Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1690 – 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: **28-29 July 2022**

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 of cilta-cel for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM), who have received at least three prior lines of therapy, including a proteasome inhibitor (PI); an immunomodulatory agent (IMiD); and an anti-CD38 antibody was received from Janssen-Cilag Pty Ltd by the Department of Health. 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).

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 did not support 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 three prior lines of therapy, including a PI, an IMiD and an anti-CD38 antibody. MSAC considered 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 is comparatively safe, effective and cost-effective over the modelled time horizon. MSAC also considered the low level of clinical evidence in support of cilta-cel to be 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.

Consumer summary

This is an application from Janssen-Cilag Pty Ltd requesting public funding of ciltacabtagene autoleucel (cilta-cel) to treat adults with myeloma that is refractory (has not responded to previous treatment) or relapsed (come back after treatment).

Myeloma is a type of blood cancer that develops from a type of white blood cell found in the bone marrow. The cancerous cells spread through the bone marrow and cause lesions in the bones. When there are myeloma lesions in many bones of the body, this is called multiple myeloma. As a result of myeloma, patients experience pain and bone fractures. Also, there is not enough space for normal blood cells to grow, resulting in bleeding problems, frequent infections, and patients feeling unwell.

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. As these are new treatments, they are currently used in patients who don't respond to, or relapse after, other types of treatment, such as chemotherapy (i.e. 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 so that they can attack the cancer cells when re-introduced into the patient's body. The patient's altered T cells are infused back into their body through a large vein to target and kill the cancer cells in the patient's body.

MSAC noted that there are many treatment options for people with RRMM, and new treatments are developed often. MSAC thought that the low level of clinical evidence in the application was not strong enough in this context, and the benefits of using cilta-cel as the fourth line of treatment (or later) were very uncertain. MSAC also thought that the total cost of cilta-cel was very high and uncertain, and there was not sufficient evidence to support funding of this application.

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

MSAC did not support funding cilta-cel for the treatment of RRMM through the National Health Reform Agreement. MSAC did not accept that cilta-cel was comparatively safe or effective in these patients, who have many other treatment options. MSAC also did not consider that cilta-cel provided good evidence on value for money.

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

MSAC noted that the purpose of this application was to seek funding under the National Health Reform Agreement (NHRA) for cilta-cel for the treatment of adult patients with RRMM who have received at least three prior lines of therapy, including a PI (bortezomib, carfilzomib); an IMiD (lenalidomide, pomalidomide), and an anti-CD38 antibody (daratumumab).

MSAC noted that, similar to other CAR-T therapies, cilta-cel involves extracting the patient's blood through apheresis and exporting the apheresis product ██ ██ ██ ██ ██ ██ ██, where the T cells are genetically modified to bear a CAR that targets the B-cell maturation antigen (found on multiple myeloma cells). The patient is preconditioned with chemotherapy before a one-off infusion of the modified cells. Also similar to other CAR-T therapies, there is a recognised risk of serious adverse events such as cytokine release syndrome and immune-mediated neurotoxicity (Immune effector cell-associated neurotoxicity syndrome [ICANS]).

MSAC recalled that it had previously supported public funding of three other CAR-T therapies since 2019 for lymphoma and/or leukaemia: applications 1519, 1519.1 (Kymriah), 1587 (Yescarta) and 1647 (Tecartus). MSAC noted the large amount of consultation feedback from more than 300 consumers and several organisations. All submissions were supportive of the application. MSAC noted that CAR-T therapy is strongly promoted by organisations such as Myeloma Australia.

MSAC considered the clinical need for treatment of RRMM with cilta-cel. Around 2,423 new cases of MM are diagnosed per year in Australia, with a median patient age of 70 years. The incidence rate peaks at age 85–89 years. MSAC noted the substantial increase in relative 5-year survival in Australian patients, from 28% in 1988–1992 to 54% in 2013–2017. MSAC considered that interventions for multiple myeloma and RRMM represent a rapidly developing field, with many alternative treatment options available in multiple lines of therapy which has improved patient outcomes.

MSAC noted the clinical management algorithm, in which cilta-cel is the fourth line of therapy. MSAC noted that cilta-cel was still under TGA consideration. The United States Food and Drug Administration (FDA) had recommended cilta-cel in February 2022 after four or more prior lines of therapy. MSAC noted the applicant's pre-MSAC response, which stated that the European Commission had granted marketing authorisation of cilta-cel in May 2022 for adults with RRMM after at least three prior lines of therapy (as proposed in the TGA indication and this application). MSAC also noted the recent Pharmaceutical Benefits Advisory Committee (PBAC) recommendations for new triple therapies for patients with RRMM, which could result in cilta-cel moving further down the line of therapies. MSAC considered that this may mean that patients are less well when they receive cilta-cel therapy (as their disease has progressed), which may mean reduced effectiveness of cilta-cel therapy for the same cost and toxicities, representing less value for money. MSAC noted the pre-MSAC response, which stated that the data suggest that the efficacy of cilta-cel is robust regardless of the number of prior lines of therapy. However, MSAC considered that there was high uncertainty about 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.

MSAC noted the comparator in the application, which was carfilzomib with dexamethasone (Cd) and pomalidomide with dexamethasone (Pd).

MSAC noted the evidence for cilta-cel in the application, which included one Phase 1b/2 single-arm study (CARTITUDE-1) with a median follow-up of less than two years. The pre-ESC and pre-MSAC response provided updated safety and efficacy results from longer median follow-up of 26.8 months. The intention-to-treat (ITT) population comprised 113 patients, of which 97 underwent the infusion (modified ITT [mITT]) providing the basis for most of the comparisons. MSAC noted CARTITUDE-1 patients had extensive inclusion and exclusion criteria and were more highly selected than patients in the comparator studies.

MSAC noted the issues raised by ESC for comparative safety. MSAC considered that comparative safety was unclear, as the intervention and comparators have substantially different adverse event profiles. Treatment with cilta-cel was associated with a high incidence of cytokine release syndrome (95%), which is usually treated with steroids and tocilizumab (IL-6 blocker). Compared with comparator studies, patients treated with cilta-cel were more likely to experience Grade 5 treatment emergent adverse events (TEAEs) (12.4% in CARTITUDE-1 vs. 5% in MM-003) and have TEAE's that result in death (9.3% in CARTITUDE-1 vs. 3.6 - 7.7% in MM-003 and LocoMMotion, respectively). MSAC noted the ADAR relied on the CARTITUDE-1 mITT analysis which therefore excluded adverse events (such as cytopaenias) in subjects who had apheresis and pre-conditioning

chemotherapy but did not proceed to infusion. Thus, MSAC considered the toxicity of the conditioning treatments would not have been captured.

MSAC noted the data on comparative effectiveness, which showed significant differences in all survival outcomes and across all naïve and indirect comparisons (including studies using inverse probability of treatment weighting [IPTW] to adjust for confounding), favouring cilta-cel. Median progression-free survival could not be calculated due to the relatively short follow-up of the CARTITUDE-1 study, and median overall survival was not reached in the follow-up duration. MSAC agreed with ESC and considered that effectiveness is likely lower in the real world than presented in the applicant-developed assessment report (ADAR) due to the reliance on naive comparisons of single-arm studies. MSAC noted the concerns from ESC that patients in CARTITUDE-1 were relatively robust and able to tolerate intensive treatment, and that this may not reflect the eligible population in Australia and may bias the effect in favour of cilta-cel. MSAC noted the pre-MSAC response, in which the applicant disagreed that comparative effectiveness was overestimated citing that the heavily pre-treated patients included in CARTITUDE-1 would bias against cilta-cel (i.e. median number of prior LOTs was 6 in CARTITUDE-1 vs. 3 to 5 in the comparator studies). The applicant contended that the number of prior therapies, and refractoriness of a person's MM to existing therapies (e.g. PIs, IMiDs, anti-CD38 monoclonal antibodies), is a stronger indicator of poor prognosis in MM (and response to next therapy) compared with age, ECOG status and co-morbidities. However, MSAC did not accept the applicant's justifications as addressing the concern regarding applicability to the Australian population, and the differences in patient's use of prior therapies across studies would be negated by the healthier status of patients in CARTITUDE-1.

Overall, MSAC was concerned that the nature of the comparisons meant that the extent of benefit of cilta-cel compared with Pd and Cd cannot be accurately quantified and it has likely been overestimated in the ADAR. A further concern was the lack of data on the durability of benefit of cilta-cel. MSAC considered that these concerns had significant implications for the interpretation of the incremental cost-effectiveness ratio (ICER).

MSAC noted the economic evaluation, which was a cost-utility analysis. MSAC considered the extrapolation of quality-adjusted life years (QALYs) over a time horizon of 25 years was the largest source of uncertainty and very optimistic, as for many patients, this would extrapolate beyond the average life expectancy in Australia. The ICER was highly sensitive to the type of distribution used to fit the data, which also led to substantial uncertainty in the economic evaluation. MSAC noted in response to the ESC's concern associated with costing of resources associated with cilta-cel, the pre-MSAC response presented multivariate sensitivity analysis to include the total direct medical costs associated with cilta-cel (including tocilizumab hospital distribution, rates of admission to intensive care units, use of intravenous immunoglobulin [IVIg] and anti-infective prophylaxis, cost of neurotoxicity AEs, 100% proportion of patients receiving cilta-cel in an inpatient setting) which increased the ICER by 6.0% (minimum cost adjustment) to 16.2% (accounting for all cost adjustments) (see Table 15). Overall, MSAC considered that the ICERs were high and likely to be underestimated.

MSAC noted the proposed risk-sharing arrangement, in which █████ ██ ███ ██ ███ ███ ████ ██ ███ ████ ██. MSAC noted that the cost of cilta-cel is linked to ███ ███, but it was not clear whether any adjustment had been made in the economic model (for both costs and health outcomes) to account for any differences between the Australian population and the participants in the CARTITUDE-1 study. The applicant noted in the pre-MSAC response that it was agreeable to developing risk-sharing arrangements to manage any utilisation beyond the estimates.

MSAC noted the financial and budgetary estimates. The net financial impact to health budgets was estimated at $███ in Year 1, increasing to $███ in Year 6. MSAC noted the revised financial

estimates in the pre-MSAC response to address ESC's concern that the number of patients was overestimated based on patient suitability and uptake. This resulted in a relative change for Years 1 to 5 of ███% for the number of patients infused and ███% for the cost to the NHRA (see Table 17).

MSAC noted that, under the NHRA, state health authorities pay 50% of the costs for High Cost Highly Specialised Therapies. MSAC noted submissions were received from New South Wales and Queensland, both of which did not support public subsidy of this therapy at this point in time. The jurisdictions noted that compared to the previous CAR-T therapies MSAC has considered, the RRMM population was significantly larger and therefore a greater threshold of evidence would be required to support public funding of cilta-cel for this indication. NSW recommended the application not be reconsidered by MSAC until a properly controlled phase II or higher trial to establish the efficacy and safety of cilta-cel against standard treatment in this large patient cohort was conducted, noting this was feasible given the size of the eligible population. Both submissions also questioned the treatment effectiveness reported, considering it was likely optimistic, particularly when compared to actual outcomes reported for CAR-T use in Australia and that review of the real-world evidence around the effectiveness of CAR-T therapies was yet to be assessed. Jurisdictions also raised concerns that the costs included in the submission were underestimated compared to the real cost of service provision in the public hospital setting and that given the large patient population substantial implementation challenges would need to be addressed in order to allow for an expansion of current services and addition of new treatment sites. Overall, MSAC considered that the lack of States' support for cilta-cel presented a barrier to successful implementation of funded treatment.

MSAC considered the jurisdiction's views and agreed that although the quality of evidence presented in the application was similar to that presented for other supported CAR-T therapies, the clinical context of RRMM differs substantially to that of previously supported indications. MSAC noted that compared to tisagenlecleucel, which was supported for the treatment of children and young adults with acute lymphoblastic leukaemia which is a small population with a high unmet clinical need and very limited treatment options, the RRMM population is substantially larger and older, with a number of alternative treatment options available as later line therapy.

Overall, MSAC did not accept that cilta-cel is comparatively safe, effective and cost-effective in the proposed context. MSAC considered the low level of clinical evidence in support of cilta-cel to be 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.

MSAC noted that results from a randomised controlled trial (CARTITUDE-4; NCT04181827) in an earlier treatment line than proposed in this application is expected in 2026.

4.   Background

The listing of cilta-cel was requested on the basis of a cost-utility analysis versus carfilzomib with dexamethasone (Cd) and pomalidomide with dexamethasone (Pd) as the main and only comparators. Cilta-cel has not previously been considered by MSAC in any indication. However, other 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's therapies that have been 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

Source: Table 1-3, Section 1 of the ADAR.
CAR-T = chimeric antigen receptor T-cells; MSAC = Medical Services Advisory Committee

5.   Prerequisites to implementation of any funding advice

Cilta-cel is in the process of being considered by the Therapeutic Goods Administration (TGA). The TGA application was on the ███ ███ ███. The TGA submission number is ███ and the TGA application number is ███. The proposed TGA indication is "cilta-cel is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody". The TGA has not advised when to expect any interim document or approval.

Cilta-cel has been recommended a conditional marketing authorisation by the European Medicines Association (EMA) (25 March 2022) for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies and whose cancer has worsened since they received their last treatment[1].

Cilta-cel was granted by the Food and Drug Administration (FDA) (28 February 2022) "for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody". The decision to restrict cilta-cel to fifth-line and later settings was not specified but appeared to be based on the high number of prior therapies patients had received in the pivotal trial, CARTITUDE-1. According to the FDA's approved product information, CARTITUDE-1 included patients who had received a "median of six prior treatment regimens (range, 3-18), with 82% of patients receiving 4 or more prior lines of therapy, 90% of patients had received prior autologous stem cell transplantation (ASCT) and 8% of patients received an allogeneic transplant". As CARTITUDE-1 was conducted in the USA, where patients with RRMM have more lines of effective treatment options available than Australian RRMM patients, cilta-cel patients may be used in less heavily treated patients.

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

The ADAR noted that previous MSAC advice for CAR-T therapies have included several requirements for public funding (p23 Axicabtagene ciloleucel PSD, January 2020; p19 Tisagenlecleucel PSD, April 2019):
- Treatment to be delivered by a haematologist working in a multi-disciplinary team specialising in CAR-T cell therapy;
- Treatment must be delivered in a tertiary public hospital with appropriate credentials;

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

- Governance and prescribing rules to ensure treatment is directed to patients most likely to benefit;
- Payment only on successful infusion (e.g. patient is infused with a clinically acceptable cell dose which is consistent with the expected cell dose specified prior to apheresis);
- Treatment to be limited to a single dose, as there is no evidence currently available informing the effectiveness or safety of multiple doses;
- A full review of clinical effectiveness, cost-effectiveness and budget impact will be conducted by the MSAC after 2 or 3 years post the commencement of public subsidy. It should be noted that these reviews are yet to be undertaken despite available data meeting the 3 year time point;
- Data on the use of CAR-T therapies in Australia should be recorded by the Australian Bone Marrow Transplant Recipient Registry (ABMTRR), with the cost of data collection met by the applicant – which ensures a single Australia source of data for all CAR-T therapies in all indications and from all treatment centres;
- A definition of an acceptable responder status for patients who undergo CAR-T therapy within the context of the disease; and
- Risk Share Arrangements to manage utilisation beyond the estimates.

