

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

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

pERC Final Recommendation

This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Pralatrexate (Folotyn)	
Submitted Reimbursement Request: for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)	
Submitted By: Servier Canada Inc.	Manufactured By: Servier Canada Inc.
NOC/c Date: October 26, 2018	Submission Date: June 1, 2018
Initial Recommendation: January 31, 2019	Final Recommendation: April 4, 2019

Approximate per Patient Drug Costs	Pralatrexate costs \$2,108.63 for a single dose vial of 20 mg. At the recommended dose of 30 mg/m ² IV once weekly for six weeks in seven week cycles, pralatrexate costs: \$16,486.33 per month (excluding wastage)
---	---

<p>pERC RECOMMENDATION</p>	<p>pERC recommends the reimbursement of pralatrexate (Folotyn) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) only if the following conditions are met:</p> <ul style="list-style-type: none"> the public drug plan cost of pralatrexate should not exceed the public drug plan cost of romidepsin cost-effectiveness being improved to an acceptable level. <p>If the aforementioned conditions cannot be met, pERC does not recommend reimbursement of pralatrexate. Reimbursement should be for patients with relapsed or refractory PTCL who have undergone previous systemic therapy, none of which include romidepsin. pERC made this decision because all patients in the PROPEL trial were treated with systemic chemotherapy and none of the patients received romidepsin before initiating treatment with pralatrexate. Patients should have a good performance status. Treatment with pralatrexate should continue until disease progression or unacceptable toxicity.</p> <p>pERC made this decision because the Committee considered that there may be a net clinical benefit of pralatrexate based on the durable activity seen in patients that achieved a response. pERC also considered that the clinical course of PTCL is aggressive, there are limited effective treatment options available, and the side effect profile of pralatrexate is manageable. Additionally, the patient population to whom this recommendation applies is small.</p> <p>pERC agreed that pralatrexate aligns with patient values in that it offers a choice of treatment that has the potential for disease control with</p>
-----------------------------------	--

manageable side effects.

pERC concluded that at the submitted price, pralatrexate could not be considered cost-effective compared with chemotherapy and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. Additionally, pERC noted that there was considerable uncertainty in the cost-effectiveness estimates of pralatrexate compared with chemotherapy and romidepsin because of a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements of Pralatrexate to Improve Cost-Effectiveness

Given that pERC was satisfied that there may be a net clinical benefit of pralatrexate, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness to an acceptable level. To offset the considerable uncertainty in the magnitude and direction of benefit, pERC concluded that the public drug plan cost of pralatrexate should not exceed the public drug plan cost of romidepsin.

Choice Between Pralatrexate and Romidepsin

pERC noted that there is currently insufficient evidence to make an informed recommendation regarding the choice between pralatrexate and romidepsin for the treatment of relapsed/refractory PTCL. However, pERC felt that given the uncertainty in the comparative effectiveness data and similar costing of these two treatments, it is uncertain whether pralatrexate is more costly and less effective than romidepsin or less costly and more effective than romidepsin. pERC noted that the choice between pralatrexate and romidepsin for relapsed or refractory PTCL will likely depend upon the relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to adverse events. pERC noted that there is currently no evidence in support of or against the use of pralatrexate after romidepsin or the use of romidepsin after pralatrexate.

Collecting Prospective Evidence to Reduce Uncertainty in the Magnitude of Benefit and Cost-Effectiveness

pERC noted that pralatrexate was issued a Notice of Compliance with conditions by Health Canada pending the results of trials to confirm clinical benefit. Given the considerable uncertainty in the magnitude of clinical benefit of pralatrexate in patients with relapsed or refractory PTCL, pERC concluded that additional prospective evidence should be collected to confirm the clinical benefit and better inform the true cost-effectiveness of pralatrexate.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Peripheral T-cell lymphoma (PTCL) is an uncommon but aggressive malignancy. The number of patients with relapsed/refractory PTCL in Canada was estimated to be 600 in 2018. The current standard of treatment in Canada for patients with relapsed/refractory PTCL is romidepsin or conventional treatments, including chemotherapy. Results with these regimens have relatively low response rates, short duration of response, and poor overall survival. Therefore, pERC agreed with the pCODR Clinical Guidance Panel (CGP) and the registered clinicians that PTCL has an aggressive clinical course and there is a need for more effective palliative treatment options.

Two non-randomized studies of pralatrexate in patients with relapsed/refractory PTCL were identified in the pCODR systematic review (PROPEL trial and PDX-JP1). pERC noted that the PDX-JP1 trial was a phase I /II trial conducted in Japan that had a very small sample size compared with the PROPEL trial, a phase II non-randomized international study. Given the limitations of trials with small sample sizes and the risk of providing unreliable estimates of efficacy, the Committee focused their deliberations on the PROPEL trial. pERC noted there were modest overall response rates and durable response observed in a proportion of patients that responded to treatment with pralatrexate. pERC considered that in a heavily pre-treated population of patients with an aggressive disease, it is uncommon to observe long durations of response. The Committee also considered that romidepsin appears to demonstrate similar rates of response and long duration of response. pERC also discussed that the observed median overall survival (OS) was long for such a heavily pre-treated patient population with aggressive relapsed/refractory disease. pERC noted that there may have been selection bias for patients with less aggressive disease compared with those patients observed in a real-world treatment setting.

