estimated in a retrospective analysis of SEER-Medicare data (130, 131).

Figure 18b presents the modeled base-case OS curves for pembrolizumab and routine surveillance alongside early Kaplan-Meier data for OS from KN-564. Compared with observed OS, the modeled OS curve is well-aligned for routine surveillance and slightly underpredicted for pembrolizumab, supporting the expectation that the base case provides a reasonable estimate of incremental effectiveness with pembrolizumab vs. routine surveillance.



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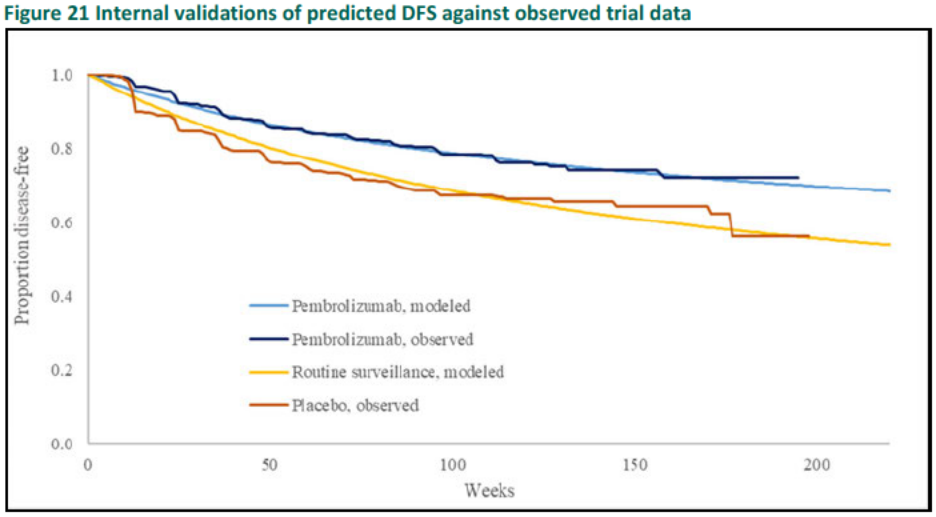
**Figure 21 Internal validations of predicted DFS against observed trial data**




*Note:* Parametric curves for transition probabilities starting from the DF state are fitted using KEYNOTE-564 trial data up to the data cutoff date of June 14, 2021. The internal validation figure above plots the modeled DFS curves against the Kaplan-Meier DFS curves based on the same data cutoff date.

#### 8.3.2.3 Alternative parametric distributions tested in scenario analyses

In scenario analyses, alternative parametric distributions are tested for the cause-specific hazards of DF → LR and DF → DM in the pembrolizumab and placebo arms.

[redacted]



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[redacted]

### 8.3.3 Transitions from locoregional recurrence to distant metastases and death

In KN-564, follow-up imaging assessment was terminated once patients had experienced LR as their first event. As a result, the subsequent time-to-event outcomes (DM or death) were unavailable from the trial. In light of this, an exponential model is fitted for the transition from LR to DM through a retrospective analysis of SEER-Medicare data. The exponential distribution is commonly assumed when estimating transition probabilities starting from intermediate health states in a Markov model, as the hazard rate does not depend on time since entry into the health state(132).

Patients who meets the following inclusion and exclusion criteria were considered in this analysis:

- Diagnosis record of RCC with clear cell component in the SEER registry between 2007 and 2015
- ≥ 66 years old at the first observed diagnosis of RCC
- Intermediate-high risk or high risk, non-metastatic RCC at diagnosis as defined by pathological TNM and Fuhrman grading status
- Received either a radical nephrectomy or a partial nephrectomy after the first observed diagnosis of RCC
- No other (non-renal) cancers before the earliest claim for nephrectomy
- No diagnoses of secondary malignant neoplasm prior to or within 30 days of nephrectomy

In total, 2,437 patients met the above criteria; 74 were further identified as having a LR, of whom 32 had continuous eligibility between initial nephrectomy and date of local recurrence and were included in the transition probability estimation. LR was identified by an additional nephrectomy after a 90-day treatment-free interval and/or a diagnosis for secondary disease of kidney or renal pelvis or intra-abdominal lymph nodes at least 30 days after the earliest claim for nephrectomy. DM were identified by a diagnosis for metastatic disease at least 30 days after the earliest claim for nephrectomy or initiation of an FDA-approved treatment for metastatic RCC after a 90-day treatment-free interval.

To avoid any immortal time bias, no minimum follow-up requirements are applied after the first LR date. When modeling the cause-specific hazards of LR → DM, patients are censored at the earliest of death, loss of follow-up, and end of data. Given the small sample size of the SEER-Medicare cohort, the cause-specific hazards of LR → death is set equal to the exponential rate of the DF → death transition in the routine surveillance arm (as estimated from KN-564 trial data). Within each cycle, the transition probability from LR → death is set equal to the maximum of the estimated probability based on parametric modeling and background mortality.

The cause-specific hazards of LR → DM and LR → death are shown below.

[redacted]



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[redacted]

### 8.3.4 Transitions from distant metastases to death

In each adjuvant treatment arm, the transition probability from DM to death is assumed to depend on the distribution of first-line treatments for advanced RCC received in that arm. First-line treatment options included the following: sunitinib, tivozanib, pazopanib, cabozantinib and nivolumab/ipilimumab. (As described in section 8.5.2, the base-case analysis also considers the cost of second-line therapies for advanced RCC in each adjuvant treatment arm; however, survival within the DM state was assumed to depend on the choice of first-line therapy).

*Estimation of mean survival by first-line treatment for advanced RCC*

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

- For sunitinib in the advanced RCC setting, exponential rates of OS and PFS failure are computed based on the observed median OS and PFS in the sunitinib arm of KN-426(133), a phase III randomized, open-label, multicenter, global trial to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for advanced RCC(134). The resulting exponential curves are plotted in Figure 22 alongside digitized Kaplan-Meier curves for sunitinib in the KN-426 trial to illustrate visual fit. The use of exponential distributions to model OS and PFS for sunitinib in the advanced RCC setting is also consistent with a previously published cost-effectiveness analysis based on the KEYNOTE-426 trial(135).
- For other advanced treatment regimens, HRs for OS and PFS versus sunitinib are each obtained from a NMA of trials conducted in advanced RCC. For each comparator, the model applies time-constant HRs estimated through fixed-effects NMAs of OS and PFS(136). Trials included in the NMAs were identified through a systematic literature review of randomized controlled trials of first-line treatments in patients with locally advanced or metastatic RCC with clear-cell histology(136).
- Optionally, a proportion of patients may be assumed to receive no subsequent treatment for metastatic RCC. PFS and OS for these patients is estimated using an analysis of the SEER-Medicare database. This subset of patients entering the distant metastases health state include patients who do not receive first-line treatment in the metastatic setting, either because they are under active surveillance or receiving best supportive care.

Table 26 reports the exponential rates of OS and PFS failure estimated for sunitinib and the no treatment option in the advanced setting. Table 27 summarizes the HRs of OS and PFS failure with other treatment regimens versus sunitinib obtained from the NMA and resulting estimates of mean OS and PFS (in weeks) for each regimen, and Table 28 provides an overview of the number of patients in the used studies.

[redacted]



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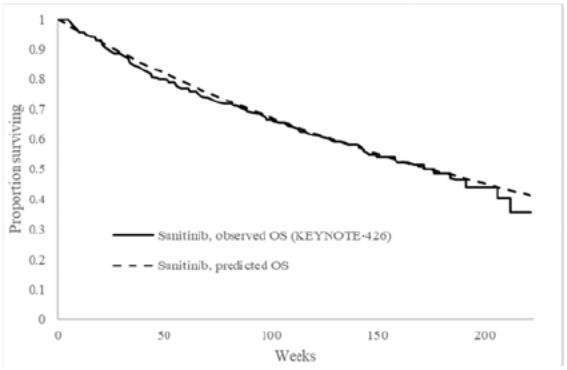
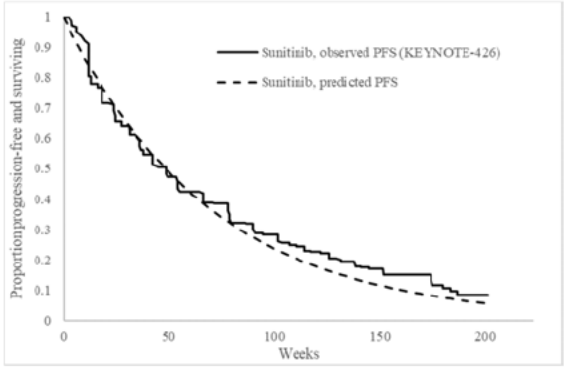
**Figure 22 Exponential models of OS and PFS compared with Kaplan-Meier curve extractions for sunitinib in the 1L advanced RCC setting**

OS:




PFS:




*Abbreviations*: 1L, first-line; OS, overall survival; PFS, progression-free survival.

**Table 27 HRs of OS and PFS failure with other treatment regimens vs. sunitinib in the 1L advanced RCC setting**

| Advanced regimen | HR of death vs. sunitinib | | HR of progression or death vs. sunitinib | | Expected survival in distant metastases state (weeks) | |
|---|---|---|---|---|---|---|
| | *HR* | *SE of ln(HR)* | *HR* | *SE of ln(HR)* | *OS* | *PFS* |
| **Sunitinib** | 1.00 | - | 1.00 | - | 252 | 70 |
| **Tivozanib** | 1.33 | 0.27 | 1.19 | 0.26 | 189 | 59 |
| **Pazopanib** | 0.92 | 0.08 | 1.05 | 0.08 | 273 | 66 |
| **Cabozantinib** | 0.80 | 0.21 | 0.48 | 0.22 | 314 | 145 |
| **Nivolumab/ipilimumab** | 0.72 | 0.08 | 0.89 | 0.08 | 349 | 78 |

*Abbreviations*: 1L, first-line; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SE, standard error.

**Table 28 Number of patients in the respective studies concerning OS and PFS in other treatment regimens vs. sunitinib in the 1L advanced RCC setting**

| Study | Ref | Intervention 1 | N (Ref) | N (Intervention) |
|---|---|---|---|---|
| **CheckMate 214** | Sunitinib | Nivolumab+ ipilimumab | 546 | 550 |
| **COMPARZ** | Sunitinib | Pazopanib | 554 | 557 |
| | **Sunitinib vs. Tivozanib** | | | |
| **Motzer 2007** | Sunitinib | IFN | 335 | 327 |
| **Escudier 2009** | IFN | Sorafenib | 92 | 97 |
| **TIVO-1** | Sorafenib | Tivozanib | 257 | 260 |
| **Alliance A031203 CABOSUN** | Sunitinib | Cabozantinib | 78 | 79 |

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

In each adjuvant treatment arm, the exponential hazard rate of DM → death is assumed to depend on: the market shares of first-line treatments received for advanced RCC (Table 29); and the expected survival associated with each advanced RCC treatment regimen (Table 27 above). Specifically, expected OS (starting from DM) is calculated in each adjuvant treatment arm as a weighted average of expected OS associated with different first-line treatments for advanced RCC, based on the market shares of first-line advanced treatments in that arm. Expected OS in each adjuvant treatment arm is then translated into a weekly hazard rate (Table 30). Expected PFS is similarly estimated for each adjuvant treatment arm based on the distributions of first-line treatments received, and the ratio of mean PFS to mean



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OS was estimated for each arm (Table 30); this ratio was used to calculate utility values and weekly disease management costs in each adjuvant treatment arm, as described in sections 8.4.1 and 8.5.4.2 of this report.

In the base case, market shares in each adjuvant treatment arm are estimated based on the following assumptions:

- In the intervention (pembrolizumab) arm, immunotherapies (IOs) are assumed to be available in the first-line advanced RCC setting, 24 months after adjuvant treatment initiations. However, for the comparator arm (routine surveillance) immunotherapies are available as first line treatment for advanced RCC as soon as the patients enter the DM state. All the market shares for 1L metastatic state are based on Danish expert clinical input. The market share of IO eligible arm for pembrolizumab is redistributed according to the global model market share and take into account the list of treatment available up to 24 months of adjuvant treatment initiation Table 29.

**Table 29 Market shares of first-line regimens for advanced RCC by adjuvant treatment arm**

| First-line regimens in advanced setting by adjuvant treatment arm (%) | First-line market shares, | | |
|---|---|---|---|
| | Pembrolizumab IO eligible | Pembrolizumab IO ineligible | Routine surveillance IO eligible |
| **Sunitinib** | 3.4% | 9.4% | 3.4% |
| **Tivozanib** | 25.6% | 71.1% | 25.6% |
| **Pazopanib** | 7.0% | 19.4% | 7.0% |
| **Cabozantinib** | 0.0% | 0.0% | 0.0% |
| **Nivolumab / ipilimumab** | 64.0% | 0.0% | 64.0% |

*Source*: Based on Danish expert clinical input

*Abbreviations*: DM, distant metastases; IO, immunotherapy; RCC, renal cell carcinoma.

**Table 30 Hazards of death from distant metastases by adjuvant treatment arm, based on first-line treatments received for advanced RCC**

| Adjuvant regimen | Eligibility for rechallenge / IOs in the advanced RCC setting | Expected survival in distant metastases state (weeks): *Weighted average based on first-line advanced treatment market shares* | | | Distant metastases → death: *Exponential hazard rate based on expected OS* |
|---|---|---|---|---|---|
| | | OS | *PFS* | Ratio of PFS to OS | |
| **Pembrolizumab** | IO-eligible | 300 | 72 | 0.24 | 0.0033 |
| **Pembrolizumab** | IO-ineligible | 211 | 61 | 0.29 | 0.0047 |
| **Routine surveillance** | IO-eligible | 300 | 72 | 0.24 | 0.0033 |

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

Health state utility inputs for the base case and scenario analyses are derived through primary analyses of EuroQol-Five Dimension-Five Level (EQ-5D-5L) data collected from the KN-564 trials and additional evidence from literature. 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 (137).

Three approaches are considered for defining health state utilities. These are based on:

- Health state
- Aging



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- AEs

In the KEYNOTE-564 trial, EQ-5D assessments continued until disease recurrence or start of a new anticancer treatment. Based on this protocol-defined assessment schedule, trial-based estimates of utility in the distant metastases state may not accurately reflect health-related quality of life during the entire period from distant metastases until death. Consequently, the base-case analysis used results from the KEYNOTE-426 trial to inform utility in the distant metastases state. Scenario analyses were also undertaken using several alternative sources for health state utilities, and the results supported the base-case cost-effectiveness conclusions.

Impact of different sources like Tivozanib NICE submission (TA512) and Pazopanib NICE submission (TA215) were tested in the DSA/scenario analyses. They had minor impact and resulted in a reduced ICER. These studies were considered in scenarios as they were approved by NICE for 1L metastatic RCC, and provided a reasonable source of utility information for the health state. Thus, MSD considers both studies to give the most appropriate results for DM state utilities as both of these are performed on advanced RCC patients. TA512 and TA215 are both described more in detail in Appendiks N Description of TA512 and TA215

The table below clarifies which analyses (base case and scenarios) draw on which data sets.

**Table 31 Data sources for different health states and analyses**

| Health state | Base case utilities (DK Algorithm) | | Scenario 1: Pre-progression DM state utility based on KEYNOTE-426 (Row 85 of <DSA Results> sheet) | | Scenario 2: DM state utilities based on Tivozanib NICE submission (TA512) (Row 86 of <DSA Results> sheet) | | Scenario 3: DM state utilities based on Pazopanib NICE submission (TA215) (Row 87 of <DSA Results> sheet) | |
|---|---|---|---|---|---|---|---|---|
| | Value | Source | Value | Source | Value | Source | Value | Source |
| Disease-free (without toxicity) | 0.914 | KEYNOTE-564 (data cutoff date: 14 Dec 2020) | 0.914 | KEYNOTE-564 (data cutoff date: 14 Dec 2020) | 0.914 | KEYNOTE-564 (data cutoff date: 14 Dec 2020) | 0.914 | KEYNOTE-564 (data cutoff date: 14 Dec 2020) |
| Locoregional recurrence | 0.897 | | 0.897 | | 0.897 | | 0.897 | |
| Distant metastases (pre-progression) | 0.851 | | 0.803 | KEYNOTE-426 (data cutoff date: 24 Aug 2018) | 0.726 | Tivozanib NICE submission (TA512) | 0.700 | Pazopanib NICE submission (TA215) |
| Distant metastases (post-progression) | 0.851 | | 0.851 | KEYNOTE-564 (data cutoff date: 14 Dec 2020) | 0.649 | | 0.590 | |

### 8.4.1 Utilities by health state

The EQ-5D-5L is the Danish preferred measure of health-related quality of life in adults (107) (138). Base-case utility values by health state are therefore derived through repeated measures regression analyses of patient-level EQ-5D-5L data from the KN-564 trial (for all the health states) and apply country-specific algorithm (Table 36). At each visit where health state was assessed, the corresponding EQ-5D-5L score was used to characterize utility. Patient-visits with missing EQ-5D-5L responses were excluded.

The schedule (study visits and estimated study times) and mapping of study visit to analysis visit for PRO data collection is provided in the table below.



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**Table 32 The schedule for PRO data collection**

| Study Week | Week 0 (Baseline) | Week 12 | Week 24 to Week 36 (Every 12 weeks) | Week 48 | Week 52 | Week 104 to Week 520 (Every 52 weeks) |
|---|---|---|---|---|---|---|
| Study Day | 1 | 85 | Week number *7+1 | 337 | 365 | Week number *7+1 |
| Day Range | <=1 | [2, 126] | [Week number*7-41, week number*7+42] | [295, 351] | [352, 546] | [Week number*7-181, week number*7+182] |

Total number of patients responding to EQ-5D-5L questionnaire are given in the table below.

**Table 33 Total number of patients responding to EQ-5D-5L questionnaire**

| Expected number of questionnaires/number of patients | Pembrolizumab *n* = 484 | Placebo *n* = 493 |
|---|---|---|
| Baseline | 484 | 493 |
| Week 12 | 483 | 493 |
| Week 24 | 458 | 452 |
| Week 36 | 399 | 423 |
| Week 48 | 358 | 394 |
| Week 52 | 353 | 384 |
| Week 104 | 115 | 109 |

Compliance and completion rates with regards to the EQ-5D-5L questionnaire are presented in table below.

**Table 34 Compliance and completion rates for EQ-5D-5L questionnaire**

| | Pembrolizumab *n* = 484 | | Placebo *n* = 493 | |
|---|---|---|---|---|
| n (%) | Completed | Compliance | Completed | Compliance |
| Baseline | 446 (92.1) | 446 (92.1) | 460 (93.3) | 460 (93.3) |
| Week 12 | 437 (90.3) | 437 (90.5) | 464 (94.1) | 464 (94.1) |
| Week 24 | 390 (80.6) | 390 (85.2) | 418 (84.8) | 418 (92.5) |



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| | Pembrolizumab | | Placebo | |
|---|---|---|---|---|
| | *n* = 484 | | *n* = 493 | |
| Week 36 | 333 (68.8) | 333 (83.5) | 361 (73.2) | 361 (85.3) |
| Week 48 | 252 (52.1) | 252 (70.4) | 311 (63.1) | 311 (78.9) |
| Week 52 | 301 (62.2) | 301 (85.3) | 327 (66.3) | 327 (85.2) |
| Week 104 | 91(18.8) | 91(79.1) | 91(18.5) | 91(83.5) |

Missing number table is given below.

**Table 35 Missing numbers for EQ-5D-5L questionnaire**

| | Pembrolizumab | Placebo |
|---|---|---|
| | *n* = 484 | *n* = 493 |
| Baseline | 0 (0.0) | 0 (0.0) |
| Week 12 | 1 (0.2) | 0 (0.0) |
| Week 24 | 26 (5.4) | 41 (8 .3) |
| Week 36 | 85 (17 .6) | 70 (14 .2) |
| Week 48 | 126 (26.0) | 99 (20 .1) |
| Week 52 | 131 (27.1) | 109 (22.1) |
| Week 104 | 369 (76.2) | 384 (77.9) |

Linear mixed-effects models with patient-level random effects are used to account for the correlation among repeated measures within an individual. The dependent variable is EQ-5D-5L utility score. The utility for disease-free (without toxicity) is estimated from a regression model that was restricted to patient-visits within the disease-free state, and that incorporated an independent variable for the presence/absence of all cause grade 3+ AE(s) at each patient-visit. The utility for locoregional recurrence is estimated from a regression model in which the independent variable was a categorical variable indicating health state at a given patient-visit (disease-free, locoregional recurrence, or distant metastases). To estimate the utility for DM, regression specification was fitted using all patient-visits with a utility measurement (N=977 patients, with 5,070 unique patient-visits). Independent variables included binary indicators for: being in the locoregional recurrence state during the patient-visit; and being in the distant metastases state during the patient-visit. Using the regression output provided below, the DM utility equaled the sum of the intercept and the coefficient for being in the DM state (i.e., 0.9011-0.05019= 0.85091).



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Pre-progression means patients progressed into distant metastases, started 1L treatment and remained progression free. Post-progression means that these patients progressed on 1L treatment. The same utility value has been used for both the pre and post-progression because in KN564, there is no data collected post distant metastases to differentiate the progression in that health state. Therefore, the utilities are based on the overall distant metastases state. The model allows the flexibility to differentiate pre-and post- progression when using literature-based utilities. Based on the DSA/scenario analyses, using different sources of utility (i.e., identical, or different pre-and post- progression utility values) has minor impact on the ICER results.

**Table 36 Health state utilities in the base case and EQ-5D change from baseline to week 52**

| Health state | Utilities | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Value | SE | Total number of patients | Number of responses | Total number of patients | Number of responses | Confidence Interval (95%) | |
| | | | Based on health state occupancy | | Based on regression | | | |
| Disease-free (without toxicity) | 0.914 | (0.005) | 972 | 4,795 | 977 | 5070 | 0.90 | 0.92 |
| Locoregional recurrence | 0.897 | (0.020) | 28 | 48 | 977 | 5070 | 0.86 | 0.94 |
| Distant metastasis (pre-progression) | 0.851 | (0.009) | 135 | 227 | 977 | 5070 | 0.83 | 0.87 |
| Distant metastasis (post-progression) | 0.851 | (0.009) | 135 | 227 | 977 | 5070 | 0.83 | 0.87 |

Source: KN-564 (data cutoff date: 14 Dec 2020)

| Treatment | Baseline | | Week 52 | | Change from baeline to Week 52 | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | N | LS mean (95% CI)[a] |
| Pembrolizumab | 446 | 0.91 (0.14) | 301 | 0.89 (0.15) | 484 | -0.02 (-0.04, -0.01) |
| Placebo | 460 | 0.91 (0.15) | 327 | 0.91 (0.15) | 493 | -0.02 (-0.03, -0.00) |

| Pairwise comparison | Difference in LS means (95% CI)[a] | p value |
|---|---|---|
| Pembrolizumab vs. placebo | -0.01 (-0.03, 0.01) | 0.4390 |

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.

For baseline and Week 52, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Two-sided p-value.

Source: Based on Danish EQ-5D-5L Mapping Algoritm (PRO FAS Population) and KN-564 (data cutoff date: 14 Dec 2020)

In the KEYNOTE-564 study, no meaningful differences between treatment arms were observed in LSM change from baseline to Week 52 in EORTC QLQ-C30 GHS/QoL or physical functioning scales, or the FKSI-DRS. No meaningful differences were observed between groups in the other EORTC QLQ-C30 functional or symptom scales or in the EQ-5D VAS (Table 37 and Table 38). Further, the empirical mean change from baseline in the EORTC QLQ-C30 GHS/QoL and physical functioning scales, and FKSI-DRS remained stable through week 104 for both pembrolizumab and placebo groups. Although patients in the placebo group did not receive active treatment, PRO outcomes were comparable between groups. Therefore, pembrolizumab did not have a negative impact on HRQoL.



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Table 37 Change from Baseline in EQ-5D-5L Utility Score to Week 12, 24, 36, 48 and 52

| Treatment | Baseline | | Week | | Change from Baseline to Week 52 | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | N | LS Mean (95% CI)[a] | Difference in LS Means[a] (95% CI) | p-Value[a] |
| **Week 12** | | | | | | | | |
| Pembrolizumab | 446 | 0.91 (0.14) | 437 | 0.90 (0.16) | 476 | -0.02 (-0.03, -0.01) | -0.01 (-0.03, 0.01) | 0.2335 |
| Placebo | 460 | 0.91 (0.15) | 464 | 0.91 (0.14) | 490 | -0.01 (-0.02, 0.00) | | |
| **Week 24** | | | | | | | | |
| Pembrolizumab | 446 | 0.91 (0.14) | 390 | 0.89 (0.17) | 482 | -0.03 (-0.04, -0.02) | -0.03 (-0.04, -0.01) | 0.0029 |
| Placebo | 460 | 0.91 (0.15) | 418 | 0.92 (0.12) | 491 | -0.01 (-0.02, 0.01) | | |
| **Week 36** | | | | | | | | |
| Pembrolizumab | 446 | 0.91 (0.14) | 333 | 0.89 (0.15) | 483 | -0.03 (-0.04, -0.02) | -0.01 (-0.03, 0.01) | 0.2628 |
| Placebo | 460 | 0.91 (0.15) | 361 | 0.91 (0.15) | 491 | -0.02 (-0.03, -0.00) | | |
| **Week 48** | | | | | | | | |
| Pembrolizumab | 446 | 0.91 (0.14) | 252 | 0.89 (0.19) | 484 | -0.04 (-0.06, -0.02) | -0.02 (-0.04, 0.00) | 0.0788 |
| Placebo | 460 | 0.91 (0.15) | 311 | 0.91 (0.13) | 493 | -0.02 (-0.03, -0.00) | | |
| **Week 52** | | | | | | | | |
| Pembrolizumab | 446 | 0.91 (0.14) | 301 | 0.89 (0.15) | 484 | -0.02 (-0.04, -0.01) | -0.01 (-0.03, 0.01) | 0.4390 |
| Placebo | 460 | 0.91 (0.15) | 327 | 0.91 (0.15) | 493 | -0.02 (-0.03, -0.00) | | |

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.

For baseline and Week 12, 24, 36, 48, and 52, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Two-sided p-value.

Database Cutoff Date: 14DEC2020.

Table 38 Change from Baseline in EQ-5D-5L VAS to Week 12, 24, 36, 48 and 52

| Treatment | Baseline | | Week | | Change from Baseline to Week 52 | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | N | Mean (SD) | N | LS Mean (95% CI)[a] | Difference in LS Means[a] (95% CI) | p-Value[a] |
| **Week 12** | | | | | | | | |
| Pembrolizumab | 446 | 84.02 (13.97) | 437 | 80.67 (15.39) | 476 | -3.19 (-4.55, -1.83) | -1.79 (-3.56, -0.02) | 0.0475 |
| Placebo | 460 | 83.12 (14.63) | 464 | 82.03 (15.22) | 490 | -1.40 (-2.72, -0.07) | | |
| **Week 24** | | | | | | | | |
| Pembrolizumab | 446 | 84.02 (13.97) | 390 | 82.33 (14.04) | 482 | -2.04 (-3.37, -0.70) | -0.39 (-2.11, 1.34) | 0.6591 |
| Placebo | 460 | 83.12 (14.63) | 418 | 82.34 (14.84) | 491 | -1.65 (-2.94, -0.36) | | |
| **Week 36** | | | | | | | | |
| Pembrolizumab | 446 | 84.02 (13.97) | 333 | 81.51 (14.77) | 483 | -3.13 (-4.65, -1.61) | -1.53 (-3.50, 0.43) | 0.1263 |
| Placebo | 460 | 83.12 (14.63) | 361 | 82.58 (14.84) | 491 | -1.60 (-3.07, -0.13) | | |
| **Week 48** | | | | | | | | |
| Pembrolizumab | 446 | 84.02 (13.97) | 252 | 82.58 (15.08) | 484 | -2.75 (-4.41, -1.08) | -0.55 (-2.67, 1.57) | 0.6101 |
| Placebo | 460 | 83.12 (14.63) | 311 | 82.09 (14.45) | 493 | -2.20 (-3.74, -0.65) | | |
| **Week 52** | | | | | | | | |
| Pembrolizumab | 446 | 84.02 (13.97) | 301 | 80.75 (15.76) | 484 | -3.36 (-4.90, -1.82) | -1.58 (-3.59, 0.42) | 0.1220 |



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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 460 | 83.12 (14.63) | 327 | 82.52 (14.87) | 493 | -1.78 (-3.27, -0.29) | | |

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.

For baseline and Week 12, 24, 36, 48, and 52 N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Two-sided p-value.

Database Cutoff Date: 14DEC2020.

It is not uncommon that utility from adjuvant trials are relatively high. For example, the utility for adjuvant melanoma for respectively recurrence free and locoregional recurrence is 0.912 and 0.858 based on KEYNOTE-054, which is close to the current case (104). It can be because the quality of life is not impaired significantly for patients who are in non-metastasis state compared to the general population. Also the utilities from a trial population may have limitations because it may not fully reflect the patients in real world due to selection and control environment. These limitations are addressed in the model by using different sources of utilites in the scenario analyses, for example, utilities for DM based on literature (139, 140).

The utility in the DF state per treatment arm can be seen in the table below.

**Table 39 DF state utility per treatment arm**

| | Pooled (recommend) | Pembrolizumab | Placebo |
|---|---|---|---|
| DF utility without grade 3+ AEs | 0.91392 | 0.90876 | 0.91880 |
| Disutility of grade 3+ AEs | 0.06202 | 0.06136 | 0.06136 |

Below is a table with number of AEs in the DF state per treatment arm.

**Table 40 DF state number of AEs per treatment arm**

| | | Pembrolizumab | | Placebo | |
|---|---|---|---|---|---|
| Health state | AE | N, records | N, patients | N, records | N, patients |
| Disease-free | During Grade 3+ AE | 180 | 94 | 81 | 36 |
| Disease-free | During Other Grade 3+ AE | 1399 | 391 | 1241 | 358 |
| Disease-free | Without AE | 782 | 403 | 1112 | 443 |

### 8.4.2 Utilities related to aging

**Error! Reference source not found.** describes the utilities associated with different age brackets, are extracted from guidelines based on Danish Medicines Council. These utilities are further used to calculate the age related dis-utilities in each cycle and are applied within the model to account for disutility related to aging of the cohort over time (141).



