PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Romidepsin (Istodax) for Peripheral T-Cell Lymphoma

May 19, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of romidepsin (Istodax) when used in the relapsed/refractory setting for patients with peripheral t-cell lymphoma who are ineligible for transplant and who have undergone systemic therapy.

Romidepsin is a histone deacetylase (HDAC) inhibitor and has a Health Canada indication for the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two single arm, multicentered, phase two studies of romidepsin in relapsed/refractory PTCL patients.[1-3] Patients in both studies received romidepsin 14 mg/m^2 intravenously over 4 hours on days 1, 8 and 15 of each 28-day cycle.

The studies were similarly designed.

- The Coiffier et al study included 130 patients with PTCL. The majority of patients in the study were male (68%), had an ECOG PS of 0 (43%), 1(49%) and 2(9%), had a primary diagnosis of PTCL, unspecified or NOS (57%), angioimmunoblastic T-cell lymphoma (15%) or ALK-1-negative ALCL (4%) and had received a median of 2 prior systemic therapies. An independent review committee was used to assess tumour response.
- The Piekarz et al study included 47 patients with PTCL. The majority of patients in the study were male (53%), had an ECOG PS of 0 (35%), 1(51%) and 2(13%), had a primary diagnosis of PTCL, unspecified or NOS (53%), angioimmunoblastic T-cell lymphoma (21%) or ALK-1-negative ALCL (16%) and had received a median of 3 prior systemic therapies. Results from the Piekarz study are based on an interim analysis.

Efficacy

The primary outcome in the Coiffier et al study was complete response/complete unconfirmed response (CR/CRu) as confirmed by an independent review committee. Among all patients in the study, 15% (n=19) achieved CR/CRu. For the secondary outcomes, among 33 (25%) patients that achieved objective disease response (ORR: CR/CRu + PR), the median durability of response was 28 months (range, < 1-48+). The median durability of response had not been reached for those patients who achieved CR/CRu (n = 19).[3] Response rates were similar across the three major subtypes of PTCL in the study (unspecified or NOS, angioimmunoblastic T-cell lymphoma and ALK-1-negative ALCL). The durability of response was not significantly different based upon the number of prior therapies (1, 2 or $\geq$3). However, patients who had received more prior therapies discontinued treatment more frequently.[4]

The primary outcomes in the Piekarz et al study were overall response rate, complete response rate and duration of response. Among all patients in the study, 18% achieved CR and 38% (95%CI, 24% - 53%) achieved ORR. In the 8 patients who had a complete response the median duration of response was 29.7 months (range 3-74).[1]

Harms

In the Coiffier et al study, 8 patients (6%) died within 30 days of the last study drug dose. One of these deaths was regarded as possibly being treatment related with the patient dying 3 weeks after the last dose from multi-organ failure with sepsis and progressive disease. In the Piekarz et al study, 2 deaths occurred during the study and 5 additional deaths occurred within 30 days of removal from the study. Of the two patients who died while on the study, 1 had rapid progressive disease with a pericardial effusion. The second patients was reported to have had a significant cardiac history.

In the Coiffier et al study, the most common adverse events were nausea, infections, fatigue, thrombocytopenia, vomiting, and diarrhea. The most common grade ≥ 3 adverse events were thrombocytopenia, neutropenia, and infection of any type. These can be seen in table 3.[2] In the Piekarz et al study, the rates of adverse events are in line with the Coiffier et al study except for the rates of leukopenia which was much higher in the Piekarz et al study, occurring in 21(44.7%) of patients compared to 8(6%) in the Coiffier et al study.

ECG abnormalities were uncommon and observed in 8 (6%) of patients in the Coiffier study.[2] In the Piekarz study one patient had an asymptomatic, nonrecurrent, 12-beat run of ventricular tachycardia during an ECG, but this patient was found to have abnormal magnesium, and potassium levels during this event.[1]

1.2.2 Additional Evidence

pCODR did not receive input on romidepsin (Istodax) for PTCL from any patient advocacy groups, as of the deadline date of December 15, 2014 for input on this review. However, an extensive search was conducted by pCODR of the literature to help inform this review. Provincial Advisory Group input was obtained from all nine of the nine provinces participating in pCODR.

In addition, the following information relevant to the pCODR review of romidepsin is discussed as supporting information.

- A summary of a systematic review conducted which included thirty-three studies assessing treatment options for peripheral T-cell lymphoma.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

There will be about 8000 new diagnoses of non-Hodgkin lymphoma (NHL) in Canada this year.[5] Among these, there will be approximately 600 new cases of PTCLs (at 5-10% of all NHLs). Approximately 70% (400) of these PTCL patients will experience relapsed/refractory disease and potentially be candidates for further therapy. [6] Despite frontline therapy and transplant as consolidation in first or second remission for selected patients, relapses are common with PTCL. For these patients' conventional doses of anti-cancer drugs are frequently used, as single agents or in combination, largely based on phase II data or using regimens borrowed from those used to treat B-cell lymphomas. Results have generally been disappointing, with most regimens giving relatively low response rates, short response durations and poor survival rates. Patients with relapsed/refractory PTCL have a very poor prognosis, with survival typically measured in months and are therefore in need of therapies that will prolong their survival with manageable toxicity.

Effectiveness

Drugs for relapsed/refractory PTCL generally have response rates that are less than 50%, as is observed for romidepsin where the objective response rate (ORR) was 25% and 38% in the Coiffier and Piekarz studies, respectively. The patients who do respond to therapy with romidepsin can often have a meaningful survival duration. Among the substantial minority of patients who responded to therapy with romidepsin, median duration of response (DoR) was 17 months in the original publication of the Coiffier study, revised to 28 months in the updated publication; and 8.9 months in the smaller Piekarz study. In this, the largest study ever conducted in relapsed/refractory PTCL by Coiffier, with independent response evaluation, the DoR is dramatically longer for romidepsin than what has ever been reported for other treatments in this disease and the response rate is comparable to that seen with other regimens. The CGP however noted that there is no clear way to distinguish which patients will respond to treatment with romidepsin.

While conventional measures of efficacy in single arm phase II studies include response rates, progression-free survival, and overall survival, considering that approximately half of the patients had no response to romidepsin, the median PFS and OS in this case, is going to be driven by the patients who do not respond to therapy, and will be unimpressively short.

Safety

The toxicity profile of romidepsin is quite manageable relative to the toxicity profiles of conventional chemotherapy drugs that are currently used to treat relapsed/refractory PTCL. The most common adverse events with romidepsin in the clinical trials were hematological and gastrointestinal. The CGP agreed that the nature, frequency and severity of these events are quite familiar and acceptable to hematologists and oncologists.

While quality of life data were not reported in these trials, it is anticipated given the toxicity profile that the use of romidepsin would be associated with the maintenance of a meaningful quality of life for patients, particularly for those who responded to therapy and had improvement in disease-related symptoms.

1.3 Conclusions

The lymphoma Clinical Guidance Panel concluded that there is a net clinical benefit to the use of romidepsin for the treatment of relapsed and refractory PTCL. This conclusion is based on two published single arm, phase II clinical trials of romidepsin monotherapy for this indication. The response rate to romidepsin in these trials was clinically significant, and most importantly, those responses were of meaningful, unprecedented duration. The toxicity of romidepsin in these trials was manageable.

The Clinical Guidance Panel also considered that from a clinical perspective:

- The level of evidence in support of this conclusion is limited as there are no randomized trials evaluating romidepsin for relapsed/refractory PTCL. However, there are no other treatments for these patients that have been reported to provide such durable responses to therapy as romidepsin, there is no standard comparator treatment for this patient population, and the small size of the patient group precludes the conduct of randomized trials.
- It would be reasonable for both romidepsin and brentuximab vedotin monotherapy to be made available to patients with relapsed/refractory CD30+ T-cell lymphoma,

as the mechanism of action of the two drugs are different and most patients will experience relapse following, or be refractory to, one or both agents. There is however no evidence to inform the optimal sequencing of these therapies.

- It is reasonable from a clinical perspective to allow for treatment until disease progression or unacceptable toxicity occurs, as this is how the treatment was prescribed in the clinical trials.
- This conclusion is not meant to apply to the mycosis fungoides (MF) type of cutaneous T-cell lymphoma, which was not the subject of this review. It is reasonable however to include transformed MF in the list of indications for romidepsin, as it behaves like other aggressive PTCL types and was covered under the scope of the current review.
- Other types of cutaneous T-cell lymphoma were included in the trials by Coiffier and Piekarz and do fall under the scope of this review and conclusion.
- This conclusion certainly applies to patients who have had prior stem cell transplant, who were included in both trials.

2 CLINICAL GUIDANCE

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 romidepsin (Istodax) for peripheral T-cell lymphoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding romidepsin (Istodax) conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review is fully reported in Sections 6. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on romidepsin (Istodax) and a summary of submitted Provincial Advisory Group Input on romidepsin (Istodax) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group, collectively comprising 5-10% of all non-Hodgkin lymphomas in Canada. Historically, the treatment of PTCLs 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 PTCLs, although these regimens have been less effective for PTCLs than B-cell lymphomas even prior to the era of targeted B-cell lymphoma therapy beginning with rituximab.[7] These treatments were developed in the era prior to rigorous pathological lymphoma classification, and so their benefit relative to other approaches specifically for PTCLs was not rigorously evaluated. The addition of etoposide has prolonged event-free but not overall survival, and some clinicians incorporate etoposide into front line therapy as a result.[8]

High dose chemotherapy and autologous stem cell transplant is sometimes incorporated into front-line therapy for PTCL, as consolidation of response to initial chemotherapy. There are no phase III trials demonstrating the superiority of this approach over conventional dose chemotherapy, but the phase II 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.[9,10]

Unfortunately, despite frontline therapy and transplant as consolidation in first or second remission for selected patients, relapses are the rule more than the exception with PTCL. For patients whose PTCL is relapsed/refractory despite prior autologous and/or allogeneic transplant, or who is not a candidate for a transplant, conventional doses of anti-cancer drugs are frequently used, as single agents or in combination, largely based on phase II data or using regimens borrowed from those used to treat B-cell lymphomas.[8] Results have generally been disappointing, with most regimens giving relatively low response rates, short response durations and poor survival rates.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness and safety of romidepsin in the relapsed/refractory setting for patients with peripheral t-cell lymphoma that are ineligible for transplant and who have undergone systemic therapy.

See Table 8 in Section 6.2.1 for outcomes of interest and appropriate comparators.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Two single arm, open label, multicentered, phase II studies of romidepsin in relapsed/refractory PTCL patients met the inclusion criteria for this systematic review. [1-3] For a more detailed description of the trials' designs and patient characteristics, please see Table 9 in the *Systematic Review* (Section 6.3.2.1). The studies were similarly designed, with the exception being that the Coiffier study had tumour responses assessed by an independent review committee. Patients in both studies received romidepsin 14 mg/m^2 intravenously over 4 hours on days 1, 8 and 15 of each 28-day cycle.

The primary outcome in the Coiffier et al trial was the percentage of patients with a complete response as defined by the International Workshop Response Criteria (IWC) for Non-Hodgkin's Lymphomas (NHL). An Independent Review Committee (IRC) assessed this outcome.[2] Secondary outcomes included the percentage of participants with objective disease response, the duration of objective disease, the duration of complete disease response, the time to disease progression and change in ECOG performance status.[11]

In the study by Piekarz et al. the primary outcomes were overall response rate, complete response rate and duration of response.[12] Response in patients with nodal disease was assessed using the International Working Group Guidelines (IWG) and response in participants with skin or visceral lesions were assessed using Response Evaluation Criteria in Solid Tumours (RECIST).[1] The secondary outcome in this study was to evaluate the tolerability of romidepsin with extended cycles of therapy and to examine the molecular effects of the drug.[12]

The key efficacy results for both studies are summarized in Table 1. A pooled analysis for the two trials shows an overall response rate of 31% and a complete response (CR) rate of 15%.[13]

Table 1: Response rates in the Coiffier and Piekarz et al studies[1,2]

Response	Coiffier et all study Independent assessment N=130 (%)	Coiffier et all study Investigator's assessment N=130 (%)	Piekarz study N=45 (%)
ORR	33 (25)	38(29)	38% (95%CI, 24% - 53%)
CR/CRu	19(15)	21(16)	NR
CR	13(10)	19(15)	8 (18)
CRu	6(5)	2(2)	NR
PR	14(11)	17(13)	9 (20)
SD	33(25)	22(17)	5 (11)
PD or N/E*	64 (49)	70 (54)	PD 18 (40)

Response	Coiffier et all study Independent assessment N=130 (%)	Coiffier et all study Investigator's assessment N=130 (%)	Piekarz study N=45 (%)
			NE 5(11)

Abbreviations: CR = complete response; CRu = unconfirmed complete response; N/E = not evaluable; NR = not reported; PD = progressive disease; PR = partial response; SD = stable disease
* Insufficient efficacy data to determine response because of early termination (i.e., includes patients determined to have PD by investigators prior to first post baseline assessment and therefore assessed as N/E according to the IRC).

