pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Idelalisib (Zydelig)

Submitted Funding Request:
For the treatment of patients with follicular lymphoma who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent

Submitted By: Gilead Sciences, Inc.	**Manufactured By:** Gilead Sciences, Inc.
NOC Date: March 27, 2015	**Submission Date:** April 12, 2016
Initial Recommendation: August 5, 2016	**Final Recommendation:** September 29, 2016

pERC RECOMMENDATION	pERC does not recommend reimbursement of idelalisib for the treatment of patients with follicular lymphoma (FL) who have had at least two prior systemic regimens and whose disease is refractory to both rituximab and an alkylating agent. The Committee made this recommendation because it was not satisfied that there is a net clinical benefit of idelalisib compared with best supportive care (BSC). The Committee concluded that there was considerable uncertainty in the evidence available on outcomes important to decision-making, such as overall survival, progression-free survival, and quality of life. pERC also noted that idelalisib had risk of significant toxicities requiring additional monitoring compared with BSC. In addition, pERC concluded that idelalisib only partially aligned with patient values. The Committee noted that, based on the information provided, idelalisib was not cost-effective in this population compared with BSC.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

pERC noted that FL is the most common type of indolent non-Hodgkin lymphoma (NHL), and the second most common NHL, accounting for approximately 35% of cases. Approximately 2,800 patients were diagnosed with FL in 2015. The prognosis of patients ranges from a 10-year survival rate of 84% in patients with low-risk disease to 42% in those with high-risk disease. Given the incurable nature of the disease, and its indolent clinical course, treatment is typically initiated at onset of symptomatic disease, while patients with asymptomatic progression will remain in observation. There is no standard of care for treating relapsed disease, with various chemotherapy regimens used to treat symptomatic relapses. Superiority of one regimen over the other is unknown, and eventually patients may develop disease that is refractory to standard therapies such as alkylators and rituximab. Treatment options and life expectancy are limited in this stage of the trajectory of illness. pERC therefore agreed that there is a need for new therapies with novel mechanisms of action in this patient population.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon one phase 2, non-randomized trial, DELTA, which administered idelalisib to adult patients with a confirmed diagnosis of indolent B-cell NHL who had received at least two prior systemic therapies and whose disease was refractory to both rituximab and an alkylating agent. Specifically, pERC deliberated upon the results of a subgroup of patients with FL from the DELTA trial and concluded that there may be a net clinical benefit with idelalisib. Given that the DELTA trial was a small, non-randomized study, designed with objective response rate (ORR) as the primary outcome in the full intention-to-treat (ITT) population, pERC expressed concern about drawing a conclusion based on post-hoc exploratory analyses within a smaller subgroup of patients with FL. pERC acknowledged that improvements in ORR within the FL subgroup of patients were consistent with the overall trial results; however, uncertainty remained due to the sample size of the study and the exploratory nature of the outcomes in the subgroup analysis. pERC also noted that the majority of patients in the DELTA trial were asymptomatic and somewhat younger than patients in the typical clinical setting. In the opinion of pERC, and consistent with Canadian clinical practice, asymptomatic patients may remain in observation for a number of years until the development of symptomatic disease. Based on this, pERC noted that the patient population studied in the DELTA trial was more favourable than patients in the clinical setting. Patients with symptomatic disease may be more susceptible to toxicity and have greater overall tumour burden than asymptomatic patients. Therefore, pERC agreed that the evidence in the DELTA trial was not sufficient to generalize the efficacy and safety outcomes to the symptomatic clinical population. Although patient-reported outcomes were measured in the trial, the Committee was uncertain as to how to interpret median best change from baseline as an outcome, given the selective reporting of only the best scores. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding the definition of symptomatic disease and the proportion of patients in the subgroup analysis who had symptomatic disease (i.e., patients requiring initiation of treatment). pERC considered additional comments provided by the pCODR Clinical Guidance Panel (CGP) and agreed that having FL that is refractory to rituximab, has progressed to stage III or IV, is associated with an elevated lactate dehydrogenase (LDH), is bulky, is associated with a high Follicular Lymphoma International Prognostic Index (FLIPI) score, or is associated with asymptomatic cytopenia does not, by itself, justify treatment. However, the presence of disease-related symptoms, which include any symptoms, not just B symptoms, would be the indication for the initiation of treatment. Based on this definition, disease-related symptoms were present in only approximately 18% of patients in the subgroup of patients with FL and therefore required treatment initiation. pERC reiterated that the majority of patients in the FL subgroup are not representative of the Canadian clinical population that fits this definition. pERC also considered feedback from the manufacturer regarding the consistency of decisions pERC made in reviews where ORR was the primary outcome and the pivotal data presented were from a non-randomized study. pERC noted that, as a principle, the Committee considers a review based on its own merits and the evidence presented for the agent under and diagnosis consideration. pERC agreed that there are considerations beyond the response rate and non-randomized design of the study that go into making recommendations, such as — but not limited to — feasibility of conducting a randomized trial, availability of alternative treatments, etc. In this instance pERC was not satisfied there is a net clinical benefit in favor of idelalisib over best supportive care.

