Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Pralatrexate

Proprietary Product Name: Folotyn

Sponsor: Mundipharma Pty Ltd

March 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations 4

1. Clinical rationale 7

1.1. Peripheral T-cell lymphoma 7

1.2. Currently available treatment for PTCL 7

1.3. The rationale for the clinical development of pralatrexate for use in PTCL 7

1.4. Orphan drug designation 8

1.5. Guidance 8

2. Contents of the clinical dossier 8

2.1. Scope of the clinical dossier 8

2.2. Paediatric data 10

2.3. Good clinical practice 11

3. Pharmacokinetics 11

3.1. Studies providing pharmacokinetic data 11

3.2. Summary of pharmacokinetics 13

3.3. Evaluator's overall conclusions on pharmacokinetics 23

4. Pharmacodynamics 25

4.1. Studies providing pharmacodynamic data 25

4.2. Summary of pharmacodynamics 25

4.2.2. Pharmacodynamic effects 26

4.3. Evaluator's overall conclusions on pharmacodynamics 30

5. Dosage selection for the pivotal studies 31

6. Clinical efficacy 32

6.1. Peripheral T-cell lymphoma in adults 32

6.2. Evaluator's conclusions on clinical efficacy for PTCL 55

7. Clinical safety 58

7.1. Studies providing evaluable safety data 58

7.2. Pivotal studies that assessed safety as a primary outcome 61

7.3. Patient exposure 62

7.4. Adverse events 65

7.5. Laboratory tests 75

7.6. Post-marketing experience 82

7.7. Safety issues with the potential for major regulatory impact 82

7.8. Other safety issues 85

7.9. Evaluator's overall conclusions on clinical safety 88

8. First round benefit-risk assessment ____ 90
8.1. First round assessment of benefits ____ 90
8.2. First round assessment of risks ____ 90
8.3. First round assessment of benefit-risk balance ____ 91
9. First round recommendation regarding authorisation ____ 91
10. Clinical questions ____ 91
10.1. Efficacy ____ 91
11. References ____ 92

List of abbreviations

Abbreviation	Meaning
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
BCRP	breast cancer resistance protein
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CER	clinical evaluation report
CR	complete response
CRu	complete response unconfirmed
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DHAP	dexamethasone, cisplatin and cytarabine
DHF	dihydrofolate
DHFR	dihydrofolate reductase
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Meaning
EMA	European Medicines Agency
EPOCH	infusional etoposide, doxorubicin, vincristine plus bolus cyclophosphamide and prednisone
EU	European Union
FPGS	folylpolyglutamyl synthetase
GARFT	glycinamide ribonucleotide formyltransferase
GCP	good clinical practice
hERG	human ether-a-go-go-related gene
Hcy	homocysteine
IC_{50}	the concentration of an inhibitor causing 50% inhibition
ICE	ifosfamide, carboplatin and etoposide
IND	investigational new drug (USA)
LC/MS/MS	liquid chromatography–tandem mass spectrometry
LLOQ	lower limit of quantification
MMA	methylmalonic acid
MRP	multidrug resistance-associated protein
MTD	maximum tolerated dose
NSCLC	non small cell lung cancer
NHL	non-Hodgkin's lymphoma
OAT	organic anion transporter
OCT	organic cation transporter
OS	overall survival
pB-LBL	precursor B-cell lymphoblastic lymphoma
PDX	pralatrexate
PET	Positron-emission tomography
PFS	progression-free survival
P-gp	P-glycoproteins

Abbreviation	Meaning
PIP	paediatric investigation plan
PPF	pre-submission planning form (TGA)
PTCL	peripheral T-cell lymphoma
PR	partial response
PR interval	time from the beginning of the P wave to the QRS complex of an ECG
QT interval	time between the beginning of the Q wave and the end of the T wave of an ECG
QTcF	Fridericia's rate-corrected QT interval
QTcB	Bazett's rate-corrected QT interval
RR interval	time duration between two consecutive R waves of an ECG
RFC-1	reduced folate carrier 1
RT-PCR	reverse transcription combined with polymerase chain reaction
SCT	stem cell transplant
TCC	transitional cell carcinoma
TGA	Therapeutic Goods Administration
T-LBL	T-cell lymphoblastic lymphoma
THF	tetrahydrofolate
TS	thymidylate synthase
WHO	World Health Organization

1. Clinical rationale

The sponsor provided a detailed and well argued clinical rationale for the development of pralatrexate as a treatment for peripheral T-cell lymphoma (PTCL). Key elements of the sponsor's rationale are presented below.

1.1. Peripheral T-cell lymphoma

PTCL is a rare, heterogeneous group of aggressive non-Hodgkin's lymphomas (NHLs) with a generally poorer prognosis than their B-cell counterparts. The natural history and outcome of PTCL varies widely with various histological subtypes. Patients with anaplastic large cell lymphoma (particularly the subtype positive for anaplastic lymphoma kinase [ALK+]) have better survival that those with other subtypes, with 5-year survival being reported as high as 70% (Vose *et al*., 2008). However, for other subtypes in patients characterised as high risk by the International Prognostic Index (IPI) (Shipp, 1994), 5-year survival has been reported to be as low as 6% (Sonnen *et al*., 2005). Several clinical studies have reported a median survival of less than 2 years for patients with T-cell neoplasms and 5-year survival rates of less than 30% (Armitage & Weisenburger, 1998; Lopez-Guillermo *et al*., 1998; Rudiger *et al*., 2002).

1.2. Currently available treatment for PTCL

Currently there are no therapies specifically approved for the treatment of PTCL. Given the aggressive clinical course and generally poor outcomes with PTCL, treatment typically involves combination chemotherapy regimens. However, the regimens used have been based largely on their utility and benefit in B-cell diseases. The majority of patients are initially treated with standard regimens of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy (Savage, 2007). A variety of other anthracycline-based combination therapies have also been utilised as first-line treatments (Fisher *et al*., 1993). The first-line response rates for CHOP chemotherapy in patients with PTCL have been reported to range between 50% and 70%. However, patients often relapse soon after responding to first-line treatments (Vose *et al*., 2008).

Also, there have been relatively few studies of potential therapeutic agents for use in relapsed or refractory PTCL - gemcitabine (Sallah *et al*., 2001), denileukin diftitox (Dang *et al*., 2007), deoxycoformycin (Dang *et al*., 2003; Dearden *et al*., 1991; Mercieca *et al*., 1994) and lenalidomide (Dueck *et al*., 2009). However, these studies have commonly included indolent tumour types, such as non-transformed mycosis fungoides, and none included more than 30 patients with the more aggressive PTCL subtypes.

1.3. The rationale for the clinical development of pralatrexate for use in PTCL

Pralatrexate is a 10-deazaaminopterin analogue of the widely used antifolate/antimetabolite, methotrexate that inhibits the enzyme dihydrofolate reductase (DHFR). Antifolates are well established as effective anticancer agents in the treatment of malignancies such as acute lymphoblastic leukaemia, lymphomas, and breast and lung cancer (Walling, 2006).

During the preclinical development program a range of *in vitro* and *in vivo* pharmacodynamic studies of pralatrexate were performed using model systems of a variety of solid tumour types and haematological malignancies. The sponsor reported these studies demonstrated pralatrexate has a broad and potent cytotoxic activity as a single agent as well as in combination with a variety of currently used chemotherapeutic agents. Of note, i*n vitro* studies in CCRF-CEM human leukaemia cells demonstrated that pralatrexate is 14 times more efficiently transported into the cells and 10 times more efficiently polyglutamated than methotrexate (Sirotnak *et al*.,

1998). These results were reflected in a 30-fold improvement in cytotoxic activity of pralatrexate compared with methotrexate in these cells. Also, after 5 days of continuous *in vitro* exposure, pralatrexate demonstrated an 8- to 20-fold greater potency than methotrexate in 5 lymphoma cell lines. It was also reported by the sponsor that this greater efficacy was confirmed by *in vivo* animal studies that used human lymphoma xenografts. A clinical development program was then initiated to determine potential efficacy in patients with refractory Hodgkin's and non-Hodgkin's lymphomas, and solid tumours (including non small cell lung cancer, malignant pleural mesothelioma, metastatic breast cancer and transitional cell carcinoma of the urinary bladder). An early clinical study in which a variety of refractory lymphoma patients were treated with pralatrexate (PDX-02-078) found that PTCL patients responded particularly well. Consequently, in view of the strong clinical need for more effective treatments, a specific clinical development program for PTCL commenced.

1.4. Orphan drug designation

Pralatrexate was granted orphan drug status in Australia for the "t*reatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated)*" in September 2011. Although the wording of the proposed indication is slightly different to the wording of the orphan drug designation, the meaning is the same.

It has been estimated that the prevalence of PTCL in Australia in 2010 was approximately 840 patients.

1.5. Guidance

The TGA-adopted EU guidelines applicable to this submission are:

- Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr), effective June 2006; and
- Appendix 2 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev. 3) on Confirmatory studies in Haematological Malignancies, effective 17 December 2010;
- Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005), effective December 2006; and
- Points to Consider on Validity and Interpretation of Meta-analyses, and One Pivotal Study (CPMP/EWP/2330/99), effective 27 March 2002.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Clinical pharmacology:
  - Pharmacodynamic (PD) data from a Phase I/II trial in lymphoma patients (PDX-02-078);
  - One study examining effects of pralatrexate on QT interval (PDX-007 QTc);
  - One mass balance study in advanced cancer patients (PDX-016);
  - One integrated analysis of pharmacokinetic (PK) data derived from three Phase I/II clinical studies (PDX-008, PDX-007 and PDX-99-083);
  - One full population PK (POPPK) analysis;

- Protocol for an ongoing open-label, Phase I study to evaluate the safety and PKs of pralatrexate in cancer patients with mild, moderate and severe renal impairment (PDX-019) that is in the earliest stages of enrolment with no data generated as yet.

· Efficacy/safety studies:

- One ongoing **pivotal** Phase II study involving 115 patients with relapsed or refractory PTCL, of whom 111 were treated with pralatrexate (PDX-008, also known as PROPEL). Enrolment was completed and a full clinical study report (CSR) was submitted;
- One Phase I/II study involving 72 adult patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma, of whom 36 (50%) had T/natural killer (NK)-cell lymphoma (PDX-02-078 – also listed under clinical pharmacology studies above). This study was completed and a full CSR was submitted;
- Twelve Phase I/II studies (1 controlled; 11 uncontrolled) in varied stages of completion, conducted in other cancer indications and using treatment regimens other than that proposed, and which have been evaluated only from a safety point of view in this CER:
  - § pralatrexate combined with gemcitabine for treatment of relapsed of refractory lymphoproliferative malignancies (PDX-009 - enrolment ongoing, interim CSR submitted);
  - § relapsed or refractory cutaneous T-cell lymphoma (PDX-010 – study ongoing, interim CSR submitted);
  - § advanced solid tumours (PDX-97-006, PDX-01-014 - both studies completed, abbreviated CSRs submitted);
  - § stage IIIB or IV non small cell lung cancer (PDX 99-053 - study completed, abbreviated CSR submitted; PDX-007 - study completed, full CSR submitted; PDX-012 – comparative ongoing study of PDX versus erlotinib interim CSR submitted);
  - § pralatrexate combined with a taxane (paclitaxel or docetaxel) for treatment of "advanced cancer" (PDX 99-083 - study completed, abbreviated CSR submitted);
  - § unresectable malignant pleural mesothelioma (PDX-01-076- study completed, abbreviated CSR submitted);
  - § advanced or metastatic relapsed transitional cell carcinoma of the urinary bladder (PDX-011 – enrolment ongoing, interim CSR submitted);
  - § advanced or metastatic breast cancer (PDX-014 – enrolment ongoing, synopsis of interim CSR submitted); and
  - § relapsed or refractory B-cell NHL (PDX-015 – enrolment ongoing, synopsis of interim CSR submitted).
- Details (but no data) were also submitted for two confirmatory Phase III, controlled clinical studies pertinent to the proposed indication of PTCL:
  - § PDX-017 (Protocol submitted) – a randomised, study of sequential pralatrexate versus observation in patients with previously undiagnosed PTCL who achieved a response after completing at least 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based treatment. The study is open to enrolment in the US, UK and Australia with a target of 549 patients randomised 2:1 to pralatrexate or observation, with follow-up through 7 years post-randomisation.
  - § PDX-3501 (Protocol synopsis submitted) – a randomised, comparative, open-label, study of pralatrexate versus treatment of physician's choice in patients who have progressed after at least one prior therapy for PTCL. This study is currently in the

planning and initiation stages. It is planned that 148 adult patients will be enrolled to obtain 108 events (deaths). Subjects will be randomised in a 1:1.

- an *Integrated Summary of Safety Tables* which comprised a collation of summary safety tables for the various treatment populations in the clinical development program and a document titled *Updated Safety Tables, Listings and Narratives* that presented supplemental tables and listings generated in response to the European Day 120 List of Questions;
- Post-marketing safety data from seven post-marketing safety update reports (PSURs) covering the period September 2009 to June 2011; and
- 348 literature references.

2.2. Paediatric data

The submission did not include paediatric data. However, the sponsor has, appropriately, developed a paediatric investigation plan (PIP) for pralatrexate. The indications targeted by the PIP are the treatment of paediatric patients aged 3 to 18 years with:

- first relapse or primary refractory mature B-cell NHL;
- peripheral T-cell lymphoma (nodal, other extranodal and leukaemic disseminated); and
- lymphoblastic NHL.

The plan proposes to use 2 pharmaceutical forms - solution for infusion for intravenous use and a solution for injection for intrathecal use (to be developed).

Three clinical studies are proposed in the PIP:

- an open-label multicentre, single arm, dose-finding study to evaluate the safety, pharmacokinetics and activity of high-dose pralatrexate with and without leucovorin in 36 patients aged 3 -18 years with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma (ALCL), T-cell lymphoblastic lymphoma (T-LBL) or precursor B-cell lymphoblastic lymphoma (pB-LBL);
- a randomised, controlled, centrally blinded non-inferiority study comparing the pharmacodynamics, efficacy and safety of high-dose pralatrexate with leucovorin rescue in at least 260 patients aged 3 -18 years with relapsed or primary refractory DLBCL, ALCL, T-LBL or pB-LBL; and
- an open-label dose-finding study to evaluate the pharmacokinetics, safety and maximum tolerated dose (MTD) in patients aged 3 -18 years with CNS involvement of DLBCL, ALCL, T-LBL or pB-LBL previously treated with one or more systemic treatment that included intrathecal methotrexate.

The PIP was approved by the EMA in November 2010 but the completion of the studies was deferred until 2021.

Also, waivers were granted on the grounds that clinical studies could not be expected to be of significant therapeutic benefit to or fulfil a need for the following paediatric populations:

- Hodgkin's lymphoma; and
- children aged less than 3 years with first relapse or primary refractory mature B-cell non-Hodgkin lymphoma, treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic disseminated) and treatment of lymphoblastic non-Hodgkin lymphoma.

2.3. Good clinical practice

The PTCL clinical study program for pralatrexate comprised 2 efficacy/safety studies – PDX-02-078 and PDX-008, both of which were conducted in compliance with the principles of ICH Good Clinical Practice (GCP) and the Declaration of Helsinki. The supporting studies undertaken in various other indications were also conducted according to GCP principles and the Declaration of Helsinki.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the available data relating to each pharmacokinetic (PK) topic and the location of each study summary.

Table 1. Submitted pharmacokinetic data

PK topic	Subtopic	Study ID	*
Healthy adults	General PK	Nil studies	
Target population §	Single dose PKs	PDX-008	
	Multiple dosing PKs	PDX-008	
Other oncology populations	Single dose PKs	PDX-007	
		PDX-99-083	
		PDX-016	*
	Multiple dosing PKs	PDX-99-083	
Special populations	Hepatic impairment	Nil studies	
	Renal impairment	Nil studies	
	Neonates/infants/children/adolescents	Nil studies	
	Elderly	Nil studies	
Genetic/gender PKs		Nil studies	
Drug-drug interaction studies		Nil studies	
Population PK analyses	Healthy subjects	Nil analyses	
	Oncology population		
	Integrated PK report	-	*
	Population PK analysis	POPPK	*

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Pralatrexate is a cytotoxic agent, so no studies have been performed in healthy volunteers.

PK data for the two pralatrexate diastereomers PDX-10a and PDX-10b were provided from two Phase I clinical studies (PDX-007 [patients with advanced non-small cell lung cancer] and PDX-99-083 [patients with advanced cancer]) and one Phase II study (PDX-008 [patients with relapsed or refractory PTCL]). Of note, only Study PDX-008 included patients from the target

population (that is, the proposed indication of PTCL). These PK data were generated with a fully validated LC/MS/MS assay method that quantified both pralatrexate diastereomers.

In addition, the sponsor provided two pooled PK analyses as follows:

- a pooled, non-compartmental, integrated covariate analysis, comprising all patients from studies PDX-008, -007 and -99-083 who completed a dense PK plasma sampling schedule over 24 - 72 hours (n=54); and
- a POPPK analysis population was performed to estimate population parameters for pralatrexate diastereomers PDX-10a and PDX-10b, including typical values, inter-individual variation, and residual variability after administration of pralatrexate to cancer patients, and to estimate the effects of individual-specific covariate factors that may be predictive of the unexplained random variability in pralatrexate PK. This analysis included all patients from the 3 studies with PK data, including those with sparse PK plasma sampling (n=154).

