Medicinrådet

# Bilag til Medicinrådets vurdering af ciltacabtagene autoleucel (cilta-cel) til behandling af patienter med recidiverende og refraktær knoglemarvskræft, som er refraktære overfor lenalidomid

*Vers. 1.0*

# Bilagsoversigt

1. Ansøgers notat til Rådet vedr. ciltacabtagene autoleucel (cilta-cel)
2. Forhandlingsnotat fra Amgros vedr. ciltacabtagene autoleucel (cilta-cel)
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Janssen-Cilag A/S
jnj.com

29. august 2025

Til Medicinrådet

**Vedr. tilbagemelding på Medicinrådets udkast til vurdering af cilta-cel (Carvykti) til patienter med recidiverende og refraktær knoglemarvskræft, som er refraktære overfor lenalidomid**

Johnson & Johnson takker for det grundige udkast til vurdering af cilta-cel. Vi sætter stor pris på den konstruktive dialog i forløbet.

## Formål og datagrundlag

Cilta-cel har været anbefalet som behandling i fjerde linje siden november 2024, og implementeringen er forløbet med stor professionalisme og engagement fra alle involverede parter. Det har sikret, at patienter har kunnet modtage behandling siden marts i år.

I det tilsendte vurderingsudkast omtales den aktuelle ansøgning som en "fremrykning" til 2L og 3L. Vi anerkender, at behandlingen i praksis gradvist kan tages i brug tidligere og dermed opfattes som en fremrykning. Samtidig vil vi gerne fremhæve, at der formelt er tale om en indikationsudvidelse, og at patientpopulationen i CARTITUDE-4 adskiller sig væsentligt fra den i CARTITUDE-1 og er mindre restriktiv.

De usikkerheder, der tidligere var forbundet med det enkeltarmede CARTITUDE-1, er nu i høj grad reduceret med data fra det randomiserede fase 3-studie CARTITUDE-4 (n > 400), som dokumenterer statistisk signifikant forbedring i både PFS og OS. Som Medicinrådets analyser viser, er cilta-cel forbundet med en betydelig sundhedsgevinst målt i QALY.

Som det også fremgår af Medicinrådets udkast, findes ikke studier, der belyser effekten af at "flytte" behandling fra 4L til 2L/3L. Vi finder, at det er metodisk problematisk at inkludere 4L-patienter i vurderingen. Effekt, sikkerhed og den tilhørende modellering er baseret på 2L/3L-patienter, og det skal understreges, at patienter ikke vil blive genbehandlet med cilta-cel. Der vil med stor sandsynlighed fortsat være patienter, som først får cilta-cel i fjerde linje, selv efter en udvidelse til anden og tredje linje som følge af et gradvist stigende markedsoptag.

## Patientestimat og vurdering af budgetkonsekvenser

Det er afgørende, at vurderingen af cilta-cel hviler på et beslutningsgrundlag, der afspejler den kliniske virkelighed. Estimaterne bør tage højde for den faktiske kapacitet, den gradvise opskalering og de kliniske forhold, herunder, at CAR-T-behandling også anvendes til andre patientgrupper end multipel myelom.

Erfaringer fra 4L-implementeringen i Danmark viser, at opskalering sker gradvist og afhænger af både kapacitet og klinisk praksis. Det samme billede ses internationalt: I Belgien vurderes under halvdelen af patienterne i 2L–5L som egnede til CAR-T; i Frankrig har 71 % ECOG 0–1; og i Tyskland skelnes eksplicit mellem 2L–4L og 5L+ populationer uden antagelser om fuld opskalering. Det understreger, at ikke alle patienter med lenalidomid-refraktaritet er kandidater til CAR-T, og at implementeringen afhænger af lokale forhold.

På den baggrund stiller vi spørgsmålstegn ved det patientestimat, der ligger til grund for budgetanalysen – særligt fordi det inkluderer patienter, der allerede behandles i dag i 4L og hvor sundhedsvæsenet dækker omkostningerne, og fordi der antages fuld opskalering allerede fra år 1. Det vurderer vi ikke som realistisk.

Hertil kommer, at en betydelig andel af patienterne vil indgå i kliniske studier, hvor behandlingen gives uden omkostninger – bl.a. QUINTESSENTIAL (arlo-cel) og MAJESTEC (tec ± daratumumab), som begge kører på flere danske afdelinger. Blenrep er desuden under vurdering i Medicinrådet og relevant for samme population. Samtidig vil anbefalingen af DaraLenDex i 1L fra maj 2025 medføre længere remissioner og dermed færre patienter i 2L over tid.

Disse forhold bør indtænkes for at undgå overestimering og afledt utilsigtet begrænsning af patientadgang.

Skulle det – mod vores forventning – vise sig, at op til 145 patienter skal behandles årligt, kan vi fra virksomhedens side garantere den nødvendige kapacitet og levering.

## Fra pris til praksis

[redacted]

Cilta-cel er en kompleks og højtspecialiseret [redacted] Vi står fortsat klar med støtte til implementering, herunder logistik, klinisk support og garanteret leveringstid på niveau med eller hurtigere end i kliniske studier.

[redacted] Vi lever dermed op til Medicinrådets krav om dokumentation og ser dette som en model for ansvarlig introduktion af avanceret behandling.

Der er tale om en omlægning af ressourcer og en investering der falder tidligt. Vores forventning er, at patienter, der behandles med cilta-cel med én infusion, opnår en dyb og langvarig respons over mange år – uden at belaste sundhedsvæsenets ressourcer.

Som inspiration kan nævnes de norske retningslinjer (Handlingsprogram for myelomatose, maj 2025), hvor en trinvis tilgang anbefales – med udgangspunkt i de mest robuste patienter – som en pragmatisk løsning under kapacitetsopbygning. En trinvis tilgang, hvor man starter med de mest robuste patienter, kan være en pragmatisk løsning, indtil eventuelle kapacitetsudfordringerne er håndteret.

Behandling med cilta-cel er allerede i dag på Rigshospitalet, Aarhus Universitetshospital og Odense. [redacted]

Vi ser frem til at sagen behandles på rådsmødet den 24. september 2025, og står naturligvis til rådighed for eventuelle spørgsmål eller behov for suplerende oplysninger.

**Bilag**

[redacted]

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DBS/LSC

# Forhandlingsnotat

| | |
|---|---|
| Dato for behandling i Medicinrådet | 24.09.2025 |
| Leverandør | Johnson & Johnson |
| Lægemiddel | Carvykti (ciltacabtagene autoleucel) |
| Ansøgt indikation | Behandling af patienter med recidiverende og refraktær knoglemarvskræft, som har fået mindst 1 tidligere behandlingslinje, herunder et immunmodulerende middel og en proteasomhæmmer, har udvist sygdomsprogression under den sidste behandlingslinje og er refraktære overfor lenalidomid. |
| Nyt lægemiddel / indikationsudvidelse | Indikationsudvidelse (CAR-T) |

## Prisinformation

Amgros har tidligere forhandlet pris på Carvykti (ciltacabtagene autoleucel).
[redacted].

*Tabel 1: Forhandlingsresultat*

| Lægemiddel | Styrke (paknings-størrelse) | AIP (DKK) | Nuværende SAIP, (DKK) | Forhandlet rabat ift. AIP |
|---|---|---|---|---|
| Carvykti | CAR-positive T-celler, 1 stk. | 2.931.194,45 | [redacted] | [redacted] |

[redacted]

## Aftaleforhold

[redacted]

## Informationer fra forhandlingen

[redacted]

## Konkurrencesituationen

Der findes flere behandlingsalternativer til patientgruppen, og der er flere nye behandlinger under vurdering i Medicinrådet. Carvykti er dog på nuværende tidspunkt den eneste CAR-T behandling til knoglemarvskræft, som har været vurderet i Medicinrådet. Abecma (idecabtagene vicleucel) har indikation til patienter med knoglemarvskræft, som har fået mindst to tidligere behandlingslinjer, men leverandøren har ikke anmodet om vurdering i Medicinrådet.

Ifølge Medicinrådets behandlingsvejledning for knoglemarvskræft anbefales følgende behandlinger i 2. linje:

- DaraLenDex: Daratumumab (Darzalex) + lenalidomid + dexamethason
- DaraBorDex: Daratumumab (Darzalex) + bortezomib + dexamethason
- EloLenDex/CarLenDex: Elotuzumab (Empliciti) *eller* carfilzomib (Kyprolis) + lenalidomid + dexamethason

Ifølge Medicinrådets behandlingsvejledning for knoglemarvskræft anbefales følgende behandlinger i 3. linje:

- PomBorDex: pomalidomid + bortezomib + dexamethason
- CarDex: carfilzomib (Kyprolis) + dexamethason
- PomDex: pomalidomid + dexamethason

Tabel 2 viser lægemiddeludgiften i første år for Carvykti i relation til DaraBorDex, PomBorDex og CarDex, da det er disse behandlinger, der er medtaget i Medicinrådets vurdering af Carvykti til knoglemarvskræft i 2./3. linje. Det skal bemærkes, at Carvykti er en engangsbehandling, hvorfor det kan være svært at sammenligne med lægemiddeludgiften for DaraBorDex, PomBorDex og CarDex der gives i længere tid.

*Tabel 2: Sammenligning af lægemiddeludgifter pr. patient*

| Lægemiddel | Styrke (pakningsstørrelse) | Dosering | Pris pr. pakning (SAIP, DKK) | Lægemiddeludgift pr. år (SAIP, DKK) |
|---|---|---|---|---|
| Carvykti | 1 stk. | Engangsbehandling | [redacted] | [redacted] |
| DaraBorDex | | | | [redacted] |

| | | | | |
|---|---|---|---|---|
| Darzalex | 1.800 mg, 1 stk. hætteglas | 1800 mg (s.c.) én gang ugentligt i de første 9 uger, derefter hver 3. uge i 15 uger, og herefter én gang hver 4. uge. | [redacted] | [redacted] |
| Bortezomib "Stada"* | 2,5 mg/ml, 1,4 ml. hætteglas | 1,3 mg/m$^2$ (i.v.) dagligt på dag 1, 4, 8 og 11 i 8 cyklusser. | [redacted] | [redacted] |
| Dexamethason "Abcur" | 1 mg, 20 stk. tabletter | 20 mg (PO) på dag 1, 2, 4, 5, 8, 9, 11 og 12 i 8 cyklusser. | [redacted] | [redacted] |
| PomBorDex | | | | [redacted] |
| Pomalidomid "Sandoz" | 4 mg, 21 stk. kapsler | 4 mg (PO) én gang dagligt på dag 1 til 14, efterfulgt af en uges pause. | [redacted] | [redacted] |
| Bortezomib "Stada"* | 2,5 mg/ml, 1,4 ml. hætteglas | 1,3 mg/m$^2$ (i.v.) dagligt på dag 1, 4, 8 og 11 i cyklus 1-8, og derefter på dag 1 og 8 i de efterfølgende cyklusser. | [redacted] | [redacted] |
| Dexamethason "Abcur" | 1 mg, 20 stk. tabletter | 20 mg (PO) på dag 1, 2, 4, 5, 8, 9, 11 og 12 i cyklus 1-8, og derefter på dag 1, 2, 8 og 9 i de følgende cyklusser. | [redacted] | [redacted] |
| CarDex | | | | [redacted] |
| Kyprolis | 30 mg, 1 stk. hætteglas | 20 mg/m$^2$ (i.v.) på dag 1, 2, og derefter 56 mg/m$^2$ på dag 8, 9, 15 og 16, og efterfølgende cyklusser | [redacted] | [redacted] |
| Dexamethason "Abcur" | 1 mg, 20 stk. tabletter | 20 mg (PO) på dag 1, 2, 8, 9, 15 og 16 | [redacted] | [redacted] |

*BSA = 1,90 m2, baseret på CARTITUDE4-studiet

[redacted]

Tabel 3 viser lægemiddeludgiften på Carvykti i relation til andre CAR-T behandlinger der er anbefalet i Medicinrådet.

*Tabel 3: Sammenligning af lægemiddeludgifter pr. patient*

| Lægemiddel | Indikation | Pris pr. pakning (SAIP, DKK) | Lægemiddeludgift pr. behandling (SAIP, DKK) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Carvykti | Recidiverende og refraktær knoglemarvskræft | [redacted] | [redacted] |
| Kymriah | B-celle akut lymfatisk leukæmi (ALL) patienter ≤ 25 år | [redacted] | [redacted] |
| Breyanzi | Diffust storcellet B-celle lymfom (DLBCL) 2./3.linje | [redacted] | [redacted] |
| Yescarta | Diffust storcellet B-celle lymfom (DLBCL) 2./3.linje | [redacted] | [redacted] |

[redacted]

## Status fra andre lande

*Tabel 4: Status fra andre lande*

| Land | Status | Link |
|---|---|---|
| **Norge** | Under vurdering | Link til status |
| **England** | Ikke ansøgt | |
| **Sverige** | Anbefalet | Link til anbefaling |

## Opsummering

[redacted]

[redacted]

# Application for the assessment of Carvykti® (ciltacabtagene autoleucel) for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide

| Color of highlighted text | Definition of highlighted text |
| --- | --- |
| | Confidential information |

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# Tables and Figures

# Abbreviations

| Abbreviation | Explanation |
|---|---|
| **1L** | First line |
| **2L** | Second line |
| **3L** | Third line |
| **AE** | Adverse event |
| **AIC** | Akaike information criterion |
| **ANC** | Absolute neutrophil count |
| **ATC** | Average treatment effect in the control |
| **ATT** | Average treatment effect in the treated |
| **BCMA** | B-cell maturation antigen |
| **BIC** | Bayesian information criterion |
| **BICR** | Blinded Independent Central Review |
| **CAR-T** | Chimeric Antigen Receptor T-cell |
| **CD38** | Antigen 38 |
| **CHMP** | Committee for Medicinal Products for Human use |

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|---|---|
| **CI** | Confidence interval |
| **Cilta-cel** | Ciltacabtagene autoleucel |
| **COMP** | For orphan medicinal products |
| **CR** | Complete response |
| **CRS** | Cytokine Release Syndrome |
| **DCO** | Data cut-off |
| **DKK** | Danish krone |
| **dL** | Decilitre |
| **DKd** | Daratumumab + carfilzomib + dexamethasone |
| **DMSG** | Danske Multidisciplinære Cancer Gruppe |
| **DPd** | Daratumumab + pomalidomide + dexamethasone |
| **DRd** | Daratumumab + lenalidomide + dexamethasone |
| **DRG** | Diagnosis-Related Group |
| **DVd** | Daratumumab + bortezomib + dexamethasone |
| **ECOG** | Eastern cooperative oncology group |
| **EMA** | European medicines agency |
| **EORTC** | European Organisation for Research and Treatment of Cancer |
| **EQ-5D-5L** | EuroQol 5-Dimensions 5-Levels |
| **HRQoL** | Health related quality of life |
| **HR** | Hazard ratio |
| **HSUV** | Health state utility values |
| **ICER** | Incremental cost-effectiveness ratio |
| **IMWG** | International Myeloma Working Group |
| **IMiD** | Immunomodulatory drug |

| | |
|---|---|
| **IPD** | Individual patient data |
| **IPTW** | Inverse probability of treatment weighting |
| **ISS** | International staging system |
| **IgG** | Immunoglobin G |
| **IgA** | Immunoglobin A |
| **ITC** | Indirect treatment comparison |
| **ITT** | Intention to treat |
| **IV** | Intravenous |
| **IVIG** | Intravenous immunoglobulin |
| **JNHB** | Joint Nordic assessment |
| **Kd** | Carfilzomib + dexamethasone |
| **KDd** | Carfilzomib + daratumumab + dexamethasone |
| **Kg** | Kilogram |
| **KM** | Kaplan Meier |
| **L** | Liter |
| **LOT** | Line of therapy |
| **LY** | Life years |
| **$m^2$** | Square meter |
| **mg** | Milligram |
| **MGUS** | Gammopathy of undetermined significance |
| **ml** | Millilitre |
| **MM** | Multiple myeloma |
| **MMRM** | Mixed-model repeated measures |
| **MRD** | Minimal residual disease |
| **MySIm-Q** | Myeloma Symptom and Impact Questionnaire |

| | |
|---|---|
| **NICE** | National Institute for Health and Care Excellence |
| **NICE DSU** | National Institute for Health and Care Excellence Decision Support Unit |
| **NA** | Not applicable |
| **NR** | Not reported |
| **OOS** | Out-of-specification |
| **OR** | Odds ratio |
| **ORR** | Overall response rate |
| **OS** | Overall survival |
| **PC** | Physician's choice |
| **Pd** | Pomalidomide + dexamethasone |
| **PD** | Progressed disease |
| **PF** | Progression free |
| **PFS** | Progression free survival |
| **PFS2** | Progression free survival on next line of therapy |
| **PGIS** | Patient Global Impression of Severity |
| **PI** | Proteasome inhibitor |
| **PL** | Prior lines |
| **PO** | Per oral |
| **PPS** | Post progression state |
| **PR** | Partial response |
| **PRO** | Patient reported outcome |
| **PRO-CTCAE** | Patient reported Outcomes version of the Common Terminology Criteria for Adverse Events |
| **PSA** | Probabilistic sensitivity analysis |

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|---|---|
| **PSM** | Partitioned survival model |
| **PVd** | Pomalidomide + bortezomib + dexamethasone |
| **QALY** | Quality adjusted Life Year |
| **R** | Lenalidomide |
| **RRMM** | Refractory multiple myeloma |
| **RRs** | Response rate ratios |
| **Rd** | Lenalidomide + dexamethasone |
| **SAEs** | Serious adverse events |
| **SC** | Subcutaneous injection |
| **sCR** | Stringent complete response rate |
| **SD** | Standard deviation |
| **SE** | Standard error |
| **sIPTW-ATT** | Stabilized Inverse Probability of Treatment Weighting for the Average Treatment effect on the Treated |
| **SMD** | Standardized mean difference |
| **SmPC** | Summary of product characteristics |
| **TEAE** | Treatment emergent adverse event |
| **TTNT** | Time to next treatment |
| **ULN** | Upper limit of normal. |
| **V** | Bortezomib |
| **VGPR** | Very good partial response |
| **VRd** | Bortezomib + lenalidomide + dexamethasone |
| **mg** | milligram |

# 1. Regulatory information on the medicine

| Overview of the medicine | |
|---|---|
| **Proprietary name** | Carvykti® |
| **Generic name** | Ciltacabtagene-autoleucel (cilta-cel) |
| **Therapeutic indication as defined by EMA** | Cilta-cel is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least one prior therapy, including an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI), have demonstrated disease progression on the last therapy, and are refractory to lenalidomide. |
| **Marketing authorization holder in Denmark** | Janssen-Cilag International NV; a company of Johnson & Johnson |
| **ATC code** | L01XL05 |
| **Combination therapy and/or co-medication** | Pre-treatment with a lymphodepleting regimen before treatment with cilta-cel |
| **(Expected) Date of EC approval** | The indication expansion was approved on 19 April 2024 [1] |
| **Has the medicine received a conditional marketing authorization?** | No. Carvykti® received a conditional marketing authorization valid throughout the EU on 25 May 2022. This was switched to a full standard marketing authorization on 19 April 2024 [1] |
| **Accelerated assessment in the European Medicines Agency (EMA)** | N/A |
| **Orphan drug designation (include date)** | Yes, on 28 February 2020, orphan designation EU/3/20/2252 was granted for cilta-cel [2]. On 27 February 2024, the Committee for Orphan Medicinal Products (COMP) concluded that the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated orphan medicinal product for cilta-cel with a maintained orphan designation [3]. |
| **Other therapeutic indications approved by EMA** | Cilta-cel was first approved in EU for the indication: treatment of adult patients with relapsed and refractory multiple myeloma MM (RRMM) who have received at least three prior therapies, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy [4, 5] |
| **Other indications that have been evaluated by the DMC (yes/no)** | Yes, cilta-cel was assessed and recommended by the DMC for the first approved indication of adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI and |

| | |
|---|---|
| | an anti-CD38 antibody and have demonstrated disease progression on the last therapy [6, 7]. |
| **Joint Nordic assessment (JNHB)** | No. Due to different approvals in the separate national medical councils the standard of care in not the same in the Nordics. As a result, cilta-cel is not suitable for a JNHB. Cilta-cel is currently under separate assessment in each Nordic country. |
| **Dispensing group** | BEGR |
| **Packaging – types, sizes/number of units and concentrations** | The medicinal product is packaged in one infusion bag. Cilta-cel $3.2 \times 10^6 – 1 \times 10^8$ cells dispersion for infusion. An infusion bag contains 30 mL or 70 mL of dispersion for infusion [8] |

# 2. Summary table

| Summary | |
|---|---|
| **Indication relevant for the assessment** | According to the EMA indication extension: Cilta-cel is indicated for the treatment of adult patients with RRMM, who have received at least one prior therapy, including an IMiD and a PI, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide |
| **Dosage regiment and administration** | Cilta-cel is intended for autologous use and for intravenous use only. The target dose is 0.75 x $10^6$ CAR-positive viable T cells/kg of body weight (not exceeding 1 × $10^8$ CAR-positive viable T cells) [8].<br>• Patients 100 kg and below: 0.5 - 1 x $10^6$ CAR-positive viable T cells/kg body weight.<br>• Patients above 100 kg: 0.5 - 1 x $10^8$ CAR-positive viable T cells (non-weight based).<br>***Pre-treatment (lymphodepleting regimen):*** A lymphodepleting regimen of cyclophosphamide 300 mg/$m^2$ intravenous and fludarabine 30 mg/$m^2$ intravenous should be administered daily for 3 days. Cilta-cel infusion should be administered 5 to 7 days after the start of the lymphodepleting regimen. [8].<br>***Premedication:*** The following pre-infusion medications should be administered to all patients 30 to 60 minutes before cilta-cel infusion [8]:<br>• Antipyretic (oral or intravenous paracetamol 650 to 1,000 mg).<br>• Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent). |

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|---|---|
| | The use of prophylactic systemic corticosteroids should be avoided as it may interfere with the activity of cilta-cel [8].<br><br>***Bridging therapy:*** Consider bridging therapy according to prescriber's choice prior to infusion with cilta-cel to reduce tumour burden or stabilise the disease [8] |
| **Choice of comparator** | Physician's choice (PC) of DVd or PVd. Kd is tested in a scenario |
| **Prognosis with current treatment (comparator)** | Estimating the prognosis for the target patient population of PI-exposed and lenalidomide-refractory MM patients with at least one prior line of therapy receiving PC is challenging, as no data for this population are available for Denmark. However, prognosis has been shown to worsen with each progressive line of therapy, with poorer survival outcomes and limited treatment options [9]. Patients with lenalidomide refractory MM have an estimated OS of just 14.7 months following lenalidomide failure after a median of two prior LOT [10]. With currently available or recommended treatments, the median PFS for patients with lenalidomide-refractory MM is less than 10 months [11]. |
| **Type of evidence for the clinical evaluation** | Head-to-head study: CARTITUDE-4 (NCT04181827), an ongoing, Phase 3, open-label, multicentre clinical trial investigating cilta-cel in the treatment of relapsed and lenalidomide-refractory MM.<br><br>Efficacy data from an indirect comparison (ITC) is used for a scenario analysis with carfilzomib and dexamethasone (Kd) as a comparator, based on individual patient data (IPD) from CARTITUDE-4 (for cilta-cel) and CANDOR (for Kd) |
| **Most important efficacy endpoints (Difference/gain compared to comparator)** | Results for key efficacy endpoints from CARTITUDE-4 data cut-off (DCO) 01 May, 2024:<br><br>Median PFS was 11.8 months (95% CI: 9.66, 14.00) for the PC arm and not reached for the cilta-cel arm NE (95% CI: 34.50, NE), HR 0.29 (95% CI: 0.22, 0.39, p<0.0001).<br><br>Median OS was not reached for the PC arm (95% CI: 37.75, NE) or the cilta-cel arm NE (95% CI: NE,NE), HR 0.55 (95% CI: 0.39, 0.79), p-value 0.0009<br><br>The overall MRD negativity rate, defined as the proportion of participants with MRD-negative status (as $10^{-5}$), was 39 (18.5%) (95% CI: 13.5%, 24.4%) for the PC arm and 129 (62.0%) (95% CI: 55.0%, 68.6%) for cilta-cel arm, OR 7.6 (95% CI: 4.8, 12.0), p-value <0.0001. |
| **Most important serious adverse events for the intervention and comparator** | In the safety analysis set (n=208 each for PC and cilta-cel arm), from CARTITUDE-4, DCO 01 May 2024, serious TEAEs were reported for 47.1% of participants in both arms. Pneumonia (PC arm: 6.7%; cilta-cel arm: 3.8%) and |

| | |
|---|---|
| | COVID-19 pneumonia (PC arm: 5.8%, cilta-cel arm: 5.8%) were the only AEs that meet the threshold of serious TEAEs for ≥5% of participants, in either treatment arm. |
| **Impact on health-related quality of life** | Clinical documentation: EQ-5D-5L data was collected in CARTITUDE-4. The EQ-5D-5L index scores from CARTITUDE-4 were used as utility weights in the health economic analysis, which were derived using Danish specific preference weights. Mean values (95%CI): PF = 0.8575 (0.8449, 0.8653), PD = 0.7954 (0.7643, 0.8265).<br><br>Health economic model: The health economic model uses health state specific utilities for progression free and progressed disease and a separate calculation related to adverse events disutilities. |
| **Type of economic analysis that is submitted** | Cost-utility analysis using a partitioned survival model (PSM) |
| **Data sources used to model the clinical effects** | Base case analysis: Direct evidence from CARTITUDE-4 (NCT04181827) for cilta-cel versus PC.<br><br>Scenario analysis: An ITC using IPD from CARTITUDE-4 (for cilta-cel) and CANDOR (for Kd) |
| **Data sources used to model the health-related quality of life** | In the health economic model, EQ-5D-5L data from CARTITUDE-4 was used for deriving health state specific utilities for progression free and progressed disease, using Danish specific preference weights. |
| **Life years gained** | 4.60 years |
| **QALYs gained** | 3.85 QALY |
| **Incremental costs** | DKK 767,708 |
| **ICER (DKK/QALY)** | DKK 199,393/QALY |
| **Uncertainty associated with the ICER estimate** | The parameter that had the most influence on ICER was model time horizon. Other parameters that effected the ICER was weekly subsequent therapy costs for PC, discount rate of QALYs and duration of subsequent treatment for PC. |
| **Number of eligible patients in Denmark** | Out of 140 with RRMM who progress to 2L and are both bortezomib-exposed and lenalidomide-refractory, 70 are expected to be eligible for CAR-T per year. A gradual increase of treated patients from years 1 to 4 is anticipated. |
| **Budget impact (in year 5)** | The budget impact of implementing cilta-cel was [redacted] DKK at year five |

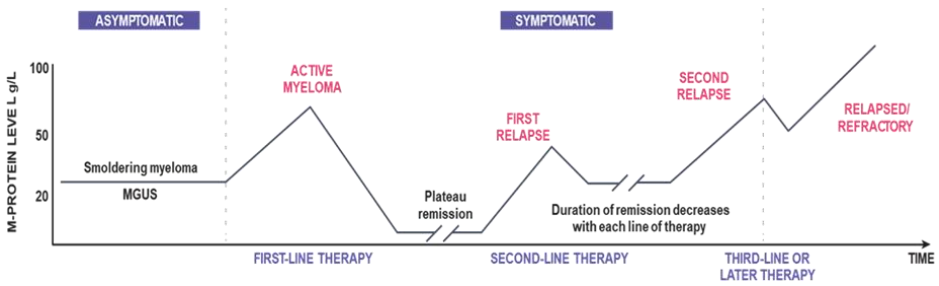
# 3. The patient population, intervention, choice of comparator(s) and relevant outcomes

## 3.1 The medical condition

Multiple Myeloma (MM) is a rare and genetically complex haematological cancer [12]. The disease initiates in plasma cells, a type of white blood cell responsible for producing antibodies (immunoglobulins). Due to MM being a clonal malignancy, it arises when a single plasma cell undergoes an oncogenic event that leads to its over-proliferation. This results in an abnormally high number of plasma cell clones in the bone marrow, leaving less space for healthy cells and interfering with the production of other blood cells, such as red blood cells and platelets. The expansion of malignant plasma cells in the bone marrow and the increasing levels of M protein in plasma and/or urine can lead to bone lesions, increased susceptibility to infections, anaemia, hypercalcemia, and renal insufficiency [12]. Patients with symptomatic MM can eventually develop plasma cell leukaemia, an advanced disease stage that is characterised by the presence of extramedullary clones (tumour sites established outside of the bone marrow) and rapid progression to death [13].

Due to its heterogeneity, MM can follow a different clinical course in each patient. Over time, patients typically experience worsening responses to treatment, characterised by shorter duration and shallower depth of response, faster disease progression, and poorer survival outcomes with each successive line of therapy (LOT). Most patients eventually become refractory to treatment (Figure 1) [14-16]. In a chart review study of MM patients conducted across seven European countries, the median duration of therapy, treatment-free interval, time to progression, and depth of response all decreased with each additional LOT [15].

**Figure 1 Trajectory of MM and RRMM—cycles of response, remission, and relapse in the presence of treatment and clonal evolution**



Abbreviations: MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; RRMM=relapsed or refractory multiple myeloma. Source: Kurtin, S., et al. [14]

Patients with newly diagnosed multiple myeloma are split into two distinct groups: eligible or ineligible for high-dose chemotherapy and autologous stem cell transplantation [17]. When the disease progresses after or during the first LOT, it is termed relapsed refractory multiple myeloma (RRMM) [18].

Most patients will experience disease relapse, and the disease will gradually become refractory to the different antimyeloma drugs. This phenomenon is driven mainly by genetic heterogeneity and clonal evolution [18]. This makes RRMM increasingly challenging to treat, where each relapse is associated with reduced response, requiring the development of treatments with new mechanisms of action.

The prognosis of MM is dependent on several factors, including intrinsic tumour cell characteristics (cytogenetic abnormalities), tumour burden (stage), patient characteristics (age, comorbidities, frailty), and response to therapy [19, 20].

The five-year survival rate for Danish patients with MM has improved significantly over time. However, prognosis remains poor, with 54% of patients alive at five years [21]. Estimating the prognosis for the target patient population of PI-exposed and lenalidomide-refractory MM patients with at least one prior line of therapy is challenging, as there is no available survival data for this specific population for Denmark.

The prognosis of survival has shown to worsen with each treatment line, and the number of available treatment options becomes increasingly limited [15]. Patients with lenalidomide-refractory MM have an estimated OS of just 14.7 months following lenalidomide failure (after having received a median of two prior lines of therapy) [10]. With currently available or recommended treatments, median PFS in the lenalidomide refractory setting is less than 10 months [22].

MM has historically been associated with the lowest patient health-related quality of life (HRQoL) of all haematological cancers [23]. It has been shown that patient well-being declines with disease duration, progression, and line of treatment [24-29]. Patients with relapsed MM have worse HRQoL than those in a treatment-free interval [24, 28, 30], as well as relative to individuals in the general population [31, 32] and patients with other cancer types [31, 33]. In addition, after treatment failure, patients may experience feelings of hopelessness about further treatment options and their future [34].

## 3.2 Patient population

The relevant population in this assessment includes adult Danish patients with RRMM who have received at least one prior therapy, including an IMiD and a PI, have demonstrated disease progression on their last therapy, and are refractory to lenalidomide. The relevant population is aligned with the population in the pivotal trial, CARTITUDE-4 [35].

Since 2018, the incidence of MM in Denmark has remained stable at approximately 350 new cases per year. However, the prevalence has increased by 25% since 2018, rising to

around 2,000 cases in 2021. The estimated incidence and prevalence rates of MM in Denmark over the past five years are presented in Table 1 [36].

Lenalidomide (R or Len), an IMiD, is commonly used as first-line therapy for the treatment of MM, often in combination with bortezomib (V or Bor), a PI[37, 38]. Thus, a high number of patients are exposed to both drugs early in their treatment course [37, 38]. Every year, 350 individuals begin 1L treatment for MM in Denmark. Of these, 234 will eventually experience disease relapse and move on to 2L therapy, while the remaining patients die before progression. As all patients with MM eventually experience disease relapse, the epidemiology of RRMM is assumed to be similar to that of MM [14].

Johnson & Johnson estimates that of the 234 patients progressing to 2L each year, 140 will be bortezomib-exposed and lenalidomide-refractory. This estimate includes the complete high-dose chemotherapy with autologous stem cell rescue cohort of younger patients, representing approximately one-third of the total patients (1/3 of 234; n=78). The estimate also covers two-thirds of elderly patients receiving bortezomib-lenalidomide-dexamethasone (VRd) or lenalidomide-dexamethasone (Rd), estimated to account for 40% (2/3 of 234 x 0.4; n=62). Among these 140 patients, Johnson & Johnson estimates that 70% of younger patients (n=55) and 25% of elderly patients (n=15) will be eligible for CAR-T treatment every year, resulting in 70 patients once treatment has been fully scaled up by year 4.

The estimated number of patients eligible for treatment with cilta-cel is shown in Table 2. These estimates reflect an increased number of patients treated from year 1 to year 4 but do not account for capacity and resource constraints, which may potentially reduce the number of patients treated. Additionally, patient estimates may vary based on the DMC's re-assessment of lenalidomide, potentially leading to fewer lenalidomide-refractory patients in 2L treatment but more in 3L, still totalling 70 patients.

**Table 1 Incidence and prevalence in the past 5 years**

| Year | 2019 | 2020 | 2021 | 2022 | 2023* |
|---|---|---|---|---|---|
| **Incidence in Denmark [36]** | 4.4/100,000 | 3.9/100,000 | 4.4/100,000 | 4.8/100,000 | 4.8/100,000 |
| **Prevalence in Denmark [36]** | 22.5/100,000 | 23.4/100,000 | 24.4/100,000 | 25.6/100,000 | 25.6/100,000 |

* Data for 2023 not available, assumed to be the same as for 2022

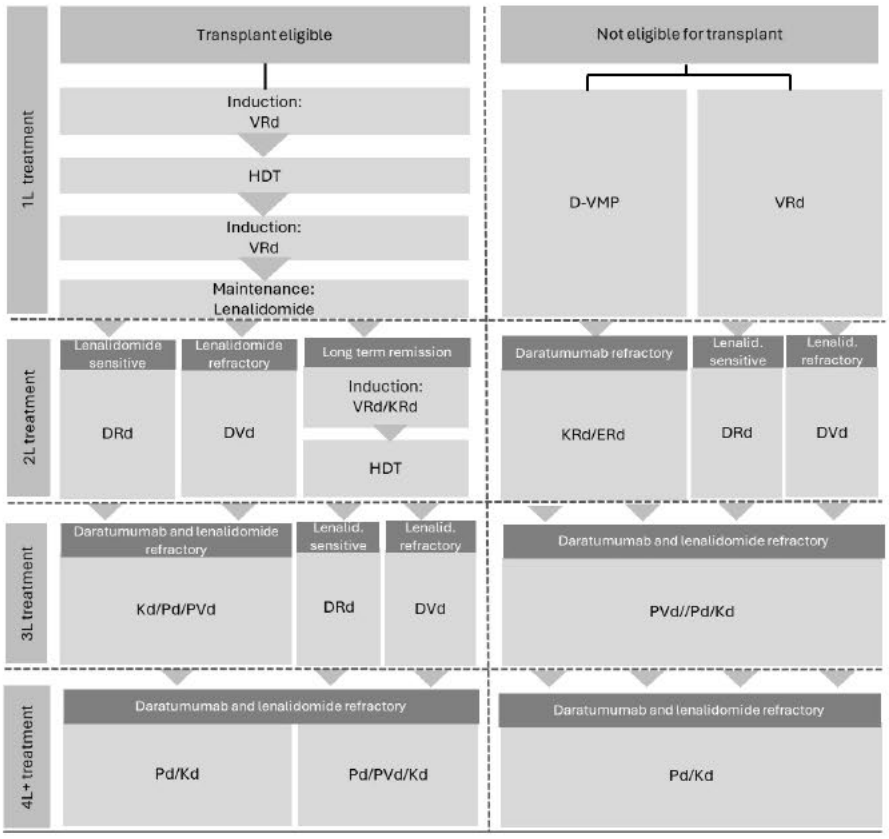
**Table 2 Estimated number of patients eligible for treatment**

| Year | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Number of patients in Denmark who are eligible for treatment in the coming years** | 6 | 40 | 55 | 70 | 70 |

## 3.3 Current treatment options

Figure 2 provides an overview of the MM treatment algorithm from the DMC treatment guideline, valid since 2022 and latest updated on 1st of January 2025 [39] The treatments recommended by DMC in 2L and later for patients who are lenalidomide refractory include daratumumab + bortezomib + dexamethasone (DVd or DaraBorDex), pomalidomide + bortezomib + dexamethasone (PVd or PomBorDex) and carfilzomib + dexamethasone (Kd or CarDex), and pomalidomide + dexamethasone (Pd or PomDex) [40]. The choice of treatment should be based on prior therapies, with no repeat treatment using the same therapy [40]. The "Danske Multidisciplinære Cancer Grupper" (DMSG) has also presented a treatment algorithm for relapsed MM, which closely aligns with the treatment recommendations given by the DMC [41].