pERC further considered the toxicity profile of idelalisib and expressed concern with the 7% treatment-related death rate in the FL population, considering it to be a dramatic drug-related toxicity when contrasted with the uncertainty in the clinical benefit of idelalisib. Furthermore, pERC noted that first-line studies using idelalisib have been stopped early due to safety concerns, and agreed that concerns remain with the toxicity profile of idelalisib. Overall, pERC agreed that idelalisib is an active agent that demonstrates some anti-tumour activity; however, due to the limitations in the available evidence and risk of significant toxicities, the Committee could not conclude that there is a net clinical benefit with idelalisib. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding the number of treatment-related deaths with idelalisib. pERC noted the CGP's response to this feedback indicating that currently available data are not sufficient to determine whether there is clear evidence that single-agent idelalisib increases mortality compared with other idelalisib-containing regimens. In the absence of comparative safety data, pERC remained concerned with the proportion of patients who died in the DELTA trial. Additionally, given the number of patients diagnosed with FL annually, pERC noted that it would have been feasible to conduct a randomized controlled trial (RCT) in this population in order to determine the comparative efficacy of idelalisib in relation to available treatment options or BSC. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding the feasibility of an RCT in this setting. Given that FL is the most common form of indolent NHL and that there is a large prevalent population, among whom at least 15% to 20% will eventually develop resistance to rituximab and an alkylating agent, pERC agreed with the CGP and reiterated that an RCT would have been feasible in this population and setting.

pERC deliberated upon input from one patient advocacy group. pERC noted that patients value extending life, bringing about remission, and controlling disease symptoms as the most important aspects of FL to be controlled by a new therapy. Patients expressed a willingness to tolerate drug-related toxicities as a trade-off for benefit in terms of survival, remission, and quality of life. Given that considerable uncertainty remained in the interpretation of efficacy and safety results from the DELTA trial, the Committee could not conclude that idelalisib aligned with these patient values. However, pERC acknowledged that the oral route of administration and the availability of a targeted treatment option do align with patient values. Overall, due to the limitations in the evidence supporting the efficacy and safety of idelalisib, pERC concluded that idelalisib only partially aligns with patient values.

pERC deliberated on the cost-effectiveness of idelalisib and concluded that idelalisib is not cost-effective. pERC made this conclusion noting the significant uncertainty in the incremental cost-effectiveness ratio due to the clinical trial data. Most notably, the Committee shared the concern of the pCODR Economic Guidance Panel (EGP) over the use of non-responders from the DELTA trial as a proxy for patients in a BSC arm. pERC agreed that patients with FL that is refractory to alkylators and rituximab, but sensitive to idelalisib, cannot plausibly be considered to be comparable to patients with FL that is refractory to alkylators, rituximab, and idelalisib. In the absence of an alternative data source, pERC noted that the EGP could not capture this uncertainty in the reanalysis estimates. Additionally, pERC noted that the methods of extrapolation of the survival benefit had a large impact on the incremental cost-effectiveness ratio. Overall, due to the large degree of uncertainty in the clinical effect estimates, pERC agreed that idelalisib could not be considered cost-effective.

pERC discussed factors that could affect the feasibility of implementing a funding recommendation for idelalisib for the treatment of FL. pERC discussed the limited evidence available in the DELTA trial and noted that an RCT would have been feasible in patients with FL. pERC noted the issuance of regulatory safety alerts and acknowledged that the use of idelalisib plus rituximab combination therapy likely contributed to the overall toxicity observed with the use of idelalisib. The Committee also noted that the rate of idelalisib-related death in the DELTA trial for patients with FL was 7%. The Committee, therefore, remained concerned about the number of drug-related deaths in the trial, particularly when coupled with the uncertain clinical benefit. pERC noted that being an oral drug, idelalisib would be easier for patients to access, especially for patients who live in rural communities or at a distance from cancer centres.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the *Clinical Guidance Report* that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group, Lymphoma Canada (LC)
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Input from the PAG
- One patient advocacy group (LC)
- The submitter (Gilead Sciences, Inc.)

