CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pralatrexate (Folotyn) for Peripheral T-cell Lymphoma

April 4, 2019

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List of Abbreviations

AE(s)	Adverse event(s)
AITL	Angioimmunoblastic peripheral T-cell lymphoma
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ASCT	Autologous stem cell transplant
CHOP	Cyclophospmamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CMCA	Case match control analysis
CR	Complete response
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
DBL	Database lock
DOR	Duration of response
EATL	Enteropathy associated T-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
HCy	Homocysteine
HR	Hazard ratio
HRQOL	Health-related quality of life
HTLV1+ ATLL	Human T-cell leukemia virus type 1 adult T-cell lymphoma/leukemia
ICE	Ifosfamide, carboplatin, etoposide
INV	Investigator assessment
IPD	Individual patient data
ITC	Indirect treatment comparison
IWC	International Workshop Criteria
LC	Lymphoma Canada
MAIC	Matching adjusted indirect treatment comparison
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmalonic acid
NCI	National Cancer Institute
N/K	Natural/Killer T-cell
ORR	Objective response rate
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PD	Progressive disease
PE	Pharmacoeconomic
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma - not otherwise specified
RCT(s)	Randomized controlled trial(s)
REAL WHO	Revised European-American Lymphoma and World Health Organization classification system
rr	Relapsed/refractory
RWE	Real world evidence
SAE(s)	Serious adverse event(s)
SCT	Stem cell transplant
SAP	Statistical analysis plan
SPTCL	Subcutaneous panniculitis-like T-cell lymphoma

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 pralatrexate (Folotyn) for peripheral T-cell lymphoma (PTCL). 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 pralatrexate (Folotyn) for PTCL conducted by the Lymphoma 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 pralatrexate (Folotyn) for PTCL, a summary of submitted Provincial Advisory Group Input on pralatrexate (Folotyn) for PTCL, and a summary of submitted Registered Clinician Input on pralatrexate (Folotyn) for PTCL, 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 pralatrexate (Folotyn) for the treatment of patients with relapsed or refractory (rr) PTCL.

Pralatrexate is indicated for the treatment of patients with rr PTCL, and has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two clinical trials were identified that met the selection criteria of the pCODR systematic review, PROPEL (PDX-008)[1] and NCT02013362 (PDX-JP1).[2] PROPEL (n=111) is the pivotal trial that was included as evidence in the pCODR submission. Comparatively, NCT02013362 (PDX-JP1) is a smaller phase 1/2 trial (n=25) conducted solely in Japanese patients. Due to the small sample size of this trial and the associated risk of providing unreliable estimates of efficacy,[3] the pCODR review and critical appraisal focused on the PROPEL trial. Refer to Section 6 and Appendix B of this report for more information on NCT02013362 (PDX-JP1).[2]

PROPEL was a phase 2, non-randomized, single-group, open-label multi-centred international trial conducted in 25 centres in the United States, Europe and Canada, that evaluated the efficacy and safety of pralatrexate in patients with rrPTCL.[1] Patients enrolled in PROPEL met the following key criteria:

- Male or female, aged at least 18 years with PTCL according to the Revised European-American Lymphoma (REAL) World Health Organization (WHO) disease classification
- Disease progression after at least one prior therapy
- No upper limit on the number of previous therapies
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- Patients who had prior allogeneic stem cell transplant (SCT) were excluded

Pralatrexate was administered to patients as an intravenous 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 (PD), initiation of other anti-cancer therapy, unacceptable toxicity, withdrawal of consent, investigator/Sponsor decision, or death. The median duration of treatment with pralatrexate was 70 days (95% confidence interval [CI], 39 to 86) or 2.0 cycles;[4] and the relative dose intensity (delivered versus planned doses administered) was 80%. Vitamin supplementation of B_{12} and folic acid were given to patients with elevated levels of methylmalonic acid (MMA) and homocysteine (HCy) at trial screening and were required for at least 10 days prior to pralatrexate administration. Once on study, all patients received vitamin supplementation for the duration of the treatment phase of the trial.[5]

The primary outcome of the trial was objective response rate (ORR; complete response [CR] + CR unconfirmed + partial response [PR]), which was assessed centrally by independent review of imaging and clinical data according to International Workshop Criteria (IWC). Imaging was performed every 14 weeks during treatment and then every 12 weeks until disease progression or initiation of subsequent therapy. ORR was also assessed by treating investigators (INV). The secondary outcomes of the trial included duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety. Health-related quality of life (HRQOL) was not evaluated.

The required sample size of PROPEL was determined using a 2-stage Simon design, which considered a ORR of 15% for the null hypothesis and a ORR of 27% as the alternate hypothesis. With 100 patients, the trial had 84% power to reject the null hypothesis. The primary efficacy analysis (and regulatory approval) of the PROPEL trial was based on a database lock (DBL) of January 2009.[6] An updated efficacy analysis was performed with a DBL of August 2009, which corresponds to the trial publication[1] and was the focus of reporting in the pCODR review. The median follow-up times of both analyses, considering all trial patients, were not reported and could not be confirmed by the Submitter.[4] The median follow-up time of patients still alive at the updated DBL was 18 months.

Of 115 enrolled patients, 111 patients received ≥1 dose of pralatrexate and were evaluable for safety and 109 patients were deemed evaluable for efficacy. At the updated DBL there were four patients remaining on treatment and 105 who had discontinued.[7] The primary reason for treatment discontinuation was disease progression (n=64) followed by adverse events (AEs; n=26); fewer patients discontinued due to investigator (n=8) or patient decision (n=6). A total of 27 patients remained on study; and 82 patients had terminated the study due to death (n=62), completion of the 24-month follow-up period (n=15) and other reasons (n=5).[7]

The median age of trial patients was approximately 58 years (range, 21to 85), with 36% of patients over the age of 65.[7] The majority of patients were male (68%), white (72%), ECOG performance status of 0 or 1 (84%),[7] and had PTCL subtype not otherwise specified (NOS;53%). Most other PTCL subtypes were represented in the trial. The median time from diagnosis of PTCL was 15.6 months. The patient sample was heavily pretreated at baseline with a median number of three prior systemic therapies (range, 1 to 13); and 18% of the trial population had been treated with ≥ 5 prior regimens.[7] Among patients included in efficacy analyses (n=109), 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 autologous stem cell transplant (ASCT) prior to enrollment in the trial.

For the pCODR Methods Team's critical appraisal of the PROPEL trial, refer to section 6.3.2.1 (e). The key outcomes of the PROPEL trial are summarized in Table 1.

Table 1: Highlights of Key Outcomes in the PROPEL trial.[1]

Key Outcomes	**Pralatrexate Monotherapy (n=109)**	
Efficacy		
DBL	August 2009	
Median follow-up	NA	
Primary Outcome	Central Assessment by IWC	Investigator Assessment
ORR, n (%; 95% CI)	32 (29; 21-39)	43 (39; 30-49)
Best clinical response n (%)		
CR	11 (10)	17 (16)
CR unconfirmed	1 (1)	3 (3)
PR	20 (18)	23 (21)
SD	21 (19)	21 (19)
PD	40 (37)	40 (37)
NE	2 (2)	0
Secondary Outcomes		
Median DOR, in months (95% CI)	10.1 (3.4-NE)	8.1 (NR)
PFS		
Median follow-up, in months	NA	
No. of PFS events (%)	70 (64)	NR
Median PFS, in months	3.5 (1.7-4.8)	4.0 (NR)[7]
OS		
Median follow-up, in months	NA	
No. deaths (%)	62 (57)	
Median OS in months (95% CI)	14.5 (10.6-22.5)	
Proportion of patients receiving SCT after pralatrexate		
Received SCT, n (%)	6 (6)	
Harms		
TEAE, n (%) – all grade / grade 3-4	111 (100) / 82 (74)	
Thrombocytopenia	45 (41) / 36 (33)	
Mucositis	79 (71) / 24 (22)	
Neutropenia	28 (25) / 24 (22)	
Anemia	38 (34) / 20 (18)	
Treatment-related AEs	106 (95)	
TEAE resulting in dose modification	35 (32)	
TEAE resulting in treatment discontinuation	26 (23)	
SAE	45 (50)	

Abbreviations: AEs – adverse events; **CI** – confidence interval; **CR** – complete response; **DBL** – database lock; **DOR** – duration of response; **IWC** – International Workshop Criteria; **NA** – not available; **NE**– not estimable; No. – number; **NR** – not reported; **ORR** – objective response rate; **PD** – progressive disease; **PR** – partial response; **OS** – overall survival; **PFS** – progression-free survival; **SAE** – serious adverse event; **SCT** – stem cell transplant; **SD** – stable disease; **TEAE** – treatment-emergent adverse events.

Efficacy

Primary Outcome – ORR

The trial met its primary outcome at the primary analysis based on the a priori statistical hypotheses specified in the statistical analysis plan (SAP). At the updated DBL, the ORR by IWC was 29% (n=32; 95% CI, 21% to 39%), and the confidence limits excluded the null value of 15%. The ORR by IWC was driven by PRs (18%; n=20), with fewer patients obtaining a CR (10%; n=11). The proportion of patients with SD (by IWC) was 19% (n=21). Of the 69 patients who did not have a response to their most recent prior therapy, 17 patients (25%) demonstrated a response to pralatrexate. Considering the 26 patients who were refractory to previous therapies, five (19%) responded to pralatrexate.

Among the 32 patients who responded to pralatrexate, 16 (50%) eventually progressed or died, five (16%) were alive and remained in response, and 11 (34%) were censored due to subsequent treatment (n=7), which included ASCT (n=2) and allogeneic SCT (n=2), or study termination (n=4). Of the 11 patients who achieved a CR, two developed PD.

Among the various patient subgroups examined, the ORR ranged from 8% to 38%. The ORRs obtained for the subgroups should be interpreted with caution considering a lack of adjustment for multiple comparisons (type 1 error) and small sample sizes, which can lead to unreliable estimates.

Secondary Outcomes – DOR, PFS, OS

The median DOR by IWC (among responders) was 10.1 months (95% CI, 3.4 months to not estimable). The United States Food and Drug Administration (FDA) review[8,9] of the PROPEL trial noted major concerns related to the determination of response and DOR in the trial (refer to section 6.3.2.2 for details) and consequently calculated a durable response rate among confirmed responders (n=16/29), which was defined as the proportion of responses that lasted at least 14 weeks and were confirmed by a subsequent scan. The durable response rate was calculated to be 12% (n=13; 95% CI, 7% to 20%).

At the updated DBL a total of 70 (64%) PFS events (PD: n=63, 58%; death: n=7, 6%) had occurred and the remaining patients (n=39) were censored. 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.

A total of 62 deaths (57%) occurred in the trial. The median OS was 14.5 months (95% CI, 10.6 to 22.5) and ranged from 1.0 to 24.1 months.

Harms

Treatment emergent adverse events (TEAEs) occurred in all patients treated with pralatrexate. The most common AEs of any grade included mucositis (71%), nausea (41%), thrombocytopenia (41%), and 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 ≥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 adverse events (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 mainly occurred due to mucositis (6%) and thrombocytopenia (5%). There were eight patient deaths within 30 days of the last dose of pralatrexate; seven patient deaths were attributed to PD and one patient died after cardiopulmonary arrest after approximately three weeks of their last dose of pralatrexate while hospitalized for mucositis and febrile neutropenia.

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 patient group input from Lymphoma Canada (LC), there is a need for more choice in drug therapies for patients with 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. LC noted that patient respondents were willing to tolerate significant side effects in new drug therapies. 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 blood platelet counts.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pralatrexate:

Clinical factors:

- Clarity of eligible patient population
- Place in therapy
- Comparison to romidepsin

Economic factors:

- Weekly dosing administration
- Drug wastage

Registered Clinician Input

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. Referring to this trial, clinicians stated that pralatrexate induced durable responses irrespective of age, histologic subtype, amount of prior therapy, prior methotrexate, and prior ASCT, making it an option worth considering for any patient with

rrPTCL. It was also reported that toxicities seem to be manageable with pralatrexate. Clinicians providing input also noted that pralatrexate has a quick infusion time. 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 rrPTCL setting. No companion diagnostic testing is required.

Summary of Supplemental Questions

Critical appraisal of a Case Match Control Analysis (CMCA) comparing patients treated with pralatrexate (PROPEL) to historical controls

In the absence of randomized controlled trials (RCTs) comparing pralatrexate to relevant comparators (romidepsin, chemotherapy), a CMCA was performed to provide an estimate of the treatment effect of pralatrexate compared to historical control patients treated with conventional treatments (mainly chemotherapy).[10] The CMCA was funded through a research grant from Spectrum Pharmaceuticals Inc. Historical controls were identified from an international database that was comprised of real world evidence (RWE) from four datasets (two in the United States, and one each in Europe and Korea). Only data on OS were analyzed since other outcomes of interest (response, PFS) were not collected in a consistent manner across datasets. The CMCA used propensity score matching 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 to historical control treatments. The median OS estimate for patients treated with pralatrexate was 15.2 months (95% CI, 11.4 to 25.6) compared to 4.1 months (95% CI, 2.6 to 5.8) with control treatments. The quality of the CMCA was appraised according to best practice principals for indirect treatment comparisons (ITC) and matching using propensity scores. The pCODR Methods Team identified a number of limitations of the CMCA that should be considered when interpreting the results; the most significant of these included 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 obtained.

See section 7.1 for more information.

Critical appraisal of the Manufacturer's submitted Matching Adjusted Indirect Comparison (MAIC) of pralatrexate (PROPEL) to romidepsin (NCT00426764)

At the request of pCODR, the Submitter conducted an ITC in the form of a MAIC to evaluate the relative efficacy between pralatrexate and romidepsin.[11] The MAIC was based on the efficacy results from the PROPEL trial and a single phase 2 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. Individual patient data (IPD) 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, naïve ITC (unadjusted for differences in baseline characteristics) results were consistent with the MAIC results with the former being of slightly greater magnitude. 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 quality of the MAIC was appraised according to best practice principles. 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; these included limitations in the OS data of both trials, and possible bias introduced by unknown cross-trial differences.

See section 7.2 for more information.

Comparison with Other Literature

The pCODR CGP and Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 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).

Table 2: Assessment of Factors that May Affect Generalizability in the PROPEL trial.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the PROPEL trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>PTCL Subtype</td><td>The most common (58%) PTCL subtype in the PROPEL trial was NOC. The percentages of patients with other subtypes are available in Section 6 of the Clinical Guidance Report, Table 9: Baseline characteristics of patients included in the PROPEL trial.</td><td>Does PTLC subtype limit the interpretation of the trial results with respect to the target population?</td><td>Given the largely shared clinical characteristics, responses to treatment, prognoses and behaviours after relapse, it is reasonable to consider the results seen in the PROPEL trial representative of those one would expect across the full PTCL class of lymphomas, including the much more rare subtypes.</td></tr>
<tr><td>ECOG Performance Status</td><td>The trial limited eligibility to patients with an ECOG performance status of ≤2.
<table><tr><th>ECOG Performance Status</th><th>Efficacy analysis set (n=109) n, (%)</th></tr><tr><td>0</td><td>42 (39)[7]</td></tr><tr><td>1</td><td>49 (45)[7]</td></tr><tr><td>2</td><td>18 (17)[7]</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The PROPEL results cannot be generalized to patients with performance status 3 or worse.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the PROPEL trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Age</td><td>The trial did not limit eligibility by patient age; 36% (n=40) of patients included in the trial were aged ≥65 years.

Subgroup analyses were pre-specified and conducted by age group:

<table><tr><td>Age group</td><td>ORR by IWC (95% CI)</td></tr><tr><td><65 years</td><td>27 (17 to 39)</td></tr><tr><td>≥65 years</td><td>33 (19 to 50)</td></tr></table></td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>There is no reason to expect an age-related impact on generalizability, in isolation. Age related decline in performance status or due to comorbidities need to be considered independent of age.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td>The trial limited eligibility to patients with adequate hematologic, hepatic, and renal function.</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population?</td><td>The PROPEL results cannot be safely extrapolated to patients with clinically significantly impaired hematologic, renal or hepatic dysfunction.</td></tr>
<tr><td></td><td>Exclusion of patients with allogeneic transplant</td><td>Patients with prior allogeneic SCT were excluded from the trial.</td><td>Did the exclusion of patients prior allogeneic SCT limit the interpretation of the trial results with respect to the target population?</td><td>Although patients with prior allogeneic transplant were excluded from the trial, it would still be reasonable to extend the trial's findings to include them. Similar to age there is no reason to expect an allogeneic transplant-related impact on generalizability, in isolation. Allogeneic transplant-related decline in performance status or due to comorbidities need to be considered independent of the allogeneic transplant.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the PROPEL trial[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2"></td><td>Ethnicity or Demographics</td><td>The ethnicity of included patients were as follows:

<table><tr><th>Ethnicity</th><th>Safety analysis set (n=111)
n, (%)</th></tr><tr><td>White</td><td>80 (72)</td></tr><tr><td>African American</td><td>14 (13)</td></tr><tr><td>Asian</td><td>6 (5)</td></tr><tr><td>Hispanic</td><td>9 (8)</td></tr><tr><td>Other</td><td>1 (<1)</td></tr><tr><td>Unknown</td><td>1 (<1)</td></tr></table></td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.</td><td>International studies did not reveal any ethnicity-related differences in PTCL behaviour or response to treatment so ethnicity should not, in isolation, affect generalizability.</td></tr>
<tr><td>Prior lines of therapy</td><td>The trial did not impose an upper limit for the number of prior lines of therapy patients could have.

The median number of prior systemic therapies was three (range, 1 to 13). 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%).</td><td>Are the results of the trial generalizable to other lines of therapy?</td><td>Yes. Pralatrexate should be an option for rrPTCL patients regardless of the number of prior systemic therapies.</td></tr>
<tr><td>Comparator</td><td>The PROPEL trial was a non-comparative, phase 2, non-randomized, single-group, open-label trial</td><td>In the absence of RCTs comparing pralatrexate to relevant available comparators in the Canadian setting (romidepsin, chemotherapy), a CMCA was performed by the Submitter to provide an estimate of the treatment effect of pralatrexate when compared to historical controls treated with conventional treatments. In addition, a MAIC to evaluate the relative efficacy between pralatrexate and romidepsin was performed by the Submitter. Details of the analyses and results are reported in Section 7 of the Clinical Guidance Report.</td><td>Was the chosen comparator a standard of care? If not a Canadian standard of care, could it be considered a reasonable alternative to that used in Canada?</td><td>The indirect comparison of pralatrexate with romidepsin implied similar rates of response and response duration. Since romidepsin is available in Canada it is the most reasonable comparator available.</td></tr>
</table>

Domain	Factor	Evidence from the PROPEL trial[1]	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Appropriateness of Primary and Secondary Outcomes	The primary outcome of the trial was ORR (CR + CR unconfirmed + PR). The secondary outcomes of the trial included DOR, PFS, OS and safety.	Were the primary and secondary outcomes appropriate for the trial design?	The cited outcomes were appropriate for the patient population.
Setting	Countries participating in the Trial	The trial was conducted at trial sites in Canada (n=9; 8%), the United States (n=80; 70%) and Europe including France (n=17; 15%), Italy (n=5; 4%), Belgium (n=3; 3%), and the UK (n=1; 1%).[8]	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	PROPEL and the indirect comparator trial of romidepsin were conducted in healthcare systems sufficiently similar to Canada to allow generalization.
	Location of the participating centres	A total of 25 institutions centers in the United States, Europe, and Canada enrolled 115 patients. The Submitter noted that sites were primarily academic/research-based centres, reflecting their interest and ability to recruit in a rare disease population.[4]	If the trial was conducted only in academic centres are the results applicable in the community setting?	rrPTCL treatment in Canada is provided at specialized centers or under the guidance of specialists at such centers, making it reasonable to generalize the PROPEL results.
	Supportive medications, procedures, or care	Concomitant procedures/medications permitted in the trial included platelet transfusions, antiemetics, erythropoietin, hematopoietic growth factors, appetite stimulating hormones, and prophylactic antibiotics.[5]	Are the supportive medications, procedures, or care used with the intervention in the trial the same as those used in Canadian clinical practice?	rrPTCL treatment in Canada is provided at centers or under the guidance of specialists with experience managing rrPTCL, including appropriate use of supportive care measures, making it reasonable to generalize the PROPEL results.