The contributions of the three clinical studies to these analyses were as follows:

- PDX-008 (n=109)
  - 10 of the 109 patients provided full plasma PK data and 8 provided urine PK data for the integrated, non-compartmental PK analysis;
  - The remaining 99 patients provided sparse plasma PK data;
  - All 109 patients provided PK data for the POPPK analysis.
- PDX-007 (n=39)
  - 38 of the 39 patients provided full plasma PK data and 33 provided urine PK data for the integrated, non-compartmental PK analysis;
  - All 39 patients provided PK data for the POPPK analysis.
- PDX-99-083 (n=51)
  - 6 patients provided full PK data for both non-compartmental PK and POPPK analyses.

Demographic and clinical characteristics of patients with full PK profiling in each of the studies are summarised in Table 2 which shows they were predominantly Caucasian, aged 50+ years, with normal hepatic and renal function.

Table 2. Characteristics of patients with full PK profiling of pralatrexate diastereomers

		PDX-008 (n=10)	PDX-007 (n=38)	PDX-99-083 (n=6)
Tumour type		PTCL	NSCLC	Solid tumours
Age (yrs)	mean ± SD	52.3 ± 14.7	61.1 ± 9.2	61.5 ± 13.6
	median	51	62	66.5
	range	24-75	40-77	37-76
Gender	Male : Female	7 : 3	16 : 22	3 : 3
Race	Caucasian	6	34	4
	Negro	3	4	1
	Asian	-	-	1
	Unknown	1	-	-
BSA (m^2)	mean ± SD	1.99 ± 0.24	1.84 ± 0.22	1.82 ± 0.26
	median	2.0	1.87	1.86
	range	1.52 – 2.4	1.36 – 2.45	1.45 – 2.10
Serum creatinine (mg/dL)	mean ± SD	1.16 ± 0.26	0.96 ± 0.24	0.88 ± 0.3
	median	1.15	0.9	0.9
	range	0.8 – 1.7	0.5 – 1.6	0.5 – 1.3
Creatinine clearance (mL/min)	mean ± SD	86.8 ± 23.5	88.6 ± 21.7	90.8 ± 27.3
	median	90.5	83.0	93
	range	53 - 130	59 - 130	60 - 130
Total bilirubin (mg/dL)	mean ± SD	0.56 ± 0.24	0.73 ± 0.28	0.70 ± 0.17
	median	0.5	0.7	0.65
	range	0.3 – 1.0	0.2 – 1.6	0.5 – 0.9
ALT (IU/L)	mean ± SD	35.5 ± 42.7	24.3 ± 12.6	24.0 ± 10.8
	median	21	23	22.5
	range	10 – 154	5 - 72	12 - 41
AST (IU/L)	mean ± SD	34.3 ± 19.6	25.0 ± 9.2	26.7 ± 12.4
	median	32	23	27
	range	10 - 79	11 - 59	12 - 47

PTCL = peripheral T-cell lymphoma NSCLC = non small cell lung cancer

3.2. Summary of pharmacokinetics

The information in the following summary is derived from clinical efficacy/safety studies in which PK profiling was undertaken in a subset of patients, and from *in vitro* studies using human biomaterials. As noted previously, the *in vitro* studies have not been evaluated as part of this CER and the information pertaining to these studies has been taken directly from the sponsor's *Summary of Clinical Pharmacology Studies* (Module 2.7.2).

3.2.1. Pharmacokinetics in the target population

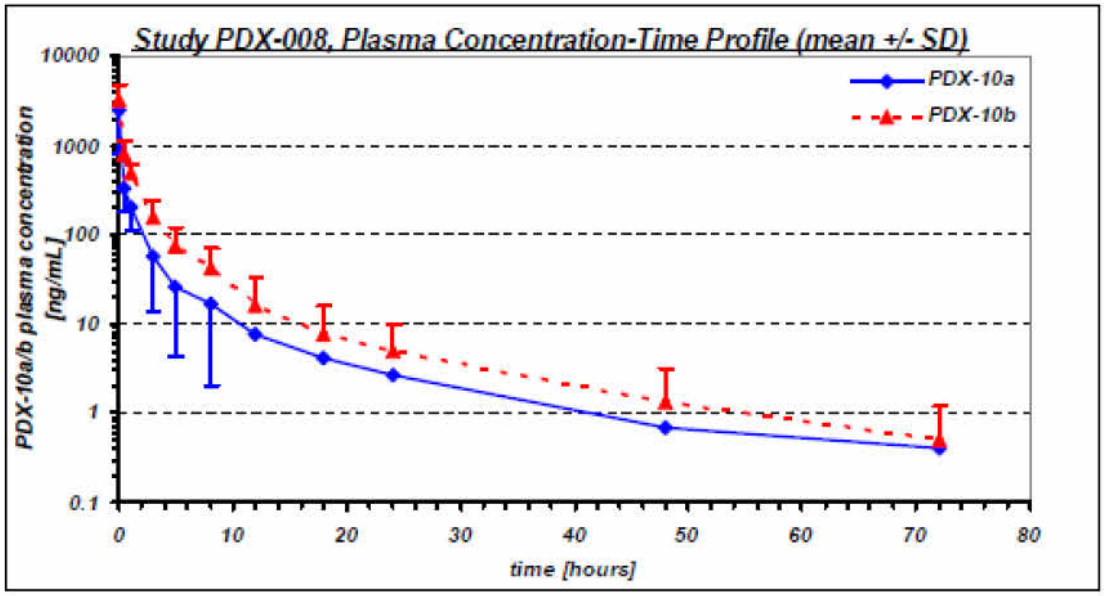
Pralatrexate Solution for Infusion is intended for intravenous administration only. It is a simple solution and is administered by injection into an IV line over 3 to 5 minutes. Thus, absorption characteristics, bioavailability and bioequivalence, and food effects are not applicable.

3.2.2. Single dose pharmacokinetics

The mean plasma concentration-time profile for the diastereomers PDX-10a and PDX-10b obtained following IV push in 10 patients with PTCL (PDX-008) are shown in **Figure 1**, below. There was a multiphasic decline in plasma concentrations, characterised by an initial rapid decline, likely to reflect clearance of pralatrexate from the body by renal and non-renal mechanisms, and a slow terminal phase which probably reflects return of pralatrexate from a deep body compartment, for example, intracellular compartments, after deglutamylation, and/or enterohepatic recycling of drug following biliary excretion into the gastrointestinal tract.

The key pharmacokinetic parameters in patients with PTCL are shown in **Table 3**, which also summarises the data obtained from non small cell lung cancer (NSCLC) patients (PDX-007) and patients with advanced solid tumours (PDX-99-083). The concentration-time profiles and PK parameters for other patient groups were similar to those observed in Study PDX-008. However, it should be noted that the results shown for Study PDX-007 in Table 3 are combined for all doses (150-325 mg/m^2) and for all regimens (3-5 minute IV push and 60 minute IV infusion). Also, patients in Study PDX-99-083 received concomitant docetaxel. The sampling schedule was significantly shorter in this study, with the result that the slow terminal phase was poorly characterised. This may explain the observation that the total clearance was higher and Vd_{ss} and terminal half life lower than observed in studies PDX-008 and PDX-007.

Figure 1. Study PDX-008 - Plasma concentration-time profiles for PDX-10a and PDX-10b after a single dose of pralatrexate (30 mg/m^2) in patients with PTCL



SD = standard deviation, PDX = pralatrexate, ng = nanogram, mL = milliliter

Table 3. Key pharmacokinetic parameters for pralatrexate

	Study PDX-008		Study PDX-007		Study PDX-99-083	
Study description	Efficacy/safety study		Dose escalation study		Dose escalation study #	
Total enrolled	109		39		48	
Full plasma profile (n)	10		38*		6	
Full urine profile (n)	8		33		0 (NC)	
Pralatrexate dose(s)	30 mg/m^2		150-325 mg/m^{2*}		120 mg/m$^{2\#}$	
Pharmacokinetic results [mean (%CV)]	**PDX-10a**	**PDX-10b**	**PDX-10a**	**PDX-10b**	**PDX-10a**	**PDX-10b**
C_{max} (ng/mL)	2478 (68)	3337 (41)			7034 (42)	10733 (27)
AUC (ng.min/mL)	93900 (55)	173954 (41)			225382 (53)	556663 (35)
Clearance (mL/min)						
Total clearance	417 (62)	191 (38)	496 (58)	226 (40)	615 (48)	217 (33)
Renal clearance	119 (68)	70 (61)	127 (73)	74 (61)		
Non-renal clearance	251 (65)	110 (44)	369 (63)	149 (51)		
Vd_{ss} (L)	105 (75)	37 (53)	112 (131)	38 (85)	65 (51)	26 (40)
terminal $t_{1/2}$ (min)	1078 (120)	714 (62)	1423 (115)	1137 (92)	419 (28)	383 (13)
% excreted unchanged in urine	31 (47)	38 (45)	25 (43)	33 (40)	NC	NC

*Dose regimens: 150 mg/m^2 IV push n=1; 190 mg/m^2 IV push n=3; 230 mg/m^2 IV push n=5; 270 mg/m^2 IV push n=16; 325 mg/m^2 IV push n=3; 190 mg/m^2 IV infusion n=5; and 230 mg/m^2 IV infusion n=5.

Parallel group, no cross over. Results are for all doses and all regimens. # All patients with PK profiling received 120 mg/m^2 pralatrexate and 35 mg/m^2 docetaxel.

NC not collected

Both the renal and non-renal clearance of PDX-10b was approximately 50% lower than that of PDX-10a and the volume of distribution at steady state (Vdss) for PDX-10b was one third of that for PDX-10a. These differences are reflected in a 2-fold higher plasma exposure of PDX-10b compared with PDX-10a. However, the plasma concentration-time profiles for both diastereomers decline in parallel, and terminal elimination half-life for both diastereomers is virtually identical. The stereo-selectivity was observed across all 3 studies and its biological cause is unknown.

The effect on the PK profile of prolonging the 3-5 minute IV injection to a 60-minute infusion was examined in Study PDX-007 using supra-clinical doses (190 and 230 mg/m^2) of pralatrexate in patients with non small cell lung cancer. The 60-minute IV infusion showed a less-pronounced multiphasic decline than IV push over 3-5 minutes, possibly as a result of drug distribution having reached equilibrium during the infusion and, apart from a lower C_{max} and longer T_{max} following an infusion (as could be expected), there were no major differences in

exposure. It was not possible to draw firm conclusions from the study because of low patient numbers and the use of a parallel group rather than cross-over design.

3.2.3. Multiple dosing pharmacokinetics

Full pralatrexate pharmacokinetic profiles for Doses 1 and 6 of Cycle 1 (C1D1 and C1D6, respectively) were obtained in 5 patients with PTCL (Study PDX-008). Repeat profiling at C1D6 showed no potential for clinically significant accumulation of pralatrexate with a weekly 30 mg/m^2 dose over the course of a single cycle of treatment. The mean AUC_∞ accumulation ratios (C1D6/C1D1) were 0.99 for PDX-10a and 0.98 for PDX-10b, whilst the mean C_{max} accumulation ratios were 0.79 for PDX-10a and 0.85 for PDX-10b.

Evaluator's comment:

The above data are based on this evaluator's own calculations from individual patient data reported for Study PDX-008. These figures differ from the sponsor's analysis set out in the Integrated PK Report, for two reasons:

- the sponsor's analysis appeared to contain an error, whereby the data for patient 109 (Study PDX-008) had been entered incorrectly in the sponsor's metrics distributions in the Integrated PK Report (this is discussed further in Section 18.1.1); and
- the sponsor's analysis used pooled data from all patients with repeat dosing, irrespective of the number of doses (and therefore cycles) received. Five patients had received 6 doses (1 completed cycle) and one patient had received 12 doses (2 completed cycles) before repeat profiling.

This evaluator concludes there was no clinically significant accumulation of pralatrexate with a weekly administration schedule over the course of a single cycle of treatment. (The sponsor reached the same conclusion from its analysis).

The situation with regard to repeated cycles of treatment is somewhat less clear. The patient who had repeat full PK profiling beyond the first cycle of treatment exhibited a marked increase in both C_{max} and AUC_∞ values for both diastereomers at Dose 6 of Cycle 2 (C2D6) compared to C1D1, without significant deterioration in renal or hepatic function from C1D1 to C2D6. The C2D6/C1D1 ratio for AUC_∞ in this patient was 1.9 and 1.35 for PDX-10a and PDX-10b, respectively, and the corresponding ratios for C_{max} were 3.2 and 2.3. However, there were no detectable pre-dosing levels of pralatrexate at C2D6 in this patient. These observations could, in fact, simply reflect intra-subject variability. Furthermore, the C_{max} and AUC_∞ values for both diastereomers at C2D6 in this patient were well within the range of values obtained at C1D1 for other patients, so that even if accumulation were occurring it would not appear to be clinically significant.

3.2.4. Linearity of dose-concentration relationship

Pralatrexate PKs appear to be dose-proportional and linear over a wide range of doses (30 - 325 mg/m^2; studies PDX-008, -007 and -99-083). Regression plots for the total clearance and Vdss for PDX-10a are shown in Figure 2 and Table 4, below (Note: pictorial results for PDX-10b were not available in the Integrated PK Report). The associated table summarises the slope, correlation coefficient (r), coefficient of determination (r^2) and p value of the regression plots for total clearance, renal clearance, non-renal clearance and Vdss for both pralatrexate diastereomers.

Figure 2. Linearity of PDX-10a clearance and volume of distribution

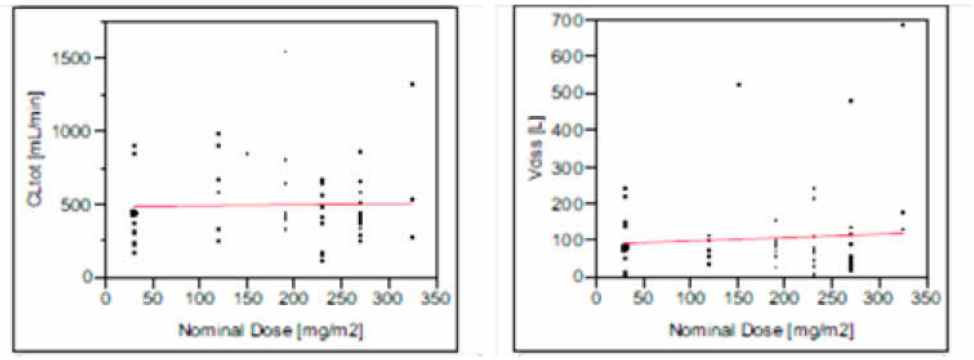


Table 4. Total clearance, renal clearance, non-renal clearance and Vdss for pralatrexate diastereomers

	Intercept	Slope	r	r^2	p-value
PDX-10a					
Cl_{tot} (mL/min) versus dose	482	0.07	0.022	0.0005	0.872
Cl_{renal} (mL/min) versus dose	118.1	0.03	0.036	0.0013	0.820
$Cl_{non\text{-}renal}$ (mL/min) versus dose	271.0	0.37	0.154	0.0238	0.335
Vd_{ss} (L) versus dose	87.5	0.10	0.071	0.005	0.619
PDX-10b					
Cl_{tot} (mL/min) versus dose	201.4	0.09	0.087	0.0075	0.532
Cl_{renal} (mL/min) versus dose	68.8	0.02	0.050	0.0025	0.754
$Cl_{non\text{-}renal}$ (mL/min) versus dose	116.3	0.12	0.158	0.0252	0.322
Vd_{ss} (L) versus dose	42.2	-0.03	0.102	0.0104	0.463

Evaluator's comment:

The correlation coefficient (r) is a measure of the linear association between dose and the parameter, whilst the coefficient of determination (r^2) indicates the proportion of variation in the PK parameter that is due to variation in dose. Conversely, 1-r^2 indicates what proportion is due to 'random' variation. The linear association of the PK parameters with dose is not strong (low r values) due to considerable inter-individual variability of pralatrexate PKs. Also, it can be appreciated that there is considerable variation in the pralatrexate PKs due to factors other than dose (low r^2 values).

3.2.4.1. Distribution

3.2.4.1.1. Volume of distribution

The steady state volume of distribution (Vd_{ss}) in patients with PTCL was 105L for PDX-10a and 37L for PDX-10b (Study PDX-008; n=10). Similar values were obtained for patients with non

small cell lung cancer (NSCLC), where the mean Vd_{ss} calculated from data obtained across a range of doses (150-325 mg/m^2) and regimens (that is, IV push and IV infusion) was 112L for PDX-10a and 38L for PDX-10b (Study PDX-007; n=38).

