CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

idecabtagene vicleucel (Abecma)

Indication: For the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and who are refractory to their last treatment.

Recommendation: Do not reimburse

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Single Technology

IDECABTAGENE VICLEUCEL (ABECMA — CELGENE Inc., a Bristol Myers Squibb company)

Therapeutic Area: Multiple Myeloma

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that idecabtagene vicleucel should not be reimbursed for the treatment of relapsed or refractory multiple myeloma (RRMM).

Rationale for the Recommendation

pERC reviewed one phase 2, open-label, single arm study (KarMMa, N = 140) of idecabtagene vicleucel in patients with RRMM. At a median follow-up of 11.3 months, the overall response rate (ORR) was 81.5% (95% CI: 68.6 to 90.7) and the complete response (CR) was 35.2% (95% CI: 22.7 to 49.4) in patients who received the target dose of 450 × 10^6 chimeric antigen receptor (CAR) T- cells. Although results of the KarMMa study appear to suggest that treatment with idecabtagene vicleucel is associated with an improvement in ORR and CR in patients with RRMM, the study was associated with major limitations, specifically the single-arm design and lack of a control group. These limitations contribute to the lack of confidence in the observed effects and lead to considerable uncertainty in the results. Duration of response (DOR), time to progression (TTP), overall survival (OS), and progression free survival (PFS) were evaluated as secondary outcomes in the KarMMa study, but none of these outcomes were controlled for multiplicity. Results of health-related quality of life (HRQoL) outcomes were reported descriptively and could not be interpreted due to missing data. Based on input received by CADTH, patients expressed the need for effective treatments that offer prolonged remission and better control of symptoms with fewer side effects and better quality of life. Idecabtagene vicleucel offers a subsequent therapy for a heavily pretreated population in the form of a single treatment. However, pERC was unable to determine whether treatment with idecabtagene vicleucel would definitively meet patients' needs due to limitations of the trial design and with the statistical analyses. In addition, as limited evidence was available regarding the long-term treatment effects of idecabtagene vicleucel, whether responses observed in the KarMMa study would be maintained beyond 16 months (at the trial data cutoff corresponding to a median follow-up of 11.3 months) was uncertain.

Indirect evidence suggested that treatment with idecabtagene vicleucel may be associated with improvements in survival outcomes, ORR, and DOR. However, these results must be considered within the context of methodological limitations such as risk of bias due to inherent design differences in the bodies of evidence that cannot be adjusted for statistically, the potential impact of unmeasured and unaccounted prognostic factors and effect modifiers in the models, and undermined generalizability by the inclusion of irrelevant comparators.

The submitted price of idecabtagene vicleucel is $545,000 per infusion (target dose of 450×10^6 CAR T-cells, within a range of 275 to 520×10^6 CAR T-cells). CADTH was unable to estimate the cost-effectiveness of idecabtagene vicleucel due to the lack of comparative clinical information and the extent of clinical benefit predicted beyond the trial observation period (i.e., more than 94% of the quality-adjusted life years (QALYs) associated with idecabtagene vicleucel occurring beyond one year).

Discussion Points

- pERC discussed that idecabtagene vicleucel is a complex therapy involving high resource utilization. Lymphodepleting chemotherapy (LDC) consisting of cyclophosphamide and fludarabine is required prior to treatment with idecabtagene vicleucel. Further, bridging therapy may be administered for disease control, at the discretion of the physician, after leukapheresis is completed and prior to the initiation of LDC.
- Given the lack of long-term evidence and the single-arm study design of the pivotal trial, there is substantial uncertainty associated with the clinical and economic evidence.
- pERC noted that treatment with idecabtagene vicleucel was associated with undesirable effects, as observed in the KarMMa study, including notable toxicity and adverse events, such as febrile neutropenia, neurotoxicity (including confusional state and encephalopathy), and cytokine release syndrome.
- pERC acknowledged that idecabtagene vicleucel offers a subsequent, single therapy for a heavily pre-treated population that may offer respite from frequent hospitalization. However, this complex therapy may pose significant hardship and financial burden, and inequitable access to patients and caregivers who have to travel to distant centres.
- pERC discussed ethical concerns driven by the high cost of idecabtagene vicleucel, limited number of centres that are authorized to administer the therapy, and geographic constraints on access. It was noted that patients from remote areas would need to have a prolonged stay at or near specialized centres and that relocation and interprovincial travel would be required for some patients to access this therapy. Travel costs for patients and their caregivers and the requirement for time spent away from work may disproportionately affect certain populations. Furthermore, pERC agreed with clinical experts that some provinces would not have capacity to assess patients' eligibility for treatment with idecabtagene vicleucel, which would result in substantive out-of-pocket costs for patients travelling out of province to meet the eligibility requirements.

