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CADTH Reimbursement Recommendation

Ibrutinib (Imbruvica)

Indication: Ibrutinib in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukemia, including those with 17p deletion

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Imbruvica?

CADTH recommends that ibrutinib, in combination with venetoclax, should be reimbursed by public drug plans for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion only if certain conditions are met.

Which Patients Are Eligible for Coverage?

In combination with venetoclax, Ibrutinib should only be covered to treat adult (≥ 18 years) patients with previously untreated CLL, including those with 17p deletion. Patients receiving Imbruvica should be in relatively good health (i.e., have a good performance status, as determined by a specialist). Patients with major surgery within 4 weeks of the first dose of study treatment, bleeding disorder, central nervous system involvement, Richter syndrome, or uncontrolled autoimmune hemolytic anemia or thrombocytopenia should not be eligible for coverage.

What Are the Conditions for Reimbursement?

Imbruvica in combination with venetoclax should only be reimbursed if prescribed by hematologists or oncologists with expertise and experience in the treatment of CLL and monitoring of therapy and if the drug program cost of Imbruvica in combination with venetoclax does not exceed the drug program cost of treatment with the least costly comparator that is reimbursed for the treatment of CLL. Patients who experience disease progression while taking Imbruvica in combination with venetoclax or who cannot tolerate the drug would not be eligible for continued coverage.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Imbruvica in combination with venetoclax resulted in added clinical benefit for patients with CLL.
- Based on CADTH's assessment of the health economic evidence, Imbruvica in combination with venetoclax, may not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a higher cost for Imbruvica in combination with venetoclax compared with other comparators reimbursed for the treatment of CLL throughout treatment.
- Imbruvica, in combination with venetoclax, meets patients' needs for more treatment options for CLL that are better tolerated with favourable

Summary

toxicity profiles compared to current chemoimmunotherapy and Bruton tyrosine kinase inhibitor (BTKi) monotherapies.

- Based on public list prices, Imbruvica, in combination with venetoclax, is estimated to cost the public drug plans approximately $15.4 million over the next 3 years. The estimated budget impact is strongly influenced by assumptions about the proportion of prevalent CLL patients who would initiate treatment following a watch-and-wait period.

Additional Information

What Is CLL?

CLL is a condition with excessive growth and buildup of small mature B-cells in various body parts, like the blood, bone marrow, lymph nodes, and lymphoid tissue. Patients with CLL may experience symptoms similar to lymphoma, such as fever, chills, night sweats, and unintentional weight loss. Other common signs include fatigue, enlarged lymph nodes, or an enlarged spleen. However, some patients may not show any noticeable symptoms at all. CLL is the most common type of leukemia in Western countries; the 2018 Canadian cancer statistics show that the incidence of newly diagnosed CLL is 6.0 per 100,000 population (1,725 new cases).

Unmet Needs in CLL

There are no curative treatments for patients with CLL; therefore, patients require continuous ongoing treatment. In addition, patients may stop responding or relapse on current treatments due to tumour cell resistance. Patients may not tolerate the toxicity and drug interactions of current treatments.

How Much Does Imbruvica Cost?

Treatment with Imbruvica in combination with venetoclax is expected to cost approximately $214,852 for a course of fifteen 28-day cycles.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that ibrutinib in combination with venetoclax be reimbursed for the treatment of adult patients with previously untreated CLL, including those with 17p deletion only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, open-label randomized controlled trial (RCT; GLOW) and 1 phase II multicohort international trial (CAPTIVATE) demonstrated that treatment with ibrutinib plus venetoclax (I+V) resulted in added clinical benefit for patients with CLL. In fludarabine-ineligible patients with CLL without 17p deletion (del[17p]), the GLOW trial (N = 211) demonstrated a statistically significant difference (P < 0.0001) in progression-free survival (PFS) between the I+V and chlorambucil plus obinutuzumab (C+O) treatment arms. In the GLOW trial, the median PFS had not yet been reached in the I+V arm, while the median PFS was 21.0 months (95% confidence interval [CI]: 27.53 months to 28.58 months) in the C+O arm. The hazard ratio (HR) for PFS per independent review committee (IRC) comparing I+V with C+O was 0.216 (95% CI, 0.131 to 0.357; P < 0.0001) in favour of I+V. In fludarabine-eligible patients with CLL without del(17p), the CAPTIVATE fixed-duration (FD) cohort (N = 159) showed that I+V demonstrated a clinically relevant complete response (CR) rate per investigator assessment (IA) of 55.9% (95% CI, 47.5% to 64.2%), which exceeded the prespecified minimum CR rate of 37% (P < 0.0001). The investigator-assessed CR rate was 55.3% (95% CI, 47.6% to 63.1%) in the all-treated patients and 50.0% (95% CI, 28.1% to 71.9%) in patients with del(17p). However, no definitive conclusions could be made about the relative benefit of I+V compared to existing BTKi options (i.e., ibrutinib, zanubrutinib, and acalabrutinib), bendamustine-rituximab (BR), and venetoclax in combination with obinutuzumab (VO) in fludarabine-ineligible or -eligible patients with CLL due to significant limitations of the indirect treatment comparisons (ITCs) using a matching-adjusted indirect treatment comparisons (MAICs) and individual patient data (IPD) observational studies.

pERC recognized the need for more treatment options for patients with CLL, notably for treatments that are better tolerated with favourable toxicity profiles compared to current chemoimmunotherapy and BTKi monotherapies. Within this context, patients with CLL and clinicians recognize the added clinical value of I+V as a targeted and oral FD therapy considered well-tolerated in this patient population. Input from patient groups indicated the need for time-limited treatment options that provide more prolonged remission and symptom control and improved quality of life with fewer side effects. Given the totality of the evidence, pERC concluded that I+V met some of the needs identified by patients as it provides an additional treatment option for oral FD administration with the potential for more prolonged remission.

Due to limitations in the pharmacoeconomic model, estimating the incremental cost-effectiveness of I+V relative to any other comparator treatment was impossible. pERC, therefore, considered the results of a cost comparison analysis considering drug costs alone. At the sponsor-submitted price for ibrutinib and venetoclax and publicly listed prices for other comparator regimens, I+V had higher drug acquisition costs than C+O and VO in the fludarabine-ineligible population and higher drug acquisition costs than BR and

fludarabine, cyclophosphamide, and rituximab (FCR) in the fludarabine-eligible population. The per-cycle drug cost of I+V is higher than that of acalabrutinib monotherapy or ibrutinib monotherapy. Because no conclusions can be drawn about the comparative effectiveness of I+V relative to other comparators, the total drug cost of I+V should not exceed the total drug cost of the lowest-cost alternative reimbursed for patients in this setting.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult (≥ 18 years) patients with previously untreated CLL, including those with 17p deletion	Evidence from the GLOW trial and CAPTIVATE FD cohort showed that I+V demonstrated clinically meaningful benefits for fludarabine-ineligible patients with CLL when compared to C+O, and in fludarabine-eligible patients with CLL compared to a prespecified threshold.	—
2. Patients must have a good ECOG performance status.	No evidence demonstrated a benefit of I+V in patients with ECOG PS greater than 2 at baseline. The GLOW trial and CAPTIVATE FD cohort only included patients with an ECOG PS of 0, 1, or 2.	—
3. Patients must not have any of the following: 3.1. Major surgery within 4 weeks of first dose of study treatment 3.2. Bleeding disorder 3.3. CNS involvement 3.4. Richter's syndrome 3.5. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia	No evidence was identified to demonstrate a benefit of I+V in patients with major surgery within 4 weeks of the first dose of study treatment, bleeding disorder, CNS involvement, Richter's syndrome, or uncontrolled autoimmune hemolytic anemia or thrombocytopenia, as these patients were not enrolled in the GLOW trial and CAPTIVATE FD cohort.	—
Renewal		
4. Renewal of I+V should be based on assessments as per clinical standard of care to be performed every 1 to 3 months.	The clinical expert consulted by CADTH indicated that response to treatment is assessed by changes in peripheral blood counts, which can easily be documented by clinicians looking after patients. The clinical expert stated that repeat bone marrows are not often performed in clinical practice but were required as part of the formal response criteria for clinical trials.	—
Discontinuation		
5. Treatment with I+V should be discontinued upon the occurrence of any of the following: 5.1. Progression of disease	No evidence was identified to demonstrate that continuing treatment with I+V in patients whose disease has progressed is effective.	—