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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) (112, 142).

**Table 41 Age-related disutility**

| Age | 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 |

### 8.4.3 Disutility related to AEs

AE-related disutility is applied as a one-time QALY decrement in the first model cycle. Disutility associated with AEs is calculated in each treatment arm as a function of: treatment-specific AE risks (Adverse reaction outcomes section 8.2.2.5); the mean durations of these AEs per affected patient in KEYNOTE-564 (section 8.2.2.5); and the estimated disutility associated with an active all-cause grade 3+ AE based on regression analyses of EQ-5D-5L data from the KN-564 trial [redacted]). The formula for calculating the AE-related QALY decrement is as follows: Total AE related QALY decrement = the sum-product (risk % of each treatment-specific AE * mean duration of each AE) * AE disutility.

[redacted]

In the base case, the disutility of active grade 3+ AE is obtained from the same regression model used to estimate the health state utility for disease-free (without toxicity). This regression model includes an intercept term along with two coefficients estimating the impact associated with the presence and absence of grade 3+ AE. The value of the coefficient associated with the presence of any grade 3+ AE(s) is used to source the disutility of the active grade 3+ AE in the model. The number of QALYs lost due to Grade 3+ AE is estimated by multiplying the disutilities with the average durations of grade 3+ AEs for pembrolizumab and routine surveillance observed in KN-564, which were 0.005 and 0.0018 years for pembrolizumab and routine surveillance, respectively.



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In the regression model built for disutility, independent variables are binary indicators for, the absence of any AE during the patient-visit in the disease-free state; and the presence of any other-grade (i.e., grade less than 3) AE during the patient-visit in the disease-free state.

From this regression equation we obtain the disutility of grade 3+ AEs as the difference in utility associated with disease-free (without toxicity) (0.8519+0.06202 = 0.91392) vs. disease-free (during any grade 3+ AE) (0.8519) in KEYNOTE-564. Thus, disutility becomes 0.06202 (0.91932-0.8519).

It is applied to all patients when they enter the model in the DF state. Hence, the model is considering AEs related to DF state only.

The table below summarizes average duration of adverse reactions, estimated disutility from regression, and final disutility value for each treatment arm.

**Table 44 average duration of adverse reactions, estimated disutility from regression, and disutility value for each treatment arm**

| AE type | Mean duration (weeks) | Source | Disutility (SE) |
|---|---|---|---|
| Abdominal pain | 4.9 | Mean duration of each grade 3-5 AE type was obtained from KEYNOTE-564 and reflects the average weeks per unique all-cause event multiplied by the mean number of unique all-cause events per patient who had a particular AE type. For AE types that did not occur in KEYNOTE-564 as of the current data cut-off, mean duration was assumed to be equal to the mean duration of grade 3+ AEs (all types). Mean durations of AEs are based on all-cause, grade 3-5 events, regardless of whether all-cause or drug-related AE risks are considered. | -0.062 (0.009) |
| Alanine aminotransferase increased | 18.6 | | |
| Arthralgia | 10.1 | | |
| Aspartate aminotransferase increased | 5.6 | | |
| Asthenia | 66.1 | | |
| Back pain | 13.7 | | |
| Blood creatinine increased | 3.6 | | |
| Constipation | 4.9 | | |
| Decreased appetite | 19.3 | | |
| Diarrhoea | 9.3 | | |
| Dizziness | 4.0 | | |
| Dry mouth | 81.0 | | |
| Dyspnoea | 0.3 | | |
| Fatigue | 46.9 | | |
| Hyperglycaemia | 22.7 | | |
| Hypertension | 35.0 | | |
| Hyperthyroidism | 5.0 | | |
| Hypothyroidism | 171.9 | | |
| Influenza-like illness | 0.7 | | |
| Myalgia | 168.3 | | |
| Nausea | 1.8 | | |
| Pain in extremity | 55.4 | | |
| Pruritus | 10.9 | | |
| Pyrexia | 0.4 | | |
| Rash | 38.0 | | |
| Upper respiratory tract infection | 3.1 | | |
| Urinary tract infection | 1.1 | | |
| Vomiting | 0.4 | | |
| Total AE-related QALY decrement (pembrolizumab): | | | **-0.0050** |



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| | |
|---|---|
| Total AE-related QALY decrement (routine surveillance): | **-0.0018** |

To estimate the disutility related to grade 3+ AEs, a regression model was fitted to patient-visits with a utility measurement that occurred during each patient's disease-free period (N=972 patients, with 4,795 unique patient-visits). Independent variables included binary indicators for: the absence of any AE during the patient-visit; and the presence of any other-grade (i.e., grade less than 3) AE during the patient-visit. This approach captures the disutility related to grade 3+ AE happened with adjuvant pembrolizumab.

AE-related disutility in the model incorporated the whole AE risks happening during the study treatments and the duration of AEs. Specifically, the cumulative risks of AE reflect the number of events occurred at any time during the study treatments. Since the exact week when each AE occurs was not available from the trial, and nearly all AEs have a duration less than 1 year, it is considered reasonable to apply all AE-related disutility as a one-off value at the beginning of the model for calculation simplicity.

## 8.5 Resource use and costs

All the costs are estimated from the Danish limited societal perspective (107). Direct medical costs along with patient costs are included in the base-case model. In this section, all costs are according to 2022 Danish kroner. The following main cost components are considered within the model:

- Drug acquisition cost and drug administration costs for adjuvant therapy – Danish Medicines Agency
- Drug acquisition cost and drug administration costs for subsequent therapies – Danish Medicines Agency
- AE management costs – based on the DRG rates from The Danish Health Data Authority
- State-specific disease management costs – based on the DRG rates from The Danish Health Data Authority
- Terminal care costs – based on the DRG rates from The Danish Health Data Authority
- Patient costs – based on the Danish Medicines Council.

### 8.5.1 Drug acquisition and administration costs for adjuvant treatment

Drug acquisition and administration costs per infusion of adjuvant pembrolizumab are calculated in the model as a function of the pharmacy price per drug unit, defined dosing schedule, relative dose intensity, and unit cost of drug administration. The proportion of patients remaining on pembrolizumab treatment over time is based on the observed Kaplan-Meier curve for time on treatment up to 1 year in KN-564. Additional details are provided in the sub-sections below.

#### 8.5.1.1 Unit drug costs, dosing schedule, relative dose intensity and per cycle cost

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 (143).

The defined dosing schedule of pembrolizumab in the adjuvant setting is a flat dose of 200 mg every 3 weeks (Table 45), consistent with the treatment protocol used in the KN-564 trial (144). In the base case, the relative dose intensity (as reflected in the pembrolizumab arm of KN-564) is applied to the drug acquisition cost per infusion of adjuvant pembrolizumab to account for any delays or interruptions in administration (e.g., due to AEs). 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.



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The number of vials administered per patient was 1.7, with an average cost per dose of DKK 38,968. No vial wastage is associated with pembrolizumab. The cost per admin for each cycle is given in Table 46.

**Table 45 Unit drug cost for adjuvant treatments**

| Drug | Unit drug costs | |
|---|---|---|
| | Strength per unit (mg) | Cost per unit (DKK) |
| Pembrolizumab | 100 | 23,204.61 |

Source: The Danish Medicines Agency

**Table 46 Dosing schedule, relative dose intensity and pr cycle cost for adjuvant treatments**

| Adjuvant regimen | Dosing schedule desription | Total mg per administration | Total vials required per admin | Relative dose intensity (%) | Drug acquisition cost per admin (2022, DKK) |
|---|---|---|---|---|---|
| Pembrolizumab | 2 mg/kg Q3W for up to 17 weeks | 170 | 1.7 | 98.9 | 38,968 |

Abbreviations: Q3W, once every 3 weeks.

Sources for relative dose intensity: KEYNOTE-564 (data cutoff date: June 14, 2021)

#### 8.5.1.2 Drug administration cost

Drug administration cost per infusion of pembrolizumab is based on the 2022 DRG-rates from the Danish Health Data Authority given that the time required per administration of pembrolizumab is 30 minutes (145).

**Table 47 Unit cost per administration of adjuvant treatments**

| Adjuvant regimen | Route | Type of administration | Unit cost per administration or pharmacy dispensing (DKK) | DRG code | Soruce |
|---|---|---|---|---|---|
| Pembrolizumab | IV | Simple parental chemoterapy | 2,038.00 | 11MA98 | DRG-rates from the Danish Health Data Authority |

Abbreviations: IV, intravenous; DRG, Diagnosis related group

#### 8.5.1.3 Time on treatment

The proportion of patients remaining on adjuvant pembrolizumab at each scheduled infusion is based on the observed Kaplan-Meier curve for time to treatment discontinuation in the KN-564 trial. In the trial, patients randomized to adjuvant pembrolizumab received treatment for a maximum of 17 doses (approximately 1 year). Based on this maximum duration, there were no patients remaining on treatment as of the data cutoff date; thus, the observed Kaplan-Meier curve for time on adjuvant treatment is fully mature and could be used directly, without the need for extrapolation.

The number of events for time on treatment (ToT) is defined as the number of patients who discontinued or completed the primary study protocol at the time of the database cut-off. Patients without events have been censored at the earliest after the last known treatment date or the database's cut-off date, whichever occurred first.



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At the database cut-off, each patient had either completed or discontinued treatment, and therefore no patients were censored.

The number of 'no. at risk' at each point in time is graphically illustrated for each of the treatment arms in the graph below. Note that placebo arm ToT is not used in the economic model because there are no drug-specific costs associated with placebo (i.e. routine surveillance) in clinical practice.

As illustrated in Figure 24, a small percentage of patients in the pembrolizumab arm of KN-564 (data cutoff date: June 14, 2021) remains on adjuvant therapy beyond 1 year, as the protocol allowed patients to complete all 17 doses past the 1-year point if there had been earlier delays in treatment. Within the model, the costs of adjuvant pembrolizumab treatment are modeled based on a fixed interval of every 3 weeks, and so the costs of the 17$^{th}$ dose are applied at t = 48 weeks from baseline for the percentage of patients still on adjuvant treatment at this time point. Therefore, the model does not use the portion of the Kaplan-Meier curve beyond the scheduled 51-week treatment period (represented by the dashed line in the figure below).



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### 8.5.2 Drug acquisition and administration cost for subsequent treatment

Within the model, drug acquisition and administration costs associated with subsequent therapies (including both first-line and second-line subsequent therapies) are applied as a one-time cost upon entry into the distant metastases state. All the patients who entered the distant metastases state are assumed to receive an active first-line treatment for advanced RCC. Among patients who received first-line therapy for advanced RCC, the costs of second- and later-line treatments for advanced RCC are also considered.

The model considers first-line and later-lines treatment options for advanced RCC, based on the clinician inputs of Denmark.

#### 8.5.2.1 Unit drug costs and dosing schedule

Drug acquisition cost per cycle for drugs in the advanced RCC setting are calculated in the model as a function of the unit drug cost, defined dosing schedule, patients weight (for IV) and relative dose intensity.

Unit drug costs are provided in Table 48, and were retrieved from The Danish medicine Agency (143).

**Table 48 Unit drug costs for first-line and second-line therapies for advanced RCC**

| Drug | Unit drug costs | |
|---|---|---|
| | Strength per unit (mg) | Cost per unit (DKK) |
| Sunitinib | 50 | 1,022.54 |
| Axitinib | 7 | 666.73 |
| Tivozanib | 1.34 | 1,180.90 |
| Pazopanib | 400 | 307.84 |
| Cabozantinib | 60 | 1,646.67 |



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| Drug | Unit drug costs | |
|---|---|---|
| | Strength per unit (mg) | Cost per unit (DKK) |
| Nivolumab | 240 | 22,003.74 |
| Ipilimumab | 200 | 102,385.55 |

Abbreviation: MU, million units.

Source: Danish medicines agency

Dosing schedules and relative dose intensity are shown in Table 49. The dosing schedules are based on NICE guidelines (146) for treatments recommended for advanced RCC in the UK and on treatment protocols in pivotal clinical trials (147, 148) for other subsequent treatments.

For intravenous drugs (nivolumab + ipilimumab) with weight-based dosing, the base-case analysis assumed that vial-sharing is allowed. Under this assumption, the number of vials required per infusion are calculated based on average body weight of patients in in the model cohort. Number of vials is calculated as patient weight in kilograms (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).

As a scenario analysis, the assumption of no vial sharing is tested. Under this scenario, the number of vials required per infusion is estimated based on a log-normal distribution of patient weight. 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 interval.

For each first-line and later-line treatment, the mean relative dose intensity (i.e., proportion of planned dose consumed) is applied to the drug acquisition cost. Relative dose intensities account for the fact that patients may not take the full planned dosage due to dose interruption or reduction associated with AEs or non-compliance. Relative dose intensities are obtained from pivotal clinical trials in advanced RCC settings. Relative dose intensities for nivolumab/ipilimumab have not been reported and are therefore assumed equal to the relative dose intensity of pembrolizumab. The cost per administration for each cycle for first-line and second-line therapies for advanced RCC is given in Table 49.

**Table 49 Dosing schedules and relative dose intensity for first-line and second-line therapies for advanced RCC**

| Regimen | Drug component | Dosing schedule | Total mg per administration | Total vials required per admin | Relative dose intensity (%) | Drug acquisition cost per admin (2022, DKK) |
|---|---|---|---|---|---|---|
| **First-line therapies** | | | | | | |
| **Sunitinib** | Sunitinib | 50 mg QD orally for 4 weeks, then 2 weeks off treatment | 1,400 | 28.00 | 74.7% | 21,387.36 |
| **Tivozanib** | Tivozanib | 1.34 mg QD orally for 3 weeks followed by 1 week without treatment | 28 | 21.00 | 94.0% | 23,311.06 |



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| Regimen | Drug component | Dosing schedule | Total mg per administration | Total vials required per admin | Relative dose intensity (%) | Drug acquisition cost per admin (2022, DKK) |
|---|---|---|---|---|---|---|
| **Pazopanib** | Pazopanib | 800 mg QD orally | 22,400 | 56.00 | 86.0% | 14,825.60 |
| **Cabozantinib** | Cabozantinib | 20/40/60 mg QD orally | 1,680 | 28.00 | 94.3% | 43,478.59 |
| **Nivolumab/ipilimumab** | Nivolumab (in combination) | 3 mg/kg IV Q3W for up to 4 doses | 255 | 1.06 | 94.8% | 22,137.19 |
| | Ipilimumab | 1 mg/kg IV Q3W for up to 4 doses | 85 | 0.42 | 94.8% | 41,202.61 |
| | Nivolumab (maintenance) | 480 mg IV Q4W starting 6 weeks after the last combination dose | 480 | 2.00 | 94.8% | 41,719.09 |
| **Second-line therapies** | | | | | | |
| ***PD-1/PD-L1 inhibitors*** | | | | | | |
| **Nivolumab** | Nivolumab | 480 mg IV Q4W or 240 mg IV Q2W | 480 | 2.00 | 92.0% | 40,486.88 |
| ***VEGF/VEGFR inhibitors*** | | | | | | |
| **Axitinib** | Axitinib | 5 mg orally BID | 280 | 40.00 | 102.0% | 27,202.67 |
| **Cabozantinib** | Cabozantinib | 60 mg orally QD | 1,680 | 28.00 | 100.0% | 46,106.67 |
| **Pazopanib** | Pazopanib | 800 mg orally QD | 22,400 | 56.00 | 86.0% | 14,825.60 |
| **Sunitinib** | Sunitinib | 50 mg orally QD for 4 weeks, then 2 weeks off treatment | 1,400 | 28.00 | 74.7% | 21,387.36 |
| ***Other treatments*** | | | | | | |
| **Everolimus** | Everolimus | 10 mg orally QD | 280 | 28.00 | 91.8% | 17,928.11 |

#### 8.5.2.2 Drug administration cost or pharmacy dispensing fees

Unit costs of intravenous drug administration are based on 2022 DRG-rates from the Danish Health Data Authority, depending on the specific treatment (Table 50, Table 51) (145). The cost of IV administration is irrespective of infusion hours or whether drugs are given as a combination therapy or monotherapy. Also, there is no cost for oral drug administration in Denmark.



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**Table 50 Unit costs of drug administration in the advanced RCC setting**

| Route | Type of administration | Unit cost per administration or pharmacy dispensing (DKK) | DRG code | Source |
|---|---|---|---|---|
| IV | Simple parenteral chemotherapy | 2,038.00 | 11MA98 | DRG-rates from the Danish Health Data Authority |
| IV | Complex parenteral chemotherapy | 2,038.00 | 11MA98 | DRG-rates from the Danish Health Data Authority |

Abbreviations: DRG, Diagnosis related group.

Abbreviations: IV, intravenous.

**Table 51 Drug administration type by treatment regimen for advanced RCC**

| Regimen | Drug component | Type of administration |
|---|---|---|
| **First-line therapies** | | |
| **Sunitinib** | Sunitinib | Oral drug dispensing |
| **Tivozanib** | Tivozanib | Oral drug dispensing |
| **Pazopanib** | Pazopanib | Oral drug dispensing |
| **Cabozantinib** | Cabozantinib | Oral drug dispensing |
| **Nivolumab/ipilimumab** | Nivolumab (in combination) | Complex parenteral chemotherapy |
| | Ipilimumab | Assumed to be covered by same administration cost |
| | Nivolumab (maintenance) | Simple parenteral chemotherapy |
| **Second- and later-line therapies** | | |
| ***PD-1/PD-L1 inhibitors*** | | |
| **Nivolumab** | Nivolumab | Simple parenteral chemotherapy |
| ***VEGF/VEGFR inhibitors*** | | |
| **Axitinib** | Axitinib | Oral drug dispensing |
| **Cabozantinib** | Cabozantinib | Oral drug dispensing |
| **Pazopanib** | Pazopanib | Oral drug dispensing |
| **Sunitinib** | Sunitinib | Oral drug dispensing |
| ***Other treatments*** | | |
| **Everolimus** | Everolimus | Oral drug dispensing |



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#### 8.5.2.3 Time on treatment, market shares, and total regimen costs

Durations of first-line treatment regimens for advanced RCC are modeled using the exponential rates of PFS failure (as described in section 8.3.4) to approximate treatment discontinuation rates. Some regimens or components of regimens are subject to a maximum treatment duration based on the dosing schedules recommended by NICE (149) (Table 52).

To estimate mean ToT for each subsequent-line treatment, median ToT data is collected from relevant second-line clinical trials (150-154) conducted in advanced RCC populations (Table 53). In the absence of clinical data in the second-line setting, median ToT is extracted from a combined first-(155)/second-line trial (156) for pazopanib. Mean ToT for each subsequent therapy is calculated as a function of median ToT, based on an assumption of constant hazards.

Based on the estimated discontinuation rate and (when applicable) the maximum duration of each drug component in a regimen, the model estimates the mean total cost of each treatment regimen in the first- and second-line setting. The mean cost of first- and second-line treatment is then calculated for each adjuvant treatment arm as a weighted average based on the first- and second-line market shares within each adjuvant treatment arm. Base-case market shares in the first-line setting are described previously in Table 29 of section 8.3.4. Base-case market shares in the second-line setting (Table 54) are estimated using similar approaches. The market shares of later-line therapies in the advanced RCC setting are based on Danish clinical expert input.

**Table 52 Maximum durations of first-line treatment regimes in the advanced RCC setting**

| Regimen | Drug component | Maximum ToT (weeks) |
|---|---|---|
| **Sunitinib** | Sunitinib | No max |
| **Tivozanib** | Tivozanib | No max |
| **Pazopanib** | Pazopanib | No max |
| **Cabozantinib** | Cabozantinib | No max |
| **Nivolumab/ipilimumab** | Nivolumab (in combination) | 12 |
| | Ipilimumab | 12 |
| | Nivolumab (maintenance) | No max |

Abbreviations: ToT, time on treatment.

**Table 53 Time on treatment for second-line treatment regimes in the advanced RCC setting**

| Second-line treatment regimen | Drug component | Maximum ToT (months) | | Source |
|---|---|---|---|---|
| | | Median | Mean | |
| ***PD-1/PD-L1 inhibitors*** | | | | |
| **Nivolumab** | Nivolumab | 23.9 | 34.5 | Motzer et al. (2015) [CheckMate 025] |
| ***VEGF/VEGFR inhibitors*** | | | | |
| **Axitinib** | Axitinib | 35.7 | 51.4 | Motzer et al. (2013) [AXIS] |



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| Second-line treatment regimen | Drug component | Maximum ToT (months) | | Source |
|---|---|---|---|---|
| | | Median | Mean | |
| **Cabozantinib** | Cabozantinib | 36.5 | 52.7 | Motzer et al. (2018) [METEOR] |
| **Pazopanib** | Pazopanib | 32.2 | 46.4 | Sternberg et al. (2013) [VEG105192] |
| **Sunitinib** | Sunitinib | 32.2 | 46.4 | Assume same median ToT as pazopanib |
| ***Other treatments*** | | | | |
| **Everolimus** | Everolimus | 19.1 | 27.6 | Motzer et al. (2018) [METEOR] |

**Table 54 Market shares of second- and later-line regimes for advanced RCC by adjuvant treatment arm**

| Later-line regimes in advanced setting | Later-line market shares, by adjuvant treatment arm (%) | | |
|---|---|---|---|
| | Median IO eligible | Mean IO ineligible | Routine surveillance IO eligible |
| ***PD-1/PD-L1 inhibitors*** | | | |
| **Nivolumab** | 20.0% | 0.0% | 20.0% |
| ***VEGF/VEGFR inhibitors*** | | | |
| **Axitinib** | 3.2% | 4.0% | 3.2% |
| **Cabozantinib** | 64.0% | 80.0% | 64.0% |
| **Pazopanib** | 6.4% | 8.0% | 6.4% |
| **Sunitinib** | 4.8% | 6.0% | 4.8% |
| ***Other treatments*** | | | |
| **Everolimus** | 1.6% | 2.0% | 1.6% |

Source: Based on Danish clinical expert input.

### 8.5.3 Costs of AEs

As described in section 8.2.2.5, the types of AEs included in the model included those considered likely to have a significant impact in terms of either resource utilization or health-related quality of life. Unit costs per episode are based on the 2022 DRG rates from the Danish Health Data Authority. The model considers AEs occurring in the adjuvant setting. The AE costs are applied as a one-off cost in the model.

**Table 55 Unit costs of AE**

| AE type | Cost per event (DKK) | DRG code |
|---|---|---|
| **Abdominal pain** | 2,415.00 kr. | DR100/23PR01 |



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| AE type | Cost per event (DKK) | DRG code |
|---|---|---|
| **Alanine aminotransferase increased** | 4,460.00 kr. | DR740B/23MA03 |
| **Arthralgia** | 2,015.00 kr. | DM255/08MA17 |
| **Aspartate aminotransferase increased** | 4,460.00 kr. | DR740B/23MA03 |
| **Asthenia** | 4,460.00 kr. | DR539A/23MA03 |
| **Back pain** | 3,050.00 kr. | DM54/08SP03 |
| **Blood creatinine increased** | 4,460.00 kr. | 23MA03 |
| **Constipation** | 4,460.00 kr. | DK590/23MA03 |
| **Decreased appetite** | 4,460.00 kr. | DR630B/23MA03 |
| **Diarrhoea** | 6,756.00 kr. | DK529B1/06MA11 |
| **Dizziness** | 5,926.00 kr. | DR42/03MA02 |
| **Dry mouth** | 1,364.00 kr. | DR682/03MA09 |
| **Dyspnoea** | 2,180.00 kr. | DR060/04MA98 |
| **Fatigue** | 4,460.00 kr. | DR539A/23MA03 |
| **Hyperglycaemia** | 4,460.00 kr. | DR739/23MA03 |
| **Hypertension** | 16,630.00 kr. | DI109/05MA11 |
| **Hyperthyroidism** | 1,845.00 kr. | DE059/10MA01 |
| **Hypothyroidism** | 1,845.00 kr. | :DE032/10MA01 |
| **Influenza-like illness** | 4,460.00 kr. | DJ10/23MA03 |
| **Myalgia** | 2,415.00 kr. | DM791/23PR01 |
| **Nausea** | 4,460.00 kr. | DR119B/23MA03 |
| **Pain in extremity** | 2,415.00 kr. | DM796/23PR01 |
| **Pruritus** | 5,789.00 kr. | DL29/09PR09 |
| **Pyrexia** | 2,513.00 kr. | DR502/18MA98 |
| **Rash** | 5,789.00 kr. | DR21/09PR09 |
| **Upper respiratory tract infection** | 2,217.00 kr. | DJ00-DJ06/03MA98 |
| **Urinary tract infection** | 27,401.00 kr. | DN390/11MA07 |



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| AE type | Cost per event (DKK) | DRG code |
|---|---|---|
| **Vomiting** | 4,460.00 kr. | DR119C/23MA03 |

Source: DRG-rates from the Danish Health Data Authority (145)

### 8.5.4 Disease management cost by health state

Unit costs for resource use elements in the disease-free, locoregional recurrence, and distant metastases states are obtained from 2022 DRG-rates from the Danish Health Data Authority (Table 56).

**Table 56 Unit costs of healthcare resources**

| Resource use element | Unit cost (DKK) | Source (145) |
|---|---|---|
| Surgery kidney, malignant disease, with robot | 90,823.00 kr. | DRG-rate 2021: 11MP07 |
| Surgery kidney, malignant disease | 86,375.00 kr. | DRG-rate 2021: 11MP08 |
| **Outpatient visits** | | |
| Medical oncologist | 2,038.00 kr. | DRG-rate 2022: 11MA98 |
| Radiation oncologist | 2,038.00 kr. | DRG-rate 2022: 11MA98 |
| General practitioner | 148.35 kr. | Honorar table, Lægeforeningen (157) |
| Palliative care, physician outpatient visit | 2,038.00 kr. | DRG-rate 2022: 11MA98 |
| Psychologist | 2,038.00 kr. | DRG-rate 2022: 11MA98 |
| Cancer specialist nurse | 550.00 kr. | Kommunerne og regionernes løndatakontor (158) |
| **Inpatient stays** | | |
| Oncology/general ward | 2,038.00 kr. | DRG-rate 2022: 11MA98 |
| Palliative care unit – inpatient | 4,746.00 kr. | DRG-rate 2022: 26MP45 |
| **Home care** | | |
| Palliative care physician | 19,330.00 kr. | DRG-rate 2022: 26HJ01 |
| Palliative care nurse | 12,886.00 kr. | DRG-rate 2022: 26HJ02 |
| Home aide visits | 0.00 | |
| **Laboratory tests** | | |
| Complete blood count | 1,515.00 kr. | DRG-rate 2022: 23MA04 |
| Complete metabolic panel | 2,038.00 kr. | DRG-rate 2022: 11MA98 |
| Urinalysis | 0.00 | |



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| Resource use element | Unit cost (DKK) | Source (145) |
|---|---|---|
| **Radiologic exams** | | |
| CT scan of abdomen/pelvis | 1,979.00 kr. | DRG-rate 2022: 30PR07 |
| CT scan of chest | 1,979.00 kr. | DRG-rate 2022: 30PR07 |
| MRI of brain | 2,057.00 kr. | DRG-rate 2022: 30PR03 |
| CT scan of brain | 1,979.00 kr. | DRG-rate 2022: 30PR07 |
| PET/CT scan | 1,979.00 kr. | DRG-rate 2022: 30PR07 |
| Bone scintigraphy | 4,344.00 kr. | DRG-rate 2022: 30PR15 |
| X-ray | 1,640.00 kr. | DRG-rate 2022: 30PR18 |

#### 8.5.4.1 Disease management costs in the disease-free and locoregional recurrence states

Medical resource use per week in the disease-free state includes laboratory test like complete blood count, CT scan of abdomen/pelvis and X ray (Table 57). The frequencies of these resource use elements are based on opinion of Danish clinical experts.

The schedule of follow-up in the locoregional recurrence state is also informed by input from Danish clinical experts. Resource use in the locoregional recurrence state also includes one-time costs of kidney surgery (both with and without robot) (nephrectomy) for a proportion of patients who enter this state. The state also includes resource use like complete blood count test and CT scan of abdomen/pelvis. Frequencies of salvage surgery and other resource use for the locoregional recurrence state are based on the opinion of Danish clinical experts.

**Table 57 Frequencies of resource use in the disease-free state**

| Resource use element | Disease-free- monthly resource use up to year 2 | | Disease-free – monthly resource use, years 2-5 | | Disease-free – monthly resource use, years 5+ | |
|---|---|---|---|---|---|---|
| | % patients | Resource use | % patients | Resource use | % patients | Resource use |
| **Laboratory tests** | | | | | | |
| Complete blood count | 100% | 0.167 | 100% | 0.083 | 100% | 0.083 |
| **Radiologic exams** | | | | | | |
| CT scan of abdomen/pelvis | 100% | 0.167 | 100% | 0.083 | 100% | 0.083 |
| X-ray | 0% | 0.000 | 0% | 0.000 | 100% | 0.042 |
| **Total cost per 1-week cycle (DKK)** | **133.92 per week** | | **66.96 per week** | | **82.80 per week** | |

Source: Danish clinical expert input



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Table 58 Frequencies of resource use in the locoregional recurrence state

| Resource use element | Locoregional recurrence – salvage surgery and other one-time resource use upon entering health state | | Locoregional recurrence – monthly resource use | |
|---|---|---|---|---|
| | % patients | Resource use | % patients | Resource use |
| **Surgery** | | | | |
| Surgery kidney, malignant disease, with robot | 7.5% | 1.000 | | |
| Surgery kidney, malignant disease | 7.5% | 1.000 | | |
| **Laboratory tests** | | | | |
| Complete blood count | 100% | 1.00 | 100% | 0.250 |
| **Radiologic exams** | | | | |
| CT scan of abdomen/pelvis | 100% | 1.000 | 100% | 0.250 |
| **Total cost (DKK)** | **15,268.85 one-time cost** | | **200.89 per week** | |

Source: Danish clinical expert opinion

### 8.5.4.2 Disease management costs in the distant metastases state

Medical resource use in the distant metastases state includes outpatient provider visits (e.g., medical oncologists, cancer specialist nurse), palliative care unit stay, complete blood count, CT scan of abdomen/pelvis and MRI of brain. Medical resource use frequencies per month are based on the opinion of Danish clinical experts.