The Committee also discussed the Clinical Guidance Panel (CGP)'s conclusions and agreed with the CGP that pralatrexate may also have a clinical benefit in patients with any PTCL subtype who have undergone any number of previous systematic therapies. As well, pERC noted that because patients in the PROPEL trial were treated with various chemotherapy regimens and did not have previous treatment with romidepsin, the Committee agreed that pralatrexate should only be considered for patients who have undergone at least one previous systematic therapy, none of which include romidepsin.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the submitter requesting that the Committee reconsider the reimbursement criteria to remove the restriction for patients who have previously been treated with romidepsin. The submitter indicated that excluding previous systemic therapy with romidepsin as a criterion for reimbursement does not align with the need for additional treatment options and will create a barrier for patients who have failed romidepsin and require additional therapy. pERC also considered that the patient group disagreed with the restriction and argued that patients with relapsed/refractory PTCL have few treatment options and should have the choice to access both pralatrexate and romidepsin. Furthermore, the submitter noted that the choice of pralatrexate or romidepsin should not restrict the subsequent use of the other based on different mechanism of action and the timing that the trials for pralatrexate and romidepsin were conducted. pERC also noted the CGP's clinical opinion in the Final Clinical Guidance Report who agreed with the submitter and the patient group. Additionally, the submitter noted there is no evidence to suggest that one therapy is more effective than the other.

pERC discussed that the evidence from the phase II non-randomized PROPEL trial demonstrated modest overall response rates and durable response in patients who were relapsed or refractory to various chemotherapy regimens before receiving pralatrexate. In addition, pERC noted that patients in the PROPEL trial were not treated with romidepsin and that there was no evidence submitted to support or refute the use of pralatrexate in patients who have been treated with romidepsin. pERC restated its conclusion that while there may be a net clinical benefit of pralatrexate, it could not recommend removing the restriction for patients previously treated with romidepsin without evidence.

[pERC's Deliberative Framework](#) for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC also discussed that the submitter did not provide any evidence to support or refute the use of pralatrexate and romidepsin or vice versa in sequence. The Committee noted that the submitted economic analysis assumed best supportive care and did not assume any active therapy in the post-progression setting. Moreover, the submitted budget impact considered a mix of all available treatments including romidepsin in the market share. The Committee also reiterated the fact that the submitted budget impact analysis did not consider the sequencing of available therapies, which would have a substantial impact on the budget. Overall, the Committee reiterated that there is currently insufficient evidence to make an informed recommendation regarding the choice between pralatrexate and romidepsin for the treatment of relapsed/refractory PTCL. The Committee also recognized that the registered clinicians' feedback agreed that there is insufficient evidence to make an informed choice between pralatrexate and romidepsin. In conclusion, pERC restated that the choice between pralatrexate and romidepsin for relapsed or refractory PTCL will likely depend upon the relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to adverse events.

pERC discussed the safety profile of pralatrexate and noted that the most common grade 3 to grade 4 adverse events were thrombocytopenia, mucositis, neutropenia, and anemia. While they noted that these adverse events can have a marked impact on a patient's functioning, the Committee concluded that the side effects of pralatrexate could be effectively managed with dose delays. Additionally, pERC noted that quality of life (QoL) data were not collected in the identified trials and considered that the impact of pralatrexate on a patient's quality of life is unknown. Therefore, pERC could not comment on how treatment with pralatrexate impacts a patient's QoL.

In the absence of a direct comparison of pralatrexate with other relevant therapies in Canada, pERC considered evidence from two submitted indirect treatment comparisons (ITCs). The first analysis was a case matched control analysis (CMCA) to provide an estimate of the treatment effect of pralatrexate compared with an historical control group treated with conventional treatments (chemotherapy). The Committee acknowledged that there were a number of limitations, including selection bias inherent to retrospective studies and the omission of important variables for matching that raised considerable uncertainty in the comparative estimates of OS. pERC noted it was challenging to interpret the submitted data and that limited conclusions could be drawn. pERC also discussed a second analysis, a matched adjusting indirect comparison (MAIC) that compared pralatrexate to romidepsin in patients with relapsed or refractory disease. The Committee agreed with the CGP that this was the most relevant comparison. The Committee considered that the baseline characteristics of patients in the PROPEL trial and the romidepsin trial were similar and that the MAIC demonstrated no significant differences between the treatment groups for OS and PFS. The Committee also noted limitations in the MAIC analysis including uncertainty in the OS data from both trials, and possible bias introduced by unknown cross-trial differences. Overall, the Committee concluded that it was unable to draw a firm conclusion concerning the comparative effectiveness of pralatrexate for relapsed/refractory PTCL.