Reimbursement condition	Reason	Implementation guidance
according to iwCLL response assessment criteria 5.2. Unacceptable toxicity		
Prescribing		
6. I+V should only be prescribed by hematologists/oncologists with expertise and experience in treating CLL and monitoring therapy.	To ensure that I+V is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
7. I+V should be negotiated so that it does not exceed the drug program cost of treatment, with the least costly comparator reimbursed for the treatment of CLL.	There is insufficient evidence to justify a cost premium for I+V over the least expensive comparator reimbursed for CLL. This is due to the limitations within the direct head-to-head evidence and the inability to conclude the indirect comparison. I+V is a fixed-dose regimen, so a price reduction may be required to ensure similar health care system costs compared to other regimens.	Per-cycle drug costs for I+V are higher than per-cycle drug costs for C+O and VO and higher than per-cycle drug costs for BR and FCR. These are also fixed-dose regimens. Per-cycle drug costs for I+V are higher than per-cycle drug costs for acalabrutinib monotherapy and ibrutinib monotherapy. These regimens are administered until progression. Consequently, the total health care system cost of these regimens depends on the progression-free survival duration.
Feasibility of adoption		
8. The feasibility of the adoption of I+V must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

CLL = chronic lymphocytic leukemia; CNS = central nervous system; C+O = chlorambucil plus obinutuzumab; del(17p) = deletion of 17p; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FD = fixed duration; I+V = ibrutinib plus venetoclax.

Discussion Points

- pERC discussed the potential of I+V meeting patients' needs and to be cost-saving, with I+V being a fixed duration and entirely oral regimen. According to clinical expert opinion, patients exhibiting good responses will likely be offered the same treatment again as those patients are not necessarily resistant, which could be an advantage compared to continuous BTKi treatments. Overall, the clinical expert commented to pERC that an FD treatment (i.e., I+V) might be attractive and used for older or higher-risk patients who have impaired renal function and/or atrial fibrillation, as those patients are more likely to experience adverse events if they have been exposed to BTKis for a long time.
- pERC noted that although the Health Canada–approved indication includes patients with del(17p), there was a limited number of patients with del(17p) included in the CAPTIVATE FD cohort (n = 20),

which may have contributed to inconsistent results in the subgroup analysis of patients with del(17p); therefore, it was uncertain whether the benefit of I+V would be consistent in patients with del(17p). pERC heard from the clinical expert who expressed confidence in the efficacy of BTKis in CLL patients with del(17p) based on the available evidence on BTKi monotherapies in CLL, particularly in genetically high-risk patients.

- pERC discussed the control arm of the GLOW trial (i.e., C+O), which does not reflect the current standard of care. pERC heard from the clinical expert that C+O is an old historic treatment being used occasionally as a standard therapy in an older population of CLL patients but not necessarily in a younger population of CLL patients. The clinical expert added that continuous BTKi (ibrutinib, acalabrutinib, and zanubrutinib) would be considered more relevant comparators. The clinical expert indicated that ibrutinib and venetoclax as monotherapies, chemoimmunotherapy such as BR, and venetoclax in combination with obinutuzumab (VO), and other BTKis (i.e., acalabrutinib and zanubrutinib) would be more appropriate comparators in the first-line setting for patients with CLL. pERC noted that although C+O is not commonly used as a first-line standard option, it was the control arm of many pivotal trials in first-line CLL for patients who were ineligible for fludarabine. Of note, acalabrutinib is approved for treating CLL based on a phase III trial (ELEVATE TN) of acalabrutinib versus acalabrutinib-obinutuzumab versus C+O.
- The sponsor submitted 2 MAICs and 2 IPD observation studies of I+V to relevant comparators in Canada. Still, there were significant limitations of the analyses, which may limit the interpretability of the comparative efficacy results and compromise the generalizability of the results to the patients across Canada. Overall, pERC concluded that limited conclusions could be made on the relative benefit of ibrutinib compared to existing BTKi (i.e., acalabrutinib and zanubrutinib), BR, or VO in fludarabine-ineligible or -eligible patients with CLL based on the submitted indirect comparative evidence.
- pERC discussed the feedback from patient groups emphasizing their experience of better tolerability with I+V over other treatment options. Improving survival, control of disease symptoms, longer remission, and better quality of life while minimizing side effects were all identified by patients as important outcomes. However, given the limitations of the trials and ITC evidence, pERC concluded that only limited interpretations could be made on the benefits of I+V on HRQoL or adverse effects over the other available treatment options.
- pERC noted the Study CLL17, which is an ongoing phase III, multicentre, randomized, prospective, open-label trial comparing the efficacy of continuous ibrutinib monotherapy with FD VO and FD I+V, and may address the evidence gap of direct comparisons between I+V and relevant comparators.
- The pharmacoeconomic model lacked sufficient rigour to estimate the cost-effectiveness of I+V relative to any of the included comparators due to the presence of 2 serious methodological limitations. First, the methods used to determine state membership were inconsistent with the requirements of the declared model structure. Second, the model failed to incorporate the desired treatment-free interval following first-line progression, revealing additional concerns about the

model's face validity. pERC could not draw any conclusions about the incremental cost-effectiveness or magnitude of the necessary price reduction.

- The per-cycle drug cost of I+V is higher than that of acalabrutinib monotherapy or ibrutinib monotherapy. However, because I+V is a fixed-dose regimen, the total drug costs among patients who remain progression-free for longer than 2.2 years are expected to be lower for patients receiving I+V than they are for patients receiving acalabrutinib monotherapy. Conclusions about overall cost savings to the health care system are difficult to draw since they will depend on the relative effectiveness of each regimen and the risk of adverse events.
- The budget impact estimate was subject to considerable uncertainty surrounding the number of existing cases initiating treatment after a watch-and-wait period. Clinical experts consulted by CADTH suggested this estimate was too low and that a much higher proportion of prevalent cases may be expected to initiate treatment following a watch-and-wait period. This would increase the costs for all treatments and increase the overall budget impact of I+V.