In the Coiffier et al. study baseline characteristics, prior regimens and number of prior therapies did not have an impact on the ability of patients to respond to romidepsin. There were no meaningful differences in ORR or CR/CRu rates based on sex, age, number of prior therapies, prior stem cell transplantation, type of prior therapy, or whether the patient was refractory to their last prior therapy.[2]

In the Piekarz study the overall response rate was 38% (94% CI, 24% - 53%). Eight patients had a complete response, with three patients are still remaining on protocol. Nine patients had partial responses and one patient is still remaining on treatment.[1]

Duration of responses

The independent review committee reported that the median time to response was 1.8 months (range, 1.4-5.3 months) in the Coiffier study.[3] The median duration of response for all patients who achieved a response as measured by the independent review committee (n = 33) was 28 months (range, < 1-48+). The median duration of response had not been reached (range, < 1-48+) for those patients who achieved CR/CRu (n = 19).[3]

In the Piekarz et al. study the overall median duration of response was 8.9 months (range 2-74) and the median time to response was 1.8 months. All patients achieved response within 2 months except for 3 patients who achieved response at 4, 8 and 11 months respectively.[1]

Progression free survival and overall survival

In the Coiffier study a longer progression free survival (PFS) was seen in patients who achieved a CR/CRu than in patients in other response categories. The independent review committee also observed that for patients with CR/CRu the median PFS was 29 months.[3] The independent review committee found that the overall median PFS was 4 months. Overall survival and progression free survival in the Coiffier study can be seen in Table 2. Progression free survival and overall survival were not reported in the Piekarz study.

Table 2: Overall survival and progression free survival [2,3]

	Objective responders (CR/CRu = PR; n=33)	CR/CRu ≥ 12 months (n=10)	CR/CRu < 12 months (n=9)	PR N=14)	SD90 N=23	SD<90/PD/ NE (n=74)
Median OS, months (range)	30 (2.0-49.5)	NR (21.2-49.5)	NR (9.2-32.0)	18 (2.0-38.8)	NR (8.1-44.6)	5 (0.3-29.3)
Median PFS, months (range)	20 (1.6-49.8)	29 (17.6-49.8)	13 (1.6-26.0)	7 (1.9-18.1)	7 (3.3-37.7)	2 (0.3-14.4)

	Objective responders (CR/CRu = PR; n=33)	CR/CRu ≥ 12 months (n=10)	CR/CRu < 12 months (n=9)	PR N=14)	SD90 N=23	SD<90/PD/ NE (n=74)
Abbreviations: CR/CRu = confirmed/unconfirmed complete response; NR = not reached; OS = Overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease; SD90 = SD for greater than 90 days						

Responses by prior therapy

In the Coiffier study the durability of response and survival rates were not significantly different for patients who received one, two or over three prior therapies. However patients who had received more prior therapies discontinued treatment more frequently.[4]

ECOG status

Eighty-two patients had a baseline performance status of more than 0 and also available post-baseline data in the Coiffier study. Of these patients 34 (41%) had a documented improvement in ECOG performance status. Improvements correlated with responses and were noted in 83%, 60%, 52%, and 18% of patients with CR/CRu, PR, SD, and PD or not evaluable, respectively.[3]

Harms

The most common adverse events in the Coiffier study were nausea, infections, fatigue, thrombocytopenia, vomiting, and diarrhea. The most common grade ≥ 3 adverse events were thrombocytopenia, neutropenia, and infection of any type. These can be seen in Table 3.[2] In the Piekarz study the rates of adverse events are in line with the Coiffier trial except for the rates of leukopenia. This was much higher in the Piekarz study.[1]

Adverse events from ECG abnormalities were uncommon and observed in 8(6%) of patients in the Coiffier study. Four patients (3%) reported prolonged QTc intervals of grades 1 and 2. None of these patients had any other cardiac adverse events. A review of the QTcF and QTcB intervals over the first 4 cycles showed no clinically significant changes across treatment cycles for these limitations.[2] In the Piekarz study one patient had an asymptomatic, nonrecurrent, 12-beat run of ventricular tachycardia during an ECG, but this patients was found to have abnormal magnesium, and potassium levels during this event.[1] An abstract from 2009 states that romidepsin has a slight effect on prolongation of the QT interval, but the effect was mild and below the level of clinical concern and not associated with any observed clinical cardiovascular events.[14]

Table 3: Adverse events reported for the Coiffier et al and Piekarz et al studies.

	All events (%) Grade ≥3 N=131[2]	Drug related events (%) Grade ≥3 N=131[2]	Grade 3 and 4 Adverse events (%) N=47[15]
Nausea	3(2)	2(2)	6(6.4)
Infections	25(19)	8(6)	13(27.7)
Asthenia/fatigue	11(8)	7(5)	9 (19.1)
Thrombocytopenia	32(24)	30(23)	17(36.2)
Vomiting	6(5)	5(4)	4(8.5)
Diarrhea	3(2)	2(2)	1(2.1)
Pyrexia	7(5)	5(4)	8(17)
Neutropenia	26(20)	24(18)	22(27.8)
Anemia	14(11)	7(5)	13(27.7)
Leukopenia	8(6)	8(6)	21(44.7)

In the Coiffier study, eight patients (6%) died within 30 days of the last study drug dose. However, seven of these patients died more than three weeks after their last dose. For three patients, progressive disease was the only cause of death reported. For the other five patients, an infection or incident that occurred during infection was reported as a cause of death. One of these deaths was regarded as possibly being treatment related. The patient received two doses of the drug before withdrawing consent. The patient died three weeks after the last dose from multi-organ failure with sepsis and progressive disease.[2]

Two deaths occurred during the study in the Piekarz et al report and five deaths occurred within 30 days of removal from the study. One patient who died during the study had rapid progressive disease with a pericardial effusion. This patient died five days after the first dose. The second patients who died on study had a past significant cardiac history. After the death of this patient the study protocol changed to exclude patients with significant cardiac histories.[1] Four out of five of the other deaths occurred in patients with disease progression. The other patient achieved a complete response, but developed high-grade fevers, thrombocytopenia elevated liver function tests after his first dose of the 15th cycle. The biopsy suggests that this patient had Epstein Barr positive NK-T lymphoma and died of hemophagocytosis syndrome.[1]

2.1.4 Comparison with Other Literature

Thirty-three studies were identified in a systematic review of treatment for peripheral T-cell lymphoma. The external consulting group Amaris prepared this document for the manufacturer.[16] The following databases were searched: Medline 1949-August 2014, EMBASE 1947-August 2014, the Cochrane Library - August 2014, and EconLit to August 2014. The websites of health authorities and clinical trials registries were also searched to capture additional data. This document addressed two objectives: to investigate the burden and progression of disease on patients with relapsed/refractory PTCL and to inform a cost-effectiveness model assessing the effect of romidepsin on patients with relapsed/refractory PTCL.[16] A total of 1029 unique citations were found. Of these 369 were identified for full text review. Two independent analysts screened the data. A third reviewer resolved discrepancies. Forty-three clinical studies were included in this systematic review. Ten studies were observational and will not be discussed any further. Details of the included clinical trials can be seen in Table 4

Table 4: Details of studies included in the systematic review[16]

Author	Year	Treatment	Study size
Single Agent chemotherapy			
Damaj	2013	Bendamustine	45
Czuczmann	2077	Nelabrine	8
Sarris	2002	TMTX	5
Single agent "other"			
Huang	2002	13-cRA	17
Enblad	2004	Alemtuzumab	14

Author	Year	Treatment	Study size
Zinzani	2005	Alemtuzumab	6
Barr	2014	Alisertib	37
Pro	2012	Brentuximab	58
Horwitz	2014	Brentuximab	35
Bartlett	2014	Brentuximab	29
Cooper	1993	Cyclosporin	5
Dang	2006	Denileukin difitox	26
Janik	2009	Denileukin difitox	8
Dueck[17]	2010	Lenalidomide	39
Morschhauser	2013	Lenalidomide	54
Ishida	2012	KW-0761 (Mogamulizumab)	27
Ogura	2014	KW-0761 (Mogamulizumab)	29
Tsimberidou	2004	Pentostatin	5
Ferme	2009	Plitdepsin	19
O'Connor	2011	Pralatrexate	111
Coffier	2012	Romidepsin	130
Piekarz	2011	Romidepsin	47
Forero-Torres	2009	SGN-30	41
Witzing	2011	Tipifarnib	10
d-Amore	2010	Zanolimumab	21
Combination chemotherapies			
Weidmann	2010	Alemtuzumab, fludaribine, cyclophosphamide and doxorubucub	11
Evens	2013	Bortezomib + gemcitabine	16
Mahadevan	2013	Cisplatin + Etoposide + Gemcitabine + methylprednisolone	33
Niitsu	2007	CMD (CPT-11+MIT+DEX)	30
Kim	2012	Vinorelbine, gemcitabine and filgrastim	24

Author	Year	Treatment	Study size
Spencer	2007	Vinorelbine, gemcitabine and filgrastim	10
Hopfinger	2014	Voronistat + lenalidomide	8
Other combination therapies			
Chen	2011	CsA, prednisolone and monthly high dose immunoglobulin	12

The studies identified are all single arm, phase 1 or 2 studies. Most of the studies included between 10 and 30 patients. Two studies included over 100 patients (Coiffer and O'Connor) and another two included over 50 patients (Pro and Morschhauser). The rest of the studies included fewer than 50 patients. Such small sample sizes increase the likelihood of type II errors, the power of studies may be low, and the chance of finding significance is difficult. In addition many of these studies did not report on certain patient characteristics such as; median time to diagnosis, previous lines of therapy, and performance status. No methodological filters were in place to exclude studies therefore the study quality is low.[16]

Outcomes

Most of the studies reported the response rate. The median overall survival was assessed in 12 of 33 studies and the median PFS was assessed in 16 out of 33 studies. Overall response was reported in 30 or 33 trials. The outcome results can be seen in Table 5. Many of the results are missing or not reported.[16]

Table 5: Outcomes of interest in the systematic review[16]

Reference	Treatment	N	CR/ CRu	PR	SD	PD/ NE	TTR (days)	DOR (mo)	OS (mo)	PFS (mo)	TTP (days)
Single Agent chemotherapy											
Damaj	Bendamustine	45									
Czuczmann	Nelabrine	8	-	13%		-		-	1.5	1.2	-
Sarris	TMTX	5	0%	40%	-	-	-	-	-	-	-
Single agent "other"											
Huang	13-cRA	17	0	29%	-	-	75	3	3.6	2.7	76
Enblad	Alemtuzumab	14	21%	14%	29%	36%	-	6	-	-	-
Zinzani	Alemtuzumab	6	33%	17%	-	-	-	-	-	-	-
Barr	Alisertib	37	-	7%	-	-	-	-	-	-	-
Pro	Brentuximab	58	57%	29%	3%	5%	-	12.6	-	13.3	-
Horwitz	Brentuximab	35	24%	18%	18%	41%	-	7.6	-	2.6	-

