CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Tafasitamab (Minjuvi)

Indication: In combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, who are not eligible for ASCT.

Sponsor: Incyte Biosciences Canada Corporation

Recommendation: Do Not Reimburse

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that tafasitamab not be reimbursed in combination with lenalidomide for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, who are not eligible for autologous stem cell transplant (ASCT).

Rationale for the Recommendation

One phase II, single-arm, open-label study (L-MIND; N=81) evaluated the efficacy and safety of tafasitamab in combination with lenalidomide in adult patients with DLBCL who had relapsed after or were refractory to 1 to 3 previous systemic regimens and who were not candidates for ASCT. Although 57.5% (95% CI: 45.9%, 68.5%) of patients from the L-MIND study showed an objective response, there was a high degree of uncertainty regarding the magnitude of clinical benefit directly attributable to tafasitamab plus lenalidomide due to the non-randomized, non-comparative, open-label study design and the small sample size. Further, due to the absence of a comparator arm, the potential clinical benefit of tafasitamab plus lenalidomide compared to other relevant treatment comparators was unknown. Health-related quality of life (HRQoL) was also not assessed in the L-MIND study. The sponsor submitted three indirect treatment comparisons (ITCs) that compared patients in the L-MIND study to patients treated with other therapies. However, given the methodological limitations of the analyses (i.e., heterogeneity, matching based on a limited number of variables, and small sample sizes), pERC was unable to determine the comparative efficacy of tafasitamab plus lenalidomide relative to other therapies. There were limited comparative data on harms; thus, no conclusions could be drawn regarding the relative safety of tafasitamab in combination with lenalidomide compared to other therapies.

Patients expressed a need for treatments that prolong survival and remission, control disease symptoms, improve HRQoL, and have fewer side effects compared to current therapies. While recognizing the need for additional effective treatment options for this vulnerable patient population, pERC was uncertain whether tafasitamab plus lenalidomide meets these important therapeutic needs given the limitations associated with the evidence reviewed.