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

6.   Proposal for public funding

Summary of request for public funding via the NHRA

Table 2 summarises the eligibility criteria for treatment with cilta-cel under the NHRA.

Table 2: Eligibility criteria for cilta-cel treatment under the NHRA

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 three prior lines of therapy AND Patient must have previously had treatment with a proteasome 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 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 ADAR.
ECOG= CAR-T= chimeric antigen receptor T-cells; Eastern Cooperative Oncology Group; MM= multiple myeloma; NHRA= National Health Reform Agreement; PBS= Pharmaceutical Benefit Scheme.

MSAC has also previously noted that there were substantial equity issues with regards to treatment with patients from non-treating states and in rural/remote communities having to travel for treatment (p23 Axicabtagene ciloleucel PSD, January 2020; p19 Tisagenlecleucel PSD, April 2019)

Proposed fee

The total cost proposed for cilta-cel was $███. The ADAR proposed ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ██.

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In CARTITUDE-1, the rate of successful infusion with cilta-cel was 86% (97/113) in all patients that underwent apheresis (ITT population) and 100% (97/97) in all successfully infused patients (mITT population). ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████ ████. Based on data from CARTITUDE-1 the total cost of cilta-cel per apheresed patient was $██ and $██ per successfully infused patient. The cost of $██ per a successfully infused patient was applied in the economic model and the cost of $██ per apheresed patient was applied in the financial estimates. It should be noted that the economic model stratified cilta-cel patients according to whether they were successfully infused or not.

7.   Population

It is expected that cilta-cel would be an alternative to the combination of Pd and Cd for the treatment of RRMM in patients who have received at least 3 prior therapies, that include a PI, an IMID and an anti-CD38 inhibitor (see Figure 1). Cilta-cel in fourth line would partly replace but also possibly displace Cd and Pd to a further line in therapy. Given that newer 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 a later than fourth line. This would be consistent with the FDA decision to restrict access to cilta-cel to ≥ 5 prior lines of therapy. The population described in the ADAR was consistent with that proposed in the Ratified PICO.

It is anticipated that the use of other MBS and PBS services will increase if cilta-cel gets approved, mainly: in hospital services (a proportion of patients will require hospitalisation), infusion-related

services, drugs for the management of AEs, drugs used as conditioning therapy and drugs used as bridging therapies. In addition, in the Ratified PICO, the applicant advised that most patients treated in the fourth line setting would already be on IVIG, either due to the disease or because of prior treatment. The applicant also suggested the incremental change in IVIG use was likely to be a small increase (approximately 5-10%); and the impact of changes to IVIG use was tested as a sensitivity analysis in the pre-ESC and pre-MSAC responses. Furthermore, there is some evidence that CAR-T-cell therapy may have potential long-term adverse events, such as prolonged cytopenia and immune deficiency, as well as infections. A study showed that patients experienced a long period of hypogammaglobulinemia, suggesting a profound and lasting humoral immune deficiency after CAR-T-cell therapy. The duration of the event and consequent need for prophylactic treatment remains uncertain however may not be disregarded.

The ADAR broadly addressed the requirements outlined in the Ratified PICO.

Figure 1 Proposed clinical algorithm
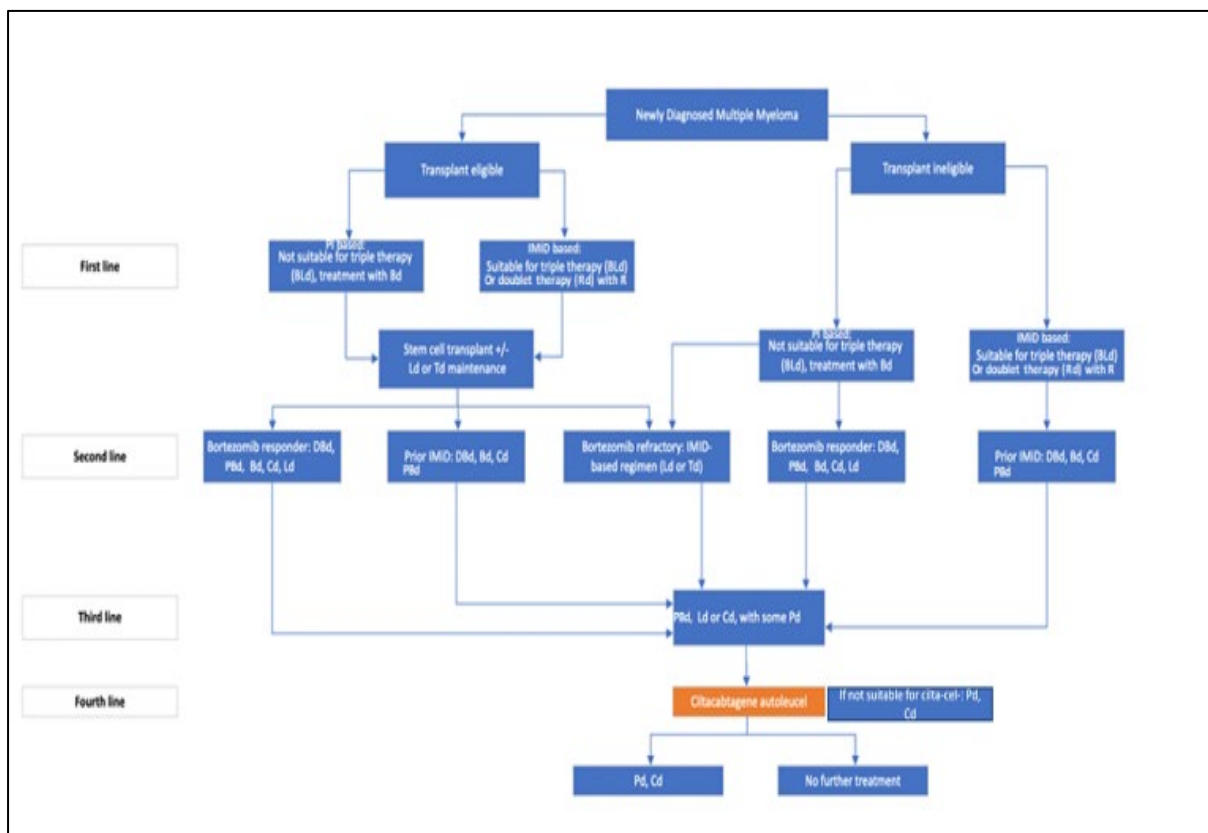
Source: Figure 1-17 of the ADAR.
Bd = bortezomib and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; cilta-cel = ciltacabtagene autoleucel; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; IMiDs = immunomodulator drugs; Ld = lenalidomide and dexamethasone; MM = multiple myeloma; Pd = pomalidomide and dexamethasone; Td = thalidomide plus dexamethasone; PBd = pomalidomide, bortezomib plus dexamethasone.

8.   Comparator

The ADAR proposed Pd and Cd as the main comparators. The ADAR presented data from the 10% PBS sample that showed that Pd (42%) and Cd (34%) were most commonly used to treat RRMM patients in the fourth line setting. Similarly, both Pd and Cd are the most commonly used therapies in the fifth line and later settings too.

The ADAR noted that PBd was PBS listed recently and that it was anticipated to be used in the third-line setting. This may increase the use of Cd in the fourth-line setting as a consequence. The ADAR stated that the use of PBd required patients to have been previously treated with lenalidomide as the backbone therapy. Given the triple combination of lenalidomide in combination with bortezomib and dexamethasone (LBd) was listed in newly diagnosed patients, it is likely most patients will meet this eligibility criterion. However, the latter does not limit its use as a different line in therapy. It should be noted that more recently several triple therapies have been assessed and recommended by the PBAC that may increase the pool of alternative therapies available. For example, the PBAC has recommended elotuzumab in combination with lenalidomide and dexamethasone (ELd) (p17, elotuzumab PSD, July 2021) and considered though not recommended others (i.e. ixazomib in combination with lenalidomide and dexamethasone (ILd) (p32, ixazomib PSD, November 2020). All of these therapies have been considered for use in second or later line, which is not the line in therapy aimed for cilta-cel. However, it is expected that they will increase the treatment options available in the RRMM setting and may push the use of cilta-cel to a further than fourth-line therapy.

This new possible scenario may push the use of Cd and Pd to a further line of treatment. Additionally, cilta-cel may also be used in later than fourth-line settings depending on the clinician's benefit risk assessment for each patient.

PASC accepted that Pd and Cd were reasonable comparators. These comparators are currently reimbursed through the PBS for the same patient population targeted in this ADAR.

9. Summary of public consultation input

Consultation feedback received post-PASC was from 283 consumers and 83 carers (total 366), two (2) individual specialists and four (4) organisations:

- Barwon Health
- Haematology Society of Australia and New Zealand (HSANZ) – updated previous feedback
- Myeloma Australia
- Myeloma Australia's Medical and Scientific Advisory Group (MSAG) – further comments.

Targeted consultation feedback received prior to PASC was from one (1) individual specialist and four (4) organisations:

- Australian Leukaemia and Lymphoma Group (ALLG)
- Haematology Society of Australia and New Zealand (HSANZ)
- Leukaemia Foundation
- Myeloma Australia's Medical and Scientific Advisory Group (MSAG).

All consultation feedback received was supportive of making this therapy available to patients with multiple myeloma (MM).

Advantages related to the proposed application were perceived to be:

- All respondents agreed that the proposed intervention satisfies an unmet need in the proposed population. Benefits included perceived improved prognosis, potential reduction or deferral of future lines of therapy, longer treatment free periods, domestic expertise and experience with CAR-T therapies and related toxicities, and reduced burden of care.
- A single treatment with ciltacabtagene autoleucel could provide MM patients with improved quality of life and a prolonged treatment free interval which would reduce the high treatment and financial burden of care
- This therapy is a significant advance, with an acceptable safety profile, for heavily pre-treated patients with relapsed/refractory MM who have few other treatment options, especially at the third or fourth line
- Its use may potentially lead to long-term remission for some patients and represents a vast improvement on other currently available therapies beyond third line treatment
- There will be less demand and cost savings in other areas of the public health system with these patients in remission following CAR-T cell therapy such as outpatient services, blood products, inpatient admissions for infections and supportive care medications.
- Subsidised ciltacabtagene autoleucel would enable equitable patient access.

Disadvantages related to the proposed application were noted to be:

- MSAG, ALLG, the Leukemia Foundation, Myeloma Australia and individuals have pointed out the recognised adverse events (AEs) related to CAR-T therapy, specifically ICANS and CRS, however, also noted that these AEs are known with established management protocols
- Feedback from the organisations commented on the population, agreeing that the proposed population in alignment with the CARTITUDE -1 trial was appropriate. However, the Leukaemia Foundation stated that limiting cilta-cel to those who have previously undergone CD-38 therapy should be reconsidered to avoid reducing access
- Further to this, infrastructure and staff requirements were stated by the individual to be a potential barrier to access for patients due to the highly specialised requirements needed to provide the proposed intervention.
- MM patients and their carers tend to be older, so delivery of therapy at a distant site from the place of residence and toxicity management of CRS and ICANS which requires patients to be managed close to the specialist facility for a minimum period of 30 days post infusion with a full-time carer available will be a higher burden for this group of patients
- MM patients are heavily pre-treated and immunosuppressed so it is likely that more patients will need IVIG and other infectious prophylaxis measures
- That treatments used as bridging therapy, such as carfilzomib or pomalidomide, are not subsequently lost as treatment options if a patient subsequently progresses post cilta-cel
- The identified patient population requires prior treatment with an anti-CD38 monoclonal antibody, i.e. daratumumab which effectively excludes some patients who have not been treated with daratumumab. Patients who have already received a second-line therapy (or beyond) who have not had access to daratumumab, therefore would be ineligible to receive cilta-cel as a fourth line therapy under the proposed indication.

Other comments raised were:

- Myeloma Australia, consumers and carers considered that this therapy should be made available early in the treatment cycle for MM patients given the significant impact it can have on the quality of life of the patient. It should not just be available as a last resort therapy.
- Consumers and carers recognise that cilta-cel is an expensive treatment and is beyond most patients reach if it doesn't have government funding.
- Feedback from Barwon Health stated that it proposes to establish a CAR T-Cell collection and reinfusion centre in regional Victoria (Geelong) to service patients in Western Victoria.
- MSAG further comments noted the changes to international regulations in the US and Europe relating to cilta-cel in the treatment of MM, and that in the rapidly evolving regulatory landscape the ideal bridging therapy may change, however currently a schedule of pomalidomide, daratumumab and dexamethasone or carfilzomib, daratumumab and dexamethasone is appropriate.

10. Characteristics of the evidence base

Summary of the clinical evidence

The ADAR's safety and efficacy evidence of cilta-cel for the treatment of RRMM in patients who had received at least 3 prior lines of therapy, was based on one single-arm study, CARTITUDE-1. The ADAR presented comparative clinical evidence from:

- Naïve (unanchored) indirect comparisons between CARTITUDE-1 versus MM-003 (only the Pd arm of the RCT) and the MRDR (Australian registry); and
- Unanchored indirect comparisons using inverse probability of treatment weighting (IPTW) to adjust for confounding, of patients who (mostly) met the CARTITUDE-1 eligibility criteria and required 4th and later lines of treatment. The sources used to conduct these indirect comparisons were:
  - Physician's choice cohort from follow-up data of three daratumumab RCT (POLLUX, CASTOR and EQUULEUS);
  - FLATIRON (USA registry);
  - LocoMMotion (prospective observational cohort).

Table 3 summarises the key features of the ADAR's clinical evidence that compared cilta-cel with Pd and Cd.