Reference	Treatment	N	CR/ CRu	PR	SD	PD/ NE	TTR (days)	DOR (mo)	OS (mo)	PFS (mo)	TTP (days)
Bartlett	Brentuximab	29	-	55%	20%	33%	-	12(HL) 7(ALCL)	-	9/9 (HL) 12.9 (ALCL)	-
Cooper	Cyclosporin	5	0%	0%	0%	100 %	-*	-	-	-	-
Dang	Denileukin difitox	26	23%	27%	23%	27%	42	-	-	6.0	-
Janik	Denileukin difitox	8	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dueck[17]	Lenalidomide	39	8%	18%	8%	26%	-	-	12	4	-
Morschhauser	Lenalidomide	54	26%	26%	57%	56%	-	3.6 (ITT) 3.6 (AITL)		2.5 (ITT) -(AITL)	-
Ishida	KW-0761 (Mogamulizumab)	27	50%	-	-	-	-	-	13.7	5.2	-
Ogura	KW-0761 (Mogamulizumab)	29	17%	17%	31%	34%	-	-	14.2	2	-
Tsimberidou	Pentostatin	5	40%	40%	-	-	-	-	-	-	-
Ferme	Plitdepsin	19	13%	13%	19%	56%	-	6	11	1	61
O'Connor	Pralatrexate	111	11%	18%	19%	51%	46	10	14.5	3.5	-
Coffier 2012	Romidepsin	130	15%	11%	25%	49%	-	16.1	-	<2	-
Piekarz	Romidepsin	47	18%	20%	11%	51%	55	9	-	-	-
Forero-Torres	SGN-30	41	5%	12%	15%	68%	-	-	-	-	-
Witzing	Tipifarnib	10	30%	10%	-	-	-	-	-	-	-
d-Amore	Zanolimumab	21	10%	14%	-	-	-	2	-	-	-
Combination chemotherapies											
Weidmann	Alemtuzumab, fludaribine, cyclophosphamide and doxorubucub	11	27%	27%	0%	45%	-	-	6.1	2.5	-
Evens	Bortezomib + gemcitabine	16	-	-	-	-	-	8, 12 and 39	6.3	1.6	
Mahadevan	Cisplatin + Etoposide + Gemcitabine + methylprednisolone	33	-	-	-	-	-	-	12	-	-
Niitsu	CMD (CPT-11+MIT+DEX)	30	37%	23%	-	-	-	-	-	-	-

Reference	Treatment	N	CR/ CRu	PR	SD	PD/ NE	TTR (days)	DOR (mo)	OS (mo)	PFS (mo)	TTP (days)
Kim	Vinorelbine, gemcitabine and filgrastim	24	-	38%	15%	7%	-	2.93	6	-	-
Spencer	Vinorelbine, gemcitabine and filgrastim	10	40%	30%	0%	30%	-	-	-	-	-
Hopfinger	Voronistat + lenalidomide	8	-	14%	14%	57%	-	11	6.7	2.2	-
Other combination therapies											
Chen	CsA, prednisolone and monthly high dose immunoglobulin	12	-	60%	-	8.3 %	-	20	-	25.5	-

Abbreviations: 13-cRA=13-cis-retinoic acid; AITL=Angioimmunoblastic T-cell lymphoma; ALCL= anaplastic large cell lymphoma; CMD (CPT-11+MIT+EX=irinotecan (CPT-11), mitoxantrone and dexamethasone;CR/CRu = confirmed/unconfirmed complete response; CsA=Cyclosporin A; DOR=Duration of Response; HL=Hodgkin's lymphoma; ITT=intention to treat; NE=Not evaluable; NR = not reached; OS = Overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease; TTR=time to response; TTP time to progression

According to the Clinical Guidance Panel (CGP) the following regimens are used in Canada to treat PTCL: gemcitabine, gemcitabine/dexamethasone/cisplatin, docetaxel/cisplatin/ dexamethasone, gemcitabine/oxaliplatin, ifosfamide/carboplatin/ etoposide, and brentuximab (for the CD30+ subset of PTCL). No data within the systematic review was found on these regimens with the exception of brentuximab. Three small, single arm studies evaluated brentuximab. The specific studies can be seen in Table 6. The results varied widely between the studies and therefore it is difficult to draw any conclusions.

Table 6: Brentuximab treatment [16]

Reference	Treatment	N	CR/ CRu	PR	SD	PD/ NE	DOR (mo)	OS (mo)	PFS (mo)
Pro	Brentuximab	58	57%	29%	3%	5%	12.6	-	13.3
Horwitz	Brentuximab	35	24%	18%	18%	41%	7.6	-	2.6
Bartlett	Brentuximab	29	-	55%	20%	33%	12(HL) 7(ALCL)	-	9/9 (HL) 12.9 (ALCL)

Abbreviations: ALCL= anaplastic large cell lymphoma; CR/CRu = confirmed/unconfirmed complete response; DOR=Duration of Response; HL=Hodgkin's lymphoma; NE=Not evaluable; OS = Overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease; TTR=time to response; TTP time to progression

Overall, it is difficult to make generalizations with the results of the Amaris systematic review. Most of the studies are small and there is a lot of missing data. There is considerable data that is missing as it relates to the description of patient characteristics and the results. Descriptions of the treatments themselves are also missing (dosages and

duration of the treatments are not listed). Without this information on treatments, it is difficult to know if the patients received the correct dosage and for how long. Furthermore the appropriate statistical representation of confidence intervals and hazard ratios are missing for the available data. Therefore this makes it difficult to draw conclusions from the data. While the authors of this systematic review searched and found the studies for inclusion in a proper and comprehensive way, the data presented is incomplete and presented in a manner that does not show key facts and tables upfront. Furthermore when the authors present the results in the systematic review they do not always properly reference the study in the written narrative. This makes it hard to follow the data. In conclusion, this systematic review is of low quality.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review

2.1.6 Other Considerations

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

Patient Advocacy Group Input

pCODR did not receive input on romidepsin (Istodax) for PTCL from any patient advocacy group(s), as of the deadline date of December 15, 2014 for patient advocacy group input on this review. However, an extensive search was conducted by pCODR of the literature to help inform this review.

pCODR found two relevant articles on treatment protocol for PTCL and one document from a national patient advocacy group website reporting on patients and caregivers' experiences with PTCL and romidepsin. pCODR also found personal accounts from three individual patients on their experiences with romidepsin for the treatment of PTCL. Because PTCL is an uncommon and aggressive cancer with many sub-types, these reports suggest that PTCL patients want the opportunity to have choice of treatments with proven efficacy, including for those patients who have the poorest prognostic factors. According to the summary report published by this national patient advocacy group, patients described that it is important for a new drug to be "able to control" specific aspects associated with their disease. These patients would be willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life. One national patient advocacy group offered that there is a need for access to therapies that will offer disease control, deeper longer lasting remissions and an improved quality of life while offering increased efficacy, minimal toxicity and manageable side effect profiles relative to other treatments. According to the information gathered from the different sources, patients reported side-effects with using romidepsin, such as, chills, headaches, rigors and night sweats, broken sleep, loss of appetite and taste, extreme fatigue and emotional distress; however, these patients noted for the most part that the side-effects were tolerable, and based on their own experiences with the treatment could permit patients to regain a satisfactory quality of life.

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 romidepsin:

Clinical factors:

- Romidepsin could fill the gap in therapy for patients with PTCL.
- Clarity requested on group of patients who would be eligible for treatment with romidepsin.
- Unknown duration of treatment.

Economic factors:

- Small patient population.
- Drug wastage likely.

2.2 Interpretation and Guidance

Burden of Illness and Need

Patients with relapsed/refractory PTCL who have not been cured with frontline combination chemotherapy or stem cell transplant are incurable and have a short life expectancy, and are in need of therapies that will prolong their survival with manageable toxicity.

Romidepsin is proposed as a treatment for patients with PTCL whose disease is relapsed and/or refractory to least one line of conventional chemotherapy, who are candidates for further treatment, and who have failed (or are ineligible for) autologous or allogeneic stem cell transplant. As outlined in section 3.3, it is estimated that approximately 400 patients per year would be candidates for romidepsin therapy in Canada for relapsed/refractory PTCL. Patients with relapsed PTCL have disease progression despite number of prior therapies. Patients with refractory PTCL have disease progression during prior therapy, or no response to prior therapy.

The population with relapsed/refractory PTCL is small. Consequently, clinical trials for this population have typically included less than 60 patients (range: 5-58 patients), with two exceptions. The Coiffier study of romidepsin for relapsed/refractory PTCL is the largest clinical trial ever reported for this population, at 130 patients. A study with pralatrexate included over 111 patients.[18] With these patient numbers, statistical power is insufficient for randomized trial designs. Consequently, the quality of the evidence informing treatment decisions for these patients is limited to indirect comparisons of single arm phase II studies. Patients with rare diseases ought still to be studied and eligible for access to effective new therapies, despite the limited quality of evidence that is possible to inform treatment recommendations.

Effectiveness:

Conventional measures of efficacy in single arm phase II studies include response rates, progression-free survival, and overall survival. It is clear from the literature that patients with relapsed/refractory PTCL have a very poor prognosis, with survival typically measured in months. The disease tends to be rapidly progressive and those patients who do not respond to therapy, or who are not given any therapy, do particularly poorly. It is also clear that drugs for relapsed/refractory PTCL have response rates that are less than 50%, including romidepsin where the ORR was 25% (Coiffier) and 38% (Piekarz). In these studies approximately half of the patients had no response to romidepsin, so the median PFS and OS in this case, is going to be driven by the patients who do not respond to therapy, and will be unimpressively short.

On the other hand, the patients who do respond to therapy with romidepsin can often have a meaningful survival duration. This has been captured in the reported trials of romidepsin under the outcome measure Duration of Response (DoR), defined as the time from achievement of at least a partial response until disease progression or (for those who have not yet progressed) the most recent disease assessment. The CGP however noted that there is no clear way to distinguish which patients will respond to treatment with romidepsin. For the substantial minority of patients (25%) who respond to romidepsin, median DoR was 17 months in the original publication of the Coiffier study, revised to 28 months in the updated publication; and 8.9 months in the smaller Piekarz study. It is remarkable that in the largest study ever conducted in relapsed/refractory PTCL by Coiffier, with independent response evaluation, the DoR is dramatically longer for romidepsin than what has ever been reported for other treatments in this disease and the response rate is comparable to that seen with other regimens.

The CGP agreed that patients with all the PTCL subtypes included in the study should qualify for treatment with romidepsin. Among these, for the small subset of PTCL patients with relapsed/refractory CD30+ T-cell lymphoma, the Clinical Guidance Panels noted that pCODR has previously reviewed the use of brentuximab vedotin, and this treatment is now available in many provinces. Given that the mechanism of action of the two drugs (brentuximab vedotin and romidepsin) are completely different, the CGP agreed that it would be reasonable to try one of these drugs and switch to the other if a patient doesn't respond. Patients with this subset of PTCL are expected to be few. The CGP however agreed that there is no evidence to inform the optimal sequencing of these two therapies.

Safety

The toxicity profile of romidepsin is quite manageable relative to the toxicity profiles of conventional chemotherapy drugs that are currently used to treat relapsed/refractory PTCL. Withdrawal from study due to treatment related adverse events was not common. Dose reductions were not unexpectedly frequent and the majority of patients in both trials tolerated full dose therapy. The most common adverse events with romidepsin in the clinical trials were hematological and gastrointestinal. The CGP agreed that the nature, frequency and severity of these events are quite familiar and acceptable to hematologists and oncologists. As with many new cancer drugs, prolongation of the QT interval has been monitored for patients on romidepsin trials for PTCL. While the QT interval was prolonged in some patients, the frequency of QT prolongation was low; the amount of prolongation was usually small; and there is evidence that this prolongation is mainly attributable to the anti-emetics used with the treatment, and not due to the romidepsin itself.

While quality of life data were not reported in these trials, it is anticipated given the toxicity profile that the use of romidepsin would be associated with the maintenance of a meaningful quality of life for patients, particularly for those who responded to therapy and had improvement in disease-related symptoms.

Based on the Coiffier and Piekarz clinical trials, the expected dose, schedule and duration of romidepsin therapy would be 14 mg/m2 iv on days 1, 8 and 15 of a 28 day cycle until disease progression or unacceptable treatment toxicity occurred. In the Piekarz study, 1062 doses were administered to 47 patients, for an average of 22.5 doses per patient. In the Coiffier study, the mean treatment duration was 4 months and 28% of patients received more than 6 cycles of therapy.

2.3 Conclusions

The lymphoma Clinical Guidance Panel concluded that there is a net clinical benefit to the use of romidepsin for the treatment of relapsed and refractory PTCL. This conclusion is based on two published single arm, phase II clinical trials of romidepsin monotherapy for this indication. The response rate to romidepsin in these trials was clinically significant, and most importantly, those responses were of meaningful, unprecedented duration. The toxicity of romidepsin in these trials was manageable.