The pERC Initial Recommendation was to not recommend reimbursement of idelalisib for the treatment of patients with follicular lymphoma (FL) who have had at least two prior systemic regimens and whose disease is refractory to both rituximab and an alkylating agent. Feedback on the pERC Initial Recommendation indicated that the manufacturer disagreed with the Initial Recommendation, the patient advocacy group agreed in part with the Initial Recommendation, and the PAG agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and effectiveness of idelalisib (Zydelig) compared with an appropriate comparator, for the treatment of patients with FL who have received at least two prior systemic regimens and whose disease is refractory to both rituximab and an alkylating agent.

Studies included: One single-arm, phase 2 study

The pCODR systematic review included one non-randomized, single-arm, phase 2 study (DELTA) that enrolled 125 patients with a confirmed diagnosis of indolent B-cell non-Hodgkin lymphoma (NHL) who had received at least two prior systemic therapies and whose disease was refractory to both rituximab and an alkylating agent. Specifically, pERC considered the population of patients with FL (n = 72) from the DELTA trial. Idelalisib was administered orally at a dose of 150 mg twice daily, until the disease progressed, unacceptable toxic effects developed, or the patient died.

pERC noted that patients with small lymphocytic lymphoma and other indolent lymphomas were also included in the trial, but it acknowledged that the current review focused on FL and it would not be appropriate to generalize results to the broader population.

Patient populations: Mostly asymptomatic patients

The subgroup of patients with FL enrolled in the DELTA trial included 39 men and 33 women with a median age of 62 years (range, 33 to 84). The majority of these patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 (43%; 31/72) or 1 (49%; 35/72), were Caucasian (90%; 64/72) and were refractory to their most recent treatment regimen (86%; 62/72). A high Follicular Lymphoma International Prognostic Index (FLIPI) risk score at baseline — defined as having three or more of the following five adverse prognostic factors: age > 60 years, Ann Arbor stage III to IV, hemoglobin < 12g/dL, number of nodal areas > 4, and serum lactate dehydrogenase (LDH) above normal — was reported in 54% (39/72) of patients.

Of note, 18% (13/72) of patients were symptomatic with either B symptoms or other disease-related symptoms at baseline, while 82% of FL patients were asymptomatic. Based on the opinion of the pCODR Clinical Guidance Panel (CGP) and pERC and consistent with Canadian clinical practice, asymptomatic patients may remain in observation for a number of years until the development of symptomatic disease. Based on this, pERC noted that the population studied in the DELTA trial was more favourable than patients encountered in clinical practice. Patients with symptomatic disease may be more susceptible to

toxicity and have greater overall tumour burden. Therefore, pERC agreed that the evidence in the DELTA trial was not sufficient to generalize the efficacy and safety outcomes to the symptomatic clinical population. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding the definition of symptomatic disease and the proportion of patients in the subgroup analysis who had symptomatic disease (i.e., patients requiring initiation of treatment). pERC considered additional comments provided by the CGP and agreed that having FL that is refractory to rituximab, has progressed to stage III or IV, is associated with an elevated LDH, is bulky, is associated with a high FLIPI score, or is associated with asymptomatic cytopenia does not, by itself, justify treatment. However, the presence of disease-related symptoms, which includes any symptoms, not just B symptoms, would result in the initiation of treatment. Based on this definition, disease-related symptoms were present in only approximately 18% of patients in the subgroup of patients with FL and therefore required treatment initiation. pERC reiterated that the majority of patients in the FL subgroup are not representative of the clinical population.