Abbreviations: CMCA – Case Match Control Analysis; **CR** – complete response; **DOR** – duration of response; **ECOG** – Eastern Cooperative Oncology Group; **IWC** – International Workshop Criteria; **NOS** – not otherwise specified; **ORR** – objective response rate; OS – overall survival; **MAIC** – Matched Adjusted Indirect Treatment Comparison; **PFS** – progression-free survival; PR – partial response; **PTCL** – peripheral T-cell lymphoma; **RCTs** – randomized controlled trials; **rr** – relapsed/refractory; **SCT** – stem-cell transplant.

1.2.4 Interpretation

Patients with rrPTCL rapidly become symptomatic, experience progressive organ dysfunction and usually succumb to their disease in a matter of months.[12-14] Interventions modelled on successful treatment of B-cell lymphoma are often employed for the treatment of such patients but have proven to have very limited usefulness. Currently, only one chemotherapeutic agent for the treatment of rrPTCL, romidepsin, has undergone formal assessment by pCODR/pERC, resulting in a recommendation for its approval for this indication. However, romidepsin has only a modest level of effectiveness for rrPTCL (ORR, 25%; CR/CR unconfirmed, 15%)[15,16] and the duration of response is short (median of 28 months).[15,16] Patients with rrPTCL have a major unmet need and it is urgent to bring additional effective therapies to their care.

Effectiveness. The effectiveness of pralatrexate for rrPTCL has been assessed in the PROPEL phase 2 clinical trial and the results from this trial, reviewed in detail below (section 6), are the evidence supplied by the Submitter in support of their request for funding of pralatrexate for rrPTCL. In summary, the PROPEL trial[1] enrolled patients with diagnoses across the spectrum of PTCL; however, reflecting the relative incidence of these lymphomas, most (92%) of the 109 evaluable patients had PTCL NOS (53%); angio-immunoblastic (AITL) PTCL (12%); systemic anaplastic large cell lymphoma (ALCL;16%); or large-cell transformation of mycosis fungoides (11%). Given the largely shared clinical characteristics, responses to treatment, prognoses and behaviours after relapse, it is reasonable to consider the results seen in the PROPEL trial representative of those one would expect across the full PTCL class of lymphomas, including the much rarer subtypes. Single-agent pralatrexate was administered as a brief intravenous injection weekly for six weeks of each seven-week cycle of treatment and was continued until progression of the lymphoma or unacceptable toxicity occurred. At the updated analysis, independently assessed responses (by IWC) were seen in 29% of patients (CR/CR unconfrimed 11%; PR 18%) and occurred approximately equally across all subtypes (~30%) with the exception of AITL (8%). Responses typically occurred early, in the first one or two cycles, with a median number of cycles received across all enrolled patients of approximately two (12 doses). The median DOR was approximately 10 months; median PFS was 3.5 months; and median OS was 14.5 months. Because the PROPEL trial enrolled rrPTCL patients with a median of three prior lines of treatment (range 1 to 13) it is possible to determine that number of prior lines of treatment did not affect likelihood of response (the ORR was 35% after failure of one prior line of treatment and 30% after three or more lines of treatment.[1]

The PROPEL trial did not include a HRQOL assessment because it was a single arm trial seeking primarily to determine response rates and duration and, without a comparator to serve as a baseline for comparison, relative HRQOL cannot be determined. However, for non-Hodgkin lymphoma, for which identification of an objective response requires at least a 50% reduction in tumour burden, there is a good correlation between ORR and relief from disease-related symptoms. Thus, it is reasonable to assume that the 29% of patients found to have a PR or CR experienced clinically meaningful improvement in disease-related symptoms.

Some of the measures used to determine effectiveness were criticized by the United States FDA when the PROPEL study was assessed. However, the criticism was directed at the technical aspects of determining response and DOR and focused on the lack of confirmatory scans to document response and the imprecision in determining response duration when the planned interval between scan-based assessments was 14 weeks. While this criticism is valid, it is important to remember that these are technical issues. Confirmatory scans are not required in the standard response criteria for lymphoma[17] and performing scans more often than every two cycles of treatment would have been considered excessive by investigators. Ultimately, the FDA did not consider these technical flaws to be substantive and ruled in favour of approval of pralatrexate for rrPTCL because the more clinically relevant endpoints of standard response assessment and PFS were not affected by them.

The gold standard for assessment of effectiveness of oncologic agents is a prospective RCT. However, such trials have not been performed for rrPTCL and are very unlikely to be performed for several reasons: first, rrPTCL is rare, making performance of prospective trials impractical; second, there is no consensus among potential investigators as to the appropriate control arm because no agents have demonstrated adequate levels of effectiveness to be considered standard and current patterns of practice vary markedly around the world – ramifying the impracticality of attempting a RCT; third, there is not even a consensus around appropriate primary treatment of PTCL, such that what might be an acceptable second-line treatment in one region could not be used in another region because that very treatment is the local first-line treatment; finally, there is no consensus about the appropriate timing or even use of high-dose chemotherapy and ASCT for rrPTCL, with that approach being considered a reasonable component of primary treatment in some regions and being reserved for third-line or later line treatment in other regions.

In the absence of prospective RCTs evaluating pralatrexate and relevant comparators (chemotherapy and romidepsin), comparative effectiveness of pralatrexate for rrPTCL was assessed by performing two ITCs: first, with a basket of 386 matched historical control patients (CMCA)[10] with rrPTCL treated with a variety of investigator-chosen systemic therapies, assembled from Memorial Sloan Kettering Cancer Center (MSKCC), University of Nebraska Medical Center (UNMC), Groupe d'Etude des Lymphomes de l'Adulte (GELA); and Samsung Medical Centre SMC; and second, with a subset of the patients enrolled in the phase 2 trial of romidepsin for rrPTCL (MAIC) [15,16] that was part of the supportive evidence leading to pCODR/pERC approval of that drug for that indication. These two detailed ITCs are reported below in section 7 and with results briefly summarized in Table 3.

Table 3: Comparison of Key Outcomes in the CMCA and MAIC Submitted as Supportive Evidence for the pCODR Submission.

	CMCA[10]	MAIC[15,16]	PROPEL trial[1]
N	80	82	109
Median follow-up in months	NR	22.3	18
OS HR (95% CI)	0.43 (0.30-0.63)*	0.88 (0.63-1.23)**	NR
Median OS in months (95% CI)	4.1 (2.6-5.8)*	NR	14.5 (10.6-22.5)
PFS HR (95% CI)	NR	1.28 (0.94-1.73)**	NR

Abbreviations: CI - confidence interval; CMCA – Case Match Control Analysis; HR -hazard ratio; NR - not reported; PFS – progression-free survival.
Notes:
* Based on comparison of the 80 CMCA and 80 PROPEL patients who could be matched.
** Based on comparison of the 82 MAIC and 109 PROPEL patients who could be matched.

Essentially, these two ITCs indicate that historically matched patients in the PROPEL trial appear to have had outcomes superior to those seen in a set of patients managed with a variety of systemic agents in the more distant past (1990s-2000s) and equivalent to those seen in a set of more contemporaneous patients treated with romidepsin in the more recent past (2010s).

Safety: Pralatrexate was generally well tolerated by patients in the PROPEL trial. The incidence of any grade 3 or grade 4 toxicity was 42% and 32%, respectively, and 68% required one or more dose omissions; however, relative dose intensity was 80%, drug discontinuations, 23% and no toxic deaths occurred. Most patients were able to take most of their prescribed doses. As expected with an anti-metabolite anti-folate agent, mucositis was the most frequent toxicity, reaching grade 3 in 18% and grade 4 in 4%. Hematologic toxicity was infrequent, reaching grade 3 or grade 4 for platelets in 14% and 19% of patients, respectively, and for hemoglobin in 16% and 2%, and for neutrophils in 14% and 8%. Only 2% of patients had a grade 3 infection. Anti-folate agents can

cause gastrointestinal, hepatic and renal toxicity but few grade 3 (4% to 5%) and no grade 4 events occurred.

Burden of illness: As explained in more detail in section 2 below, it is reasonable to anticipate that, at most, 600 new cases of rrPTCL will be seen in Canada each year. Older age (> 60 years), frailty and concurrent organ dysfunction are often present in these patients (e.g. hepatic, renal, gastrointestinal), all of which make pralatrexate a much less attractive treatment option or even contraindicate its use. For those reasons and in light of the modest response rate to pralatrexate and availability of alternative treatments such as romidepsin, at most, only approximately half of rrPTCL patients will be thought suitable candidates for pralatrexate. Therefore, less than half of 600 equals 300 patients per year will be given pralatrexate (CGP best estimate). Since the median number of doses of pralatrexate typically administered is 10-12, approval of funding should lead to delivery of fewer than 3,000 doses (10 x 300) annually for the entire country.

Need: As explained above, patients with rrPTCL are in urgent need of effective treatment. Although, in general, patients with relapsed lymphoma of any type are often considered for high dose chemotherapy followed by ASCT this approach has very limited usefulness for rrPTCL because the large majority of patients with rrPTCL are ineligible for ASCT because of age, comorbidity and/or lack of disease chemo-sensitivity and at least some of the potentially eligible patients will have already undergone ASCT as part of their primary treatment. For those same reasons pralatrexate will seldom be considered as a potential bridge to ASCT. While the response rate and response duration for pralatrexate are both modest, availability of pralatrexate will expand the potential treatments for such patients beyond the few currently available in Canada. This expansion of potential treatment alternatives will allow lymphoid cancer experts greater flexibility in the management of these severely ill, symptomatic patients.

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 include 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 addition, the Submitter noted that given the timing of the trials for pralatrexate (PROPEL start August 2006, complete January 2009) and romidepsin (NCT00426764 start June 2007, complete November 2010),[6,18] it is unlikely that either trial would have enrolled many patients who had been treated with the opposing therapy. Furthermore, the Submitter noted that romidepsin [histone deacetylase (HDAC) inhibitor] and pralatrexate (antifolate) have two different mechanisms of action with non-over-lapping side-effect profiles[19,20] and that these differences support the rational for studying the combination of romidepsin and pralatrexate for the treatment of patients with relapsed/refractory lymphoid malignancies (NCT01947140).[21]

In response to the Submitter's feedback, the CGP note that the practical effect of the pERC recommendation will be to preclude the use of pralatrexate for any patient with relapsed PTCL who has previously received romidepsin, either as part of primary treatment, an unlikely scenario in Canada, or for a previous relapse, a common practice in Canada. This recommendation against the use of pralatrexate after romidepsin has failed is not supported by any evidence and will harm patients.

Romidepsin is a histone deacetylase inhibitor (HDACi) and pralatrexate is an anti-folate antimetabolite. Thus, they work by entirely different mechanisms. There is no scientific rationale to think resistance to romidepsin will result in or predict for resistance to pralatrexate. Indeed, the opposite is most likely. The likelihood of response to pralatrexate should be unaffected by prior resistance to an HDACi. Available evidence supports this assertion.

If romidepsin resistance correlated with pralatrexate resistance, the effect of the combination of the two drugs should not be additive because at least some of the cancers resistant to romidepsin should also be resistant to pralatrexate and vice versa. In fact, however, the effect of the combination or romidepsin and pralatrexate on PTCL is more than additive; it is synergistic in both preclinical models[22] and phase I-II testing.[23] Since the phase II response rate to romidepsin is 25% and to pralatrexate 29% any cross-resistance shared by the two drugs should lead to an overall response rate to the combination of less than 54%. In actual fact, the response rate to the combination is 71% with 22% complete responses.[23] Thus, available evidence provides no support for the hypothesis that pralatrexate will be less effective for PTCL after romidepsin has failed to control the disease.

The rationale for pERC's recommendation that pralatrexate only be funded for relapse of PTCL when patients 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, this lack of prior exposure to romidepsin is simply 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. This lack of evidence is definitely not evidence of a lack of effect.

As documented in the pCODR review of pralatrexate for relapsed 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. Denying these patients access to pralatrexate if they have previously received romidepsin will deny them the possibility of having a clinically useful response to pralatrexate. pERC is recommending that pralatrexate be funded for the treatment of patients with relapsed PTCL when they have not previously received romidepsin, presumably to address their unmet need. It seems contradictory to deny access to pralatrexate when the patient has already received romidepsin when such patients have an even greater unmet need but no diminished likelihood of responding to the pralatrexate.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit from the use of pralatrexate in the treatment of symptomatic patients with rrPTCL. This conclusion is based on:

- Data from one phase 2 clinical trial of pralatrexate[1] for patients with PTCL who had relapsed or were refractory to at least one prior systemic therapy.
    - An ORR of 29% in trial patients
    - CR/CR unconfirmed rate of 11%
    - Median DOR of approximately 10 months
    - Median PFS of 3.5 months
    - Median OS of 14.5 months
    - Acceptable level of AEs
- Two ITCs: one in which pralatrexate provided superior control of rrPTCL when compared with a matched set of historical control patients treated with a variety of systemic agents; and a second in which pralatrexate provided equivalent control of rrPTCL patients treated with romidepsin.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma CGP. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

PTCLs are a heterogeneous group of non-Hodgkin lymphomas, collectively comprising 5-10% of all non-Hodgkin lymphomas in Canada. The term PTCL is used to denote a family of mature T-cell lymphoid malignancies with relatively aggressive behaviour including, in order of frequency of diagnosis in Canada, peripheral T-cell lymphoma, PTCL NOS; AITL; ALCL (both ALK [anaplastic large cell kinase]-positive and ALK-negative subtypes); extranodal Natural Killer (N/K)/T-cell lymphoma, nasal type; enteropathy associated T-cell lymphoma (EATL); hepatosplenic T-cell lymphoma; and subcutaneous panniculitis-like T-cell lymphoma (SPTCL).[24] The most common histological subtypes are PTCL NOS, AITL, and ALCL, comprising approximately 80% of all PTCLs.[14] As a group, PTCLs are considerably more treatment resistant and have inferior survivals compared to B-cell lymphomas. As examples, in the original 2008 publication of the International Peripheral T-cell Lymphoma Project, five-year survival rates were 32% for PTCL NOS and AITL, 70% for ALK-positive ALCL, 49% for ALK-negative ALCL, 20% for EATL and 7% for hepatosplenic T-cell lymphomas.[25] Like other lymphomas, PTCLs typically present with lymphadenopathy, hepatosplenomegaly, visceral or marrow involvement, and constitutional symptoms (weight loss, fever, night sweats). In addition, some PTCLs have characteristic clinical presentations, such as the rash, hemolysis, hypergammaglobulinemia, constitutional symptoms and hepatosplenomegaly seen in AITL;[24] gluten enteropathy with EATL;[24] nasal mass and extensive local invasion with extranodal NK/T-cell lymphoma, nasal type;[24] and painful subcutaneous nodules with subcutaneous panniculitis-like T-cell lymphoma.[24] Accurate diagnosis is necessary for appropriate clinical management and requires an adequate incisional or excisional biopsy and the experience and diagnostic techniques available to experienced hematopathologists.

Of the 8,300 annual incident cases of non-Hodgkin lymphoma in Canada, approximately 12% are of T-cell origin, therefore approximately 1,000, of which approximately900 fall into the categories typically included in the PTCL group described above.[26] Approximately 300 of these patients have stage 1 or 2 (limited stage) and 600, stage 3 or 4 disease (advanced stage)[i]. Since approximately half of patients with limited stage and 75% of patients with advanced stage PTCL harbor disease refractory to primary treatment or relapse after primary treatment (rrPTCL) it is reasonable to expect that approximately 600 new cases of rrPTCL will require management in Canada each year.

2.2 Accepted Clinical Practice

Historically, the treatment of PTCL has mirrored that of the more common B-cell lymphomas. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy or CHOP-like regimens have historically been considered the standard front-line therapy for PTCL, although these regimens are much less effective for PTCL than B-cell lymphomas.[25,27] More recent analysis suggests that anthracyclines (e.g., doxorubicin), the cornerstone of CHOP-like chemotherapy, may not impact treatment outcomes in PTCL.[25,27] The addition of etoposide has prolonged event-free but not OS, and some clinicians incorporate etoposide into front-line therapy as a result.[28] Phase 3 trials have been or are being conducted adding alemtuzumab, brentuximab vedotin, romidepsin or T-cell specific monoclonal antibodies to

[i] Extrapolated from the BC Cancer lymphoid cancer database.

CHOP induction;[16,28-30] however, none has shown sufficiently consistent improvement to be routinely included in standard practice.

High-dose chemotherapy and ASCT is sometimes incorporated into front-line therapy for PTCL, as consolidation of response to initial chemotherapy, or employed at the time of first relapse.[30-33] There are no phase 3 trials demonstrating the superiority of this approach over conventional dose chemotherapy, but the phase 2 results are sufficiently compelling for some clinicians to consider this approach as the best available therapy for fit patients, particularly in the poorer prognosis PTCL histologies.[30-33]

For extranodal NK/T-cell lymphoma, regimens incorporating L-asparaginase/ methotrexate/steroid and combinations of etoposide/ifosfamide/platinum agent/corticosteroid have become widely adopted rather than CHOP-like regimens.[34-37]

The goal of front-line therapy for PTCL is durable remission and hopefully cure. For patients with PTCL that has relapsed following front-line therapy or is refractory to initial therapy, autologous or allogeneic transplantation is often considered as consolidation if a response to conventional dose second-line therapy can be attained.[31-33] Long-term remissions have been achieved in the chemosensitive relapse setting with autologous or allogeneic transplant.

Despite front-line therapy and transplant as consolidation in first or second remission for selected patients, relapses are common with PTCL. For patients whose PTCL has relapsed or was refractory despite prior autologous and/or allogeneic transplant, or who are not candidates for transplant, conventional doses of anti-cancer drugs are frequently used, as single agents or in combination, largely based on phase 2 data or using regimens borrowed from those used to treat B-cell lymphomas. Results have generally been disappointing, with most regimens and new agents giving relatively low response rates, short response durations and poor survival rates. There are no randomized trials of treatment for rrPTCL to guide treatment choices. In Canada, commonly used agents include gemcitabine, cisplatin, oxaliplatin, etoposide, cyclophosphamide, methotrexate, romidepsin and etoposide. Brentuximab vedotin is also being assessed for its usefulness for CD30+ PTCL.

Apart from drug therapy, radiotherapy may be used as consolidation following systemic therapy for PTCL or palliation of localized, bulky or residual masses after chemotherapy. Radiotherapy is particularly important in the initial management of early stage extranodal NK/T-cell lymphoma.[37-39] Surgery has a limited role in the treatment of PTCL or other lymphomas being used primarily to establish the diagnosis.

The only agent that has been formally reviewed by pCODR for rrPTCL is romidepsin. In May 2015 pERC recommended funding of single-agent romidepsin for patients with rrPTCL who have received prior systemic treatment and are not candidates for high-dose chemotherapy and hematopoietic SCT to be used if a favourable response occurs for as long as that response is maintained without unacceptable toxicity. Subsequently, most provinces have provided such funding. If recommended for funding by pERC, pralatrexate will become the second agent recommended for this indication in Canada.

2.3 Evidence-Based Considerations for Funding Population

There will be about 8,300 new diagnoses of non-Hodgkin lymphoma (NHL) in Canada in 2018[40] of which there will be approximately 900 new cases of PTCL. At least two-thirds of these patients will experience rrPTCL and potentially become candidates for further therapy. Thus, it is reasonable to project that approximately a maximum of 600 patients may become candidates for pralatrexate treatment in Canada each year. Eligible patients would have rrPTCL despite at least one prior line of systemic therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

It is unlikely that pralatrexate will be used for any indications other than PTCL. It has no currently proposed uses for non-malignant diseases and is perceived to be of little use for types of lymphoma (B-cell non-Hodgkin lymphoma, Hodgkin lymphoma) other than PTCL since other more effective, better established agents are available. The possible exception is cutaneous T-cell lymphoma (CTCL), which is usually considered separately from the PTCLs and has been found to have modest responsiveness to pralatrexate.[41] In situations when all available standard agents currently in use for CTCL have been exhausted, clinicians may request access to pralatrexate. Given the rarity of CTCL and the availability of several other agents specific for this type of lymphoma any use of pralatrexate for CTCL will be quite limited.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Lymphoma Canada (LC) provided input on pralatrexate as treatment for PTCL and their input is summarized below.