pERC acknowledged that because of the non-randomized phase II study design of the PROPEL trial, there was considerable uncertainty in the magnitude of clinical benefit of pralatrexate in comparison with chemotherapy and compared with romidepsin. Nevertheless, pERC concluded that there may be a net clinical benefit of treatment with pralatrexate based on the durable activity observed in patients who achieved a response. pERC agreed that the clinical course of PTCL is aggressive, there are limited effective treatment options available, and the side effect profile of pralatrexate is manageable. Given the considerable uncertainty in the magnitude of clinical benefit of pralatrexate in patients with relapsed or refractory PTCL, pERC concluded that additional prospective evidence should be collected to confirm the clinical benefit of pralatrexate.

pERC deliberated on input from one patient advocacy group concerning pralatrexate. pERC noted that a small number of patients who provided input had direct experience with pralatrexate. pERC discussed that patients value having choice in treatment options, longer survival, longer remission and better disease control. pERC also noted that some patients valued the shorter infusion times offered, such as with pralatrexate, compared with the longer infusion times with other available therapies including chemotherapy and romidepsin. The Committee acknowledged that patients with relapsed/refractory PTCL are willing to tolerate significant side effects of treatment with proven efficacy. Overall, pERC concluded that pralatrexate aligns with patient values in that it offers a choice of treatment that has the potential for disease control with manageable side effects.

The Committee deliberated upon the cost-effectiveness of pralatrexate. pERC noted that the submitted base-case analysis compared pralatrexate with best supportive care (conventional chemotherapies). A scenario analysis comparing pralatrexate with romidepsin was also provided. For the comparison of pralatrexate with BSC, pERC noted the Economic Guidance Panel (EGP's) wide range of incremental cost-effectiveness (ICER) estimates, all of which pERC considered not cost-effective. pERC acknowledged that, because of the non-comparative phase II trial design and the limitations in the CMCA analysis informing the comparative efficacy of pralatrexate to BSC (conventional chemotherapies), there is considerable uncertainty in the magnitude of benefit and therefore considerable uncertainty in the incremental cost-effectiveness of pralatrexate. The Committee discussed that the factor that most influences the incremental cost is the duration of treatment with pralatrexate. The factors that most influence the incremental effect are the long-term benefit of pralatrexate, the time horizon and the survival extrapolation method. Overall, pERC noted that the magnitude of long-term benefit associated with pralatrexate is unknown, given the lack of long-term data. Therefore, pralatrexate could not be considered cost-effective compared with BSC at the submitted price.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the submitter noting that they disagreed with the EGP's best estimate of reducing the clinical benefit beyond two years while maintaining an assumed high cost for pralatrexate due to long-term treatment. The submitter noted that if the assumption that the benefit beyond two years for pralatrexate is reduced by 50%, then the treatment duration for pralatrexate should not exceed that observed in the clinical trial.

pERC considered the EGP's response to the feedback in the Final Economic Guidance Report. pERC noted that the EGP provided reanalysis estimates with the assumption that patients would receive treatment with pralatrexate for a maximum of two years. Based on the EGP's reanalysis of the upper bound ICER, pERC noted that pralatrexate is still not cost-effective compared with BSC at the submitted price.

For the comparison of pralatrexate with romidepsin, pERC noted that in several reanalyses, the EGP's best estimates of the incremental cost-effectiveness indicated that pralatrexate was dominated by romidepsin (i.e., pralatrexate was more costly and less effective than romidepsin) while the submitter's estimate of the incremental cost-effectiveness suggested that pralatrexate was dominant compared with romidepsin (i.e., pralatrexate was less costly and more effective than romidepsin). The Committee considered that the submitted MAIC analysis demonstrated no significant differences between pralatrexate and romidepsin for OS and PFS. pERC agreed with the EGP that there is a high level of uncertainty in the comparative efficacy estimates and therefore a high level of uncertainty in the cost-effectiveness estimates. In addition, pERC agreed with the EGP that wastage significantly impacts the incremental cost of pralatrexate compared with BSC and romidepsin, since vial sharing is unlikely to happen in this small patient population. Overall, due to the considerable uncertainty in the magnitude of and direction of benefit, pERC concluded that the public drug plan cost of pralatrexate should not exceed the public drug plan cost of romidepsin.

pERC discussed factors that could impact the feasibility of implementing a positive conditional reimbursement recommendation for pralatrexate for the treatment of relapsed/refractory PTCL. The Committee discussed that pralatrexate is administered by intravenous (IV) push and has shorter chair time than current treatments which pERC considered an enabler to implementation. Additionally, pERC discussed the Provincial Advisory Group's (PAG's) request for clarity on sequencing for patients who are treated with other therapies, the duration of treatment with pralatrexate and eligibility criteria for patients with relapsed/refractory PTCL. pERC noted there is currently insufficient evidence to make an informed decision regarding the choice between pralatrexate and romidepsin for the treatment of relapsed/refractory PTCL. However, pERC felt that given the uncertainty in the comparative effectiveness data and similar costing of these two treatments, it is uncertain whether pralatrexate is more costly and less effective than romidepsin or less costly and more effective than romidepsin. pERC noted that the choice between these two drugs will likely depend upon relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to adverse events. Additionally, pERC agreed with the CGP that given the shared clinical characteristics, responses to treatment, prognoses and behaviours after relapse, it is reasonable to consider the results observed in the PROPEL trial representative of those one would expect across the full PTCL class of lymphomas, including the much more rare subtypes.

