Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1690.1 – Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T cell to treat refractory or relapsed multiple myeloma

Applicant: **Janssen-Cilag Pty Ltd**

Date of MSAC consideration: **23-24 November 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1.   Purpose of application

An application requesting public funding was received from Janssen-Cilag Pty Ltd by the Department of Health and Aged Care. The application concerned ciltacabtagene autoleucel (cilta-cel) for the treatment of adult patients with RRMM who have received at least 4 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody. The sponsor is seeking public funding for cilta-cel in patients with RRMM through the National Health Reform Agreement (NHRA).

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice for public funding of ciltacabtagene autoleucel (cilta-cel), a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy, for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM), who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody. MSAC considered that the clinical place of cilta-cel and the proposal for its use as a later line of therapy in the context of RRMM for patients who have a high unmet clinical need was reasonable. MSAC noted limitations in the clinical evidence but accepted the clinical claim that cilta-cel had superior effectiveness in terms of durable survival outcomes and a different safety profile compared with standard of care therapies. However, MSAC considered the incremental cost-effectiveness ratio (ICER) was both unacceptably high and underestimated. ███████████████████████████████, ███████████████████████ ██████████████████████████████. MSAC noted that the jurisdictions considered substantial price reduction was required for public funding to be supported.

MSAC considered that the estimated costs associated with cilta-cel therapy were highly uncertain and underestimated. MSAC deferred its advice to see whether a lower ICER could be achieved through adjusting inputs in the economic model (particularly hospital costs and health benefits gained - to be verified by jurisdictions) and for a significant price reduction to be offered by the company. MSAC advised that an ICER in the range of those for other treatments in later line RRMM recommended by PBAC would be more likely to be acceptable. Furthermore, MSAC requested the Department negotiate a pay-for-performance arrangement to incentivise payment on the performance of the deeper level of clinical response achieved at 12-months after cilta-cel infusion.

Consumer summary

This was an application from Janssen-Cilag Pty Ltd requesting public funding of ciltacabtagene autoleucel (cilta-cel) to treat adults with myeloma that has not responded to previous treatment (refractory) or has come back after treatment (relapsed). This is the second time that MSAC has considered this application. In July 2022, MSAC did not support funding of cilta-cel for this condition.

Multiple myeloma, also known as myeloma, is a form of blood cancer that develops from a type of white blood cell found in the bone marrow (soft matter within bones where blood cells are made). The cancerous cells spread through the bone marrow and cause lesions that weaken the bones, which can result in there not being enough normal blood cells to grow. As a result of myeloma and its lesions, patients experience pain, bone fractures, bleeding problems and frequent infections.

Chimeric antigen receptor T cell (CAR-T cell) therapies such as cilta-cel are used to treat patients with some types of cancer, such as myeloma. They are currently used in patients who don't respond to, or who relapse after, other types of treatment, usually chemotherapy (called relapsed or refractory multiple myeloma [RRMM]). CAR-T cell therapy involves taking some of the patient's own blood, which is then sent to a laboratory where the T cells (a type of white blood cell) are extracted and genetically altered to express a chimeric antigen receptor (CAR) that helps the T cells target specific proteins and attack the myeloma cancer cells. The patient's altered T cells are infused back into their body target and kill the cancer cells.

This application is to use cilta-cel as a fifth-line treatment, which means after four other treatments have already been tried and have not resulted in remission (disappearance of evidence of cancer). MSAC considered that the side effects from CAR-T therapies, including cilta-cel, can be serious, including most patients having a severe inflammatory reaction following infusion (cytokine release syndrome) which can be life-threatening, as well as potentially severe brain inflammation and neurological and blood related effects. Long term side-effects could also be severe but are currently uncertain due to the newness of these treatments. MSAC considered that cilta-cel should not be used until after other, more established options have already been tried.

MSAC acknowledged that there are few other options available as fifth and sixth-line therapies, and that the evidence presented supported the benefit of cilta-cel treatment over conventional therapies for RRMM, with benefits observed in terms of response to treatment, extending life and preventing disease recurrence, and therefore there is a clinical need for cilta-cel for some people. However, MSAC considered the actual cost of cilta-cel to be too high, and this affected MSAC's view about the value for money offered by cilta-cel, as the cost of cilta-cel was much higher than alternative RRMM treatments when measured against health benefits. Therefore, MSAC determined that additional work should be done on the price and how payments to the drug company for cilta-cel would be made.

MSAC noted the significant volume of consumer support for this application, all of which was supportive of making this therapy available to patients with RRMM. MSAC also noted that the four submissions from States and Territories as joint funders of this highly specialised therapy via the National Health Reform Agreement (NHRA) were not supportive of the application unless the price of cilta-cel was to be significantly reduced.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC deferred its decision on whether to support cilta-cel for use as fifth-line therapy for people with RRMM. MSAC considered that the treatment was effective and safe enough for

Consumer summary
people as a fifth-line therapy, but was concerned that the price was too high for it to be cost-effective. MSAC advised negotiating on the cost so that the treatment is good value for money.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Janssen-Cilag Pty Ltd was for using ciltacabtagene autoleucel (cilta-cel) to treat adult patients with RRMM who have received at least four prior lines of therapy (i.e., fifth line treatment), including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody. The sponsor is seeking public funding for cilta-cel in patients with RRMM as a Highly Specialised Therapy through the National Health Reform Agreement (NHRA).

MSAC recalled that it did not support public funding of Application 1690[1] in July 2022 as MSAC did not accept that cilta-cel is comparatively safe, effective and cost-effective over the modelled time horizon for adult patients with RRMM who have received at least three prior lines (4L) of therapy. MSAC considered that there was low level clinical evidence, a large and uncertain financial impact, and there were other treatment options available for late line disease. Public funding for cilta-cel was also not supported by the jurisdictions, and it was undergoing Therapeutic Goods Administration (TGA) review at the time.

MSAC noted three key differences in this resubmission compared to the original submission:

- cilta-cel has been placed as fifth-line (5L) or later therapy instead of 4L or later for adult RRMM patients who have received treatments including a PI, an IMiD and an anti-CD38 antibody
- longer follow-up data were available from the key clinical trial CARTITUDE-1, a single-arm study (33.4 months follow-up compared with 21.7 months follow-up in the original submission), although the data for 5L + MM supplied by the sponsor had not yet been peer reviewed or published
- the comparator arm included an additional comparator (selinexor plus dexamethasone; Sd).

In addition, MSAC noted that the TGA has now approved cilta-cel for adult RRMM patients who have received at least three prior lines of therapy, including a PI, an IMiD and an anti-CD38 antibody.

MSAC noted the significant volume of support for the application from clinicians, patients and patient support groups, who argued that a treatment option is needed for patients who have survived four lines of therapy, especially younger patients. MSAC agreed that there is a clinical need for cilta-cel as a treatment option in the later course of RRMM disease.

MSAC noted the ongoing reluctance from the states and territories to support the public funding of cilta-cel, with most citing the prohibitive cost of the therapy. Most states and territories considered that the hospital costs were underestimated and therefore did not view cilta-cel as cost-effective, and the place in therapy was uncertain. Some jurisdictions considered that the proposed model of 70%:30% (inpatient:outpatient) CAR-T service delivery would require additional support services to implement a change in the model of care. MSAC's July 2023

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[1] MSAC application 1690 PSD -available at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1690-public

review of the CAR-T therapy tisagenlecleucel, that was listed in 2019, highlighted that the true program cost of providing tisagenlecleucel for paediatric acute lymphoblastic leukaemia was substantially higher than expected, which was concerning for jurisdictions. MSAC noted issues in the data collected via the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) on tisagenlecleucel due to its incompleteness, inconsistency, and accessibility. MSAC noted that the applicant suggested exploring data collection using a disease specific registry such as the Myeloma and Related Diseases Registry (MRDR). MSAC noted issues related to data collection for currently approved CAR T-cell therapies and considered it will be important that data collection is standardised going forward.

MSAC noted that the clinical criteria for eligibility of cilta-cel treatment under the NHRA had been further defined. In addition to the previous requirements and the change to 5L or later line therapy, eligible patients must also have a creatinine clearance of 40 mL/min or greater and liver function test results of no more than 3.0 times the upper limit of normal. These stricter requirements meant that there was a 43% reduction in the estimated number of eligible patients because there will be fewer patients who would be healthy enough to qualify for cilta-cel therapy.

MSAC noted that multiple myeloma is a mostly incurable and very heterogeneous disease with highly variable treatment pathways. MSAC noted the clinical management algorithm, in which cilta-cel is proposed as the fifth or sixth line of therapy for adult RRMM patients. MSAC considered that the clinical place of cilta-cel and the proposal for its use as a later line of therapy in the context of RRMM for patients who have a high unmet clinical need was reasonable. MSAC noted the comparators in the application, carfilzomib with dexamethasone (Cd), pomalidomide with dexamethasone (Pd) and selinexor with dexamethasone (Sd) were anticipated to be replaced and/or displaced by cilta-cel.

MSAC noted limitations in the clinical evidence presented in the applicant-developed assessment report (ADAR) which included the phase 1b/2 single arm study (CARTITUDE-1). MSAC also noted clinical evidence from the phase 3 randomised control trial CARTITUDE-4, that compared cilta-cel to standard of care (SoC) combination therapy (pomalidomide, bortezomib and dexamethasone (PVd); or daratumumab, pomalidomide and dexamethasone (DPd), as per physician's choice) in the lenalidomide-refractory RRMM population (an earlier line than the proposed line of therapy in this application) where:

- the median follow-up was 15.9 months (range of 0.1–27.3 months)
- more patients in the cilta-cel group had an overall response (84.6% v 67.3%) and complete remission (CR) (73% v 22%)
- most patients reported grade 3 or 4 adverse events (AEs).

MSAC considered that the CARTITUDE-4 data in the earlier line less resistant population provided some reassurance of the clinical efficacy of cilta-cel. MSAC considered the true magnitude and durability of the benefit in terms of overall survival (OS) and progression-free survival (PFS) outcomes based on the data presented in the ADAR remained uncertain due to data being heavily censored. MSAC noted the applicant's pre-MSAC response, that pointed to the 33.4-month data-cut to support the superiority claim by stating that while the number of patients at risk significantly dropped from the 33.4 month point, it did indicate durability of response over the observed trial period and showed that the trends observed in the earlier July 2021 data cut off continued in the October 2022 data cut off. MSAC agreed with the Evaluation Sub-committee (ESC) that there was strong evidence to support the ADAR's claims of superiority of cilta-cel against current Australian SoC therapies.

MSAC noted the frequency of AEs, including those of Grade 3 or higher and of serious AEs, was high in both CARTITUDE-1 and comparator studies. MSAC noted the safety data from the CARTITUDE-1 trial, including the risk of cytokine release syndrome (CRS; 95%), immune effector cell-associated neurotoxicity syndrome (ICANS; 17–21%) and cytopenia (100%) in cilta-cel–treated patients in the short term. In the medium term, 40–50% of patients experienced

neurological AEs including parkinsonism like effects and haematological AEs. MSAC noted that the parkinsonism signs and symptoms were not modelled in terms of quality of life (QoL), nor mentioned in the ADAR. MSAC noted the pre-MSAC response where the applicant stated that based on findings of CARTITUDE-1, AE high risk patient management strategies had been implemented across the CARTITUDE program that reduced the incidence of parkinsonism from 6% to <0.5% in new and ongoing studies. MSAC considered that the registry could capture these types of AEs. Long-term possibly severe AEs include secondary malignancies, but more (i.e., 15-year follow-up) data were needed on these. Overall, MSAC considered that uncertainty regarding safety and effectiveness remained, but that the additional data from the sponsor and the latest data cut provided reassurance that there appeared to be a clinical benefit for cilta-cel. MSAC noted that CARTITUDE-1 and local expert opinion indicated that two cycles of bridging therapy are required for each patient. The bridging therapy agent may include any previously used agent (in 3L or 4L) such as Pd, Cd, lenalidomide and dexamethasone (Ld), bortezomib and dexamethasone (Bd), Sd, elotuzumab or dexamethasone monotherapy. The Pharmaceutical Benefits Scheme (PBS) restrictions for some of these agents may not allow patients to use them as bridging therapy because patients are only eligible to receive these therapies once. MSAC noted that the sponsor sought advice on how PBS restrictions may be amended to allow these drugs for (re)treatment as bridging therapy prior to CAR-T infusion, and also for use after progression on CAR-T therapy.

MSAC noted that ESC queried whether production issues were affecting the ability of manufacturers to meet demand for CAR-T therapies noting National Institute for Health and Care Excellence (NICE) submission for cilta-cel was withdrawn by Janssen. ███ ████ █
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MSAC noted that the economic evaluation was a cost-utility analysis using a decision-tree and partitioned-survival model including OS, PFS and a post-progression state (PPS). The approach used for the economic model was consistent with previous CAR-T therapies considered by MSAC. This approach was also consistent with the initial ADAR, with differences being in the use of cilta-cel as 5L treatment and the use of Sd as an additional comparator; more mature data from CARTITUDE-1 study and STORM (a single-arm open-label trial assessing the efficacy and safety of Sd); and the revision of MRDR cohorts to align with 5L use. The ADAR also used new time-dependent weighting (infused to non-infused). MSAC queried this, as using fixed weights would better align with the model over time. MSAC considered that the economic model may favour cilta-cel. MSAC noted several additional updates to the model from the initial submission, including inpatient length of stay and outpatient time ratios, and the inclusion of intravenous immunoglobulin (IVIg) costs. However, MSAC noted that several uncertainties in the economic model remained, including the number of apheresis procedures required per patient, and the likely underestimation of ongoing and recurrent AEs for both cilta-cel and the comparators. In addition, neurotoxicity monitoring had not been captured, which MSAC assumed would affect cilta-cel's cost-effectiveness, perhaps significantly. MSAC also noted that the ADAR did not take into account any change in QoL for a later treatment (5L vs 4L), and MSAC considered that, for younger patients who do respond to cilta-cel, it was reasonable to assume they could have a good QoL post-treatment. MSAC noted the base case incremental cost-effectiveness ratio (ICER) of $████, with PFS utilities and time horizon being the main drivers of the ICER. MSAC noted the pre-ESC response provided additional modelling including a revised base case to address the assessment groups concern regarding the application of utilities (including PFS health state values based on 5L+ subgroup data) and the application of the PFS/OS curves in the comparator arm resulting in an ICER of $████ (2.4% higher than the base case ICER). MSAC noted ESC's concern about the extrapolation and time horizons used in the model. The applicant justified the extrapolation in its pre-MSAC response by stating that "the lognormal distribution for extrapolation of OS and PFS Kaplan-Meier (KM) data could be justified based on the available evidence, and clinical expert validation". They also stated "as the lognormal distribution reflects a

decrease in hazard over time, as compared to the exponential (constant risk) and Weibull (an increase in hazard with time), based on the observed trend in the hazard in both of these trials, provide strong support for the OS and PFS extrapolations". The applicant justified the modelled time horizon by stating that 25 years was reasonable for younger patients and the time horizon was considerably shorter than the time horizons (that is, 44–50 years) of the economic evaluations accepted by MSAC for other CAR-Ts for conditions with patients of a similar average age to RRMM populations. MSAC accepted the economic model, but considered the extrapolations to be ambitious, that the OS and PFS estimates for the comparator were too conservative and the benefit attributed to cilta-cel too generous, and advised that the base case should be modified to address this. In addition, MSAC queried the accuracy of the input costs, pointing out that the true delivery costs in other approved CAR-T therapies were not adequately captured.

MSAC noted that the total number of patients had been reduced in this ADAR ██████ ██████ ██████ ██████ ██████ ██████ compared to the previous submission ██████ ██████ ██████ ██████ ██████ ██████. This represented a 43% reduction in the estimated number of cilta-cel–treated patients over 5 years compared to the previous ADAR. Patient suitability in 5L and 6L was lower than in 4L RRMM because patients in this setting were less likely to be able to tolerate cilta-cel. The uptake rate for 5L used in this ADAR was ████% in year 1 increasing to ████% by year 3, and the uptake rate of 6L was assumed equal to the uptake rate of 5L from the previous ADAR (that is, ████% in year 1 decreasing to ████% in year 5). However, MSAC considered the proposed uptake rate remained highly uncertain, and pointed to other CAR-T predicted versus actual usage data showing that the estimated patient numbers were generally not reached.