The Clinical Guidance Panel also considered that from a clinical perspective:

- The level of evidence in support of this conclusion is limited as there are no randomized trials evaluating romidepsin for relapsed/refractory PTCL. However, there are no other treatments for these patients that have been reported to provide such durable responses to therapy as romidepsin, there is no standard comparator treatment for this patient population, and the small size of the patient group precludes the conduct of randomized trials.
- It would be reasonable for both romidepsin and brentuximab vedotin monotherapy to be made available to patients with relapsed/refractory CD30+ T-cell lymphoma, as the mechanism of action of the two drugs are different and most patients will experience relapse following, or be refractory to, one or both agents. There is however no evidence to inform the optimal sequencing of these therapies.
- It is reasonable from a clinical perspective to allow for treatment until disease progression or unacceptable toxicity occurs, as this is how the treatment was prescribed in the clinical trials.
- This conclusion is not meant to apply to the mycosis fungoides (MF) type of cutaneous T-cell lymphoma, which was not the subject of this review. It is reasonable however to include transformed MF in the list of indications for romidepsin, as it behaves like other aggressive PTCL types and was covered under the scope of the current review.
- Other types of cutaneous T-cell lymphoma were included in the trials by Coiffier and Piekarz and do fall under the scope of this review and conclusion.
- This conclusion certainly applies to patients who have had prior stem cell transplant, who were included in both trials.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group, collectively comprising 5-10% of all non-Hodgkin lymphomas in Canada. The most common histological subtypes are PTCL Not Otherwise Specified (PTCL NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T cell lymphoma (AITL). ALCL can be further subclassified based on the presence of ALK expression, which confers a superior prognosis. Other PTCL subtypes include hepatosplenic T-cell lymphoma, enteropathy-associated T-cell lymphoma, subcutaneous panniculitis-like T cell lymphoma, rare subtypes of primary cutaneous T cell lymphoma (not to be confused with mycosis fungoides), and extranodal NK/T cell lymphomas. As a group, PTCLs have inferior prognosis 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+ ALCL, 49% for ALK- ALCL, 20% for enteropathy-associated and 7% for hepatosplenic T-cell lymphomas.[6] Like other lymphomas, PTCLs present with lymphadenopathy, hepatosplenomegaly, visceral or marrow involvement, and constitutional symptoms. Some PTCLs occasionally have more characteristic clinical presentations, such as the rash, hemolysis and hypergammaglobulinemia seen in some cases of AITL,[19] or the association of enteropathic T-cell lymphoma with celiac disease in about one third of cases.[20] Extranodal NK/T cell lymphoma and HTLV-I associated Adult T-cell leukemia/lymphoma (ATLL) are much more common in Asia than in North America.[6]

3.2 Accepted Clinical Practice

Historically, the treatment of PTCLs 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 PTCLs, although these regimens have been less effective for PTCLs than B-cell lymphomas even prior to the era of targeted B-cell lymphoma therapy beginning with rituximab.[7] These treatments were developed in the era prior to rigorous pathological lymphoma classification, and so their benefit relative to other approaches specifically for PTCLs was not rigorously evaluated. More recent analysis suggests that anthracyclines, the cornerstone of CHOP-like chemotherapy, may not impact treatment outcomes in PTCL.[6] The addition of etoposide has prolonged event-free but not overall survival, and some clinicians incorporate etoposide into front line therapy as a result.[8] Phase III trials are underway adding alemtuzumab, brentuximab or romidepsin to CHOP induction, and adding pralatrexate as maintenance therapy following CHOP induction.[21-23]

High dose chemotherapy and autologous stem cell transplant is sometimes incorporated into front line therapy for PTCL, as consolidation of response to initial chemotherapy. There are no phase III trials demonstrating the superiority of this approach over conventional dose chemotherapy, but the phase II 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.[9,10]

For extranodal NK/T-cell lymphoma, regimens incorporating L-asparaginase/ methotrexate/steroid and combinations of etoposide/ifosfamide/platinum agent/steroid

have become widely adopted rather than CHOP-like regimens.[24,25] For ATLL, antiretroviral therapy and interferon are commonly used for chronic or leukemic disease, while CHOP-like regimens are also used for lymphoma presentations.[26,27]

The goal of frontline therapy is durable remission and hopefully cure. For patients with PTCL that is relapsed following frontline therapy, or refractory to initial therapy, and if a response to conventional dose second line therapy can be attained, autologous or allogeneic transplantation are often considered as consolidation. Long term remissions have been achieved in the chemosensitive relapse setting with autologous or allogeneic transplant.[9,10,26,28]

Unfortunately, despite frontline therapy and transplant as consolidation in first or second remission for selected patients, relapses are the rule more than the exception with PTCL. For patients whose PTCL is relapsed/refractory despite prior autologous and/or allogeneic transplant, or who is not a candidate for a transplant, conventional doses of anti-cancer drugs are frequently used, as single agents or in combination, largely based on phase II data or using regimens borrowed from those used to treat B-cell lymphomas.[8] Results have generally been disappointing, with most regimens giving relatively low response rates, short response durations and poor survival rates. There are no randomized trials of treatment for relapsed/refractory PTCL to guide treatment choices. In Canada, commonly used regimens include gemcitabine, GDP, GemOx, ICE, and relatively gentle oral therapy with cyclophosphamide, methotrexate or etoposide. In BC, Brentuximab is available for CD30+ PTCL.

Apart from drug therapy, radiotherapy is commonly used as consolidation following systemic therapy for PTCL that is localized, bulky at presentation, or for residual masses. Radiotherapy is particularly important in the initial management of early stage extranodal NK/T cell lymphoma.[8] Surgery has a limited role in the treatment of PTCL or other lymphomas.

Romidepsin could potentially be added as a new line of therapy for patients with relapsed/refractory PTCL. There is not yet the expectation that romidepsin would be used in combination, or in place of existing therapies. It would probably be used as second or third line therapy after front line CHOP like chemotherapy and (for fit patients) autologous or allogeneic stem cell transplant. It could potentially be used later in the course of treatment, as it is not clear in which order the available treatments are best used.

3.3 Evidence-Based Considerations for a Funding Population

There will be about 8000 new diagnoses of non-Hodgkin lymphoma (NHL) in Canada this year.[5] There will therefore be approximately 600 new cases of PTCLs (at 5-10% of all NHLs, taking the mean of this estimate). Approximately 70% of these patients will experience relapsed/refractory disease[6] and potentially be candidates for further therapy. It is projected on this basis that perhaps 400 patients would be candidates for romidepsin treatment in Canada each year. Eligible patients would have relapsed/refractory PTCL despite at least one prior line of systemic therapy.

3.4 **Other Patient Populations in Whom the Drug May Be Used**

Romidepsin has generally been studied in patients without further treatment options, including those who have had prior autologous or allogeneic stem cell transplant or are ineligible for such therapy. The drug could potentially be used to induce a response to therapy in order to facilitate getting a patient to autologous or allogeneic transplant, particularly in cases where the PTCL was demonstrably refractory to conventional chemotherapy.[29]

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

As of the deadline date of December 15, 2014 for patient advocacy group input on romidepsin (Istodax) for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL), pCODR had not received any patient evidence submissions. To help inform pERC's deliberations on the alignment with patient values component of their Deliberative Framework, pCODR has conducted an extensive literature search through Medline and PubMed, and supplemented by a "grey literature" search of national and international patient advocacy group websites and cancer forums. The search parameters were from the last five years and was in English only. The search resulted in 102 references in total. pCODR has compiled the most relevant information to help illustrate some of the patient experiences and perspectives on PTCL and romidepsin.

pCODR found two relevant articles on treatment protocol for PTCL and one document from a national patient advocacy group website reporting on patients and caregivers' experiences with PTCL and romidepsin. pCODR also found personal accounts from three individuals patients on their experiences with romidepsin for the treatment of PTCL. Because PTCL is an uncommon and aggressive cancer with many sub-types, these reports suggest that PTCL patients want the opportunity to have choice of treatments with proven efficacy, including for those patients who have the poorest prognostic factors. According to the summary report published by this national patient advocacy group, patients described that it is important for a new drug to be "able to control" specific aspects associated with their disease. These patients would be willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life. One national patient advocacy group offered that there is a need for access to therapies that will offer disease control, deeper longer lasting remissions and an improved quality of life while offering increased efficacy, minimal toxicity and manageable side effect profiles relative to other treatments. According to the information gathered from the different sources, patients reported side-effects with using romidepsin, such as chills, headaches, rigors and night sweats, broken sleep, loss of appetite and taste, extreme fatigue and emotional distress; however, these patients noted for the most part that the side-effects were tolerable, and based on their own experiences with the treatment could permit patients to regain a satisfactory quality of life.

Experiences Patients Have with PTCL

The treatment of PTCL remains a challenging endeavor. Compared with the more common aggressive B-cell lymphomas, more patients with PTCL become refractory to initial therapy and those who achieve responses often will have shorter progression-free survival. *(Source: Lunning MA, Horwitz S. Treatment of peripheral T-cell lymphoma: are we data driven or driving the data? Curr Treat Options Oncol. 2013 Jun;14(2):212-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3938283*).

This clinical assessment is aligned with the findings of one national patient advocacy group. According to this patient advocacy group, PTCL can occur from young adulthood to old age and is slightly more common in men than in women. Patient ages as specified by participants ranged between 15 and 74 years of age. Signs and symptoms of PTCL vary according to subtype; some common symptoms include 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 can also be affected. *(Source: http://www.lymphoma.ca/sites/default/files/images/presentations/lymphoma_canada_romidepsin_pcodr_submission_web.pdf)*

Patients' Experiences with Current Therapy for PTCL

Based on the reported findings from Lunning et al., the addition of etoposide to standard regimens and consolidation of first remissions with autologous stem cell transplantation (autoSCT) provides the best outcome in patients with PTCL and currently use CHOEP followed by ASCT for eligible patients with the common PTCL subtype: PTCL-NOS, AITL, and ALK negative ALCL. *(Source: Lunning MA, Horwitz S. Treatment of peripheral T-cell lymphoma: are we data driven or driving the data? Curr Treat Options Oncol. 2013 Jun;14(2):212-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3938283)*.

In recent years there has been a plethora of novel agents showing activity in PTCL, often in patients with advanced relapsed or refractory disease. These agents include antifolate drugs (pralatrexate), histone deacetylase inhibitors (vorinostat, romidepsin, panobinostat and belinostat), nucleoside analogues (gemcitabine, forodesine and clofarabine), monoclonal antibodies (anti-CD52, anti-CD4 and anti-CD2), fusion toxins (denileukin diftitox), immunomodulatory agents (lenalidomide) and proteasome inhibitors (bortezomib). *(Source: Howman RA, Prince HM. New drug therapies in peripheral T-cell lymphoma. Expert Rev Anticancer Ther. 2011 Mar;11(3):457-72.)*

According to one national patient advocacy group, there is no current standard of care for patients with most subtypes of PTCL. Anthracycline-containing regimens such as CHOP are commonly used. Although most patients achieve a response with induction chemotherapy, responses are typically brief and many patients experience relapse or become refractory to treatment. *(Source: http://www.lymphoma.ca/sites/default/files/images/presentations/lymphoma_canada_romidepsin_pcodr_submission_web.pdf)*

Impact of PTCL and Current Therapy on Caregivers

One national patient advocacy group reported that there was a large impact on day-to-day life of caregivers, such as, ability to travel, ability to volunteer, ability to spend time with family and friends, ability to work, ability to concentrate, ability to exercise, ability to attend to household chores and ability to fulfill family obligations. It was also reported that these caregivers had difficulties with managing "side effects" of the treatment, as well as difficulties with accessibility of treatment. The accessibility issues ranged from financial burden in caring for the patient to travelling to a cancer centre for treatment. *(Source: http://www.lymphoma.ca/sites/default/files/images/presentations/lymphoma_canada_romidepsin_pcodr_submission_web.pdf)*

Patient Experiences to Date with Romidepsin

pCODR has extracted the following excerpts describing the personal experiences from patients who have used romidepsin for the treatment of PTCL. These patients reported on their experiences with PTCL, treatment regimens, side-effects and response to the treatment under review.

