

## CADTH Reimbursement Recommendation

# Tafasitamab (Minjuvi)

**Indication:** In combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma not otherwise specified, including diffuse large B-cell lymphoma arising from low grade lymphoma, who are not eligible for autologous stem cell transplant.

**Sponsor:** Incyte Biosciences Canada Corporation

**Final recommendation:** Do not reimburse

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## What Is the CADTH Reimbursement Recommendation for Minjuvi?

CADTH recommends that Minjuvi, in combination with lenalidomide, not be reimbursed by public drug plans for the treatment of 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).

## Why Did CADTH Make This Recommendation?

- The clinical evidence reviewed by CADTH was not strong enough to show whether treatment with Minjuvi in combination with lenalidomide benefits patients with R/R DLBCL. It is not known if Minjuvi in combination with lenalidomide would lead to better outcomes for patients compared to currently available treatments.
- Patients identified a need for treatments that prolong survival and remission, control disease symptoms, improve health-related quality of life (HRQoL), and have fewer side effects compared to current therapies. It is not clear whether Minjuvi in combination with lenalidomide meets these needs.

## Additional Information

### What Is DLBCL?

DLBCL is a cancer of the lymphatic system that develops when the body makes abnormal B lymphocytes. DLBCL is a fast-growing type of non-Hodgkin lymphoma (NHL). If DLBCL comes back after or does not respond to first-line chemotherapy treatment, it is considered R/R. It was estimated that 11,100 people in Canada would be diagnosed with NHL and 2,900 people in Canada would die from NHL in 2021. DLBCL is the most common subtype of NHL, constituting 30% to 40% of cases in Canada. Approximately 30% to 50% of patients in Canada experience R/R disease after treatment with standard first-line chemotherapy.

### Unmet Needs in DLBCL

Patients with R/R DLBCL have limited treatment options, 1 of which is ASCT. However, not all patients are eligible for ASCT. Prognosis of patients with R/R DLBCL remains poor, particularly for those who are not eligible for ASCT. Furthermore, not every patient's disease responds to currently available treatments for R/R DLBCL and remission duration is often short.

### How Much Does Minjuvi Cost?

Treatment with Minjuvi is expected to cost between \$11,679 and \$31,422 per patient per 28-day cycle.

## Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that tafasitamab not be reimbursed 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.

## 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 (i.e., tafasitamab plus 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% confidence interval [CI], 45.9% to 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 nonrandomized, noncomparative, 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. HRQoL was also not assessed in the L-MIND study. The sponsor submitted 3 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 was limited comparative data on harms; thus, no conclusions could be drawn regarding the relative safety of tafasitamab plus 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 (DOR), 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, which is a phase II, single-arm, 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 who were ineligible for ASCT included those who were older than 70 years, had organ dysfunction or comorbidities precluding the use of high-dose chemotherapy and ASCT, had failed a 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 antitumour activity based on the objective response rate (ORR) observed in the L-MIND study. However, pERC noted that the results of the L-MIND study were based on descriptive analyses and did not include formal statistical significance testing; therefore, no robust conclusions could be drawn regarding the efficacy of tafasitamab plus lenalidomide. The committee was concerned about the limitations and inherent biases (e.g., patient selection bias) of noncomparative studies and their risk of providing unreliable efficacy estimates in light of the favourable population of patients enrolled in the L-MIND study. Furthermore, 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 progression-free survival (PFS) times observed in the L-MIND trial were longer than typically expected in patients with R/R DLBCL who are ineligible for ASCT. However, pERC was uncertain whether the OS and PFS results were due to the effects of tafasitamab plus lenalidomide because L-MIND was a single-arm study without a comparator. 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 would be generalized. The clinical experts highlighted that the general population of people living in Canada with R/R DLBCL who are ineligible for ASCT has a greater proportion of patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 2 or greater, relapse within 6 months of completion of initial therapy (primary refractory and early relapse), and have failed prior ASCT or have unfavourable cytogenetics. However, pERC acknowledged that some patients with factors associated with being high risk were enrolled in the L-MIND study, despite the trial eligibility criteria. Also, 10% of the patients included had non-DLBCL lymphomas upon central pathology review, which would be expected to have longer PFS and OS based on natural history, and which would have biased the results. pERC concluded that the generalizability of the PFS and OS results from the L-MIND study to the patient population of those living in Canada 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, or the individual regimens bendamustine plus rituximab (BR), rituximab plus gemcitabine plus oxaliplatin (R-GemOx), polatuzumab vedotin 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, timing of 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 PS (e.g., an ECOG greater than 2) or comorbidities (e.g., clinically significant cardiovascular or thromboembolic events, 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 who are not eligible for ASCT want 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 HRQoL, and insufficient comparative safety data, pERC was uncertain whether tafasitamab plus lenalidomide meets these important patient needs.
- pERC discussed each of the issues identified by the sponsor in their request for reconsideration, which included [REDACTED] [REDACTED]. pERC also considered input received from patient and clinician groups on the draft recommendation issued in April 2022, and feedback from clinical experts and the public drug programs related to the sponsor's reasons for requesting a reconsideration. Due to the limitations of the available evidence from the L-MIND study and ITCs, pERC remained uncertain whether tafasitamab plus lenalidomide meets important therapeutic needs for this patient population that is not eligible for ASCT and has limited treatment options.