**Figure 2 DMC treatment algorithm for newly diagnosed multiple myeloma**



Source: Adapted from DMC treatment algorithm [40]. Abbreviations: D-VMP= daratumumab + bortezomib + melphalan + prednisol, DVd=daratumumab; bortezomib, dexamethasone; DRd=daratumumab, lenalidomide, dexamethasone; ERd=elotuzumab, lenalidomide, dexamethasone; HDT=High-dose therapy with autologous stem-cell rescue; Kd=carfilzomib, dexamethasone; KRd=carfilzomib, lenalidomide, dexamethasone; Pd=pomalidomide, dexamethasone; PVd= Pomalidomide, bortezomib, dexamethasone; VRd= Bortezomib, lenalidomide, dexamethasone.

## 3.4 The intervention

An overview of the intervention is given below in Table 3.

**Table 3 Overview of Carvykti® (ciltacabtagene autoleucel)**

| Overview of intervention | |
|---|---|
| **Indication relevant for the assessment** | In line with the EMA indication: Adult patients with RRMM, who have received at least one prior therapy, including an IMiD and a PI, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide. |
| **ATMP** | Carvykti® (ciltacabtagene autoleucel, cilta-cel) is a BCMA-directed, genetically modified autologous T cell immunotherapy [42]. |
| **Method of administration** | IV |
| **Dosing** | The target dose is 0.75 x $10^6$ CAR-positive viable T cells/kg of body weight (not exceeding 1 × $10^8$ CAR-positive viable T cells) [42]. Patients 100 kg and below: 0.5 - 1 x $10^6$ CAR-positive viable T cells/kg body weight. Patients above 100 kg: 0.5 - 1 x $10^8$ CAR-positive viable T cells (non-weight based). |
| **Dosing in the health economic model (including relative dose intensity)** | As per dosing schedule [42]. The proportion receiving cilta-cel after apheresis is assumed to be 94.23% based on CARTITUDE-4. |
| **Should the medicine be administered with other medicines?** | Patients should receive pre-treatment (lymphodepleting regimen). Consists of cyclophosphamide 300 mg/$m^2$ intravenous and fludarabine 30 mg/$m^2$ intravenous should be administered daily for 3 days. Cilta-cel infusion should be administered 5 to 7 days after the start of the lymphodepleting regimen. In addition, pre-infusion medications should be administered to all patients 30 to 60 minutes before cilta-cel infusion [42]: Antipyretic (oral or intravenous paracetamol 650 to 1,000 mg) and antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent). |

| | |
|---|---|
| | The use of prophylactic systemic corticosteroids should be avoided as it may interfere with the activity of cilta-cel [42]. |
| **Treatment duration / criteria for end of treatment** | A single infusion of treatment on day 5-7 following pre-treatment. |
| **Necessary monitoring, both during administration and during the treatment period** | Patients are monitored daily at a qualified clinic during treatment and for 14 days following treatment. An additional 14 days of periodic check-ups are required, during which patients need to stay in close proximity to the treatment site. |
| **Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?** | NA |
| **Package size(s)** | The medicinal product is packaged in one infusion bag. cilta-cel $3.2 \times 10^6 – 1 \times 10^8$ cells dispersion for infusion. An infusion bag contains 30 mL or 70 mL of dispersion for infusion [42]. |

### 3.4.1 Description of ATMP

Carvykti® (ciltacabtagene autoleucel, cilta-cel) is an anti-B cell maturation antigen (BCMA)-directed, genetically modified autologous T cell immunotherapy. It involves reprogramming a patient's T cells with a transgene that encodes a chimeric antigen receptor (CAR), enabling these cells to identify and eliminate cells expressing BCMA. BCMA is primarily found on the surface of malignant multiple myeloma B-lineage cells, late-stage B cells and plasma cells. The T-cells, transduced ex vivo, use a replication-incompetent lentiviral vector that encodes a BCMA.

## 3.5 Choice of comparator(s)

Due to the absence of a single standardised treatment for the trial patient population, the comparator to cilta-cel in the CARTITUDE-4 trial was physician's choice (PC) of PVd or DPd. The lack of standard treatment is reflected in the current treatment landscape in Denmark for the corresponding population, where cilta-cel may replace DVd, PVd, Pd, or Kd. In the second line of therapy, DVd is typically chosen, whereas in the third line, DVd, PVd, Pd, and Kd are all viable options. Treatment choice depends on the patient's age, overall health, prior therapies, toxicity profiles, comorbidities, and preferences. Consequently, all these combinations may be considered potential comparators.

Given the several potential comparators to cilta-cel for the current indication, feedback was obtained from the DMC expert committee. The expert committee identified DVd, PVd, and/or Kd as the most relevant comparators in this context (as per e-mail DMC/Johnson and Johnson October 8, 2024)]. The comparable efficacy of DVd and DPd [43] supported the use of PC from CARTITUDE-4 as the comparator in the base case of

the economic analysis, with the cost of DPd replaced by the cost of DVd to align with Danish clinical practice. This adjustment does not affect the relative effect used in the model, which remains consistent with the head-to-head comparison in CARTITUDE-4.

As a supportive clinical analysis, cilta-cel was compared to Kd, as recommended by the DMC. In the absence of direct head-to-head evidence, the relative efficacy was estimated through an indirect treatment comparison (ITC) using individual patient data (IPD) from CARTITUDE-4 and CANDOR [44]. However, because of the number of eligible patients from the Kd arm in the CANDOR trial the analysis cannot be limited to third line patients.

Table 1 presents the comparators selected for the health economic base case and scenario analysis.

**Table 4 Summary of comparators used in the health economic assessment**

| Scenario | Comparator | Efficacy source |
|---|---|---|
| **Base case** | Physician's choice of DVd (86.7%) or PVd (13.3%) | CARTITUDE-4 |
| **Scenario** | Kd | CARTITUDE-4 and CANDOR |

Table 5 below gives an overview of the respective comparator in the base case and scenario analysis.

**Table 5 Overview of comparators**

| Overview of comparator(s) | | | |
|---|---|---|---|
| **Generic name** | Pomalidomide+ bortezomib + dexamethasone (PVd/PomBorDex)[45-47] | Daratumumab + bortezomib + dexamethasone (DVd/ DaraBorDex) [45, 46, 48] | Carfilzomib + dexamethasone (Kd/CarDex)[47, 49] |
| **ATC code** | L04AX06+ L01XG01+ H02AB02 | L01FC01+ L01XG01+ H02AB02 | L01XG02+ H02AB02 |
| **Mechanism of action** | Bortezomib inhibits the proteasome, leading to cell cycle arrest and apoptosis, while pomalidomide inhibits tumour cell proliferation, induces apoptosis, enhances immune response, and blocks angiogenesis; | Daratumumab, a monoclonal antibody targeting the CD38 protein on MM cells, disrupts its biological functions. Bortezomib inhibits the proteasome, leading to cell cycle arrest and apoptosis. Together daratumumab and | Carfilzomib, a proteasome inhibitor that targets the 20S proteasome, delaying tumour growth in MM. Combined with dexamethasone, it enhances cell death, reduces drug resistance, and suppresses the |

| | | | |
|---|---|---|---|
| | together, they disrupt myeloma cell survival and synergize with dexamethasone to target lenalidomide-resistant cells. | bortezomib disrupt myeloma cell survival and synergize with dexamethasone to target lenalidomide-resistant cells. | inflammatory tumour environment. |
| **Method of administration** | Pomalidomide (PO), bortezomib (IV or SC), dexamethasone (PO) | Daratumumab (SC), bortezomib (IV or SC), dexamethasone (PO) | Carfilzomib (IV), dexamethasone (PO) |
| **Dosing** | Administered in 21-day cycles.<br><br>Pomalidomide (4 mg) taken once daily on days 1 to 14, followed by one week rest period.<br><br>Bortezomib (1.3 $mg/m^2$) administered daily on days 1, 4, 8 and 11 in cycle 1-8, thereafter on day 1 and 8 in following cycles.<br><br>Dexamethasone (20 mg) administered on the same days as bortezomib and the day after, i.e., taken on days 1, 2, 4, 5, 8, 9, 11 and 12 in cycle 1.8 and thereafter on days 1, 2, 8, and 9 in following cycles. | Administered in 21-day cycles.<br><br>Daratumumab (16mg/kg) administered once weekly for the first 9 weeks, thereafter every 3 weeks for 15 weeks, thereafter once every 4 weeks.<br><br>Bortezomib (1.3 mg/ $m^2$) administrated on days 1, 4, 8 and 11 for 8 cycles.<br><br>Dexamethasone (20 mg) taken on days 1, 2, 4, 5, 8, 9, 11 and 12 for 8 cycles. | Administered in 28-day cycles.<br><br>Carfilzomib administered on days 1, 2, 8, 9, 15 and 16 followed by a 12-rest period. Carfilzomib is administered at a starting dose of 20 $mg/m^2$ (maximum dose of 44 mg) on days 1 and 2 of cycle 1. If this dose is well-tolerated, it is increased to 56 $mg/m^2$ (maximum dose of 123 mg) starting on day 8 of cycle 1.<br><br>Dexamethasone (20 mg) administered twice weekly, on days 1, 2, 8, 9, 15, 16, 22 and 23. |
| **Dosing in the health economic model (including relative dose intensity)** | As per SmPC (see section 11.1) | As per SmPC (see section 11.1) | As per SmPC (see section 11.1) |
| **Should the medicine be administered with other medicines?** | Ciprofloxacin, enoxacin, and fluvoxamine can be given together with pomalidomide. If given, the dose of pomalidomide should be reduced by 50% [45]. | Pre-infusions of corticosteroid, paracetamol and diphenhydramine (or equivalent) should be administrated. Post-infusion of methylprednisolone (or equivalent) might be needed. | Antiviral prophylaxis and thromboprophylaxis can be given to patients being treated with carfilzomib in combination with dexamethasone. |

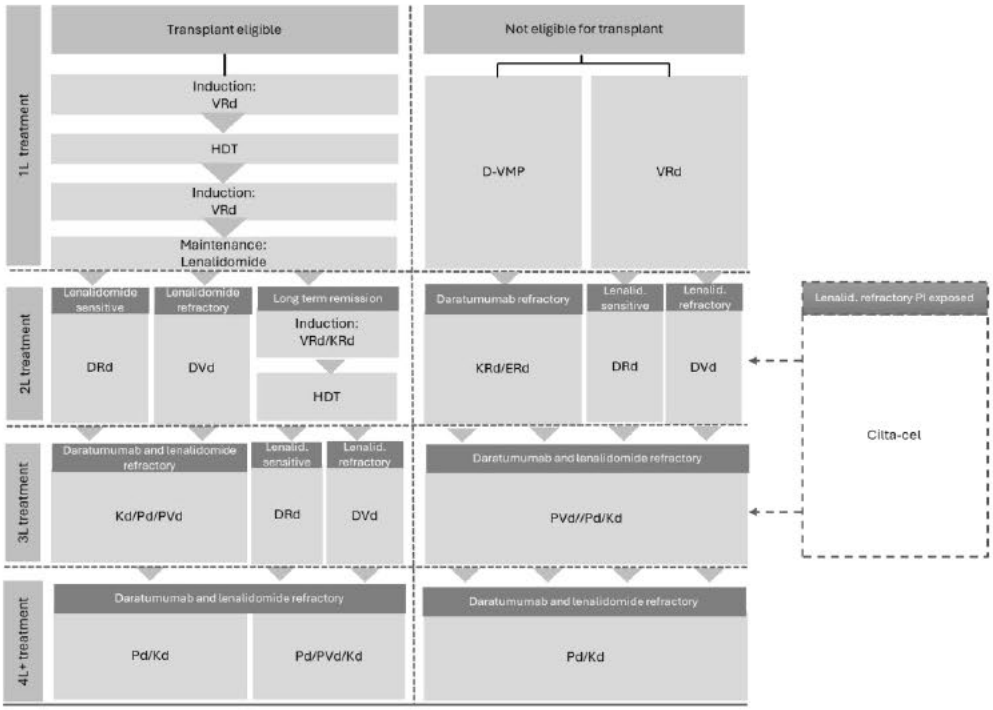
| | | | |
|---|---|---|---|
| **Treatment duration/ criteria for end of treatment** | A 21-day cycle. PFS is the main criteria for end of treatment and the secondary end of treatment is OS. | 21-days cycle for cycles 1 to 8 and then 28 days cycle. Treatment until progressed disease or unacceptable toxicity. | A 21-day cycle. Treatment for maximum 5 years, until progressed disease or unacceptable toxicity. |
| **Need for diagnostics or other tests (i.e. companion diagnostics)** | No | No | No |
| **Package size(s)** | Pomalidomide: 14 capsules of 4 mg each.<br>Bortezomib: One vial containing 3.5 mg of powder for solution for injection.<br>Dexamethasone: 100 tablets of 4 mg each. [50]. | Daratumumab: One vial of concentrate for solution for infusion of 20 mg/ml.<br>Bortezomib: One vial containing 3.5 mg of powder for solution for injection.<br>Dexamethasone: 100 tablets of 4 mg each [50]. | Carfilzomib: One vial containing 60 mg of powder for solution for infusion<br>Dexamethasone: 100 tablets of 4 mg each [50]. |

Abbreviations: Intravenous=IV, mg=milligram, PO=per oral, OS=overall survival, PFS=progression-free-survival, POM=pomalidomide, SC=subcutaneous injection, SmPC=summary of product characteristics.

### 3.5.1 The intervention in relation to Danish clinical practice

The current DMC treatment guideline, updated in January 2025, recommends DVd, Kd or a pomalidomide regimen, i.e., PVd or Pd, [39] in lenalidomide refractory RRMM [22] in 2L or later. For the specific targeted population within this application, only one regimen, DPd, has marketing authorisation in the EU, but is not recommended by the DMC [22]. The expected place in the current treatment algorithm is presented in Figure 3.

**Figure 3 Place in the current treatment algorithm**




Abbreviations: 1L=first line, 2L=second line, 3L=third line, cilta-cel= ciltacabtagene autoleucel, DRd= daratumumab + lenalidomide + dexamethasone, DVd=daratumumab + bortezomib + dexamethasone, D-VMP = daratumumab + bortezomib + melphalan + prednisol, ERd= elotuzumab +lenalidomide + dexamethasone, HDT= high dose therapy, Kd= carfilzomib + dexamethasone, lenalid= lenalidomide, Pd= pomalidomide + dexamethasone, PI= proteasome inhibitor, PVd= pomalidomide + bortezomib + dexamethasone, VRd=bortezomib + lenalidomide + dexamethasone.

## 3.6 Cost-effectiveness of the comparator(s)

The comparators, PC (PVd or DVd) in the base case and Kd in the scenario analysis, are all recommended by the DMC treatment guideline. They are considered standard of care in Denmark [39].

### 3.6.1 Definition of efficacy outcomes included in the application

In the base case analysis, cilta-cel is compared against PC. The efficacy outcomes of the intervention and base case comparators are all based on the CARTITUDE-4 trial. The relevant efficacy outcomes are presented in Table 6.

**Table 6 Efficacy outcome measures relevant for the application CARTITUDE-4 study**

| Outcome measure | Time point | Definition | How was the measure investigated/method of data collection |
|---|---|---|---|
| **Progression-free survival (PFS)**<br><br>**CARTITUDE-4** | Median follow-up of 33.6 months, | PFS is defined as the time from the date of randomisation to the date of first documented disease | Investigated and defined according to the IMWG criteria |

| | | | |
|---|---|---|---|
| | study up to 6 years. | progression, or death due to any cause, whichever occurs first. | |
| **Overall survival (OS)**<br><br>**CARTITUDE-4** | Median follow-up of 33.6 months, study up to 6 years. | OS is measured from the date of randomisation to the date of the participant's death. If the participant is alive or the vital status is unknown, then the participant's data will be censored at the date the participant was last known to be alive. | Investigated and defined according to the IMWG criteria |
| **Complete Response (CR) or Stringent Complete Response Rate (sCR)**<br><br>**CARTITUDE-4** | Median follow-up of 33.6 months, study up to 6 years. | The CR or sCR rate is the percentage of participants who achieve a CR or sCR response. | Investigated and defined according to the IMWG criteria |
| **Overall response rate (ORR)**<br><br>**CARTITUDE-4** | Median follow-up of 33.6 months, study up to 6 years. | ORR is the percentage of participants who achieve a partial response or better. | Investigated and defined according to the IMWG criteria |
| **Overall Minimal Residual Disease (MRD)** | Median follow-up of 33.6 months, study up to 6 years. | Overall MRD negativity the percentage of participants who achieve MRD negativity at any time after the date of randomisation before initiation of subsequent therapy. | Investigated and defined according to the IMWG criteria |

Abbreviations: CR = Complete response, IMWG = International Myeloma Working Group, MRD = Minimal residual disease, ORR = Overall response rate, OS = Overall survival, PFS = Progression-free survival, sCR = Stringent complete response rate.

**Validity of outcomes**

According to EMA best clinical practice [51], PFS and OS are considered valid outcomes in anti-cancer trials. ORR is commonly used as an endpoint to assess the clinical benefit of drug approvals [51]. According to the International Myeloma Working Group's (IMWG) definition, MRD is the persistence or re-emergence of very low levels of cancer cells in complete remission patients with about 1 tumour cell in at least $10^{-5}$ normal bone marrow cells [52]. The clinical implication of MRD (within both newly diagnosed MM and RRMM) has been recognized; sustained MRD after treatment indicates that the tumour cells are not entirely eradicated, and a relapse in the near future is expected. Studies

have shown that MRD negativity is a superior prognostic factor for both PFS and OS [53-55] recently also recognized by the FDA.

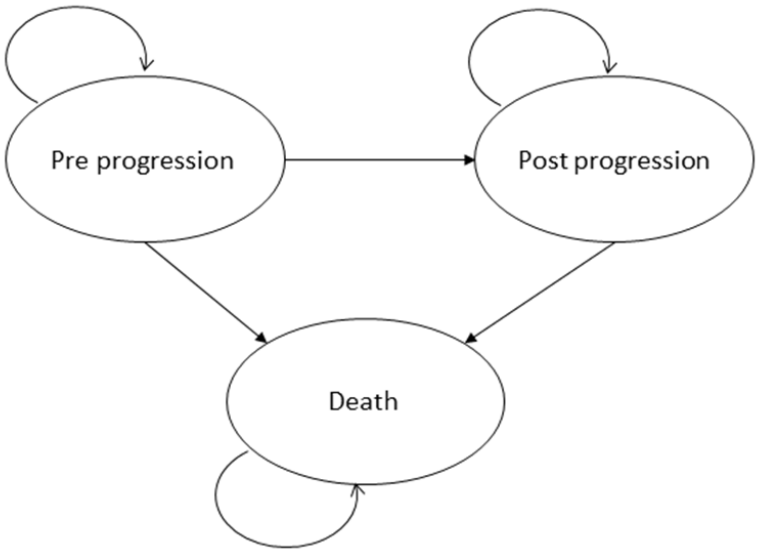
# 4. Health economic analysis

## 4.1 Model structure

A three-health state partitioned survival model (PSM) was developed. The health states progression-free (PF), post-progression/progressed (PD), and death represent the disease development (Figure 4). The model structure is consistent with previous models in RRMM, including models analysing CAR-T use in Denmark. Treatment-specific acquisition, administration, resource use, and AE costs are incurred as patients receive active therapy. The 'post-progression' state also captures costs associated with subsequent treatment. Each health state is related to a utility and disutility of AEs is captured in the first cycle of the model.

In a PSM, OS and PFS are modelled independently, and the proportions of patients in each health state over time are derived directly from the OS and PFS projections using an area-under-the-curve approach. The proportion of patients who are dead in each model cycle is estimated by one minus estimated survival, and the proportion of those in the post-progression state is estimated by the difference between OS and PFS projections.

**Figure 4 Model structure - partitioned survival model (PSM)**



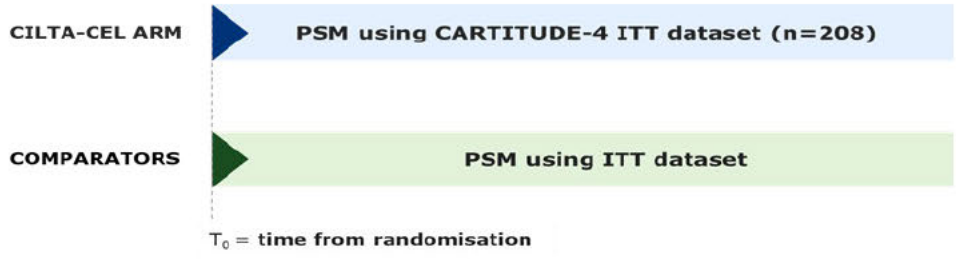

Abbreviations: OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model

All patients enrolled in CARTITUDE-4 were modelled as a single cohort, regardless of whether they received a cilta-cel infusion. This approach uses the CARTITUDE-4 intention-to-treat (ITT) efficacy data, which includes PFS and OS for all patients enrolled in CARTITUDE-4. Patients enter the PSM beginning at the time of randomisation for the

intervention and comparators. Time 0 is the point of apheresis for cilta-cel ITT data and the start of treatment for non-CAR-T arms (Figure 5).

Patients in the cilta-cel arm are assigned the costs of apheresis, bridging therapy, lymphodepleting-conditioning therapy and post-monitoring costs in addition to the CAR-T infusion costs (including drug acquisition and inpatient administration).

**Figure 5 Simple PSM model structure timeline and dataset where ITT dataset is used**




## 4.2 Model features

Table 7 presents a summary of the model features. The economic evaluation is based on a limited societal perspective with a time horizon of 40 years to capture costs and outcomes over a patient's lifetime. Given the mean starting age of 60 years in the population of interest, 40 years was considered to be adequate follow-up time for a lifetime analysis.

The cycle length selected for the model is one week, as this allows for capturing the varied dosing schedules of therapies included as a comparator. A half-cycle correction is applied to the calculation of costs and health effects accrued throughout each cycle to account for the transition of patients from one health state to another happening in a continuous process. This correction represents an average transition halfway through a cycle (i.e., not at the beginning or end of a cycle).

Following DMC guidelines costs and health effects were discounted at a rate of 3.5%. The discount rate does not consider different timing of health benefits and the costs of treatments like cilta-cel with high upfront cost and long-term benefits. This leads to a likely undervaluation of long-term benefits and potentially labelling effective therapies as less cost-effective [56] .The DMC's recent decision to apply a flat discount rate of 3.5% for all years rather than decreasing it after year 35 worsens this situation. Research shows that using differential discount rates for costs and benefits can more accurately reflect the long-term benefits, as implemented in e.g., Belgium (3% for cost and 1.5% for benefits), the Netherlands (4% for costs and 1.5% for benefit) and Poland (5% for costs and 3.5% for benefits) [57]. Johnson & Johnson would like to highlight the importance of scenario analyses on discount rates, as these analyses significantly influence the evaluation [56, 58] to ensure that ATMPs are not assessed unfairly compared to non-ATMP treatments.

**Table 7 Features of the economic model**

| Model features | Description | Justification |
|---|---|---|

| | | |
|---|---|---|
| Patient population | Adult patients with RRMM who have previously received 1–3 prior lines of therapy that included a PI and an IMiD and who are refractory to lenalidomide. | According to EMA indication (see also section 3.2) |
| Perspective | Limited societal perspective | According to DMC guidelines |
| Time horizon | Lifetime (40 years) | To capture all health benefits and costs in line with DMC guidelines.<br>Based on mean age at diagnosis/model starting age (60 years). |
| Cycle length | 1 week | This allows for capturing the varied dosing schedules of therapies included comparators. |
| Half-cycle correction | Yes | A half-cycle correction is applied to the costs and health effects, to account for the transition of patients from one health state to another happening in a continuous process, representing an average transition of halfway through a cycle (i.e., not at the beginning or end of a cycle). |
| Discount rate | 3.5 % | A discount rate of 3.5 % for cost and health effects for all years should be applied according to DMC guidelines, discount rate from and the Danish Ministry of Finance.<br>Different discounting (1.5% and 0%) for costs and benefits are tested in scenario |
| Intervention | Cilta-cel | According to CARTITUDE-4 and approved indication by EMA |
| Comparator(s) | DVd<br>PVd | According to DMC treatment guidelines for MM. |
| Outcomes | OS, PFS | PFS and OS, are used to calculate the time patients spend in each model health state, which ultimately drives the aggregated costs, LYs, and QALYs. |

# 5. Overview of literature

## 5.1 Literature used for the clinical assessment

The clinical efficacy and safety of cilta-cel and the base case comparators, PC, was based on the latest data cut-off (DCO) 01 May 2024 from the ongoing head-to head trial, CARTITUDE-4. CARTITUDE-4 is a phase 3, randomised, open-label, parallel, multicentre trial and the pivotal clinical trial for cilta-cel in this population, including adult patients with RRMM, who have received at least one prior therapy, including an IMiD and a PI, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide [59].

In the scenario analysis with Kd as a comparator, the clinical efficacy for cilta-cel and Kd was based on an ITC, using IPD from CARTITUDE-4 (cilta-cel) and CANDOR (Kd) [44] (see further Appendix C). A systematic literature review was not the basis for selecting efficacy sources for the ITC. The availability of IPD for both studies allowed for the matching of populations, resulting in a more robust comparison. The median follow-up for patients in CANDOR was 16.9 months (DCO: July 14, 2019) (Appendix C).

Table 8 below is an overview of the relevant literature used for the clinical assessment of efficacy and safety in the base case and scenario analysis.

**Table 8 Relevant literature included in the assessment of efficacy and safety**

| Reference | Trial name | NCT identifier | Dates of study | Used in comparison of |
|---|---|---|---|---|
| San-Miguel J, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med*. 2023;389(4):335-347 [60]<br><br>J&J Data on file (2024) Ciltacabtagene autoleucel ( Carvykti® A Phase 3 Randomized study comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide Refractory Multiple Myeloma [59] | CARTITUDE-4 | NCT04181827 | Start: 30/06/20<br><br>Data cut-off 01/11/22 and 01/05/24<br><br>Completion: Ongoing | Cilta-cel vs. PC of DVd and PVd |
| Usmani SZ, et al. (2023) Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study [44] | CANDOR | NCT03158688 | Start: 13/06/2017<br><br>Completion: 14/06/21 | Efficacy for Kd from CANDOR used in the ITC |
| J&J Data on file. (2024) Efficacy of Carvykti® in CARTITUDE-4 versus Other Conventional Treatment Regimens for Lenalidomide-Refractory Multiple Myeloma Using Inverse Probability of Treatment Weighting [61]. | CARTITUDE-4<br><br>CANDOR | NCT04181827<br><br>NCT02136134 | Data cut-off CARTITUDE-4: 01/05/24<br><br>Data cut-off CANDOR: 15/04/22 | ITC of cilta cel versus Kd (CANDOR) |

Abbreviations: DPd = daratumumab + pomalidomide + dexamethasone, DVd =daratumumab + bortezomib + dexamethasone, ECOG = Eastern Cooperative Oncology Group, IMiD = Immunomodulatory drug, Kd = carfilzomib + dexamethasone, KdD = carfilzomib + daratumumab + dexamethasone, PI = proteasome inhibitor, PVd = pomalidomide + bortezomib + dexamethasone, RRMM = relapsed and refractory multiple myeloma

## 5.2 Literature used for the assessment of health-related quality of life

Patient HRQoL was assessed in CARTITUDE-4 [62]. The index scores from the EuroQol Five Dimension Questionnaire (EQ-5D-5L) were used to derive Danish-specific health state utility values (HSUV) in patients with PF and PD. Utility decrements due to AEs were sourced from publications and previous HTA submissions, while the duration of the AE was based on the CARTITUDE-4 trial.

Table 9 below is an overview of the literature used for the assessment of HRQoL.

**Table 9 Relevant literature included for (documentation of) health-related quality of life (See section 10)**

| Reference | Health state/Disutility | Reference to where in the application the data is described/applied |
|---|---|---|
| Data on file. Unpublished data 2024: Utility from CARTITUDE-4 weighted for the Danish population [63]. | Progression-free: 0.858<br>Progressed disease: 0.795 | Section 10.2.3 |
| Howell, T. A., Matza, L. S., Jun, M. P., Garcia, J., Powers, A., & Maloney, D. G. (2022). Health State Utilities for Adverse Events Associated with Chimeric Antigen Receptor T-Cell Therapy in Large B-Cell Lymphoma. PharmacoEconomics - open, 6(3), 367–376. https://doi.org/10.1007/s41669-021-00316-0 [64] | CRS, Grade 1-2: -0.050<br>CRS, Grade 3+: -0.8575 | Section 10.2.3 |
| Assumed to be captured as part of CRS disutility | Neurotoxicity, Grade 1-2: 0.00<br>Neurotoxicity, Grade 3+: 0.00 | Section 10.2.3 |
| Ossa DF, Briggs A, McIntosh E, Cowell W, Littlewood T, Sculpher M. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality-of-life assessment using direct utility elicitation and discrete choice experiment methods. Pharmacoeconomics. 2007;25(3):223-37. doi: | Anaemia: -0.310<br>Thrombocytopenia: -0.310 | Section 10.2.3 |

| | | |
|---|---|---|
| 10.2165/00019053-200725030-00005. PMID: 17335308.[65] | | |
| Launois R, Reboul-Marty J, Henry B, Bonneterre J. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine. Pharmacoeconomics. 1996 Nov;10(5):504-21. doi: 10.2165/00019053-199610050-00008. PMID: 10169397. [66] | Febrile neutropenia: -0.390 | Section 10.2.3 |
| Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, Engelgau MM, Kaplan RM, Herman WH. Valuing health-related quality of life in diabetes. Diabetes Care. 2002 Dec;25(12):2238-43. doi: 10.2337/diacare.25.12.2238. PMID: 12453967. [67] | Leukopenia: -0.065<br>Lymphopenia: -0.065 | Section 10.2.3 |
| Cykert S, Joines JD, Kissling G, Hansen CJ. Racial differences in patients' perceptions of debilitated health states. J Gen Intern Med. 1999 Apr;14(4):217-22. doi: 10.1046/j.1525-1497.1999.00320.x. PMID: 10203633; PMCID: PMC1496565. [70] | Lower respiratory infection: -0.1900<br>Respiratory infection: -0.1900 | Section 10.2.3 |
| Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006 Sep 18;95(6):683-90. doi: 10.1038/sj.bjc.6603326. PMID: 16967055; PMCID: PMC2360509. [68] | Nausea: -0.100<br>Neutropenia: -0.150 | Section 10.2.3 |

## 5.3 Literature used for inputs for the health economic model

The clinical inputs (PFS and OS) used in the health economic model were based on CARTITUDE-4 [62] and the clinical inputs were extrapolated over time (see section 8). For the scenario analysis (cilta-cel versus Kd), clinical inputs were based on the ITCs using efficacy inputs (PFS and OS) from CARTITUDE-4 and CANDOR [71].

Unit cost inputs were based on publicly available literature relevant to Denmark with 2025 prices, e.g., medicinpriser.dk, the DMC "Valuation of unit costs" (Værdisætning af enhedsomkostninger), and DRGs from Sundhedsdatastyrelsen.

The relevant model inputs and associated literature used in the health economic model are listed in Table 10.

**Table 10 Relevant literature used for input to the health economic model**

| Reference (Full citation incl. reference number) | Input/estimate | Method of identification | Reference to where in the application the data is described/applied |
|---|---|---|---|
| J&J Data on file (2024). Ciltacabtagene autoleucel ( Carvykti®). A Phase 3 Randomized study comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide Refractory Multiple Myeloma [59]. | PFS for intervention and comparator<br>OS for intervention and comparator | Based on direct evidence from CARTITUDE-4 and extrapolated | Section 6.1.4 and for parametric survival modelling 8 |
| J&J Data on file. (2024). Efficacy of Carvykti® in CARTITUDE-4 versus Other Conventional Treatment Regimens for Lenalidomide-Refractory Multiple Myeloma Using | PFS for intervention and comparator in scenario analysis<br>OS for intervention and comparator scenario analysis | Based on ITCs and extrapolated | Section 7.1.3 and for parametric survival modelling 8 |

| | | | |
|---|---|---|---|
| Inverse Probability of Treatment Weighting [61] | | | |
| medicinpriser.dk | Drug acquisition cost | Based on DMC guidelines and Værdisætning af enhedsomkostninger 2024 | Section 11 |
| laeger.dk / rigshospitalet.dk | Costs of laboratory test | | |
| sundhedsdatastyrelsen.dk | Resource use and AE cost using DRGs | | |
| medicinraadet.dk | Administration cost and patient costs | | |

# 6. Efficacy

## 6.1 Efficacy of cilta-cel compared to physician's choice of DVd or PVd in adult patients with RRMM, who have received at least one prior therapy, including an IMiD, and a PI, have demonstrated disease progression in the last therapy, and are refractory to lenalidomide

### 6.1.1 Relevant studies

As previously described, CARTITUDE-4, is the main data source for the base case comparison used to model the efficacy of cilta-cel compared to PC. The primary outcome of CARTITUDE-4 is PFS, with secondary outcomes including, but not limited to, OS, MRD negativity, and ORR. Data from the latest DCO (May 01 2024) are presented below, with a median follow-up time of 33.6 months [71]. An overview of CARTITUDE-4 is presented in Table 11 and in detail in Appendix A [62, 71].

In the scenario analysis, IPD from the CARTITUDE-4 and the clinical trial, CANDOR [44, 72], was used in an ITC to determine the efficacy of cilta-cel against Kd. CANDOR was a randomised, multi-centre, open-label phase 3 study, outlined in detail in Appendix A. CANDOR evaluated the efficacy and safety of carfilzomib in combination with daratumumab and dexamethasone (KDd) versus Kd alone, including patients who were anti-CD38 naïve. The results from the ITC is presented in Appendix C.

**Table 11 Overview of study design for studies included in the comparison**

| Trial | Study design | Study duration | Patient population | Intervention | Comparator | Outcomes and follow-up time |
|---|---|---|---|---|---|---|
| CARTITUDE-4<br><br>(NCT04181827) | Phase lll / open label / parallel/ multicentre trial | Ongoing, latest data-cut May 1, 2024 | RRMM patients with 1-3 prior LOT that are refractory to lenalidomide. | Cilta-cel (intravenous) 0.75 x 106 CAR-positive viable T cells/kg of body weight. Patients ≤100 kg and below: 0.5 - 1 x 106 CAR-positive viable T cells/kg body weight. Patients > 100 kg: 0.5 - 1 x 108 CAR-positive viable T cells (non-weight based).<br><br>Pretreatment of lymphodepleting regimen of cyclophosphamide (intravenous) 300 mg/$m^2$ intravenous and fludarabine 30 mg/ $m^2$administered daily for 3 days. Cilta-cel should be administered 5 to 7 days after lymphodepleting regimen start.<br><br>Pre-infusion 30 to 60 minutes before cilta-cel infusion: Antipyretic (oral or intravenous paracetamol 650 to 1,000 mg) and Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent). Consider bridging therapy according to prescriber's choice prior to infusion with Carvykti® to reduce tumour burden or stabilise the disease. | PVd dosing: Pomalidomide (orally) 4 mg/day once daily on Days 1 to 14 of repeated 21- day cycles. Bortezomib (intravenous or subcutaneous) 1.3 mg/ $m^2$ once daily on day 1, 4, 8 and 11 in cycle 1-8, then on day 1 and 8 in the following cycles. Dexamethasone (orally) 20 mg/day (10 mg/day for age > 75 years) once daily on day 1, 2, 4, 5, 8, 9, 11 and 12 in cycle 1-8, then on day 1, 2, 8 and 9 in the following cycles.<br><br>DPd dosing: Daratumumab (subcutaneous) 1,800 mg/day on day 1, 8, 15 and 22 in cycle 1-2, then on day 1 and 15 in cycle 3-6, and then on day 1 in the following cycles. Pomalidomide (orally) 4 mg/day once daily on Days 1 to 14 of repeated 21- day cycles. Dexamethasone (orally) 40 mg/day (20 mg/day for age> 75 years) on day 1, 8, 15 and 22. | PFS (median follow-up 33.6 months), Overall MRD negative rate (measured for all patients at 6,12,18 and 24 months (±21), and then yearly (± 3 months)), Cilta-cel group was also assessed at day 56 after infusion), Rate of MRD negativity in participants with CR/sCR (at 12 months and followed up yearly (±3 months)), Rate of sustained MRD negative status (at 12 months ± 3months) , OS (median follow-up 33.6 months), ORR (until end of study), PFS2 (median follow-up 25.3 months) |

Abbreviations: cilta-cel= ciltacabtagene autoleucel, CR = complete response, EORTC QLQ-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, EQ-5D-5L = EuroQol 5-Dimension 5-Level, IMiD = Immunomodulatory drug, Kd = carfilzomib + dexamethasone, IV = intravenous infusion, kg= kilogram, LOT = lines of therapy, $m^2$= square meter, mg=milligram, MRD= minimal residual disease, MySIm-Q = Multiple Myeloma Symptom and Impact Questionnaire, ORR= overall response rate, OS= overall survival,

PFS=progression-free-survival, PFS2= progression-free-survival on next line of therapy, PGIS = Patient Global Impression of Severity, PRO = patient reported outcome, PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, PVd= pomalidomide + bortezomib + dexamethasone, RRMM= relapsed and refractory multiple myeloma, Vd= bortezomib + dexamethasone.