MSAC noted the ████ of cost proposed as part of the risk-sharing agreement ████ ████ ██████. The applicant confirmed there would be a limit of one treatment per patient per lifetime. MSAC noted that out-of-pockets costs were not included in the ADAR.

MSAC considered that different risk-sharing arrangements may be preferred for different CAR T treatments and indications depending on their different characteristics, and in this case a PfP arrangement to incentivise payment on the performance of the deeper level of clinical response achieved at 12 months post cilta-cel infusion may be appropriate, noting the applicant's willingness to negotiate on structure and timing of a payment model. MSAC considered that comparison with funding arrangements for other late line RRMM treatments recommended by the PBAC would be informative to determine an appropriate basis for funding cilta-cel, and that an ICER in the range of $75,000 (upper limit of PBAC ICER range[2]) aligning with these treatments would be more likely to be reasonable. MSAC considered the basis for funding cilta-cel should also be benchmarked against other CAR-T therapies currently funded through the NHRA.

MSAC deferred its decision for funding cilta-cel. MSAC accepted that cilta-cel is clinically effective for 5L or later line of therapy for a small subset of patients. MSAC considered that the claim of QALYs gained for the intervention and comparator needed to be revisited and adjusted, and that the estimated costs associated with cilta-cel therapy were highly uncertain and underestimated and a revised economic analysis with inputs verified by jurisdictions was required. MSAC considered the ICER was both unacceptably high and underestimated and advised that a lower

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[2] Selinexor March 2022 PSD: Base case ICER per QALY ranges of $55,000 to < $75,000; PBAC recommendation based on ICER of $60,000 per QALY

ICER be achieved by reducing the proposed cost of the therapy. MSAC requested further clarification and justification about the proposed patient uptake rates so that a more accurate financial impact could be calculated, and considered negotiation of a PfP arrangement that places more emphasis on the achievement of a deeper (sustained) clinical response (i.e. payment 2) may be appropriate. MSAC advised that if the above issues are addressed, reconsideration of this application could bypass ESC and be made directly to MSAC.

4. Background

Cilta-cel was considered by the Medical Services Advisory Committee (MSAC) in July 2022 for the treatment of adult patients with RRMM who have received at least 3 prior lines of therapy, including a PI, an IMiD and an anti-CD38 antibody. MSAC did not support funding cilta-cel for the treatment of RRMM through the NHRA as MSAC did not accept that cilta-cel is comparatively safe or effective for these patients and considered that this population has many other treatment options. MSAC also did not consider that cilta-cel represented good value for money.

This applicant developed assessment report (ADAR) sought to address the issues highlighted in the previous submission (see Table 17). The applicant is now requesting funding for cilta-cel as a later line therapy for RRMM, for adults who have received at least 4 prior lines of therapy (i.e., fifth-line or more advanced multiple myeloma, or 5L+ multiple myeloma (MM)).

Chimeric antigen receptor T cell (CAR-T) therapies have previously been considered by MSAC for other indications (Table 1). These therapies received public funding via the NHRA.

Table 1   Overview of CAR-T therapies considered by MSAC

Application	Application title	MSAC meetings
1519	Tisagenlecleucel (CTL019) for treatment of refractory CD19-positive leukaemia and lymphoma	9 April 2019, 28-29 March 2019, 22-23 November 2018
1519.1	Tisagenlecleucel (CTL019) for treatment of relapsed or refractory diffuse large B-cell lymphoma	28-29 November 2019, 1-2 August 2019
1587	Axicabtagene ciloleucel [KTE-C19] for the treatment of refractory or relapsed CD19-positive lymphoma	16 January 2020, 28-29 November 2019
1647	Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma	29-30 July 2021
1723	Brexucabtagene autoleucel for adult relapsed or refractory B-precursor acute lymphoblastic leukaemia	24-25 November 2022

Source: Table 1-2, Section 1 of the resubmission ADAR.
Abbreviations: CAR-T = chimeric antigen receptor T cell; MSAC = Medical Services Advisory Committee

5. Prerequisites to implementation of any funding advice

Cilta-cel qualifies as a high-cost, highly specialised therapy as per the NHRA definition (Addendum to the NHRA 2020–2025 (NHRA 2020–2025).

TGA details

Cilta-cel (CARVYKTI®) was included on the Australian Register of Therapeutic Goods (ARTG) on 6 June 2023. Cilta-cel was registered on the ARTG as a Class 4 biological.[3]

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[3] https://www.tga.gov.au/resources/artg/410143

The TGA approved indication is: 'cilta-cel is indicated for the treatment of adult patients with RRMM, who have received at least 3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 antibody.'[4]

Janssen notes that other CAR-T therapies have been approved by the TGA and MSAC for use in acute lymphoblastic leukaemia (ALL), diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL). These therapies target CD-19.

Additionally, since the initial evaluation, European Medicines Agency (EMA) approval was granted. An updated summary of approved indications from the TGA, EMA and FDA are provided in Table 2.

Table 2   Updated summary of cilta-cel, tisagenlecleucel, and axicabtagene ciloleucel approved indications in Australia, Europe and USA

Approval	Cilta-cel	Tisagenlecleucel	Axicabtagene ciloleucel
ATC code	L0XX	L01XX71	L01X
TGA	Adult patients with RRMM who have received ≥3 prior lines of therapy, including PI, IMiD and anti-CD38 antibody.	Paediatric and young adult patients up to age 25 with B-cell precursor ALL that is refractory, in relapse post-transplant, or in second or later relapse. Adult patients with relapsed or refractory DLBCL after ≥2 lines of systemic therapy. Not indicated for patients with primary central nervous system lymphoma.	Relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
EMA	Adult patients with RRMM who have received ≥3 prior therapies, including IMiD, PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	Paediatric and young adult patients up to and including age 25 with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse. Adult patients with relapsed or refractory DLBCL after ≥2 lines of systemic therapy.	Adult patients with relapsed or refractory DLBCL and PMBCL, after ≥2 lines of systemic therapy.
FDA	Adult patients with RRMM after ≥4 prior lines of therapy, including PI, IMiD and an anti-CD38 monoclonal antibody.	Patients up to age 25 with B-cell precursor ALL that is refractory or in second or later relapse. Adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Limitation of Use: Tisagenlecleucel (KYMRIAH®) is not indicated for treatment of patients with primary central nervous system lymphoma	Adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Source: Constructed during the evaluation based on publications from TGA, EMA and FDA
Abbreviations: ATC = anatomical therapeutic chemical; ALL = acute lymphoblastic leukaemia; cilta-cel = ciltacabtagene autoleucel; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; FDA = Food and Drug Administration; PMBCL = primary mediastinal B-cell lymphoma; TGA = Therapeutic Goods Administration; RRMM = relapsed or refractory multiple myeloma; PI = proteasome inhibitor.

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[4] https://www.ema.europa.eu/en/news/new-gene-therapy-treat-adult-patients-multiple-myeloma

Consistent with other CAR-T therapies previously considered by MSAC, the ADAR has requested public funding via the NHRA. The proposed funding mechanism is appropriate and consistent with previous MSAC advice for CAR-T cell therapies.

The ADAR noted that previous MSAC advice for CAR-T therapies included the following requirements for public funding (p23 Axicabtagene ciloleucel Public Summary Document (PSD), January 2020; p19 Tisagenlecleucel PSD, April 2019):

- treatment must be delivered by a haematologist working in a multidisciplinary team specialising in CAR-T cell therapy
- treatment must be delivered in a tertiary public hospital with appropriate credentials
- governance and prescribing rules to ensure treatment is directed to patients most likely to benefit
- payment only upon successful infusion (i.e., patient infused with a clinically acceptable cell dose consistent with the expected cell dose specified prior to apheresis)
- treatment to be limited to a single dose (no currently available evidence informing the effectiveness or safety of multiple doses)
- full review of clinical effectiveness, cost-effectiveness and budget impact to be conducted by MSAC 2–3 years post-commencement of public subsidy
- data on the use of CAR-T therapies in Australia to be recorded by the Australian Bone Marrow Transplant Recipient Registry (ABMTRR), with the cost of data collection to be met by the applicant (ensuring a single Australian source of data for all CAR-T therapies for all indications and from all treatment centres)
- definition of an acceptable responder status for patients undergoing CAR-T therapy within the context of the disease
- risk share arrangements to manage utilisation beyond the estimates.

Data collection via ABMTRR registry

MSAC advises that the use of CAR-T therapies in Australia should be registered with the ABMTRR, which provides specific data collection for CAR-T cell therapies. It should be noted that there is another registry in Australia for patients with MM—the Myeloma and Related Diseases Registry (MRDR), a prospective, clinical-quality registry of newly diagnosed cases of plasma cell disorders. MRDR was established in 2012 and operates at 44 sites in Australia, and more recently in New Zealand. The ADAR constructed 2 alternative comparator arms from this registry, the MRDR main cohort and the MRDR modified cohort, for use in the economic model.

The applicant noted issues with the use of the ABMTRR that have been raised with Australia and New Zealand Transplant and Cellular Therapies (ANZTCT) by Medicines Australia. The current registry was not enabling the industry to meet obligations required by TGA and MSAC, and various State and Territory Agreements that relate to commercial CAR-T therapies. No response from ANZTCT was provided in the submission. The applicant stated a keenness to resolve registry challenges to enable efficient and timely data entry of the mandated patient-level data from CAR-T centres and meet contractual obligations. The applicant requested further advice from MSAC on this matter.

6.   Proposal for public funding

Public funding of one-off cilta-cel treatment is specifically requested for patients with RRMM, who have received at least 4 prior lines of therapy, including a PI, IMiD and an anti-CD38 antibody (i.e., 5L+ RRMM, Table 3). This request is narrower than the approved TGA indication.

The proposed eligibility criteria for cilta-cel treatment in this ADAR has been updated to reflect the revised population requested for funding (i.e., 5L+ RRMM), and the additional criteria

proposed by Myeloma Australia's Medical and Scientific Advisory Group (MSAG) related to creatine clearance and liver function. The remaining criteria is consistent with the previous submission. Janssen is willing to work with the MSAC Secretariat and the Department to ensure that cilta-cel is used in the intended population and has proposed the below eligibility criteria for funding via the NHRA.

Table 3 Eligibility criteria for cilta-cel treatment under the NHRA (italicised are changes compared with previous submission)

Component	Description
Treatment criteria	Patient must be treated in a tertiary public hospital with appropriate credentials AND Patient must be treated by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy
Clinical criteria	The condition (MM) must be confirmed by a histological diagnosis AND Patient must have progressive disease after at least *four* prior lines of therapy AND Patient must have previously had treatment with a protease inhibitor, immunomodulatory (ImiD) drug, and an anti-CD38 therapy AND Patient must not be receiving concomitant PBS-subsidised therapies AND Patient must have an ECOG score of 0 or 1 AND *Patient must have a creatinine clearance of 40 mL/min or greater* *AND* *Patient must have a liver function of 3.0 x upper limit of normal or less* AND Patient must not have received successful treatment with cilta-cel before, (i.e. treatment is limited to one successful infusion per lifetime)

Source: Table 1-11, Section 1.10 of the 1690 ADAR
Abbreviations: CAR-T= chimeric antigen receptor T-cells; ECOG = Eastern Cooperative Oncology Group; MM = multiple myeloma; NHRA= National Health Reform Agreement; PBS = Pharmaceutical Benefits Scheme.

Proposed fee

Treatment is proposed to be limited to one successful infusion per lifetime. ▮▮▮▮ ▮▮▮▮▮▮
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Implications of NHRA listing of cilta-cel for PBS-subsidised MM therapies

The process of delivering cilta-cel requires that a patient receives bridging therapy between the point of cell collection to cilta-cel infusion and the purpose is to achieve disease control of the myeloma ahead of CAR-T infusion.

In the CARTITUDE-1 study the average duration of bridging therapy was 15 days. However, it is anticipated based on local clinical expert advice that on average around 2 cycles of bridging therapy will be required for each patient receiving cilta-cel.

As bridging therapy, patients may be treated with any previously used agent resulting in stable disease or a therapy they are previously naïve too should they have not exhausted all PBS options. Relevant bridging therapies in Australia are anticipated to include Pd, Cd, Ld, Bd, Sd, elotuzumab or dexamethasone monotherapy.

Janssen sought advice on how the PBS restrictions for the relevant appropriate MM therapies be amended to allow for the use as a bridging therapy ahead of ciltacabtagene autoleucel infusion as clinical experts noted a need to not restrict the use of MM therapy after progression on CAR-T therapy, or in the case that these MM therapies have been previously used, to allow their retreatment as an appropriate means for bridging therapy ahead of CAR-T infusion.

7.   Population

The requested treatment population for funding of cilta-cel is patients with RRMM previously treated with 4 lines of therapy including PI, IMiD and an anti-CD38 inhibitor. Thus, the earliest that patients can receive cilta-cel will be as a 5L MM treatment.

The ADAR stated that prior to the 5L setting, patients will have received treatment regimens that include these 3 classes of MM medicine (i.e., PI, IMiD and an anti-CD38 inhibitor), potentially receiving some of them more than once; for example, lenalidomide and pomalidomide (IMiDs), bortezomib and carfilzomib (PIs) and daratumumab and elotuzumab (monoclonal antibodies). These treatment options may have been exhausted as patients become refractory. The applicant stated that the unmet need for 5L+MM patients is more significant relative to the 4L+MM population. The 4L+MM patients would have failed 3 prior lines of treatment and in significant need for superior treatments that could extend survival and improve their quality of life. In the case of further 4L treatment failure, the available treatment options were limited.

This resubmission ADAR addressed some of the elements prespecified in the PICO confirmation ratified by PICO Advisory Sub-committee (PASC) in December 2021. The intervention and outcomes were consistent with those ratified; however, the population and comparators had been updated in the resubmission (Table 4) in response to issues raised by MSAC in its initial consideration of cilta-cel in July 2022 regarding an unacceptably low level of clinical evidence in support of cilta-cel in the context of late-line treatment where other treatment options were available. The requested 5L+ population is at a later line of therapy, and consequently there were fewer treatment options as they have exhausted and become refractory to even more therapies (than people with 4L+ RRMM). As such, the applicant stated that there is a greater clinical need

for additional treatments in later-line RRMM. The change in the PICO had not been ratified by PASC but the MSAC Executive was informed of the proposed change on 26 May 2023.

Cilta-cel is anticipated to both replace and displace comparator treatments (i.e. Cd, Pd and Sd).

Table 4   PICO included in the resubmission

Component	Description
Population	Adult patients with relapsed or RRMM, who have received at least 4 prior lines of therapy, including: 1) a proteasome inhibitor; 2) an immunomodulatory agent (IMiD); and 3) an anti-CD38 antibody.
Intervention	Ciltacabtagene autoleucel (also known as cilta-cel)
Comparator/s	Pomalidomide with dexamethasone, or carfilzomib with dexamethasone, or selinexor with dexamethasone.
Outcomes	Clinical effectiveness outcomes: • Complete response/stringent complete response. • Overall response rate. • Very good partial response or better response rate. • Duration of response, time to response. • Minimal residual disease negativity. • Progression free survival. • Overall survival. • Health-related quality of life. Safety outcomes: • Rate of AE and serious AE. • Incidence of AEs of special interest. • Incidence of cytokine release syndrome. • Incidence of neurological toxicity- CAR-T cell-related neurotoxicity (ICANS) and other neurological toxicities. • Incidence of tumour lysis syndrome, incidence of cytopenia. • Incidence of hypogammaglobulinemia. Cost-effectiveness: • Cost (including cost of additional pre-infusion and post infusion interventions). • Cost per life year gained. • Cost per quality-adjusted life year. • Incremental cost-effectiveness ratio. Financial implications: • Number of patients suitable for treatment. Number of patients who receive treatment.