Background

CLL is a lymphoproliferative B-cell malignancy characterized by the progressive expansion of monoclonal B lymphocytes in the blood, bone marrow, lymph nodes, or other lymphoid tissue. CLL is a rare disease with low prevalence and incidences worldwide. However, it is the most common adult leukemia in Canada. In 2018, 1,725 patients were diagnosed with CLL (1,095 men and 630 women). Several genetic alterations can influence prognosis, including the deletion of 17p (del[17p]), resulting in the loss of tumour protein 53 (TP53), which is 1 of the poorest prognostic factors for CLL. Other genetic alterations, including TP53 mutation without del(17p), unmutated immunoglobulin gene heavy chain variable region (IGHV), deletion of 11q (del[11q]), and complex karyotype (i.e., > 3 cytogenetic aberrations) are associated with a poor prognosis in CLL. For many patients with CLL, the disease burden is increased by the presence of major comorbidities and frailty, as well as toxicities associated with standard-of-care chemotherapy-based regimens. CLL is generally considered incurable. The 5-year net survival for CLL is 83%, and in 2020, 554 Canadians died from CLL. Median life expectancy for patients with the del(17p) or TP53 mutation is fewer than 2 to 3 years from initial diagnosis. Among patients deemed ineligible for FCR, treatment with chemoimmunotherapy (CIT) such as chlorambucil plus obinutuzumab (C+O), venetoclax-obinutuzumab (VO), and continuous BTK inhibitors (e.g., ibrutinib or acalabrutinib) may be used. For patients with high-risk features (i.e., del(17p) and/or TP53 mutation) regardless of age/fitness, BTK inhibitors are the preferred treatment option even though VO is still available. Among younger patients (ages 18 to 64) without del(17p) or TP53 mutations, FCR is recommended as a first-line treatment for those with mutated IGHV. For younger patients who are fit, with unmutated IGHV, BTK inhibitors are preferred over FCR. VO is a treatment option for these patients, albeit with less durable remission than BTKi, and is not reimbursed publicly. Based on clinician input collected by CADTH, continuous BTK inhibitors are most commonly used in Canada for younger patients with higher-risk mutations such as TP53 mutations, 11q mutations, or unmutated IGHV genes.

Ibrutinib, combined with venetoclax, has been approved by Health Canada for treating adult patients with previously untreated CLL, including those with del(17p). Ibrutinib is an oral, first-in-class, targeted Bruton's tyrosine kinase inhibitor (BTKi). Venetoclax is an oral inhibitor of B-cell lymphoma-2. For treatment of untreated CLL with an ibrutinib and venetoclax combination, the recommended dosing schedule is ibrutinib 420 mg (three 140 mg capsules) administered orally once daily for three 28-day cycles, followed by ibrutinib 420 mg plus venetoclax 400 mg, administered orally daily for twelve 28-day cycles. Venetoclax dosing should be initiated in cycle 4 with a dose ramp-up over 5 weeks (20 mg, 50 mg, 100 mg, 200 mg, and 400 mg daily) and continued at 400 mg daily from cycle 5 onward.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, open-label multicentre RCT (GLOW) in patients who are fludarabine-ineligible and 1 phase 2 multicohort international trial (CAPTIVATE) in patients who are fludarabine-eligible
- patients' 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 1 clinical specialist with expertise in diagnosing and treating patients with CLL
- input from 2 clinician groups, including Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee and a group of 2 clinicians who treat CLL and small lymphocytic lymphoma in Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

LC is a national charity that engages in education, support, advocacy, and research activities for the patients and lymphoma community. LC conducted an online anonymous patient survey between March 22, 2023 and May 2, 2023. A total of 87 patients, including 49 Canadians. responded to the survey. As most patients with CLL experience no or minor symptoms, many respondents indicated that CLL did not strongly impact their daily activities at diagnosis. A total of 64 respondents rated fatigue (47%), high white blood cell counts (26%), body aches and pains (25) as highly negative impacts (3 to 5 out of 5) at diagnosis. Among 71 respondents who reported psychosocial effects of CLL diagnosis, anxiety and worry (61%), stress of diagnosis (59%), and difficulty sleeping (28%) were the most common. The most highly rated negative physical symptoms (3 to 5 out of 5) among 70 respondents included fatigue (44%), body aches and pains (27%), and indigestion, abdominal pain, or bloating (17%). Most negatively rated effects on quality of life among 87 respondents included anxiety and worry (42%), difficulty sleeping (31%), and stress of diagnosis (28%). When considering

a novel CLL treatment, respondents cited living longer (81%), controlling symptoms (75%), longer remission (71%), better quality of life (66%), and fewer side effects (35%) as extremely important.

Of 10 patients with CLL with specific experience with I+V regimen, 5 patients are in remission for 2 to 5 years. In 10 patients treated with I+V regimen, improvement has been noted in high white blood counts (80%), enlarged lymph nodes (70%), low platelet and red blood cell counts (60%), and weight loss (30%).

The input highlighted that a time-limited, oral I+V therapy option would be especially beneficial for those living in rural areas and cost-saving for health care system. Of note, 24% of the respondents noted a positive of the fixed duration of treatment. Also, 55% of patients reported that having more treatment options is very important.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH indicated that the most important goals of treatment of patients with CLL is to reverse symptoms and control the disease for as long as possible with treatments that have minimal toxicity and do not have a significant negative impact on the quality of life. The clinical expert stated that the most significant limitation to current treatments for patients with CLL is that tumour cell resistance usually occurs, and patients stop responding or relapse on therapy. Other limitations include toxicity and drug interactions, the requirement for continuous ongoing treatment, and there are no curative treatments for patients with CLL. The clinical expert stated that other considerations might be addressed, including the opportunity for FD treatment versus continuous treatment and achieving undetectable minimal residual disease. The clinical expert stated that this combination therapy could be used as a first-line setting and possibly in recurrent disease and in patients with CLL who have some level of resistance or at least have been exposed to the drugs in the combination. In addition, the clinical expert speculated that it is potentially possible that this combination therapy could be used in patients who are resistant to 1 of the drugs in the combination. However, this would have to be shown in evidence. Overall, the clinical expert stated that I+V could be used in patients exposed but not necessarily resistant to either of these drugs. The clinical expert stated that there is a possible shift in the current treatment paradigm with the combination therapy; this is because the drugs are stopped after a fixed period, which is different than the paradigm of continuous therapy that is used for the different BTK inhibitors. The clinical expert commented that older or younger patients with a high Cumulative Illness Rating Scale (CIRS) score or reduced creatinine clearance, regardless of the del(17p)/TP53 mutations status, should be suited for I+V. In addition, patients with bulky disease or high lymphocyte counts, or impaired creatinine clearance, which are considered at higher risk for tumour lysis syndrome, would also be suitable for I+V as ibrutinib was given before the venetoclax to reduce the risk of tumour lysis. The clinical expert mentioned that there were no factors identified in the subgroup analysis indicating any subset of patients who would be most likely to respond or conversely, less likely to respond to the combination therapy. All symptomatic patients with CLL need treatment. The clinical expert indicated that response to treatment is assessed by changes in peripheral blood counts, which can easily be documented by clinicians looking after patients. In addition, as per feedback for the clinical expert, minimal residual disease (MRD) assessments were also used from peripheral blood and bone marrow using

2 technologies: Next generation sequencing and multicolour flow cytometry. The clinical expert stated that death and disease progression, measured by increasing lymphocyte count or enlarging lymph nodes or spleen, are major reasons for discontinuing the treatment of ibrutinib in combination with venetoclax. Similar to other BTKis, the clinical expert stated that ibrutinib in combination with venetoclax treatment should be managed by a specialist (i.e., hematologist or medical oncologist) who is familiar with this class of drugs to manage toxicities and dosing optimally.