Table 3: Key features of the ADAR's clinical evidence that compared cilta-cel with Pd and Cd

Study	Study Design	Risk of bias (evaluator's assessment)	Population	Intervention/comparator	Outcomes	Results used in the economic model
Intervention: cilta-cel						
CARTITUDE-1 ITT = 113 mITT = 97	Phase 1b/2 OL, single-arm clinical study Median follow-up: 21.7 months	Serious to critical	RRMM, ≥3 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-1, NYHA stage ≤II, creatinine ≤ 2 mg/dL, no other serious underlying medical condition.	ITT: 100% (n = 113) all enrolled/apheresed patients mITT: infused patients only (97/113)	Primary: ORR Secondary: sCR, SCR rate at 12 months, AEs, CR, MRD negativity, HRQoL, DoR, PFS, OS, AE's	PFS, OS, sCR rate at 12 months, AEs.
Comparators: Pd and Cd						
Naive indirect comparison						
MM-003 (Pd arm only) ITT=302	Phase 3, OL, RCT Median follow-up: 15.9 months	Low to moderate	RRMM, ≥ 2 prior lines (PI, IMiD), ECOG 0-2.	Pd arm: 100% (n =302) received Pd.	Primary: PFS Secondary: ORR, sCR, CR, DoR, OS, AEs	PFS, OS
MRDR main cohort ITT= 42	Retrospective analysis of MM registry data Median follow-up: NR	Unacceptable	RRMM, ≥ 3 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-2	Pd and Cd: 35.7% Not PBS listed:14.3%	ORR, CR, PFS, OS	PFS, OS
MRDR modified cohort ITT= 125			Same as above except for prior use of anti-CD38 antibody	Pd and Cd: 40.8% Not PBS listed: 5.6%	ORR, CR, PFS, OS	PFS, OS
Indirect treatment comparison using IPTW						
Physician's Choice Cohort ITT = 632 mITT = 434	Retrospective analysis of 3 daratumumab RCT Median follow-up: NR	Acceptable	RRMM, ≥ 3 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-1, creatinine ≤ 2 mg/dL	Pd and Cd: 42.6% Not PBS listed: 12.6%	ORR, CR, PFS, OS	PFS, OS
FLATIRON ITT = 482 mITT = 336	Retrospective analysis of registry data Median follow-up: NR	Acceptable	RRMM, ≥ 3 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-1, creatinine ≤ 2 mg/dL	Pd and Cd: 54.2% Not PBS listed: 21.3%	ORR, CR or better, PFS, OS.	PFS, OS
LocoMMotion ITT =248 mITT = 170	Prospective cohort study Median follow-up: 11 months	Acceptable	RRMM, received ≥ 3 prior lines (PI, IMiD, anti-CD38 antibody), ECOG 0-1	Pd and Cd: 55.2% not PBS listed: 15.8%	Primary: ORR Secondary: sCR, CR, DoR, OS, PFS, HRQoL, AEs	Not used

Source: Constructed during evaluation based on data in Section 2 of the ADAR.

Cd = carfilzomib plus dexamethasone; cilta-cel = ciltacabtagene autoleucel; CR = complete response; IMiD = immunomodulatory agent; ECOG = Eastern Cooperative Oncology Group; IPTW = inverse probability treatment weighting; ITT = intention-to-treat [a] ; KM = Kaplan-Meier; mITT [b]= modified intention-to-treat; NYHA = New York Heart Association; ORR = overall response rate; OS = overall survival; Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; PI = proteasome inhibitor; RRMM = relapsed or refractory multiple myeloma; sCR = stringent complete response

Notes:

a: Included in the analysis as the ITT population (underwent apheresis or enrolled)

b: Included in the analysis as the mITT population (received treatment with citla-cel infusion therapy or did not die or progressed or withdraw consent before receiving citla-cel infusion therapy or within 47 days (physician's choice cohort FLATIRON) or 52 days (LocoMMotion) of starting treatment.

c: CARTITUDE-1 used ROBINS-1 Risk of Bias Tool, MM-003 used the Cochrane Risk of Bias Tool, CE-MRDR. Physician's Cohort Study, FLATIRON and LocoMMotion used SIGN checklist for cohort studies

The ADAR relied on the modified intention to treat (mITT) analysis (infused only patients); however, efficacy outcomes of the ITT analysis (all enrolled patients all of which underwent apheresis) were also reported in the ADAR. It should be noted that the results from the latest data cut-off in July 2021 was not available for all the outcomes and analyses (Table 4). In contrast, safety was only reported in the mITT analysis of CARTITUDE-1 and the ITT analyses of LocoMMotion and MM-003.

Table 4: Datasets used by the ADAR to construct efficacy and safety information for ITT and mITT population in CARTITUDE-1

Outcome	ITT		mITT	
	Data-set	Data available for evaluation?	Data-set	Data available for evaluation?
Efficacy data	CARTITUDE-1 IPD July 2021 Data cut off	No	CSR July 2021	Yes
Safety data	NR	NA	CARTITUDE-1 IPD July 2021 Data cut off	No

Source: constructed during the evaluation.
CSR= clinical study report; IPD= individual patient data; ITT= intention to treat; mITT= modified intention to treat; NA= not applicable; NR= not reported.

For the studies used in the naive indirect comparison: MM-003 (only the Pd arm) and MRDR (Australian registry database), only the ITT results were available. Hence, the ADAR compared these results with both ITT and mITT results of CARTITUDE-1. This was reasonable.

For studies used in in the indirect comparison following IPTW, both ITT (i.e. patients who met the CARTITUDE-1 eligibility criteria and required 4th and later lines of treatment) and mITT (patients who did not die or progressed or withdraw consent within 47 days (physician's choice, FLATIRON) or 52 days (LocoMMotion) since initiating the corresponding therapy) results were presented. The number of patients who dropped out in the mITT population due to death or progression in the first 47 to 52 days of commencing fourth line was higher in some of the comparator studies (Physician's Choice Cohort = 18% and LocoMMotion = 31%) than in CARTITUDE-1 (14%). This may be due to patients in CARTITUDE-1 generally being healthier, younger and with fewer markers that suggested a more aggressive disease.

The evidence presented to build the comparator arm differed in terms of: (1) type of analyses, (2) eligibility criteria across trials, and (3) baseline characteristics of patients all of which contributed to transitivity issues from CARTITUDE-1 to the comparator studies.

Differences in the type of analysis: number of observations/line of therapies (LOTs) versus patient numbers

In CARTITUDE-1, MM-003 (Pd arm only), CE-MRDR and LocoMMotion, the reported number of observations related to the number of patients in the studies. However, in the physician's choice cohorts (long-term follow up of the daratumumab trials) and FLATIRON, the number of line of therapies (LOTs) after patients had failed after their third-line of treatment were used. The latter meant that the same patients could appear multiple times in the comparator studies if they required further than four lines of therapy. For example, a patient who received six lines of therapy, could have been included three times in the analysis (see Figure 2). The ADAR argued that the reason why they followed this approach was to account for the following inherent differences between CARTITUDE-1, the pooled data of the three daratumumab studies and FLATIRON:

- The physician's choice cohort (from the daratumumab trials) and the FLATIRON cohort were both retrospectively assessed to be included into the indirect comparison; hence, this method allowed to determine the earliest LOT from which the patient met the CARTITUDE-1 eligibility criteria.

- CARTITUDE-1 patients may have received multiple LOTs since they first became eligible and the time they were enrolled into the clinical trial.

Figure 2 An Example Participant from the Physician's Choice Cohort with Multiple Index Dates
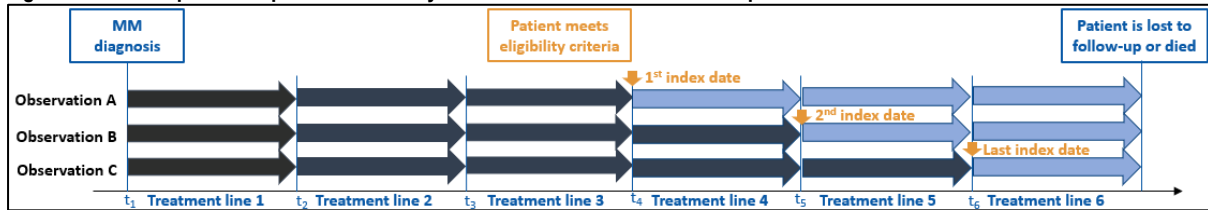
Source: Figure 1 of Attachment A.9 of the ADAR.
ITT= intention-to-treat; mITT= modified intention-to-treat; MM= multiple myeloma
Note: This example shows a participant becoming eligible after line 3 and having index dates t4, t5, and t6. This participant would be included three times in the analysis which considers all index dates with T0 = t4 (Observation A), T0 = t5 (Observation B), and T0= t6 (Observation C), respectively. For the analysis which considers only the first index date, this participant would be included once with T0 = t4 (Observation A). The index date, T0, was defined as the start of the relevant LOT (ITT population) or as the start of the relevant LOT + 47 days (mITT population

The ADAR argued that this approach was the most statistically efficient approach relative to including only the first or last eligible LOT (Backenroth 2021) (Phillippo, Ades et al. 2018) and has been peer reviewed. In contrast, the use of only the first eligible LOT may have biased the results in favour of the comparator arm, given that patients in the comparator arm would been exposed to fewer prior lines, on average, compared to patients in the treatment arm. However, it was also unclear if patients who failed further lines of therapy (>4) continued to meet the eligibility criteria to support this approach.

Patients were first selected based on whether they met CARTITUDE-1 eligibility criteria (unadjusted analysis). The imbalance across patient's baseline characteristics was then adjusted using the IPTW methodology. The ADAR presented both, the unadjusted and adjusted results as well as conducted several sensitivity analyses. The base case scenario weighted participants on the following factors: refractory status, cytogenetic profile, ISS stage, extramedullary plasmacytomas, time to progression on last regimen, number of prior LOTs, years since MM diagnosis, and age. The fully adjusted scenario weighted participants on hemoglobin, prior stem cell transplant, ECOG score, race, sex, and type of MM, in addition to the base case variables. The approach followed by the ADAR to identify and select these variables was appropriate.

Key differences in study eligibility criteria

Relative to the comparator studies, CARTITUDE-1 had extensive inclusion and exclusion criteria where patients were:

- required to have an Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) of 0-1 while MM-003, CE-MRDR cohorts included patients with an ECOG PS of 0-2. In CARTITUDE-1, 4% of patients had an ECOG PS of 2 while in the comparator studies this value ranged from 7-17%. This difference may suggest that patients in the control arms may have been sicker than in CARTITUDE-1;
- required to have received at least 3 prior lines of therapy while patients in MM-003 had received two prior lines before initiating treatment with Pd;
- required to have a creatinine ≤ 2 mg/dL. Renal function was not a requirement in MM-003, CE-MRDR cohorts or LocoMMotion.
- required to have prior treatment with anti-CD38 antibodies. Patients in MM-003 and CE-MRDR (modified cohort) were likely not treated with anti-CD38 antibodies;

Overall, patients were more highly selected in CARTITUDE-1. In additional to the above, patients in CARTITUDE-1 had to be classified as New York Heart Association (NHYA) ≤II, no history of toxicity

to anticancer therapies and not have other serious underlying medical illness. In contrast, some patients in the comparator groups were selected from registry databases (with limited available clinical information) from where it is unclear if patients would have been considered too sick for treatment with cilta-cel (and therefore excluded from CARTITUDE-1).

Key differences in baseline characteristics

Patients in CARTITUDE-1 were likely healthier (i.e. both younger and able to undergo ASCT therapy) than patients in the comparator studies, despite been more heavily treated:

- The median age was 61 years in CARTITUDE-1 versus 65 years in the comparator studies
- 90% of patients in CARTITUDE-1 had received a prior ASCT versus 55% to 78% in the comparator studies.
- The median number of prior LOTs was 6 in CARTITUDE-1 versus 3 to 5 in the comparator studies.
- Other differences in distribution of patient characteristics were noted. Fewer patients in CARTITUDE-1 relative to the comparators:
    - Had an International Staging System (ISS) stage III (14% versus a range from 11-34%);
    - had and ECOG PS of 2 (4% versus a range from 7-17%);
    - were triple or quad refractory (43% versus a range 38-78%).

Given that the ADAR adjusted for baseline characteristics in the IPTW indirect comparison (Physician's Cohort Study, FLATIRON and LocoMMotion) these differences in populations were unlikely to bias the results.

Main transitivity issues

The non-comparative nature of the evidence of CARTITUDE-1 and the above-mentioned differences in baseline characteristics and eligibility criteria across the studies, translated into substantial transitivity issues, mainly:

- CARTITUDE-1 had an extensive eligibility criteria to ensure that patients were fit and healthy enough to withstand treatment with cilta-cel.
- CARTITUDE-1 was powered to detect changes in ORR, whilst MM-003 (Pd arm from RCT) was powered to detect differences in PFS. The other comparator studies had no defined primary outcome as they were registry datasets (MRDR and FLATIRON) and cohort studies (Physician's Choice Cohort and LocoMMotion).
- The time when the studies were conducted. MM-003 was conducted earlier (2011-2012) and may not reflect contemporary clinical practice of treating RRMM than the other studies (2016 and later), as newer treatments are now available to treat patients in subsequent relapses. This would favour cilta-cel.
- Country specific settings determine access to different treatment options in patients with RRMM. CARTITUDE-1, Physician's Cohort Study, FLATIRON and LocoMMotion were conducted in the USA and Europe, where the treatment available may differ to that in Australia.
- Comparisons made using mITT results from CARTITUDE-1 against ITT results from MM-003 and MRDR are likely to suffer from survivorship bias. CARTITUDE-1 patients were required not to progress prior to receiving cilta-cel which lasted a median of 47 days (from apheresis to infusion). In MM-003 and CE-MRDR there was no such requirement prior to treatment.

Cilta-cel (CARTITUDE-1) vs. LCAR-B38M (LEGEND-2)

An additional clinical study (LEGEND-2) was identified but was excluded by the ADAR. LEGEND-2 was a phase I single-arm study conducted in China that enrolled 74 adults with RRMM who had progressive disease after at least 3 prior therapies (including a PI, an IMiD, and an anti-CD38 antibody). LEGEND-2 was designed to explore safety (primary outcome) and CR (secondary outcome). The ADAR considered that the results of LEGEND-2 clinical study (Zhao, Liu et al. 2018) were not relevant to support the clinical claim given differences compared to CARTITUDE-1, mainly:

- patients in LEGEND-2 were less heavily treated and generally younger.
- LEGEND-2 used cyclophosphamide alone as conditioning therapy. In contrast, CARTITUDE-1 used cyclophosphamide and fludarabine to achieve lymphodepletion.
- all patients that were enrolled were infused compared to 86% in CARTITUDE-1. This difference is likely due to differences in the study protocol that may arise from the experience (i.e. safety) in LEGEND-2 that translated into a different protocol for CARTITUDE-1.
- LEGEND-2 started to enrol patients in 2015, when other therapies (such as IMiD) may not have been available (Zhao, Liu et al. 2018).

In addition to the differences in the protocol and patient characteristics, the ADAR argued that LCAR-B38M was not the exact same product as cilta-cel. This was due to the differences in the manufacturing and scale up processes, and clinical and administration processes. LEGEND-2 explored the differences between a single and a three CAR-T cell infusion approach with varying doses ($0.2\text{-}2.0 \times 10^6$ CAR-T cells/kg). Furthermore, the target dose in CARTITUDE-1 was 0.75×10^6 CAR-positive viable cells per kg (range $0.5 \times 10^6 – 1.0 \times 10^6$) of cilta-cel and the target dose in LEGEND-2 was 0.5×10^6 (range $0.07 - 2.1 \times 10^6$). Hence, the therapy used in LEGEND-2 corresponds to an earlier version of cilta-cel.