## Background

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 people in Canada would be diagnosed with NHL and 2,900 people in Canada would die from NHL that year. 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 R/R disease after treatment with standard first-line chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or a similar regimen.

Patients with R/R DLBCL have limited treatment options, which range from supportive care to conventional salvage therapy and ASCT. Eligibility for this salvage approach depends on PS, age, and comorbidities, and eligibility for ASCT is also dependent on the response to salvage chemotherapy. The prognosis of patients with DLBCL who have relapsed and do not undergo high-dose therapy and ASCT is poor. Even for those patients who 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. pola-BR is an option for people in Canada in this setting, if funded, according to 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 its recommendation, the committee considered the following information:

- a review of 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 2 clinical specialists with expertise in 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.

After the draft recommendation for tafasitamab was issued in April 2022, the sponsor filed a request for reconsideration. In the meeting to discuss the sponsor’s request for reconsideration, the committee considered the following information:

- input from the sponsor, which included comments on the L-MIND study design, the patient population enrolled in the L-MIND study compared to the population of patients with R/R DLBCL living in Canada, the clinical relevance of the outcomes in the L-MIND study, the methodology of the 3 ITCs, and the safety profile of tafasitamab plus lenalidomide in the absence of an HRQoL assessment in the L-MIND study
- feedback on the draft recommendation from 1 patient group, LC
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise in diagnosing and treating patients with DLBCL
- feedback on the draft recommendation from 2 clinician groups, the OH-CCO Hematology Cancer Drug Advisory Committee and LC.

## 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 patients with DLBCL responded to the surveys, of which 2 (1%) indicated they had received tafasitamab therapy. Commonly reported symptoms affecting patients' 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 the Clinical Experts Consulted by CADTH

The clinical experts reported that the goal of treatment in patients with R/R DLBCL who are not eligible for intensive therapies (i.e., ASCT and/or CAR T-cell therapy) is to control symptoms with minimal toxicity 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). Per the clinical experts, most currently used treatment options have short durations of response.

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

The clinical experts indicated that patients who would most likely benefit from tafasitamab plus lenalidomide are those with relapsed DLBCL, including those with underlying indolent lymphomas. The clinical experts thought that tafasitamab plus 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 plus lenalidomide before treatment because there is no data on which patient or tumour characteristics are optimal for this treatment compared to other options. The clinical experts noted that patients with primary refractory DLBCL would be least suitable for treatment with tafasitamab plus lenalidomide and 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 CT or PET scans every 3 to 4 months (or sooner if there is a change in the patient's clinical status), with a clinical exam and bloodwork drawn before each treatment. The clinical experts indicated that a clinically meaningful response