Clinician Group Input

Seven clinicians from Ontario (Cancer Care Ontario) Hematology Cancer Drug Advisory committee (OH-CCO Hem DAC) and 2 clinicians who treat CLL and small lymphocytic lymphoma (SLL) in Canada submitted 2 separate clinician group input. The 2 clinician groups and a clinical expert consulted by CADTH agree that I+V would be the first-line option for patients with CLL and also suitable for later settings in specific clinical situations. OH-CCO Hem DAC added that I+V may be limited to healthy populations, i.e., younger populations, due to safety concerns around cardiovascular adverse effects. All clinicians agreed that having a time-limited treatment option is an unmet need, discontinuing therapy would be considered in case of disease progression, and hematologists and/or medical oncologists should be involved in managing patients with CLL being treated with I +V. Additionally, the clinical expert consulted by CADTH stated that the development of tumour cell resistance, drug interactions, and a lack of curative therapy are also unmet needs. Both clinician groups and the clinical expert consulted by CADTH agree that symptom control, disease control (undetectable MRD), and time off treatment are important therapy goals for I+V treatment. The 2 clinician groups added that improvement in PFS and quality of life, along with minimal toxicity from I+V treatment, as added by the clinical expert, are the desired goals of therapy. None of the clinicians had experience in treating CLL with the I+V combination.

Drug Program Input

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

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
Relevant funded comparators include acalabrutinib, ibrutinib monotherapy, venetoclax plus obinutuzumab, obinutuzumab plus chlorambucil (comparator in GLOW trial), and other rituximab-based chemoimmunotherapy combinations (e.g., bendamustine-rituximab, chlorambucil-rituximab). Zanubrutinib is currently going through CADTH review for previously untreated and relapsed-refractory CLL-SLL in adult patients, but a recommendation has not yet been issued.	Comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
Ibrutinib+venetoclax is given as a fixed duration. For patients whose disease recurs after the completion of therapy, is there evidence to support re-treatment? The CAPTIVATE study gave specific details on re-treatment: "After completion of the FD regimen, patients who subsequently had confirmed progressive disease (PD) by iwCLL criteria could be retreated with single-drug ibrutinib until PD or unacceptable toxicity." Is there evidence to support the re-treatment with single-drug ibrutinib?	The clinical expert consulted by CADTH stated that there is no evidence yet. However, if patients have a durable response to first treatment (i.e., at least 3 years DOR) then the clinical expert would speculate that re-treatment with ibrutinib + venetoclax would be considered. pERC acknowledged the clinical expert's recommendation but determined that a 1-year DOR to first treatment would suffice for re-treatment with ibrutinib + venetoclax to be considered. pERC also noted that the assessment of single-drug ibrutinib as re-treatment was beyond the scope of this review.
Other BTK inhibitors approved in Canada (ibrutinib and acalabrutinib) are currently reimbursed for both CLL and SLL, though Health Canada has approved none for use in SLL. Would it be appropriate to extend reimbursement of ibrutinib with venetoclax to patients with SLL?	CADTH would like to note that ibrutinib, combined with venetoclax, has received approval from Health Canada for treating adult patients with CLL. The indication did not include patients with SLL. Acknowledging that usage would be off-label in Canada, pERC noted that jurisdiction could consider extending reimbursement of ibrutinib in combination with venetoclax to patients with SLL for the following reasons: • Clinical experts consulted by CADTH noted that CLL and SLL are treated the same in Canadian clinical practice. • SLL is rare condition and there are no BTK inhibitors treatments and venetoclax-based regimens specifically approved for use in these patients in Canada. • Ibrutinib is another BTK inhibitor that is currently reimbursed by the participating plans.
Considerations for prescribing of therapy	
Ibrutinib should be administered as a single drug at a dose of 420 mg once daily for three 28-day cycles, followed by ibrutinib 420 mg plus venetoclax 400 mg daily for twelve 28-day cycles. Venetoclax should be initiated at cycle 4 with dose ramp-up over 5 weeks.	Comment from the drug programs to inform pERC deliberations.
If a patient experiences intolerance to ibrutinib, can treatment with venetoclax monotherapy be continued?	The clinical expert consulted by CADTH confirmed that treatment with venetoclax monotherapy should be continued if a patient experiences intolerance to ibrutinib because venetoclax monotherapy is an active therapy in treating patients with CLL. The clinical expert noted that patients receiving venetoclax monotherapy may have an elevated risk of tumour lysis syndrome at the beginning of the treatment. pERC agreed with the clinical expert that administering ibrutinib in combination with venetoclax would reduce the risk of tumour lysis syndrome in patients with CLL. If patients have to stop ibrutinib due to intolerance, it is safe to continue venetoclax as monotherapy.
Generalizability	
Should patients currently receiving ibrutinib monotherapy and have not experienced disease progression be eligible for the addition of venetoclax?	pERC cannot comment on this specific enquiry as no data are available. However, pERC asserts that, as a general rule, patients who are already responding to therapy and are not experiencing

Drug program implementation questions	Clinical expert response
	toxicity should remain on the current therapy without adding a new treatment.
Funding algorithm (oncology only)	
Drugs may change place in therapy of comparator drugs	Comment from the drug programs to inform pERC deliberations.
Under what clinical circumstances would ibrutinib-venetoclax be used over existing first-line drugs? • Need clarity on the eligible patient population • Will impact downstream sequencing	pERC agreed with the clinical expert consulted by CADTH that several treatments are currently available for first-line treatment. pERC also noted that using I+V as a first-line treatment for CLL would impact subsequent treatment sequencing. Further, it is unclear how BTK inhibitors compare to venetoclax-based combination therapies as first-line treatment.
Care provision issues	
Ibrutinib is a 140 mg capsule in a bottle of 90 capsules. The product monograph indicates to store at room temperature between 15°C to 30°C.	Comment from the drug programs to inform pERC deliberations.
Ibrutinib has the potential for drug-drug, drug-food, drug-herb, and drug-laboratory interactions, requiring assessment and/or intervention.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
Feasibility of adoption (budget impact) is a concern.	Comment from the drug programs to inform pERC deliberations.

BTK = Bruton Tyrosine Kinase; CLL-SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DOR = duration of response; I+V = ibrutinib plus venetoclax; PFS = progression-free survival.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

The GLOW trial is a multicentre, randomized, open-label phase III study that compared the efficacy and safety of the combination of I+V to C+O for the first-line treatment of patients with CLL. GLOW enrolled patients from a population of older patients with previously untreated CLL who were unable to be treated with a fludarabine-based regimen. Patients with del(17p) or known TP53 mutation were excluded because these aberrations are associated with inferior outcomes with chemoimmunotherapy (i.e., C+O). Patients (N = 211) were randomized 1:1 to receive I+V (n = 106) or C+O (n = 105). The CAPTIVATE trial is a multicentre, phase II, single-arm study, also assessing time-limited treatment with the combination of I+V of patients with treatment-naive CLL-SLL in either an MRD-guided discontinuation cohort (N = 164) or a FD cohort (N = 159), sequentially enrolled. The MRD cohort will not be further discussed as the sponsor is not proceeding with this treatment regimen. This review focuses on the CAPTIVATE FD cohort, which enrolled 159 patients eligible for the fludarabine-based regimen. Eligible patients for the CAPTIVATE FD cohort were 18 to 70 years of age with previously untreated CLL or SLL requiring treatment per the international workshop on chronic lymphocytic leukemia (iwCLL) criteria. They had measurable nodal disease by CT, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 2, and adequate hepatic, renal, and hematologic

function. There were 2 study Canadian sites included in the GLOW trial and no sites in Canada for the CAPTIVATE FD cohort.