A naïve comparison between CARTITUDE-1 and LEGEND-2 was conducted by the evaluation (see Table 5). Overall, the results suggested that cilta-cel may be superior in terms of PFS, CR and ORR. In terms of safety, the results suggested cilta-cel was inferior to LCAR-B38M (as the rates of adverse events were generally higher for patients treated cilta-cel). However, the results should be interpreted with caution as the comparison was naïve and due to the transitivity issues discussed above.

Table 5: Naïve comparison between CARTITUDE-1 and LEGEND-2

Outcome, % (n/N)	CARTITUDE-1 N=113	LEGEND-2 N=57
Apheresis	100% (113)	NR - Unknown
Received CAR-T infusion	97 (86)	57 (100)
Target CAR-T dose (range)	0.75×10^6 ($0.5 - 1.0 \times 10^6$)	0.5×10^6 ($0.07 - 2.1 \times 10^6$)
Administration cilta-cel/LCAR-B38M	Single infusion	3 infusions over 7-day period (20, 30, and 50% of total dose).
Median follow-up	22.7 months	8 months
Median age (range)	61(56–68) years	54 (27-72) years
Median N of prior lines of therapy (range)	6 (4 to 8)	3 (1 to 9)
Prior therapies, % (n/N) - Proteasome inhibitors - Immunomodulatory agents - Anti-CD38 antibody	 92% (95/113) 96% (99/113) 94% (97/113)	 68% (39/57) 86% (49/57) NR
mITT results % (n/N)		
Overall response rate	97% (91/99)	88% (76/95)
Complete response or better	83% (80/97)	68% (39/57)
Median PFS (95% CI)	NE (22.8, NE)	15 months (11, NE)
Minimal residual disease negativity	62% (56/97)	63% (56/57)
Median OS (95% CI)	NE (27.24, NE)	Median not reached
Any TEAE	100% (97/97)	100% (57/57)
Any serious TEAE	55% (53/97)	≥ Grade 3 TEAE: 65% (37/57)
CRS	95% (92/97)	90% (51/97)
≥ Grade 3 CRS	5% (5/97)	7% (4/57)
≥ Grade 3 TEAS		
Neutropenia	95% (92/97)	NR
Anaemia	68% (66/970)	18% (10/57)
Thrombocytopenia	60% (58/97)	23% (13/57)
Leukopenia	61% (59/97)	30% (17/57)

Source: constructed during evaluation from (Zhao, Liu et al. 2018, Berdeja, Madduri et al. 2021); CARTITUDE-1 CSR
CAR-T= chimeric antigen receptor; CI= confidence interval; citla-cel= ciltacabtagene autoleucel; CRS= cytokine release syndrome; NE = not estimable, NR= not reported; ORR= overall response rate; PFS= progression-free survival; TEAE= treatment emergent adverse event

Overall, it was considered reasonable that the ADAR excluded this study from Section 2. It should be noted that excluding LEGEND-2 likely favoured cilta-cel as the results from LEGEND-2 are less favourable compared to CARTITUDE-1 in terms of PFS, CR and ORR. However, LEGEND-2 were used to validate the modelled survival curves in Section 3 given the longer term follow-up available. This was considered appropriate.

11. Comparative safety

Table 6 presents the naïve comparison between CARTITUDE-1 and the comparator studies for which safety data was presented in the ADAR, MM-003 and LocoMMotion.

Table 6: Summary of adverse events in CARTITUDE-1, MM-003 and LocoMMotion (naïve indirect comparison)

Outcome, % (n/N)	Cilta-cel	Comparator studies: Pd and Cd	
	CARTITUDE-1 mITT (n=97)	MM-003 ITT (N= 302)	LocoMMotion ITT (N= 248)
Median follow-up (months)	21.7	15.9	11
Patients who progressed/died before cilta-cel	9.7% (11/113)	NR	NR
Any TEAE	100% (97/97)	NR	83.5% (207/248)
Any serious TEAE	54.6% (53/97)	61.0% (183/302)	33.9% (84/248)
Cytokine Release Syndrome	94.9% (92/97)	NR	NR
Cytokine Release Syndrome (≥ Grade 3)	5.2% (5/97)	NR	NR
Maximum severity of any TEAE			
Grade 1	0% (0/97)	NR	NR
Grade 2	0% (0/97)	NR	NR
Grade 3	1.0% (1/973)	NR	NR
Grade 4	86.6% (84/97)	NR	NR
Grade 5	12.4% (12/97)	5.0% (15/302)	NR
TEAE with outcome death	9.3% (9/97)	3.6% (11/302)	7.7% (19/248)
Grade 3 or 4 TEAEs			
Neutropenia	94.8% (92/97)	48.0% (143/302)	13.3% (33/248)
Anaemia	68.0% (66/97)	33.0% (99/302)	10.9% (28/248)
Thrombocytopenia	59.8% (58/97)	22.0% (67/302)	17.7% (44/248)
Leukopenia	60.8% (59/97)	8.7% (26/302)	4.8% (12/248)
Febrile Neutropenia	50.5% (49/97)	9.3% (28/302)	NR

Source: constructed during evaluation based on data presented in Section 2.3.3
Cd =carfilzomib plus dexamethasone; ITT= intention to treat; mITT= modified intention to treat; NR = not reported; Pd = pomalidomide plus dexamethasone; TEAE = treatment emergent adverse events.

The results of the naïve indirect comparison between CARTITUDE-1 versus MM-003 and LocoMMotion suggested that patients treated with cilta-cel were more likely to experience Grade 5 TEAE (12.4% versus 5%) and have TEAE's that result in death (9.3% versus 3.6 - 7.7%). Patients treated with cilta-cel were also more likely to experience hematologic AEs.

12. Comparative effectiveness

The results presented herein correspond to the ORR, sCR, CR or better(≥CR), PFS and OS. Further discussion regarding other outcomes can be found in the main body of the ADAR. A summary of the efficacy results for CARTITUDE-1 versus the comparator studies are provided in Table 7 (ITT) and Table 8 (mITT). It should be noted that the ADAR relied on the mITT results rather than the ITT.

Follow-up was 21.7 months in CARTITUDE-1, 15.9 months in MM-003, 18.2 months in the Physician's Choice cohort and 11 months in LocoMMotion. Follow-up was not reported in the MRDR registry (however, most patients had progressed by 6 months) nor the FLATIRON registry.

ORR, ≥CR and sCR

Overall, the results presented by the ADAR for ORR, ≥CR and sCR suggested that treatment with cilta-cel was superior to Pd and Cd. The ITT analysis showed that ORR for patients treated with cilta-cel was 80.4% versus 17.2 to 31.5% for patients treated with Pd and Cd in the comparator studies (see Table 7). The ≥CR rate was 70.8% in patients treated with cilta-cel vs 0.0 to 9.3% in the comparator studies. The sCR was 70.8% for cilta-cel vs. 0.0 to 1% for the comparator studies

In the mITT population, the ORR for patients treated with cilta-cel was 97.9% versus 17.2 to 42.9% for patients treated with Pd and Cd in the comparator studies (see Table 8). Similar outcomes were observed in the mITT population relative to the CR and sCR (82.5% vs 0% to 9.3% and 82.5% vs. 0 to 1%, respectively). Further, each of the risk difference (RD) estimates were statistically significant and in favour of treatment with cilta-cel.

Progression-Free Survival

Data from CARTITUDE-1 mITT analysis showed that the 12-month PFS rate was 76% (95% CI: 67, 84) and 18-month PFS rate was 67% (95% CI: 57, 75). It should be noted that the median time to PFS was not reached in the mITT analysis (95% CI: 22.8, NE) hence the comparative efficacy against the mITT analysis showed should be interpreted with caution. The median time to event in the ITT analysis was 27.4 (22.4, NE) with substantial censoring after 24 months which translated into a 12-month PFS rate was 70% (95% CI: 61, 78) and 18-month PFS rate was 62% (95% CI: 52, 70).

The PFS results were consistent across all comparisons and showed that cilta-cel produced superior PFS. For all the indirect comparisons, the Kaplan-Meier (KM) curves separated early and did not cross at any timepoint and favouring cilta-cel. Given the similarity observed across all comparisons, KM curves accounting for the MRDR registry only (main and modified cohorts) are presented below. The estimated hazard ratios (HR) were statistically significantly favouring cilta-cel in both the ITT and mITT comparisons.

CARTITUDE-1 versus MM-003 and CE-MRDR (main and modified cohorts) – naïve indirect comparison

It should be noted that only the ITT results were available for the comparators where median PFS was 4.0 months in the MM-003 and ▇▇▇ and ▇▇▇ in the MRDR main and modified cohorts. The HR estimated when comparing CARTITUDE-1 against MM-003, MRDR main cohort and MRDR modified cohort were ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇, respectively (see Table 7).

Figure 3 (ITT) and Figure 4 (mITT) present the KM curves for PFS in CARTITUDE-1 MRDR (main and modified cohorts). Please notes these figures are redacted.

Figure 3: PFS Kaplan–Meier curves for CARTITUDE-1 vs. MRDR – ITT results
REDACTED

Source: Figure 2-31 of the ADAR.
ITT= intention to treat; MRDR= Myeloma and Related Diseases Registry; PFS= progression-free survival.

Figure 4: PFS Kaplan–Meier curves for CARTITUDE-1 MRDR – mITT results
REDACTED

Source: Figure 2-31 of the ADAR.
mITT= modified intention to treat; MRDR= Myeloma and Related Diseases Registry; PFS= progression-free survival.

CARTITUDE-1 vs. Physician's Choice Cohort, FLATIRON and LocoMMotion –ITC using IPTW

The results showed that cilta-cel had superior PFS relative to all the comparator studies in both the adjusted and unadjusted results.

The ITT analysis showed that the median PFS ranged from 3.5 months (adjusted FLATIRON) to ▇▇▇ (unadjusted Physician's Choice cohort) in the comparator studies. However, the lower bound of the 95% CI KM estimate in CARTITUDE-1 was 22.8 months which compared favourable to the highest upper bound of the comparator arms (▇▇▇ in the physician's cohort study). Despite the immaturity of the CARTITUDE-1 data, the KM curves suggested that PFS was superior with cilta-cel.

Overall Survival

Data from CARTITUDE-1 mITT analysis showed that the 12-month OS rate was 87.6% (95% CI; 79.2, 92.8) and 18-month PFS rate was 81.4% (95% CI; 72.2, 87.9). The ITT analysis showed a 12-month OS rate was 81% (95% CI: 73, 88) and 18-month PFS rate was 76% (95% CI: 66, 83).

OS results were consistent across all comparisons and showed that cilta-cel produced superior OS. For all the indirect comparisons the KM curves separated early and did not cross at any timepoint with a HRs statistically significant favouring cilta-cel in both the ITT and mITT comparisons. However, the OS KM curves for cilta-cel should be interpreted with caution as OS was not reached in either of the analyses with substantial censoring after 24 months. With the data available, it can't be said whether the curves at this point start to flatten.

CARTITUDE-1 versus CE-MRDR (main and modified cohorts) – naïve comparison

It should be noted that only the ITT results were available for the comparators for which median OS was 12.7 months in the MM-003 and ███ and ███ ███ in the MRDR main and modified cohorts. The HR estimated for the ITT analysis when comparing CARTITUDE-1 against MM-003, MRDR main cohort and MRDR modified cohort were ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██, respectively (Table 7). The HR estimated for the mITT analysis when comparing CARTITUDE-1 against MM-003, MRDR main cohort and MRDR modified cohort were ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██, respectively (Table 8).

Figure 5 (ITT) and Figure 6 (mITT) present the KM curves for OS in CARTITUDE-1 and CE-MRDR (main and modified cohorts). Please notes these figures are redacted. As with PFS, only ITT data was available in MM-003 and CE-MRDR cohorts. Further, there appeared to be an error in the number of patients at risk reported in the MRDR arm. The number reported likely relates to probability of event rather than actual patients at risk.

Figure 5: OS Kaplan–Meier curves for CARTITUDE-1 vs. MRDR – ITT results

REDACTED

Source: Figure 2-42 and Figure 2-43 of the ADAR

Figure 6 OS Kaplan–Meier curves for CARTITUDE-1 vs. MRDR – mITT results

REDACTED

Source: Figure 2-42 and Figure 2-43 of the ADAR

The ADAR stated that 49% patients having died by 12 months follow-up in MM-003. Despite no follow-up being reported in the MRDR, most patients had died by 12 months, with only ██ ██ ██ ██ ██ ██ of patients alive at 12 months. Hence, this data was considered relatively mature.

Overall, the results showed that cilta-cel had superior OS based on a naïve comparison. It should be noted that OS was immature as median OS had not been reached in CARTITUDE-1 in either the mITT or ITT analysis, hence results should be interpreted with caution. However, the lower bound of the 95% CI KM for the ITT comparison was 28.7 months which was favourable when compared to the highest upper bound reported for the comparators (15.5 in MM-003 or FLATIRON).

CARTITUDE-1 vs. Physician's Choice Cohort, FLATIRON and LocoMMotion – ITC using IPTW

The ITT and mITT results showed that cilta-cel was superior OS based on both an unadjusted and adjusted IPTW indirect comparisons with each of the comparator studies. It should be noted that these results are uncertain as median time to OS had not been reached. Similarly, median time to

OS was not reached in LocoMMotion. However, the lower bound of the 95% CI KM estimate in CARTITUDE-1 was 28.7 months which compared favourable to the highest upper bound of the comparator arms (15.47 months in FLATIRON) which resulted in a median time to OS 1.9 times higher in the ITT analysis. Similarly, if the mITT analysis were considered (lower bound = 27.2), the median time to OS would 1.3 times (upper bound = 17.8 in FLATIRON). Despite the immaturity of the CARTITUDE-1 data, the KM curves suggested that OS was superior with cilta-cel.

Clinical claim

The ADAR claimed that cilta-cel had a different safety profile to Pd and Cd

The ADAR's argument to justify this claim was that AEs may occur during the initial period of therapy compared with an ongoing and cumulative basis compared with Pd and Cd. However, the results presented in Table 6, suggested cilta-cel had an inferior safety profile. The following should be considered regarding the safety claim:

- the results should be interpreted with caution given the naïve nature of the comparison and the differences in follow-up observed across the studies. The longer follow-up in CARTITUDE-1 may explain these differences as patients were more exposed to suffer AEs compared to MM-003 and LocoMMotion.
- safety results were provided for the mITT analysis only which considers patients that were infused with cilta-cel but not all the patients that underwent apheresis. This was considered inappropriate as patients eligible for cilta-cel required apheresis and potentially conditioning treatment and bridging therapy. The pre-ESC response provided a summary of the safety results of patients in the ITT population who underwent apheresis. Some prior CAR-T applications considered by MSAC have presented safety results for the mITT population (i.e. MSAC 1519) (p12, tisagenlecleucel PSD, April 2019). However, the axicabtagene ciloleucel application presented both, ITT and mITT results (Table 6, p14 of 1587 PSD).
- safety data came from the CARTITUDE-1 IPD July 2021 Data cut off, which was not provided in the ADAR, hence could not be verified by the evaluation.

