CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Idelalisib (Zydelig) for Follicular Lymphoma

September 29, 2016

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding idelalisib (Zydelig) for follicular lymphoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding idelalisib (Zydelig) for follicular lymphoma conducted by the Lymphoma/Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on idelalisib (Zydelig) for follicular lymphoma, a summary of submitted Provincial Advisory Group Input on idelalisib (Zydelig) for follicular lymphoma, and a summary of submitted Registered Clinician Input on idelalisib (Zydelig) for follicular lymphoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of idelalisib (Zydelig) as monotherapy 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. There is no standard comparator for idelalisib in this treatment setting.

Idelalisib is a selective inhibitor of the PI3Kδ isoform that reduces intracellular signaling via the B cell receptor (BCR), and reduces BCR and chemokine receptor activation of the AKT and MAPK/ERK pathways that are important for cell proliferation. The recommended dose for idelalisib is 150mg taken twice daily until disease progression.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one non-randomized, non-comparative, open-label Phase II study (DELTA) examining the use of idelalisib in patients (n=125) with indolent non-Hodgkin's lymphoma (iNHL) who had at least 2 prior lines of treatment and were refractory to both rituximab and an alkylating agent. Refractoriness is defined in Section 6.3.2.1. While the trial included various histological subtypes of iNHL, the focus of this systematic review is on those patients with follicular lymphoma (FL).

Of the 125 patients enrolled in the DELTA study, 72 had FL. Patients were administered 150 mg of idelalisib orally, twice daily until disease progression or the patient withdrew from the study. The median age of FL patients was 62 years (range, 33 to 84 years). The majority of FL patients had an ECOG performance status of 0 or 1 (92%). Of note, 82% of patients were asymptomatic at baseline, while 18% (13/72) of patients were considered symptomatic (11/72 (15%) of follicular lymphoma patients had baseline B-symptoms (fever, weight loss, night sweats) and 2/72 (3%) had other (skin lesions, pruritus, unknown) symptoms)[43]. Most patients (83%) had stage III or IV disease at baseline and 75% had baseline cytopenia.

The median time since diagnosis for FL patients was 4.7 years (range, 0.8 to 18.4 years). The median number of prior treatments was 4 (range, 2 to 12). The majority of patients (69%, 50/72) with FL had received prior treatment with bendamustine, of which 32 patients were refractory to bendamustine monotherapy and 23 patients were refractory to bendamustine + rituximab. Most FL patients were also refractory to at least 2 regimens (80%) and this was also true for the ITT population of patients with iNHL (79.2%). Among the 125 patients enrolled, most were refractory to the most recent regimen (90%). This was also true for the FL subgroup of patients (86.1%). The median duration of treatment was 6.5 (range, 0.6 to 31.0) months.

Of the 125 patients enrolled, 2 did not meet the eligibility criteria, leaving 123 patients to be included in the primary efficacy analysis. Patients with FL made up the greatest subpopulation of patients by disease type, representing 59% (72/123) of the study population. At the time of data cut-off (June 11, 2014), 7/72 (9.7%) patients with FL continued treatment.[6] In the overall ITT population (at the data cut-off of June 25, 2013), 40 patients (32%) were continuing with their treatment.[1] As such, 65 (90%) of patients with FL discontinued treatment due to progressive disease (53%), adverse events (21%), investigator request (6%), death (7%),[6] or because the patient withdrew consent (4%).

[Table 1]: Highlights of Key Outcomes

Table 10. Efficacy outcomes in patients with iNHL and the subgroup of patients with follicular lymphoma

	ITT, iNHL (n=125)[1]	Patients with FL (n=72)[43]
PFS, months, (median, range)	11.0 (0.03-16.6)	11.0 (0-30.6)
ORR (% and 95% CI %)	56.8 % (n=71/125; 95% CI 47.6-65.6, p<0.001)	55.6% (n=40/72; 95% CI 43.4-67.3, p<0.001)
DOR, months (median, range)	12.5 (0.03-14.8)[1]	10.8 (0-26.9)
Follow up, months (median, range)	9.7[1]	19.4 (0.7-35.6)
OS, months, (median, range)	20.3 (0.7-22.0)[1]	Not reached
OS rate		
1 year	80%[1]	88.1%[2]
1.5 years	NA	74.2%[2]
2 years	NA	69.8%[2]
Harms Outcome, n (%)	**iNHL (ITT) Patients**	**FL Patients**
Deaths	28 (22%)	12 (16%)[7]
Death due to AE's	8 (6%)	5 (7%)[6]
Grade ≥3	68 (54)	47 (65.3)
AE (any grade)	103 (82)	71 (98.6)

Abbreviations: CI = confidence interval; DOR = duration of response; FL = follicular lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; AE = adverse event; NA: not available
Note: data was collated from a variety of sources and presented as presented in the original sources.

Efficacy

The primary outcome was the overall rate of response. Key secondary outcomes included: the duration of response, progression-free survival, and safety. A significant overall response rate was reported both in the ITT population of patients with iNHL and FL as 57% and 56%, respectively. Ten patients (14%) with FL had a complete response and 30 (42%) had a partial response, while 8 (11%) patients had progressive disease and 23 (32%) patients had stable disease. The median PFS for the FL patients was 11.0 (0-30.6) months, which was comparable to that of the overall population (11.0 (0-16.6)). The median duration of response in the FL subset of patients was 10.8 months (range, 0-26.9 months).

Harms

Patients were regularly assessed for safety and toxicities. Deaths was reported in 12/72 patients with FL.[7] Among these, 5/72 (7%) were due to adverse events (one each of cardiac arrest, drug-induced pneumonitis, splenic infarction/acute abdomen, heart failure and unknown).[6] The most common adverse events of any grade were diarrhea (51%) and neutropenia (51%), with 14% of patients FL experiencing ≥Grade 3 diarrhea and 22% experiencing ≥Grade 3 neutropenia. Grade 3 or higher elevations in aminotransferase levels were also observed in 14% of patients with FL.

Key Limitations

The Gopal 2014 study is a non-comparative study, any comparisons with other treatments would have a high risk of bias, thus making it difficult to draw any conclusions. There is however no current standard of care for patients in this setting.

Data on efficacy and safety of idelalisib in the FL subset was assessed as an unplanned *subgroup* analysis, which has limitations:

- The overall study was powered to detect a treatment effect in the overall study population (*all* patients with iNHL) and the study sample size calculations were performed accordingly. However, in order to detect an interaction effect of the same magnitude in the FL subgroup, the sample size would need to be largely inflated.[3] Whether or not the effect varies by the severity of the disease is also difficult to determine with the sample sizes of these *subgroups* of patients with FL being relatively small.
- While the authors report a consistent effect between disease subgroups (FL, small lymphocyctic lymphoma, marginal-zone lymphoma, lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia), there is no evidence on the external consistency of the results since no other studies were identified. At best, post-hoc subgroup analyses should be considered exploratory and interpreted with caution.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

According to Lymphoma Canada (LC), patients with early stage FL who participated in the survey reported minimal symptoms associated with their disease and tended to report a good quality of life. However, for those with relapsed disease, their quality of life was impacted more significantly. LC noted that patients commonly reported fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, as well as muscle and joint pain. Some patients with FL expressed difficulties with memory, concentration, anxiety, depression, insomnia and intimacy. LC also noted that there were additional complications reported which included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia), and easy bruising (caused by low platelet counts). LC stated that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day activities. Respondents reported that treatment options for recurrent FL include: single agent or combination chemotherapy, anti CD 20 monoclonal antibodies (alone or in combination), or radiation therapy. According to LC, these treatment options tend to be associated with increased toxicity, reduced anti-tumour

activity and unpleasant side effects. In terms of expectations for a new therapy, respondents reported that they are seeking treatment that will prolong their life, offer disease control, bring about a remission and improve quality of life. As an oral therapy, LC indicated that idelalisib could reduce drug administration costs (e.g., no chemo chair time) and reduce the financial burden for patients and their caregivers (i.e., reduce the need for patients and caregivers to travel to receive treatment). Furthermore, LC added that some patients treated with idelalisib may be eligible for a potentially curative allogeneic transplant; and therefore, idelalisib may also help some transplant patients bridge to a donor lymphocyte infusion.

Provincial Advisory Group (PAG) Input

Input was obtained from all the provinces participating in pCODR. PAG identified the following as factors that could impact the implementation of idelalisib for follicular lymphoma (FL):

Clinical factors:

- Clarity of the recommended population and definition of refractory to rituximab
- Safety and risks of treatment given the recent alert issued by the Food and Drug Administration in the U.S. and the stopping of several ongoing trials
- Lack of comparative data and long-term data

Economic factors:

- Large prevalent patient population
- Duration of treatment until disease progression or unacceptable toxicities

Registered Clinician Input

Registered clinician input was not received on this submission.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

Table 2.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

1.2.3 Factors Related to Generalizability of the Evidence

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Symptomatic Disease	Among the subgroup of 72 patients with FL, 13 (18.1%) patients had disease-related symptoms (11/72 (15%) of follicular lymphoma patients had baseline B-symptoms (fever, weight loss, night sweats) and 2/72 (3%) had other (skin lesions, pruritus, unknown) symptoms)[43] and 59 (81.9%) patients did not have disease-related symptoms present at enrollment. The submitter defined "disease-related symptoms" as B-symptoms (eg. fever, weight loss, night sweats) and other symptoms (eg. skin lesions, pruritus, etc). Additional clinical manifestations of the disease such as lesions, lymphadenopathy, cytopenias, extranodal involvement, bone marrow, performance status, stage, LDH, and progressive disease may also be used to determine initiation of treatment. The submitter further noted that the majority of patients had bulky lymphadenopathy and 83.3% had Ann Arbor stage III-IV disease. Many had intermediate (25.0%) or high (54.2%) risk FLIPI scores and ECOG performance scores of 0 (43.1%), 1 (48.6%) or 2 (8.3%). The median time since completion of their last therapeutic regimen was 4.3 months and 86% of the patients were refractory to this regimen.	Are the trial results generalizable to patients with symptomatic disease	Indication for therapy included symptomatic disease, cytopenias secondary to disease, bulky adenopathy, or risk of other organ compromise due to extranodal disease. Whether these patients would have been offered treatment outside of the clinical trial is unclear. Although the majority of patients did not have symptoms, it is the opinion of the CGP that the response can likely be generalized to patients with symptomatic disease. There is no reason why having symptomatic disease would lessen the response to therapy.
	Other iNHL's	The study included other subtypes of indolent non-Hodgkin lymphoma, including small lymphocytic lymphoma, marginal zone lymphoma, and lymphoplasmacytic lymphoma.	Are the results generalizable to other types of lymphoma?	Due to the low number of patient with subtypes of lymphoma other than follicular lymphoma, the results cannot be generalized to these patient populations.
	Age	Within the trial, 26 patients (36%) were ≥65 years. Subgroup analyses were available for this population. ORR was 62% (16/26) (95% CI 40.6-79.8) in patient's ≥65 years. However, limitations exist on the interpretation of these data because the results are based on a subgroup of 26 patients within an unplanned post hoc analysis of 72 patients with FL. Results were however consistent across all subgroups in the full cohort.	Are the trial results generalizable to patients with FL who are refractory to an alkylator and bendamustine and are ≥65 years old	Yes. The results are generalizable to patients over the age of 65. There is no data within this study or in other studies using Idelalisib that would suggest efficacy would be different in patients >65.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Patients not refractory to both rituximab and an alkylating agent	All patients included in the trial were refractory to both rituximab and an alkylating agent	Are the trial results generalizable to patients who are not refractory to both rituximab and an alkylating agent?	No. The results are specific to patients with refractory disease, and cannot be generalized to patients that are not refractory. There are no studies addressing the non-refractory group, and therefore, extrapolation is not possible.
	ECOG PS of 2 or greater	Within the trial, 6 patients (8.3%) had an ECOG PS of 2. Given the sample size, it is not clear whether the overall effect would also be similar in patients with an ECOG PS of 2.	Are the trial results generalizable to patients with an ECOG PS of 2?	Yes. For disease-related compromise of performance status, it is the opinion of the CGP that this therapy could be generalized to patients with ECOG >2.

1.2.4 Interpretation

Burden of Illness and Need:

In 2015, approximately 2800 patients were diagnosed with follicular lymphoma in Canada.[4] Despite significant advancement in treatment, it still remains an incurable disease. For patients with advanced disease, after frontline therapy, all patients will eventually relapse. Various chemotherapy regimens can be used to treat symptomatic relapses. Superiority of one regimen over the other is unknown, and eventually, refractory disease to standard therapies such alkylators and rituximab may occur. Treatment options are limited in this patient group, and life expectancy is shortened. Finding novel therapies for this patient group is a continued need. Using novel targeted therapy, such as idelalisib, may lead to improvement in outcomes, as demonstrated in this review.