to treatment would include improvement in survival as well as DOR, which would usually correlate with an improvement in symptom burden. 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, and indicated 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 OH-CCO Hematology Cancer Drug Advisory Committee and a group of 4 clinicians whose submission was coordinated by LC. The clinician groups agreed that tafasitamab plus 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 patients with DLBCL who have progressed on CAR T-cell 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 a protocol amendment changed the definition of primary refractory disease. The drug programs noted that patients with a history of double- or triple-hit genetics DLBCL, central nervous system lymphoma involvement, and other histological types of lymphoma (e.g., primary mediastinal B-cell lymphoma or Burkitt lymphoma) were also 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 during the trial for more than 28 days for the same persistent toxicity, then the treatment was discontinued.
- 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 plus lenalidomide at the time of public funding if this was reimbursed.
- The drug programs noted that, if reimbursed, tafasitamab plus 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 plus 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, was reviewed. The primary objective of the L-MIND study was to determine the activity of tafasitamab plus lenalidomide in terms of ORR (CR plus PR) in adult patients with R/R DLBCL. Patients received IV tafasitamab (12 mg/kg) and oral lenalidomide (25 mg per 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 end point was ORR by independent review committee (IRC). Other efficacy outcomes assessed included ORR by investigator assessment, OS, PFS, time to progression (TTP), event-free survival (EFS), complete response rate (CRR), 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%), had Ann Arbor stage III or IV disease (75.3%), and did not have a prior ASCT (88.9%). Overall, 54.3% of the enrolled patients were male, 55.6% had an ECOG PS of 1, 50.6% had an International Prognostic Index score of 3 to 5, and 46.9% had disease of germinal centre B-cell like cell origin by immunohistochemistry. Mean time since first DLBCL diagnosis was 39.6 months (standard deviation [SD] = 34.8). All (100%) patients had experience with 1 or more prior anti-cancer medications; 50.6% of patients had received 2 or more 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 chemo-refractory (22.5%).

#### Efficacy Results

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

#### *Overall Survival*

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

#### *Progression-Free Survival*

At the primary analysis, median PFS by IRC was 11.6 months (95% CI, 5.7 to NR) with a median follow-up time of 17.6 (95% CI, 14.1 to 21.2) months. As of the most recent analysis, median PFS by IRC was 11.6 months (95% CI, 6.3 to 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 to NR). TTP results were not reported in the subsequent interim analyses.

### ***Event-Free Survival***

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

### ***Objective Response Rate***

ORR by IRC was the primary end point in the L-MIND trial. At the primary analysis, the ORR by IRC was 60.0% (95% CI, 48.4 to 70.8). The best objective response for patients was CR for 34 out of 80 (42.5%) patients and PR for 14 out of 80 (17.5%) patients. As of the most recent interim analysis, ORR by IRC was 57.5% (95% CI, 45.9 to 68.5) and 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 to NR) months. Median DOR by IRC in patients with PR was 4.4 months (95% CI, 2.0 to 9.1) and NR (95% CI, 21.7 to NR) in patients with CR. As of the most recent interim analysis, median DOR by IRC was 43.9 (95% CI, 26.1 to NR) months. Median DOR by IRC in patients with PR was 5.6 (95% CI, 2.2 to NR) months compared to NR (95% CI, 43.9 to 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 to NR) months. At the second analysis, median TTNT was ████████ months. TTNT results were not reported in the most recent interim analysis.

### ***Health-Related Quality of Life***

HRQoL was not assessed in the L-MIND trial.

## **Harms Results**

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

### ***Adverse Events***

All 81 (100%) patients enrolled in the L-MIND trial experienced 1 or more treatment-emergent adverse event (AE). The most common AEs were neutropenia (n = 41; 50.6%), anemia (n = 37; 37.0%), diarrhea (n = 29; 35.8%), thrombocytopenia (n = 25; 30.9%), and cough (n = 22; 27.2%).

## **Serious Adverse Events**

Overall, 53.1% of patients enrolled in the L-MIND study experienced 1 or more 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 more than 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 the study drug in more than 1 patient was neutropenia (n = 3; 3.7%).