### 6.1.2 Comparability of studies

In the ITC for cilta-cel versus Kd (described further in Appendix C), patients in CANDOR were matched to the population in CARTITUDE-4, having received 1-3 prior LOT, including a PI and IMiD, refractory to lenalidomide, and having ECOG scores of <2. In CARTITUDE-4, subjects had no previous exposure to anti-CD38 therapies, while subjects in the CANDOR trial were allowed pre-exposure to anti-CD38 therapies, but only one patient in the DKd arm was pre-exposed to anti-CD38.

#### 6.1.2.1 Comparability of patients across studies

The baseline characteristics of patients included in CARTITUDE-4 [62, 71] are presented in Table 12.

For CANDOR, see Appendix A.2 and Appendix C.4.1.1.

**Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety**

| | CARTITUDE-4 | |
|---|---|---|
| | **Cilta-cel** | **PC** |
| **Median age, years (range)** | 61.5 (27-78) | 61.0 (35-80) |
| **Female, n (%)** | 44.2 | 41.2 |
| **Body weight, n (%)** | 78.45 (18.50) | 76.64 (15.32) |
| **Body surface area, mean (SD); $m^2$** | 1.91 (0.259) | 1.89 (0.225) |
| **ECOG performance status, n (%)** | | |
| **0** | 114 (54.8) | 121 (57.3) |
| **1** | 93 (44.7) | 89 (42.2) |
| **2** | 1 (0.5) | 1 (0.5) |
| **Number of prior lines, n (%)** | | |
| **1** | 68 (32.7) | 68 (32.2) |
| **2** | 83 (39.9) | 87 (41.2) |
| **3** | 57 (27.4) | 56 (26.5) |
| **Prior PI, n (%)** | | |
| **Bortezomib** | 203 (97.6) | 205 (97.2) |

| | CARTITUDE-4 | |
|---|---|---|
| | Cilta-cel | PC |
| **Carfilzomib** | 77 (37.0) | 66 (31.3) |
| **Ixazomib** | 21 (10.1) | 21 (10.0) |
| **Prior IMiD, n (%)** | | |
| **Lenalidomide** | 208 (100.0) | 211 (100.0) |
| **Pomalidomide** | 8 (3.8) | 10 (4.7) |
| **Thalidomide** | 100 (48.1) | 82 (38.9) |

Abbreviations: cilta-cel= ciltacabtagene autoleucel, DPd= daratumumab + pomalidomide + dexamethasone, ECOG= Eastern Cooperative Oncology Group, IMiD= Immunomodulatory drug, NA = not applicable, NR=not reported, PC= physicians' choice, PI= proteasome inhibitor, PVd= pomalidomide + bortezomib + dexamethasone, SD= standard deviation

### 6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The population in the health economic model aligns with the expected patient population in Denmark, cilta-cel's approved indication and the CARTITUDE-4 population, including adult patients who had received at least one prior therapy, including an IMiD and a PI, and have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

The model inputs concerning patient characteristics comprise age, gender, and body weight based on CARTITUDE-4 population characteristics (Table 13). In Danish clinical practice, the percentage of females (45%) aligns with that in CARTITUDE-4. While the median age at MM diagnosis for Danish patients is 72 years. Patients considered for a CAR T are generally expected to be slightly younger than the overall MM population [73]. In the health economic analysis, the impact of cohort age is tested a scenario analysis.

**Table 13 Characteristics in the relevant Danish population and in the health economic model**

| | Value in Danish population (assumed as per CARTITUDE-4) | Value used in health economic model |
|---|---|---|
| Age (mean) | 60 years | 60 years |
| Gender (% of female) | 42.7% | 42.7% |
| Patient weight (mean) | 77.54 kg | 77.54 kg |
| Body surface area (mean) | 1.9m$^2$ | 1.9m$^2$ |

### 6.1.4 Efficacy – results per CARTITUDE-4

The efficacy results presented in the following section for cilta-cel and PC are from the latest DCO 01 May 2024 from CARTITUDE-4, (overall efficacy results for the comparative analysis are summarized in the next chapter, Table 18). The following sections present results for the key outcomes PFS, OS, overall MRD negativity, PFS2, and ORR. The presented outcomes are accounting for all events from randomisation.

#### 6.1.4.1 Progression-free Survival

The primary efficacy outcome for the CARTITUDE-4 study was PFS. At a median follow-up of 33.6 months, PFS events were reported in 72.5% of PC arm participants and 42.8% of cilta-cel arm participants, 31 and 24 events, respectively (Table 14). The 36-month PFS rates were 22.9% and 56.0% for PC and cilta-cel, respectively (Table 14). The median PFS was 11.8 months (95% CI: 9.66, 14.00) for the PC arm and not reached for cilta-cel NE (34.50, NE), with a hazard ratio of 0.29 (95% CI: 0.22, 0.39, $p$<0.0001).

A KM plot for PFS is shown in Figure 6 (Data on file). The KM PFS curves crossed three months after randomisation, mainly due to an imbalance in PFS events before the cilta-cel infusion. Both groups received the same therapy for the first eight weeks (PVd/PDd); however, there were more PFS events (22 events) in the cilta-cel group occurring before the cilta-cel infusion, with most patients showing disease progression about one month after randomisation. This imbalance may be attributed to the cilta-cel group receiving approximately [redacted] during bridging therapy.

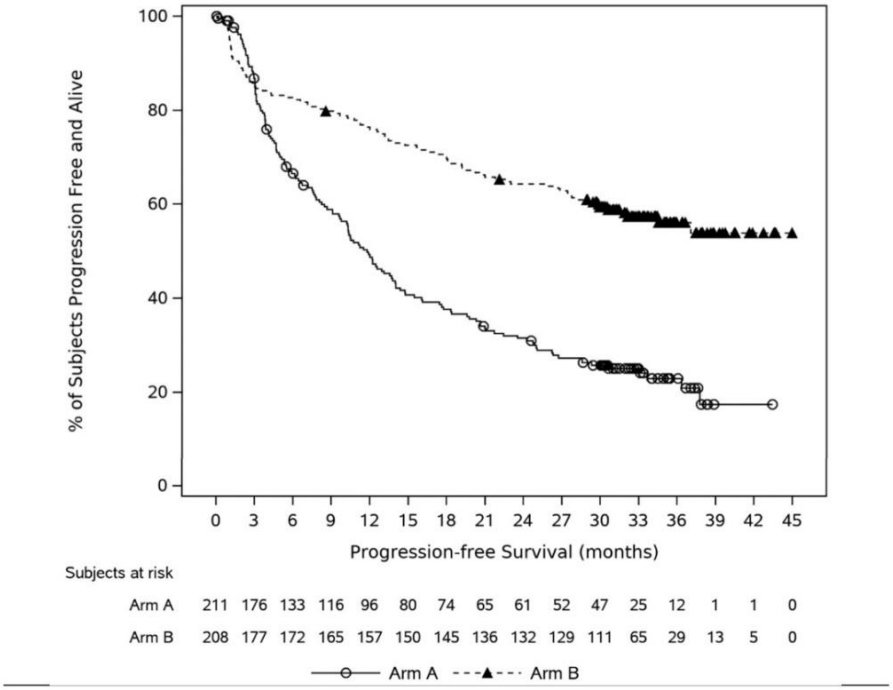
**Table 14 PFS results in CARTITUDE-4 Intent-to-treat analysis set (DCO 01 May 2024)**

| PFS results | PC (N=211) | Cilta-cel (N = 208) |
|---|---|---|
| Number of events (%) | 153 (72.5%) | 89 (42.8%) |
| Number of censored (%) | 58 (27.5%) | 119 (57.2%) |
| Median Kaplan-Meier estimate, months | 11.79 | NE |
| (95% CI) | (9.66, 14.00) | (34.50, NE) |
| *P*-value [a] | | <0.0001 |
| Hazard ratio (95% CI)[b] | | 0.29 (0.22, 0.39) |
| 12-month PFS rate % (95% CI) | 48.7 (41.7, 55.5) | 75.9 (69.5, 81.2) |
| 24-month PFS rate % (95% CI) | 31.4 (25.1, 38.0) | 64.3 (57.4, 70.4) |
| 36-month PFS rate % (95% CI) | 22.9 (16.9, 29.4) | 56.0 (48.6, 62.9) |

Abbreviations: PC=Physician choice of PVd = pomalidomide-bortezomib-dexamethasone or DPd = daratumumab-pomalidomide-dexamethasone, CI = confidence interval; CPW=constant piecewise weighted.

Note: [a]p-value is based on the CPW log-rank test (weight=0 in the log-rank statistic for the first 8 weeks post-randomization, and 1 afterwards) stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized. [b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized, including only PFS events that occurred more than 8 weeks post-randomization. A hazard ratio <1 indicates an advantage for cilta-cel.

**Figure 6 Kaplan-Meier Plot for Progression-free Survival, Intent-to-Treat Analysis Set (DCO 01 May 2024)**

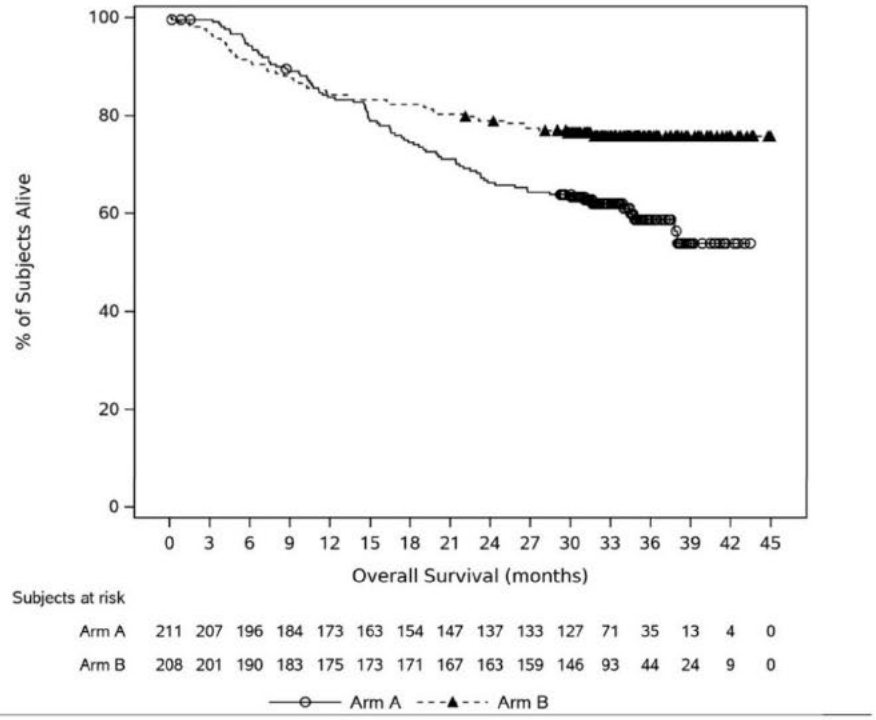



Abbreviations: Arm A = PC of PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion; PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.

### 6.1.4.2 Overall Survival

By the updated DCO of 01 May 2024, 83 participants (39.3%) in the PC arm and 50 participants (24.0%) in the cilta-cel arm had died. At the median follow-up of 33.6 months, the median OS was not met for either arm. The HR for OS in the cilta-cel arm compared to the PC arm was 0.55 (95% CI: 0.39, 0.79), with a p-value of 0.0009, crossing the boundary of 0.0108. This showed a 45% reduction in death risk for the cilta-cel arm (Figure 7). The 36-month OS rates were 58.7% for the PC arm and 75.7% for the cilta-cel arm (Table 15).

**Figure 7 Kaplan-Meier Plot for Overall Survival; Intent-to-Treat Analysis Set (DCO 01 May 2024)**




Abbreviations: Arm A = PC of PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion; PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.

**Table 15 Summary of Overall Survival; Intent-to-Treat Analysis Set (DCO 01 May 2024)**

| OS results | PC (N=211) | Cilta-cel (N=208) |
|---|---|---|
| Number of events, n (%) | 83 (39.3%) | 50 (24.0%) |
| Number of events censored, n (%) | 128 (60.7%) | 158 (76.0%) |
| Median Kaplan-Meier estimate, months<br>(95% CI) | NE<br>(37.75, NE) | NE<br>(NE, NE) |
| Hazard ratio (95% CI) | - | 0.55 (0.39, 0.79) |
| 12-month OS rate, % (95% CI) | 83.6 (77.9, 88.0) | 84.1 (78.4, 88.4) |
| 24-month OS rate, % (95% CI) | 66.2 (59.3, 72.2) | 78.8 (72.6, 83.8) |
| 36-month OS rate, % (95% CI) | 58.7 (51.0, 65.6) | 75.7 (69.2, 81.0) |

Abbreviations: cilta-cel = ciltacabtagene autoleucel, CI = confidence interval, DPd = Daratumumab +Pomalidomide + dexamethasone, OS = overall survival, PC = physician's choice, PVd = Pomalidomide + Bortezomib + dexamethasone. Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I,

II, III) and number of prior lines (1 vs. 2 or 3) as randomised. A hazard ratio <1 indicates an advantage for cilta-cel.

#### 6.1.4.3 Overall MRD negativity

Minimal residual disease negativity is a superior prognostic factor for both PFS and OS. In CARTITUDE-4, MRD was assessed for all participants at suspected complete response (CR) or stringent complete response (sCR), as well as 6, 12, 18, and 24 months from Cycle 1 Day 1 for the PC arm, and from cilta-cel infusion for cilta-cel arm, regardless of CR status. After 24 months, MRD was checked annually until disease progression for participants in CR or sCR. In the cilta-cel arm, MRD was also assessed at Day 56 post-infusion. The overall MRD negativity rate, defined as the proportion of participants with MRD-negative status (as $10^{-5}$), was 18.5% for the PC arm and 62.0% for cilta-cel arm, with an odds ratio (OR) of 7.6 (95% CI: 4.8, 12.0) (Table 16). In participants with evaluable samples, the MRD negativity rate at the $10^{-5}$ threshold was significantly higher in the cilta-cel arm (89.0%) compared to the PC arm (37.9%), with an OR of 13.3 (95% CI: 6.8, 25.8).

**Table 16 Summary of MRD Negativity Rate at $10^{-5}$ in Bone Marrow; Intent-to-Treat Analysis Set (DCO 01 May 2024)**

| | PC (N=211) | Cilta-cel (N=208) |
|---|---|---|
| MRD negativity, n (%) (95% CI[a]) | 39 (18.5%) (13.5%, 24.4%) | 129 (62.0%) (55.0%, 68.6%) |
| OR (95% CI[a]) | - | 7.61 (4.83, 12.00) |
| P-value[b] | - | <0.0001 |

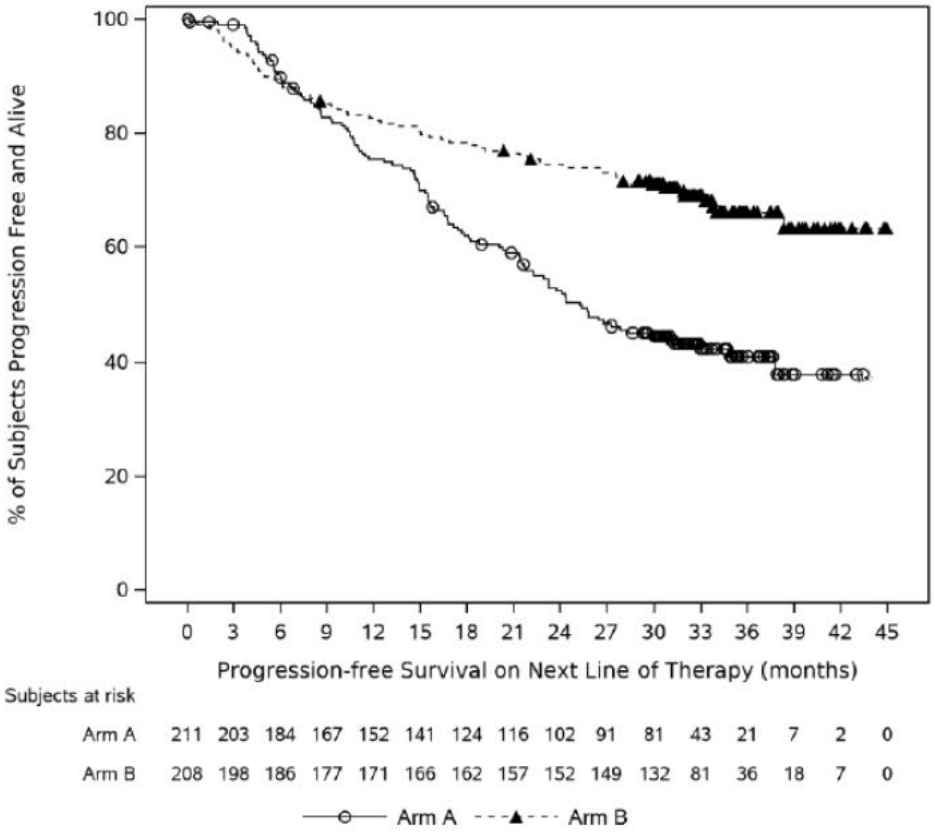
Note: Overall MRD negativity rate is defined as the proportion of subjects who have MRD negative status (at $10^{-5}$) by bone marrow aspirate at any time after the date of randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy [a]. Exact 95% confidence interval. [b]Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

Abbreviation: PVd = pomalidomide-bortezomib-dexamethasone, DPd = daratumumab-pomalidomide-dexamethasone, CI = confidence interval, MRD = minimal residual disease.

#### 6.1.4.4 Progression-free Survival on Next Line Therapy (PFS2)

The cilta-cel arm had fewer PFS2 events (32.2%) compared to the PC arm (55.0%), with a hazard ratio of 0.46 (95% CI: 0.34, 0.63), and the median PFS2 was 25.3 months for the PC and not reached for the cilta-cel arm (data on file), see Figure 8 and Table 17.

**Figure 8 Kaplan-Meier Plot for Progression-free survival on next line of therapy; Intent-to-Treat Analysis Set (DCO 01 May 2024)**




**Key:** Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.

**Key:** PVd=pomalidomide-bortezomib-dexamethasone; DPd=daratumumab-pomalidomide-dexamethasone.

**Note:** Intent-to-treat analysis set consists of subjects who were randomized in the study.

**Table 17 Summary of Progression-free survival on next line of therapy; Intent-to-Treat Analysis Set (DCO 01 May 2024)**

| | Arm A | Arm B |
|---|---|---|
| Analysis set: intent-to-treat | 211 | 208 |
| Progression-free survival on next line of therapy | | |
| Number of events (%) | 116 (55.0%) | 67 (32.2%) |
| Number of censored (%) | 95 (45.0%) | 141 (67.8%) |
| Kaplan-Meier estimate (months) | | |

| | | |
|---|---|---|
| 25% quantile (95%% CI) | 12.68 (10.15, 15.47) | 22.70 (14.75, 31.90) |
| Median (95% CI) 25.30 (21.59, 32.89) NE (NE, NE) | 25.30 (21.59, 32.89) | NE (NE, NE) |
| 75% quantile (95% CI) | NE (NE, NE) | NE (NE, NE) |
| P-value[a] | - | <0.0001 |
| Hazard ratio (95%)[b] | - | 0.46 (0.34, 0.63) |
| 6- month PFS2 rate % (95% CI) | 90.2 (85.3, 93.6) | 89.4 (84.4, 92.9) |
| 12- month PFS2 rate % (95% CI) | 75.4 (68.8, 80.7) | 82.7 (76.8, 87.2) |
| 18- month PFS2 rate % (95% CI) | 62.0 (54.9, 68.2) | 78.3 (72.1, 83.3) |
| 24- month PFS2 rate % (95% CI) | 52.3 (45.2, 58.9) | 74.4 (67.9, 79.8) |
| 30- month PFS2 rate % (95% CI) | 44.6 (37.5, 51.3) | 71.0 (64.3, 76.7) |
| 36- month PFS2 rate % (95% CI) | 41.0 (33.7, 48.1) | 66.0 (58.5, 72.5) |

**Key:** Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.

**Key:** PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.

**Key:** CI = confidence interval.

**a** p-value is based on the log-rank test stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.

**b** Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for Arm B.

**Note:** Intent-to-treat analysis set consists of subjects who were randomized in the study.

#### 6.1.4.5 Overall Response rate

ORR did not change in the new DCO 01 May 2024, and remained at 67.3% (95% CI:60.5%, 73.6%) for the PC arm and 84.6% (95% CI: 79.0%, 89.2%) for the cilta-cel arm. The odds ratio was 3.0 (95% CI: 1.8, 5.0; p<0.0001).

# 7. Comparative analyses of efficacy

As the effect in the base case is based on the head-to-head trial CARTITUDE-4, the following sections in chapter 7 are not applicable. The results from the comparative analysis of CARTITUDE-4 are presented in Table 18.

In a scenario analysis cilta-cel was compared to Kd, based on an ITC. The methods and results are presented in Appendix C.

### 7.1.1 Differences in definitions of outcomes between studies

For the ITC, see Appendix C.1.4

### 7.1.2 Method of synthesis

For the ITC, see Appendix C.1.5

### 7.1.3 Results from the comparative analysis

Results from the relevant efficacy endpoints in from CARTITUDE-4 are presented in Table 18.

**Table 18 Results from the comparative analysis of cilta-cel vs. PC from CARTITUDE-4, for adult patients with RRMM, who have received at least one prior therapy, including an IMiD, and a PI, have demonstrated disease progression in the last therapy, and are refractory to lenalidomide**

| Outcome measure | Cilta-cel (N=155) | PC (N=156) | Result |
|---|---|---|---|
| **PFS** | Median: NE<br>(95% CI: 34.5, NE) | Median: 11.8 mo.<br>(95% CI: 9.7, 14.0) | NE, HR: 0.29 (95% CI: 0.22, 0.39, *p*<0.0001) |
| **OS** | Median: NE<br>(95% CI: NE, NE) | Median: NE<br>(95% CI: 37.75, NE) | NE, HR: 0.55 (95% CI: 0.39, 0.79) |
| **PFS2** | Median: NE<br>(95% CI: NE, NE) | Median: 25.3 mo.<br>(95% CI: 21.6, 32.9) | NE |
| **ORR** | Median: 84.6%<br>(95% CI: 79.0%, 89.2%) | Median: 67.3%<br>(95% CI:60.5%, 73.6%) | 17.3%, OR 3.0 (95% CI: 1.8, 5.0; p<0.0001) |
| **Overall MRD negativity** | 39 (18.5%)<br>(95% CI: 13.5%, 24.4) | 129 (62.0%)<br>(95% CI: 55.0%, 68.8%) | 43.5%, 7.61 (4.83, 12.00) |

Note: *ATT adjusted results. Abbreviations: CI= confidence interval, cilta-cel= ciltacabtagene autoleucel, DPd= daratumumab + pomalidomide + dexamethasone, DVd=daratumumab + bortezomib + dexamethasone, Kd =

carfilzomib + dexamethasone, MRD= minimal residual disease, NA= not applicable, NE= not estimable, PFS=progression-free-survival, PFS2= progression-free-survival on next line of therapy, ORR= overall response rate, OS= overall survival, PVd = pomalidomide + bortezomib + dexamethasone.

### 7.1.4 Efficacy – results per PFS and OS

See Appendix C.4 for results from the ITC.

# 8. Modelling of efficacy in the health economic analysis

## 8.1 Presentation of efficacy data from the clinical documentation used in the model

The clinical data from the CARTITUDE-4 trial, based on the DCO of May 1, 2024, were used to model PFS and OS for cilta-cel and PC. Standard survival models, including exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, and generalised gamma, were fitted to individual trial data. The selection of distributions followed the guidance provided by the DMC and NICE Decision Support Unit [74, 75].

Model performance and the selection of base case was assessed through:

- **Visual comparison** with the Kaplan-Meier (KM) estimate (KM curves) and non-parametric hazards.
- **Goodness-of-fit** using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC).
- **Clinical plausibility** of the hazard function's shape and the estimated future event rates.

Mortality estimates were constrained by age- and gender-specific general mortality rates from the current Danish life tables [76].

## 8.2 Calculation of transition probabilities N/A

Not applicable.

**Table 19 Transitions in the health economic model N/A**

| Health state (from) | Health state (to) | Description of method | Reference |
|---|---|---|---|
| Disease-free survival | Recurrence | N/A | |
| | Death | N/A | |

| | | |
|---|---|---|
| Recurrence | Death | N/A |
| Health state/ Transition | | N/A |

### 8.2.1 Extrapolation of efficacy data

#### 8.2.1.1 Extrapolation of progression-free survival

A summary of assumptions associated with the extrapolation of PFS for cilta-cel and PC is presented below in Table 20.

**Table 20 Summary of assumptions associated with extrapolation of PFS**

| Method/approach | Description/assumption |
|---|---|
| Data input | Clinical data from CARTITUDE-4 (NCT04181827) [60] DCO 01 May 2024. |
| Model | The seven standard survival models were fitted to the individual subject data in CARTITUDE-4. The survival times were assumed to follow one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma. |
| Assumption of proportional hazards between intervention and comparator | No |
| Function with best AIC fit | Intervention: Lognormal<br>Comparator: Lognormal |
| Function with best BIC fit | Intervention: Lognormal<br>Comparator: Lognormal |
| Function with best visual fit | Intervention: Lognormal<br>Comparator: Lognormal |
| Function with best fit according to evaluation of smoothed hazard assumptions | Intervention: Lognormal<br>Comparator: Lognormal |
| Validation of selected extrapolated curves (external evidence) | N/A |
| Function with the best fit according to external evidence | N/A |
| Selected parametric function in base case analysis | Intervention: Lognormal<br>Comparator: Lognormal |

| | |
|---|---|
| Adjustment of background mortality with data from Statistics Denmark | Yes |
| Adjustment for treatment switching/cross-over | No |
| Assumptions of waning effect | No |
| Assumptions of cure point | No |

The primary endpoint of the CARTITUDE-4 trial was PFS, as assessed by blinded independent central review (BICR). At the latest DCO, PFS data for cilta-cel showed that 42.8% (89/208) of events had been observed. In comparison, the data for PC showed a higher level of events observed with 72.5% (153/211) of events observed. Extrapolation was necessary to estimate the unrestricted mean difference in PFS for the economic analysis. Additional details, including goodness-of-fit metrics, predicted landmark PFS rates, and the median and estimated mean for each survival model in each treatment arm, are provided in Appendix D.

Figure 9 and Figure 10 show the PFS KM curves for cilta-cel and PC, respectively, along with the fitted standard survival models.

For cilta-cel, most distributions, except the exponential, visually aligned well with the underlying KM curve. In contrast, the exponential distribution showed a poor fit to the KM curve. While most distributions provided similar survival estimates during the period covered by the KM data, their predictions for PFS diverged significantly beyond this period.

For PC, the visual fit of all distributions to the KM-curve was comparable. However, as with cilta-cel, the survival curves diverged beyond the KM curve. For PC, the curves formed three distinct clusters, with relatively consistent PFS estimates within each cluster.

[redacted]

[redacted]

The estimated goodness-of-fit statistics, AIC and BIC, for PFS are reported in [redacted] for cilta-cel and PC, respectively.

For cilta-cel, the lognormal distribution provided the best fit according to AIC, followed by the generalised gamma and log-logistic distributions. All three distributions showed similar PFS rates at the 1-, 5-, and 10-year landmarks (Table 66), although the generalised gamma distribution estimated higher PFS rates than the other two after the 1-year landmark. The hazard shapes of these functions closely aligned with the smoothed non-parametric hazard from the trial, confirming their suitability (see Figure 33).

In contrast, the exponential distribution showed the worst fit based on AIC and BIC for cilta-cel. Additionally, the constant hazard of the exponential model was inconsistent with the shape of the smoothed non-parametric hazard and did not show a good visual fit to the KM curve.

For PC, the same three distributions as for cilta-cel, lognormal, log-logistic, and generalised gamma provided the best statistical fit based on AIC, in that order. Similar to cilta-cel, the exponential distribution also provided a poor statistical fit for PC, with only the Weibull and gamma distributions performing worse. The visual comparison of hazard rates against the smoothed non-parametric hazard was consistent with the goodness-of-fit statistics (see Figure 34).

Clinically, it is plausible for the hazard to decrease over time, as suggested by the CARTITUDE-4 data. The decline of the hazard over time may be attributed to:

- **Treatment effect**, reducing the risk of progression or death over time.
- **Patient selection:** patients who remain event-free for extended periods may have inherently better prognoses, either due to favourable biological characteristics or positive responses to treatment.

Both arms of CARTITUDE-4 show a declining hazard with time; for PC, it occurs after an initial increase in the hazard rate. This is consistent with the prediction of a lognormal distribution.

The lognormal distribution's fit according to both AIC and BIC, regardless of the treatment arm, means it also provides the best fit when the total stratified fits are examined (see [redacted]). The exponential distribution provided the worst fit, with the largest distance from the minimum AIC and /or BIC estimates, making it an unsuitable selection for extrapolation of PFS.

Alongside the lognormal distribution, the loglogistic and generalized gamma distributions emerged as viable alternatives based on goodness-of-fit statistics and hazard development. Considering the eligibility solely on the plausibility of hazard development, the Weibull and Gamma distributions could also be seen as potential alternatives. However, after a thorough evaluation of the selection criteria, the lognormal distribution was ultimately chosen for extrapolating PFS for both treatment arms in the base case analysis. This decision was validated by internal Danish medical experts, who confirmed the plausibility of the hazard shape. Additionally, the lognormal distribution's strong statistical fit and visual alignment further substantiated its selection.

#### 8.2.1.2 Extrapolation of overall survival

A summary of assumptions associated with the extrapolation of OS for cilta-cel and PC are presented in Table 21.

**Table 21 Summary of assumptions associated with extrapolation of OS**

| Method/approach | Description/assumption |
|---|---|
| **Data input** | Clinical data from CARTITUDE-4 (NCT04181827) DCO 01 May, 2024 [71] |
| **Model** | The seven standard survival models; exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma, were fitted to the individual subject data in CARTITUDE-4 and the ITC. |
| **Assumption of proportional hazards between intervention and comparator** | No |
| **Function with best AIC fit** | Intervention: Gompertz<br>Comparator: log-logistic |
| **Function with best BIC fit** | Intervention: Gompertz<br>Comparator: exponential |
| **Function with best visual fit** | Intervention: Gompertz<br>Comparator: generalized gamma |
| **Function with best fit according to evaluation of smoothed hazard assumptions** | Intervention: Gompertz<br>Comparator: generalized gamma |
| **Validation of selected extrapolated curves (external evidence)** | NA |
| **Function with the best fit according to external evidence** | NA |
| **Selected parametric function in base case analysis** | Intervention: Lognormal<br>Comparator: Lognormal |
| **Adjustment of background mortality with data from Statistics Denmark** | Yes |
| **Adjustment for treatment switching/cross-over** | No |
| **Assumptions of waning effect** | No |
| **Assumptions of cure point** | No |

At the most recent DCO on May 1, 2024, OS data showed that 24.0% (50/208) of events were observed in the cilta-cel arm and 39.3% (83/211) in the PC arm. Consequently, extrapolation was necessary to estimate the unrestricted mean difference in OS between the treatment arms. Detailed extrapolation data, including information on goodness-of-fit, predicted landmark OS rates, and the estimated median and mean for each survival model in both treatment arms, are presented in Appendix D.

[redacted] display the OS KM curves for cilta-cel and PC and the fitted standard survival models.

For cilta-cel, most distributions provided a relatively good visual fit to the KM curves, except the exponential and gamma distributions. Generally, simple distributions (constant or monotonically increasing or decreasing) provided a poorer fit than the more complex ones. The best visual fit was the Gompertz distribution, followed by the generalised gamma. Beyond the KM curve, the curves predict highly variable survival rates. Although the Gompertz distribution has the best visual fit to the KM curve, it predicts that an implausible high proportion, over 70%, has no further events after approximately six years. Except for the Gompertz, the more complex and visually better-fitting distributions provided more optimistic long-term survival estimates than the less complex distributions.

For PC, all distributions generally provided a good visual fit to the Kaplan-Meier estimates. Similar to cilta-cel, while the distributions provided similar estimates for the period covered by the KM curve, the curves diverge after the final KM estimate, though to a lesser degree than for cilta-cel. The trend for the long-term survival estimates is similar to cilta-cel in that the more complex distributions provide more optimistic long-term estimates. However, the simplest distribution, the exponential, is not the worst but instead provides estimates in the middle of all distributions.

[redacted]

[redacted]

For cilta-cel, the best statistical fits estimated by both AIC and BIC were the Gompertz and the lognormal, followed by the generalised gamma and the log-logistic distributions (see [redacted] This was consistent with the visual fit to the KM curve.

The shapes of the smoothed non-parametric hazards ([redacted]) both display an initial increase in hazard followed by a decline after reaching a maximum. This

[redacted]

is aligned with the observation that complex or non-monotonic distributions better fit the KM curve.

The Gompertz distribution had the best statistical fit and a good visual fit to the KM curve for cilta-cel. However, the extrapolation of the hazard was not clinically plausible, with no more events after approximately six or seven years. Further, with its monotonically decreasing hazard, the Gompertz distribution was inconsistent with the smoothed non-parametric hazard (Figure 44).

The lognormal distribution [redacted]) had the best stratified overall fit. It was also a good visual fit to the KM curves for both arms and the smoothed non-parametric hazard. The shape of the hazard is also clinically plausible based on the same reasoning as for PFS: treatment effect and patient selection.

The exponential distribution had a poor visual fit to the KM curves and had the worst statistical fit for cilta-cel (see [redacted]). The shape of Its hazard was also the least plausible, considering the shape of the non-parametric hazard (see Figure 41).

When comparing the predicted survival estimates of the two best-fitting (with a clinically plausible shape) distributions, generalized gamma and lognormal, at the five-year mark, the predicted percentage of OS was roughly similar, around 70%. However, over time, these two curves diverged. At 40 years, the end of the time horizon, the generalised gamma predicted approximately 47% of patients alive versus 34% for lognormal.

For PC the log-logistic, exponential, and lognormal distributions exhibit the best overall statistical fits (see Table 71). However, the exponential distribution assumes a constant hazard, which is generally not considered clinically plausible. The lognormal and log-logistic distributions predict very similar OS rates at 5, 10, and 40 years, with approximately 40%, 20%, and 7% of patients alive, respectively. In the CASTOR clinical trial, the pivotal trial for DVd in the RRMM setting, follow-up data up to 6 years (72 months) are available to validate the OS of PC. Based on this DCO in CASTOR, the OS rate for treatment with DVd was slightly above 40% at the five-year mark and approximately equal to 40% at the six-year mark, supporting the predictions of the lognormal log-logistic distributions.

Based on the above, the lognormal distribution was selected to extrapolate OS for both treatment arms in the base case. This aligns with NICE's recommendation to use the same distribution for all treatment arms unless there is strong evidence to the contrary. Other distributions (Weibull, loglogistic, gamma and generalised gamma) were considered based on the criteria enumerated in section 8.1. However, even if all of them at least partly fulfilled these, they all fared worse than the lognormal distribution.

Given the immaturity of the data and the fact that both arms have received CAR-T therapies either as an intervention or as a subsequent treatment, reducing their hazards to below the hazard of the general population may be expected, as the response to treatment with CAR-T may reduce the disease-specific hazard (dying due to RRMM) below the hazard of competing events in all-cause mortality. The hazard of death is not allowed to go below that of the general population at any time in the analysis.

## 8.3 Presentation of efficacy data from [additional documentation]

Not applicable.

## 8.4 Modelling effects of subsequent treatments

The effects of subsequent treatments were not modelled explicitly but are included in the OS endpoint.

## 8.5 Other assumptions regarding efficacy in the model

Not applicable.

## 8.6 Overview of modelled average treatment length and time in model health state

The estimates for the modelled average and modelled median of PFS and OS for both arms as predicted by the extrapolation, are presented in Table 22. These have not been modified with discounting or half-cycle correction but are adjusted for Danish background mortality in line with the DMC template.

