Australian Government

Department of Health

MSAC Application 1690:

Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) to treat refractory or relapsed multiple myeloma (RRMM)

Ratified

PICO Confirmation

Summary of PICO/PPICO criteria to define questions to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for ciltacabtagene autoleucel in fourth line or later multiple myeloma

Component	Description
Population	Adult patients with relapsed or refractory multiple myeloma (RRMM), who have received at least three prior lines of therapy, including: 1) a proteasome inhibitor (PI); 2) an immunomodulatory agent (IMiD); and 3) an anti-CD38 antibody.
Intervention	Ciltacabtagene autoleucel (also known as cilta-cel and brand nameREDACTED)
Comparator/s	Pomalidomide with dexamethasone or carfilzomib with dexamethasone.
Outcomes	<u>Clinical Effectiveness Outcomes:</u> • Complete response/stringent complete response (CR/sCR). • Overall response rate (ORR). • Very good partial response (VGPR) or better response rate. • Duration of response, time to response. • Minimal residual disease (MRD) negativity. • Progression free survival (PFS). • Overall survival (OS). • Health-related quality of life. <u>Safety Outcomes:</u> • Rate of adverse events (AE) and serious adverse events (SAE). • Incidence of AEs of special interest. • Incidence of cytokine release syndrome (CRS). • Incidence of neurological toxicity- CAR-T cell-related neurotoxicity (ICANS) and other neurological toxicities. • Incidence of tumour lysis syndrome, incidence of cytopenia. • Incidence of hypogammaglobulinemia. <u>Cost-effectiveness:</u> • Cost (including cost of additional pre-infusion and post infusion interventions). • Cost per life year gained (LYG). • Cost per quality-adjusted life year (QALY) or disability adjusted life year (DALY). • Incremental cost-effectiveness ratio (ICER). <u>Financial implications:</u> • Number of patients suitable for treatment. • Number of patients who receive treatment.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of ciltacabtagene autoleucel versus pomalidomide plus dexamethasone or carfilzomib plus dexamethasone in fourth line or later treatment of multiple myeloma?

Purpose of application

An application requesting public funding (under the National Health Reform Agreement) of ciltacabtagene autoleucel for the treatment of relapsed or refractory multiple myeloma (RRMM) after failure of three or more lines of therapy was received from the Janssen-Cilag Pty Ltd by the Department of Health.

The clinical claim in the application is that the use of ciltacabtagene autoleucel results in superior health outcomes compared to the current therapies in the RRMM setting.

The application notes that ciltacabtagene autoleucel has a manageable safety profile. The application does not specify an inferiority, non-inferiority or superiority claim for safety. The applicant indicated that a claim for safety will be addressed in the assessment report.

PICO criteria

Population

Multiple Myeloma

Multiple Myeloma (MM) is a plasma cell malignancy. It may be accompanied by complications of enhanced bone loss associated with diffuse osteopenia or focal lytic lesions, renal failure, hypercalcaemia, immune suppression and anaemia. As of 2017, approximately 2100 new cases are diagnosed in Australia each year, with median age at diagnosis of approximately 70 years (AIHW 2018; Quach 2019).

MM follows a relapsing and remitting course and patients may receive multiple lines of therapy. Although treatments for MM may result in remission, most patients will relapse as there is no cure for the disease. The duration of response and remission typically decreases with each line of therapy due to plasma cell clonal evolution. There is significant patient attrition at each line of therapy, as patients become unsuitable for further therapy and succumb to the disease (Zhao 2019).

The application notes that relapsed MM is defined as the reoccurrence of the disease after partial or complete remission and refractory MM is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy.

The application notes that in the PBS restrictions for MM therapies, progressive disease is defined as at least 1 of the following (as stated in daratumumab PBS restriction [Item 12220E]):

a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or
b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or
c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or
d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or
e) an increase in the size or number of lytic bone lesions (not including compression fractures); or
f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or

g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).

The application considers that if patients reach the fourth line setting, they may be assessed for eligibility for ciltacabtagene autoleucel and referred to a treating public hospital by their haematologist or haematological oncologist. The application noted that patients will progress quickly through lines of MM therapy.

Fourth line or later

The application proposes that the medical service is intended for patients with multiple myeloma (MM) who have received at least three prior lines of therapy, including:

1) a proteasome inhibitor (PI);
2) an immunomodulatory agent (IMiD); and
3) an anti-CD38 inhibitor.