LC conducted two anonymous online surveys—one for patients with PTCL and one for patients with PTCL who have experience with pralatrexate—from May 15 to June 10, 2018. Links to the surveys were sent via e-mail to patients registered on the LC database. The links were also made available via LC Twitter and Facebook accounts, Canadian and American Cancer Society message boards, Facebook groups organized for lymphoma patients and survivors, and international lymphoma organizations' own contacts. The surveys had a combination of multiple choice, rating and open ended questions. Open-ended responses to survey questions and quotes obtained from interviews were also included verbatim to provide a deeper understanding of patient perspectives.

LC noted that it had difficulty in finding patient respondents despite their effort. Overall, eight PTCL patients and one caregiver of a deceased PTCL patient provided input for this submission. Among the nine respondents, LC reported three have relapsed/refractory PTCL, three do not have rrPTCL, and three did not indicate whether or not they are rrPTCL. There were three PTCL patients and one caregiver of a patient with pralatrexate experience who responded to the survey, one of whom (patient respondent) also participated in a phone interview. The one caregiver included in the submission responded to the patient survey on behalf of a patient who passed away from PTCL. Therefore, this caregiver represented the perspective of a patient and not a caregiver. There were five PTCL patients without pralatrexate experience who responded to the survey. Four respondents identified as male, and three as female; their ages ranged from 25 years to 74 years. The remaining two respondents did not to provide this information. Of the nine respondents, three were from Canada (Ontario & Quebec), three were from the US, one was from Australia, and two did not provide information about their country location.

According to LC, there is a need for more choice in drug therapies for patients with 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. LC noted that patient respondents were willing to tolerate significant side effects in new drug therapies. 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 blood platelet counts.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with PTCL

All nine respondents answered the questions about their experience with PTCL.

The respondents to this survey were diagnosed with the following PTCL subtypes: AITL, human T-cell leukemia virus type 1 adult T-cell lymphoma/leukemia (HTLV1+ ATLL), SPTCL, or PTCL-NOS. Refer to *Table 4: Number of respondents with specified PTCL subtypes for more details.* Among

the nine respondents, LC reported that three have rrPTCL, three do not have rrPTCL, and three did not indicate whether or not they are rrPTCL.

Table 4: Number of respondents by PTCL subtypes.

PTCL Subtypes	Number of Respondents
AITL	3
HTLV1+	1
PTCL-NOS	2
SPTCL	1
AITL & PTCL-NOS	1
Not Specified	1

LC noted the following symptoms reported by respondents, which varied according to subtype: fatigue, swelling in the neck, armpit, groin, near ears or near elbows (due to enlarged lymph nodes), night sweats, rash, fever and weight loss. Bone marrow, liver, spleen, stomach and skin were also affected, according to some of the respondents.

The following were quotes from respondents:

- "*Fatigue was overwhelming. Rapid weight loss sapped my strength.*" (Male, 55-64, United States, AITL)
- "*When diagnosed, he was incredibly unwell and we didn't think he'd make it through. He had a massive disease burden and was hospitalised for weeks.*" (Caregiver to Male, 45-54, Australia, PTCL-NOS)
- "*Any swelling in lymph nodes now brings anxiety.*" (Female, 55-64, Canada, AITL)

3.1.2 Patients' Experiences with Current Therapy for PTCL

Seven of the nine respondents answered the questions about their experience with current therapies. According to LC, there is currently no standard of care for patients with most subtypes of PTCL who relapse after one or more lines of previous therapy. LC noted that anthracycline-containing regimens such as CHOP are commonly used. Refer to *Table 5: Reported Treatment by PTCL Subtype* for details related to the type of treatment received by patient respondents. Although most patients achieve a response with induction chemotherapy, responses are typically brief and many patients experience relapse or become refractory to treatment.

Table 5: Reported Treatment by PTCL Subtype.

PTCL Subtypes	Treatment by Subtype as Reported by Patients
AITL	CHOP, CHOEP, EPOCH, GVD, romidepsin, belinostat, alisertib, TREC, mesna, cyclophosphamide, fludarabine, allogeneic bone marrow/stem cell transplant
HTLV1+	Allogeneic bone marrow/stem cell transplant

PTCL Subtypes	Treatment by Subtype as Reported by Patients
PTCL-NOS	CHOEP, DHAP, allogeneic bone marrow/stem cell transplant
SPTCL	EPOCH
Abbreviations: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone) GVD (gemcitabine , vinorelbine , and pegylated liposomal doxorubicin) TREC (bendamustine, rituximab, etoposide, and carboplatin) DHAP (dexamethasone, high-dose cytarabine, cisplatin) EPOCH (etoposide-prednisone-Oncovin-cyclophosphamide-hydroxydaunorubicin)	

In terms of current therapy symptom management, when patient respondents were asked to rate how much their current therapies were able to manage their PTCL symptoms on a scale of 1 (Strongly Disagree) to 10 (Strongly Agree), the average score was 8. Further, more than 70% of respondents provided a score of '9' or '10', suggesting these patients were satisfied with their current symptom management. Some of the patient respondent comments include:

- "*I am just over one year out from my last treatment and am doing well, my oncologist said three years out is the best measure. Also, there is presently only one other option if it does return.*" (Female, 55-64, Canada, AITL)
- "*At present, the treatments have worked. However, I understand that the only way to truly ensure it does not come back is for a stem cell transplant which happens later this month.*" (Female, 35-44, Canada, HTLV1+)

With regard to side effects of current therapies, patient respondents identified a variety of side effects from their current therapies:

- "*Low immunity causing isolation. Nausea on first and last rounds of treatment. Insomnia. Neuropathy in one hand and mild concentration/brain fog issues.*" (Female, 55-64, Canada, AITL)
- "*CHOEP was hard on his body, DHAP was really rough and pralatrexate was really good apart from 2 bouts of mucositis which took about a week to reside.*" (Caregiver to Male, 45-54, Australia, PTCL-NOS)
- "*Positive : in remission! Negatives: osteoporosis, AVN from Prednisone, lung infection, daily 4-hr. IVs for two years, severe GVHD*" (Male, 55-64, United States, AITL) [GVHD = graft-versus-host disease]

Patient respondents also elaborated on the different ways in which these side effects interfered with day-to-day activities:

- "*Treatment consumed all my time and energy. Unable to work due to severe GVHD, 4-hr. IVs every day, need to keep away from public area.*" (Male, 55-64, United States, AITL)
- "*I was unable to work, volunteer, travel and fulfill some family obligations during treatment. Concentration was also an issue as my mind kept going back to my diagnosis and whether the treatment was working and would it be enough.*" (Male, 55-64, United States, AITL)

When patient respondents were asked about the importance of having choice in deciding which drug to take based on known side effects and expected outcomes of treatment, on a scale of 1 (Not Important as Long There is at Least One Treatment Choice) to 10 (Extremely Important to

Have Choice of Treatment), the average score was 8.25. Additionally, all respondents felt there is currently a need for more choice in drug therapies for patients with PTCL.

LC expressed that patient respondents were willing to tolerate significant side effects in new drug therapies. All respondents answered with '9' or '10' when asked if they would be willing to tolerate side effects with a new drug approved by Health Canada for the treatment of PTCL on a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects). When asked why they would be willing to tolerate these side effects, some of the patient respondents' comments included:

- "*Depending on the side effects that are possible, I think feeling poorly for a day or two but gaining time and quality of life in the longer run, is a fair trade*." (Female, 35-44, Canada, HTLV1+)
- "*I feel my life and family are worth trying whatever is available to best treat my cancer*." (Male, 55-64, United States, AITL)
- "*To survive*." (Male, 55-64, United States, AITL)

When patients were asked to rate how important it is for a new drug to be "able to control" specific aspects associated with their disease on a scale of 1 (Not important To Control) to 10 (Very Important To Control), all of the results were highly rated, with more importance assigned to bringing about remission and living longer (rated 10/10):

Importance of a New Drug to be 'Able to Control'	Rating Average
Bring about a remission	10
Control disease and symptoms associated with the disease	9.5
Live longer	10
Improve blood counts	8.8
Improve quality of life	8.8

According to LC, these results suggest that patient respondents prioritize longevity and disease control over other considerations.

When asked about other aspects of PTCL that they would consider as being important for a new drug to control, patient respondents commented:

- "*I would be looking for a substantial and immediate response from the lymphoma to the drug*" (Male, 65-74, United States, AITL & PTCL-NOS)
- "*Maybe skip CHOP, which had no effect but bad side effects, and go straight to second-line treatment*." (Male, 55-64, United States, AITL)
- "*I would like to see a drug that cures, instead of one that simply manages the symptoms*." (Female, 35-44, Canada, HTLV1+)
- "*All aspects are important for a healthy life, mentally and physically*." (Female, 55-64, Canada, AITL)

3.1.3 Impact of PTCL and Current Therapy on Caregivers

The one caregiver included in the submission responded to the patient survey on behalf of a patient who passed away from PTCL. Therefore, this caregiver represented the perspective of a patient and not a caregiver. Thus, no details on the impact of PTCL and current therapy on caregivers were included in the submission.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Pralatrexate

LC highlighted the following from the five patient respondents with experience with pralatrexate.

A male patient respondent from the United States, 65-74 years of age, completed the survey and was later interviewed. This patient was diagnosed in 2008 with AITL and PTCL-NOS. He was heavily pre-treated prior to his treatment with pralatrexate, including: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone), romidepsin, GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin), belinostat, alisertib, TREC, mesna, cyclophosphamide and fludarabine. He is currently in remission following an allo-transplant.

A male patient respondent from Australia, 45-54 years of age completed the survey. This patient was diagnosed in 2016 with PTCL-NOS and was pre-treated with six cycles of CHOEP and one cycle of DHAP (dexamethasone, high-dose cytarabine, P–cisplatin) prior to pralatrexate and an allotransplant. He went into complete remission within 6 weeks of using pralatrexate and remains cancer free. Comments are excerpted with his permission from a submission made to the Australian government supporting public funding for pralatrexate.

A female patient respondent from Sherbrooke, Quebec, 55-64 years of age, participated in the survey. She was diagnosed in 2017 and has been treated with 12 rounds of radiation in addition to pralatrexate and an unknown number of other therapies.

A fourth survey was completed by the mother of a male patient identified as 25-34 years of age who died from SPTCL. This patient was treated with EPOCH. The pralatrexate was used as a bridge to an allo-transplant.

In terms of side effects, LC noted that mouth sores and mucositis were the most commonly reported side effects, followed by anemia as well as low white blood cell and blood platelet counts. When asked about the tolerability of the side effects associated with pralatrexate on a scale of 1 (completely tolerable) to 10 (completely tolerable), patient respondents gave an average score of 5. Patient respondents commented that:

- "*My only side effects were a couple of episodes of mucositis which were pretty bad at the time. I had experienced severe mucositis whilst on CHOEP and so I was familiar with it. I just had to wait for the mucositis to run its course and get better, which it did.*" (Male, 45-54, Australia PTCL-NOS)

- "*[Side effects] weren't intolerable but they were a challenge*" (Male, 65-74, United States, AITL & PTCL-NOS)

Respondents were asked if they would recommend pralatrexate to other patients with PTCL based on their personal experiences. All three patient respondents who responded to this question responded 'Yes'. One patient respondent commented that:

- "*It worked and just didn't seem to be harsh on my body. It was a fast process as well with a weekly 10 minute infusion so I was only half a day not working each week. I stayed on it for months whilst waiting for my donor transplant and stayed in CR. After my initial mucositis, I had a near normal life back.*" (Male, 45-54, Australia PTCL-NOS)

3.3 Additional Information

LC expressed that the majority of PTCL patients will die from their disease within two years of diagnosis. LC highlighted that there has been little improvement in PTCL outcomes in the last two decades and that patients are in need of additional treatment options to prolong their life.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The PAG 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 nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pralatrexate for PTCL:

Clinical factors:

- Clarity of eligible patient population
- Place in therapy
- Comparison to romidepsin

Economic factors:

- Weekly dosing administration
- Drug wastage

Please see below for more details.

4.1 Currently Funded Treatments

The current standard of care for rrPTCL is romidepsin. PAG noted that the PROPEL trial being submitted for review is a phase 2 non-comparative trial and is seeking information on the comparison of pralatrexate with romidepsin.

4.2 Eligible Patient Population

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 pervious treatments used.

4.3 Implementation Factors

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 B_{12} injections also need to be administered intramuscularly and folic acid would need to be taken concomitantly.

PAG is also seeking clarify on the treatment duration.

4.4 Sequencing and Priority of Treatments

PAG noted that there are different therapies available for different histologic subtypes of T-cell lymphoma. PAG is seeking clarity on the place in therapy of pralatrexate among the different treatments available and the possible sequencing of treatments.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided: one from an individual oncologist and one group input.

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. Referring to this trial, clinicians stated that pralatrexate induced durable responses irrespective of age, histologic subtype, amount of prior therapy, prior methotrexate, and prior ASCT, making it an option worth considering for any patient with rrPTCL. It was also reported that toxicities seem to be manageable with pralatrexate. Clinicians providing input also noted that pralatrexate has a quick infusion time. 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 rrPTCL setting. No companion diagnostic testing is required.

Please see below for details from the clinician inputs. Quotes are reproduced as they appeared in the original input, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

5.1 Current Treatment(s) for rrPTCL

In one clinician input, it was stated that romidepsin or a first-line CHOP-based chemotherapy (e.g. CHOP – etopiside) is the current standard of care, while in the other clinician input, it was stated that there is currently no standard of care for rrPTCL in Canada. In one clinician input, it was reported that 75% of rrPTCL patients in the pivotal study for this therapy were non-responders, indicating limitations with romidepsin.

It was reported that for transplant-eligible patients with chemosensitive disease, consolidation with high dose chemotherapy/ASCT is often recommended following first relapse. It was stated that even when a transplant is appropriately offered, few patients will undergo a transplant due to having highly refractory and PD. To add to this, it was reported that allo-transplant may be considered in younger patients with refractory disease; however, its use is limited by availability of stem cell donors and toxicity related to graft-vs-host disease. It was also reported that for transplant-ineligible patients, participation in a clinical trial is recommended, and that palliative chemotherapy or romidepsin may also be prescribed.

In addition, one clinician noted that brentuximab vedotin has good efficacy in ALCL; however, systemic ALCL represents only 10% of the PTCL population, and the impact of brentuximab vedotin is more modest in other CD30+ PTCLs and most patients do not express this marker.

5.2 Eligible Patient Population

It was reported by the clinicians providing input that the patient population in the funding request meets the needs in the clinical practice setting. It was indicated that the population that would receive romidepsin (indicated as a current treatment) is very similar to the PROPEL study. Clinicians providing input noted that the PROPEL study included patients with all aggressive subtypes of PTCL, including challenging entities such as blastic N/K T-cell lymphoma, transformed mycosis fungoides, and HTLV-1 ATLL), which are often excluded from trials. It was indicated that the heavily treated population in the trial is

reflective of the patient population seen in clinical practice. Furthermore, clinicians stated that pralatrexate induced durable responses irrespective of age, histologic subtype, amount of prior therapy, prior methotrexate, and prior ASCT, making it an option worth considering for any patient with rrPTCL. It was also noted that pralatrexate provides an option as a bridge to SCT for patients who are chemo-insensitive.

According to one of the clinicians providing input, the criteria that patients must have received one prior therapy seems reasonable and that the population in the trial for romidepsin is very similar to the population in the trial for pralatrexate. It was also expressed that the PTCL category is used loosely in the pralatrexate trial, but seems reasonable.

5.3 Relevance to Clinical Practice

It was reported by the clinicians providing input that there is an unmet need for the specified patient population. More specifically, clinicians indicated that because most patients undergoing treatment for PTCL do not achieve complete remission or will ultimately relapse, consequently new therapies are needed.

Further to this, it was stated that patients who have PTCL have an inferior prognosis compared to patients who have aggressive B-cell lymphomas and that there has been little improvement in PTCL clinical outcomes in the last two decades. It was stated: "*Approximately 25% of patients experience a long-term remission following induction therapy and outcomes for relapsed PTCL are dismal—median PFS is less than 4 months and median OS is ~6.5 months.*"

It was noted that it is unclear, however, how pralatrexate compares to romidepsin. In terms of the benefit of this therapy, it was noted that pralatrexate has a quick infusion. In addition, clinicians noted that toxicities seemed comparable across the trials.

Clinicians felt that the major benefit from this therapy are high response rates and durable responses in a heavily pre-treated patient population. It was also reported that toxicities seem to be very manageable with pralatrexate. As well, it was noted that pralatrexate has an advantage compared to other therapy with respect to chair time.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

It was noted by one clinician that, currently, there are no data on sequencing. However, the other clinician providing input reported that pralatrexate would provide an additional treatment option to patients in the relapsed and refractory PTCL setting, in which the current therapies offer limited efficacy. The PROPEL trial was referenced, and it was indicated that, based on the trial, pralatrexate provides a viable treatment option as a bridge to SCT.

5.5 Companion Diagnostic Testing

None required.

5.6 Additional Information

No additional comments provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of pralatrexate (FOLOTYN) for the treatment of adult patients with rrPTCL.

Supplemental Questions most relevant to the pCODR review and to the PAG were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of a CMCA comparing patients treated with pralatrexate (PROPEL) to historical controls
- Critical appraisal of the Manufacturer's submitted MAIC comparing pralatrexate (PROPEL) to romidepsin (NCT00426764)

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. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6: Trial Selection Criteria.