3.2.4.1.2. Plasma protein binding

Binding of racemic pralatrexate to human plasma proteins was investigated by equilibrium dialysis using carbon-14 (^{14}C)-pralatrexate and by ultrafiltration using pralatrexate (studies PDX-K-06029-U, PDX-K-07043-U, PDX-K-07049-U, and PDX-K-08066-U). These *in vitro* studies indicated that racemic pralatrexate is moderately bound (67-86%) to human plasma proteins and that albumin appears to be one of the major binding proteins. Pralatrexate binding was constant in the concentration range 5-100 μg/mL (~10-210 μM), indicating no saturation of the binding sites.

Plasma protein binding of the individual pralatrexate diastereomers, PDX-10a and PDX-10b has not been assessed.

3.2.4.1.3. Erythrocyte distribution

There was insignificant (<4%) partitioning of racemic pralatrexate (5, 25 and 100 μg/mL) into the red blood cells of 3 different blood samples obtained from 3 healthy volunteers (*in vitro* Study PDX-K-08067-U).

3.2.4.1.4. Tissue distribution

The magnitude of the volume of distribution at steady state suggests there is moderate tissue distribution of both pralatrexate diastereomers.

3.2.4.2. Metabolism

3.2.4.2.1. Interconversion between enantiomers

This has not been assessed formally in either *in vitro* or *in vivo* studies.

3.2.4.2.2. Sites of metabolism and mechanisms / enzyme systems involved

In vitro studies using human hepatic biomaterials (hepatocytes, liver microsomes and liver S9 fractions) suggest that racemic pralatrexate is not subject to significant metabolism by Phase I hepatic CYP450 isoenzymes or Phase II hepatic glucuronidases (Studies PDX-K-06028-U, PDX-K-07030-U, PDX-K-08061-U and PDX-K-08062-U).

3.2.4.2.3. Non-renal clearance

60-70% of pralatrexate is eliminated by non-renal clearance (Studies PDX-008 and PDX-007). The non-renal clearance in 10 patients with PTCL was 119 mL/min for PDX-10a and 70 mL/min for PDX-10b. Similar results were obtained for patients with NSCLC. In the absence of Phase I or Phase II metabolism, and extrapolating from the results of mass balance studies in rats, the non-renal clearance of pralatrexate is thought to be largely via hepatobiliary excretion. (Note: a mass balance study in humans has not been completed).

3.2.4.2.4. Metabolites identified in humans

No metabolites have been identified.

3.2.4.2.5. Pharmacokinetics of metabolites

Not applicable.

3.2.4.2.6. Consequences of genetic polymorphism

Nil identified to date. However, 3 patients were observed to have very low urinary excretion of pralatrexate despite normal renal function. The cause was not elucidated and could be a manifestation of genetic polymorphism. This issue is discussed further below.

3.2.4.3. Excretion

3.2.4.3.1. Routes and mechanisms of excretion

Approximately 30% of pralatrexate is eliminated by renal excretion (Studies PDX-008 and PDX-007; see Table 3, above). The mean total systemic clearance of pralatrexate diastereomers was 417 mL/min for PDX-10a and 191 mL/min for PDX-10b in 10 patients with PTCL. The mean fraction of unchanged pralatrexate diastereomers excreted in urine following a pralatrexate dose of 30 mg/m^2 administered as an IV infusion over 3-5 minutes was 31% for PDX-10a and 38% for PDX-10b. Non-renal clearance (thought to be hepatobiliary excretion) accounts for the remaining two-thirds.

3.2.4.3.2. Mass balance studies

At the time of data cut-off for the submission, 2 patients had been enrolled in an ongoing mass balance study (PDX-016). However, these results are considered unreliable because the ^{14}C radioactivity recovery results suggest that the current positioning of the radiolabel may not be sufficiently stable.

3.2.4.3.3. Renal clearance

The renal clearance in 10 patients with PTCL was 119mL/min for PDX-10a and 70mL/min for PDX-10b. Similar results were obtained for patients with NSCLC. Urinary excretion data for pralatrexate have been generated from 41 patients (33 in Study PDX-007 and 8 in PDX-008). About one third of both pralatrexate diastereomers were excreted unchanged in urine. Renal clearance values corrected for plasma protein binding suggest there is net renal tubular secretion.

Of note, 3 patients had very low urinary excretion of pralatrexate despite normal renal function (creatinine clearance (CrCl)) and normal urinary volumes throughout the urine collection periods:

- Patient A in Study PDX-007 (CrCl 130mL/min) received a 270 mg/m^2 dose of pralatrexate as an IV push. The fraction of unchanged pralatrexate diastereomers excreted in urine (f_e) was only 2% for PDX-10a and 3% for PDX-10b. Concomitant medications at the time of PK sampling were omeprazole, enoxaparin, atenolol, oxycodone, zolpidem and bupropion;
- Patient B in Study PDX-007 (CrCl 75mL/min) received a 270 mg/m^2 dose of pralatrexate as an IV push. The f_e was only 1% for PDX-10a and 2% for PDX-10b. Concomitant medications were pantoprazole, ondansetron, docusate sodium, mineral oil, senna and fentanyl;
- Patient C, Study PDX-008 (CrCl 84mL/min) received a 30 mg/m^2 dose of pralatrexate. The f_e was only 0.4% for PDX-10a and 0.9% for PDX-10b. Concomitant medications at the time of PK sampling were pantoprazole, azithromycin, allopurinol and paracetamol.

Evaluator's comment:

Within-study performance of the assay for PDX-10a and PDX-10b in urine was acceptable in the two studies. This leaves pharmacogenetic or drug-drug interaction factors as possible explanations for this finding.

It is of note that all three patients received a concomitant proton pump inhibitor (PPI) prior to and at the time of PK sampling. PPIs were not included in the sponsor's examination of potential drug-drug interaction covariates in the pooled and POPPK analyses. Interestingly, the co-administration of PPIs has been shown to delay the clearance of high dose methotrexate (which is structurally similar to pralatrexate) and, correspondingly, increase methotrexate plasma concentration (Suzuki *et al*., 2008). It has been postulated that this may be due to inhibitory activity of PPIs on breast cancer resistance protein (BCRP) or due to polymorphism of CYP2C19. *In vitro* studies were reported by the sponsor to have shown that pralatrexate is not a substrate for the CYP450 system, is a weak

inhibitor of CYP2C19 and is a low to moderate substrate for BCRP, a moderate to low substrate for OATP1B1 and a moderate substrate for OATP1B3.
An exploratory examination of f_e by this evaluator found that the mean f_e in patients receiving PPIs (n=16) was lower than in patients not receiving concomitant PPIs (n=25) for both PDX-10a (19.7% versus 30.7%; t-test p = 0.002) and PDX-10b (27.7% versus 38.5%; t-test p = 0.01). However, the clinical significance of this finding is unclear. Firstly, for the individual patients identified above, total clearance of each of the diastereomers was within the range of values reported for patients with "normal" f_e values, suggesting any decrease in renal clearance was offset by increased non-renal excretion. The overall systemic exposure (AUC) in these patients was also well within the range of values reported for other patients. Secondly, this evaluator found no difference between those patients receiving and not receiving PPIs for the mean total clearance of PDX-10a (462.8 versus 476.2mL/min; t-test p=0.89) and PDX-10b (214.6 versus 214.7mL/min; t-test p=0.99. All but 2 of the patients who received concomitant PPIs were from Study PDX-007 and therefore received higher than recommended doses of pralatrexate, ranging from 190-270 mg/m^2.

The POPPK analysis found a study-specific effect on PDX-10a and PDX-10b clearance, whereby clearance was reduced by a factor of 0.581 and 0.682, respectively, for Study PDX-008. The sponsor considered this effect was most likely an artefact of sparse sampling as it could be shown that patients with full PK sampling in PDX-008 (n=10) were adequately described in further simulations that did not include a study specific effect on clearance. This conclusion seems reasonable and is in keeping with the findings of the non-compartmental, integrated covariate analysis of patients with full PK data, where there was no significant correlation between study and the total clearance of either PDX-10a or PDX-10b.

3.2.4.4. Intra- and inter-individual variability of pharmacokinetics

Table 3 shows there was substantial inter-individual variability, reflected in the high coefficients of variation (%CV) for all PK parameters after a single dose of pralatrexate. In Study PDX-008, the CVs exceeded 40% for all PK parameters.

Intra-individual variability could be assessed only in the context of repeat dosing in a small number of patients.

3.2.5. Pharmacokinetics in other special populations

No studies in specific populations were performed and, consequently, limited data are available on pralatrexate PK in those populations.

3.2.5.1. Pharmacokinetics in patients with impaired hepatic function

No studies have been performed in patients with hepatic impairment.

The selection criteria used in the studies were such that no patients who underwent PK profiling had a baseline serum bilirubin level above 1.3mg/dL. Furthermore, only two patients had ALT and/or AST levels greater than 1.5 x ULN - patient 109 in Study PDX-008, who had a baseline ALT of 4.2 x ULN and an AST of 2.1 x ULN; and patient 22 in Study PDX-007, who had a baseline ALT of 1.9 x ULN and an AST of 1.6 x ULN. Patient 22 had PK parameters that were well within the range of values obtained from all patients. Interestingly, patient 109 had the highest non-renal clearance as well as the highest renal and total clearance, and the lowest AUC values for both pralatrexate diastereomers among all the patients who had both plasma and urine PK profiling in Study PDX-008.

Neither the non-compartmental, integrated covariate analysis nor the POPPK analysis identified total bilirubin or transaminase levels as significant covariates for pralatrexate clearance. However, given that 60-70% of pralatrexate is eliminated by non-renal clearance, and that this is likely to be largely via hepatobiliary excretion, a risk for increased exposure in patients with hepatic impairment cannot be excluded. The proposed Product Information (PI) appropriately

advises that the administration of pralatrexate to patients with hepatic impairment should be done with caution and that liver function and adverse events should be monitored closely.

3.2.5.2. Pharmacokinetics in patients with impaired renal function

No studies have been performed in patients with renal impairment.

The selection criteria used in the studies were such that only 3 patients who underwent full PK profiling had a baseline serum creatinine level above 1.5 mg/dL. The PK parameters obtained from these patients (patients 41 and 47 in Study PDX-007 and patient 7 in Study PDX-008) were well within the range of values obtained from all patients in these studies, suggesting it is unlikely there are any appreciable changes in the PKs of pralatrexate in patients with mild renal impairment. However, given the significant contribution of renal excretion of pralatrexate to overall clearance of pralatrexate, it is possible that moderate to severe renal impairment may increase exposure to the drug. In this regard, both the sponsor's non-compartmental, integrated covariate analysis and POPPK analysis identified creatinine clearance as a covariate for pralatrexate clearance. In particular, the POPPK analysis estimated that the clearances of PDX-10a and PDX-10b would decrease by 21% and 24%, respectively, in a patient with a creatinine clearance of 30 mL/min.

Patients with renal impairment have been identified as a special population of interest and the sponsor submitted the protocol for a study in patients with advanced cancer and mild, moderate, and severe renal impairment (Study PDX-019). This study is in the earliest stages of enrolment and no data had been generated at the time of submission. The proposed PI appropriately advises that the administration of pralatrexate to patients with moderate to severe renal impairment should be done with caution and that renal function and adverse events should be monitored closely.

3.2.5.3. Pharmacokinetics according to age

PK data were obtained from patients aged 21-85 years, with an average age of 60 years. In the sponsor's POPPK analysis, models that included age as a covariate were unsuccessful, most likely due to the high degree of correlation between age and creatinine clearance. After accounting for renal function, age was not a relevant covariate. Consequently, creatinine clearance was deemed a more clinically important predictor and was selected to represent both renal function and age dependencies in the POPPK model. Whilst no dosage adjustments are recommended for age *per se*, age-related decline in renal function could potentially lead to reduced clearance. This is reflected appropriately in the proposed PI.

3.2.5.4. Pharmacokinetics related to genetic factors

Specific pharmacogenetic studies of pralatrexate have not been conducted.

3.2.5.5. Pharmacokinetics according to gender and race

There were no significant gender or racial/ethnic differences observed in the non-compartmental, integrated covariate analysis or POPPK analysis. Of note though, the patient population enrolled in the 3 contributing studies was predominantly Caucasian.

3.2.6. Pharmacokinetic interactions

3.2.6.1. Pharmacokinetic interactions demonstrated in human studies

No formal drug-drug interaction studies have been performed.

Co-administration of probenecid resulted in dose-dependent reduction in clearance of pralatrexate and a commensurate increase in systemic exposure and half-life, and reduced tolerability of pralatrexate (Study PDX-01-014). Although this study was conducted using a non-validated, non-chiral assay, and there was no control group, the results are consistent with those observed when probenecid is co-administered with methotrexate (Aherne *et al*., 1978).

Therefore, the sponsor has included precautionary information about the co-administration of these agents in the proposed PI. This is reasonable.

Pralatrexate was studied in combination with docetaxel in 6 patients enrolled in Study PDX-99-083. As previously mentioned, the sampling schedule was significantly shorter in this study than in studies PDX-008 and PDX-007. Furthermore, there was no patient cross-over and no patients received either pralatrexate or docetaxel alone. Consequently no firm conclusions can be made about the effect of docetaxel on pralatrexate pharmacokinetics and vice versa.

Covariate PK analyses of potential drug-drug interactions did not show any significant correlation between pralatrexate and the concomitant administration of diuretics, non-steroidal anti-inflammatory drugs (NSAIDS), sulfonamides, and penicillin. However, these medicines were used infrequently and the available information for the analysis was suboptimal (there was scant information about the actual NSAIDs or their dose/duration). The sponsor considered that the analysis had not excluded the possibility of underlying drug-drug interactions and, given the significant contribution of renal excretion to the overall clearance of pralatrexate, has appropriately, included precautionary statements that concomitant administration of drugs that affect glomerular filtration and/or renal tubular secretion, and nephrotoxic drugs (aminoglycosides, loop diuretics, platinum compounds, cyclosporine) could also potentially result in reduced clearance of pralatrexate.

3.2.6.2. Clinical implications of in vitro findings

3.2.6.2.1. Protein binding

In the *in vitro* Study PDX-K-07043-U, racemic pralatrexate at a test concentration of 17 μM was not significantly displaced from its human plasma protein binding sites by phenytoin (albumin site I), warfarin (albumin site I), ceftriaxone (albumin site II), digoxin (albumin site III), disopyramide (α1-acid glycoprotein and albumin) or propranolol (α1-acid glycoprotein, albumin and lipoproteins). Of note, the pralatrexate concentration used in this study approximated the mean *in vivo* C_{max} (sum of both stereo-isomers) of 13 μM (~6 μg/mL) observed in the pivotal Study PDX-008.

Conversely, in Study PDX-07049-U, racemic pralatrexate at a concentration of 160 μg/mL did not significantly displace these same reference drugs (change in unbound fraction ≤ 2%). Of note, the highest observed C_{max} (sum of both stereo-isomers) in Study PDX-008 was 11.11 μg/mL ~23 μM (in patient 93) which is approximately 14 times lower than the concentration used in this study.

On the basis of these findings , it is unlikely that pralatrexate at therapeutic concentrations will be displaced from human plasma proteins by other drugs (phenytoin, warfarin, ceftriaxone, digoxin, propranolol, and disopyramide) or cause clinically relevant increases in unbound drug concentrations of other drugs as a result of their displacement from plasma proteins.

3.2.6.2.2. CYP450 interaction

Pralatrexate is not a substrate for the CYP450 microsomes (Study PDX-K-08062-U). Five *in vitro* studies examined the potential of pralatrexate to inhibit the CYP450 system. Key findings from these studies were:

- There was no significant inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2D6, or CYP2E1 by pralatrexate at concentrations of 20, 50 and 100 μM (Study PDX-K-07032-U) and no significant inhibition of CYP1A2, CYP2C8, CYP2C9 or CYP3A4 at a pralatrexate concentration of 100 μM (Study PDX-K-07033-U);
- Pralatrexate has very weak inhibitory potential on CYP2B6, shown by an IC_{50} > 5000 μM (Study PDX-K-11089)
- Pralatrexate produced >50% inhibition of CYP2C19 at concentrations ≥ 50 μM (Study PDX-K-07032-U), including 53% inhibition at 100 μM Study PDX-K-07033-U. Furthermore,

pralatrexate was found to inhibit CYP2C19 by either a mixed or a non-competitive model, with a K_i of CYP2C19 inhibition > 1mM (Study PDX-K-07044-U). Based on the highest observed C_{max} in Study PDX-008, pralatrexate is unlikely to inhibit CYP2C19 *in vivo* when used at the recommended dose of 30 mg/m^2; and

- Further to Study PDX-K-07044-U, the IC_{50} values of pralatrexate for CYP2C19 in human liver microsomes were found to be high (>3500 μM) under both reversible and irreversible incubation conditions, indicating that the inhibition of CYP2C19 by pralatrexate is very weak (Study PDX-K-11090).

Also, pralatrexate at concentrations of 2, 10 and 50μM did not induce CYP1A2, CYP2C19 or CYP3A4 when tested in fresh hepatocytes from 3 human donors (Study PDX-K-08060-U).

The maximum pralatrexate concentrations used in these studies were in access of maximum plasma concentrations achieved in the pivotal clinical Study PDX-008. Therefore, pralatrexate is not likely to affect CYP450-mediated metabolism of other drugs when used at the doses recommended for the proposed clinical indication.