Effectiveness:

Progression-free Survival (PFS):

After a median follow up of 9.7 months, the median progression free survival in patients treated in the phase II trial of Idelalisib was 11 months (0-30.6 months). Since this was a phase II study, there is no comparator. Prior to entering the study, the median PFS for the most recent regimen was 5.1 (4.4-6.0) months. A PFS of 11 months for idelalisib confirms this drug has activity in patients with refractory disease. How this compares to other therapies is unknown.

Overall Survival (OS):

Median overall survival was not reached for this study. The one-year overall survival was 88.1%, and the 2 yr. overall survival was 69.8%. The life expectancy for untreated patient's refractory to alkylators and rituximab is uncertain, as this patient group has not been specifically studied in other clinical trials.

Overall Response rate (ORR) – Primary Outcome:

The overall response rate to idelalisib as determined by an independent review committee was 55.6% (n=40/72; 95% CI 43.4-67.3, p<0.001). This included 10 patients with a complete response (CR), and 30 patients with a partial response (PR). The clinical significance of the response rate is uncertain.

Given that Study 101-09 was a non-randomised study, results with idelalisib were presented in comparison to the last prior therapy patients had received.[5,6] In a study such as this in which eligibility requires demonstration of lack of response (refractoriness) to a prior agent, comparison to the last prior line of treatment is not informative. Within the trial, 86.1% of patients with FL were refractory to their most recent regimen. This is a select patient population resistant to a specific therapy, but the response to the last prior therapy does not necessarily represent the response to other chemotherapy regimens. Consequently, there is no appropriate comparator in this phase II study.

Quality of Life (QOL) analysis:

Health related quality of life data shows no impairment in QOL with idelalisib. There is clinically meaningful improvement in several subscales including emotional and functional wellbeing, additional concerns, trial outcome index score, and for the FACT-G total score subscales. The CGP noted that results were reported using best change from baseline as an endpoint. The CGP was concerned that this endpoint may have reported selective results that favour idelalisib, presenting the most optimistic interpretation. These quality of life changes are clinically relevant as they reflect a meaningful improvement compared to the pre-treatment baseline assessment for the patients in this study. The

improvements seen are in keeping with patient wishes for lymphoma therapy based on the feedback from patient advocacy groups. The wishes expressed include having more choice in treatment options with an acceptable side effect profile, and an improvement in quality of life after therapy.

Safety:

Toxicity:

Clinically relevant serious adverse events (SAE), grade 3 or higher, include diarrhea (14%), neutropenia (22%), and elevated liver enzymes (14%). Pneumonitis occurred in 4% of participants. Heightened awareness and prompt investigation is appropriate if symptoms occur due to reported cases of fatality from infection, colitis, hepatotoxicity and pneumonitis in other studies.

Death:

Twelve deaths were reported in the 72 patients with follicular lymphoma enrolled in the study.[7] While most of these deaths were due to disease progression, 5 of these deaths were reported as an adverse event. This is a rate of 6.9% for an adverse events causing death. In light of the recent studies combining idelalfisib with chemotherapy causing increased mortality, these results require further follow-up and monitoring to better clarify at-risk populations. Treatment with idelalisib should be confined to patient populations where benefit, and safety has been confirmed. Using idelalisib in combination with other therapies should be done only in the setting of a clinical trial.

Following the posting of the Initial recommendation and the receipt of feedback from stakeholders, the CGP addressed the following concerns in response to feedback:

- As related to the number of treatment related deaths in the trial (7% in the FL population), based on data that have been made available thus far, there is no clear evidence to say that single-agent idelalisib increases mortality compared to other regimens. Without a control arm, it is therefore difficult to say whether a 7% mortality rate is greater than what would be expected with other treatments in this setting. Prescribers should however be aware of this limitation, and proceed with a heightened level of awareness.
- As related to the comparative efficacy of idelalisib with other available treatment options, the CGP noted that potential next treatments for this population include purine analogues (e.g. fludarabine, cladribine, pentostatin); pulse high dose corticosteroids (e.g. prednisone, dexamethasone); newer anti-CD20 monoclonal antibodies (e.g. ofatumomab, obinotuzumab); other less commonly used anti-lymphoma agents (e.g. bendamustine, gemcitabine, etoposide and others); combinations of agents; and experimental or off label agents (e.g. ibrutinib, venetoclax, clinical trial drugs). The CGP is unaware of any evidence to support the notion that idelalisib will definitely perform better than any of those agents. The current study confirms that Idelalisib has activity in follicular lymphoma and that it is a reasonable treatment option for patients with disease resistant to alkylators and rituximab. How it compares to other regimens is however unknown. Based on the current evidence, idelalisib would at best be included as another option for patients, in addition to the options outlined above.
- As related to the proportion of patients in the trial who had symptomatic disease and were in need of treatment, the CGP agree that having follicular lymphoma that is refractory to rituximab, has spread 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 and in the absence of disease related symptoms, justify treatment. The CGP however agreed that having disease-related symptoms, which includes any symptoms, not

just B symptoms, does justify treatment. The current evidence indicates that disease-related symptoms were only present in ~18% of patients.

- As related to the feasibility of an RCT in this population, the CGP noted that the Canadian incidence of follicular lymphoma — approximately 2800 new cases per year — is not particularly relevant to the current question as the key population is defined by prevalence. With a median overall survival exceeding 10 years, as is now true in Canada, the Canadian prevalent population is approximately 30,000. Since follicular lymphoma is not curable, most patients relapse, often multiple times, and eventually the lymphoma becomes resistant to alkylators and rituximab. It is therefore not unreasonable to consider that at least 15% to 20% of the prevalent population of follicular lymphoma patients eventually develop alkylator/rituximab resistant disease and require treatment, providing a potential population of at least several thousand for a trial such as the current one. The CGP agreed that this would have been sufficient for a randomized controlled trial. It is also notable that other groups have been able to conduct RCTs in this population. Even if considering the available number of patients as defined by the submitter's feedback, 90 patients could have been enrolled since 2015, 45 patients in each arm. An international trial involving the US and Europe could have accrued many more patients in the same period of time. The CGP also cite their own clinical experience in which at least one, often two or three, open, prospective randomized clinical trials accruing patients with relapsed follicular lymphoma have been open continuously for the past 5-10 years in their respective practices. Such trials have opened and closed approximately on time, with adequate accrual for interpretation. It is therefore not appropriate to confidently state that idelalisib is more effective than current options without an RCT.
- Lastly, as related to the comparison of the trial data to patient's last line of prior treatment, the CGP re-iterate that this is an inappropriate comparison. The CGP agree that results obtained through such a comparison would be dependent on the clinician's choice of last prior treatment to be used and the patient's disease course (e.g., whether the patient has slowly or rapidly progressive disease). The CGP noted the submitter's feedback pointing out that "47 different prior therapeutic regimens" had been used in patients on the trial. The CGP however agreed that such a large number of effective options are not available in this setting. Therefore most of these regimens would likely have been ineffective options to which the submitter is trying to make a comparison. As an example Table 8 (Section 6 of this report) shows that only 34% of patients had received a purine analogue as part of their prior therapy. A purine analog is a class of drugs with known activity in lymphoma yet the majority of patients had not received this treatment yet. Therefore the number of drugs used in prior therapy is irrelevant if one is using drugs that are ineffective, and passing up drugs that have known activity. Therefore the CGP agreed that demonstrating efficacy compared to an ineffective treatment is not sufficient evidence of effectiveness.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to idelalisib in the treatment of follicular lymphoma. From this study it is clear that idelalisib is an active drug in follicular lymphoma based on the response rate and PFS. However, without a comparator arm, the magnitude of benefit is difficult to determine. An 11-month median progression free survival in the refractory patient population is likely clinically meaningful. A randomized clinical trial comparing Idelalisib to other agents in this setting would be ideal. Based on these data, idelalisib is a reasonable option for patients with follicular lymphoma when other treatment options have been exhausted.

In making this conclusion, the Clinical Guidance Panel also considered the following:

- The subgroup analysis of patients with follicular lymphoma were not pre-planned and is based on relatively small patient numbers. Conventionally subgroup analyses are used for hypothesis generation and require future validation in larger studies. Thus far, confirmatory phase III studies of the benefits of idelalisib in patients with FL have not been reported. Although not randomized against other agents, a phase III dose optimization trial in patients with refractory FL is underway with an estimated completion date in June 2019 (NCT02536300)[8]

- Due to the long survival and indolent nature of follicular lymphoma, PFS is a clinically relevant outcome used widely in indolent non-Hodgkin lymphoma studies.

- This study focuses on a refractory patient population where there is no standard of care. There are no other studies that address other treatment options in this highly specific patient group. A meaningful interpretation of PFS in comparison to other regimens cannot be given. Eighty-six percent of patient entered in the trial were refractory to their last prior treatment, but the duration or response to the last prior therapy does not necessarily represent the response to other chemotherapeutic agents.

- The majority of patients tolerate this drug without significant adverse events. However, life threatening toxicities can occur, and further study is necessary to define populations at risk.

- Treatment with idelalisib should be as a single agent in patients with lymphoma. Combination with rituximab or other chemotherapy regimens for low grade lymphoma should be within the context of a clinical trial.

- Idelalisib use should be restricted to patients having failed two or more prior lines of therapy, refractory to rituximab and alkylators (both bendamustine and cyclophosphamide) and when other treatment options have been exhausted.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma/Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (NHL), and the second most common NHL, accounting for approximately 35% of cases. Non-Hodgkin lymphoma made up 4.5% of all new cancers in Canada in 2015, and it is estimated that more than 2800 Canadians are diagnosed with follicular lymphoma every year.[4] It is usually diagnosed in patients, over the age of 50 and it is uncommon in young people. Prognosis is estimated by the Follicular Lymphoma-specific International Prognostic Index (FLIPI) which incorporates patient-specific, and disease-specific features at the time of diagnosis. Based on this model, prognosis varies from a 10 yr. survival of 84% in the low risk group, to 42% in the high risk group.[9]

The Diagnosis of follicular lymphoma is typically made on an excisional lymph node biopsy. The lymphoma is classified according to the World Health Organization based on histologic features of the lymph node. Grade 1, 2, and 3a lymphoma is determined based on the number of blast cells seen under high power microscopy. Regardless of the grading, these subtypes are all considered indolent lymphoma and are managed identically. The majority of clinical opinion classifies grade 3b follicular lymphoma, with characteristic sheets of blast cells, as an aggressive lymphoma, and as a result, is managed differently than the indolent subtypes. Initial investigations for staging of the disease include a CT scan of the chest, abdomen and pelvis as well as a bone marrow biopsy. Stage I and II disease, as defined by the Ann Arbour staging system, has disease confined to the same side of the diaphragm. Stage III disease is defined as widespread adenopathy above and below the diaphragm, and stage IV disease includes patients with bone marrow or diffuse extralymphatic organ involvement. Non-bulky stage I or II disease may be eligible for radiation as a potentially curable option. Advanced stage follicular lymphoma, defined as bulky disease, or stage III or IV disease are considered incurable. Indication for treatment is for symptomatic disease, and typically involves chemoimmunotherapy to treat the widespread burden of illness.

2.2 Accepted Clinical Practice

There is significant heterogeneity with respect to the clinical course of advanced stage lymphoma. Given the incurable nature of the disease, and its indolent clinical course, treatment is typically initiated at onset of symptomatic disease. This 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. Early chemoimmunotherapy intervention for patients with asymptomatic disease has not been associated with an improvement in survival compared to a "watch and wait" strategy.[10] However, early intervention in asymptomatic patients using single agent rituximab immunotherapy resulted in improved progression-free survival (PFS).[11] Long-term outcomes of such therapy remains uncertain.

When a patient develops symptomatic disease, chemoimmunotherapy is the treatment of choice. Several studies have been done confirming the addition of rituximab to chemotherapy significantly improves response rate, duration of response and overall survival.[12] Although many chemotherapies have been combined with rituximab, the use of an alkylator combined with rituximab has emerged as the standard of care. Historically, the most commonly used alkylator was cyclophosphamide. In an attempt to determine optimal first-line therapy, a phase III study compared R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), R-CHOP (rituximab,

cyclophosphamide, doxorubicin, vincristine, prednisone), and R-FM (rituximab, fludarabine, mitoxantrone) chemotherapy.[13] The results confirmed R-CHOP as the regimen of choice with a longer remission compared to R-CVP, and less toxicity compared to R-FM. More recently, bendamustine, a cytotoxic bifunctional alkylating agent combined with rituximab has become the standard first-line therapy for follicular lymphoma across Canada.[12] When compared to R-CHOP, bendamustine and rituximab (BR) had an improvement in PFS (not reached (NR), vs. 40.9 months for R-CHOP, HR 0.61, $p<0.0072$), and improved time to next treatment (NR vs. 42.3 months, HR=0.52, $p<0.001$).[14] Bendamustine and rituximab also had an improved toxicity profile, making this the preferred regimen for first-line therapy in follicular lymphoma.