Patient #1

One patient shared the following experience on Cancer Survivor Network: *I have only recently joined, but can offer hope for those who are diagnosed with this rare and aggressive cancer. The prognosis is consistently given as poor, although this is changing. In mid-2008, I was diagnosed*

with Peripheral T-Cell Lymphoma - NOS. This cancer is rare, so there exists no standardized therapy to use against it. It is aggressive, and so time is of the essence in combating it. CHOP is often mentioned, or even administered, but PTCL, in the words of my oncologist, "laughs at it".

At that time, doctor decided on two different courses of aggressive chemotherapy, given back to back over four months. The first course was CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone), followed by GVD (Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin). This course of therapy may not be appropriate for any other individual, since this cancer's immunophenotype can vary widely within its rather broad ("NOS") category.

In any event, my disease responded to the combination of eight anti-cancer drugs. I was blessed with what appeared to be a complete response after four months. I do not maintain that this was an easy course of therapy, but that it was a necessary one. It was discontinued at the end due to cumulative toxicity. A scan two months later showed that the cancer had come right back. At that time, I was offered the "salvage therapy" of in-patient ICE (ifosfamide, carboplatin and etoposide). This offered only limited effectiveness, since I had already received etoposide, one of ICE's components, as part of the primary therapy.

Providentially, at that time, two clinical trials were offered to me. One did not appear to be suited to my case, but the other seemed to offer promise. It was for a biological (non-chemotherapy) drug called Romidepsin (aka Istodax, Depsipeptide, FK228). It offered a high-30% chance of response. I entered into the trial and subsequent scans revealed that the disease responded well to it. The median time of response to the drug was 13 months. After that, half of the patients relapsed.

Well, to shorten this, it is now 33 months after I began treatment and I remain cancer-free. Doctor states that the prognosis improves with the passage of time. Quite a change from the "very poor" prognosis I received in February, 2009 after the immediate relapse. Romidepsin is now FDA approved for both Cutaneous T-Cell lymphoma (CTCL) and PTCL. Additionally, there is a cousin of Romidepsin (Belinostat) available, as well as a new chemotherapy drug, Folotyn (Pralatrexate). (Source: http://csn.cancer.org/node/230058)

Patient #2

A male patient, in Canada (51 years old) who identifies as being diagnosed with PTCL-NOS in June 2012 on a publicly available cancer forum. He provides a very detailed account about his experiences with romidepsin from May to Nov 2014 (currently 7 treatment cycles completed).

This patient describes being heavily pre-treated prior to romidepsin (4 x CEOP, poor response; 2 cycles of GDP then ASCT in Nov 2012; relapse in April 2013; 6 cycles GDP ending Oct 2013). The patient reported the following side effects during the first cycle with romidepsin, including rigors, night sweats, broken sleep, anorexia and extreme fatigue. After 2 cycles were completed he was feeling much better and the side effects had lessened. He reported the CT showed some shrinkage of his tumours. On the second dose of cycle 3 he reported tolerating romidepsin much better. He also stated the side effects were almost all gone and at day three after his dose, he has good energy and no loss of appetite. In November 2014, he reported completing 7 cycles of romidepsin and is doing well. *(Source: www.cancerforums.net/threads/38666-PCTL-NOS-and-Romidepsin)*.

Patient #3

A third male patient reported the following experience with romidepsin: *In the early afternoon I was introduced to Romidepsin, my new chemotherapy drug. The treatment starts off with a couple of premeds, and then the main course is served over a 4 hour infusion. Sitting in that treatment chair for 5 straight hours is not a highly recommended way to spend an afternoon. While my past experience with chemotherapy drugs has been quite good, in terms of avoiding side effects, Romidepsin may prove to be a different animal. Immediately after the infusion I felt very blah and drained. I climbed into bed with a headache, and began having chills. The thermometer registered 101.3, and a quick call to the oncologist-on-call suggested we watch it and head to the ER if it continued to increase. Fortunately it passed after a short time and the night was restful. In the morning the blahs and aches and pains had returned, but over the next couple of hours I began to feel better, and by early afternoon was more "normal'. Today has been much better and hopefully my negative reactions were just an introductory experience, not to be repeated after each treatment. Time will tell.*

Last Tuesday was my second Romidepsin treatment and it seems to have gone a little better than the first one. No nighttime chills and fever spikes, and the next-day-blahs didn't last as long. But I did still have a drained feeling, and my sense of taste suffered for a couple of days, but then returned to normal. Overall not as bad as the first time around, so maybe my body is adapting to this new chemo drug. If this is as bad as it gets, I'll consider myself lucky and focus on other things.

My blood tests revealed that my platelet count had dropped very low, so after my Romidepsin on Tuesday, I was treated to a platelet infusion for desert. A low platelet count means that your blood does not clot as efficiently and quickly as normal, and the implications of this can be quite severe. Hopefully by my next treatment the counts will be closer to normal.

At the present time there are five main aspects of my disease that I tend to focus on.

My first aspect is the cancer itself. I am being treated with a chemo drug called Romidepsin, which I trust is doing a good job of eradicating all the cancer cells in my body. Unfortunately it takes time for progress to be detectable, so I will not receive any reassessment testing/scans for 8 weeks. Depending on the reassessment results, I expect to receive this treatment for probably the next 6 months. In the meantime I just need to trust that my team is winning. Unfortunately, this drug is causing certain side effects that were not present with some of my earlier drugs. The main ones are cold chills at night and my sense of taste is getting all beaten up.

The second aspect is my lower back and spine area, which is where the initial tumor was detected. While the tumor itself has been effectively dealt with, and is no longer a direct factor, the residual damage it caused is taking time to heal and rehab.

The third aspect is the strength and flexibility of my right leg. The tumor caused spinal nerve pressure in my right leg and the resulting pain and lack of use are still impacting my movement and mobility.

I would say without question that the biggest factor currently affecting my daily life is fatigue. During my first round of cancer treatments, fatigue was my constant companion from day one, and seemed fairly consistent, rated most of the time as a 4 on a 10 scale (1 being no fatigue and 10 being extreme). This time around it seems to be at about a 7 or 8. Getting dressed in the morning is exhausting. Fixing a sandwich in the kitchen for lunch is taxing. The fatigue is a

natural side effect of cancer, and results from many chemotherapy drugs. Romidepsin in particular can cause extreme fatigue in some patients.

The final aspect would be my mental outlook. I am a fairly positive glass-half-full kind of guy to start with. And I tend to apply about 110% effort to whatever tasks I undertake. Because of the implications of this battle I may have jacked up the bar to about 125%. But I find that this second set of treatments are requiring more effort to stay positive. My pain and discomfort, extreme fatigue and some added side effects, all being present 24/7 since before Christmas, are adding to my mental challenge. But I also believe that the back and leg pain, and the mobility issues will be resolved in the next several weeks. That should provide an added big boost.

(Source: http://www.lymphomainfo.net/blogs/s/day-1-cycle-1; http://www.lymphomainfo.net/blogs/s/treatment-2; http://www.lymphomainfo.net/blogs/s/the-many-aspects-of-cancer)

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca). 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 romidepsin:

Clinical factors:

- Romidepsin could fill the gap in therapy for patients with PTCL.
- Clarity requested on group of patients who would be eligible for treatment with romidepsin.
- Unknown duration of treatment.

Economic factors:

- Small patient population.
- Drug wastage likely.

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that there is no current standard of care for this patient population. Romidepsin is a new class of drug that could fill the gap in therapy for patients with PTCL who have received one prior therapy. This would be an enabler.

PAG indicated that a barrier could be the single arm trial on romidepsin for relapsed/refractory PTCL. As there are no comparative trials, PAG questioned the overall response rate versus the current treatment options.

5.2 Factors Related to Patient Population

PAG noted that the very small patient population would be an enabler. However, PAG noted that romidepsin is approved in the USA for treatment of cutaneous T-cell lymphoma and that Canadian clinicians have been accessing romidepsin via Special Access Program for this indication. Thus, PAG has concerns for use in cutaneous T-cell lymphoma, which has not been submitted for pCODR review.

PAG also noted that patients who respond to romidepsin have the option to continue treatment, beyond the six cycles, as maintenance therapy. Although early identification of responders is possible after two months of treatment and would enable early assessment of benefit, the unknown duration of treatment is an implementation barrier.

PAG is requesting clarity around the definition of “patients who have received at least one prior therapy” versus “relapsed or refractory patients” as the trial includes patients who had one prior systemic therapy. PAG noted some patients are given one dose of systemic

treatment to become eligible as having received at least one prior therapy, although patients may not have progressed.

PAG questioned whether patients who have had a stem cell transplant would be suitable for treatment with romidepsin.

5.3 Factors Related to Dosing

None identified.

5.4 Factors Related to Implementation Costs

There is only one vial size available and since the dose is calculated based on body surface area (BSA), a partial vial would be required to make the patient's dose in many cases. The short stability of the vial after reconstitution and the infusion solution, in addition to the small patient population, would make it difficult for vial sharing. PAG also noted that the full 2mL volume of the reconstituted vial cannot be completely withdrawn due to the viscosity of the reconstituted solution. There would be drug wastage from the inability to use the full volume and the poor stability of the reconstituted solution, which is a barrier to implementation.

5.5 Factors Related to Health System

Romidepsin, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of infusion related reactions. Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients which is an enabler. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to implementation.

For some jurisdictions, administration in the smaller outreach clinics may be a barrier due to the lack of resources who would be familiar with the drug and the disease.

Romidepsin is administered by intravenous infusion over 4 to 4.5 hours. This would be a barrier as there would be increased chemotherapy chair utilization, increased pharmacy preparation time and increased nursing resources.

PAG also noted the multiple drug-drug interactions and the additive effect with other drugs that prolong QT interval may present a challenge to monitor safety.

5.6 Factors Related to Manufacturer

PAG identified that the availability of romidepsin in only one vial size could be a barrier to implementation due to the potential for drug wastage.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of romidepsin when used in in the relapsed/refractory setting for patients with peripheral t-cell lymphoma that are ineligible for transplant and who have undergone systemic therapy.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 7. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized control trials In the absence of RCT data, clinical trials investigating the efficacy of romidepsin should be included. Reports of trials with only a dose-escalation design should be excluded. Reports of trials with a mixed design are to be included only if separate data were reported for the cohort of patients who were included in the efficacy-determining phase of the study.	Relapsed or refractory patients with peripheral t-cell lymphoma that are ineligible for transplant and who have undergone systemic therapy	Romidepsin 14 mg/m^2 administered intravenously over 4 hours on days 1, 8 and 15 of a 28-day cycle.	-CHOP -EPOCH -HyperCVAD, - DHAP -Gemcitabine -Gemcitabine + methylprednisolone and cisplatin -Gemcitabine, dexamethasone and cisplatin -Brentuximab - Gemcitabine + or – other therapy -Oxaliplatin -ICE -Bendamustine - Alisertib. Other experimental therapies that could be used -VIP-rABVD -Pralatrexate -Alemtuzumab -Denileukin and diftitox and interferon -Interferon -Bexarotene -Lenalidomide dexamethasone and cisplatin -Pentostatin	-**Overall survival** -Progression free survival -Overall response rate -**Grade 3-4 adverse events**, including nausea, fatigue, thrombocytopenia, infection, vomiting and diarrhea, infusion reaction, prolonged QT interval -**Quality of life** -subgroups including: anaplastic ALK+, anaplastic ALK-, PTCL NOS, angioimmunoblastic, hepatosplenic, enteropathic

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
			-Best supportive Care - No comparator in the case of single arm studies	

Notes: **CHOP**= CHOP cyclophosphamide, doxorubicin, vincristine, prednisone; **DHAP** = dexamethasone, high-dose cytarabine (ARA-C) and cisplatin Platinol; **EPOCH**= etoposide, prednisone, vincristine (Oncovin) and doxorubicin hydrochloride (hydroxydaunorubicin hycrochloride; **HyperCVAD**= cyclophosphamide, vincristine, doxorubicin and dexamethasone, administered on a hyperfractionated schedule; **ICE** = Ifosfamide, carboplatin and etoposide; **VIP-rABVD** = ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine;

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

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; 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 [romidespin or istodax] and (peripheral T-cell lymphoma].

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of April 2, 2015.

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 - clinicatrials.gov and Ontario Institute for Cancer Research - Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and [Include other conferences as per the guidance provided in S2 on tumour type, e.g. ESMO, ASH, SABCS] were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members 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.