Finally, pERC also considered the submitted budget impact analysis (BIA) and noted that the projected market share of pralatrexate is underestimated because the submitter underestimated the market share and the number of patients eligible to be treated with pralatrexate. Moreover, the submitted budget

impact considered a mix of all available treatments including romidepsin in year one to year three in the market share. pERC also discussed the fact that the BIA did not consider the sequencing of available therapies, which would have a substantial impact on the budget.

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (Lymphoma Canada [LC])
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, Lymphoma Canada.
- One clinician group, Cancer Care Ontario Hematology DAC.
- The PAG.
- The submitter, Servier Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of pralatrexate (Folotyn) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) conditional on the public drug plan cost of pralatrexate being lower than the public drug plan cost of romidepsin.

Feedback on the pERC Initial Recommendation indicated that the manufacturer, PAG and the patient group agreed in part with the Initial Recommendation and the registered clinician group agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pralatrexate (Folotyn) for patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Studies included: One phase II non-randomized study was the focus of deliberation

The pCODR systematic review included two clinical trials: PROPEL and PDX-JP1. The pCODR review focused on the PROPEL trial because the PDX-JP1 trial was a small phase I / II study (n = 25) with a very small sample size which was considered associated with the risk of providing unreliable estimates of efficacy. Therefore, the pCODR systematic review, critical appraisal and pERC deliberations focused on the larger phase II trial, the PROPEL trial (n = 111).

The PROPEL was a phase II, non-randomized, single-group, open-label multi-centred international trial conducted in 25 centres in the US, Europe, and Canada, that evaluated the efficacy and safety of pralatrexate in patients with relapsed or refractory PTCL.

The pCODR review also provided contextual information on two submitted indirect treatment analyses in the absence of randomized controlled trials (RCTs) comparing pralatrexate with relevant comparators, including a case matched control analysis (CMCA) comparing patients treated with pralatrexate to historical controls treated with chemotherapy and a matching adjusted indirect comparison (MAIC) comparing pralatrexate to romidepsin.

Patient populations: Heavily pre-treated at baseline with a median of three prior systemic therapies

Key eligibility criteria included patients aged at least 18 years of age with PTCL according to the Revised European-American Lymphoma and World Health Organization (REAL WHO) disease classification, disease progression after at least one prior therapy with no upper limit on the number of previous therapies, and ECOG performance status of 0 to 2. Patients who had a previous allogeneic stem cell transplant (SCT) were excluded.

The median age of patients in the PROPEL trial was 58 years (range, 21 to 85), with 36% of patients over the age of 65. The majority of patients were male (68%), white (72%), ECOG performance status of 0 or 1 (84%), and had PTCL subtype NOS (53%). The median time from diagnosis of PTCL was 15.6 months. The patient sample was heavily pretreated at baseline with a median of three prior systemic therapies (range, 1 to 13); and 18% of the trial population had been treated with ≥ 5 prior regimens. 24% (n = 26) were refractory to all previous therapies and did not demonstrate any evidence of response; while 63% (n = 69) were unresponsive to their most recent prior therapy. There were 18 patients (16%) who had relapsed after ASCT prior to enrolment in the trial.

The submitter provided feedback on pERC's Initial Recommendation regarding the reimbursement criteria that pralatrexate should be reimbursed for patients with relapsed or refractory PTCL who have undergone systemic therapy, none of which included romidepsin. The submitter indicated that the criteria of excluding romidepsin as a previous systemic therapy does not align with the need for additional treatment options and will create a barrier for patients who have failed romidepsin and require additional therapy.

In response to the submitter's feedback, the CGP noted pERC's rationale for limiting pralatrexate to patients that have not received prior romidepsin appears to reflect the fact that none of the patients enrolled in the pivotal phase II trial of pralatrexate for relapsed PTCL had previously received romidepsin. However, the CGP note that this lack of prior exposure to romidepsin is an artifact of the timing of the pivotal clinical trials, not a reflection of any evidence that prior romidepsin reduces or eliminates responsiveness to pralatrexate. The phase II trial of pralatrexate was conducted before romidepsin became widely used for PTCL. Patients with relapsed PTCL have a large unmet need for effective treatments. This same unmet need is at least as great in patients whose relapsed PTCL is not controllable by romidepsin. Limiting these patients' access to pralatrexate if they have previously received romidepsin will deny them the possibility of having a clinically useful response to pralatrexate.

The Committee noted the feedback from the submitter and the CGP's opinion regarding the use of pralatrexate after romidepsin. However, pERC restated its conclusion that while there may be a net clinical benefit of pralatrexate, it could not recommend removing the restriction for patients previously treated with romidepsin without evidence.