Upon entering the distant metastases state, a proportion of patients are assumed to incur one-time costs of kidney surgery (both with and without robot). The percentage of patients with surgery among those who experienced distant metastases are based opinion of Danish clinical experts.

The distant metastases state in the present model encompasses both pre- and post-progression distant metastases. Therefore, in each adjuvant treatment arm, disease management costs per week in the distant metastases state are computed as a weighted average of resource use associated with pre- versus post-progression distant metastases, based on the estimated proportion of time spent progression-free within the distant metastases state (Table 60).

Table 59 Frequencies of resource use in distant metastases state

| Resource use element | Distant metastases (pre progression) – salvage surgery (one-time resource use upon entering health state) | | Distant metastases (pre progression) – subsequent monthly resource use | | Distant metastases (post progression) – monthly resource use | |
|---|---|---|---|---|---|---|
| | % patients | Resource use | % patients | Resource use | % patients | Resource use |
| **Surgery kidney, malignant disease, with robot** | 7.5% | 1.000 | | | | |



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| Resource use element | Distant metastases (pre progression) – salvage surgery (one-time resource use upon entering health state) | | Distant metastases (pre progression) – subsequent monthly resource use | | Distant metastases (post progression) – monthly resource use | |
|---|---|---|---|---|---|---|
| | % patients | Resource use | % patients | Resource use | % patients | Resource use |
| Surgery kidney, malignant disease | 7.5% | 1.000 | | | | |
| Outpatient visits | | | | | | |
| Medical oncologist | 0% | 0.00 | 100% | 1.00 | 100% | 0.250 |
| Cancer specialist nurse | 0% | 0.00 | 100% | 0.250 | 100% | 0.250 |
| Inpatient stays | | | | | | |
| Oncology/general ward | 0% | 0.000 | 0% | 0.000 | 15% | 1.000 |
| Home care | | | | | | |
| Palliative care physician | 0% | 0.000 | 0% | 0.000 | 20% | 1.000 |
| Laboratory tests | | | | | | |
| Complete blood count | 0% | 0.000 | 100% | 1.000 | 100% | 0.333 |
| Radiologic exams | | | | | | |
| CT scan of abdomen/pelvis | 0% | 0.000 | 100% | 0.333 | 100% | 0.333 |
| MRI of brain | 0% | 0.000 | 0% | 0.00 | 7% | 0.333 |
| Total cost (DKK) | 13,289.85 one-time cost | | 531.75 per week | | 1387.09 per week | |

Source: Danish clinical expert opinion

Under base case market shares in Table 29.

**Table 60 Overall disease management cost per week in distant metastases, by adjuvant treatment arm**

| Adjuvant regimen | Eligibility for rechallenge / Ios in the advanced RCC setting | Ratio of PFS:OS in DM state: *Based on advanced treatment market shares* | Overall disease management costs per week in DM state: *Weighted average of pre- and post-progression costs (kr.)* |
|---|---|---|---|
| Pembrolizumab | IO-eligible | 0.24 | 1,181.44 per week |
| Pembrolizumab | IO-ineligible | 0.29 | 1,139.98 per week |
| Routine surveillance | IO-eligible | 0.24 | 1,181.44 per week |



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### 8.5.5 Terminal care costs

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 61 Terminal care costs**

| Resource | Unit cost (DKK) | DRG code | Frequency of use (number per week) | Source for unit cost (including codes if available) |
|---|---|---|---|---|
| **One time Terminal care cost** | 28,154.00 | 15MP01 | Lump-sum cost (assumption of 14 days care) | DRG-rates from the Danish Health Data Authority (145) |

### 8.5.6 Patient cost

According to requirements of the Danish Medicines Council and as a part of a Danish 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 (159). Also, a time cost of DKK 179 based on the average hourly wage (after tax) is applied to the patients for taking into account per hour infusion time and time spend at follow up visit (159). The transportation cost and infusion time cost are considered once in three weeks for adjuvant pembrolizumab according to the dosing schedule mentioned in Table 62.

**Table 62 IV infusion time and transportation cost according to treatments**

| Cost per patient | Treatment cycles (weeks) | Patient hours required per administration | Hours spent per week | Cost per infusion (DKK) | Transportation cost per administration (DKK) |
|---|---|---|---|---|---|
| **Pembrolizumab (adjuvant therapy)** | 3 | 0.50 | 0.17 | 29.83 | 33.33 |

Additionally, for time spend at follow up visit is given in Table 63.

**Table 63 Follow up visit cost (using frequency resource use, patient hours, and % of patients)**

| Resource use | Patient hours |
|---|---|
| **For DF state** | |
| Complete blood count | 0.5 |
| CT scan of abdomen/pelvis | 1 |
| X-ray | 0.5 |
| **For LR state** | |
| Surgery kidney, malignant disease, with robot | 36 |
| Surgery kidney, malignant disease | 36 |
| Complete blood count | 0.5 |



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| Resource use | Patient hours |
|---|---|
| CT scan of abdomen/pelvis | 1 |
| **For DM state** | |
| Surgery kidney, malignant disease, with robot | 36 |
| Surgery kidney, malignant disease | 36 |
| Medical oncologist visit | 1 |
| Cancer specialist nurse visit | 0.5 |
| Oncology/general ward stay | |
| Palliative care physician | 1 |
| Complete blood count | 0.5 |
| CT scan of abdomen/pelvis | 1 |

Considering all the patient hours of follow up visit, resource use frequency and % of patients taking the follow up visit (Table 57, Table 58, Table 59) we are calculating the follow up visit cost for different states. A transportation cost is also added to the patients when they are going for follow up visits. The costs of different states are given in Table 64.

**Table 64 State-wise cost of hours spend at follow up visits**

| Health state | Patient Follow Up Cost (kr.) | | | Transportation Cost (kr.) | | |
|---|---|---|---|---|---|---|
| | Up to 3 years | Years 3-5 | Subsequent years | Up to 3 years | Years 3-5 | Subsequent years |
| **Disease-free** | 6.86 | 3.43 | 3.43 | 33.33 | 33.33 | 33.33 |
| **Locoregional recurrence** | One-time resource cost upon entering health state | Subsequent weekly resource cost | | One-time resource cost upon entering health state | Subsequent weekly resource cost | |
| | 1,145.60 | 10.29 | - | 115.00 | 11.50 | - |
| **Distant metastases** | One-time resource cost upon entering health state | Subsequent weekly resource cost (pre-progression) | Subsequent weekly resource cost (post-progression) | One-time resource cost upon entering health state | Subsequent weekly resource cost (pre-progression) | Subsequent weekly resource cost (post-progression) |
| | 966.60 | 13.72 | 255.51 | 15.00 | 36.41 | 35.42 |



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### 8.5.7 Results

### 8.5.8 Base case overview

The model calculates expected costs, LY gained, QALYs, and incremental cost-effectiveness ratios (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.

**Table 65 Base case overview**

| | |
|---|---|
| Comparator | Routine surveillance |
| Type of model | Markov model |
| Time horizon | 41.1 years (life time) |
| Cycle length | The present model uses a weekly cycle length to allow for precise calculation of drug acquisition and administration costs. |
| Treatment line | Adjuvant treatment. Subsequent treatments are also included |
| Measurement and valuation of health effects | Health-related quality of life measured with EQ-5D-5L in KN564. Danish population weights were used to estimate health-state utility values |
| 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:<br>• Drug acquisition and administration costs for adjuvant therapy<br>• Drug acquisition and administration costs for subsequent therapy<br>• Disease management costs<br>• AE-related costs<br>• Terminal care costs<br>• Transportation cost and time spent by patients<br>The costing year of the analysis is 2022. |
| Dosage of pharmaceutical | Pembrolizumab:<br>• 2 mg/kg (IV) every 3rd week for up to 17 series of administration (approx. one year) OR 4 mg/kg (IV) every 6th week for up to 9 series of administration (approx. one year). |
| Average time on treatment | Pembrolizumab: 11.1 months/17 cycles |
| Transition probabilities | Transition probabilities starting from the disease-free state are estimated based on survival analyses of individual patient-level data from the KN-564 trial, following the parametric multistate modelling approach described by Williams et al. ((111) (112) |



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| | |
|---|---|
| Transition probabilities from DFS | In accordance with recommendations of Danish medicines council ((107), base-case parametric functions are selected such that the same functional form is used to model each health state transition in both the pembrolizumab (intervention) and the routine surveillance (comparator) arm. The rationale for this approach is to prevent the extrapolated portion of the DFS curves from following drastically different trajectories between the two model arms.<br><br>Parametric proportional hazards models with a time-varying treatment effect (before and after year 1) with A) an exponential function for disease-free → locoregional recurrence and B) Gompertz function for disease-free → distant metastases. |
| Transition probabilities from LR | For transitions probabilities from LR to different health states we use exponential rates due to lack of data from the KN564 trial. |
| Transition probabilities from DM | Transitions probabilities from DM to death state are modelled using the exponential hazard rate for each adjuvant regimen (based on HRs of advanced treatments obtained from NMA for OS and PFS vs. sunitinib) and the market shares of advanced regimens. |
| IO therapy as 1L treatment option | In the intervention (pembrolizumab) arm, immunotherapies (IOs) are assumed to be available in the first-line advanced RCC setting, 24 months after adjuvant treatment initiations. However, for the comparator arm (routine surveillance) immunotherapies are available as first line treatment for advanced RCC as soon as the patients enter the distant metastases state. |

### 8.5.9 Base case results

Base-case results (with 3.5% discounting of costs and health benefits) are presented in Table 66. Over a 41.1-year time horizon, total costs are 1,136,705 kr. for pembrolizumab and 946,641 kr. for routine surveillance. Total QALYs over this time horizon are estimated to be 10.92 for pembrolizumab and 9.65 for routine surveillance. Total LYs are estimated to be 12.25 and 10.89 years, respectively, for pembrolizumab vs. routine surveillance. The proportion of total LYs spent in the disease-free state is 82.0% in the pembrolizumab arm compared with 66.4% in the routine surveillance arm.

The resulting ICER in terms of incremental cost per QALY gained is 149,523 kr. for pembrolizumab vs. routine surveillance. The ICER in terms of incremental cost per LY gained is estimated to be 138,784 kr. (Table 66). These results indicate that pembrolizumab is cost-effective as an adjuvant treatment of RCC following nephrectomy (as it is within the threshold of 3 times GDP per capita of Denmark).

Differences in total costs across the treatment arms are largely driven by adjuvant treatment costs and by subsequent treatment costs in the advanced RCC setting (the latter being lower for pembrolizumab; Table 67). Disease management costs (excluding anti-cancer treatment) are also lower in the pembrolizumab arm (156,888 kr.) vs. the routine surveillance arm (220,632 kr.), reflecting the lower incidence of disease recurrence achieved with pembrolizumab. This is also true for terminal care costs, which were lower for pembrolizumab than routine surveillance (9,213 kr. vs. 13,261 kr.). The patient cost is also lower for pembrolizumab as compared to routine surveillance arm (21,599 kr. vs. 35,609 kr.).



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**Table 66 Base case results**

| | Total costs (kr.) | Total QALYs | Total LYs | ΔCosts (kr.) | ΔQALYs | ΔLYs | ICER of pembrolizumab vs. comparator (kr./QALY) | ICER of pembrolizumab vs. comparator (kr./LY) |
|---|---|---|---|---|---|---|---|---|
| **Pembrolizumab** | 1,136,705 | 10.92 | 12.25 | - | - | - | - | - |
| **Routine surveillance** | 946,641 | 9.65 | 10.89 | 190,064 | 1.27 | 1.37 | 149.523 | 138,784 |

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

**Table 67 Base-case disaggregated costs and effectiveness**

| Outcomes | Pembrolizumab | Routine surveillance |
|---|---|---|
| **Total costs (kr.)** | 1,136,705 | 946,641 |
| Adjuvant treatment costs | 553,833 | 0 |
| *Drug acquisition costs* | 526,308 | 0 |
| *Drug administration costs* | 27,526 | 0 |
| Subsequent treatment costs | 393,956 | 676,409 |
| *Drug acquisition costs* | 388,119 | 660,193 |
| *Drug administration costs* | 5,837 | 16,217 |
| Adverse event costs | 1,215 | 730 |
| Disease management costs | 156,888 | 220,632 |
| Terminal care costs | 9,213 | 13,261 |
| Patient cost | 21,599 | 35,609 |
| **Quality-adjusted life years** | 10,92 | 9,65 |
| *Disease-free* | 9,06 | 6,54 |
| *Locoregional recurrence* | 0,53 | 0,86 |
| *Distant metastases* | 1,34 | 2,25 |
| *AE-related disutility* | -0,0050 | -0,0018 |
| *Age-related disutility* | -0.15 | -0.10 |
| **Life years** | 12.25 | 10.89 |
| *Disease-free* | 10.05 | 7.23 |



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| Outcomes | Pembrolizumab | Routine surveillance |
|---|---|---|
| *Locoregional recurrence* | 0.61 | 0.98 |
| *Distant metastases* | 1.59 | 2.68 |

#### 8.5.9.1 Main driver behind difference between disease management costs in the two arms

Disease management costs are lower in the pembrolizumab arm vs. the routine surveillance arm, as there is lower incidence of disease recurrence and progression associated with pembrolizumab use. We can also see from the DFS curve that more patients remain in the DFS state in pembrolizumab arm compared to the routine surveillance arm at all time points. This results in a higher resource utilization in routine surveillance arm (as they move to LR and DM state) in this arm. Additionally, the cost of managing patients in the LR (15,268.85 kr. one-time cost upon entering health state + 200.89 kr. per week) and DM states (13,289.85 kr. one-time cost upon entering health state + 959.42 kr. per week) is higher vs. the DF state (74.88 kr. per week on an average).

#### 8.5.9.2 Main driver behind difference between terminal care cost in the two arms

In this model, only those patients who die from DM state are assumed to incur a one-time cost associated with palliative/terminal care to account for disease linked mortality. In Denmark, terminal care costs are based on costs during the 14 days before death and taken the same for both the arms. Over the time horizon, it can be observed from the OS curve, that the survival with pembrolizumab use is higher vs. routine surveillance. More patients die from DM state in the routine surveillance arm as compared to the pembrolizumab arm attaching a higher terminal care cost to it (13,261 kr. vs. 9,213 kr., respectively).

#### 8.5.9.3 Main driver behind difference between subsequent treatment cost in the two arms

In the model, drug acquisition and administration costs associated with subsequent therapies (including both first-line and second-line subsequent therapies) are applied as a one-time cost upon entry into the distant metastases state. This cost would apply to the % of patients that make a transition to DM state in each cycle. The analysis shows that more patients transition to the DM state in the routine surveillance arm as compared to the pembrolizumab arm. This is due to the fact that transition probabilities to DM state are higher for routine surveillance arm. The DM state occupancy at each time point can be observed to be higher in the routine surveillance arm vs. pembrolizumab attaching a higher subsequent treatment cost to the former.

#### 8.5.9.4 Main driver behind difference between patient cost in the two arms

The patient cost can be bifurcated into two parts, one is the infusion time cost, and the other is the patient follow-up time cost. Also, a transportation cost was incurred by the patients at the time of treatment administration and at the time of follow up. The main driving factor for higher patient cost in routine surveillance arm is the patient follow up cost and transportation cost in the LR and DM state. it can be observed that the LR and DM state occupancy is higher for the routine surveillance arm compared to the pembrolizumab arm. Hence, the patient cost in the routine surveillances arm is higher than pembrolizumab arm.



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## 8.6 Sensitivity analyses

### 8.6.1 Deterministic sensitivity analyses

To assess the robustness of the model results, deterministic sensitivity analyses (DSAs) are conducted by varying one model input or assumption at a time. Table 68 summarizes the variables assessed and the resulting ICERs. DSA results are also shown graphically in tornado diagrams (Figure 25). Sensitivity analyses in the tornado diagrams are sorted from the widest to narrowest range of ICER values to highlight parameters with the strongest influence on the cost-effectiveness results.

Table 68 shows that across the sensitivity analyses, the incremental cost per QALY for pembrolizumab vs. routine surveillance ranges from 48,075 kr. to 416,005 kr. The ICER is comparable to the base-case value when using a 30-year time horizon (158,589 kr./QALY) and increases in the scenario that used a short time horizon of 20 years (235,861 kr./QALY). Because large proportions of patients in both arms are expected to survive beyond 20 and 30 years, these alternative time horizons are considered as scenario analyses only. The ICER decreased to 48,075 kr./QALY when applying no discounting to costs and effectiveness and 84,871 kr./QALY when using a 1.5% (rather than 3.5%) annual discount rate, as the costs of adjuvant therapy are incurred upfront in year 1 and these scenarios assigns a higher present value to long-term QALY gains with pembrolizumab relative to routine surveillance.

ICERs of pembrolizumab vs. the routine surveillance arm are also sensitive to parameters determining transition probabilities starting from the disease-free state. Across the five scenarios that uses alternative parametric distributions to model transitions from the disease-free state, the ICER varies from 173,575 kr./QALY to 416,005 kr./QALY, with all five scenarios yielding an ICER below a willingness-to-pay threshold of 1,199,894 kr./QALY. This threshold approximately corresponds to the World Health Organization recommended threshold of three times gross domestic product [GDP] per capita.(160) GDP per capita in the Denmark is 399,965 kr. (160) GDP per capita in the Denmark is 399.965 kr. in 2020 according to the World Bank.(161) The most conservative of these scenarios uses separately fitted exponential distributions for disease-free → locoregional recurrence and generalized gamma distributions for disease-free → distant metastases in each treatment arm. Under this alternative set of parametric distributions, the model predicts a 11 percentage-point difference in DFS between pembrolizumab and routine surveillance at 7 years, on par with the observed DFS benefit of sunitinib vs. placebo at 7 years in the S-TRAC trial. Given that the observed effect size on DFS is larger for pembrolizumab vs. placebo in KEYNOTE-564 (37% reduction in the hazards of recurrence or death) than for sunitinib vs. placebo in S-TRAC (24% reduction in hazards of recurrence or death), this scenario is included as the lower limit of incremental effectiveness with pembrolizumab relative to routine surveillance.

The ICER of pembrolizumab vs. routine surveillance increases slightly when excluding the costs of second-line treatments in the distant metastases state. The ICER moderately decreases in scenarios that did not apply age-related disutility, or that used prior NICE appraisals (TA512 or TA215) as the source for utility values in the distant metastases state. However, the ICER is not very sensitive to high/low variation in state-specific utility values. The cost-effectiveness results also are not very sensitive to the assumption of 100% relative dose intensity for adjuvant pembrolizumab, or to variations in: transition probabilities from the locoregional recurrence state; the efficacy (in terms of PFS and OS) of subsequent treatments for RCC in the distant metastases state; drug administration costs; state-specific disease management costs; terminal care costs; or AE-related costs and disutilities.



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**Table 68 Tabular DSA and scenario analysis results**

| | Change | ICER (DKK/QALY) | % Change vs. Base-case |
|---|---|---|---|
| **Base case** | | 149,523 | |
| **Time horizon and discounting** | Time horizon: 30 years | 158,589 | 5.7 |
| | Time horizon: 20 years | 235,861 | 57.8 |
| | Annual discount rate: 0.0% | 48,075 | -68 |
| | Annual discount rate: 1.5% | 84,871 | -43.5 |
| **Efficacy and transition probabilities** | DF→LR, DF→DM: Exponential, Generalized gamma (separately fitted) | 416,005 | 178 |
| | DF→LR, DF→DM: Exponential, Gompertz (separately fitted) | 349,085 | 133.4 |
| | DF→LR, DF→DM: Exponential, Gompertz (jointly fitted, time-constant HR) | 173,575 | 16.1 |
| | DF→LR, DF→DM: Weibull, Gompertz (jointly fitted, time-constant HR) | 194,607 | 30.2 |
| | DF→LR, DF→DM: Weibull, Gompertz (jointly fitted, time-varying HR) | 194,017 | 29.8 |
| | Exponential rates of LR→DM and LR→Death +/- 20% | 142,343 / 159,883 | -4.8 / 6.9 |
| | Exponential rates of OS and PFS failure with treatments for advanced RCC +/- 20% | 164,348 / 121,090 | 9.9 / -19 |
| **Subsequent therapies for advanced RCC** | Include costs of first-line advanced regimens only | 215,233 | 43.9 |
| **Drug acquisition and administration costs** | Unit cost of simple IV drug administration +/- 20% | 152,499 / 146,546 | 2 / -2 |
| | Unit cost of complex IV drug administration +/- 20% | 149,244 / 149,801 | -0.2 / 0.2 |
| | Unit cost of oral drug dispensing +/- 20% | 149,523 / 149,523 | -0.2 / 0 |
| | Mean patient weight +/- 20% | 223,677 / 75,368 | 49.5 / -49.5 |
| | Do not apply relative dose intensity | 144,294 | -3.5 |
| | Do not allow vial-sharing | Dominant | |
| **Disease management costs** | Medical management costs in DF state per week (up to year 2) +/- 20% | 149.654 / 149.391 | 0.1 / -0.1 |



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| | Change | ICER (DKK/QALY) | % Change vs. Base-case |
|---|---|---|---|
| | Medical management costs in DF state per week (years 2-5) +/- 20% | 149,720 / 149,325 | 0.1 / -0.1 |
| | Medical management costs in DF state per week (years 5+) +/- 20% | 151,120 / 147,925 | 1.1 / -1.1 |
| | Salvage surgery costs upon LR state entry (one-time cost) +/- 20% | 149,278 / 149,767 | -0.2 / 0.2 |
| | Medical management costs in LR state (per week) +/- 20% | 148,911 / 150,134 | -0.4 / 0.4 |
| | Medical management costs upon DM state entry (one-time cost) +/- 20% | 149,145 / 149,900 | -0.3 / 0.3 |
| | Medical management costs in pre-progression DM state (per week) +/- 20% | 148,520 / 150,525 | -0.7 / 0.7 |
| | Medical management costs in post-progression DM state (per week) +/- 20% | 139,803 / 159,242 | -6.5 / 6.5 |
| | Terminal care cost (one-time cost) +/- 20% | 148,886 / 150,159 | -0.4 / 0.4 |
| **AE-related costs** | Cost of AEs +/- 20% | 149,599 / 149,446 | 0.1 / -0.1 |
| | Do not consider costs of AE management | 149.141 | -0.3 |
| | Consider drug-related AE risks | 149.185 | -0.2 |
| **Utilities** | Utility in DF state (95% CI) | 146,611 / 152,552 | -2 / -2.1 |
| | Utility in LR state (95% CI) | 151,212 / 147,870 | 1.1 / -1.1 |
| | Utility in pre-progression DM state (95% CI) | 150,016 / 149,032 | 0.3 / -0.3 |
| | Utility in post-progression DM state (95% CI) | 151,376 / 147,714 | 1.3 / -1.2 |
| | All health state utilities based on KEYNOTE-564 (incl. post-progression DM) | 149,523 | 0 |
| | Pre-progression DM state utility based on KEYNOTE-564 | 148,259 | -0.9 |
| | DM state utilities based on Tivozanib NICE submission (TA512) | 129,240 | -13.7 |
| | DM state utilities based on Pazopanib NICE submission (TA215) | 124,507 | -16.9 |
| | Do not apply age-adjusted disutility | 143,630 | -3.4 |



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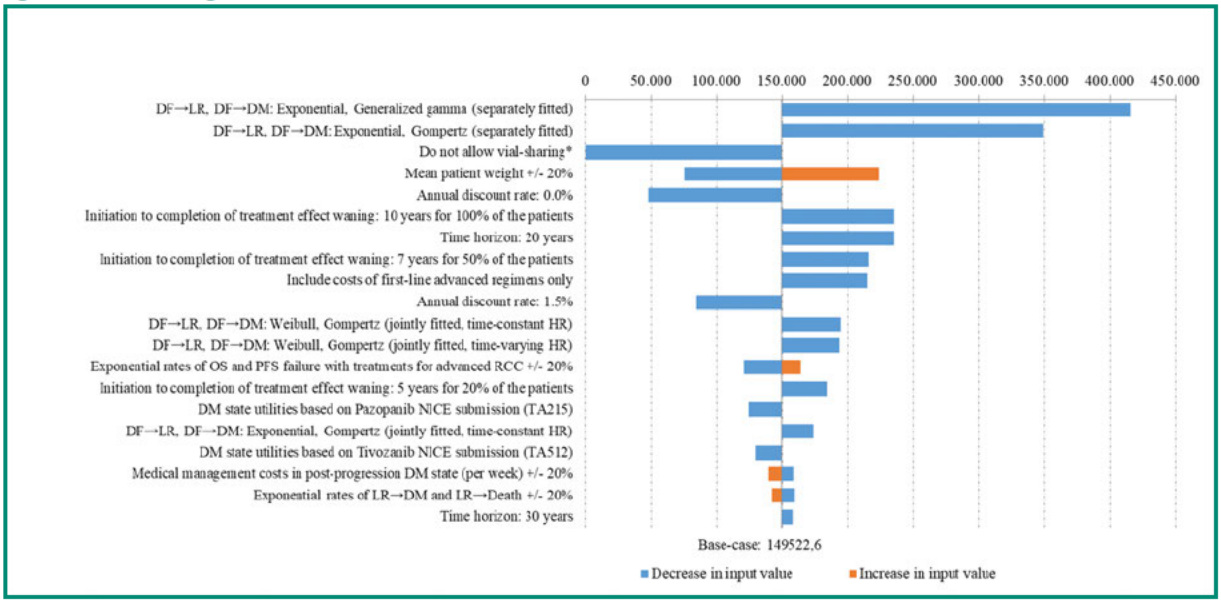
| Change | ICER (DKK/QALY) | % Change vs. Base-case |
|---|---|---|
| Disutility from AEs +/- 20% | 149,599 / 149,446 | 0.1 / -0.1 |
| Do not apply AE-related disutility | 149,143 | -0.3 |

**Figure 25 Tornado diagram**



*Abbreviations*: CI, confidence interval; DF, disease-free; DM, distant metastases; HR, hazard ratio; LR, locoregional recurrence; OS, overall survival; PFS, progression-free survival.

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

### 8.6.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) is conducted to estimate the probability of pembrolizumab being cost-effective based on different willingness-to-pay thresholds. A Monte-Carlo simulation with 1,000 iterations is conducted. In each iteration, the model inputs are randomly drawn from the distributions specified in Appendix J.

Uncertainty in the transition probabilities from the disease-free health state is represented using multivariate normal distributions (or univariate normal for the exponential rates), as this distribution reasonably describes the sampling distribution of the mean for many variables.

Exponential rates of transitions from the locoregional recurrence health state are modeled with normal distributions. For exponential rates of OS and PFS failure with sunitinib in the advanced RCC setting, normal distributions are used. Log-normal distributions are assumed for HRs of OS and PFS for other advanced RCC treatments vs. sunitinib. Gamma distributions are assumed for medical management, drug administration, and adverse event cost parameters that can range between zero and infinity. Beta distributions are assumed for utilities of health states and utilities according to age group, to reflect their allowable range between zero and one. For dis-utilities associated with adverse events, normal distributions are used.

Whenever available, the standard error of the selected distribution is obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, the standard error for each cost parameter is assumed to be equal to 20% of the mean value.

Across the 1,000 iterations of the PSA, the average incremental cost is 193,922 kr. and the average incremental QALY gain is 1.24 for pembrolizumab vs. routine surveillance. The resulting probabilistic ICER per QALY for pembrolizumab vs. routine surveillance is 156,940 kr. and is within a close range to the base case results (149,523 kr./QALY).

Figure 26 presents the scatterplot of the simulated incremental cost and QALY pairs for pembrolizumab vs. routine surveillance. The cost-effectiveness acceptability curve in Figure 27 show the probability of pembrolizumab being cost-effective vs. routine surveillance over a range of different willingness-to-pay thresholds. Based on a willingness-to-pay threshold of 1,199,894 kr. per QALY (3 times GDP per capita) gained, pembrolizumab has a 98.4% probability of being cost-effective vs. routine surveillance.



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**Figure 26 Scatterplots of incremental costs and effectiveness for pembrolizumab vs. routine surveillance across 1,000 iterations of the PSA**

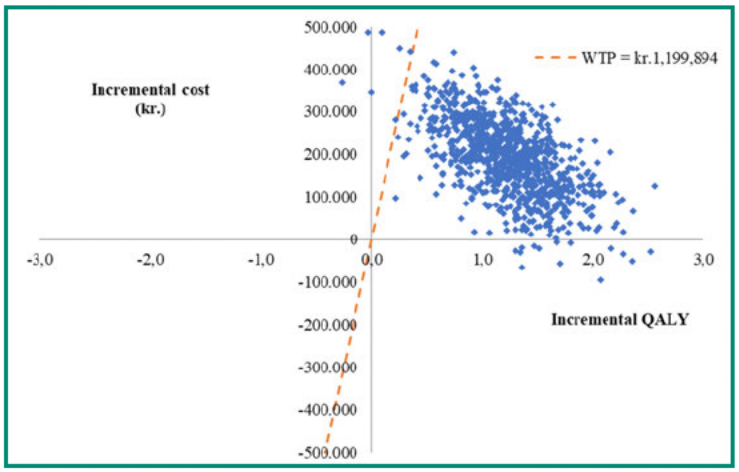
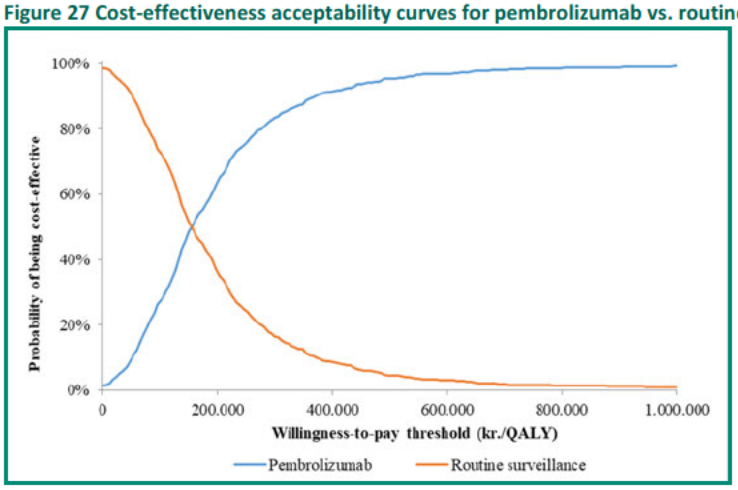



**Figure 27 Cost-effectiveness acceptability curves for pembrolizumab vs. routine surveillance**




The significance of the drug price for the ICER is illustrated by the table and graph below showing ICER's estimated at different prices going from AIP to a price where the ICER becomes negative.