Notably, only patients who have received prior anti-CD38 will be eligible for ciltacabtagene autoleucel. Daratumumab is the only anti-CD38 treatment listed on the PBS and is restricted to second line therapy; daratumumab was listed on the PBS from January 2021. The application noted there will be a delay in the timing of when all Australian RRMM patients meet the proposed clinical criteria for ciltacabtagene autoleucel. However, in further discussion with the applicant (at the pre-PASC teleconference), the applicant stated that daratumumab has been administered to patients in later lines of therapy as part of a compassionate use program outside of the PBS. The applicant further confirmed in its response to the Pre-PASC PICO that it has provided daratumumab compassionately as a later line therapy since 2017 and will continue to do so meaning all Australian patients with MM have the option to benefit from an anti-CD38 therapy. Consequently, the applicant considers that the PBS restriction of daratumumab would not constitute a barrier to access for ciltacabtagene autoleucel.

The intended population is consistent with the proposed TGA indication (approval expected 31 August 2022):

> Cilta-cel *[ciltacabtagene autoleucel]* 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 requested population is also consistent with the population enrolled in the CARTITUDE-1 study that assessed ciltacabtagene autoleucel among patients aged 18 years or older with a diagnosis of MM and an Eastern Cooperative Oncology Group performance status score of zero or one, who received three or more previous lines of therapy or were double-refractory to a PI and an IMiD, and had received a PI, IMiD, and anti-CD38 antibody.

Stem cell transplant status

The application requests ciltacabtagene for patients who have received stem cell transplant and those who have not. The CARTITUDE-1 study (Usmani 2021) indicates that 90% of total patients had previously received autologous stem cell transplantation, and 8% had received allogenic stem cell transplantation. In further discussion with the applicant, they considered that this reflected the differing survival and attrition between transplant eligible and ineligible patients, with a greater number of patients who received a stem cell transplant being sufficiently fit to receive fourth line or later treatment.

Measures of fitness

The application does not include specific criteria for assessing fitness of patients to receive ciltacabtagene autoleucel. The CARTITUDE-1 study included patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤1, as noted above.

PASC considered that the population was well defined, noting the definition of the population was consistent with PBS restrictions for treatments for multiple myeloma, and was broadly consistent with the population enrolled in CARTITUDE-1.

Intervention

Mechanism of action

Ciltacabtagene autoleucel is a chimeric antigen receptor-T cell (CAR-T) therapy. Ciltacabtagene autoleucel is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. *PASC questioned whether there would be a requirement for additional testing for BCMA or whether it was expressed in all MM.* The applicant advised there was no requirement for additional testing as all MM expressed BCMA. Ciltacabtagene autoleucel is prepared from the patient's peripheral blood mononuclear cells obtained via a leukapheresis. The mononuclear cells are enriched for T cells and genetically modified *ex vivo* by transduction with a replication incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain. The transduced anti-BCMA CAR-T cells are then expanded and infused and formulated into a suspension prior to infusion back into the patient, where the anti-BCMA CAR-T cells can recognise and eliminate BCMA expressing target cells.

Dose

The application states that ciltacabtagene autoleucel is to be administered as a single dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T-cells. The dose is $0.5\text{-}1.0\times10^6$ CAR-positive viable T-cells per kilogram (kg) of body weight, with a maximum dose of 1×10^8 CAR-positive viable T-cells per single infusion. The infusion should be given 5 to 7 days after the start of the lymphodepleting regimen. The maximum dose in the application was higher than the range of doses given in CARTITUDE ($0.5\text{-}1.0\times10^6$ CAR-positive viable T-cells per kg of body weight). *PASC questioned whether the proposed maximum dose of 1×10^8 CAR-positive viable T cells per kg of body weight was greater than that used in CARTITUDE-1 ($0.5\text{-}1.0\times10^6$ CAR-positive viable T cells per kg of body weight).* The applicant advised the proposed dose range was consistent with CARTITUDE-1.

The application proposes, consistent with the MSAC recommendation for Kymriah® in diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL) (MSAC 1519.1, November 2019) and Yescarta® in these same indications as well as high grade B-cell lymphoma (HGBCL) (MSAC 1587, January 2020), that patients would be limited to one successful CAR-T infusion per lifetime. The application defines a successful infusion as when the patient with RRMM has been infused with the optimal ciltacabtagene autoleucel dosage as per the recommend dose above.

Description of procedure*:*

The application notes that other CAR-T therapies have already been approved by the TGA and MSAC for use in acute lymphoblastic leukaemia (ALL; MSAC 1519), DLBCL (MSAC 1519.1, MSAC 1587) and PMBCL. (MSAC 1519.1, MSAC 1587). These therapies target CD-19.