The ADAR claimed that cilta-cel was superior in terms of efficacy to Pd and Cd.

The ADAR's claim of superior efficacy was plausible and supported by the evidence for the first 2 years of data. However, transitivity issues identified above limit the interpretation of comparative effectiveness mainly because patients in CARTITUDE-1 appeared to be healthier (despite being more heavily treated), with less progressive disease than patients in the comparator studies and because CARTITUDE-1 had a stringent eligibility criteria, which ensured patients were able to withstand treatment with cilta-cel.

Table 7: Results from CARTITUDE-1 vs. comparator studies (ITT comparison)

Outcome, % (n/N)	CARTITUDE-1	MM-003	CE-MRDR (main cohort)	CE-MRDR (modified cohort)	Physician's Choice Cohort		FLATIRON		LocoMMotion	
Treatment	Cilta-cel	100% Pd	▓▓▓	▓▓▓	▓▓		Cd or Pd (54.2%)		Cd or Pd (55.2%)	
Number	113	302	▓▓▓▓▓				248	117	482	111
Comparison	-	Naïve	Naïve	Naïve	Unadjusted IPTW	Adjusted IPTW	Unadjusted IPTW	Adjusted IPTW	Unadjusted IPTW	Adjusted IPTW
Median follow-up	21.7 months	15.9 months	▓▓▓▓				Unknown		11 months	
Treatment response										
ORR	84.1% (95/113)	31.% (95/302)	▓▓	▓▓	▓▓		NR	NR	29.8% (74/248)	NR
ORR RD	-	▓▓	▓▓	▓▓	▓▓	▓▓	NR	NR	**2.82 (1.59, 4.99)**	NR
sCR	70.8% (80/113)	1% (3/302)	▓	▓▓▓			NR	NR	0% (0/248)	NR
≥ CR	70.8% (80/113)	1% (3/302)	▓	▓▓			NR	NR	0.4% (1/248)	NR
≥ CR RD	-	▓▓	▓▓	▓▓	▓▓		NR	NR	NR	NR
Progression-free-Survival										
Number of events % (n/N)	41.5% (47/113)	78.8% (238/302)	▓▓	▓▓	▓▓		NR	NR	NR	NR
Median KM estimates (95% CI)	NE (22.8, NE)	4.0 (3.6, 4.7)	▓▓▓	▓▓▓	▓▓▓	▓▓▓	3.88 (3.29, 4.40)	3.48 (2.89, 4.57)	4.6 (3.9, 5.6)	4.1 (2.9, 5.1)
HR (95%)	-	▓▓	▓▓	▓▓	▓▓	▓▓	**0.21 (0.16, 0.29)**	**0.21 (0.14, 0.32)**	**0.23 (0.16, 0.33)**	**0.19 (0.11, 0.32)**
Overall Survival										
Number of events	46.0% (52/113)	50.7% (153/302)	▓▓	▓▓	▓▓		NR	NR	NR	NR
Median KM estimates (95% CI)	NE (28.70, NE)	12.7 (10.4, 15.5)	▓▓	▓▓▓	▓▓▓	▓▓▓	12.25 (9.9, 14.2)	12.29 (9.7, 15.5)	12.4 (10.3, NE)	11.76 (7.2, NE)
HR (95% CI)	-	▓▓▓	▓▓▓	▓▓▓	▓▓▓	▓▓▓	**0.29 (0.20, 0.44)**	**0.31 (0.18, 0.53)**	**0.32 (0.20, 0.50)**	**0.32 (0.14, 0.58)**

Source: constructed during evaluation from Section 2.3.2

Cd = carfilzomib plus dexamethasone; cilta-cel = ciltacabtagene autoleucel; ≥ *CR* = *complete response or better; CI = confidence interval;* KM = Kaplan-Meier; IPTW = inverse probability treatment weighting; ITT = intention-to-treat HR = hazard ratio; MRD = minimal residual disease; mITT = modified intention-to-treat; Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; OR = odds ratio; ORR = overall response rate; sCR = stringent clinical response; RD = risk difference; CI = confidence interval; Bold = statistically significant at p-value<0.05.

Table 8: Results from CARTITUDE-1 vs. comparator studies (mITT comparison)

Outcome, % (n/N)	CARTITUDE-1	MM-003	CE-MRDR (main)	CE-MRDR (modified)	Physician's Choice Cohort		FLATIRON		LocoMMotion	
Treatment	Cilta-cel	100% Pd	■■■■	■	‖‖		Cd or Pd (54.2%)		Cd or Pd (55.2%)	
Number	97	302	■■■■■■■■■				336	95	170	108
Comparison	-	Naïve	Naïve	Naïve	Unadjusted IPTW	Adjusted IPTW	Unadjusted IPTW	Adjusted IPTW	Unadjusted IPTW	Adjusted IPTW
Median follow-up	21.7 months	15.9 months	■■■■	■	■■		Unknown		11 months	
Population	mITT	ITT	■■■■				mITT		mITT	
Treatment response										
ORR	97.9% (95/97)	31.% (95/302)	‖	■‖	■■■■		NR	NR	42.9% (73/170)	31.4% (34/108)
ORR RD	-	■‖	■‖	■■	‖‖‖	■■■■	NR	NR	**3.12 (2.24, 4.00)**	NR
sCR	82.5% (80/97)	1% (3/302)	‖	■■■■			NR	NR	0% (0/248)	0% (0/108)
≥ CR	82.5% (80/97)	1% (3/302)	‖	■‖	■■■■		NR	NR	0.6% (1/248)	0% (0/108)
≥ CR RD	-	■‖	■■■■	■■	‖	■‖	NR	NR	NR	NR
Progression-free-Survival										
Number of events	37.1% (36/97)	78.8% (238/302)	‖	■‖	■■■■		NR	NR	NR	NR
Median KM estimates (95% CI)	NE (22.8, NE)	4.0 (3.6, 4.7)	■■■	■■■	■■■	■■■	4.47 (3.78, 5.03)	4.50 (2.40, 5.85)	4.3 (3.7, 5.6)	2.7 (2.4, 4.8)
HR (95%)	-	■‖	■‖	■■■	■‖■	■■■	**0.20 (0.14, 0.28)**	**0.18 (0.12, 0.27)**	**0.19 (0.12, 0.29)**	**0.15 (0.08, 0.29)**
Overall Survival										
Number of events	23.7% (23/97)	50.7% (153/302)	‖	■‖	■■■■		NR	NR	NR	NR
Median KM estimate (95% CI)	NE (27.24, NE)	12.7 (10.4, 15.5)	‖	■■■	‖	■‖	14.78 (12.29, 17.84)	13.24 (9.17, 21.29)	NE (12.12, NE)	11.33 (5.45, NE)
HR (95% CI)	-	■‖	■‖	■■	■‖	■■	**0.27 (0.17, 0.42)**	**0.24 (0.13, 0.43)**	**0.28 (0.16, 0.49)**	**0.20 (0.09, 0.41)**

Source: constructed during evaluation from Section 2

Cd = carfilzomib plus dexamethasone; cilta-cel = ciltacabtagene autoleucel; ≥ CR = complete response or better; CI = confidence interval; KM = Kaplan-Meier; IPTW = inverse probability treatment weighting; ITT = intention-to-treat HR = hazard ratio; MRD = minimal residual disease; mITT = modified intention-to-treat; Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; OR = odds ratio; ORR = overall response rate; sCR = stringent clinical response; RD = risk difference; CI = confidence interval; Bold = statistically significant at p-value<0.05

13. Economic evaluation

The ADAR presented a cost-utility analysis (CUA) of cilta-cel versus the nominated comparators Pd and Cd. Given that the different sources used to compile data for the comparator arms (some of which were patient registries) reflect the treatment choice that physicians would have made for a particular line in treatment, the Applicant referred to the comparator arm as 'physician's choice'. The presentation of a CUA was consistent with the superiority claim proposed in the ADAR. This was also consistent with the approach followed by other CAR-T therapies previously considered by MSAC (tisagenlecleucel 1519, 1519.1, axicabtagene ciloleucel 1587, and brexucabtagene autoleucel 1647). It should be noted that given some of the evidence presented in Section 2 was based on the comparisons of single arm studies, the CUA was subject to the same transitivity issues presented in Section 2. A summary of key components of the economic evaluation is presented in Table 9. All components of the economic evaluation were considered appropriate.

Table 9   Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Adult patients with RRMM, who had ≥3 prior lines of therapy or were double refractory to a PI and IMiD[a], and whose prior regimens included a PI, IMiD and an anti-CD38 therapy, with disease progression on or after the last regimen[a]
Comparator	Pd and Cd (labelled as Physician's choice in the economic model) in the base-case.
Type of analysis	Cost-utility analysis
Outcomes	QALYs and (LYs
Time horizon	Lifetime horizon (defined as 25 years) in base-case
Computational method	Hybrid model (Decision tree + Partitioned survival model)
Health states	Partitioned survival model has following health states: • Pre-progression • Post-progression • Death
Cycle length	1 week
Transition probabilities	Primary data source for cilta-cel: CARTITUDE-1 Data sources for the comparator arm: • CE-MRDR (main and modified cohorts) • Post daratumumab trials • FLATIRON • MM-003 (reflects Pd only)
Discount rate	5% for both costs and outcomes
Software	Excel 2016

Source: Table 3-1 of the ADAR.

IMiD= Immunomodulatory drug; LY= life year; PI= Proteasome inhibitor; RRMM= Relapsed or refractory multiple myeloma; PICO= Population, Intervention, Comparator and Outcome; QALY= quality adjusted life year.

[a] This corresponds the patient population as per CARTITUDE-1 protocol but is not consistent with the proposed restriction for MBS listing.

CARTITUDE-1 provided the key clinical evidence for the cilta-cel arm and the local registry (MRDR) in particular cohort 2, was included in the base case as the clinical evidence for the comparator arm. The MRDR-Cohort 2 (main cohort) was considered by the ADAR to most closely align to the CARTITUDE-1 patient population and had the requirement for prior anti-CD38 exposure. The main cohort population was a relatively small population group of 42 patients, of which 15 patients received either carfilzomib or pomalidomide (i.e. 8 and 7 patients, respectively).

The ADAR presented a range of incremental cost effectiveness ratios (ICER) based on most of the comparative evidence presented in Section 2 as the base case to show a relevant and appropriate plausible ICER range for cilta-cel. However, the evaluation considered that the different sources used actually represented sensitivity analyses, rather than alternative base cases as they are

indicating how sensitivity the ICER is to the assumed efficacy of the comparator. Given that the ADAR relied on the main cohort (Cohort 2) of the MRDR for the purpose of presenting their results, this was considered by the evaluation as the base case. Other comparative studies included:

- MRDR- Cohort 4 ('modified' cohort; excludes requirement for anti-CD38 exposure). By excluding this requirement, the sample size increased from 42 (main cohort) to 125 patients (modified cohort).
- FLATIRON and Physician's choice cohort (three daratumumab trials) through adjusted IPTW ITCs using a constant cumulative HR of physician's choice versus cilta-cel, and
- Pd (alone), whereby the PFS and OS transition estimates were based on the study-arm of Miguel 2013 (phase-3 RCT comparing Pd versus high-dose dexamethasone alone for patients with RRMM who had previously received a PI and IMID).

Economic model

The economic model in the ADAR was developed using a hybrid model approach which included a decision tree and a partitioned survival model (PSM) component (Figure 7). It should be noted that PSM analyses rely on within-trial relationships between non-mutually exclusive survival curves to determine health state membership. Thus, the use of different sources to derive the OS and PFS curves for cilta-cel and its comparators means that the relationship between the OS and PFS curved may be confounded by differences between the studies leading to uncertainties in the interpretation of the results.

Figure 7 Economic Model Structure (cilta-cel arm)
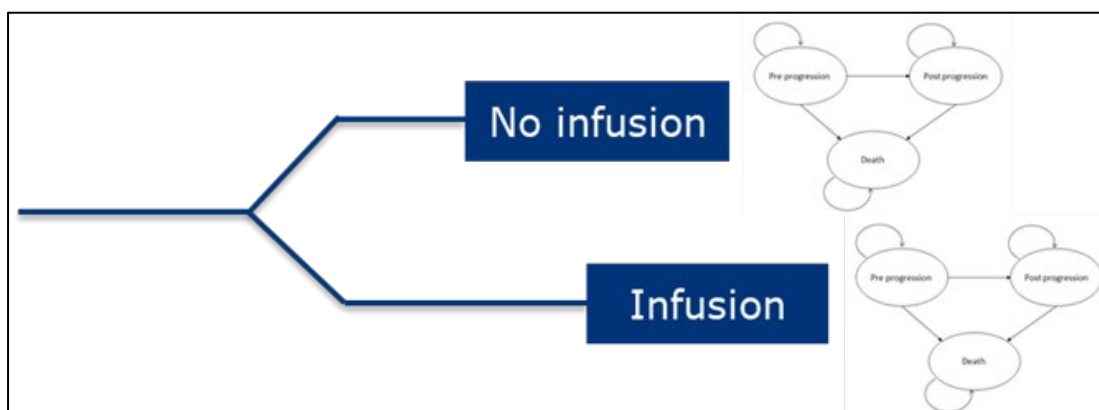
Source: Figure 3-1 of the ADAR.

The model structure was based on combining costs and outcomes in two cohorts: non-infused patients and infused patients. PFS and OS mITT data (KM and extrapolation) were used for the infused patients (data cutoff July 2021) for the entirety of the model. However, data from non-infused patients relied on the 6-month KM data (PFS and OS). Beyond this period, all non-infused patients were assumed to have died, hence, from this point onwards, PFS and OS reflected outcomes in infused patients only. Clinical outcomes for the non-infused group could not be source verified during the evaluation. Structural uncertainty could not be tested to assess the impact of utilising the ITT analysis (infused and non-infused patients) where all enrolled patients (N=113) entered the PSM and both infused and non-infused patients were followed up consistently.

Model inputs and assumption

The ADAR's base-case economic model considered a lifetime horizon defined as 25 years. The application of a lifetime horizon was consistent with other CAR-T therapies previously considered by MSAC. However, it should be noted that the clinical data presented for CARTITUDE-1 was immature and time to event for OS had not been reached in the mITT analysis. At a median follow-up of 21.7 months, 23 patients (23.7%) who had received cilta-cel had died and 74 patients

(76.3%) remained alive (p27, CARTITUDE-1 CSR July 2021 data cutoff) whilst 36 patients (37.1%) experienced progression and 61 patients (62.9%) were progression-free (p24, CARTITUDE-1 CSR July 2021 data cutoff). Shorter time horizons were tested in a sensitivity analysis.