**Table 22 Estimates in the model**

| | Modelled average [effect measure] (reference in Excel) | Modelled median [effect measure] (reference in Excel) | Observed median from relevant study |
|---|---|---|---|
| Cilta-cel - PFS | 122 months [Partitioned Survival Model M21] | 51 months [Partitioned Survival Model M20] | NE (34.50, NE) |
| PC - PFS | 28 months [Partitioned Survival Model M23] | 12 months [Partitioned Survival Model M22] | 12 months |
| Cilta-cel - OS | 186 months [Partitioned Survival Model N21] | 178 months [Partitioned Survival Model N20] | NE (NE, NE) |
| PC - OS | 95 months [Partitioned Survival Model N23] | 49 months [Partitioned Survival Model N22] | NE (37.75, NE) |

| | | | |
|---|---|---|---|
| Cilta-cel – TTD | N/A | N/A | N/A |
| PC – TTD | 28 months [Partitioned Survival Model M23] | 12 months [Partitioned Survival Model M22] | 12 months |

Abbreviations: Cilta-cel=ciltacabtagene autoleucel, OS = overall survival, PC = physician's choice, PFS= progression-free survival, NE= Not estimable.

Table 23 provide the modelled average treatment length and time in model health as prescribed by DMC guidelines.

**Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half-cycle correction**

| Treatment | Treatment length [months] | PFS [months] | OS [months] |
|---|---|---|---|
| Cilta-cel | NA | 122 | 186 |
| PC | 28 | 28 | 95 |

Abbreviations: cilta-cel= ciltacabtagene autoleucel, NA=Not available

# 9. Safety

## 9.1 Safety data from the clinical documentation

The main source of safety data comes from CARTITUDE-4 with the latest available DCO 01 May 2024, which provided a median follow-up of 33.6 months (PC arm: 33.5 months; cilta-cel arm: 33.7 months). In CARTITUDE-4, the group of 416 patients (PVd/DPd N = 208; cilta-cel N = 208) who received any part of study treatment constituted the safety analysis set [59]. All participants in the safety analysis experienced at least 1 treatment-emergent adverse event (TEAE). Serious TEAEs were reported for 47.1% of participants in both arms (at least 1 serious TEAE related to cilta-cel: 24.0%). Grade 3 or 4 TEAEs were reported for 97.1% and 96.6% of participants in PC arm and in the cilta-cel arm, respectively. Moreover, 134 patients who received cilta-cel as study treatment suffered from cytokine release syndrome (CRS) and 36 patients reported CAR-T Cell neurotoxicity [59].

The overview of the safety events from CARTITUDE-4 is presented in Table 24.

**Table 24 CARTITUDE-4 Overview of safety events. State the time period the table covers [71]**

| | Cilta-cel (N=208) | PC (N=208)[71] | Difference, % (95 % CI) |
|---|---|---|---|
| Number of adverse events, n | NA | NA | NA |

| | Cilta-cel (N=208) | PC (N=208)[71] | Difference, % (95 % CI) |
|---|---|---|---|
| Number and proportion of patients with ≥1 adverse events, n (%) | 208 (100.0%) | 208 (100.0%) | 0 |
| Number of serious adverse events*, n | NA | NA | NA |
| Number and proportion of patients with ≥ 1 serious adverse events*, n (%) | 67 (32.2%) | 54 (26.0%) | 7, 6.2% (4.99% 7.41%) |
| Number of CTCAE grade ≥ 3 events, n | NA | NA | NA |
| Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%) | 201 (97%) | 202 (97%) | 1, 0% ( -2.20%, 2.20%) |
| Number of adverse reactions, n | NA | NA | NA |
| Number and proportion of patients with ≥ 1 adverse reactions, n (%) | 171 (82.2%) | 204 (98.1%) | 33, -16% (-18.02%,-13.78%) |
| Number and proportion of patients who had a dose reduction, n (%) | NA | NA | NA |
| Number and proportion of patients who discontinue treatment regardless of reason, n (%) | 0 (0%) | 165 (79.3%) | 165, -79% (-80.70%, -77.90%) |
| Number and proportion of patients who | 0 | 43 (21%) | 43, -21% (-21.72%,-20.28%) |

| | Cilta-cel (N=208) | PC (N=208)[71] | Difference, % (95 % CI) |
|---|---|---|---|
| discontinue treatment due to adverse events, n (%) | | | |

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available.

The frequency of all serious TEAEs with frequency of ≥ 5% recorded in the CARTITUDE-4 are presented in

Table 25. Serious TEAEs were reported for 47.1% of participants in both arms. Pneumonia (PC arm: 6.7%; cilta-cel arm: 3.8%) and COVID-19 pneumonia (PC arm: 5.8%, cilta-cel arm: 5.8%) were the only AEs that meet the threshold of serious TEAEs for ≥5% of participants, in either treatment arm. For a full list of all serious adverse events (SAEs) in CARTITUDE-4 see Appendix 0.

**Table 25 CARTITUDE-4 Serious adverse events (33.6 months follow up)**

| Adverse events | Cilta-cel (N=208) | | PC (N=208) | |
|---|---|---|---|---|
| | Number of patients with adverse events | Number of adverse events | Number of patients with adverse events | Number of adverse events |
| Adverse event, n (%): Total | 86 (41.3%) | NA | 73 (35.1%) | NA |
| COVID- 19 pneumonia | 12 (5.8%) | NA | 10 (4.8%) | NA |
| Pneumonia | 12 (5.8%) | NA | 6 (2.9%) | NA |

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

In the health economic model, AEs of at least grade 3 with an incidence of at least 5% in either treatment arms of the CARTITUDE-4 trial were included. However, CRS and neurotoxicity were included in the health economic analysis regardless of incidence and grade because these are AEs commonly associated with CAR-T that can lead to severe, life-threating outcomes. These AEs are detailed in Table 26.

In the scenario analysis for cilta-cel versus Kd, AEs from CANDOR were applied (see Appendix E.1 for a summary), and application in the scenario available in the CE-model.

**Table 26 CARTITUDE-4 Adverse events used in the health economic model**

| Adverse events | Cilta-cel | PC | | |
|---|---|---|---|---|
| **Adverse event, n (%)** | **Frequency used in economic model for intervention** | **Frequency used in economic model for comparator** | **Source** | **Justification** |
| CRS, Grade 1-2 | 63% | 0% | CARTITUDE-4 | >5% |
| CRS, Grade 3 + | 1% | 0% | CARTITUDE-4 | Commonly associated with CAR-T |
| Neurotoxicity, Grade 1-2 | 15% | 0% | CARTITUDE-4 | >5% |
| Neurotoxicity, Grade 3+ | 2% | 15% | CARTITUDE-4 | >5% |
| Anaemia | 36% | 1% | CARTITUDE-4 | >5% |
| Febrile neutropenia | 5% | 0% | CARTITUDE-4 | >5% |
| Infusion-related reaction | 0% | 5% | CARTITUDE-4 | >5% |
| Leukopenia | 12% | 5% | CARTITUDE-4 | >5% |
| Lower respiratory tract infection | 1% | 12% | CARTITUDE-4 | >5% |
| Lymphopenia | 21% | 1% | CARTITUDE-4 | >5% |
| Nausea | 0% | 82% | CARTITUDE-4 | >5% |
| Neutropenia | 90% | 6% | CARTITUDE-4 | >5% |
| Respiratory infection | 1% | 20% | CARTITUDE-4 | >5% |
| Thrombocytopenia | 42% | 2% | CARTITUDE-4 | >5% |
| Hypogammaglobulinemia | 8% | 4% | CARTITUDE-4 | >5% |

## 9.2 Safety data from external literature applied in the health economic model N/A

Not applicable.

**Table 27 Adverse events that appear in more than X % of patients N/A**

| Adverse events | Intervention (N=x) | | | Comparator (N=x) | | | Difference, % (95 % CI) | |
|---|---|---|---|---|---|---|---|---|
| | Number of patients with adverse events | Number of adverse events | Frequency used in economic model for intervention | Number of patients with adverse events | Number of adverse events | Frequency used in economic model for comparator | Number of patients with adverse events | Number of adverse events |
| Adverse event, n | | | | | | | | |

# 10. Documentation of health-related quality of life (HRQoL)

HRQoL was evaluated in CARTITUDE-4 using several patient-reported outcome measures. For this application, we present EQ-5D-5L (Table 28).

**Table 28 Overview of included HRQoL instruments**

| Measuring instrument | Source | Utilization |
|---|---|---|
| EQ-5D-5L | CARTITUDE-4 | EQ-5D-5L data was used to calculate health state utility values |

## 10.1 Presentation of the health-related quality of life EQ-5D-5L

### 10.1.1 Study design and measuring instrument

HRQoL was assessed in the CARTITUDE-4 trial using EQ-5D-5L, which is a standardized generic instrument used to measure HRQoL. The instrument includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on five levels of severity, ranging from no problems to extreme problems, enabling a detailed assessment of an individual's health [77]. The a priori expectations were that patients in the cilta-cel arm would have a higher HRQoL due to longer progression free survival. The choice of patient-reported outcome (PRO) is not expected to introduce any risk of bias. EQ-5D is a validated and widely used instrument specifically designed to assess HRQoL across diverse patient populations. In this assessment, the efficacy of cilta-cel is evaluated using the ITT population. However, for HRQoL analysis, EQ-5D-5L data were included only from patients who completed the questionnaires, resulting in a smaller sample size attributable to missing data. This may affect the health economic analysis by limiting representativeness and introducing potential bias.

### 10.1.2 Data collection

In the CARTITUDE-4 clinical trial, EQ-5D data was collected from subjects at each cycle until disease progression warranted discontinuation or unacceptable. The HRQoL-evaluable population was defined as those in the ITT population who had completed at least one EQ-5D-5L measurement. The two treatment arms were well-balanced regarding demographics and baseline clinical characteristics [62]. The ITT population comprised 419 subjects: 208 in the cilta-cel group and 211 in the PC group. Of these, 191 individuals in the cilta-cel group and 182 in the PC group contributed to the EQ-5D-5L measurement (see Table 29 and Table 30 for the time points for data collection are along with the completion rates for cilta-cel and PC, respectively).

Available data decreased over time, and the completion rate was similar in both groups until the last timepoint. At 30 months, the completion rate was higher in the PC group compared to the cilta-cel group. Missing EQ-5D-5L data were not imputed; instead, it was assumed that the characteristics of patients with missing data were consistent with those of patients with no missing data.

**Table 29 Pattern of missing data and completion cilta-cel**

| Time point (months) | HRQoL population N | Missing N (%) | Expected to complete N | Completion N (%) |
|---|---|---|---|---|
| | Number of patients at randomization | Number of patients for whom data is missing (% of patients at randomization) | Number of patients "at risk" at time point X | Number of patients who completed (% of patients expected to complete) |
| **Baseline** | 208 | 17 (8.2%) | 208 | 191 (91.8%) |
| **Cycle 3** | 208 | 76 (36.5%) | 173 | 132 (76.3%) |
| **Cycle 6** | 208 | 76 (36.5%) | 166 | 132 (79.5%) |
| **Cycle 9** | 208 | 81 (38.9%) | 162 | 127 (78.4%) |
| **Cycle 12** | 208 | 92 (44.2%) | 155 | 116 (74.8%) |
| **Cycle 18** | 208 | 106 (51.0%) | 140 | 102 (72.9%) |
| **Cycle 24** | 208 | 109 (52.4%) | 130 | 99 (76.2%) |
| **Cycle 30** | 208 | 130 (62.5%) | 116 | 78 (67.2%) |
| **Cycle 36** | 208 | 171 (82.2%) | 51 | 37 (72.5%) |
| **Cycle 42** | 208 | 200 (96.2%) | 11 | 8 (72.7%) |
| **Cycle 48** | 208 | 208 (100%) | 2 | 0 |

**Table 30 Pattern of missing data and completion PC**

| Time point (months) | HRQoL population N | Missing N (%) | Expected to complete N | Completion N (%) |
|---|---|---|---|---|
| | Number of patients at randomization | Number of patients for whom data is missing (% of patients at randomization) | Number of patients "at risk" at time point X | Number of patients who completed (% of patients expected to complete) |
| **Baseline** | 211 | 28 (13.3%) | 209 | 183 (87.6%) |
| **Cycle 3** | 211 | 74 (35.1%) | 161 | 137 (85.1%) |
| **Cycle 6** | 211 | 98 (46.4%) | 128 | 113 (88.3%) |
| **Cycle 9** | 211 | 112 (53.1%) | 112 | 99 (88.4%) |
| **Cycle 12** | 211 | 135 (64.0%) | 93 | 76 (81.7%) |
| **Cycle 18** | 211 | 153 (72.5%) | 74 | 58 (78.4%) |
| **Cycle 24** | 211 | 165 (78.2%) | 57 | 46 (80.7%) |
| **Cycle 30** | 211 | 171 (81.0%) | 48 | 40 (83.3%) |
| **Cycle 36** | 211 | 200 (94.8%) | 13 | 11 (84.6%) |
| **Cycle 42** | 211 | 211 (100%) | 1 | 0 |
| **Cycle 48** | 211 | 211 (100%) | 0 | 0 |

### 10.1.3 HRQoL results

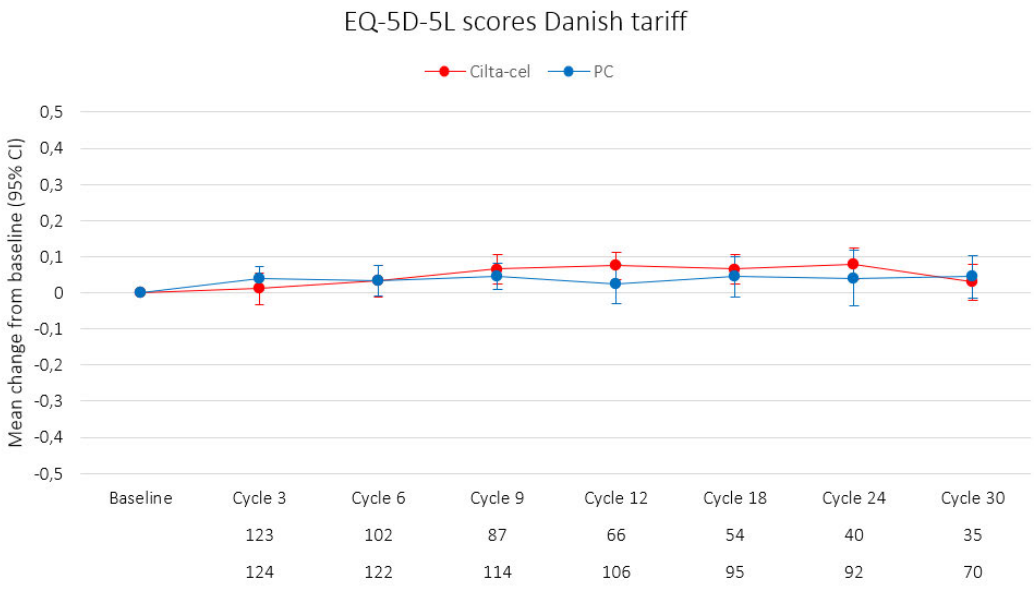



**Figure 13 Mean EQ-5D-5L score change from baseline for cilta-cel and PC**

Table 31 shows the EQ-5D-5L indexes for the cilta-cel arm and PC arm. The estimated differences between arms are overall not statistically significant, indicating that the HRQoL is comparable for the cilta-cel arm and the PC arm. Data from baseline until cycle 30 is presented, as the number of observations past cycle 30 is limited.

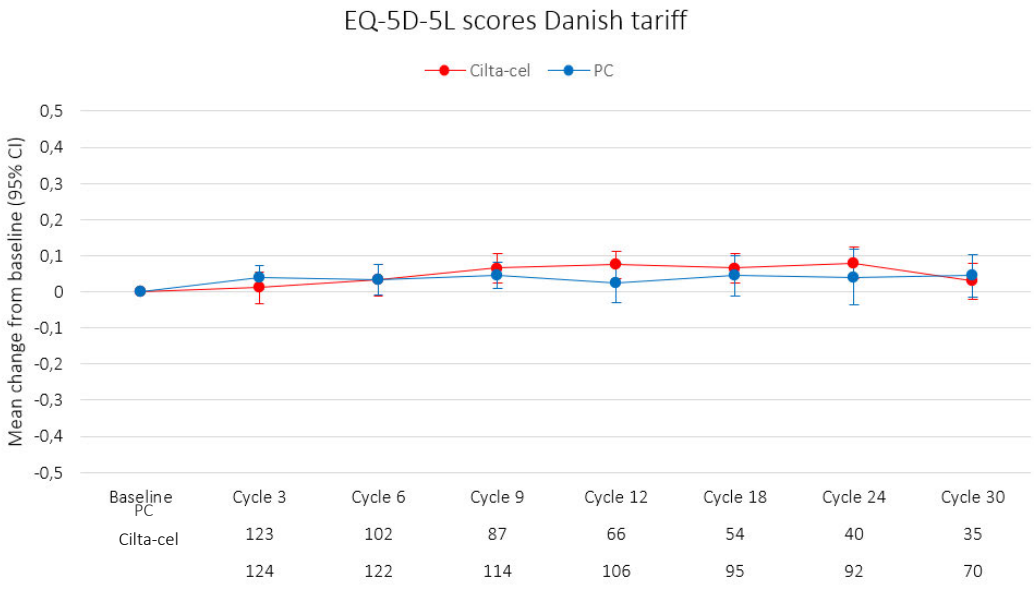



**Figure 13 Mean EQ-5D-5L score change from baseline for cilta-cel and PC**

**Table 31 HRQoL EQ-5D-5L summary statistics**

| | Cilta-cel | | PC | | Cilta-cel vs. PC |
|---|---|---|---|---|---|
| | N | Mean (SE) | N | Mean (SE) | Difference (95% CI) p-value |
| **Baseline** | 191 | 0.77(0.02) | 181 | 0.81 (0.02) | -0.04 (-0.09, 0.01), 0.09 |
| **Cycle 3** | 132 | 0.81 (0.02) | 137 | 0.87 (0.02) | -0.06 (-0.10, -0.01), 0.03 |
| **Cycle 6** | 132 | 0.85 (0.02) | 113 | 0.85 (0.02) | 0.00 (-0.05, 0.05), 0.97 |
| **Cycle 9** | 127 | 0.88 (0.01) | 99 | 0.86 (0.02) | 0.02 (-0.03, 0.06), 0.41 |
| **Cycle 12** | 116 | 0.87 (0.02) | 76 | 0.84 (0.02) | 0.03 (-0.02, 0.09), 0.25 |
| **Cycle 18** | 102 | 0.89 (0.01) | 58 | 0.86 (0.02) | 0.03 (-0.01, 0.08), 0.15 |
| **Cycle 24** | 99 | 0.89 (0.02) | 46 | 0.83 (0.03) | 0.07 (0.00, 0.13), 0.04 |
| **Cycle 30** | 73 | 0.86 (0.02) | 39 | 0.89 (0.02) | -0.03 (-0.08, 0.03), 0.38 |

## 10.2 Health state utility values (HSUVs) used in the health economic model

Utility values were applied to each health state in the model to capture the quality of life associated with treatment and disease outcomes. HRQoL data from CARTITUDE-4 were pooled across treatment arms to estimate HSUVs for PF and PD. No treatment-specific utilities were applied, so there is only one value for PF and one value for PD, regardless of the treatment arm.

### 10.2.1 HSUV calculation

PF and PD state utilities were estimated from EQ-5D-5L assessed while patients were PF (and not censored for progression) and after patients had progressed, in the CARTITUDE-4 trial, respectively. The HSUVs are estimated based on data from baseline to cycle 30, as the number of observations past cycle 30 is limited. Mixed-model repeated measures (MMRM) accounting for correlations between measurements from the same patients were used. The EQ-5D-5L index scores used as utility weights in the health economic analysis, were derived using the 01 May 2024 DCO of the CARTITUDE-4 study and Danish-specific preference weights. These were then age-adjusted according to the DMC guidelines.

For PF, cycle-specific MMRM analyses were conducted so that utility estimates of patients who have progressed before a cycle do not influence the utility estimate for that cycle. First, for each EQ-5D-5L collection time point, a separate MMRM was fit using

information only from patients who stayed progression-free until that time point, including all their available EQ-5D-5L results up to and including that time point, and using the visit as a categorical predictor, to get time specific utility estimates. Second, from each of these MMRMs, the least squares mean estimate of the last time point was used as the utility estimate for that time point.

The choice of covariance structure for the MMRM models was based on the model that incorporated all PRO values during PFS and had the lowest AIC. The unstructured covariance matrix had the lowest AIC, with this approach estimating a unique correlation coefficient for each pair of time points, allowing the ability to model the observed data closely. No covariates were included in the analysis, as any relevant covariates are expected to be balanced across the treatment arms due to randomisation.

The area under the curve of the PF estimates was used to estimate the mean utility value for the PF state. A single MMRM model was used to estimate the mean utility value in the PD health state.

#### 10.2.1.1 Mapping

Not applicable.

### 10.2.2 Disutility calculation

In CARTITUDE-4, the duration of AEs was assessed, making it relevant to include utility decrements associated with the AEs to capture their impact on quality of life during treatment. Utility decrements due to AEs were not measured in CARTITUDE-4 but were sourced from publications and previous HTA submissions. The duration of AEs was, as previously stated, based on CARTITUDE-4 for all AEs, except for cardiac disorders and infusion-related reactions, where data from CARTITUDE-1 [78] was used since it was not available in CARTITUDE-4. In the health economic model, AE-related utility decrements were calculated by dividing the duration of the AE by 365.25 (one year) and then multiplying the result by the associated disutility value. Details on the AEs included in the health economic model are presented in Table 32.

**Table 32 Summary of adverse event disabilities applied in the model**

| Adverse event | Duration of AEs (days) | Disutility | AE-related utility decrement |
|---|---|---|---|
| CRS, Grade 1-2 | 3.58 | -0.0500 | -0.0005 |
| CRS, Grade 3+ | 5.00 | -0.7862 | -0.0108 |
| Neurotoxicity, Grade 1-2 | 131.52 | 0.0000 | 0.0000 |
| Neurotoxicity, Grade 3+ | 16.20 | 0.0000 | 0.0000 |

| | | | |
|---|---|---|---|
| Anaemia | 16.78 | -0.3100 | -0.0139 |
| Febrile neutropenia | 6.90 | -0.3900 | -0.0071 |
| Infusion-related reaction | 4.25 | 0.0000 | 0.0000 |
| Leukopenia | 37.31 | -0.0650 | -0.0019 |
| Lower respiratory tract infection | 19.00 | -0.1900 | -0.0099 |
| Lymphopenia | 65.26 | -0.0650 | -0.0114 |
| Nausea | 10.00 | -0.1000 | -0.0027 |
| Neutropenia | 45.56 | -0.1500 | -0.0162 |
| Respiratory infection | 9.25 | -0.1900 | -0.0048 |
| Thrombocytopenia | 51.36 | -0.3100 | -0.0412 |
| Hypogammaglobulinemia | 136.44 | 0.0000 | 0.0000 |

### 10.2.3 HSUV results

The HSUVs are presented in Table 33.

**Table 33 Overview of health state utility values and disutilities**

| | Results (95% CI) | Instrument | Tariff | Comments |
|---|---|---|---|---|
| **HSUVs** | | | | |
| Progression-free | 0.8575<br>(0.8449-0.8653) | EQ-5D-5L | DK | Estimate is based on pooled PF data for both trial arms |
| Progressed disease | 0.7954<br>(0.7643-0.8265) | EQ-5D-5L | DK | Estimate is based on pooled PD data for both trial arms |
| **Disutilities** | | | | |

| | | | | |
|---|---|---|---|---|
| CRS, Grade 1-2 | -0.0500 | EQ-5D-5L | UK | Based on CRS grade 2 disutility [64] |
| CRS, Grade 3+ | -0.8575 | EQ-5D-5L | DK | Assumed equal to PF HSUV |
| Neurotoxicity, Grade 1-2 | 0.0000 | N/A | N/A | Assumed to be captured as a part of CRS disutility |
| Neurotoxicity, Grade 3+ | 0.0000 | N/A | N/A | Assumed to be captured as a part of CRS disutility |
| Anaemia | -0.3100 | EQ-5D | Unknown | Estimated as an average based on moderate and severe anaemia [65] |
| Febrile neutropenia | -0.3900 | Study specific standard gamble questionnaire | N/A | Difference between *before starting chemotherapy* and *febrile neutropenia with hospitalisation [66]* |
| Infusion-related reaction | 0.0000 | | N/A | |
| Leukopenia | -0.0650 | QWB-SA | N/A | Assumed equal to the disutility of neuropathy [67] |
| Lower respiratory tract infection | -0.1900 | Study specific standard gamble questionnaire | N/A | Assumed equal to the disutility of pneumonia [70] |
| Lymphopenia | -0.0650 | QWB-SA | N/A | Assumed equal to the disutility of neuropathy [67] |
| Nausea | -0.1000 | EQ-5D | Unknown | Assumed equal to the disutility of vomiting [68] |
| Neutropenia | -0.1500 | EQ-5D | Unknown | [68] |
| Respiratory infection | -0.1900 | Study specific standard gamble questionnaire | N/A | Assumed equal to the disutility of pneumonia [70] |
| Thrombocytopenia | -0.3100 | EQ-5D | Unknown | Estimated as an average based on moderate and severe anaemia [65] |

| | | |
|---|---|---|
| Hypogammaglobulinemia | 0.0000 | N/A |

## 10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy N/A

Not applicable.

### 10.3.1 Study design N/A

Not applicable.

### 10.3.2 Data collection N/A

Not applicable.

### 10.3.3 HRQoL Results N/A

Not applicable.

### 10.3.4 HSUV and disutility results N/A

Not applicable.

**Table 34 Overview of health state utility values [and disutilities] N/A**

| | Results [95% CI] | Instrument | Tariff (value set) used | Comments |
|---|---|---|---|---|
| N/A | | | | |

**Table 35 Overview of literature-based health state utility values N/A**

| | Results [95% CI] | Instrument | Tariff (value set) used | Comments |
|---|---|---|---|---|
| N/A | | | | |

# 11. Resource use and associated costs

The health economic analysis adopts a limited societal perspective. Costs considered in the base case included drug acquisition, the pre-treatment for patients in the cilta-cel

arm, co-medications, drug administration, disease management, AE management, and patient cost including transportation and patient time, reflecting the time spent in connection with treatment. All costs were reported in DKK from 2024.

Pre-treatment costs included leukapheresis, bridging therapy, and conditioning therapy (cyclophosphamide and fludarabine). Based on patients originally assigned to receive cilta-cel in the CARTITUDE-4 trial, these costs were applied to 107% (a proportion of patients had leukapheresis twice), 100% and 94.2%, respectively. The drug acquisition and infusion costs of cilta-cel were applied as a one-time cost to 94.2% (196/208) of patients on the cilta-cel model arm, representing the proportion of patients infused in CARTITUDE-4.

## 11.1 Medicines - intervention and comparator

Medicines for the intervention and comparator used in the model are presented in Table 36. The dosing was based on clinical trials or the respective regimen's SmPC. As per DMC guidelines, all drug acquisition unit costs included in the model are found in the CE-model sheet 'Medicines'. The medicine with the lowest price per mg was chosen for drugs with multiple package sizes available. The cost for cilta-cel was applied as a one-off cost at the time of infusion for the proportion of patients who received cilta-cel in CARTITUDE-4 (see further section 11.1.1).

Wastage was accounted for in the base case analysis as a conservative assumption for the real-world clinical setting, where vial sharing is not always feasible. Relative dose intensity was not included, but dose skipping was applied as the proportion of dose administered, representing the probability that a given administration will not take place. Dose skipping was based on the clinical trial data in four steps: First, the number of doses administered to all patients were summed. Second, the total number of doses that were expected to be administered while the patients have been on treatment according to dosing schedule was calculated. Third, the sum of administered doses was divided by the sum of expected doses to calculate the proportion of expected doses that were administered. For cilta-cel 94.23% included the proportion of patients receiving infusion with cilta-cel after undergone apheresis.

**Table 36 Medicines used in the model**

| Medicine | Dose | Relative dose intensity[1] | Frequency | Vial sharing |
|---|---|---|---|---|
| **Ciltacabtagene autoleucel** | 0.75 x $10^6$ CAR-positive viable T cells/kg[2] | 94.23% | Single dose | No |
| **DVd** | | | Administrated in 21-day cycles. | |

| | | | | |
|---|---|---|---|---|
| Daratumumab | 16 mg/kg | 90% | Administered once weekly for the first 9 weeks, then every 3 weeks for 15 weeks, and thereafter once every 4 weeks. | No |
| Bortezomib | 1.3 $mg/m^2$ | 77% | Administered on days 1, 4, 8, and 11 for 8 cycles. | No |
| Dexamethasone | 20 mg | 100% | Taken on days 1, 2, 4, 5, 8, 9, 11 and 12 for 8 cycles. | No |
| **PVd** | | | Administered in 21-day cycle. | |
| Pomalidomide | 4 mg | 88% | Taken once daily on days 1 to 14, followed by one week rest period. | No |
| Bortezomib | 1.3 $mg/m^2$ | 77% | Administered daily on days 1, 4, 8 and 11 in cycle 1-8, thereafter on day 1 and 8 in following cycles. | No |
| Dexamethasone | 20 mg | 100% | Administered on the same days as bortezomib and the day after, i.e., taken on days 1, 2, 4, 5, 8, 9, 11 and 12 in cycle 1.8 and thereafter on days 1, 2, 8, and 9 in following cycles. | No |
| **Kd** | | | Administered in 28-day cycles. | |
| Carfilzomib | 20/56 $mg/m^2$ | 77% | Carfilzomib administered on days 1, 2, 8, 9, 15 and 16 followed by a 12-rest period. Carfilzomib is administered at a starting dose of 20 $mg/m^2$ (maximum dose of 44 mg) on days 1 and 2 of cycle 1. If this dose is well-tolerated, it is increased to 56 $mg/m^2$ (maximum dose of 123 mg) starting on day 8 of cycle 1. | No |
| Dexamethasone | 20 mg | 100% | Dexamethasone (20 mg) administered twice weekly, on days 1, 2, 8, 9, 15, 16, 22 and 23. | No |

Note: [1] Dose skipping are presented here, as one minus the proportion of doses skipped, that represents the probability that a given administration will not take place. For cilta-cel this represent the proportions of patients receiving cilta-cel after having undergone apheresis. [2] Not exceeding 0.75 x $10^8$ CAR-positive viable T cells.

Abbreviations: Cilta-cel= ciltacabtagene autoleucel, kg = kilogram, mg=milligram, $m^2$ =square meter

### 11.1.1 Total cost of cilta-cel procedure

The total costs associated with cilta-cel treatment was 3,023,314 DKK and was applied as a one-off cost on the cilta-cel model arm. The total cost for cilta-cel included the price for cilta-cel (2,945,000 DKK), costs associated with co-medication, apheresis, conditioning, and bridging therapy (see details in following sections). Please note that the acquisition cost of CAR-T in the model is based on the price for cilta-cel but adjusted for product being out of specification (OSS [cost DKK 1,000 per OOS]) and the proportion of patients that are initially selected to treatment that actually receives an infusion (94.23%).

## 11.2 Medicines– co-administration

### 11.2.1 Pre-treatment cost

Patients treated with cilta-cel should receive a sequence of apheresis, bridging therapy and conditioning regimen (cyclophosphamide and fludarabine) before cilta-cel infusion. The resource use associated with the pre-treatment period is presented in Table 37.

Apheresis was costed as a procedure based on DRG 16MP05 (25,006 DKK). In CARTITUDE-4, 193 patients (92.8%) underwent a single apheresis attempt, and 15 patients (7.2%) underwent two apheresis attempts. Therefore, assuming this may also be the case in Danish clinical practice, the model assumed 1.07 apheresis per patient. Further, 94.2% of patients received the conditioning regimen of cyclophosphamide IV 300 mg/$m^2$ and fludarabine IV 30 mg/$m^2$ daily). Conditioning therapy costs included three days of cyclophosphamide and three days of fludarabine based on CARTITUDE-4.

Bridging therapy was to be started after apheresis. As per the CARTITUDE-4 trial, 100% of the patients in the Carvykti® arm of the model are assumed to receive bridging therapy for a mean duration of 7.75 weeks. In CARTITUDE-4 bridging therapy was given with either DPd, 182 patients (87.5%) or PVd, 26 patients (12.5%). Based on Danish clinical praxis, 87.5% was assumed receiving DVd for bridging therapy and 12.5% PVd.

Table 38 present the unit cost of conditioning therapy.

**Table 37 Apheresis, bridging therapy, and conditioning therapy resource use**

| | Value | Source |
|---|---|---|
| Unit cost apheresis (DKK) | 25,006 DKK | DRG 16MP05 |
| % receiving apheresis | 100% | CARTITUDE-4 |
| Average number of apheresis procedures per patient | 1.07 | CARTITUDE-4 |

| | | |
|---|---|---|
| % receiving PVd bridging | 12.5% | Assumption based on CARTITUDE-4 with local adaptation |
| % receiving DVd bridging | 87.5% | Assumption based on CARTITUDE-4 with local adaptation |
| The average duration of bridging therapy | 7.75 weeks | CARTITUDE-4 (based on 2 cycles of PVd and DPd) |
| Percentage of patients receiving bridging therapy | 100% | CARTITUDE-4 |
| % receiving conditioning of patients that received apheresis | 94.2% | CARTITUDE-4 |
| Duration of conditioning therapy | 3 days | CARTITUDE-4 |

**Table 38 Conditioning therapy drug acquisition unit costs**

| Drug | Type of admin | Drug units (vials per pack) and Strength | Price per pack (DKK) | Dose | Relative dose intensity | Frequency | Source |
|---|---|---|---|---|---|---|---|
| Fludarabine | IV | 5 x 2 ml<br>25 mg/ml | 6,550.50 | 30 $mg/m^2$ | 100% | 0.43 weeks | Medicinpriser.dk - Fludarabinphosphat Ebewe, Varenummer: 492479[79] |
| Cyclophosphamide | IV | 1 x 500 mg | 192 | 300 $mg/m^2$ | 100% | 0.43 weeks | Medicinpriser.dk - Sendoxan Varenummer: 020307[79] |

### 11.2.2 Infusion cost

Patients receiving cilta-cel infusion were assumed to be hospitalised for the procedure. The cost was derived from the Danish-specific DRG (16MA11), which included 16 days of hospitalisation. This was also the approximate average number measured in CARTITUDE-4 (16.6 days). The cost related to hospital stay was 60,906 DKK (see Table 39).

**Table 39 Cilta-cel infusion cost**

| | Frequency | Unit Cost (DKK) | DRG code | Reference |
|---|---|---|---|---|
| Hospital inpatient stay | Once | 69,813 | DRG 16MA11 | DRG 2025 |

### 11.2.3 Concomitant Medication

Concomitant medications were defined as any drugs given in addition to the active treatment regimens, excluding any drugs prescribed to manage AEs. CAR-T-related prophylaxis and other associated costs encompassed expenses for intravenous immunoglobulin, prophylactic antiviral, antibacterial, and antifungal therapies. Based on CARTITUDE-4, the model includes the costs of intravenous immunoglobulin (IVIG) and prophylactic treatments in the cost of concomitant medications, Table 40 present the use of concomitant medications based on the CARTITUDE-4 trial applied in the model – the incremental difference is used in the model.

Table 41 presents dosing, treatment duration and price assumptions used in the model for IVIG and prophylactic treatments.

**Table 40 Prophylactic use in CARTITUDE-4**

| Treatment | Cilta-cel (N=208) | PC (N=208) | Difference |
|---|---|---|---|
| Intravenous immunoglobulin | 42.8% | 18.3% | 25.0% - units |
| Prophylactic antiviral: aciclovir | 98.6% | 97.1% | 1.5% - units |
| Prophylactic anti-bacterial: levofloxacin | 92.2% | 64.4% | 27.8% - units |
| Prophylactic antifungal: fluconazole | 52.2% | 6.3% | 45.9% - units |

**Table 41 Dosing and cost information for IVIG and prophylactic treatments**

| Treatment | Drug Units per Package | Strength (mg) | Price per Pack (DKK) | Dose per Admin (mg) | Number of Admins per Course | Total Cost per Course (DKK) | Reference [79] |
|---|---|---|---|---|---|---|---|
| IVIG | 1 x 5 ml | 200 mg/ml | 503.73 | 1,000 mg infusion | 16.9 | 8,513 | Medicinpriser.dk, Hizentra, Varenummer 426888 |
| Antiviral: aciclovir | 100 | 200 mg | 62.10 | 400 mg 4 times daily for 14 days | 56 | 69.55 | Medicinpriser.dk, Aciclovir "1A Farma" Varenummer 590036 |
| Antibacterial: levofloxacin | 10 tablets | 500 mg | 497.00 | 500 mg | 14 | 695.80 | Medicinpriser.dk, Levofloxacin "Nordic Prime, Varenummer 494622 |
| Antifungal: fluconazole | 28 tablets | 50 mg | 152.00 | 400 mg daily for at least 7 days (assumed 14 days) | 14 | 608.00 | Medicinpriser.dk, Fluconazol "HEXAL" Varenummer 149783 |

Abbreviations: IVIG = intravenous immunoglobulin, mg = milligram.