Discussion Points

- pERC recognized that patients with R/R DLBCL who are unfit or ineligible for intensive therapies (i.e., ASCT or chimeric antigen receptor [CAR] T-cell therapy) have limited treatment options with low response rates and short duration of response, and acknowledged that ineligibility for intensive therapies is often due to comorbidities in this vulnerable patient population. pERC also considered input from the clinician groups that indicated tafasitamab plus lenalidomide would be a treatment option for patients who may not have access to ASCT or CAR T-cell therapy due to strict eligibility criteria or geographical limitations. The committee agreed with the clinical experts and patient groups that there is a significant unmet need for effective treatment options in this patient population.
- pERC deliberated on the results of L-MIND – a phase II, single-arm, and open-label study that assessed the efficacy and safety of tafasitamab plus lenalidomide in adult patients with R/R DLBCL who were not candidates for ASCT. Patients ineligible for ASCT included patients who were older than 70 years, had organ dysfunction or comorbidities precluding the use of high-dose chemotherapy or ASCT on the basis of unacceptable risk of treatment, failed previous ASCT, did not respond to salvage therapy, refused ASCT, or were unable to receive ASCT because of an inability to successfully collect peripheral blood stem cells. pERC considered that tafasitamab plus lenalidomide produced anti-tumour activity based on the objective response rate (ORR) observed in the L-MIND study. However, pERC noted that the submitted reports for the L-MIND study, including the trial publications, did not include formal statistical significance testing of the results and therefore no robust conclusions could be drawn regarding the anti-tumour activity of tafasitamab plus lenalidomide. The committee was concerned about the limitations and inherent biases (e.g., patient selection bias) of non-comparative studies and their risk of providing unreliable efficacy estimates in light of the favourable population of patients enrolled in the L-MIND study. Further, pERC was uncertain if the observed ORR for tafasitamab plus lenalidomide would translate into benefits in HRQoL as the L-MIND study did not assess HRQoL.
- pERC considered that the median overall survival (OS) and median progression-free survival (PFS) observed in the L-MIND trial were longer than typically expected survival rates in patients with R/R DLBCL who are ineligible for ASCT. However, pERC agreed with the clinical experts consulted by CADTH that patients in the L-MIND study represented a more favourable subset of patients than the general population of patients for whom these results could be generalized. The clinical experts highlighted that, when compared with patients enrolled in L-MIND study, the population of Canadian patients with R/R DLBCL who are ineligible for ASCT has a greater proportion of patients with an ECOG PS of 2 or greater, more patients may experience relapse within 6 months of completion of initial therapy (primary refractory and early relapse), and more patients would have failed prior ASCT or have unfavourable cytogenetics, with a higher proportion of non-GCB cell of origin subtype and double or triple hit lymphoma, (who were excluded from the L-MIND trial). As well, 10% of the patients included had non-DLBCL lymphomas upon central pathology review, which would be expected to have longer PFS and OS with this regimen and bias the results. pERC concluded that the generalizability of the PFS and OS results from the L-MIND study to the Canadian patient population was limited, as a large proportion of patients normally seen in Canadian practice would not have been eligible for participation in the L-MIND study.
- In the absence of a direct comparison of tafasitamab plus lenalidomide to currently available treatments in Canada, pERC considered the sponsor-submitted ITCs. Results from the ITCs suggested that tafasitamab plus lenalidomide may be associated with an improvement in clinical outcomes compared to lenalidomide monotherapy, systemic therapies pooled, bendamustine + rituximab (BR), rituximab + gemcitabine + oxaliplatin (R-GemOx), polatuzumab plus BR (pola-BR), and CAR T-cell therapies. However, there were substantial methodological limitations associated with the ITCs including heterogeneity (e.g., study design, outcome definitions, data collection methods, or assessments), matching based on a limited number of variables, and small sample sizes. More specifically, pERC discussed the notable differences in eligibility criteria between the L-MIND study and the external observational cohorts (RE-MIND and RE-MIND2) used for the indirect comparisons and noted that patients included in RE-MIND and RE-MIND2 could have worse performance status (e.g., ECOG greater than 2) or comorbidities (e.g., clinically significant cardiovascular or thromboembolic events, severe hepatic impairment) that would have excluded them from participating in the L-MIND study. pERC also discussed the impact of confounding factors that were not accounted for in the matching (e.g., ECOG PS, double- or triple-hit disease, cell of origin), and agreed that these limitations could have biased the ITC results in favour of tafasitamab plus lenalidomide. In addition, pERC noted that some of the comparators in the ITCs are not commonly used in Canada (e.g., lenalidomide monotherapy, BR). In view of the substantial uncertainty in the ITC results, pERC was unable to draw any definitive conclusions regarding the efficacy of tafasitamab plus lenalidomide compared to other therapies in patients with R/R DLBCL who are not eligible for ASCT.
- Input from patient groups indicated that patients with R/R DLBCL desire treatments that prolong survival and remission, control disease symptoms, improve HRQoL, and have fewer side effects compared to current therapies. Given the

considerable uncertainty around the clinical efficacy results, lack of data on HR-QoL, and insufficient comparative safety data, pERC was uncertain whether tafasitamab plus lenalidomide meets these important patient needs.

Background

Non-Hodgkin lymphoma (NHL) is a cancer of the immune system that encompasses more than 60 types of cancers affecting the lymphocytes. In 2021, it was estimated that 11,100 Canadians would be diagnosed with NHL and 2,900 Canadians would die from NHL that year. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, constituting 30 to 40% of cases in Canada. DLBCL represents a heterogeneous group of aggressive B-cell malignancies. Some types of indolent B-cell lymphomas can transform into DLBCL (e.g., follicular lymphoma). Although the curability rate of DLBCL is high, approximately 30 to 50% of patients in Canada experience relapsed or refractory (R/R) disease after treatment with standard first-line chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or a similar regimen.

Patients with R/R DLBCL have limited treatment options, ranging from supportive care to conventional salvage therapy and autologous stem cell transplant (ASCT). Eligibility for this salvage approach depends on performance status, age, and comorbidities, and eligibility for ASCT is also dependent on the response to salvage chemotherapy. The prognosis of relapsed DLBCL patients who do not undergo high-dose therapy and ASCT is poor. Even for those patients that respond to salvage chemotherapy and undergo ASCT, 50% are likely to relapse following ASCT. In patients with R/R DLBCL who are not eligible for intensive therapies, there is no standard treatment approach. There are numerous chemotherapy options, but response rates are generally low and remission duration is short. Polatuzumab vedotin, bendamustine and rituximab (pola-BR) is an option for Canadians in this setting if funded, as per the clinical experts consulted by CADTH.

Tafasitamab has been approved by Health Canada in combination with lenalidomide for the treatment of adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, who are not eligible for ASCT. Tafasitamab is a monoclonal antibody. It is available as an IV infusion and the dosage recommended in the product monograph is 12 mg/kg body weight. There is currently no Health Canada approved indication for lenalidomide monotherapy in lymphoma.