The ADAR stated that cilta-cel is expected to be administered to most patients in the outpatient setting. After the infusion (day 1), 6 days of outpatient follow-up are expected. A small proportion of patients who will be at high risk of AEs are expected to be hospitalised for up to 2 weeks (14 days) after receiving an infusion of cilta-cel (the latter would apply to 20% of patients as informed by local clinical advice). The ADAR stated that this was communicated by local clinical experts as reflected of current experience in Australia with CAR-T therapies. For the base case analysis, the ADAR assumed that 80% of patients will receive cilta-cel infusion in an outpatient setting and remaining 20% in an inpatient setting.

The pre-MSAC response stated that the applicant consulted Australian clinical experts at a recent Advisory Board on whether patients would be managed in inpatient or outpatient setting following cilta-cel infusion. The clinical advisors noted that the protocol for managing patients following cilta-cel infusion has evolved over the clinical development program. For example, in the CARTITUDE-4 study (NCT04181827) which included Australian sites, admission was mandated following the infusion, however, patients could be discharged before 14 days. As experience has increased, clinicians have identified that achievement of good disease control following bridging therapy is crucial for determining whether a patient can be managed on an inpatient or outpatient basis. The applicant also acknowledged that there is a degree of variability in how Australian clinical experts considered how patients will be managed in clinical practice post cilta-cel infusion, with the proportion of patients managed in the inpatient stay potentially higher than 20%, but with a much shorter inpatient stay than that assumed within the economic and financial models. As such, the applicant considered that the overall economic impact and cost for the post infusion management of cilta-cel is likely to be similar to that estimated in the ADAR.

For costing purposes, the comparators were weighted as 50.0% Pd and 50.0% Cd. The submission justified the choice of the weighted assignment of Pd and Cd based on the MRDR registry data where Cd and Pd were used by 19.0% and 16.7% of patients, respectively (main Cohort). These percentages increased to 20.8% and 20.0% in the modified cohort for Cd and Pd, respectively. However, the 10% PBS sample demonstrated a slightly higher utilisation of Pd compared to Cd (42% versus 34%, respectively). A higher rate of Pd use may be justified based on the different route of administration between the regimens whereby Pd is an oral regimen and Cd required intravenous drug administration. The proportion of Pd versus Cd use was tested in a sensitivity analysis, but had a minor impact on the ICER.

Furthermore, the ADAR assumed the twice weekly dosing regimen of carfilzomib (i.e., 56 mg/m^2 twice weekly) as opposed to the once weekly regimen (70 mg/m2), which was recommended by the PBAC at the July 2020 PBAC Meeting and projected to result in a net cost saving for the PBS/RPBS (p9, carfilzomib PSD, July 2020 PBAC Meeting). The cost saving is likely to also be reflected in MBS costs as the frequency of intravenous administration would also be reduced from twice weekly to once weekly. Thus, the consideration of the twice-weekly carfilzomib regimen alone in the economic model is likely to overestimate the costs associated with Cd administration. The latter would have biased the results in favour of cilta-cel by resulting in greater cost-offsets for the comparator arm than would otherwise occur with once weekly dosing of Cd.

In calculating health utilities, the ADAR appropriately applied Australian tariffs to the EuroQol Group-5 Dimension 5 Level (EQ-5D-5L) data collected from the CARTITUDE-1 trial, whilst post progression survival health state utility was sourced from the literature (The National Institute for Health and Care Excellence, NICE, technology appraisals). However, the justification for the use of EQ-5D-5L at 1-year (based on availability of CARTITUDE-1 data) during the progression-free period to estimate the PFS (off treatment) utility value was not well supported. The reason for this is that the majority of patients in CARTITUDE-1 would have remained progression-free at 12 months (12-month PFS estimate was 79.4%). Thus, the utility value associated with PFS (off treatment) was

likely an overestimation, and likely favoured cilta-cel. In addition, in calculating AEs' disutilities, each disutility was multiplied by the respective AE rate (grade >3 with incidence of greater than 5%) and added to each treatment arm as one-time utility decrements at the beginning of the model. This was reasonable for cilta-cel therapy. However, a one-time utility decrement does not account for a particular patient experience with the same AE occurring more than once during several cycles of Cd or Pd administration.

The ADAR stated the KM estimates of PFS and OS from CARTITUDE-1 and MRDR main cohort (and other comparators) were used for the initial period of the analysis, followed by extrapolation using parameterised survival curves after the 20% at risk point on the KM curve. The KM cut off points applied to CARTITUDE-1 was at 107 weeks for OS and 104 weeks for PFS, at which point event free probability based on KM was 74.0% for survival and 60.5% for PFS. For one of the comparator arms, the MRDR main cohort, the cut-off points applied were at 70 weeks for OS and 24 weeks for PFS. At these cut offs the event free probability based on KM was 29.0% for OS and 24.6% for PFS.

Beyond the cut-off points, a parametric function was adjusted to extrapolate the results. The base case economic model used a lognormal distribution to extrapolate OS and PFS from CARTITUDE-1 and an exponential distribution for the extrapolation of OS and PFS for the comparators. In the context of immature data, an informed choice of the best parametric fit was limited given the extensive extrapolation to the 25-year time horizon (considering a median time to follow-up of 21.7 months in CARTITUDE-1 and was not reported in the MRDR registry). Furthermore, sensitivity analyses conducted by the ADAR and the evaluation which used the MRDR main cohort as the comparator arm, showed that the ICER was highly sensitive to the parametric function adopted, particularly with respect to the extrapolation of OS for cilta-cel (see Table 12).

Several issues were identified during the evaluation regarding health care resource use:

- The model base case accounted for one apheresis procedure. This was reasonable but may have underestimated the overall cost of apheresis due to the potential for multiple apheresis attempts per patient. In CARTITIUDE-1, from those who underwent apheresis (113 patients), three patients (2.7%) required 2 apheresis attempts and 1 patient (0.9%) required 3 attempts at apheresis (the remaining 109 patients required a single apheresis).

- It was assumed that patients would receive Pd and Cd in equal proportions as bridging therapy in Australia according to local clinical advice. Details of the local clinical advice were not provided in the ADAR, hence its applicability and representativeness could not be appraised. In CARTITUDE-1, the most common agents used as bridging therapy (≥ 20% of patients in the mITT) included: dexamethasone 63.9%, bortezomib 26.8%, cyclophosphamide 22.7% and pomalidomide 21.6%. As these agents are also available on the PBS for this indication, the rationale as to why the choice of therapy would be different in Australia was unclear.

- The drug cost considerations for tocilizumab may not be appropriate given that:
  - Tocilizumab is not PBS listed for the management of CAR-T associated CRS. The PBS item codes applied was for the clinical indication of severe active juvenile idiopathic arthritis and thus not reflective for the use within the ADAR.
  - The economic model derived the proportion of patients receiving treatment in the public and private setting based on Medicare statistics. However, it appears implausible that whilst the ADAR stated that cilta-cel will be administered in the public setting only and assumed that 100% of bridging and conditioning therapy would occur in the public setting, that the treatment of CAR-T associated CRS would occur in both the public and private setting. It may have been more appropriate to assume that tocilizumab administration would occur 100% in the public setting.

- In July 2021 Roche (Sponsor of tocilizumab) notified the TGA of shortages of multiple presentations of tocilizumab due to global demand in response to the COVID-19 pandemic. Thus, whilst the submission applied an AEMP for tocilizumab of $405.39, Section 19A supply of tocilizumab (i.e. supplying substitute medicines when registered medicines are unavailable or in short supply) has an AEMP of $2,259.08 (PBS item 12694D). Noting that the current supply issue may be transitory and potentially resolved by the time cilta-cel becomes available (if supported by MSAC), there is potential that the cost of tocilizumab may still be high should the shortage be expected to last longer than anticipated.

- eviQ guidelines recommend the consideration of transfer to ICU for patients with grade 2 CRS, and ICU admission for grade > 3. However, in the submission ICU costs were applied to patients with grade > 3 CRS, potentially underestimating costs associated with CRS management. Assuming that all Grade 2 CRS events required ICU was tested in a sensitivity analysis during the evaluation with a minor impact on the results. According to the Ratified PICO, MSAC stated that the rate of ICU support was not wholly covered in the intervention (p19, Ratified PICO confirmation).

- The cost of neurotoxicity was not considered as it was assumed that the cost of managing CRS captured the cost of neurotoxicity. This may not be reasonable as CRS and neurotoxicity may be treated separately owing to its distinct timing and response to intervention. The justification may be reasonable if neurotoxicity occurred concurrent to CRS, however if it occurs separate to CRS, this is likely an underestimation of neurotoxicity management. According to eviQ, management of neurotoxicity with no concurrent CRS may include (depending on grade) ICU admission, high dose corticosteroid, periodic neuroimaging, and treatment of convulsive status epilepticus. The pre-ESC and pre-MSAC response investigated the impact of including the cost of neurotoxicity AEs in sensitivity analyses (see pre-MSAC response results in Table 15).

- The ADAR did not consider costs associated with IVIG based on the rationale that most patients treated in the fourth line setting would already be on IVIG, either due to disease or because of prior treatment (p9 Ratified PICO confirmation). MSAG considered that the rate of IVIG use and anti-infective prophylaxis was not wholly covered in the intervention (p19, Ratified PICO confirmation). This is also consistent with the evidence presented by the evaluation in Section 1 that suggests a profound and lasting humoral immune deficiency after CAR-T therapy that may require the use of IVIG. The pre-ESC and pre-MSAC response investigated the impact of including the cost of IVIG therapy costs in sensitivity analyses (see pre-MSAC response results in Table 15).

The unit cost of cilta-cel proposed by the ADAR was $██.███.
The cost under the Risk Sharing Agreement are presented in Table 10.

Table 10 Cilta-cel cost at each payment timepoint under Risk Sharing Agreement

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

Source: Table 3-29 of the ADAR.
Abbreviations: RSA, Risk sharing agreement; sCR, Stringent complete response

The results of the stepped economic evaluation are summarised in Table 11. Given that the ADAR has suggested the use of different sources to build the comparator arm, it also suggested that instead of a single ICER, a range was presented to reflect the base case. The ADAR stated that the base case corresponded to Step 4, where the outcome was measured in QALYs and the time

horizon was set to lifetime, with an ICERs ranging from \$███ to \$███ per additional QALY. The ADAR nominated the MRDR Cohort 2 as the main cohort for the comparative data (forming the basis for Steps 1, 2 and 3 in the table below (as well as the sensitivity analyses) and thus this can be interpreted as the base case result.

Table 11 Results of the stepped economic analysis

Steps	Costs			Health Outcomes			ICER
	Cilta-cel	Comparator	Incremental Costs	Cilta-cel	Comparator	Incremental Health Outcomes	
Step 1: Incremental cost/PFLY gained, over 2 years' time horizon							
Step 1	\$██	\$█	\$█	PFLYs: 1.43	PFLYs: 0.48	PFLYs: 0.95	\$█ [\$/PFLY gained]
Step 2: Incremental cost/LY gained, over 2 years' time horizon							
Step 2	\$██	\$█	\$█	LYs: 1.59	LYs: 0.90	LYs: 0.69	\$█ [\$/LY gained]
Step 3: Incremental cost/LY gained, over a lifetime horizon of 25 years							
Step 3	\$██	\$█	\$█	LYs: 5.45	LYs: 1.02	LYs: 4.43	\$█ [\$/LY gained]
Step 4 (Base-case): Incremental cost/QALY gained, over a lifetime horizon of 25 years							
Step 4(i): Comparator data source: MRDR (Cohort 2)	\$██	\$█	\$█	**QALYs: 4.00**	**QALYs: 0.66**	**QALYs: 3.34**	\$█ [\$/QALY gained]
Step 4(ii): Comparator data source: MRDR (Cohort 4)	\$██	\$█	\$█	QALYs: 4.00	QALYs: 0.80	QALYs: 3.20	\$█ [\$/QALY gained]
Step 4(iii): Comparator data source: Flatiron Health	\$██	\$█	\$█	QALYs: 4.00	QALYs: 1.09	QALYs: 2.92	\$█ [\$/QALY gained]
Step 4(iv): Comparator data source: Post daratumumab trials	\$██	\$█	\$█	QALYs: 4.00	QALYs: 0.90	QALYs: 3.10	\$█ [\$/QALY gained]
Step 4(v): Alternate comparator: Pd alone; Data source: MM-003 trial	\$██	\$█	\$█	QALYs: 4.00	QALYs: 0.90	QALYs: 3.10	\$█ [\$/QALY gained]

Source: Table 3-50 of the ADAR.

Abbreviations: ICER, incremental cost effectiveness ratio; OS, Overall survival; LY, Life-year; Pd, pomalidomide + dexamethasone; PFLY, progression-free life-year; QALY, Quality-adjusted life year

Note: Includes pre-infusion cost (cost of apheresis, bridging therapy, and conditioning therapy), cilta-cel acquisition cost, and cilta-cel infusion cost

A summary of the key drivers of the model is presented in Table 12. As expected, all key drivers relate to the uncertainty of the available data and its substantial extrapolation. The evaluation considered that, in the context of immature OS data and anticipated superior clinical outcomes compared to current anti-myeloma therapies in the later stage of MM, in principle, use of the Weibull distribution may have been more reasonable. The Weibull better reflects the fact that these patients have advanced disease and are likely to progress overtime. In contrast, the exponential, as applied in the ADAR, assumes event rates remain constant over time. Different time horizons

were tested in the ADAR to account for the uncertainty around the extrapolation of the data, ranging from 10 years up to 40 years. When brexucabtagene autoleucel was considered by MSAC, the impact of a 10-year time horizon was tested as a way to assess the effect on the ICER of a shorter time horizon (point 14, p30 of the brexucabtagene autoleucel PSD, July 2021).

Table 12 Key drivers of the model

Description	Method/Value	Impact Base case: $▇ gained [a]
Extrapolation	Parametric models for extrapolation were selected based on AIC and BIC, in addition to assessment of plausibility in comparison to LEGEND-2.	High, favoured cilta-cel. Application of exponential (least conservative but best goodness of fit statistics as per AIC/BIC) and Weibull distribution for cilta-cel OS increased the ICER to $▇ and $▇, respectively.
Time Horizon	25 years	Moderate, favoured cilta-cel. A time horizon of 10 and 20 years increased the ICER to $▇ and $▇ respectively.

Source: compiled during the evaluation using Section 3 worksheet
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian information criterion; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; TTD = time to discontinuation
Note: [a] based on MRDR Cohort 2 as comparator
[b] Refers to all comparators except FLATIRON and daratumumab trials: for MRDR Cohort 2 (70 weeks at which point event free probability based on KM was 29.0%); for MRDR Cohort 4 or modified cohort (80 weeks at which point event free probability based on KM was ≈26.0%); for Pd based on MM-003 (57 weeks at which point event free probability based on KM was ≈ 55%).