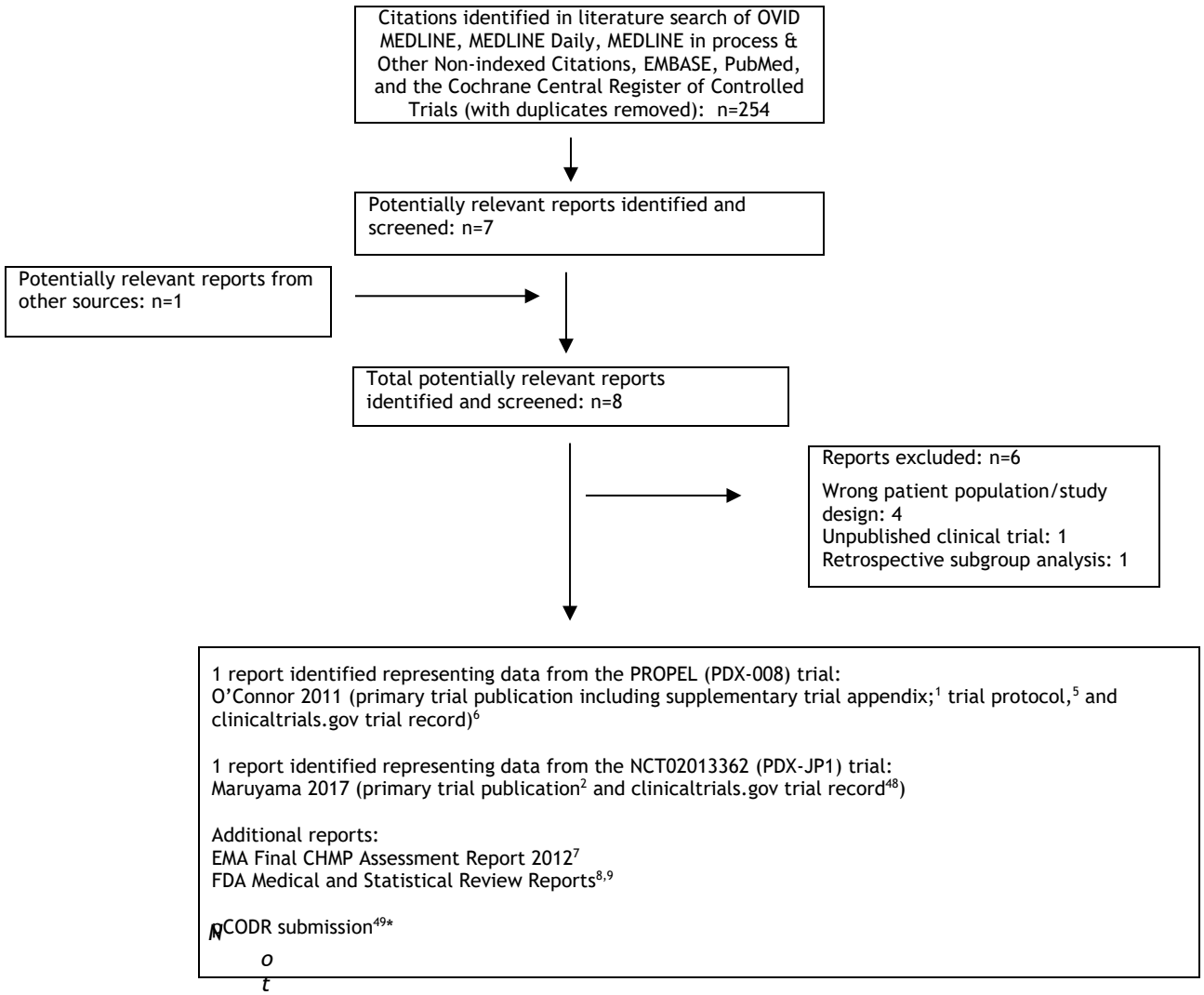
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs • In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of pralatrexate should be included	• Patients with PTCL who have documented disease progression after ≥1 prior systemic therapy	• Pralatrexate	• Romidepsin • Chemotherapy • Belinostat	• ORR • DOR • **OS** • **PFS** • HRQOL Safety • AEs • SAEs • WDAEs • Myeloid, GI and renal toxicities
Abbreviations: **AE(s)** – adverse event(s); **DOR** – duration of response; GI – gastrointestinal; **HRQOL** – health-related quality of life; **ORR** – objective response rate; **OS** – overall survival; **PFS** – progression-free survival; **PTCL** – peripheral T-cell lymphoma; **SAE(s)** – serious adverse events; **WDAEs** – withdrawals due to adverse events.				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Of the 255 potentially relevant reports identified, eight were selected for full-text review; of these, two were included in the pCODR systematic review[1,2] and six were excluded. Reports were excluded because they included the wrong patient population and/or study design,[42-45] they were unpublished clinical trials (only available in abstract form),[46] and reported results of a retrospective subgroup analysis of the PROPEL trial data.[47]

Figure 1. PRISMA Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to the PROPEL trial were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

Two clinical trials, PROPEL (PDX-008)[1] and NCT02013362 (PDX-JP1),[2] were identified that met the selection criteria of the pCODR systematic review. PROPEL (n=111) is the pivotal trial that was included as evidence in the pCODR submission. Comparatively, NCT02013362 (PDX-JP1) is a smaller trial (n=25) conducted solely in Japanese patients. Due to the small sample size of this trial and the associated risk of providing unreliable estimates of efficacy,[3] the pCODR review and critical appraisal focused on the PROPEL trial. Data from NCT02013362 (PDX-JP1) have been summarized in this report for reference; and additional trial data, in terms of baseline characteristics, outcomes and safety, are available in Appendix B. Key characteristics of both trials, including design, eligibility criteria and outcomes of interest, are summarized in Table 7 below.

6.3.2.1 Detailed Trial Characteristics

a) Trials

PROPEL (PDX-008)[1]

PROPEL was a phase 2, non-randomized, single-group, open-label multi-centred international trial that evaluated the efficacy and safety of pralatrexate in patients with rrPTCL.[1] The trial was conducted in 25 centres in the United States (15), Europe (8) and Canada (2).[6] The trial included nine Canadian patients.[6]

Funding

The PROPEL trial was funded by Allos Therapeutics Inc. The trial authors were responsible for all aspects of trial conduct, including design, recruitment of patients, data collection, analysis and interpretation, and the final manuscript. Almost all trial authors reported potential conflicts of interest related to compensation from the Manufacturer for employment and stock ownership (one author), or consultancy fees, honoraria and research funding.

Eligibility Criteria

Patients enrolled in PROPEL met the following key criteria:

- Male or female, aged at least 18 years with PTCL according to the REAL WHO disease classification
- Disease progression after at least one prior therapy
- No upper limit on the number of previous therapies
- ECOG performance status of 0 to 2
- Patients who had prior allogeneic SCT were excluded

For a more detailed list of the key eligibility criteria used in the trial refer to Table 7.

Outcomes and Disease Assessment

The primary outcome of the trial was ORR (CR + CR unconfirmed + PR), which was assessed centrally by independent review of imaging and clinical data according to IWC developed by the National Cancer Institute-sponsored International Working Group. ORR was also assessed by treating investigators. The secondary outcomes of the trial included DOR, PFS, OS and safety. HRQOL was not evaluated.

PTCL was confirmed centrally based on a histopathologic evaluation and adjucated by an independent hematopathologist if required. After treatment was initiated, the first tumour response assessment was performed within seven days prior to the

first projected dose of the second treatment cycle; subsequent assessments were performed within seven days before the first projected dose of every even numbered cycle; therefore, response assessment occurred every 14 weeks (prior to cycles 4, 6, 8 etc.). After treatment imaging was performed every 12 weeks until disease progression or initiation of subsequent therapy. PD was documented according to trial site local practice; if PD was clearly documented, a confirmatory assessment was not required. Unscheduled tumour response assessments were also submitted for central review. Response evaluations included computed tomography (CT) imaging of the chest, neck, abdomen and pelvis, and other disease sites by imaging if applicable,[5] as well as physical examination with skin photography, bone marrow aspirate/biopsy (if indicated). Whole body positron emission tomography (PET) imaging was performed and evaluated as an exploratory analysis.

After treatment discontinuation, patients attended a safety visit within 35 days (±5 days) of the last dose of pralatrexate, and then entered follow-up, with visits occurring every three months (±2 weeks) until PD or subsequent treatment. If subsequent treatment for PTCL was initiated, patients were then followed for OS every six months for up to two years after the first dose of pralatrexate.

Table 7: Summary of Key Trial Characteristics of the Included PROPEL (PDX-008)[1] and NCT02013362 (PDX-JP1)[2] trials.

Trial Design	Eligibility Criteria	Intervention	Trial Outcomes
PROPEL (PDX-008) NCT00364923 Phase 2, non-randomized, single-group, open-label trial N enrolled=115 N treated=111 (safety) N evaluable=109 (efficacy) 25 centres in US (n=15), Europe (N=8) and Canada (N=2)[6] Patient Enrolment: August 2006 to April 2008 Data cut-off dates: • January 2009[6] • August 2009 Trial completion date: February 2012[6] Funding: Allos Therapeutics Inc.[5]	<u>Key Inclusion Criteria:</u> • ≥ 18 years of age with PTCL according to the REAL WHO disease classification[a] • Documented disease progression after ≥1 prior treatment and recovered from toxic effects of prior therapy • At least 4-weeks between receipt of prior chemotherapy or radiation therapy and initiation of pralatrexate • No upper limit on number previous therapies • ECOG performance status ≤2 • Adequate hematologic, hepatic, and renal function[b] • Patients with pleural effusions or ascites were permitted on study • Informed consent[5] <u>Key Exclusion Criteria:</u> • Other pre-specified T/NK-cell neoplasms[d] • Active concurrent malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix); if history of prior malignancy, patient must be disease-free for ≥5 years[5] • CHF class III/IV according to NYHA heart failure guidelines; or uncontrolled hypertension[5] • Brain or CNS metastases[5] • Prior allogeneic SCT • Relapse less than 75 days post-ASCT • Major surgery within 2 weeks of study entry • Investigational drugs, biologics, or devices as the only prior therapy • Any conventional chemotherapy or radiation therapy ≤ 4 weeks before study treatment • Receipt of corticosteroids ≤ 7 days before study treatment, unless taking continuous dose of ≤ 10 mg/day of prednisone for at least 1 month • Previous exposure to pralatrexate[5] • Pregnant or lactating	• Pralatrexate IV push over 3-5 minutes at 30 mg/m^2 for 6 weeks followed by 1 week rest (7-week cycle), with treatment continuing until PD, unacceptable toxicity or patient/physician decision. • Maximum duration of 2 years[5] • Vitamin supplementation of B_{12} 1 mg IM every 8-10 weeks and daily folic acid 1.0-1.25 mg per day[5] required to improve mucositis[c]	<u>Primary:</u> • ORR (CR+CRU+PR)[e] <u>Secondary:</u> • DOR • PFS • OS
NCT02013362 (PDX-JP1) Phase 1/2, non-randomized, single-group, open-label	<u>Key Inclusion Criteria:</u> • ≥ 20 years of age with histologically confirmed PTCL according to 2008 WHO disease classification[f] • Relapsed or refractory disease after	• Pralatrexate IV push over 3-5 minutes at 30 mg/m^2 for 6 weeks followed by 1 week rest (7-week cycle), with	<u>Primary:</u> • ORR (CR + PR)[i] <u>Secondary:</u>

trial N enrolled=25 • Phase 1 (n=3) • Phase 2 (n=22) N treated=25 (safety) N evaluable=20 (efficacy) 12 centres in Japan[48] Patient Enrolment: • March 2014 to September 2015 Data cut-off date: • December 28, 2015 Trial completion date: • September 2017[48] Funding: Mundipharma K.K.	≥1 prior antitumour therapy • Measurable disease >1.5 cm in diameter by CT according to IWC • At least 21 days between receipt of prior chemotherapy, high-dose systemic corticosteroid therapy or radiation therapy and initiation of pralatrexate; and at least 100 days for antibody therapy or ASCT • ECOG performance status ≤2 • Adequate hematologic, hepatic, and renal function[g] • Informed consent <u>Key Exclusion Criteria:</u> • Previous exposure to pralatrexate • Active concurrent cancers or history of other cancer within previous five years • Active or history of brain or CNS metastases • Prior allogeneic SCT • Severe CVD • Uncontrolled hypertension or diabetes mellitus despite adequate therapy • Positive CMV or HBV surface antigen test • Positive hepatitis C virus or HIV antibody test • Positive HBV surface or HBV core antibody test with results above the detection sensitivity of the HBV-DNA quantitative test • Infectious disease currently required IV antibiotics or antifungal or antiviral treatment • Interstitial pneumonia or pulmonary fibrosis • Pregnant or lactating	treatment continuing until PD, unacceptable toxicity, drug omissions due to AEs for three consecutive visits, pregnancy, patient/physician decision, withdrawal of consent • Vitamin supplementation of B_{12} 1.0 mg IM every 8-10 weeks and daily folic acid 1.0-1.25 mg per day until 30 days after last dose[h]	• ORR by investigator assessment • ORR by FDG-PET/CT • DOR and time-to-response • PFS • OS

Abbreviations: **ASCT** – autologous stem cell transplant; **CHF** – congestive heart failure; **CMV** – cytomegalovirus; **CR** – complete response; **CRU** – complete response unconfirmed; **CT** – computed tomography; **CVD** – cardiovascular disease; **DNA** – deoxyribonucleic acid; **DOR** – duration of response; **FDG** –fluorodeoxyglucose; HIV - human immunodeficiency virus; **HBV** – hepatitis B virus; **IM** – intramuscular; **IV** – intravenous; **T/NK** – T-cell/natural killer cell; **NYHA** – New York Heart Association; **ORR** – overall response rate; **PD** – progressive disease; **PFS** – progression-free survival; **PR** – partial response; **PTCL** – peripheral T-cell lymphoma; **REAL** - Revised American Lymphoma; **SCT** – stem cell transplant; **WHO** – World Health Organization.

Notes:

[a] – T/NK-cell leukemia/lymphoma, adult T-cell lymphoma/leukemia (human T-cell leukemia virus [HTLV] 1+), angioimmunoblastic T-cell lymphoma, blastic NK lymphoma (with skin, lymph node, or visceral involvement), anaplastic large cell lymphoma, primary systemic type, PTCL – unspecified, T/NK-cell lymphoma – nasal, enteropathy-type intestinal lymphoma, hepatosplenic T-cell lymphoma, extranodal peripheral T/NK-cell lymphoma – unspecified, subcutaneous panniculitis T-cell lymphoma, transformed mycosis fungoides.

[b] – absolute neutrophil count ≥1000/μL, platelet count ≥100,000/μL, total bilirubin ≤1.5 mg/dL, AST and ALT ≤2.5 upper limit of normal, and creatine ≤1.5 mg/dL.

[c] - Elevated methylmalonic acid (>200 nmol/L) and/or homocysteine (>μmol/L) at screening required initiation of vitamins ≥10 days before the first dose of pralatrexate.

[d] – Other pre-specified T/NK-cell neoplasms include: precursor T/NK neoplasms (with the exception of blastic NK lymphoma), T-cell prophylactic leukemia, T-cell large granular lymphocytic leukemia, mycosis fungoides

(other than transformed mycosis fungoides), Sézary syndrome, primary cutaneous CD30+ disorders, including anaplastic large cell lymphoma and lymphomatoid papulosis.
[e] –Assessed by central review imaging and clinical data according to International Workshop Criteria (IWC) developed by the National Cancer Institute-sponsored International Working Group; and by PET imaging, which was for exploratory purposes.
[f] – PTCL – unspecified, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, extranodal T/NK-cell lymphoma, nasal type, enteropathy-associated TCL, hepatosplenic T-cell lymphoma, subcutaneous panniculitis T-cell lymphoma, and transformed mycosis fungoides.
[g] - Neutrophil count ≥1000/mm3 without granulocyte stimulating factor, platelet count ≥100,000/mm3 without blood transfusion, total bilirubin ≤1.5 mg/dL, AST and ALT ≤2.5 upper limit of normal, or <5 x upper limit of normal if hepatic involvement by lymphoma.
[h] - Recommended prevention and treatment of mucositis included professional oral care prior to initiation of study treatment, with ongoing consultation during study treatment.
[i] –Assessed by central review imaging and clinical data according to IWC.

Sample Size and Statistical Analyses

The required sample size of the PROPEL trial was determined using a 2-stage Simon design, which considered a ORR of 15% for the null hypothesis, and a ORR of 27% as the alternate hypothesis (Table 8). These response rates were chosen based on the assumption that a response rate of 20% was considered a good indication of activity with any new treatment in patients with PTCL. Under the 2-stage design, at least four of 35 enrolled patients had to experience a response (CR, CR unconfirmed, or PR) in stage 1 for the trial to proceed to stage 2. Patient enrollment was not stalled for this interim analysis.[50] In stage 2, an additional 65 patients would be enrolled. In order to reject the null hypothesis, a minimum of 23 out of 100 patients had to achieve a response in order to enable a 95% CI that excluded 15%. With 100 patients, the trial had 84% power to reject the null hypothesis.

The primary analysis of ORR, DOR and PFS were based on central review of tumour assessments; all evaluations that showed evidence of disease at screening were repeated for subsequent response assessments.[5] The primary efficacy analysis (ORR) was planned to occur once the last responding patient had at least six months of follow-up on their duration of response.

Efficacy analyses included all evaluable patients, which comprised of patients who received at least one dose of pralatrexate and met the major inclusion criterion of a centrally confirmed diagnosis of an allowed PTCL histopathologic subtype.[50]

The primary outcome of ORR was defined as the sum of CR, CR unconfirmed and PR by central review, divided by the number of patients. The 95% CI for the ORR was calculated using the binomial density function.[50] DOR was measured from the first day of documented response to PD or death. Patients who received subsequent therapy or withdrew consent prior to PD were censored at the last prior response assessment. Patients who discontinued treatment prior to PD or subsequent treatment without withdrawing consent were followed for disease status. The trial protocol also pre-specified subgroup analyses of the primary outcome according to the following patient groups: age (<65 versus ≥65 years), race (white versus non-white, with the possibility of adding categories), and gender. It was noted in the protocol that additional subgroups may be considered.[50]

PFS and OS were measured from the first day of treatment until an event (PD or death, respectively) or censoring, whichever occurred first; both outcomes were estimated using the product-limit estimator.[50] Patients undergoing transplant or any other subsequent therapy prior to documentation of PD were censored for PFS.

The analysis of safety was carried out on all patients who received at least one dose of pralatrexate (n=111). AEs were graded according to National Cancer Institute toxicity criteria for AEs version 3.0 and coded according to MedDRA version 11.0.

The primary efficacy analysis (and regulatory approval) of the PROPEL trial was based on a DBL of January 2009. An updated efficacy analysis was performed with a DBL date of August 2009, which corresponds to the trial publication.[1] Reporting of trial results in this report is focused on the trial publication; however, efficacy results of the primary analysis have been included for reference. Of note, an interim analysis of the data (DBL unknown) was used to inform the pharmacoeconomic (PE) model and report submitted for this pCODR submission;[51] however, these data have not been included in this report due to limited (abstract-level) reporting but they align with results of the January and August DBLs.

Additional public data sources (European Medicines Agency [EMA] and FDA reports) have also been referenced to augment reporting.[7-9]

Protocol Amendments

A total of six amendments were made to the PROPEL trial protocol.[7] One amendment, amendment 6, was made after patients were enrolled into the trial; this amendment permitted treatment beyond 24 months if patients were judged by the treating investigator to be experiencing clinical benefit.

Table 8: Select quality characteristics of the PROPEL trial.

Trial Quality Characteristics	PROPEL Trial (PDX-008)[1]
Treatment versus Comparator	• Pralatrexate monotherapy • Non-comparative (no control group)
Primary outcome	• ORR (central review by IWC)
Required sample size	• 2-stage Simon design • Required sample size was based on a null hypothesis of a true response rate of 15% and an alternative hypothesis of 27% • Stage 1 (interim analysis): at least 4 out of 35 patients were required to experience a response (CR, Cru, or PR) for the trial to move onto stage 2 • Stage 2 (primary analysis): 65 additional evaluable patients were enrolled; and at least 23 of 100 patients were required to have a response to enable a 95% CI to exclude the ORR=15% • Stage 2 of the trial had 84% power to reject the null hypothesis
Randomization method	• Not applicable
Allocation concealment (yes/no)	• No
Blinding	• Open label • Central (independent) outcome assessment
ITT analysis (yes/no)	• No
Efficacy analyses	• Efficacy analyses were pre-specified to occur after all patients had been followed for a minimum of one year after enrollment or until study endpoints were met, whichever occurred first. • Primary efficacy analysis DBL: January 2009 • Updated efficacy analysis DBL: August 2009 (trial publication)
Final analysis (yes/no)	• Yes
Early termination (yes/no)	• No
Ethics approval (yes/no)	• Yes
Abbreviations: CI – confidence interval; **CR** – complete response; **CRu** – complete response unconfirmed; **DBL** – database lock; **ITT** – intent-to-treat; **IWC** – International Workshop Criteria; **ORR** – overall response rate; **PR** – partial response.	

NCT02013362 (PDX-JP1)[2]

Trial NCT02013362[2] was an open-label, non-randomized, multicentre phase 1/2 trial, which proceeded PROPEL, and enrolled patients between March 2014 and September 2015 from 12 centres in Japan. The phase 2 portion of the trial was designed to evaluate the efficacy and safety of pralatrexate in patients with rrPTCL after at least one prior anti-tumour therapy. The trial was funded by Mundipharma K.K.

The key eligibility criteria of the trial are summarized in Table 7, and closely align with the inclusion and exclusion criteria used in the PROPEL trial.

The primary outcome was ORR (CR + PR) based on CT imaging and assessed by independent central review. Secondary outcomes included ORR by investigator assessment, ORR by fludeoxyglucose (FDG)-PET/CT, DOR, PFS, OS and safety. Response to treatment was assessed by CT and FDG-PET/CT at week seven of odd-numbered cycles according to IWC and Revised Response Criteria for Malignant Lymphoma, respectively.