Sources of Information Used by the Committee

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

- A review of the 1 single-arm, open-label, phase II clinical study in adult patients with DLBCL who had relapsed after or were refractory to 1 to 3 previous systemic regimens (with at least 1 anti-CD20 therapy), and who were not candidates for high-dose chemotherapy (HDC) and subsequent ASCT
- Patient perspectives gathered by 1 patient group, Lymphoma Canada (LC)
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Input from two clinical specialists with expertise diagnosing and treating patients with DLBCL
- Input from 2 clinician groups, including the Ontario Health-Cancer Care Ontario (OH-CCO) Hematology Drug Advisory Committee and a group of 4 clinicians whose submission was coordinated by LC
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

One patient advocacy group provided input on tafasitamab for the treatment of DLBCL in adult patients. LC conducted 4 anonymous online surveys. Overall, 150 DLBCL patients responded to the surveys, of which 2 (1%) indicated they had received tafasitamab therapy. Commonly reported symptoms affecting patients' health-related quality of life (HRQoL) at diagnosis included fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, unexplained weight loss, loss of appetite, flu-like symptoms, and persistent cough. Patients also described mental and emotional problems associated with their disease and treatment that negatively

impacted their quality of life. Patients rated longer survival and remission than with current therapies and controlling disease symptoms as the most important outcomes for a new therapy. Better HRQoL and fewer side effects compared to current therapies were also important considerations.

Clinician input

Input from clinical experts consulted by CADTH

The clinical experts reported that the goal of treatment in patients with R/R DLBCL that are not eligible for intensive therapies (i.e., ASCT and or chimeric antigen receptor T-cell [CAR T-cell] therapy) is to control symptoms with minimal toxicity in order to improve HRQoL, delay disease progression, and prolong life. The clinical experts noted that ASCT and CAR T-cell therapy both have toxicity and feasibility issues that limit broad application. Of the available options for patients who are not eligible for intensive therapies, or relapse after these therapies, there is no standard of care treatment and there is no treatment that is curative (i.e., patients are treated with palliative intent). As per the clinical experts, most currently used treatment options have short durations of response.

The clinical experts indicated that tafasitamab in combination with lenalidomide (tafasitamab + lenalidomide) would be an option at relapse for second-line therapy in patients who are not eligible for intensive therapy. Tafasitamab + lenalidomide treatment could also be used in the third-line or later setting for patients who relapse after ASCT.

The clinical experts thought that patients who would most likely benefit from tafasitamab + lenalidomide are those with relapsed DLBCL, including those with underlying indolent lymphomas. The clinical experts thought that tafasitamab + lenalidomide may be considered in patients who are not eligible for ASCT or CAR T-cell therapy, or who decline either of these treatments. The clinical experts indicated that it is not possible to identify patients who are most likely to respond to tafasitamab + lenalidomide prior to treatment because there is no data on which patient or tumour characteristics are optimal for this treatment compared to other options. The clinical experts thought that patients with primary refractory DLBCL would be least suitable for treatment with tafasitamab + lenalidomide. In addition, the clinical experts noted that patients who cannot come in for frequent IV infusions would not be suitable for this treatment.

The clinical experts consulted by CADTH reported that standard of care for assessing treatment response would be imaging with computed tomography/positron emission tomography (CT/PET) every 3 to 4 months (or sooner if there is a change in the patient's clinical status), and a clinical exam and bloodwork before each treatment. The clinical experts indicated that a clinically meaningful response to treatment would include improvement in survival as well as duration of response (DoR), which would usually correlate with an improvement in symptom burden. As per the clinical experts, meaningful response would include complete response (CR), partial response (PR), or stable disease with a tolerable toxicity profile.

The clinical experts noted that any disease progression should be an indication for treatment discontinuation. The clinical experts thought that recurrent infections, serious infection due to B-cell depletion, and hypogammaglobulinemia may also be considerations for discontinuation.