## **Mortality**

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

## **Notable Harms**

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

Regarding myelosuppression, 50.6% (n = 41) of patients experienced neutropenia, 37.0% (n = 30) experienced anemia, 30.9% (n = 25) experienced thrombocytopenia, 14.8% (n = 12) experienced leukopenia, 12.3% (n = 10) experienced febrile neutropenia, and 7.4% (n = 6) experienced lymphopenia.

One (1.2%) patient developed worsening progressive multifocal leukoencephalopathy. [REDACTED] experienced hepatitis B virus reactivation. Five (6.2%) patients experienced an infusion-related reaction. No patients experienced grade 3 or higher 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 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-based nearest neighbour 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 patients with R/R DLBCL not eligible for HDC followed by ASCT by comparing a matched cohort with the efficacy outcomes observed for tafasitamab plus lenalidomide therapy in the L-MIND trial. The primary end point was ORR. Other end points assessed included OS, CRR, DOR, PFS, TTNT, and EFS. Data from the L-MIND study used in RE-MIND were from the November 30, 2018, data cut-off (primary analysis).

RE-MIND2 was designed to characterize the effectiveness of systemically administered therapies in the treatment of patients with R/R DLBCL (second line, third line, and fourth line) by generating a real-world, synthetic control group for comparison with the L-MIND trial. Eligible systemic therapies for comparison included regimens administered in routine clinical care according to the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines for patients with R/R DLBCL who were not eligible for ASCT. This study included the following treatment cohorts: systemic therapies pooled, BR, R-GemOx, CAR T-cell therapy, and pola-BR. The primary end point was OS. Other end points 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]

Unanchored MAICs of tafasitamab plus 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 plus lenalidomide. End points assessed included OS, PFS, DOR, ORR, and CRR. Data were used from the L-MIND study analysis with the October 30, 2020, data cut-off.

## Efficacy Results

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

In RE-MIND2, patients in the tafasitamab plus lenalidomide cohort showed an improvement in OS compared to the cohorts of systemic therapies pooled (HR = 0.553; 95% CI, 0.358 to 0.855;  $P = 0.0076$ ), BR (HR = 0.418; 95% CI, 0.272 to 0.644;  $P < 0.0001$ ), and R-GemOx (HR = 0.467; 95% CI, 0.305 to 0.714;  $P = 0.0004$ ). An improvement was also observed for PFS in the tafasitamab plus lenalidomide cohort compared with the cohorts of systemic therapies pooled (HR = 0.424; 95% CI, 0.278 to 0.647;  $P < 0.0001$ ), BR (HR = 0.527; 95% CI, 0.344 to 0.809;  $P = 0.0033$ ), and R-GemOx (HR = 0.433; 95% CI, 0.288 to 0.653;  $P < 0.0001$ ). The ORR was higher in the tafasitamab plus 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 plus lenalidomide cohort compared to the BR cohort ([REDACTED]  $P = 0.1810$ ).