**Table 69 ICER's estimated at different prices**

| Pembrolizumab Cost (kr. for 100 mg) | Discount Rate | ICER (kr./QALY) |
|---|---|---|
| 23,205 | 0% | 148,523 |
| 22,044 | 5% | 128,196 |
| 20,884 | 10% | 107,594 |
| 19,724 | 15% | 86,992 |
| 18,564 | 20% | 66,390 |
| 17,403 | 25% | 45,789 |
| 16,243 | 30% | 25,187 |



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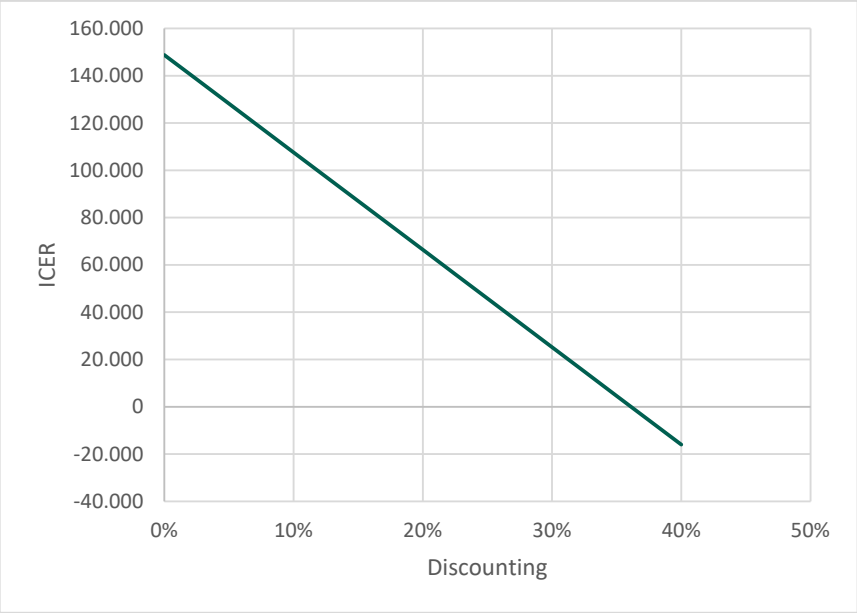
| | | |
|---|---|---|
| 15,083 | 35% | 4,585 |
| 13,923 | 40% | Dominant (-16,017) |

**Figure 28 ICER's at different discounting**




## 8.7 Model validation

### 8.7.1 Verification

To verify the results of the cost-effectiveness model, both internal and external quality control procedures were undertaken. Internally, the model developer team took actions to ensure that the mathematical calculations are performed correctly and are consistent with the model's specifications. The model was also independently reviewed by health economists external to the company that built the model, who evaluated the model from an overall health economics perspective in addition to checking for implementation errors.

### 8.7.2 Internal validation

The internal validity of the model was also assessed by comparing modelled efficacy outcomes against the original sources that informs the efficacy inputs. The present economic model was developed using efficacy data from the recent efficacy update report from KEYNOTE-564 (data cutoff date: June 14, 2021), representing 30.1 months of median follow-up (defined as the time between the date of randomization until the database cutoff date). Specifically, the DFS curves predicts for two arms of KEYNOTE-564 were plotted alongside the observed Kaplan-Meier curves for DFS to ensure that the curves are well-aligned during the trial period. Similar comparisons were conducted between the predicted and observed cumulative incidence curves for each individual transition from the disease-free state (i.e., disease-free to locoregional recurrence, disease-free to distant metastases, and disease-free to death).



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### 8.7.3 External validation

Model predictions were also compared against observed data from external studies. For example, data from the placebo arms of previous adjuvant TKI inhibitor trials were used to validate the model predictions for DFS and OS in the placebo arm. Details are provided in section 5.3.1.3 and Appendiks L Overview of clinical trials used for external validation.

Additionally, clinical experts were consulted to validate the efficacy inputs (including the plausibility of long-term DFS and OS) and other key model decisions (e.g., assumptions about post-recurrence treatments) from a clinical perspective.

### 8.7.4 Cross-validation

A targeted literature review did not identify any prior cost-effectiveness studies of adjuvant treatments for RCC. Consequently, there is limited potential for cross-validation of the current model results against other, independently developed economic evaluations in the same indication. However, prior HTAs and published cost-effectiveness studies in other adjuvant oncology indications, including the NICE appraisal of pembrolizumab as adjuvant treatment of resected stage III melanoma (TA553) (162) provide support and precedence for the assumptions used in the current model.

# 9. Budget impact analysis

## 9.1 Budget impact analysis overview

The budget impact analysis is added in the KN564 cost effectiveness model, adapted with local Danish inputs which estimates the five-year budgetary impact for 143 annual ccRCC patients, who are eligible for adjuvant RCC 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 is not available as an adjuvant treatment for RCC. Only routine surveillance is available as an adjuvant treatment.
2. *New scenario*: Pembrolizumab is available as an adjuvant treatment for RCC alongside the other treatment option; routine surveillance.

The overall model schematic overview of the model is shown in

**Figure 29**.



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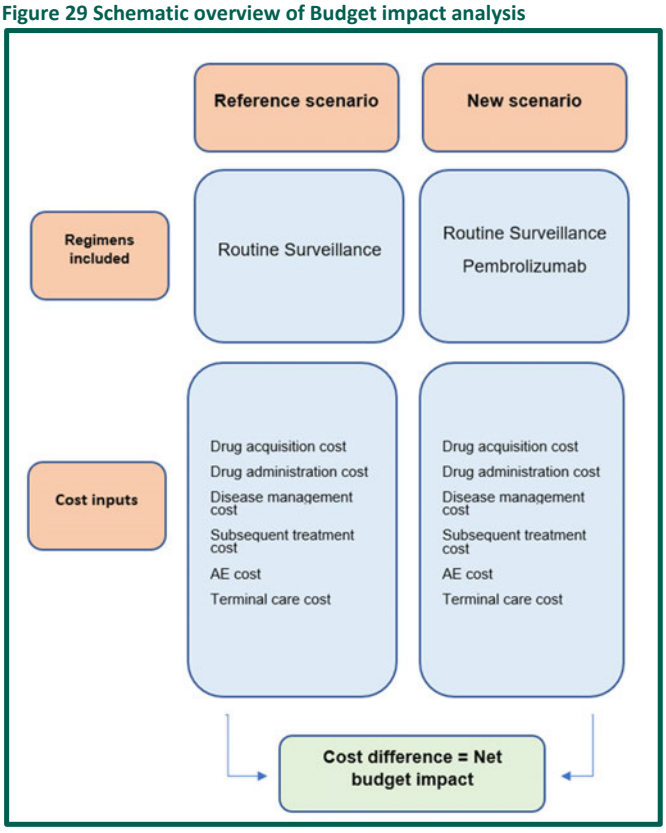
Figure 29 Schematic overview of Budget impact analysis




## 9.2 Calculations of the Budget impact analysis

The expected number of patients entering the target population is calculated according to the patient population (section 8.2.2.1 ) 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 70, Table 71).

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



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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. Specifically, the cost in each category (adjuvant drug acquisition and administration costs, testing costs, disease management costs, AE-related costs and terminal care costs) are calculated for different years from the cost effectiveness model. 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.

### 9.2.1 Patient population

The model uses 240 patients at risk. Out of these, 70% (n=161) is diagnosed with ccRCC, which is the patient population included in KEYNOTE-564. 85% (n=137) have been assessed as suitable candidates for adjuvant treatment. Based on clinical data from adjuvant melanoma, 54% of the eligible patients will receive treatment based on patient/doctor preferences. This ends up with 143 eligible patients (11, 76). The number of patients each of the 5 years are given below Table 70.

**Table 70 Number of patients expected to be treated over the next five-year period**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Patients diagnosed with adjuvant RCC** | 240 | 240 | 240 | 240 | 240 |
| **Eligible population to receive Pembrolizumab** | 143 | 143 | 143 | 143 | 143 |

### 9.2.2 Market shares

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 as an adjuvant treatment for RCC patients. Market share values are based on market research data from Denmark. The current and projected market shares are shown in Table 71.

**Table 71 Projected Market Shares**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| | | | **Reference scenario** | | |
| Routine surveillance | 100.00% | 100.00% | 100.00% | 100.00% | 100.00% |
| Pembrolizumab | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Total | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| References | *Danish Expert Input* | | | | |
| | | | **New scenario** | | |



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| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Routine surveillance | 66.70% | 25.00% | 0.00% | 0.00% | 0.00% |
| Pembrolizumab | 33.30% | 75.00% | 100.00% | 100.00% | 100.00% |
| Total | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| References | *Danish Expert Input* | | | | |

Table 72 shows the number of patients in each year of Reference and New scenario.

**Table 72 Number of patients in each scenario**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Reference scenario** | | | | | |
| Routine surveillance | 143 | 143 | 143 | 143 | 143 |
| Pembrolizumab | 0 | 0 | 0 | 0 | 0 |
| Total | 143 | 143 | 143 | 143 | 143 |
| **New scenario** | | | | | |
| Routine surveillance | 95 | 36 | 0 | 0 | 0 |
| Pembrolizumab | 48 | 107 | 143 | 143 | 143 |
| Total | 143 | 143 | 143 | 143 | 143 |

### 9.2.3 Cost calculation of Budget impact analysis

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

## 9.3 Budget impact analysis results

To calculate the total budget per patient cost is multiplied by the number of patients each year (Table 72). The total annual cost for new and reference scenarios are given in Table 73. Base-case results for budget impact analysis are presented in Table 74.

**Table 73 Annual Budget**

| | Pembrolizumab | Routine surveillance | Total |
|---|---|---|---|
| **With introduction of pembrolizumab** | | | |



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| | Pembrolizumab | Routine surveillance | Total |
|---|---|---|---|
| **Year 1 (kr.)** | 31.651.170 | 20.367.422 | 52.018.593 |
| **Year 2 (kr.)** | 74.583.395 | 20.346.078 | 94.929.473 |
| **Year 3 (kr.)** | 105.386.208 | 13.333.262 | 118.719.470 |
| **Year 4 (kr.)** | 113.692.696 | 9.688.207 | 123.380.904 |
| **Year 5 (kr.)** | 120.351.486 | 7.697.559 | 128.049.045 |
| | | **With no introduction of pembrolizumab** | |
| **Year 1 (kr.)** | 0 | 30.535.865 | 30.535.865 |
| **Year 2 (kr.)** | 0 | 49.594.504 | 49.594.504 |
| **Year 3 (kr.)** | 0 | 62.440.984 | 62.440.984 |
| **Year 4 (kr.)** | 0 | 72.151.010 | 72.151.010 |
| **Year 5 (kr.)** | 0 | 80.052.139 | 80.052.139 |

**Table 74 Annual Budget with No Pembrolizumab in market**

| | Year 1 (kr.) | Year 2 (kr.) | Year 3 (kr.) | Year 4 (kr.) | Year 5 (kr.) | Total | Average |
|---|---|---|---|---|---|---|---|
| **Pembrolizumab** | 31.651.170 | 74.583.395 | 105.386.208 | 113.692.696 | 120.351.486 | 445.664.955 | 89.132.991 |
| **Routine surveillance** | -10.168.443 | -29.248.426 | -49.107.722 | -62.462.803 | -72.354.580 | -223.341.974 | -44.668.395 |
| **Total budget impact** | **21.482.727** | **45.334.969** | **56.278.486** | **51.229.894** | **47.996.906** | **222.322.982** | **44.464.596** |

**Table 75 Costs per patient per year - if the pharmaceutical is recommended**

| | Year 1 (kr.) | Year 2 (kr.) | Year 3 (kr.) | Year 4 (kr.) | Year 5 (kr.) |
|---|---|---|---|---|---|
| **For the pharmaceutical under consideration, costs per patient** | 221,647 | 522,293 | 737,999 | 796,167 | 842,798 |
| For **competitive pharmaceutical 1** | 142,629 | 142,480 | 95,331 | 68,580 | 53,904 |
| For **competitive pharmaceutical 2 (etc.)** | - | - | - | - | - |

**Table 76 Costs per patient per year - if the pharmaceutical is NOT recommended**

| | Year 1 (kr.) | Year 2 (kr.) | Year 3 (kr.) | Year 4 (kr.) | Year 5 (kr.) |
|---|---|---|---|---|---|
| **For the pharmaceutical under consideration, costs per patient** | 0 | 0 | 0 | 0 | 0 |



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| | Year 1 (kr.) | Year 2 (kr.) | Year 3 (kr.) | Year 4 (kr.) | Year 5 (kr.) |
|---|---|---|---|---|---|
| For **competitive pharmaceutical 1** | 213,837 | 347,300 | 437,262 | 505,259 | 560,589 |
| For **competitive pharmaceutical 2 (etc.)** | - | - | - | - | - |

# 10. Discussion on the submitted documentation

## 10.1 Results summary

Over a lifetime model horizon, adjuvant pembrolizumab is expected to yield substantial improvements in QALYs and LYs relative to routine surveillance in patients with RCC post-nephrectomy. In the base case, the incremental costs per QALY gained is 149.523 kr. for pembrolizumab vs. routine surveillance. Results from the DSA support the base-case findings, with most variation observed in sensitivity analyses that varied the DFS-related parameters, annual discount rate, time horizon and assumptions regarding subsequent treatments. In the PSA, the average ICER per QALY across all 1,000 iterations is consistent with the base-case ICER. At a willingness-to-pay threshold of 1,199,894 kr. (3 times GDP per capita of Denmark) per QALY gained, pembrolizumab has a 98.4% probability of being cost-effective vs. routine surveillance.

The impact of introducing pembrolizumab as adjuvant treatment (for 143 patients) will lead to an average increase of 44,289,665 kr. in the budget. The budget increase is driven largely by the projection that more patients will be receiving immunotherapies including 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

The Markov cohort structure is a well-established modeling approach that has been commonly used in published cost-effectiveness analyses and prior health technology appraisals of adjuvant/neoadjuvant therapies in other oncology indications. Previous HTA appraisals of pembrolizumab in a different adjuvant indication (resected high-risk stage III melanoma) employs an analogous 4-state Markov model framework and used the same multi-state parametric modeling approach for the estimation of transition probabilities 90-92.

Efficacy inputs for the pembrolizumab and routine surveillance arms are based on patient-level data from the randomized controlled KEYNOTE-564 trial. Consistent with methodological guidance from the NICE DSU49,93, the selection of parametric functions to model transitions starting from the disease-free state are based on goodness of fit with the observed data, and clinical plausibility of long-term extrapolations assessed using external data and clinical expert opinion. Long-term DFS and OS predictions in the routine surveillance arm closely aligns with placebo arm results from multiple prior trials of adjuvant therapies for RCC.

Given the 1-year maximum duration of adjuvant pembrolizumab, time on treatment in the adjuvant pembrolizumab arm is precisely estimated based on observed, mature Kaplan-Meier data from KEYNOTE-564, without the need for extrapolation.



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OS and PFS within the distant metastases state are modeled based on the market shares of first-line treatments for advanced RCC. Consequently, it is possible to conduct meaningful sensitivity analyses that varied assumptions regarding the mix of subsequent treatments received in each adjuvant treatment arm. The base-case market shares of subsequent treatments are supported by Denmark clinical expert opinion.

Utility and AE-related disutility inputs are directly obtained from the KEYNOTE-564 trial, and are measured using the EQ-5D, the utility measure preferred by Danish medicines council. The QALY decrement associated with AEs is considered in each treatment arm, accounting for the mean duration of each included AE and treatment-specific risk of each AE.

### 10.3 Limitations of the economic evaluation

As with any pharmacoeconomic evaluation, this model is subject to some limitations. KEYNOTE-564 data are not used to model transition probabilities starting from the locoregional recurrence and distant metastases states due to: (i) the per-protocol termination of scheduled imaging follow-up at the time of locoregional recurrence, which prevented the estimation of transition probabilities starting from the locoregional recurrence state; and (ii) the immaturity of OS data as of the current data cutoff date. Because supplemental data sources (i.e., the SEER-Medicare database and results from clinical trials in the advanced RCC setting) are used to inform transition probabilities starting from locoregional recurrence and distant metastases, the model conservatively assumes that adjuvant pembrolizumab will have no ongoing therapeutic benefit once patients experience either of these DFS failure events. Based on comparisons against the observed OS Kaplan-Meier curves from KEYNOTE-564, the predicted OS curve is well-aligned for routine surveillance and slightly underpredicted for pembrolizumab. OS predictions from the model should be validated against longer-term OS results from KEYNOTE-564 as this data becomes available.

Another limitation is the need to extrapolate long-term DFS based on DFS data during the available follow-up period from KEYNOTE-564. Given the uncertainty inherent in the extrapolation of survival outcomes, alternative distributional assumptions are tested in scenario analyses, including two highly conservative scenarios in which the incremental DFS benefit of pembrolizumab vs. routine surveillance at 7 years is similar to that observed for sunitinib vs. placebo in the S-TRAC trial. The available data from KEYNOTE-564 supports a larger incremental benefit for pembrolizumab than sunitinib, given the reported hazard ratios of DFS failure (0.63 for pembrolizumab vs. placebo in KEYNOTE-564 vs. 0.76 for sunitinib vs. placebo in S-TRAC). Across all plausible and conservative scenario analyses conducted on DFS, the resulting ICERs of pembrolizumab are below the willingness-to-pay threshold, supporting the robustness of the base-case ICER.

### 10.4 Conclusion

There are currently limited options available for adjuvant treatment of RCC following nephrectomy. In the KEYNOTE-564 trial, 33% of patients randomized to placebo experienced DFS failure (i.e., locoregional recurrence, distant metastases, or death) by 2 years. Among patients in the placebo arm who had a DFS failure by the end of follow-up, the large majority (79%) experienced distant metastases as their first DFS failure event. There is ongoing need for effective adjuvant therapies to reduce the risk of disease recurrence and thereby improve overall survival in patients who have undergone nephrectomy for RCC.

This economic evaluation, conducted from a limited Danish societal perspective, finds adjuvant pembrolizumab to be highly cost-effective over a lifetime horizon compared with routine surveillance. The ICER is favorable for



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pembrolizumab with a cost per quality adjusted life year on 149,523 kr. compared with current Danish standard clinical practice. The ICER should be seen as an outcome in a continuum of several economic outcomes that are affected by e.g. the number of long-term survivors, which in this analysis is based on a parametric function based on data from other adjuvant indications, clinical expert inputs and observed Kaplan-Meier curves. The ICER will thus be either slightly higher or lower than 149.523 kr., but the result supports that there is a reasonable relationship between the effect and cost of using pembrolizumab for adjuvant treatment of ccRCC patients, as this is significantly lower than ICERs in previously approved Medicines Council recommendations.

The DSA demonstrated that the cost-effectiveness of pembrolizumab is robust across a range of plausible input values and alternative scenarios. In the PSA, pembrolizumab has a 98.4% probability of being cost-effective vs. routine surveillance at a willingness-to-pay threshold of 1,199,894 kr. per QALY gained. Pembrolizumab therefore represents a clinically effective and cost-effective adjuvant treatment option in Denmark.

In budget impact analysis it is estimated that the introduction of pembrolizumab as an adjuvant treatment of RCC patients will lead to increase in current health expenditure of Denmark 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

Speciallæge, Ph.D., Niels Fristrup, Kræftafdelingen på Aarhus Universitetshospital

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## Appendiks A – Litteratursøgning efter effekt og sikkerhed ved intervention og komparator(er)

Da der i KN564 studiet er foretaget en direkte sammenligning mellem den nye behandling og den relevante komparator, er der ikke foretaget en systematisk søgning efter dokumentation for effekt og sikkerhed, da søgningen ikke forventes at tilvejebringe yderligere relevant dokumentation for effekt og sikkerhed for både intervention og komparator.

Det relevante studie der ligger til grund for denne ansøgning blev publiceret i New England Journal of Medicine og er: Choueiri TK, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma, N Engl J Med. 2021 Aug 19;385(8):683-694. doi: 10.1056/NEJMoa2106391(2). NCT-nummer: NCT03142334. Studiestart den 9. Juni 2017 og primær studie slutdato 14. december 2020. Estimeret endelig slutdato 28. december 2025. For fuld liste af studiekarakteristika, se appendix B.

Data brugt til denne ansøgning er data on file fra ovenstående publikation (2). Desuden den fra EMA udarbejdede EPAR samt den opdaterede analyse med 6 måneders ekstra opfølgning (European updated report; EUR) og den fra KN564 udarbejdede clinical study report (CSR) (29, 30, 86).



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## Appendiks B Hovedkarakteristika ved inkluderede undersøgelser

| **Forsøgets navn:** Safety and Efficacy Study of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (MK-3475-564/KEYNOTE-564) | **NCT-nummer: NCT03142334** |
|---|---|
| **Objektiv** | *The purpose of this study is to evaluate the safety and efficacy of pembrolizumab (MK-3475) in the adjuvant treatment of adult participants who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 no evidence of disease (M1 NED) renal cell carcinoma (RCC) with clear cell component.*<br><br>*The primary study hypothesis is that pembrolizumab is superior to placebo with respect to Disease-free Survival (DFS) as assessed by the Investigator in male and female participants with intermediate-high risk, high risk and M1 NED RCC.* |
| **Publikationer – titel, forfatter, tidsskrift, årstal** | *Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma, Choueiri K et al., N Engl J Med. 2021 Aug 19;385(8):683-694*<br><br>*Prevalence, Disease-free, and Overall Survival of Contemporary Patients With Renal Cell Carcinoma Eligible for Adjuvant Checkpoint Inhibitor Trials, Marconi L et al., Clin Genitourin Cancer. 2021 Apr;19(2):e92-e99.* |
| **Studietype og design** | *A Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy Eligible patients were randomized 1:1 to receive either 200 mg pembrolizumab or placebo (normal saline) by intravenous (i.v.) infusion every 3 weeks. The intervention model was a parallel assignment and masking was quadruple (participant, care provider, investigator, and outcomes assessor). Participants was assigned to receive study treatment until disease recurrence, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the participant, noncompliance with study treatment or procedural requirements, administrative reasons requiring cessation of treatment, or until the participant has received 17 cycles of study treatment (approximately 1 year). Each cycle is 3 weeks long.*<br><br>*With Protocol Amendment 02 (dated 04 Sep 2019), the secondary study objectives for the evaluation of pharmacokinetic (PK) parameters and the presence of pembrolizumab antidrug antibodies (ADA) were reclassified as tertiary study objectives.* |
| **Stikprøvestørrelse (n)** | 994 participants |
| **De vigtigste inklusions- og eksklusionskriterier** | ***Inclusion Criteria:***<br>• *Has histologically confirmed diagnosis of renal cell carcinoma (RCC) with clear cell component with or without sarcomatoid features*<br>• *Female participants of childbearing potential must be willing to use an adequate method of contraception, for the course of the study through 120 days after the last dose of study treatment*<br>• *Male participants of childbearing potential must agree to use an adequate method of contraception, starting with the first dose of study treatment through 120 days after the last dose of study treatment*<br>• *Has intermediate-high risk, high risk, or M1 no evidence of disease (NED) RCC as defined by the following pathological tumor-node-metastasis and Fuhrman grading status:*<br>1. *Intermediate-high risk RCC: pT2, Grade 4 or sarcomatoid, N0, M0; pT3, Any Grade, N0, M0*<br>2. *High risk RCC: pT4, Any Grade N0, M0; pT Any stage, Any Grade, N+, M0*<br>3. *M1 NED RCC participants who present not only with the primary kidney tumor but also solid, isolated, soft tissue metastases that can be completely resected at one of the following: the time of nephrectomy (synchronous) or, ≤1 year from nephrectomy (metachronous)*<br>• *Has received no prior systemic therapy for advanced RCC* |



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- *Has undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins*
- *Must have undergone a nephrectomy and/or metastasectomy ≥28 days prior to signing informed consent and ≤12 weeks prior to randomization*
- *Must be tumor-free as assessed by the Investigator and validated by either computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain and chest, abdomen, and pelvis and a bone scan ≤28 days from randomization*
- *Must have provided adequate tissue per the following: Nephrectomy only: tissue from nephrectomy (required); Synchronous M1 NED: tissue from nephrectomy (required) AND, metastasectomy tissue (if available); Metachronous M1 NED: tissue from metastasectomy (required) AND, nephrectomy tissue (if available)*
- *Has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1*
- *Has adequate organ function*

***Exclusion Criteria:***

- *Has had major surgery, other than nephrectomy and/or resection of pre-existing metastases for M1 NED participants, within 12 weeks prior to randomization*
- *Has received prior radiotherapy for RCC*
- *Has pre-existing brain or bone metastatic lesions*
- *Has residual thrombus post nephrectomy in the vena renalis or vena cava*
- *Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior 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). Replacement therapy is allowed*
- *Has a known additional malignancy that is progressing or required active treatment ≤3 years ago. Exceptions include early-stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, in situ prostate cancer, or in situ breast cancer that has undergone potentially curative therapy*
- *Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis*
- *Has an active infection requiring systemic therapy*
- *Has a history of, or is currently on, dialysis*
- *Has a known history of human immunodeficiency virus (HIV) infection*
- *Has known active hepatitis B or hepatitis C virus infection*
- *Has a known history of active tuberculosis (Bacillus tuberculosis)*
- *Has had a prior solid organ transplant*
- *Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients*
- *Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening visit through 120 days after the last dose of study treatment*
- *Has received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-programmed cell death-ligand 1 (anti-PD-L1), or anti-programmed cell death-ligand 2 (anti-PD-L2) agent or with an agent directed to another co-inhibitory T-cell receptor*



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| | |
|---|---|
| | *(i.e., cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX-40, CD137 [tumor necrosis factor receptor superfamily member 9 (TNFRSF9)]) or has previously participated in a Merck pembrolizumab (MK-3475) clinical trial*<br>• *Has received prior anticancer therapy, monoclonal antibody, chemotherapy, or an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) before first dose of study treatment or not recovered (i.e., must be ≤ Grade 1 or at Baseline) from AEs due to previously administered agents*<br>• *Has received a live vaccine within 30 days prior to the first dose of study treatment*<br>• *Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment* |
| **Indgreb** | *496 participants started in the experimental arm. 488 participants treated: Participants receive pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 17 cycles (up to approximately 1 year).* |
| **Komparator(er)** | *498 participants started in the placebo arm. 496 participants treated. Participants receive placebo (saline solution) via IV infusion on Day 1 of each 3-week cycle for up to 17 cycles (up to approximately 1 year).* |
| **Opfølgningstid** | *Median follow up of 24,1 months (range 14,9 to 41,5).* |
| **Anvendes undersøgelsen i den sundhedsøkonomiske model?** | *Ja* |
| **Primære, sekundære og sonderende endepunkter** | ***Primary Endpoints***<br>1. ***Disease-free Survival (DFS) as Assessed by the Investigator [ Time Frame: Up to approximately 42 months (database cutoff date 14 Dec 2020) ]*** *DFS, as assessed by the investigator, is defined as the time from randomization to the first documented local recurrence, distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 no evidence of disease (NED) by investigator) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 versus 1), United States (US) participant (Yes versus No) within M0 group by investigator was used to report hazard ratio (HR) and 95% confidence intervals (CIs).*<br><br>***Key Secondary Endpoint***<br><br>2. ***Overall Survival (OS) [ Time Frame: Up to approximately 72 months ]*** *OS was defined as the time from randomization to death due to any cause.*<br><br>***Other Secondary Endpoints***<br><br>3. ***Number of Participants Who Experienced an Adverse Event (AE) [ Time Frame: Nonserious AEs: Up to 30 days after last dose of study treatment (Up to approximately 13 months); Serious AEs: Up to 90 days after last dose of study treatment (Up to approximately 15 months) ]***<br>*An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. Participants are monitored for the occurrence of nonserious AEs for up to 30 days after last dose of study treatment and of serious AEs for up to 90 days after last dose of study treatment. The number of participants who experience an AE will be assessed.*<br><br>4. ***Number of Participants Who Discontinued Study Drug Due to an AE [ Time Frame: Up to approximately 12 months ]****An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. The number of participants who discontinue study treatment due to an AE will be assessed.* |



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5. ***First Local Disease Recurrence-specific Survival (DRSS1) as Assessed by the Investigator [ Time Frame: Up to approximately 72 months ]*** *DRSS1 is defined as the time from randomization to the first documented local recurrence of RCC as assessed by the investigator. For DRSS1, only local recurrence is counted as an event.*

6. ***Second Disease Recurrence-Specific Survival (DRSS2) as Assessed by the Investigator [ Time Frame: Up to approximately 72 months ]*** *DRSS2 is defined as the time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first, as assessed by the investigator.*

7. ***Event-Free Survival (EFS) as Assessed by the Blinded Independent Central Review (BICR) [ Time Frame: Up to approximately 72 months ]****EFS is defined as time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants which by BICR were considered disease-free at baseline (M0/M1 NED); or disease progression among participants which by BICR were considered to have baseline disease (M1), or death due to any cause, whichever occurs first.*

8. ***DFS According to Participant Programmed Cell Death-Ligand 1 (PD-L1) Expression Status (Positive, Negative) as Assessed by the Investigator [ Time Frame: Up to approximately 72 months ]*** *DFS, as assessed by the investigator, is defined as the time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. The PD-L1 expression status is based on combined positive score (CPS). If CPS is ≥ 1, PD-L1 expression status is positive and if the CPS is <1, PD-L1 expression status is negative.*

9. ***OS According to Participant PD-L1 Expression Status (Positive, Negative) [ Time Frame: Up to approximately 72 months ]*** *OS is defined as the time from randomization to death due to any cause. The PD-L1 expression status is based on combined positive score (CPS). If CPS is ≥ 1, PD-L1 expression status is positive and if the CPS is <1, PD-L1 expression status is negative.*

10. ***Change From Baseline in the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) Total Score [ Time Frame: Baseline and Week 52 ]*** *The QLQ-C30 quality of life (QOL) questionnaire contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain) and single symptom items (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. Items are scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much). The QLQC30 also contains 2 global health status scales that use 7-point scale scoring (1=very poor and 7=excellent). The change from baseline in the 2-item global health status/QOL life scale (range: 2-14) will be presented, with a higher score representing a higher QOL.*

11. ***Change From Baseline in the Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) Index Score [ Time Frame: Baseline and Week 52 ]*** *The FKSI-DRS index consists of a 9-item questionnaire that assesses the extent of participant symptoms from kidney cancer over the previous 7 days. Responses are scored on a 5-point scale (0=Not at all to 4=Very much) and summed to generate an index symptom score. These scores can range from 0 to 36, with a higher score indicating more favorable kidney cancer symptom status. The change from baseline in the FKSI-DRS index score will be presented.*

*Primary endpoints included in the current application:*

1. ***Disease-free Survival (DFS) as Assessed by the Investigator [ Time Frame: Up to approximately 42 months (database cutoff date 14 Dec 2020) ]*** *DFS, as assessed by the*



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| | |
|---|---|
| | *investigator, is defined as the time from randomization to the first documented local recurrence, distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 no evidence of disease (NED) by investigator) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 versus 1), United States (US) participant (Yes versus No) within M0 group by investigator was used to report hazard ratio (HR) and 95% confidence intervals (CIs).*<br><br>2. ***Overall Survival (OS) [ Time Frame: Up to approximately 72 months ]*** *OS was defined as the time from randomization to death due to any cause.*<br>3. ***Adverse Events***<br>4. ***QoL defined by Least means squares from baseline to week 52 using FKSI-DRS and EORTC-QLQ-C30*** |
| | *Efficacy will be assessed in the intent-to-treat population (all randomly assigned patients) and analyzed by randomized treatment group. Safety will be assessed in all randomly assigned patients who received at least one dose of study drug and will be analyzed by treatment received (APaT population).*<br>*Kaplan–Meier method is used to estimate rates of progression-free survival and overall survival.* |
| **Analyser af undergrupper** | *In the current application subgroup analyses were performed for the primary efficacy outcome measure (DFS). The study was not powered to show a statistical difference in these subgroups and as such these analyses are of post hoc nature, any given p-values nominal and results hypothesis driving.* |
| **Andre relevante oplysninger** | |

**Stratificering:**

- M0 vs M1 NED
- For M0 gælder yderligere:
    - ECOG Performance status 0 vs 1
    - Patienter fra USA vs patienter ikke fra USA (5, 11)

**Statistisk analyseplan**

I den statistiske analyseplan for KN564 var hypotese 1 (H1): Der er i højere grad forbedret DFS ved adjuverende behandling med pembrolizumab end ved placebo, og H2 ligeledes at der i højere grad er forbedret OS ved adjuverende behandling med pembrolizumab end ved placebo(2). Det primære endepunkt (DFS) har allokeret 2.5% alpha (1-sidet test), og hvis H0 forkastes, kan alpha recirkuleres til OS-analysen, som er det vigtigste sekundære endepunkt. Dette betyder også, at hvis det primære endepunkt, DFS, er signifikant bedre for pembrolizumab-armen versus placebo-armen, vil det understøtte studiets overordnede hypotese og studiet vil konkluderes som et positivt studie. Studiet har 95% power til at vise en effekt på DFS på HR=0.7 med en 1-sidet alpha på 2,5%.