Background

Idecabtagene vicleucel has a Health Canada indication for the treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and who are refractory to their last treatment. Idecabtagene vicleucel is a cell therapy formed by chimeric antigen receptor (CAR)-positive T cells directed against the B-cell maturation antigen (BCMA). It is available as a cell suspension in one or more patient specific infusion bag(s), and the Health Canada–approved target dose is 450×10^6 CAR T-cells, within a range of 275 to 520×10^6 CAR T-cells, for intravenous infusion.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of one single-arm, phase 2, clinical study (KarMMa) in patients with multiple myeloma who have been previously treated with at least 3 previous regimens, and a review of two indirect comparisons.
- Patients' perspectives gathered from one patient group, *Myeloma Canada*.
- Three clinical specialists with expertise diagnosing and treating patients with multiple myeloma.
- Input from 2 clinician groups, including the Canadian Myeloma Research Group (CMRG) and the Ontario Health group (previously Cancer Care Ontario).
- A review of the pharmacoeconomic model and report submitted by the sponsor
- A review of relevant ethical issues related to idecabtagene vicleucel from published literature

Patient Input

One patient group (Myeloma Canada) provided input for this submission. Patient perspectives were obtained from a patient survey accessed through email and social media from December 17th, 2020 to January 4th, 2021. A total of 388 individuals with myeloma responded to the survey. The following is a summary of key input from the perspective of the patient group:

- Overall, patients described the negative impact of myeloma on daily life, including their ability to work, travel, and exercise. Patients who have been heavily treated expect new treatment options to provide prolonged remission, better quality of life and overall health, better control of myeloma symptoms, and fewer side effects.

- Myeloma Canada surveyed patients' understanding of CAR T-cell therapy and concluded that more than half of participants understand the process involved. More than half felt that CAR T-cell immunotherapy could improve their long-term health outlook, although they had concerns about the possibility of requiring bridging therapy, and about potential side effects.
- The patient group highlighted that many Canadians are looking for new options for effective treatments, especially when they reach the point of multiple therapies with remission and refractoriness to the regimens available. Myeloma Canada stated that CAR T-cell therapy represents an important benefit to these patients, despite the number and severity of the side effects.

Drug Plan Input

The drug programs raised questions concerning how to identify patients for whom treatment with idecabtagene vicleucel would be most appropriate and noted that the choice of comparator in the submitted trial would need special consideration as there is no clear standard of care (i.e., when reaching fourth line of therapy). They also noted that access to treatment with idecabtagene vicleucel may be limited due to jurisdictional capacity and that out of province care may be needed for proper administration. PAG raised concerns that idecabtagene vicleucel is a resource-intensive therapy given the need for leukapheresis, cell processing, lymphodepleting chemotherapy, potential use of bridging therapy, and management of adverse effects.

Clinical Evidence

Clinical Trials

The systematic review included one single-arm, phase 2, clinical study (KarMMa) in patients with multiple myeloma who have been previously treated with at least 3 previous regimens, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody were refractory to their last treatment. The main objective of the study was to evaluate the efficacy and harms of idecabtagene vicleucel. Enrolled patients (N = 140) underwent leukapheresis (i.e., drug manufacturing) and, if necessary, a bridging therapy (with corticosteroids, alkylating agents, immunomodulatory agents, PIs, and/or anti-CD38 antibodies alone or in combination) while the idecabtagene vicleucel was manufactured. All patients were required to undergo LDC with cyclophosphamide and fludarabine 5 days before the idecabtagene vicleucel infusion. Of the 140 patients from the enrolled population, 128 received the idecabtagene vicleucel infusion and were included as the idecabtagene vicleucel-treated population for the primary analysis of efficacy and safety. Patients received target doses of 150×10^6, 300×10^6, or 450×10^6 CAR T-cells and were followed for at least 24 months and then asked to participate in a separate long-term follow-up study. The median age of the 140 enrolled patients was 60.5 years (range 33 to 78), 82 (58.6%) were male, with a median of 6 years since diagnosis (range 1 to 18 years), 46 (32.9%) with a high cytogenetic risk, and 131 (93.6%) have received a stem cell transplant.