The primary end points were PFS per IRC in the GLOW trial and CR rate per IA in the CAPTIVATE FD cohort. Other secondary or exploratory outcomes of interest included the PFS per IA, overall survival (OS), overall response rate (ORR; per IRC and IA), CR rate per IRC, improvement in hematological parameters(secondary outcome for the GLOW trial; exploratory outcome for the CAPTIVATE FD cohort), duration of response (DOR; per IRC and IA), time to subsequent treatment (TTNT, GLOW only), MRD negativity rate, tumour lysis syndrome (TLS) risk reduction, and health-related quality of life (HRQoL; GLOW only).

For the fludarabine-ineligible patients included in the GLOW trial, the majority of patients enrolled were men (57.8%) who were white (95.7%), 42.2% of patients were female, 0.5% of patients were Asian, 0.5% of patients were multiple races, and 3.3% of patients did not report their race. Median age was 71 years (range: 47 to 93), with 87.2% of patients at least 65 years of age and 34.1% of patients at least 75 years of age. Advanced-stage disease at baseline was reported for 54.8% of patients based on Rai Stage III-IV disease and 42.1% of patients based on Binet Stage C disease. About half of the patients had a baseline ECOG PS of 1 (53.1%). Overall, the proportion of patients with high-risk disease, defined by the presence of del(11q), unmutated IGHV, or TP53 mutation, was similar between treatment arms (59.4% versus 57.1% for I+V versus C+O). For fludarabine-eligible patients included in the CAPTIVATE FD cohort, the median age at baseline was 60.0 years (range: 33 to 71 years), with 28.3% of patients at least 65 years of age. More patients were male (66.7%), and most were white (92.5%). At baseline, more patients (69.2%) had an ECOG PS score of 0. Cytogenetic characteristics indicative of poor prognosis (per hierarchical classification) were del(17p) (12.6%) and del(11q) (17.6%). Other poor prognostic characteristics included TP53 mutated (10.1%), del(17p)/TP53 mutated (17.0%), unmutated IGHV (56.0%), and complex karyotype (19.5%).

Efficacy Results

Progression-Free Survival

In the GLOW study, PFS per IRC was the primary end point. At the time of primary analysis (data cut-off: February 26, 2021), the data recorded a median follow-up time of 27.7 months (95% confidence interval [CI], 27.50 to 27.83) in the I+V arm and 27.89 months (95% CI, 27.53 to 28.58) in the C+O arm. The median PFS per IRC was not reached for the I+V arm and was 21.0 months for the C+O arm. Based on IRC assessment, the HR for PFS events was 0.216 (95% CI, 0.131 to 0.357; $P < 0.0001$). Events of disease progression or death were reported for 20.8% of patients in the I+V arm (13 disease progression events and 9 deaths) and 63.8% of patients in the C+O arm (65 disease progression events and 2 deaths). Subgroup analyses and prespecified sensitivity analyses of PFS per IA in the primary analysis were generally consistent with the primary analysis across all prespecified subgroups except for race and disease diagnosis at baseline. Generally, results were similar during the extended follow-up (data cut-off: August 25, 2022).

In the CAPTIVATE fixed-duration cohort, the primary analysis (data cut-off: November 12, 2020), median PFS by IRC assessment was not reached in the all-treated FD cohort based on an overall median follow-up of 27.9 months. The PFS event rate probabilities in the all-treated FD cohort were 14.5% (21 disease progression events and 2 deaths) at the time of primary analysis. Of note, results for median PFS per IRC for all patients

and for patients with del(17p) were based on an immature time point after the median follow-up and were therefore considered to be unreliable by the sponsor. Generally, similar results were observed with PFS per IA and in the extended follow-up analysis (data cut-off: August 04, 2021).

Overall Survival

In the GLOW study, in the primary analysis (data cut-off: February 26, 2021), the median OS was not reached in either arm. With a median follow-up of 27.7 months for the I+V arm and 27.89 months for the C+O arm, there were 11 (10.4%) deaths observed in the I+V arm and 12 (11.4%) deaths observed in the C+O arm (HR = 1.048, 95% CI, 0.454 to 2.419; nominal P = 0.9121). Similarly, median OS was not reached in either arm in the extended follow-up analysis (data cut-off: August 25, 2022)

In the CAPTIVATE FD cohort, in the primary analysis (data cut-off: November 12, 2020), median OS was not reached in the all-treated FD cohort based on an overall median follow-up of 27.9 months, there were 3 deaths (1.9%) reported in the all-treated FD cohort, and no death reported in patients with del(17p). Most patients were alive and on study with OS probabilities of 98.1% at 24 months at the primary data cut-off date and at 36 months at the extended follow-up analysis data cut-off date (August 4, 2021) for the all-treated FD cohort. All patients with del(17p) were alive and on study at the primary data cut-off date and at the extended follow-up analysis data cut-off date.

Overall Response Rate

At the GLOW primary analysis (data cut-off: February 26, 2021), the IRC-assessed ORR (of partial response [PR]or better) was similar between the I+V and C+O arms (86.6% versus 84.8% for I+V versus C+O; relative response = 1.02, 95% CI, 0.92 to 1.14; P = 0.6991). Similar results were observed in the ORR based on IA. Generally similar results were observed in the extended follow-up analysis (data cut-off: August 25, 2022). Of note, as the difference in ORR based on IRC assessment between treatment arms was not statistically significant (P = 0.6991) in the primary analysis, the hierarchical statistical testing strategy ended at ORR per IRC. The remaining key secondary end points (i.e., OS, sustained hematological improvements, and time to improvement in the Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue Score) and ORR per IA were considered not statistically significant.

In the CAPTIVATE FD cohort, in the primary analysis (data cut-off: November 12, 2020), the ORR per IRC assessment was 96.2% (95% CI, 93.3% to 99.2%) for all treated patients and 100.0% (95% CI, 100.0% to 100.0%) for patients with del(17p). Generally, similar results were observed with ORR per IA and in the extended follow-up analysis (data cut-off: August 04, 2021).

Complete Response (CR, including CR and complete response with an incomplete marrow recovery [CRi]) rate

In the GLOW study, in the primary analysis (data cut-off: February 26, 2021), the IRC-assessed CR rate was higher in the I+V arm compared with the C+O arm (38.7% versus 11.4% for I+V versus C+O; relative response = 3.43; 95% CI, 1.91 to 6.15; P < 0.0001). Similar results were observed at the time of the 18-month extended follow-up (data cut-off: August 25, 2022) and with CR rate per IA.

In the CAPTIVATE FD cohort, CR rate by IA was assessed as the primary end point. In patients without del(17p) in the FD cohort, CR rate per IA was met at 55.9% (95% CI, 47.5% to 64.2%), which exceeded the prespecified minimum CR rate of 37% (1-sided P < 0.0001) in the primary analysis (data cut-off: November 12, 2020). Similar results were observed in the extended follow-up analysis (data cut-off: August 04, 2021) with a CR rate of 58.1% (95% CI, 49.8% to 66.4%) based on IA. The investigator-assessed CR rate in the all-treated patients was 55.3% (95% CI, 47.6% to 63.1%) in the primary analysis and 57.2% (95% CI, 49.5% to 64.9%) in the extended follow-up analysis. For those patients with del(17p), the CR rates per IA were identical with 50.0% (95% CI, 28.1% to 71.9%) in the primary analysis and in the extended follow-up analysis.