Eventually, patients with advanced disease at initial presentation will develop progressive disease. Asymptomatic progression can be observed, with chemotherapy reserved for patients with symptoms as outlined above. There is no standard of care for treating relapsed disease. Numerous regimens have been tried but never compared against each other. Cytotoxic drugs in combination with rituximab is recommended if the duration of remission is greater than 6 months after receiving a rituximab containing regimen. Many of the same chemoimmunotherapy protocols used in first line therapy have demonstrated activity in second line phase II studies with response rates varying from 65-90%. Such examples include BR,[15] CVPR,[16] and R-CHOP.[17] Consequently, the choice of treatment may be based on what was given in the past, incorporating a drug with a different mechanism of action. Purine analogues have also shown activity in relapsed follicular lymphoma with complete response rates as high as 74% using FCR (fludarabine, cyclophosphamide, rituximab), and could also be used in the relapsed setting.[18]

The role of stem cell transplantation in follicular lymphoma is controversial. For select patients, it may provide prolonged PFS, and potentially cure the disease if an allogeneic stem cell transplant is considered. However, there is no consensus regarding which patients might benefit from this approach and the utilization of high dose chemotherapy is decreasing since the introduction of rituximab in the treatment paradigm.[19] Based on consensus opinion, autologous stem cell transplant may be considered in first or second chemo-sensitive relapse for young, healthy patients, with high risk disease. This patient group is defined as under the age of 70, with high risk disease based on the FLIPI score, or relapsed disease within 3 years after first-line chemoimmunotherapy. However, the benefits of this approach in the rituximab era are less certain, and the risks of high dose chemotherapy need to be balanced against the benefit. Consensus opinion also suggests the use of allogeneic stem cell transplant for healthy patients under the age of 40, with progressive disease post-autologous stem cell transplant.[19] The number of patients eligible for such a procedure would be small, and the magnitude of benefit is uncertain.

Although follicular lymphoma is considered a chemotherapy-sensitive disease, it remains an incurable disease for patients not eligible for allogeneic stem cell transplant, and resistance occurs with re-treatment, and multiple lines of therapy. New treatments with a novel mechanism of action are necessary for patients with refractory disease. Radioimmunotherapy using a radiolabeled monoclonal antibody, such as Yttrium-90 (90Y)-labelled ibritumomab, has some evidence of activity in patients with relapsed disease.[20] However, concerns regarding long-term hematologic toxicity, and a restricted indication for patients with low burden of disease in the marrow have limited its utilization. Other drugs with novel mechanisms of action, such as bortezomib and lenalidomide look promising, but there is insufficient data to consider these agent as standard care.

A number of cellular pathways have been identified that are responsible for the proliferation, migration and survival of B-lymphocytes. One in particular is the presence of constitutive activation of the phosphoinositide-3 kinase (PI3K) family of proteins. The PI3K δ isoform is restricted to hematopoietic cells, and CLL cells appear to be dependent on its expression for

survival. Idelalisib is a selective inhibitor of the PI3K δ isoform, and does not appear to inhibit normal T or NK cell function. Idelalisib reduces intracellular signaling via the B cell receptor (BCR), and reduces BCR and chemokine receptor activation of the AKT and MAPK/ERK pathways that are important for cell proliferation. Research is ongoing to determine the magnitude of impact this drug has on B-cell lymphoid neoplasms.

Targeting the PI3K δ pathway may provide a new therapeutic option for patients with previously treated follicular lymphoma. For patients with resistant disease, defined as progression within 6 months of receiving rituximab, and previously had treatment with an alkylating agent, there is no standard of care. This patient group has not been isolated from the relapsed follicular lymphoma studies previously published. Historically, treatment would be based on choosing a regimen where cross-resistance is less likely (i.e. using a purine analogue if cyclophosphamide and bendamustine have already been used). Idelalisib monotherapy may be a treatment option for this group. A recent phase II study looked specifically at the relapsed and rituximab-refractory group.[1] The results of this study is the topic of this review.

TableXX: Standard therapy and proposed idelalisib therapy for transplant-ineligible patients with follicular lymphoma

Line of Therapy	Standard chemotherapy options
1st-Line	Bendamustine-Rituximab
Maintenance	Rituximab
2nd-Line	Alkylator + Rituximab (ie. Cyclophosphamide or chlorambucil)
3rd-line (non-refractory to alkylator and rituximab)	Purine-analogue +/- Rituximab (ie. Fludarabine)
3rd line therapy (Refractory to alkylator and rituximab)	Purine analogue Or Idelalisib

2.3 Evidence-Based Considerations for a Funding Population

The population under consideration here includes patients with resistant disease, defined as progression within 6 months of receiving rituximab, and previously having had treatment with an alkylating agent. This includes treatment with both cyclophosphamide and bendamustine.

2.4 Other Patient Populations in Whom the Drug May Be Used

The benefits of single agent idelalisib in patients with relapsed FL but not rituximab-resistant is unknown. At the present time, there is no indication to use idelalisib in this group. Similarly, the benefits of idelalisib in combination with rituximab is an area of ongoing research.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lymphoma Canada (LC), provided input on idelalisib for the treatment of patients with relapsed/refractory follicular lymphoma (FL). LC conducted an online survey and interviewed FL patients and caregivers about the impact of FL on their lives and the effects of treatments for their lymphoma. The total number of respondents is reported in the table below.

Gender	Age	Nationality					
		Canada	USA	UK	Italy	South Africa	Did not specify
Patients without idelalisib experience (Survey)							
Male	**35-44**	3	-	1	-	-	Data not available
	45-54	3	1	1	-	-	
	55-64	10	-	1	-	-	
	65-74	5	-	-	-	-	
	75+	3	-	1	-	-	
Female	**35-44**	5	1	-	-	1	
	45-54	8	2	6	1	-	
	55-64	30	6	5	-	-	
	65-74	12	4	1	-	-	
	75+	1	-	-	-	-	
Skipped		1	-	-	-	-	
Patients WITH Idelalisib experience (Survey)							
Female	**55-64**	1	-	-	-	-	-
Caregivers (Survey)							
Male	**35-44**	-	-	-	-	-	Data not available
	45-54	2	-	-	-	-	
	55-64	-	1	-	-	-	
	65-74	-	1	-	-	-	
	75+	-	-	-	-	-	
Female	**25-34**	2	-	-	-	-	
	35-44	1	-	1	-	-	
	45-54	1	-	1	-	-	
	55-64	5	-	1	-	-	
	65-74	1	-	-	-	-	
	75+	-	-	-	-	-	
Patients without idelalisib experience (Interviews)							
Male	**55-64**	1	-	-	-	-	-
Female	**55-64**	1	-	-	-	-	-
Patient WITH idelalisib experience (Online forum)							
Gender/age not available		-	1	-	-	-	-

The patient and caregiver survey links were sent via e-mail on March 19th, 2016 to patients and caregivers registered on the LC database and were also made available via LC twitter and Facebook accounts, as well as through FL patient forums and the Lymphoma Association (UK). The

survey links were shared on FL patient forums between March 19th and March 24th, 2016. The surveys were open from March 18th to April 7th, inclusive.

The surveys had a combination of multiple choice, rating and open-ended questions. There was skipping logic questions built into the surveys to allow respondents to answer questions which were relevant only to them. Open-ended responses to surveys and quotes obtained from interviews that reflected the sentiment of respondents are included verbatim in order to provide a deeper understanding of patient and caregiver perspectives.

The table below provides information regarding respondent participation by country and their experience with and without idelalisib.

From a patient's perspective, the physical and emotional impact of living with FL was varied.

LC indicated that 33 of the 137 (24.1%) respondents reported they had relapsed FL. LC stated that for those respondents with relapsed disease, quality of life was impacted more significantly than those who indicated they did not have relapsed FL.

According to LC, patients with early stage FL who participated in the survey reported minimal symptoms associated with their disease and tended to report a good quality of life. However, for those with relapsed disease, their quality of life was impacted more significantly. LC noted that patients commonly reported fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, as well as muscle and joint pain. Some patients with FL expressed difficulties with memory, concentration, anxiety, depression, insomnia and intimacy. LC also noted that there were additional complications reported which included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia), and easy bruising (caused by low platelet counts). LC stated that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day activities. Respondents reported that treatment options for recurrent FL include: single agent or combination chemotherapy, anti CD 20 monoclonal antibodies (alone or in combination), or radiation therapy. According to LC, these treatment options tend to be associated with increased toxicity, reduced anti-tumour activity and unpleasant side effects. In terms of expectations for a new therapy, respondents reported that they are seeking treatment that will prolong their life, offer disease control, bring about a remission and improve quality of life. As an oral therapy, LC indicated that idelalisib could reduce drug administration costs (e.g., no chemo chair time) and reduce the financial burden for patients and their caregivers (i.e., reduce the need for patients and caregivers to travel to receive treatment). Furthermore, LC added that some patients treated with idelalisib may be eligible for a potentially curative allogeneic transplant; and therefore, idelalisib may also help some transplant patients bridge to a donor lymphocyte infusion.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Follicular Lymphoma

According to LC, respondents with early stage FL who participated in the survey reported minimal symptoms associated with their disease and tended to report a good quality of life. The respondents commonly reported fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, muscle and joint pain. Some respondents with FL expressed difficulties with memory,

concentration, anxiety, depression, insomnia and intimacy. Additional complications reported included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts).

LC also asked respondents about the impact of FL on day-to-day life. Respondents were asked to rate on a scale of 1 (no impact) to 10 (very significant impact), how much the symptoms associated with FL have impacted or limited their day-to-day activities and quality of life.

The table below provides further information regarding various impacts on day-to-day life and the corresponding rating by respondents. LC indicated that for those factors with a rating average ≥5, it was deemed to be a greater than neutral impact on the day-to-day life.

Impact on Day-to-Day Life of R/R FL Patient Participants (N= 32*)	**Rating of ≥7 n (%)**	**Rating Average**	**Impact on Day-to-Day Life of all other FL Patient Participants (N=93)**	**Rating of ≥7 n (%)**	**Rating Average**
Ability to work	15 (46.9%)	6.2	Ability to work (*N=92)	33 (35.9%)*	5.1
Ability to travel	15 (46.9%)	5.6	Ability to travel	25 (26.9%)	4.6
Ability to exercise	12 (37.5%)	5.6	Ability to concentrate	26 (28.0%)	4.5
Ability to attend to household chores	11 (34.4%)	5.3	Ability to exercise	25 (26.9%)	4.5
Ability to fulfill family obligations	13 (40.6%)	5.1	Ability to contribute financially to household expenses	25 (26.9%)	4.2
Ability to spend time with family & friends	11 (34.4%)	5.1	Ability to volunteer *(N=90)	27 (30.0%)*	4.2
Ability to contribute financially to household expenses (*N=31) (* 1 skipped)	11 (35.5%)*	5.0	Ability to attend to household chores	16 (17.2%)	4.1
Ability to concentrate	11 (34.4%)	4.9	Ability to spend time with family & friends	21 (22.6%)	3.9
Ability to volunteer	13 (40.6%)	4.8	Ability to fulfill family obligations	15 (16.1%)	3.8
Notes:* One R/R FL participant did not respond to this question					

Below were some of the key responses as reported by three (3) respondents to help illustrate the impacts in regards to their experiences with FL:

- *"Critical reduction in oxygen absorption rate. Movement from chair rest to bathroom and back left me breathless and starving for oxygen. Was placed on oxygen supply at home with some improvement. Second round of chemo seems to have resolved the issue for the most part. Having just completed six months of treatment (monthly infusions and biweekly pill regimen), I do not know what will happen when the swelling may return to limit the exchange of oxygen."(Male; 65-74; Canada)*

- *"The second time I relapsed it was after birthing my third child and it was a nightmare. Mental Health is definitely impacted even after being in remission for 10 years. I could not attend to my children for two years due to the side effects of chemo and everything associated to having lymphoma."(Female; 35-44; Canada)*
- *"When symptoms were at their worst, before treatments began, I had chronic bladder/kidney infections, a build up of fluids due to difficulty urinating, and discomfort wherever the tumours happened to be pressing, night sweats, heaviness and weakness in legs which made walking and stairs difficult, as well as cracked and bleeding feet. I stopped working, cut back on commitments to family and friends as I was able." (Female; 55-64; Canada)*

3.1.2 Patients' Experiences with Current Therapy for Follicular Lymphoma

According to LC, while current treatment options can work initially, patients with FL usually relapse after treatment and in most cases each period of remission becomes shorter. LC indicated that treatment options for recurrent FL include: single agent or combination chemotherapy, anti CD 20 monoclonal antibodies (alone or in combination), or radiation therapy. Thirty-three (33) respondents indicated they had relapsed FL of which 29 (87.9%) provided the names of the treatment(s) that they had received.

The table below lists current treatments received by respondents.