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

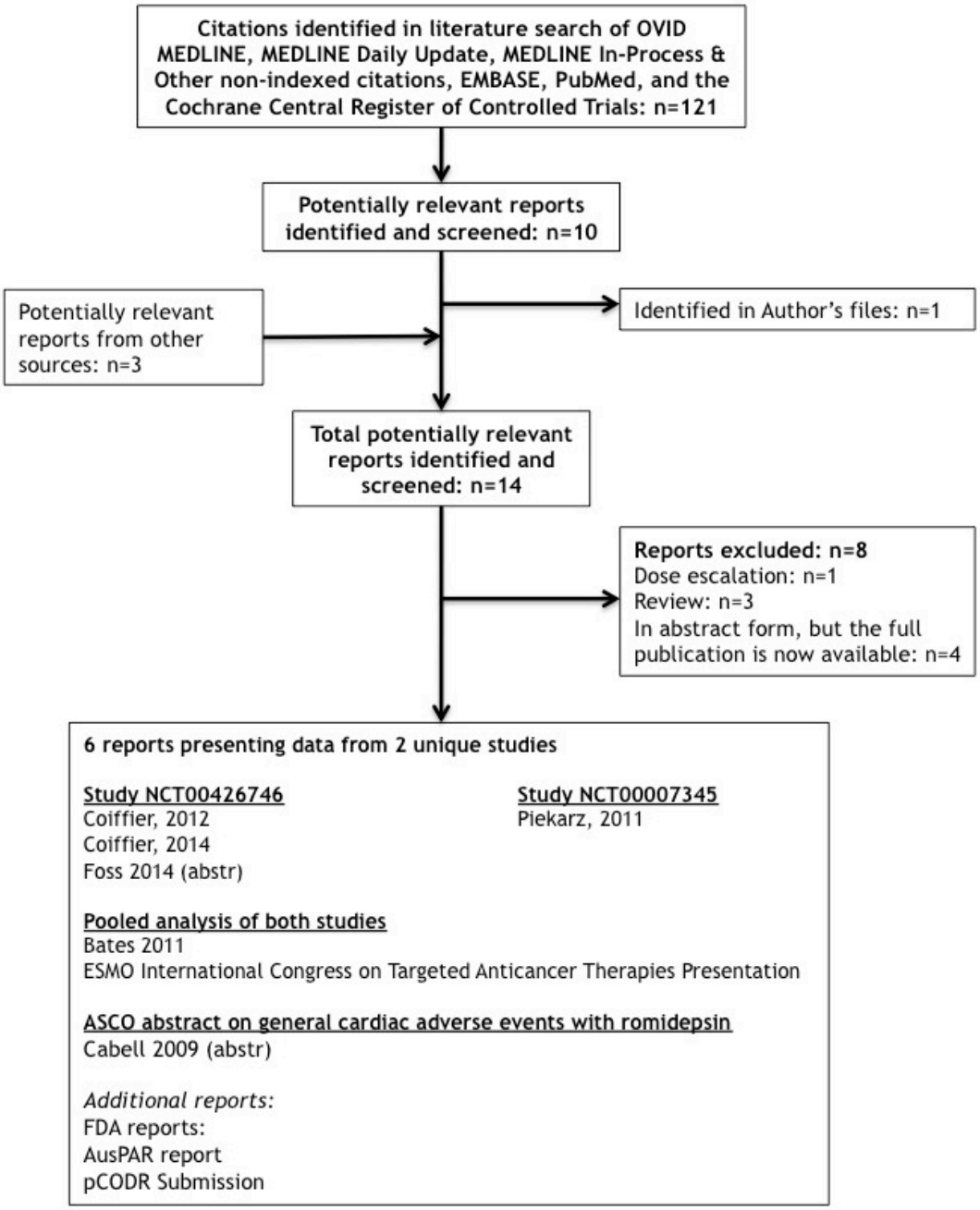
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 14 potentially relevant reports identified, 6 studies were included in the pCODR systematic review [1-4,13 14] and 8 studies were excluded. Studies were excluded because they were [dose escalation studies, 30], [reviews, 31-33], [relevant abstracts were found but they were superseded by more recent full publications, [34-37].

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies.



Note: Additional data related to the Coiffer et al. and Piekarz et al. studies were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

Provide a brief statement summarizing the number and type of included studies.

6.3.2.1 Detailed Trial Characteristics

Table 8. Summary of Trial characteristics of the included Study[11,12]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
GPI-06-0002[11] NCT00426764 Coiffier et al. Phase 2 open label multicentre study N=131 71 centres in 11 countries: Australia, the Czech republic, France, Germany, Italy Poland, Spain, Sweden, Ukraine, the United Kingdom and the United States of America Study start date: June 2007, Study completion date: December 2014 Funded by: Celgene Corporation	**Inclusion Criteria:** • Histologically confirmed PTCL • Written informed consent. • Progressive disease following at least one systemic therapy or refractory to at least one prior systemic therapy. • Measurable disease • ECOG performance status of 0-2. • Serum potassium ≥3.8 mmol/L and magnesium ≥0.85 mmol/L • Negative pregnancy test • Must use an effective barrier method of contraception. **Exclusion Criteria:** • Central nervous system lymphoma • Chemotherapy or immunotherapy within 4 weeks of study entry • Initiation of corticosteroids during study • Concomitant use of any other anti-cancer therapy or investigational agent • Any known cardiac abnormalities • Serum potassium <3.8 mmol/L or serum magnesium <0.85 mmol/L • Concomitant use of drugs that may cause a significant prolongation of the QTc, use of CYP3A4 significant or moderate inhibitors, use of therapeutic warfarin or another anticoagulant due to a potential drug interaction. • Clinically significant active infection • Previous extensive radiotherapy involving ≥30% of bone marrow, • Major surgery within 2 weeks of study entry • Previous allogeneic stem cell transplant • Inadequate bone marrow or other organ function	Romidepsin 14 mg/m^2 intravenously over 4 hours on Days 1, 8 and 15 of each 28-day cycle.	**Primary Outcome Measure** • Percentage of Participants With a Complete Response According to the International Workshop Response Criteria (IWC) for Non-Hodgkin's Lymphomas (NHL) Assessed by an Independent Review Committee **Secondary Outcome Measures** • Percentage of Participants With Objective Disease Response • Duration of Objective Disease • Duration of Complete Disease Response • Time to Disease Progression • Change in Eastern Cooperative Oncology Group (ECOG) Performance Status

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	• Patients who are pregnant or breast-feeding; • Coexistent second malignancy or history of prior solid organ malignancy within previous 3 years • Significant medical or psychiatric condition • Prior exposure to romidepsin		
NCT00020436[12] Piekarz et al. Phase 2 open label multicentre study N=63 total Peripheral T-Cell Lymphoma n=47 3 centres in Australia, 10 centres in the United States of America Study start date: December 2000 Study completion date: December 2015 Funded by: National Cancer Institute (NCI)	**Inclusion Criteria** • Relapsed or refractory peripheral T-cell lymphoma, cutaneous T cell lymphoma, mature T cell lymphoma • Disease measurable by radiographic imaging. • age ≥ to 18 years • ECOG performance status of 0-2 • No serious or intercurrent illness, a life expectancy of > than 12 weeks • written informed consent • negative pregnancy test • sexually active participants must use effective contraception • Laboratory values within limits • Cardiac studies within limits **Exclusion criteria** • Unconfirmed diagnosis, or with B-cell lymphomas • Prior or concurrent malignancies that have not been curatively treated. • Known CNS lymphoma. • Chemotherapy within 4 weeks • HIV seropositivity. • Pregnant or breast-feeding patients. • Major surgery within 21 days. • Uncontrolled infection or uncontrolled medical illness. • Known cardiac abnormalities	Romidepsin 14 mg/m^2 intravenously over 4 hours on Days 1, 8 and 15 of each 28-day cycle.	Primary Outcome Measures: • Overall response rate. • Complete response rate. • Duration of response. Secondary Outcome Measure: • To evaluate the tolerability of romidepsin with extended cycles of therapy. To examine the molecular effects of romidepsin.
ECOG= Eastern Cooperative Oncology Group			

a) Trials

Two single arm, open label phase two studies met the inclusion criteria for this systematic review, GPI-06-0002 by Coiffier et al.[2,3] and another study by Piekarz et al.[1] Both studies included patients with previously treated relapsed or refractory peripheral T-cell lymphoma and both studies used International Working group (IWC) criteria) guidelines for the evaluation of disease.[38] The study by Piekarz et al also included patients with primary cutaneous anaplastic large cell lymphoma and other mature T-cell lymphomas. However, only the results for peripheral T-cell lymphomas will be discussed and presented. Patients in both studies received

romidepsin 14 mg/m^2 intravenously over 4 hours on days 1, 8 and 15 of each 28-day cycle. Both studies were described as being open-label. However, GPI-06-0002 by Coiffier et al assessed tumour response by an independent review committee.[3]

Both studies were multicentre studies: GPI-06-0002 by Coiffier et al was conducted in 71 centres in 11 countries: Australia, the Czech republic, France, Germany, Italy Poland, Spain, Sweden, Ukraine, the United Kingdom and the United States of America and was funded by Celgene Corporation. The study by Piekarz et al.[12] was conducted in three centres in Australia and 10 in the United States and was funded by the National Cancer Institute.[12]

The primary outcome in the Coiffier et al trial was the percentage of patients with a complete response as defined by the International Workshop Response Criteria (IWC) for Non-Hodgkin's Lymphomas (NHL). An Independent Review Committee (IRC) assessed this outcome.[2] Complete response was defined as a: ">75% decrease in size aggregate of nodal index lesions (large and small), complete disappearance of extranodal and non-index lesions; total disappearance of clinical disease including skin involvement; disease-related signs and symptoms, normalization of biochemical abnormalities and reduction in size of spleen or liver so no longer palpable. Unconfirmed complete response was defined as: all above criteria except all nodal index lesions must have regressed >75% in the sum of the product diameters (SPD) from baseline. Individual nodes previously confluent must have regressed by >75% in their SPD."[11] Secondary outcomes included the percentage of participants with objective disease response, the duration of objective disease, the duration of complete disease response, the time to disease progression and change in ECOG performance status.[11]

In the study by Piekarz et al. the primary outcomes were overall response rate, complete response rate and duration of response.[12] Response in patients with nodal disease was assessed using the International Working Group Guidelines (IWG) and response in participants with skin or visceral lesions were assessed using Response Evaluation Criteria in Solid Tumours (RECIST). [1] The secondary outcome in this study was to evaluate the tolerability of romidepsin with extended cycles of therapy and to examine the molecular effects of the drug.[12]

Neither study was terminated early. The final completion date for the GPI-06-0002 study by Coiffier et al was December 2014, although data collection for the primary outcome was completed in October of 2010.[11] The final completion date for the study by Piekarz et al is December 2015 and the completion date for the primary outcome was January 2015.[12] Therefore, this data is based on an interim analysis.[38]

In both trials, time to event data was summarized using Kaplan-Meier methods.[1,2] In the study by Piekarz et al, response durations were censored at the time of first recurrence and patients were allowed to restart therapy if they were in long-term remission and discontinued therapy for reasons other than disease progression.[1] No information was provided on whether the results were censored at the time of the first recurrence in the Coiffier et al study.

b) Populations

A total of 131 patients were included in the GPI-06-0002 study by Coiffier et al and 47 patients with PTCL (63 total study population) were included in the study by Piekarz et al. Patient characteristics can be seen in Table 9.