Clinician group input

Clinician input on the review of tafasitamab for the treatment of adult patients with R/R DLBCL was received from 2 groups: the Ontario Health-Cancer Care Ontario (OH-CCO) Hematology Drug Advisory Committee and a group of 4 clinicians whose submission was coordinated by LC. The clinician groups agreed that tafasitamab + lenalidomide would be recommended in patients with DLBCL who do not respond to or relapse after first-line therapies. There were differing opinions on which patients are unsuitable for tafasitamab. The clinicians from OH-CCO shared that DLBCL patients who have progressed on CAR-T therapies would be least suitable for this therapy while the LC-coordinated group maintained that there are no specific parameters that deem a patient to be unsuitable for this therapy.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for tafasitamab:

- The drug programs noted that the L-MIND study eligibility criteria excluded patients with primary refractory DLBCL and noted that there was a change in definition of primary refractory disease in a protocol amendment. The drug programs noted that patients with a history of double/triple hit genetics DLBCL, CNS lymphoma involvement, and other histological types of lymphoma (e.g., primary mediastinal B-cell lymphoma or Burkitt lymphoma) also were excluded from the L-MIND study.
- The drug programs noted that, in the L-MIND study, the investigator was able to decide if the patient should continue further tafasitamab in the case of disease progression. Also, if both drugs needed to be interrupted for more than 28 days for the same persistent toxicity, then the treatment was discontinued in the L-MIND trial.
- The drug programs noted that patients who have received more than 3 prior lines of treatment but who would otherwise fit the trial criteria would have a time-limited opportunity to receive tafasitamab in combination with lenalidomide at the time of public funding if this was reimbursed.
- The drug programs noted that, if reimbursed, tafasitamab in combination with lenalidomide may need to be sequenced with pola-BR and CAR T-cell therapy.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

One single-arm, multicentre, open-label, phase II study (L-MIND, N=81) of tafasitamab + lenalidomide in adult patients with DLBCL who had relapsed after or were refractory to 1 to 3 previous systemic regimens (with at least 1 anti-CD20 therapy), and who were not candidates for HDC and subsequent ASCT. The primary objective of the L-MIND study was to determine the activity of tafasitamab + lenalidomide in terms of objective response rate (ORR) (complete response [CR] + partial response [PR]) in adult patients with R/R DLBCL. Patients received IV tafasitamab (12 mg/kg) and oral lenalidomide (25 mg/day) for up to 12 cycles (28 days each), followed by tafasitamab monotherapy in patients with stable disease or better until disease progression. The primary endpoint was ORR by independent review committee (IRC). Other efficacy outcomes assessed included ORR by investigator assessment, overall survival (OS), progression-free survival (PFS), time to progression (TTP), event-free survival (EFS), complete response rate (CRR), duration of response (DoR), time to response (TTR), and time to next treatment (TTNT). Harms outcomes were also examined. HRQoL outcomes were not assessed.

In the L-MIND study, the mean age of patients was 69.3 years. Most patients were White (88.9%), Ann Arbor Stage III or IV (75.3%), and did not have a prior ASCT (88.9%). Overall, 54.3% of the enrolled patients were male, 55.6% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1, 50.6% had an International Prognostic Index (IPI) score of 3 to 5, and 46.9% had disease of germinal centre B-cell like (GCB) cell origin by immunohistochemistry. Mean time since first DLBCL diagnosis was 39.6 months (standard deviation [SD]: 34.8). All (100%) patients had ≥1 prior anti-cancer medication; 50.6% of patients had received ≥ 2 prior therapy lines, and 44.4% were refractory to their most recent previous therapy. The most common reasons for ASCT ineligibility were older age (46.3%) and being chemorefractory (22.5%).

Efficacy Results

Three analyses were conducted based on 3 data cuts. The primary analysis had a data cutoff date of November 30, 2018. Two additional interim analyses, which were not prespecified in the study protocol, were conducted with data cutoff dates of November 30, 2019 and October 30, 2020. A final analysis is planned with the final data cutoff at study completion (anticipated for November 2022).

Overall Survival

At the primary analysis, median OS was not reached (NR) (95% confidence interval [CI]: 18.3, NR) with a median follow-up time of 19.6 (95% CI: 15.3, 21.9) months. As of the most recent analysis, the median OS was 33.5 months (95% CI: 18.3, NR) with a median follow-up time of 42.7 (95% CI: 38.0, 47.2) months.

Progression-Free Survival

At the primary analysis, median PFS by IRC was 11.6 months (95% CI: 5.7, NR) with a median follow-up time of 17.6 (95% CI: 14.1, 21.2) months. As of the most recent analysis, median PFS by IRC was 11.6 months (95% CI: 6.3, 45.7) with a median follow-up time of 33.9 ([redacted]) months.

Time to Progression

At the primary analysis, median TTP was 16.2 months (95% CI: 7.4, NR). TTP results were not reported at the subsequent interim analyses.