Treatments Received (N= 29)	n	Treatments Received	n
R-CHOP; ASCT	2	Bendamustine-Rituximab	1
R-CHOP; Rituximab maintenance	2	R-CVP; Bendamustine-Rituximab	1
CVP; R-CHOP	2	CVP; FCM; Rituximab maintenance	1
Bendamustine-Rituximab; R-CHOP; R-GDP	1	R-CHOP; Radiation	1
Ritxumab; R-CHOP; R-CVP; Bendamustine; ASCT	1	CHOP; R-CHOP	1
CHOP; DHAP; Fludarbine; Interferon; B-R	1	CHOP; Rituximab	1
R-CHOP; DHAP; FCR; SCT (with total body irradiation)	1	R-CVP; Rituximab maintenance	1
Rituximab alone; CVP; GA-101; Bendamustine	1	R-CHOP; Radiation	1
CHOP; R-Galiximab; Radiation	1	R; Chlorambucil	1
CHOP; Zevalin; Bendamustine-Ritxuimab	1	R-GDP	1
CHOP; R-CVP; Rituximab Maintenance	1	Rituximab alone	1
Radiation; CVP; CHOP	1	Rituximab maintenance	1
Rituximab; Bendamustine-Rituximab	1	R-CHOP	1
Please note: ASCT = Autologous Stem Cell Transplant; SCT = Stem Cell Transplant.			

LC noted that for side effects of treatments, respondents listed both positive (disease control) and negative side effects (disease progression; adverse events; discontinue treatment due to side effects) of treatment.

Below were some of the key responses reported by five (5) respondents with relapsed FL to help describe perspectives regarding their experience with their current treatments:

- *"I feel like I'm wading through water. Dry mouth. Fatigue. My body injures and bruises easily. It takes a long time to recover. Just in case no one asks it has ruined my sex life*

because of the above symptoms". (Female; 45-54; UK; R-CHOP; Radiation)

- *"GDP-R was my last therapy. I found it becoming more difficult to rebound after each cycle. My hemoglobin and platelets were so low I had to have a few blood transfusions. At the end of it all my cancer was larger." (Male; 55-64; Canada; Bendamustine-Rituximab, CHOP-R, GDP-R)*
- *"The cancer never went away it just shrunk. Radiation had no effect whatsoever on the tumours. Of the different drugs I was given prednisone was the most difficult drug. I was unable to sleep or relax for five days. I can't imagine ever having to take that truck again. I lost my hair but I really didn't find that such a big deal. I found being hooked up to an IV line for 3 to 4 hours very difficult." (Female; 55- 64; Canada; CHOP; R-CVP; Rituximab Maintenance)*
- *"Bendamustine/rituximab was not so toxic as the CHOP regime, 12 years ago, although it seems I have had a reaction to Rituximab and was not allowed to continue with maintenance treatment as I developed numerous chest infections and bronchiectasis. My lymphocyte level is still very low. (0.02) and I take antibiotics and antivirals on a daily basis." (Female; 65-74; UK; CHOP; Zevalin; B-R)*
- *"It is potentially life threatening. So being denied treatment due to criteria funding is distressing." (Female; 55-64; Canada; CHOP; DHAP; Fludarabine, Interferon; Bendamustine-Rituximab)*

With respect to current therapy symptom management, LC reported that treatment options available in Canada for relapsed disease tend to be associated with increased toxicity, reduced anti-tumour activity and unpleasant side effects. LC submits that for Canadian FL patients refractory to both rituximab and an alkylating agent, there are currently no effective treatment options available in the third line setting with the exception of a stem cell transplant for those who are eligible. LC asked respondents to rate their level of agreement with how much their current therapy (ies) are (or most recent therapy (ies) was) able to manage symptoms associated with their FL with 1 (strong disagree) to 10 (strongly agree). LC reported that the 20 patient respondents living in Canada who identified as having relapsed FL who answered this question rated much lower (rating average 6.15) than the 38 patient respondents living in Canada who identified as not having relapsed FL (rating average 8.0).

In terms of choice of treatment, LC asked respondents how important it is for them and their physician to have a choice in deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 (not important as long as there is at least one treatment choice) to 10 (extremely important to have choice of treatment). LC reported that eighty-six (86) of the 117 respondents (73.5%) who answered this question gave this a rating of 8 or higher. According to LC, a rating average of 8.6, means a large proportion felt that choice was very important based on known side effects and expected outcomes of a drug. LC also asked respondents if they feel there is currently a need for more choice in drug therapy (ies) for patients with FL. The vast majority of the 117 respondents (112, 95.7%) who answered this question felt there is a definitive need for more therapies. One respondent stated: *"I am running out of options." (Male; 55-64; Canada; Bendamustine- Rituximab; R-CHOP; R-GDP).*
LC also asked respondents how difficult it was to access their current or most recent therapy (ies). LC reported that 40 (51.3%) of respondents answered 'not difficult at all', 22 (28.2%) answered 'not very difficult', 11 (14.1%) answered somewhat difficult, and 5 (6.4%) answered 'very difficult'. Overall, LC reported that 16 (20.5%) Canadian respondents who selected 'somewhat difficult' or 'very difficult' were included as respondents who experienced difficulties with access.

Difficulties expressed by respondents included the need to: travel great distances to receive treatments in Canada, meet specific provincial drug funding criteria, and pay out-of-pocket costs for treatments and associated travel.

Below were some of the key responses as described by four (4) Canadian respondents:

- *"I have 3 days in hospital instead of 2, I used to do bloodwork, see the Dr & have chemo in one day then chemo the next day, so only 2 days of travel & time spent in hospital. Now it's one day for bloodwork & Dr & then back 2 more days for chemo. Extra wear & tear on us, our car & our pocketbook for parking." (Female; 55-64; Canada)*
- *"Not difficult to get to London Regional Cancer Clinic and oncologists outstanding, the only challenge was the government's refusal to fund my maintenance Rituxin. That has been distressing."(Female; 55-64; Canada)*
- *"There were not volunteer drives that were accessible. I had to stay 3-5 hours past their return departure time. My therapy caused huge reactions so I had to stay overnight after treatment. We couldn't afford the lodge or motel bills. I had no one else willing to drive me to appointments. There were so many cancer patients at the cancer centre that I had to always make sure the times they scheduled me actually worked for bloodwork deadlines before treatment and giving enough time for slowed-down infusions before closing. If I didn't alert staff immediately that the booked times did not work out, I could lose my place for treatment that day or that week and would have to prolong my treatment cycle. My world revolved totally around my medical appointments and chemotherapy and that was not helpful. Staff were overworked." (Female; 45-54; Canada)*
- *"Having to go to Toronto for the best part of the day is very tiring when you are having chemo and therefore it is not advisable to drive yourself. Therefore, I had to have someone take me. I did not feel well enough to use public transit as I never knew how sick I would be on the way home."(Female;65-74; Canada)*

3.1.3 Impact of Follicular Lymphoma and Current Therapy on Caregivers

There were a total of 19 caregiver respondents who participated in the survey. LC noted that seven (36.8%) respondents were retired at the time of completing the survey and 12 (63.2%) were still working. LC asked respondents to rate on a scale of 1 (no Impact) to 10 (very significant impact) how caring for the person with FL has impacted their day-to-day life.

The table below provides further details on the impact of day-to-day life of caregivers from the perspective of being retired and those who were still working, and their corresponding ratings. According to LC, for those factors with a rating average of ≥5, it was deemed to be a greater than neutral impact on the day-to-day life.

Impact on Day-to-Day Life of Retired Caregivers (N= 7)	**Rating of ≥7 n (%)**	**Rating Average**	**Impact on Day-to-Day Life of <u>Not</u> Retired Caregivers (N=12)**	**Rating of ≥7 n (%)**	**Rating Average**
Ability to volunteer	3 (42.9%)	7.4	Ability to travel	5 (41.7%)	5.8
Ability to travel *1 skipped	4 (66.7%)*	6.8*	Ability to Work	4 (33.3%)	5.4
Ability to concentrate	2 (28.6%)	4.6	Ability to concentrate	4 (33.3%)	5.3
Ability to fulfill family obligations	2 (28.6%)	4.3	Ability to volunteer	3 (25.0%)	5.0
Ability to spend time with family & friends	2 (28.6%)	4.1	Ability to exercise	5 (41.7%)	4.9

Impact on Day-to-Day Life of Retired Caregivers (N= 7)	Rating of ≥7 n (%)	Rating Average	Impact on Day-to-Day Life of Not Retired Caregivers (N=12)	Rating of ≥7 n (%)	Rating Average
Ability to exercise	2 (28.6%)	4.0	Ability to fulfill family obligations	4 (33.3%)	4.8
Ability to attend to household chores	1 (14.3%)	3.6	Ability to spend time with family & friends	3 (25.0%)	4.7
Ability to contribute financially to household expenses	1 (14.3%)	2.1	Ability to contribute financially to household expenses	2 (16.7%)	3.6
Ability to work	Not asked		Ability to attend to household chores	2 (16.7%)	3.5

When asked about challenges caregivers face in caring for patients with this type of cancer, the following responses were noted below as described by three (3) caregiver respondents:

- *"Self-employed family business, husband on treatment and unable to take sick leave. Caring for husband attending hospital plus running company/staff/clients - friends and family mean well but are emotionally needy asking and worrying and constantly calling/telephoning... Hospitals and appointments are very slow and not time efficient...Communication between different hospitals, GP and clinicians not good due to being different areas/foundation trusts etc…Travel and parking is an additional burden on time and most hospitals have limited spaces so drive round and round constantly seeking parking...Cancer isn't 9-5 and many people still need to work to survive in addition to being treated and struggling to stay alive." (Wife; Not Retired; 45-54; UK)*
- *"The biggest impact for me as a spouse has been the emotional/psychological impact...There has been nothing offered support wise to help us cope with the reality that his life has been shortened by decades." (Wife; Not Retired; 35-44; Canada)*
- *"When my husband was first diagnosed the life we knew ended. Period. Everything changed. Our children were greatly affected also. We live in a rural area so we had to travel 30 min (family doctor) to 3 hours (oncologist - Cancer Center) for every doctor appointment/treatment so time & cost is a huge factor. My responsibilities doubled as I took on everything my husband used to do. Which wasn't easy as I was also a 24/7 caregiver. The medication regime was so extensive that I had to keep a paper on the fridge & reminders on my phone so we wouldn't miss a dose. I cannot imagine a person with cancer going thru treatments without someone to keep track of medications, appointments, driving the patient around & insuring there is proper food always available…Now that my husband is in remission things have gotten a lot better, but when he was first diagnosed "the not knowing" almost killed us both!!... The worst thing with fNHL is there is no cure... Do I think more funding is needed for this disease? Absolutely!! With all my heart!!" (Wife; Not Retired; 55-64; Canada)*

When asked about side effects, LC stated that caregivers reported difficulties managing the "side effects" of treatment, as described by three (3) caregivers in the responses provided below:

- *"The nausea at the time of treatment was a huge factor. He had to eat "as soon as" he felt hungry or he would loose (sic) his appetite. I would pre make meals that could be quickly heated. The "chemo brain" has made it frustrating for both of us because he couldn't remember things. The neuropathy in his feet has just made it uncomfortable for him."*

(Female; Spouse/Partner; Not Retired; 55-64; Canada)

- *"My dad got really sick at his first treatment and had an incredibly bad reaction to the drugs. As his daughter it was pretty scary to see my dad at his most vulnerable and so helpless."(Female; Daughter; Not Retired 25-24; Canada)*
- *"Small challenges were encountered choosing a menu that would appeal during the CVP-R treatments, dealing with the fatigue and mild depression during and after treatment." (Female; Spouse/Partner; Retired; 55-64; Canada)*

LC also noted that caregivers reported difficulties with "accessibility". According to LC, the most commonly reported factors were financial burden and distance to receive the drug treatment. Some caregivers had to take time off work to assist in taking care of the patient (loss of income). Other caregivers reported the drug was difficult to access because they had to travel to a cancer centre far from home.

To help illustrate the challenges noted above, caregiver respondents reported the following:

- *"It was a long drive. We had to be there for hours so we had to be there early in the morning. I had to take at least one day off work and sometimes two days." (Spouse /Partner; Not Retired; Male; 45-54; Canada)*
- *"We had to apply for income support and a drug card for my child as they had no coverage. I am currently off work on LTD while treatment is occurring."(Parent; Not Retired; Female; 45-54; Canada)*
- *"Can't concentrate on work, 1-hour and fifteen minutes to cancer treatments, health care needs improvements, finances a struggle, the process is not easy. There should be financial help for people." (Spouse /Partner; Not Retired; Male; 45-54; Canada)*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Idelalisib (Zydelig)

For respondents who have not used idelalisib, LC asked respondents to rate on a scale of 1 (Not Important) to 10 (Very Important), how important it is for a new drug to be able to control specific aspects associated with their FL. According to LC, the vast majority of respondents who answered this question assigned a rating of '10' to all aspects.