3.2.6.2.3. Interaction with transporter systems

Study PDX-K-08059-U demonstrated that pralatrexate is not a substrate for P-gp, and does not significantly inhibit or induce P-gp. The maximum concentration (500 μM) used in this study far exceeded the highest observed C_{max} in the pivotal clinical Study PDX-008 (~ 23 μM [mean C_{max}: ~ 13 μM]). Thus, it is unlikely that pralatrexate will affect excretion of other drugs *in vivo* through an interaction with P-gp.

Pralatrexate was found to be a low-to-moderate substrate for the membrane efflux transporters BCRP, MRP2 and MRP3 (Studies PDX-K-10078-U and PDX-K-10081-U). Study PDX-K-10078-U also demonstrated that pralatrexate is a not a significant inhibitor of BRCP but is a moderate inhibitor of MRP2 (IC_{50} = 43.5 μM) and a potent inhibitor of MRP3 (IC_{50} < 0.3 μM). Clinically significant inhibition of MRP2 by pralatrexate is most unlikely occur with the recommended dosing regimen, given the highest C_{max} of 23 μM achieved in Study PDX-008. However, the finding that pralatrexate is a potent inhibitor of MRP3 at concentrations readily achieved with the recommended dosing regimen for PTCL has significance with respect to the potential effects from concomitant use of a number of other oncologic agents that are thought to rely on this liver transporter. These agents include etoposide, teniposide and methotrexate. The proposed PI appropriately includes a cautionary statement about the co-administration of such agents.

Pralatrexate was also found to be a moderate-to-low affinity substrate and a very weak inhibitor of OATP1B1 (IC_{50} > 100 μM), whilst methotrexate was neither a substrate nor a significant inhibitor at concentrations ≤ 100 μM (Study PDX-K-11080-U). Also, pralatrexate was not a significant substrate for OCT2, OAT1, OAT3 and a moderate affinity substrate for OATP1B3 (Study PDX-K-11088-U). In the same study methotrexate was shown to be a significant substrate for OCT2, OAT1 and OATP1B3, and a low affinity substrate for OAT3. Pralatrexate did not exhibit concentration-dependent inhibition of OCT2, OAT1, OAT3 or OATP1B3 in the range 0.3 – 100 μM, with IC_{50} values >100 μM for each of the transporters (Study PDX-K-11084-U). Thus, it is unlikely that pralatrexate will affect excretion of other drugs *in vivo* through an interaction with these transporters.

3.3. Evaluator's overall conclusions on pharmacokinetics

Pralatrexate Solution for Infusion contains pralatrexate as an approximately 1:1 racemic mixture of the *S*- and *R*- configurations at C10 (known as PDX-10a and PDX-10b, respectively). The PKs of these pralatrexate diastereomers have been reasonably well characterised using data from subsets of oncology patients who underwent full plasma profiling in 3 efficacy/safety studies. It has been demonstrated that pralatrexate has stereo-selective pharmacokinetics, the biological cause of which is unknown.

Following IV push over 3-5 minutes there is a multiphasic decline in the levels of both pralatrexate diastereomers, characterised by an initial rapid fall in plasma concentrations followed by a slow terminal phase. The decline of both diastereomers occurs in parallel, with a 2-fold higher plasma exposure of PDX-10b compared with PDX-10a. Approximately one third of pralatrexate clearance is via renal excretion and two thirds by non-renal mechanisms. Of note, a mass balance study is yet to be completed. It is apparent however, that both renal and non-renal clearance of PDX-10b is approximately 50% lower than that of PDX-10a. Also, the volume of distribution indicates that pralatrexate has moderate tissue distribution (with PDX-10a > PDX-10b).

The rapid drop in plasma concentrations is thought to reflect clearance of pralatrexate from the body by renal and non-renal mechanisms, whilst the slow terminal phase could reflect return of pralatrexate from intracellular compartments, after deglutamylation, and/or enterohepatic recycling of drug following biliary excretion into the gastrointestinal tract. The slow terminal phase does not appear to contribute significantly to total exposure to the drug. Furthermore, there was no accumulation of pralatrexate with repeated dosing over the course of a single cycle of treatment in a small number of patients with PTCL. Of note, the effect of repeat dosing beyond the first cycle of treatment was assessed in only one patient who exhibited an increase in both AUC and C_{max} at Dose 12 relative to Dose 1. The potential for accumulation of pralatrexate in third space compartments (such as pleural effusion and ascites) has not been assessed.

It appears that the PKs of pralatrexate are linear over doses ranging from 30 to 325 mg/m^2. However, it is clear from the data submitted that there is considerable inter-individual variability in the PKs of pralatrexate and the observation of linearity needs to be interpreted in that light. It must also be remembered that the data were generated in sick patients taking multiple medications, so it is not entirely clear what the sources of variability in the PKs are. For example, 3 patients were noted to have very low urinary excretion of pralatrexate, despite normal renal function and urinary volumes during the collection period. This raises the possibility of pharmacogenetic issues and/or drug-drug interactions. Specific pharmacogenetic studies of pralatrexate have not been conducted. Furthermore, formal drug-drug interaction studies have not been performed. A population PK analysis of potential drug-drug interactions did not show any significant correlation between pralatrexate and the concomitant administration of diuretics, non-steroidal anti-inflammatory drugs (NSAIDS), sulfonamides, and penicillin. However, these analyses were limited by less than optimal data and the sponsor considered that the analyses had not excluded the possibility of underlying drug-drug interactions. Given the significant contribution of renal excretion to the overall clearance of pralatrexate, and the fact that pralatrexate undergoes net renal tubular secretion, the sponsor has appropriately included precautionary statements about the concomitant administration of drugs that affect glomerular filtration and/or renal tubular secretion, and nephrotoxic drugs.

In vitro studies have indicated that, at the doses intended for use in patients with PTCL, there would be low potential for clinically significant drug-drug interactions on the basis of protein binding displacement, or as a result of interactions affecting the CYP450 system and P-gp transporter system. However, pralatrexate is a potent inhibitor of MRP3 at concentrations readily achieved with the recommended dosing regimen for PTCL. Although pralatrexate is intended for use as a single agent, this finding nevertheless has significance with respect to the potential effects of other oncologic agents, such as etoposide, teniposide, and methotrexate, which are thought to rely on this liver transporter. The proposed PI appropriately includes a cautionary statement about the co-administration of such agents.

No specific population studies have been conducted and, otherwise, only limited PK data are available for such populations. The sponsor's population PK analysis identified creatinine clearance as a covariate for pralatrexate clearance. In particular, it was estimated that the clearances of PDX-10a and PDX-10b would decrease by 21% and 24%, respectively, in a patient

with a creatinine clearance of 30 mL/min. After accounting for renal function, age was not a relevant covariate. These findings are appropriately reflected in the proposed PI which cautions that the administration of pralatrexate to patients with moderate to severe renal impairment should be done carefully and that renal function and adverse events should be monitored closely. The PI also advises that whilst no dosage adjustments are recommended for age *per se*, age-related decline in renal function could potentially lead to reduced clearance.

Neither the non-compartmental, integrated covariate analysis nor the POPPK analysis identified total bilirubin or transaminase levels as significant covariates for pralatrexate clearance. However, given that 60-70% of pralatrexate is eliminated by non-renal clearance, and that this is likely to be largely via hepatobiliary excretion, a risk for increased exposure in patients with hepatic impairment cannot be excluded. This is adequately reflected in the proposed PI.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 5 (below) shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 5. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Biomarker–tumour response relationship	PDX-008 PDX-007 PDX-99-083	
Secondary Pharmacology	Effect on QT interval	PDX-007 (QT_c)	*
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	Nil studies	
	Effect of age	Nil studies	
PD Interactions	Nil studies		
Population PD and PK-PD analyses	Healthy subjects	Nil analyses	
	Target population (PTCL) §	PDX-008	
	Oncology (NHL and Hodgkin's lymphoma) patients	PDX-02-078 (Mould *et al*., 2009)	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

4.2.1. Mechanism of action

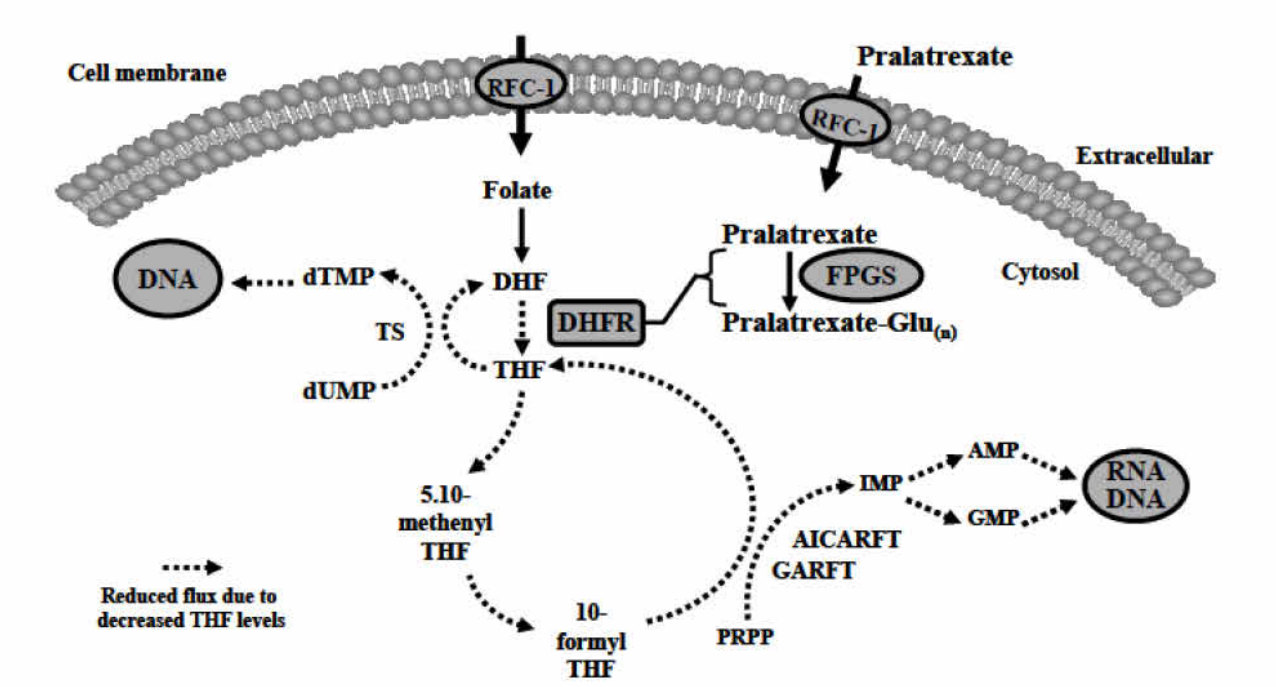
Pralatrexate is an antineoplastic folate analogue that exerts its activity through competitive inhibition of the enzyme dihydrofolate reductase (DHFR) in the folic acid metabolic pathway (Figure 3, below). Inhibition of DHFR leads to depletion of tetrahydrofolate (THF) which is required for the synthesis and catabolism of several amino acids; the formation of creatine and

choline; the synthesis of purines; the methylation of ribonucleic acids (RNAs); and the synthesis of deoxythymidine monophosphate (dTMP) and deoxyribonucleic acid (DNA). In most cancer cells the inhibition of DNA synthesis leads to cell cycle arrest and/or programmed cell death.

Pralatrexate also undergoes polyglutamylation by folylpolyglutamyl synthetase (FPGS), which results in prolonged intracellular retention and accumulation within tumour cells and enhanced inhibition of DHFR.

The two C10 diastereomers were reported to have similar cytotoxic activity *in vitro*.

Figure 3. Folic acid metabolism



AICARFT = aminoimidazolecarboxamide ribonucleotide formyl transferase, AMP = adenosine monophosphate, DHF = dihydrofolate, DHFR = dihydrofolate reductase, DNA = deoxyribonucleic acid, dTMP = deoxythymidine monophosphate, dUMP = deoxyuridine monophosphate, FPGS = folylpolyglutamyl synthetase, GARFT = glycinamide ribonucleotide formyltransferase, $Glu_{(n)}$ = polyglutamate, GMP = guanosine monophosphate, IMP = inosine monophosphate, PRPP = phosphoribosyl pyrophosphate, RFC-1 = reduced folate carrier-1, RNA = ribonucleic acid, THF = tetrahydrofolate, TS = thymidylate synthase

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

It has been hypothesised that a number of targets within the folate metabolic pathway which regulate internalisation of pralatrexate, its mechanism of action, and subsequent retention through formation of polyglutamylated metabolites may correlate with pralatrexate anti-tumour activity. Consequently, tumour tissue gene expression analysis was undertaken in several studies with the aim of identifying predictors of pralatrexate response, focusing on components of the folate metabolic pathway as follows:

- RFC-1, the membrane transporter protein responsible for cellular uptake of pralatrexate;
- FPGS, the enzyme responsible for polyglutamylation of pralatrexate and consequently, its intracellular retention and accumulation;
- dihydrofolate reductase (DHFR), the enzyme necessary for conversion of folic acid to dihydrofolate (DHF) and tetrahydrofolate (THF) for nucleotide base and deoxyribonucleic acid (DNA) synthesis;

- thymidylate synthase (TS), an enzyme for the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate for DNA synthesis;
- glycinamide ribonucleotide formyltransferase (GARFT), an enzyme involved in an alternate path for THF production; and
- gammaglutamyl hydrolase (GGH, also known as FPGH), the enzyme that cleaves the glutamate residues from pralatrexate, reducing the DHFR inhibitory activity of pralatrexate and enabling pralatrexate elimination from the cell.

Tumour samples were analysed using a quantitative polymerase chain reaction (PCR) assay. The relative expression of each biomarker was quantified in each tissue sample using the delta cycle threshold (delta CT) method with β-actin as the internal control. Disappointingly, the data were of limited value because of the low number of patients consenting to such analyses (a separate consent was required for the analysis) and the low response rates in the studies:

- PDX-008 - 6 patients with PTCL consented and provided tumour tissue for analyses, the results of which are shown in Table 6, below. Three of these patients achieved a partial response; two had stable disease and one had disease progression. Of note, the collection dates of the samples predated the study enrolment date for all patients and therefore may not have been a true indicator of gene expression at baseline;
- PDX-007 - 6 patients with NSCLC provided tumour tissue and there were only 2 objective responses to treatment in the whole study (and it was not stated whether these patients were among those in the gene expression analysis);
- PDX-99-083 - 7 patients with NSCLC provided tumour tissue. The biomarkers did not appear to be either over-expressed or under-expressed when compared to the expression observed in reference tissue samples. However, no normal lung tissue was available for comparison and there was no clinical response to pralatrexate amongst the 7 patients.

Table 6. Gene expression profiles in patients with PTCL (Study PDX-008)

Gene	Tissue	-(Delta Delta CT)	2^(-Delta Delta CT)	(95% CI)
DHFR	D. Colon	-0.56	0.68	(0.36, 1.28)
	Lung	1.07	2.10	(1.11, 3.97)
	A. Liver/St. Universal	-2.62	0.16	(0.08, 0.32)
FPGS	D. Colon	0.77	1.70	(1.07, 2.69)
	Lung	1.10	2.15	(1.36, 3.40)
	A. Liver/St. Universal	0.56	1.47	(0.92, 2.34)
GARFT	D. Colon	-1.11	0.46	(0.35, 0.61)
	Lung	-0.62	0.65	(0.50, 0.85)
	A. Liver/St. Universal	-2.49	0.18	(0.14, 0.23)
GGH	D. Colon	-0.71	0.61	(0.41, 0.92)
	Lung	-0.57	0.68	(0.45, 1.02)
	A. Liver/St. Universal	-4.82	0.04	(0.02, 0.08)
RFC1	D. Colon	-1.64	0.32	(0.26, 0.39)
	Lung	-0.56	0.68	(0.55, 0.84)
	A. Liver/St. Universal	-2.46	0.18	(0.12, 0.27)
TS	D. Colon	-1.55	0.34	(0.20, 0.59)
	Lung	1.88	3.67	(2.11, 6.40)
	A. Liver/St. Universal	-0.17	0.89	(0.34, 2.31)

The sponsor acknowledged that a larger patient data set of biomarker expression in pralatrexate responders and non-responders is needed to determine the utility of each

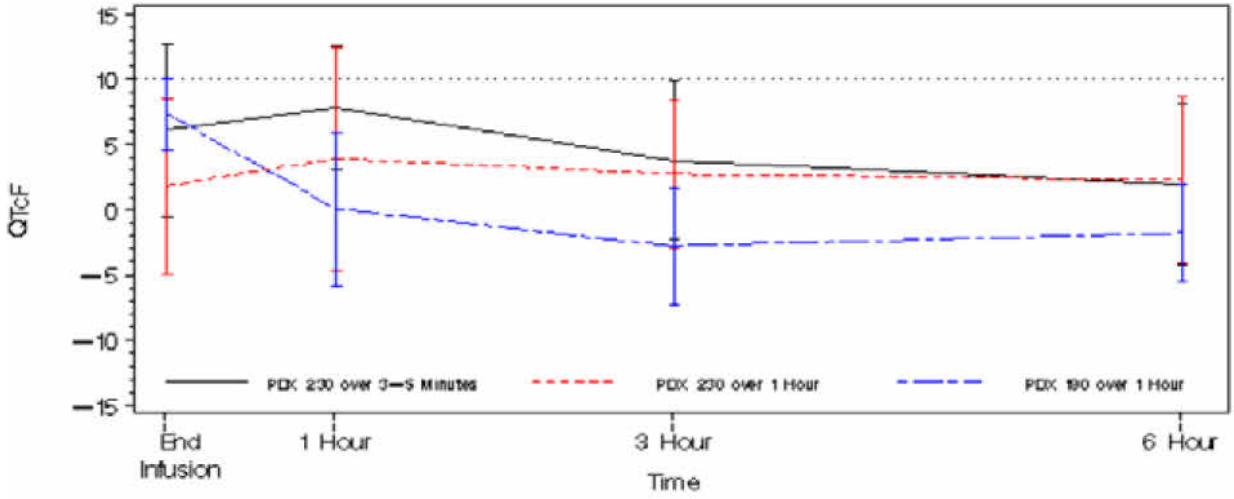
biomarker, its change and/or combination of biomarker changes to predict pralatrexate efficacy or identify cancer types that may be most responsive to pralatrexate.