Subgroup analyses of CR rate per IA, sensitivity analyses using CR rate per IRC and duration of CR, and supportive analysis of duration of CR were generally consistent with the primary analysis. The subgroup analysis results were consistent across all prespecified subgroups except for bulky disease. Refer to Appendix 1 for the detailed subgroup analyses data.

Sustained Hematologic Improvement

In the GLOW study, in the primary analysis (data cut-off: February 26, 2021), the proportion of patients with sustained improvement in hemoglobin was similar for I+V compared with C+O (44.3% versus 50.5% for I+V versus C+O; nominal P = 0.3854). The proportion of patients with sustained platelet improvement was similar for I+V compared with C+O (24.5% versus 29.5% for I+V versus C+O; nominal P = 0.4346). Similar results were observed at the time of the 18-month extended follow-up (data cut-off: August 25, 2022).

In the CAPTIVATE FD cohort, in the primary analysis (data cut-off: November 12, 2020), the proportion of patients achieving a sustained improvement in hemoglobin was 41.5% (95% CI, 33.9% to 49.2%) in all treated patients and 60.0% (95% CI, 38.5% to 81.5%) in patients with del(17p). The proportion of patients with sustained improvement in platelets was 17.6% (95% CI, 11.7% to 23.5%) in all treated patients and 15.0% (95% CI, 0 to 30.6%) in patients with del(17p). Similar results were observed in the extended follow-up analysis (data cut-off: August 04, 2021).

Duration of Response

In the GLOW study, as of the data cut-off for the primary analysis (February 26, 2021), with an overall median follow-up of 27.7 months, the median DOR for patients who achieved an IRC-assessed PR or better was 28.9 months (95% CI, 28.7 to not estimable [NE]) in the I+V arm and 21.1 months (95% CI,15.9 to 25.1) in the C+B arm. Similar results were observed in the time of the 18-month extended follow-up (data cut-off: August 25, 2022) and with the DOR per IA.

In the CAPTIVATE FD cohort, in the primary analysis (data cut-off: November 12, 2020), with a median follow-up of 27.9 months, the median DOR per IRC assessment for the FD cohort were not reached for all patients and patients with del(17p) (with the lower end of the 95% CI of 18.9 months). Of note, the median DOR per IRC for patients with del(17p) in the primary was considered not reliable due to the limited number (n = 2) of patients at risk at 36 months after the initial response. Generally, similar results were observed with DOR per IA and in the extended follow-up analysis (data cut-off: August 04, 2021).

Time to Next Treatment

At the GLOW primary analysis (data cut-off: February 26, 2021), fewer patients in the I+V arm received subsequent anticancer therapy compared to that in the C+O arm (3.8% versus 25.7% for I+V versus C+O; HR = 0.143, 95% CI, 0.050 to 0.410; nominal P < 0.0001). Similar results were observed in the extended follow-up analysis (data cut-off: August 25, 2022).

TTNT was not reported in the CAPTIVATE FD cohort.

MRD Negativity

In the GLOW trial, higher proportion of patients reported negative overall MRD by next-generation sequencing in the I+V arm compared to that in the C+O arm in bone marrow (55.7% versus 21.0% for I+V versus C+O; relative response = 2.65; 95% CI, 1.75 to 3.99; P < 0.0001) and in peripheral blood (59.4% versus 40.0% for I+V versus C+O; nominal P = 0.0055) in the primary analysis (data cut-off: February 26, 2021). MRD negativity rate was not assessed in the extended follow-up analysis (data cut-off: August 25, 2022).

In the all-treated FD cohort of the CAPTIVATE trial, the overall MRD negativity rates by flow cytometry were as follows: 59.7% (95% CI, 52.1% to 67.4%) for all patients, and 45.0% (95% CI, 23.2% to 66.8%) for patients with del(17p) in the bone marrow (BM); 76.7% (95% CI, 70.2% to 83.3%) for all patients and 80.0% (95% CI, 62.5% to 97.5%) for patients with del(17p) in the peripheral blood. The extended follow-up analysis reported Identical results for the overall MRD negativity rate (data cut-off: August 4, 2021).

TLS Risk Reduction

In the I+V arm of the GLOW study, 26 (24.5%) patients had high TLS risk by tumour burden at baseline. After ibrutinib lead-in, 22 (20.8%) patients shifted to medium or low risk in the primary analysis (data cut-off: February 26, 2021). The extended follow-up analysis did not assess TLS risk reduction (data cut-off: August 25, 2022).

In the FD cohort of the CAPTIVATE study, high tumour burden was observed for 34 (21.4%) all treated patients, among them, 1 (5%) patient had del(17p) at baseline, after 3 cycles of single-drug ibrutinib lead-in therapy, 33 (20.8%) patients shifted to medium-low risk in the primary analysis (data cut-off: November 12, 2020), among them, 1 (5%) patient had del(17p). The extended follow-up analysis did not assess TLS risk reduction (data cut-off: August 04, 2021).

Health-Related Quality of Life (HRQoL)

In the GLOW trial, HRQoL was a secondary outcome. Generally, in the primary analysis of the GLOW trial (data cut-off: February 26, 2021), patients in the I+V arm had early deteriorations and later improvements in HRQoL compared to patients in the C+O arm as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) Global Health Status, EuroQol five-dimensional five-level questionnaire visual analogue scale (EQ-5D-5L VAS), EQ-5D-5L Utility Score, and FACIT-Fatigue Scale. All the HRQoL results were considered not statistically significant according to the prespecified hierarchical statistical testing strategy as ORR per IRC failed to demonstrate statistical significance. The time to worsening/improvement in EORTC Global Health Status, EQ-5D-5L VAS, EQ-5D-

5L Utility, and FACIT-Fatigue were not assessed in the extended follow-up analysis (data cut-off: August 25, 2022).

HRQoL was not measured in the CAPTIVATE FD cohort.

Harms Results

In fludarabine-ineligible patients reported in the GLOW trial, at least 1 adverse event (AE) was reported for a similar proportion of patients in the I+V arm compared with the C+O arm (99.1% versus 94.3% for I+V versus C+O) in GLOW. The AEs of any grade were reported more frequently in the I+V arm include: diarrhea (50.9% versus 12.4% for I+V versus C+O), infections and infestations nausea (60.4% versus 48.6% for I+V versus C+O), metabolism and nutrition disorders (42.5% versus 23.8% for I+V versus C+O), respiratory, thoracic and mediastinal disorders (35.8% versus 28.6% for I+V versus C+O), musculoskeletal and connective tissue disorders (34.0% versus 25.7% for I+V versus C+O), and nervous system disorders (30.2% versus 20.0% for I+V versus C+O).