Key efficacy results: Exploratory secondary end point in a subgroup analysis

The primary outcome in the DELTA trial was objective response rate (ORR). The ORR for the subgroup of patients with FL was 55.6% (95% confidence interval [CI], 43.4 to 67.3; $P < 0.001$), which included 10 complete responses and 30 partial responses. This was reported as consistent with the ORR for the overall study population and all subgroups. pERC acknowledged that improvements in ORR within the FL subgroup of patients were consistent with the overall trial results, agreeing that idelalisib has some anti-tumour activity. However, pERC noted that data on efficacy and safety of idelalisib in the FL subset were assessed as a post-hoc subgroup analysis, which undermined the Committee's certainty in the reported results. Furthermore, the small sample size of the study and the use of a one-sided alpha level of 0.1 in the ITT analysis increased the chance of detecting a statistical difference in ORR where there is no real difference. Given these limitations, pERC expressed concern in drawing conclusions from these data.

Secondary end points within the subgroup of patients with FL included progression-free survival (PFS) and overall survival (OS). Median PFS was 11 months (range, 0 to 30.6). Median OS was not reached in the FL subgroup of patients and was 20.3 months (range, 0.7 to 22.0) in the ITT analysis. pERC considered the reporting of secondary exploratory end points within a subgroup analysis, in a small non-randomized trial, and agreed that the data could not be interpreted, given the considerable uncertainty. Additionally, in the absence of a comparator arm, pERC could not determine the significance of the reported changes in PFS and OS. Furthermore, given the number of patients diagnosed with FL annually, pERC agreed that a randomized controlled trial could have been conducted in this population to determine the comparative efficacy of idelalisib in relation to available treatment options or best supportive care (BSC). Overall, pERC agreed that idelalisib is an active anti-tumour agent; however, there were considerable limitations to the available clinical evidence.

Quality of life: Best change from baseline as an outcome

Health-related quality of life (HRQoL) was measured using the validated 42-item Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym), which comprises the following FACT-G subscales: Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and the Lymphoma subscale (LymS). A higher score indicates a higher HRQoL. Results were reported as best change from baseline for both the overall and FL populations. Minimally important differences were reported based on best median change from baseline.

pERC considered whether best change from baseline accurately represents the impact of idelalisib on patient-reported outcomes, or whether median change from baseline would be more valid. pERC agreed that best change from baseline may selectively report only the best scores and agreed that conclusions could not be drawn on the reported minimally important differences using these data.

Safety: High risk of significant toxicity, including death

pERC considered the toxicity profile of idelalisib and noted that the number of drug-related deaths occurring in 7% (5/72) of patients was high in this mostly asymptomatic population. pERC was uncertain how symptomatic patients, who may be more susceptible to toxicity and have greater overall tumour burden, would tolerate idelalisib. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding the number of treatment-related deaths measured with idelalisib. pERC noted the CGP's response to this feedback indicating that currently available data are not sufficient to determine whether there is clear evidence that single-agent idelalisib increases mortality compared with other idelalisib-containing regimens. In the absence of comparative safety data, pERC

remained concerned with the proportion of patients who died in the DELTA trial. Furthermore, pERC noted that Health Canada has issued an alert that idelalisib users are at an increased risk of fatal and serious infections. In addition, patients had decreased OS compared with control patients in a phase 3 trial that evaluated the addition of idelalisib to standard therapies for first-line treatment of chronic lymphocytic leukemia (CLL) and early-line treatment of relapsed indolent NHL. This has subsequently led to the stopping of all ongoing trials of idelalisib in first-line treatment of CLL and early-line treatment of indolent NHL. pERC acknowledged that the use of idelalisib plus rituximab combination therapy likely contributed to the overall toxicity observed with the use of idelalisib and the issuance of safety alerts. Additionally, pERC noted that 65% (47/72) of patients experienced grade 3 or higher toxicities with idelalisib. The most common grade 3 or higher toxicities reported by patients receiving idelalisib were diarrhea, pyrexia, and nausea. Overall, the Committee remained concerned with the toxicity profile of idelalisib, particularly the number of drug-related deaths in the trial when coupled with the uncertainty in clinical benefit.