Source: Table 1-5, Section 1.6 of the ADAR
Abbreviations: AE = adverse event, cilta-cel = ciltacabtagene autoleucel, IMiD = immunomodulatory agent, RRMM = relapsed or refractory multiple myeloma.

8.   Comparator

The comparators under evaluation in this ADAR have been updated from the ADAR lodged in February 2022. While both pomalidomide plus dexamethasone (Pd) and carfilzomib plus dexamethasone (Cd), remain as comparators, the ADAR also included the addition of selinexor plus dexamethasone (Sd) following its Pharmaceutical Benefit Schedule (PBS) listing for the 5L+ MM population in 2022.

The ADAR stated that there is a lack of standard of care (SoC) in the treatment setting and patients lack effective options. Pd and Cd were previously accepted as relevant comparators for cilta-cel for 4L+ MM by PASC and remained relevant comparators for cilta-cel for the 5L+ MM population.

Sd had been listed on the PBS for 5L+ MM since the initial ADAR was submitted in February 2022. Penta-refractory (PR) MM and triple-class refractory (TCR) MM are terms used to describe this population. The PBAC noted that selinexor was the first in a new class of anti-myeloma drugs known as selective inhibitors of nuclear export (SINE), and that there was a high clinical need for effective therapies for patients with TCR and PR MM. The commentary noted Selinexor plus dexamethasone had been included as a relevant comparator in the ADAR.

9.   Summary of public consultation input

A summary of previous consultation feedback received for MSAC Application 1690 is available in the Public Summary Document. Please refer to application 1690 PSD July 2022 (pp10-12)[1].

Consultation input further to this resubmission was received from 2 consumer organisations, five health professional organisations and 425 individuals, 2 of whom were medical professionals with the remainder consumers, friends and family of consumers and a charity worker. The organisations that submitted input was:

- The Leukaemia Foundation
- Myeloma Australia
- Haematology Society of Australia and New Zealand (HSANZ)
- The Australasian Leukaemia and Lymphoma Group (ALLG)
- Blood Transplant and Cell Therapies, Westmead Hospital
- Peter MacCallum Cancer Centre
- Myeloma Australia – Medical and Scientific Advisory Group (MSAG)

All consultation feedback received was supportive of making this therapy available to patients with refractory or relapsed multiple myeloma (RRMM).

Key Benefits of the proposed treatment were identified as stemming from the inadequacy/ disadvantages of current therapeutic options, as well as the potential efficacy of CAR-T.

Inadequacy/ disadvantages of current therapeutic options included:

- The challenges of undergoing current treatment options including induction therapy, stem cell transplant, and chemotherapy

    - The difficulty and inconvenience of frequent hospital/clinic visits
    - The pain and discomfort of the procedures

- The ongoing side effects of the therapies, including pain, fatigue, damage to organs and how this affects quality of life
- The significant cost

- The limitations of current myeloma treatments for remission and longevity of life. Some of the feedback that expressed concerns about current treatments suggested CAR-T should be available earlier in the treatment cycle.

- The Centre for Excellence for Cellular Immunotherapy noted that patients with RRMM after 4 therapies have poor outcomes with current therapies due to multidrug resistance, genetic complexities and increasing co-morbidities due to increasing age.

Potential efficacy of CAR-T included:

- Growing clinical evidence of the efficacy of CAR-T and the need to provide another treatment option for myeloma patients who may have exhausted all other current therapies.

"There is an urgent and unmet clinical need for novel therapies including BiTE and CAR-T for multiply relapsed/ refractory MM. The evidence supporting efficacy and safety continues to grow and is quite compelling, reflecting widespread approvals internationally." (Haematology Society of Australia and New Zealand).

"…with my first-hand experience in caring for these patients I am a wholehearted advocate for more funding to be channelled into this exciting research so as to create a mainstream CAR-T treatment off-trial." (Clinical Trials Co-ordinator)

"For my myeloma mates CAR-T is now the best - Or in some cases only - treatment to prevent their lives being cut short."
- MSAG noted Cilta-cel is game changing therapy for those patients with late-stage disease. Current available therapies for patients on 5th line treatment have survival in the range of 3-6 months compared to 3-4 years with Cilta-cel.
- The advantage that is a one-off procedure with potentially fewer side effects, which affords patients a higher quality of life.
- Evidence of CAR-T adoption in other countries.
- Improved strategies for managing the side effects of CAR-T
- The Leukaemia Foundation provided a patients account of their prior treatments and subsequent CAR-T treatment, which they state '…*seemingly provided this patient with another chance at life'*.
- Myeloma Australia noted that Cilta-cel brings hope to patients for extended life expectancy and relief from the burden of continuous therapy regimens, with associated physical and psychological benefits.

Potential disadvantages of the proposed therapeutic device were identified as:

- Cilta-cel is not currently publicly funded raising concerns for the significant cost of cilta-cel to treat most patients creating a health equity access issue.

- CAR T therapy is a specialised service generally only available in tertiary centres in Australia, adding to equity issues as patients will have to travel significant distances to access the service and remain in close proximity to the treating hospital after treatment for a period of time. This could have financial implications for patients and families.

- Potential medical risk associated with the procedure and side effects including cytokine release syndrome, neurotoxicity, infection and cytopenias. CAR T therapy is also

accompanied by specific acute and longer-term toxicity and risk, which may mean it is not suitable for all patients with a diagnosis of myeloma.

Other

Respondents clarified that sCR is a well-established, relevant standardised measure used as end point across most centres in Australia to monitor the response to treatment for RRMM although it may not be typically assessed in 5th-line+ RRMM patients in clinical practice. MSAG also advised that sCR at 12 months is the correct proxy endpoint for PFS and OS. Furthermore, responses clarified that measurable residual disease (MRD) is not currently used in 5L+ RRMM treatment as a measure for response to treatment partly because MRD testing is not Medicare Benefits Schedule (MBS) funded and the technology (specifically Next generation sequencing [NGS]) is not widely accessible across Australia to assess MRD. Respondents also indicated that NGS testing and Flow MRD both would be appropriate methods for MRD testing in RRMM patients.

Respondents noted that post-apheresis, patient management is highly individualised, contingent on multiple factors including co-morbidities, response to previous therapies and disease trajectory. However, patients are generally expected to receive bridging therapy, which typically involves anti-myeloma therapy and the use of steroids.

Other comments noted from the feedback included the urgent and unmet clinical need for novel therapies including bi-specific T-cell engager (BiTE) and CAR-T for RRMM patients who often have very few effective treatment options available. Regarding CAR-T treatments, a respondent highlighted the undocumented burden of disease morbidity and cost to health care should be considered and the profound immeasurable social and psychological impact of disease burden are to be noted. Regarding BiTE treatments, the responses noted that BiTE treatments, if available, would offer the advantage of rapid access as an "off-the-shelf" treatment and might be a suitable therapy to consider earlier in the treatment process than CAR-T especially for individuals who experience rapid relapse, patients deemed frail, and patients for whom CAR-T therapy may not be considered suitable such as for patients with advanced organ dysfunction, Plasma cell leukaemia, CNS involvement etc. In addition, a respondent suggested that CAR-T may be more suitable over BiTEs for patients from regional Australia as BiTEs require ongoing treatment.

The Blood Transplant and Cell Therapies, Westmead Hospital noted that they are in the currently in the process of transitioning to outpatient CAR-T infusion for suitable low risk patients. They also raised concern about moving the proposed line of therapy from 4L+ to 5L+, noting that a large proportion of patients will not remain eligible for treatment after failing the 4th line of therapy. The ALLG noted a disadvantage of treating the more heavily pre-treated patients with CAR-T therapy include poor performance status and treatment outcomes that would be not as good as expected. Respondents noted that they would like to see Cilta-cel available to patients in earlier lines of therapy.

A respondent noted that there are current ongoing trials for use of CAR-T in earlier lines potentially offering a more favourable prognosis with respect to PFS. However, the results of these trials are pending and benefits in earlier lines of therapy remain to be fully understood.

10.   Characteristics of the evidence base

Summary of the clinical evidence

The comparative safety and efficacy of cilta-cel for the treatment of RRMM in patients who have received at least 4 prior lines of therapy was based on data from the single-arm clinical trial, CARTITUDE-1. In contrast to the ADAR lodged in February 2022, the resubmission included trial data up to October 2022 (additional 12 months, i.e., median follow up: 33.4 vs 21.7 months).

Based on the systematic literature review, 5 studies met the inclusion criteria for assessing the effectiveness and safety of cilta-cel compared to commonly used 5L+ RRMM therapies in Australia (Pd, Cd, Sd). Four of the 5 comparator sources were the same as those presented in the original ADAR submission. This included the POLLUX/CASTOR/EQUULEUS clinical trials and real-world data from Australia/New Zealand (CARTITUDE-1-eligibile Myeloma and Related Diseases Registry (CE-MRDR) cohort), USA (FLATIRON) and USA/Europe (LocoMMotion). The new comparator study, STORM, was a single-arm open-label trial assessing the efficacy and safety of Sd. Table 5 summarises the key features of each study used in the ADAR to compare the safety and efficacy of cilta-cel to current 5L+ RRMM standard of care (SoC) therapies.

Table 5   Key features of studies used in the ADAR

Trial/Study	Study design	Population (5L+)	Intervention	Key outcomes	Analysis populations
CARTITUDE-1 (NCT03548207)	Phase 1b-2, open-label, single-arm multicentre study, median follow-up 33.4 months	RRMM, ≥4 prior lines (PI, IMiD, anti-CD38 antibody), Eastern Cooperative Oncology Group (ECOG) 0-1, NYHA stage ≤II, creatinine ≤2 mg/dL, no other serious underlying medical condition.	ITT: 100% (n = 93) all-enrolled/apheresed patients mITT: cilta-cel infused patients only (n = 80)	ORR (Primary endpoint), CR, sCR rate at 12 months, AEs, CR, MRD negativity, HRQoL, DoR, PFS, OS	ITT: patients who underwent apheresis; mITT: patients receiving cilta-cel at target dose
Physician's choice cohort – POLLUX/CASTOR/ EQUULEUS	Retrospective analysis of long-term follow-up data from: POLLUX (Phase 3 Randomised controlled trials (RCT); NCT02076009) CASTOR (Phase 3 RCT; NCT02136134) EQUULEUS (Phase 1b non-randomised trial; NCT01998971), median follow-up NR	RRMM, ≥4 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-1, creatinine ≤2 mg/dL	ITT: 14.6% received Cd, 19.1% Pd, 2.4% Sd mITT: 16.9% received Cd, 23.6% Pd, 2.0% Sd	ORR, CR, PFS, OS	ITT 5L+: all patients who satisfied the eligibility criteria

Trial/Study	Study design	Population (5L+)	Intervention	Key outcomes	Analysis populations
CE-MRDR	Retrospective analysis of multicentre registry data (Australia/New Zealand), median follow-up NR	RRMM, ≥4 prior lines (PI, IMiD, and anti-CD38 antibody; ITT only), ECOG 0-2	ITT: 21.4% received Cd, 17.9% Pd, 17.9% Sd mITT: 21.9% received Cd, 19.3% Pd, 8.8% Sd	ORR, CR, PFS, OS	Main cohort: 4+ treatment regimens including an IMID and PI and anti-CD38; Modified cohort: 4+ treatment regimens including an IMID and PI
FLATIRON	Retrospective analysis of multicentre registry data (USA), median follow-up NR	RRMM, ≥4 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-1, creatinine ≤2 mg/dL	ITT: 21.2% received Cd, 24.7% Pd, 8.0% Sd mITT: 20.7% received Cd, 27.1% Pd, 7.3% Sd	ORR, CR or better, PFS, OS.	ITT 5L+: all patients who satisfied the eligibility criteria
LocoMMotion	Prospective, non-interventional, multinational study (USA/Europe), median follow-up 26.4 months	RRMM, ≥4 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-1	ITT: 22.3% received Cd, 26.1% Pd, 1.1% Sd mITT: 23.3% received Cd, 29.2% Pd, 0% Sd	Primary: ORR Secondary: sCR, CR, DoR, OS, PFS, HRQoL, AEs	ITT 5L+: all patients who satisfied the eligibility criteria
STORM	Phase 2b, single-arm, open-label study, median follow-up NR	RRMM, ≥6 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-2.	TCR/PR: 100% (n = 122) received Sd	Primary: ORR Secondary: OS, PFS, AEs	ITT TCR/PE: total enrolled population; ITT TCR/PR: enrolled patients who were triple class or penta-refractory

Source: Adapted from Table 2-1 from Section 2.2.1 and Table A 4 from Appendix B of the ADAR.
Abbreviations: AE = adverse event, Cd = carfilzomib, CE-MRDR= CARTITUDE-1-eligible Myeloma and Related Diseases Registry; CR = complete response, DoR = durability of response, ECOG = Eastern Cooperative Oncology Group, HRQoL = health-related quality of life, IMiD = immunomodulatory drug, ITT= intention-to-treat, mITT= modified intention-to-treat, MRD = measurable residual disease (previously known as minimal residual disease), MRDR = Myeloma and Related Diseases Registry, NYHA = New York Heart Association functional class, ORR = overall response rate, OS = overall survival, Pd = pomalidomide, PFS = progression-free survival, PR = penta-refractory, PE = penta-exposed, RRMM = relapsed or refractory multiple myeloma, Sd = selinexor, sCR = stringent complete response, TCR = triple-class refractory.

Key differences in inclusion/exclusion criteria

The ECOG scoring system is a scale used to assess a patient's disease progression, effect of disease on daily living abilities, and determination of appropriate treatment and prognosis. Lower scores generally align with patients being less impaired and having better prognoses. The CARTITUDE-1 study required patients to have an ECOG score of 0–1, while CE-MRDR and STORM required an ECOG score of 0–2. CARTITUDE-1 listed extensive exclusion criteria regarding patient disease history. Patients had to be classified as New York Heart Association (NYHA) functional class ≤ II, have no history of toxicity to anticancer therapies, and no other serious underlying medical illness. Collectively, the more restrictive eligibility criteria of CARTITUDE-1 likely select for more robust patients than those enrolled in the comparator studies.

Key differences in baseline characteristics

The commentary noted that between CARTITUDE-1, CE-MRDR and STORM there were imbalances in the key prognostic factors identified by MSAC, such as median time from diagnosis (a proxy for time taken to reach 5L therapy) and PI + IMiD + anti-CD38 antibody refractory status/penta-refractory status.

- Median time from diagnosis = CARTITUDE-1 (5L+ population): 6.19–6.71 years, CE-MRDR: 3.7–3.4 years, STORM: 6.6 years
- PI + IMiD + anti-CD38 antibody refractory status = CARTITUDE-1 (5L+ population): 91.3–91.4%, CE-MRDR: 32.5–66.1%, STORM: 100%
- Penta-refractory status = CARTITUDE-1 (5L+ population): 48.8–51.6%, CE-MRDR: 7.0–14.3%, STORM: 68%.

The CARTITUDE-1 cohort had a greater proportion of patients with an International Staging System (ISS) staging of 1 (51.6–60%) than the STORM (16.4%), CE-MRDR (22.7–30.1%), physician's choice (39.4–42.5%), FLATIRON (35.7–36.8%%) and LocoMMotion (33.7–36.4%) cohorts.

Patients in CARITIUDE-1 (median age 62 years) tended to be younger than those in the comparator studies: median age 65 years in STORM and 66 years (mITT: 67 years) in the CE-MRDR cohort.

Patients in CARTITUDE-1 on average had received fewer prior treatments than those enrolled in STORM, and more than those included in CE-MRDR. The median number of prior treatments at baseline was 6 for patients in CARTITUDE-1, 7 for STORM and 4 for CE-MRDR. The proportion of patients who had received ≥6 prior lines of treatment was 58.1–61.3% in CARTITUDE-1, 42.9–45.8% in the physician's choice cohort and 50.6–52.4% in FLATIRON. The proportion of patients who had received ≥6 prior lines of treatment was not publicly available for STORM.