The application states that treatment will be prescribed and monitored by an experienced haematologist working in a multidisciplinary team specialising in the provision of CAR-T cell therapy.

The application notes that most of the medical service will be rendered in Australia, with the exception being the manufacturing of ciltacabtagene autoleucel CAR-T product which occurs in the Janssen manufacturing centre in Raritan (New Jersey, USA).

The application notes that, similar to previously approved CAR-T therapies, ciltacabtagene autoleucel involves the following

1) Apheresis: a standard leukapheresis procedure is used to obtain a patient's peripheral blood mononuclear cells. Various specialised apheresis systems are available for this process. The apheresis machine is a multi-use consumable. Single-use consumables include tubing, sets, bowls, anticoagulant and replacement fluids.

   Bridging therapy: the patients may receive bridging therapy as per clinical indication to maintain disease stability during the period of production of ciltacabtagene autoleucel. Bridging therapy will be a short-term treatment (i.e. approximately up to 6 weeks) and is currently funded on the PBS.

2) Manufacture of ciltacabtagene autoleucel: The mononuclear cells are enriched for T cells and genetically modified *ex vivo* by transduction with a replication incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain. The transduced anti-BCMA CAR-T cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The drug product infusion bag is individually packed in an aluminium cryo cassette prior to cryopreservation. Once the CAR-T product is manufactured, it will undergo full quality assurance (QA) release at Raritan, then be transported directly to hospital in Australia.

3) Conditioning (lymphodepletion): A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously is administered daily for 3 days. Ciltacabtagene autoleucel infusion is administered 5 to 7 days after the start of the lymphodepleting regimen. Standard single-use consumables for an intravenous (IV) infusion include sterile alcohol wipes, plastic wrap, film dressing, gauze wipes, tubing adhesive tape, spill kit, preparation mats, labels, transport bag, and latex gloves.

4) Ciltacabtagene autoleucel infusion: Ciltacabtagene autoleucel infusion includes standard single-use consumables typical to an IV infusion, as listed above.

5) Monitoring after infusion: tocilizumab or methylprednisolone may be administered via IV infusion for the management of cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS). Standard single-use consumables for an IV infusion will be required, as listed above. *PASC noted the monitoring requirements for CRS and ICANS.*

Figure 1: REDACTED
PASC noted the intervention consisted of multiple steps.

Co-administered PBS therapies

Table 2 presents the relevant PBS item codes for medicines that may be required for the delivery of ciltacabtagene autoleucel.Table 1

Table 2: List of relevant PBS item codes for medicines that may be required for the delivery of ciltacabtagene autoleucel

Pharmaceutical	Usage	PBS item code
Cyclophosphamide	Chemotherapy for public hospital use, alkylating agent	4327R (unrestricted item)
Fludarabine	Chemotherapy for public hospital use, antimetabolite	4393F (unrestricted item)
Tocilizumab	Treatment of cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Funding costs based on PBS codes:1056G, 1058J, 10060L, 10064Q, 10068X, 10071C, 10072D, 10073E, 10077J, 10078K, 10079L, 10081N *Note: The above PBS item numbers are not indicated for CRS or ICANS.*
Methylprednisolone	Treatment of cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	5263B (unrestricted item) 11739W (unrestricted item) 5264C (unrestricted item)

Source: Table 1, p6 of the application

The application, however, also notes that tocilizumab is not PBS-funded for these uses.

PASC noted that the intervention did not include use or change in use of intravenous immunoglobulin (IVIg). 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 suggested the incremental change in IVIg use is likely to be a small increase (approximately 5-10%).

Uptake

The application states that the uptake of ciltacabtagene autoleucel over the next three years is anticipated to have an upper limit of REDACTED per year across Australia. The application states that this estimate is informed by local expert opinion and that most patients in clinical practice will have received daratumumab (either at second line on the PBS which was agreed with the PBAC in determining the financial estimates for daratumumab or compassionately as a later line therapy). Furthermore, the application states that uptake will be moderated by:

1) the requirement that only patients who have received a CD38 inhibitor (ie, daratumumab) will be allowed to access ciltacabtagene autoleucel. This would unlikely be an issue, if as the applicant stated in further discussion, patients may access daratumumab as part of compassionate use programme in later lines of therapy.
2) the fitness of patients required for treatment and to travel to a treatment centre.

Comparators

The application nominates pomalidomide with dexamethasone or carfilzomib with dexamethasone as the main comparators. The application based selection of the comparator on the PBS restrictions of available MM therapies and estimates of use from a 10% PBS sample of MM therapies.