The trial's sample size was estimated based on the ORR obtained in the PROPEL trial (29% [95% CI, 21-39]); 18 patients were required to provide 80% power to detect an ORR that was above an alternative threshold of 10% with a one-sided alpha error of 0.1. The analyses of efficacy and safety were pre-specified to occur when all patients included in the phase 2 portion of the trial had completed three treatment cycles. Efficacy was evaluated in all patients who received at least one dose of pralatrexate, had a post-baseline efficacy assessment, and met all eligibility criteria. Safety was evaluated in all trial patients. Analyses were performed based on a DBL date of December 28, 2015.

b) Populations

PROPEL (PDX-008)[1]

The baseline characteristics of patients in the PROPEL trial are summarized in Table 9. Overall, it was reported that the baseline demographic and prognostic characteristics of included patients were reflective of patients with PTCL in the western hemisphere. The median age of the patient sample was approximately 58 years (range, 21 to 85), with 36% of patients over the age of 65.[7] The majority of patients were male (68%), white (72%), ECOG performance status of 0 or 1 (84%),[7] and had PTCL subtype NOS (53%). Most other PTCL subtypes were represented in the trial; the percentages of patients with other subtypes are available in Table 9. The median time from diagnosis of PTCL was 15.6 months. The patient sample was heavily pretreated at baseline with a median number of three prior systemic therapies (range, 1 to 13); and 18% of the trial population had been treated with ≥ five prior regimens.[7] 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%). Romidepsin was not identified as a prior therapy for any patient in the PROPEL trial. Among patients included in efficacy analyses (n=109), 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 enrollment in the trial.

Table 9: Baseline characteristics of patients included in the PROPEL trial.

Table 1. Baseline Characteristics of Patients

Parameter	Patients (N = 111) No.	%
Sex		
Male	76	68
Female	35	32
Ethnicity		
White	80	72
African American	14	13
Asian	6	5
Hispanic	9	8
Other	1	< 1
Unknown	1	< 1
Mean age, years	57.7	
Range	21-85	
≥ 65	40	36
Median No. of prior therapies for PTCL	3	
Range	1-13	
Median No. of prior systemic therapies for PTCL	3	
Range	1-12	
Type of prior therapy for PTCL		
Local therapy		
Radiation therapy	25	23
Photopheresis	10	9
Topical nitrogen mustard	4	4
Systemic therapy		
CHOP	78	70
Platinum-containing multi-agent chemotherapy	45	41
Non-platinum-containing multi-agent chemotherapy	43	39
Single-agent chemotherapy	36	32
Autologous stem cell transplant	18	16
Bexarotene	15	14
Other	13	12
Corticosteroids alone*	8	7
HyperCVAD	8	7
Denileukin diftitox	7	6
Systemic investigational agents	7	6
Histopathology per central review		
PTCL unspecified	59	53
Anaplastic large cell lymphoma, primary systemic type*	17	15
Angioimmunoblastic T-cell lymphoma	13	12
Transformed mycosis fungoides	12	11
Blastic NK lymphoma (with skin, lymph node, or visceral involvement)	4	4
Other	2†	2
T/NK-cell lymphoma nasal	2	2
Extranodal peripheral T/NK-cell lymphoma unspecified	1	< 1
Adult T-cell leukemia/lymphoma (HTLV-1+)	1	< 1

NOTE. Patients treated with corticosteroids alone received other systemic therapies.
Abbreviations: PTCL, peripheral T-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HyperCVAD, hyperfractionated cyclophosphamide with vincristine, doxorubicin, and corticosteroids; NK, natural killer; HTLV, human T-lymphotropic virus; ALK, anaplastic lymphoma kinase.
*Eleven patients were ALK negative, four were ALK positive, two did not have ALK status determined.
†Ineligible for study due to diagnosis of mycosis fungoides not transformed and nondiagnostic pathologic lymphoid infiltrate.

Source: O'Connor, O et al: J Clin Oncol, Vol.29 (9), 2011: 1182-1189.

NCT02013362 (PDX-JP1)[2]

The baseline characteristics of patients in phase 2 of the trial are summarized in Appendix B. The median age was 71 years (range, 42 to 83) with 72% of patients aged 65 years or older. Compared to the PROPEL trial, fewer histologic subtypes were included; the most common were PTCL-NOS (48%), AITL (36%), and ALCL ALK-negative (8%). Patients had received a median of three prior therapies (range, 1 to 8), with all patients having received chemotherapy and two patients had undergone prior ASCT. Just over half of patients (56%) had no evidence of response to their most recent prior therapy. All patients had an ECOG status of 0-1.

c) Interventions

PROPEL (PDX-008)[1]

Prior to the first dose of pralatrexate, MMA and HCy levels were assessed at screening to determine the need for vitamin supplementation. If MMA and HCy levels of patients were elevated at trial screening (>200 nmol/L and >10 µmol/L, respectively), vitamin supplementation of B_{12} (1 mg IM every 8 to 10 weeks) and folic acid (1.0 to 1.25 mg PO every day) were required for at least 10 days prior to pralatrexate administration. Once on study, all patients received vitamin supplementation for the duration of the treatment phase of the trial.[5] Pralatrexate was administered to patients as an intravenous push over three to five minutes at a dose of 30 mg/m^2 per week for six weeks followed by one week off treatment (seven week cycle).

Dose Delay, Dose Modification, and Treatment Duration

Dose delays and reductions of pralatrexate were permitted in the trial in the event of AEs, with protocol-specific guidelines for treatment modification.[5] Treatment was administered up to a maximum duration of two years, and was discontinued in the event of PD, initiation of other anti-cancer therapy, development of an AE indicating intolerance at the lowest study dose permitted in the trial (20 mg/m^2/week), three sequential missed doses or a ≥3 week lapse between doses due to AEs, withdrawal of consent, investigator/Sponsor decision, or death.[5]

It was reported that 68% of patients (n=76) remained at the target dose of pralatrexate (30 mg/m^2) for the duration of treatment, and the same proportion of patients had at least one missed dose due to AEs. Mucositis was identified as the most common reason for dose modification (23%; n=25). Abnormal liver function test results, thrombocytopenia, and fatigue (two patients each, 2%), and herpes zoster, leucopenia, neutropenia and rash pruritic (one patient each, 1%) caused dose modification much less frequently.

Among evaluable patients, the median duration of treatment with pralatrexate was 70 days (95% CI, 39 to 86) or 2.0 cycles;[4] and the median dose administered was 207.9 mg/m^2. The relative dose intensity (delivered versus planned doses administered) was 80%.[4] The FDA reported that 41% of trial patients (n=45) were off treatment before cycle 2; and 78% (n=85) were off treatment before cycle 4.[8]

Concomitant Procedures and Medications

The concomitant procedures/medications permitted in the trial (at the discretion of treating investigators) included platelet transfusions, antiemetics, erythropoietin, hematopoietic growth factors, appetite stimulating hormones, and prophylactic antibiotics.[5] The most frequently used concomitant medications used by patients in the trial were consistent with those used to treat AEs associated with pralatrexate administration, which included stomatological preparations (65%), drugs for peptic ulcer and gastro-esophageal reflux (56%), opioids (52%, antiemetic/anti-nauseants (52%), and analgesics/antipyretics (48%).[4] During treatment with pralatrexate the use of steroids was not allowed for prophylaxis or for treatment; as well, any additional therapy for T-cell lymphoma including radiation therapy, other cytotoxic agents, biologic, or immune response modifiers were prohibited.[7]

NCT02013362 (PDX-JP1)[2]

The dosing and administration of pralatrexate and vitamin supplementation in NCT02013362 (PDX-JP1) was the same as the PROPEL trial (Table 7). Patients

received a median of one treatment cycle (range, 1 to 9) and four doses (range, 1 to 48) of pralatrexate; median treatment duration was 49 days (range, 12 to 445). Dose reductions and missed doses due to AEs occurred in 27% (n=6) and 91% (n=20) of patients, respectively; and 55% (n=12) of patients were off treatment before cycle 2.

In terms of concomitant medications, professional oral care was administered to patients before and during study treatment for the prevention and treatment of mucositis. Prophylaxis against pneumocystis jiroveci pneumonia with sulfamethoxazole-trimethoprim and/or varicella zoster virus infection were permitted at the discretion of treating investigators.

d) Patient Disposition

PROPEL (PDX-008)[1]

Patient disposition in the PROPEL trial, based on the August 2009 DBL, is depicted in Figure 2.[7] A total of 130 patients were screened for enrollment into PROPEL, of whom 115 were enrolled. The reasons for the 15 screening failures related to patients not meeting inclusion criteria and refusal to participate/withdrawal of consent. Of the 115 enrolled patients, 111 patients received ≥1 dose of pralatrexate and were evaluable for safety and 109 patients were deemed evaluable for efficacy. Four patients did not receive allocated treatment and were excluded from the safety analysis; while two patients were excluded from the efficacy analysis for not having a centrally confirmed diagnosis of PTCL (Figure 2).

At the updated DBL there were four patients remaining on treatment and 105 who had discontinued.[7] The primary reason for treatment discontinuation was disease progression (n=64) followed by AEs (n=26); fewer patients discontinued due to investigator (n=8) or patient decision (n=6). A total of 27 patients remained on study; and 82 patients had terminated the study due to death (n=62), completion of the 24 month follow-up period (n=15) and other reasons (n=5).

Protocol Deviations

Major protocol deviations, which were deviations considered to potentially affect the overall inference and conclusions of the trial, occurred in a total of two patients (2%); both deviations related to the receipt of prohibited concomitant medications.[4]

Subsequent Treatment

After discontinuing treatment with pralatrexate, 69% of trial patients (n=75) went on to subsequent therapy.[8] The types of subsequent therapies received as first therapy after pralatrexate are summarized in Table 10 (based on the January 2009 DBL). Most patients received a combination chemotherapy regimen with or without a platinum agent (30%), followed by single-agent chemotherapy (13%). Six patients (6%) received a SCT as initial subsequent therapy; while 13 patients (12%) received a subsequent transplant any time post-pralatrexate treatment. The Submitter confirmed that one patient in the trial received romidepsin after treatment with pralatrexate.[4]

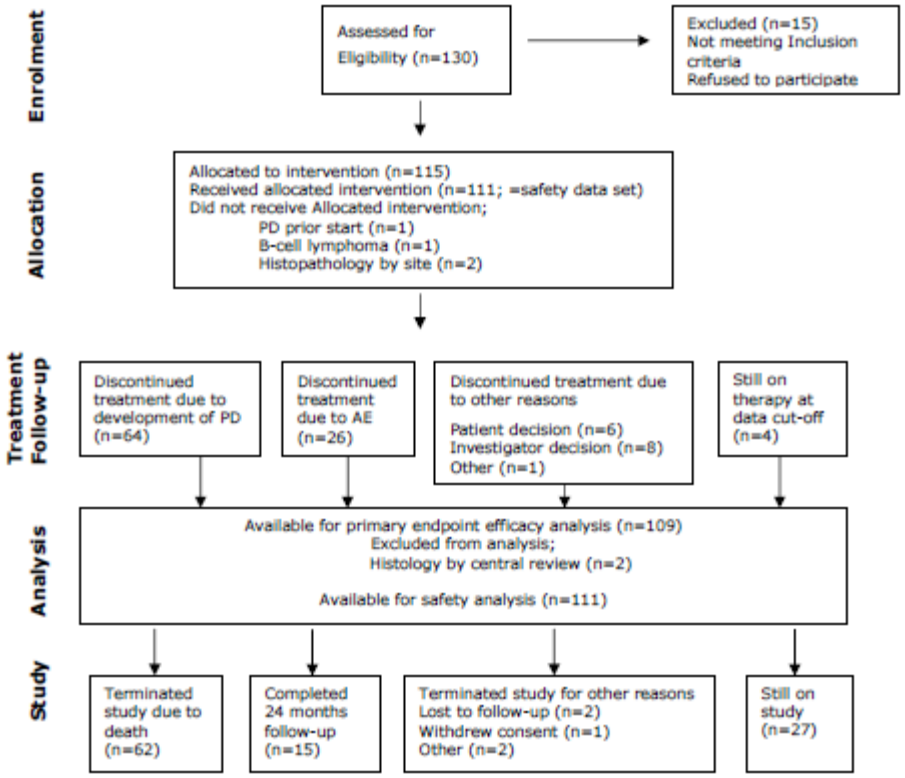


Figure 2: Patient disposition in the PROPEL trial (August 2009 DBL).[7]

Table 10: Subsequent therapies received by patients after treatment with pralatrexate in the PROPEL trial (January 2009 DBL).[8]

	Subsequent Therapy for PTCL	Efficacy Analysis Set (N=109) n (%)
Initial Subsequent Treatment for PTCL	Non platinum-containing multi-agent chemotherapy	19 (17)
	Platinum-containing multi-agent chemotherapy	14 (13)
	Single-agent chemotherapy	14 (13)
	Systemic investigational agents	8 (7)
	Stem cell transplant	6 (6)
	Radiation therapy with or without systemic treatment	4 (4)
	Steroids alone	4 (4)
	CHOP	2 (2)
	Other	2 (2)
	Bexarotene	1 (<1)
	Denileukin diftitox	1 (<1)
Subsequent Stem Cell Transplant at Any Time		13 (12)

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone

NCT02013362 (PDX-JP1)[2]

Of the 22 patients enrolled in the phase 2 portion of the trial, two were excluded from the analysis of efficacy for not having a centrally confirmed diagnosis of PTCL. Therefore the efficacy analysis was based on 20 evaluable patients, and the safety analysis was based on all patients treated with pralatrexate (n=25). At the time of the data cut-off date (DBL December 28, 2015) four patients remained on treatment. No other information on patient disposition, including any subsequent treatments received, was reported.

e) Limitations/Sources of Bias

The pCODR submission was based on data from the PROPEL trial, which was a global, single-group, open-label, phase 2 trial with no active treatment or placebo control group. The pCODR Methods Team acknowledges that the rarity and heterogeneity of rrPTCL, along with variability in the treatments used to treat the disease, pose challenges in terms of conducting trials with a more robust design. Nevertheless, ascertaining the magnitude of clinical benefit associated with pralatrexate based on the PROPEL trial evidence is difficult in the absence of a direct comparison to currently available options (e.g., romidepsin, chemotherapy), and considering other identified limitations, which include the following:

- The pCDOR Methods Team questions the appropriateness of attributing clinical benefit to pralatrexate on the basis of the primary outcome results (ORR determined by IWC criteria):
    - ORR is a surrogate outcome that may not translate to benefits in PFS and OS. The clinical benefit associated with the ORR obtained in the PROPEL trial, in terms of PFS and OS, cannot be confirmed since PFS and OS data are uninterpretable in a non-comparative trial design.
    - The FDA identified issues relating to the determination of tumour response in the trial (refer to proceeding section 6.3.2.2 under subheading “Issues with Response Determination and DOR identified by the FDA”) that raises doubt around the reliability of the tumour assessments that were performed. As well, due to the length of the time interval between imaging scans (14 weeks) and the absence of protocol mandated confirmatory scans, the FDA concluded a valid estimate of DOR could not be determined. The FDA calculated a durable response rate to estimate the clinical benefit of pralatrexate in the trial, which was calculated to be 12% (n=13; 95% CI, 7 to 20%) among a subgroup (approximately half; n=16/29) of the responding patients in the trial.
    - The ORRs obtained in the trial for patient subgroups should be interpreted with caution considering a lack of adjustment for multiple comparisons (type 1 error) and small sample sizes, which can lead to unreliable estimates.
- The median follow-up times considering all trial patients for both efficacy analyses (primary and updated) are unknown and could not be confirmed by the Submitter.

- The OS estimates obtained in the trial are confounded by the subsequent therapies received by patients after treatment with pralatrexate.
- Data on patient-reported HRQOL, an important outcome, was not collected in the trial; as such, the impact of pralatrexate on the HRQOL of patients in the trial is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

PROPEL (PDX-008)[1]

As previously indicated, the primary efficacy analysis of the PROPEL trial was based on a trial DBL of January 2009; and the updated efficacy analysis (PROPEL trial publication) was based on a DBL of August 2009.[1] The median follow-up times of both analyses, considering all trial patients, were not reported and could not be confirmed by the Submitter.[4] The median follow-up time of patients still alive at the updated analysis DBL was 18 months.[1] Of note, the efficacy results discussed below pertain to the updated analysis unless otherwise specified.

NCT02013362 (PDX-JP1)[2]

The primary efficacy analysis was based on a trial DBL of December 28, 2015. The primary outcome was assessed after three treatment cycles. For the assessment of OS, median follow-up time was 181 days for censored patients. The median follow-up time for the other time-to-event outcomes was not reported.

Efficacy Outcomes

PROPEL (PDX-008)[1]

ORR (primary outcome) and DOR

Table 11 summarizes the response outcomes obtained in the PROPEL trial by method of analysis (IWC, INV, and IWC plus PET) at the updated analysis August 2009 DBL.[1] For comparison, the primary analysis results are available in Table 12 (January DBL) and show response outcomes very similar to the updated analysis.[8]

The trial met its primary outcome at the primary analysis based on the a priori statistical hypotheses specified in the SAP. At the updated analysis, the ORR by IWC was 29% (n=32; 95% CI, 21% to 39%), and the confidence limits excluded the null value of 15%. The ORR by IWC was driven by PRs (18%; n=20), with fewer patients obtaining a CR (10%; n=11). The proportion of patients with SD (by IWC) was 19% (n=21). Of the 69 patients who did not have a response to their most recent prior therapy, 17 patients (25%) demonstrated a response to pralatrexate. Considering the 26 patients who were refractory to previous therapies, five (19%) responded to pralatrexate.

Among the various patient subgroups examined, the ORR ranged from 8% to 38% (Table 13). The ORRs obtained for the subgroups should be interpreted with caution considering a lack of adjustment for multiple comparisons (type 1 error) and small sample sizes, which can lead to unreliable estimates. The ORRs obtained by INV and IWC plus PET were 39% (95% CI not reported) and 26% (95% CI not reported), respectively (Table 11).

It was reported that the majority of responding patients achieved a response quickly; 63% of all responses occurred within the first treatment cycle of pralatrexate, and responses were also observed as late as treatment cycle 7. The

median DOR by IWC (among responders) was 10.1 months (95% CI, 3.4 months to not estimable; Figure 3B) or 306 days (range, 1 to 673). The median DOR for the other two methods of assessment was 12.7 months (IWC plus PET) and 8.1 months (INV).

Among the 32 responding patients, 16 (50%) progressed or died, five (16%) were alive and remained in response, and 11 (34%) were censored due to subsequent treatment (n=7), which included ASCT (n=2) and allogeneic SCT (n=2), or study termination (n=4). Of note, of the 11 patients who achieved a CR, there were two who developed PD.

Issues with Response Determination and DOR identified by the FDA

After its review of the primary efficacy analysis data on ORR (January 2009 DBL), the FDA noted major concerns related to the determination of response and DOR in the trial.[8,9] Tumour response was evaluated by imaging at the end of cycle one and every 14 weeks thereafter. The trial protocol did not require confirmatory imaging be performed after an initial response was designated by IWC criteria. Further, determination of PD was performed according to local practice at trial sites; and if PD was clearly documented, confirmatory scans were not required. The FDA cited that over half of responders (52%; n=15/29) had their responses adjucated due to disagreements between central reviewers, which raised concern over the reliability of response designation. The FDA was able to confirm IWC response for 16 of the 29 responders but not for the remaining 13 patients. Further, owing to the long interval between scans (end of cycle one, then every 14 weeks thereafter) which made it difficult to determine the true time of when a response or PD occurred, and that a majority of patients were designated responders by IWC at or prior to the first scan (69%; n=20), the FDA concluded a valid estimate of DOR could not be determined. Consequently, the FDA calculated a durable response rate to estimate the clinical benefit of pralatrexate in the trial, which was defined as the proportion of responses that lasted at least 14 weeks and was confirmed by a subsequent scan; the durable response rate was calculated to be 12% (n=13; 95% CI, 7 to 20%).