Event-Free Survival

At the primary analysis, median EFS was 8.7 (95% CI: 5.3, 21.0) months with a median follow-up time of 19.7 (95% CI: 14.3, 22.0) months. EFS results were not reported at the subsequent interim analyses.

Objective Response Rate

ORR by IRC was the primary endpoint in L-MIND. At the primary analysis, the ORR by IRC was 60.0% (95% CI: 48.4, 70.8). The best objective response for patients was CR for 34/80 (42.5%) patients and PR for 14/80 (17.5%) patients. As of the most recent interim analysis, ORR by IRC was 57.5% (95% CI: 45.9, 68.5) 32 (40.0%) patients had CR and 14 (17.5%) patients had PR.

Duration of Response

At the primary analysis, median DoR by IRC was 21.7 (95% CI: 21.7, NR) months. Median DoR by IRC in patients with PR was 4.4 months (95% CI: 2.0, 9.1) and NR (95% CI: 21.7, NR) in patients with CR. As of the most recent interim analysis, median DoR by IRC was 43.9 (95% CI: 26.1, NR) months. Median DoR by IRC in patients with PR was 5.6 (95% CI: 2.2, NR) months compared to NR (95% CI: 43.9, NR) in patients with CR.

Time to Response

At the primary analysis, median TTR (CR or PR) based on IRC evaluation was 2.0 months (range: 1.7 to 16.8 months). At the second analysis, median TTR based on IRC evaluation was 2.0 months (range: 1.7 to 16.8). TTR results were not reported at the most recent interim analysis.

Time to Next Treatment

At the primary analysis, median TTNT was 15.4 (95% CI: 7.6, NR) months. At the second analysis, median TTNT was [redacted] months. TTNT results were not reported at the most recent interim analysis.

Health-Related Quality of Life

HRQoL was not assessed in L-MIND.

Harms Results

Harms data from the L-MIND study safety analysis set (N=81) as of the most recent analysis (October 30, 2020 data cutoff) are summarized below. As of both the primary analysis and most recent analysis, the median duration of exposure to the study treatment (tafasitamab + lenalidomide) was 9.2 months.

Adverse Events

All 81 (100%) patients enrolled in L-MIND experienced ≥1 treatment-emergent adverse event (AE). The most common AEs were neutropenia (50.6%), anemia (37.0%), diarrhea (35.8%), thrombocytopenia (30.9%), and cough (27.2%).

Serious Adverse Events

Overall, 53.1% of patients enrolled in L-MIND experienced ≥1 serious adverse event (SAE). The most common SAEs were pneumonia (n=7, 8.6%), febrile neutropenia (n=5, 6.2%), and pulmonary embolism (n=3, 3.7%). Other SAEs reported in >1 patient included bronchitis, lower respiratory tract infection, atrial fibrillation, and congestive heart failure (n=2, 2.5% each).

Withdrawals Due to Adverse Events

Overall, 20 (24.7%) patients permanently discontinued treatment with 1 or both study drugs due to AEs: [redacted], and 10 (12.3%) discontinued both study drugs. The only AE that led to permanent discontinuation of study drug in >1 patient was neutropenia (n=3, 3.7%).

Mortality

In total, 42 (51.9%) patients enrolled in L-MIND had died as of the October 30, 2020, data cutoff date. [redacted].

Notable Harms

Overall, [redacted] of patients enrolled in L-MIND experienced an infection. The most common types of infections were urinary tract infection (17%), and respiratory tract infections of all grades, including pneumonia and bronchitis (53.1%).

Regarding myelosuppression, 50.6% of patients experienced neutropenia, 36.0% experienced anemia, 30.9% experienced thrombocytopenia, 14.8% experienced leukopenia, 12.3% experienced febrile neutropenia, and 7.4% experienced lymphopenia.

One (1.2%) patient developed progressive multifocal leukoencephalopathy (PML). [redacted] patients experienced hepatitis B virus (HBV) reactivation. Five (6.2%) patients experienced an infusion-related reaction. No patients experienced Grade ≥ 3 tumour lysis syndrome or cytokine release syndrome. Tumour lysis syndrome or cytokine release syndrome events of any grade were not reported.

Indirect Comparisons

Description of studies

Three sponsor-submitted indirect treatment comparisons (ITCs) were included in this review: 2 retrospective observational studies (RE-MIND and RE-MIND2) that were used as external cohorts for indirect comparison with patients enrolled in the L-MIND study, using estimated propensity score (ePS)-based Nearest Neighbour (NN) 1:1 matching methodology, and 1 ITC that used unanchored matching-adjusted indirect comparisons (MAICs). These ITCs were used to inform the pharmacoeconomic models.