Factors Associated with Long-term Health and Well-being	Rating of 10 n (%)	Rating Average
Allow me to live longer (N=119)	109 (91.6%)	9.66
Bring about a remission (N=119)	105 (88.2%)	9.59
Control disease and symptoms associated with the disease (N=119)	102 (85.7%)	9.56
Improve Quality of Life (N =119)	96 (80.7%)	9.46
Improve blood counts (N = 117)	83 (70.9%)	8.90

One respondent from the interview stated: "*I did not take idelalisib, but I looked it up on the internet. If it comes on the market, this is my next drug because as you know it is not curable.*" (Male; 58; Canada) Another respondent indicated: "*Well if it's going to help patients with lymphoma and put them into a remission and gives them more time and improves their overall health. I can understand why someone would be willing to say they would be willing to have side effects. As long as it is not detrimental to their health and it is not on-going.*" (Female; 67; Canada)

LC stated that respondents were asked on a scale of 1 (will not tolerate any side effects) to 10 (will tolerate significant side effects) to rate the extent extent to which they would be willing to tolerate side effects if they were to consider having treatment with a new drug approved by Health Canada for the treatment of their FL. Of the 81 respondents living in Canada who answered this question, 39 (48.1%) respondents gave a rating of 8 or higher (rating average 6.9). According to LC, many respondents described they would be willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life.

Below were some key responses as reported by 5 (five) respondents:

- *"I would hope they were only short term and that side effects from treatment would be less debilitating than the symptoms of the disease. The best of the two evils I suppose!" (Female; 65-74; Canada)*
- *"If it will make you sicker than a dog then all of a sudden you are not going to get better, then I probably would not want to tolerate that too much. I will take side effects, but not massive side effects. I would not want to be laid up in bed." (Male; 58; Canada)*
- *"If the drugs give me more time to live I will certainly strongly consider putting up with side effects." (Female; 65-74; Canada)*
- *"Finding a control/remission would be worth the side effects. Having a choice of drugs to treat this disease would be helpful." (Female; 55-64; Canada)*
- *"My quality of life was drastically reduced during my treatment. I had complications which impacted my health. Since I have finished my treatment I have been determined to do everything I can to improve my health and well-being. I am now feeling better and working towards staying positive and regaining my life." (Female; 45-54; Canada)*

According to LC, from a patient and caregiver perspective, patients seek individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments. LC indicated that as an oral therapy, it is easier for patients to use, without the necessity to keep track of treatment cycles common to other treatments. It can be taken in the comfort of a patient's home. Moreover, patients and caregivers who live far from treatment facilities and the elderly would particularly benefit from an oral medication.

LC also stated that in Canada, there is a need for access to targeted oral therapies that have proven to be effective at stopping FL disease progression and maintaining a good quality of life (especially after other treatments have failed due to relapses in disease and all other currently available treatment options have been exhausted).

Respondents who have experiences with idelalisib

LC reported that, one (1) patient with experience with idelalisib as a single agent for R/R FL completed the survey (Female; 55-64; Canada). She was diagnosed with FL in 2006. Her previous treatments included: R-CVP; Rituximab; Bendamustine. She commenced treatment with idelalisib in May of 2015 and was still taking idelalisib as of March 20th, 2016 (date survey was completed).

When this respondent was asked how idelalisib compares in terms of side effects, with other treatments she had taken for FL, on a scale of 1 - 10, with 1 being (Far Less Side Effects) and 10 being (Many More Side Effects). She rated idelalisib as "1 -far less side effects". LC reported that she experienced a body rash but stated it was not severe and was seen to be an acceptable side effect.

In order to provide additional context regarding side effects, LC found the following posting in an online forum from another respondent who reported:

- *"I have been on various treatments for follicular lymphoma since the dx in 2011...bendamustine, clinical trials, r- chop, autologous transplant... For six months I have been taking Zydelig (American name- I'm in California) or idelisimab [m]- two pills a day, few side effects and it seems like it's keeping the lymphadenopathy at bay. Not shrinking, nor growing according to a PET scan. I've had few if any side effects - but sometimes get inordinately fatigued which could be a medication side effect. Or is it from the lymphoma? How do I know? And I am wondering what treatment will work if and when this one stops working. Thanks!" (January 2016)*

  Source: https://community.macmillan.org.uk/cancer_types/follicular_lymphoma/f/34644/t/104368

In terms of an improvement in symptoms, when the respondent who have experience with idelalisib was asked on a scale of 1 (No Improvement) to 10 (Very Significant Improvement) for each of the following symptoms associated with FL, how much each symptom has improved with idelalisib, she provided the following ratings as noted in the table below.

Symptoms	Rating	Symptoms	Rating
Aches and/or pains	Not Applicable to Me	Low platelet counts (thrombocytopenia)	Not Applicable to Me
Enlarged lymph node(s)	9	Low red blood cell counts (anemia)	Not Applicable to Me
Enlarged spleen	Not Applicable to	Night sweats	9
Fatigue	5	Reduced appetite	Not Applicable to Me
Fever	Not Applicable to	Weight loss	Not Applicable to Me
High white blood cell counts (leukocytosis)	Not Applicable to Me		

In terms of quality of life, on a scale of 1 (Severely Negatively Impacted) to 10 (Normal Living), LC stated that this respondent rated her Quality of Life while having treatment with idelalisib as a "10 - normal living". LC reported that that she attributed idelalisib to reducing her night sweats and also stated that the swelling of the lymph nodes in her groin had shrunk.

LC also stated that this respondent was asked how idelalisib changed or is expected to change her long-term health and well-being in which she selected "Control disease and symptoms associated with the disease." Based on her personal experiences with idelalisib, LC stated that she would recommend idelalisib to other FL patients because it is "very effective".

According to LC, as an oral therapy, idelalisib could reduce the associated drug administration costs (e.g., no chemo chair time) and reduce the need for patients and caregivers to travel to receive treatment. Furthermore, LC added that some patients treated with idelalisib may be eligible for a potentially curative allogeneic transplant. LC also believes that idelalisib may also help some transplant patients bridge to a donor lymphocyte infusion.

3.3 Additional Information

None provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all the provinces participating in pCODR. PAG identified the following as factors that could impact the implementation of idelalisib for follicular lymphoma (FL):

Clinical factors:

- Clarity of the recommended population and definition of refractory to rituximab
- Safety and risks of treatment given the recent alert issued by the Food and Drug Administration in the U.S. and the stopping of several ongoing trials
- Lack of comparative data and long-term data

Economic factors:

- Large prevalent patient population
- Duration of treatment until disease progression or unacceptable toxicities

Please see below for more details.

4.1 Factors Related to Comparators

For previously treated and refractory FL, treatment varies across the jurisdictions and there is no standard of care. Treatments available include chemotherapy, such as cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP), cyclophosphamide/vincristine/prednisone (CVP), bendamustine or fludarabine/cyclophosphamide/mitoxantrone (FCM).

4.2 Factors Related to Patient Population

PAG noted that a large prevalent number of patients with FL may be eligible to receive treatment with idelalisib, given the course of the disease and the limited options for refractory disease. In addition, idelalisib is an oral drug that could fill the gap in therapy for FL patients who are refractory to both rituximab and an alkylating agent.

PAG noted that the pivotal trial being submitted is a small phase II trial where patients with other types of low grade lymphomas were included. PAG has concerns there may be pressure from clinicians and patients to use idelalisib for small lymphocytic lymphoma and other indolent lymphomas. In addition, there may be interest in the use of idelalisib for patients who are not refractory to both rituximab and an alkylating agent or in patients who relapsed after six months of last treatment. PAG is seeking clarity on the group of patients who would be eligible for treatment with idelalisib and the definition of refractory to rituximab.

PAG also noted that there were a small number of patients with FL (n=72) in the pivotal trial submitted and is seeking information on whether comparative data from a phase III trial would be available, given the number of prevalent patients with refractory FL.

4.3 Factors Related to Dosing

The dose of idelalisib is same for all patients and one dose reduction is supported. These are enablers to implementation.

PAG noted there are two tablet strengths available to accommodate for dose reductions. However, PAG has some concerns with drug wastage if dose reductions require change in tablet strength prior to the previously dispensed strength being all used.

4.4 Factors Related to Implementation Costs

Idelalisib is the first in a new class of drug. Health care professionals would need to become familiar with monitoring and managing toxicities and drug-drug interactions associated with idelalisib. PAG noted the black box warnings for fatal and serious hepatotoxicities, severe diarrhea, colitis, pneumonitis, and intestinal perforation. Additional health care resources would be required to monitor and treat these and other adverse events. In addition, the Food and Drugs Administration in the U.S. issued an alert regarding reports of increased rate of adverse events, including deaths. Although the alert was issued for clinical trials with idelalisib in combination with chemotherapy, PAG would like the benefits versus safety of treatment of FL with idelalisib be addressed given the uncertainty of adverse events.

The unknown number of patients who would be eligible and treatment duration are barriers to implementation as it is difficult to determine the budget impact. PAG noted that there could be a large incremental budget impact.

4.5 Factors Related to Health System

PAG noted that idelalisib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.6 Factors Related to Manufacturer

PAG noted the high cost of idelalisib would also be a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

A registered clinician input was not received on the review for idelalisib (Zydelig) for the treatment of follicular lymphoma.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of Idelalisib (Zydelig) as monotherapy for the treatment of follicular lymphoma in patients who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent. This will include patients that are refractory to both agents in combination or to each agent sequentially.

No supplemental Questions and Comparison with Other Literature relevant to the pCODR review and to the Provincial Advisory Group were identified

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

[Table 3]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published non-comparative clinical trials investigating the efficacy of idelalisib were to be included. Exclude reports of trials with only a dose-escalation design. Reports of trials with a mixed design[†] were to be included only if separate data were reported for the cohort of patients who received the study intervention.	Patients with FL who have had at least 2 prior systemic regimens and are refractory to both rituximab and an alkylating agent Studies of patients with small lymphocytic lymphoma were excluded. Subgroups: • Age • Comorbidities • Symptomatic vs. asymptomatic disease • Organ function (liver and kidney) • ECOG PS	Idelalisib monotherapy at a starting dose of 150mg administered orally as a single tablet bid	No consensus on current standard of care Chemotherapies include: • CHOP • FCM • Single agent bendamustine • Single agent fludarabine • Gemcitabine • No active therapy/symptom management • Observation[&]	Primary • **Progression free survival** • Treatment-free survival • **Toxicity (Grade 3 or 4 AE)** Additional Outcomes of Interest: • Overall survival • Quality of life • Response rate (CR, PR) • Duration of response • Time to symptomatic disease • Time to next treatment
AE = adverse events; bid = twice daily; CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone; CR = complete response; CVP = cyclophosphamide + vincristine + prednisone; FCM = bendamustine or fludarabine + cyclophosphamide + mitoxantrone; FL = follicular lymphoma; PR = partial response; RCT = randomized controlled trial				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

[†]A mixed design was defined as a trial with a dose-escalation phase followed by an efficacy-determining phase in which the study intervention was administered at the same dose and schedule to all patients (generally the maximum tolerated dose determined in the dose-escalation phase).

[&] only in patients that have asymptomatic disease

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (February 2016) via OVID; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were idelalisib (Zydelig) and follicular lymphoma.

No filters were applied to limit retrieval by study type. The search was limited to English-language documents, but not limited by publication year. The search is considered up to date as of July 7, 2016.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. On member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review

A data audit was conducted by another member of the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