The Submitter indicated to the pCODR Methods Team that the analysis of PFS was not affected by the limitations associated with DOR since clinical progression lead to discontinuing patients from treatment and study, which preceded imaging determination.[4]

Subsequent Transplant

As indicated in Table 10 (subsequent therapies), there were six patients (6%) in the trial who proceeded to SCT as subsequent treatment after discontinuing pralatrexate. Five of these patients had a response to pralatrexate per IWC, and four were still in response when they went onto SCT. At the time of last follow-up, these four patients remained alive and had received no further therapy.[1]

Table 11. Response outcomes in the PROPEL trial based on the updated analysis August 2009 DBL.

Table 2. Best Response to Treatment and Time-to-Event Data

Response and Time to Event (Total N = 109)	Central Review: IWC No.	IWC %	IWC + PET No.	IWC + PET %	Local Investigator No.	Local Investigator %
Best response						
CR + CRu + PR	32	29	28	26	43	39
CR	11	10	15	14	17	16
CRu	1	1	0	0	3	3
PR	20	18	13	12	23	21
SD	21	19	18	17	21	19
PD	40	37	31	28	40	37
UE	2	2	18	17	0	0
Missing, off treatment in cycle 1	14	13	14	13	5	5
Time-to-event	32		28		43	
Median time to response, days						
First response	46		48		50	
Range	37-349		37-248		38-358	
Best response	141		136		51	
Range	37-726		37-542		38-542	
Median duration of response, months	10.1		12.7		8.1	
Median duration of response, days	306		386		246	

Abbreviations: IWC, International Workshop Criteria; PET, positron emission tomography; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease; UE, unevaluable.

Source: O'Connor, O et al: J Clin Oncol, Vol.29 (9), 2011: 1182-1189.

Table 12: Response outcomes in the PROPEL trial based on the primary efficacy analysis (January 2009 DBL).[8]

		Efficacy Analysis Set (N=109) n	(%)	(95% CI)
Best Response per Central Review - IWC	CR+CRu+PR	29	(27)	(19, 36)
	CR	7	(6)	
	CRu	2	(2)	
	PR	20	(18)	
	SD	24	(22)	
	PD	40	(37)	
	UE	2	(2)	
	Missing: off-treatment in cycle 1	14	(13)	
Best Response per Central Review - IWC+PET	CR+CRu+PR	26	(24)	(16, 33)
	CR	14	(13)	
	PR	12	(11)	
	SD	20	(18)	
	PD	31	(28)	
	UE	18	(17)	
	Missing: off-treatment in cycle 1	14	(13)	
Best Response per Local Investigator	CR+CRu+PR	42	(39)	(29, 48)
	CR	15	(14)	
	CRu	4	(4)	
	PR	23	(21)	
	SD	22	(20)	
	PD	40	(37)	
	UE: off-treatment in cycle 1	5	(5)	

CI = confidence interval; IWC = International Workshop Criteria; CR = complete response; CRu = complete response unconfirmed; PR = partial response; SD = stable disease; PD = progressive disease; UE = unevaluable; PET = positron emission tomography

Table 13: Response by patient subgroup in the PROPEL trial based on the updated analysis (August 2009 DBL).

Table 3. Response Analyses by Key Subsets

Parameter	No.	%	IWC Response Rate No.	IWC Response Rate %	95% CI
Region					
North America	85	78	27	32	22 to 43
Europe	24	22	5	21	7 to 42
Age, years					
< 65	70	64	19	27	17 to 39
≥ 65	39	36	13	33	19 to 50
Prior systemic therapy					
1 regimen	23	21	8	35	16 to 57
2 regimens	29	27	7	24	10 to 44
> 2 regimens	57	52	17	30	18 to 43
Prior transplant					
Yes	18	17	6	33	13 to 59
No	91	83	26	29	20 to 39
Prior methotrexate					
Yes	21	19	5	24	8 to 47
No	88	81	27	31	21 to 41
Histology					
PTCL NOS	59	54	19	32	21 to 46
Angioimmunoblastic	13	12	1	8	0 to 36
Anaplastic LC	17	16	6	35	14 to 62
Transformed MF	12	11	3	25	5 to 57
Other	8	7	3	38	9 to 76

Abbreviations: IWC, International Workshop Criteria; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; LC, large cell; MF, mycosis fungoides.

Source: O'Connor, O et al: J Clin Oncol, Vol.29 (9), 2011: 1182-1189.

PFS

At the time of the updated analysis a total of 70 (64%) PFS events (PD: n=63, 58%; death: n=7, 6%) had occurred; the remaining patients (n=39) were censored (based on central review of response using IWC) because they had not yet progressed (n=5; 5%), had received other anti-cancer therapy (n=26; 24%) prior to PD assessment, terminated study follow-up for response (n=4; 4%), and received a SCT (n=4; 4%).[7] The median PFS among evaluable patients was 3.5 months (95% CI, 1.7 to 4.8) and ranged from 1.0 to 23.9 months (Figure 2 C). The median PFS by INV was 4.0 months (range, 1 to 726 days).[7]

OS

A total of 62 deaths (57%) occurred in the trial; the remaining patients (n=47; 43%) were censored because they were still alive. The median OS was 14.5 months (95% CI, 10.6 to 22.5) and ranged from 1.0 to 24.1 months (Figure 2 D).

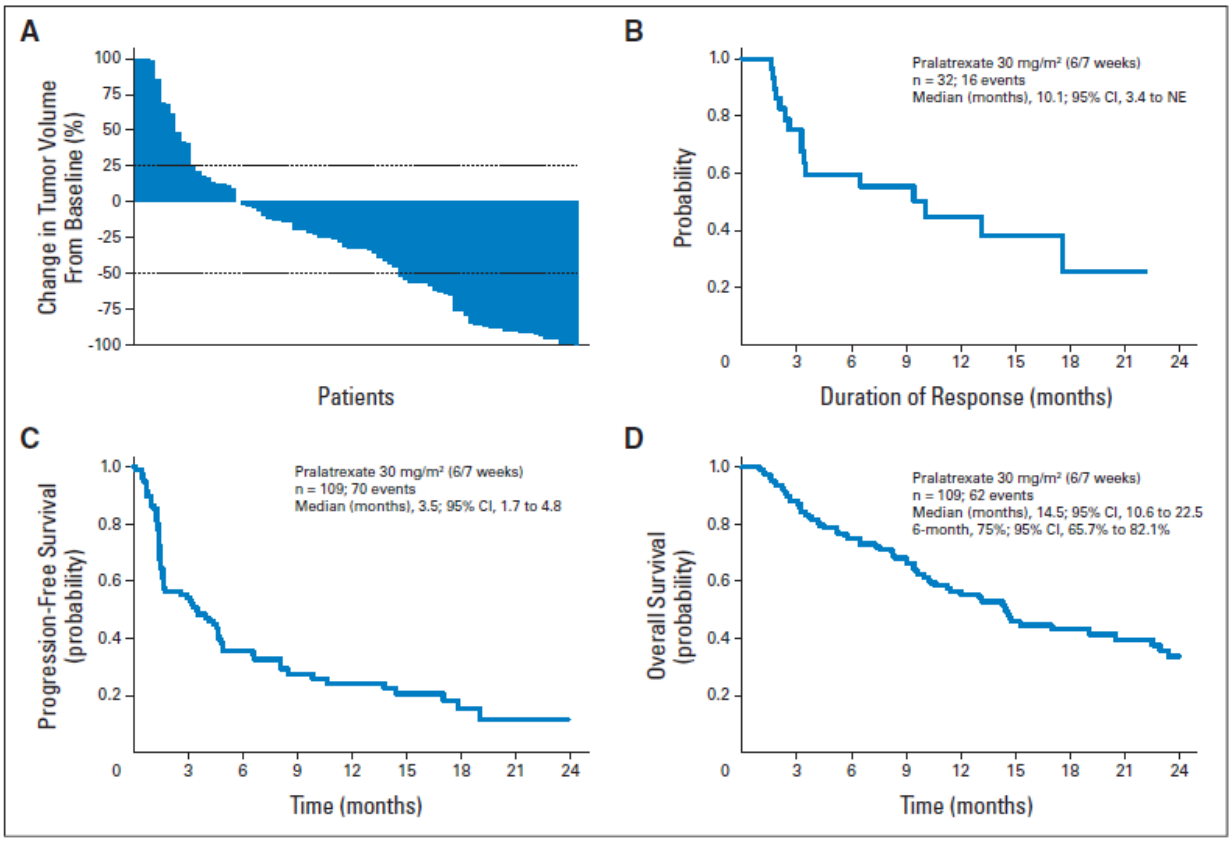


Fig 1. (A) Maximum change from baseline in tumor volume (sum of the products of the greatest diameter). (B) Kaplan-Meier estimate of duration of response per central review. (C) Kaplan-Meier estimate of progression-free survival per central review. (D) Kaplan-Meier estimate of overall survival per central review.

Figure 3: Kaplan Meier estimates of DOR (B), PFS (C), and OS (D) in the PROPEL trial.

Source: O'Connor, O et al: J Clin Oncol, Vol.29 (9), 2011: 1182-1189.

NCT02013362 (PDX-JP1)[2]

A summary of the efficacy outcomes of NCT02013362 are summarized in Appendix B. Among evaluable patients (n=20), the ORR by CT imaging and central review was 45% (n=9; 90% CI, 26% to 65%) and comprised of two CRs and seven PRs. In exploratory patient subgroup analyses, ORRs ranged from 25% to 71% but these analyses are based on very small numbers of patients (the number of patients in subgroups ranged from 2 to 16). The ORR by INV was also 45% (90% CI not reported). It was noted that including FDG-PET/CT imaging to response criteria did not change the results significantly (data not reported). Median DOR was not reached in the trial (range, 1 to 358 days); median PFS was approximately five months (150 days; 95% CI, 43 to 183) and median OS was not reached (range, 41 to 470 days). The number of deaths observed in the trial was not reported.

Harms Outcomes

PROPEL (PDX-008)[1]

The AEs, regardless of causality, occurring in ≥ 10% of patients in the PROPEL trial are summarized in Table 14. 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 ≥2 mucositis was 14 days. Other frequently reported AEs (e.g., pyrexia, constipation, edema) were generally mild to moderate in severity (Table 14). Most patients (n=106, 95%) experienced at least one AE that was considered by investigators to be possibly, probably, or definitely related to pralatrexate.[9] The frequency of 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.

Cumulative myelosuppression was not observed in the trial; thrombocytopenia, anemia and neutropenia were noted as rarely being symptomatic and requiring supportive measures; 15% and 10% of patients received a platelet transfusion and filgrastim, respectively.

Treatment discontinuations attributable to AEs occurred in 23% of patients (n=26); and mainly occurred due to mucositis (6%) and thrombocytopenia (5%). There were eight patient deaths within 30 days of the last dose of pralatrexate; seven patient deaths were attributed to PD and one patient died after cardiopulmonary arrest after approximately three weeks of their last dose of pralatrexate while hospitalized for mucositis and febrile neutropenia. This latter patient death was considered possibly related to study treatment.

Table 14: Adverse events reported in the PROPEL trial at the updated analysis (August 2009 DBL).

Table 4. Adverse Events (safety population) in ≥ 10% of Patients

Event	Total		Grade 3		Grade 4	
	No.	%	No.	%	No.	%
Any event	111	100	47	42	35	32
General events and administration site conditions						
Mucositis*	79	71	20	18	4	4
Fatigue	40	36	6	5	2	2
Pyrexia	38	34	1	1	1	1
Edema*	34	31	1	1	0	0
Hematologic events						
Thrombocytopenia*†	45	41	15	14	21	19
Anemia*	38	34	18	16	2	2
Neutropenia*	28	25	15	14	9	8
Leukopenia*	12	11	4	4	4	4
GI events						
Nausea	46	41	4	4	0	0
Constipation	38	34	0	0	0	0
Vomiting	28	25	2	2	0	0
Diarrhea	25	23	2	2	0	0
Dyspepsia*	11	10	0	0	0	0
Respiratory, thoracic, and mediastinal events						
Cough	32	29	1	1	0	0
Epistaxis	29	26	0	0	0	0
Dyspnea	21	19	8	7	0	0
Skin and subcutaneous tissue events						
Rash	17	15	0	0	0	0
Pruritus*	16	14	2	2	0	0
Night sweats	12	11	0	0	0	0
Infections						
Upper respiratory tract infection	12	11	1	1	0	0
Sinusitis	11	10	1	1	0	0
Other conditions						
Hypokalemia*	18	16	4	4	1	1
Anorexia*	18	16	3	3	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal*	14	13	6	5	0	0
Back pain	14	13	3	3	0	0
Abdominal pain	13	12	4	4	0	0
Headache	13	12	0	0	0	0
Pain in extremity	13	12	0	0	0	0
Asthenia	12	11	2	2	0	0
Tachycardia	11	10	0	0	0	0

NOTE. Patients could have > 1 adverse event. Included in this Table are all patients who received ≥ 1 dose of the study drug.
*Included a grouping of similar preferred terms.
†Platelet count < 10,000 μL was seen in five patients.

Source: O'Connor, O et al: J Clin Oncol, Vol.29 (9), 2011: 1182-1189.

NCT02013362 (PDX-JP1)[2]

Refer to Appendix B for a summary of the AEs that occurred in ≥ 20% of trial patients. All patients in the trial (n=25) experienced an AE. The most commonly reported AEs of any grade were mucositis (88%), thrombocytopenia (68%), liver function test abnormalities (64%), anemia (60%), and lymphopenia (56%), while the most common grade 3-4 AEs were lymphopenia (52%), thrombocytopenia (40%), and leukopenia (28%). SAEs were experienced by 48% of patients. Dose reductions, omissions, and treatment discontinuations attributable to AEs occurred in 28%, 88%, and 24% of patients, respectively. One patient death occurred due to pneumonia with underlying pulmonary infiltrate by PTCL and was not attributed to study treatment.

6.4 Ongoing Trials

No ongoing RCTs evaluating pralatrexate as monotherapy in rrPTCL were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of pralatrexate for the treatment of patients with rrPTCL:

- Critical appraisal of a CMCA comparing patients treated with pralatrexate (PROPEL) to historical controls
- Critical appraisal of the Manufacturer's submitted MAIC comparing pralatrexate (PROPEL) to romidepsin (NCT00426764)

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Case Match Control Analysis (CMCA)

7.1.1 Objective

In the absence of RCTs comparing pralatrexate to relevant comparators (romidepsin, chemotherapy), a CMCA was performed to provide an estimate of the treatment effect of pralatrexate compared to historical controls treated with conventional treatments. The CMCA was recently published by the PROPEL trial lead author and funded through a research grant from Spectrum Pharmaceuticals Inc.[10]

7.1.2 Findings

Rationale for CMCA

The ability to conduct RCTs, which is most often the regulatory standard for the approval of new cancer drugs, is challenging in rare and heterogeneous malignancies like PTCL. A strategy to assess or benchmark the potential OS benefit associated with new drugs in rare diseases is to conduct a CMCA based on large international databases of RWE. The aforementioned CMCA was performed to derive an estimate of OS in patients treated with pralatrexate in the PROPEL trial relative to historical controls identified from an international database that was comprised of RWE from four datasets (two in the United States, and one each in Europe and Korea).

Source

The recent publication of the CMCA was used as the basis of pCODR's review and critical appraisal; the Submitter could not confirm the DBL used in the analysis.[4]

Methods

Selection of Historical Controls

A total of 859 historical control patients with PTCL were identified from four datasets:

- MSKCC: 171 patients treated between June 1997 and July 2011
- UNMC: 67 patients diagnosed between July 1984 and May 2010
- GELA: 117 patients whose first-line treatment was administered under four clinical trials conducted between December 1997 and April 2008
- SMC: 504 patients contributed data; retrospective data were collected between 1995 and 2007, and prospectively collected data starting in 2008

Of the 859 historical control patients, 386 patients (69, 44, 110, and 163 from MSKCC, UNMC, GELA and SMC datasets, respectively) met the pre-specified selection criteria for inclusion into the CMCA; the criteria included the following:

- Histologies consistent with the inclusion criteria of the PROPEL trial
- Patients who received at least two prior therapies
- Patients who had not received pralatrexate

Reported efficacy outcomes were not considered as criteria to select patients as historical controls. Data on OS were reported in all four datasets while response rates and PFS were not collected in a consistent manner across the datasets, and therefore could not be analyzed. Table 15 summarizes the patients excluded from the CMCA based on the selection criteria. Most excluded patients were from the MSKCC and SMS datasets; exclusions were primarily based on receiving only one prior treatment regimen.

Table 15: Summary of patients excluded from historical control datasets.

Characteristics	MSKCC (n= 171)	UNMC (n= 67)	GELA (n= 117)	SMC (n= 504)
Histology not included in PROPEL	2	8	3	74
Only 1 regimen received	68	17	3	319
Received prior Pralatrexate	30	1	3	0
One or more of the above criteria	102	23	7	341

Source: O'Connor, O et al; Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study, JNCI Cancer Spectr, 2018, Volume 2, Issue 4, pky038, online supplement, by permission of Oxford University Press.

Matching and Statistical Analyses

The CMCA used propensity score matching to derive a comparative estimate of OS between patients treated with pralatrexate and historical controls.[52] The propensity score is a measure of the likelihood of treatment assignment (case or control) conditional on observed baseline characteristics; therefore, among a group of patients who have the same propensity score, the distribution of observed baseline characteristics will be approximately the same.[53] Thus, matching cases to controls on the propensity score serves to mimic randomization by balancing known (measured) baseline demographic and clinical characteristics in case and control groups and reduces any bias imposed by an imbalance in known prognostic variables and treatment effect modifiers.

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 rationale for the selection of the specific variables for matching was not provided. After a request for further information, the Submitter confirmed that variable selection was based on the eligibility criteria from the PROPEL trial and whether data were available across the different datasets. No statistical analyses were performed (e.g. multivariate regression model analyses) to identify a subset of variables most predictive of outcome to include for matching.[4] Further, it is unknown how missing data on variables used for matching were handled in the analysis.

A propensity score was generated using multivariate logistic regression for each patient in the dataset; the score, which ranges between 0 and 1, represents the relationship between multiple characteristics and the dependent variable (case or control) as a single characteristic. Matched sets of cases and controls (1:1) were derived using an "8 to 1 Digit Match" algorithm that makes "best" matches first and then "next-best" matches in a hierarchical sequence until no more matches can be made. Best matches are those with the highest digit match on the propensity score (8 digits). For those cases that do not match, cases are then matched to controls based on 7 digits of the propensity score, and so on sequentially, until the lowest digit match (1 digit).

Details of the statistical methods used to generate treatment effect estimates were not reported and could not be confirmed by the Submitter.[4] OS estimates derived from the CMCA were presented as HRs with corresponding 95% CIs. Subgroup analyses did not appear to be prospectively defined, however, they were performed by age interval (age at diagnosis in every 10 years and ≥ 65 years) and histological subtype (PTCL NOS and AITL).

A separate analysis was performed that was restricted to patients in the PROPEL trial in order to compare the PFS patients experienced with pralatrexate compared to prior systemic therapy. Using the methods of von Hoff, the PFS of patients on study treatment is compared to the PFS on their most recent line of therapy. In this analysis patients serve as their own control. If the resulting PFS ratio is greater than 1.3, the difference in outcome is considered statistically significant. This analysis is based on the premise that successive lines of treatment rarely produce greater clinical benefit than that observed with previous lines of treatment. The von Hoff analysis was used to assess PFS in the subgroup of patients in the trial with refractory disease (n=68) who responded to pralatrexate (n=16).