4.2.2.2. Secondary pharmacodynamic effects

4.2.2.3. Effect on QT interval

The effect of pralatrexate on QT interval was assessed in a sub-study of PDX-007 (PDX-007 QT_c) in which 14 evaluable patients with non-small cell lung cancer underwent intensive electrocardiographic evaluations prior to and after receiving pralatrexate doses of either 190 mg/m^2 administered IV over 60 minutes (n=4) or 230 mg/m^2 administered IV over 3 - 5 minutes (n=5) or 60 minutes (n=5). Infusion of pralatrexate was associated with a repolarisation delay in all 3 cohorts, as shown by the changes in Fridericia's rate-corrected QT interval (QT_cF) from pre-injection levels in Figure 4. The thresholds at which there would be a modest regulatory concern regarding QT prolongation are mean increases in QT_cF > 5ms or an upper bound of the two sided 90% CI (= upper bound of a one-sided 95% CI) >10msec.

Figure 4. Study PDX-007(QT_c) - Mean (90%CI) change from pre-injection QT_cF (msec) by treatment group



The greatest effect on QT_cF was observed with the highest dose (230 mg/m^2) administered via IV push over 3-5 minutes. The upper bound of the two-sided 90% CI for the mean change from pre-injection in QT_cF interval in this group was 12.7 ms at the end of the injection and this persisted at 1 hr post injection. The mean change from pre-injection QT_cF in this cohort also exceeded 5 ms at both time points. Changes observed in the cohort that received 190 mg/m^2 also exceeded both these thresholds at the end of infusion but returned to pre-injection levels by 1 hr post infusion (that is, more rapidly than doses of 230 mg/m^2). However, cohorts and times were not compared statistically.

Although on face value the data may suggest some concern, it should be appreciated that:

- the doses used and, consequently the maximum pralatrexate concentrations achieved in the study far exceeded those expected for the target PTCL population;
- the data are pre-post data only and generated in parallel groups and, because of the study population, it was not possible to analyse the time-matched baseline-corrected drug-placebo difference in QT_c interval that would account for diurnal effects as a dependent variable (as suggested by the ICH-E14 Guideline). This was a terminal oncology population and provision of placebo was unethical, and the underlying disease was progressive, so the assumption of disease stability usually required for cross-over designs could not be met;

- when data for all cohorts were combined, the mean changes in QT_cF at end-injection, and at 1, 3 and 6 hours post injection and the upper bounds of the corresponding 90% CIs were all below 5ms and 10msec, respectively;
- no relationship was found between pralatrexate C_{max} or AUC values and either the maximum or mean QT_cF interval changes, possibly reflective of a plateau on the dose-response curve;
- there were no significant changes in the mean HR, PR interval, RR interval or QRS-interval; and
- in terms of categorical analyses, no patient had a post injection absolute QT_c interval > 470 ms; only 1 patient (who received 190 mg/m^2 over 1 hr) exhibited a post-injection absolute QT_c interval > 450 ms; no patient exhibited an increase in QT_c from baseline of > 18.4 ms; and no pathological U waves were observed in the study.

Furthermore, 2 evaluable patients had other predisposing risks. One patient had low potassium levels prior to injection and another was taking long term azithromycin (at an unspecified dose) for 'dyspnoea'. These patients had maximal increases in QT_cF of 8.9 and 3.3 ms, respectively, with corresponding absolute QTcF values of 405 and 410.7 ms (occurring at the end of the infusion).

Overall these findings, together with findings of *in vitro* studies that were reported to show that pralatrexate does not inhibit the human ether-a-go-go-related gene (hERG) or affect dog Purkinje fibre action potential at concentrations well above the clinically observed C_{max}, suggest that pralatrexate is unlikely to markedly delay cardiac repolarisation in PTCL patients treated with pralatrexate doses ≤ 30 mg/m^2.

Relationship between drug concentration and pharmacodynamic effects

4.2.2.4. Relationship between pralatrexate exposure and tumour response

Doses of pralatrexate used in the clinical development program ranged from 10 to 325 mg/m^2, mostly administered IV over 3-5 minutes on weekly schedules. Doses in patients with haematological malignancies were generally lower (mostly 10-45 mg/m^2, although some patients received doses as high as 270 mg/m^2 (Study PDX-02-078)). Patients with solid tumours received higher individual doses of pralatrexate (150 – 325 mg/m^2).

Two studies enrolled patients with PTCL who were treated with pralatrexate as a single agent (PDX-008 and PDX-02-078). No formal exposure-tumour response assessments were performed for these patients. However, data from the two studies were used for separate population PK-PD exposure-response analyses for safety (see immediately below).

4.2.2.5. Relationship between pralatrexate exposure and mucositis and thrombocytopenia

As can be predicted from its antifolate activity, the main toxicities of pralatrexate manifest as mucosal inflammation (stomatitis, mucositis) and myelotoxicity (neutropaenia and thrombocytopaenia). Indeed, early studies (PDX-97-006 and PDX-99-053) established mucositis as the dose limiting toxicity of pralatrexate at doses of 135-150 mg/m^2 in patients with NSCLC. Furthermore, the initial incidence of mucositis in lymphoma patients receiving 135 mg/m^2 pralatrexate was considerably higher than seen in the NSCLC population (PDX-02-078). In Study PDX-008, which used a much lower dose of 30 mg/m^2 in patients with PTCL, the most frequent adverse events reported as the reason for withdrawal from treatment were mucosal inflammation (n = 7, 6%) and thrombocytopaenia (n = 6, 5%). Population PK modelling for patients with PTCL showed the severity of mucositis and thrombocytopaenia trended to correlate with pralatrexate exposure. The mean estimated $AUC_{0-\infty}$ values were higher in patients who had Grade 3+ mucosal inflammation or thrombocytopaenia than in patients who did not. Similar findings were observed for C_{max} values but these were less pronounced than for AUC.

Correlations between total pralatrexate AUC and mucosal inflammation were also observed in several studies that employed non chiral assays, including a population PK-PD analysis of data from Study PDX-02-078 (reported by Mould *et al*., 2009), which used a dihydrofolate reductase base assay similar to that used for the quantification of methotrexate and validated for pralatrexate; and an analysis of pooled data from studies PDX-97-006 and PDX-99-053, although the two latter studies used a non validated pralatrexate assay. The importance of Study PDX-02-078 is that a preliminary analysis of the plasma PK data suggested that those patients with the highest 8 hr pralatrexate plasma levels were at higher risk of developing mucositis. Furthermore, the results suggested there is a correlation between baseline serum methylmalonic acid levels and the risk of developing mucositis. Folate levels have been correlated with mucositis in patients treated with methotrexate for head and neck cancer and homocysteine and MMA levels are frequently elevated in folate-deficient states (Savage & Lindenbaum 1994). Patients with high levels of MMA and Hcy who experienced mucositis, who consecutively began vitamin supplementation with folic acid and vitamin B12 and corrected their abnormally high levels of MMA and Hcy, did not experience recurrence of their mucositis on re-challenge with pralatrexate. The latter observation provided evidence for routine vitamin B12 and folic acid supplementation with pralatrexate administration.

4.3. Evaluator's overall conclusions on pharmacodynamics

Pralatrexate is an antineoplastic folate analogue that exerts its activity through competitive inhibition of the enzyme dihydrofolate reductase (DHFR) in the folic acid metabolic pathway. As with the PK data, PD data were collected from subsets of oncology patients enrolled in clinical efficacy/safety studies. These data were supplemented by population PK/PD analyses.

No formal analysis of exposure-response for efficacy was performed for patients with PTCL. Also, attempts to examine gene expression of key targets in the folate metabolic pathway as potential markers of tumour response were unsuccessful. Of note, the protocols for some of the more recently initiated studies have allowed for an exploratory evaluation for the presence of a single nucleotide polymorphism for the RFC-1 biomarker in peripheral blood (PDX-010, PDX-011). Interestingly, it has been recently demonstrated that acquired resistance to pralatrexate in human cancer cell lines was associated with decreased RFC-1 expression, in contrast to resistance to methotrexate which was correlated with increased DHFR expression (Serova *et al* 2011)[1].

Correlations between total pralatrexate AUC and mucosal inflammation were observed in several population PK-PD models, including modelling based on data from patients with PTCL in the pivotal study (PDX-008), and the supportive study in haematological malignancies (PDX-02-078). Results from Study PDX-02-078 also suggested there is a correlation between baseline serum methylmalonic acid levels and the risk of developing mucositis. Patients with high levels of methylmalonic and homocysteine who experienced mucositis, who consecutively began vitamin supplementation with folic acid and vitamin B12 and corrected their abnormally high levels of MMA and Hcy, did not experience recurrence of their mucositis on re-challenge with pralatrexate. The latter observation provided evidence for the routine supplementation with vitamin B12 and folic acid with pralatrexate administration.

Effects of pralatrexate on the QT interval were examined in a small sub-study of PDX-007 in patients with non-small cell lung cancer. Given the study population, it was not possible to conduct the study to the standard normally required to examine QT interval effects of new chemical entities. In particular, the study was not placebo controlled and not of a cross over design, such that possible diurnal effects were not accounted for. Although pralatrexate at doses

[1] Furthermore, acquired resistance to methotrexate affects each known step in methotrexate action, including impaired transport of methotrexate into cells, production of altered forms of DHFR that have less affinity for methotrexate and decreased ability to synthesize methotrexate polyglutamates (Goodman and Gilman, 2011)

190 mg/m^2 and 230 mg/m^2 were associated with a repolarisation delay in their respective cohorts, when data for all cohorts were combined, the mean changes in QT_cF at end-injection, and at 1, 3 and 6 hr post injection and the upper bounds of the corresponding 90% CIs were all below the thresholds of 5 ms and 10 ms, respectively. Furthermore, none of the categorical thresholds for concern (that is, QT_c interval > 500 ms or increase in QT_c interval > 30 ms) were observed in any patient. No correlation was observed between either the maximum or mean change in QT_cF and pralatrexate exposure (C_{max} and AUC). Of note, the doses used and, consequently the maximum pralatrexate concentrations achieved in the study far exceeded those expected for the target PTCL population. Thus, this evaluator agrees with the sponsor that pralatrexate is unlikely to markedly delay cardiac repolarisation in PTCL patients treated with doses ≤ 30 mg/m^2.

5. Dosage selection for the pivotal studies

The following summary of results from Phase I and II studies gives an understanding of how the dosage regimen for pralatrexate changed over the course of the clinical development program, ultimately leading to dose selection for the pivotal study in patients with PTCL (Study PDX-008).

The first Phase I study, PDX-97-006, was conducted exclusively in patients with NSCLC, who had been previously treated with a median of 2 prior chemotherapy regimens. Initially, pralatrexate was administered IV at a dose of 30 mg/m^2 weekly for 3 weeks out of 4 weeks without vitamin B12/ folate supplementation (n=6). Stomatitis requiring dose reduction and/or delay in the first cycle occurred in 4 of 6 patients treated at the initial dose level (30 mg/m2), making this an intolerable dose of pralatrexate given on this schedule. The dose escalation scheme was modified consequently to a biweekly schedule (every 2 weeks in a 4 week cycle) and dose escalation proceeded from 15 to 30 mg/m^2 and then proceeded in approximately 10 mg/m^2 increments to 170 mg/m^2. Both patients treated at the 170 mg/m^2 dose developed dose limiting toxicities and the 150 mg/m^2 cohort was expanded with 6 additional patients enrolled. Only 1 of these 6 patients developed a dose limiting toxicity. Thus, the 150 mg/m^2 dose was defined as the maximum tolerated dose of the study and the dose recommended for Phase II studies.

A subsequent single-agent Phase II study in patients with Stage IIIB or IV NSCLC (PDX-99-053) used pralatrexate at doses up to 150 mg/m^2 every 2 weeks of a 4 week cycle with folate supplementation for patients experiencing significant stomatitis. This study yielded results that were considered to be consistent with the activity of other single agents in this setting (4 partial responses out of 39 treated patients).

Study PDX-02-078 was the first study of pralatrexate as a single agent in patients with relapsed or refractory haematological malignancies (Hodgkin's lymphoma and NHL) and began as a Phase II study using a slightly lower initial starting dose (135 mg/m^2 every other week) than identified in the NSCLC Phase II study because of the greater number of prior therapies these patients had received compared to patients with NSCLC. The protocol was subsequently amended to include inter-patient dose escalation (a Phase I activity) to determine the optimal dose and schedule of pralatrexate, using an initial dose of 30 mg/m^2 weekly for 3 weeks of a 4 week cycle, with subsequent increases in the number of consecutive doses (from 3 to 6 doses) and dose amount (15 mg/m^2 increments). These changes were in response to a higher than anticipated incidence of Grade 3 or 4 stomatitis in patients with Hcy and MMA concentrations > 10 µmol/L and >200 nmol/L, respectively, and because many patients with palpable disease had responses that were suggestive of cytokine failure (that is, they experienced marked reductions in their disease by Day 7 but these grew back to baseline levels by Day 15). Importantly, the study was also amended to include a requirement for normalised Hcy and MMA levels or a 10 day course of folic acid/vitamin B12 repletion prior to study entry. The overall response rate for the study was 33%, including a response rate of 60% among 20 evaluable patients with PTCL. In the Phase I part of the study, 5 dose-limiting toxicities and 2

patient deaths were experienced with 45 mg/m^2 weekly for 6 doses/7-week cycle treatment group (n = 11 treated patients). The maximum tolerated dose was declared as the dose level below this, that is, 30 mg/m^2 weekly for 6 doses/7 week cycle which was used in the Phase II part of the study and also used subsequently in Study PDX-008 along with routine supplementation of vitamin B12 and folic acid.

6. Clinical efficacy

6.1. Peripheral T-cell lymphoma in adults

6.1.1. Pivotal efficacy study

6.1.1.1. Study PDX-008 - aka PROPEL (Pralatrexate in Patients with Relapsed Or Refractory PERipheral T-cell Lymphoma)

6.1.1.1.1. Study design, objectives, locations and dates

This Phase II, single arm, non-randomised, open-label study was conducted across 35 study sites in Europe, the USA and Canada from August 2006 to August 2009 with the objective of evaluating the efficacy, safety and pharmacokinetic profiles of pralatrexate when administered with concurrent vitamin B12 and folic acid supplementation in patients with relapsed or refractory PTCL.

The study was designed as a confirmatory efficacy study following the observation of tumour responses in 12/20 (60%) evaluable patients with T/natural killer (NK)-cell lymphoma in Study PDX-02-078. It employed a 2-stage design (Simon, 1989) that required at least 4/35 evaluable patients to experience a response in Stage 1 for the study to proceed to Stage 2, with a minimum of 100 evaluable patients overall. An independent Data Monitoring Committee (DMC) that comprised 3 haematologists/oncologists, with experience in managing T-cell lymphoma who were not directly involved with the conduct of the study performed safety assessments after the first 10, 35 and 65 patients had completed their first cycle of treatment. The DMC recommended study continuation after each of these safety reviews.

6.1.1.1.2. Inclusion and exclusion criteria

Participants were required to be aged 18 years or older and have:

- histologically/cytologically confirmed PTCL of the following subtypes according to the Revised European American Lymphoma (REAL) World Health Organization (WHO) disease classification, with at least 1 biopsy from initial diagnosis or in the relapsed setting to confirm the diagnosis of PTCL;
  - T/NK-cell leukaemia/lymphoma;
  - Adult T-cell lymphoma/leukaemia (ATLL) (human T-cell leukaemia virus [HTLV] 1+);
  - Angioimmunoblastic T-cell lymphoma;
  - Blastic NK lymphoma (with skin, lymph node, or visceral involvement);
  - Anaplastic large cell lymphoma (ALCL), primary systemic type;
  - PTCL – unspecified;
  - T/NK-cell lymphoma – nasal;
  - Enteropathy-type intestinal lymphoma;
  - Hepatosplenic T-cell lymphoma;
  - Extranodal peripheral T/NK-cell lymphoma – unspecified;

- Subcutaneous panniculitis T-cell lymphoma;
- Transformed mycosis fungoides; and

· received at least 1 prior non-experimental, non-biological treatment, with clear disease progression after the last treatment received; and

· an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2; and

· absolute neutrophil count (ANC) > 1,000/μL; and

· platelet count > 100,000/μL; and

· serum alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 times upper limit of normal (ULN) or < 5 times ULN if there was documented hepatic involvement with lymphoma; and

· total serum bilirubin < 1.5 mg/dL; and

· serum creatinine concentration < 1.5 mg/dL, or creatinine clearance ≥ 50 mL/min in the event that if the patient's serum creatinine was > 1.5 mg/dL; and

· medically acceptable contraception, unless surgically sterile.