RE-MIND was designed to characterize the effectiveness of lenalidomide monotherapy in the treatment of R/R DLBCL patients not eligible for HDC followed by ASCT. The primary endpoint was ORR. Other endpoints assessed included OS, complete response rate (CRR), DoR, PFS, TTNT, and EFS. Data from the L-MIND study used in RE-MIND were from the November 30, 2018 data cutoff (primary analysis).

RE-MIND2 was designed to characterize the effectiveness of systemically administered therapies in the treatment of R/R DLBCL patients (second-line [2L], third-line [3L], fourth-line [4L]). Eligible systemic therapies included regimens administered in routine clinical care according to National Comprehensive Cancer Network (NCCN)/European Society for Medical Oncology (ESMO) guidelines for patients who were not eligible for ASCT. This study included the following treatment cohorts: systemic therapies pooled, bendamustine + rituximab (BR), rituximab + gemcitabine + oxaliplatin (R-GemOx), CAR T-cell therapy, and pola-BR. The primary endpoint was OS. Other endpoints assessed included ORR, CRR, DoR, PFS, [redacted]. Data from the L-MIND study used in RE-MIND2 were from the [redacted]. The prespecified main analysis was

conducted for systemic therapies pooled, BR, and R-GemOx. [redacted] pola-BR and CAR T-cell therapy [redacted] analyses were conducted.

Unanchored MAICs of tafasitamab + lenalidomide in the L-MIND study versus comparator therapies using prospective studies were conducted. In total, 5 prospective studies reporting data for lenalidomide monotherapy, pola-BR, BR, and R-GemOx were selected for the MAICs against tafasitamab + lenalidomide. Endpoints assessed included OS, PFS, DoR, ORR, and CRR. Data were used from the L-MIND study analysis with the October 30, 2020, data cutoff.

Efficacy Results

In RE-MIND, ORR was 67.1% (95% CI: 55.4, 77.5) in the tafasitamab + lenalidomide cohort compared to 34.2% (95% CI: 23.7, 46.0) in the lenalidomide monotherapy cohort (odds ratio [OR]: 3.885; 95% CI: 1.900, 8.142; P<0.0001). Median OS was NR (95% CI: 15.5, NR) in the tafasitamab + lenalidomide cohort and 9.4 (95% CI: 5.1, 20.0) months in the lenalidomide monotherapy cohort (hazard ratio [HR]: 0.499; 95% CI: 0.317, 0.785; P=0.0026). Median PFS was 12.1 (95% CI: 5.9, NR) months in the tafasitamab + lenalidomide cohort and 4.0 (95% CI: 3.1, 7.4) months in the lenalidomide monotherapy cohort (HR: 0.463; 95% CI: 0.307, 0.698; P=0.0002). Median DoR was 20.5 (95% CI: 12.3, NR) months in the tafasitamab + lenalidomide cohort and 6.6 (95% CI: 4.1, 17.2) months in the lenalidomide monotherapy cohort (P[redacted]).

In RE-MIND2, patients in the tafasitamab + lenalidomide cohort showed an improvement in OS compared to the cohorts of systemic therapies pooled (HR: 0.553; [redacted]; P=0.0076), BR (HR: 0.418; [redacted]; P<0.0001), and R-GemOx (HR: 0.467; [redacted]; P=0.0004). An improvement was also observed for PFS in the tafasitamab + lenalidomide cohort compared with the cohorts of systemic therapies pooled (HR: 0.424; 95% CI: 0.278, 0.647; P<0.0001), BR (HR: 0.527; 95% CI: 0.344, 0.809; P=0.0033), and R-GemOx (HR: 0.433; 95% CI: 0.288, 0.653; P<0.0001). The ORR was higher in the tafasitamab + lenalidomide cohort compared to the cohorts of systemic therapies pooled ([redacted]; P=0.0323) and R-GemOx ([redacted]; P=0.0076). There was no difference in ORR in the tafasitamab + lenalidomide cohort compared to the BR cohort ([redacted]; P=0.1810).

In the MAICs, [redacted]. For the comparisons of tafasitamab + lenalidomide to pola-BR, no differences were observed for OS, PFS by IRC, ORR, and CRR. Overall, the results of some of the comparisons to BR favoured tafasitamab + lenalidomide, whereas others indicated no difference. Lastly, in the MAIC of tafasitamab + lenalidomide versus R-GemOx, results indicated no difference between tafasitamab + lenalidomide and R-GemOx for all outcomes assessed.