The application notes that, as patients are required to have accessed at least three prior lines of therapy, the earliest patients can receive ciltacabtagene autoleucel will be as a fourth line MM treatment. Prior to the fourth line setting, patients will have typically received regimens which include lenalidomide (an IMiD), bortezomib (a PI) and daratumumab (an anti-CD38 inhibitor) in Australian clinical practice.

The application presents PBS 10% sample data demonstrating that the current standard therapy most commonly utilised for RRMM patients in the fourth line setting is pomalidomide ; the next most commonly utilised is carfilzomib.

Figure 2: REDACTED

PASC noted the relative use of MM therapies in the fourth and fifth line settings.

The application considers that the use of carfilzomib will increase in the third line setting as a consequence of the recent PBS listing of MM therapies in the first line and second line settings. Thus, this should further increase the uptake of pomalidomide in the fourth line MM setting. *PASC noted the new PBS listing of pomalidomide, bortezomib and dexamethasone.* The applicant indicated that this regimen was typically used as a third line treatment. The applicant further indicated that those receiving this regimen in third line would be unlikely to receive pomalidomide as a fourth line treatment and be treated with carfilzomib with dexamethasone in that treatment setting.

In further discussion, the applicant considered that ciltacabtagene autoleucel would both replace and displace comparator treatments. For some patients, after failure of ciltacabtagene autoleucel, they will be treated with pomalidomide with dexamethasone or carfilzomib with dexamethasone. For others, the application considered that based on the duration of response of ciltacabtagene autoleucel in the CARTITUDE-1 study, the high attrition rates between lines of therapy, and the general health of patients after a fourth line of treatment for MM, ciltacabtagene autoleucel would be the patients' final line of treatment, and thus the comparator would be replaced. Further support for the nominated comparators comes from Martin (2021). The authors reported an analysis comparing patients from the USA in CARTITUDE-1 to a real-world patient cohort who met the CARTITUDE-1 criteria in the Flatiron database (a primarily US based MM registry). Among those in the registry, standard of care regimens included pomalidomide (33%), carfilzomib (32%), daratumumab (13%), elotuzumab (16%), and ixazomib (8%).

PASC accepted that pomalidomide with dexamethasone and carfilzomib with dexamethasone were reasonable comparators.

<u>Supplementary/ near market comparator:</u>

In March 2021, the FDA approved idecabtagene vicleucel, another BCMA CAR-T therapy for MM with at least three prior lines of therapy. In further discussion, the applicant noted that idecabtagene vicleucel is not TGA approved and that no record of a TGA application has been identified. However, the applicant was open to including idecabtagene vicleucel as a supplementary comparator.

In response to the Pre-PASC PICO, the applicant noted in regard to idecabtagene vileucel that this intervention is not TGA approved or currently being evaluated by the TGA based on information in the public domain. The applicant notes that a matching-adjusted indirect comparison (MAIC) of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma has been published (Martin 2021a).

The applicant indicated that an updated MAIC based on more mature evidence for this clinical comparison will be provided in the assessment report.

Outcomes

The application includes the following outcomes. Other outcomes considered to be relevant were also included during the development of the PICO.

Intervention outcomes

- Incidence of manufacturing failure resulting in no product infusion or out of spec product infusion.
- Incidence of patient deterioration between apheresis and infusion such that infusion cannot proceed.

PASC noted the PICO included additional outcomes relating to the intervention (e.g. manufacturing outcome, patient deterioration between apheresis and treatment). PASC considered that the given high cost of the intervention, these are important outcomes to consider.

Effectiveness Outcomes:

- Complete response/stringent complete response (CR/sCR).
- Overall response rate (ORR)[1].
- Very good partial response (VGPR) or better response rate.
- Duration of response, time to response.
- Minimal residual disease (MRD) negativity.
- Progression free survival (PFS).
- Overall survival (OS).
- Health-related quality of life.

PASC acknowledged that some of the nominated outcomes would not be available for the comparators (e.g. MRD).

Safety Outcomes:

- Rate of adverse events (AE)[1] and serious adverse events (SAE).
- Incidence of AEs of special interest.
- Incidence of CRS.
- Incidence of neurological toxicity - CAR-T cell-related neurotoxicity (ICANS) and other neurological toxicities.
- Incidence of tumour lysis syndrome, incidence of cytopenia.
- Incidence of hypogammaglobulinemia.

Cost-effectiveness:

- Cost (including cost of additional pre-infusion and post infusion interventions).
- Cost per life year gained (LYG).
- Cost per quality adjusted life year (QALY) or disability adjusted life year (DALY).
- Incremental cost-effectiveness ratio (ICER).