## 11.3 Administration costs

Drug administration cost for infusion treatment is included in the analysis, based on the DRG 17MA98, see Table 42.

**Table 42 Administration costs used in the model**

| Administration type | Frequency | Unit cost [DKK] | DRG code | Reference |
|---|---|---|---|---|
| **Administration** | According to product dosing frequency, see Table 36 | 2,136 | 17MA98, MDC17 1-dagsgruppe, pat. Mindst 7 år. | DRG 2025 |

## 11.4 Disease management costs

The model captures routine monitoring and follow-up care costs post-infusion for cilta-cel (Table 43) and routine monitoring costs during the PF and PD state for cilta-cel and PC (Table 44).

Post-infusion monitoring costs for cilta-cel were applied to all infused patients, starting from discharge on Day 17 to Day 112 after cilta-cel administration. The frequency of resource use was based on CARTITUDE-4 CSR and included a haematology visit and lab test at intervals that averaged [redacted] week. The cost was based on the DRG 17MA98, and the lab test was assumed to be covered within the DRG cost for the haematology visit.

Routine monitoring during the PF state and PD state for cilta-cel and PC included a haematology visit once every month (0.25 times per week), an assumption based on the same frequency that was applied in the DMC teclistamab assessment [80].

**Table 43 Weekly resource use for cilta-cel specific monitoring post infusion day 17 to day 112**

| Activity | Frequency | Unit cost [DKK] | Reference |
|---|---|---|---|
| **Outpatient visit (Haematologist visit)** | 0.29 per week | 2,136 | DRG 2025: 17MA98 [81]<br>Frequency based on CARTITUDE-4 |
| **Biochemistry** | | 0 | Assumed covered in DRG 2025: 17MA98.<br>Frequency based on CARTITUDE-4 |
| **Vital signs, including oxygen saturation** | | 0 | |
| **Quantitative immunoglobulin** | | 0 | |
| **Protein electrophoresis** | | 0 | |
| **24-hour urine protein electrophoresis sample** | | 0 | |
| **Serum calcium corrected for albumin** | | 0 | |

**Table 44 Weekly resource use for routine follow-up care cilta-cel and PC**

| Activity | Frequency | | Unit cost [DKK] | Reference |
|---|---|---|---|---|
| | PFS | PPS | | |
| **Outpatient visit (Haematologist visit)** | Once per month (0.25 per week) | Once per month (0.25 per week) | 2,136 | DRG 2025: 17MA98 |

| | |
|---|---|
| | Frequency based on teclistamab evaluation [80]. |

## 11.5 Costs associated with management of adverse events

Costs associated with AEs were included in the analysis and are presented in Table 45. The latest available DRG weights (2024) were used following Danish guidelines [82].

Costs associated with AEs were applied as one-off costs in the first cycle of the model. The frequency of AEs is presented in section 9.

**Table 45 Costs associated with the management of adverse events**

| | DRG code | Unit cost/DRG tariff |
|---|---|---|
| **CRS, Grade 1-2** | DRG 18MA04 divided by Trimpunkt 6 | DKK 3,849.50 |
| **CRS, Grade 3+** | DRG 18MA04 | DKK 23,097.00 |
| **Neurotoxicity, Grade 1-2** | DRG 21MA05 | DKK 13,784.00 |
| **Neurotoxicity, Grade 3+** | DRG 21MA07 | DKK 19,963.00 |
| **Anaemia** | DRG 16MA05 | DKK 43,485.00 |
| **Asthenia** | DRG 49SP01 | DKK 8,449.00 |
| **Febrile neutropenia** | DRG 49PR07 | DKK 20,988.00 |
| **Infusion-related reaction** | DRG 09MA09 | DKK 2,441.00 |
| **Insomnia** | Assumed to not be associated with any additional costs | DKK 0.00 |
| **Leukopenia** | DRG 17MA05 | DKK 49,350.00 |
| **Lower respiratory tract infection** | DRG 04SP01 | DKK 4,077.00 |
| **Lymphopenia** | DRG 17MA05 | DKK 49,350.00 |
| **Nausea** | DRG 06MA17 | DKK 3,402.00 |
| **Neutropenia** | DRG 49PR07 | DKK 20,988.00 |
| **Respiratory infection** | DRG 04SP01 | DKK 4,077.00 |
| **Thrombocytopenia** | DRG 16MA03 | DKK 37,482.00 |

| | DRG code | Unit cost/DRG tariff |
|---|---|---|
| **Hypogammaglobulinemia** | DRG 16MP02 | DKK 35,286.00 |

* 35,000 SEK inflated to 2024 (24.18% increase (SCB 2023[83])) and converted to DKK (exchange rate 0.65).

## 11.6 Subsequent treatment costs

The choice subsequent treatment impacts costs but not survival outcomes in the model. The cost of subsequent treatment is applied as a one-off cost upon disease progression and has three important components:

- The proportion of the cohort who will receive subsequent treatment
- The distribution of different subsequent treatment regimens
- The expected duration of subsequent treatment

For each model cycle, the change in PFS state membership is calculated (i.e. PFS survival in cycle *i* minus PFS survival in cycle *i-1*). In the base case scenario, this difference is then multiplied by the proportion of deaths where the cause of progression was recorded as death relative to the total number of deaths (20%, pooled from both treatment arms). This calculation yields the count of new progressors (those transitioning to PPS) to estimate costs associated with subsequent treatments. This value is then multiplied by the percentage receiving subsequent treatment estimated from the CARTITUDE-4 trial.

A total of 52 participants in the cilta-cel and 138 in the PC arm received subsequent anti-myeloma therapy, while 68 and 147 patients survived their progression event. Over both arms, 190 (52 + 138) received subsequent therapy of a total of 215 (68 + 147). The proportion of patients alive receiving subsequent was thus estimated to 190/215 = 0.8837 (88.37%) and applied to both arms of the model.

The composition of subsequent treatments was based on the CARTITUDE-4 trial but adjusted to reflect the Danish clinical practice presented in Table 46.

The average duration of subsequent treatment was estimated based on the time patient spend in the post-progression health state but adjusted to account for treatment-free intervals, using data from CARTITUDE-4. For the cilta-cel arm this rendered an average duration of subsequent treatment to 29 months, while the corresponding duration for the PC arm was 30 months.

The dosing schedule for the subsequent treatments is presented in Table 47. In the base case scenario, wastage is assumed.

**Table 46 Subsequent treatment**

| Subsequent medicine | Prior treatment | Prior treatment |
|---|---|---|
| | **Cilta-cel** | **PC of DVd and PVd** |
| **Cilta-cel** | 1.88% | 22.03% |

| | | |
|---|---|---|
| **Teclistamab** | 20.91% | 32.77% |
| **Kd** | 38.60% | 22.59% |
| **Pd** | 38.60% | 22.59% |

Abbreviations: cilta-cel = ciltacabtagene autoleucel, Kd=carfilzomib + dexamethasone, Pd= pomalidomide + dexamethasone

**Table 47 Medicines of subsequent treatments**

| Medicine | Dose | Relative dose intensity[1] | Frequency | Vial sharing |
|---|---|---|---|---|
| **Cilta-cel** | 0.75 x $10^6$ CAR-positive viable T cells/$kg^2$ | 94.23% | Single dose | No |
| **Teclistamab** | 0.06/0.3/1.5 mg/kg | 93% | 0.06 and 0.3 mg/kg priming dose in week 1; 1.5 mg/kg once weekly thereafter | No |
| **Kd** | | | | |
| Carfilzomib | 20/56 mg /$m^2$ | 77% | Twice weekly for 3 weeks, followed by 1 week rest period | No |
| Dexamethasone | 20 mg | 100% | Twice weekly | No |
| **Pd** | | | | |
| Pomalidomide | 4 mg | 86% | Daily for 3 weeks, followed by 1 week rest period | No |
| Dexamethasone | 40 mg | 100% | Weekly | No |

Note: [1] Dose skipping are presented here, as one minus the proportion of doses skipped, that represents the probability that a given administration will not take place. For cilta-cel this represent the proportions of patients receiving cilta-cel after having undergone apheresis. [2] Not exceeding 0.75 x 108 CAR-positive viable T cells

Abbreviations: cilta-cel = ciltacabtagene autoleucel, Kd=carfilzomib + dexamethasone, kg = kilogram, mg=milligram, $m^2$ =square meter, Pd= pomalidomide + dexamethasone.

## 11.7 Patient costs

The analysis adopts a limited societal perspective, accounting for non-medical costs i.e. as patient costs for time spent receiving treatment, e.g., in relation to administration of drugs and travel costs to and from the hospital. The cost of patient time and transportation costs were estimated using the hourly wage of DKK 188 [84] and

transportation costs DKK 140 per round trip based on from *Værdisætning af Enhedsomkostninger* 2024 [84] (Table 48)

For cilta-cel, patient time and patient transportation costs were included for the pre-treatment (apheresis, infusion and conditioning). For apheresis and conditioning this included a visit, each of 4 hours respectively, along with the associated transportation costs (a roundtrip). For clita-cel, as patients are hospitalised for 16 days in connection with the infusion, 16 days x 24h of patient time and transportation cost (one roundtrip) was assumed.

For PC and subsequent therapies each drug administration included 4 hours of patient time and a round trip.

Monitoring in PF and PD state included a haematology visit once per month, both in the PC arm and the cilta-cel arm. Patient time of 4 hours per visit and one round trip was assumed for monitoring in both arms (see Table 44).

**Table 48 Patient costs used in the model**

| Activity | Time spent [minutes, hours, days] | Unit cost |
|---|---|---|
| **Cilta-cel apheresis** | 4 hours x 1 time at apheresis | 188 DKK per hour + 140 DKK (roundtrip) |
| **Cilta-cel conditioning** | 4 hours x 1 time at conditioning | 188 DKK per hour + 140 DKK (roundtrip) |
| **Cilta-cel infusion** | 384 hours (16 days x 24 hours) time | 188 DKK per hour + 140 DKK (roundtrip) |
| **Drug administration (non CAR T)** | 4 hours x every 21-day cycle as per dosing schedule | 188 DKK per hour + 140 DKK (roundtrip) |
| **Monitoring PF and PD** | 4 hours once per month | 188 DKK per hour + 140 DKK (roundtrip) |

## 11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not included.

# 12. Results

## 12.1 Base case overview

The base case overview is presented in Table 49.

**Table 49 Base case overview**

| Feature | Description |
|---|---|
| Comparator | Physician's choice of DVd and PVd |
| Type of model | Markov model with PSM structure |
| Time horizon | 40 years (lifetime) |
| Discount rate | 3.5 % for costs and health effects |
| Treatment line | 2L and 3L |
| Measurement and valuation of health effects | EQ-5D-5L with Danish population weights were used to estimate health-state utility values |
| Costs included | Medicine costs<br>Hospital costs<br>Costs of adverse events<br>Patient costs |
| Dosage of medicine | Based on weight |
| Average time on treatment | Intervention: N/A<br>Comparator: 2.35 (PFS) |
| Parametric function for PFS | Intervention: lognormal<br>Comparator: lognormal |
| Parametric function for OS | Intervention: lognormal<br>Comparator: lognormal |
| Inclusion of waste | No |
| Average time in model health state | Progression free: cilta-cel = 10.2 years; PC =0.6 years.<br>Progressed: cilta-cel = years; PC= years.<br>Overall survival: cilta-cel = 15.5 years; PC = 7.9 years |

### 12.1.1 Base case results

Table 50 include the base results for cilta-cel versus PC of DVd and PVd over a lifetime from a Danish limited societal perspective.

The ICER of cilta-cel was estimated to DKK 342,471/QALY (DKK 286,632/LY) compared to PC of DVd and PVd. There was a substantial gain in QALYs for patients who received cilta-cel compared with those who received PC. The base case result showed that cilta-cel resulted in an additional 3.85 QALYs (4.60 LYs), compared to PC alone. The incremental cost of the cilta-cel compared to PC was DKK 767,708.

**Table 50 Base case results, discounted estimates**

| | Cilta-cel | PC of DVd and PVd | Difference |
|---|---|---|---|
| Medicine costs | [redacted] | [redacted] | [redacted] |
| Administration | 65,785 | 117,011 | 51,225 |
| Disease management costs | 291,591 | 169,746 | 121,844 |
| Costs associated with management of adverse events | 76,506 | 41,692 | 34,814 |
| Subsequent treatment costs | [redacted] | [redacted] | [redacted] |
| Patient costs | 217,966 | 141,288 | 76,678 |
| Palliative care costs | 0 | 0 | 0 |
| **Total costs** | [redacted] | [redacted] | [redacted] |
| Life years gained (PFS) | 7.27 | 2.08 | 5.19 |
| Life years gained (PPS) | 3.42 | 4.01 | -0.59 |
| **Total life years** | **10.69** | **6.09** | **4.60** |
| QALYs (PFS) | 6.13 | 1.78 | 4.36 |
| QALYs (PPS) | 2.66 | 3.15 | -0.49 |
| QALYs (adverse reactions) | -0.04 | -0.03 | -0.02 |
| **Total QALYs** | **8.75** | **4.90** | **3.85** |
| **Incremental costs per life year gained** | | | **286,632** |

| | |
|---|---|
| **Incremental cost per QALY gained (ICER)** | **342,741** |

## 12.2 Sensitivity analyses

### 12.2.1 Deterministic sensitivity analyses

**The uncertainty in a single parameter on the on ICER was tested in a one-way sensitivity (OWSA). The results of the OWSA analyses are presented in**

**Table 51 and**

Figure 14.

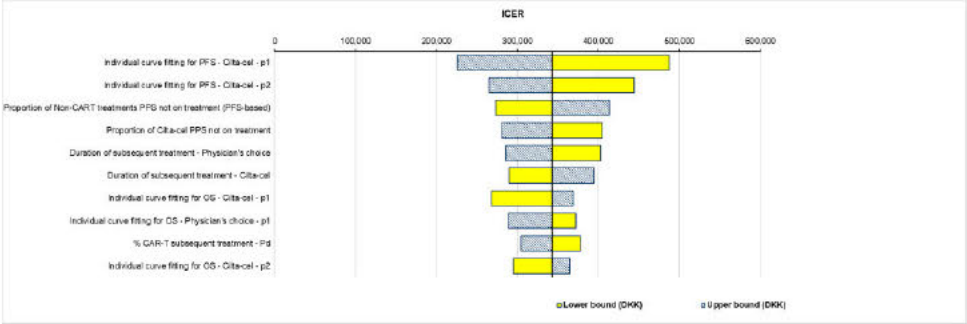
The parameter with the most significant influence on the ICER was the *individual curve fitting for PFS – cilta-cel – p1*. This parameter pertains to the first parameter of the lognormal survival model, specifically for the PFS outcome measure in the cilta-cel arm (the lognormal survival model is characterized by two parameters). Overall, the parameters of the survival model related to both key outcome measures (OS and PFS), as well as those parameters influencing subsequent treatment costs, exert the greatest impact on the ICER.

Table 51 One-way sensitivity analyses results

| | Base Case | Change (lower/upper) | Reason / Rational / Source | Incremental cost (DKK) | Incremental benefit (QALYs) | ICER (DKK/QALY) |
|---|---|---|---|---|---|---|
| **Base case** | - | - | - | [redacted] | **3.85** | **342,471** |
| **Individual curve fitting for PFS – cilta-cel – p1** | [redacted] | [redacted] | Uncertainty about long-term PFS; CARTITUDE-4 | [redacted] | [redacted] | 487,667 |
| | | [redacted] | | [redacted] | [redacted] | 226,018 |
| **Individual curve fitting for PFS – cilta-cel – p2** | [redacted] | [redacted] | Uncertainty about long-term PFS; CARTITUDE-4 | [redacted] | [redacted] | 444,148 |
| | | [redacted] | | [redacted] | [redacted] | 264,864 |
| **Proportion of Non-CART treatments PPS not on treatment (PFS-based)** | [redacted] | [redacted] | Uncertainty about treatment free intervals in PPS; CARTITUDE-4 | [redacted] | [redacted] | 273,111 |
| | | [redacted] | | [redacted] | [redacted] | 413,553 |
| **Proportion of cilta-cel PPS not on treatment** | [redacted] | [redacted] | Uncertainty about treatment free intervals in PPS; CARTITUDE-4 | [redacted] | [redacted] | 404,778 |
| | | [redacted] | | [redacted] | [redacted] | 281,224 |
| **Duration of subsequent treatment – PC** | [redacted] | [redacted] | Uncertainty about the duration of | [redacted] | [redacted] | 402,392 |
| | | [redacted] | | [redacted] | [redacted] | 286,049 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | subsequent treatments; CEM | | | |
| **Duration of subsequent treatment – cilta-cel** | [redacted] | [redacted] | Uncertainty about the duration of subsequent treatments; CEM | [redacted] | [redacted] | 289,664 |
| | | [redacted] | | [redacted] | [redacted] | 394,172 |
| **Individual curve fitting for OS – cilta-cel – p1** | [redacted] | [redacted] | Uncertainty about long-term OS; CARTITUDE-4 | [redacted] | [redacted] | 268,030 |
| | | [redacted] | | [redacted] | [redacted] | 368,478 |
| **Individual curve fitting for OS – PC – p1** | [redacted] | [redacted] | Uncertainty about long-term OS; CARTITUDE-4 | [redacted] | [redacted] | 372,178 |
| | | [redacted] | | [redacted] | [redacted] | 288,681 |
| **% CAR-T subsequent treatment – Pd** | [redacted] | [redacted] | Uncertainty about the subsequent treatment composition | [redacted] | [redacted] | 378,265 |
| | | [redacted] | | [redacted] | [redacted] | 304,323 |
| **Individual curve fitting for OS – cilta-cel – p2** | [redacted] | [redacted] | Uncertainty about long-term OS; CARTITUDE-4 | [redacted] | [redacted] | 294,944 |
| | | [redacted] | | [redacted] | [redacted] | 364,411 |

**Figure 14 Tornado diagram**




Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties relevant for the Danish clinical setting, these included assumptions around, comparator, discount rate, time horizon, parametric distributions used to extrapolate PFS and OS and time dependent utilities. Testing different discount rates is of particular interest as lower, or zero, discount rates may better reflect the sustained impact of treatment, ensuring that long-term health gains are not undervalued [85].

The ICER was robust in most scenarios tested, as the variations in the results across different scenarios do not show extreme or unreasonable fluctuations.

**Table 52 Scenario analysis**

| | Setting | Δ LYs | Δ QALYs | Δ Costs | ICER |
|---|---|---|---|---|---|
| **Base case** | - | 4.60 | [redacted] | [redacted] | 342,471 |
| **Discount rate cost and effects** | 3.5%, 1.5% | 6.05 | [redacted] | [redacted] | 262,745 |
| | 1.5%, 0% | 7.58 | [redacted] | [redacted] | 227,719 |
| **Time horizon** | 30 years | 4.47 | [redacted] | [redacted] | 337,323 |
| | 20 years | 3.56 | [redacted] | [redacted] | 365,762 |
| | 15 years | 2.70 | [redacted] | [redacted] | 452,603 |
| | 10 years | 1.64 | [redacted] | [redacted] | 716,428 |
| **Cilta-cel and PC OS extrapolation** | Loglogistic | 4.69 | [redacted] | [redacted] | 346,712 |
| **Cilta-cel OS extrapolation** | Gompertz | 5.98 | [redacted] | [redacted] | 377,483 |
| **Cilta-cel and PC PFS extrapolation** | Loglogistic | 4.60 | [redacted] | [redacted] | 380,235 |

| | | | | | |
|---|---|---|---|---|---|
| **Cilta-cel OS and PFS extrapolation** | Weibull | 3.55 | [redacted] | [redacted] | 504,836 |
| **Utility** | Time dependent | 4.60 | [redacted] | [redacted] | 333,772 |

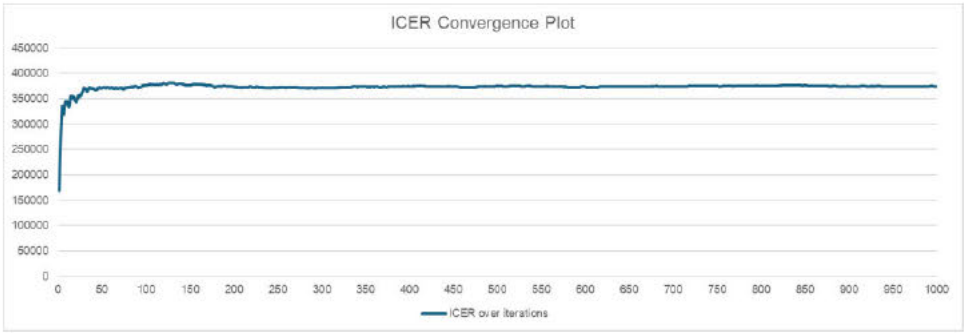
### 12.2.2 Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) shows the overall uncertainty of the incremental cost-effectiveness results for cilta-cel compared with PC of DVd and PVd. Further details are listed in Appendix G.

The PSA, which was run for 1,000 simulations, produced results consistent with the deterministic result. [redacted] displays the PSA iterations in a cost-effectiveness plane. The PSA iterations consistently demonstrated that cilta-cel was more costly and more effective compared to PC.

[redacted]

**Figure 16 ICER Convergence Plot**



# 13. Budget impact analysis

**Number of patients (including assumptions of market share)**

Below in Table 53 the estimated eligible patients are presented in the scenario where cilta-cel is recommended a market share of 50% at year 5 was assumed, with eligible patients in line with those described in section 3.2.

**Table 53 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| | | | **Recommendation** | | |
| **Cilta-cel** | 6 | 40 | 55 | 55 | 70 |
| **PC of DVd/PVd** | 134 | 100 | 85 | 85 | 70 |
| | | | **Non-recommendation** | | |
| **Cilta-cel** | 0 | 0 | 0 | 0 | 0 |
| **PC of DVd/PVd** | 140 | 140 | 140 | 140 | 140 |

**Budget impact**

[redacted] present the budget impact of recommending cilta-cel with all relevant costs included, as per DMC guidelines. The budget impact of recommending cilta-cel is [redacted]

[redacted]

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| The medicine under consideration is recommended | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| The medicine under consideration is NOT recommended | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Budget impact of the recommendation** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

# 14. List of experts

Not applicable.

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# Appendix A. Main characteristics of studies included

## A.1 CARTITUDE-4

**Table 55 Main characteristic of CARTITUDE-4**

| Trial name: CARTITUDE-4 | NCT04181827 |
|---|---|
| **Objective** | The primary objective of the trial was to compare the efficacy of cilta-cel with standard therapy (PVd or DPd), in terms of PFS. |
| **Publications – title, author, journal, year** | Unpublished data 2024.: Ciltacabtagene autoleucel ( Carvykti®). A Phase 3 Randomized study comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide Refractory Multiple Myeloma [62]. |
| **Study type and design** | CARTITUDE-4 is an ongoing, open-label, multicentre, phase III randomized controlled trial. It aims to evaluate the efficacy and safety of cilta-cel, a CAR-T cell therapy, compared to SoC treatments (PVd or DPd). The trial involves patients with relapsed or lenalidomide-refractory MM who have received 1-3 PLs of therapy. There was no crossover. |
| **Sample size (n)** | N=419 (Cilta-cel=208, PVd or DPd= 211) |
| **Main inclusion criteria** | -At least 18 years old.<br>-Documented diagnosis of MM according to International Myeloma Working Group (IMWG).<br>-Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.<br>-Measurable disease at screening is defined by one of the following: percentage of serum M- paraprotein 1.0 g/dL, urine M-protein level 200mg/24 hours, or light chain MM with serum free light chain 10 mg/dL and an abnormal serum free light chain ratio.<br>-Received 1 to 3 PLs including a PI and an IMiD, in which at least 1 complete cycle of each PL must have been completed. Exception made if PD was the best response to the line of therapy.<br>-Refractory to lenalidomide according to IMWG criteria.<br>**Fulfil clinical values during screening phase:**<br>-Hemoglobin ≥8 g/dL, absolute neutrophil count (ANC) ≥1 x $10^9$/L, platelet count ≥75 x $10^9$/L in patients in whom <50% of bone marrow nucleated cells are plasma cells; platelet count ≥50 x $10^9$/L in patients in whom ≥50% of bone marrow nucleated cells are plasma cells. |

| Trial name: CARTITUDE-4 | NCT04181827 |
|---|---|
| | -Lymphocyte count ≥0.3 x $10^9$/L<br><br>-Aspartate aminotransferase ≤0.3 x ULN<br><br>-Alanine aminotransferase ≤0.3 x ULN<br><br>-Total bilirubin ≤2.0 x ULN, exemption in patients with congenital bilirubinemia.<br><br>-Glomerular filtration rate 40mL/min per 1.73 $m^2$.<br><br>-Women of childbearing potential must have two negative pregnancy tests before receiving PVd or DPd treatment. These women must also restrain from heterosexual intercourse or agree to using two different contraceptives for the entire course of treatment and an additional 3 months if received daratumumab or bortezomib, and instead 28 days if patient has received pomalidomide.<br><br>-Men must abstain from heterosexual intercourse or use contraception.<br><br>-No donation of eggs or sperm is permitted during the study and at least 3 months if patient has received daratumumab or bortezomib, and instead 28 days if patient has received pomalidomide. |
| **Main exclusion criteria** | -Any prior CAR-T therapy.<br><br>-Any prior therapy in which BCMA is targeted.<br><br>-Toxicity levels due to previous anticancer therapy that has not reached baseline or to Grade 1 or less, exemption: alopecia.<br><br>-Subjects with Grade 1 peripheral neuropathy with pain or Grade 2+ neuropathy cannot receive PVd but may receive DPd as standard or bridging therapy.<br><br>-Seven days prior to randomization received corticosteroids equivalent to ≥70mg of prednisone.<br><br>-Vaccinated with live attenuated vaccines within 4 weeks prior to randomization.<br><br>-Pregnant, breast-feeding or planning to become pregnant during time of study or within 3 months of receiving the last does of pomalidomide, or within 1 year after receiving JNJ-68284528 infusion.<br><br>For the full list of exclusion criteria please view the attachment "protocol" in the publication [60]. |
| **Intervention** | The intervention, cilta-cel was administered to 208 patients.<br><br>A pretreatment of lymphodepleting regimen of cyclophosphamide 300 mg/$m^2$ intravenous and fludarabine 30 mg/$m^2$ intravenous was administered daily for 3 days. A single infusion of cilta-cel was administered 5 to 7 days after the start of the lymphodepleting regimen.<br><br>-Patients ≤100 kg received 0.5 - 1 x $10^6$ CAR-positive viable T cells/kg body weight. |

| Trial name: CARTITUDE-4 | NCT04181827 |
|---|---|
| | -Patients > 100 kg received 0.5 - 1 x $10^8$ CAR-positive viable T cells (non-weight based).<br><br>The following pre-infusion medications was administered to all patients 30 to 60 minutes before cilta-cel infusion:<br><br>-Antipyretic (oral or intravenous paracetamol 650 to 1,000 mg).<br><br>-Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).<br><br>(Bridging therapy was administered to patients as needed to control disease progression between leukapheresis and the infusion of cilta-cel.) |
| **Comparator(s)** | **PVd dosing (28 patients)**:<br><br>-Pomalidomide 4 mg/day taken orally once daily on Days 1 to 21 of repeated 28- day cycles.<br><br>-Bortezomib 1.3 mg/ $m^2$administered intravenously or subcutaneously on days 1, 4, 8 and 11 in cycle 1-8, then on days 1 and 8 in the following cycles<br><br>-Dexamethasone 20 mg/day (10 mg/day for age > 75 years) taken orally or intravenously on days 1, 2, 4, 5, 8, 9, 11 and 12 in cycles 1-8, then on day 1, 2, 8 and 9 in the following cycles.<br><br>**DPd dosing (183 patients):**<br><br>-Daratumumab 1,800 mg/day subcutaneous injection, administered on days 1, 8, 15 and 22 in cycle 1-2, then on days 1 and 15 in cycle 3-6, and then on day 1 in the following cycles.<br><br>-Pomalidomide 4 mg/day taken orally once daily on Days 1 to 21 of repeated 28- day cycles.<br><br>-Dexamethasone 40 mg/day (20 mg/day for age> 75 years) on day 1, 8, 15 and 22. |
| **Follow-up time** | In the publication the median follow-up time was 15.9 months (range 0.1-27.3). While in this dossier we use the latest data cut-off 01 May 2024, in which the median follow-up time is 33.6 months. |
| **Is the study used in the health economic model?** | Yes |
| **Primary, secondary and exploratory endpoints** | Primary endpoint<br><br>-PFS<br><br>Secondary endpoints<br><br>-Rate of complete response (CR)/stringent complete response (sCR)<br><br>-Rate of minimal residual disease (MRD) negative rate<br><br>-Rate of MRD negativity in participants with CR/sCR at 12 ± 3 months |

| Trial name: CARTITUDE-4 | NCT04181827 |
|---|---|
| | -Rate of sustained MRD negative status<br><br>-OS<br><br>-Overall response rate (ORR)<br><br>-PFS on next line of therapy (PFS2)<br><br>-Incidence and severity of AEs<br><br>-Pharmacokinetic and pharmacodynamic markers including but not limited, to systemic cytokine concentrations, and markers of CAR-T cells, T cell expansion (proliferation), and persistence via monitoring CAR-T positive cell counts and CAR transgene level<br><br>-Presence of anti-cilta-cel antibodies<br><br>-Time to worsening of symptoms using the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) total symptom score.<br><br>-Change from baseline in health-related quality of life (HRQoL) subscale scores from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, (MySIm-Q), EuroQol Five Dimension Questionnaire (EQ-5D-5L), Patient Global Impression of Severity (PGIS), and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) items.<br><br>**Endpoints included in this application:**<br><br>The primary endpoint was PFS as assessed by the investigator, according to RECIST version 1.1. Secondary outcomes used were OS, Response outcomes, MRD negativity, patient-reported outcomes, AEs.<br><br>***Other endpoints:***<br><br>NA |
| **Method of analysis** | All efficacy analysis was performed on the intention-to-treat population. The Kaplan-Meier survival was used to estimate and assess the primary outcome PFS. Hazard rations and 95% CI were calculated using a Cox proportional hazards model to compare survival outcomes between the two treatment arms. Additionally, secondary outcomes including ORR, CR, and MRD negativity were analysed using weighted logistic regression models. When comparing outcomes between treatment groups, inverse probability of treatment weighting was used to adjust for potential confounding variables. |
| **Subgroup analyses** | NA |
| **Other relevant information** | NA |

Abbreviations: AEs= adverse events, ANC= absolute neutrophil count, BCMA=B-cell maturation antigen, CI= confidence interval, cilta-cel= ciltacabtagene autoleucel, CR= complete response ,dL= decilitre, DPd= daratumumab + pomalidomide + dexamethasone, ECOG PS= Eastern Cooperative Oncology Group Performance Status EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, EQ-5D-5L= EuroQol 5-Dimension 5-Level, g=gram, IMWG= International Myeloma Working Group, L=litre, kg= kilogram, $m^2$=square meter, mg= milligram, mL=millilitre, MM=multiple myeloma,

MRD=minimal residual disease, MySIm-Q= Multiple Myeloma Symptom and Impact Questionnaire, NA= not applicable, ORR= overall response rate, OS= overall survival, PFS2= progression-free-survival on next line of therapy, PGIS= Patient Global Impression of Severity, PL= prior lines, PRO-CTCAE= Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, PVd= pomalidomide + bortezomib + dexamethasone, RECIST= Response Evaluation Criteria in Solid Tumours, sCR= stringent complete response, SoC= standard of care, ULN= upper limit of normal.

## A.2 CANDOR

**Table 56 Main characteristics CANDOR**

| Trial name: CANDOR | NCT03158688 |
|---|---|
| **Objective** | The objective of the trial was to evaluate the efficacy and safety of KdD compared to Kd in patients with RRMM with 1 to 3 prior LOTs. |
| **Publications – title, author, journal, year** | Quach H, Nooka A, Samoylova O, et al. Carfilzomib, dexamethasone and daratumumab in relapsed or refractory multiple myeloma: results of the phase III study CANDOR by prior lines of therapy. *Br J Haematol*. 2021;194(4):784-788. doi:10.1111/bjh.17541<br><br>Siegel D, Weisel K, Zahlten-Kumeli A, Medhekar R, Ding B, Leleu X. Health-related quality of life outcomes from the CANDOR study in patients with relapsed or refractory multiple myeloma. *Leuk Lymphoma*. 2021;62(12):3002-3010. doi:10.1080/10428194.2021.1941927<br><br>Suzuki K, Min CK, Kim K, et al. Carfilzomib, dexamethasone, and daratumumab in Asian patients with relapsed or refractory multiple myeloma: post hoc subgroup analysis of the phase 3 CANDOR trial. *Int J Hematol*. 2021;114(6):653-663. doi:10.1007/s12185-021-03204-9<br><br>Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. *Lancet Oncol*. 2022;23(1):65-76. doi:10.1016/S1470-2045(21)00579-9<br><br>Landgren O, Weisel K, Rosinol L, et al. Subgroup analysis based on cytogenetic risk in patients with relapsed or refractory multiple myeloma in the CANDOR study. *Br J Haematol*. 2022;198(6):988-993. doi:10.1111/bjh.18233<br><br>Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study [published correction appears in Lancet. 2020 Aug 15;396(10249):466. doi: 10.1016/S0140-6736(20)31669-X]. *Lancet*. 2020;396(10245):186-197. doi:10.1016/S0140-6736(20)30734-0<br><br>Leleu X, Beksac M, Chou T, et al. Efficacy and safety of weekly carfilzomib (70 mg/m$^2$), dexamethasone, and daratumumab (KdD70) is comparable to twice-weekly KdD56 while being a more convenient dosing option: a cross-study comparison of the CANDOR and EQUULEUS |

| | |
|---|---|
| | studies. *Leuk Lymphoma*. 2021;62(2):358-367. doi:10.1080/10428194.2020.1832672<br><br>Usmani SZ, Quach H, Mateos MV, et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. *Blood Adv*. 2023;7(14):3739-3748. doi:10.1182/bloodadvances.2023010026 |
| **Study type and design** | CANDOR is a completed phase III, randomized, open-label trial. Participants were randomized in 1:2 ratio to arms Kd vs KdD after being stratified by 1) International Staging System (ISS) stage (Stage 1-2 vs Stage 3) at screening, 2) prior PI exposure (yes/no), 3) number of prior lines of therapy (1 vs ≥ 2), and 4) prior cluster differentiation antigen 38 (CD38) antibody therapy (yes/no). No crossover was allowed. No masking. |
| **Sample size (n)** | N = 466, KdD = 312, and Kd = 154 |
| **Main inclusion criteria** | Inclusion criteria for patients included being aged ≥18 years with RRMM, having an ECOG performance status from 0 to 2, having undergone between 1 and 3 prior lines of therapy, and having experienced a partial or better response to at least 1 previous therapy. |
| **Main exclusion criteria** | Patients were excluded if they had received antimyeloma immunotherapy or chemotherapy within 21 days or high-dose steroids within 14 days before randomization. |
| **Intervention** | Patients that allocated to KDd received Carfilzomib as an intravenous infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20mg/$m^2$ on days 1 and 2 of cycle 1 and 56 mg/$m^2$ thereafter). The patients received dexamethasone as oral or IV infusion weekly at 40 mg (20 mg for patients aged >75 years). A split dose of 20 mg dexamethasone each day was administered when taken on successive days. Patients also received daratumumab as an IV infusion of 8 mg/kg on days 1 and 2 of cycle 1, 16 mg/kg once weekly for the remaining doses of the first 2 cycles, then every 2 weeks for 4 cycles (cycles 3-6), and every 4 weeks thereafter. |
| **Comparator(s)** | Patients that allocated to Kd received Carfilzomib as an intravenous infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20mg/$m^2$ on days 1 and 2 of cycle 1 and 56 mg/$m^2$ thereafter). The patients received dexamethasone as oral or IV infusion weekly at 40 mg (20 mg for patients aged >75 years). A split dose of 20 mg dexamethasone each day was administered when taken on successive days |
| **Follow-up time** | Median follow-up time was 50.6 in the KdD group and 50.1 months for the Kd group. |
| **Is the study used in the health economic model?** | Yes. |

| | |
|---|---|
| **Primary, secondary and exploratory endpoints** | **Endpoints included in this application:** The primary endpoint PFS and the secondary endpoint OS are included in this assessment.<br><br>**Other endpoints:** OR, MRD negative at 12 months, number of participants with TEAEs, Kaplan-Meier Estimate for DOR, Kaplan-Meier Estimate Time to Next Treatment (TTNT), Kaplan-Meier Estimates for TTP, Time to Overall Response, Percentage of Participants who Achieved and Maintained MRD negative for 12 months or more, Percentages of Participants with a CR, and Percentages of Participants who achieved MRD negative status as assessed by next generation. |
| **Method of analysis** | All efficacy analyses were intention-to-treat analyses. The Kaplan-Meier method was used to estimate rates of PFS and OS. A weighted Cox stratified model was used to estimate the adjusted HR for treatment effect |
| **Subgroup analyses** | The pre-specified subgroup analyses were ISS stage at screening, age (≥ 65 or not), region (North America, Europe or Asia-Pacific), baseline ECOG, baseline CrCl, cytogenic risk group, number of prior LOTs, previous PI, refractory to PI, previous IMiD, refractory to IMiD, previous lenalidomide, refractory to lenalidomide, one prior therapy (lenalidomide naïve, prior lenalidomide exposure, refractory to lenalidomide) and two or three prior therapies ( lenalidomide naïve, prior lenalidomide exposure, refractory to lenalidomide). |
| **Other relevant information** | NA |

Abbreviations: CR= complete response, CrCl= creatine clearance, DOR= duration of response, ECOG= Eastern Cooperative Oncology Group, HR=Hazard ratio, IMiD=Immunomodulatory drug, ISS=International staging system, IV=intravenous infusion, Kd= carfilzomib + dexamethasone, KdD= carfilzomib + daratumumab + dexamethasone, LOT= lines of therapy, MRD= minimal residual disease, NA= not applicable, OR=overall response, OS=overall survival, PFS=progression-free-survival, PI=proteasome inhibitor, RRMM=relapsed and refractory multiple myeloma, TEAE=treatment emergent adverse event, TTNT=time to next treatment, TTP=time to progression, kg=kilogram, $m^2$= square meter, mg=milligram.