Assessment of comparative efficacy

In the absence of head-to-head trial data, the applicant used a series of indirect treatment comparisons to support the clinical claim that cilta-cel has superior efficacy in terms of ORR, PFS and OS compared to Australian SoC therapies for adult patients with 5L+ RRMM (most commonly Pd, Cd and Sd). These comparisons included:

- Naïve (unanchored) indirect treatment comparison (ITC) of CARTITUDE-1 (5L+ population) versus:
  - updated CE-MRDR data (Australian registry 5L+ population)
  - STORM (Sd single-arm trial data from PBAC public summary documents) and relevant trial publications informing the PBS-listed population (i.e.TCR/PR population)
- Unanchored ITCs using an inverse probability of treatment weighting (IPTW) method between CARTITUDE-1 and:
  - physician's choice cohort from follow-up data of 3 daratumumab RCTs (POLLUX, CASTOR and EQUULEUS; 5L+ population)
  - FLATIRON (5L+ population; USA registry)
  - LocoMMotion (5L+ population) prospective observational cohort (data available to October 2022).

Where possible, the applicant presented indirect comparisons for both populations: ITT—all-enrolled patients who underwent apheresis, and mITT—infused patients only (Table 6). Descriptions of ITT and mITT populations for the comparator studies are presented in Table 5.

Table 6   Summary of CARTITUDE-1 and comparator study populations compared in ITC

	STORM	CE-MRDR	POLLUX/ CASTOR/ EQUULEUS	FLATIRON	LocoMMotion
CARTITUDE-1	ITT 5L+ vs TCR/PR (where available)	ITT 5L+ vs main and modified CE-MRDR 5L+ cohorts	ITT 5L+ vs ITT 5L+	ITT 5L+ vs ITT 5L+	ITT 5L+ vs ITT 5L+
	mITT 5L+ vs TCR/PR (where available)	mITT 5L+ vs main and modified CE-MRDR 5L+ cohorts	mITT 5L+ vs mITT 5L+	mITT 5L+ vs mITT 5L+	mITT 5L+ vs mITT 5L+

Source: Adapted from Table 2-5 from Section 2.3.2 of the ADAR.
Abbreviations: CE-MRDR= CARTITUDE-1-eligible Myeloma and Related Diseases Registry; ITT = intention-to-treat, mITT = modified intention-to-treat, TCR/PR = triple-class refractory, penta-refractory

Transitivity issues

The clinical evidence for cilta-cel as a treatment for RRMM still relied on the results of CARTITUDE-1 and unanchored, naïve ITC for an estimation of comparative efficacy. As such, the commentary noted that transitivity issues identified as part of the original submission remained. In brief, the main transitivity issues identified previously were:

- The strict inclusion/exclusion criteria of CARTITUDE-1 selected for patients who are generally fitter than the average 5L+ RRMM population in Australia.
- Naïve comparisons conducted between CARTITUDE-1 and comparators are likely to be biased by imbalances in key prognostic factors. The potential impact of imbalances in patient characteristics was assessed through the application of IPTW to match patient characteristics; however, bias introduced by the presence of unobserved confounders and differences in study design cannot be ruled out.
- Comparisons made using the mITT population of CARTITUDE-1 against ITT populations of STORM (TCR/PR) and CE-MRDR are likely to suffer from survivorship bias.
- Country-specific settings determine access to different treatment options in patients with RRMM. Much of the clinical evidence presented in the ADAR was collected in the USA and Europe, where treatment availability may differ to that in Australia.

Assessment of comparative safety

Only CARTITUDE-1, STORM and LocoMMotion reported results of safety outcomes relevant to 5L+ patients. Thus, the applicant was only able to present analyses of comparative safety based on these studies. Table 7 summarises the populations considered in the naïve comparisons of safety outcomes. Despite presenting adverse event rates related to apheresis, bridging therapy and conditioning regimen for the ITT population of CARTITUDE-1, comparisons were made only against the mITT population (as was done in the original ADAR submission). The previous concerns raised by MSAC as to the appropriateness of the comparisons based on this population remained, given that all patients eligible for cilta-cel will had undergone apheresis and were likely to have received conditioning treatment/bridging therapy.

Table 7   Summary of safety data used in naïve comparison between CARTITUDE-1, STORM, and LocoMMotion

	CARTITUDE-1	STORM	LocoMMotion
Adverse events	mITT, mITT 5L+	All-treated (TCR/PE)	All-treated
Treatment-emergent adverse events (TEAEs)	mITT	5L+ TCR/PR	All-treated
Serious AEs	mITT	All-treated (TCR/PE)	All-treated
Cytopenic AEs	mITT	-	All-treated
Deaths	mITT, mITT 5L+	-	All-treated

Source: Adapted from Table 2-65, and Table 2-70 from Section 2.3.3 of the ADAR.
Abbreviations: AE = Adverse event, mITT = modified intent-to-treat, TEAE = treatment-emergent adverse event; TCR/PE = triple-class refractory, penta-exposed

11.   Comparative safety

The commentary noted results of the naïve comparison of safety outcomes reported in the ADAR (Table 8) suggested that the likelihood of experiencing any TEAEs and serious AEs was similar between the patient populations of CARTITUDE-1 and STORM. In contrast, when compared to LocoMMotion, CARTITUDE-1 was associated with a higher proportion of patients reporting TEAEs. The commentary considered these results should be interpreted with caution, given differences in the follow-up of the 2 studies (CARTITUDE-1: median follow-up 33.4 months; LocoMMotion 26.4 months). Furthermore, based on the updated safety data of CARTITUDE and LocoMMotion (as of October 2022), the ADAR demonstrated stability over time for the number of reported safety outcomes for cilta-cel, while those for SoC treatment worsened over time. This is consistent with one-off exposure to cilta-cel treatment versus continuous and cumulative exposure to other RRMM SoC therapies. Fewer patients experienced fatal TEAE in CARTITUDE-1 than both STORM and LocoMMotion cohorts. Patients receiving cilta-cel were more likely to experience serious TEAE than patients treated in LocoMMotion, and less likely than patients treated with Sd in STORM. The most common Grade 3 or 4 TEAE for patients treated with cilta-cel was neutropenia, experienced by 94.8% of infused patients, in contrast with 17.3% and 24.1% in LocoMMotion and STORM, respectively. Overall, the commentary agreed that the available data supported the conclusion of a different safety profile for cilta-cel, both with respect to timing and nature of TEAEs experienced. It was noted that neurocognitive and hypokinetic movement disorders with features of parkinsonism after BCMA-targeting CAR-T cell therapy have been reported[5]. There were 25 patients in the CARTITUDE-1 study who experienced neurotoxicity, of which five male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS. Neurologic toxicity with parkinsonism had been reported in other ongoing trials of ciltacabtagene autoleucel[6].

In the pre-MSAC response, the applicant stated that based on the findings of CARTITUDE-1, patient management strategies in patients with 2 or more risk factors were implemented across the cilta-cel development program to prevent or reduce the incidence and severity of neurological AEs/parkinsonism. Since implementation, approximately 250 patients have been dosed across the CARTITUDE program, reducing the incidence of parkinsonism from 6% to <0.5% in new and ongoing studies (Martin et al. 2022)[7].

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[5] Van Oekelen, O., *et al.* (2021) Neurocognitive and hypokinetic movement disorder with features of parkinsonism after BCMA-targeting CAR-T cell therapy. *Nat Med* **27**, 2099–2103. https://doi.org/10.1038/s41591-021-01564-7

[6] https://www.fda.gov/media/156560/download

[7] Martin et al. 2022. Ciltacabtagene Autoleucel, an Anti–B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. J Clin Oncol 41:1265-1274.

Table 8 Summary of safety outcomes across CARTITUDE-1, LocoMMotion, STORM

Analysis set	CARTITUDE-1		LocoMMotion	STORM	
	mITT (n=97)	mITT 5L+ (n=80)	All-treated (n=248)	All-treated (TCR/PE) (n=123)	TCR/PR subgroup (n=83)
Incidence of TEAEs					
Any TEAE	97 (100.0%)	███ ██	215 (86.7%)	123 (100%)	NR
Any serious TEAE	53 (54.6%)	███ █	91 (36.7%)	78 (63.4%)	NR
TEAE with outcome death	6 (6.2%)	███ ██	21 (8.5%)	12 (9.8%)	NR
Grade 3 or 4 TEAEs reported at ≥25% frequency in any arm^					
Neutropenia	92 (94.8%)	NR	43 (17.3%)	NR	20 (24.1%)
Anaemia	66 (68.0%)	NR	27 (10.9%)	NR	40 (48.2%)
Thrombocytopenia	58 (59.8%)	NR	48 (19.4%)	NR	52 (62.7%)
Leukopenia	59 (60.8%)	NR	15 (6.0%)	NR	15 (18.1%)
Lymphopenia	48 (49.5%)	NR	19 (7.7%)	NR	NR

Source: Table ES-3 from the ADAR Executive Summary.
Abbreviations: mITT = modified intention-to-treat; TEAE = treatment-emergent adverse event; TCR/PE = triple-class refractory, penta-exposed

12. Comparative effectiveness

Overall response rate, complete response and stringent complete response

The commentary considered overall, the results presented by the ADAR for ORR, ≥CR and sCR supported the claim that treatment with cilta-cel is superior to Pd, Cd and Sd in a 5L+ RRMM patient population. In the CARTITUDE-1 ITT 5L+ population, the ORR was ████ %, with most patients (████ %) achieving at least very good partial response (VGPR) and ████ % achieving sCR. This increased to ████ %, ████ % ████ ████ % of patients achieving OR, VGPR and sCR, respectively, in the mITT 5L+ patient population (Table 9).

Cilta-cel compared favourably with available 5L+ RRMM treatments based on naïve treatment comparisons with STORM and CE-MRDR. The proportion of patients in the ITT 5L+ population of CARTITUDE-1 who achieved an OR was ████ ████ ████ than the Sd arm of the STORM trial ██ respectively.

Table 9   Comparison of ORR, CRR and ≥CR rates in CARTITUDE-1 vs CE-MRDR and STORM

	CARTITUDE-1		CE-MRDR		STORM (Sd arm)
	ITT/all-enrolled 5L+ population n (%)	mITT/all-treated 5L+ population n (%)	main 5L+ cohort n (%)	modified 5L+ cohort n (%)	TCR/PR population n (%)
Number of patients (N)	███ ███	███ ███	███ ███ ██ ██	███ ███ ███ ██	83 (100)

	CARTITUDE-1		CE-MRDR		STORM (Sd arm)
	ITT/all-enrolled 5L+ population n (%)	mITT/all-treated 5L+ population n (%)	main 5L+ cohort n (%)	modified 5L+ cohort n (%)	TCR/PR population n (%)
Overall response (sCR + CR + VGPR + PR)	███	███	███	███	21 (25.3)
VGPR or better (sCR + CR + VGPR)	███	███	███	███	NR
CR or better (sCR + CR)	███	███	███	███	NR

Source: Adapted from Table 2-29, Section 2.3.2.3. of the ADAR.

Abbreviations: CR = complete response, ITT = intent-to-treat, mITT = modified intent-to-treat, sCR = stringent complete response, PR= penta-refractory; TCR/PR = triple-class refractory, penta-refractory; VGPR = very good partial response; NR = not reported

PFS

Based on a naïve comparison of CARTITUDE-1 versus the CE-MRDR 5L+ cohort and the STORM TCR/PR population, the PFS of patients treated with cilta-cel improved compared to other 5L+ RRMM therapies (Table 10). ███████████████████████████████ ███████ Median PFS for CE-MRDR was ████████████████████ for the main 5L+ cohort, which was consistent with the median PFS of 2.8 months (95% CI: 1.9, 4.2) observed in STORM. This corresponded to improved median PFS in patients treated with cilta-cel of ████ and ████ months for ITT and mITT 5L+ populations, respectively, compared with STORM and the CE-MRDR main 5L+ cohort.

Table 10   PFS comparison between CARTITUDE-1, STORM and CE-MRDR

	CARTITUDE-1		STORM	CE-MRDR	
	ITT/all-Enrolled 5L+ analysis Set	mITT/all-Treated 5L+ analysis Set	TCR/PR population	Main 5L+ cohort	Modified 5L+ cohort
Number of patients (N)	███	███	83	███	███
Number of events	███	███	40	███	███
Kaplan-Meier estimate (median months; 95% CI)	███ ███	███ ███	2.8 (1.9, 4.2)	███ ███	███ ███
6-month PFS rate %	███	███	~18	███	███
9-month PFS rate %	███	███	~12	███	███
12-month PFS rate %	███	███	NE	███	███
18-month PFS rate %	███	███	NE	███	███
24-month PFS rate %	███	███	NE	███	███
30-month PFS rate %	███	███	NE	███	███

Source: Table 2-7, Section 2.3.2.1. of the ADAR.

Note: *Approximation presented in ADAR based on recreated individual patient data (IPD)

Abbreviations: CE-MRDR= CARTITUDE-1-eligible Myeloma and Related Diseases Registry; CI= confidence interval; NR = not reported; NE = not estimable; PFS= progression free survival; TCR/PR = triple-class refractory, penta-refractory

Estimated hazard ratios (HRs) when comparing the ITT 5L+ populations of CARTITUDE-1 to CE-MRDR and STORM were ███ ████████████████ and ████████████ ████, respectively (Figure 1, Figure 2, Table 11). Similarly, the results of the unadjusted and adjusted ITCs between CARTITUDE-1, the physician's choice cohort, FLATIRON and LocoMMotion also demonstrated statistical superiority of cilta-cel versus 5L+ RRMM therapies for the outcome of PFS. HRs estimated from the adjusted analyses comparing the ITT 5L+ populations of CARTITUDE-1, physician's choice cohort, FLATIRON and LocoMMotion were ████████ ████ ████ ████ ████████ ████████ and ████ ████ ████████ ████, respectively.

Figure 1   Kaplan-Meier curves of PFS for the ITT 5L+ population of CARTITUDE-1 vs STORM (TCR/PR)

REDACTED

Source: Figure 2-2, Section 2.3.2.1. of the ADAR.

Figure 2   Kaplan-Meier curves of PFS for the ITT 5L+ population of CARTITUDE-1 vs CE-MRDR main cohort

REDACTED

Source: Figure 2-3, Section 2.3.2.1. of the ADAR.

Table 11   HRs of CARTITUDE-1 vs STORM (TCR/PR) and CE-MRDR for the outcome of PFS, based on naïve comparison

	HR (95% CI); p value	N CARTITUDE-1	N comparator
STORM (TCR/PR)			
ITT 5L+ population			
-	████ ████ ████ ████	████	83
████ ████ ████			
-	████ ████ ████	████	83
████ ████			
████ ████ ████			
Main CE-MRDR cohort	████ ████ ████ ████	████	56
Modified CE-MRDR cohort	████ ████ ████ ████	████	114
████ ████ ████			
Main CE-MRDR cohort	████ ████ ████ ████	████	56
Modified CE-MRDR cohort	████ ████ ████ ████	████	114

Source: Adapted from Table 2-8 and Table 2-9, Section 2.3.2.1 of the ADAR.
Abbreviations: CI= confidence interval; CE-MRDR = CARTITUDE-1-eligibile Myeloma and Related Diseases Registry; HR= Hazard ratio; ITT= intention-to-treat; mITT= modified intention-to-treat; TCR/PR = triple-class refractory, penta-refractory

OS

Based on a naïve comparison of CARTITUDE-1 versus the CE-MRDR 5L+ cohorts and the STORM TCR/PR population, the OS of patients treated with cilta-cel improved compared to other 5L+ RRMM therapies (Table 12). The median OS for cilta-cel had not been reached at the time of the

October 2022 database lock for either the ITT or mITT 5L+ populations. Median OS for patients treated with Sd in STORM was 8.4 months (95% CI: 5.9, 11.2, TCR/PR, Figure 3, Figure 4). Median OS for CE-MRDR was ████ █████ ████████████████ in the main 5L+ cohort and ████ ████ ████ ████ in the modified cohort. Based on the estimated lower limit of 95% CI for OS in the ITT population of CARTITUDE-1 of ██████████, cilta-cel is estimated to increase OS by at least █████ and █████ months compared with STORM and CE-MRDR, respectively, based on the naïve comparison.