[1] Primary outcome in CARTITUDE-1 (NCT03548207)

Financial implications:

- Number of patients suitable for treatment.
- Number of patients who receive treatment.

PASC noted that the PICO includes a thorough list of relevant outcomes.

As noted in the Public Summary Document for MSAC 1519.1 (p24), in consideration of tisagenlecleucel for treatment of relapsed or refractory DLBCL, clinical, economic, and financial outcomes should include intention to treat (ITT) outcomes, as opposed to outcomes for only patients who successfully complete treatment.

Clinical management algorithms

Figure 3 and Figure 4 present the current and proposed clinical management algorithms. *PASC accepted the current and proposed clinical management algorithms.*

The applicant generally agreed with the clinical management algorithms, noting the following:

- In the first-line setting, if a patient is not suitable for triple therapy with bortezomib, lenalidomide and dexamethasone (BLd), they will have a doublet therapy, which may be bortezomib with dexamethasone (Bd) or lenalidomide with dexamethasone (Ld). Thus, it is not restricted to Bd alone. If a person with MM has been treated with an immunomodulator (IMiD; lenalidomide) in the first line setting, a patient will switch class of therapy in the relapse setting (i.e. at second line). If a person with MM has been treated with a proteasome inhibitor (PI) in the first line setting (i.e. bortezomib), they may still receive a PI or bortezomib at relapse due to the fixed-duration nature of the bortezomib with dexamethasone regimen, provided the patient's MM was not refractory to bortezomib.
- In the proposed clinical algorithm which includes ciltacabtagene autoleucel at fourth line; it should be noted that ciltacabtagene autoleucel will not have 100% uptake in this setting, and thus a patient may still be treated with pomalidomide with dexamethasone (Pd), or carfilzomib with dexamethasone (Cd), if they are not of suitable fitness for ciltacabtagene autoleucel therapy.

The applicant further noted that use of thalidomide in clinical practice is low, and is diminishing, due to its toxicity. As noted in the comparator section, pomalidomide, bortezomib and dexamethasone may now be used in relapsed/refractory MM following its recent PBS listing (note: pomalidomide is an IMiD).