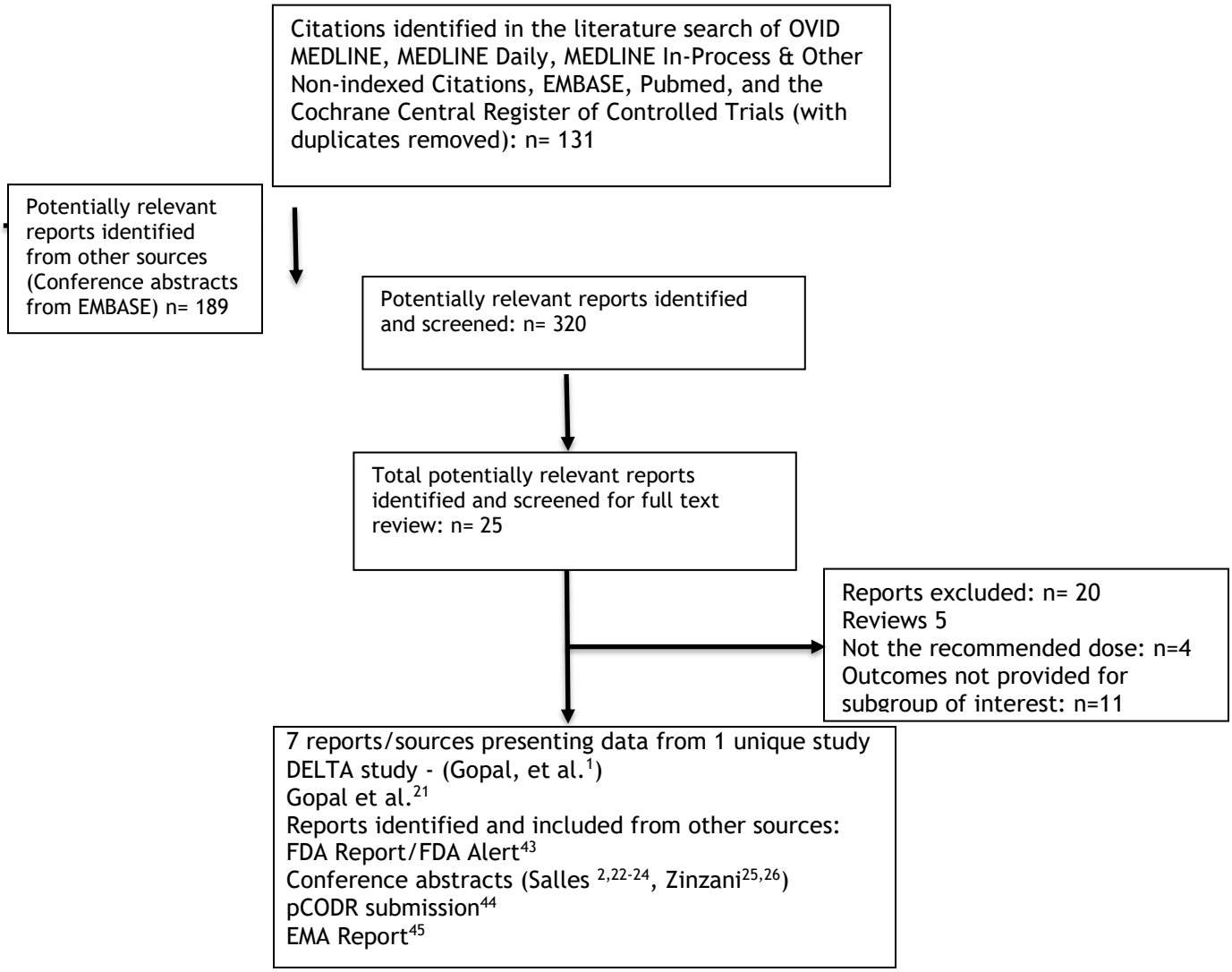
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 320 potentially relevant reports identified, 7 reports/sources presenting data from 1 unique study were included in the pCODR systematic review.[2,21-26] Studies were excluded because they did not evaluate patients with FL as a population or a subgroup[27-29] they were review or opinion articles[30-34] a different dose of idelalisib was used,[35-38] or they were follow-up studies of the included Gopal et al. study but did not report any data on the FL subset of patients.[21,22,39-42]

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the Gopal et al.[1] study were also obtained through requests to the Submitter by pCODR[7]

6.3.2 Summary of Included Studies

One non-randomized, single arm, Phase II interventional study, DELTA, was identified that met the eligibility criteria and is included in this systematic review.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Trial Outcomes
DELTA 101-09 (NCT01282424) Single group, open-label Phase II study Enrolment: n pts with iNHL enrolled= 125; subgroup of pts with FL enrolled = 72 41 centres in the United States and Europe Patient Enrolment Dates: April 2011 – October 2012 Data cut-off: June 25, 2013 Final Analysis Date (subgroup analysis): June 30, 2015 Funding: Gilead Sciences	• Age ≥18 years • Confirmed diagnosis of B-cell iNHL[A] without evidence of histologic transformation[B] • Radiographically measurable disease[C] • Having received at least 2 prior systemic therapies for iNHL • Refractory[D] to both rituximab and an alkylating agent[E] • KPS of 60 or higher • Absolute neutrophil count of $1.0x10^9$ per litre or higher • Platelet count of $50x10^9$ per litre or higher <u>Key Exclusion Criteria:</u> • Active CNS lymphoma • Prior history of hepatic dysfunction • Active systemic infections (HIV, Hep B or C virus)	<u>Intervention</u> Idelalisib: 150mg administered orally twice daily until disease progression, unacceptable toxicity, or death or withdrawal of consent No comparators were used in this study	<u>Primary:</u> • Overall response rate[F] (CR and PR) <u>Secondary:</u> • Time to response • Duration of response[G] • Progression-free survival • Overall survival • Adverse events
Abbreviations: CNS = central nervous system; CR = complete response; FL = follicular lymphoma; Hep = Hepatitis; HIV = human immunodeficiency virus; iNHL = indolent non-Hodgkin's KPS = Karnofsky performance score; lymphoma; n = number; PR = partial response; pts = patients; WHO = World Health Organization;			
Notes: [A] histologic types included follicular lymphoma (Grade 1, 2, or 3a), small cell lymphocytic lymphoma, splenic, nodal, or extranodal marginal-zone lymphoma, or lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia [B]according to WHO 2008 classification [C]defined as the presence of ≥1 lymph node with perpendicular dimensions measuring ≥2.0x≥1.0 cm [D] refractory was defined as less than a PR or progression of disease within 6 months after completion of a prior therapy [E] administered together or in successive treatments [F] Tumour response and progression were evaluated by CT, laboratory testing, and physical exam at screening and at weeks 8, 16 ,24, 36, and 48 and every 12 weeks thereafter [G] measured from the onset of response to disease progression			

a) Trials

DELTA was a phase II, interventional, single-arm study in which patients with a confirmed diagnosis of indolent B-cell non-Hodgkin's lymphoma who had received at least two prior systemic therapies and were refractory to both rituximab and an alkylating agent (e.g., bendamustine, cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, nitrosoureas),[43] were administered idelalisib orally at a dose of 150mg twice daily. The focus

was to evaluate the safety and efficacy of idelalisib in this patient population. The primary outcome was the overall response rate.

The DELTA study was sponsored by Gilead Sciences and Calistoga Pharmaceuticals (which was acquired by Gilead Sciences in 2011). DELTA was a multi-centered trial taking place at 41 sites across the United States and Europe. While the study locations were not indicated in the trial report, the clinicaltrials.gov website listed the sites, which included the United States, Germany, Italy, France, England, and Poland.

To be eligible for this non-comparative study, all patients must have had a confirmed diagnosis of B-cell iNHL, without evidence of histologic transformation, according to the WHO 2008 classification. Grades 1-3a follicular lymphoma were among the included histological subtypes, along with small lymphocytic lymphoma, splenic, nodal, or extranodal marginal-zone lymphoma, or lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia. Patients must also have had radiographically measurable disease, which was defined as the presence of ≥ 1 lymph node with perpendicular dimensions measuring ≥ 2.0 x ≥1.0cm. While the intention to treat (ITT) results for the iNHL population will be provided, the focus of this review will be in the sub-population of patients with follicular lymphoma.

Table 5: Select quality characteristics of the included DELTA trial of Idelalisib in patients with indolent non-Hodgkin's' lymphoma.

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
Delta	Idelalisib No comparator	ORR	In the ITT population, 100 patients required to provide 90% power to test the hypothesis that the RR would be 39% or higher against the null hypothesis that it would be 20% or lower, at a one-sided level of significance of 0.005	125 patients with iNHL enrolled 122 patients evaluated • 72 patients with FL evaluated[1]	Trial not randomized	No	No	Yes	Yes	No	Yes
Abbreviations: CR = complete response; FL = follicular lymphoma; iNHL = indolent non-Hodgkin's lymphoma; ITT = intention to treat analysis; ORR = overall response rate (CP and PR); PR = partial response; RR = response rate											
Notes: [1] Sample size calculations were performed only for the overall population of patients with iNHL, not for subgroups. Subgroup analysis were unplanned											

a) Populations

In the DELTA study, a total of 125 patients with iNHL were enrolled of which 72 had follicular lymphoma. This included 39 men and 33 women with a median age of 62 (range, 33-84). The majority (90%) of patients were Caucasian. Baseline demographics of patients can be found in Table 6.

The baseline disease status of patients with follicular lymphoma in the DELTA study is presented in Table 7. Of note, 18% (13/72) of patients were symptomatic ((11/72 (15%) of follicular lymphoma patients had baseline B-symptoms (fever, weight loss, night sweats) and 2/72 (3%) had other (skin lesions, pruritus, unknown) symptoms)[43], while 82% of FL patients

were asymptomatic. The submitter defined "symptomatic" disease to be "disease-related symptoms" as reported in Study 101-09. These reflect B-symptoms (eg. fever, weight loss, night sweats) and other symptoms (eg. skin lesions, pruritus, etc), and not characteristics or manifestations such as disease stage, lymphadenopathy, cytopenias, organ compromise/enlargement, performance status, or progressive disease.[7] The submitter noted that additional clinical manifestation of the disease could also be used to determine initiation of treatment and some variation exists across different guidelines on when to initiate treatment.

The treatment history of patients with FL on idelalisib is presented in Table 8. Refractory disease was defined as:[43]

Rituximab (without chemotherapy)

- Lack of a complete response (CR) or partial response (PR) during rituximab therapy comprising ≥4 doses of ≥375 mg/m2 given weekly, or
- Occurrence of progressive disease (PD) within 6 months of the completion of a regimen of rituximab therapy comprising ≥4 doses of ≥375 mg/m2 given weekly, or
- Occurrence of PD during rituximab maintenance therapy or within 6 months of completion of rituximab maintenance therapy

Rituximab (with chemotherapy)

- Lack of a CR or PR during rituximab-containing therapy comprising ≥2 doses of ≥375 mg/m2, or
- Occurrence of PD within 6 months of the completion of a regimen of rituximab-containing therapy comprising ≥2 doses of ≥375 mg/m2, or
- Occurrence of PD during rituximab maintenance therapy or within 6 months of completion of rituximab maintenance therapy

Alkylating agent (administered with or without rituximab)

- Lack of a CR or PR during alkylating-agent-containing therapy comprising ≥2 cycles of treatment, or
- Occurrence of PD within 6 months of the completion of a regimen of alkylating agent-containing chemotherapy comprising ≥2 cycles of treatment.
- It should be noted that the majority of patients (69%, 50/72) with FL had received prior treatment with bendamustine, of which 32 patients were refractory to bendamustine monotherapy and 23 patients were refractory to bendamustine + rituximab.

Table 6: Baseline demographics of patients in the study of idelalisib in patients with iNHL who are refractory to rituximab and an alkylating agent.

Characteristic	ITT, iNHL (n=123)[46]	FL (n=72)[43]
Age		
Median (range) age, y	64 (33-87)	62 (33-84)
Mean (SD)	62 (11)	61 (12)
Groups		
< 40	3	3
40-64	65	43
≥ 65	55	26
Male, n (%)	80 (64)	39 (54.2)
Female	45 (36)	33 (45.8)
Caucasian, n (%)	110 (89.4)	64 (88.9)
Asian	3 (2.4)	3 (4.2)
African American	2 (1.6)	0 (0)
Other	9 (7.3)	4 (5.6)

Abbreviations: n = number; SD = standard deviation; y = years;

Table 7. Baseline disease status of patients in the DELTA study.

Characteristic	ITT[43], iNHL (n=123)	FL (n=72)[43]
Target Lesions, count		
Median (range)	5 (1-6)	5 (1-6)
Mean (SD)	4 (2)	4 (2)
SPD, cm^2		
Median (range)	26.9 (1.9-224.3)	22.7 (3.2-199.5)
Mean (SD)	40.7 (41.2)	34.0 (33.8)
Lymphadenopathy		
Diameter of largest node, cm		
Median (range)	4.1 (1.6-17.4)	3.9 (2-17.2)
Mean (SD)	4.7 (2.4)	4.5 (3.4)
Extranodal Involvement, n (%)		
Liver nodules	2 (2)	1 (1.4)
Spleen nodules	19 (15)	11 (15.3)
Other[1]	24 (20)	12 (16.7)
Bone Marrow		
Infiltrate present	55 (45)	19 (26.4)
Biopsy or aspirate collected	118 (96)	71 (98.6)
Disease-related symptoms		
B-symptoms[2]	21 (17)	11 (15.3)
Other[3]	3 (2)	2 (2.8)
Disease Burden, n (%)		
Stage III or IV	111 (89)[1]	60 (83.3)
Elevated LDH	38 (30)[1]	21 (29.2)
Bulky Disease[4]	33 (26)[1]	16 (22.2)
High FLIPI risk score at baseline[5], n (%)	NA	39 (54.2)
ECOG Performance Score, n (%)[6]		
2	8 (7)	6 (8.3)
1	115 (30)	35 (48.6)
0		31 (43.1)
Baseline cytopenia, n (%)	90 (73.2)[43]	54 (75.0)[43]
Hemoglobin <125g/L	61 (49.6)	28 (38.9)
Platelets (Grade 1: LLN to $75x10^9$/L; Grade 2: <75 to $50x10^9$/L)	NA	24 (33.3)[47]
Neutrophils (Grade 2: <$1.5x10^9$/L to $1.0x10^9$/L)	NA	17 (23.6)[47]

Abbreviations: FL = follicular lymphoma; g/L = grams per litre; FLIPI score = Follicular Lymphoma International Prognostic Index; LDH = lactate dehydrogenase; LLN = lower limit of normal; n = number; SPD = sum of the product of the diameters of index lesions; NA: not available; ECOG: Eastern Cooperative Oncology Group

[1] Partial list: soft tissue, peritoneum, lung, skin, muscle, kidney

[2] B-symptoms included fever, weight loss, night sweats

[3] Included skin lesions, pruritus, unknown

[4] Bulky disease was defined as the presence of one or more nodes with at least one dimension of 7cm or more.