Figure 3   Kaplan-Meier curves of OS for the ITT 5L+ population of CARTITUDE-1 vs STORM (TCR/PR)

REDACTED

Source: Figure 2-10, Section 2.3.2.2. of the ADAR.

Figure 4   Kaplan-Meier curves of OS for the ITT 5L+ population of CARTITUDE-1 vs CE-MRDR main cohort

REDACTED

Source: Figure 2-11, Section 2.3.2.2. of the ADAR.

Table 12   OS comparison between CARTITUDE-1, STORM and CE-MRDR

	CARTITUDE-1		STORM	CE-MRDR	
	ITT/all-enrolled 5L+ analysis set	mITT/all-treated 5L+ analysis set	TCR/PR population	main 5L+ cohort	modified 5L+ cohort
Number of patients (N)	████	████	83	████	████
Overall survival (OS)	████	████	NR	████	████
Kaplan-Meier estimate (median months; 95% CI)	████ ████ ████	████ ████ ████	8.4 (5.9, 11.2)	████ ████ ████	████ ████ ████
6-month OS rate % (95% CI)	████ ████ ████	████ ████ ████	~58	████	████
12-month OS rate % (95% CI)	████ ████ ████	████ ████ ████	~37	████	████
18-month OS rate % (95% CI)	████ ████ ████	████ ████ ████	~29	████	████
24-month OS rate % (95% CI)	████ ████ ████	████ ████ ████	~29	████	████
30-month OS rate % (95% CI)	████ ████ ████	████ ████ ████	NE	████	████

Source: Table 2-18, Section 2.3.2.2 of the ADAR.
Abbreviations: CE-MRDR = CARTITUDE-1-eligible Myeloma and Related Diseases Registry; NR = not reported; NE = not estimable; TCR/PR = triple-class refractory, penta-refractory

For OS, naïve comparisons between CARTITUDE-1, CE-MRDR and STORM demonstrated statistical superiority of cilta-cel treatment over 5L+ RRMM therapies. The estimated HR for the ITT 5L+ populations of CARTITUDE-1 and CE-MRDR was ████ ████████ ████ ████ ████ ████ ████ when compared to STORM.

Unadjusted and adjusted ITCs between CARTITUDE-1, physician's choice cohort, FLATIRON and LocoMMotion showed better OS in patients treated with cilta-cel in comparison with real-world evidence describing currently available treatments for 5L+ RRMM. The commentary noted

conclusions were also robust to adjusted analyses based on IPTW to reduce bias introduced as a result of imbalances in patient characteristics. Estimated HRs from the adjusted analyses comparing the ITT 5L+ populations of CARTITUDE-1, physician's choice cohort, FLATIRON and LocoMMotion were ███ ████ ████ █████ ████ ████ ███ ██████████████ ████, respectively.

Table 13   HRs of CARTITUDE-1 vs STORM (TCR/PR), CE-MRDR, POLLUX/CASTOR/EQUUELUS and FLATIRON for OS

	HR (95% CI)	p value	N CARTITUDE-1	N comparator
STORM (TCR/PR)				
ITT 5L+ population				
	███	<0.001	███	83
mITT 5L+ population				
	███	<0.001	███	83
CE-MRDR				
ITT 5L+ population				
Main CE-MRDR cohort	███	p<0.001	███	56
Modified CE-MRDR cohort	███	p<0.001	███	114
mITT 5L+ population				
Main CE-MRDR cohort	███	p<0.001	███	56
Modified CE-MRDR cohort	███	p<0.001	███	114
POLLUX/ CASTOR/ EQUUELUS				
ITT 5L+ population				
Unadjusted	███	p<0.0001	███	465
Adjusted (IPTW)	███	p<0.0001	███	188
mITT 5L+ population				
Unadjusted	███	p<0.0001	███	301
Adjusted (IPTW)	███	p<0.0001	███	90
FLATIRON*				
ITT 5L+ population				
Unadjusted	███	p<0.0001	███	947
Adjusted (IPTW)	███	p=0.0002	███	436
mITT 5L+ population				
Unadjusted	███	p<0.0001	███	672
Adjusted (IPTW)	███	p<0.0001	███	216

Source: Adapted from Table 2-19, Table 2-20, Table 2-21 and Table 2-22, Section 2.3.2.2 of the ADAR.
Abbreviations: CE-MRDR = CARTITUDE-1-eligibible Myeloma and Related Diseases Registry; CI= Confidence Interval; ITT= intention-to-treat, mITT= modified intention-to-treat; IPTW = inverse probability of treatment weighting; HR = hazard ratio

CARTITUDE-4

MSAC previously noted the direct RCT (CARTITUDE-4[8]) evaluating cilta-cel or standard care in lenalidomide-refractory RRMM (i.e., an earlier treatment line, have received 1 to 3 prior therapies including a PI and an IMiD in CARTITUDE-4 vs at least 3 prior therapies including a PI, IMiD, anti-CD38 antibody in CARTITUDE-1). Standard care was physician's choice of pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd). Of the patients in the standard care group, 183 received DPd and 28 received PVd. The commentary noted that the results of comparative efficacy and safety have read out from the interim analysis.

At a median follow-up of 15.9 months (range, 0.1 to 27.3), the median PFS was not reached in the cilta-cel group and was 11.8 months in the standard-care group (HR, 0.26; 95% CI, 0.18 to 0.38), More patients in the cilta-cel group than in the standard-care group had an overall response (84.6% vs. 67.3%), a complete response or better (73.1% vs. 21.8%), and an absence of minimal residual disease (60.6% vs. 15.6%). Death from any cause was reported in 39 patients and 46 patients, respectively (HR, 0.78; 95% CI, 0.5 to 1.2). Most patients reported Grade 3 or 4 adverse events during treatment.

The authors concluded that the results from CARTITUDE-4 confirmed the efficacy observed in heavily pre-treated patients who received cilta-cel in CARTITUDE-1. The authors also noted that lower rates of cytopenias, cytokine release syndrome, and CAR-T–related neurotoxicity were seen in CARTITUDE-4 than in CARTITUDE-1, which suggested that cilta-cel may have a better side-effect profile when used earlier in treatment.

Clinical claim

Considering the consistency of evidence presented across the comparative efficacy analyses (both naïve and indirect comparisons, including those using IPTW to adjust for confounding), there was strong evidence to support the ADAR's claims of superiority of cilta-cel against current Australian SoC therapies. Furthermore, CARTITUDE-4 had demonstrated the comparative efficacy of cilta-cel in the context of a randomised controlled trial. However, the commentary considered the true magnitude and durability of the benefit in terms of OS and PFS outcomes based on the data presented in the ADAR remained uncertain, given the nature of ITCs and the identified transitivity issues regarding patient fitness in CARTITUDE-1 relative to the comparator studies. As the inclusion criteria for CARTITUDE-1 was more stringent than applied for comparator studies (as described in Section 0), it is likely that the estimated treatment benefit for cilta-cel was overestimated, however the extent of this overestimate was uncertain.

13. Economic evaluation

Cost-utility analysis

The ADAR presented a cost-utility analysis to quantify the additional costs and benefits of treatment with cilta-cel in patients with 5L+ RRMM in comparison with the physician's choice. The approach used was consistent with the original ADAR, with cost-utility analysis based on a decision-tree and partitioned-survival model including OS, PFS and a post-progression state (PPS) (Figure 5). Transitions between health states were informed by analysis of CARTITUDE-1 IPD for cilta-cel and real-world evidence (CE-MRDR) for the physician's choice comparator. Health states were assigned costs and utility values sourced from published literature and CARTITUDE-1, with

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[8] San-Miguel et al. (2023) Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med*. Jul 27;389(4):335-347. doi: 10.1056/NEJMoa2303379. Epub 2023 Jun 5. PMID: 37272512.

time spent by patients in each health state informing overall costs and benefits accrued over a lifetime model horizon. A one-week model cycle length was applied.

Figure 5   Economic model structure
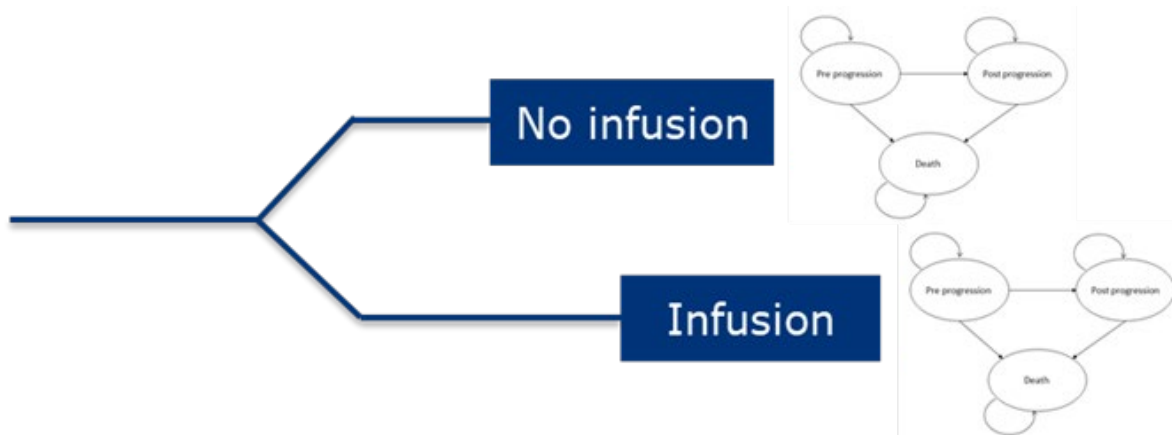
Source: Figure 3-3 from Section 3.2.3 of the ADAR.

The cost-utility analysis primarily differed from the original ADAR in terms of the population evaluated (5L+ versus 4L+ RRMM), and the comparators considered, which had been revised to include Sd (Section 6) in line with the update to the proposed positioning of cilta-cel as a 5L+ treatment. Underlying evidence sources have correspondingly been revised to include more mature data from CARTITUDE-1 and STORM, and a revision of the CE-MRDR cohorts aligned to 5L+ use of cilta-cel (Section 8). The following additional sources of data for the comparator arm were also provided for sensitivity analyses:

- MRDR Cohort 4 ('modified' cohort; excludes requirement for anti-CD38 exposure) to increase the sample size of the analyses and modelling
- Pooled data from 3 comparator sources including Flatiron Health, daratumumab trials and LocoMMotion study, through ITC using a constant cumulative HR of physician's choice versus cilta-cel
- Selinexor plus dexamethasone (alone), whereby the PFS and OS transition estimates were based on the penta-refractory population of the STORM trial.

The commentary noted the approach used for the economic model was consistent with previous CAR-T therapies considered by MSAC. The commentary believed that the overall approach was appropriate for the evaluation of cilta-cel as a treatment for 5L+ RRMM. However, uncertainties regarding the comparative efficacy and durability of effect based on the single-arm CARTITUDE-1 trial and naïve comparisons against real-world and clinical trial evidence introduced significant uncertainty in assessing the cost-effectiveness of cilta-cel. These uncertainties had not been addressed in comparison with the original ADAR. As described in Sections 8–10, there remained significant heterogeneity between study designs and enrolled patient characteristics, which had the potential to confound the comparison between cilta-cel and the comparator of physician's choice. The commentary believed that, in aggregate, these uncertainties would tend to bias results in favour of cilta-cel, with the modelled cohort achieving significant benefits in terms of OS and PFS prior to infusion with cilta-cel. Outcomes between apheresis and infusion were anticipated to be, at best, non-inferior to physician's choice for patients treated with cilta-cel, given the potential for bridging therapy to cease prior to infusion. However, the economic model estimated significant benefits in OS and PFS over the first 50 days of the model horizon (Figure 6). Differences in the enrolled patient populations and associated transitivity issues between trials could explain this difference and result in an overestimation of benefits associated with cilta-cel treatment. The pre-ESC response proposed additional modelling to address this concern in scenario analysis (and this scenario also included in the revised base case model) which

applied the assumption of no PFS/OS events in the comparator arm until day 50 (i.e. the time of cilta-cel infusion) reducing the ICER to $_____ (-1.2%).

Figure 6   Modelled OS and PFS for cilta-cel and physician's choice

REDACTED

Source: Attachment 3.3 of the resubmission ADAR: health economic model.

Model inputs and assumptions

The commentary noted consistent with the original ADAR, the model considered a lifetime horizon, defined as 25 years from baseline. The commentary agreed with this approach as being appropriate to capture all incremental costs and benefits associated with cilta-cel; however, this required significant extrapolation beyond the follow-up of CARTITUDE-1. While a more mature cut of data from CARTITUDE-1 had been provided in the resubmission ADAR (additional 12 months in comparison with the original ADAR), survival data was still immature, with median OS still unavailable. This meant that the model required significant extrapolation to estimate long-term cost-effectiveness of cilta-cel. Furthermore, the additional follow-up data was not able to provide sufficient evidence to identify a parametric distribution that accurately fits the data. All available distributions remained tightly grouped and overlapping in the region prior to cut-off and only diverge in the longer-term stages. The commentary noted this situation was consistent with that of the modelled survival of the original ADAR.

Base-case model extrapolations of OS and PFS were based on parametric survival analysis of CARTITUDE-1 and CE-MRDR to estimate long-term patient outcomes. The commentary agreed with the choice of statistical methods used in the ADAR; however, given the limited follow-up available in the context of the large potential clinical benefit for cilta-cel, there remained significant uncertainty in assessing long-term cost-effectiveness. The estimated cost-effectiveness of cilta-cel was highly sensitive to the choice of parametric distribution. Given the immaturity of the data, there was a limited rationale for an informed choice of which parametric model distribution is most appropriate, as no meaningful distinction in model fit was observed within trial follow-up, including longer-term follow-up data from LEGEND-2, where none of the parametric survival models captured the observed OS plateau from approximately 36 months onwards (Figure 7). Limited scenario analysis exploring the impact of different parametric curves was provided in the ADAR so further scenarios were explored in the additional analysis conducted as part of the commentary.

Figure 7 CARTITUDE-1 versus LEGEND-2 OS comparison

REDACTED

Red: CARTITUDE-1 OS and 95% CI (October 2022 data-cut); Black: GEFOS02_LEGEND-2 OS and 95% CI (Long-term f/u data).

Source: Figure 3-8, ADAR Section 3.2.5.3

The commentary also noted that the base-case analysis provided in the ADAR assumed the most optimistic survival distribution for cilta-cel OS, and the second-most optimistic for PFS. Conversely, outcomes for the physician's choice comparator arm assumed the most conservative parametric distributions for extrapolating both OS and PFS. The commentary noted this meant that equally plausible estimates of the cost-effectiveness of cilta-cel, based on different choices of parametric distributions, could be significantly higher than those presented in the ADAR (Table 15).

The ADAR applied a new approach of time-dependent weighting to determine the ratio of infused and non-infused patients at various time-points within the economic model. This differed in

comparison with the original submission which used a fixed ratio of infused to non-infused throughout the modelled time period. The commentary considered the rationale for this approach was not clear as the fixed-weight approach better aligned with the model structure, and the proportion of patients in the infused and non-infused groups would change over time given differing survival prognosis. Furthermore, the commentary noted relevant calculations associated with the time-dependent weighting did not seem to be applied consistently throughout the model and resulted in a more favourable result for cilta-cel. In the pre-ESC response, the applicant reasoned that a time dependent approach provides a more robust estimation of the of the PFS and OS for cilta-cel than the constant weight approach due to superior alignment to the ITT KM OS and PFS curves.

Quality of life

The commentary noted no changes were made regarding quality of life or utility inputs in the ADAR in comparison with the previous submission.

The commentary believed that the approach taken to estimate health state utility values from CARTITUDE-1 had the potential to bias results in favour of cilta-cel. The ADAR calculated PFS off-treatment utility based on responses collected on day 352 of CARTITUDE-1, however, patients infused with cilta-cel would initially experience a reduction in utility, which would gradually increase over time prior to disease progression. Selecting the utility estimate for this health state based on a single timepoint, meant that this initial utility decrement was not captured in the economic model outside of the inclusion of adverse event utility decrements, and presented an optimistic scenario with respect to quality-of-life in cilta-cel infused patients. The commentary conducted an additional scenario analysis that used a weighted average of all post infusion utility estimates, which is believed to present a more representative PFS off-treatment utility value (Figure 8), however still with the potential to be optimistic.