In the MAICs, [REDACTED]. For the comparisons of tafasitamab plus 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 plus lenalidomide, whereas others indicated no difference. Lastly, in the MAIC of tafasitamab plus lenalidomide versus R-GemOx, results indicated no difference between tafasitamab plus 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 AEs in the tafasitamab plus 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 plus lenalidomide cohort was longer (approximately 10 months) compared to the cohorts of systemic therapies pooled (2.4 months), BR (3.2 months), and R-GemOx (2.9 months). 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 trial cohort and observational cohorts could not be accounted for with the methods used. Although the eligibility criteria for enrolment 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 lactate dehydrogenase). Other known confounders were not accounted for in the matching (e.g., ECOG PS, International Prognostic Index 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, according to the clinical experts. RE-MIND2 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. They 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 plus lenalidomide in patients who 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. They also indicated that they would not consider using tafasitamab plus lenalidomide in patients who were eligible for CAR T-cell therapy. There are also concerns of whether the systemic therapies pooled cohort adequately reflects current contemporary practice and 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 end point 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 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 previously described. 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 R/R DLBCL who are not eligible for autologous stem cell transplant
Treatment	Tafasitamab in combination with lenalidomide
Dose regimen	Tafasitamab is given at a dose of 12 mg/kg. It is infused on days 1, 4, 8, 15, and 22 in the first 28-day cycle; on days 1, 8, 15, and 22 in the second and third cycles; and on days 1 and 15 in cycle 4 and beyond. Patients self-administer lenalidomide capsules at a starting dose of 25 mg daily on days 1 through 21 of each 28-day cycle for up to 12 cycles. Lenalidomide dosing may be titrated per the product monograph. Treatments are to be used until disease progression or unacceptable toxicity.
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	<ul style="list-style-type: none"> <li>Clinical inputs were derived from the single-arm L-MIND trial, RE-MIND2, and a sponsor-submitted MAIC.</li> <li>Utility values were taken from the NICE review of tisa-cel.</li> </ul>
Submitted results	ICER = \$199,353 per QALY compared with GDP (incremental cost = \$503,073; incremental QALYs = 2.52). Scenario analysis: ICER is \$162,718 per QALY compared with pola-BR.
Key limitations	<ul style="list-style-type: none"> <li>The clinical effects of tafasitamab in combination with lenalidomide are based on a phase II, open-label, single-arm trial of 80 patients, of whom approximately 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.</li> <li>The comparative clinical effectiveness of tafasitamab in combination with lenalidomide compared with relevant treatments for R/R DLBCL is unknown due to substantial limitations with the evidence used to</li> </ul>

Component	Description
	<p>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.</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• The sponsor’s PSM structure (based on progression-free survival and overall survival) was not appropriate given the available clinical data for tafasitamab in combination with 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.”</li> <li>• Key assumptions regarding resource use underestimated relative costs associated with tafasitamab in combination with lenalidomide, and in the case of subsequent treatments costs, did not incorporate different efficacy assumptions.</li> </ul>
<p><b>CADTH reanalysis results</b></p>	<p>CADTH could not address the key limitations associated with the sponsor’s economic evaluation pertaining to the clinical evidence and model structure.</p> <p>As such, a CADTH base case was not able to be determined.</p> <p>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 in combination with lenalidomide compared with relevant comparators, if tafasitamab in combination with lenalidomide was considered to provide additional benefit compared with relevant comparators. If that assumption does not hold, tafasitamab in combination with lenalidomide is dominated (i.e., more costly and associated with equal or fewer QALYs).</p>

axi-cel = axicabtagene ciloleucel; CAR T = chimeric antigen receptor T-cell; DLBCL = diffuse large B-cell lymphoma; GDP = gemcitabine plus dexamethasone plus cisplatin; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; NOC/c = Notice of Compliance with Conditions; pola-BR = polatuzumab vedotin plus bendamustine plus rituximab; PSM = partitioned survival model; QALY = quality-adjusted life-year; R-GDP = rituximab plus gemcitabine plus dexamethasone plus cisplatin; R-GemOx = rituximab plus gemcitabine plus oxaliplatin; R/R = relapsed or refractory; tisa-cel = tisagenlecleucel.

## 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 who received first-line therapy were underestimated, subsequent therapies were not modelled appropriately, CAR T-cell therapies are unlikely to be displaced, the market uptake of tafasitamab plus 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 patients with NHL who have DLBCL, increasing the proportion of patients with DLBCL who receive a first-line therapy, removing CAR T-cells as direct comparators, and reducing the market uptake of tafasitamab plus lenalidomide and its displacement of pola-BR. Under these alterations, CADTH reanalyses reported that the reimbursement of tafasitamab plus 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.

## 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.

#### **Initial meeting date: April 13, 2022**

Regrets: One expert committee member did not attend.

Conflicts of interest: None.

#### **Reconsideration meeting date: September 13, 2022**

Regrets: Three expert committee members did not attend.

Conflicts of interest: None.