More patients in I+V arm experienced at least 1 serious adverse event (SAE) of any grade than the C+O arm (46.2% versus 27.6% for I+V versus C+O). More patients reported AEs leading to discontinuation in the I+V arm (20.8% versus 7.6% for I+V versus C+O). There were 11 (10.4%) of patients in the I+V arm and 12 (11.4%) of patients in the C+O arm died during the study period and AE was the most frequently cause of death in the I+V arm (6.6% versus 1.9% for I+V versus C+O). In GLOW, more patients report atrial fibrillation (14.2% versus 1.9% for I+V versus C+O). Grades 3 or 4 atrial fibrillation was reported in 2 (1.9%) of patients in the I+V arm while no patients in the C+O arm. Similarly, higher proportion of patients reported major hemorrhage in the I+V than the C+O arms (3.8% versus1.0% for I+V versus C+O).

In fludarabine-eligible patients reported in the CAPTIVATE FD cohort, at least 1 AE was reported in 158 (99.5%) patients and AEs of Grades 3 or 4 were reported in 98 (61.6%) patients. The most commonly reported AEs were diarrhea (62.3%), nausea (42.8%), neutropenia (41.5%), and arthralgia (33.3%). Grades 3 or 4 neutropenia was reported in 52 (32.7%) patients. There were 36 (22.6%) patients who experienced at least 1 SAEs of any grade and 30 (18.9%) of patients experienced at least 1 SAEs of Grades 3 or 4; 8 (5.0%) of patients had adverse events leading to ibrutinib discontinuation, while 3 (1.9%) had adverse events leading to venetoclax discontinuation; 3 (1.9%) of patients died during the study period, and 7 (4.4%) of patients had atrial fibrillation, 2 (1.3%) of which were Grades 3 or 4. And major hemorrhage was reported in 3 patients (1.9%).

Critical Appraisal

Fludarabine-Ineligible Population

The open-label design of the GLOW trial had the potential to introduce reporting bias in the assessment of subjective outcomes reported by patients such as HRQoL and AEs. Disease response outcomes (PFS, ORR, DOR, CR rate) were assessed by investigator assessments and an IRC to help mitigate the biases associated with the open-label study design for the GLOW trial. In the GLOW trial, the overall median duration of exposure was substantially longer for the I+V arm (13.8 months) than for the C+O arm (5.1 months), which may bias the results in favour of I+V. In addition, fewer patients in the C+O arm discontinued from treatment

due to adverse events compared to the I+V arm, and a higher proportion of patients completed the study treatment in the C+O arm than the I+V arm, which indicates that patients in the C+O arm had better treatment compliance than the I+V arm in the GLOW trial, which may bias the results against the I+V arm. A higher proportion of patients in the C+O arm received subsequent anticancer therapy compared to the I+V arm. The clinical expert CADTH consulted indicated that subsequent therapies would influence OS. The CADTH review team agrees with the clinical expert and notes that subsequent anticancer therapy results in an indirectness of the estimated OS effect. It is difficult in this setting to isolate the direct effect of I+V treatment on OS due to the intercurrent use of subsequent anticancer therapies. The median of OS was not reached in the I+V arm in the GLOW trial in the primary analysis, so the OS data were considered immature.

Fludarabine-Eligible Population

The FD cohort in the CAPTIVATE trial was designed as a single-arm study, given the lack of a comparator arm, the ability to make definitive conclusions on the comparative efficacy of I+V in fludarabine-eligible patients with CLL is limited. In addition, the open-label design had the potential to introduce reporting bias in the assessment of subjective outcomes reported by patients (i.e., AEs). Disease response outcomes (PFS, ORR, DOR, CR rate) were assessed by investigator assessments and an IRC to help mitigate the biases associated with the open-label study design for the FD cohort in the CAPTIVATE trial. The median of OS and PFS were not reached in the CAPTIVATE FD cohort in the primary analysis, so the OS data were considered immature. In addition, the CADTH review team would like to note that although the CAPTIVATE FD cohort included a subgroup of patients with del(17p); however, there was no formal statistical testing performed between subgroups and the sample size for patients with del(17p) is small (n = 20), thus, no conclusions can be drawn from the study results for patients with del(17p). Although the subgroup analyses were prespecified, no evidence exists that the studies were powered to detect subgroup differences. HRQoL is considered a relevant outcome by patients with CLL and clinicians. However, there was no assessment for HRQoL in the CAPTIVATE FD cohort; thus, it is uncertain whether the treatment with I+V would improve HRQoL in fludarabine-eligible patients with CLL.

Both the GLOW trial and CAPTIVATE FD cohort required eligible patients to have measurable nodal disease. However, according to the clinical expert consulted by CADTH, there is a small proportion of patients who only have elevated white cell counts and cytopenia and may not have an enlarged lymph node in clinical practice; these patients are important and would fit in the patient population for the I+V regimen. The clinical expert stated that there is a more diversified patients population including patients from Asia and other parts of the world in their clinical practice compared to the patient population in the GLOW trial and CAPTIVATE FD cohort. The baseline characteristics of the 2 studies may be indicative of the overrepresentation of white patients (≥ 92%) with CLL in both fludarabine-eligible and fludarabine-ineligible populations and thus present an evidence gap in patients' generalizability. Though the inclusion criteria mandated eligible patients in the GLOW trial to have creatinine clearance of less than 70 mL/min and/or a cumulative illness rating scale (CIRS) score more than 6, the baseline creatinine clearance for both treatment arms are higher than what the clinical expert would expect in high-risk patients with CLL who are ineligible to FCR in clinical practice, which may indicate that patients in the GLOW trial have better kidney functions than patients in clinical practice. This may compromise the study results to the general fludarabine-ineligible patients with CLL. Generally, the

risk profile of patients in the CAPTIVATE FD cohort is what the clinical expert would expect in fludarabine-eligible patients with CLL in clinical practice.

Indirect Comparisons and Observational Studies

Description of Studies

In patients who were ineligible to receive fludarabine, the sponsor provided 2 ITCs and 2 IPD observational studies that evaluated the efficacy and safety of I+V versus BR, ibrutinib, VO, and acalabrutinib. In fludarabine-eligible patients, an IPD analysis was conducted comparing I+V versus FCR) The ITC analyses were based on MAIC methods (comparison with acalabrutinib and VO) and the IPD were based on propensity score methods (comparison with BR, ibrutinib, and FCR). All comparisons included patients with untreated CLL but varied in terms of age (all adults or ≥ 65 years only), presence of comorbidities and high-risk mutations, such as del(17p) and TP53. The median follow-up duration ranged from 38 months to 54.4 months, depending on the treatment group and the analysis. The base case MAIC models were adjusted for 4 covariates (age, ECOG performance score, CIRS score and TP53 status); whereas, the IPD analyses controlled for 11 potential confounders, including age, ECOG score, renal function, and high-risk mutations (TP53, del(11q) and IGHV).

Efficacy Results

Fludarabine-Ineligible Population

For I+V versus acalabrutinib, the time-varying analysis of PFS estimated an HR of [redacted] for the base case model. The comparison with VO reported the base case PFS HR of [redacted].

The observational study comparing I+V versus BR estimated PFS HR of [redacted] for the base-case analysis. For the comparison of I+V versus ibrutinib, [redacted] of patients in the I+V and ibrutinib groups, respectively [redacted] reported a progression event (HR and 95% CI not reported).

For all comparisons in the fludarabine-ineligible population, the comparative efficacy of I+V on OS was unclear, as the results had high uncertainty due to the low number of events, limited sample size, and in many cases, [redacted] and lacked precision.

Fludarabine-Eligible Population

In the base-case analysis for PFS, the model estimated an HR of [redacted] The analysis of OS [redacted] but was limited by small sample size and low event rates, and thus should be interpreted with caution.