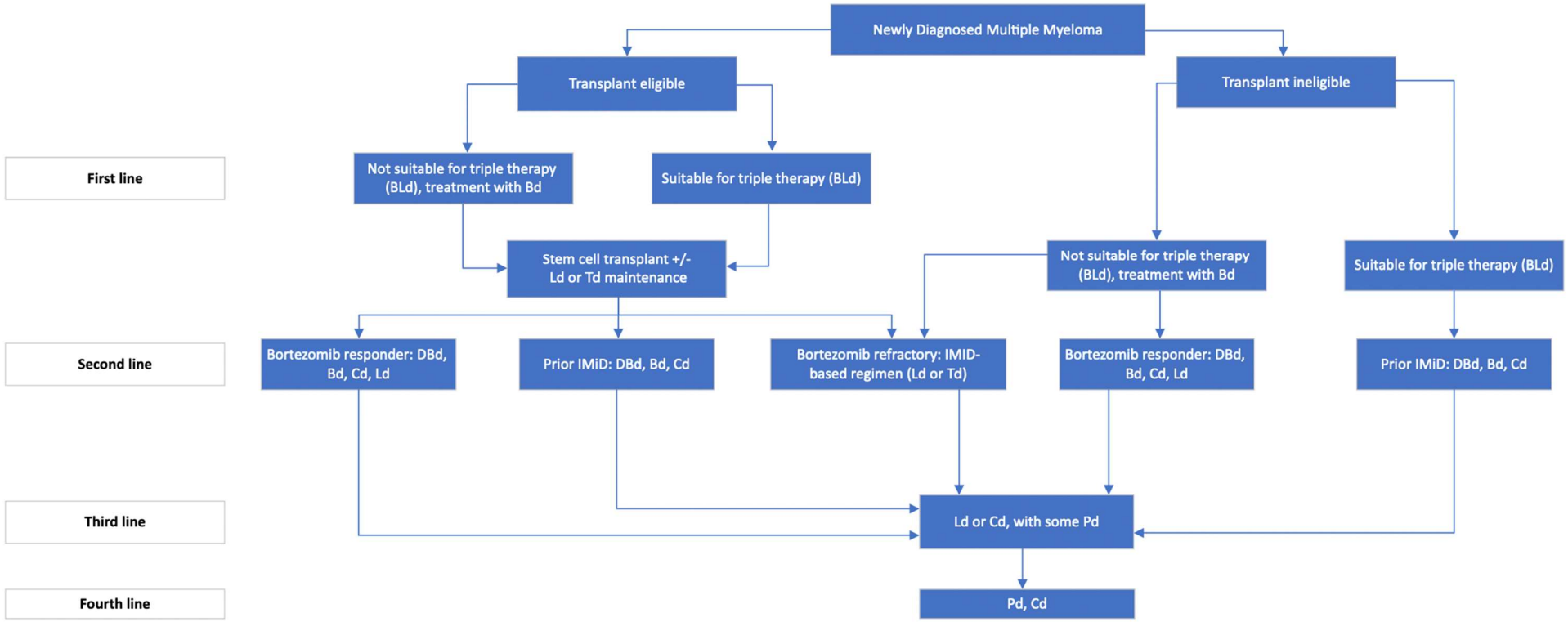

Figure 3: Current clinical management algorithm

Source: adapted from Figure 8, p24 of the application.

Bd = bortezomib and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; 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.

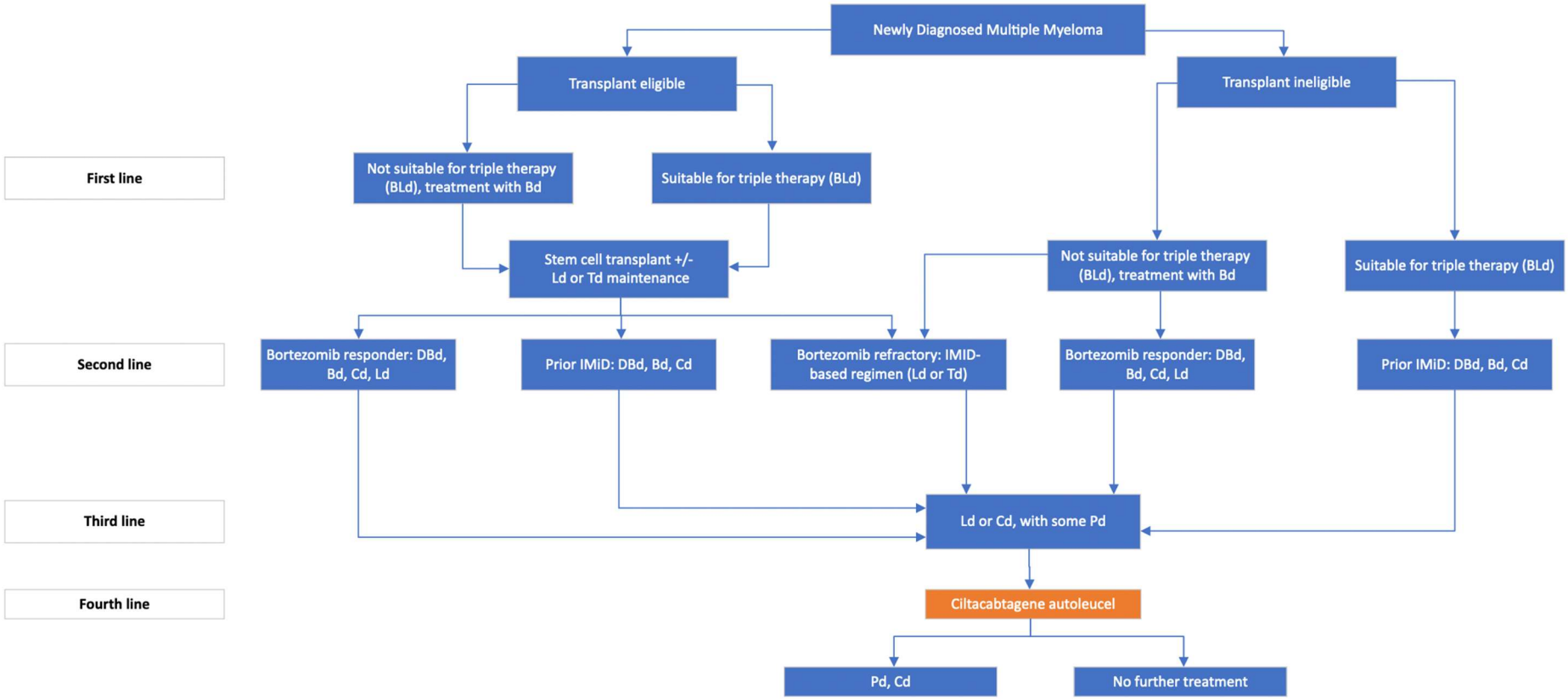

Figure 4: Proposed clinical management algorithm

Source: adapted from Figure 8, p24 of the application.

Bd = bortezomib and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; 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.