The results of the key sensitivity analyses from the ADAR and those prepared by the commentary are summarised in Table 13. The change in the ICER was estimated based on the ADAR's results assuming the comparator was modelled using the MRDR main cohort data.

Table 13 Sensitivity analyses

Analysis	Incremental cost	Incremental QALY	Incremental cost per QALY	Change in ICER
Results as per the ADAR using MRDR cohort 2 as comparator data source)	$▇	3.34	$▇	N/A
Time horizon (base case 25 years)				
10 years	$▇	2.41	$▇	38%
Additional analyses conducted during the evaluation				
Parametric Function for OS and PFS (base case cilta-cel lognormal and MRDR cohort 2 exponential distribution)				
Cilta-cel exponential distribution for both OS (best fit AIC/BIC) and PFS (best fit BIC) [a]	$▇	2.63	$▇	27.8%
Cilta-cel Exponential distribution for OS only	$▇	2.78	$▇	19%
Cilta-cel Exponential distribution for PFS only	$▇	3.17	$▇	7%
Cilta-cel Weibull distribution for both OS and PFS [a]	$▇	2.11	$▇	57.8%
Cilta-cel Weibull distribution for OS only	$▇	2.20	$▇	49.7%
Cilta-cel Weibull distribution for PFS only	$▇	3.14	$▇	8.0%
MRDR (cohort 2) lognormal distribution for OS (best fit BIC) and loglogistic distribution for PFS (best fit AIC/BIC) [a]	$▇	3.14	$▇	-5.5%
MRDR (cohort 2) lognormal distribution for OS only	$▇	3.18	$▇	5%
MRDR (cohort 2) loglogistic distribution for PFS	$▇	3.32	$▇	-7%
MRDR (cohort 2) generalized gamma distribution for OS (best fit AIC) and loglogistic distribution for PFS (best fit AIC/BIC)	$▇	2.70	$▇	9.2%

Source: Table 3-56 of the ADAR and developed during the evaluation
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan Meier; MRDR, Myeloma and Related Diseases Registry; N/A, not applicable; OS, overall survival; PFS, progression-free survival
Note: [a] these were multi-variate sensitivity analyses as the parametric distribution for both OS and PFS of the respective arms were tested.

The pre-ESC response presented a sensitivity analysis including IVIG related costs (Table 14), which were not evaluated. This was based on use of IVIG therapy in CARTITUDE-1 and assumption that that patients who received IVIG therapy as prophylaxis will receive therapy for 12 months whereas patients who received IVIG therapy in response to adverse events will be on therapy for 6 months and is supported by AustralianGuidelines(https://www.blood.gov.au/pubs/ivig/conditions-for-which-IVIg-has-an-established-therapeutic-role.html).

Table 14 Results of sensitivity analysis- Pre-ESC response

Sensitivity Analysis	Incremental Costs	Incremental QALY	ICER	% Change from base case
Base Case	$█	3.34	$█	NA
Include IVIG therapy costs (12 and 6 months for prophylaxis and adverse events, respectively) No. of IVIG treatment cycles: 10.37	$█	3.34	$█	2.9%
Include the cost of neurotoxicity adverse event • Incidence: 5.2% (=5/97) • Cost: $28, 900.96 (assumed equal to cost of CRS event)	$█	3.34	$█	0.4%

The pre-MSAC response presented additional multivariate sensitivity analyses to address ESC's concerns about model costings (Table 15), which were not evaluated.

Table 15 Applicant pre-MSAC response multivariate sensitivity analyses results (Table 2A and B)

Table 2A: Impact of cost modifications on ICER				
Base Setting/Model Settings	**Inc Cost**	**Inc QALY**	**ICER**	**%Change**
• **MRDR (cohort 2)**	$█	3.34	$█	NA
• **MRDR (cohort 4)**	$█	3.20	$█	NA
• **Flatiron health**	$█	2.92	$█	NA
• **Post daratumumab trials**	$█	3.10	$█	NA

AE COST MODIFICATIONS
 • Tocilizumab hospital distribution
   o Public- 100% (base case: 56.1%)
   o Private – 0% (base case: 43.9%)
 • Apply ICU admission cost to 100% of grade 2 CRS patients (base case: 0%)
 • Include IVIG therapy costs (12 and 6 months for prophylaxis and AEs, respectively)
   o No. of IVIG treatment cycles: 10.37
 • Include the cost of neurotoxicity AE
   o Incidence: 5.2% (=5/97)
   o Cost: $28, 900.96 (assumed equal to CRS cost)
	MRDR (cohort 2)			

	$█	3.34	$█	6.0%
	MRDR (cohort 4)			
	$█	3.20	$█	6.5%
	Flatiron health			
	$█	2.92	$█	7.0%
	Post daratumumab trials			
	$█	3.10	$█	7.6%
NON-AE COST MODIFICATIONS • 45% and 55% of patients using twice and once weekly Cd, respectively (base case: 100% using twice weekly dosing) • Proportion of patients receiving cilta-cel infusion in an inpatient setting: 100% (base case: outpatient 80%, inpatient 20%)	MRDR (cohort 2)			
	$█	3.34	$█	3.9%
	MRDR (cohort 4)			
	$█	3.20	$█	5.3%
	Flatiron health			
	$█	2.92	$█	6.8%
	Post daratumumab trials			
	$█	3.10	$█	8.6%
ALL COST MODIFICATIONS • All the above amendments	MRDR (cohort 2)			
	$█	3.34	$█	9.9%
	MRDR (cohort 4)			
	$█	3.20	$█	11.7%

	Flatiron health		
$■	2.92	$■	13.8%
	Post daratumumab trials		
$■	3.10	$■	16.2%

Table 2B: Impact of all cost modifications on costs of providing cilta-cel & AE management (excl. acquisition cost)			
Model Settings (all modifications applied)	**Base case**	**Scenario**	**Change**	**%Change**

• Tocilizumab hospital distribution
  ○ Public- 100% (base case: 56.1%)
  ○ Private – 0% (base case: 43.9%)
• Apply ICU admission cost to 100% of grade 2 CRS patients (base case: 0%)
• Include IVIG therapy costs (12 and 6 months for prophylaxis and AEs, respectively)
  ○ No. of IVIG treatment cycles: 10.37
• Include the cost of neurotoxicity AE
  ○ Incidence: 5.2% (=5/97)
  ○ Cost: $28, 900.96 (assumed equal to CRS cost)
• 45% and 55% of patients using twice and once weekly Cd, respectively (base case: 100% using twice weekly dosing)
• Proportion of patients receiving cilta-cel infusion in an inpatient setting: 100% (base case: outpatient 80%, inpatient 20%)
	Total cilta-cel cost (excl. acquisition cost)		

	$■	$■	$■	**64.6%**
	Apheresis cost		
	$■	$■	$■	0.0%
	Bridging therapy cost		
	$■	$■	$■	-13.2%
	Conditioning therapy cost		
	$■	$■	$■	0.0%
	IVIG therapy cost*		
	$■	$■	$■	NA
	Cilta-cel infusion cost		
	$■	$■	$■	262.9%
	Post- CART monitoring cost		
	$■	$■	$■	0.0%
	Adverse event management cost		
	$■	$■	$■	139.7%

Source: Table 2A and B, p7 of pre-MSAC response

14. Financial/budgetary impacts

The financial implications of listing cilta-cel to the state and commonwealth health budgets are summarised in Table 16. Consistent with the economics, the ADAR assumed 80% of infusions can be given and monitored in the outpatient setting for 7 days, based on the advice of local clinicians with expertise and experience in treating MM.

Table 16 Net financial implications of publicly funding cilta-cel to the state and commonwealth health budgets

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total eligible patients						
Total suitable patients						
Patients that underwent patient's apheresis						
Successfully infused patients						
Estimated use and cost of the proposed health technology						
Patients that underwent patient's apheresis						
Successfully infused patients						
Patients with sCR at 12-months post-treatment						
Cost for patients successfully infused	$	$	$	$	$	$
Cost for patients with sCR at 12-months post-treatment	$	$	$	$	$	$
Cost for cilta-cel	$	$	$	$	$	$
Change in use and cost of other health technologies						
Cost to PBS	$	$	$	$	$	$
Offsets to PBS	$	$	$	$	$	$
Net cost to PBS	$	$	$	$	$	$
Cost to MBS	$	$	$	$	$	$
Offsets to MBS	$	$	$	$	$	$
Net cost to MBS	$	$	$	$	$	$
Cost to hospitals	$	$	$	$	$	$
Offsets to hospitals	$	$	$	$	$	$
AE treatment in hospitals	$	$	$	$	$	$
Net cost to hospitals	$	$	$	$	$	$
Net financial impact to Health Budgets	$	$	$	$	$	$

Source: Table 4-22, Section 4 of the ADAR

The ADAR estimated that the total cost of publicly funding cilta-cel was $███ ███ over the 6-year period. The total cost of cilta-cel (product costs) was $███ ███ (over the 6-year period). The overall net cost to the health budgets over 6 years of was $███ to the PBS, $███ to the MBS and $███ to hospitals. Overall, the evaluation considered that the financial estimates likely overestimated mainly due to an overestimation of the number of eligible patients and optimistic assumptions around uptake. The following arguments were proposed for the overestimation of the financial estimates:

- The ADAR estimated alive and progression-free patients potentially eligible for cilta-cel from the OS and PFS curves from different sources using an exponential model derived from median time to corresponding event. By assuming an exponential model, the event rate (progression and death) occurs at a constant rate, meaning that the transition probability is also constant. This may not reflect the way RRMM patients progress and die in their disease

- The patient numbers from Janssen's daratumumab monotherapy compassionate access program informed the sixth line eligible pool of patients in the financial model. However, it

was uncertain what proportion of patients receiving daratumumab monotherapy would be suitable candidates for treatment with cilta-cel.

- The proportion of patients suitable for treatment with cilta-cel in fourth-line settings was likely overestimated (▮% in Year 1 increasing to ▮% by Year 4), as only ▮% of patients in FLATIRON, a registry database (which is more representative of real-world patients), met CARTITUDE-1's eligibility criteria for use of cilta-cel as a subsequent therapy in a fourth line setting (Table 56). The suitability and uptake rate was higher at 70% in the physician's choice cohort of clinical trials (▮%). It was unknown what proportion of patients would be eligible for subsequent therapy with cilta-cel in fifth and/or sixth line; however, it is likely this will be less than what the ADAR proposed (▮% of fifth line patients and ▮% of sixth line patients).

- The ADAR assumed uptake would be ▮% in Year 1, increasing to ▮% by Year 5 in fourth-line settings, ▮% in Year 1, and decreasing to ▮% by Year 6 in fifth-line settings, and decreasing to ▮% in Year 5 in sixth line settings. However, new triple therapies for RRMM patients are currently under consideration by the PBAC which may push cilta-cel to a later line setting. The latter is consistent with the restriction from the FDA that limited the use of cilta-cel to fifth-line therapy.

The pre-MSAC response presented revised financial estimates, which were not evaluated. The applicant acknowledges the ESC's concern that the number of eligible patients are overestimated, given US FLATIRON registry data shows a lower eligibility rate (46%). As such, the applicant reduced the uptake rates at fourth-line by approximately ▮% (absolute reduction) each year (Table 17).

Table 17: Revised financial estimates based on reduced suitability for 4L MM

	Year 1	Year 2	Year 3	Year 4	Year 5	Years 1-5
Suitability rate at 4L MM (ADAR)	▮%	▮%	▮%	▮%	▮%	
Suitability rate at 4L MM (pre-MSAC)	▮%	▮%	▮%	▮%	▮%	
Change (relative reduction)	▮%	▮%	▮%	▮%	▮%	
Number of patients infused (ADAR)						
Number of patients infused (pre-MSAC)						
Change (relative reduction)	▮%	▮%	▮%	▮%	▮%	▮%
Cost to the NHRA (ADAR)	$▮	$▮	$▮	$▮	$▮	$▮
Cost to NHRA (pre-MSAC)	$▮	$▮	$▮	$▮	$▮	$▮
Change (relative reduction)	▮%	▮%	▮%	▮%	▮%	▮%

Source: Table 1, p6 of the pre-MSAC response

15. Other relevant information

Nil

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

Reliance on naive comparisons of single-arm studies – Effectiveness is likely lower in the real world than presented in the ADAR. The evidence base was from a single case series including patients who were younger and more robust than the expected treatment population. The comparative efficacy is likely to be overestimated as the comparator studies contained a wide spectrum of patients who were older and less healthy. This may bias the effect in favour of cilta-cel. Thus, there is uncertainty in the magnitude of the efficacy benefit which has implications for the ICER (which is likely to be optimistic).

Place in clinical management algorithm may change – With approval of new treatments and combinations for multiple myeloma, Cilta-cel may be pushed beyond fourth-line therapy as of 2022. Moving to a later line of therapy may result in reduced efficacy with the same costs and toxicities, which leads to uncertain value for money. Due to strong consumer advocacy and perception of benefit, there is likely to be demand for cilta-cel earlier in the disease course, however efficacy and cost-effectiveness as an earlier line of therapy have not been examined.

Safety profile appears worse than other fourth-line therapies – High rates of cytokine release syndrome, neurotoxicity and repeat admissions are not adequately costed for in the application. Further analyses should include the costs of these adverse events. The cost of long term IVIG was also not included in the ADAR.

Economic issues:

Extrapolation leads to significant uncertainty – Extrapolated estimates of survival were out to 25 years which is not clinically feasible and appear to be optimistic. The ICER may be substantially higher than estimated.

Multivariate sensitivity analyses should be considered to explore the combined impact of the univariate sensitivity analyses.

Financial issues:

There is an overestimation of the number of eligible patients and optimistic assumptions in terms of patient suitability and uptake.

The proposed cost of cilta-cel is high and costs of procedures are underestimated.

Other relevant information:

Strong opposition to the application from the States – Feedback from NSW and Qld outlined legitimate concerns regarding high product cost, costing data are underestimated, uncertain value for money based on case series data only, lack of infrastructure to deliver these therapies, particularly in light of larger populations than previous CAR-T cell therapies, issues with data reporting and access to the mandatory registries.

Cost-effectiveness of other CAR-T therapies may be less than predicted – A review of previously approved CAR-T therapies in Australia is needed to assist risk mitigation, and data is collected but may not be available until 2023. States and Territories are collecting data which indicate higher mortality than the single study evidence base and would be informative.

Leakage to a broader group of patients is likely – Previous CAR-T therapies have more restricted access through tighter eligibility criteria. States have suggested a cap on the number of patients.

Use of tocilizumab to treat cytokine release syndrome is not PBS-listed for this indication but is used universally for treatment with proposals to use prophylactically in the future.