The main limitation of the KarMMa trial is the lack of a comparator arm. Only the outcomes of ORR and CR were adjusted for multiplicity. Effect estimates on HRQoL were uncertain due to increasing missing data at later time points of measurement.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. The committee discussed the following: overall response rate (ORR) as the primary outcome, complete response rate (CRR) as a key secondary outcome, and other secondary outcomes included the duration of response (DoR), time to response (TTR), time to progression (TTP), minimal residual disease negative status (MRD), overall survival (OS), progression-free survival (PFS), and health-related quality of life (HRQoL) measured with the European Organization for Research and Treatment of Cancer – Quality of Life C30 (EORTC-QLQ-C30) Questionnaire, the European Organization for Research and Treatment of Cancer – Quality of Life Multiple Myeloma (EORTC-QLQ-MY20) Module, and the EuroQoL 5 dimension 5-scale (EQ-5D-5L) questionnaire.

Efficacy

At a median follow-up of 11.3 months, the ORR in the total idecabtagene vicleucel-treated population was 73.4% (95% CI: 65.8 to 81.1; $p < 0.0001$) and 81.5% (95% CI: 68.6 to 90.7) in the target dose of 450×10^6 CAR T-cells group. Given that the test for ORR (primary endpoint) was positive, the key secondary efficacy endpoint of complete response (CR) rate was tested. In the total

idecabtagene vicleucel-treated group, 40 of 128 patients achieved a CR, equivalent to a CR rate of 31.3% (95% CI: 23.2 to 39.3 ; p < 0.0001) while in the target dose of 450 × 10^6 CAR T-cells group, the CR was 35.2% (95% CI: 22.7 to 49.4).

Duration of response (DoR), time to response (TTR), and time to progression (TTP) were evaluated in the KarMMa trial as secondary endpoints. In the target dose of 450 × 10^6 CAR T-cells population, the median DoR was 11.30 months (95% CI: 9.17 to 11.43), and the TTR was 1.0 month (range 0.9 to 2.0). TTP was not assessed in the target dose group of 450 × 10^6 CAR T-cells. Further, an MRD negative status with a complete response or better was observed in 13 of 54 (24.1%) patients in the target dose of 450 × 10^6 CAR T-cells.

In the all-treated population, the observed median OS was 18.2 months (95% CI: 18.0 to NE), with 77% of individuals alive at 12 months. The OS was not estimable in patients in the target dose of 450 × 10^6 CAR T-cells group. Similarly, based on the KM estimates, the median progression-free survival (PFS) was 8.6 months (95% CI: 5.6 to 11.3) with 34% of patients event-free at 12 months in the idecabtagene vicleucel treated group, and 11.3 months (95% CI: 8.8 to 12.4) in the target dose of 450 × 10^6 CAR T-cells group, denoting a likely meaningful benefit for patients treated with idecabtagene vicleucel.

For HRQoL outcomes, results of the KarMMa trial suggest that idecabtagene vicleucel treatment may be associated with improvements in the Fatigue, Pain, Physical Functioning, and Global Health/QoL subscales of the EORTC QLQ-C30 by reaching points of meaningful clinical significance above the thresholds of probably benefit according to MIDs established in the literature. On average, no clinically meaningful deterioration in the EORTC QLQ-C30 Cognitive Functioning and EORTC QLQ-MY20 Disease Symptoms and Side Effects subscales were observed posttreatment. When addressing the EQ-5D-5L subscales, no changes from baseline were observed in any subscales of this measurement.

Harms (Safety)

AEs were reported in all 128 (100%) patients treated with idecabtagene vicleucel. Most adverse events, with the exception of hypogammaglobulinemia and infections, occurred within the first 8 weeks after infusion. Most commonly reported AEs were hematologic toxic effects, including neutropenia in 117 patients (91.4%), CRS in 107 patients (83.6%), anemia in 89 patients (69.5%), and thrombocytopenia in 81 patients (63.3%). A total of 86 (67.2%) patients had at least one SAE. The most frequently reported SAEs (≥ 5% of patients) were CRS in 22 patients (17.2%), general physical health deterioration in 13 (10.2%) patients, pneumonia in 11 (8.6%) patients, and febrile neutropenia in 9 (7.0%) patients.