[5] A high FLIPI risk score at baseline was defined as having ≥3 out of 5 of the following adverse prognostic factors: age >60 years, Ann Arbor stage III-IV, hemoglobin <12g/dL, number of nodal areas >4, and serum LDH above normal.

[6] The inclusion criteria for the trial specified that patients have a Karnofsky score of >60 to be enrolled in the trial. The data reported with Table 7 is based on data reported in the FDA report, which used ECOG PS

Table 8. Treatment history of patients on idelalisib in the DELTA study.		
Characteristic	**ITT, iNHL (n=122)[43]**	**Patients (n=72)[43]**
Median (range) time since diagnosis, y Mean (SD)	5.2 (0.4-18.4) 5.8 (4)	4.7 (0.8-18.4) 5.9 (4.2)
Median (range) n of previous treatments Mean (SD)	4 (2-12) 4.2 (2.1)	4 (2-12) 4.2 (2.2)
	ITT, iNHL (n=125)[1]	**Patients (n=72)**
Prior Therapy, n (%)		
Bendamustine	81 (65)	50 (69.4)
Anthracycline	79 (63)	51 (70.8)
Purine analog	42 (34)	17 (23.6)
Autologous stem cell transplantation	14 (11)	12 (16.7)
Prior Therapy to Which Disease was Refractory, n/N (%)		
Bendamustine	61/81 (75)	32/50 (64.0)
Bendamustine + rituximab	47/60 (78)	23/36 (72.2)
R-CHOP	40/56 (71)	23/35 (65.7)
R-CVP	29/36 (81)	15/20 (75.0)
Refractory to ≥2 regimens, n (%)	99/125 (79)	57 (79.2)
Refractory to most recent regimen, n (%)	112/125 (90)	62 (86.1)
Abbreviations: n = number; R-CHOP = rituximab + cyclophosphamide + doxorubicin + prednisone; R-CVP = rituximab + cyclophosphamide + prednisone; SD = standard deviation,		

b) Interventions

Details on the dosing and administration of the drug regimen used in the DELTA study can be found in Table 3. In this study, all patients were started on 150mg twice daily oral administration of idelalisib. Patients did not keep a medication diary but adherence to the recommended dose was inferred from dispensing of the tablets, which was done at 4-week intervals for the first 24 weeks and at 12-week intervals thereafter. The protocol included two dose level reductions (first to 100mg BID and then to 75mg BID) for adverse events, which were graded according to NCI CTCAE 3.0. Patients were instructed to withhold idelalisib and reduce the dose for Grade 3 and 4 non-hematologic adverse events and for Grade 4 hematologic events. Doses were not increased after a reduction. Idelalisib treatments were given indefinitely until disease progression, unacceptable toxicity at the lowest dose level, or withdrawal of consent. The median duration of treatment was 6.5 (range 0.6-31.0) months.[43]

All concomitant drugs taken during the course of the study were recorded. Routine and appropriate supportive care was allowed if clinically indicated and in accordance with standard care. Systemic corticosteroids were to be avoided, but could be administered for severe conditions. Anticancer therapies of any kind were prohibited during the study period.[43]

Patients were assessed for safety every 2 weeks for 3 months, then every 4 weeks for 3 months, then every 6 weeks for 6 months, and then every 12 weeks. Efficacy was assessed at 2, 4, 6, 9, and 12 months and then every 3 months. Long term follow up will be conducted for all patients at 6 to 12 month intervals until 5 years.[1,43]

According to the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), there is no standard of care for relapsed, refractory iNHL.[51, 52]

c) Patient Disposition

The DELTA trial enrolled 125 patients with iNHL from 40 sites in 6 countries. Two patients did not meet the eligibility criteria and therefore 123 patients were included in the primary efficacy analysis. The subpopulation of patients with follicular lymphoma represented 59% (72/123) of the subjects enrolled. While data is presented for both iNHL and FL patient populations, only the FL data is discussed as it is the focus of this review.

As reported at the ASCO meeting held in May 2015,[2] at the time of data cut-off (June 11, 2014) 7 patients (9.7%) in the FL subpopulation continued on treatment while 65 (90.3%) had discontinued. The most frequent reason for discontinuation was due to progressive disease (52.8%). The median duration of treatment was 6.5 months (range, 0.6-31 months). Details on patient disposition can be seen in Table 9.

Table 9. Disposition of patients in DELTA study.

Disposition	ITT, iNHL (n=125)[1]	FL (n=72)[6]
Ongoing treatment (n, %)	**40 (32)**	**7 (9.7%)**
Discontinued treatment (n, %)	**85 (68)**	**65 (90.3%)**
Progressive disease	41 (33)	38 (52.8)
Adverse event(s)	25 (20)	15 (20.8)
Investigator request	7(6)	4 (5.6)
Death	8 (6)	5 (6.9)
Withdrew consent	4 (3)	3 (4.2)

d) Limitations/Sources of Bias

Overall, results from the Gopal et al 2014 study are limited by the level of evidence and lack of comparative efficacy data for idelalisib, compared to any appropriate comparator, in the relapsed refractory follicular lymphoma setting. Therefore, the following biases and limitations should be noted:
The Gopal 2014 study is a single-arm non-randomized open-label trial in which neither participants nor investigators in the trial were blinded, and as such, are at risk for a number of different biases that can affect the internal validity. Two such biases include patient selection as part of inclusion criteria for eligibility and performance bias due to knowledge of the study treatment. It is important to note that investigators, study personnel, clinicians and patients involved in the trial were aware of the study drug assigned, which can introduce the potential to bias results and outcomes in favour of idelalisib if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. This limits the robustness of the efficacy results. To reduce the impact of this bias however, the investigators used a blinded independent review committee to evaluate responses using standardized criteria, in an unbiased manner. The single-arm non-randomized design also makes interpreting the efficacy and safety events attributable to idelalisib challenging, since all patients received the same treatment.

The Gopal 2014 study is a non-comparative study, any comparisons with other treatments would have a high risk of bias, thus making it difficult very difficult to draw any conclusions. There is however no current standard of care for patients in this setting.

It must be noted that data on efficacy and safety of idelalisib in the FL subset was assessed as a *subgroup post-hoc* analysis, both of which have their limitations. First, the overall study was powered to detect a treatment effect in the overall study population (*all* patients with iNHL) and the study sample size calculations were performed accordingly. However, in order to detect an interaction effect of the same magnitude in the FL subgroup, the sample size would need to be largely inflated.[3] Whether or not the effect varies by the severity of the disease is also difficult to determine with the sample sizes of these *subgroups* of patients with FL being relatively small. Second, while the authors report a consistent effect between disease subgroups (FL, small lymphocyctic lymphoma, marginal-zone lymphoma, lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia), there is no evidence on the external consistency of the results since no other studies were identified. At best, post-hoc subgroup analyses should be considered exploratory and interpreted with caution.

Patient reported outcomes (PROs) were collected in the form of measurement of HRQL using the validated 42-item Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) scale. Results were, however, reported using the best response from baseline as an endpoint. It is unclear how meaningful this endpoint is, given that it is selectively reporting the best results and that not all experiences patients had with idelalisib as related to patient reported outcomes.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Responses were assessed based on revised criteria for malignant lymphoma.[48] As such, a complete response was defined as the disappearance of all evidence of disease and a partial response was defined as regression of measureable disease and no new sites. Stable disease was defined as a failure to attain a complete or partial response or progressive disease, and the appearance of any new lesion or an increase by 50% of previously involved sites from nadir was considered to be progressive disease. A summary of efficacy results can be found in Table 10.

Overall Response Rate (Complete Response and Partial Response)

The ORR (95% CI) for the FL subset of patients was 55.6% (43.4-67.3, p<0.001), which included 10 complete responses and 30 partial responses. Median (range) time to response was Kaplan-Meier estimated at 2.6 months (1.6-11 months).[5] The median time to the first CR ranged from 1.9-19.2 months, while the median time to PR was 3.3 (1.6-11.0) months. This was reported as consistent with the ORR for the overall study population and all subgroups, regardless of disease subtype, number of prior regimens, refractoriness to last prior therapy, refractoriness to bendamustine, bulky status, age, and gender. Lymph node size decreased during treatment by ≥50% SPD in 57% of patients.

Data were available for ORR based on patients that had symptomatic versus asymptomatic disease. Symptomatic disease was defined as "disease-related symptoms" as reported in Study 101-09. These reflect B-symptoms (eg. fever, weight loss, night sweats) and other symptoms (eg. skin lesions, pruritus, etc), and not characteristics or manifestations such as disease stage, lymphadenopathy, cytopenias, organ compromise/enlargement, performance status, or progressive disease.[7] Of note, 18% (13/72) of patients were symptomatic ((11/72 (15%) of follicular lymphoma patients had baseline B-symptoms (fever, weight loss, night

sweats) and 2/72 (3%) had other (skin lesions, pruritus, unknown) symptoms)[43], while 82% of FL patients were asymptomatic.

Duration of Response

Responses to idelalisib were rapid, with the majority of responses evident at the first response evaluation.[1, 7] Median response duration was 10.8 (range 0-26.9) months; 27 months in patients with a complete response.[5]

Overall, patients experienced a relatively short exposure to idelalisib and a short duration of response. For example, only 24 patients with FL remained on idelalisib longer than 6 months, of whom only 5 were treated for more than 12 months. Only 6 patients with FL had a duration of response of less than 2 months.

Table 10. Efficacy outcomes in patients with iNHL and the subgroup of patients with follicular lymphoma

	ITT, iNHL (n=125)[1]	**Patients with FL (n=72)[43]**
PFS, months, (median, range)	11.0 (0.03-16.6)	11.0 (0-30.6)
ORR (% and 95% CI %)	56.8 % (n=71/125; 95% CI 47.6-65.6, p<0.001)	55.6% (n=40/72; 95% CI 43.4-67.3, p<0.001)
CR, n (%)	7 (5.6)	10 (13.9)
PR, n (%)	63 (50.4)	30 (41.7)
PD, n (%)	10 (8.0)	8 (11.1)
SD, n, (%)	42 (33.6)	23 (32.0)
DOR, months (median, range)	12.5 (0.03-14.8)[1]	10.8 (0-26.9)[5]
Follow up, months (median, range)	9.7[1]	19.4 (0.7-35.6)
≥50% SPD reduction in lymph node size	NA	57%
OS, months, (median, range)	20.3 (0.7-22.0)[1]	Not reached
OS rate		
1 year	80%[1]	88.1%[2]
1.5 years	NA	74.2%[2]
2 years	NA	69.8%[2]

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; FL = follicular lymphoma; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; SPD = sum of the product of the diameters of index lesions; NA: not available
Note: data was collated from a variety of sources and presented as presented in the original sources.

Progression-free Survival

For the overall patient population, the median progression-free survival (a secondary outcome) was 11 months (0-16.6). At 1 year, 47.7% of patients were progression free.[2] The median PFS for the FL patients was 11.0 (0-30.6) months. In the absence of a comparator arm, the results of the study were compared to the last prior line of treatment (LPT) patients would have received before entry into the study. Of note, the median (range) progression-free survival associated with the LPT before the study was 5.1 (4.4-6.0) months[2] in the FL population and 3.9 (0.7- 41.4)[49] in the overall iNHL population.[5,6]

Treatment-free Survival[47]

Treatment free survival was defined by Gopal et al.[1] as the interval from the end of idelalisib treatment to the earlier of first documentation of antitumour therapy or death from any cause. At the June 30, 2015 data cut-off, post-study treatment free survival data were

available for 93% (67/72) of patients with FL. Overall, the median (95% CI) Kaplan Meier estimate of treatment free survival was 1.7 (1, 3.6) months, with a range of 0.0 to 35.5 months.[7] Among these, 40/67 (60%) patients received another anti-tumour treatment, median time from last idelalisib treatment to next therapy 1.35 months (range 0-13.1), 11/67 (16%) died (median time from last idelalisib treatment to death was 0.8 months (range 0.1-25.5), 6/67 (9%) were in long term follow up (median time from last idelalisib treatment to June 20, 2015 data cut-off was 21.75 months (range 15.2-35.5 months)) and 10/67 (15%) discontinued long term follow up (median time from last idelalisib treatment to discontinuation of long term follow up was 1.05 months (range 0-12.8 months).[7]

Time to Symptom Progression

The time until the emergence of B symptoms (eg. fever, weight loss, night sweats) and other symptoms (eg. skin lesions, pruritus, etc.) was not a pre-specified endpoint for the study and no such data are available for the FL subgroup or the study population as a whole.

Overall Survival

Overall survival (OS), was a secondary endpoint in the study. Median OS was not reached in the subgroup of patients with FL, but Kaplan-Meier estimated overall survival at 1, 1.5, and 2 years was 88.1%, 74.2%, and 69.8%, respectively in the FL population.[5,6]

Safety:

Deaths[1]

In the overall ITT population, a total of 28 deaths (22%) were reported. Eleven deaths occurred while the patient was receiving the study drug or within 30 days after the last dose. The causes of death were progressive disease (3 patients), pneumonia (3 patients), and cardiac arrest, cardiac failure, splenic infarction, septic shock, and pneumonitis (1 patient each). The remaining 17 deaths, due predominantly to progressive disease, occurred during follow-up.