Pralatrexate was administered to patients as an intravenous (IV) push over three to five minutes at a dose of 30 mg/m² per week for six weeks followed by one week off treatment (seven week cycle). Treatment was administered up to a maximum duration of two years, and was discontinued in the event of progressive disease, initiation of other anti-cancer therapy, unacceptable toxicity, withdrawal of consent, investigator/sponsor decision, or death. A protocol amendment was issued to permit treatment beyond 24 months if patients were judged by the treating investigator to be experiencing clinical benefit. The median duration of treatment in the PROPEL trial was 70 days (95% CI, 39 to 86) or 2.0 cycles. The relative dose intensity (delivered versus planned doses administered) was 80%. All patients received vitamin supplementation consisting of B12 and folic acid for the duration of treatment with pralatrexate. Vitamin supplementation of B12 and folic acid were given to patients with elevated levels of methylmalonic acid (MMA) and homocysteine (HCy) prior to initiating pralatrexate.

Key efficacy results: Moderate ORR and Meaningful Long Duration of Response

The key efficacy outcome deliberated on by pERC was objective response rate (ORR) (CR + CR unconfirmed + PR), the primary outcome of the trial and duration of response (DOR), a secondary outcome of the trial.

At the updated database lock in August 2009, the ORR by International Workshop Criteria (IWC) was 29% (n = 32; 95% CI, 21% to 39%) with the majority of patients achieving a PR (18%; n = 20), and with fewer patients obtaining a CR (10%; n = 11). Of the 69 patients who did not have a response to their most recent prior therapy, 17 patients (25%) demonstrated a response to pralatrexate. Of the 26 patients who were considered refractory to previous therapies, five (19%) responded to pralatrexate. Subgroups analyses demonstrated that the ORR ranged from 8% to 38%.

Key secondary outcomes deliberated on by pERC were DOR, PFS and OS. Among responders, the median DOR by IWC was 10.1 months (95% CI, 3.4 months to not estimable). The median PFS by IWC among evaluable patients was 3.5 months (95% CI, 1.7 to 4.8) and ranged from 1.0 to 23.9 months. The median OS was 14.5 months (95% CI, 10.6 to 22.5) and ranged from 1.0 to 24.1 months.

Patient-reported outcomes: Not measured.

Quality of life and patient-reported outcomes were not measured in the PROPEL trial. Therefore, pERC was not able to comment on the impact of pralatrexate on quality of life.

Limitations: No direct comparative data to relevant comparators (chemotherapy or romidepsin)

In the absence of RCTs comparing pralatrexate with relevant comparators (romidepsin, chemotherapy), a CMCA was performed to provide an estimate of the treatment effect of pralatrexate compared with historical controls treated with conventional treatments (mainly chemotherapy). Historical control patients were identified from an international database of real-world evidence from four datasets in the US, Europe and Korea. Only data on OS were analyzed since other outcomes of interest including response rates, safety, quality of life and, PFS were not collected consistently across datasets. Propensity score matching was performed to derive a comparative estimate of OS between patients treated with pralatrexate and historical controls. Historical control patients were matched to patients in the PROPEL trial based on the following variables: WHO histology, number of previous treatments received, age at diagnosis, and sex. The matching process reduced the effective sample size from 386 to 80 historical control patients, and from 109 to 80 PROPEL patients (total n = 160). The CMCA produced a hazard ratio (HR) of 0.43 (95% CI, 0.30 to 0.63), suggesting a significant OS benefit in favour of pralatrexate when compared with historical control treatments. The median OS estimate for patients treated with pralatrexate was 15.2 months (95% CI, 11.4 to 25.6) compared with 4.1 months (95% CI, 2.6 to 5.8) with control treatments. The pCODR Methods Team identified a number of limitations of the CMCA including the high risk of selection bias owing to the retrospective nature of the historical comparator data, and the omission of important variables from the matching process, which may confound the treatment effect estimates.

At the request of pCODR, the submitter conducted an indirect treatment comparison (ITC) in the form of a MAIC to evaluate the relative efficacy between pralatrexate and romidepsin, a relevant comparator identified by PAG and the Clinical Guidance Panel. The MAIC was based on the efficacy results from the PROPEL trial and a single phase II trial of romidepsin (NCT00426764). The baseline characteristics of patients in the two trials were generally similar in terms of demographics and clinical characteristics. The outcomes evaluated in the MAIC included OS and PFS. Other outcomes of interest including response rates, safety, and quality of life were not evaluated. Individual patient data from the PROPEL trial were reweighted using inverse propensity score weights; the reweighted population matched the romidepsin trial in terms of the distributions of matched variables, which included age, sex, race, performance status, histopathology subtype, previous treatment exposure, refractory to most recent therapy, and prior SCT. Post-matching, the effective sample size of patients treated with pralatrexate in the PROPEL trial was reduced to 82.05. For both OS and PFS, naive ITC (unadjusted for differences in baseline characteristics) results were consistent with the MAIC results. Both ITC analyses demonstrated no significant differences between pralatrexate and romidepsin for OS [MAIC: HR = 0.88 (0.63 to 1.23)] and PFS [MAIC: 1.28 (0.94 to 1.73)]. The pCODR Methods Team considered a MAIC of the two trials appropriate based on their similarity but noted some limitations that should be considered when interpreting the results including limitations in the OS data of both trials, and possible bias introduced by unknown cross-trial differences.