Figure 8 Mean utility derived from CARTITUDE-1 EQ-5D-5L by timepoint, illustrating the approach used in the ADAR base case analysis for PFS (off-treatment), and the scenario analysis conducted by the assessment group

REDACTED

The ADAR also did not include age related utility decrements, which meant that background dropped in utility associated with aging were not captured. This was relevant as the evaluation extrapolated outcomes over a lifetime model horizon, and consequently, would overestimate the benefits of treatment with cilta-cel. Additional scenario analyses were conducted to reflect reductions in population utility according to Australian population norms.[9]

The ADAR also noted that quality of life analysis was not reconducted in the 5L+ subgroup of CARTITUDE-1 to maintain overall sample size for the analysis. While the commentary acknowledged that most of CARTITUDE-1 met 5L+ criteria, it would be expected that this patient population would have a poorer quality of life in comparison with patients prior to 5L. As such, current estimates of utility derived from CARTITUDE-1 may overestimate patient health-related quality of life at 5L+, and consequently overestimate the benefits of treatment, given the expectation that cilta-cel would extend patient PFS and OS. Additional analysis had been presented in the ADAR of quality-of-life in the 5L+ patient population, which indicated that this is unlikely to have a significant impact on cost-effectiveness, however, robust inclusion in the economic model would reduce uncertainty. This also applied to transitivity concerns with respect to the enrolled patient population, with more robust patients likely to report improved health-related quality of life. The commentary considered this uncertainty should be interpreted in the context of the sensitivity analysis conducted in the ADAR showing that modelled cost-

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[9] McCaffery, et al (2016). Health-related quality of life measured using the EQ-5D–5L: South Australian population norms. *Health and Quality of Life Outcomes,* 14.

effectiveness was highly sensitive to the value of health state utilities for PFS and PPS (Figure 9). The pre-ESC response proposed additional modelling to address this concern in scenario analyses (and also included in the revised base case model) which applied the PFS health state values based on 5L+ subgroup and applied age-related utility decrements increasing the ICER to $██████ (3.3%) and $██████ (2.6%) respectively.

Resource use and costs

██
██
██

Table 14   Cilta-cel cost at each payment timepoint under risk-sharing agreement

Description	Cost	Notes
███ ███ ███	██	██ ███ ███ ███ ███ ███
███ ███ ███ ███ ███ ██	██	███ ███ ███ ██
███ ███ ███ ███ ███ ███ ███ ██	██	███ ██ ██ ██ ███ ███
███ ███ ███ ███ ███ ██	██	██ ███ ███ ███ ███ ███
███ ███ ███ ███ ███	██	██ ██ ███ ███ ███ ███

Source: Table 3-37 from Section 3.2.7 of the ADAR and economic model spreadsheet
Abbreviation: RSA = Risk Share Arrangement, sCR = SCR = stringent complete response
████████████████████

The commentary noted in general, costs and resource used assumptions and inputs consistent with the previous ADAR. However, the following revisions have been included in the updated economic model in addition to costs being updated to reflect more current data sources:

- Weighted costs associated with the physician's choice comparator arm had been updated to include Sd, reflecting the new proposed position of cilta-cel at 5L+, with costs weighted to reflect a 40:40:20 distribution of Pd:Cd:Sd. The commentary noted that this was not aligned with the distribution of treatments observed in CE-MRDR used to inform efficacy for the comparator arm, where 17.9%, 21.4% and 17.9% received Pd, Cd and Sd, respectively, corresponding to a ratio of approximately 38:31:31. This approach may underestimate the cost of treatment in the comparator arm and bridging therapy. The pre-ESC response proposed additional modelling to address this concern in scenario analyses (and also included in the revised base case model) which applied the composition of physician's choice treatments based on MRDR cohort treatment distribution (38:31:31) reducing the ICER to $ ██████ (-1.7%).
- The model now included additional costs associated with intravenous immunoglobulin (IVIG) therapy as part of the pre-treatment costs associated with cilta-cel.
- Carfilzomib dosing was updated by the applicant to include the potential for once-weekly dosing in addition to the existing twice-weekly dosing regimen.
- The proportion of patients receiving cilta-cel in an outpatient setting was revised to 30%, with the remainder (70%) receiving cilta-cel in an inpatient setting, based on a survey of NHRA-funded CAR-T therapy sites.

- The length of inpatient stay associated with cilta-cel infusion was reduced from the 14 days included in the previous ADAR to 8.83 days, based on a survey of NHRA-funded CAR-T therapy sites.
- An additional cost reflecting admission to an intensive care unit for 4.5 days was included for managing grade 2 CRS in alignment with eviQ guidelines.
- Addition of costs associated with neurotoxicity occurring independently of CRS.

As raised in the previous MSAC consideration of cilta-cel for RRMM, the model base-case analysis still assumed only one apheresis procedure is required, despite multiple procedures being required in 3.6% of patients enrolled in CARTITUDE-1. This assumption had the potential to underestimate the overall costs associated with cilta-cel treatment.

The commentary also concluded that costs associated with managing AEs for both patients treated with cilta-cel and relevant comparators were likely to be underestimated. The model considered the incidence of TEAEs as one-off events in the first model cycle, despite the results of CARTITUDE-1 showing patients with prolonged and recurrent cytopenias, and also the potential for ongoing development of TEAEs associated with cumulative exposure to Pd, Cd, and Sd. Furthermore, additional monitoring for the onset of neurotoxicity associated with cilta-cel infusion was not explicitly captured, however, as the model analysis included significant inpatient stay associated with both cilta-cel infusion and the onset of cytopenias, the commentary considered aggregate impact on cost-effectiveness of these assumptions was unlikely to be significant.

Scenario and sensitivity analysis

The results of the scenario analyses were presented as part of the ADAR (see Table 15 below). These scenarios had been supplemented by additional scenario analyses conducted as part of the Commentary. Percentage change in the incremental cost-effectiveness ratio (ICER) was calculated with reference to the base-case submitted in the ADAR, which corresponded to the CE-MRDR main cohort.

Table 15   Results of model scenario analyses

| Base-case setting | Scenario setting | Incremental | | ICER (Cost/QALY) | % change in ICER from base-case |
		Costs	QALYs		
Base-case		■	3.25	■	
Discount rate 5% per annum	No discounting	■	4.84	■	-31.8%
	3.5% discounting	■	3.62	■	-9.9%
Time horizon 25 years	Time horizon 10 years	■	2.39	■	34.8%
	Time horizon 20 years	■	3.10	■	4.7%
	Time horizon 30 years	■	3.33	■	-2.3%
	Time horizon 40 years	■	3.35	■	-2.8%
Cilta-cel OS and PFS extrapolation: KM + individual fitting using lognormal distribution; MRDR (cohort 2) OS and PFS extrapolation: KM + individual fitting using exponential distribution	Cilta-cel OS and PFS extrapolation: individual fitting using lognormal distribution; MRDR (cohort 2) OS and PFS extrapolation: individual fitting using exponential distribution	■	3.20	■	0.2%

| Base-case setting | Scenario setting | Incremental | | ICER (Cost/QALY) | % change in ICER from base-case |
		Costs	QALYs		
Cilta-cel OS extrapolation: KM + individual fitting using lognormal distribution	Cilta-cel OS extrapolation: KM + individual fitting using exponential distribution (best fit based on AIC/Bayesian information criterion (BIC) values)	■	2.70	■	19.7%
Cilta-cel PFS extrapolation: KM + individual fitting using lognormal distribution	Cilta-cel PFS extrapolation: KM + individual fitting using exponential distribution (best fit based on BIC value)	■	3.09	■	5.5%
MRDR (cohort 2) OS extrapolation: KM + individual fitting using exponential distribution	MRDR (cohort 2) OS extrapolation: KM + individual fitting using lognormal distribution (best fit based on BIC value)	■	3.03	■	7.3%
MRDR (cohort 2) PFS extrapolation: KM + individual fitting using exponential distribution	MRDR (cohort 2) PFS extrapolation: KM + individual fitting using Gompertz distribution (best fit based on AIC/BIC values)	■	3.24	■	-2.5%
PFS utility data source: CARTITUDE-1 EQ-5D-5L analysis using Australian preference weights	PFS utility data source: CARTITUDE-1 EQ-5D-5L analysis using UK preference weights	■	3.27	■	-0.6%
PPS utility data source: NICE TA427	PPS utility data source: ENDEAVOR trial (NICE TA657)	■	3.27	■	-0.6%
Cilta-cel PFS and OS extrapolation using time dependent weights approach	Cilta-cel PFS and OS extrapolation using the original fixed weight approach	■	3.04	■	6.8%
CAR-T treatment costing approach: micro-costing	CAR-T treatment costing approach: fixed cost of $75,000 based on Queensland Health Department feedback	■	3.25	■	9.3%
% patients in hospital setting for CAR-T infusion: Outpatient: 30% Inpatient: 70% Duration of inpatient stay: 8.83 days	% patients in hospital setting for CAR-T infusion: Outpatient: 0% Inpatient: 100% Duration of inpatient stay: 14 days	■	3.25	■	1.3%

| Base-case setting | Scenario setting | Incremental | | ICER (Cost/QALY) | % change in ICER from base-case |
		Costs	QALYs		
% patients in hospital setting for CAR-T infusion: Outpatient: 30% Inpatient: 70% Duration of inpatient stay: 8.83 days	% patients in hospital setting for CAR-T infusion: Outpatient: 80% Inpatient: 20% Duration of inpatient stay: 14 days	██	3.25	██	-0.5%
Payment for outcome discount applied	Payment for outcome discount not applied	██	3.25	██	31.6%
Additional scenarios conducted as part of the Commentary					
███ ██ ██	██ ██ ██	██	3.25	██	-33.2%
	██ ██ ██	██	3.25	██	-42.6%
	██ ██ ██	██	3.25	██	-54.1%
	██ ██ ██	██	3.25	██	-57.9%
	██ ██ ██	██	3.25	██	-2.4%
Cilta-cel OS: KM + individual lognormal Cilta-cel PFS: KM + individual lognormal MRDR (cohort 2) OS: KM + individual exponential MRDR (cohort 2) PFS: KM + individual exponential	Cilta-cel OS: KM + individual exponential Cilta-cel PFS: KM + individual exponential MRDR (cohort 2) OS: KM + individual lognormal MRDR (cohort 2) PFS: KM + individual Gompertz (best fits based on AIC/BIC values)	██	2.31	██	31.0%
Treatment distribution for Pd, Cd, and Sd of 40:40:20 from local clinical advice	Treatment distribution for Pd, Cd, and Sd of 38:31:31 from MRDR	██	3.25	██	-2.4%
Proportion receiving subsequent therapy based on entire patient population (61.1%)	Proportion receiving subsequent therapy based on 5L+ patient population; new data cut (58.5%)	██	3.25	██	-0.1%
PFS off-treatment utility based on mean at Day 352 (0.80)	PFS off-treatment utility based on weighted average of post-infusion responses (0.77)	██	3.15	██	3.2%

Base-case setting	Scenario setting	Incremental		ICER (Cost/QALY)	% change in ICER from base-case
		Costs	QALYs		
Fixed health state utilities applied over model time horizon	Age dependent utility decrement applied as cohort age	■■■■	3.17	■■■■	2.6%
PFS off-treatment utility based on mean at Day 352 (0.80); Fixed health state utilities applied over model time horizon	PFS off-treatment utility based on weighted average of post-infusion responses (0.77); Age dependent utility decrement applied as cohort age	■■■■	3.07	■■■■	6.0%
Use of time dependent weights for cilta-cel PFS and OS extrapolation	Use of constant weights	■■■■	3.04	■■■■	6.8%

Abbreviations: QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; KM = Kaplan-Meier; MRDR = Myeloma and Related Diseases Registry; AIC = Akaike information criterion; BIC = Bayesian information criterion; PPS = post-progression survival

Note * Selinexor March 2022 PSD: Base case ICER per QALY ranges of $55,000 to < $75,000; PBAC recommendation based on ICER of $60,000 per QALY

The ADAR presented the results of a one-way sensitivity analysis to identify the most influential model parameters in determining cost-effectiveness in the context of uncertainty (Figure 9). Health state utility values for PFS and PPS were among the most influential model parameters, with lower utility values decreasing cost-effectiveness of cilta-cel. In addition, one-way sensitivity analyses showed that cilta-cel was more cost-effective in younger patients.

Figure 9   Tornado diagram (base-case using MRDR cohort 2 as comparator data source) of one-way sensitivity analysis

REDACTED

Source: ADAR figure 3-22, section 3.3.2.2.

14. Financial/budgetary impacts

The overall net cost to the health budget associated with cilta-cel is $ ■■■■■■■ in Year 1, increasing to $ ■■■■■■ in Year 5, reaching a total of $ ■■■■■■ over 5 years (Table 16). The net cost over 5 years is $ ■■■■■■ to the PBS, $ ■■■■■■ to the MBS (i.e., minor savings) and $ ■■■■■■ to hospitals.

The 5-year overall net cost to the health budget represented a 38% reduction to the estimate presented in the initial ADAR considered by MSAC in July 2022. These cost savings were mostly driven by the removal of patients receiving cilta-cel as 4th line therapy.

In line with the July 2022 ADAR evaluation, the assessment group considered that the financial impact was still overestimated. Although reasonable adjustments have been made to account for the new proposed positioning of cilta-cel as a 5th line + (5L+) treatment, the estimated number of eligible patients was still likely an overestimate, taking into account the following points:

- The total number of 5L+ patients possibly treated in 2024 is likely overestimated as cilta-cel may only become available in May 2024 at the earliest. The calculations do not account for this.
- In the July 2022 ADAR evaluation, it was highlighted that only 46% of patients in the FLATIRON registry met CARTITUDE-1 eligibility criteria in the 4L+ setting. Therefore, the presented proportion of patients suitable for cilta-cel treatment in 5L+ (55.7%) is likely overestimated given that these patients are likely less 'fit' than 4L+ patients. The pre-ESC response sought to address this issue by highlighting that analysis of the 5L+ MM cohorts of the FLATIRON and post daratumumab trials, and the proportion that met the CARTITUDE-1 eligibility criteria which validated the suitability estimates applied in the ADAR resubmission.
- Patient numbers calculated for 'daratumumab compassionate access' scheme appear to be based on linear extrapolations. It is unclear why the extrapolated numbers for years 2023 to 2029 have remained unchanged, given that values for 2020, 2021 and 2022 were reduced by ██, respectively. It is likely that the extrapolation may overestimate the number of patients.
- Given that the approach to estimating alive and progression-free patients remains unchanged from the previous ADAR, the associated uncertainties remain.

████ ████ █████ ████ ██ ███ ████ %. No compelling rationale was provided for ████ the ████ to the Australian healthcare system.

Table 16   Net financial implications of cilta-cel to the Commonwealth and state/territory health budgets, comparison to initial ADAR 1690

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Current ADAR						
Enrolled patients	▌	▌	▌	▌	▌	▌
Infused patients	▌	▌	▌	▌	▌	▌
Cost to NHRA*	▌	▌	▌	▌	▌	▌
Initial ADAR	▌	▌	▌	▌	▌	▌
Change in use and cost of other health technologies						
Increased cost to PBS	▌	▌	▌	▌	▌	▌
Decreased cost to PBS	▌	▌	▌	▌	▌	▌
Net cost to PBS	▌	▌	▌	▌	▌	▌
Initial ADAR	▌	▌	▌	▌	▌	▌
Increased cost to MBS	▌	▌	▌	▌	▌	▌
Decreased cost to MBS	▌	▌	▌	▌	▌	▌
Net cost to MBS	▌	▌	▌	▌	▌	▌
Initial ADAR	▌	▌	▌	▌	▌	▌
Cost to hospitals	▌	▌	▌	▌	▌	▌
AE treatment in hospitals	▌	▌	▌	▌	▌	▌
Net cost to hospitals	▌	▌	▌	▌	▌	▌
Initial ADAR	▌	▌	▌	▌	▌	▌
Net financial impact to health budgets*	▌	▌	▌	▌	▌	▌
*Net financial impact to health budgets in initial ADAR**	▌	▌	▌	▌	▌	▌
Relative reduction (%) compared to the initial ADAR 1690						
Net financial impact to health budgets*	34%	44%	37%	35%	38%	40%

Source: Worksheet 'Section 4.3'; ADAR section 4.4.
Note: * ▋▋▋▋▋▋▋▋▋▋▋▋.
Abbreviations: ADAR = Applicant Developed Assessment Report; NHRA = National Health Reform Agreement; PBS = pharmaceutical benefits schedule; MBS = medicare benefits schedule AE = adverse events; sCR = Stringent complete response

15. Other relevant information

Equality considerations

The applicant stated that the setting of care for cilta-cel will be the same as for current CAR-T therapies funded under NHRA. There are possible inequality issues associated with this as some patients may have difficulties accessing these sites and associated travel costs may prohibit treatment. However, the MSAG report stated that 'Australia has enough CAR-T centres and scale-up capacity to deliver cilta-cel to patients. Future investment in sovereign manufacturing capability will be required.'