In the subgroup of patients with FL, 12 deaths were reported in patients with FL. The causes of death reported for these patients were disease progression (n=7), and were adverse events(n=5).[7] Deaths due to adverse events included one each of cardiac arrest, drug-induced pneumonitis, splenic infarction/acute abdomen, heart failure and unknown.[6]

Grade 3 or 4 Adverse Events

Details on adverse events found in >10% of the FL population can be found in Table 11. The most common adverse events of any grade were diarrhea (51%), cough (32%), pyrexia (29%), fatigue (28%), nausea (28%), and neutropenia (51%). Severe (≥Grade 3) adverse events included diarrhea (14%), pyrexia (4%), and nausea (3%). Rates of ≥Grade 3 transaminase elevation, pneumonitis, neutropenia, anemia, and thrombocytopenia were 14%, 4%, 22%, 3%, and 6%, respectively.[5,6]

While idelalisib was generally well tolerated and had an acceptable safety profile during the trial, it should be noted that on May 3, 2016, Health Canada issued an alert that idelalisib users are at increased risk of fatal and serious infections and that patients also had a decreased overall survival compared to control patients in a Phase III trial that evaluated the addition of idelalisib to standard therapies for first-line treatment of CLL and early line treatment of relapsed iNHL.[50] As a result, Gilead stopped all ongoing clinical trials using idelalisib for first-line treatment of CLL and early line treatment of iNHL and is amending the

trial documentation and the Zydelig Product Monograph to reflect the new safety information.

Table 11. Adverse Effects Reported in ≥10% Patients				
	iNHL (ITT) Patients[43]		FL Patients	
Event, n (%)	Any	Grade ≥3	Any	Grade ≥3
All AE's	103 (82)	68 (54)	71 (98.6)	47 (65.3)
Diarrhea	54 (43)	16 (13)	37 (51.4)	10 (13.9)
Cough	36 (29)	0	23 (31.9)	0
Pyrexia	35 (28)	2 (2)	21 (29.2)	3 (4.2)
Fatigue	37 (30)	2 (2)	20 (27.8)	0
Nausea	37 (30)	2 (2)	20 (27.8)	2 (2.8)
Anemia	35 (28)	2 (2)	25 (34.7)	2 (2.8)
Neutropenia	70 (56)	34 (27)	37 (51.4)	16 (22)
Thrombocytopenia	32 (26)	8 (6)	17 (23.6)	4 (5.6)
Increased ALT/AST	ALT 59 (47) AST 44 (35)	ALT 16 (13) AST 10 (8)	38 (52.8)	10 (13.9)
Dyspnea	22 (18)	4 (3)	14 (19.4)	2 (2.8)
Rash	16 (13)	2 (2)	14 (19.4)	2 (2.8)
Decreased appetite	22 (18)	1 (1)	13 (18.1)	0
Vomiting	19 (15)	3 (2)	12 (16.7)	2 (2.8)
Night sweats	14 (11)	0	11 (15.3)	0
URTI	18 (14)	0	11 (15.3)	0
Weight decreased	17 (14)	0	11 (15.3)	0
Abdominal pain	20 (16)	3 (2)	10 (13.9)	2 (2.8)
Headache	13 (10)	1 (1)	10 (13.9)	1 (1.4)
Back pain	NR	NR	9 (12.5)	1 (1.4)
Asthenia	14 (11)	3 (2)	8 (11.1)	0
Constipation	NR	NR	8 (11.1)	0
Pneumonia	14 (11)	9 (7)	8 (11.1)	5 (6.9)

Abbreviations: AE = adverse events; ALT = alanine aminotransferase, AST aspartate aminotransferase; FL = follicular lymphoma; iNHL = indolent non-Hodgkin's lymphoma; ITT = intention to treat; n = number; NR = not reported; URTI = upper respiratory tract infection
Note: data was collated from a variety of sources and presented as presented in the original sources.

Quality of Life

Health-related quality of life (HRQL) 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). The FACT-Lym was scored based on the FACIT (Functional Assessment of Chronic Illness Therapy) scoring guideline and user manual. Repeated measured mixed-effects models were used to asses mean change from baseline within the treatment arm.[22] The Trial Outcome Index (TOI) is PWB + FWB + LymS. The higher the score, the higher the reflection of HRQL. The FACT-Lym was administered every 4 weeks (0-24 weeks),[41] then every 6 weeks (30-48 weeks), and again at week 60. Based on the study protocol, change in scores from baseline to each subsequent assessment and the best change from baseline during the study were to be summarized. The method of last observation carried forward was to be used to impute values for missing data.[1] Based on published results, only best change from baseline was reported for both the overall and FL populations.

Kaplan-Meier estimates of median time to improvement and best change from baseline in FACT-Lym scores are shown in Table 12. While minimally important differences were reported using the FACT-Lym scoring system for emotional and functional well-being, additional concerns, trial outcome index score, and for the FACT-G total score subscales (Table 12),[6] it is notable that they were based on the best change from baseline, defined as the highest change score post baseline. It is unclear as to whether this measure, best change from baseline, represents the impact of idelalisib on patient reported outcomes, as would be captured using the median change from baseline. Information was not provided on completion rates for the questionnaires.

Table 12. KM-Estimated Median Time to Improvement and Best Change from Baseline in FACT-Lym Scores in the subgroup of patients with FL.

Median (range) FACT-Lym Score	Best Change From Baseline* (n=72)	Median Time to Improvement†, mo (n=72)	Minimally Important Difference
Physical well-being	1.0 (-12.0-11.0)	NR (0.0 to 30.6)	2-3
Social/family well-being	1.0 (-4.7-11.0)	NR (0.0 to 30.6)	2-3
Emotional well-being	3.0 (-9.0-12.0)	NR (0.0 to 30.6)	2-3
Functional well-being	2.0 (-10.0-14.0)	NR (0.0 to 30.6)	2-3
Additional concerns	5.0 (-17.0-19.0)	4.2 (0.0 to 27.9)	3-5
Trial outcome index score	6.0 (-34.0-35.0)	2.8 (0.0 to 30.6)	7-8
FACT-G total score	4.0 (-29.7-31.0)	6.9 (0.0 to 30.6)	3-7
FACT-Lym total score	7.5 (-39.0-47.0)	1.9 (0.0 to 30.6)	10-11

Abbreviations: FACT-G = Functional Assessment of Cancer Therapy, General; FACT-Lym = Functional Assessment of Cancer Therapy, Lymphoma; KM = Kaplan-Meier; NR = not reached
*Defined as the highest change score post baseline.
†Calculated as (date of first symptom improvement − date of first dose of idelalisib + 1) ÷ 30.4375.

Best change from baseline values were also reported for the overall iNHL patient population and no information was available on median changes from baseline. LymS change scores exceeded the minimum important difference for at least 90% of the patients, indicating a clinically significant improvement in lymphoma-related concerns at some point in the study. There was no information to determine whether this minimum important difference occurred at one or multiple time points of measure for PRO's. The median best changes from baseline for the FACTG, FACTLym, and TOI total scores were 5.0, 8.3, and 6.0, respectively.[41]

6.4 Ongoing Trials

One phase III, randomized, double-blind dose optimization study of idelalisib in patients with relapsed, refractory (twice-pretreated) follicular lymphoma and small lymphocytic lymphoma is currently active and recruiting patients. The primary objective of this parallel assignment study in which patients will be randomized to receive a starting dose of either 100mg or 150mg of idelalisib is to optimize the safety and efficacy of chronic administration of idelalisib in patients with follicular lymphoma or small lymphocytic lymphoma and evaluate the overall safety profile of idelalisib and overall response rate by Week 24. In this study, patients will be response assessed at the 8-week mark, after which patients in the 150mg starting arm will be discontinued from the study or may receive blinded open-label idelalisib 150mg bid. Patients in the 100mg starting arm will either be dose escalated to open-label 150mg bid or maintain blind and continue on the 100mg dose bid. Further details of this trial are provided in Table 13 below.

Table 13. Ongoing trials of idelalisib in patients with follicular lymphoma.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT02536300 Phase III, multicenter, randomized, double-blind parallel assignment study Previously treated patients with FL or SLL (Estimated enrollment, N= 240) Status: active, recruiting patients Study locations: USA, Australia, France, Israel, Italy, Poland, Romania, Spain, UK Estimated completion date: June 2019	<u>Key Inclusion Criteria:</u> • Histologically confirmed FL (Grade 1,2, or 3A) or small lymphocytic lymphoma • Refractory to and disease progression within 6m from the last dose of at least 2 lines of prior therapy • Stage 3 or 4 disease <u>Key Exclusion Criteria:</u> • Hx of lymphoid malignancy other than FL • Known hx of CNS lymphoma or leptomeningeal lymphoma • Known presence of intermediate or high-grade myelodysplastic syndrome • Known hx or serious allergic rxn • Hx of a non-lymphoid malignancy except for allowed exceptions • Evidence of current systemic bacterial, fungal, or viral infection • Known hx of liver disease	Experimental Arm 1: Idelalisib 150mg PO bid Based on response, pts will be discontinued or receive blinded or open-label idelalisib 150mg bid Experimental Arm 2: Idelalisib 100mg PO bid Based on response, pts will be dose escalated to open-label 150mg bid or maintain blind	<u>Primary:</u> • Safety • ORR (CR or PR) by week 24 <u>Secondary:</u> • Time to AE onset, rate of AEs of interest, rate of drug interruptions • PFS • DoR • OS • PK

Table 13. Ongoing trials of idelalisib in patients with follicular lymphoma.			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Trial Outcomes**
Study Sponsor: Gilead Sciences	• Hx of drug-induced pneumonitis, or IBD • Known HIV infection	and continue on 100mg bid	

Abbreviations: AE = adverse event(s); bid = twice daily; CNS = central nervous system; CR = complete response; DoR = duration of response; FL = follicular lymphoma; HIV = human immunodeficiency virus; hx = history; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PO = orally; PR = partial response; SLL = small lymphocytic lymphoma

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma/Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on idelalisib (Zydelig) for follicular lymphoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lymphoma/Myeloma Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2016**, Embase** 1974 to 2016 April 21**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Idelalisib* or zydelig* or CAL-101 or CAL101 or GS1101 or GS-1101 or YG57I8T5M0 or 870281-82-6).ti,ab,ot,kf,hw,rn,nm.	1480
2	Lymphoma, Follicular/ or Lymphoma, Non-Hodgkin/	68499
3	(lymphom* or lymphogranuloma* or granuloma*).ti,ab,kf.	481615
4	(brill symmers adj2 disease*).ti,ab,kf.	426
5	or/2-4	500819
6	1 and 5	571
7	6 use pmez,cctr	100
8	*idelalisib/	265
9	(Idelalisib* or zydelig* or CAL-101 or CAL101 or GS1101 or GS-1101 or YG57I8T5M0 or 870281-82-6).ti,ab,kw.	934
10	8 or 9	945
11	follicular lymphoma/ or nonhodgkin lymphoma/	68160
12	(lymphom* or lymphogranuloma* or granuloma*).ti,ab,kw.	485623
13	(brill symmers adj2 disease*).ti,ab,kw.	426
14	or/11-13	503849
15	10 and 14	401
16	15 use oemezd	313
17	7 or 16	413
18	limit 17 to english language	400
19	remove duplicates from 18	316

20	19 not conference abstract.pt.	127
21	19 not 20	189

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Add to builder	Query	Items found	Time
#25	Add	Search **(((#21) AND (Lymphoma, Follicular[mh] OR Lymphoma, Non-Hodgkin[mh:noexp] OR brill symmers disease*[tiab] OR lymphom*[tiab]))) AND (publisher[sb] OR 2016/04/13:2016/04/20[edat])**	4	13:44:05
#24	Add	Search **publisher[sb] OR 2016/04/13:2016/04/20[edat]** Sort by: **PublicationDate**	503880	13:43:56
#23	Add	Search **(#21) AND (Lymphoma, Follicular[mh] OR Lymphoma, Non-Hodgkin[mh:noexp] OR brill symmers disease*[tiab] OR lymphom*[tiab])**	95	13:43:33
#22	Add	Search **Lymphoma, Follicular[mh] OR Lymphoma, Non-Hodgkin[mh:noexp] OR brill symmers disease*[tiab] OR lymphom*[tiab]** Sort by: **PublicationDate**	158824	13:43:23
#21	Add	Search **idelalisib[Supplementary Concept] OR Idelalisib*[tiab] OR zydelig*[tiab] OR CAL-101[tiab] OR CAL101[tiab] OR GS 1101[tiab] OR GS-1101[tiab] OR YG57I8T5M0[rn] OR 870281-82-6[rn]** Schema: **syn** Sort by: **PublicationDate**	255	13:42:22

3. Cochrane Central Register of Controlled Trials (Central)

Searched via OVID.

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

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