The histological subtypes allowed in the study were chosen by the sponsor because they have a relatively homogenous prognosis and outcome; they are among the most common PTCL subtypes; and they are representative of the larger PTCL patient population. Patients with subtypes that have a highly aggressive nature (such as T-cell prolymphocytic leukaemia (T-PLL)) were excluded from the study, as were patients with subtypes that have a natural history of an indolent and prolonged course, such as:

· T-cell large granular lymphocytic leukaemia;

· Mycosis fungoides (except transformed mycosis fungoides);

· Sézary syndrome; and

· Primary cutaneous CD30+ disorders.

Other key exclusion criteria included active concurrent malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix); previous allogeneic stem cell transplantation; history of, brain metastases or central nervous system disease; receipt of any conventional chemotherapy or radiation therapy (RT) within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study treatment or planned use during the course of the study; and receipt of corticosteroids within 7 days of study treatment, unless patient had been taking a continuous dose of no more than 10 mg/day of prednisone for at least 1 month.

The diagnosis of eligible peripheral T-cell lymphoma (PTCL) histopathological subtype was confirmed by central pathology review. In cases where the diagnosis provided by the investigator of histopathological subtype could not be confirmed, the relevant slides and pathology reports were referred for an independent third party pathology assessment (adjudication).

6.1.1.1.3. Study treatments

Patients received pralatrexate 30 mg/m^2 administered IV once weekly for 6 consecutive weeks followed by 1 week of rest for a 7 week cycle. Dose reductions to 20 mg/m^2 or dose omissions were allowed according to pre-defined criteria for haematological toxicities, mucosal inflammation, and other treatment-related non-haematological toxicities. Vitamin administration began after blood was collected for measurement of MMA and Hcy levels. If these levels were normal, patients could proceed to pralatrexate treatment and concurrent folic acid (1 - 1.25 mg PO daily) and vitamin B12 (1 mg IMI every 8 - 10 weeks). If the patient's MMA

levels were >200 nmol/L and/or Hcy >10 µmol/L, vitamin supplementation was given for at least 10 days prior to the first administration of pralatrexate.

Patients were treated with pralatrexate for 24 months or until they experienced any of the following, whichever occurred first:

- disease progression;
- initiation of radiotherapy or systemic chemo/biologic therapy for T-cell lymphoma;
- developed a treatment related toxicity indicating intolerance of the lowest study dose allowed (20 mg/m^2/week), namely the second occurrence of thrombocytopenia Grade 4; the occurrence of either grade neutropaenia and fever or Grade 4 neutropaenia despite cytokine support; or the occurrence of any Grade 4 non-haematological toxicity at that dose;
- omission of 3 sequential doses of pralatrexate due to a treatment-related AE;
- > 3-week lapse between pralatrexate doses; or
- development of an AE, intercurrent illness, condition, or procedural complication that interfered with the patient's ongoing participation.

Other treatments allowed during the study included:

- palliative and supportive care, as clinically indicated, and in accordance with the standard practices of the institution;
- prophylaxis and treatment of nausea and vomiting, according to the standard of care within the institution;
- erythropoietin, if judged by the investigator to be in the best interest of the patient (for example, for patients with underlying anaemia or unacceptable haematological toxicity);
- other haemopoietic growth factors (for example, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), except for pegfilgrastim, in accordance with the instructions for treatment modification for haematological toxicities as specified in the protocol;
- appetite stimulating hormones (for example, megestrol acetate) to control anorexia and cachexia;
- prophylactic antibiotics, at the discretion of the investigator; and
- transfusions at the discretion of the investigator.

6.1.1.1.4. Efficacy variables and outcomes

The following procedures/tests were performed for evaluation of tumour response:

- **physical examination** to assess liver, spleen, lymph nodes, and skin lesions. This included medical photography with ruler measurements for documentation of any skin lesions;
- **radiographic imaging** (using the same imaging technique as for screening):
  - CT of chest, neck, abdomen, and pelvis
  - Other imaging techniques documenting disease site(s) other than chest, neck, abdomen, or pelvis, if applicable.
  - Whole body positron-emission tomography (PET) scans (from base of skull to mid thigh). This was done for an exploratory analysis. PET imaging was not necessary if there was disease progression according to the International Workshop Criteria (IWC) documented by clinical examination, CT or other imaging technique);
- **LDH level** determination; and

- **bone marrow biopsy**; if the patient's screening bone marrow biopsy/aspirate results were positive or indeterminate and the patient had a confirmed complete response, a repeat bone marrow biopsy and aspirate assessment was to be performed.

Evaluation of response was performed within 7 days prior to the projected first dose of the second cycle and then within 7 days prior to the projected first dose of every even-numbered subsequent cycle (Cycles 4, 6, 8, etc), that is, every 14 weeks, although unscheduled radiological response assessments were performed earlier if clinical progression was suspected. Patients were to attend a safety follow-up visit 35 days after the last dose of pralatrexate followed by routine follow-up every 3 months until PD or subsequent therapy. Patients were then followed for survival and first subsequent therapy for T-cell lymphoma every 6 months for a total duration of 2 years after the first dose of pralatrexate.

Tumour response was performed centrally by Princeton Radiology Pharmaceutical Research, LLC (RadPharm) using a comprehensive charter based on the International Workshop Criteria (IWC) developed by the National Cancer Institute (NCI)-sponsored International Working Group (Cheson *et al*., 1999), that also took into account skin involvement. RadPharm evaluated all radiological data, photographs for patients with cutaneous disease, clinical data, LDH and bone marrow biopsies. Investigator assessment of response was also documented.

The **primary efficacy endpoint** was the overall response rate defined as complete response (CR), complete response unconfirmed (CRu) or partial response (PR). The criteria used by RadPharm for determining responder status were included with the submission.

Overall, 3 methods were used to assess response to treatment:

- Response according to IWC (central review) – this was the primary analysis;
- Response according to IWC plus PET scans (central review) – this was an exploratory analysis; and
- Response according to the local investigator.

Other efficacy outcomes included:

- duration of response - measured from the first day of documented response until either disease progression or death due to any cause (only calculated for patients who responded);
- progression-free survival (PFS) - calculated as the number of days from treatment Day 1 to the date of disease progression or death, regardless of cause; and
- overall survival (OS) - calculated as the number of days from treatment Day 1 to death or censoring, whichever occurred first.

6.1.1.1.5. Randomisation and blinding methods

Not applicable to the study design.

6.1.1.1.6. Analysis populations

The efficacy analysis was conducted on patients who had received at least 1 dose of pralatrexate and met the major inclusion criterion, that is, the diagnosis of allowed PTCL histopathological subtype confirmed by independent central pathology review. All patients who received at least one dose of pralatrexate were included in the safety analysis population.

6.1.1.1.7. Sample size

For the primary endpoint of overall response rate, the study was designed to test a null hypothesis of a true response rate of 15% and an alternative hypothesis of a true response rate of 27%. Under these assumptions, the one tail type I error was 2.2% and the power was 84.3%. It was determined *a priori* that a minimum of 100 patients were needed with a response rate of 23% for the lower bound of the 95% confidence interval (CI) to exceed 15%. The target

response rates were chosen by the sponsor following discussions with leading lymphoma experts to determine what would be considered a clinically meaningful response rate.

6.1.1.1.8. Statistical methods

Response rate was calculated from the number of responders (CR + CRu + PR) divided by the number of evaluable patients, using response data received from central review. The 95% CI for response rate was calculated using the binomial density function. Response rate was also estimated by level/subgroup according to age (< 65 years old versus ≥ 65 years old); race; and gender. Response rate based on investigators' assessments were also be reported and a summary of discrepancies between central review and local investigator was provided.

Duration of response, PFS and OS were each estimated using the Kaplan-Meier method. Patients receiving subsequent therapy, including transplant before disease progression was documented, were censored for response duration and PFS. For PFS, patients who were alive without disease progression were censored at the last disease assessment date or the date of first dose, whichever was later. Patients who withdrew consent to participate in the study prior to disease progression were censored at the date of their last disease assessment or treatment Day 1, whichever was later. Patients who withdrew from treatment prior to disease progression without withdrawing consent were followed for disease status and survival whenever possible. These patients were censored at their last tumour assessment or initiation of subsequent anti-cancer therapy, whichever came first, if they did not progress by that time. Patients who did not have response assessments after baseline were censored at treatment Day 1. For OS, patients who had not died (no record of death) or were lost to follow-up were censored at the date of last contact. Patients who withdrew consent to participate in the study were censored on the date of withdrawal. Patients who withdrew from treatment without withdrawing consent were followed for survival status whenever possible.

An evaluation of the relationship between response and survival was also undertaken to gain a better understanding of the value of the response rate as an end point in patients with PTCL. Two methods were used:

- *Cox model* with a single time-dependent covariate for each patient's status over time.
- Initially, all patients were labelled as non-responders and once a patient responded, he/she moved to a response state where he/she remained for all subsequent times. At each death time a relative risk of death (hazard ratio [HR]) was calculated for patients who achieved a best response of CR or PR versus those who had not, as well as an overall HR which represented an average relative risk of death for patients who had responded versus those who had not.
- *Landmark method*, where a time-point, or landmark, in this case Day 53, was chosen post enrolment and all patients who are alive at that time-point are categorized as either responders or non-responders.
- This categorisation can be used as a binary covariate in a Cox model in the usual manner where the responder status is considered a "baseline" covariate relative to survival subsequent to the landmark. This method does not include all patients since generally not all patients are alive at the landmark chosen. Day 53 was chosen because it coincided with the first response assessment, and all patients who had a response assessment at the completion of Cycle 1 had that assessment prior to Day 53. Patients who died or did not have a response assessment before day 53 were excluded from the analyses.

6.1.1.1.9. Participant flow

A total of 130 patients were screened for study eligibility and 115 patients were enrolled at 25 of the 35 study centres. Of the 115 enrolled patients:

- 4 never received treatment with pralatrexate.

- The investigator decided not to treat Patient 003 due to the presence of B-cell lymphoma and Patient 051 developed disease progression prior to starting pralatrexate treatment. Patients 032 and 104 were also considered not evaluable due to their histopathology assessment by the site;
- 111 patients received at least one dose of pralatrexate and were included in the safety analysis; and
- 109 patients had a diagnosis of PTCL confirmed by central pathology review and were included in the efficacy analysis.
- Two patients were considered not to have an eligible PTCL subtype by the central review and adjudication process and were, therefore, excluded from the efficacy analysis. One of these patients was reported by the investigator as having angioimmunoblastic T-cell lymphoma, but histopathology was deemed indeterminate on central review and was reported only as having non-diagnostic patchy lymphoid infiltrate by the adjudicator. The other patient was reported by the investigator as having transformed mycosis fungoides but neither central pathology review nor the adjudicator could confirm that the mycosis fungoides was transformed.

Of the 111 patients who received at least one dose of pralatrexate, 4 remained on therapy at time of database cut-off date (17 August 2009) and 107 had discontinued study treatment. The most common reasons for study treatment discontinuation were disease progression (n=65; 59%) adverse event (n=26; 23%), investigator decision (n=8; 7%) and patient decision (n=6; 5%). The reasons for investigator decisions for discontinuation included: proceeding to stem cell transplant (SCT) for 4 of the 8 patients; 2 patients received a concomitant steroid (concomitant therapy was a specified reason for treatment discontinuation), 1 patient had stable disease (SD) but was not responding adequately to proceed to SCT, and no reason was provided for 1 patient. No details were available for those patients who discontinued due to patient reasons.

At database cut-off 83 (75%) patients had terminated the study. Reasons for terminating the study were death (n=63; 57%); completed follow-up of 24 months (n=15; 14%), withdrawal of consent (n=1; <1%), loss to follow up (n=2; 2%) and other (n=2; 2%).

6.1.1.1.10. Major protocol violations/deviations

There were no major protocol deviations. Minor deviations included:

- failure to meet entry criteria; this occurred in 7 patients. Five of the patients did not meet the specific haematological, hepatic, or renal function criteria at screening and within 3 days prior to start of treatment. An exemption from the criterion was granted for 3 of these patients prior to enrolment. The remaining 2 of 7 patients either did not stop or failed to stop other chemotherapeutic agents within the required time frame before starting pralatrexate;
- use of a prohibited concomitant medication; this occurred in 6 patients, all of whom received concurrent systemic corticosteroids; and
- failure to adhere to protocol-specified dose modification rules; this occurred in 17 patients (4 patients had 2 deviations each), of whom 12 did not have a protocol specified dose omission, 7 did not have a protocol-specified dose reduction, and 2 did not have protocol-specified treatment termination. Also 13 patients were granted exemptions to dose modification (1 patient was granted 3 exemptions).

6.1.1.1.11. Baseline data

Patient demographics and disease subtype and status are summarised in Table 7, below. The study population was predominantly male (n=76; 68%) and Caucasian (n=80; 72%), with an

average age of 57.7 years (range 21-85). Just over a third of patients (n=40; 36%) were aged 65 years or older. The commonest disease subtypes according to central review assessment were PTCL-unspecified (n=59; 53%); ALCL, primary systemic type (n=17; 15%); angioimmunoblastic T-cell lymphoma (n=13; 12%); and transformed mycosis fungoides (n=12; 11%).

Patients were heavily pre-treated prior to study entry. The median number of prior therapies in the 111 treated patients was 3 (range 1-13) and 27 patients (24%) had received at least 5 prior therapies. Most prior therapies were systemic in nature (median 3, range 1-12), with the most common treatment comprising CHOP (n=78; 70%). Stem cell transplantation (SCT) had been used in 18 (16%) patients, of whom 9 had had a CR in response to their transplant but had relapsed prior to study entry. Twenty-seven patients (24%) had previously received treatment with methotrexate (either as a single agent or in a combination regimen). Seventy patients (63%) did not have evidence of response to their most recent prior therapy before entering the study and 27 (24%) did not have evidence of response to any previous therapy. ECOG performance status was 0 in 43 (39%) patients, 1 in 49 (44%) patients and 2 in 19 (17%) patients.

Table 7. Study PDX-008 - Baseline patient demographics and disease characteristics

Demographics		n=111
Gender	Male	76 (68%)
	Female	35 (32%)
Race	Caucasian	80 (72%)
	Negro	14 (13%)
	Asian	6 (5%)
	Hispanic	9 (8%)
	Other	1 (<1%)
***Age* (years)**	Mean ± SD	57.7 ± 15
	Median	59.0
	Range	21-85
	< 65 years	71 (64%)
	≥ 65 years	40 (36%)
Disease characteristics		n=111
Tumour histopathology	PTCL-unspecified	59 (53%)
(Central Review)	Anaplastic large cell lymphoma, primary systemic type	17 (15%)
	Angioimmunoblastic T-cell lymphoma	13 (12%)
	Transformed mycosis fungoides	12 (11%)
	Blastic NK lymphoma (skin, lymph node or visceral involvement)	4 (4%)
	T/NK-cell lymphoma nasal	2 (2%)
	Extranodal peripheral T/NK-cell lymphoma unspecified	1 (<1%)
	Adult T-cell leukaemia/lymphoma (HTLV1++)	1 (<1%)
	Other	2 (2%)
Time since diagnosis (months)	Mean ± SD	30.8 ± 43.2
	Median	15.6
	Range	0.8 – 322.3
Prior systemic therapy	1	23 (21%)
	2	30 (27%)
	3	23 (21%)
	4	14 (13%)
	≥ 5	21 (19%)
	Median	3.0
	Range	1 – 12
	Patients with no evidence of response to immediate prior therapy	70 (63%)
	Patients with no evidence of response to any prior therapy	27 (24%)
ECOG performance status	0	43 (39%)
	1	49 (44%)
	2	19 (17%)

6.1.1.1.12. Results for the primary efficacy outcome

Table 8 below summarises the best overall response for all 3 methods of assessment; IWC, IWC plus PET scans and investigator. The response rate per the primary analysis (independent central review using IWC) was 29% (n = 32) with a 95% CI of 21 – 39%. More than half of the responders had a partial response. The time to first response among the 32 responders ranged from 37 to 349 days (median 45 days).