Andre sekundære endepunkter var antal patienter med hhv. alle bivirkninger, alvorlige bivirkninger og bivirkninger der ledte til afbrydelse af behandling. Desuden hhv. antal patienter med lokal og fjern recidiv (kaldet disease recurrence-specific survival 1 (DRSS1) og -2), event free survival (EFS) ved BICR, DFS og OS stratificeret på PD-L1 status (CPS </>1), samt QoL (gennemsnitlig ændring fra baseline ved EORTC-QLQ-C30 global sundhedsstatus og fysisk funktion samt FKSI-DRS score).

For IA1 blev der udført analyser af effekt på 'intention-to-treat' (ITT) populationen, og der blev udført analyser af sikkerhed på 'All Participants as Treated' (APaT) populationen, som omfattede alle randomiserede deltagere, der modtog mindst 1 dosis af studieintervention (2). DFS og OS blev evalueret ved at sammenligne pembrolizumab med placebo ved hjælp af en stratificeret log-rangeringstest. Estimering af hazard ratioen (HR) blev udført ved hjælp af en



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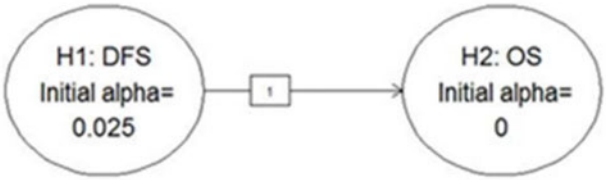
stratificeret Cox regressionsmodel. Event-rater over tid blev estimeret inden for hver behandlingsgruppe ved hjælp af Kaplan-Meier (KM)-metoden. Maurer- og Bretz-multiplicitetsstrategien for gruppe-sekventielt design blev anvendt til det primære slutpunkt DFS og det vigtigste sekundære endepunkt OS med henblik på at have en stærk kontrol for type I-fejl (27, 86).




DFS blev testet ved efter IA1 og var præspecificeret ved ca. 265 tilfælde af recidiv svarende til 80% af det estimerede antal recidiv ved den endelig analyse (final analysis). Desuden vises DFS fra 6 måneders yderligere opfølgning efter IA1 efterspurgt af EMA i forbindelsen med processen om godkendelse herfra(27). OS-data er stadig præmature med kun 51 events (26% af de planlagte OS-events der forventes til final analysis) i den oprindelige publikation(2) samt 66 ved de ekstra 6 måneders opfølgning svarende til 33% af de 200 events der er præspecificeret ved den endelige OS analyse.

## Appendiks C Baselinekarakteristika hos patienter i undersøgelser, der anvendes til sammenlignende analyse af effekt og sikkerhed

| Baseline karakteristika for ITT populationen som blev anvendt ved effekt sammenligninger. Der er ikke angivet særskilte baseline karakteristika for APaT populationen, der dog kun tæller 10 færre patienter end ITT og derfor anses nedenstående tabel for at være dækkende for begge populationer. | | | |
|---|---|---|---|
| | KEYTRUDA (n=496) | Placebo (n=498) | Total (N=994) |
| Male, n (%) | 347 (70.0) | 359 (72.1) | 706 (71.0) |
| Age | | | |
| Median (range), years | 60.0 | 60.0 | 60.0 |
| ≥65, n (%) | 158 (31.9) | 172 (34.5) | 330 (33.2) |
| Race | | | |
| White race, n (%) | 372 (75.0) | 377 (75.7) | 749 (75.4) |
| Asian, n (%) | 63 (12.7) | 75 (15.1) | 138 (13.9) |
| American Indian or Alaska Native | 10 (2.0) | 2 (0.4) | 12 (1.2) |
| Black or African American | 7 (1.4) | 5 (1.0) | 12 (1.2) |
| Multiple | 8 (1.6) | 5 (.0) | 13 (1.3) |
| Missing | 36 (7.3) | 34 (6.8) | |
| Region, n (%) | | | |
| North America | 133 (26.8) | 125 (25.1) | 258 (26.0) |
| European Union | 188 (37.9) | 187 (37.6) | 375 (37.7) |
| Rest of the world | 175 (35.3) | 186 (37.3) | 361 (36.3) |
| ECOG PS, n (%) | | | |
| 0 | 421 (84.9) | 426 (85.5) | 847 (85.2) |
| 1 | 75 (15.1) | 72 (14.5) | 147 (14.8) |
| Type of nephrectomy, n (%) | | | |
| Partial | 37 (7.5) | 38 (7.6) | 75 (7.5) |
| Radical | 559 (92.5) | 460 (92.4) | 919 (92.5) |
| PD-L1 status, n (%) | | | |
| CPS <1 | 124 (25.0) | 113 (22.7) | 237 (23.8) |
| CPS ≥1 | 365 (73.6) | 383 (76.9) | 748 (75.3) |
| Missing | 7 (1.4) | 2 (0.4) | 9 (0.9) |
| Primary tumor, n (%) | | | |
| T1 | 11 (2.2) | 15 (3.0) | 26 (2.6) |
| T2 | 27 (5.4) | 33 (6.6) | 60 (6.0) |
| T3 | 444 (89.5) | 437 (87.8) | 881 (88.6) |



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| Baseline karakteristika for ITT populationen som blev anvendt ved effekt sammenligninger. Der er ikke angivet særskilte baseline karakteristika for APaT populationen, der dog kun tæller 10 færre patienter end ITT og derfor anses nedenstående tabel for at være dækkende for begge populationer. | | | |
|---|---|---|---|
| T4 | 14 (2.8) | 13 (2.6) | 27 (2.7) |
| Tumor Grade | | | |
| Grade 1 | 19 (3,8) | 16 (3,2) | 35 (3,5) |
| 2 | 153 (30,8) | 150 (30,1) | 303 (30,5) |
| 3 | 219 (44,2) | 213 (42,8) | 432 (43,5) |
| 4 | 103 (20,8) | 119 (23,9) | 222 (232) |
| Missing | 2 (0,4) | 0 (0,0) | 2 (0,2) |
| Metastatic Staging, n (%) | | | |
| M0 | 467 (94.2) | 469 (94.2) | 936 (94.2) |
| M1 NED | 29 (5.8) | 29 (5.8) | 58 (5.8) |
| RCC Risk Category, n (%) | | | |
| M0-Intermediate-High Risk | 422 (85.1) | 433 (86.9) | 855 (86.0) |
| M0-High Risk | 40 (8.1) | 36 (7.2) | 76 (7.6) |
| M0-Others | 5 (1.0) | 0 (0.0) | 5 (0.5) |
| M1 NED | 29 (5.8) | 29 (5.8) | 58 (5.8) |
| Lymph node stage, n (%) | | | |
| N0 | 465 (93.8) | 467 (93.8) | 932 (93.8) |
| N1 | 31 (6.3) | 31 (6.2) | 62 (6.2) |
| Sarcomatoid Feature | | | |
| Presence | 52 (10.5) | 59 (11.8) | 111 (11.2) |
| Absence | 417 (84.1) | 415 (83.3) | 832 (83.7) |
| Unknown | 27 (5.4) | 24 (4.8) | 51 (5.1) |

Source: EPAR (29). Note: Participants in M0-Intermediate-high risk are pT2 (Grade 4 or sarcomatoid), N0, M0 or pT3 (Any Grade), N0, M0. Participants in M0-high risk are pT4 (Any Grade), N0, M0 or pT Any (Any Grade), N1 or greater, M0. Participants in M1 NED are participants who present not only with the primary kidney tumor but also solid, isolated, soft tissue metastases that were completely resected at the time of nephrectomy (synchronous) or <=1 year from nephrectomy (metachronous). Participants in M0-Others are T2 (grade <= 3)N0 M0 or T1 N0 M0.

CPS: Combined positive score; ECOG PS: European Cooperative Oncology Group Performance Score; ITT: Intention-to-treat; NED: No evidence of disease; PD-L1: Programmed death ligand 1; RCC: Renal cell carcinoma

### Sammenlignelighed af patienter på tværs af studier

N/A



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### Sammenlignelighed af undersøgelsespopulationerne med danske patienter, der er berettiget til behandling

KN564 var et international studie med deltagelse af 21 lande. Ovenfor ses at populationen der indgik havde en stor overvægt af patienter med kaukasisk oprindelse (>75%), samt at over 1/3 af patienterne var fra Europa, hvorfor patientgruppen overordnet vurderes til fint at repræsentere den danske patientpopulation. Derudover ses at medianalderen i KN564 var 60 år mod 66 år for kirurgisk behandlede RCC patienter i Danmark, der dog ikke kan sammenlignes direkte da medianalderen for danske patienter for de præcise inklusionskriterier i KN564 ikke findes. Dog har flere eksperter vurderet KN564 populationen til at være yngre end tilsvarende patienter der opereres i dansk klinisk praksis, men da både danske og internationale eksperter har udtalt at der vil være en tendens til at behandle flere yngre patienter med adjuverende immunterapi da risikoen for at dø af sin nyrecancer frem for af andre årsager (cardiovaskulære etc.) stiger med alderen, og derfor vil en anslået risk/benefit analyse af adjuverende behandling forskydes jo ældre patienten er. Derfor er det ikke overraskende at median alderen i KN564 er lidt lavere end den generelle median alder for alle danske patienter der behandles med kurativt intenderet kirurgi, da eksperter vurderer at ikke alle patienter der er egnede til adjuverende pembrolizumab ifølge KN564 kriterier vil blive behandlet i Danmark, ligesom det også har været tilfældet for adjuverende behandling mod melanom (76).

I KN564 har langt hovedparten af inkluderede patienter pT3, hvilket også er tilfældet i Danmark når pT1 patienter sorteres fra de kirurgisk behandlede patienter. Den næstmest hyppige patientgruppe ifht. pT-stadie i KN564 er pT2, hvilket også afspejles i den danske population af kirurgisk behandlede patienter i Darencas seneste årsrapport (2, 11).



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## Appendiks D Effektivitets- og sikkerhedsresultater pr. undersøgelse

**Definition, validitet og klinisk relevans af inkluderede resultatmål**

| Outcome measure | Definition |
|---|---|
| **Disease Free Survival (DFS).**<br><br>**Primary endpoint** | DFS, as assessed by the investigator, is defined as the time from randomization to the first documented local recurrence, distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 no evidence of disease (NED) by investigator) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 versus 1), United States (US) participant (Yes versus No) within M0 group by investigator was used to report hazard ratio (HR) and 95% confidence intervals (CIs).<br><br>For RCC patients after nephrectomy the fear of recurrence is a major contributor to negative QoL. Patients with recurrence experience symptoms, 3 times increased risk of death, shorter OS, poorer QoL and impose higher costs on health systems compared to patients with no recurrence. As many patients are still in the labor force and have good performance status, physical/psychological wellbeing in the form of delaying/preventing recurrence is the key clinical endpoint, whereas OS is secondary due to the relatively long life expectancy of these patients. |
| **Overall Survival (OS)**<br><br>**Key secondary endpoint** | OS was defined as the time from randomization to death due to any cause. The goal of cancer treatment is to prolong overall survival a t minimal AE burden, so despite DFS being the preferred primary endpoint OS is still a key endpoint |
| **Safety, Adverse Events (AE)** | An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study treatment, whether or not considered related to the use of study treatment. Participants are monitored for the occurrence of nonserious AEs for up to 30 days after last dose of study treatment and of serious AEs for up to 90 days after last dose of study treatment. The number of participants who experience an AE will be assessed:<br><br>Number of Participants Who Experienced an Adverse Event (AE) [ Time Frame: Nonserious AEs: Up to 30 days after last dose of study treatment (Up to approximately 13 months); Serious AEs: Up to 90 days after last dose of study treatment (Up to approximately 15 months) ]<br><br>Number of Participants Who Discontinued Study Drug Due to an AE [ Time Frame: Up to approximately 12 months ] |

| Outcome measure | Definition |
|---|---|
| **Quality of Life (QoL)** | The **EORTC QLQ-C30** was developed to assess the quality of life of patients with cancer. It contains 30 questions (items), 24 of which aggregate into nine multi-item scales representing various aspects, or dimensions, of quality of life (QOL): one global scale, five functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain), and six additional single-symptom items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease. Individual items are scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Raw scores for each scale are standardized into a range of 0 to 100 by linear transformation; a higher score on the global and functional scales represents a higher ("better") level of functioning, and a higher score on the symptom scale represents a higher ("worse") level of symptoms<br><br>The FKSI-DRS is a reliable, valid, and responsive brief index of the most important symptoms associated with advanced kidney cancer – it was developed to follow the symptoms particularly caused by the disease and not the treatment by answering 9 questions found via clinician and patient interviews. Individual items are scored on a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). Scores fall between 0-36 with higher scores meaning less symptoms and expectedly higher QoL.<br><br>It is important to bear in mind that these instruments have been developed for patients with active cancer disease and also in an era where chemotherapy was a predominant treatment regimen. Hence, they are not developed nor validated for adjuvant treatment of disease free patients, and the results should be viewed in that light. |



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**Resultater pr. undersøgelse**

**Tabel A3a Resultater af KN564 (NCT03142334) – IA1 follow up 24,1 months**

| | | | | 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** | **1-sidet *P* value** | | |
| *(DFS) rates* | Pembrolizumab | 496 | 109 events (22,0%) | 42 events (8,3%) | N/A | N/A | HR: 0,68 | 0.,53-0,87 | 0.001 | *The disease free survival (DFS) 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.* | 1 |
| | Placebo | 498 | 151 events (30,3%) | | | | | | | | |
| *24 month (DFS)* | Pembrolizumab | 496 | 77,3% (72,8–81,1) | 9,2% ARR | N/A | N/A | N/A | N/A | N/A | *The disease free survival (DFS) 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.* | 1 |
| | Placebo | 498 | 68,1% (63,5–72,2) | | | | | | | | |
| *Overall survival (OS)* | Pembrolizumab | 496 | 18 events (3,6%) | 15 events (3,0%) | N/A | N/A | HR: 0,54 | 0,30-0,96 | 0,0164 | *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.* | 1 |
| | Placebo | 498 | 33 events (6,6%) | | | | | | | | |
| *24 month OS* | Pembrolizumab | 496 | 96,6% (94,3-98,0) | 3,1% ARR | N/A | N/A | N/A | N/A | N/A | *The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.* | 1 |
| | Placebo | 498 | 93,5 (90,5-95,6) | | | | | | | | |
| *All cause safety grade 3-4*<br>*as-treated population* | Pembrolizumab | 488 | 158 events (32,4%) | -14,7 absolute risk reduction | N/A | N/A | [redacted] | [redacted] | [redacted] | *Safety will be assessed in all randomly assigned patients who received at least one dose of study drug and will be analyzed by treatment received. Safety will be monitored throughout the study and for 30 days after the end of treatment (90 days for serious adverse events). Safety analysis will include the incidence, causality and outcome of adverse events; changes in vital signs; and* | 1, (86) |
| | Placebo | 496 | 88 events (17,7%) | | | | | | | | |



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**Tabel A3a Resultater af KN564 (NCT03142334) – IA1 follow up 24,1 months**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | *changes in laboratory values. Adverse events will be graded and recorded throughout the trial and follow-up period per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4* | |
| | | | | **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** | **1-sidet *P* value** | | |
| *EORTC QLQ-C30 global health status/QoL scores Baseline – week 52* | Pembrolizumab | 484 | -4,25 (-6,32, -2,19) | -2,57 | -5,22, 0,08 | 0,0571 | N/A | N/A | N/A | *PROs were assessed at Cycles 1, 5, 9, 13, and 17, as well as at discontinuation, 30-day follow-up, and annually during post-treatment follow-up until disease recurrence or new anticancer treatment was initiated for all patients receiving at least 1 dose of study treatment. The 3 prespecified PRO endpoints were mean change from baseline in FKSI-DRS score, EORTC-QLQC30 global health status/quality of life scores, and EORTC-QLQ-C30 physical functioning scale. Nominal p-values were computed for between-treatment group comparisons. Results were not adjusted for multiplicity, and therefore should be interpreted with caution. Pairwise comparisons of least square means differences were performed.* | (29) |
| | Placebo | 492 | -1.68 (-3.69, 0.32) | | | | | | | | |
| *EORTC QLQ-C30 physical* | Pembrolizumab | 484 | -1,81 (-3,19, --0,43) | -0,91 | [redacted] | [redacted] | N/A | N/A | N/A | *PROs were assessed at Cycles 1, 5, 9, 13, and 17, as well as at discontinuation, 30-day follow-up, and annually during post-treatment follow-up until disease recurrence or new anticancer* | 1, (86) |
| | Placebo | 492 | -0,9 (-2,23, 0,44) | | | | | | | | |



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| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *functioning scale Baseline – week 52* | | | | | | | | | | *treatment was initiated for all patients receiving at least 1 dose of study treatment. The 3 prespecified PRO endpoints were mean change from baseline in FKSI-DRS score, EORTC-QLQC30 global health status/quality of life scores, and EORTC-QLQ-C30 physical functioning scale. Nominal p-values were computed for between-treatment group comparisons. Results were not adjusted for multiplicity, and therefore should be interpreted with caution. Pairwise comparisons of least square means differences were performed.* |
| *FKSI-DRS Baseline – week 52* | Pembrolizumab | 483 | -1,12 (-1,53, -0,71) | -0,67 | -1,23, -0,12 | 0,017 | N/A | N/A | N/A | *PROs were assessed at Cycles 1, 5, 9, 13, and 17, as well as at discontinuation, 30-day follow-up, and annually during post-treatment follow-up until disease recurrence or new anticancer treatment was initiated for all patients receiving at least 1 dose of study treatment. The 3 prespecified PRO endpoints were mean change from baseline in FKSI-DRS score, EORTC-QLQC30 global health status/quality of life scores, and EORTC-QLQ-C30 physical functioning scale. Nominal p-values were computed for between-treatment group comparisons. Results were not adjusted for multiplicity, and therefore should be interpreted with caution. Pairwise comparisons of least square means differences were performed.* |
| | Placebo | 492 | -0,45 (-0,84, 0,05) | | | | | | | |

## Appendiks E Sikkerhedsdata for intervention og komparator(er)

### Adverse event summary

AEs were coded using MedDRA (Version 23.1). AEs were monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE Version 4.0.AEs were coded using MedDRA (Version 23.1). AEs were monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE Version 4.0.

**Table 77 Adverse Event Summary (APaT Population)**

| | KN564 Data for Pembrolizumab | | KN564 Data for Placebo | | Reference Safety Dataset for Pembrolizumab | | Cumulative Running Safety Dataset for Pembrolizumab | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 470 | (96.3) | 452 | (91.1) | 5,690 | (96.7) | 8,890 | (96.4) |
| with no adverse event | 18 | (3.7) | 44 | (8.9) | 194 | (3.3) | 328 | (3.6) |
| with drug-relateda adverse events | 386 | (79.1) | 265 | (53.4) | 4,132 | (70.2) | 6,375 | (69.2) |
| with toxicity grade 3-5 adverse events | 158 | (32.4) | 88 | (17.7) | 2,829 | (48.1) | 4,444 | (48.2) |
| with toxicity grade 3-5 drug-related adverse events | 92 | (18.9) | 6 | (1.2) | 913 | (15.5) | 1,490 | (16.2) |
| with serious adverse events | 100 | (20.5) | 56 | (11.3) | 2,266 | (38.5) | 3,449 | (37.4) |
| with serious drug-related adverse events | 59 | (12.1) | 1 | (0.2) | 656 | (11.1) | 1,049 | (11.4) |
| who died | 2 | (0.4) | 1 | (0.2) | 312 | (5.3) | 484 | (5.3) |
| who died due to a drug-related adverse event | 0 | (0.0) | 0 | (0.0) | 39 | (0.7) | 66 | (0.7) |
| discontinued drug due to an adverse event | 101 | (20.7) | 10 | (2.0) | 790 | (13.4) | 1,215 | (13.2) |
| discontinued drug due to a drug-related adverse event | 86 | (17.6) | 3 | (0.6) | 410 | (7.0) | 676 | (7.3) |
| discontinued drug due to a serious adverse event | 49 | (10.0) | 5 | (1.0) | 572 | (9.7) | 855 | (9.3) |
| discontinued drug due to a serious drug-related adverse event | 37 | (7.6) | 0 | (0.0) | 245 | (4.2) | 392 | (4.3) |

[a] Determined by the investigator to be related to the drug.

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

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

### Most common Adverse Events

The most frequently reported AEs (incidence ≥20%) in the pembrolizumab arm of study KN564 were fatigue, diarrhoea, pruritus, arthralgia, hypothyroidism, and rash. The AEs with greatest percentage difference (risk difference of approximately ≥10%) between the pembrolizumab and placebo groups were hypothyroidism, hyperthyroidism, pruritus, and rash (see Figure “Between-treatment Comparisons in Grade 3-5 Adverse Events Selected Adverse Events (≥ 1%Incidence) and Sorted by Risk Difference”).

The observed incidences of hypothyroidism (21.1% vs 11.1%) and hyperthyroidism (11.9% vs 4.2%) were higher in the Indication Dataset than in the RSD; all hypothyroidism and hyperthyroidism events in the Indication Dataset were Grade 1 and Grade 2 except for 1 participant each with Grade 3 hypothyroidism and Grade 3 hyperthyroidism. Blood creatinine increased (10.2% vs 4.4%) were also higher in the Indication Dataset than in the RSD; however, participants in study KN564 had prior nephrectomy (rate of blood creatinine increase was 8.5% in the placebo arm).

**Table 78 Participants With Adverse Events (Incidence ≥10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)**

| | KN564 Data for Pembrolizumab [a] | | KN564 Data for Placebo [b] | | Reference Safety Dataset for Pembrolizumab [c] | | Cumulative Running Safety Dataset for Pembrolizumab [d] | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 470 | (96.3) | 452 | (91.1) | 5,690 | (96.7) | 8,890 | (96.4) |
| with no adverse events | 18 | (3.7) | 44 | (8.9) | 194 | (3.3) | 328 | (3.6) |
| Fatigue | 145 | (29.7) | 120 | (24.2) | 1,884 | (32.0) | 2,789 | (30.3) |
| Diarrhoea | 124 | (25.4) | 111 | (22.4) | 1,200 | (20.4) | 1,870 | (20.3) |
| Pruritus | 111 | (22.7) | 65 | (13.1) | 1,060 | (18.0) | 1,591 | (17.3) |
| Arthralgia | 108 | (22.1) | 93 | (18.8) | 1,104 | (18.8) | 1,593 | (17.3) |
| Hypothyroidism | 103 | (21.1) | 18 | (3.6) | 651 | (11.1) | 1,034 | (11.2) |
| Rash | 98 | (20.1) | 53 | (10.7) | 904 | (15.4) | 1,291 | (14.0) |
| Nausea | 80 | (16.4) | 48 | (9.7) | 1,213 | (20.6) | 1,861 | (20.2) |
| Cough | 76 | (15.6) | 50 | (10.1) | 1,148 | (19.5) | 1,639 | (17.8) |
| Headache | 69 | (14.1) | 62 | (12.5) | 711 | (12.1) | 989 | (10.7) |
| Hyperthyroidism | 58 | (11.9) | 1 | (0.2) | 247 | (4.2) | 435 | (4.7) |
| Asthenia | 50 | (10.2) | 36 | (7.3) | 666 | (11.3) | 1,051 | (11.4) |
| Blood creatinine increased | 50 | (10.2) | 42 | (8.5) | 256 | (4.4) | 455 | (4.9) |
| Back pain | 49 | (10.0) | 64 | (12.9) | 662 | (11.3) | 1,023 | (11.1) |
| Vomiting | 41 | (8.4) | 28 | (5.6) | 732 | (12.4) | 1,173 | (12.7) |
| Constipation | 35 | (7.2) | 40 | (8.1) | 995 | (16.9) | 1,530 | (16.6) |
| Decreased appetite | 35 | (7.2) | 10 | (2.0) | 1,136 | (19.3) | 1,749 | (19.0) |
| Dyspnoea | 31 | (6.4) | 27 | (5.4) | 989 | (16.8) | 1,323 | (14.4) |
| Pyrexia | 31 | (6.4) | 23 | (4.6) | 746 | (12.7) | 1,135 | (12.3) |
| Anaemia | 20 | (4.1) | 18 | (3.6) | 836 | (14.2) | 1,340 | (14.5) |

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

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.