ESC discussion

ESC noted that the purpose of this application is to seek public funding for ciltacabtagene autoleucel (cilta-cel) to treat refractory or relapsed multiple myeloma (RRMM) in adults under the National Health Reform Agreement (NHRA) as a High Cost Highly Specialised Therapy (HST). ESC noted that, under the NHRA, state health authorities are required to pay 50% of the costs for HSTs. Cilta-cel is proposed as a fourth line of therapy, after a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody. Cilta-cel has not yet been registered with the Therapeutic Goods Administration.

ESC noted that, similar to other chimeric antigen receptor T cell (CAR-T) therapies, cilta-cel involves extracting the patient's blood through apheresis and exporting the apheresis product overseas (in this case to the United States), where the T cells are genetically modified to bear a CAR that targets B-cell maturation antigen (found on multiple myeloma cells). The patient is preconditioned with chemotherapy before one-off infusion of the modified cells. Also similar to other CAR-T therapies, ESC noted that the cilta-cel procedure has a high cost ($⬛⬛) and a risk of serious adverse events such as cytokine release syndrome and immune-mediated neurotoxicity.

ESC noted that MSAC has previously approved three other CAR-T therapies since 2019 for lymphoma and/or leukaemia: applications 1519 (Kymriah), 1587 (Yescarta) and 1647 (Tecartus). This application differs in terms of higher cost and larger expected population. ESC noted the requirements set by MSAC before funding could be approved for prior applications included that patients must meet strict eligibility criteria (clinical and laboratory parameters) and that payment is made only after successful infusion, that data are recorded in the Australian Bone Marrow Transplant Recipient Registry, and that MSAC would conduct a full review of clinical effectiveness, cost-effectiveness and budget impact after 2–3 years. These reviews are yet to be undertaken.

ESC noted the large amount of consultation feedback from more than 300 members of the public and several organisations. All submissions were supportive of the application. Common issues raised in submissions included reducing the burden of care, as well as concerns about equitable patient access. Importantly, many submissions considered that patient access to this therapy should not be restrictive, and it should not be used as a last resort simply because it is new and expensive. ESC also noted that CAR-T therapy is strongly promoted by organisations such as Myeloma Australia.

ESC noted the clinical management algorithm. ESC considered the appropriateness of limiting cilta-cel funding to patients who have failed daratumumab (anti-CD38) therapy. Currently, PBS funding requirements are that daratumumab is used as second-line treatment with bortezomib. However, some patients cannot tolerate bortezomib due to neuropathy. In addition, given this was only recently funded, some patients have missed out on this as a second line of therapy, but have had three or more lines of therapy and have refractory disease, so would otherwise be eligible for cilta-cel. The applicant developed assessment report (ADAR) stated that the sponsor will continue to provide daratumumab under compassionate access. ESC noted consultation feedback that limiting cilta-cel to those who had previously had anti-CD38 therapy would unfairly restrict patient access.

ESC also noted the recent PBAC recommendations for new triple therapies for patients with RRMM, which may mean that cilta-cel would move further down the line of therapies. This has occurred in the United States, where the Food and Drug Administration approved cilta-cel as a fifth line of therapy, not fourth line. ESC considered that this may mean that patients are less well when they

receive cilta-cel therapy (as their disease has progressed), which may mean reduced effectiveness of cilta-cel therapy for the same cost and toxicities, representing less value for money[2].

ESC noted the evidence for cilta-cel in the application, which included one Phase 1b/2 single-arm study (CARTITUDE-1) with a median follow-up of just less than two years. The intention-to-treat (ITT) population comprised 113 patients, of which 97 underwent the infusion (modified ITT [mITT]) providing the basis for most of the comparisons. ESC noted that the eligibility criteria included patients with RRMM who had undergone ≥ 3 lines of therapy (median= 6, range= 3, 18). These three prior lines of therapy included a PI, an IMiD (thalidomide or analogue) and an anti-CD38 antibody. ESC noted that industry had funded the study and prepared the manuscript for publication. ESC also noted the high risk of bias inherent in the single-arm study.

ESC considered that patients in CARTITUDE-1 were relatively robust and therefore able to tolerate intensive treatment. This was the result of their relatively young age (median 61 years) and high (90%) prior use of autologous stem cell transplant (ASCT), and other eligibility criteria. As a consequence, ESC considered that these findings may not be applicable to the broader eligible Australian RRMM population.

ESC noted the ADARs comparative clinical evidence from:

- A naive (unanchored) indirect comparison that compared cilta-cel (CARTITUDE-1) with: the pomalidomide arm of the MM-003 trial; and the Myeloma and Related Diseases Registry, a myeloma registry from Australia and New Zealand.
- An indirect treatment comparison using inverse probability treatment weighting (IPTW) that compared cilta-cel (CARTITUDE-1) with: the Physician's Choice cohort (follow-up data from three trials of daratumumab (POLLUX, CASTOR and EQUULEUS), the LocomMotion study (myeloma cohort) and FLATIRON (a US-based registry).

ESC noted that the IPTW method was used to create a group of patients more similar to those in CARTITUDE-1, by weighting for prognostic factors such as age and disease burden. ESC considered the MM-003 study from 2012 was slightly outdated and may not be reflective of contemporary practice.

ESC considered that the patients in the comparator studies were less healthy than the cilta-cel study which may bias the effect in favour of cilta-cel. ESC noted that some of the comparator studies held almost double the rate of Stage III disease (31% vs 14%), had worse Eastern Cooperative Oncology Group (ECOG) Performance Status scores and were older (median age 65 vs. 61 years). The pre-ESC response stated that that there are additional patient characteristics which potentially bias the indirect comparisons against cilta-cel and in favour of the comparator; for example, patients in CARTITUDE-1 were more heavily pre-treated (median of 6) compared to MM-003 (median of 5) and the MRDR (median of 3-4), which biases the comparison against cilta-cel[3]. However, ESC considered that the potential impact of this bias is likely negated by their younger age, better ECOG status and relative lack of co-morbidities, as these factors would increase a participant's ability to withstand the rigors of treatment.

ESC noted the results of the clinical comparisons, which showed significant differences in all survival outcomes and across all comparisons, favouring cilta-cel. ESC recalled that MSAC

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[2] In the pre MSAC response, the applicant contended that the results of CARTITUDE-1 do not support this statement. Refer to Section 3 of the PSD for MSAC's consideration.

[3] In the pre MSAC response, the applicant contended that the number of prior therapies, and refractoriness of a person's MM to existing therapies (e.g. PIs, IMiDs, anti-CD38 monoclonal antibodies), is a stronger indicator of poor prognosis in MM (and response to next therapy) compared with age, ECOG status and co-morbidities. Refer to Section 3 of the PSD for MSAC's consideration.

previously preferred the ITT approach. ESC noted the point estimate for hazard ratios for progression-free survival (PFS) and overall survival (OS) were similar (0.18 and 0.23, respectively). Median progression-free survival could not be calculated due to the relatively short follow-up of the CARTITUDE-1 study, and median overall survival was not reached in the follow-up duration. Overall, ESC considered that effectiveness is likely lower in the real world than presented in the ADAR due to the reliance on naive comparisons of single-arm studies.

For comparative safety, ESC considered that cilta-cel is likely to be inferior ESC noted there was a high incidence of cytokine release syndrome (CRS) in the study (95%), which is usually treated with steroids and tocilizumab (IL-6 blocker). In CARTITUDE-1, 70% of patients received tocilizumab whilst 20% received Anakinra. ESC noted that toculizumab is not PBS-listed for this indication. ESC also noted as tocilizumab is used to manage COVID-19, there is currently a worldwide shortage of this drug. ESC noted that patients experiencing CRS of Grade 2 or higher are recommended for ICU support; however, the ADAR only included costs for Grade 3 patients and above (5%). Comparative safety was difficult to assess as the patients from registry and trial data had a variety of drugs with variable side effect profiles.

ESC noted that neurotoxicity (Immune effector cell-associated neurotoxicity syndrome [ICANS] occurred in around 21% of patients in CARTITUDE-1 and required intensive care unit (ICU) treatment, steroids and anticonvulsants. ESC noted that the cost of managing ICANS was not included in the ADAR as it was assumed this would occur in tandem with CRS. However, ESC did not consider this was always the case. ESC noted that 'other' neurotoxicities occurred in 12% of patients, of which 50% lasted for a median duration of 74 days. For the other half (50%), symptoms never resolved and consequently most of those patients died. ESC noted the consultation comment from a specialist haematologist that 'other' neurotoxicities could be reduced in the future with improved bridging chemotherapy, however there were no data to support this currently. The ADAR also excluded adverse events such as cytopaenias in subjects who had apheresis and pre-conditioning chemotherapy but did not proceed to infusion. ESC considered the toxicity of the conditioning treatments would not have been captured. Treatment related adverse events that result in death was around 9% from the CARTITUDE-1 study compared with about 3-7% in the other registry studies. ESC considered rates of some adverse events (such as cytopenias) would not be well captured in registry studies that informed the comparator.

ESC noted the economic evaluation, which was a cost-utility analysis, and considered this to be appropriate. ESC noted that the health states in the economic model (pre-progression, progression and death) relied on within-trial relationships with overall survival and progression-free survival curves, which are not mutually exclusive. This results in potential for confounding.

ESC noted the proposed risk-sharing arrangement, ███████████████████████████████ ███. ESC noted that the cost of cilta-cel is linked to ████████, but it was not clear whether any adjustment had been made in the economic model (for both costs and health outcomes) to account for any differences between the Australian population and the participants in the CARTITUDE-1 study.

ESC noted that the economic model extrapolated quality-adjusted life years (QALYs) over a lifetime time horizon (25 years). Although this is consistent with previous CAR-T applications, ESC considered that this extrapolation was highly uncertain, as the CARTITUDE-1 study had a median follow-up of 22 months (and a log normal distribution was applied beyond that time point). The commentary was unable to verify the extrapolation sources for the non-infused group. The pre-ESC response included additional data to 26 months, but this had little effect on these uncertainties. ESC noted that the ICER is highly sensitive to the type of distribution applied to fit the data, and this is a key uncertainty in the economic evaluation. ESC also noted the submission from

Queensland Health, which commented that the extrapolation was optimistic as the rate of decline in overall survival beyond 10 years was less than the proportion of patients with progressed disease. Overall, ESC considered that the ICERs in the ADAR were high and likely to be underestimated.

ESC considered that the high rates of CRS, neurotoxicity and repeat admissions and long term IVIG are not adequately accounted for in the ADAR. Further analyses should include the costs of these adverse events. ESC also noted that there was uncertainty regarding the public/private split for managing CAR-T associated CRS with tocilizumab. ESC noted the pre-ESC response, which included sensitivity analyses to include costs for IVIg use and neurotoxicity adverse events. These increased the ICER by 0.4–2.9% (see Table 15).

ESC suggested that multivariate sensitivity analyses should be conducted to explore the combined impact of the univariate sensitivity analyses.

ESC noted that the number of eligible patients may be overestimated based on patient suitability and uptake. Data from the FLATIRON registry in the US indicates that 46% of patients would be eligible for cilta-cel, but the ADAR proposes ███–███% of patients over 5 years.

ESC noted that the economic results using the confidential pricing for Pd and Cd (that were lower than the published price), increased the ICER from around █ to █%. For the financial estimates this led to a reduction in PBS cost offsets (e.g. net cost to PBS ████████████████).

ESC considered that leakage to a broader group of patients is likely. Previous CAR-T therapies have more restricted access through tighter eligibility criteria.

Previous applications for CAR-T therapies have not been supported by state governments (i.e. jurisdictions) due to high costs, uncertain value for money and lack of infrastructure. ESC noted that submissions from New South Wales and Queensland for this application expressed a strong opposition to funding under the NHRA. These submissions highlighted that cilta-cel differs from other CAR-T therapies in its indication and has a substantially larger potential population size, and it was unclear whether existing health services could deliver the intense in-hospital support required. States suggested a cap on the number of patients. Queensland Health reported that estimates of treatment effectiveness are overly optimistic – 12-month mortality following CAR-T therapy in Queensland is around 33%, compared to the 10% assumed in the model. Queensland Health also estimated the actual price of delivering the therapy to be around $75,000 per patient (rather than $████ in the applicant-developed assessment report [ADAR]), as every patient is admitted for 14 days, rather than 20% of patients as stated in the ADAR. It was also noted that other costs (such as for specialised staff, use of intravenous immunoglobulin [IVIg] and anti-infective prophylaxis) are not adequately included in the application. States also reasoned that the evidence base is weak, costs are underestimated, and there is a lack of consultation with states regarding costs. New South Wales Health also reported numerous issues including delays in access to data, data not being shared outside the registry or funder, and complaints from clinicians about excessive data recording.

ESC noted that, for Kymriah and Yescarta, patients are requested to stay within 1 hour of the treatment centre for 1 month after treatment, to manage any adverse events. ESC queried how this would be funded for cilta-cel, given the larger patient population size than for other CAR-T therapies. ESC also noted that people in remote communities would likely experience issues accessing cilta-cel, as for other CAR-T therapies.

ESC noted that the Department has requested that the applicant clarify in its pre-MSAC response whether patients would be admitted and treated with cilta-cel (delivery of the infusion and potentially a period of monitoring) mainly as inpatients (as stated in the application form), or

outpatients (as stated in the ADAR and modelled in the application). ESC noted the feedback received from the jurisdictions, that whilst other countries may be transitioning to an outpatient setting to deliver CAR-T therapy, this is not yet standard practice in Australia and patients would receive treatment in an admitted, inpatient setting. Given the economic model and financials were primarily based on an outpatient delivery setting, this would require them to be corrected. If cilta-cel was to be provided in the outpatient setting, it would have implications as to the appropriate funding source.

17.   Applicant comments on MSAC's Public Summary Document

Janssen Australia is disappointed that the Medical Services Advisory Committee (MSAC) has not supported the funding of CAR T-cell therapy ciltacabtagene autoleucel for Australians with multiple myeloma who have received at least three prior lines of therapy. Further, Janssen does not agree with MSAC's consideration that the evidence base is insufficient for determining the comparative safety and effectiveness, and note that single arm clinical trials have been the accepted evidence base for all previously approved CAR-T therapies considered by MSAC. Janssen is also disappointed that MSAC have not fully recognised the clinical need for new effective therapies in this population. The MSAC submission highlighted that while typically half of these patients will currently die within one year on current therapies, with ciltacabtagene autoleucel 70% patients are alive after over 2 years of median treatment follow-up[4]. Janssen sincerely thanks those clinicians, patients and advocacy groups who provided submissions to MSAC in support of ciltacabtagene autoleucel in the public consultation. Janssen will review the details of MSAC's advice and remain committed to working with all stakeholders to ensure equitable and timely access to ciltacabtagene autoleucel in Australia.

18.   Further information on MSAC

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

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[4] 1.   Usmani et al. Phase 1b/2 Study of Ciltacabtagene Autoleucel, a BCMA-Directed CAR-T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma (CARTITUDE-1): 2 Years Post LPI. Presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7; Chicago.