Need: Treatment options, improved survival and toxicity profile

pERC noted that FL is the most common type of indolent NHL, and the second most common NHL, accounting for approximately 35% of cases. Approximately 2,800 patients were diagnosed with FL in 2015. The prognosis of patients ranges from a 10-year survival rate of 84% in those with low-risk disease to 42% in those with high-risk disease. Given the incurable nature of the disease, and its indolent clinical course, treatment is typically initiated at the onset of symptomatic disease, while patients with asymptomatic progression can be in observation. The appearance of symptomatic disease includes B symptoms such as fevers, unexplained weight loss, and drenching sweats at night, or bulky adenopathy causing symptoms. Marked cytopenias due to bone marrow involvement may also be an indication for therapy, if severe and/or progressive. There is no standard of care for treating relapsed disease. Various chemotherapy regimens are used to treat symptomatic relapses; however, the superiority of one regimen over the other is unknown, and eventually, disease that is refractory to standard therapies such as alkylators and rituximab may develop. Treatment options are limited in this patient group and life expectancy is short. pERC therefore agreed that there is a need for new therapies with novel mechanisms of action in this patient population.

PATIENT-BASED VALUES

Values of patients with follicular lymphoma: Reduced ability to perform day-to-day activities

Patients providing input noted that they have minimal symptoms and good quality of life associated with disease in early stages. For those with relapsed disease, fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, and muscle and joint pain were the most commonly reported symptoms. Patients also indicated that their disease affected their ability to work, travel, exercise, attend to household chores, spend time with family and friends, and contribute financially to household expenses. While the majority of patients reported that access to treatment was not difficult, 20% reported that the need to travel, drug reimbursement criteria, and costs made treatment difficult.

Caregivers stated that caring for a loved one with FL had the most impact on their ability to volunteer, travel, concentrate, and work. They also found it difficult to manage side effects and deal with time off work to care for patients and with the financial burden and need to travel to receive treatment. pERC discussed patient and caregiver experience with FL and acknowledged the significant impact on day-to-day life and quality of life. pERC acknowledged that idelalisib demonstrates anti-tumour activity, but the Committee was unable to reconcile the limitations associated with the design of the DELTA trial, which introduced considerable uncertainty regarding the reported results for clinical efficacy and safety.

Patient values on treatment: Fewer side effects and increased normal living

Patients reported that current treatment options can be effective, but relapse eventually occurs and each period of remission becomes shorter. Current treatments for relapsed disease were reported to be associated with increased toxicity, reduced anti-tumour activity, and unpleasant side effects. A majority of patients providing input expressed a need for additional treatment options and the ability to choose a treatment based on its toxicity profile. Some patients also indicated that current therapies are difficult to access due to travel distances, and having to meet specific funding criteria and pay out-of-pocket costs for treatments and travel. As idelalisib is an oral therapy, pERC noted that it would align with the patient value of having more accessible treatment options.

pERC considered the efficacy and toxicity profile of idelalisib in relation to the expressed values for a new treatment; i.e., extends life, brings about remission, and controls disease symptoms of FL. pERC also noted patients' willingness to tolerate side effects with a new treatment option if they could live longer, achieve remission, control their disease, or have improved quality of life. One patient had direct experience with idelalisib as a single agent for relapsed FL and indicated that idelalisib had far fewer side effects than other treatments for FL, and equated the experience on idelalisib with normal living. While pERC appreciated individual patient experience on idelalisib, it remained concerned by the significant risk for death, as reported in the trial population and in regulatory alerts. pERC also acknowledged that the clinical evidence for efficacy was not sufficient to draw a conclusion on the net clinical benefit of idelalisib in this patient population. Overall, pERC agreed that idelalisib aligned only partially with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis of idelalisib compared with BSC for patients with FL who have received at least two prior systemic regimens and whose disease is refractory to both rituximab and an alkylating agent.

Basis of the economic model: DELTA trial

Costs included were cost of the drugs, adverse event costs, and monitoring costs. pERC noted that the factor most significantly affecting cost was the drug cost. Key clinical effects considered in the analysis were obtained from the DELTA trial. pERC noted that the clinical effect estimates for modelling the BSC arm created the uncertainty in the clinical inputs. Additionally, the method of extrapolation of OS data had a large impact on the results.

pERC noted that the submitted primary analysis focused on a comparison to last line of prior therapy. In accordance with input from the CGP, the EGP did not consider this analysis further, because the results from the DELTA trial did not support the use of idelalisib in place of currently available treatment options. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer related to the appropriateness of making a comparison to a patients' last line of prior treatment. pERC echoed the CGP's response to this feedback and agreed that a comparison to the last line of prior treatment is contingent on the choice of therapy patients receive and whether or not a reasonable treatment option was used. pERC noted the CGP's comments that most of the 47 treatments used in the last line of prior treatment for patients in the trial would likely constitute ineffective treatments since few effective treatment options are available in this setting. pERC noted that purine analogues, which are effective in this setting, were used in only 34% of patients, and agreed that a comparison to a group of patients who mostly received an ineffective last line of prior treatment is not appropriate and will skew the results in favour of idelalisib.