Safety: Manageable safety profile

Treatment emergent AEs occurred in all patients treated with pralatrexate in the PROPEL trial. The most common AEs of any grade included mucositis (71%), nausea (41%), thrombocytopenia (41%), fatigue (36%); while the most common grade 3/4 AEs were thrombocytopenia (33%), mucositis (22%), neutropenia (22%), and anemia (18%). The mean duration of grade \geq 2 mucositis was 14 days.

Most patients (n = 106, 95%) experienced at least one AE that was considered by investigators to be possibly, probably, or definitely related to pralatrexate. The frequency of serious AEs (SAEs) was 45% (n = 50) in the trial; the most common SAEs included pyrexia (7%), mucositis (5%), febrile neutropenia (5%), dehydration (4%), and dyspnea (4%), with the majority considered reversible or manageable through dose modification.

Treatment discontinuations attributable to AEs occurred in 23% of patients (n = 26) and were due to mucositis (6%) and thrombocytopenia (5%). There were eight patient deaths within 30 days of the last dose of pralatrexate.

Need and burden of illness: Aggressive disease with limited treatments available

Peripheral T-cell lymphoma is an uncommon but aggressive malignancy. The number of patients with relapsed/refractory PTCL is relatively small with an estimated 600 patients in Canada in 2018. The current standard of treatment in Canada is romidepsin for patients with relapsed/refractory PTCL or conventional doses of chemotherapies. Results with these treatments have relatively low response rates, short duration of response and poor overall survival. Therefore, there is a need for more effective palliative treatment options.

Registered clinician input: Need for more treatment options for PTCL patients who will eventually relapse

Clinicians indicated that the major benefits from pralatrexate are high response rates and durable responses in a heavily pre-treated patient population, as demonstrated in the PROPEL trial. The clinicians stated that pralatrexate induced durable responses irrespective of age, histologic subtype, amount of prior therapy, prior methotrexate, and prior autologous stem-cell transplant, making it an option worth considering for any patient with relapsed or refractory PTCL. It was also reported that toxicities seem to be manageable with pralatrexate. The need for new treatments in this patient population was emphasized as most patients undergoing treatment for PTCL do not achieve complete remission, or will ultimately relapse. The clinicians providing input reported that pralatrexate would provide an additional option to patients in the relapsed and refractory PTCL setting.

PATIENT-BASED VALUES

Patient values on treatment: More choices for treatment, longer remission, longer survival

According to Lymphoma Canada (LC), there is a great need for more treatment options for patients with relapsed/refractory PTCL. There is currently no standard of care for patients with most subtypes of PTCL who relapse after one or more lines of previous therapy. Fatigue, swelling in the neck, armpit, groin, near ears or near elbows (due to enlarged lymph nodes), night sweats, rash, fever, and weight loss were among the symptoms reported by patient respondents. Bringing about remission and living longer were of high importance to patient respondents. Among the patient respondents with experience with pralatrexate, mouth sores and mucositis were the most commonly reported side effects, followed by anemia, low white blood cell and platelet counts. It was reported that patients with relapsed/refractory PTCL were willing to tolerate significant side effects of treatment with proven efficacy. In addition, some patients valued the shorter infusion time with pralatrexate compared with longer infusion times with available therapies including chemotherapy and romidepsin.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR EGP assessed a cost-utility analysis of pralatrexate compared with best supportive care (BSC) comprising of mainly chemotherapies as well as a scenario analysis of pralatrexate compared with romidepsin in patients with relapsed or refractory PTCL. The model was comprised of three health states: pre-progression, progression (or post-progression), and death.

Basis of the economic model: Indirect treatment comparisons (CMCA and MAIC)

Costs considered in the analysis included drug costs, administration costs and ongoing medical care costs.

The clinical effect considered in the analysis was based on projected overall survival, progression-free survival and utilities.

The efficacy and safety parameters for pralatrexate were based on the PROPEL trial. The PFS and OS were extrapolated using parametric functions fitted to the patient-level trial data. A CMCA encompassing a multi-cohort retrospective analysis of multiple registries of data was used to inform OS in BSC. The non-responders group from pralatrexate group was used as a proxy for extrapolating PFS for BSC. For the

scenario analysis of pralatrexate compared with romidepsin, a submitted MAIC analysis based on the efficacy results from the PROPEL trial and a single phase II trial of romidepsin (NCT00426764) was used.

The model assumed that after disease progression, all patients would receive best palliative care until death (i.e., no subsequent active cancer therapy assumed).

Drug costs: High drug costs

Pralatrexate costs \$2,108.63 for a single dose vial of 20 mg. At the recommended of 30 mg/m² IV once weekly for six weeks in seven week cycles and a dose intensity of 80% as per PROPEL trial, pralatrexate costs: \$16,486.33 per month (excluding wastage).