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

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

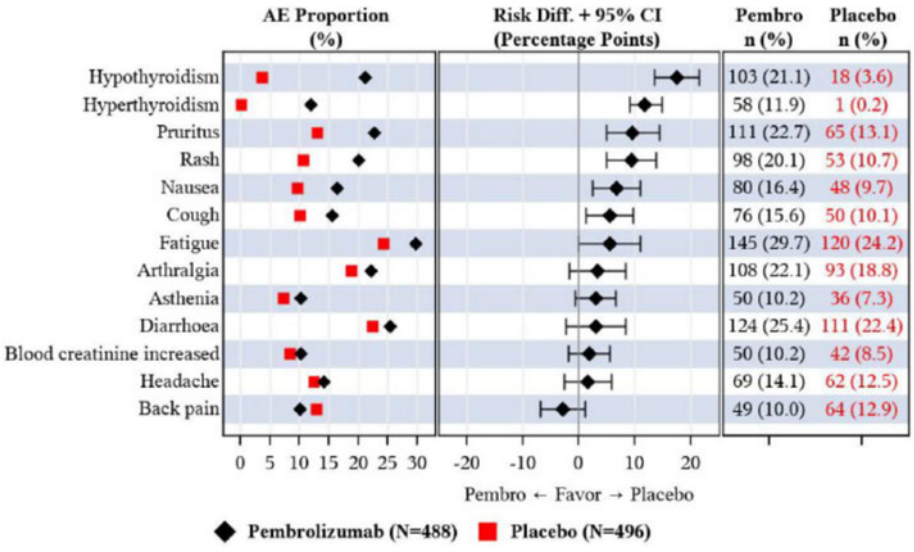


**Figure 30 Between-treatment Comparisons in AEs; Selected AEs (≥ 10% Incidence) and Sorted by Risk**

| | KN564 Data for Pembrolizumab [a] | | KN564 Data for Placebo [b] | | Reference Safety Dataset for Pembrolizumab [c] | | Cumulative Running Safety Dataset for Pembrolizumab [d] | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 386 | (79.1) | 265 | (53.4) | 4,132 | (70.2) | 6,375 | (69.2) |
| with no adverse events | 102 | (20.9) | 231 | (46.6) | 1,752 | (29.8) | 2,843 | (30.8) |
| Fatigue | 99 | (20.3) | 71 | (14.3) | 1,170 | (19.9) | 1,686 | (18.3) |
| Pruritus | 91 | (18.6) | 57 | (11.5) | 836 | (14.2) | 1,230 | (13.3) |
| Hypothyroidism | 86 | (17.6) | 13 | (2.6) | 565 | (9.6) | 895 | (9.7) |
| Diarrhoea | 77 | (15.8) | 51 | (10.3) | 630 | (10.7) | 956 | (10.4) |
| Rash | 73 | (15.0) | 36 | (7.3) | 676 | (11.5) | 957 | (10.4) |
| Hyperthyroidism | 50 | (10.2) | 0 | (0.0) | 219 | (3.7) | 384 | (4.2) |
| Arthralgia | 46 | (9.4) | 43 | (8.7) | 464 | (7.9) | 673 | (7.3) |
| Nausea | 39 | (8.0) | 23 | (4.6) | 535 | (9.1) | 748 | (8.1) |
| Myalgia | 30 | (6.1) | 20 | (4.0) | 232 | (3.9) | 341 | (3.7) |
| Asthenia | 28 | (5.7) | 23 | (4.6) | 363 | (6.2) | 545 | (5.9) |
| Decreased appetite | 15 | (3.1) | 2 | (0.4) | 461 | (7.8) | 657 | (7.1) |

**Grade ≥3 Adverse Events**

Table: Participants With Grade 3-5 Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term

| | KN564 Data for Pembrolizumab | | KN564 Data for Placebo | | Reference Safety Dataset for Pembrolizumab | | Cumulative Running Safety Dataset for Pembrolizumab | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 158 | (32.4) | 88 | (17.7) | 2,829 | (48.1) | 4,444 | (48.2) |
| with no adverse events | 330 | (67.6) | 408 | (82.3) | 3,055 | (51.9) | 4,774 | (51.8) |
| Hypertension | 14 | (2.9) | 13 | (2.6) | 102 | (1.7) | 152 | (1.6) |
| Alanine aminotransferase increased | 11 | (2.3) | 1 | (0.2) | 61 | (1.0) | 120 | (1.3) |
| Aspartate aminotransferase increased | 8 | (1.6) | 1 | (0.2) | 65 | (1.1) | 141 | (1.5) |
| Diarrhoea | 8 | (1.6) | 1 | (0.2) | 79 | (1.3) | 129 | (1.4) |
| Hyperglycaemia | 7 | (1.4) | 3 | (0.6) | 64 | (1.1) | 111 | (1.2) |
| Pneumonia | 7 | (1.4) | 1 | (0.2) | 242 | (4.1) | 351 | (3.8) |
| Adrenal insufficiency | 6 | (1.2) | 1 | (0.2) | 18 | (0.3) | 32 | (0.3) |
| Lipase increased | 6 | (1.2) | 0 | (0.0) | 16 | (0.3) | 27 | (0.3) |
| Acute kidney injury | 5 | (1.0) | 0 | (0.0) | 51 | (0.9) | 86 | (0.9) |
| Diabetic ketoacidosis | 5 | (1.0) | 0 | (0.0) | 9 | (0.2) | 17 | (0.2) |
| Fatigue | 5 | (1.0) | 0 | (0.0) | 144 | (2.4) | 224 | (2.4) |
| Colitis | 4 | (0.8) | 0 | (0.0) | 60 | (1.0) | 93 | (1.0) |
| Pulmonary embolism | 3 | (0.6) | 3 | (0.6) | 91 | (1.5) | 133 | (1.4) |
| Vomiting | 3 | (0.6) | 0 | (0.0) | 42 | (0.7) | 89 | (1.0) |
| Abdominal pain | 2 | (0.4) | 1 | (0.2) | 42 | (0.7) | 106 | (1.1) |
| Arthralgia | 2 | (0.4) | 2 | (0.4) | 58 | (1.0) | 75 | (0.8) |
| Hypokalaemia | 2 | (0.4) | 1 | (0.2) | 58 | (1.0) | 89 | (1.0) |
| Hyponatraemia | 2 | (0.4) | 6 | (1.2) | 153 | (2.6) | 231 | (2.5) |
| Pneumonitis | 2 | (0.4) | 0 | (0.0) | 83 | (1.4) | 109 | (1.2) |
| Urinary tract infection | 2 | (0.4) | 3 | (0.6) | 73 | (1.2) | 104 | (1.1) |
| Anaemia | 1 | (0.2) | 0 | (0.0) | 233 | (4.0) | 427 | (4.6) |
| Asthenia | 1 | (0.2) | 1 | (0.2) | 58 | (1.0) | 108 | (1.2) |
| Back pain | 1 | (0.2) | 1 | (0.2) | 64 | (1.1) | 97 | (1.1) |
| Blood alkaline phosphatase increased | 1 | (0.2) | 0 | (0.0) | 48 | (0.8) | 95 | (1.0) |
| Decreased appetite | 1 | (0.2) | 0 | (0.0) | 74 | (1.3) | 120 | (1.3) |
| Dehydration | 1 | (0.2) | 0 | (0.0) | 62 | (1.1) | 102 | (1.1) |
| Dyspnoea | 1 | (0.2) | 0 | (0.0) | 131 | (2.2) | 177 | (1.9) |
| Pleural effusion | 1 | (0.2) | 1 | (0.2) | 68 | (1.2) | 100 | (1.1) |

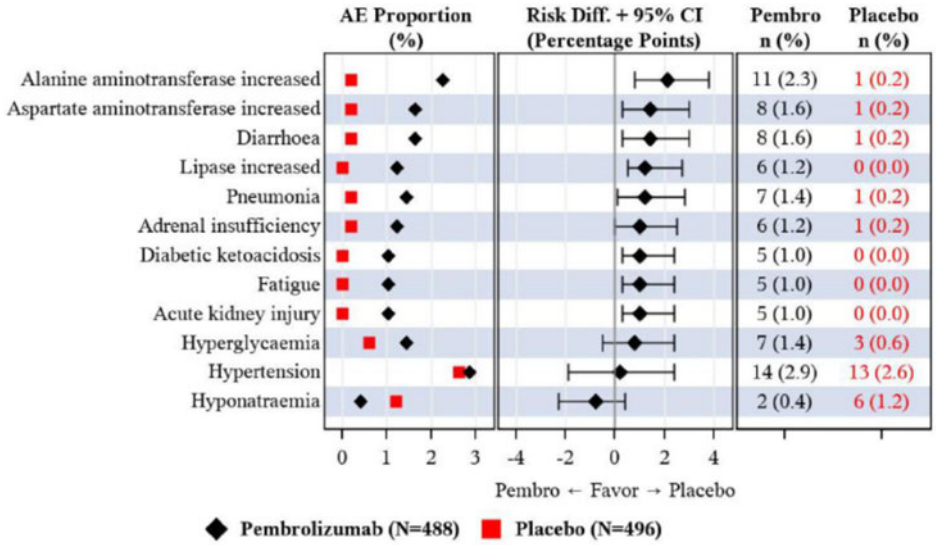


**Figure 31 Between-treatment Comparisons in Grade 3-5 Adverse Events Selected Adverse Events (≥ 1%Incidence) and Sorted by Risk Difference**

**Table 79 Treatment-related Grade ≥3 Adverse Events Participants With Grade 3-5 Drug-Related Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term**

| | KN564 Data for Pembrolizumab | | KN564 Data for Placebo | | Reference Safety Dataset for Pembrolizumab | | Cumulative Running Safety Dataset for Pembrolizumab | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 92 | (18.9) | 6 | (1.2) | 913 | (15.5) | 1,490 | (16.2) |
| with no adverse events | 396 | (81.1) | 490 | (98.8) | 4,971 | (84.5) | 7,728 | (83.8) |
| Alanine aminotransferase increased | 9 | (1.8) | 1 | (0.2) | 35 | (0.6) | 68 | (0.7) |
| Diarrhoea | 8 | (1.6) | 0 | (0.0) | 55 | (0.9) | 86 | (0.9) |
| Adrenal insufficiency | 6 | (1.2) | 0 | (0.0) | 13 | (0.2) | 25 | (0.3) |
| Aspartate aminotransferase increased | 6 | (1.2) | 0 | (0.0) | 35 | (0.6) | 69 | (0.7) |
| Diabetic ketoacidosis | 5 | (1.0) | 0 | (0.0) | 8 | (0.1) | 16 | (0.2) |
| Fatigue | 4 | (0.8) | 0 | (0.0) | 63 | (1.1) | 100 | (1.1) |
| Pneumonitis | 2 | (0.4) | 0 | (0.0) | 78 | (1.3) | 103 | (1.1) |

## Serious adverse event/deaths/other significant events

## Serious Adverse Events (SAEs)

**Table 80 Participants With Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term**

| | KN564 Data for Pembrolizumab [a] | | KN564 Data for Placebo[b] | | Reference Safety Dataset for Pembrolizumab[c] | | Cumulative Running Safety Dataset for Pembrolizumab [d] | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 100 | (20.5) | 56 | (11.3) | 2,266 | (38.5) | 3,449 | (37.4) |
| with no adverse events | 388 | (79.5) | 440 | (88.7) | 3,618 | (61.5) | 5,769 | (62.6) |
| Acute kidney injury | 6 | (1.2) | 0 | (0.0) | 50 | (0.8) | 95 | (1.0) |
| Adrenal insufficiency | 6 | (1.2) | 0 | (0.0) | 18 | (0.3) | 32 | (0.3) |
| Pneumonia | 6 | (1.2) | 1 | (0.2) | 246 | (4.2) | 348 | (3.8) |
| Colitis | 5 | (1.0) | 1 | (0.2) | 59 | (1.0) | 88 | (1.0) |
| Diabetic ketoacidosis | 5 | (1.0) | 0 | (0.0) | 9 | (0.2) | 17 | (0.2) |
| Pneumonitis | 3 | (0.6) | 0 | (0.0) | 117 | (2.0) | 157 | (1.7) |
| Diarrhoea | 1 | (0.2) | 0 | (0.0) | 59 | (1.0) | 84 | (0.9) |
| Dyspnoea | 1 | (0.2) | 0 | (0.0) | 81 | (1.4) | 97 | (1.1) |
| Pleural effusion | 1 | (0.2) | 1 | (0.2) | 83 | (1.4) | 113 | (1.2) |
| Pulmonary embolism | 1 | (0.2) | 3 | (0.6) | 71 | (1.2) | 99 | (1.1) |
| Urinary tract infection | 1 | (0.2) | 2 | (0.4) | 59 | (1.0) | 83 | (0.9) |
| Anaemia | 0 | (0.0) | 0 | (0.0) | 59 | (1.0) | 101 | (1.1) |
| Pyrexia | 0 | (0.0) | 1 | (0.2) | 67 | (1.1) | 102 | (1.1) |

## Drug-related Serious Adverse Events (SAEs)

**Table 81 Participants With Drug-related SAEs Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term**

| | KN564 Data for Pembrolizumab [a] | | KN564 Data for Placebo [b] | | Reference Safety Dataset for Pembrolizumab [c] | | Cumulative Running Safety Dataset for Pembrolizumab [d] | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 59 | (12.1) | 1 | (0.2) | 656 | (11.1) | 1,049 | (11.4) |
| with no adverse events | 429 | (87.9) | 495 | (99.8) | 5,228 | (88.9) | 8,169 | (88.6) |
| Adrenal insufficiency | 6 | (1.2) | 0 | (0.0) | 14 | (0.2) | 26 | (0.3) |
| Colitis | 5 | (1.0) | 1 | (0.2) | 51 | (0.9) | 78 | (0.8) |
| Diabetic ketoacidosis | 5 | (1.0) | 0 | (0.0) | 8 | (0.1) | 16 | (0.2) |
| Pneumonitis | 3 | (0.6) | 0 | (0.0) | 111 | (1.9) | 150 | (1.6) |

**Deaths**

The incidence of deaths (up to 90 days after the last dose of study intervention) due to AEs was 0.4% (n=2) in the Indication Dataset compared with 5.3% in the RSD.

The two deaths in the Indication Dataset were reported due to AEs with PTs of pneumonia and multiple organ dysfunction syndrome; and 1 death due to AEs was reported in the placebo group (PT: hemorrhage intracranial). None of the deaths were considered treatment related by the investigator. Other significant events - Adverse Events of Special Interest (AEOSI) AEOSI are immune-related events and infusion-related reactions associated with pembrolizumab.

**Table 82 Adverse Event Summary AEOSI (APaT Population)**

| | KN564 Data for Pembrolizumab | | KN564 Data for Placebo | | Reference Safety Dataset for Pembrolizumab | | Cumulative Running Safety Dataset for Pembrolizumab | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | | 9,218 | |
| with one or more adverse events | 173 | (35.5) | 34 | (6.9) | 1,475 | (25.1) | 2,295 | (24.9) |
| with no adverse event | 315 | (64.5) | 462 | (93.1) | 4,409 | (74.9) | 6,923 | (75.1) |
| with drug-related adverse events | 155 | (31.8) | 22 | (4.4) | 1,282 | (21.8) | 2,005 | (21.8) |
| with toxicity grade 3-5 adverse events | 44 | (9.0) | 3 | (0.6) | 381 | (6.5) | 603 | (6.5) |
| with toxicity grade 3-5 drug-related adverse events | 43 | (8.8) | 0 | (0.0) | 331 | (5.6) | 532 | (5.8) |
| with serious adverse events | 41 | (8.4) | 1 | (0.2) | 381 | (6.5) | 583 | (6.3) |
| with serious drug-related adverse events | 39 | (8.0) | 1 | (0.2) | 337 | (5.7) | 522 | (5.7) |
| who died | 0 | (0.0) | 0 | (0.0) | 11 | (0.2) | 20 | (0.2) |
| who died due to a drug-related adverse event | 0 | (0.0) | 0 | (0.0) | 11 | (0.2) | 20 | (0.2) |
| discontinued drug due to an adverse event | 39 | (8.0) | 0 | (0.0) | 232 | (3.9) | 372 | (4.0) |
| discontinued drug due to a drug-related adverse event | 38 | (7.8) | 0 | (0.0) | 228 | (3.9) | 367 | (4.0) |
| discontinued drug due to a serious adverse event | 21 | (4.3) | 0 | (0.0) | 156 | (2.7) | 238 | (2.6) |
| discontinued drug due to a serious drug-related adverse event | 21 | (4.3) | 0 | (0.0) | 154 | (2.6) | 236 | (2.6) |

**Table 83 Participants With AEOSI (Incidence > 0% in One or More Treatment Groups) By AEOSI Category (APaT Population)**

| | KN564 Data for Pembrolizumab | | KN564 Data for Placebo | | Reference Safety Dataset for Pembrolizumab ¶ | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | |
| with one or more adverse events | 173 | (35.5) | 34 | (6.9) | 1,475 | (25.1) |
| with no adverse events | 315 | (64.5) | 462 | (93.1) | 4,409 | (74.9) |
| Adrenal Insufficiency | 10 | (2.0) | 1 | (0.2) | 47 | (0.8) |
| Colitis | 8 | (1.6) | 1 | (0.2) | 110 | (1.9) |
| Encephalitis | 1 | (0.2) | 0 | (0.0) | 3 | (0.1) |
| Guillain-Barre Syndrome | 0 | (0.0) | 0 | (0.0) | 4 | (0.1) |
| Hepatitis | 5 | (1.0) | 0 | (0.0) | 56 | (1.0) |
| Hyperthyroidism | 58 | (11.9) | 1 | (0.2) | 247 | (4.2) |
| Hypophysitis | 2 | (0.4) | 0 | (0.0) | 36 | (0.6) |
| Hypothyroidism | 103 | (21.1) | 18 | (3.6) | 652 | (11.1) |
| Infusion Reactions | 7 | (1.4) | 5 | (1.0) | 138 | (2.3) |
| Myasthenic Syndrome | 3 | (0.6) | 0 | (0.0) | 3 | (0.1) |
| Myocarditis | 1 | (0.2) | 0 | (0.0) | 5 | (0.1) |
| Myositis | 2 | (0.4) | 1 | (0.2) | 19 | (0.3) |
| Nephritis | 3 | (0.6) | 0 | (0.0) | 23 | (0.4) |
| Pancreatitis | 0 | (0.0) | 0 | (0.0) | 18 | (0.3) |
| Pneumonitis | 11 | (2.3) | 5 | (1.0) | 264 | (4.5) |
| Sarcoidosis | 4 | (0.8) | 0 | (0.0) | 10 | (0.2) |
| Severe Skin Reactions | 8 | (1.6) | 2 | (0.4) | 97 | (1.6) |
| Thyroiditis | 6 | (1.2) | 1 | (0.2) | 58 | (1.0) |
| Type 1 Diabetes Mellitus | 9 | (1.8) | 0 | (0.0) | 20 | (0.3) |
| Uveitis | 0 | (0.0) | 1 | (0.2) | 21 | (0.4) |
| Vasculitis | 2 | (0.4) | 0 | (0.0) | 2 | (0.0) |

**Table 84 Participants With grade 3-4 AEOSI (Incidence >0% in Indication Dataset)**

| | KN564 Data for Pembrolizumab | | KN564 Data for Placebo | | Reference Safety Dataset for Pembrolizumab[¶] | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5,884 | |
| with one or more Grade 3-4 adverse events | 44 | (9.0) | 3 | (0.6) | 370 | (6.3) |
| Adrenal Insufficiency | 6 | (1.2) | 1 | (0.2) | 23 | (0.4) |
| Colitis | 5 | (1.0) | 0 | (0.0) | 67 | (1.1) |
| Encephalitis | 1 | (0.2) | 0 | (0.0) | 2 | (0.0) |
| Hepatitis | 4 | (0.8) | 0 | (0.0) | 44 | (0.7) |
| Hyperthyroidism | 1 | (0.2) | 0 | (0.0) | 7 | (0.1) |
| Hypophysitis | 2 | (0.4) | 0 | (0.0) | 20 | (0.3) |
| Hypothyroidism | 1 | (0.2) | 0 | (0.0) | 7 | (0.1) |
| Infusion Reactions | 2 | (0.4) | 0 | (0.0) | 14 | (0.2) |
| Myocarditis | 1 | (0.2) | 0 | (0.0) | 5 | (0.1) |
| Nephritis | 1 | (0.2) | 0 | (0.0) | 16 | (0.3) |
| Pneumonitis | 4 | (0.8) | 0 | (0.0) | 82 | (1.4) |
| Severe Skin Reactions | 8 | (1.6) | 2 | (0.4) | 74 | (1.3) |
| Thyroiditis | 2 | (0.4) | 0 | (0.0) | 1 | (0.0) |
| Type 1 Diabetes Mellitus | 9 | (1.8) | 0 | (0.0) | 19 | (0.3) |
| Vasculitis | 1 | (0.2) | 0 | (0.0) | 1 | (0.0) |

**Table 85 Time to Onset and Duration of AEOSI**

| | KN564 Data for Pembrolizumab[c] | | KN564 Data for Placebo[d] | | Reference Safety Dataset for Pembrolizumab[e] | | Cumulative Running Safety Dataset for Pembrolizumab[f] | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 488 | | 496 | | 5884 | | 9218 | |
| Participants with AEOSI | 173 | (35.5) | 34 | (6.9) | 1475 | (25.1) | 2295 | (24.9) |
| Time to Onset of First AEOSI (days)[a] | | | | | | | | |
| Mean (Std) | 100.9 (94.8) | | 146.4 (89.1) | | 117.9 (121.0) | | 116.5 (123.1) | |
| Median | 64.0 | | 147.5 | | 79.0 | | 71.0 | |
| Range | 1 to 426 | | 1 to 364 | | 1 to 787 | | 1 to 787 | |
| Total episodes of AEOSI | 292 | | 39 | | 2105 | | 3297 | |
| Average Episodes per participant | 1.69 | | 1.15 | | 1.43 | | 1.44 | |
| Episode duration (days)[b] | | | | | | | | |
| Median | 101.0 | | 42.0 | | 86.0 | | 88.0 | |
| Range | 1 to 1148+ | | 1 to 1022+ | | 1 to 1640+ | | 1 to 1640+ | |

(%) = Number of participants with AEOSI / Number of participants in population.

[a] Time to onset statistics are based on number of participants with AEOSI.

[b] From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the participant died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.

+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.

Std = Standard Deviation.

## Appendiks F Sammenlignende analyse af effektivitet og sikkerhed

Da en direkte sammenligning af de to grupper, adjuverende pembrolizumab vs. placebo fra KN564 studiet blev anvendt, og der ikke har været lavet indirekte sammenligninger eller metaanalyser, er dette appendix ikke relevant for ansøgningen da en litteratursøgning ikke forventes at bringe yderligere information frem.



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# Appendiks G – Ekstrapolering

The current appendix contains the additional information referred to in 8.3.1.

## 12.1 Additional information concerning transitions from disease-free state

### 12.1.1 Calculation of transition probabilities based on cause-specific hazards

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

1. For each cause of DFS failure *k* (i.e., LR, DM, or death), the average cause-specific hazard within the cycle from week *(t-1)* to *t* was calculated as:
$$\bar{h}_k(t) = H_k(t) - H_k(t-1)$$
where $H_k(.)$ is the cause-specific cumulative hazard of cause *k* (based on the parametric function selected to model cause *k*).
2. The average hazard of any DFS failure within the cycle from week *(t-1)* to *t*, denoted $\bar{h}_{DFS}(t)$, is calculated as the sum of the average cause-specific hazard for all three causes within that cycle. This hazard is converted into a probability using the formula:
$$1 - e^{-\bar{h}_{DFS}(t)}$$
3. In each cycle, the relative contribution of each cause *k* to the overall hazard of DFS failure is derived as:
$$\frac{\bar{h}_k(t)}{\bar{h}_{DFS}(t)}$$
This represents the probability of having had an DFS failure of type *k* given that an DFS failure has occurred within the cycle (163). The relative contribution of cause *k* is then multiplied by the probability of any DFS failure within the cycle to obtain the transition probability corresponding to cause *k*.

Within each cycle, the transition probability from DF → death is set equal to the maximum of the estimated probability based on parametric modeling and background mortality, given the age and gender distribution of the cohort by that cycle. All-cause mortality rates by age for men and women in Denmark are obtained from the Statistics Denmark (164).

### 12.1.2 Selection of base-case parametric functions

The exhaustive list of the distributions considered under each approach and step referred to in 8.3.2.2 is presented below.

**Table 86 Selected parametric distributions for of DF → LR and DF → DM in Step 0**

| | DF → LR | DF → DM |
|---|---|---|
| Approach 1: | | |
| 1. | Gen. gamma | Gen. gamma |
| 2. | Gompertz | Gen. gamma |
| 3. | Log-normal | Gen. gamma |
| 4. | Exponential | Gen. gamma |
| 5. | Log-logistic | Gen. gamma |
| 6. | Weibull | Gen. gamma |
| 7. | Gen. gamma | Gompertz |
| 8. | Gompertz | Gompertz |
| 9. | Log-normal | Gompertz |
| 10. | Exponential | Gompertz |
| 11. | Log-logistic | Gompertz |
| 12. | Weibull | Gompertz |
| 13. | Gen. gamma | Log-normal |
| 14. | Gompertz | Log-normal |
| 15. | Gen. gamma | Log-logistic |
| 16. | Log-normal | Log-normal |



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| | | |
|---|---|---|
| 17. | Exponential | Log-normal |
| 18. | Log-logistic | Log-normal |
| 19. | Weibull | Log-normal |
| 20. | Gen. gamma | Weibull |
| 21. | Gompertz | Log-logistic |
| 22. | Log-normal | Log-logistic |
| 23. | Exponential | Log-logistic |
| 24. | Log-logistic | Log-logistic |
| 25. | Weibull | Log-logistic |
| 26. | Gompertz | Weibull |
| 27. | Log-normal | Weibull |
| 28. | Exponential | Weibull |
| 29. | Log-logistic | Weibull |
| 30. | Weibull | Weibull |
| 31. | Gen. gamma | Exponential |
| 32. | Gompertz | Exponential |
| 33. | Log-normal | Exponential |
| 34. | Exponential | Exponential |
| 35. | Log-logistic | Exponential |
| 36. | Weibull | Exponential |
| Approach 2: | | |
| 37. | Exponential | Gompertz |
| 38. | Weibull | Gompertz |
| 39. | Gompertz | Gompertz |
| 40. | Gompertz | Weibull |
| 41. | Weibull | Weibull |
| 42. | Exponential | Weibull |
| 43. | Gompertz | Exponential |
| 44. | Weibull | Exponential |
| 45. | Exponential | Exponential |
| Approach 3: | | |
| 46. | Exponential | Exponential |
| 47. | Gompertz | Exponential |
| 48. | Weibull | Exponential |
| 49. | Exponential | Weibull |
| 50. | Exponential | Gompertz |
| 51. | Gompertz | Weibull |
| 52. | Weibull | Weibull |
| 53. | Weibull | Gompertz |
| 54. | Gompertz | Gompertz |

**Table 87 Selected parametric distributions for of DF → LR and DF→ DM in Step 1**

| | DF → LR | DF → DM |
|---|---|---|
| Approach 1: | | |
| 1. | Gen. gamma | Gen. gamma |
| 2. | Log-normal | Gen. gamma |
| 3. | Exponential | Gen. gamma |
| 4. | Log-logistic | Gen. gamma |
| 5. | Weibull | Gen. gamma |
| 6. | Gen. gamma | Gompertz |
| 7. | Log-normal | Gompertz |
| 8. | Exponential | Gompertz |
| 9. | Log-logistic | Gompertz |
| 10. | Weibull | Gompertz |
| 11. | Gen. gamma | Log-normal |
| 12. | Gompertz | Log-normal |
| 13. | Gen. gamma | Log-logistic |
| 14. | Log-normal | Log-normal |
| 15. | Exponential | Log-normal |
| 16. | Log-logistic | Log-normal |
| 17. | Weibull | Log-normal |
| 18. | Gen. gamma | Weibull |
| 19. | Gompertz | Log-logistic |
| 20. | Log-normal | Log-logistic |
| 21. | Exponential | Log-logistic |
| 22. | Log-logistic | Log-logistic |
| 23. | Weibull | Log-logistic |
| 24. | Gompertz | Weibull |
| 25. | Log-normal | Weibull |
| 26. | Exponential | Weibull |



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| | | |
|---|---|---|
| 27. | Log-logistic | Weibull |
| 28. | Weibull | Weibull |
| 29. | Gen. gamma | Exponential |
| 30. | Gompertz | Exponential |
| 31. | Log-normal | Exponential |
| 32. | Exponential | Exponential |
| 33. | Log-logistic | Exponential |
| 34. | Weibull | Exponential |
| Approach 2: | | |
| 35. | Exponential | Gompertz |
| 36. | Weibull | Gompertz |
| 37. | Gompertz | Gompertz |
| 38. | Gompertz | Weibull |
| 39. | Weibull | Weibull |
| 40. | Exponential | Weibull |
| 41. | Gompertz | Exponential |
| 42. | Weibull | Exponential |
| 43. | | |
| Approach 3: | | |
| 44. | Exponential | Exponential |
| 45. | Gompertz | Exponential |
| 46. | Weibull | Exponential |
| 47. | Exponential | Weibull |
| 48. | Exponential | Gompertz |
| 49. | Gompertz | Weibull |
| 50. | Weibull | Weibull |
| 51. | Weibull | Gompertz |
| 52. | Gompertz | Gompertz |

**Table 88 Selected parametric distributions for of DF → LR and DF→ DM in Step 2 & 3**

| | DF → LR | DF → DM |
|---|---|---|
| Approach 1: | | |
| 1. | Gen. gamma | Gompertz |
| 2. | Log-normal | Gompertz |
| 3. | Exponential | Gompertz |
| 4. | Log-logistic | Gompertz |
| 5. | Weibull | Gompertz |
| 6. | Gen. gamma | Gen. gamma |
| 7. | Log-normal | Gen. gamma |
| 8. | Exponential | Gen. gamma |
| 9. | Log-logistic | Gen. gamma |
| 10. | Weibull | Gen. gamma |
| Approach 2: | | |
| 11. | Exponential | Gompertz |
| 12. | Weibull | Gompertz |
| 13. | Gompertz | Gompertz |
| Approach 3: | | |
| 14. | Exponential | Gompertz |
| 15. | Weibull | Gompertz |
| 16. | Gompertz | Gompertz |

**Table 89 Selected parametric distributions for of DF → LR and DF→ DM in Step 4a**

| | DF → LR | DF → DM |
|---|---|---|
| Approach 1: | | |
| 1. | Exponential | Gen. gamma |
| 2. | Exponential | Gompertz |
| Approach 2: | | |
| 3. | Exponential | Gompertz |
| 4. | Weibull | Gompertz |
| Approach 3: | | |
| 5. | Exponential | Gompertz |
| 6. | Weibull | Gompertz |

**Table 90 Selected parametric distributions for of DF → LR and DF→ DM in Step 4b & 5**

| | DF → LR | DF → DM |
|---|---|---|
| Approach 3: | | |
| 1. | Exponential | Gompertz |



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The selection process detailed below starts with a total of 54 candidate combinations, including 36 under Approach #1, 9 under Approach #2, and 9 under Approach #3. [redacted] and [redacted] list all candidate combinations of parametric functions in each treatment arm, including the rankings in terms of MSE in each model arm and long-term predictions of DFS and OS.

Initial exclusions based on clinical plausibility: When fitting separate parametric curves to each arm of KN-564 (i.e., Approach #1), there are 2 combinations of parametric distributions that results in higher long-term survival predictions for routine surveillance than pembrolizumab, as shown in [redacted] and [redacted] These combinations of distributions are excluded from further consideration due to clinical implausibility.