Table 9: Patients Characteristics

Characteristics	Coiffier et al N (%)[2,11]	Piekarz et al N (%)[1]
Sex		
male	88(68)	25 (53)
female	42(32)	22 (47)
Ethnicity		
white	116(89)	NR
Black	7	NR
Asian	3	NR
Other	4	NR
Age, years		
median	61	59
range	20-83	27-84
ECOG Performance Status		
0	46(35)	20 (43)
1	66(51)	23(49)
2	17(13)	4(9)
Primary diagnosis		
PTCL, unspecified or NOS	69 (53)	27 (57)
Angioimmunoblastic T-cell lymphoma	27 (21)	7(15)
ALK-1-negative ALCL	21(16)	2(4)
Enteropathy type T-cell lymphoma	6(5)	0
Subcutaneous panniculitis-like t-cell lymphoma	3(2)	0
ALK-1-positive ALCL *	1(1)	2(4)
Cutaneous gamma/delta T-cell lymphoma	1(1)	0
Extranodal NK/T-cell lymphoma, nasal type	1(1)	0
Transformed mycosis fungoides	1(1)	0
Primary cutaneous anaplastic large T-cell	0	2(4)
Cutaneous T-cell	0	2(4)
Hepatosplenic PTCL	0	1(2)
Enthrophy associated T-cell lymphoma	0	1(2)
PTCL unspecified of the skin	0	1(2)
CD30 lymphoproliferative disorder	0	1(2)

Characteristics	Coiffier et al N (%)[2,11]	Piekarz et al N (%)[1]
Diffuse large B-cell lymphoma	0	1(2)
Type of Prior therapy		
Chemotherapy	129(99)	47(100)
Monoclonal antibody therapy	20(15)	2[38]
Other types of therapy	14(11)	9((18)
Stem cell transplant	21(16)	18(38)
Number of prior systemic therapies		
Median [range]	2 [1-8]	3 [1-11]
NR: not reported		

c) *Interventions*

Romidepsin was administered at the same dose and schedule in both studies. Patients in both arms received romidepsin 14 mg/m^2 intravenously over 4 hours on days 1, 8 and 15 of each 28-day cycle.

In the GPI-06-0002 study by Coiffier et al the majority of the patients tolerated the full dose. Sixty-one patients (47%) needed at least dose interruption and 14 (11%) required a dose reduction to 10 mg/m^2 due to adverse events.[2] At a median follow-up of 22.3 months all of the study patients received a median of 2 treatment cycles (range <1-54)[3] The median dose was 144.4 mg and the mean number of cycles was 2.0.[15]

In the study by Piekarz et al, the following percentages of doses were administered: 48% full doses, 13% escalated doses and 39% reduced doses.[1] Doses could be reduced or held for adverse events. Patients received a median of 3 (1-57) cycles, and 9 (1-169) doses. The median cumulative dose was 112 mg/m^2.[1]

d) *Patient Disposition*

In the GPI-06-0002 study by Coiffier et al 131 patients were enrolled. The analysis is based on 130 patients since one patient with a diagnosis of large B-cell lymphoma was excluded from the efficacy analysis.[2] Fifty patients received 4 or more treatment cycles and 35 patients received 6 or more treatment cycles. As of October 31, 2010, thirty-three patients completed the study after 6 cycles and 98 patients did not complete the study. The patients did not complete the study due to the following reasons; 72 patients had progressive disease; 19 due to adverse events, 3 withdrew, 1 withdrew because of a physician decision; 1 protocol violation and 2 for other reasons. No patients were lost to follow-up.[11]

In the study by Piekarz et al the protocol was initially limited to patients who had not received more than two chemotherapy regimens. The protocol was amended to include patients with any subtype of PTCL and any number of prior treatments since six of the initial 16 patients demonstrated a response to the treatment. Two deaths occurred while the patients were on the study and five occurred within 30 days after removal from the study.[1] Fifteen patients completed 6 cycles of treatment. Thirty two patients did not complete the treatment; 24 had

progressive disease; 2 stopped treatment due to adverse events; two had complicating disease, 2 patients died and 2 stopped treatment for other reasons.[15]

e) Limitations/Sources of Bias

Both studies were single arm, open label, phase II studies and, therefore, there was no comparator arm. Since there is no comparative evidence for romidepsin, the efficacy of romidepsin versus current treatments is uncertain. Additionally there were no independent assessments of the Piekarz et al study and investigators provided the analyses. The GPI-06-0002 study by Coiffier et al had independent investigators review the primary outcome. The independent assessment consisted of a blinded central radiology assessment of medical imaging data by radiologists with experience in lymphoma, followed by a review by two hematologic oncologists.[2] Most of the study data from the Piekarz et al study is also based on interim analyses. This can lead to biases as the study is not yet completed and results could change during the final analyses. [38]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Response

The response rates in the study by Coiffier et al were independently assessed. They can be seen in Table 10. Response rates in the Piekarz et al study were not independently assessed and can also be seen in Table 10. A pooled analysis for the two trials shows an overall response rate of 31% and a CR rate of 15%.13

Table 10: Response rates in the Coiffier et al and Piekarz et al studies

Response	Coiffier et al study Independent assessment N=130 (%)[2]	Coiffier et al study Investigator's assessment N=130 (%)[2]	Piekarz et al study N=45 (%)[1]
CR/CRu	19(15)	21(16)	NR
CR	13(10)	19(15)	8 (18)
CRu	6(5)	2(2)	NR
PR	14(11)	17(13)	9 (20)
ORR (CR/CRu + PR)	33 (25)	38(29)	38% (95%CI, 24% - 53%)
SD	33(25)	22(17)	5 (11)
PD or N/E*	64 (49)	70 (54)	PD 18 (40) NE 5(11)

Abbreviations: CR = complete response; CRu = unconfirmed complete response; N/E = not evaluable; NR = not reported; ORR: objective response rate; PD = progressive disease; PR = partial response; SD = stable disease

* Insufficient efficacy data to determine response because of early termination (i.e., includes patients determined to have PD by investigators prior to first post baseline assessment and therefore assessed as N/E according to the IRC).

In the Piekarz study the overall response rate was 38% (94% CI, 24% - 53%). Eight patients had a complete response, with three patients are still remaining on protocol. Nine patients had partial responses and one patient is still remaining on treatment.[1]

In the Coiffier et al study all patients received a median of two treatment cycles (range <1-54) at a median follow-up of 22.3 months. Patients who had a response (CR/CRu or PR, n= 33) received a median of 8 treatment cycles (range <1-54). Patients who had a CR/CRu (n=15) received a median of 19 cycles (range 2-54).

Overall responses by different subgroups in the Coiffier et al study can be seen in Table 11. They were similar across the three most common PTCL subgroups (NOS, AITL, ALK-1 negative ALCL) and no significant differences in objective response rate or rates of CR/CRu were seen.[3] In the 13 patients with rarer subtypes responses were not observed. However, in patients who were refractory to their last prior therapy, 14 of 49 (29%) responded (including 9 patients who achieved CR/CRu).[2]

Table 11: responses by subgroup in the Coiffier et all study[3]

Response	PTCL-NOS n=60 (%)	AITL n=27 (%)	ALK-1 Negative ALCL n=21 (%)
CR/CRu	10 (14)	5(19)	4(19)
PR	10(14)	3(11)	1(5)
ORR (CR/CRu + PR)	20(29)	8(30)	5(24)
SD	16(23)	9(33)	5(24)
Disease Control (ORR + SD90)	34(49)	12(44)	8(38)
PD/NE*	33(48)	10(37)	11(52)

Abbreviations: AITL angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; CR/CRu = confirmed/unconfirmed complete response; NE = not evaluable, ORR = objective response rate; PD = progressive disease; PR = partial response; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified; SD = stable disease; SD90 = SD for greater than 90 days; * insufficient efficacy data to determine response because of early termination.

In the Coiffier et al study baseline characteristics, prior regimens, and number of prior therapies did not have an impact on the ability of patients to respond to romidepsin. There were no meaningful differences in ORR or CR/CRu rates based on sex, age, number of prior therapies, prior stem cell transplantation, type of prior therapy, or whether the patient was refractory to their last prior therapy. However, objective responses could be seen in five (25%) of 20 patients (including four patients with CR/CRu) who received prior monoclonal antibody therapy, two (14%) of 14 patients (both CR/CRu) who previously received other types of immunotherapy, and five (24%) of 21 patients (including two patients with CR/CRu) who received prior stem cell transplantation. In patients who had received one, two, three, four, or more than four prior lines of systemic therapy the rates of CR/CRu were 13%, 14%, 11%, 27%, and 14%, respectively.[2]

Durability of responses

Most of the responses were noticed at the first response assessment, which was at 2 months. The independent review committee reported that the median time to response was 1.8 months (range, 1.4-5.3 months).[3] The median durability of response for all patients who achieved a response as measured by the independent review committee (n = 33) was 28 months (range, < 1-48+). The median duration of response had not been reached (range, < 1-48+) for those patients who achieved CR/CRu (n = 19).[3] One patient with a documented durability of response of less than 1 month discontinued treatment to receive a stem cell transplant after the first response assessment of a complete response. Of the 19 patients who achieved

CR/CRu, 53% had a durability of response ≥ 12 months and 32% had a durability of response ≥ 24 months. [3] No statistically significant differences in durability of response were seen across the three most comment PTCL subgroups, however the responses were durable.[3] In patients who had progressive disease to their last prior therapy (n = 49), the median durability of response had not yet been reached for all patients who achieved a response (n = 14) or for patients who achieved CR/CRu (n = 9).[3]

In the Piekarz et al study the overall median duration of response was 8.9 months (range 2-74) and the median time to response was 1.8 months. All patients achieved response within 2 months except for 3 patients who achieved response at 4, 8 and 11 months respectively.[1] In the 8 patients who had a complete response the median duration of response was 29.7 months (range 3-74). At the time of this report three patients are still continuing on treatment with two remaining in complete response.[1] In the 9 patients with partial responses the median duration of response was 5.2 months (range 2-23). The median time to progression is 7.4 months and at the time of this report one patient remains on study. Stable disease was seen in five patients. The median time to response was 6 months (range3-12).[1] In the Piekarz study the responses and duration by subgroups can be seen in Table 12.

Table 12: responses by subgroup in the Piekarz et al study[1]

	Number or responses	Duration of CR (mo)	Duration of PR (mo)
PTCL-NOS n=27	11	3,3,12,13,74	2,3,5,6,9,12
AITL n=6	1		23
ALK-1 Negative ALCL n=2	2	6	3

AITL angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; CR = complete response; PR = partial response; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified

Progression free survival and overall survival

In the Coiffer study a longer progression free survival was seen in patients who achieved a CR/CRu than in patients in other response categories. The independent review committee also observed that for patients with CR/CRu the median PFS was 29 months.[3] The independent review committee found that the overall median progression free survival was 4 months. Overall survival and progression free survival can be seen in Table 13.

Table 13: Overall survival and progression free survival in the Coiffier et al study[3]

	Objective responders (CR/CRu = PR; n=33)	CR/CRu ≥ 12 months (n=10)	CR/CRu < 12 months (n=9)	PR N=14)	SD90 N=23	SD<90/PD/ NE (n=74)
Median OS, months (range)	30 (2.0-49.5)	NR (21.2-49.5)	NR (9.2-32.0)	18 (2.0-38.8)	NR (8.1-44.6)	5 (0.3-29.3)
Median PFS, months (range)	20 (1.6-49.8)	29 (17.6-49.8)	13 (1.6-26.0)	7 (1.9-18.1)	7 (3.3-37.7)	2 (0.3-14.4)

	Objective responders (CR/CRu = PR; n=33)	CR/CRu ≥ 12 months (n=10)	CR/CRu < 12 months (n=9)	PR N=14)	SD90 N=23	SD<90/PD/ NE (n=74)
Abbreviations: CR/CRu = confirmed/unconfirmed complete response; NR = not reached; OS = Overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease; SD90 = SD for greater than 90 days						

Responses by prior therapy

In the Coiffier et al. study the durability of response and survival rates were not significantly different for patients who received one, two or over 3 prior therapies. However patients who had received more prior therapies discontinued treatment more frequently.[4] This can be seen in Table 14.