Table 4 in the attachment presents a comparison of the algorithm and the PBS restrictions for the described therapies. Overall, the application's current algorithm is consistent with the PBS restrictions for the included therapies.

Proposed economic evaluation

Based on the claim of superior effectiveness, a cost utility analysis is the most appropriate type of economic evaluation. *PASC noted that a claim of comparative safety (superior, non-inferior, inferior) needed to be addressed.*

PASC agreed that based on a claim of superior effectiveness, a cost utility analysis was the appropriate economic evaluation.

Table 3 provides a guide for determining which type of economic evaluation is appropriate.

Table 3 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The proposed mechanism for public funding is the National Health Reform Agreement (NHRA) which includes funding from both the Commonwealth Government (50%) and the governments of the relevant states and territories (50%), and which other CAR-T therapies have been funded under. This appears to be based on the Addendum to National Health Reform 2020-2025 that states (p57) that "… funding arrangements for new high cost, highly specialised therapies (HSTs), recommended for delivery in a public hospital setting by the Medical Services Advisory Committee, will be determined on the basis of hospital funding contributions specified in Schedule A with the following exceptions for the term of this Addendum: (a) the Commonwealth, for these types of therapies, will provide a contribution of 50 per cent of the growth in the efficient price or cost (including ancillary services), instead of 45 per cent …"

As such, the application considers that an MBS descriptor is not applicable. The application does not specify a fee or an amount to be charged. *PASC accepted that an MBS item descriptor was not relevant*

given funding was requested via the National Health Reform Agreement (NHRA). Despite an item descriptor not being relevant, PASC advised that the population needed to be clearly defined in the assessment report.

PASC also advised that a definition of 'response', preferably considering a time point, be addressed in the assessment report.

Summary of public consultation input

Input was received from the following four (4) organisations and one (1) individual:

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

The consultation feedback was supportive of the application.

Benefits

All respondents agreed that the proposed intervention satisfies an unmet need in the proposed population. Benefits included 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.

Disadvantages

MSAG, ALLG, the Leukemia Foundation and the individual 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.

All feedback 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.

Further comments

Other services identified in the feedback are haematology services, apheresis units, cellular laboratories, ward and outpatient services, pharmacy services, intensive care, emergency, designated respiratory physicians, neurologists, infectious disease physicians, rehabilitation specialists, paramedical services, dietetics, physiotherapy, radiology services, and occupational therapy.

The individual and ALLG stated that carfilzomib and dexamethasone are used as 3rd and 4th line therapy, thus should be included as a comparator.

The Leukemia foundation suggested that the applicants confirm whether treatments used as bridging therapy in the proposed intervention, such as carfilzomib or pomalidomide, are lost as treatment options if a patient progresses post cilta-cel.

MSAG stated that the rate of ICU support, IVIG use and anti-infective prophylaxis is not wholly covered in the intervention.

PASC noted that the consultation feedback was generally supportive with concerns around access to ciltacabtagene autoleucel (due to the proposed population eligibility criteria and limited treatment sites) and additional costs for access and resulting flow-on treatment.

Next steps

The applicant advised this will be progressing as an ADAR (applicant-developed assessment report).

References

Addendum to National Health Reform 2020-2025. https://federalfinancialrelations.gov.au/sites/federalfinancialrelations.gov.au/files/2021-07/NHRA_2020-25_Addendum_consolidated.pdf

Australian Institute of Health and Welfare (AIHW) 2018. ACIM (Australia Cancer Incidence and Mortality Book, AIHW: Canberra.

Kumar SJ et al. Multiple Myeloma Version 3. *Journal of the National Comprehensive Cancer Network*. 2020; 18 (12): 1685-1717.

Martin TG, et al. Comparison of outcomes with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-1 versus real-world standard of care (RW SOC) for patients (pts) with triple-class exposed relapsed/refractory multiple myeloma (RRMM). ASCO 2021 conference (Abstract 8045).

Martin T, et al. Matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma. *Current Medical Research and Opinion.* 2021a, 37(10): 1779-1788.

Quach H. and Prince H.M. on behalf of MSAG 2019. Clinical Practice Guideline. Multiple Myeloma. Updated 2019.

Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1. (2021): 8005-8005. ASCO 2021 conference. Data cut-off Feb 11, 2021.

Zhao J et al. Real-world treatment patterns in relapsed/refractory multiple myeloma in Australia: results from the Myeloma and Related Diseases Registry. Abstract presented (O051) at Blood 2019 on 21/10/2019, Perth Convention & Exhibition Centre, 20 - 23 October 2019.