[redacted]

[redacted]



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Visual assessment of fit: During the trial period, [redacted] and [redacted] show the observed cumulative incidence of transitions from DF → LR in the pembrolizumab and routine surveillance arms, respectively, alongside the predicted cumulative incidence from different combinations of parametric functions. In the pembrolizumab arm, all combinations of parametric functions produce a close visual fit to the observed cumulative incidence of DF → LR. In the routine surveillance arm, combinations that use Gompertz for DF → LR appear to achieve the best fit with the observed cumulative incidence of DF → LR, although reasonably close fits were achieved with all combinations of functions.

Analogous figures are presented for the cumulative incidence of DF → DM in each treatment arm ([redacted] and [redacted] In the pembrolizumab arm, visual fit is closest when using Gompertz or generalized gamma (under Approach #1) or Gompertz (under Approach #2), while all combinations of parametric functions under Approach #3 produces a close fit. In the routine surveillance arm, visual assessment strongly favored combinations of parametric functions that used either Gompertz or generalized gamma (under Approach #1) or Gompertz (under Approach #2 or 3) for DF → DM. Thus, given the requirement of consistent distribution types in both arms, visual inspection supports the exclusion of all but 16 combinations of parametric distributes. These remaining 16 combinations included those using generalized gamma or Gompertz for DF → DM (minus the two combinations excluded previously based on crossing DFS curves).

As shown in Figur 8, the DFS Kaplan-Meier curves for pembrolizumab and placebo separates early and remained separated in KN-564. The difference in the DFS rates between the treatment groups at 12, 18, and 24 months ranged from 9.5% to 11.0%. Log-cumulative hazard plots, presented in Figure 20 or the DF → LR and DF → DM transitions, show minimal deviations from parallel lines beyond approximately week 12. The lack of separation between the curves prior to week 12 may reflect the protocol-defined timing of the first imaging scan for disease recurrence (week 12 in KN-564). The estimates in the tails of these plots are based on censored data, are not stable, and should be interpreted with caution. The log-cumulative hazard plots favored Approach #3 (which allowed the treatment effect to differ before vs. after 1 year) over Approach #2, but generally

supported the use of proportional hazards models to represent the cause-specific hazards of these transitions. Thus, no further exclusions are applied based on these findings.

[redacted]



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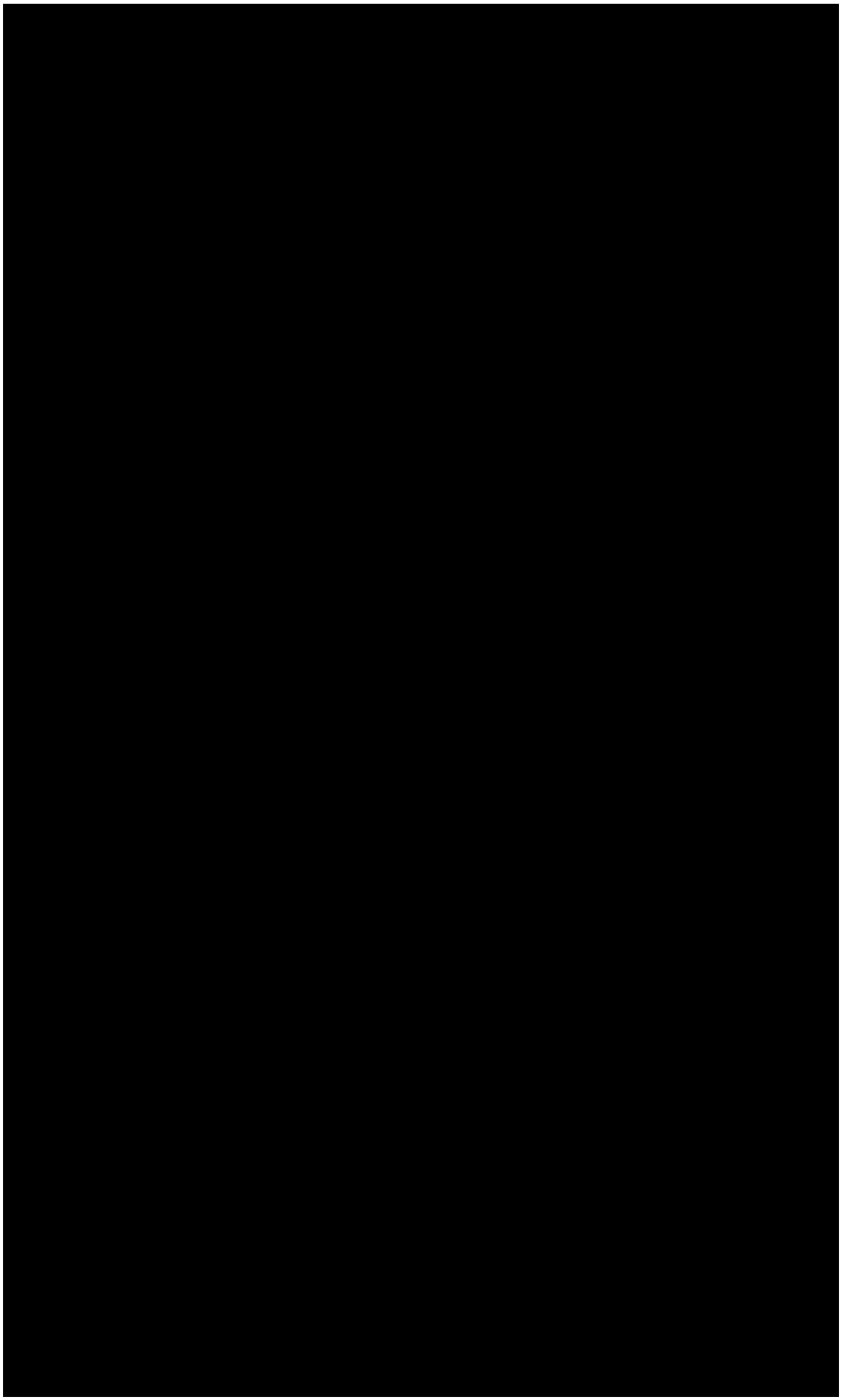



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[redacted]



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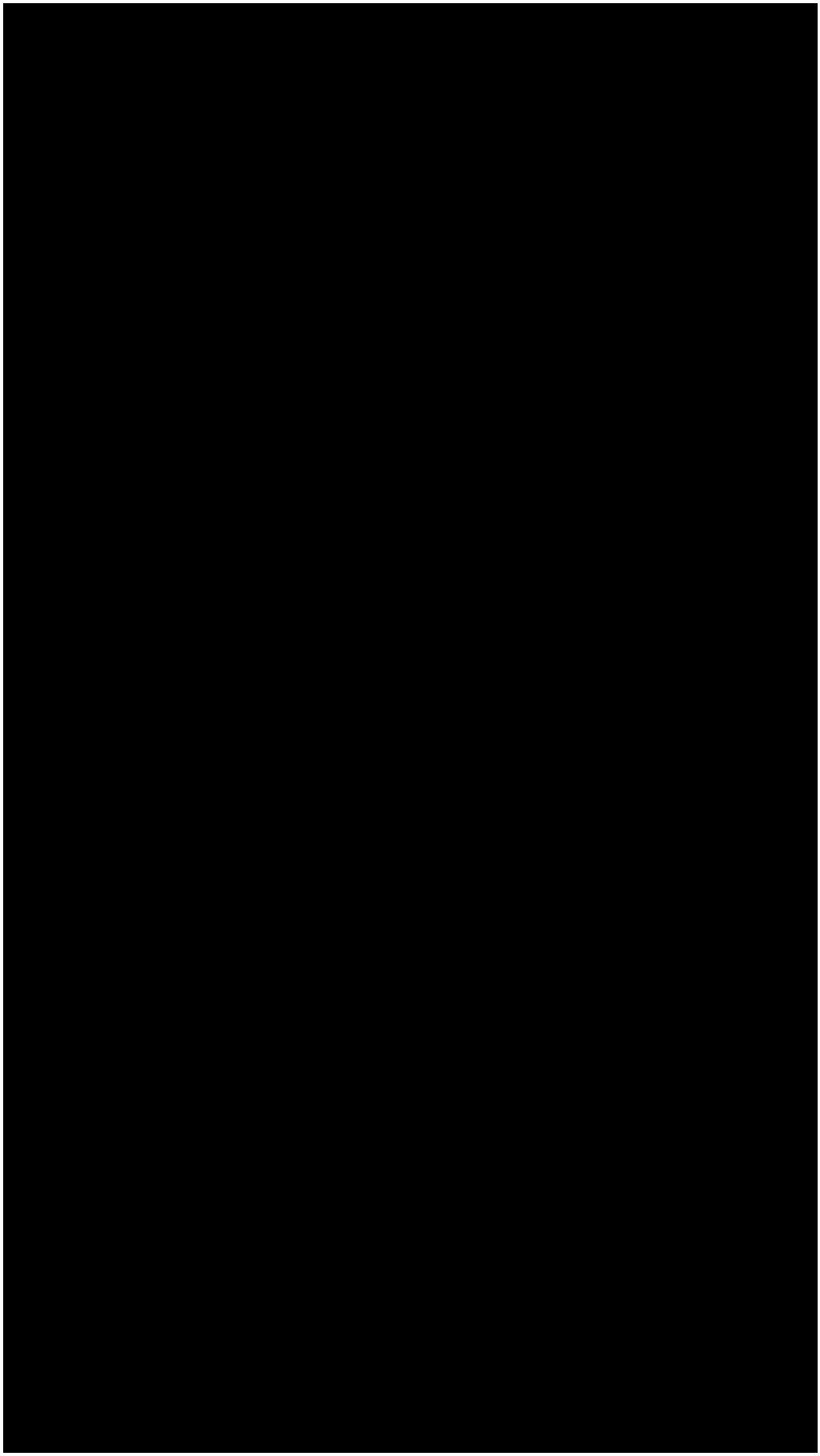



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[redacted]



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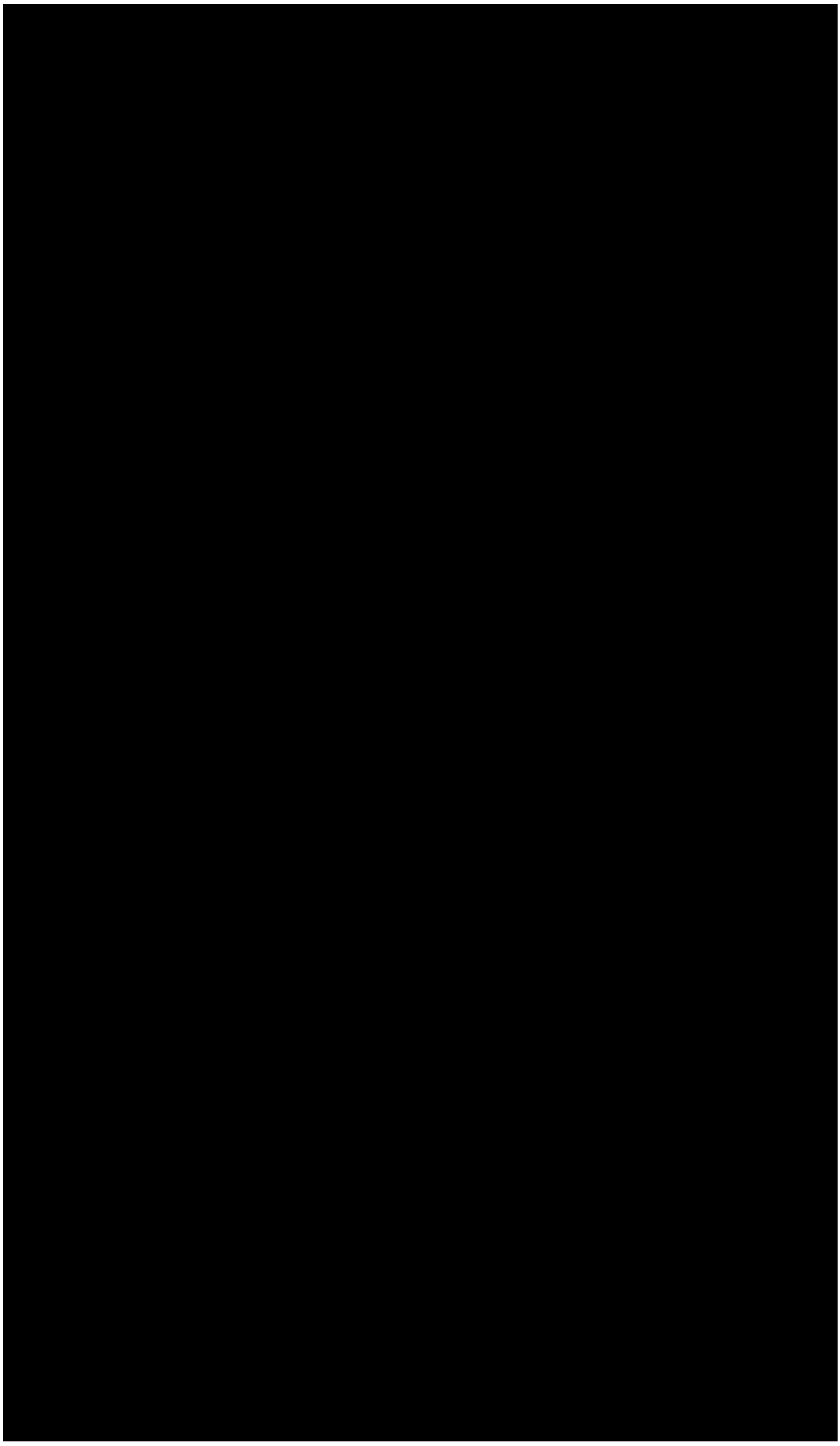



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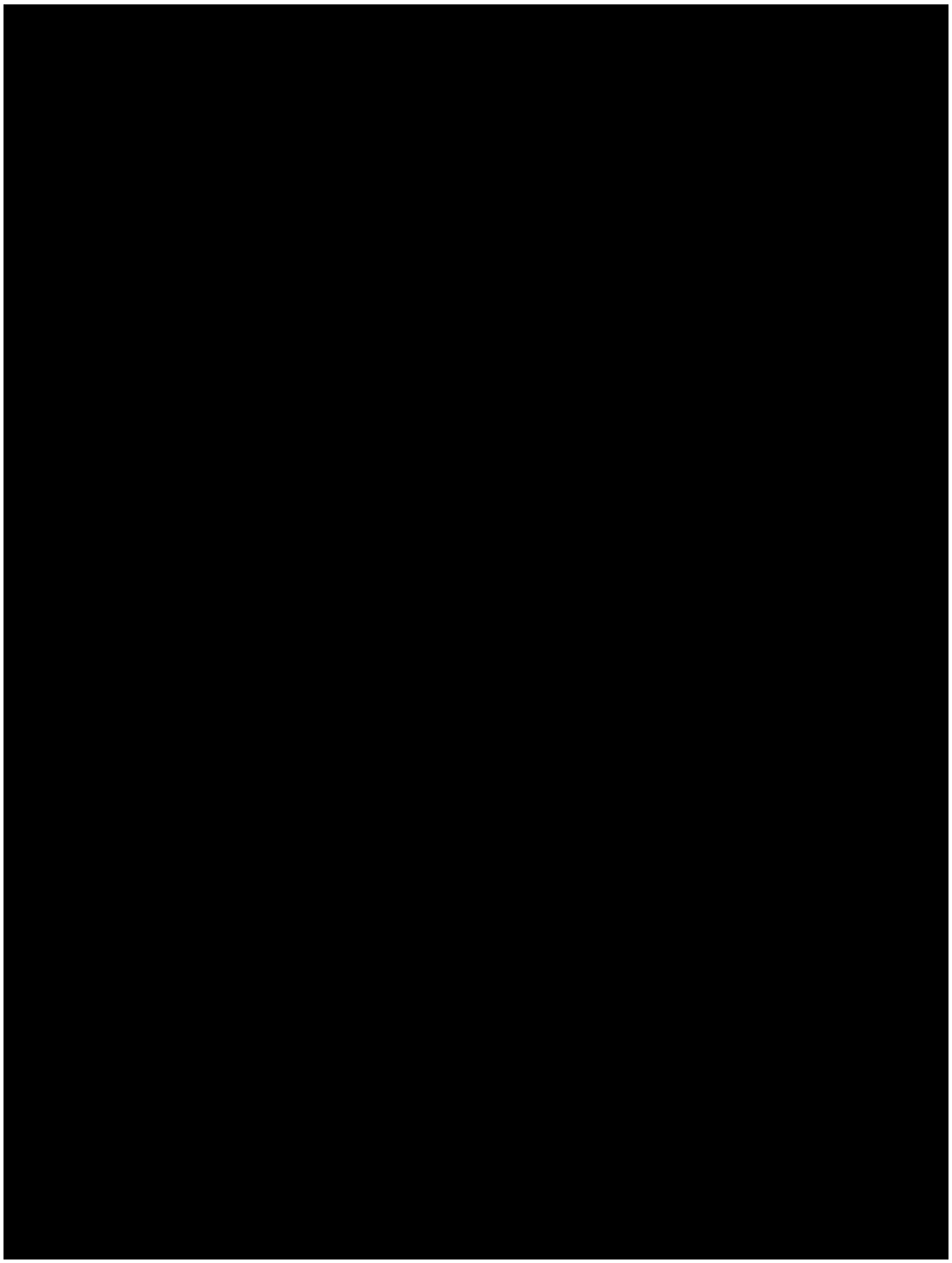



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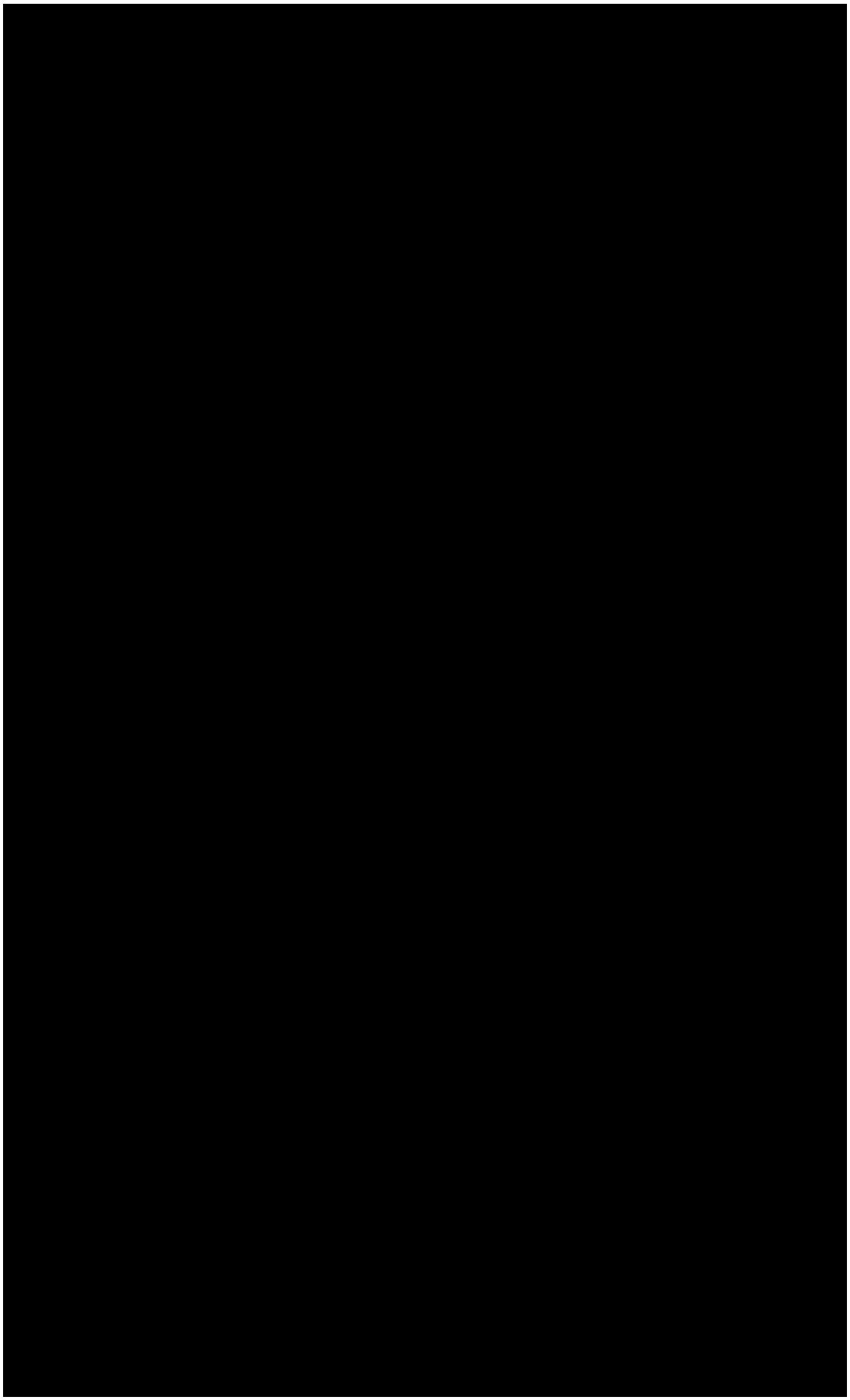



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[redacted]

Fit statistics: As shown in [redacted] and [redacted] the MSE statistics align with findings from visual assessment, with all 16 remaining combinations ranking within the top 50% (i.e., 27th best-fitting or better) of all 54 candidate distributions based on the fit of predicted vs. observed DFS.

Based on statistical fit, visual assessment, and the initial exclusions due to crossing survival curves, further assessments of external validity focus primarily on the 16 aforementioned combinations of distributions for DF → LR and DF → DM.
Under the final selected base case (i.e., Exponential/Gompertz under Approach #3), [redacted] illustrates the close visual alignment between predicted versus observed cumulative incidences of all three individual transitions starting from the DF state. [redacted] og [redacted] presents the alignment between predicted versus observed DFS during the trial period. Close fits are similarly achieved with the other 6 combinations of distributions listed above ([redacted]

External validations of predicted DFS and OS for routine surveillance: Across the S-TRAC, ASSURE (high-risk, clear cell RCC subset), and PROTECT trials, 5-year DFS for placebo ranges narrowly from 50.6% to 51.3% (simple average: 50.9%). Thus, to better ensure externally valid extrapolations in the routine surveillance arm, further exclusions are applied based on the requirement that predicted 5-year DFS should fall within a range of 50.9% +/- 2.5 percentage-points (i.e., 48.4% to 53.4%). This criterion results in the exclusion of an additional 10 combinations of distributions that overpredicted DFS in the routine surveillance arm to varying degrees. The remaining 6 combinations of distributions include:

- Exponential/Generalized gamma under Approach #1 (separately fitted)
- Exponential/Gompertz under Approach #1 (separately fitted)
- Exponential/Gompertz under Approach #2 (jointly fitted, time-constant treatment effect)
- Weibull/Gompertz under Approach #2 (jointly fitted, time-constant treatment effect)
- Exponential/Gompertz under Approach #3 (jointly fitted, time-varying treatment effect)
- Weibull/Gompertz under Approach #3 (jointly fitted, time-varying treatment effect)

[redacted] presents additional data points from external studies alongside predicted DFS under these 6 combinations. Of these 6 combinations, Exponential/Gompertz under Approach #3 provides the closest fit to the external DFS at year 3.5, 5 and 7, followed by Exponential/Gompertz under Approach #2. The other 4 combinations deviate further from external DFS in an overestimated direction. Therefore, Exponential/Gompertz under Approach #3 is considered in the model as base case.

[redacted] plots base-case DFS predictions for routine surveillance against external, digitized DFS data from the placebo arms of prior adjuvant therapy trials in RCC, as well as the DFS Kaplan-Meier curve from KN-564 (data cutoff date: June 14, 2021). [redacted] plots base-case OS predictions for routine surveillance against external, digitized OS data from the same trials (where available). For both survival endpoints, the observed Kaplan-Meier curves from external studies closely align with and surrounded the modeled survival projections for routine surveillance.

[redacted]

[redacted]



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[redacted]

[redacted]



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[redacted]

[redacted]

## 12.2 Additional information concerning included studies in the health economic analysis

### 12.2.1 Network Meta Analysis used for advanced RCC

For each advanced RCC treatment option, exponential models of OS and progression-free survival (PFS) were estimated. For sunitinib in the advanced RCC setting, exponential rates of OS and PFS failure were computed based on the observed median OS and PFS in the sunitinib arm of KEYNOTE-426 trial. HRs for OS and PFS versus sunitinib are each obtained from a NMA of trials conducted in advanced RCC. For each comparator, the model applies time-constant HRs estimated through fixed-effects NMAs of OS and PFS. Trials included in the NMAs were identified through a systematic literature review of randomized controlled trials of first-line treatments in patients with locally advanced or metastatic RCC with clear-cell histology (108).

### 12.2.2 Methodology/evidence acquisition

A living, interactive systematic review (LISR) and network meta-analysis was created for first-line treatment of mRCC using data from randomized controlled trials comparing contemporary treatment options with single-agent tyrosine kinase inhibitors. An advanced programming and artificial intelligence was applied – framework for evidence synthesis to create a living search strategy was assisted, to facilitate screening and data extraction using a graphical user interface, automate the frequentist network meta-analysis, and display results in an interactive manner.

### 12.2.3 Results synthesis

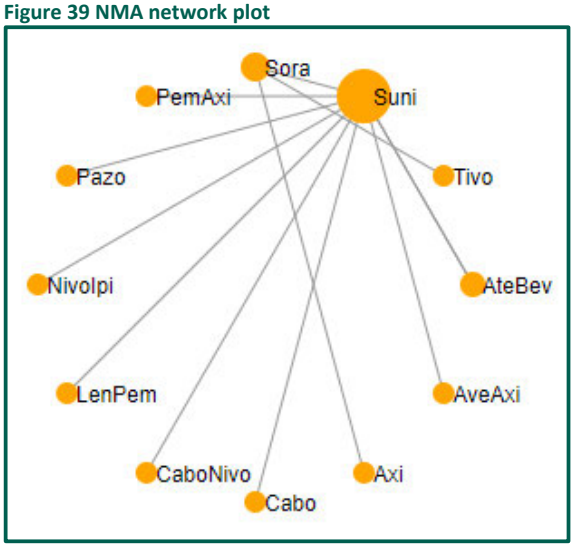
As of October 22, 2020, the LISR includes data from 14 clinical trials and the living NMA includes 11 trials excluding the trials that evaluated crossover sequential treatments. Baseline characteristics are summarized in an interactive table, but a screen dump is provided below. In sum, the all trials cover 7520 patients. All trials except one were two-arm trials, and one trial contained three arms. All trials followed an open-label, randomized design. Patient population consisted of 74% males ranging from 68% to 83%, and the median age in the included trials ranged from 58 to 68. Network meta-analysis results are summarized as interactive tables and plots, GRADE summary-of-findings tables, and evidence maps (108).

**Table 96 Summary of trial characteristics in living, interactive systematic review (LISR)**

| Study | Trial name | Phase | Males (%) | MA (yr) | Treatment arm | Control arm | Organs involved (%) | Prior nephrectomy (%) | Prognostic risk model | Prognostic risk (%) | PD-L1 score >1% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Choueiri 2020 [8] | CHECKMATE 9ER | 3 | 74 | 62 | Nivolumab + cabozantinib | Sunitinib | Lung: 75<br>N: 40<br>Bone: 24<br>Liver: 20 | Treatment: 69<br>Control: 71 | IMDC | Favorable: 23<br>Intermediate: 58<br>Poor: 20 | 26 |
| Rini 2019 [4] | KEYNOTE 426 | 3 | 73 | 62 | Pembrolizumab + axitinib | Sunitinib | Lung: 72<br>LN: 46<br>Bone: 24<br>Adrenal:17<br>Liver: 16 | Treatment: 83<br>Control: 83 | IMDC | Favorable: 31<br>Intermediate: 56<br>Poor: 13 | 58 |
| Rini 2019 [6] | IMMOTION 151 | 3 | 73 | 61 | Atezolizumab + bevacizumab | Sunitinib | Lung: 73<br>LN: 47<br>Liver: 17 | Treatment: 74<br>Control: 72 | MSKCC | Favorable: 20<br>Intermediate: 69<br>Poor: 12 | 40 |
| Motzer 2019 [7] | JAVELIN 101 | 3 | 74 | 62 | Avelumab + axitinib | Sunitinib | NA | Treatment: 80<br>Control: 80 | MSKCC | Favorable: 21<br>Intermediate: 62<br>Poor: 16 | 63 |
| Motzer 2018 [1] | CHECKMATE 214 | 3 | 74 | 62 | Nivolumab + ipilimumab | Sunitinib | Lung: 69<br>LN: 47<br>Bone: 21<br>Liver: 19 | Treatment: 82<br>Control: 80 | IMDC | Favorable: 23<br>Intermediate: 61<br>Poor: 16 | 76 |
| Atkins 2017 [47] | IMMOTION 150 | 2 | NA | NA | Atezolizumab + bevacizumab | Sunitinib | NA | NA | MSKCC | NA | 54 |
| Choueiri 2017 [41] | CABOSUN (update 2018) | 2 | 78 | 63 | Cabozantinib | Sunitinib | Bone: 36 | Treatment: 72<br>Control: 77 | IMDC | Favorable: NA<br>Intermediate: 81<br>Poor: 19 | NA |
| Motzer 2013 [43] | COMPARZ | 2 | 73 | 62 | Pazopanib | Sunitinib | Lung: 76<br>LN: 42<br>Bone: 18<br>Liver: 18 | Treatment: 82<br>Control: 84 | MSKCC | Favorable: 27<br>Intermediate: 59<br>Poor: 11 | NA |
| Motzer 2013 [44] | NA | 3 | 72 | 59 | Tivozanib | Sorafenib | Lung: 80<br>LN: 67<br>Adrenal:26<br>Liver: 22<br>Bone: 22 | Treatment: 100<br>Control: 100 | MSKCC | Favorable: 30<br>Intermediate: 64<br>Poor: 5 | NA |
| Hutson 2013 [45] | NA | 3 | 72 | 58 | Axitinib | Sorafenib | Lung: 73<br>LN: 53<br>Bone: 28<br>Liver: 27 | Treatment: 85<br>Control: 90 | MSKCC | Favorable: 51<br>Intermediate: 43<br>Poor: 3 | NA |
| Tomita 2020 [46] | CROSS-J-RCC | 3 | 83 | 67 | Sorafenib | Sunitinib | Lung: 73<br>LN: 28<br>Bone: 28<br>Brain: 5<br>Liver: 10 | Treatment: 88<br>Control: 89 | MSKCC | Favorable: 22<br>Intermediate: 78 | NA |
| Cirkel 2017 [48] | ROPETAR [a] | 2 | 68 | 66 | Pazopanib alt. everolimus | Pazopanib | Lung: 68<br>LN: 39<br>Bone: 35<br>Brain: 1<br>Liver: 11 | Treatment: 33<br>Control: 51 | MSKCC | Favorable: 26<br>Intermediate: 58<br>Poor: 15 | NA |
| Eichelberg 2015 [49] | SWITCH [a] | 3 | 75 | 65 | Sorafenib → sunitinb | Sunitinib → sorafenib | Lung: 75<br>LN: 44<br>Bone: 15<br>Brain: 3<br>Liver: 22 | Treatment: 92<br>Control: 92 | MSKCC | Favorable: 42<br>Intermediate: 55<br>Poor: <1 | NA |
| Retz 2017 [50] | SWITCH II [a] | 3 | 72 | 68 | Sorafenib → pazopanib | Pazopanib → sorafenib | Lung: 71<br>Bone: 20<br>Liver: 18 | Treatment: 88<br>Control: 86 | MSKCC | Favorable: 49<br>Intermediate: 47<br>Poor: 2 | NA |

MA = median age; LN = lymph node; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan-Kettering Cancer Center; NA = not available; alt. = alternating with.
[a] The ROPETAR and SWITCH trials were not included in our analysis.