Harms Results

In RE-MIND2, 8 patients (14.5%, 14.5%, and 15.1% in the analysis sets for comparison to systemic therapies pooled, BR, and R-GemOx, respectively) discontinued due to the AEs in the tafasitamab + lenalidomide cohort. In the cohorts of systemic therapies pooled, BR, and R-GemOx, 5 (6.8%), 2 (2.8%), and 4 (5.4%) patients, respectively had AEs leading to permanent discontinuation of treatment. The types of AEs leading to treatment discontinuation were not reported. The median duration of exposure in the tafasitamab + lenalidomide cohort [redacted] compared to the cohorts of systemic therapies pooled [redacted], BR ([redacted]), and R-GemOx ([redacted]). Harm outcomes were not reported in RE-MIND or the MAICs.

Critical Appraisal

The RE-MIND and RE-MIND2 studies implemented multiple measures to minimize bias, however, important sources of heterogeneity between the L-MIND cohort and observational cohorts could not be accounted for with the methods used. Although the eligibility criteria for enrollment in RE-MIND and RE-MIND2 were based on the eligibility criteria used in the L-MIND study, differences related to the RE-MIND and RE-MIND2 studies being retrospective studies were noted. Comparison of data from a prospective, interventional trial to retrospective, observational studies using real-world data may be problematic as a number of notable differences in data collection, outcomes, and assessments were identified (e.g., tumour assessment frequency, imaging modalities and criteria used to assess response). Most importantly, there is the impact of potential remaining unmeasured confounding factors that were not accounted for in the matching. The RE-MIND and RE-MIND2 studies used 9 covariates for matching in their main analyses (age, Ann Arbor Stage, refractoriness to last therapy line, number of previous lines of therapy,

history of primary refractoriness, prior ASCT, neutropenia, anemia, and elevated LDH). Other known confounders were not accounted for in the matching (e.g., ECOG PS, IPI score, cell of origin, comorbidities) in the main analyses. As a result of these limitations, there is a substantial risk of bias in the RE-MIND and RE-MIND2 study results.

There are also limitations to the external validity of the RE-MIND and RE-MIND2 studies. Lenalidomide monotherapy is not used as a treatment for R/R DLBCL in Canada, as per the clinical experts. RE-MIND-2 included relevant comparators, but the clinical experts consulted by CADTH also indicated that R-GemOx and BR are not commonly used to treat patients with R/R DLBCL in Canada. The clinical experts indicated that pola-BR would be the most relevant comparator, although it is not yet funded. The clinical experts noted that the relevance of CAR T-cell therapy as a comparator for tafasitamab + lenalidomide in patients that are not eligible for ASCT was debatable. The clinical experts considered CAR T-cell therapy to be an intensive therapy and thus more comparable to ASCT. The clinical experts indicated that they would not consider using tafasitamab + lenalidomide in patients that were eligible for CAR T-cell therapy. There are also concerns of whether the systemic therapies pooled cohort adequately reflects current contemporary practice/therapies in Canada.

Although the methods used to conduct the unanchored MAICs followed technical guidance, the analyses have limitations that impact the internal and external validity. Most importantly, not all known effect modifiers and prognostic factors identified by the authors could be adjusted for in the analyses due to the availability of data. The quality of most of the comparator studies was low. Furthermore, multiple sources of heterogeneity (e.g., study design, eligibility criteria, study endpoint definitions, timing of tumour assessments) were identified that could not be accounted for in the analyses conducted. Given these issues, there is substantial concern for the risk of bias in the MAIC results. There are also limitations to the external validity of some of the comparators (i.e., lenalidomide monotherapy, BR, and R-GemOx) as described above. In addition, results may only be generalizable to patients similar to those enrolled in the comparator studies, which may not be representative of patients typically seen in Canadian practice.