Particular points to note are:

- 15 patients (5 CR; 10 PR) achieved a first response within 49 days (that is, 1 cycle of treatment). This included 3 patients (1 CR; 2 PR) who achieved a response after very limited exposure to pralatrexate (that is, ≤ 3 doses):
  - Patient C: a 60M with nodal PTCL – unspecified, an ECOG PS of 1 and an elevated LDH level (206 IU/L; normal range (NR) 60 - 200) at screening, received only a single 30 mg/m^2 dose of pralatrexate. The Week 2 dose was withheld because of mucositis. The Week 3 dose was withheld because of sepsis and the study drug was discontinued. He achieved a best response of PR at 36 days and went on to receive a stem cell transplant at Day 69. This patient had received only 1 prior course of treatment; 6 cycles of CHOP, completed 4 months prior to receiving pralatrexate and with a best response of disease progression.
  - Patient D: a 58M with PTCL – unspecified, a splenic mass on PET, an ECOG PS of 1 and a normal LDH level (171 IU/L; NR 0 - 190) at screening - received two 30 mg/m^2 doses of pralatrexate. The third dose of pralatrexate was withheld because of mucositis, neutropaenia and thrombocytopenia, and the fourth and fifth doses were also withheld because of fever and neutropaenia. Treatment was discontinued in Week 6 because of Grade 3 neutropaenia and fatigue. He achieved a best response of PR at Day 37 and had disease progression at Day 287. Previous treatment included 5 cycles of CHOP (best response PR); 2 cycles of DHAP (dexamethasone, cisplatin, cytarabine; best response PR); and, most recently, SCT 10 months before starting pralatrexate, with a best response of CR.
  - Patient E: a 71F with PTCL – unspecified, a splenic mass on PET, an ECOG PS of 1 and an elevated LDH level (679 IU/L; NR 313 - 618) at screening - received a total of 3 doses of pralatrexate. After receiving her first dose of pralatrexate, the next 2 doses were held because of Grade 2/3 oral mucositis. She received two reduced doses (20 mg/m^2) in Weeks 4 and 5 and then permanently discontinued study treatment due to recurrence of oral mucositis. She achieved PR at Day 48 and thence CRu (217 days after starting pralatrexate) and CR (399 days after starting pralatrexate). The patient subsequently remained in CR until study termination, with duration of response of 519 days. Treatment prior to study entry included CHOP (best response CR); radiotherapy (best response CR); and, most recently, combination ifosfamide, carboplatin, etoposide completed 3 months prior to treatment with pralatrexate, with best response of disease progression.

Evaluator's comment:

The issue here is whether these responses can be considered to be wholly due to pralatrexate, given such limited exposure. It is not immediately apparent what else could have influenced the disease response in these cases other than "spontaneous remission" because these patients completed their last prior treatment and relapsed well in advance of receiving pralatrexate. However, spontaneous remissions are exceedingly rare anyway, so to have 3 such occurrences in patients with very aggressive, relapsed PTCL is extremely unlikely. Thus, it is reasonable to assume that the response in these patients was due to pralatrexate activity.

Table 8. Study PDX-008 - Best response in patients with PTCL

		Efficacy Analysis Set (N=109)		
		n	(%)	(95% CI)
Best Response per Central Review - IWC	CR+CRU+PR	32	(29)	(21, 39)
	CR	11	(10)	
	CRU	1	(1)	
	PR	20	(18)	
	SD	21	(19)	
	PD	40	(37)	
	UE	2	(2)	
	Missing: off-treatment in cycle 1	14	(13)	
Best Response per Central Review - IWC+PET	CR+CRU+PR	28	(26)	(18, 35)
	CR	15	(14)	
	PR	13	(12)	
	SD	18	(17)	
	PD	31	(28)	
	UE	18	(17)	
	Missing: off-treatment in cycle 1	14	(13)	
Best Response per Local Investigator	CR+CRU+PR	43	(39)	(30, 49)
	CR	17	(16)	
	CRU	3	(3)	
	PR	23	(21)	
	SD	21	(19)	
	PD	40	(37)	
	UE: off-treatment in cycle 1	5	(5)	

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

- 5 patients (1CR; 4 PR) had a response with pralatrexate therapy when they had failed to respond to any of their earlier therapies:
  - Patient F: a 76M with transformed mycosis fungoides, cutaneous lesions, an ECOG PS of 0 and an elevated LDH (1258 IU/L; NR 313 – 618) at screening; received 2 cycles of pralatrexate (with C1D3 and C1D4 omitted because of acute cholecystitis). A best response of PR was achieved at Day 42, with duration of response of 78 days. This patient had received 2 prior treatment courses, both systemic – denileukin diftitox and bexarotene, with the most recent treatment (bexarotene) completed 6 weeks prior to receiving pralatrexate. The best response to both prior therapies was disease progression.

- Patient G: a 30M with T/NK cell lymphoma, an ECOG PS of 0 and an elevated LDH (428 IU/L; NR 313 – 618) at screening - received a total of 9 cycles of pralatrexate, with a best response of CR occurring at Day 143 and duration of response of 306 days. This patient had received a mix of systemic and local treatments prior to pralatrexate initiation, including 4 cycles of CHOP (best response stable disease) and, most recently, radiation of the nasopharynx and base of skull (best response disease progression) 4 months prior to receiving pralatrexate.

  Evaluator's comment:

  Data indicate that Patient G also had active disease in the mediastinum (PET positive nodes), which was outside the radiation field and which also appeared to respond to treatment on study (largest diameter reduced from 20 mm at screening to 9 mm at the time the response was achieved). Thus, it does not appear that the response in this patient was likely to be due to delayed radiation effects.

- Patient H: a 64M with extranodal PTCL – unspecified involving lung, liver and kidney, a ECOG PS of 2 and an elevated LDH (341 IU/L; NR 60 – 200) at screening - received 2 cycles of pralatrexate (with C1D6 omitted because of mucositis; C2D3 and C2D6 omitted because of pancytopaenia, with dose reduction at C2D4 because of mucositis). A best response of PR was achieved at Day 43 and lasted 54 days. This patient had received 2 prior treatment courses, both systemic; interferon (best response disease progression); and infusional etoposide, doxorubicin, vincristine plus bolus prednisone and cyclophosphamide (EPOCH), with the most recent treatment (EPOCH) completed 6 weeks prior to receiving pralatrexate (best response disease progression).
- Patient C: discussed above.
- Patient I: an 83M with PTCL – unspecified with lung and liver involvement on PET, an ECOG PS of 1 and normal LDH (232 IU/L; NR 100 – 250) at screening - received 2 complete cycles of pralatrexate with no dose reduction. A best response of PR was achieved at day 41 and lasted 57 days. This patient had received 3 prior treatment courses, all systemic; Rituximab x 5 cycles (best response not assessable) cyclophosphamide/vincristine/ prednisone x 8 cycles (best response stable disease); and bexarotene (best response stable disease), with the most recent treatment (bexarotene) completed 4 months prior to receiving pralatrexate.

· Four of the 11 patients who were assessed by IWC as having a CR had an earlier response assessed as a PR:

- Patient J became a CR approximately 1.5 months after assessment as a PR, 180 days after starting pralatrexate.
- Patient K became a CR approximately 10 months after assessment as a PR, 348 days after starting pralatrexate.
- Patient E: discussed above
- Patient L became a CR approximately 3 months after assessment as a PR, 140 days after starting pralatrexate.

6.1.1.1.13. IWC Response rate by patient age, gender and tumour subtype

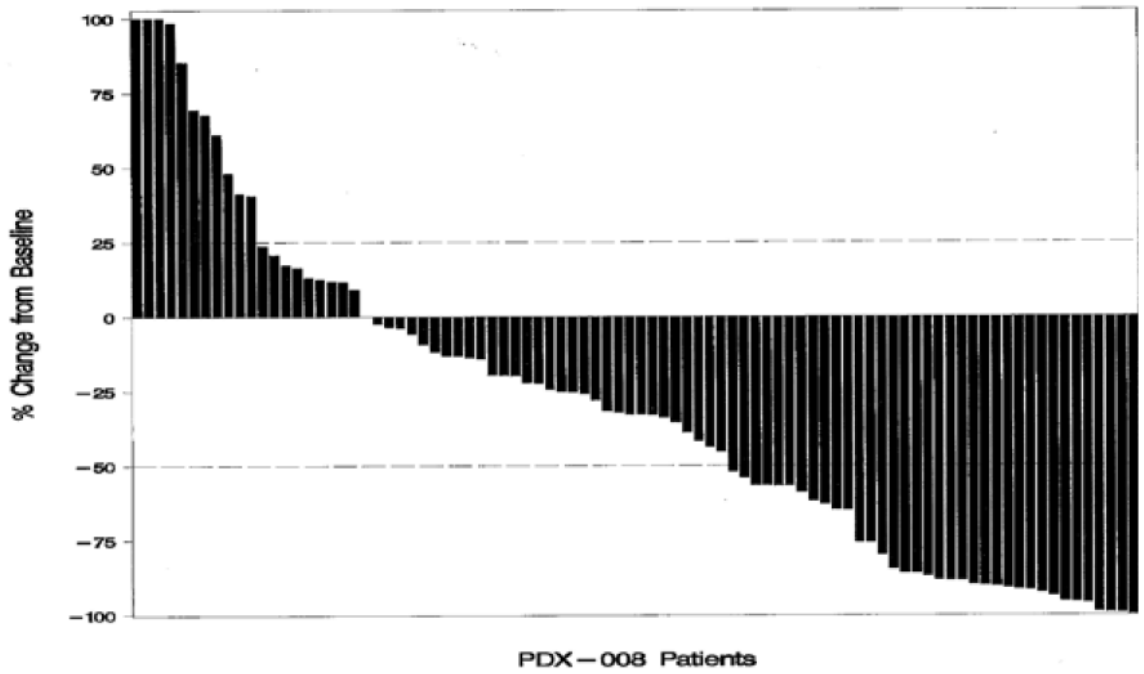
Patients aged ≥ 65 years old had a numerically higher response rate than those < 65 years old (33% versus 27%); however this was not statistically significant. Response rate was similar among the subtypes, ranging from 25% (3/12) response rate for patients with transformed mycosis fungoides to 35 % (6/17) for patients with anaplastic LCL. However, patients with angioimmunoblastic T-cell lymphoma had a response rate of only 8% (1/13). There was little or

no difference in response rate in the subsets of gender (male 30% versus female 29%); race (White 29% versus non-White 30%); or investigational sites.

6.1.1.1.14. Individual tumour response

A total of 88 patients had disease measures at both baseline and post-treatment. Of these, 67 had a decrease in tumour volume when comparing the sum of the products of the greatest diameters (SPD) at baseline and their maximum decrease during the study, including 25 patients with decreases of >75% and 11 with decreases of 50-75%. Increases in the SPD were observed in; 20 patients and 1 had no change. This is shown as a waterfall plot in **Figure 5.**

Figure 5. Study PDX-008 - Individual tumour responses measured by maximum change from baseline in the sum of products of the greatest diameter



Patients with tumour size reductions of >75% did not necessarily achieve a CR because there were multiple criteria, such as no new sites of disease (see the Appendix to this CER). For example, 4 patients who met the SPD criterion were considered to have disease progression because they developed new lesions.

No patients without pre-post treatment SPD assessments were deemed to have had a response (6 had disease progression, 2 were unevaluable and 13 did not have a post-baseline evaluation).

6.1.1.1.15. Results for other efficacy outcomes

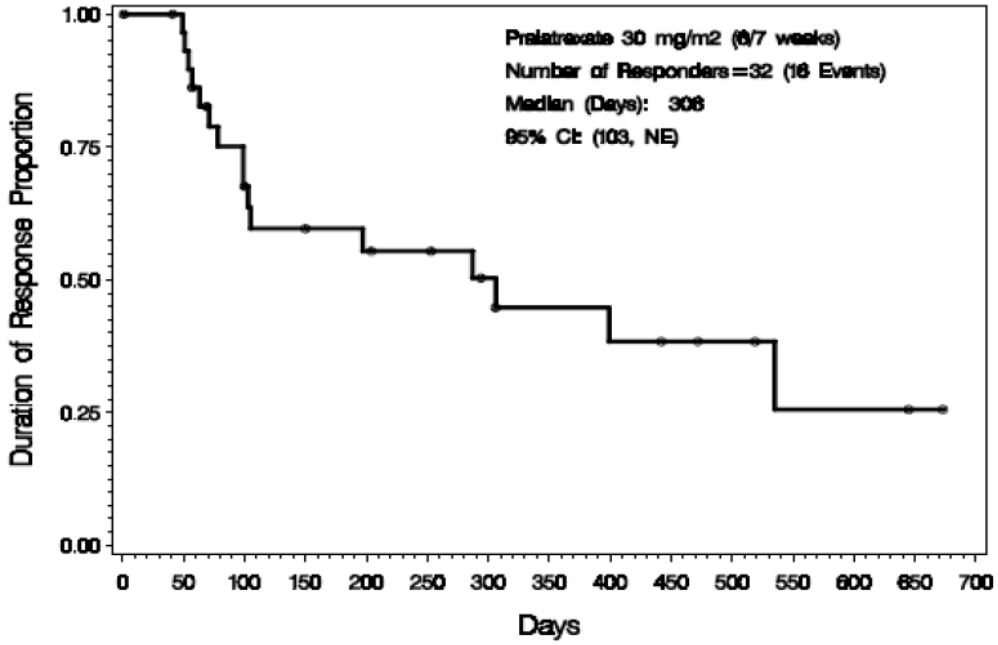
Duration of response

The median duration of response assessed per central review by IWC was 306 days (95% CI: 103 - not estimable) or 10.1 months, with a range of 1-673 days. The 6 month and 12 month Kaplan-Meier estimates for duration of response were 60% and 45%, respectively. The Kaplan-Meier plot is shown in Figure 6, below.

The median duration of response assessed by IWC plus PET (28 responders) was 386 days (95% CI: 191 - not estimable); range of 1-682 days. The median duration of response assessed by local investigator (for 43 responders) was 246 days (95% CI: 154 – 379); range of 1-677 days.

At the time of data cut off in August 2009, 14 patients had durations of response (assessed by IWC) in excess of 6 months, including 5 patients with a continued response to treatment (3CR; 2PR), ranging from 204 to 673 days. Four of these 5 patients also remained on treatment.

Figure 6. Study PDX-008 - Kaplan-Meier duration of response (IWC central review)



It should be noted that patients went to clinic weekly to receive pralatrexate, and if they had new skin lesions or disease-related symptoms, they were discussed with the treating physician, which often led to an earlier determination of PD that would have been attained by scans (that is, every 14 weeks). In fact, 45% of all the disease progression determinations by central review were based on unscheduled assessments and only 33% of disease progression events in responders as determined by central review were based on a scheduled assessment.

In an undated update of efficacy presented in the *Clinical Summary Efficacy Addendum*, the sponsor reported that in the intervening 2 years (approximately) the 5 patients with a continued response to treatment at the time of the original data cut-off all remained in response with durations ranging from 20.7 to 46.9 months (621 – 1407 days). This included 2 patients who received a stem cell transplant immediately after completion of pralatrexate treatment, with durations of response of 41.3 months (1239 days) and 44.6 months (1338 days), respectively.

Individual IWC response data and a further break down of these data according to whether there was CR/CRu or PR were included in the submission. The latter two tables include details of those covariates that might be considered to be of prognostic importance (such as age; ECOG PS; number of and best response to prior therapies; and LDH levels).

Evaluator's comment:

From the data it can be appreciated that there was a high degree of censoring for the calculation of Kaplan-Meier estimates of the median duration of response. Only 16 patients had event dates (14 disease progressions, 2 deaths). End dates for the remaining 16 responders were censored. The sponsor noted that among those patients with censored end dates, the duration of response will only change for 5 (that is, those with continuing response at time of data cut off). The duration of response will never change for the other 11 patients because 4 had gone on to transplant, 3 had started another cancer therapy, 3 had completed all protocol-required visits for follow-up, and 1 had withdrawn consent to be followed further. The 3 patients that were censored because they had started another cancer treatment are of interest to this evaluator:

- Patient G (duration of response censored at 306 days) - according to the data this patient received pralatrexate for 442 days, having first achieved a response of CR on 1 October 2007.

Pralatrexate was last administered on 25 July 2008. On 8 August 2008 treatment was permanently discontinued and the primary reason was documented to be "Other, Progression of Disease". According to the data, the therapy received subsequent to pralatrexate was combination liposomal doxorubicin and gemcitabine, commenced on 22 August 2008;

- Patient M (duration of response censored at 1 day) - according to the data this patient received pralatrexate for 246 days and the patient first achieved a response of PR on 4 March 2008. Pralatrexate was last administered on 4 March 2008. On 11 March 2008 treatment was permanently discontinued and the primary reason was documented to be "Other, Progression of Disease". According to the data, the therapy received subsequent to pralatrexate was methotrexate, aracytine and hydrocortisone, commenced on 13 August 2008;
- Patient N (duration of response censored at 1 day) - according to the data this patient received pralatrexate for 135 days, with the last dose administered on 16 January 2008. She first achieved a response of PR on 22 January 2008. On 29 January 2008 treatment was permanently discontinued and the primary reason was documented to be "Non haematological adverse event, PNEUMONITIS". According to the data, the therapy received subsequent to pralatrexate was "Steroid (UNK)", commenced on 7 February 2008.