Drug costs: High drug cost

The cost of idelalisib is $85.35 per 150 mg tablet. At the recommended dose of 150 mg twice daily, this amounts to $170.70 per day, or $4,779.60 per 28-day cycle.

Cost-effectiveness estimates: Best supportive care data, extrapolation method, and uncertainty in trial results

pERC deliberated on the cost-effectiveness of idelalisib and concluded that idelalisib is not cost-effective. pERC made this conclusion noting the significant uncertainty in the incremental cost-effectiveness ratio due to the clinical trial data. Most notably, the Committee shared the EGP's concern over the use of non-responders from the DELTA trial as a proxy for the BSC arm. pERC agreed that patients with FL that is refractory to alkylators and rituximab, but sensitive to idelalisib, cannot plausibly be considered to be the same as patients with FL that is refractory to alkylators, rituximab, and idelalisib. In the absence of an alternative data source, pERC noted that the EGP could not capture this uncertainty in the reanalysis estimates.

Additionally, pERC noted that the methods of extrapolation of the survival benefit, which used a fully parametric curve, overestimated the OS benefit. pERC agreed with the use of the trial data with extrapolation used for the remainder of the time horizon as being a more appropriate method. Furthermore, pERC noted that the efficacy and safety inputs from the DELTA trial remained uncertain,

due largely to the design of the trial. pERC noted that the EGP explored various other inputs in the economic model, many of which did not have a large impact on the incremental cost-effectiveness ratio. Overall, pERC concluded that idelalisib could not be considered cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Safety concern, phase 3 trial feasible

pERC discussed factors that could affect the feasibility of implementing a funding recommendation for idelalisib for FL. pERC reiterated that there is no standard of care for previously treated and refractory FL. The Committee acknowledged the PAG's appreciation of idelalisib's ability to fill the gap in therapy for patients whose disease is refractory to both rituximab and an alkylating agent. pERC also noted that being an oral drug, idelalisib would be easier for patients to access, especially for those living at a distance from treatment centres, but it might pose a financial or administrative burden for patients living in provinces where oral medications are not funded.

Given the large number of patients with FL, pERC highlighted that a phase 3 trial is feasible in this patient population. Furthermore, pERC echoed the PAG's concern over fatal and serious toxicities associated with idelalisib, as reported in the Health Canada and FDA alerts. pERC acknowledged that the use of idelalisib plus rituximab combination therapy likely contributed to the overall toxicity observed with the use of idelalisib and the issuance of safety alerts. The Committee remained concerned with the number of drug-related deaths in the trial, particularly when coupled with the uncertainty in clinical benefit.

DRUG AND CONDITION INFORMATION

Drug Information	• Oral, targeted inhibitor of phosphatidylinositol 3-kinase p110δ (PI3Kδ) isoform • Available as 100 mg and 150 mg tablets • The recommended dose is 150 mg administered orally twice daily
Cancer Treated	• Relapsed/refractory follicular lymphoma (FL)
Burden of Illness	• Indolent non-Hodgkin lymphoma is characterized by slow progression and frequent relapse, and is incurable • Life expectancy for patients with FL is limited and there is a high possibility of relapse
Current Standard Treatment	• There is no current standard of treatment for relapsed/refractory FL
Limitations of Current Therapy	• Limited efficacy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Paul Hoskins, Oncologist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Carole McMahon, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Scott Berry, Matthew Cheung, and Allan Grill, who were not present for the meeting
- Kelvin Chan, who was excluded from voting due to a conflict of interest
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:

- Kelvin Chan and Matthew Cheung, who were excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of idelalisib for follicular lymphoma, through their declarations, five members had a real, potential or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform their deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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