Results

The baseline characteristics of the 386 patients included in the CMCA from the PROPEL trial and historical controls prior to the matching process are summarized in Table 16.The mean age of patients ranged from 48.4 years to 55.9 years and most patients were male (range, 61.4%-69.9%). Compared to historical controls, patients in PROPEL were more heavily pretreated (median number of prior therapies was 4, compared to a median of 2-3 in historical controls) and had a longer median time from diagnosis (median 15.5 months, compared to 7.3 to 15.2 months in historical controls). Not every histological subtype of PTCL included in PROPEL was captured in each historical control data set but the major subtypes were represented across the databases (PTCL NOS, ranged from 34.4 to 63.6%; AITL, ranged from 4.5 to 50.0%; ALCL, ranged from 1.8 to 27.3%). Over 60 different prior treatment regimens were used across the four datasets with etoposide-containing regimens being the most frequently used, mostly in the form of ICE (ifosfamide, carboplatin, etoposide) chemotherapy.

The baseline characteristics of patients in the PROPEL trial and historical control dataset after the 8 to 1 digit match process was performed are summarized in Table 17. 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 successfulness of matching was based on an assessment of means and frequencies; standardized differences were not reported. Table 17 demonstrates that the matching process achieved balance between PROPEL and historical control patients for each variable selected for matching.

For the purpose of the von Hoff analysis, the outcomes of patients in the PROPEL trial as a function of line of prior therapy are available in Table 18. The PFS ratio obtained for the subset of patients with refractory disease who responded to pralatrexate was 4.63, which demonstrated superior PFS with pralatrexate compared to patients' most recent prior therapy

that was considered statistically significant and controlled for factors including number of lines prior treatment and histology.

Table 16: Baseline characteristics of historical control and PROPEL trial patients pre-matching.

Characteristics	MSKCC (n = 69)	UNMC (n = 44)	GELA (n = 110)	SMC (n = 163)	PROPEL (n = 109)
Age at diagnosis, y					
Mean	54.1	48.4	55.9	50.8	55.5
SD	17.44	13.09	14.02	13.83	14.36
Min–max	12–89	17–70	15–79	17–76	19–85
Sex, No. (%)					
Male	47 (68.1)	27 (61.4)	73 (66.4)	114 (69.9)	74 (67.9)
Female	22 (31.9)	17 (38.6)	37 (33.6)	49 (30.1)	35 (32.1)
Number of regimens No. (%) (including pralatrexate for PDX-008)					
2	37 (53.6)	21 (47.7)	55 (50.0)	76 (46.6)	23 (21.1)
3–4	24 (34.8)	21 (47.7)	49 (44.5)	87 (53.4)	52 (47.7)
≥5	8 (11.6)	2 (4.5)	6 (5.5)	0 (0.0)	34 (31.2)
Median	2.0	3.0	2.5	3.0	4.0
Min–max	2–7	2–15	2–5	2–4	2–12
Time from diagnosis to pralatrexate or last comparator therapy, months					
Median	11.0	7.5	15.2	7.3	15.5
Min–max	0.033–104	1.774–130.9	0.953–132.5	-23.1–99.42	0.854-322.4
N missing	0	1	0	0	0
Histology as per 2008 WHO classification, No. (%)					
Adult T-cell leukemia/lymphoma (HTLV 1+)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.9)
Anaplastic large cell lymphoma, primary systemic type	18 (26.1)	12 (27.3)	2 (1.8)	18 (11.0)	17 (15.6)
Angioimmunoblastic T-cell lymphoma	15 (21.7)	2 (4.5)	55 (50.0)	20 (12.3)	13 (11.9)
Blastic NK lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.7)
Enteropathy-type intestinal lymphoma	0 (0.0)	0 (0.0)	5 (4.5)	0 (0.0)	0 (0.0)
Extranodal peripheral T/NK-cell lymphoma unspecified	0 (0.0)	0 (0.0)	8 (7.3)	0 (0.0)	1 (0.9)
Hepatosplenic T-cell lymphoma	5 (7.2)	2 (4.5)	1 (0.9)	0 (0.0)	0 (0.0)
PTCL-unspecified	24 (34.8)	28 (63.6)	38 (34.5)	56 (34.4)	59 (54.1)
Subcutaneous panniculitis T-cell lymphoma	1 (1.4)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
T/NK-cell lymphoma nasal	3 (4.3)	0 (0.0)	0 (0.0)	68 (41.7)	2 (1.8)
Transformed mycosis fungoides	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	12 (11.0)
Histology classification (2008 WHO), No. (%)					
Cutaneous	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	12 (11.0)
Extranodal	9 (13.0)	2 (4.5)	15 (13.6)	68 (41.7)	7 (6.4)
Leukemic	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.9)
Nodal	57 (82.6)	42 (95.5)	95 (86.4)	94 (57.7)	89 (81.7)
Age at initiation of pralatrexate or last comparator therapy, y					
Mean	55.4	49.9	57.8	51.8	58.0
SD	17.40	13.66	14.45	14.10	14.19
Min–max	13–90	18–72	17–83	17–78	21–85
N missing	0	1	0	0	0
Response to any therapy, No. (%)					
No	7 (10.1)	6 (13.6)	19 (17.3)	79 (48.5)	21 (19.3)
Yes	62 (89.9)	38 (86.4)	91 (82.7)	84 (51.5)	88 (80.7)
Response to 2nd last therapy, No. (%)					
No	32 (46.4)	20 (45.5)	44 (40.0)	108 (66.3)	68 (62.4)
Yes	37 (53.6)	24 (54.5)	66 (60.0)	55 (33.7)	41 (37.6)

*GELA = Groupe d'Etude des Lymphomes de l'Adulte; MSKCC = Memorial Sloan Kettering Cancer Center; SMC = Samsung Medical Center; UNMC = University of Nebraska Medical Center; HTLV = Human T-cell Leukemia-Lymphoma Virus; NK = Natural Killer; WHO = World Health Organization; PTCL = peripheral T-cell lymphomas.

Source: O'Connor, O et al; Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study, JNCI Cancer Spectr, 2018, Volume 2, Issue 4, pky038, by permission of Oxford University Press.

Table 17: Baseline characteristics of historical control and PROPEL trial patients post-matching.

Matched variables	Control n = 80	PROPEL n = 80
Histology, No. (%)		
Adult T-cell leukemia/lymphoma (HTLV-1+)	0 (0.0)	1 (1.3)
Anaplastic large cell lymphoma, primary systemic type	12 (15.0)	13 (16.3)
Angioimmunoblastic T-cell lymphoma	12 (15.0)	12 (15.0)
Extranodal peripheral T/NK-cell lymphoma unspecified	0 (0.0)	1 (1.3)
PTCL-unspecified	52 (65.0)	49 (61.3)
T/NK-cell lymphoma nasal	2 (2.5)	2 (2.5)
Transformed mycosis fungoides	2 (2.5)	2 (2.5)
Sex, No. (%)		
Male	52 (65.0)	52 (65.0)
Female	28 (35.0)	28 (35.0)
Prior therapy, No. (%)		
1	19 (23.8)	20 (25.0)
2–3	47 (58.8)	46 (57.5)
≥4	14 (17.5)	14 (17.5)
Age at initiation of PROPEL or last comparator therapy		
Mean, y	55.8	58.2
Time from diagnosis to PROPEL or last comparator therapy		
Median, months	11.5	13.7

*HTLV = Human T-cell Leukemia-Lymphoma Virus; NK = Natural Killer; PTCL = peripheral T-cell lymphomas.

Source: O'Connor, O et al; Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study, JNCI Cancer Spectr, 2018, Volume 2, Issue 4, pky038, by permission of Oxford University Press.

Table 18: Outcomes of patients in the PROPEL trial as a function of line of prior therapy.

	One prior therapy n = 23		Two prior therapies n = 29		Three or more prior therapies n = 57	
Efficacy assessment	Central review	Investigator review	Central review	Investigator review	Central review	Investigator review
Overall response rate, No. (%)	8 (34.8)	10 (43.5)	7 (24.1)	11 (37.9)	17 (29.8)	23 (40.4)
Complete response, No. (%)	4 (17.4)	6 (26.1)	3 (10.3)	4 (13.8)	4 (7.0)	9 (15.8)
Progression free survival, mo	8	5.3	3.2	3.2	1.7	4.4
Duration of response, mo	NR	12.5	10	4.7	3.4	8.2

*NR = not reached.

Source: O'Connor, O et al; Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study, JNCI Cancer Spectr, 2018, Volume 2, Issue 4, pky038, by permission of Oxford University Press.

Overall Survival Analysis

The OS curves for patients in the individual historical control datasets and the PROPEL trial are shown in Figure 4. The OS KM curves clearly demonstrate overlap; the median OS (in months) of the MSKCC, UNMC, GELA, and SMC datasets was 6.1, 8.7, 4.2, and 3.7, respectively, compared to 14.7 in the PROPEL trial. It should be noted that the median OS estimates and curves do not account for differences in baseline characteristics between the five treatment groups.

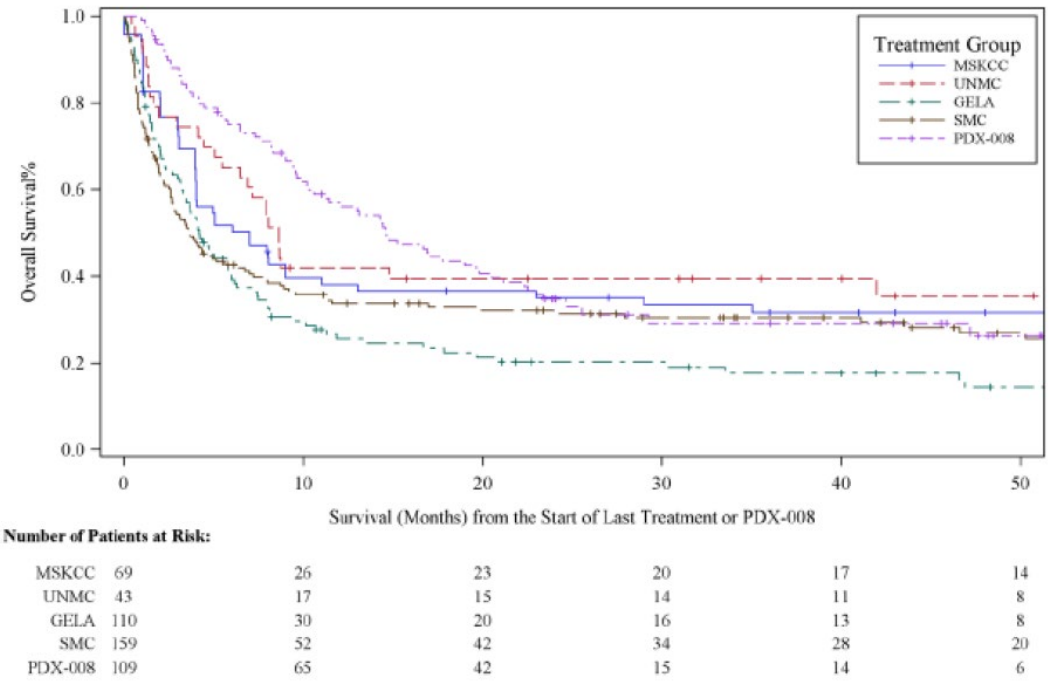


Figure 4: Overall survival (from start of last treatment) curves of individual historical control patient datasets and patients in the PROPEL trial treated with pralatrexate.

Source: O'Connor, O et al; Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study, JNCI Cancer Spectr, 2018, Volume 2, Issue 4, pky038, online supplement, by permission of Oxford University Press.

The OS curves for PROPEL trial patients treated with pralatrexate and matched historical control patients are shown in Figures 5 and 6. The CMCA, with patients matched on gender, number of prior treatments, age every 10 years, and WHO histology (n=162), produced an HR of 0.43 (95% CI, 0.30 to 0. 63), which suggests a significant OS benefit in favour of pralatrexate when compared to historical control treatments. The median OS estimate for patients treated with pralatrexate was 15.2 months (95% CI, 11.4 to 25.6) compared to 4.1 months (95% CI, 2.6 to 5.8) with control treatments. Figure 6 displays the results in patients matched for age ≥ 65 years (n=158); the CMCA produced an HR of 0.43 (95% CI, 0.29 to 0.63) in this patient subgroup. For patients with PTCL subtypes NOS (n=101) and AITL (n=24), the respective HRs for OS were 0.36 (95% CI, 0.23 to 0.58) and 0.45 (95% CI, 0.18 to 1.14).

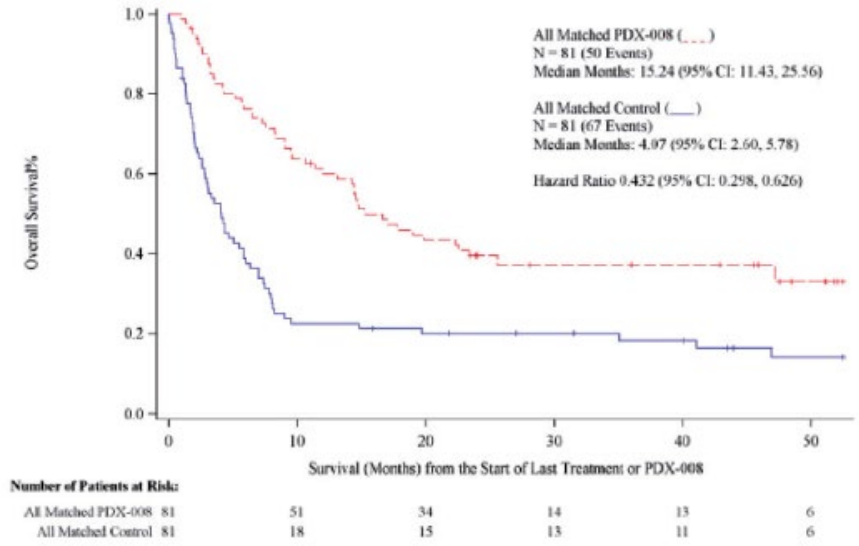


Figure 5: Overall survival (from start of last treatment) curves of patients treated in the PROPEL trial with pralatrexate versus historical control patients matched on gender, number of prior treatments, age every 10 years, and WHO histology.

Source: O'Connor, O et al; Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study, JNCI Cancer Spectr, 2018, Volume 2, Issue 4, pky038, by permission of Oxford University Press.

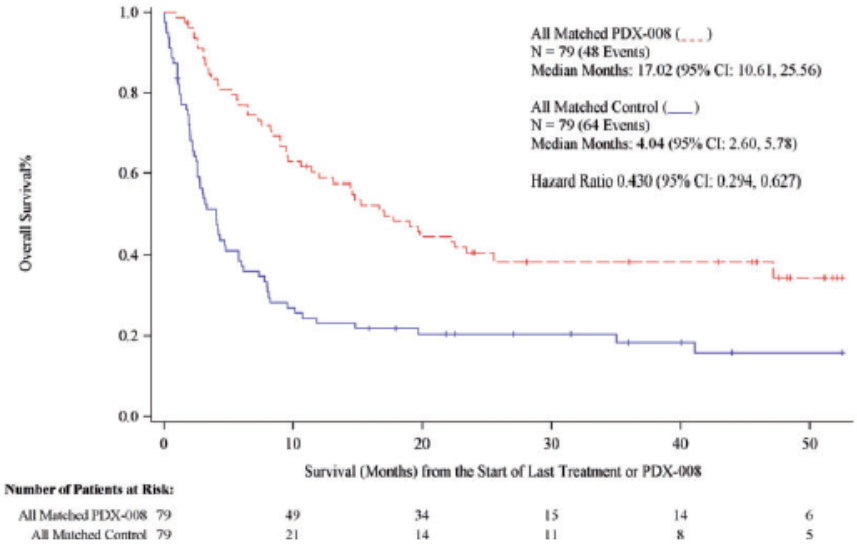


Figure 6: Overall survival (from start of last treatment) curves of patients treated in the PROPEL trial with pralatrexate versus historical control patients matched on gender, number of prior treatments, age ≥65 years, and WHO histology.

Source: O'Connor, O et al; Strategy for assessing new drug value in orphan diseases: an international case match control analysis of the PROPEL study, JNCI Cancer Spectr, 2018, Volume 2, Issue 4, pky038, by permission of Oxford University Press.

Critical Appraisal – Limitations and Sources of Bias

The quality of the CMCA was appraised according to best practice principals for ITC and matching using propensity scores.[53-55] The pCODR Methods Team identified a number of limitations of the CMCA, summarized below, which should be considered when interpreting the results.

- The CMCA indirectly compared outcomes in patients from the PROPEL trial to a historical cohort comprising of data from patients treated at four centres from 1984 to 2011. The retrospective nature of the historical data makes it highly prone to selection bias since it is unknown how patients were selected for treatment and information was not reported regarding any approaches used to mitigate bias.
- The results of the von Hoff analysis of PFS should be viewed cautiously as the PFS ratio can lead to biased estimates due to several factors including differences in PD and censoring definitions, and the exclusion of patients who die before progression and are lost to follow-up.[56] The analysis also focused on responders and not all patients.
- The methods used for the CMCA were appropriate and generally aligned with best practice; however, the following limitations regarding methodology should be noted:
    - In terms of the variables selected for matching, the Submitter confirmed that these were selected based on the PROPEL trial eligibility criteria for which data were available across all four datasets. Availability of data limited the number of variables for matching to four (histology, number of previous treatments received, age at diagnosis, and gender) and excluded other eligibility criteria including ECOG performance status, prior SCT, and other important variables, such as whether a patient was refractory to their most recent therapy. Consequently, differences between the treatment groups in these factors are not accounted for in the analysis and may confound the treatment effect estimates obtained.
    - There were gaps in reporting related to the statistical analyses performed to generate treatment effect estimates; specifically, it is unknown whether the statistical tests used accounted for the matched (paired) nature of the data.[53]

7.1.3 Summary

In the absence of RCTs comparing pralatrexate to relevant comparators (romidepsin, chemotherapy), a CMCA was performed to provide an estimate of the treatment effect of pralatrexate compared to historical control patients treated with conventional treatments (mainly chemotherapy).[10] The CMCA was funded through a research grant from Spectrum Pharmaceuticals Inc. Historical controls were identified from an international database that was comprised of RWE from four datasets (two in the United States, and one each in Europe and Korea). Only data on OS were analyzed since other outcomes of interest (response, PFS) were not collected in a consistent manner across datasets. The CMCA used propensity score matching 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 an HR of 0.43 (95% CI, 0.30 to 0. 63), suggesting a significant OS benefit in favour of pralatrexate when compared to historical control treatments. The median OS estimate for patients treated with pralatrexate was 15.2 months (95% CI, 11.4 to 25.6) compared to 4.1 months (95% CI, 2.6 to 5.8) with control treatments. The quality of the CMCA

was appraised according to best practice principals for ITC and matching using propensity scores. The pCODR Methods Team identified a number of limitations of the CMCA that should be considered when interpreting the results; the most significant of these included 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 obtained.

7.2 Matching Adjusted Indirect Comparison (MAIC)

7.2.1 Objective

In the absence of RCTs comparing pralatrexate to romidepsin, and to fulfill the pCODR request for comparative evidence between the two agents, the Submitter undertook a targeted review of clinical evidence and conducted an ITC in the form of a MAIC to evaluate the relative efficacy between pralatrexate and romidepsin.[11] Results of the MAIC were subsequently incorporated into the PE model to help inform cost-effectiveness estimates for pralatrexate.

7.2.2 Findings

Rationale for MAIC

Both the PAG and the pCODR CGP identified romidepsin as a relevant comparator to pralatrexate for rrPTCL. In Canada, romidepsin is approved (NOC/c) and has received funding in all but two CADTH participating provincial drug plans. Consequently, a comparison of the efficacy and safety of pralatrexate relative to romidepsin was deemed important to the current pCODR review. In the absence of direct evidence comparing the two agents, pCODR formally requested the Submitter provide an ITC.