### A.2.1 Baseline characteristics

**Table 57 Baseline characteristic from CANDOR**

| | CANDOR | |
|---|---|---|
| **Baseline characteristics** | **KdD** | **Kd** |
| Median age, years (range) | 64.0 (57-70) | 64.5 (59-71) |
| Female n (%) | 135 (43.00) | 63 (41.00) |
| ECOG performance status, n (%) | | |
| 0 | NA | NA |
| 0-1 | 295 (95) | 147 (95) |

| | CANDOR | |
|---|---|---|
| ≥1 | NA | NA |
| 2 | 15 (5) | 7 (5) |
| Number of prior lines, n (%) | | |
| 1 | 144 (46) | 70 (45) |
| 2 | NA | NA |
| 3 | NA | NA |
| Prior PI, n (%) | 168 (54) | 84(55) |
| Bortezomib | NA | NA |
| Ixazomib | 287 (92) | 134 (87) |
| Thalidomide | 123 (39) | 74 (48) |

# Appendix B. Efficacy results per study

## B.1 Efficacy results CARTITUDE-4

**Table 58 Results per study CARTITUDE-4**

| Result of CARTITUDE-4 (NCT04181827) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| Median PFS, months (data cut-off 01/05/24) | PVd + DPd | 211 | 11.79 (9.66–14.00) | NE | NE | NE | HR: 0.29 | 0.22–0.39 | <0.0001 | The median survival is based on the Kaplan-Meier estimator. HR and 95% CI from Cox proportional hazard model. P-value based on the constant piecewise log-rank test. | [59] |
| | Cilta-cel | 208 | NE (34.50–NE) | | | | | | | | [59] |
| Rate of CR/sCR (data | Pvd + DPd | 211 | 24.2% (18.6% - 30.5%) | 52.7 % | 44.3 % – 61.1 % | NE | OR: 11.32 | 7.08 – 18.11 | <0.0001 | Proportion of patients with CR or sCR. Mantel-Haenszel | [59] |

| Result of CARTITUDE-4 (NCT04181827) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| cut-off 01/05/24) | Cilta-cel | 208 | 76.9% (70.6%-82.5%) | | | | | | | estimate of the common odds ratio, with 95% CI, was used. P-value from the CMH test. | [59] |
| ORR (data cut-off 01/11/22[1]) | Pvd + DPd | 211 | 67.3% (60.5% – 73.6%) | 17.3% | 8.96%–25.6% | NE | OR: 3.0 | 1.8–5.0 | <0.0001 | ORR was the proportion of subjects who achieve a PR or better according to the IMWG criteria. Mantel-Haenszel estimate of the common odds ratio, with 95% CI, was used. P-value from the CMH test | [62] |
| | Cilta-cel | 208 | 84.6% (79.0%–89.2%) | | | | | | | | [62] |
| Overall MRD Negativ | PVd + DPd | 211 | 18.5 % (13.5% – 24.4 % | 43% | 34.7 %–52.2% | NE | OR: 7.61 | 4.83–12.00 | <0.0001 | Proportion of patients with MRD negative status (at $10^{-5}$) after | [59] |

| Result of CARTITUDE-4 (NCT04181827) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| ity Rate (data cut-off 01/05/24) | Cilta-cel | 208 | 62.0% (55.0% - 68.6%) | | | | | | | randomisation and before starting a subsequent therapy. Mantel-Haenszel estimate of the common odds ratio, with 95% CI, was used. P-value from Fisher's exact test. | [59] |
| Median OS, months (data cut-off 01/05/24) | PVd + DPd | 211 | NE (37.75 – NE) | NE | NE | NE | HR: 0.55 | 0.39–0.79 | 0.0009 | OS was analysed using an unweighted stratified log-rank test. HR and 95% CI from a Cox proportional hazards model. P-value based on the log-rank test. | [59] |
| | Cilta-cel | 208 | NE (NE – NE) | | | | | | | | [59] |
| Rate of MRD Negativ | PVd + DPd | 211 | 8.1 % (4.8%–12.6%) | 36.1 % | 28.1%–44.1% | NE | OR: 9.29 | 5.22–16.55 | <0.0001 | Proportion of subjects who achieved MRD-negative status (at $10^{-}$ | [59] |

| Result of CARTITUDE-4 (NCT04181827) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| ity at 12 Months ± 3 Months (data cut-off 01/05/24) | Cilta-cel | 208 | 44.2 % (37.4%–51.3%) | | | | | | | [5]) within 12 months ± 3 months, regardless of CR/sCR. Mantel-Haenszel used to estimate the common OR. Exact 95% CI. P-value from Fisher's exact test. | [59] |
| Rate of Sustained MRD-negative status (data cut-off 01/05/24) | PVd + DPd | 211 | 6.20 % (3.30%–10.30%) | 33.00% | 26.00 – 41.40 % | NA | OR: 10.11 | 5.41–18.91 | | Proportion of subjects who achieved MRD negativity, confirmed minimum 1 year apart and without any examination showing MRD-positive status in between. Mantel-Haenszel estimate of the common OR was used. P-value from Fisher's exact test. | [59] |
| | Cilta-cel | 208 | 39.9% (33.2%–46.9%) | | | | | | | | [59] |

| Result of CARTITUDE-4 (NCT04181827) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| Median time to PFS2, months (data cut-off 01/05/24) | PVd + DPd | 211 | 25.3 (21.6–32.9) | NE | NE | NE | HR: 0.46 | 0.34–0.63 | <0.0001 | Median PFS2 based on Kaplan-Meier estimate. HR and 95% CI from Cox proportional HR model- P-value based on the log-rank test. | [59] |
| | Cilta-cel | 208 | NE (NE–NE) | | | | | | | | [59] |

1: No changes reported in latest data-cut off.

Abbreviations: CI= Confidence Interval, Cilta-cel = ciltacabtagene autoleucel, CR=complete response, DPd = daratumumab + pomalidomide + dexamethasone , HR = Hazard ratio, MRD = minimal residual disease, NE = not estimable, NR = not reported, ORR = overall response rate, OS= overall survival, PD=progressed disease, PFS = progression-free-survival, PFS2= progression-free-survival on next-line therapy, PVd = pomalidomide + bortezomib + dexamethasone, sCr= stringent complete response

## B.2 Efficacy results CANDOR

In CANDOR (NCT03158688) patients with RRMM were randomly assigned 2:1 to KDd or Kd. The primary endpoint, PFS, was assessed in the ITT population. Secondary endpoints included ORR, rate of MRD-CR at 12 weeks, OS, DoR, TTNT, time to progression, and time to response.

The result from CANDOR is used in a scenario analysis, where cilta-cel is compared to Kd. The efficacy outcomes, PFS and OS, are derived from CANDOR and for the scenario analysis the efficacy of Kd is compared against cilta-cel through ITC (see Appendix C).

The OS and PFS results from CANDOR are presented below with the DCO: July 14, 2019, for the ITT population.

**Table 59 Results per study CANDOR**

| Results of CANDOR (NCT03158688) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| Median PFS, months (data cut-off 14/06/21[1]) | KdD | 312 | 28.4 (22.7 – 36.2) | 13.2 | 5.35 – 21.05 | NE | HR: 0.64 | 0.49 – 0.83 | NR | PFS was summarized descriptively using the Kaplan-Meier method with HRs estimated using a stratified Cox proportional hazards model. | [44] |
| | Kd | 154 | 15.2 ( 11.9– 19.9) | | | | | | | | [44] |
| Median OS, months (data | KdD | 312 | 50.8 (44.70– NE) | 7.2 | NE | NE | HR: 0.78 | 0.60- 1.03 | NR | OS was summarized using the Kaplan-Meier method, | [44] |

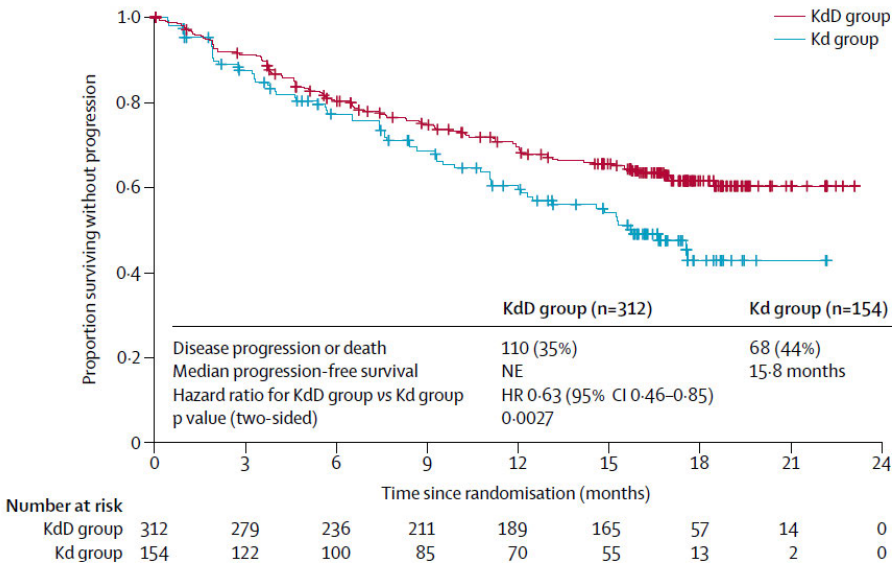
| Results of CANDOR (NCT03158688) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Description of methods used for estimation | References |
| Outcome | Study arm | N | Result (CI) | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| cut-off 15/04/22) | Kd | 154 | 43.6 (35.3–NE) | | | | | | | with a stratified Cox proportional hazards model used to estimate HR and corresponding 95% CI. | [44] |

1: Most recent data cut-off that assess PFS for all patients.
Abbreviations: HR= hazard ratio, Kd = carfilzomib + dexamethasone, KdD= carfilzomib + daratumumab + dexamethasone, NE= not estimable, NR= not reported, OS= overall survival, PFS=progression-free-survival.

### B.2.1 Progression-free Survival

The primary efficacy outcome for the CANDOR trial was PFS. After median follow-up of 16.9 in the KdD group and 16.3 months in Kd group, median PFS was not reached in the KdD group and was 15.8 months in the Kd group (HR, 0.63; 95%, CI, 0.46-0.85; p=0.0027). The Kaplan-Meier estimate is presented in Figure 17.

**Figure 17 CANDOR Kaplan-Meier estimate of PFS in the ITT population**



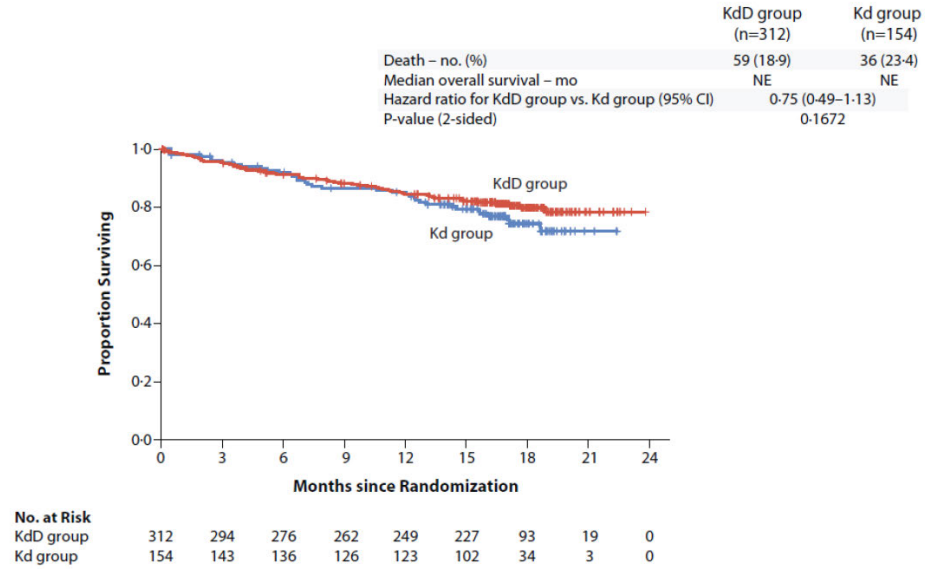

Abbreviations: CI= confidence interval, HR= Hazard ratio, Kd= carfilzomib + daratumumab, KdD= carfilzomib + daratumumab + dexamethasone, NE=not estimable, HR=Hazard ratio, PFS=Progression free survival.

### B.2.2 Overall Survival

Median overall survival was not met in the primary analysis, in either treatment groups (HR for death, 0.75; 95% CI 0.49-1.13, 9=0.17). A total of 95 deaths had occurred by the DCO, with 59 (19%) reported in the KdD group and 36 (23%) deaths reported in the Kd group. The Kaplan-Meier 18-month OS rates were 80% (95% CI 74.6 – 84.2) in the KdD group and 74% (95% CI 65.9 – 81.1) in the Kd group.

Figure 18 presents the Kaplan-Meier estimate for overall survival in the ITT population.

**Figure 18 CANDOR Kaplan-Meier estimate of overall survival in the ITT population**




Abbreviations: CI= confidence interval, HR= Hazard ratio, Kd= carfilzomib + daratumumab, KdD= carfilzomib + daratumumab + dexamethasone, NE=not estimable.

# Appendix C. Comparative analysis of efficacy

## C.1 Indirect treatment comparison (ITC) of cilta-cel versus Kd in adult patients with RRMM, who have received at least one prior therapy, including an IMiD, and a PI, have demonstrated disease progression in the last therapy, and are refractory to lenalidomide

### C.1.1 Objective

The objective of the ITCs was to estimate the relative efficacy of cilta-cel versus Kd as assessed in CANDOR), for the treatment of patients with RRMM who have received 1-3 prior LOTs that included an IMiD and a PI, and who are refractory to lenalidomide. The ITC used IPD from the CARTITUDE-4 and the daratumumab clinical trial CANDOR. Both the trials were randomized, multi-centre, open-label phase III studies.

### C.1.2 Data sources

This ITC used IPD from the CARTITUDE-4 and CANDOR, the trials are described in Appendix A and results (OS and PFS) in Appendix B. CANDOR evaluated the efficacy and safety of carfilzomib in combination with daratumumab and dexamethasone (DKd) versus dexamethasone (Kd) alone, in a total of 466 patients [86]. Full study details have been published.

### C.1.3 Outcomes

The ITC evaluated five efficacy outcomes: ORR, ≥VGPR, ≥CR, PFS and OS. ORR was defined as the proportion of patients who achieved partial response (PR) or better (stringent CR [sCR], CR, VGPR, or PR) based on IMWG consensus criteria[87]. ≥VGPR was defined as the proportion of patients who achieved a VGPR, CR, or sCR based on IMWG consensus criteria [87]. ≥CR was defined as the proportion of patients who achieved a CR or sCR based on IMWG consensus criteria [87]. PFS was defined as the time from the index date to the date of progression or death, whichever occurred first while OS was defined as the time from the index date to the date of death. If the patient was alive or the vital status was unknown, then the patient's data was censored at the date the patient was last known to be alive.

### C.1.4 Analysis Population

The cilta-cel cohort consisted of patients who were randomized to the cilta-cel arm (all patients underwent apheresis) in CARTITUDE-4, and satisfied key criteria outlined below.

- Have received 1-3 prior lines of therapy including a PI and IMiD. Patient must have undergone at least 1 complete cycle of treatment for each line of therapy, unless progressive disease was the best response to the line of therapy.

- Be refractory to lenalidomide per IMWG consensus guidelines (failure to achieve minimal response or progression on or within 60 days of completing lenalidomide therapy).[16] Progression on or within 60 days of the last dose of lenalidomide given as maintenance will meet this criterion. For patients with more than one prior line of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy. However, patients must be refractory to lenalidomide in at least one prior line.

- Have Eastern Cooperative Oncology Group (ECOG) scores <2.

Additionally, as prior exposure to anti-CD38 therapies was an exclusion factor in the daratumumab clinical trials, patients with prior exposure to anti-CD38 therapies in the cilta-cel cohort were excluded. The index date for each patient was defined as the date of randomization.

The comparator cohorts were comprised of patients who received one of the following treatments from CANDOR, DKd or Kd and met the following key inclusion criteria to align with the CARTITUDE-4 trial:

- Have received 1-3 prior lines of therapy, including a PI and IMiD.
- Refractory to lenalidomide.
- Have ECOG scores of <2.
- No prior exposure to anti-CD38 therapies.

The index date for each patient was defined as the date of randomization within each trial.

### C.1.5 Method

#### C.1.5.1 Identification and Rank Ordering of Covariates for Balancing

Comparisons of outcomes between studies may be prone to bias due to confounding if not properly adjusted [88]. Prognostic baseline characteristics for adjustment were identified and ranked in order of importance prior to the present analysis, based on input from independent clinical experts [78, 89]. The following five factors were identified as most prognostic and clinically relevant: refractory status, cytogenetic risk,[90] International Staging System (ISS) presence of plasmacytomas/extramedullary disease, and time to progression in prior line. However, due to the high proportion of patients with unknown cytogenetics in the daratumumab clinical trials (ranging from 25% to 60%), cytogenetic risk could not be included. The remaining four factors constitute the base case adjustment set. A full list of the prognostic factors and their availability is shown in Table 60.Separate sensitivity analyses included the top 8 available

factors as well as all available variables. Variables with proportions of missing values less than 25% were imputed using multiple imputation with chained equation.

**Table 60 List of covariates and usability in the ITC**

| Covariate | Used in current analyses? | Categories |
|---|---|---|
| ***Variables for base case (top 4 variables[1])*** | | |
| Refractory status[2] | Yes | < Double refractory<br>≥ Double refractory |
| ISS stage | Yes | I<br>II<br>III |
| Presence of plasmacytomas/ extramedullary disease[3] | Yes | No<br>Yes |
| Time to progression on last regimen | Yes | ≤ 6 months<br>> 6 months |
| ***Top 8 variables*** | | |
| Number of prior LOTs | Yes | 1-2<br>3 |
| Years since MM diagnosis | Yes | < 4<br>≥ 4 |
| Age (years) | Yes | <65<br>≥65 |
| Hgb | Yes | <10 g/dL<br>10-12 g/dL<br>≥12 g/dL |
| ***Additional variables*** | | |
| Creatinine clearance | Yes | < 60ml/min<br>60+ |
| Prior stem cell transplant | Yes | No<br>Yes |

| | | |
|---|---|---|
| ECOG status | Yes | 0<br>1 |
| Race | Yes | White<br>Not reported / other |
| Sex | Yes | Female<br>Male |
| Type of MM | Yes | IgG<br>IgA<br>Other |

[1] Cytogenetic risk was identified as one of the most clinically relevant variables, but was not used in the ITC.[2] Refractoriness was defined as from the case report form as progressive disease/relapsed per investigator assessment.[3] Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas[91]. Abbreviations: ECOG=Eastern Cooperative Oncology Group, Hgb= haemoglobin, ISS=International Staging System, LOTs= lines of therapy, MM= multiple myeloma, NA= not applicable, PI= proteasome inhibitor.

#### C.1.5.2 Handling Missing Data in Selected Covariates

Variables with proportions of missing values less than 25% were imputed using multiple imputation with chained equation.

#### C.1.5.3 Choice of Statistical Method

The cilta-cel cohort was compared to each of the comparator cohorts. To ensure a balance between the cilta-cel cohort and the comparator treatments, selected baseline characteristics were adjusted for using either propensity score or regression methods, following recommendations of the NICE DSU Technical Support Document 17 [92]. IPTW with average treatment effect in the treated (ATT) weighting was chosen for the main analyses. This propensity-score based method allowed the comparator cohort to be reweighted to align with the cilta-cel cohort to emulate hypothetical comparative trials in which patients were randomized to cilta-cel or one of the comparator regimens. It is important to recognize that the use of the IPTW approach with ATT weights may not be appropriate when the sample size in the comparator arm is small. The instability of results is further amplified in situations with a limited number of events, such as in the analysis of OS. To ensure reliable and robust analyses for the assessment of OS, a multivariable approach is deemed more appropriate.

IPTW with average treatment effect in the control (ATC) weights was conducted as a sensitivity analyses, where patients in the cilta-cel cohort were reweighted to reflect each of the comparator cohorts, whereas the comparator cohorts were kept as observed. ATC weights are a valid alternative when the sample size of the external cohort is small and ATT weights become unstable if adding several covariates in the PS model[93]. Multivariable regression was also conducted as a sensitivity analysis. Unlike reweighting methods, regression models estimate the conditional average treatment

effect and require a large sample compared to the number of covariates. All statistical analyses and graphical interpretation of the results were carried out with SAS 9.4 (SAS Institute, Cary, North Carolina) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

## C.2 Inverse Probability of Treatment Weighting

### C.2.1 Propensity Score Weighting

The propensity score is a balancing score defined by Rosenbaum and Rubin as the probability of treatment assignment conditional on observed baseline covariate: $e_i = Pr(Z_i = 1|X_i)$.[94] Propensity score weighting uses the PS to remove the effects of confounding when estimating the effects of treatment on the outcome. Propensity scores were estimated based on a multivariable logistic regression using a binary treatment variable as the dependent target variable and selected baseline covariates as explanatory variables. The estimated propensity scores were then used to derive weights for each participant using weighting formulas for the desired target population.

With ATT weights, patients in CARTITUDE-4 received a weight of 1 ($ATT_{w_{1k}} = 1\ (k = 1,2, \ldots, n1)$), and the weight for participants in the comparator cohort with a propensity score, $p_{0k}$, were $ATT_{w0k} = uATT_{w0k} \cdot \frac{n_0}{sum\ (uATT_{w0k})}\ (k = 1,2,..,n0)$, where $uATT_{w0k} = \frac{p_{0k}}{1-p_{0k}}$ is the unscaled ATT weight, and $n_1$and $n_0$ were the sample sizes for the cilta-cel and the comparator cohort, respectively [95]. Consequently, patients in the comparator arms with more similar baseline characteristics to the cilta-cel cohort received larger weights to balance the two groups. This estimated the treatment effect in the cilta-cel population [96].

With ATC weights, patients in the comparator treatment cohorts received a weight of 1 ($ATT_{w_{0k}} = 1\ (k = 1,2, \ldots, n0)$), while patients in CARTITUDE-4 were reweighted based on the probability of receiving treatment. Specifically, weights for participants in CARTITUDE-4 with a propensity score, $p_{1k}$, were $ATC_{w1k} = uATC_{w1k} \cdot \frac{n_1}{sum\ (uATC_{w1k})}\ (k = 1,2,..,n1)$, where $uATC_{w1k} = \frac{1-p_{1k}}{p_{1k}}$ is the unscaled ATC weight, and $n_1$and $n_0$ are the sample sizes for the cilta-cel and the comparator cohort, respectively [97] This estimated the treatment effect in the comparator treatment cohorts.

Following weighting, balance between the cilta-cel cohort and the comparator cohort was evaluated by comparing unweighted and weighted standardized mean difference (SMD) plots, with SMD ≤0.25 indicating balance between both cohorts [98]. In addition, overlap of the propensity score distributions was assessed as the area intersected by the two propensity score density functions [99, 100].

### C.2.2 Estimating Adjusted Treatment Effect

The comparative efficacy of cilta-cel versus each of the comparator treatments was determined for the following outcomes: ORR, ≥VGPR, ≥CR, PFS, and OS. Relative efficacy

was assessed for both the unadjusted comparison (i.e., cilta-cel versus comparator treatment prior to IPTW), and the adjusted comparison (i.e., with IPTW) for all outcomes. For response outcomes (ORR, ≥VGPR, and ≥CR), logistic regression (with weights applied for the adjusted comparison) was used to estimate rate ratios (RRs), odds ratios (ORs), and the corresponding 95% confidence intervals (CIs) **[101]**. Risk differences were also presented. For PFS and OS, a Cox proportional hazards model (with weights applied for the adjusted comparison) was used to derive hazard ratios (HRs) and 95% CIs.

## C.3 Model specifications and sensitivity analysis

Two separate sensitivity analyses were conducted to assess the impact of modifying various aspects of the analysis, summarized in Table 61. The first sensitivity analysis was an IPTW using ATC weights, where patients in the cilta-cel cohort were reweighted to reflect each of the comparator cohorts, whereas the comparator cohorts were kept as observed. While the primary ATT-based analyses estimate comparative efficacy in the cilta-cel population, ATC weighting provides comparative estimates in the patient cohort for the comparator. When the sample size of the external cohort is small, and ATT weights may become unstable if adding several covariates in the PS model, ATC weights are a valid alternative [102]. As sample size for some of the comparator cohorts in the current analyses was limited, IPTW-ATC allowed to additionally adjust for number of prior lines, years since diagnosis, age, and haemoglobin levels, on top of the covariates included in the base case. Finally, multivariable regression models were used as an alternative option to IPTW, as it allowed to explore the impact of further adding prior transplant, ECOG status, MM type, creatinine clearance, gender, and race as covariates.

**Table 61 Overview of sensitivity analyses**

| | Analytic Specification | | |
|---|---|---|---|
| | **Outcomes** | **Covariates** | **Statistical Method** |
| Main Analyses | ORR, ≥VGPR, ≥CR, PFS | Base Case[1] | IPTW with ATT weights |
| | OS | Base Case[1] + number of prior lines, years since diagnosis, age, haemoglobin levels, prior transplant, ECOG status, MM type, creatinine clearance, gender, and race | Multivariable regression |
| **Sensitivity Analyses** | | | |
| IPTW with ATC weighting | ORR, ≥VGPR, ≥CR, PFS, OS | Base Case[1] + number of prior lines, years since | IPTW with ATC weighting |

| | | | |
|---|---|---|---|
| | | diagnosis, age, and haemoglobin levels | |
| Multivariable Regression | ORR, ≥VGPR, ≥CR, PFS | Base Case[1] + number of prior lines, years since diagnosis, age, haemoglobin levels, prior transplant, ECOG status, MM type, creatinine clearance, gender, and race | Multivariable regression |

[1] Refractory status, International Staging System (ISS), presence of plasmacytomas/extramedullary disease, and time to progression in prior line. Abbreviations: ATC= average treatment effect in the control, ATT= average treatment effect in the treated, ≥CR= complete response or better, ECOG= Eastern Cooperative Oncology Group, IPTW= inverse probability of treatment weighting, ISS= International Staging System, LOTs= lines of therapy, MM= multiple myeloma, ORR= overall response rate, PFS= progression free survival, ≥VGPR= very good partial response or better.

### C.3.1 Assessment of Unmeasured Confounding

To assess the potential impact of unmeasured confounding, E-values for all outcomes were calculated. The E-value is defined as the minimum strength of association on the risk ratio scale that confounders would need to have with both the exposure (i.e., treatment group) and the outcome, conditional on the measured covariates, to fully explain away an observed exposure-outcome association [103]. The calculation of E-value makes no assumption on the scale and distribution of the outcomes. E-values were calculated based on the observed relative measures, i.e., RR and OR for response outcomes and HR for PFS and OS. Additionally, all combinations of values for associations of a potential unmeasured confounder with both the treatment and the outcomes of interest required to alter the conclusion on the treatment effect (of which the E-value is the specific combination with both values being equal) are presented graphically using bias plots.

### C.3.2 Assessment of Proportional Hazards

Appropriateness of the proportional hazards assumption for PFS and OS was assessed based on visual inspection of the log-cumulative hazard plot, visual inspection of the Schoenfeld residuals plot, and performance of the Grambsch-Therneau test [104] (with a *P*-value less than 0.05 considered to indicate a violation of the assumption). For all analyses, participant numbers over time were reported, and uncertainty in the survival curves over time to reflect a potential decline in participants in cohorts was presented.

## C.4 Results

### C.4.1 Efficacy of cilta-cel compared to Kd in adult patients with RRMM, who have received at least one prior therapy, including an IMiD, and a PI, have demonstrated disease progression in the last therapy, and are refractory to lenalidomide

An overview of the relevant results from the ITC are listed in Table 63.

[redacted]

| Outcome | | Absolute difference in effect | | | Relative difference in effect | | | Method used for quantitative synthesis | Result used in the health economic analysis? |
|---|---|---|---|---|---|---|---|---|---|
| | Studies included in the analysis | Difference | CI | P value | Difference | CI | P value | | |
| Cilta-cel vs Kd: Median OS | CARTITUDE-4, CANDOR | [redacted] | | | | | | [redacted] | Yes |
| Cilta-cel vs Kd: Median PFS | CARTITUDE-4, CANDOR | [redacted] | | | | | | [redacted] | Yes |

[redacted]

### C.4.1.1 Baseline characteristics before and after IPTW with ATT and ATC weighting without truncation

The ATT analyses weighed participants on the following factors: refractory status, ISS stage, time to progression on prior LOTs, and presence of plasmacytomas/extramedullary disease. The IPTW-ATC analyses adjusted for the top 8 available variables including the top 4 covariates plus number of prior lines, years since MM diagnosis, age, and haemoglobin levels.

Multiple imputation was required for the following missing variables in CANDOR: time to progression of prior line (missing 4.1% for DKd and 4.4% for Kd), years since MM diagnosis (missing 5.1% for DKd and 2.2% for Kd), and haemoglobin (missing 1% for DKd).

The population differences between the cilta-cel and Kd treatment cohort for each factor before and after adjustment with IPTW using ATT and ATC weighting with truncation, are shown in Table 63. Prior to weighting, the cilta-cel cohort had a higher proportion of patients with ISS stage I, longer time to progression in prior line, and a higher presence of plasmacytomas / extramedullary disease. After IPTW, key baseline covariates were well balanced across the cohorts, except for the presence of plasmacytomas / extramedullary disease following ATT weighting, where the SMDs remained ≥0.25 for all comparisons. This is due to few patients in the comparator cohorts with presence of plasmacytomas / extramedullary disease, suggesting that results are conservative for cilta-cel.

[redacted] presents the distributional balance of covariates, for cilta-cel versus Kd, are presented in the form of histograms.

**Table 63 Overview of baseline characteristics for cilta-cel (CARTITUDE-4) versus Kd (CANDOR) before and after adjustment with IPTW using ATT and ATC**

| Variable | Categories | Unadjusted Comparison | | | Base Case - sIPTW-ATT Truncation (4 Variables) | | sIPTW-ATC Truncation (8 Variables) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cilta-cel N=155 N (%) | Kd N=46 N (%) | SMD | Kd N=42 N (%) | SMD | Cilta-cel N=139 N (%) | Kd N=46 N (%) | SMD |
| Refractory status | < Double refractory | 82 (52.9%) | 26 (56.5%) | 0.0727 | 23 (53.9%) | 0.021 | 77 (55%) | 26 (56.5%) | 0.0301 |
| | ≥ Double refractory | 73 (47.1%) | 20 (43.5%) | | 19 (46.1%) | | 63 (45%) | 20 (43.5%) | |
| ISS stage | I | 103 (66.5%) | 23 (50%) | 0.4404 | 28 (65.5%) | 0.0208 | 74 (52.8%) | 23 (50%) | 0.1628 |
| | II | 44 (28.4%) | 15 (32.6%) | | 12 (29.3%) | | 49 (35.5%) | 15 (32.6%) | |
| | III | 8 (5.2%) | 8 (17.4%) | | 2 (5.1%) | | 16 (11.7%) | 8 (17.4%) | |
| Time to progression of prior line | < 6 months | 22 (14.2%) | 14 (30.4%) | 0.3977 | 5 (12.2%) | -0.0594 | 34 (24.5%) | 14 (30.4%) | 0.1324 |
| | ≥ 6 months | 133 (85.8%) | 32 (69.6%) | | 37 (87.8%) | | 105 (75.5%) | 32 (69.6%) | |
| Presence of plasmacytomas/ extramedullary disease | Yes | 29 (18.7%) | 3 (6.5%) | -0.3734 | 4 (9.2%) | -0.2772 | 10 (7%) | 3 (6.5%) | -0.0193 |
| | No | 126 (81.3%) | 43 (93.5%) | | 38 (90.8%) | | 130 (93%) | 43 (93.5%) | |
| Number of prior LOTs | 1-2 | 120 (77.4%) | 26 (56.5%) | -0.4557 | 25 (58.7%) | -0.4096 | 86 (61.4%) | 26 (56.5%) | -0.0994 |
| | 3 | 35 (22.6%) | 20 (43.5%) | | 17 (41.3%) | | 54 (38.6%) | 20 (43.5%) | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Years since MM diagnosis | < 4 | 101 (65.2%) | 28 (60.9%) | -0.0890 | 22 (53%) | -0.2495 | 79 (56.3%) | 28 (60.9%) | 0.0926 |
| | ≥ 4 | 54 (34.8%) | 18 (39.1%) | | 20 (47%) | | 61 (43.7%) | 18 (39.1%) | |
| Hemoglobin (g/dL) | <10 | 40 (25.8%) | 9 (19.6%) | 0.1856 | 5 (12.4%) | 0.3475 | 24 (17.4%) | 9 (19.6%) | 0.0574 |
| | 10-12 | 55 (35.5%) | 20 (43.5%) | | 18 (43.7%) | | 61 (43.8%) | 20 (43.5%) | |
| | >12 | 60 (38.7%) | 17 (37%) | | 18 (43.9%) | | 54 (38.7%) | 17 (37%) | |
| Age | < 65 | 96 (61.9%) | 28 (60.9%) | -0.0219 | 25 (58.3%) | -0.0743 | 80 (57.5%) | 28 (60.9%) | 0.0688 |
| | ≥ 65 | 59 (38.1%) | 18 (39.1%) | | 18 (41.7%) | | 59 (42.5%) | 18 (39.1%) | |
| Prior stem cell transplant | Yes | 129 (83.2%) | 21 (45.7%) | -0.8534 | 19 (45.7%) | -0.8522 | 116 (83.4%) | 21 (45.7%) | -0.8579 |
| | No | 26 (16.8%) | 25 (54.3%) | | 23 (54.3%) | | 23 (16.6%) | 25 (54.3%) | |
| ECOG status | 0 | 85 (54.8%) | 23 (50%) | -0.0970 | 19 (45.5%) | -0.1869 | 77 (55.4%) | 23 (50%) | -0.1084 |
| | 1 | 70 (45.2%) | 23 (50%) | | 23 (54.5%) | | 62 (44.6%) | 23 (50%) | |
| Type of MM | IgA | 26 (16.8%) | 10 (21.7%) | 0.2082 | 9 (20.5%) | 0.0957 | 18 (13.2%) | 10 (21.7%) | 0.3141 |
| | IgG | 86 (55.5%) | 27 (58.7%) | | 22 (53.2%) | | 78 (55.6%) | 27 (58.7%) | |
| | Other | 43 (27.7%) | 9 (19.6%) | | 11 (26.3%) | | 43 (31.2%) | 9 (19.6%) | |
| Creatinine clearance | < 60ml/min | 20 (12.9%) | 12 (26.1%) | 0.3375 | 8 (20.1%) | 0.1940 | 23 (16.7%) | 12 (26.1%) | 0.2307 |
| | 60+ | 135 (87.1%) | 34 (73.9%) | | 34 (79.9%) | | 116 (83.3%) | 34 (73.9%) | |
| Sex | Male | 86 (55.5%) | 29 (63%) | 0.1543 | 25 (58.4%) | 0.0590 | 86 (61.4%) | 29 (63%) | 0.0335 |
| | Female | 69 (44.5%) | 17 (37%) | | 18 (41.6%) | | 54 (38.6%) | 17 (37%) | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Race | White | 115 (74.2%) | 38 (82.6%) | 0.2056 | 34 (80.8%) | 0.1590 | 113 (81.4%) | 38 (82.6%) | 0.0321 |
| | Not reported / Other | 40 (25.8%) | 8 (17.4%) | | 8 (19.2%) | | 26 (18.6%) | 8 (17.4%) | |

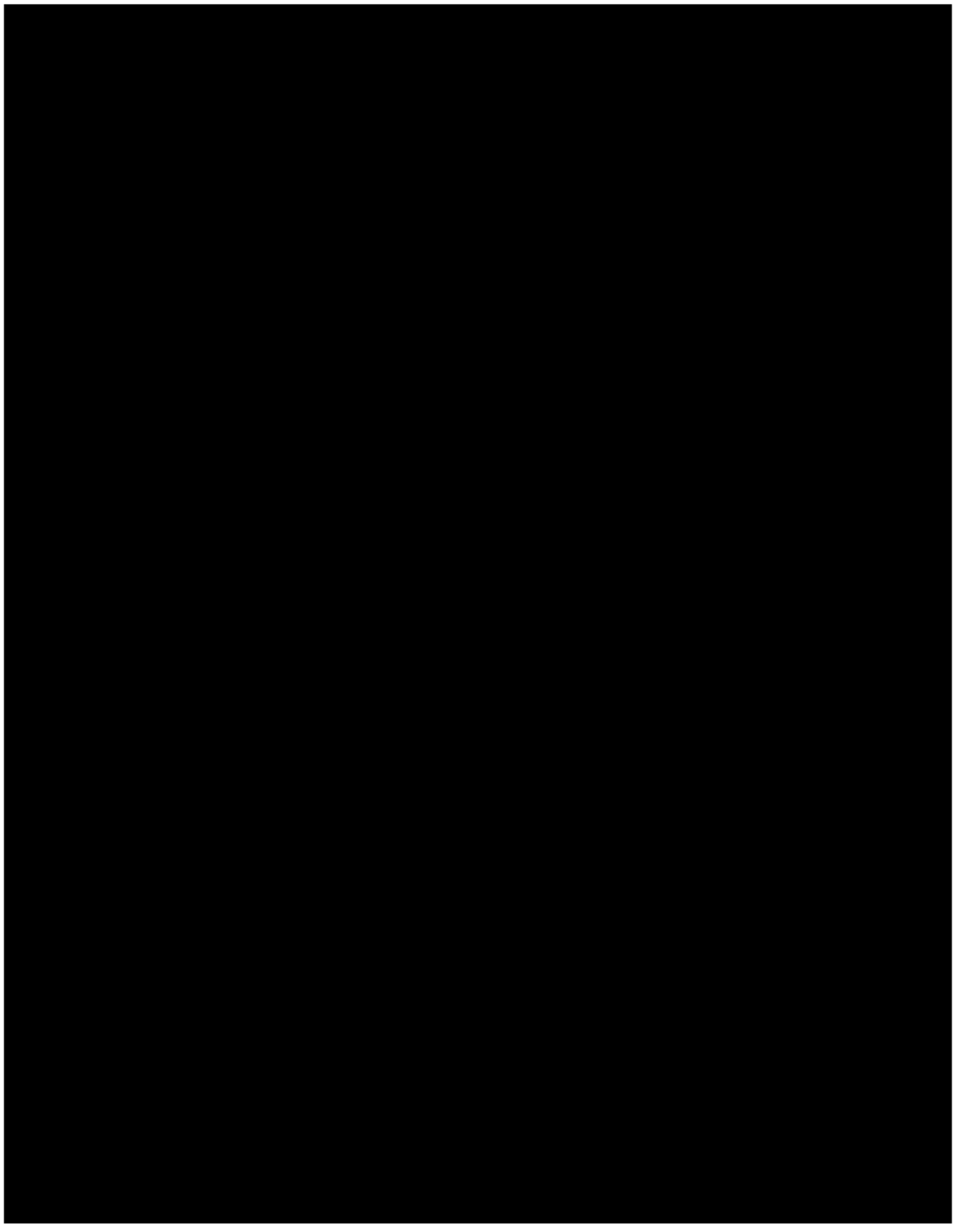
Grey cells indicate that these variables were not adjusted for in the given analysis.
SMD between 0 and 0.1 indicates a small difference, an SMD >0.1 and ≤0.2 indicates a moderate difference, and an SMD of >0.2 indicates a substantial difference [105].
Abbreviations: ATC= average treatment effect in the control, ATT= average treatment effect in the treated, ECOG= Eastern Cooperative Oncology Group, IPTW= inverse probability of treatment weighting, ISS=International Staging System, Kd=carfilzomib + dexamethasone, LOTs= lines of therapy, MM= multiple myeloma, SMD=standardized mean difference.