NICE evaluation of cilta-cel

During evaluation, the commentary noted that Janssen withdrew its submission for cilta-cel from the National Institute for Health and Care Excellence (NICE)[10]. The withdrawal was related to production issues affecting the ability of manufacturers to meet demand for CAR-T therapies as stated by Myeloma UK[11].

16. Committee-in-confidence information

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17. Attachment Executive Summary – MSAC July 2022 submission issue resolution

Table 17 presents a summary of the main issues identified in the July 2022 submission, and to what extent they have been addressed in the updated June 2023 1690.1 submission. Updates are assessed and noted as being addressed, inadequately addressed, or not addressed.

Table 17 MSAC July 2022 submission issues resolution

Main issues for MSAC consideration July 2022 – 1690	June 2023 – 1690.1 ADAR mitigation commentary	Status considered by the commentary
Clinical issues:		
Cilta-cel is under TGA review. The current request is for fourth-line therapy. The FDA restricted cilta-cel to fifth and later settings, which appeared to be based on the high number of prior therapies patients had received in the pivotal trial, CARTITUDE-1. Given that newer triple therapies are currently being assessed by the PBAC (some recommended though not yet listed), it may be possible that cilta-cel could be pushed to later than fourth-line therapy.	Janssen is requesting funding for the 5L+ MM including a PI, IMiD and anti-CD38, to address issues raised by MSAC and the states/territories in July 2022. MSAG remains supportive of a 5L+ line funding recommendation as 'a viable compromise as any access to CAR-T therapy for myeloma patients is better than none' (MSAG Clinical Expert Statement, p2; Attachment 1.2).	Addressed

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[10] National Institute for Health and Care Excellence. TA889: Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma. NICE - National Institute for Health and Care Excellence. Accessed at: https://www.nice.org.uk/guidance/ta889

[11] CGT Live. Janssen no longer seeking approval for Carvykti in the UK. CGT Live. Accessed at: https://www.cgtlive.com/view/janssen-no-longer-seeking-approval-carvykti-uk

Main issues for MSAC consideration July 2022 – 1690	June 2023 – 1690.1 ADAR mitigation commentary	Status considered by the commentary
The pivotal trial supporting the listing of cilta-cel (CARTITUDE-1) was a single-arm clinical study, hence a comparator arm was constructed based on external sources.	The pivotal trial supporting the application remains CARTITUDE-1, a single-arm study with the comparator arm constructed based on external sources. An additional 12 months of CARTITUDE-1 data were presented in the resubmission (i.e. 33.4 months follow-up vs 21.7 months f/u in the original ADAR).	Not addressed
The comparative efficacy and safety results were subject to relevant transitivity issues arising from the naïve nature of the comparison, mainly that patients in CARTITUDE-1 were healthier and fitter (i.e. greater median time since diagnosis, fewer at ISS stage III, ECOG PFS = 2 or triple or quad refractory) than were patients from the comparator studies. The latter scenario can be explained due to the different inclusion and exclusion criteria. This favours cilta-cel.	The resubmission continues to present naïve treatment comparisons between CARTITUDE-1, STORM and CE-MRDR, thus transitivity issues remain.	Not addressed
The ADAR claim for different safety profiles may not be supported by the evidence. The results of the naïve comparison between CARTITUDE-1, MM-003 (PD arm of RCT) and LocoMMotion suggested that patients in CARTITUDE-1 were more likely to experience Grade 5 TEAE (12.4% vs 5%) and have TEAE resulting in death (9.3% vs 3.6–7.7%). These results should be interpreted with caution given the naïve nature of the comparison and the differences in follow-up (21.7, 15.9 and 11 months in CARTITUDE-1, MM-003 and LocoMMotion, respectively) that bias the results against CARTITUDE-1. It should be noted that cilta-cel is a one-off therapy, while the proposed comparators (Cd and Pd) are to be administered until disease progression or unacceptable toxicities are reached.	The resubmission presents naïve treatment comparisons for safety outcomes between CARTITUDE-1, STORM and LocoMMotion, thus interpretation is still limited. Differences in follow-up between studies remain. The applicant provides some evidence to suggest stability of safety outcomes associated with cilta-cel over time, while those for 5L+ RRMM appear to worsen. This is consistent with one-off exposure to cilta-cel treatment, compared with continuous and cumulative exposure to other RRMM SoC therapies.	Not addressed
Inconsistencies were identified in CARTITUDE-1 results for the latest ITT analysis provided in the ADAR (July 2021 data cut-off). Firstly, the results showed that 52 patients (46%) died compared to 23 patients (20.4%) in the mITT population. This resulted in a difference of 29 deaths (52-23), which exceeded the 16 patients not infused with cilta-cel and excluded from the mITT population. Secondly, the number of progression events as per PFS (47/113; 41.5%) was lower than for survival events as per OS (52/113; 46.0%).	Inconsistencies regarding the number of PFS vs OS appear to have been resolved.	Addressed
Median time to OS was not reached in CARTITUDE-1 (median follow-up 21.7 months) in either the ITT or mITT analyses, hence the data for cilta-cel were considered immature. In addition, at 24 months there was substantial censoring in both PFS and OS Kaplan-Meier curves, hence it is difficult to determine whether the curve flattens or not.	The median time to OS in CARTITUDE-1 was still not reached, even after an additional 12 months of follow-up (total 33.4 months), and high censoring levels remained.	Not adequately addressed

Main issues for MSAC consideration July 2022 – 1690	June 2023 – 1690.1 ADAR mitigation commentary	Status considered by the commentary
Safety results were provided for the mITT analysis only, which considers patients infused with cilta-cel but not all patients who underwent apheresis. This was considered inappropriate, as patients may be exposed to complications from the apheresis itself and toxicities from conditioning treatment and, potentially, bridging therapies. Moreover, these patients would be eligible for Cd or Pd (the comparators) if they were to not receive cilta-cel.	The resubmission continued to present naïve treatment comparisons of safety outcomes based on the CARTITUDE-1 mITT population. While the applicant did provide further information on AE rates for those receiving apheresis and bridging therapies (see ADAR Section 2.3.1.1), these results were not included in any formal comparison of safety against comparator trials.	Not adequately addressed
Economic issues:		
The ICER was highly sensitive to the OS extrapolation of cilta-cel. Median OS (both mITT and ITT analyses) and PFS (mITT only) were not reached in CARTITUDE-1, which introduced uncertainty as these data were used to extrapolate to 25 years. Thus, there were limited data to inform the choice of the best parametric fit. Application of exponential and Weibull distribution for cilta-cel OS increased the ICER from $ ▉ to $ ▉ and $ ▉ per additional QALY, respectively.	The model is highly sensitive to the results of the survival curves, in particular OS of cilta-cel. The model extrapolates survival data for cilta-cel based on 3-year KM curves for a lifetime horizon of 25 years. Given the large extrapolation period, uncertainty in these outcomes is high. Adding to this, the base-case provided in the ADAR assumed the most optimistic extrapolations for cilta-cel OS and the second-most optimistic for cilta-cel PFS, while the comparator arm assumes the most conservative in both OS and PFS.	Not addressed
IVIG use was not accounted for in Section 3 or Section 4, but the ratified PICO stated the incremental change in IVIG would be approximately 5-10%. Hence, the cost of treatment with cilta-cel may have been underestimated.	To address this concern, in addition to the previous submission's pre-treatment costs (which precedes the cilta-cel infusion consisting of apheresis, bridging therapy, and conditioning therapy), IVIG therapy cost is also added in this ADAR.	Addressed
Financial issues:		
There appears to be an overestimation of the number of eligible patients and optimistic assumptions regarding uptake.	The assessment group believes that the financial estimates are still overstated, consistent with the July 2022 ADAR report. The anticipated number of eligible patients is still probably inflated, despite fair changes being made to reflect the new intended positioning.	Not addressed
The financial estimates include the following assumptions that impact the results:		
All patients who had accessed daratumumab monotherapy (via compassionate access) receive cilta-cel; however, some patients may be unsuitable candidates for treatment with cilta-cel.	Janssen clarified that the financial model does not assume that all patients who accessed daratumumab monotherapy receive cilta-cel. Patient numbers from Janssen's daratumumab monotherapy compassionate access program informed the 6L eligible pool of patients in the financial model. Similar to the eligible pool of patients at 5L MM, suitability and uptake rates are applied to the eligible pool of MM patients at 6L in the financial model (refer to Table 4 and 5).	Addressed

Main issues for MSAC consideration July 2022 – 1690	June 2023 – 1690.1 ADAR mitigation commentary	Status considered by the commentary
The proportion of patients suitable for cilta-cel in the fourth-line setting was likely overestimated (██% in year 1 increasing to ██% by year 4). From the FLATIRON registry, which is more representative of real-world patients, only ██% of patients met CARTITUDE-1 eligibility criteria. It is unknown what proportion of patients would be eligible for cilta-cel in the fifth and/or sixth-line setting; however, it is likely less than what was proposed by the ADAR ██% of fifth-line patients and ██% of sixth-line patients).	The total number of cilta-cel treated patients has been reduced substantially in this ADAR (████████ ████████) compared to the previous submission (████████ ████. There is a ██% reduction in the total number of cilta-cel treated patients over 5 years in this resubmission compared to the previous ADAR. The rationale for a decrease in cilta-cel treated patients in this ADAR is the removal of patients receiving cilta-cel in the 4L from the eligible patient population pool. Further, the suitability in 5L and 6L is lower compared with 4L MM because patients in this setting are less likely to be able to tolerate cilta-cel.	Addressed
The ADAR assumed uptake would be ██% in year 1, increasing to ██% by year 5 in fourth-line settings. However, new triple therapies for RRMM patients are currently under consideration by PBAC which may push cilta-cel to a later line setting. This scenario, if approved would be consistent with the restriction from the FDA limiting the use of cilta-cel to fifth-line therapy.	The proposed population eligible to receive cilta-cel includes patients who have received at least 4 prior lines of therapies for MM. The uptake rate for 5L in this ADAR is now assumed to be higher than the uptake rate for 5L patients used in the initial submission. Patients now will be receiving cilta-cel for the first time in 5L setting, therefore 5L uptake rate will be higher compared to the previous ADAR where patients could also receive cilta-cel in 4L. The uptake rate for 5L used in this ADAR is ██% in year 1, increasing to ██% by year 3. The uptake of cilta-cel in 5L will reach peak share by year 3, as clinicians seek to treat every patient with cilta-cel at 5L because they will have become refractory to all or nearly all classes of MM medicines by 5L. The uptake rate of 6L is assumed equal to the uptake rate of 5L in the previous ADAR (i.e. ██% ██ ██% ████).	Not adequately addressed

Abbreviations: ADAR = applicant developed assessment report; Cd = carfilzomib plus dexamethasone; CE-MRDR = CARTITUDE-1-eligible Myeloma and Related Diseases Registry; ECOG = Eastern Cooperative Oncology Group; FDA = Food and Drug Administration; ICER = incremental cost-effectiveness ratio; IMiD = Immunomodulatory drug; ISS = International Staging System; ITT= intention-to-treat; mITT= modified intention-to-treat; IVIG = intravenous immunoglobulin; KM = Kaplan-Meier; MSAC = Medical Services Advisory Committee; MRDR = Myeloma and Related Diseases Registry; MSAG = Myeloma Australia's Medical and Scientific Advisory Group; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PICO = population, intervention, comparator, outcomes; Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; PI = proteosome inhibitor; QALY = quality-adjusted life year; RCT = randomised controlled trial; RRMM = relapsed or refractory multiple myeloma; SoC = standard of care; TGA = Therapeutic Goods Administration; TEAE = treatment-emergent adverse events;

Source: MSAC considerations adapted from ADAR Attachment 1.8 1690 Executive Summary, updated with commentary by the assessment group.

18. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The resubmission presented longer follow-up data (33.4 months follow-up) from the CARTITUDE-1 study that suggested a durable response for cilta-cel. However, the data were heavily censored and the outcomes remained uncertain.

- Comparative efficacy appeared to support superiority of cilta-cel, but there were multiple biases that may have favoured cilta-cel.

- Transitivity issues due to naïve comparisons of single-arm studies remained in the resubmission and were not easily resolved.

- New safety data indicated neurologic toxicity with features of parkinsonism as a new adverse event that was not rare and was not accounted for in the resubmission. Use of the modified ITT population for comparative safety biased the results in favour of cilta-cel.

Economic issues:

- Uncertainties in the clinical evidence and clinical claim were carried over into the economic evaluation.

- Substantial uncertainties remained, particularly relating to the immature OS data from CARTITUDE-1 and the large extrapolation period resulting in high levels of uncertainty in the modelled outcomes. The base case ICER was highly sensitive to the choice of method for parametric extrapolation and model time horizon.

- The ICER remained high and uncertain.

Financial issues:

- The revised financial estimates to account for the new proposed positioning of cilta-cel was a 5L+ treatment may still have been overestimated and remained uncertain

Other relevant information:

- States and territories remained unsupportive of the application unless there was a significant price reduction. Amongst other issues raised by the states and territories were uncertainties in clinical evidence, economic modelling assumptions and underestimated costs. The proposed administration model of 70%:30% (inpatient: outpatient) may require additional support services.

- Unresolved issues with registry data meant that registries were unlikely to be able to provide meaningful data to inform decision making on CAR-T therapies in the short term

- A summary of the main issues identified for MSAC application 1690 and the extent they have been addressed in this resubmission were presented in Table 19.

ESC discussion

ESC noted that this resubmission is for public funding of ciltacabtagene autoleucel (cilta-cel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell [CAR-T] therapy) for the treatment of refractory or relapsed multiple myeloma (RRMM) in adults. If funded, cilta-cel would become available as a High Cost Highly Specialised Therapy (HST) under the National Health Reform Agreement (NHRA) with state and territory health authorities required to pay 50% of the costs for HSTs.

The previous submission was not supported by MSAC at its July 2022 meeting. At that time, MSAC considered that there was high uncertainty regarding the clinical place of cilta-cel and the proposal for its use as a later line of therapy in the context of RRMM, which has a long disease history with many alternative and new treatment options that have improved patient outcomes. MSAC did not accept that cilta-cel was comparatively safe, effective and cost-effective over the modelled time horizon. MSAC also considered that the low level of clinical evidence presented in support of cilta-cel was unacceptable in the context of late-line treatment where other treatment options are available, and the prevalence of RRMM being clearly beyond that of a rare disease, with a large and uncertain financial impact.

The three main differences in this resubmission were:

- cilta-cel was now placed as fifth-line (5L) therapy instead of 4L for adult patients who have received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody.

- Longer follow-up data were available from the CARTITUDE-1 single-arm study (33.4 months follow-up compared with 21.7 months follow-up in the original submission), although the data were supplied by the sponsor and have not yet been peer reviewed or published

- the comparator arm included an additional comparator (Selinexor plus dexamethasone; Sd).

ESC noted the changes to the eligibility criteria for cilta-cel treatment proposed for funding under the NHRA. The revised target population is more restrictive than the regulatory approved population.