Attachment

Table 4: Comparison of application algorithm and PBS restrictions

Treatment	Application nominated line of therapy	PBS restriction
Bortezomib	First line (in combination with lenalidomide and dexamethasone (BLd) First and second line for some patients in combination with dexamethasone (Bd)	**Multiple myeloma** (no further restriction) [Items 12219D, 12227M]
		Symptomatic MM <u>Newly diagnosed, ineligible for high dose chemo</u> • Combination with corticosteroid and melphalan or cyclophosphamide (no concomitant thalidomide or its analogues) [Items 4403R, 4429D, 7238Y, 7274W] <u>Newly diagnosed, eligible for high dose chemo and ASCT</u> • Combination with chemo (no concomitant thalidomide or its analogues) [Items 4732C, 4429D, 7275X]
		Progressive disease <u>Prior ASCT or ineligible for ASCT</u> • Monotherapy or in combination with corticosteroid and/or cyclophosphamide (no concomitant carfilzomib, thalidomide or its analogues) after at least one previous therapy [Items 4706Q, 4712B, 7268M, 7269N]
		Retreatment of progressive disease with at least at least a partial response to the most recent course of PBS-subsidised bortezomib therapy • Monotherapy or in combination with corticosteroid and/or cyclophosphamide (no concomitant carfilzomib, thalidomide or its analogues) [Items 4713C, 4725Q, 7271Q, 7272R]
Lenalidomide	First line (in combination with bortezomib and dexamethasone) (BLd) Second or third in some patients in combination with dexamethasone (Ld)	**Newly diagnosed** <u>Ineligible for ASCT</u>: • Combination with dexamethasone (no concomitant bortezomib, thalidomide or its analogues) [Items 11029L, 11036W, 11041D, 11042E, 11055W, 11062F, 11063G, 11064H] <u>Previous ASCT, no progression following ASCT</u> • Monotherapy [Items 11964Q, 11965R, 11966T, 11967W, 11968X, 11969Y] <u>Ineligible for SCT or previous SCT (does not specify)</u> • Combination with bortezomib and dexamethasone (no concomitant carfilzomib, thalidomide or its analogues, no prior lenalidomide or bortezomib) [Items 12004T, 12011E, 12012F, 12018M, 12019N, 12020P, 12026Y, 12034J, 12035K, 12036L, 12037M, 12038N, 12039P, 12050F, 12057N, 12058P, 12059Q, 12060R, 12061T, 12062W, 12068E, 12069F, 12070G, 12071H]
		Progressive disease after at least one prior therapy <u>Ineligible for SCT or previous SCT</u> • Monotherapy or combination with dexamethasone (no concomitant bortezomib, carfilzomib or thalidomide or its analogues) [Items 5783J, 5784K, 5785L, 5786M, 9642L, 9643M, 9644N, 9645P]
Daratumumab	Second line in combination with bortezomib and dexamethasone (DBd)	**Relapsed and/or refractory MM, progressive disease <u>after only one prior therapy</u> (i.e. use must be as second line drug therapy; use as third line drug therapy or beyond is not PBS-subsidised** [Items 12228N, 12230Q) • Combination with bortezomib and dexamethasone (no concomitant carfilzomib, thalidomide or its analogues and no concomitant bortezomib from week 25)
Thalidomide	Second line in bortezomib refractory patients	**Multiple myeloma** (no further restriction) [Items 6469L, 9566L, 9667T, 9684Q]
Carfilzomib	Second, third, or fourth line in combination with dexamethasone (Cd)	**Progressive disease after at least one prior therapy** <u>Ineligible for SCT or previous SCT</u> • Combination with dexamethasone (no concomitant bortezomib, thalidomide or its analogues) [Items 11229B, 11230C, 12243J, 12244K]

Treatment	Application nominated line of therapy	PBS restriction
Pomalidomide	Fourth line in combination with dexamethasone (some patients in third line in combination with dexamethasone) (Pd)	**Treatment failure with lenalidomide AND bortezomib, unless contraindicated or not tolerated according to the Therapeutic Goods Administration (TGA) approved Product Information** Ineligible for SCT or previous SCT • Combination with dexamethasone (no concomitant bortezomib, carfilzomib or thalidomide or its analogues) [Items 10387Q, 10406Q, 10417G]
		Progressive disease after at least one prior therapy that is either (i) lenalidomide monotherapy or (ii) contains lenalidomide Ineligible for SCT or previous SCT • Combination with bortezomib and dexamethasone (no concomitant carfilzomib or thalidomide or its analogues) [Items 12661J, 12665N, 12666P, 12668R]

Source: Figure 8, 24 of the application and the respective PBS restrictions for the therapies presented