[redacted]

### C.4.1.2 Overall response rate (ORR)

The observed ORR was [redacted] the cilta-cel cohort, with rates in the Kd cohorts [redacted] In the main analyses, the RRs for cilta-cel versus Kd was [redacted] Results for cilta-cel versus Kd, were statistically significantly in favour of cilta-cel across sIPTW-ATC with truncation, IPTW-ATC without truncation, and multivariable regression sensitivity analyses [redacted]

[redacted]



### C.4.1.3 Very Good Partial Response or Better (VGPR)

The observed ≥VGPR rates were 85.2% in the cilta-cel cohort and [redacted] in the Kd cohort [redacted] In the main analyses, the RRs for cilta-cel versus Kd [redacted]). All results were statistically significant.

[redacted]

[redacted]

with dexamethasone, MM= multiple myeloma, Pd= pomalidomide in combination with dexamethasone, RR= rate ratio, Vd= bortezomib with dexamethasone, VGPR= very good partial response.

### Complete or better response rate

The observed ≥CR rates were [redacted] in the cilta-cel cohort [redacted] for Kd [redacted] In the main analysis, the RRs for cilta-cel versus Kd was [redacted]). All results were statistically significant.

[redacted]

[redacted]

[redacted]

### C.4.1.4 Progression free survival (PFS)

Results from the main analysis using sIPTW-ATT weighting with truncation showed statistically significant results in favour of cilta-cel, with HRs [redacted] suggesting that cilta-cel reduces the risk of progression or death by [redacted] versus Kd ([redacted]).

[redacted]

[redacted]

Group, HR= hazard ratio, IPTW= inverse probability of treatment weighting, ISS= International Staging System, Kd= carfilzomib in combination with dexamethasone, MM= multiple myeloma, Pd= pomalidomide in combination with dexamethasone, PFS= progression-free survival, Vd= bortezomib with dexamethasone.

The ATT weighted Kaplan-Meier plots with truncation for PFS are presented for the cilta-cel versus the Kd cohorts in [redacted].

The median PFS for the cilta-cel cohort [redacted]d. The observed median PFS was [redacted]) for Kd. Following base case adjustment with truncation, the median PFS was [redacted] for Kd.

### C.4.1.5 Overall survival (OS)

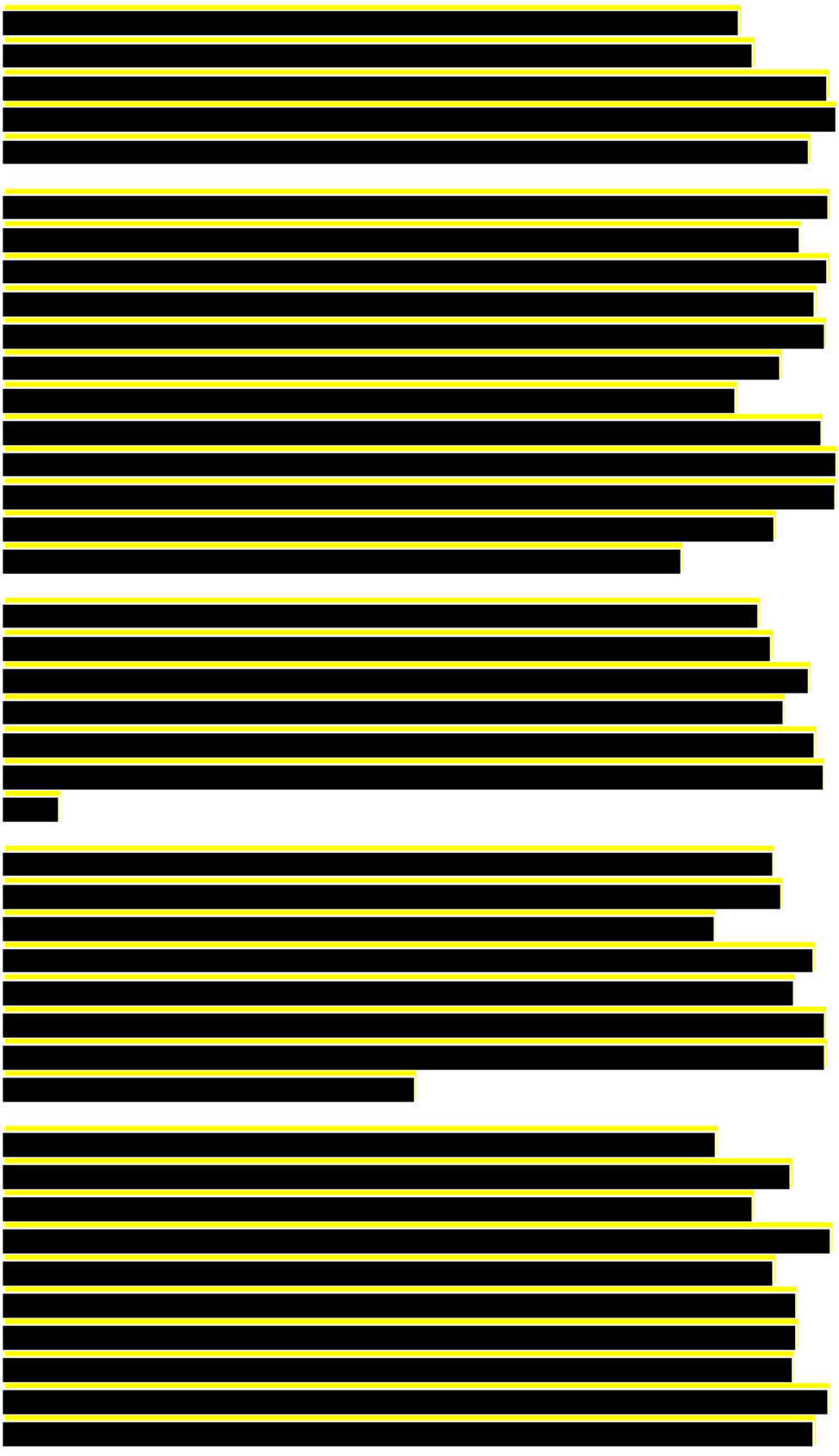
Results from the main analysis using sIPTW-ATT weighting with truncation showed statistically significant results in favour of cilta-cel versus Kd, with [redacted] suggesting that cilta-cel reduces the risk of death by [redacted]

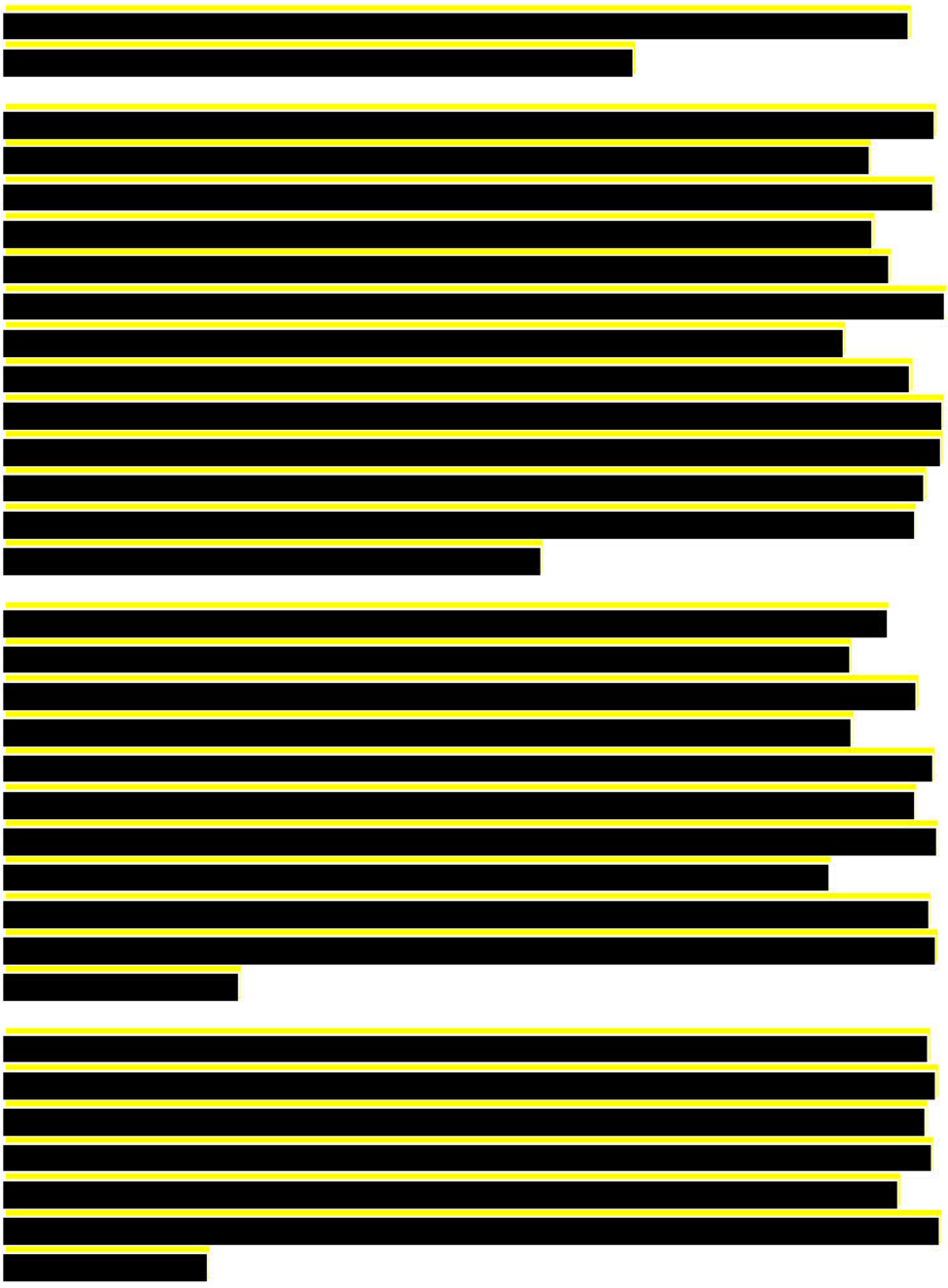
[redacted]

[redacted]

The ATT-adjusted Kaplan-Meier plots for OS with truncation are presented for the cilta-cel versus the Kd cohorts in [redacted] The median OS for the cilta-cel cohort [redacted] observed median OS was [redacted] for Kd. Following base case adjustment with truncation, [redacted] for Kd.

### C.4.2 Discussion and conclusion





## C.5 Health economic analysis, comparing cilta-cel to Kd

Kd is considered a secondary comparator. The analysis comparing cilta-cel to Kd is therefore intended to support the primary comparison, which evaluates cilta-cel against PC.

Due to the limited significance of this analysis, its description is purposefully brief, with the associated assumptions derived from those used in the base-case analysis. The

rationale for limiting the comparison between cilta-cel and Kd to a complementary sensitivity analysis is discussed in the following section.

When cilta-cel is compared to Kd, based on the adjusted Kd arm from the CANDOR trial and employing the same assumptions used in J&J's base-case comparison of cilta-cel to PC, the ICER is estimated at DKK 280,836. This figure is calculated from incremental costs of DKK [redacted]nd incremental QALYs of [redacted]Additional scenarios include the following:

- Using the most optimistic survival distributions (OS = lognormal; PFS = Gompertz) for the Kd arm from the CANDOR trial decreases the ICER for cilta-cel versus Kd to DKK 240,378.
- Conversely, applying the most conservative survival distributions (OS = Gompertz; PFS = exponential) for the Kd arm increases the ICER to DKK 325,471.

All three ICER estimates derived from this comparison are lower than J&J's base-case ICER of DKK 342,471.

An alternative method for comparing cilta-cel to Kd, which can be applied within the submitted model, assumes that the efficacy of Kd is equivalent to that of PC. In this context, cilta-cel demonstrates greater effectiveness against Kd than against PC, as indicated by the point estimates (see Table 64). Consequently, extrapolating Kd's efficacy from PC data in the CARTITUDE-4 study offers a conservative estimate of cilta-cel's relative efficacy compared to Kd. However, it is important to note that while this methodological approach may provide a conservative efficacy estimate, the resulting ICER may not necessarily be conservative. Enhanced health benefits (measured as incremental QALYs) may potentially be offset by higher associated costs.

If Kd's efficacy is extrapolated from PC data in the CARTITUDE-4 study and assumptions are aligned with J&J's base-case comparison between cilta-cel and PC, the ICER for cilta-cel versus Kd is calculated as DKK 147,594. This is based on incremental costs of [redacted]nd incremental QALYs of [redacted]otably, this ICER of DKK 147,594 is also lower than J&J's base-case ICER of DKK 342,471.

Since J&J's base-case analysis comparing cilta-cel to PC results in a higher ICER than any of the reported comparisons between cilta-cel and Kd, J&J concludes that the primary base-case analysis is sufficiently robust to support decision-making. This conclusion is based on the premise that, if cilta-cel is deemed cost-effective versus PC, it can similarly be considered cost-effective versus Kd. Therefore, restricting the comparison between cilta-cel and Kd to a complementary sensitivity analysis is seen as appropriate.

**Table 64 PFS and OS HRs for cilta-cel versus PC and cilta-cel versus Kd**

| Endpoint | Point estimate | 95% CI |
|---|---|---|
| **PFS-HR** | | |

| | | |
|---|---|---|
| Cilta-cel versus PC | 0.39 | 0.30-0.51 |
| Cilta-cel versus Kd | [redacted] | [redacted] |
| **OS-HR** | | |
| Cilta-cel versus PC | 0.55 | 0.39-0.79 |
| Cilta-cel versus Kd | [redacted] | [redacted] |

# Appendix D. Extrapolation

## D.1 Extrapolation of progression-free survival

### D.1.1 Data input

PFS was extrapolated from the subject-level data from the CARTITUDE-4 trial (

The primary endpoint of the CARTITUDE-4 trial was PFS, as assessed by blinded independent central review (BICR). At the latest DCO, PFS data for cilta-cel showed that 42.8% (89/208) of events had been observed. In comparison, the data for PC showed a higher level of events observed with 72.5% (153/211) of events observed. Extrapolation was necessary to estimate the unrestricted mean difference in PFS for the economic analysis. Additional details, including goodness-of-fit metrics, predicted landmark PFS rates, and the median and estimated mean for each survival model in each treatment arm, are provided in Appendix D.

Figure 9 and Figure 10 show the PFS KM curves for cilta-cel and PC, respectively, along with the fitted standard survival models.

For cilta-cel, most distributions, except the exponential, visually aligned well with the underlying KM curve. In contrast, the exponential distribution showed a poor fit to the KM curve. While most distributions provided similar survival estimates during the period covered by the KM data, their predictions for PFS diverged significantly beyond this period.

For PC, the visual fit of all distributions to the KM-curve was comparable. However, as with cilta-cel, the survival curves diverged beyond the KM curve. For PC, the curves formed three distinct clusters, with relatively consistent PFS estimates within each cluster.

Figure 9 and F[redacted]Survival models for both intervention and comparator were fitted independently as the curves crossed.

### D.1.2 Model

Standard parametric functions, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma, and generalised gamma, were used; see Table 65. Discussion on the selection of the preferred distributions for both arms and clinical endpoints is provided in section 8. All the parametric distributions are available in the model.

**Table 65 Parametric Survival Functions in use in the model**

| Distribution | Equation |
|---|---|
| Exponential | *S(t) = EXP(-1*(t* EXP(rate)))* |
| Weibull | *S(t) = EXP(-1*((t/exp(scale))^ EXP(shape)))* |

| | |
|---|---|
| Lognormal | *S(t) = 1-LOGNORM.DIST(t,meanlog,EXP(sdlog),TRUE)* |
| Loglogistic | *S(t) = (1/(1+(t/EXP(scale))^(EXP(shape))))* |
| Gompertz | *S(t) =EXP(-(EXP(rate)/shape)*(EXP(shape*t)-1))* |
| Gamma | *S(t)=IF(,GAMMA.DIST((1/(SQRT(1/EXP(shape))^2))*(t*EXP(-(shape-rate)))^(1/SQRT(1/EXP(shape)))^SQRT(1/EXP(shape)),1/(SQRT(1/EXP(shape))^2), 1,TRUE) when SQRT(1/EXP((shape-rate)))<0,*<br>*S(t) = 1-GAMMA.DIST((1/(SQRT(1/EXP(shape))^2))*(t*EXP(-(shape-rate)))^(1/SQRT(1/EXP(shape)))^SQRT(1/EXP(shape)),1/(SQRT(1/EXP(shape))^2), 1,TRUE)) when SQRT(1/EXP((shape-rate)))≥0* |
| Generalised gamma | *S(t) = GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE) when Q<0*<br>*S(t) = 1-GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE)) when Q≥0* |

### D.1.3 Proportional hazards

The proportional hazards assumption for PFS was evaluated using a log cumulative hazard plot (Figure 28) for cilta-cel and PC, as assessed by BICR. The log cumulative hazard plot shows the hazards crossing, which typically indicates that the assumption of proportional hazards may not hold. This violation was confirmed by the Schoenfeld residual plot and test (Figure 29); the residuals exhibit a clear non-random trend over time, and the Schoenfeld test was significant [redacted]

Figure 30 displays the quantile-quantile plot, which evaluates the appropriateness of using an accelerated failure time (AFT) model. The shape of the plot suggests that the AFT assumption does not necessarily hold (deviates from the liner trendline).

Due to these findings, models were fitted separately to the two arms of CARTITUDE-4. Furthermore, considering that the hazard plots indicate (for both arms) that the hazard rate changes over time, any model with a constant hazard (e.g., exponential) would a priori appear to be an unsuitable selection.

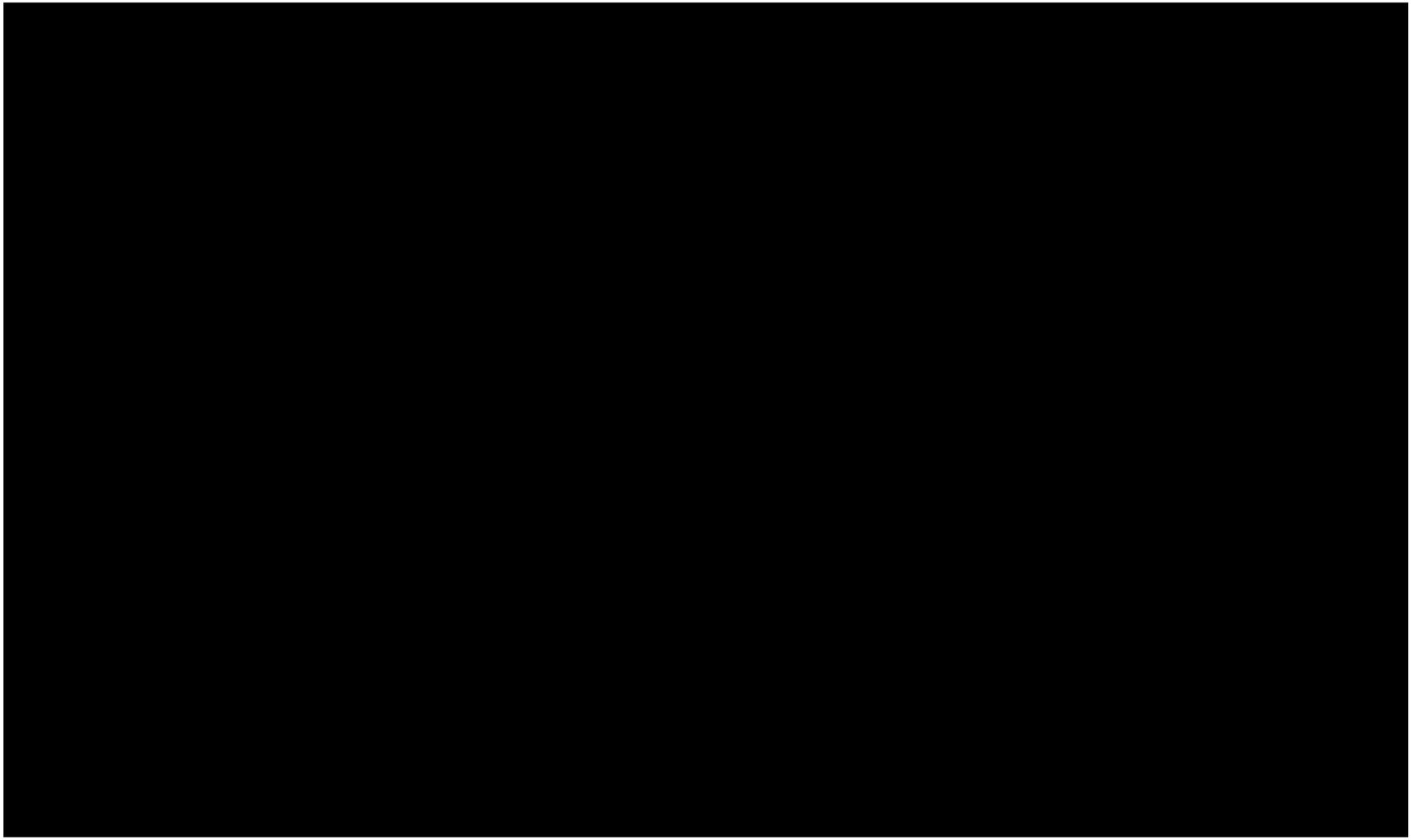
[redacted]

[redacted]

### D.1.4 Evaluation of statistical fit (AIC and BIC)

Goodness-of-fit statistics, landmark survival rates, estimated median, and estimated mean survival for cilta-cel (Table 66) and PC (Table 67) are presented below. The combined total stratified fits are shown in Table 66. A discussion on the best-fitting distributions and their clinical plausibility is available in section 8.1.2.1.

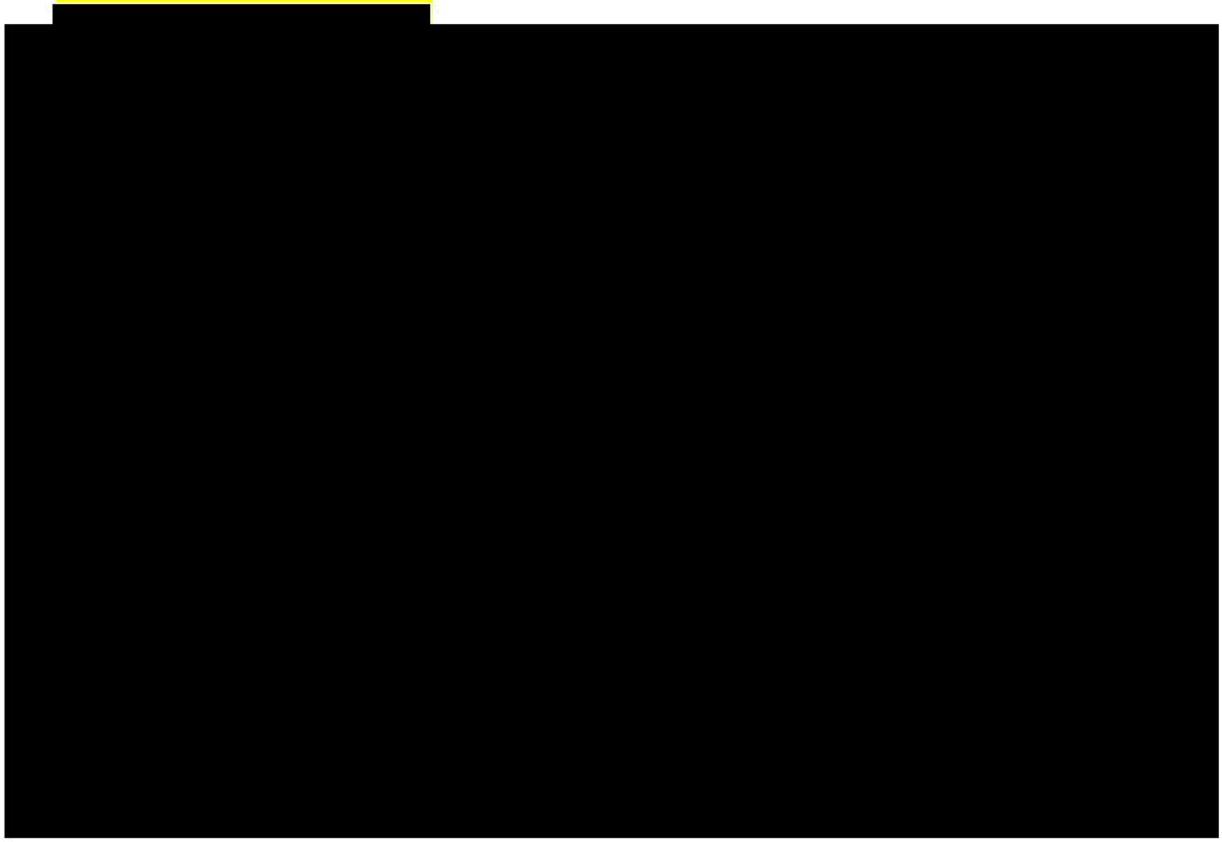
As noted in section 8.1.2.1, the statistically best-fitting distributions for both treatment arms were lognormal, log-logistic, and generalised gamma, as they had the lowest AIC and BIC values. Conversely, the exponential distribution demonstrated the worst fit for cilta-cel, while the gamma distribution provided the worst fit for PC, [redacted]



### D.1.5 Evaluation of visual fit

[redacted] and Figure 32 display time-to-event data curves for both the Kaplan-Meier estimate and the fitted parametric distributions, alongside the general population's mortality for cilta-cel and PC, respectively. The exponential model predicts the lowest PFS for cilta-cel; however, as previously noted, this is also the statistically worst-fitting distribution. Similarly, for PC, the worst-fitting distribution (gamma) also yields some of the most pessimistic PFS estimates.

[redacted]



[redacted]

### D.1.6 Evaluation of hazard functions

In [redacted], the smoothed hazards from the trial are compared with those generated by different distributions for cilta-cel and PC, respectively. In [redacted] cilta-cel, most distributions, with the exception of the exponential, provide hazard functions that align relatively well with the smoothed hazard, predicting decreasing hazards over time. However, the fit of the Gompertz distribution is noticeably worse than that of the other distributions associated with decreasing hazards. For PC, the generalised gamma and lognormal distributions are the two that most closely follow the smoothed hazard.

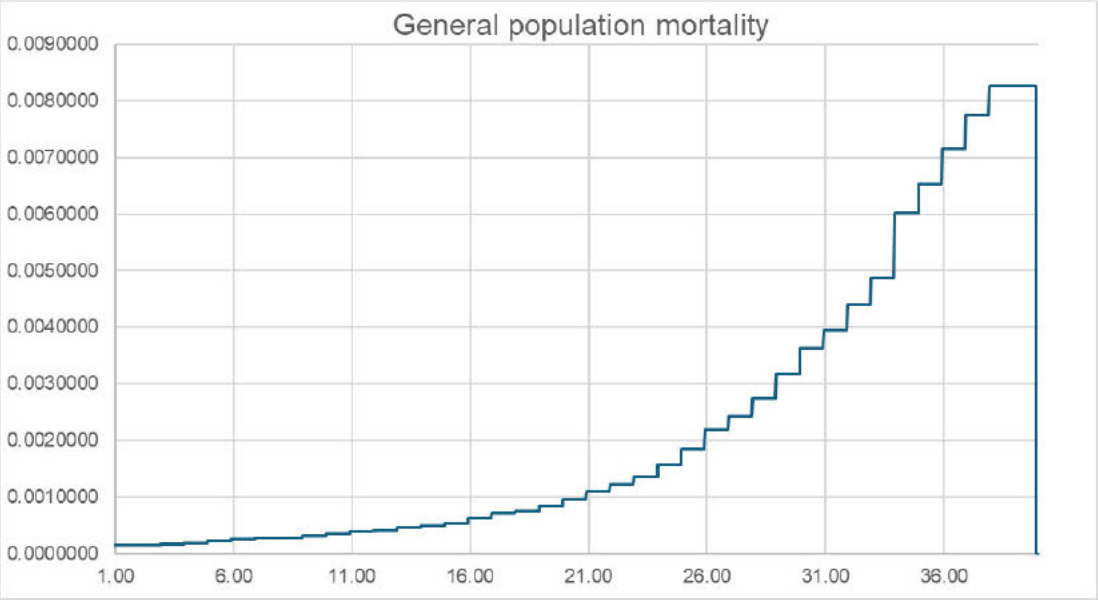
### D.1.7 Validation and discussion of extrapolated curves

See section 8.2.1.1.

### D.1.8 Adjustment of background mortality

The general mortality rates for the Danish population were applied. Figure 35 illustrates the modelled probability of death per year starting at age 60 (the cohort age at the start of the analysis).

**Figure 35 General population mortality**




### D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

### D.1.10 Waning effect

Not applicable.

### D.1.11 Cure-point

Not applicable.

## D.2 Extrapolation of overall survival

### D.2.1 Data input

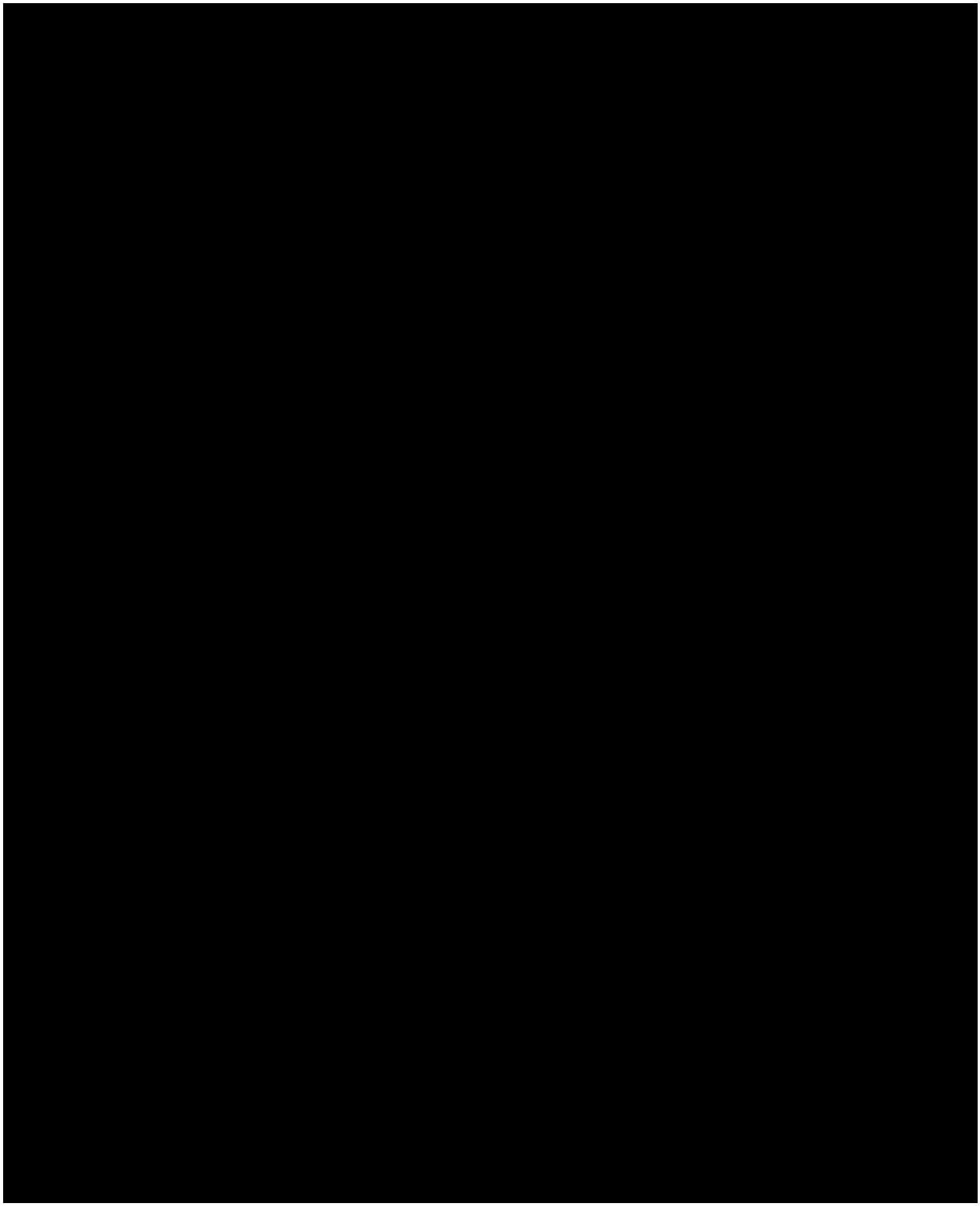
Subject-level data from the CARTITUDE-4 trial was used to extrapolate OS (Figure 11 and [redacted] Survival models for both intervention and comparator were fitted independently.