In total, 8 patients died after leukapheresis and prior to receiving idecabtagene vicleucel infusion: 5 patients (3.6%) died after leukapheresis and prior to starting LDC and 3 patients (2.1%) died after starting LDC and prior to receiving the idecabtagene vicleucel infusion. In the idecabtagene vicleucel treated population, as of the data cutoff date, 34 patients (26.6%) died on or after the idecabtagene vicleucel infusion, 24 of which were attributed to the malignant disease under study or a complication due to the malignant disease under study. Notable harms were identified according to the protocol for this review. Febrile neutropenia was present in 21 patients (16.4%) of the idecabtagene vicleucel treated population. A total of 23 patients (18.0%) in the idecabtagene vicleucel-treated population had investigator-identified neurotoxicity (iiNTs) on or after the idecabtagene vicleucel infusion. CRS on or after the idecabtagene vicleucel infusion was present in 107 patients (83.6%).

Indirect Evidence

Two sponsor submitted analyses compared the information from the single arm KarMMa study to observational evidence obtained from individual patient data or aggregated published data. The first analysis (NDS-MM-003 or KarMMa-RW) was a comparison of the 128 idecabtagene vicleucel-patients from the original KarMMa trial (i.e., the idecabtagene vicleucel treated population) with 190 patients with similar eligibility criteria obtained from a set of 'real world' (RW) patient-level data collected from various sources, including databases and clinical sites. To decrease the imbalances or differences in patients from the RWE when compared to the KarMMa population, propensity scores (PS) were created and used in an inverse probability treatment weighting (IPTW).

The second analysis was a matching adjusted indirect comparison (MAIC) that compared the idecabtagene vicleucel treated population from the KarMMa trial to aggregated data from a published RWE study (MAMMOTH). This analysis aims at providing a comparator arm, with adjustment for differences in baseline characteristics, prognostic factors, and effect modifiers, and obtained an

adjusted effect estimate for decision-makers and stakeholders, given the lack of direct, head-to-head comparison of idecabtagene vicleucel to relevant comparators.

From the NDS-MM-003 analysis, the ORR was lower in the Eligible RRMM cohort as compared with the idecabtagene vicleucel cohort (32.2% versus 76.4%; RR = 2.4; 95% CI: 1.7 to 3.3; p < 0.0001). A comparison between the 2 groups yielded an OS HR of 0.42 (95% CI: 0.26 to 0.68), favoring the idecabtagene vicleucel cohort compared with the Eligible RRMM cohort treated with available therapy (p = 0.0005). The median TTR for responders was 1.1 months (range: 0.2 to 8.6) in the Eligible RRMM cohort versus 1.0 month (range: 0.5 to 8.8) in the idecabtagene vicleucel cohort. Similarly, the HR for DoR was 0.55 (95% CI: 0.29 to 1.06; p = 0.0725) and the PFS showed a HR of 0.47 (95% CI: 0.33 to 0.67; p < 0.0001).

The second analysis using MAIC and comparing to the MAMMOTH study yielded similar results. Idecabtagene vicleucel in the treated population was more efficacious than conventional care in terms of ORR, ([redacted]) and also in the population using the target dose of 450 × 10^6 CAR+ T cells. There was also a better PFS in the idecabtagene vicleucel treated population ([redacted]) and in patients receiving the target dose of 450x10^6 CAR+T cells ([redacted]), and better OS, with the idecabtagene vicleucel treated population performing better than conventional care in the MAMMOTH treated population in the adjusted MAIC ([redacted]) and target dose ([redacted]).

Both comparisons present important limitations, such as risk of bias due to inherent design differences in the bodies of evidence, the potential impact of unmeasured and unaccounted prognostic factors and effect modifiers in the models, and undermined generalizability by the inclusion of irrelevant comparators. Given the limitations of the two ITCs and the absence of direct comparative evidence, any potential benefit of idecabtagene vicleucel over other treatment regimens used in this patient population remains unknown.

Economic Evidence

Cost and Cost-Effectiveness

The submitted price of idecabtagene vicleucel is $545,000 per infusion (target dose of 450×10^6 CAR-positive T-cells, within a range of 275 to 520 ×10^6 CAR-positive T-cells), excluding the costs associated with leukapheresis, bridging therapies, and lymphodepleting chemotherapy.

The sponsor submitted a cost-utility analysis based on a three-state partitioned survival model comparing idecabtagene vicleucel to conventional care (defined as a basket of chemotherapy regimens) for the treatment of adult patients with MM who have received at least three prior regimens, including regimens with an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody. The analysis was conducted from the perspective of a Canadian publicly funded health care system adopting a lifetime time horizon (i.e.,15 years). The proportion of patients who were progression-free, experienced progressive disease, or were dead at any time over the model time horizon was derived from non-mutually exclusive survival curves. The clinical efficacy of idecabtagene vicleucel was informed by patients who received the target dose within the KarMMa trial. To estimate the comparative treatment effects to conventional care, 190 patients within the retrospective NDS-MM-003 database were selected for meeting the key eligibility criteria of the KarMMa trial based on select baseline characteristics and trimmed stabilized inverse probability of treatment weighting was applied to patients from the NDS-MM-003 and the KarMMa treated population (i.e., those who received idecabtagene infusion). Treatment and health-state utilities were sourced from the KarMMa trial and from published studies.