**Figure 39 NMA network plot**



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## 12.3 The SEER Medicare database

The database that is included in the health economic analysis is the SEER Medicare database.

### 12.3.1 Methodology

A retrospective analysis of Surveillance, Epidemiology and End Results (SEER)-Medicare data is conducted to assess whether disease-free survival (DFS) may serve as a predictor for long-term survival among patients with intermediate-high risk or high-risk renal cell carcinoma (RCC) post-nephrectomy when OS is unavailable.

The SEER-Medicare database (2007–2016) is used to identify patients ≥66 years with non-metastatic intermediate-high risk and high risk RCC post-nephrectomy.

**Inclusion criteria**

Patients with RCC were identified from the data based on the following criteria:

- Patients had a diagnosis of RCC recorded in the SEER registry (using ICD for Oncology, 3rd Edition [ICD-O3] code: C649 with renal cell carcinoma with clear cell component: '8310') between 2007 and 2015
- Patients had intermediate-high risk or high risk, non-metastatic RCC as defined by collaborative tumor-node-metastasis (TNM) and Fuhrman grading status:
    - Intermediate-to-high risk RCC
        - T2, Grade 4 or sarcomatoid, N0, M0
        - T3, any Grade, N0, M0
    - High risk RCC:
        - T4, any Grade N0, M0
        - T any stage, any Grade, N+, M0
    - For a given diagnosis, pathological information was used to derive the collaborative TNM stage if it was available; otherwise clinical information was used to derive the collaborative TNM stage instead.
- Patients had received either a radical nephrectomy or a partial nephrectomy after the first observed diagnosis of RCC
- ≥66 years old at the first observed diagnosis of RCC

**Exclusion criteria**

Patients who meet the following criteria were excluded, unless otherwise specified:

- Patients who had metastatic disease at diagnosis
- Patients with other (non-renal) cancers before the earliest claim for nephrectomy
- Patients diagnosed with secondary malignant neoplasm prior to or within 30 days after the initial nephrectomy
- Patients diagnosed with RCC at autopsy, nursing homes, or by death certificate
- Patients enrolled in HMO anytime during the study period
- Patients who did not meet eligibility criteria for each individual analysis.

There is no single widely accepted method for evaluating the relationship between an intermediate endpoint such as DFS and OS. Therefore, several different approaches are employed to address the study objective:

- First, the association between DFS and OS for patients with RCC is assessed using the Kendall's τ correlation analysis. For this analysis, time to recurrence and time to OS are recorded relative to date of initial nephrectomy. Patients are censored at the earliest of loss of follow-up or end of data availability (as observed in Medicare data). Kendall's τ



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rank correlation is used to assess the correlation between DFS and OS from the initial nephrectomy. Kendall's τ is estimated based on a Clayton copula model. A 95% CI and p-value were obtained using a bootstrapping approach with 1,000 replications.

- Additionally, a landmark analysis is performed. Three landmark points (i.e., 1, 3, and 5 years after the initial nephrectomy) are selected to provide the balance of allowing enough time for recurrence to occur while also providing enough follow-up for analyses. Subsequent OS is described and compared between patients with recurrence and those without recurrence from each of these landmark points using Kaplan-Meier curves. Therefore, in this landmark analysis, time zero is the landmark time point being evaluated (i.e., 1, 3, or 5 years after nephrectomy). The HR associated with DFS at each landmark point is estimated using multivariable Cox models adjusting for age at nephrectomy, sex, race, disease stage at diagnosis, and CCI.
- Multivariable regression models are also used to quantify the incremental OS post-nephrectomy associated with increased time to recurrence among patients with recurrence, adjusting for baseline covariates.

The significant positive association of DFS and OS among patients with intermediate-high risk and high risk RCC post-nephrectomy observed for patients in SEER-Medicare data supports use of DFS as a potential predictor of OS for these patients when OS data are immature.

### 12.3.2 Comparability/representativeness

Research regarding the clinical and economic burden associated with recurrence in RCC is currently limited. To the best of knowledge, this study is the first to demonstrate the substantial economic and clinical burden associated with RCC recurrence using real-world data.

The table below present baseline characteristics in KN564 and the SEER-Medicare study in order to compare the two studies.

**Table 97 Comparison of baseline characteristics in KEYNOTE-564 compared with SEER-Medicare study, overall population**

| | KEYNOTE-564 | SEER-Medicare study |
|---|---|---|
| **Age:** | | |
| Mean | 58.4 | 75.5 |
| Range | 25-84 | NR |
| **Sex (%):** | | |
| Male | 72.1% | 60.7% |
| Female | 27.9% | 39.3% |
| **Nephrectomy:** | | |
| Partial | 7.6% | |
| Radical | 92.4% | NR |
| **ECOG:** | | |
| 0 | 85.5% | |
| 1 | 14.5% | NR |
| M0 Intermediate-high risk | 86.9% | 97.8% |
| M0 High risk | 7.2% | 2.2% |
| M1 NED | 5.8% | 0% |

# Appendiks H – Litteratursøgning efter HRQoL-data



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## Appendiks I Mapping af HRQoL-data

Ikke relevant.



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## Appendiks J Probabilistiske følsomhedsanalyser

**Table 98 Parameters and distributional assumptions considered in the probabilistic analysis (copied from the model sheet "PSA Setup")**

| | Input parameter | Distribution | Mean | SE | Note |
|---|---|---|---|---|---|
| Parameter estimates for DF→LR (Exponential) | Parameter A | MV normal | 0.0007 | - | Uncertainty in the cause-specific hazards of transitions from the DF state is represented by the variance-covariance matrix or SE corresponding to the parameter estimates from KEYNOTE-564 |
| | Pembrolizumab (vs. Routine surveillance) | MV normal | -0.63 | - | |
| | Pembrolizumab (vs. Routine surveillance)*Post-year 1 | MV normal | -0.183 | - | |
| Parameter estimates for DF→DM (Gompertz) | Parameter A | MV normal | -0.01 | - | |
| | Parameter B | MV normal | 0.0044 | - | |
| | Pembrolizumab (vs. Routine surveillance) | MV normal | -0.39 | - | |
| | Pembrolizumab (vs. Routine surveillance)*Post-year 1 | MV normal | -0.097 | - | |
| Parameter estimates for DF→Death (Exponential) | Parameter A | MV normal | 0.00006 | - | |
| | Pembrolizumab (vs. Routine surveillance) | MV normal | 0.63292 | - | |
| Exponential rates of LR→DM | Pembrolizumab | Normal | 0.00422 | 0.00102 | SE is based on the original source for this exponential rate, i.e., the SEER-Medicare database study. Exponential rates of LR→DM are assumed to be equal across adjuvant treatment arms, and are therefore varied together in each iteration of the PSA. |
| | Routine surveillance | Normal | 0.00422 | 0.00102 | |
| Exponential rates of LR→Death | Pembrolizumab | Normal | 0.00006 | 0.00004 | SE is based on the original source for this exponential rate, i.e., KEYNOTE-564. Exponential rates of LR→Death are assumed to be |
| | Routine surveillance | Normal | 0.00006 | 0.00004 | |

| | Input parameter | Distribution | Mean | SE | Note |
|---|---|---|---|---|---|
| | | | | | equal across adjuvant treatment arms, and are therefore varied together in each iteration of the PSA. |
| Exponential rates of OS and PFS failure with different treatments in the advanced RCC setting | Sunitinib, OS | Normal | 0.004 | 0.00027 | Exponential rates and corresponding standard errors for sunitinib were estimated based on long-term results from the KEYNOTE-426 trial; HRs for other advanced regimens vs. sunitinib were obtained from a network meta-analysis of trials in the advanced RCC setting. Percentile matching is used for each OS/PFS pair to preserve the rank of these two outcomes for each treatment regimen. |
| | Sunitinib, PFS | Normal | 0.014 | 0.00132 | |
| | Sunitinib, HR of OS vs. sunitinib | Log-normal | 1.00 | | |
| | Sunitinib, HR of PFS vs. sunitinib | Log-normal | 1.00 | | |
| | Tivozanib, HR of OS vs. sunitinib | Log-normal | 1.33 | 0.27 | |
| | Tivozanib, HR of PFS vs. sunitinib | Log-normal | 1.19 | 0.26 | |
| | Pazopanib, HR of OS vs. sunitinib | Log-normal | 0.92 | 0.08 | |
| | Pazopanib, HR of PFS vs. sunitinib | Log-normal | 1.05 | 0.08 | |
| | Cabozantinib, HR of OS vs. sunitinib | Log-normal | 0.80 | 0.21 | |
| | Cabozantinib, HR of PFS vs. sunitinib | Log-normal | 0.48 | 0.22 | |
| | Nivolumab / ipilimumab, HR of OS vs. sunitinib | Log-normal | 0.72 | 0.08 | |
| | Nivolumab / ipilimumab, HR of PFS vs. sunitinib | Log-normal | 0.89 | 0.08 | |
| Medical management costs by health state | Medical management costs in DF state per week (up to year 2) | Gamma | 133.92 | 26.78 | SE assumed to be equal to 20% of the base-case value. |



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| | Input parameter | Distribution | Mean | SE | Note |
|---|---|---|---|---|---|
| | Medical management costs in DF state per week (years 2-5) | Gamma | 66.96 | 13.39 | |
| | Medical management costs in DF state per week (years 5+) | Gamma | 82.80 | 16.56 | |
| | Salvage surgery costs upon LR state entry (one-time cost) | Gamma | 15,268.85 | 3053.77 | |
| | Medical management costs in LR state (per week) | Gamma | 200.89 | 40.18 | |
| | Medical management costs upon DM state entry (one-time cost) | Gamma | 13,289.85 | 2657.97 | |
| | Medical management costs in pre-progression DM state (per week) | Gamma | 531.75 | 106.35 | |
| | Medical management costs in post-progression DM state (per week) | Gamma | 1,387.09 | 277.42 | |
| | Terminal care cost (one-time cost) | Gamma | 28,154.00 | 5,630.80 | |
| Drug administration costs | Unit cost of simple IV drug administration | Gamma | 2038.00 | 407.60 | SE assumed to be equal to 20% of the base-case value. |
| | Unit cost of complex IV drug administration | Gamma | 2038.00 | 407.60 | |
| Relative dose intensity | Pembrolizumab | Normal | 0.99 | 0.05 | SE assumed to be 5% for all treatments. |



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| | Input parameter | Distribution | Mean | SE | Note |
|---|---|---|---|---|---|
| Cost of AEs | Pembrolizumab | Gamma | 1214.79 | 242.96 | SE assumed to be equal to 20% of the base-case value. |
| | Routine surveillance | Gamma | 729.64 | 145.93 | |
| Utilities and disutilities | Utility of DF (without toxicity) | Beta | 0.91392 | 0.00467 | SEs are based on the original sources for the utility inputs, i.e., KEYNOTE-564 and KEYNOTE-426. Percentile matching is used to preserve rank of utility values from best to worst health state. |
| | Utility of LR | Beta | 0.89663 | 0.01961 | |
| | Utility of pre-progression DM | Beta | 0.85091 | 0.00937 | |
| | Utility of post-progression DM | Beta | 0.85091 | 0.00937 | |
| | Disutility from AEs | Normal | -0.06202 | 0.00883 | |
| | Utility associated with age (18-29) | Beta | 0.871 | 0.17420 | SE assumed to be equal to 20% of the absolute value of the mean. |
| | Utility associated with age (30-39) | Beta | 0.848 | 0.16960 | |
| | Utility associated with age (40-49) | Beta | 0.834 | 0.16680 | |
| | Utility associated with age (50-69) | Beta | 0.818 | 0.16360 | |
| | Utility associated with age (70-79) | Beta | 0.813 | 0.16260 | |
| | Utility associated with age (80+) | Beta | 0.721 | 0.14420 | |



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## Appendiks K Summary of findings from the SEER-Medicare database

A retrospective analysis of Surveillance, Epidemiology and End Results (SEER)-Medicare data is conducted to assess whether disease-free survival (DFS) may serve as a predictor for long-term survival among patients with intermediate-high risk or high risk renal cell carcinoma (RCC) post-nephrectomy when OS is unavailable (110, 131).

The SEER-Medicare database (2007–2016) is used to identify patients ≥66 years with non-metastatic intermediate-high risk and high risk RCC post-nephrectomy. There is no single widely accepted method for evaluating the relationship between an intermediate endpoint such as DFS and OS. Therefore, several different approaches are employed to address the study objective:

- First, the association between DFS and OS for patients with RCC is assessed using the Kendall's τ correlation analysis. For this analysis, time to recurrence and time to OS are recorded relative to date of initial nephrectomy. Patients are censored at the earliest of loss of follow-up or end of data availability (as observed in Medicare data). Kendall's τ rank correlation is used to assess the correlation between DFS and OS from the initial nephrectomy. Kendall's τ is estimated based on a Clayton copula model. A 95% CI and p-value were obtained using a bootstrapping approach with 1,000 replications.
- Additionally, a landmark analysis is performed. Three landmark points (i.e., 1, 3, and 5 years after the initial nephrectomy) are selected to provide the balance of allowing enough time for recurrence to occur while also providing enough follow-up for analyses. Subsequent OS is described and compared between patients with recurrence and those without recurrence from each of these landmark points using Kaplan-Meier curves. Therefore, in this landmark analysis, time zero is the landmark time point being evaluated (i.e., 1, 3, or 5 years after nephrectomy). The HR associated with DFS at each landmark point is estimated using multivariable Cox models adjusting for age at nephrectomy, sex, race, disease stage at diagnosis, and CCI.
- Multivariable regression models are also used to quantify the incremental OS post-nephrectomy associated with increased time to recurrence among patients with recurrence, adjusting for baseline covariates.

A total of 643 patients were analyzed; mean age of 75 years; >95% of patients had intermediate-high risk RCC at diagnosis; 269 patients had recurrence over the course of follow-up, among which 10.8% had locoregional recurrence and 89.2% had distant metastatic recurrence. Patients with recurrence post-nephrectomy by each landmark point had shorter subsequent OS compared to patients without recurrence by the corresponding point. For patients with versus without recurrence by 1, 3, and 5 years following initial nephrectomy, the median OS after each landmark point was 2.4 vs. 9.7 years, 4.5 years vs. not reached, and 5.7 years vs. not reached, respectively (all p<0.001). Additionally, patients who experienced disease recurrence after the initial nephrectomy had an approximately 3 times increased risk of death compared with patients at the same time point who were without recurrence (adjusted hazard ratios 3.46, 2.98 and 2.70 for the landmark points 1, 3 and 5 years). The Kendall's τ correlation between DFS and OS post-nephrectomy was 0.70 (95% CI: 0.65, 0.74; p<0.001). After adjusting for baseline covariates, patients with one additional year of time to recurrence were associated with 0.73 years longer OS post-nephrectomy (95% CI: 0.40, 1.05; p<0.001).(131) When adjusting for age at recurrence instead of age at nephrectomy, the incremental OS increased from 0.73 years to 0.85 years per one additional year of DFS (95% CI: 0.52, 1.18 years; p<0.001), which reflected a negative indirect effect from time to recurrence to post-recurrence survival mediated through age.

The significant positive association of DFS and OS among patients with intermediate-high risk and high risk RCC post-nephrectomy observed for patients in SEER-Medicare data supports use of DFS as a potential predictor of OS for these patients when OS data are immature.



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# Appendiks L Overview of clinical trials used for external validation

**Table 99 Inclusion criteria and characteristics of KEYNOTE-564 and adjuvant RCC trials included in external validity assessment**

| Trial attribute | KEYNOTE-564* | ASSURE (high-risk subset) | S-TRAC | PROTECT | ATLAS | Immotion010* |
|---|---|---|---|---|---|---|
| *No. of patients* | 994 | 1,069 | 615 | 1,538 | 724 | 778 |
| *Treatment arms* | Pembrolizumab vs placebo | Sunitinib or sorafenib vs placebo | Sunitinib vs placebo | Pazopanib vs placebo | Axitinib vs placebo | Atezolizumab vs placebo |
| *Duration of adjuvant treatments, years* | 1 | 1 | 1 | 1 | 3 | 1 |
| *Inclusion criteria* | Intermediate-/high-risk RCC:<br>▪ pT2, G 4 or sarcomatoid, N0, M0;<br>▪ pT3, Any G, N0, M0<br>High-risk RCC:<br>▪ pT4, Any G N0, M0;<br>▪ pT, Any stage, Any G, N1, M0<br>M1 NED | TNM 2002 staging:<br>▪ pT3, G any, N0 or pNx, M0<br>▪ pT4, G any, N0 or pNx, M0<br>▪ pT any, G any, N1 (fully resected), M0 | TNM 2002 staging:<br>▪ pT3, G any, N0 or pNx, M0<br>▪ pT4, G any, N0 or pNx, M0<br>▪ pT any, G any, N1 (fully resected), M0 | TNM 2010 staging:<br>▪ pT2, G3-4, N0 or pNx, M0<br>▪ pT3, G any, N0 or pNx, M0<br>▪ pT4, G any, N0 or pNx, M0<br>▪ pT any, G any, N1, M0 | TNM 2010 staging:<br>▪ pT2, G any, pN0 or pNx, M0<br>▪ pT3, G any, pN0 or pNx, M0<br>▪ pT4, G any, pN0 or pNx, M0<br>▪ pT any, G any, pN1, M0 | Intermediate-/high-risk RCC:<br>▪ pT2, G 4 N0, M0;<br>▪ pT3a, G3-4 N0, M0;<br>▪ pT3b, c N0, M0;<br>▪ T4 any grade N0, M0;<br>▪ pT, Any stage, Any G, N1, M0<br>M1 NED |
| *Microscopic disease* | M1, NED after resection of oligometastatic sites <=1 year from nephrectomy | M0 patients with evidence of microscopic disease (R1) are acceptable | M0 patients with evidence of microscopic disease (R1) are acceptable | M0, resected nonmetastatic | Patients must have no evidence of macroscopic residual disease or metastatic disease | M1 NED: Patiens with synchronous metastasectomy and metachronous metastasectomy >1 year post primary surgery |
| *Histology* | Clear cell | Clear cell predominant | Clear cell predominant | Clear cell predominant (> 50%) | Clear cell predominant (> 50%) | Clear cell and/or sarcomatoid (sarcomatoid ncc allowed) |
| *Performance status* | ECOG 0-1 | ECOG 0-1 | ECOG 0-1 | Karnofsky performance score >= 80 | ECOG 0-1 | ECOG 0-1 |
| *Risk score* | TNM and Fuhrman grade | Modified UISS intermediate high to very high | Modified UISS high risk | SSIGN intermediate to high risk | TNM and Fuhrman grade | TNM and Fuhrman grade |

*Abbreviations:* ECOG, Eastern Cooperative Oncology Group; SSIGN, stage, size, grade and necrosis; UISS, University of California Los Angeles Integrated Staging System.

*Note:* The table above is adapted from Table A10 of Eisen et al. (2020)(165)

*Immotion010 was a negative trial and included adjuvant treatment with atezolizumab, and anti-PD-L1 inhibitor, in contrast to the positive KN564-trial which included adjuvant treatment with pembrolizumab, an PD-1 inhibitor. Studies in mRCC with anti-PD-L1 inhibitors have largely been less successful than have studies with anti-PD-1 inhibitors.

**Table 100 Overview of DFS estimates from different studies**

| DFS by year: | 1 | 2 | 3 | 3.5 | 4 | 5 | 7 |
|---|---|---|---|---|---|---|---|
| Pembrolizumab, modeled DFS | 86.0% | 78.1% | 72.8% | 70.8% | 69.0% | 66.0% | 61.2% |
| Pembrolizumab, observed DFS (KEYNOTE-564, data cutoff date: 14 Jun 2021) | 85.5% | 78.3% | 74.1% | 72.1% | -- | -- | -- |
| Placebo, modeled DFS | 79.6% | 67.7% | 60.1% | 57.2% | 54.8% | 50.7% | 44.5% |
| Placebo, observed DFS (KEYNOTE-564, data cutoff date: 14 Jun 2021) | 76.0% | 67.3% | 64.2% | 56.1% | -- | -- | -- |
| Placebo, observed DFS (S-TRAC) | 77.7% | 67.3% | 59.5% | 57.1% | 54.7% | 51.3% | 39.5% |
| Placebo, observed DFS (ASSURE ccRCC high risk) | 78.6% | 63.6% | 57.6% | 54.3% | 53.0% | 50.6% | 38.2% |
| Placebo, observed DFS (PROTECT) | 74.3% | 67.0% | 61.9% | 60.2% | 58.7% | 50.8% | -- |
| Placebo, observed DFS (ATLAS) | 76.7% | 65.0% | 60.2% | 59.2% | 54.3% | -- | -- |
| Placebo, observed DFS (IMMotion10) | 74.1% | 64.8% | 58.8% | 57.4% | 53.5% | 46.3% | -- |

*Sources:* Gross-Goupil et al. (2018) [ATLAS]; Haas et al. (2017) [ASSURE]; Motzer et al. (2017) [PROTECT]; Ravaud et al. (2016) [S-TRAC], Sumanta et al. (2022) [Immotion]

**Table 101 Overview of OS estimates from different studies**

| OS by year: | 1 | 2 | 3 | 3.5 | 4 | 5 | 7 |
|---|---|---|---|---|---|---|---|
| Placebo, modeled OS | 97.9% | 94.1% | 89.5% | 87.2% | 84.9% | 80.3% | 71.6% |
| Placebo, observed OS (S-TRAC) | 98.7% | 94.5% | 90.9% | 88.6% | 85.8% | 81.9% | 72.2% |
| Placebo, observed OS (ASSURE ccRCC high risk) | 97.4% | 91.3% | 86.9% | 83.4% | 82.6% | 77.5% | 67.7% |
| Placebo, observed OS (PROTECT) | 97.7% | 93.2% | 88.2% | 86.2% | 84.5% | 81.6% | 77.7% |
| Placebo, observed OS (IMMotion10) | 97.2% | 93.0% | 89.7% | 88.4% | 85.2% | 81.2% | -- |

*Sources:* Haas et al. (2017) [ASSURE]; Motzer et al. (2018) [S-TRAC]; Motzer et al. (2021) [PROTECT], Sumanta et al. (2022) [IMmotion]



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# Appendiks M, DaRenCa kliniske retningslinjer for kirurgi ved renalcellecarcinom, opsummeret

**Danske kliniske guidelines fra DaRenCa (13):**

*Udredning*

1. Sygdommen stadieinddeles ud fra billeddiagnostik med flerfaset CT-skanning af thorax og abdomen i henhold til (74)(A)
2. Hvis biopsi skønnes relevant, anbefales grovnålsbiopsi med 18 G kanyle (B)
3. Hos patienter med primær metastatisk sygdom, som er uegnede til kirurgi, men kandidater til medicinsk behandling, anbefales biopsi af tumor samt evt. metastase (B)
4. Patienter under udredning skal have taget følgende blodprøver, hvoraf resultaterne skal indrapporteres til DaRenCaData: hæmoglobin, neutrofile granulocytter, C-reaktivt protein, ioniseret calcium, lactatdehydrogenase og natrium (D)
5. Alle patienter med nyrecancer skal drøftes på multidisciplinær team (MDT) konference (D)

*Kirurgi ved lokaliseret tumor*

6. Lokaliseret renalcellekarcinom (RCC) skal fjernes kirurgisk, når det er muligt og klinisk relevant (A)
7. Partiel nefrektomi foretrækkes, når det er teknisk muligt, ellers foretages nefrektomi (A)

*Ablativ behandling*

8. Ablationsbehandling kan tilbydes selekterede patienter med cT1A tumorer, når partiel nefrektomi er uhensigtsmæssig (B). **NB – disse patienter er ikke inkluderet i nærværende ansøgning**

*Aktiv overvågning*

9. Aktiv overvågning kan tilbydes patienter med små solide tumorer (≤ 3 cm), høj alder, dårlig almen tilstand og/eller betydende co-morbiditet, såfremt behandling kan blive relevant (B)
10. Patienter i aktiv overvågning anbefales CT-scanning af thorax og abdomen hver 6.måned de første 2 år og derefter årligt (D). **NB – disse patienter er ikke inkluderet i nærværende ansøgning**

*Kirurgi ved lokalavanceret RCC*

11. Ved lokalavanceret RCC foretages laparoskopisk nefrektomi, når det er teknisk muligt (A)
12. Tumortromber i vena renalis og vener centralt herfor fjernes sammen med primærtumor, når det er teknisk muligt (B)
13. Embolisering anbefales kun som palliation hos patienter med klinisk betydende blødning, som er uegnede til kirurgi (B). **NB – disse patienter er ikke inkluderet i nærværende ansøgning**

*Lymfeknudedissektion og fjernmetastaser*

14. Lymfadenektomi anbefales ikke hos patienter med lavrisikotumorer (cT1-cT2, cN0, cM0) (A)
15. Lymfadenektomi anbefales ved mistanke om regionale lymfeknudemetastaser, enten radiologisk påvist (korteste akse > 10 mm) eller peroperativt fundne suspekte lymfeknuder, med henblik på staging og lokal kontrol (B)
16. Adrenalektomi foretages ved mistanke om metastase eller direkte indvækst (B)
17. Solitære fjernmetastaser/oligometastaser fjernes, og der tilstræbes radikalitet, når det er teknisk muligt (B)



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# Appendiks N Description of TA512 and TA215

TA512 is a technology appraisal of NICE on tivozanib (Fotivda) for treating **advanced** renal cell carcinoma in adults, whereas TA215 is a technology appraisal of NICE on pazopanib (Votrient) for previously untreated **advanced** renal cell carcinoma in adults.

**TA512**: The main clinical evidence for tivozanib for this appraisal came from TIVO-1, an open-label randomised controlled trial that primarily investigated whether tivozanib (n=260) prolongs time to disease progression compared with sorafenib (n=257). At disease progression, patients in the sorafenib group could switch (cross over) to treatment with tivozanib. Patients in the tivozanib group could also have subsequent treatment if their disease progressed. The committee considered whether this trial was relevant to clinical practice in England:

- Comparator: the comparator in TIVO-1 was sorafenib, which is not used in the NHS and was not considered a comparator in this appraisal.
- Outcome: the primary outcome was progression-free survival, but the trial also measured overall survival and health-related quality of life.
- Baseline characteristics: the clinical experts generally considered the baseline characteristics of patients in the trial to be similar to those of people who would be offered tivozanib in the NHS:

Most patients in the trial (88%) were enrolled in Central or Eastern Europe. The committee was concerned that these patients may have poorer access to second-, third- and fourth-line life-extending therapies. This would mean that the survival times in TIVO-1 might be shorter than those in England.

Patients in the sorafenib group had a better average performance status than those in the tivozanib group. In the sorafenib group, 54% had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 (meaning that they did not have any symptoms and were able to carry out usual activities unrestricted) compared with 45% in the tivozanib group. This means that the results may underestimate the effectiveness of tivozanib. The committee concluded that the comparator and location of TIVO-1 limited the generalisability of the results.

**TA215**: A systematic review was undertaken to identify clinical evidence for pazopanib and its comparators in the first-line treatment of patients with advanced/metastatic RCC. One randomised controlled trial (RCT) evaluating pazopanib in this population was identified, VEG105192 (Sternberg 2010). The placebo-controlled VEG105192 study provides the primary evidence for the efficacy and safety profile of pazopanib; results from the treatment-naive subpopulation form the main focus of this submission in line with the scope of this appraisal (first-line treatment).

A cost effectiveness analysis was also performed which was in line with the appraisal. The cost-effectiveness of pazopanib in the treatment-naïve advanced/metastatic RCC population has been examined, consistent with the scope for this appraisal. In the evaluation, a “partitioned-survival” model was used to project expected clinical and economic outcomes for patients with advanced/metastatic RCC who were assumed to receive either pazopanib or one of the comparators for this appraisal, sunitinib, IFN or BSC. The time horizon evaluated was 10 years, with no additional benefits assumed beyond this time frame. The model structure is based on PFS and OS health states, consistent with clinical outcomes employed in oncology trials, and 9 specifically with those examined in the VEG105192 trial. The model employed in this analysis contains three mutually exclusive health states: “Alive Pre-Progression”, “Alive Post-Progression”, and “Dead”. While residing in a particular health state, patients are assigned a cost of care and health-state preference weight (i.e. utility value), both of which are assumed to depend upon disease status.



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