BSC costs represented by a combination of monotherapy and combination therapy chemotherapy agents were approximately \$1,625.59 per cycle per month.

Romidepsin costs \$2,582.00 per 10 mg vial. At the recommended dose of 14 mg/m² intravenous (IV) on days 1, 8, and 15 of a 28 day cycle romidepsin costs \$20,910.64 per month (excluding wastage).

Cost-effectiveness estimates: Substantial uncertainty in the incremental effect

The EGP's ICER estimate range for the comparison of pralatrexate to BSC were wide (lower bound: \$189,133 per quality-adjusted life-year (QALY) and upper bound: \$479,307 per QALY) compared with the submitter's estimate (\$254,022 per QALY). The Committee noted the assumptions upon which the EGP's estimates were based, which included:

- A shortened time horizon from 10 years to five years to better align with the expert opinion of the clinical course of a patients with relapsed/refractory PTCL as noted by the pCODR CGP
- A reduction of the clinical benefit after the two-year trial duration to explore uncertainty in the long-term benefit of pralatrexate
- A change to the OS and PFS extrapolation methods
- Equal utilities in the pre-progression state

Due to the non-comparative phase II trial design and the limitations in the CMCA analysis informing the comparative efficacy of pralatrexate to BSC, there is considerable uncertainty in the magnitude of benefit and therefore considerable uncertainty in the incremental cost-effectiveness of pralatrexate. The EGP noted that the best estimate would likely be closer to the upper bound ICER estimate due to the considerable uncertainty in the magnitude of the long-term benefit of pralatrexate. This estimate includes the scenario of a 50% reduction of clinical benefit after the two-year trial duration, equal utilities in the pre-progression state over a five-year time horizon. Furthermore, the ICER would likely be higher because of the wastage that will be incurred as vial sharing is highly unlikely given the small number of patients who would be receiving pralatrexate. Overall, the magnitude of long-term benefit associated with pralatrexate is unknown, given the lack of long-term data. Therefore, pralatrexate could not be considered cost-effective compared with BSC (chemotherapies) at the submitted price.

The submitter provided feedback on the pERC Initial Recommendation noting that if the assumption that the benefit beyond two years for pralatrexate is reduced by 50% in the EGP's upper bound estimate, then the treatment duration for pralatrexate should not exceed that observed in the clinical trial.

In response to the feedback provided by the submitter, the EGP agreed with the submitter's comment regarding the cost of pralatrexate in the scenario analysis with a reduced clinical benefit of 50% beyond the two-year trial duration. The submitter suggested that the scenario of using 38 vials based on the median duration of treatment in the PROPEL trial should be considered. The EGP noted that the submitted economic model has the option to assume that patients will receive treatment with pralatrexate for a maximum of two years and therefore, the EGP used this option when conducting the reanalysis on the clinical benefits decreased by 50% after the 2 year trial period. The EGP disagreed with the submitter's suggestion that the estimate of the cost of pralatrexate should be based on the median duration of treatment in the PROPEL trial (i.e., 38 vials), as this does not correlate with the PFS modelled by the parametric models. Based on the EGP's reanalyses estimates, pralatrexate is still not considered cost-effective compared with BSC (chemotherapies) at the submitted price.

The EGP's ICER estimates for the scenario analysis of pralatrexate compared with romidepsin was dominated (more costly and less effective) in several reanalyses compared with the submitter's ICER that was dominant (less costly and more effective). The EGP considered that the submitted MAIC analysis, demonstrated no significant differences between pralatrexate and romidepsin for OS and PFS. Therefore, the EGP set the HR for PFS and OS equal to one for all reanalyses. In addition, different parametric curves

were used to estimate PFS and OS. The EGP cautioned that there is a high level of uncertainty in the long-term benefit of pralatrexate and therefore a high level of uncertainty in the cost-effectiveness estimates.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Wastage a concern, BIA substantially underestimated

Pralatrexate is administered by IV push and has shorter chair time than currently available treatments, which is considered an enabler to implementation. However, wastage is a concern because vial sharing is unlikely given the small patient population. The following implementation issues were identified by Provincial Advisory Group (PAG) which include: clarity on sequencing for patients treated with other therapies, clarity on the duration of treatment with pralatrexate and clarity on the eligibility criteria for patients with relapsed/refractory PTCL.

The factors that influence the budget impact include the number of patients eligible to be treated with pralatrexate and the extent of market expansion. The submitted BIA is underestimated because the projected market share of pralatrexate is underestimated. The submitter underestimated the market share and the number of patients eligible to be treated with pralatrexate. Furthermore, the BIA did not consider the sequencing of available therapies, which would have a substantial impact on the budget.

DRUG AND CONDITION INFORMATION

Drug Information

- Pralatrexate is an anti-folate or anti-metabolite (a folate analogue metabolic inhibitor)
- Recommended dosage of Pralatrexate was administered to patients at a dose of 30 mg/m² per week for six weeks followed by one week off treatment (seven week cycle) as intravenous (IV) push over three to five minutes. Treatment is administered until disease progression or unacceptable toxicity.