Harms Results

No safety data were reported in the fludarabine-ineligible population.

Among fludarabine-eligible patients, grade 3 or 4 TEAEs were reported by [redacted] of patients in the FCR group compared with [redacted] of those in the I+V group, across the base-case and sensitivity analyses

conducted. Comparative OR of grade 3 or 4 adverse events were not reported. The incidence of treatment discontinuation ranged from [redacted] for I+V versus [redacted] for FCR across the analyses.

Critical Appraisal

Fludarabine-Ineligible Population

For the MAICs comparing I+V with acalabrutinib and VO, there was poor overlap between trial populations in the GLOW study and comparator trials, which was evident given the low effective sample size after weighting ([redacted]). The comparator trials included patients with high-risk mutations who were excluded from the GLOW study, and the presence of these mutations could not be controlled for in the adjusted analyses. The ability to achieve balance in effect modifiers was also limited due to missing covariate data, and imbalances between groups were noted for important patient characteristics in the base-case analysis. [redacted], and time-varying Cox analyses showed treatment effects that lacked precision. Given these limitations, the findings of the MAIC were considered highly uncertain.

The selection of covariates for inclusion in the propensity score model is important for inference to be valid in observational studies. These analyses are unclear if all known confounders and prognostic factors were included. Moreover, there were issues with missing covariate data, which may have affected the specification of the propensity scores. The distribution of propensity scores showed a considerable proportion of patients had a very low probability of receiving the treatment (i.e., propensity score near 0). These patients appear to have been assigned extreme weights and, thus, have a disproportionate influence on the analysis. Further, the sample sizes were generally small, with only [redacted] patients in the I+V group and [redacted] patients in the comparator groups.

In the fludarabine ineligible population, none of the pairwise comparisons reported safety outcomes; thus, the comparative safety is unknown.

About external validity, there were differences in the patients included in each pairwise comparison that should be considered when interpreting the results. The comparison with BR and ibrutinib included only patients 65 years of age and older (with or without comorbidities); whereas the comparison with VO included any adult (≥ 18 years) with comorbidities (CIRS > 6 and CrCl ≤ 70 mL/min), and the comparison with acalabrutinib included all patients at least 65 years of age, but only younger adults who had comorbidities. Thus, the patients may not be comparable across analyses, and each pairwise comparison's external validity should be assessed separately.

Fludarabine-Eligible Population

The sponsor conducted an observational study based on propensity score methods because there was no randomized control group in the CAPTIVATE study. For the IPD analysis, it was unclear if all known confounders and prognostic factors were included in the model, and in addition, there were issues with missing covariate data. Therefore, there may be residual confounding from measured and unmeasured covariates that could bias the effect estimates. Also, the data were based on a small sample size (I+V [redacted] patients, FCR [redacted] patients in the base-case analysis), and OS had low event rates. Limited safety data were reported; thus, the comparative safety is unclear. The external validity of the base case findings may be

limited by including patients with comorbidities and high-risk mutations who would not be eligible to receive FCR in clinical practice.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target populations	Adults with previously untreated CLL. Two subpopulations were considered: • Fludarabine ineligible: Defined as patients older than 65 years with no 17p deletion or patients between age 18 and 64 with CIRS > 6 and creatinine clearance < 60mL/min. • Fludarabine eligible: Defined as patients with no 17p deletion with a CIRS score ≤ 6, creatinine clearance ≥ 60mL/min, and an Eastern Cooperative Oncology Group Performance Score ≤ 2.
Treatments	Ibrutinib, in combination with venetoclax (I+V)
Dose regimen	Ibrutinib: 420 mg once daily for fifteen 28-day cycles Venetoclax: Initiated on cycle 4 of ibrutinib. 20 mg once daily for 7 days, repeated for 50 mg, 100 mg and 200 mg. Maintenance dose of 400 mg once daily until cycle 15.
Submitted price	$99.74 per 140 mg capsule
Treatment cost	Regimen: $214,852 (ibrutinib: $125,793; venetoclax: $89,060)
Comparators	**Fludarabine ineligible:** • acalabrutinib • bendamustine plus rituximab (BR) • chlorambucil plus obinutuzumab (C+O) • ibrutinib • venetoclax plus obinutuzumab (VO) **Fludarabine eligible:** • FCR: fludarabine plus cyclophosphamide and rituximab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	**Fludarabine ineligible**: 20 years **Fludarabine eligible**: 30 years
Key data sources	**Fludarabine ineligible**: GLOW Trial **Fludarabine eligible**: CAPTIVATE Trial Sponsor-submitted indirect treatment comparisons. Independent estimates of relative treatment effect obtained using propensity score analysis and anchored matched-adjusted indirect comparisons.

Component	Description
Key limitations	• While direct comparative evidence was available for I+V vs. C+O, clinical expert feedback solicited by CADTH for this review suggested that C+O is rarely used in practice. Comparative efficacy for other relevant comparators was derived from indirect treatment comparisons (ITCs) submitted by the sponsor. These ITCs had a number of methodological concerns that precluded CADTH from drawing conclusions about the comparative effects of ibrutinib+venetoclax on progression-free survival (PFS) and overall survival (OS). • The methods used to determine state membership were inconsistent with the requirements for a Markov model, as time in health states could not be tracked. The sponsor's model therefore could not accurately calculate costs or QALYs. • The model assumed all second-line therapies would initiate 14 cycles after progression on first-line treatment. The inclusion of regimens with fixed durations meant that this approach failed to reflect the intended treatment-free period between regimens. This resulted in the misspecification of treatment acquisition costs for all fixed-duration regimens. In addition, the model was unable to distinguish between patients who had progressed but had yet to initiate second-line therapy.
CADTH reanalysis results	Given that CADTH was unable to address the limitations of the submitted economic evaluation, a base case could not be derived.
Key scenario analyses	The sponsor's submission claimed that I+V was cost-saving relative to acalabrutinib, which was identified by clinical experts as the most relevant comparator in the fludarabine-ineligible subpopulation. To explore this claim, CADTH conducted a scenario analysis comparing only drug costs between I+V and acalabrutinib monotherapy. In this analysis, cost savings from I+V may be realized if patients receiving acalabrutinib monotherapy remain on treatment for 2.2 years or longer. In the fludarabine-eligible subpopulation, drug costs for I+V were higher than those for FCR. Conclusions relating to the cost savings relative to the other regimens are difficult to draw as they will depend on the relative effectiveness of each regimen and the risk of adverse events.

BR = bendamustine plus rituximab; C+O = chlorambucil plus obinutuzumab; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, and rituximab; I+V = ibrutinib plus venetoclax; ITC = indirect treatment comparison; LY = life-year; OS = overall survival; PFS = progression free survival; QALY= quality-adjusted life-year; VO = venetoclax plus obinutuzumab.

Budget Impact

CADTH identified 1 key limitation in the sponsor's budget impact analysis: the under-estimation of the size of the eligible population for treatment. The sponsor's submission assumed that 20% of prevalent (existing) cases would initiate treatment after a watch-and-wait period. CADTH revised this input to 50% following consultation with clinical experts. CADTH performed a reanalysis which used this increase in the population eligible for treatment. The three-year net-budget impact was estimated to be $15,450,333 (year 1: $17,203,486; year 2: $10,241,543; year 3: -$11,994,696).

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. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: September 13, 2023

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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