Source

The MAIC was performed by the Submitter at the request of pCODR, and therefore has not been published or peer-reviewed. The Submitter's MAIC report was used as the basis of this review and critical appraisal.[11]

Methods

Trials Included in MAIC

Evidence for pralatrexate was from IPD derived from the phase 2 PROPEL trial, which is the pivotal trial informing the pCODR review. The details of the trial design have been previously described in Section 6 of this report. The MAIC was based on the efficacy results from 109 patients at the January 2009 DBL, at which point the median follow-up time for all patients who were still alive at the time of analysis was 18 months (median follow-up time considering all trial patients is unknown).[4]

One trial of romidepsin was identified by the literature search.[15] The methods used to locate and select evidence for inclusion were not described. The single trial of romidepsin in patients with rrPTCL was a single group, phase 2 trial (NCT00426764) that included 130 patients. In this trial, patients with centrally confirmed PTCL with adequate bone marrow and organ function, as well a meeting specific hematological criteria and an ECOG performance status of ≤2, received romidepsin at a dose of 14 mg/m^2 as a four-hour intravenous infusion on days 1, 8, and 15 for each 28 day cycle for up to six cycles. Patients with stable disease (SD), PR, or CR/CR uconfirmed could elect to extend therapy until PD or another treatment withdrawal criterion was met. Assessment of response was made by independent review using IWC criteria. The primary outcome of the trial was the rate of CR/CR unconfirmed. The secondary outcomes included ORR, DOR, time-to-progression, change in ECOG status, and PFS was also assessed.

The two trials included in the MAIC, PROPEL and NCT00426764, are summarized in Tables 19 (trial design) and 20 (baseline characteristics).

Table 19: Trials included in MAIC.

Trial ID	Study design (n)	Phase	Primary Outcome	Reference
Pralatrexate				
PROPEL	Single arm (n= 109)	II	Overall Response Rate	NCT00364923, O'Connor (2011)[1]
Romidepsin				
NCT00426764	Single arm (n = 130)	II	Rate of complete responses/unconfirmed complete responses as per independent review committee	NCT00426764 Coiffer (2012)[25] Coiffer (2014)[23]

The baseline characteristics of patients in the PROPEL and romidepsin trials were generally similar in terms of demographics (age, gender), with the exception of some numerical differences in the ethnicities of enrolled patients. In terms of clinical characteristics, median time since diagnosis was the same in each trial (approximately 1.3 years), and the proportions of patients within each ECOG status were generally similar between the trials, as were the proportions of patients who had prior transplant and were refractory to last therapy. In terms of notable differences, patients in PROPEL were more heavily pretreated compared to patients in the romidepsin trial (% of patients with ≥3 prior therapies was 52% in PROPEL versus 37%), and differences were observed in the proportions of patients with specific histology subtypes. Both trials enrolled a majority of PTCL-NOS, but PROPEL included a higher proportion of patients with the more aggressive transformed mycosis fungoides subtype (11% versus 1% in the romidepsin trial), while there were more patients with AITL in the romidepsin trial (21% versus 12% in the PROPEL trial). The trial populations appeared similar with respect to previous treatment histories.

Outcomes

The outcomes evaluated in the MAIC included OS and PFS; other important outcomes, including ORR, DOR, HRQOL and safety were not analyzed. The availability of outcome data of interest is summarized in Table 21. For the romidepsin trial, a curve for OS was not available nor was the PFS curve available for all patients in the trial (only for subgroups based on response status). In order to ensure a similar length of follow-up between the trials, the median OS and median PFS data from the updated analysis of the romidepsin trial were used.

Table 20: Baseline patient characteristics for included trials.

Characteristic	PROPEL (pralatrexate) n= 109	NCT00426764 (romidepsin) n = 130
Age, median (range)	59 (21 - 85)	61 (20 - 83)
Male, n (%)	74 (68)	88 (68)
White race/ethnicity (%)	79 (72)	116 (89)
ECOG, n (%)		
0	42 (39)	46 (35)
1	49 (45)	66 (51)
2	18 (17)	17 (13)
International Prognostic Index, n (%)		
<2	Not measured/reported	31 (24)
≥2	Not measured/reported	99 (76)
Prior systemic therapy regimens, n (%)		
1 regimen	23 (21)	38 (29)
2 regimens	29 (27)	44 (34)
≥3 regimens	57 (52)	48 (37)
Years since diagnosis, median (range)	1.3 (0.1 - 26.9)	1.3 (0.2 - 17.0)
Prior transplant, n (%)	18 (17)	21 (16)
Refractory to most recent therapy, n (%)	43 (39)	49 (38)
Type of prior therapy for PTCL, n (%)		
Chemotherapy	105 (95)	129 (99)
Monoclonal antibody therapy	26 (23)	20 (15)
Other type of immunotherapy	18 (16)	14 (11)
Histology based on central diagnosis, n (%)		
PTCL NOS	59 (54)	69 (53)
Anaplastic large cell lymphoma, primary systemic type	17 (16)	22 (17)
ALK-1 positive	Not reported	1 (1)
ALK-1 negative	Not reported	21 (16)
Angioimmunoblastic T-cell lymphoma	13 (12)	27 (21)
Transformed mycosis fungoides	12 (11)	1 (1)
Blastic natural killer (NK) lymphoma	4 (4)	0 (0)
Enteropathy-type T-cell lymphoma		6 (5)
T/NK-cell lymphoma nasal	2 (2)	1 (1)
Extranodal peripheral T/NK-cell lymphoma unspecified	1 (<1)	0 (0)
Adult T-cell leukemia/lymphoma (HTLV-1$^+$)	1 (<1)	0 (0)
Subcutaneous panniculitis-like T-cell lymphoma	0 (0)	3 (2)
Cutaneous gamma/delta T-cell lymphoma	0 (0)	1 (1)

Table 21: Available outcome data of interest in the included trials.

Treatment	Publication	Median Follow-Up Time	OS	PFS
Pralatrexate	PROPEL. O'Connor (2011)	18 months	KM, Median survival time	KM, Median event free time
Romidepsin	Coiffier (2012)[25]	13.4 months	Not reported	KM, Median event free time
Romidepsin	Coiffier (2014)[23]	22.3 months	Median survival time	Median event free time

Methods of MAIC

Since the included trials were single group, phase 2 trials that provided evidence in the form of IPD for one trial (PROPEL) and published aggregate data for the other (romidepsin), an anchored ITC (network meta-analysis) was not feasible. As a result, the comparative efficacy of pralatrexate to romidepsin was evaluated using both a naïve and MAIC.

A naïve ITC was performed to provide a reference case estimate of comparative efficacy between pralatrexate and romidepsin; this involved estimating an HR based on median PFS and OS. This type of ITC involves no adjustments for differences in baseline characteristics between trials.

A MAIC was performed following the methods of Signorovitch et al;[57] this method of analysis provides an estimate of relative treatment effect that has been adjusted to account for known imbalances in prognostic variables and/or treatment effect modifiers that can be influential on outcome. In the MAIC, IPD from the PROPEL trial were reweighted using inverse propensity score weights. The weights are assigned to each patient in the PROPEL trial, with the aim that the reweighted population matches the romidepsin trial in terms of the distributions of matched variables.

A disease expert consulted on the choice of relevant variables to include in the model and on validation of the final model, however, no statistical analyses (e.g., multivariate regression model analyses) were conducted to inform the final set of variables to use for matching.[4] Relevant known prognostic variables and treatment effect modifiers, for which data were available in both trials, were entered into a logistic propensity score model (using R software version 3.5.1). The following variables were included into the model for matching:

- Age (continuous in years)
- Sex (male or female)
- Race (white/non-white)
- ECOG performance status (0 or ≥1)
- Histopathology; recatagorized into the following key subtypes: PTCL NOS, AITL, ALCL (either ALK-1 positive or negative), and other subtypes
- Previous treatment exposure (>2 prior therapies versus ≤2 prior therapies); patients were defined as heavily pretreated if they had ≥3 previous therapies.
- Refractory to the most recent therapy (yes/no)
- Prior SCT (yes/no)

Details on the statistical method used to generate relative treatment effect estimates were not reported. After a request for additional information, the Submitter confirmed to pCODR that treatment effect was estimated as an HR determined by converting the median survival time into hazard rates. Associated CIs were calculated using an approximation of the standard error of the log HR based on the number of events of interest.

Results

Following matching, the effective sample size of patients treated with pralatrexate in the PROPEL trial was reduced by 25%, to 82.05. A comparison of baseline patient characteristics pre- and post-matching indicated the matching procedure was successful in achieving balance in the distribution of matched variables, with virtually no differences between the pralatrexate and romidepsin patient populations. The results of both the naïve ITC and the MAIC are presented in Table 22. For both OS and PFS, the naïve ITC results are consistent with the MAIC results with the former being of slightly greater magnitude. Both ITC analyses demonstrate no significant differences between pralatrexate and romidepsin for either outcome. The Kaplan Meier curves for the pralatrexate treated patients in PROPEL based on the MAIC and naïve ITC are presented for PFS and OS in Figures 7 and 8, respectively.

Table 22: Results of the naïve indirect treatment comparison and MAIC analyses.

Analysis	Outcome	HR for pralatrexate vs. romidepsin (95% CI)
Naïve ITC*	OS	0.78 (0.56-1.09)
	PFS	1.15 (0.85-1.56)
MAIC**	OS	0.88 (0.63-1.23)
	PFS	1.28 (0.94-1.73)
Abbreviations: CI – confidence interval; HR – hazard ratio; ITC – indirect treatment comparison; MAIC – matching adjusted indirect treatment comparison; OS – overall survival; PFS – progression-free survival; SCT – stem cell transplant.		
Notes: *Based on a sample size of 109 patients from the PROPEL trial and 130 patients from the romidepsin trial (NCT00426764). **Based on a post-matching effective sample size of 82.05; pralatrexate IPD were matched to the romidepsin trial data on the following variables: sex, race, age, PTCL subtype, >2 prior systemic therapies, ECOG performance status, refractory to most recent therapy, and prior SCT.		

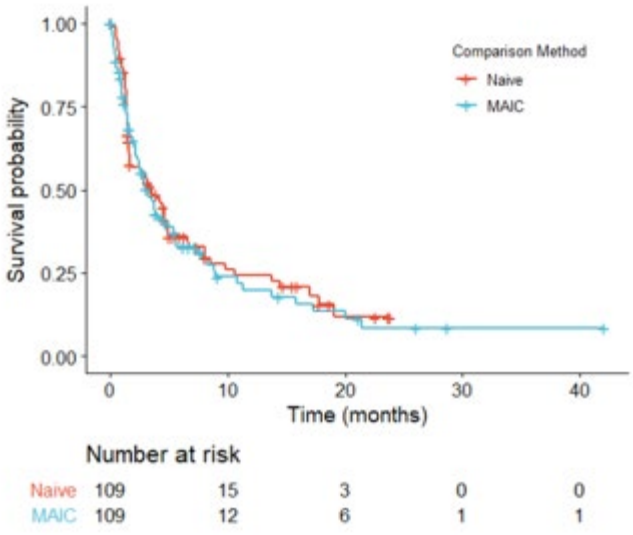


Figure 7: Kaplan Meier PFS curves for pralatrexate treated population in PROPEL based on MAIC and naïve ITC.

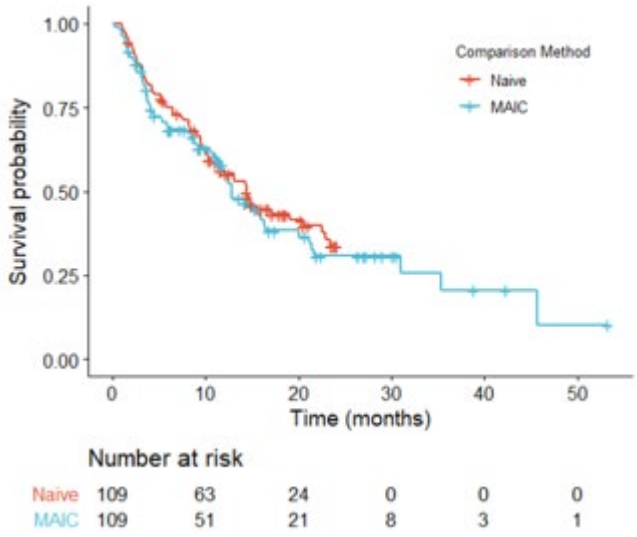


Figure 8: Kaplan Meier OS curves for pralatrexate treated population in PROPEL based on MAIC and naïve ITC.

Critical Appraisal – Limitations and Sources of Bias

The quality of the Manufacturer-submitted MAIC was appraised according to best practice principles outlined by Signorovitch et al (2012).[57] The pCODR Methods Team noted the following:

- The patient populations of the PROPEL and romidepsin trials were generally similar in terms of trial design, baseline patient characteristics, and outcomes. Upon review, the pCODR Methods Team did not identify any concerning differences in the distributions of known treatment effect modifiers between the trials. Of note, patients in PROPEL were more heavily pretreated compared to patients in the romidepsin trial, and differences were observed with respect to specific histology subtypes (PROPEL enrolled more patients with transformed mycosis fungoides subtype; and more patients in the romidepsin trial had AITL). Notwithstanding these differences, the pCODR Methods Team considered a MAIC of the two trials to be appropriate based on their similarity.
- The Submitter supplied a comparison of baseline characteristics between the trials pre- and post-matching, which indicated successful matching was obtained for the analysis. However, it also highlighted that the distributions of matched variables were very similar between the trials pre-matching and, therefore, it is debatable whether much was gained by performing a MAIC versus the naïve ITC. Comparison of the treatment effect estimates obtained by each method show similar results, where precision in the estimate (95% CI) is slightly better with the naïve indirect comparison, likely because it is based on more patients (matching on variables reduced the effective sample size of the PROPEL trial by 25%, to n=82.05).

The methods used for the MAIC were appropriate and generally aligned with best practice; however, some limitations were identified and should be considered when interpreting the results:

- The Manufacturer noted several limitations to the OS data (data immaturity, differing lengths of follow-up), particularly pertaining to the romidepsin trial (lack of an OS curve for all trial patients, which precluded reconstruction of IPD; use of crude measures of variance), which raise uncertainty regarding the treatment estimates obtained for this outcome.
- A MAIC adjusts for trial differences in known prognostic factors or treatment effect modifiers; however, it does not account for unknown cross-trial differences that may be present. Consequently, treatment effect estimates obtained by the MAIC are still susceptible to bias resulting from unknown confounding.
- It is unclear if the analysis considered differences related to outcome definitions and assessment (investigator versus independent review), which can also introduce variation across trials.

7.2.3 Summary

At the request of pCODR, the Submitter conducted an ITC in the form of a MAIC to evaluate the relative efficacy between pralatrexate and romidepsin.[11] The MAIC was based on the efficacy results from the PROPEL trial and a single phase 2 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. IPD 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, naïve ITC (unadjusted for differences in baseline characteristics) results were consistent with the MAIC results with the former being of slightly greater magnitude. 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 quality of the MAIC was appraised according to best practice principles. 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; these included limitations in the OS data of both trials, and possible bias introduced by unknown cross-trial differences.

8 COMPARISON WITH OTHER LITERATURE

No comparison to other literature was undertaken for the pCODR review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma CGP and supported by the pCODR Methods Team. This document is intended to advise the pCODR pERC regarding the clinical evidence available on pralatrexate (Folotyn) PTCL. 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

The Lymphoma CGP is comprised of three clinicians.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH 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 AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials May 2018, Embase 1974 to 2018 June 11, Ovid MEDLINE(R) ALL 1946 to June 11, 2018

#	Searches	Results
1	(Folotyn* or pralatrexate or HSDB 7786 or HSDB7786 or A8Q8I19Q20).ti,ab,ot,kf,kw,hw,rn,nm.	739
2	1 use medall	122
3	1 use cctr	23
4	2 or 3	145
5	*pralatrexate/	143
6	(Folotyn* or pralatrexate or HSDB 7786 or HSDB7786).ti,ab,kw,dq.	429
7	5 or 6	431
8	7 use oemezd	289
9	8 and conference abstract.pt.	121
10	limit 9 to yr="2013-Current"	68
11	limit 10 to english language	68
12	8 not 9	168
13	4 or 12	313
14	limit 13 to english language	300
15	remove duplicates from 14	185
16	11 or 15	253

2. Literature search via PubMed

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

Search	Query	Items found	Time
#3	Search **(#1 AND #2)**	1	12:33:53
#2	Search **publisher[sb]**	515806	12:33:40
#1	Search **("10-propargyl-10-deazaaminopterin" [Supplementary Concept] OR Folotyn*[tiab] OR pralatrexate[tiab] OR HSDB 7786[tiab] OR HSDB7786[tiab] OR A8Q8I19Q20[rn] OR 146464-95-1[rn])**	131	12:33:34

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/

Search: Folotyn, pralatrexate, peripheral t-cell lymphoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Folotyn, pralatrexate, peripheral t-cell lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Folotyn, pralatrexate, peripheral t-cell lymphoma – 2017 (ASH), 2018 (ASCO)

Detailed Methodology

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 ® ALL (1946-) via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (May 2018) 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 pralatrexate and Folotyn.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of January 3rd, 2019.

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. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. 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.

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. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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

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 Team.

Data Analysis

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

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 clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

APPENDIX B: Summary of Trial NCT02013362 (PDX-JP1)

Trial NCT02013362 (PDX-JP1)[2]	Phase 2 (n=22)	
Baseline Characteristics, n (%)		
Age in years, median (range)	71 (42-83)	
≥65	18 (72)	
Sex		
Male/Female	14 (64) /8 (36)	
ECOG		
0	11 (50)	
1	11 (50)	
2	0	
Histology		
PTCL-NOS	10 (45)	
AITL	9 (41)	
ALCL, ALK negative	1 (5)	
Other (not PTCL)	2 (9)	
Prior systemic therapy		
Median (range)	2 (1-8)	
1	4 (18)	
2	8 (36)	
3	2 (9)	
≥4	8 (36)	
Response to most recent therapy		
CR	7 (32)	
PR	3 (14)	
SD	5 (23)	
PD	2 (9)	
NE	5 (23)	
Time from most recent therapy		
<3 months	11 (50)	
≥3 months	11 (50)	
Efficacy Outcomes	**Phase 2 Efficacy Analysis Set (n=20)**	
Primary – ORR by IWC, n (%; 90% CI)	9 (45; 26-65)	
CR	2 (10)	
PR	7 (35)	
SD	4 (20)	
PD	7 (35)	
Secondary		
DOR, median (range) in days	Not reached (1-358)	
PFS, median (95% CI) in days	150 (43-183)	
OS, median (range) in days	Not reached (41-470)	
Harms	**Safety Analysis Set (n=25)**	
	Any grade	**Grade 3-4**
Any AE (occurring in ≥20% of patients)	25 (100)	NR
Mucositis*	22 (88)	5 (20)
Thrombocytopenia*	17 (68)	10 (40)
Liver function test abnormal*	16 (64)	3 (12)
Anemia*	15 (60)	5 (20)
Lymphopenia*	14 (56)	13 (52)
Neutropenia*	11 (44)	6 (24)
Leukopenia*	11 (44)	7 (28)
Fever	11 (44)	0
Malaise	9 (36)	0
Nasopharyngitis	9 (36)	0
Nausea	7 (28)	0

Rash	7 (28)	0
Vomiting	7 (28)	0
Diarrhea	6 (24)	0
Hypokalemia*	6 (24)	4 (16)
Insomnia	6 (24)	0
Edema*	5 (20)	0
SAE	12 (48)	
Treatment discontinuation due to AEs	6 (24)	
Dose reduction due to AEs	7 (28)	
Dose omission due to AEs	22 (88)	

Abbreviations: AE – adverse events; **AITL** angioimmunoblastic T-cell lymphoma; **ALCL**- anaplastic large-cell lymphoma; **ALK** – anaplastic lymphoma kinase; **CI** – confidence interval; **CR**- complete response; **DOR** – duration of response; **ECOG** – Easter Cooperative Oncology Group; **IWC** – International Workshop Criteria; **PD** – progressive disease; **NE** – not evaluable; **NOS** – not otherwise specified; **NR** – not reported; **PFS** – progression-free survival; **PR** – partial response; **PTCL**- peripheral T-cell lymphoma; **SAE** – serious adverse events; **SD** – stable disease; **ORR** – objective response rate; **OS** – overall survival.
* Includes reclassified similar AEs.

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