Cancer Treated

- Peripheral T-Cell Lymphoma (PTCL)

Burden of Illness

- PTCLs are a heterogeneous group, collectively comprising of 5% to 10% of all non-Hodgkin lymphomas in Canada

Current Standard Treatment

- Estimated that 600 patients per year would be candidates for pralatrexate therapy in Canada for relapsed/refractory PTCL

Limitations of Current Therapy

- Relatively low response rates, short duration of response, and poor overall survival

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist

Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Kelvin Chan and Dr. Winson Cheung who were not present for the meeting
- Daryl Bell who did not vote due to his role as a patient member alternate

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist

Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Kelvin Chan and Dr. Marianne Taylor who were not present for the meeting.
- Daryl Bell who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pralatrexate (Folotyn) PTCL, through their declarations, no members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of the members were excluded from voting. For the Final Recommendation, no members had a real, potential, or perceived conflict, and based on application of the pCODR Conflict of Interest Guidelines, none of the members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

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

Use of this Recommendation

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

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
<ul style="list-style-type: none"> PAG noted that the PROPEL trial is a phase II non-comparative trial and is seeking information on the comparison of pralatrexate with romidepsin, the current standard of care for relapsed or refractory PTCL. 	<ul style="list-style-type: none"> Since romidepsin is available in Canada it is the most reasonable comparator available. A naive indirect comparison of pralatrexate with romidepsin shows similar rates of response and response duration. The submitted MAIC analysis of pralatrexate and romidepsin demonstrated no difference in PFS and OS. pERC noted that there is currently insufficient evidence to make an informed recommendation regarding the choice between pralatrexate and romidepsin for the treatment of relapsed/refractory PTCL. However, pERC felt that given the uncertainty in the comparative effectiveness data and similar costing of these two treatments, it is uncertain whether pralatrexate is more costly and less effective than romidepsin or less costly and more effective than romidepsin. pERC noted that the choice between these two drugs will likely depend upon relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to adverse events.
<ul style="list-style-type: none"> PAG is seeking clarity on the eligible patient population as the funding request is broad for relapsed or refractory patients. PTCL is a heterogeneous group of aggressive lymphomas with many subtypes. It will be important to clearly specify which subtypes of PTCL are eligible for treatment with pralatrexate. PAG is seeking information on the number of previous treatment patients in the trial had received and whether there is information on the previous treatments used. 	<ul style="list-style-type: none"> Given the shared clinical characteristics, responses to treatment, prognoses and behaviours after relapse, it is reasonable to consider the results observed in the PROPEL trial representative of those expected across the full PTCL class of lymphomas, including the much more rare subtypes. Pralatrexate should be an option for relapsed or refractory patients regardless of the number of prior systemic therapies, none of which include romidepsin. In the PROPEL trial, there was a median number of three prior systemic therapies (range, 1-13); and 18% of the trial population had been treated with ≥ 5 prior regimens. Most patients had been previously treated with CHOP (70%), platinum-containing multi-agent chemotherapy (41%), non-platinum containing multi-agent chemotherapy (39%), or single-agent chemotherapy (32%). None of the patients in the trial were previously treated with romidepsin. pERC noted that because patients in the PROPEL trial were treated with various chemotherapy regimens and did not have previous treatment with romidepsin, the Committee agreed that pralatrexate should only be considered for patients who have undergone at least one previous systematic therapy, none of which include romidepsin.

<ul style="list-style-type: none"> • PAG has concerns for drug wastage as vial sharing may be difficult with a very small number of eligible patients. PAG also noted that pralatrexate is administered by intravenous push, which has shorter chair time and enables pralatrexate to be administered in smaller clinics. • Pralatrexate is administered once weekly for six weeks out of seven weeks. PAG noted that the administration schedule is not convenient for patients. PAG also noted that Vitamin B12 injections also need to be administered intramuscularly and folic acid would need to be taken concomitantly. • PAG is also seeking clarity on the treatment duration. 	<ul style="list-style-type: none"> • The ICER would likely be higher because of the wastage that will be incurred as vial sharing is highly unlikely given the small number of patients who would be receiving pralatrexate. • In the PROPEL trial, the median duration of treatment with pralatrexate was 70 days (95% CI, 39 to 86) or 2.0 cycles and the median dose administered was 207.9 mg/m². • All patients received vitamin supplementation consisting of B12 and folic acid for the duration of treatment with pralatrexate. Patients with elevated levels of MMA and HCy should be given vitamin supplementation prior to initiating pralatrexate as per the PROPEL trial.
<ul style="list-style-type: none"> • PAG is seeking clarity on the place in therapy of pralatrexate among the different treatments available and the possible sequencing of treatments. 	<ul style="list-style-type: none"> • pERC noted that there is currently no evidence in support for or against the use of pralatrexate after romidepsin or the use of romidepsin after pralatrexate.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.