Table 14: responses by prior therapies[4]

	1 prior therapy n=38 (%)	2 prior therapies n=44 (%)	≥ 3 prior therapies n=48 (%)
ORR	9(24)	10(23)	15(31)
CR/CRu	5(13)	7(16)	8(17)
DOR, median (range), mo	NE (1.9-33.9)	NE (<0.1-56.3)	16.4 (<0.1-37.3)
PFS, median (range), mo	5.4 (0.4-35.5)	3.1 (0.3-57.9)	3.8 (0.3-38.9)
OS, median (range), mo	18.2 (0.4-36.6)	9.4 (0.3-58.1)	9.2 (1.3-53.8)
Discontinuation due to AEs	6(16)	6(14)	12(25)
Abbreviations: AE= adverse event; DOR = duration of response; NE – not estimable; OS = overall survival; PFS = progression free survival			

ECOG status

Eighty-two patients had a baseline performance status of more than 0 and also available post-baseline data in the Coiffier study. Of these patients 34 (41%) had a documented improvement in ECOG performance status. Improvements correlated with responses and were noted in 83%, 60%, 52%, and 18% of patients with CR/CRu, PR, SD, and PD or not evaluable, respectively.[3]

Harms

The most common adverse events in the Coiffier study were nausea, infections, fatigue, thrombocytopenia, vomiting, and diarrhea. The most common grade ≥ 3 adverse events were thrombocytopenia, neutropenia, and infection of any type. These can be seen in Table 15.[2] Infections were common in the Coiffier et al study, however no individual infection type was reported with an incidence of 10% or more. Most of the infections were thought to be unrelated to treatment, with drug-related grade 3 to 4 infectious in 6% of the patients. Patients who had received prior monoclonal antibody therapy had a noticeably higher incidence of grade 3 to 4 infections (30% *v* 14%) as well as in those with disease involving the bone marrow (30% *v* 12%). This suggests that perhaps underlying disease, and prior therapies, may be important contributing aspects to these events.[2]

Adverse events from ECG abnormalities were uncommon and observed in 8 (6%) of patients in the Coiffier study. Four patients (3%) reported prolonged QTc intervals of grades 1 and 2. None of these patients had any other cardiac adverse events. A review of the QTcF and QTcB intervals over the first 4 cycles showed no clinically

significant changes across treatment cycles for these limitations.[2] In the Piekarz study one patient had an asymptomatic, nonrecurrent, 12-beat run of ventricular tachycardia during an ECG, but this patients was found to have abnormal magnesium, and potassium levels during this event.[1] An abstract from 2009 states that romidepsin has a slight effect on prolongation of the QT interval, but the effect was mild and below the level of clinical concern and not associated with any observed clinical cardiovascular events.[14]

In the Piekarz study the adverse events can be seen in Table 15. The rates of events are in line with the Coiffier trial except for the rates of Leukopenia. This was much higher in the Piekarz study. Overall the rate of infection for the Piekarz study was n=17 (36%).[1]

Table 15: Adverse events for both trials

	Coiffier et al. All events (%) Grade ≥3 N=131[2]	Coiffier et al. Drug related events (%) Grade ≥3 N=131[2]	Piekarz et al. Grade 3 and 4 Adverse events (%) N=47[15]
Nausea	3(2)	2(2)	6(6.4)
Infections	25(19)	8(6)	13(27.7)
Asthenia/fatigue	11(8)	7(5)	9 (19.1)
Thrombocytopenia	32(24)	30(23)	17(36.2)
Vomiting	6(5)	5(4)	4(8.5)
Diarrhea	3(2)	2(2)	1(2.1)
Pyrexia	7(5)	5(4)	8(17)
Neutropenia	26(20)	24(18)	22(27.8)
Anemia	14(11)	7(5)	13(27.7)
Leukopenia	8(6)	8(6)	21(44.7)

In the Coiffier study most of the patients tolerated the full dose of romidepsin, however, 61 patients (47%) needed at least one dose interruption and 14 (11%) needed a dose reduction to 10 mg/m^2 for controlling adverse events. Most dose interruptions were due to thrombocytopenia (18%), infections (12%), and neutropenia (11%). Thrombocytopenia was the only adverse events that required a dose reduction in more than two patients (n = 4). In most of the patients, thrombocytopenia recovered between cycles.[2]

Treatment was discontinued as a result of adverse events in 25 (19%) of 131 patients in the Coiffier study. The main events leading to drug cessation were thrombocytopenia (n=3, 2%), pneumonia (n=3, 2%) fatigue (n=2 2%), dyspnea (n=2 2%), and sepsis (n=2 2%). In addition, eight patients (6%) died within 30 days of the last study drug dose. However, seven of these patients died more than 3 weeks after their last dose. For three patients, progressive disease was the only cause of death reported. For the other five patients, an infection or incident that occurred during infection was reported as a cause of death. One of these deaths was regarded as possibly being treatment related. The patient received two doses of the drug before withdrawing consent. The patient died 3 weeks after the last dose from multi-organ failure with sepsis and progressive disease.[2]

Two deaths occurred during the study in the Piekarz et al report and five deaths occurred within 30 days of removal from the study. One patient who died during the study had rapid progressive disease with a pericardial effusion. This patient

died five days after the first dose. The second patients who died on study had a past significant cardiac history. This patient had a complete response after the first cycle but passed away during sleep 3 days after the second dose on the 5th cycle. After the death of this patient the study protocol changed to exclude patients with significant cardiac histories.[1] Four out of five of the other deaths occurred in patients with disease progression. The other patient achieved a complete response, but developed high-grade fevers, thrombocytopenia and elevated liver function tests after his first dose of the 15th cycle. The biopsy suggests that this patient had Epstein Barr positive NK-T lymphoma and died of hemophagocytosis syndrome.[1]

6.4 Ongoing Trials

Table 16. Summary of trial characteristics of ongoing studies

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Phase IIa Study on the Role of Gemcitabine Plus Romidepsin (GEMRO Regimen) in the Treatment of Relapsed/Refractory Peripheral T-cell Lymphoma Patients. (FIL_GEMRO)[39]			
NCT01822886 Location: Italy Estimated Enrolment n=20 Funding: Fondazione Italiana Linfomi ONLUS	Inclusion Criteria: • Patients with diagnosis of PTCL • Age ≥ 18 years • Relapsed (≥1) or refractory to conventional chemotherapy/radiotherapy • Stage I-IV • ECOG Performance status ≤2 • Normal renal and hepatic functions • Laboratory test results. • Adequate bone marrow reserve. • Able to adhere to study visit schedule and other protocol requirements • Cardiac ejection fraction (MUGA scan or echocardiography) > 45% • Life expectancy > 6 months • Females of childbearing potential must have a negative pregnancy test. • Patients of childbearing potential must use an effective contraceptive method during the study and for 30 days after the last dose of study drug. • Measurable disease of at least 2 cm as detected by CT scan, assessed by site radiologist • Written informed consent Exclusion Criteria: • Serious active disease or co-morbid medical condition • History of malignancies other than lymphoma unless been free of the disease for ≥ 3 years • Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form • Patients with congenital long QT syndrome, history of significant cardiovascular disease and/or taking drugs leading to significant QT prolongation • Corrected QT interval > 480 msec (using the Fredericia formula) • Low K+ (<3.8 mmol/L) and low Mg+ (<0.85 mmol/L) levels, except if corrected before beginning the chemotherapy • Previous exposure to romidepsin or gemcitabine • CNS disease • History of clinically relevant liver or renal insufficiency; significant cardiac, vascular,	Romidepsin 12 mg/m2 d.1,8, 15 for 6 cycles + Gemcitabine 800 mg/m2 d.1, 15 for 6 cycles by 28 days followed by Romidepsin 14 mg/m2 d. 1, 15 to PD.	Primary Outcome Measures: • Complete remission rate Secondary Outcome Measures: • ORR • DOR • PFS • OS • B-symptoms • Adverse events

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Phase IIa Study on the Role of Gemcitabine Plus Romidepsin (GEMRO Regimen) in the Treatment of Relapsed/Refractory Peripheral T-cell Lymphoma Patients. (FIL_GEMRO)[39]			
	pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances Active opportunistic infection		
Alisertib (MLN8237) or Investigator's Choice in Patients With Relapsed/Refractory Peripheral T-Cell Lymphoma[40]			
NCT01482962 N=271 Phase3 - RCT 30 Locations in the United States and Canada Funded by: Millennium Pharmaceuticals, Inc	Inclusion Criteria: • Age 18 or older • Patients with PTCL and have relapsed or are refractory to at least 1 prior systemic, cytoxic therapy for PTCL. Cutaneous-only disease is not permitted. Patients must have documented evidence of progressive disease. • Tumor biopsy available for central hematopathologic review • Measurable disease according to the IWG criteria • ECOG PS of 0-2 • Patients of childbearing potential must use an effective method of contraception through 30 days after the last dose of study drug. • Suitable venous access • Voluntary written consent Exclusion Criteria • Central nervous system lymphoma • Treatment within 4 weeks of first dose of study treatment or concomitant use during study • Prior administration of an Aurora A kinase-targeted agent, including alisertib; or all of the 3 comparator drugs (pralatrexate, or romidepsin or gemcitabine; or known hypersensitivity) • History of uncontrolled sleep apnea syndrome or other conditions that could result in excessive daytime sleepiness • Cardiac conditions. • Concomitant use of other medicines • Patients with abnormal gastric or bowel function who require continuous treatment with H2-receptor antagonists or proton pump inhibitors • HIV, hepatitis B virus, or hepatitis C • Autologous stem cell transplant less than 3 months prior to enrolment • Patients who have undergone allogeneic stem cell or organ transplantation any time • Inadequate blood levels, bone marrow or other organ function.	Patients randomized to receive alisertib will be administered an enteric-coated tablet formulation 5×10-mg twice daily orally for 7 consecutive days (Cycle Days 1-7) in a 21-day cycle. Patients randomized to receive Pralatrexate will be administered the drug at 30mg/m2 as an intravenous (IV) push over 3 to 5 min once weekly for 6 weeks in 7-week cycles with concurrent vitamin B12 and folic acid supplementation. Cycles should be repeated every 7 weeks Patients randomized to receive Gemcitabine will receive the drug intravenously at 1,000 mg/m2 over 30 minutes on Days 1, 8, and 15 of a 28-day cycle. Cycles should be repeated every 28 days in the absence of disease progression or unacceptable toxicity. Patients randomized to receive Romidepsin will be administered the drug intravenously at 14mg/m2 over a 4-hour period on Days 1,8,& 15 of a 28-cycle. Cycles should be repeated every 28 days.	Primary Outcome Measures: • Overall response rate (ORR) by central review + progression free survival (PFS) Secondary Outcome Measures: • Number of patients with complete response + complete response unconfirmed • Number of patients with overall survival • Time to disease progression, duration of response, and time to response • Number of adverse events, serious adverse events, assessments of clinical laboratory values and clinically important abnormalities, and vital sign measurements • Time to subsequent antineoplastic therapy • Plasma concentration-time data to contribute to future population pharmacokinetics (PK) analysis Changes in reported symptoms and Quality of Life (QOL) assessment per Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) for functioning and symptoms

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Phase IIa Study on the Role of Gemcitabine Plus Romidepsin (GEMRO Regimen) in the Treatment of Relapsed/Refractory Peripheral T-cell Lymphoma Patients. (FIL_GEMRO)[39]			
	• The patient must have recovered to NCI CTCAE Grade ≤ 1 toxicity, to patients' baseline status (except alopecia), or deemed irreversible from the effects of prior cancer therapy • Major surgery, serious infection, or infection requiring systemic antibiotic therapy within 14 days prior to the first dose of study treatment • Female patients who are breastfeeding or pregnant • Coexistent second malignancy or history of prior solid organ malignancy within previous 3 years • Serious medical or psychiatric illness or laboratory abnormality that could, in the investigator's opinion, potentially interfere with the completion of treatment according to the protocol		

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma and Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on romidepsin (Istodax) for peripheral T-cell lymphoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR 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.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature search through: Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update, EMBASE. And Cochrane Central Register of Controlled Trials (CENTRAL)

1. (peripheral T-cell lymphoma or T-cell lymphoma).mp.
2. (Istodax or romidepsin).mp.
3. (FK228 or FK 228 or Fk-228).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
4. (FR901228 or FR 901228 or FR-901228).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
5. 2 or 3 or 4
6. 1 and 5
7. remove duplicates from 6
8. limit 7 to (phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)

2. Literature Search via PubMed

1. Istodax OR romidepsin OR FK228 OR FK 228 OR Fk-228
2. peripheral T-cell lymphoma or T-cell lymphoma
3. 1 AND 2
4. publisher[sb]
5. 3 AND 4.2

3. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov
Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: Istodax OR romidepsin OR FK228 OR FK 228 OR Fk-228

Select International Agencies:

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

Search terms: Istodax OR romidepsin OR FK228 OR FK 228 OR Fk-228

Conference Abstracts:

American Society of Clinical Oncology (ASCO)

Via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

American Socety of Hematology (ASH)

Via Blood search portal: http://www.bloodjournal.org/ash-annual-meeting-abstracts?sso-checked=1

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