ESC noted that multiple myeloma is a mostly incurable and very heterogeneous disease. The clinical management algorithm is complex, patients have multiple treatment options at each stage, and treatment sequencing and duration of treatment is highly variable within the proposed population. ESC considered because the cause of the disease is so variable that it is important to clearly define the patient population eligibility for cilta-cel, including what is meant by relapse and the definition of progressive disease. ESC noted that with newer 3L and 4L therapies that have become available in recent years, the 5-year survival for myeloma patients has improved and further improvements may be expected with the emergence of new therapies for RRMM. ESC noted that response rates reduce with each subsequent line of therapy, so the number of patients reaching 5L to receive cilta-cel would be smaller than 4L. ESC noted that 5L patients are often younger and their disease more resistant to treatment, whereas older and frailer patients may not get the opportunity to receive multiple lines of therapy or, if more indolent disease, may never become eligible for treatment in 5L+, including with cilta-cel. ESC noted cilta-cel can also be used as a 6L treatment for patients who have exhausted other treatment options.

ESC noted that patients may be treated with any previously used agent (in 3L or 4L) for bridging therapy ahead of infusion with cilta-cel. ESC noted there are many different options available for bridging therapy in Australia, including on the Pharmaceutical Benefits Scheme (PBS); however the PBS restrictions for some of these drugs may not allow for patients to use as bridging therapy because patients are only eligible to receive these therapies once (i.e., they are not eligible to receive them again if they had previously progressed on or following the use of these therapies). ESC noted that any changes to PBS restrictions of bridging therapies would need to be considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

ESC noted the large amount of consultation feedback from 193 individuals including consumers, clinicians, charity workers and one organisation, all of which were supportive of the application. Input from patients emphasised the disadvantages of current therapies, as well as the value in having another treatment option available. Issues relating to cost were also highlighted.

ESC noted that the clinical claim in the ADAR resubmission was still based on unanchored indirect treatment comparisons (ITCs) between CARTITUDE-1 (5L+ population) and other

comparator studies, and therefore considered that the methodological uncertainty from the original submission remained. ESC noted that CARTITUDE-1 included a significant majority (~82%) of the requested 5L+ population. The updated analysis from CARTITUDE-1 used both the intention-to-treat (ITT) population (n = 93) from CARTITUDE-1 and the modified intention-to-treat (mITT) population of patients who had a successful infusion (n = 80) only. ESC noted comparisons made using the mITT population of CARTITUDE-1 against ITT populations of STORM (TCR/PR) and the CARTITUDE-1-eligible Myeloma and Related Diseases Registry (CE-MRDR) are likely to suffer from survivorship bias. ESC also considered that historical cohorts in the comparator group received older treatments (pre 2016), and this may have affected survival compared to newer therapies used in CARTITUDE-1 patients. ESC noted that the ITC using the inverse probability treatment weighting (IPTW) method between CARTITUDE-1 with the Physician's Choice cohort (follow-up data from three trials of daratumumab [POLLUX, CASTOR and EQUULEUS]) and FLATIRON (5L+ population from a US-based registry) adjusted for confounding prognostic factors including age, refractory status and number of prior lines of therapy. However, bias introduced by the presence of unobserved confounders such as co-morbidities of renal impairment, diabetes or frailty was not taken into account. ESC considered that this was important, as the median age at diagnosis of multiple myeloma in Australia is 70 years (compared with median age of 62 years in CARTITUDE-1), and 40% of diagnoses are in people aged 75 years or over. ESC also noted several differences in other prognostic factors between the intervention and comparator groups (such as age and Eastern Cooperative Oncology Group [ECOG] status) and considered that these differences, on balance, would bias the results in favour of cilta-cel.

In terms of comparative effectiveness, ESC noted that median overall survival (OS) still has not been reached in the more mature follow-up dataset for either ITT or mITT analyses, estimated at 33.2 months or longer in the ITT population in CARTITUDE-1 compared with <12 months in most comparator studies. Cilta-cel reduced the risk of death by 60-80% versus current 5L+ therapies. ESC noted the consistency of the evidence showing significant differences in OS and PFS between cilta-cel and the comparators presented in the ADAR. Median progression-free survival (PFS) for the ITT 5L+ population was ▮▮▮▮▮▮▮ compared with 2.8 to 6.2 months in the comparator studies. ESC considered the updated survival data was suggestive of a durable response for cilta-cel; however, the Kaplan-Meier data are heavily censored (after 24 months) and remains uncertain. Overall, ESC considered that comparative efficacy appeared to indicate superiority of cilta-cel; however, the nature of the ITCs, significant transitivity issues and multiple biases that favour cilta-cel meant there is low certainty regarding the magnitude of incremental benefit of cilta-cel compared with the comparators. ESC also considered the results from a direct randomised controlled trial (CARTITUDE-4), albeit in an earlier treatment line, may assist with understanding the comparative efficacy observed in heavily pre-treated patients who received cilta-cel in CARTITUDE-1.

ESC noted safety outcomes were available for CARTITUDE-1, LocoMMotion and STORM but it was unclear how safety data had been captured in the comparator studies. In terms of comparative safety, ESC noted that the frequency of adverse events (AEs), including those of Grade 3 or higher and of serious AEs, was high in both CARTITUDE-1 and comparator studies (nearly all patients experienced at least one treatment-emergent AEs across studies). Fewer patients experienced fatal TEAE in CARTITUDE-1 than both STORM and LocoMMotion cohorts. Patients receiving cilta-cel were more likely to experience serious TEAE than patients treated in LocoMMotion, and less likely than patients treated with Sd in STORM. ESC noted the updated safety data from CARTITUDE -1 and LocoMMotion suggested stability over time for the number of AEs reported for cilta-cel, while those for standard of care (SoC) treatment worsened over time. This is consistent with one-off exposure to cilta-cel treatment versus continuous and cumulative exposure to other RRMM SoC therapies. ESC agreed with the commentary that the available data supports the conclusion of a different safety profile for cilta-cel, both with respect to timing and nature of TEAEs experienced. ESC noted the ADAR resubmission used the mITT population for comparative safety which biases the results in favour of cilta-cel as it excludes all patients that received conditioning therapies but did not proceed to infusion.

In addition, ESC noted that CAR-T-specific adverse events (such as Cytokine Release Syndrome [CRS] and Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS] and cytopenenias) which typically occur in the short term are generally well understood. However, ESC noted 5 of 97 patients in the CARTITUDE-1 study had developed neurological toxicity with signs and symptoms of parkinsonism. ESC noted parkinsonism like side effects have also been observed in other cilta-cel studies and these effects appeared to be specific to BCMA-directed therapies. This had not been addressed in the ADAR, and quality of life as a result of this AE had not been modelled or costed, which biases in favour of cilta-cel. ESC noted that secondary malignancies are potential long-term effects of treatment with CAR-T therapies. However, the risk is currently unknown. ESC noted that FDA has previously suggested a minimum 15 year follow up to capture potential secondary malignancies.

ESC noted the economic evaluation, which was a cost-utility analysis. In the resubmission, changes had been made to the population (adult patients who had at least four lines of prior therapy), the comparator (including Sd) and the primary data sources for time-to-event data. The computational method was a hybrid model of decision tree and partition survival analyses as used in the original ADAR. However, the resubmission presented an alternative approach that calculated time-dependent weights based on the number of patients at risk for OS and PFS in both infused and non-infused groups over time. ESC noted the commentary considered that this approach was not justified, was inconsistent with the model, and favoured cilta-cel. ESC noted the pre-ESC response, which the applicant reasoned this method produced better alignment with observed OS and PFS data. ESC considered that the sensitivity analysis conducted by the commentary addressed this concern which showed that when fixed weights were applied the ICER increased by 6.8%.

ESC considered the model structure was appropriate. However, ESC noted in the economic model significant benefits in OS and PFS between apheresis and infusion in the cilta-cel arm, which may not be plausible as the intervention would be expected to be at best noninferior with comparator arm over this duration. ESC considered that the differences between enrolled patient populations and associated transitivity issues between studies could explain this difference and result in an overestimation of modelled benefits associated with cilta-cel treatment. ESC noted the pre-ESC response addressed this issue in its revised base case.

ESC noted that a lifetime horizon (defined as 25 years) in the model was a source of significant uncertainty and considered to be very optimistic by MSAC in the original Application 1690, and had not been changed in this resubmission. Given the median age at diagnosis of 70 years, for many patients, this would extrapolate beyond the average life expectancy in Australia. ESC noted that cilta-cel may be more likely to be used in younger patients than older patients in the proposed 5L+ population, which could justify the period used for the lifetime horizon.

ESC also considered that the base case extrapolation method was optimistic for cilta-cel and conservative for the comparator, and the model was highly sensitive to changes in the extrapolation method. ESC considered that the updated survival data from CARTITUDE-1 are promising in respect to showing a proportion of patients treated with cilta-cel may be cured, however the immature survival and the large extrapolation period (in the context of the time horizon) meant uncertainty in these modelled outcomes was high. The ADAR referred to the LEGEND-2 study to validate the modelled long-term OS of cilta-cel, although this study was excluded in the analyses due to a number of differences between the LEGEND-2 study and the proposed intervention. In LEGEND-2, OS plateaued after 36 months indicating that patients reached a cure state at this point. However, ESC considered that a more conservative approach may be warranted, as the LEGEND-2 data were not included in the ADAR and demonstrated the broad potential of CAR-T therapies in general, rather than cilta-cel specifically.

ESC noted some issues relating to the quality-of-life weights in the model that may have overestimated quality-adjusted life year (QALY) gains following cilta-cel; however, this did not have a large impact on the incremental cost-effectiveness ratio (ICER) (see Table 15).

ESC noted that costs in the model were generally consistent with Application 1690 and the changes made to include costs for admission to intensive care units, neurotoxicity AEs, intravenous immunoglobulin (IVIg) did not make a substantial difference to the ICER. ESC considered that the hospital and subsequent monitoring costs used in the economic model were likely to be much higher in reality, with consequences for the ICER. ESC noted that the revised model for CAR-T service delivery included a 70%:30% (inpatient:outpatient) setting based on a survey of NHRA-funded CAR-T therapy sites (compared with 20%:80% inpatient:outpatient setting in Application 1690). ESC noted that no rationale was provided in the resubmission to justify the high product cost of cilta-cel (███ ███████). ██████ ███ ███ ███ ███ ███ ███ ███ ███ ███ ██ ████ ██ ██ ██████ ███ ███ ███ ███). ESC considered that clearly defined restrictions in terms of patient eligibility would be required in any deed of agreement for cilta-cel for RRMM for the benefit of both patient and service providers. ESC noted the applicant's willingness to work with the department on the structure and timing of the payment model.

ESC noted the sensitivity and scenario analyses conducted in the resubmission and additional analyses conduced in the commentary (see Table 15). ESC noted the main drivers to the ICER were the extrapolation method and model time horizon. ██████ ███ ███ ███ ███ ███ ███ ███ ██ ██ ███ ███ ███ ███ ███ ███ ███ ESC noted the commentary conducted additional scenario analyses investigating reduced costs of cilta-cel therapy, including based on ICERs in the range of those treatments accepted by PBAC in 5L+ RRMM (selinexor March 2022 PSD).

ESC noted the applicant's pre-ESC response, including the revised base case of $ █████ gained which is 2.4% higher than the base case ICER of $ ████████. ESC agreed that the applicant had addressed a number of concerns for the model from the commentary; however, the ICER remained very high and uncertain.

ESC noted the financial impact, which was reduced compared with Application 1690 (see Table 16). ESC agreed with the commentary which considered that reasonable adjustments were made to account for the new proposed positioning of cilta-cel as a 5L+ treatment, but was likely to still be overestimated. ESC noted the pre-ESC response but considered that the uncertainties in assumptions regarding line of treatment meant that the financial impact remained uncertain. ESC noted that the projected cost to the Pharmaceutical Benefits Scheme (PBS) changed from negative (cost-saving) in Year 1, to positive by Year 6. ESC noted the Assessment Group advised that this is because the cost-offsets associated with displacement of comparators over the first 3 years outweigh the additional costs of the conditioning regimen, bridging therapies and IVIG therapy associated with cilta-cel. However, the financial analysis does assume that 100% of the conditioning, bridging, and IVIG therapy costs are incurred by the PBS, compared with between 27.7% and 69.6% of replaced therapy costs. Therefore, because the use of cilta-cel in the eligible patient population over time is anticipated to increase, the proportion of costs incurred by the PBS will also increase resulting in a net increase in costs to the PBS from Year 4 onwards.

ESC noted jurisdictional feedback from four states and territories, which considered the revised 5L+ population appeared more appropriate. One state suggested conditional support for the application based on a price reduction, updated modelling and other criteria. Three states raised concerns based on the lack of robust evidence and high costs. All four states and territories indicated that a significant price reduction would need to be negotiated if MSAC supported this application, as well as a risk sharing arrangement. One state did not support the proposed schedule of payments, suggesting payment should be linked to longer term patient survival and provision of quality-of-life outcomes. Other issues raised by jurisdictions included the sustainability of long-term funding for CAR-T therapies (given the high cost and state health budgets), that the median length of inpatient stay in one state was 17 days (not 8.83 days as presented in the resubmission model) and that the proposed administration model of 70%:30%

(inpatient: outpatient) would require a shift in the current admitted model of care for CAR-T treatments and may require additional support services .

ESC queried whether production issues were affecting the ability of manufacturers to meet demand for CAR-T therapies noting National Institute for Health and Care Excellence (NICE) submission for cilta-cel was withdrawn by Janssen. ESC also queried whether CAR-T manufacturing issue was a global issue, or specific to the United Kingdom.

ESC noted that data from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) on CAR-T therapies was incomplete and inconsistently reported between states and territories. There was insufficient information about the use of IVIG and duration of IVIG therapy, so these uncertainties remain. ESC noted that data completeness and complex contracting arrangements have impacted on data accessibility. ESC queried whether data from the Myeloma and Related Diseases Registry would be more informative for purposes of data collection as suggested by the applicant in its pre-ESC response.

ESC noted data from a review of tisagenlecleucel (tisa-cel, another CAR-T therapy) for paediatric acute lymphocytic leukaemia. In clinical practice, tisa-cel had evolved from a potentially curative treatment to becoming a bridging therapy to haematopoietic stem cell transplant (HSCT). Data from ███████ showed that ███████ patients (███%) had a second CAR-T infusion. It was not clear whether the potential for second or subsequent infusions should be a consideration for cilta-cel and the RRMM population; if yes, this could be a large number of people who receive multiple infusions at a high cost of therapy. ESC requested that the applicant provide clarification around the potential need for multiple CAR-T infusions and if this was required, the associated costs.

ESC also noted that the average cost per patient receiving tisa-cel (including the cost of the treatment and ancillary services) was $██████, ranging from $██████████ to $██████ per patient. ESC noted that the real-world evidence on CAR-T therapies in different patient populations showed that costs are much higher than the modelled costs, which means that the impact on hospitals and health systems may have been underestimated.

19. Applicant comments on MSAC's Public Summary Document

Janssen welcomes that the Medical Services Advisory Committee (MSAC) has acknowledged the unmet clinical need of the CAR T-cell therapy ciltacabtagene autoleucel for the treatment of Australians with multiple myeloma. As part of its submission to MSAC, Janssen proposed a pay for performance arrangement that sought to ensure that the Australian federal and state/territory governments will be receiving the greatest value for money for funding ciltacabtagene autoleucel by requesting the majority of the payment only if a patient has obtained a deep clinical response to therapy. Deep clinical responses are infrequently attained with current standard of care in 5L+ MM, and most patients die by 12 months with therapies currently available in Australia. Furthermore, Janssen shifted the clinical positioning from 4L+ to 5L+ MM in the November 2023 submission resulting in a ≈40% reduction in the cost to Government over 5 years versus the July 2022 submission. Janssen sincerely thanks those clinicians, patients and advocacy groups who provided over 430 submissions to MSAC all in support of ciltacabtagene autoleucel in the public consultation. Janssen remain committed to working with all stakeholders to ensure equitable and timely access to ciltacabtagene autoleucel, but its availability in Australia relies on the value of the innovation being recognised.

20. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website