Economic Evidence

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplant.
Treatment	Tafasitamab in combination with lenalidomide (tafasitamab + lenalidomide)
Submitted price	$1,167.86 per 200 mg single-use vial of tafasitamab
Treatment cost	At the submitted price, tafasitamab costs $29,196 in the first cycle, $23,357 in the second and third cycles, and $11,679 in the fourth cycle and beyond. Lenalidomide costs $2,078 per 28-day cycle for up to 12 cycles.
Comparators	Base case: R-GemOx, R-GDP, GDP Scenario analysis: Pola-BR, CAR-T (tisa-cel and axi-cel), Pooled comparator (comprising a weighing of all comparators)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	20 years
Key data sources	• Clinical inputs were derived from the single-arm L-MIND trial, RE-MIND2, and a sponsor-submitted MAIC. • Utility values were taken from the NICE review of tisa-cel.
Submitted results	ICER = $199,353 per QALY compared with GDP (incr cost = $503,073, incr QALYs = 2.52). Scenario analysis: ICER is $162,718 per QALY compared with Pola-BR.
Key limitations	• The clinical effects of tafasitamab + lenalidomide are based on a phase II, open-label, single-arm trial of 80 patients, of whom ~10% did not have the underlying condition (DLBCL) upon central pathology review. Data were analyzed descriptively, and no hypothesis testing was undertaken. As such, the clinical data for the regimen in the population under review are associated with uncertainty.

Component	Description
	• The comparative clinical effectiveness of tafasitamab + lenalidomide compared with relevant treatments for R/R DLBCL is unknown due to substantial limitations with the evidence used to inform the comparisons – matching data from the L-MIND trial to an observed cohort (RE-MIND2) and multiple MAICs, each of which were associated with several key methodological limitations. • The key comparator (Pola-BR) was not included in the sponsor's base case analysis. The incorporation of additional comparators in the model (Pola-BR, CAR-T) was not appropriate, given differences in the number of patients matched and impact on efficacy that was not addressed. • The sponsor's PSM structure (based on progression-free survival and overall survival) was not appropriate given the available clinical data for tafasitamab + lenalidomide, for which an NOC/c was given, was based on response rates. In the Product Monograph, Health Canada stated that "an improvement in progression-free survival or overall survival has not been established." • Key assumptions regarding resource use underestimated relative costs associated with tafasitamab + lenalidomide, and in the case of subsequent treatments costs, did not incorporate different efficacy assumptions.
CADTH reanalysis results	CADTH could not address the key limitations associated with the sponsor's economic evaluation pertaining to the clinical evidence and model structure. As such, a CADTH base case was not able to be determined. CADTH corrected errors in the sponsor's model which increased the ICER to $228,224 per QALY compared with GDP. CADTH undertook exploratory analyses assessing alternate efficacy assumptions which resulted in ICERs ranging from $225,000 per QALY to $490,000 per QALY for tafasitamab + lenalidomide compared with relevant comparators, if tafasitamab + lenalidomide was considered to provide additional benefit compared with relevant comparators. If that assumption does not hold, tafasitamab + lenalidomide is dominated (i.e., more costly and associated with equal or fewer QALYs).

Axi-Cel = Axicabtagene ciloleucel ; CAR-T = Chimeric Antigen-Receptor T-cell ; DLBCL = diffuse large B-cell lymphoma; GDP = Gemcitabine + dexamethasone + cisplatin ; ICER = incremental cost-effectiveness ratio; incr = incremental; LY = life-year; NOC/c = Notice of Compliance with conditions; Pola-BR = Polatuzumab + bendamustine + rituximab; PSM = partitioned survival model; QALY= quality-adjusted life-year; R-GDP = Rituximab + gemcitabine + dexamethasone + cisplatin ; R-GemOx = Rituximab + gemcitabine + oxaliplatin ; Tisagenlecleucel = Tisa-Cel.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the model lacked transparency, an updated incidence of NHL was available, the proportions of patients with DLBCL and who received first line therapy were underestimated, subsequent therapies were not modelled appropriately, CAR-T therapies are unlikely to be displaced, the market uptake of tafasitamab in combination with lenalidomide may be overestimated, the relative duration of therapy is uncertain, and the relative administration costs are uncertain.

CADTH reanalysis included updating comparator costs, updating the number of new NHL cases in the base year, increasing the proportion of NHL patients who have DLBCL, increasing the proportion of DLBCL patients who receive a first line therapy, removing CAR-Ts as direct comparators, and reducing the market uptake of tafasitamab in combination with lenalidomide and its displacement of Pola-BR. Under these alterations, CADTH reanalyses reported that the reimbursement of tafasitamab in combination with lenalidomide for adults with R/R DLBCL who are not eligible for ASCT would be associated with a budgetary increase of $14,411,397 in Year 1, $43,026,427 in Year 2, and $75,935,998 in Year 3, for a 3-year total incremental cost of $133,373,822. CADTH was unable to address uncertainties around subsequent therapies, relative duration of therapy, or relative administration costs.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: April 13, 2022

Regrets

One expert committee member did not attend.

Conflicts of Interest

None