### D.2.2 Model

See section D.1.2. Discussion on the selection of the preferred distributions for both arms and clinical endpoints is provided in section 8.2.1.2. All the parametric distributions are available in the model.

### D.2.3 Proportional hazards

The PH assumption for OS was evaluated using a log cumulative hazards plot (Figure 39) for cilta-cel and PC. The plot indicates that the hazards cross, suggesting that the PH assumption may not hold. As for PFS, the Schoenfeld test was conducted to assess the PH assumption further. In the Schoenfeld residual plot (Figure 40), the residuals displayed a clear non-random trend over time, and the Schoenfeld test was highly significant [redacted] confirming a likely violation of the PH assumption. As a result, models were fitted separately to the two arms of CARTITUDE-4.



### D.2.4 Evaluation of statistical fit (AIC and BIC)

[redacted] present the goodness-of-fit statistics, landmark survival rates, and estimated median and mean OS for cilta-cel and PC, respectively. The total stratified fits are shown in Table 69. A discussion on the best-fitting distributions and their clinical plausibility is available in section 8.2.1.2. Notably, for cilta-cel, similar to PFS, the exponential distribution is the statistically worst-fitting distribution, as indicated by the highest AIC/BIC values.

[redacted]

### D.2.5 Evaluation of visual fit

Figure 39 and Figure 40 present time-to-event data curves, illustrating both the KM estimates and the parametric distributions for OS and the general population's mortality for cilta-cel and PC, respectively. The crossing observed between the predicted OS and the general population's mortality may be attributed to the immaturity of the data. However, this crossing is not necessarily clinically implausible. The extrapolated OS from CARTITUDE-4 is dominated by the disease-specific hazard (RRMM). In time, competing hazards will become increasingly important and start dominating the hazard as cohort age increases.

### D.2.6 Evaluation of hazard functions

Smoothed hazards, along with the hazards of the parametric distributions for both treatment arms, are presented in Figure 41 for cilta-cel and Figure 42 for PC.

For cilta-cel, the exponential distribution has the least plausible hazard function as it is not able to describe the estimated smoothed hazard from the trial. The hazard functions of the Gompertz, generalised gamma, and lognormal distributions are the closest to the shape of the non-parametric smoothed hazard. However, among these three, the Gompertz distribution is the least plausible due to [redacted] of the smoothed hazard. Additionally, the figure does not show the hazards for the Gompertz distribution [redacted], causing its OS curve to become [redacted] after approximately six years.

For the PC arm, the lognormal, log-logistic, and generalised gamma distributions have hazard functions that most closely match the non-parametric smoothed hazard among all the distributions tested. Since the trial data is predicted [redacted], the Weibull, Gamma, Gompertz, and exponential distributions are unsuitable for extrapolation.

### D.2.7 Validation and discussion of extrapolated curves

Not available.

### D.2.8 Adjustment of background mortality

See section D.1.8.

### D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

### D.2.10 Waning effect

Not applicable.

### D.2.11 Cure-point

Not applicable.

# Appendix E. Serious adverse events

## E.1 Adverse Events CANDOR

In CANDOR the safety analyses, with the latest clinical DCO April 15, 2022 [44], included 466 patients for the safety analysis (intervention N=308 and comparator N=153). The total number of serious AEs were 335 (intervention N=246 (79.9%) and comparator N=89 (58.2%). Pneumonia was the only serious adverse event that affected more than 5% of patients (intervention N=52 (16.88%) and comparator N=16 (10.46%).

**Table 20 CANDOR Overview of safety events. Median follow-up 50 months.**

| | KdD (N= 308) [44] | Kd (N= 153) [44] | Difference, % (95 % CI) |
|---|---|---|---|
| Number of adverse events, n | NA | NA | NA |
| Number and proportion of patients with ≥1 adverse events, n (%) | NA | NA | NA |
| Number of serious adverse events*, n (%) | 211 (68.50%) | 80 (52.30%) | 131 (NR) |
| Number and proportion of patients with ≥ 1 serious adverse events*, n (%) | 306 (99.4%) | 149 (97.4%) | 157, 1.97% (-0.72%-4.65%) |
| Number of CTCAE grade ≥ 3 events, n | 273 (87%) | 120 (78%) | 153 (9%) |
| Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%) | NA | NA | NA |
| Number of adverse reactions, n | 306 (99%) | 149 (97%) | 157, 2.28% (-0.78%-5.28%) |
| Number and proportion of patients | NA | NA | NA |

| | KdD (N= 308) [44] | Kd (N= 153) [44] | Difference, % (95 % CI) |
|---|---|---|---|
| with ≥ 1 adverse reactions, n (%) | | | |
| Number and proportion of patients who had a dose reduction, n (%) | 141 (45.8%) | 59 (38.6%) | 82, 7.37% (-2.15%-16.88%) |
| Number and proportion of patients who discontinue treatment regardless of reason, n (%) | 308 | 153 | 155 |
| Number and proportion of patients who discontinue treatment due to adverse events, n (%) | 105 (34%) | 41 (27%) | 64, 7.01% (-1.81%-15.83%) |

Abbreviations: CI= confidence interval, KdD= Carfilzomib, daratumumab, and dexamethasone, Kd= Carfilzomib and dexamethasone, NA = Not available.

**Table 72 CANDOR Serious adverse events (median follow-up 50 months)**

| Adverse events | Intervention (N=308) | | Comparator (N=153) | |
|---|---|---|---|---|
| | Number of patients with adverse events | Number of adverse events | Number of patients with adverse events | Number of adverse events |
| Adverse event, n (%) | 211 (68.15%) | N/A | 80 (52.29%) | N/A |
| Pneumonia [109] | 52 (16.88%) | NA | 16 (10.46%) | NA |

## E.2 All Serious Adverse Events in CARTITUDE-4

All serious adverse events observed in CARTITUDE-4 [110] are presented in Table 73.

**Table 73 Treatment-emergent Serious Adverse Events**

| Analysis set: safety | Cilta-cel (n=208) | PC of PVd or DPd (n=208 |
|---|---|---|

| | | |
|---|---|---|
| **Total number of subjects with serious TEAE** | **98 (47.1%)** | **98 (47.1%)** |
| **MedDRA system organ class/preferred term** | | |
| **Infections and infestations** | **55 (26.4%)** | **64 (30.8%)** |
| COVID-19 pneumonia | 12 (5.8%) | 12 (5.8%) |
| Pneumonia | 8 (3.8%) | 14 (6.7%) |
| COVID-19 | 6 (2.9%) | 7 (3.4%) |
| Upper respiratory tract infection | 4 (1.9%) | 5 (2.4%) |
| Metapneumovirus pneumonia | 3 (1.4%) | 0 |
| Cytomegalovirus infection | 2 (1.0%) | 1 (0.5%) |
| Lower respiratory tract infection | 2 (1.0%) | 0 |
| Respiratory tract infection | 2 (1.0%) | 2 (1.0%) |
| Sepsis | 2 (1.0%) | 1 (0.5%) |
| Staphylococcal infection | 2 (1.0%) | 0 |
| Cellulitis | 1 (0.5%) | 2 (1.0%) |
| Enterocolitis viral | 1 (0.5%) | 0 |
| Escherichia urinary tract infection | 1 (0.5%) | 0 |
| Gastroenteritis Escherichia coli | 1 (0.5%) | 1 (0.5%) |
| Gastroenteritis bacterial | 1 (0.5%) | 0 |
| Gastroenteritis salmonella | 1 (0.5%) | 0 |
| Gastrointestinal infection | 1 (0.5%) | 0 |
| Haemophilus sepsis | 1 (0.5%) | 0 |
| Herpes zoster | 1 (0.5%) | 0 |
| Infection | 1 (0.5%) | 1 (0.5%) |

| | | |
|---|---|---|
| Large intestine infection | 1 (0.5%) | 0 |
| Neutropenic sepsis | 1 (0.5%) | 1 (0.5%) |
| Parainfluenza virus infection | 1 (0.5%) | 4 (1.9%) |
| Parvovirus B19 infection | 1 (0.5%) | 0 |
| Pneumocystis jirovecii pneumonia | 1 (0.5%) | 5 (2.4%) |
| Pneumonia klebsiella | 1 (0.5%) | 0 |
| Pneumonia parainfluenza viral | 1 (0.5%) | 1 (0.5%) |
| Pneumonia pseudomonal | 1 (0.5%) | 0 |
| Pneumonia respiratory syncytial viral | 1 (0.5%) | 1 (0.5%) |
| Pneumonia streptococcal | 1 (0.5%) | 1 (0.5%) |
| Pseudomonal sepsis | 1 (0.5%) | 0 |
| Respiratory tract infection viral | 1 (0.5%) | 0 |
| Rotavirus infection | 1 (0.5%) | 0 |
| Sinusitis bacterial | 1 (0.5%) | 0 |
| Staphylococcal bacteraemia | 1 (0.5%) | 0 |
| Tonsillitis | 1 (0.5%) | 0 |
| Upper respiratory tract infection bacterial | 1 (0.5%) | 0 |
| Urinary tract infection | 1 (0.5%) | 2 (1.0%) |
| Urosepsis | 1 (0.5%) | 1 (0.5%) |
| Anal abscess | 0 | 1 (0.5%) |
| Appendicitis | 0 | 1 (0.5%) |
| Bacteraemia | 0 | 1 (0.5%) |
| Bacterial pericarditis | 0 | 1 (0.5%) |

| | | |
|---|---|---|
| Cytomegalovirus chorioretinitis | 0 | 2 (1.0%) |
| Cytomegalovirus colitis | 0 | 1 (0.5%) |
| Cytomegalovirus infection reactivation | 0 | 1 (0.5%) |
| Device related sepsis | 0 | 1 (0.5%) |
| Endophthalmitis | 0 | 1 (0.5%) |
| Epiglottitis | 0 | 1 (0.5%) |
| JC virus infection | 0 | 1 (0.5%) |
| Leishmaniasis | 0 | 1 (0.5%) |
| Metapneumovirus infection | 0 | 1 (0.5%) |
| Pneumonia haemophilus | 0 | 1 (0.5%) |
| Pneumonia legionella | 0 | 2 (1.0%) |
| Pneumonia pneumococcal | 0 | 1 (0.5%) |
| Pneumonia staphylococcal | 0 | 1 (0.5%) |
| Post procedural infection | 0 | 1 (0.5%) |
| Progressive multifocal leukoencephalopathy | 0 | 1 (0.5%) |
| Pyelonephritis acute | 0 | 1 (0.5%) |
| Respiratory syncytial virus infection | 0 | 1 (0.5%) |
| Rhinovirus infection | 0 | 3 (1.4%) |
| Septic shock | 0 | 1 (0.5%) |
| Soft tissue infection | 0 | 1 (0.5%) |
| Staphylococcal skin infection | 0 | 1 (0.5%) |
| Viral uveitis | 0 | 1 (0.5%) |
| **Blood and lymphatic system disorders** | **15 (7.2%)** | **10 (4.8%)** |

| | | |
|---|---|---|
| Febrile neutropenia | 5 (2.4%) | 6 (2.9%) |
| Anaemia | 4 (1.9%) | 1 (0.5%) |
| Neutropenia | 4 (1.9%) | 1 (0.5%) |
| Cytopenia | 1 (0.5%) | 0 |
| Immune thrombocytopenia | 1 (0.5%) | 0 |
| Lymphocytosis | 1 (0.5%) | 0 |
| Thrombocytopenia | 1 (0.5%) | 0 |
| Hyperviscosity syndrome | 0 | 1 (0.5%) |
| Pancytopenia | 0 | 1 (0.5%) |
| **Nervous system disorders** | **14 (6.7%)** | **6 (2.9%)** |
| Facial paralysis | 9 (4.3%) | 1 (0.5%) |
| Facial paresis | 1 (0.5%) | 0 |
| 3rd nerve paralysis | 1 (0.5%) | 0 |
| Immune effector cell-associated neurotoxicity syndrome | 1 (0.5%) | 0 |
| Parkinsonism | 1 (0.5%) | 0 |
| Polyneuropathy | 1 (0.5%) | 0 |
| Spinal cord compression | 1 (0.5%) | 0 |
| Subdural hygroma | 1 (0.5%) | 0 |
| Trigeminal palsy | 1 (0.5%) | 0 |
| Ischaemic stroke | 0 | 2 (1.0%) |
| Syncope | 0 | 2 (1.0%) |
| General disorders and administration site conditions | 8 (3.8%) | 7 (3.4%) |

| | | |
|---|---|---|
| Pyrexia | 4 (1.9%) | 5 (2.4%) |
| General physical health deterioration | 3 (1.4%) | 0 |
| Fatigue | 1 (0.5%) | 0 |
| Chest discomfort | 0 | 1 (0.5%) |
| Chills | 0 | 1 (0.5%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **8 (3.8%)** | **9 (4.3%)** |
| Myelodysplastic syndrome | 3 (1.4%) | 0 |
| Peripheral T-cell lymphoma unspecified | 2 (1.0%) | 0 |
| Acute myeloid leukaemia | 1 (0.5%) | 0 |
| Basal cell carcinoma | 1 (0.5%) | 0 |
| Malignant pleural effusion | 1 (0.5%) | 0 |
| Myelodysplastic syndrome with multilineage dysplasia | 1 (0.5%) | 0 |
| Paraneoplastic syndrome | 1 (0.5%) | 0 |
| Epstein-Barr virus associated lymphoma | 0 | 1 (0.5%) |
| Invasive lobular breast carcinoma | 0 | 1 (0.5%) |
| Lip squamous cell carcinoma | 0 | 1 (0.5%) |
| Lung adenocarcinoma | 0 | 1 (0.5%) |
| Neoplasm of appendix | 0 | 1 (0.5%) |
| Renal cell carcinoma | 0 | 1 (0.5%) |
| Serous cystadenocarcinoma ovary | 0 | 1 (0.5%) |
| Squamous cell carcinoma of skin | 0 | 1 (0.5%) |
| Tonsil cancer | 0 | 1 (0.5%) |

| | | |
|---|---|---|
| Immune system disorders | 7 (3.4%) | 1 (0.5%) |
| Cytokine release syndrome | 7 (3.4%) | 1 (0.5%) |
| Metabolism and nutrition disorders | 7 (3.4%) | 3 (1.4%) |
| Hypercalcaemia | 5 (2.4%) | 2 (1.0%) |
| Hyperferritinaemia | 1 (0.5%) | 0 |
| Hypophosphataemia | 1 (0.5%) | 0 |
| Hyponatraemia | 0 | 1 (0.5%) |
| **Cardiac disorders** | **6 (2.9%)** | **8 (3.8%)** |
| Acute coronary syndrome | 1 (0.5%) | 0 |
| Atrial fibrillation | 1 (0.5%) | 4 (1.9%) |
| Atrial flutter | 1 (0.5%) | 1 (0.5%) |
| Atrioventricular block second degree | 1 (0.5%) | 0 |
| Pericarditis | 1 (0.5%) | 0 |
| Supraventricular tachycardia | 1 (0.5%) | 0 |
| Acute myocardial infarction | 0 | 1 (0.5%) |
| Angina pectoris | 0 | 1 (0.5%) |
| Cardiac failure | 0 | 1 (0.5%) |
| Left ventricular dysfunction | 0 | 1 (0.5%) |
| Myocardial infarction | 0 | 1 (0.5%) |
| Palpitations | 0 | 1 (0.5%) |
| Gastrointestinal disorders | 6 (2.9%) | 3 (1.4%) |
| Diarrhoea | 5 (2.4%) | 0 |
| Colitis | 1 (0.5%) | 0 |

| | | |
|---|---|---|
| Abdominal pain | 0 | 1 (0.5%) |
| Gastric haemorrhage | 0 | 1 (0.5%) |
| Ileus | 0 | 1 (0.5%) |
| **Musculoskeletal and connective tissue disorders** | **5 (2.4%)** | **3 (1.4%)** |
| Back pain | 2 (1.0%) | 0 |
| Arthralgia | 1 (0.5%) | 0 |
| Pain in extremity | 1 (0.5%) | 2 (1.0%) |
| Pathological fracture | 1 (0.5%) | 0 |
| Bone pain | 0 | 1 (0.5%) |
| **Respiratory, thoracic and mediastinal disorders** | **5 (2.4%)** | **9 (4.3%)** |
| Pleural effusion | 2 (1.0%) | 0 |
| Respiratory failure | 2 (1.0%) | 1 (0.5%) |
| Acute respiratory distress syndrome | 1 (0.5%) | 0 |
| Pulmonary embolism | 1 (0.5%) | 4 (1.9%) |
| Pulmonary oedema | 1 (0.5%) | 1 (0.5%) |
| Acute respiratory failure | 0 | 1 (0.5%) |
| Interstitial lung disease | 0 | 1 (0.5%) |
| Lung disorder | 0 | 1 (0.5%) |
| **Injury, poisoning and procedural complications** | **3 (1.4%)** | **3 (1.4%)** |
| Humerus fracture | 1 (0.5%) | 1 (0.5%) |
| Subdural haemorrhage | 1 (0.5%) | 0 |
| Tracheal obstruction | 1 (0.5%) | 0 |
| Fall | 0 | 1 (0.5%) |

| | | |
|---|---|---|
| Hip fracture | 0 | 1 (0.5%) |
| Spinal compression fracture | 0 | 1 (0.5%) |
| Psychiatric disorders | 2 (1.0%) | 2 (1.0%) |
| Disorientation | 1 (0.5%) | 0 |
| Suicidal ideation | 1 (0.5%) | 0 |
| Confusional state | 0 | 1 (0.5%) |
| Mental disorder | 0 | 1 (0.5%) |
| Renal and urinary disorders | 2 (1.0%) | 4 (1.9%) |
| Acute kidney injury | 2 (1.0%) | 3 (1.4%) |
| Haematuria | 0 | 1 (0.5%) |
| Eye disorders | 1 (0.5%) | 0 |
| Diplopia | 1 (0.5%) | 0 |
| Investigations | 1 (0.5%) | 2 (1.0%) |
| Alanine aminotransferase increased | 1 (0.5%) | 0 |
| Aspartate aminotransferase increased | 1 (0.5%) | 0 |
| Procalcitonin increased | 0 | 1 (0.5%) |
| Troponin I increased | 0 | 1 (0.5%) |
| Reproductive system and breast disorders | 1 (0.5%) | 0 |
| Pelvic pain | 1 (0.5%) | 0 |
| Hepatobiliary disorders | 0 | 2 (1.0%) |
| Cholestasis | 0 | 1 (0.5%) |
| Hyperbilirubinaemia | 0 | 1 (0.5%) |
| Vascular disorders | 0 | 4 (1.9%) |

| | | |
|---|---|---|
| Deep vein thrombosis | 0 | 2 (1.0%) |
| Hypertension | 0 | 1 (0.5%) |

Note: Safety analysis set consists of subjects who received any part of study treatment. The output includes the diagnosis of CRS and ICANS along with other AEs and the symptoms of CRS or ICANS are excluded.

# Appendix F. Health-related quality of life

Not applicable.

# Appendix G. Probabilistic sensitivity analyses

**Table 74 Overview of parameters in the PSA**

| Input parameter | Point estimate | Lower bound | Upper bound | Probability distribution |
|---|---|---|---|---|
| **Patient characteristics** | | | | |
| Age (mean) | 60.10 | [redacted] | | |
| Proportion of female | 0.43 | | | |
| Body weight (mean) | 77.54 | | | |
| Body surface area (mean) | [redacted] | | | |
| **Other Settings** | | | | |
| Drug Wastage | Yes | No | Yes | |
| **Individual curve fitting for OS** | | | | |
| Cilta-cel | Lognormal | [redacted] | | |
| Physician's choice | Lognormal | [redacted] | | |
| **Individual curve fitting for PFS** | | | | |
| Cilta-cel | Lognormal | [redacted] | | |
| Physician's choice | Lognormal | [redacted] | | |
| **HR of cilta-cel various populations versus CD38 Naïve population** | | | | |
| PFS | [redacted] | | | |
| OS | [redacted] | | | |
| **% CAR-T OOS** | | | | |

| | | | | |
|---|---|---|---|---|
| Cilta-cel | 0.041 | [redacted] | [redacted] | [redacted] |
| **N patients discontinuing prior to CAR-T infusion** | | | | |
| Cilta-cel | 12 | [redacted] | [redacted] | [redacted] |
| **CAR-T pre-infusion period** | | | | |
| Cilta-cel | 78.60 | [redacted] | [redacted] | [redacted] |
| **CAR-T infusion: cilta-cel** | | | | |
| Duration of inpatient stay for infusion (day) | 16 | [redacted] | [redacted] | [redacted] |
| **Average number of apheresis** | | | | |
| Cilta-cel | 1.07 | [redacted] | [redacted] | [redacted] |
| **CAR-T bridging therapy: Cilta-cel** | | | | |
| PVd | 0.13 | [redacted] | [redacted] | [redacted] |
| DVd | 0.875 | [redacted] | [redacted] | [redacted] |
| **CAR-T bridging therapy duration** | | | | |
| Average duration of bridging therapy (weeks) – cilta-cel | 7.75 | [redacted] | [redacted] | [redacted] |
| **Proportion starting bridging therapy** | | | | |
| Percentage patients receiving bridging therapy – cilta-cel | 1 | [redacted] | [redacted] | [redacted] |
| **CAR-T conditioning therapy: Cilta-cel** | | | | |

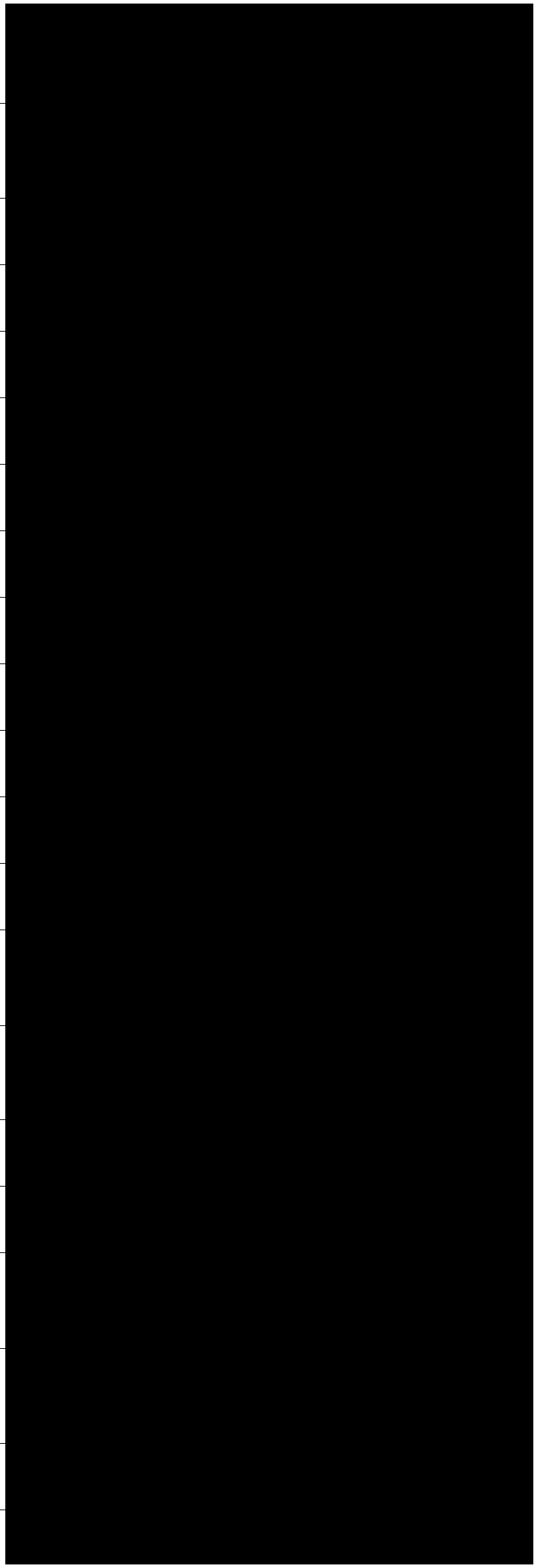
| | | | | |
|---|---|---|---|---|
| % patients receiving conditioning therapy (infused) | 0.94 | [redacted] | [redacted] | [redacted] |
| Duration of Fludarabine 30mg/m2 (day) | 3 | [redacted] | [redacted] | [redacted] |
| Duration of Cyclophosphamide 300mg/m2 (day) | 3 | [redacted] | [redacted] | [redacted] |
| **CAR-T related monitoring unit costs during the post-monitoring period** | | | | |
| Duration of post-monitoring (days) | 112 | [redacted] | [redacted] | [redacted] |
| **CAR-T related resource use during the post-monitoring period** | | | | |
| Hematologist vist | 0.29 | [redacted] | [redacted] | [redacted] |
| Biochemistry | 0.29 | [redacted] | [redacted] | [redacted] |
| Vital signs, including oxygen saturation | 0.29 | [redacted] | [redacted] | [redacted] |
| Quantitative immunoglobulin | 0.29 | [redacted] | [redacted] | [redacted] |
| Protein electrophoresis | 0.29 | [redacted] | [redacted] | [redacted] |
| 24-hour urine protein electrophoresis sample | 0.29 | [redacted] | [redacted] | [redacted] |
| **CAR-T related prophylactic and other medications: cilta-cel** | | | | |
| Intravenous immunoglobulin | 0.25 | [redacted] | [redacted] | [redacted] |
| Prophylactic antiviral: aciclovir | 0.02 | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| Prophylactic anti-bacterial: levofloxacin | 0.28 | [redacted] | [redacted] | [redacted] |
| Prophylactic antifungal: fluconazole | 0.46 | [redacted] | [redacted] | [redacted] |
| **Routine care (pre progression, on treatment)** | | | | |
| Hematologist visit | 0.25 | [redacted] | [redacted] | [redacted] |
| **Routine care (pre progression, off treatment)** | | | | |
| Hematologist visit | 0.25 | [redacted] | [redacted] | [redacted] |
| **Routine care (post progression)** | | | | |
| Hematologist | 0.25 | [redacted] | [redacted] | [redacted] |
| **Sample size for subsequent treatment** | | | | |
| Proportion of cilta-cel PPS not on treatment | [redacted] | [redacted] | [redacted] | [redacted] |
| Proportion of Non-CAR-T treatments PPS not on treatment (PFS-based) | [redacted] | [redacted] | [redacted] | [redacted] |
| Probability that progression event was death – value in use – cilta-cel | [redacted] | [redacted] | [redacted] | [redacted] |
| Probability that progression event was death – value in use – PC | [redacted] | [redacted] | [redacted] | [redacted] |
| **% treatment regimen used for subsequent treatment for CAR-T** | | | | |
| Pd | 0.39 | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| Kd | 0.39 | [redacted] | [redacted] | [redacted] |
| Teclistamab | 0.21 | [redacted] | [redacted] | [redacted] |
| **% treatment regimen used for subsequent treatment for non CAR-T** | | | | |
| Pd | 0.23 | [redacted] | [redacted] | [redacted] |
| Kd | 0.23 | [redacted] | [redacted] | [redacted] |
| Teclistamab | 0.33 | [redacted] | [redacted] | [redacted] |
| Cilta-cel | 0.22 | [redacted] | [redacted] | [redacted] |
| **% patients taking subsequent treatment upon disease progression (conditional on surviving progression event)** | | | | |
| Cilta-cel | [redacted] | [redacted] | [redacted] | [redacted] |
| PC | [redacted] | [redacted] | [redacted] | [redacted] |
| **Mean duration of subsequent treatment (week) by treatment regimen** | | | | |
| Cilta-cel | [redacted] | [redacted] | [redacted] | [redacted] |
| PC | [redacted] | [redacted] | [redacted] | [redacted] |
| **Patient time costs** | | | | |
| Hours per visit or drug administration | 4.0 | [redacted] | [redacted] | [redacted] |
| **Utility** | | | | |
| PFS, CAR-T | 0.86 | [redacted] | [redacted] | [redacted] |
| PFS, non CAR-T | 0.86 | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| Utility PPS | 0.80 | [redacted] | [redacted] | [redacted] |
| **AE duration (days)** | | | | |
| CRS, Grade 1-2 | 3.58 | [redacted] | [redacted] | [redacted] |
| CRS, Grade 3+ | 5.00 | [redacted] | [redacted] | [redacted] |
| Neurotoxicity, Grade 1-2 | 131.52 | [redacted] | [redacted] | [redacted] |
| Neurotoxicity, Grade 3+ | 16.20 | [redacted] | [redacted] | [redacted] |
| Acute renal failure | 3.00 | [redacted] | [redacted] | [redacted] |
| Anemia | 16.78 | [redacted] | [redacted] | [redacted] |
| Cardiac failure | 18.00 | [redacted] | [redacted] | [redacted] |
| Febrile neutropenia | 6.90 | [redacted] | [redacted] | [redacted] |
| Hypertension | 36.20 | [redacted] | [redacted] | [redacted] |
| Leukopenia | 37.31 | [redacted] | [redacted] | [redacted] |
| Lymphopenia | 65.26 | [redacted] | [redacted] | [redacted] |
| Neutropenia | 45.56 | [redacted] | [redacted] | [redacted] |
| Pneumonia | 16.10 | [redacted] | | |
| Respiratory infection | 9.25 | | | |
| Thrombocytopenia | 51.36 | | | |
| Hypogammaglobulinemia | 136.44 | | | |
| **AE-related disutilities** | | | | |
| CRS, Grade 1-2 | -0.05 | | | |
| CRS, Grade 3+ | -0.86 | | | |

| | |
|---|---|
| Neurotoxicity, Grade 1-2 | 0.0 |
| Neurotoxicity, Grade 3+ | 0.00 |
| Acute renal failure | -0.10 |
| Anemia | -0.31 |
| Cardiac failure | -0.10 |
| Febrile neutropenia | -0.39 |
| Hypertension | 0.00 |
| Leukopenia | -0.07 |
| Lymphopenia | -0.07 |
| Neutropenia | -0.15 |
| Pneumonia | -0.19 |
| Respiratory infection | -0.19 |
| Thrombocytopenia | -0.31 |
| Hypogammaglobulinemia | 0.00 |
| **Adverse Events Frequency, cilta-cel** | |
| CRS, Grade 1-2 | 0.63 |
| CRS, Grade 3+ | 0.01 |
| Neurotoxicity, Grade 1-2 | 0.15 |
| Neurotoxicity, Grade 3+ | 0.02 |
| Acute renal failure | 0.00 |



| | |
|---|---|
| Anemia | 0.36 |
| Cardiac failure | 0.00 |
| Febrile neutropenia | 0.05 |
| Hypertension | 0.03 |
| Leukopenia | 0.12 |
| Lymphopenia | 0.21 |
| Neutropenia | 0.90 |
| Pneumonia | 0.04 |
| Respiratory infection | 0.01 |
| Thrombocytopenia | 0.42 |
| Hypogammaglobulinemia | 0.08 |
| **Adverse Events Frequency, PC** | |
| CRS, Grade 1-2 | 0.0 |
| Anemia | 0.1 |
| Febrile neutropenia | 0.0 |
| Hypertension | 0.0 |
| Leukopenia | 0.0 |
| Lymphopenia | 0.1 |
| Neutropenia | 0.8 |
| Pneumonia | 0.1 |
| Respiratory infection | 0.0 |
| Thrombocytopenia | 0.2 |

| | | |
|---|---|---|
| Hypogammaglobulinemia | 0.0 | [redacted] |

# Appendix H. Literature searches for the clinical assessment N/A

## H.1 Efficacy and safety of the intervention and comparator(s)

Not applicable.

### H.1.1 Search strategies

Not applicable.

### H.1.2 Systematic selection of studies

### H.1.3 Not applicable Excluded full text references

Not applicable.

### H.1.4 Quality assessment

Not applicable.

### H.1.5 Unpublished data

Not applicable.

# Appendix I. Literature searches for health-related quality of life N/A

## I.1 Health-related quality-of-life search

Not applicable.

### I.1.1 Quality assessment and generalizability of estimates

Not applicable.

### I.1.2 Unpublished data

Not applicable.

# Appendix J. Literature searches for input to the health economic model N/A

## J.1 External literature for input to the health economic model

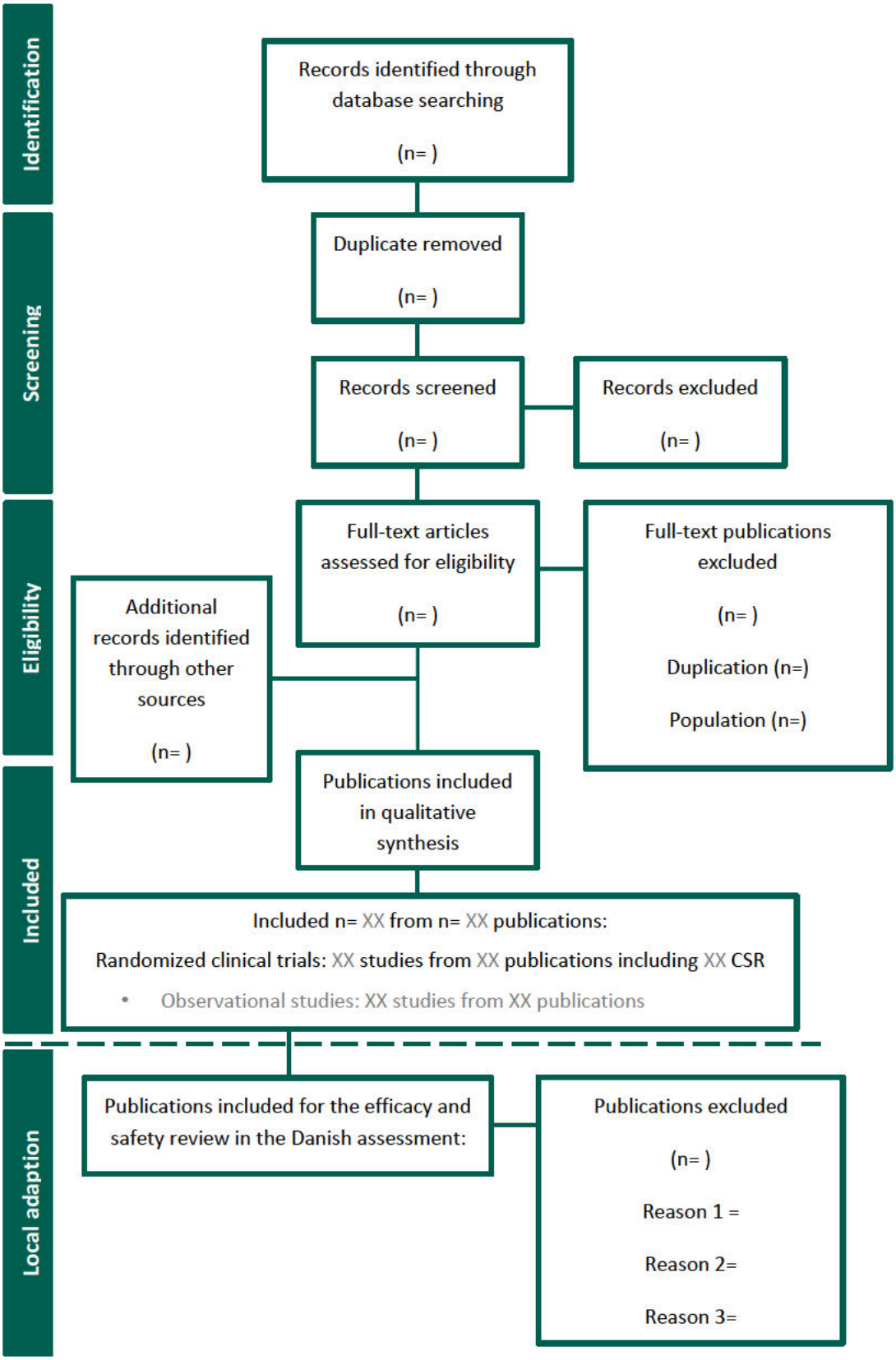
Not applicable. Example: Systematic search for […]

Not applicable.

### J.1.1 Example: Targeted literature search for [estimates]

**Not applicable.**

**Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.**



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