CADTH identified several key limitations with the submitted analysis:

- The clinical efficacy of idecabtagene vicleucel is uncertain. KarMMa is an open-label, single-arm Phase II study and the efficacy of idecabtagene vicleucel is further expected to be dependent on several implementation factors.
- Relative effectiveness estimates (i.e., PFS and OS) of idecabtagene vicleucel compared to conventional care were obtained by comparing the KarMMa treated population to a retrospective database of patients using different MM treatments. Despite adjustments for several known prognostic variables using propensity scores, there remains significant uncertainty on the relative efficacy of idecabtagene vicleucel compared with conventional care.

- Clinical experts noted that the sponsor's chosen OS and PFS curves were optimistic compared to real-world clinical experience and, given that the OS data were immature at the trial data cut-off, the true long-term effectiveness (and relative effectiveness) remains unknown.
- The comparator was a pooled strategy of different oncology regimens which does not reflect Canadian practice. Furthermore, there were inconsistencies between the regimens informing costs for conventional care and those informing clinical efficacy inputs.
- Treatment-specific utility weights were applied that lacked face validity and, in some instances, double-counted the disutility associated with adverse events and treatment administration in favour of idecabtagene vicleucel.

The issues with the clinical data prohibit a reasonable assessment of cost-effectiveness as there is no clear resolution to address the clinical uncertainties. As such, a CADTH base case could not be derived. CADTH undertook a series of exploratory reanalyses, focused on the treated population, which indicated that the ICER of idecabtagene vicleucel was likely to be higher than that estimated by the sponsor. The ICERs were very sensitive to different assumptions regarding relative efficacy and the cost of idecabtagene vicleucel. One set of exploratory reanalyses attempted to address some of the identified limitations including: adjusting the distribution of regimens informing the cost of conventional care and removing treatment-specific utilities. A different combination of possible efficacy scenarios was tested on top of the changes noted above and the deterministic ICER for idecabtagene vicleucel was found to range from $286,142 to $1,276,217 per QALY compared with conventional care. Price reductions of at least 83% to 94% would be required to achieve an ICER of $50,000 per QALY.

Budget Impact

The sponsor estimated the incremental budget impact of reimbursing idecabtagene vicleucel to be $200.2 million over 3 years, based on a health care system perspective. CADTH identified limitations with the submitted budget impact analysis and undertook re-analyses which estimated the incremental budget impact of reimbursing idecabtagene vicleucel to be $328.4 million over 3 years. The results were primarily driven by the price of idecabtagene vicleucel and the number of patients receiving idecabtagene vicleucel.

Ethical Considerations

Empirical and normative literature related to the use of idecabtagene vicleucel and experiences of adult patients with multiple myeloma were reviewed for ethical content, using methods of qualitative description to highlight ethical considerations and themes. 61 publications met inclusion criteria and were included in the report; none directly reported on the use of idecabtagene vicleucel for multiple myeloma, but instead explored multiple myeloma incidence, treatment, access, costs of therapies, clinical trial inclusion, and clinical decision making.

Findings indicate that there are disparities in the incidence, treatment and outcomes of multiple myeloma along racial, socioeconomic, age, and geographical lines. Similarly, there are disparities in access to and receipt of treatment of multiple myeloma, with older adults and racialized communities or ethnic minorities, or those of lower socioeconomic status, less likely to receive treatment. These considerations are amplified when demand for CAR T-cell therapies outstrips supply and resources. An analysis of large American clinical trials revealed that there are also disparities in inclusion in clinical trials for multiple myeloma therapies, where racial and ethnic minorities tend to be under-represented, which in turn may lead to limited understanding and elimination of the disparities identified. This under-representation may be due to racial minority groups limited access to insurance (this may not be representative of access in Canada), academic trial centres, and multiple co-morbidities that may render them ineligible.

Patients eligible for CAR T-cell therapies often face few therapeutic options and thus may be willing to pursue high risk treatments, highlighting a need to consider and identify the appropriate balance of risks and benefits for patients receiving these therapies.

pERC Members

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

May 14, 2021 Meeting

Regrets

One expert committee member did not attend.

Conflicts of Interest

None

CADTH

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