For Patients G and M the commencement of another cancer treatment occurred after the documentation of progression of disease. The censoring of these patients in preference to including them with an end date for the event of disease progression needs to be fully explained and justified by the sponsor.

Also, Patient M had a censored duration of only 1 day (although in actuality the duration may be as long as 7 days before subsequent disease progression if the dates are as recorded in the line listings). This raises the issue of whether it can be accepted that this patient had a meaningful clinical response - is it simply enough to have tumour shrinkage, for however limited a period of time, or does one need either an enduring response and/or an accompanying reduction in symptoms? Importantly, symptomatology and quality of life were not assessed in the study.

Progression free survival (PFS)

The median PFS based on response assessed by IWC, estimated by the Kaplan-Meier method (Figure 7, below), was 106 days (95% CI: 51 - 146 days) or 3.5 months, with a range of 1-726 days. Seventy patients (64%) had an event of either disease progression (n = 63, 58%) or death (n = 7, 6%) that was used to calculate their PFS. The remaining 39 patients were censored because they had either not yet progressed at the time of the data cut-off date (n = 5, 5%) or had received anti-cancer therapy before progressive disease was assessed (n = 26, 24%) or they had received a transplant (n=4, 4%) or they terminated study follow-up of response (n=4, 4%).

The median PFS based on response assessed by IWC plus PET was 141 days (95% CI: 79 - 243), with a range of 1-726 days. The median PFS based on response assessed by local investigator was 121 days (95% CI: 77-148 days), with a range of 1-726 days. The median PFS based on response assessed by IWC plus PET was 141 days (95% CI: 79 - 243), with a range of 1-726 days. The median PFS based on response assessed by local investigator was 121 days (95% CI: 77-148 days), with a range of 1-726 days.

Overall survival (OS)

As at data cut-off in August 2009, the overall survival ranged from 1.0 to 24.1 months, with median duration 14.5 months (95% CI: 10.6-22.5). Forty-seven patients (43%) were censored because they were still alive at the time of the data cut-off date. Of the 62 patients who had died, 52 (84%) were due to progression of their PTCL.

In its *Clinical Summary Efficacy Addendum* the sponsor reported that, after the intervening 2 years (approx), 12 patients were still alive with survival from Treatment Day 1 ranging from 36.0 to 52.8 months, including 5 patients with an OS of more than 4 years from Treatment Day

1. Table 9, below presents the original and updated survival rates and their 95% CIs, calculated from the beginning of pralatrexate treatment through the time of the last available follow-up.

Figure 7. Study PDX-008. Kaplan-Meier progression free survival per central review (IWC)

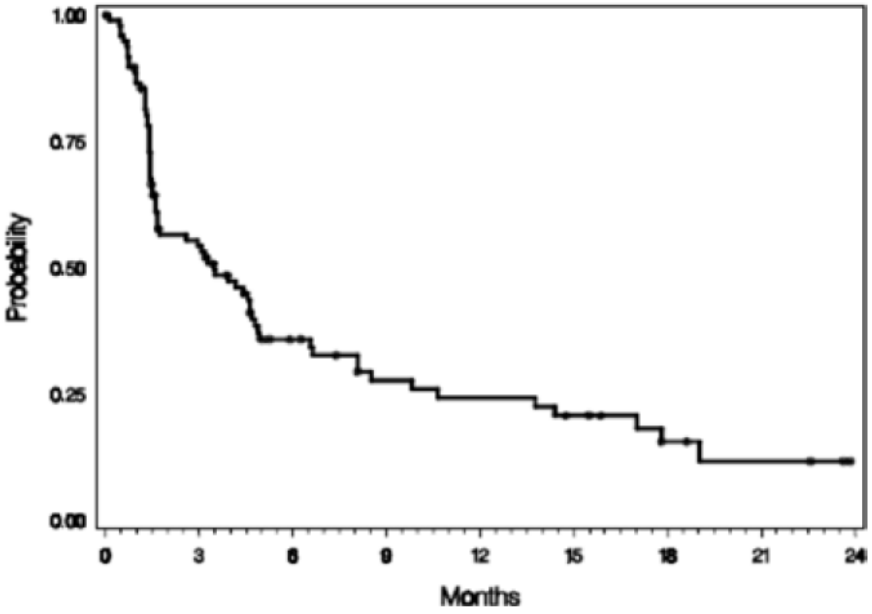


Table 9. Study PDX-008. Survival rates in PTCL patients treated with pralatrexate

	1 year	2 years	3 years	4 years
Original data (CSR)				
Rate (%)	55.3	33.7	-	-
95% CI	45.2 – 64.3	23.3 – 44.5	-	-
Updated data				
Rate (%)	56.0	34.8	28.5	24.9
95% CI	46.1 – 64.9	25.8 – 43.9	19.1 – 38.6	15.0 – 36.2

Correlation between tumour response and survival

The results of the Cox model and Landmark analyses are shown in Table 10, below. An HR <1 supports the claim that increasing response rate leads to increased survival. However, not all such results were statistically significant (and, correspondingly, the 95% CIs for the HR were quite wide) as a consequence of the small number of responders included in the analyses, particularly in the landmark analyses.

Patients treated with pralatrexate who responded at any time had a 44% (per central review) and 56% (per investigator) reduction in risk of death (Cox model p=0.07 and <0.01, respectively). Patients who responded during Cycle 1 had a 31% (per central review) and 49% (per investigator) reduction in risk of death (Landmark analysis p=0.32 and 0.03, respectively).

Table 10. Study PDX-008 - Analysis of survival by tumour response

Evaluation Method	Statistical Method	No. Patients in Analysis (Responders)	HR (95% CI)	*P* Value
Per central review	Landmark at cycle 1[a]	93 (20)	0.69 (0.33, 1.43)	0.32
	Time-dependent covariate	109 (32)	0.56 (0.30, 1.05)	0.07
Per investigator	Landmark at cycle 1[a]	91 (32)	0.51 (0.28, 0.95)	0.03
	Time-dependent covariate	109 (43)	0.44 (0.25, 0.78)	< 0.01
Per central review using IWC + PET response assessment	Landmark at cycle 1[a]	75 (18)	1.06 (0.51, 2.17)	0.88
	Time-dependent covariate	109 (28)	0.56 (0.29, 1.06)	0.08

Deaths occurring or patients without any tumor response evaluations prior to day 53 were excluded.
No. = number; HR = hazard ratio; CI = confidence interval; IWC = International Workshop Criteria; PET = positron emission tomography

Subsequent therapies

The majority of patients (n=80; 73%) went on to treatment with a subsequent therapy after discontinuing pralatrexate. Most commonly (n = 36; 33%) this comprised combination chemotherapy (with or without a platinum agent). At data cut off in August 2009, 6 (6%) patients had gone on to SCT as their initial subsequent therapy. This included 5 patients who had a response to pralatrexate per IWC (3 CR; 2 PR) and of these all but one (PR) were still in response at the time of the SCT. At the time of last contact prior to data cut-off, none of these 4 patients had received any therapy after the SCT, suggesting that all 4 remained in response. An additional 7 patients had SCT after their initial failure to respond to pralatrexate treatment. Of the 13 (12%) patients who underwent an SCT at the August 2009 cut-off date, 2 had an autologous SCT and 11 had an allogeneic SCT.

6.1.1.1.16. Retrospective analyses of data from Study PDX-008

In recognition of the limitations of data generated from a non-comparative study, the sponsor undertook a number of retrospective analyses to better define the clinical benefit of pralatrexate. These analyses employed patients as their own controls, as well as historical controls and were reported in summary form in the *Clinical Summary of Efficacy Addendum*.

Patients as their own controls

In the first analysis the sponsor examined the patterns of change in response rate and PFS with successive lines of treatment and the impact of pralatrexate relative to prior therapies. Results are shown in Table 11, below for 3 subsets of patients; those with 3 or more prior systemic therapies; those with 2 or more prior systemic therapies and all patients (that is, immediate prior therapy).

Table 11. Study PDX-008 - Response rate and progression-free survival with pralatrexate versus earlier lines of therapy

Prior systemic therapy	N	Response rate	Progression-free survival	
			PFS median (days) [95%CI]	HR [95%CI]
Patients with ≥ 3 previous treatments - 3	57	56%	213.5 [122 – 180]	*- 3 versus – 2* 0.66 [0.45 – 0.97]
- 2	57	33%	140.0 [75 – 208]	*- 2 versus – 1* 0.82 [0.57 – 1.20]
- 1	57	30%	95.0 [72 – 136]	*- 1 versus PDX* 1.12 [0.75 – 1.67]
Pralatrexate (PDX)	57	40%	134.0 [51 – 162]	
Patients with ≥ 2 previous treatments - 2	86	38%	144.0 [91 – 188]	*- 2 versus – 1* 0.79 [0.58 – 1.06]
- 1	86	29%	89.5 [72 – 123]	*- 1 versus PDX* 1.20 [0.87 – 1.66]
Pralatrexate (PDX)	86	40%	119.0 [77 – 146]	
Immediate prior treatment - 1	109	38%	114.0 [89 – 151]	*- 1 versus PDX* 1.05 [0.79 – 1.41]
Pralatrexate (PDX)	109	39%	121.0 [77 – 148]	

It is known that, generally, the response rates and progression-free survival of patients who progress through successive lines of therapy decreases with each subsequent line of therapy (so-called progressive resistance). The sponsor's analyses of data from Study PDX-008 confirmed there was a trend for decreasing response rates and PFS with successive prior treatments in patients who had 3 or more and 2 or more prior treatments. Importantly, pralatrexate appeared to reverse these trends in these two patient subsets. Also, when compared to immediate prior therapy, pralatrexate appeared to stabilise the trend, whereas ordinarily one would expect the response rate and progression free survival to have declined. It is important to remember that these were retrospective analyses and the study was not powered for such comparisons – and although the hazard ratios (HR) for comparisons involving pralatrexate were all in favour of pralatrexate, statistical significance was not achieved at a 5% level and the 95% CIs are quite wide. Another limitation with this analysis is that it was based on investigator assessments because central review was not available for prior therapies. Investigator response rates were higher than the central review rate by 10%, whilst the duration of PFS was assessed as being slightly longer by investigators compared to central review.

In the second analysis, the response to pralatrexate (response rate, PFS and time to progression) was compared with the last prior treatment regimen by regimen type (Table 12, below). Response numerically favoured pralatrexate in all the comparisons except the comparison with CHOP. Statistical significance (&/or 95% CI intervals) not reported for these analyses, but the regimen subgroups are quite small. Of particular note, half of the patients who received CHOP in the treatment immediately prior to pralatrexate, received CHOP as their first and only treatment up to that point in time, so they did not at that stage have relapsed disease and were not known to be refractory to treatment. When such patients are removed from the analysis (that is, analysis restricted to patients with ≥ 2 prior systemic therapies), there were similar outcomes for pralatrexate and COHP as a second or subsequent therapy.

Table 12. Study PDX-008 - Median progression-free survival and response rate with pralatrexate versus the immediate prior systemic regimen, by regimen

Regimen	Prior therapy	N	Response rate	Progression-free survival		Time to progression	
				Median (days)	HR	Median (days)	HR
All patients Overall	PDX	109	39%	121		142	
	- 1	109	38%	114	1.05	114	1.15
Single agent	PDX	20	50%	67.5		86	
	- 1	20	15%	82.5	1.09	82.5	1.21
CHOP	PDX	31	35%	148		150	
	- 1	31	58%	151	0.79	151	0.86
Bexarotene/denileukin diftitox	PDX	10	70%	254		254	
	- 1	10	30%	84.5	1.58	84.5	1.58
Platinum-based multi-agent	PDX	17	24%	77		77	
	- 1	17	24%	63	1.12	63	1.12
Non-platinum non-CHOP multi-agent	PDX	14	29%	57		121	
	- 1	14	43%	95.5	0.97	95.5	1.22
SCT	PDX	9	56%	324		234	
	- 1	9	56%	274	2.38	274	2.38
Patients with ≥2 prior regimens Overall	PDX	86	40%	119		127	
	- 1	86	29%	89.5	1.20	89.5	1.29
Single agent	PDX	18	44%	68.5		86	
	- 1	18	11%	81.5	1.25	81.5	1.34
CHOP	PDX	15	33%	97		127	
	- 1	15	40%	114	0.92	114	1.10
Bexarotene/denileukin diftitox	PDX	9	67%	178		178	
	- 1	9	33%	56	1.36	56	1.36
Platinum-based multi-agent	PDX	16	25%	77		77	
	- 1	16	19%	62	1.29	62	1.29
Non-platinum, non-CHOP multi-agent	PDX	12	33%	121		121	
	- 1	12	42%	87.5	1.17	87.5	1.34
SCT	PDX	9	56%	324		324	
	- 1	9	56%	274	2.38	274	2.38

The sponsor also examined the response to pralatrexate after failure of CHOP and after failure of ifosfamide/carboplatin/etoposide (ICE)-based regimens. CHOP is the most common first line treatment used for PTCL, whilst ICE-based regimens are often used in salvage situations. A total of 16 patients received pralatrexate as second-line treatment post CHOP. The response rate per central review in these patients was 44% (19% CR and 25% PR) with a median duration of response that was not estimable due to insufficient disease progression events. Among these patients were 2 who went onto to SCT and remained in CR at 20 and 21.7 months follow-up, respectively. A total of 20 patients had received a prior ICE-based regimen (9 as most recent therapy) and their overall response rate was 40% (15% CR and 25% PR) with a median duration of response of 13.1 months. 95% CI intervals for these outcomes were not reported for these analyses but could be expected to be quite wide given that the regimen subgroups are quite small. Of the 9 patients whose most recent prior therapy was ICE, 2 patients did not respond to the prior ICE-based regimen but did respond to pralatrexate (1 CR and 1 PR). Two of the 20 patients who had previously received ICE-based regimens achieved a CR on pralatrexate and proceeded to SCT; the duration of response to pralatrexate in these patients was censored (at 1.3 and 4.9 months). However, these 2 patients remain in CR and their disease-free period (duration of response: pralatrexate + transplant) at most recent follow-up is 10.9 and 30.8 months.

In order to determine whether patients who responded to pralatrexate on PDX-008 were more likely to respond due to a superior disease prognosis at study entry, the sponsor conducted a retrospective analysis comparing the PFS of pralatrexate responders according to central review (n=32) with the PFS of the same patients' most recent prior therapies. The median PFS from pralatrexate was 438 days compared to a median PFS of 242 days from the most recent prior therapy. A further subset analysis amongst patients who had responded to pralatrexate but not to their most recent prior therapy (n=17) also revealed a prolonged median PFS with pralatrexate compared to the previous treatment (419 days versus 111 days).

The sponsor considered that the data for the patients who did not respond to the most recent prior therapy were particularly important, arguing that it was reasonable to assume that the disease course was unaffected, or only minimally affected by prior therapy. In this context, a prolonged progression time following a response to pralatrexate therapy in those patients could be considered to be due to treatment with pralatrexate, not patient factors. It was further argued that, as the great majority of patients with relapsed/refractory PTCL die as a result of progression of their lymphoma, it was reasonable to assume that a positive impact on progression contributed to the improved survival observed for responding patients in the landmark analyses (Table 10).

Comparison with historical controls

The sponsor compared survival data from Study PDX-008 with data from historical controls from a number of registries and databases:

- The International T-cell Registry (Vose *et al* 2008) – comprising 1153 confirmed cases of PTCL and NK/T-cell diagnosed between January 1990 to December 2002.

  The 5-year survival from diagnosis for PTCL-U, angioimmunoblastic, and all NK/T-cell lymphomas was 32%, compared with only 14% for ATLL. Anaplastic large-cell lymphoma (ALCL), ALK+ demonstrated the best 5-year survival (70%), ALCL, ALK - had an intermediate 5-year survival (49%). This is the largest available data set and has the advantage of central review/confirmation of diagnosis. However, there were no data specifically about outcomes in relapsed/refractory patients and the data weren't contemporaneous with those from PDX-008.

- The T-cell project (Federico *et al* 2011)– comprising 524 newly diagnosed PTCL cases collected from 2006 onwards.

  The 3-year survival from initial diagnosis for the entire population was 50% (95% CI 43-56%). This dataset has the advantage of being contemporaneous with those from Study PDX-008 but does not contain information specifically about outcomes in relapsed/refractory patients;

- The Modena Cancer registry – comprising data from 104 patients with PTCL diagnosed between 1997 and 2007.

  Median survival from diagnosis in this patient group was 10 months, with a 5-year survival rate of 34.9%. There were no data available on the therapies received after progression or relapse and the data are mostly not contemporaneous with those from Study PDX-008.

- The University of Nebraska Medical Center (UNMC) database – comprising data from 76 patients diagnosed between July 1984 and May 2010, including 50 PTCL patients who received 2 or more therapies.

  The sponsor was able to access the centre's web-based oncology database and use the Patient Repository Module which allowed for accurate tracking of patients at UNMC and partner centres. Consequently, the sponsor was able to evaluate the data with a focus on survival outcomes for patients treated for relapsed or refractory disease.

  UNMC patients who received 2 or more therapies had a median survival (calculated from the initiation of last therapy to death or censoring) of 8.7 months compared to 14.5 months for patients in Study PDX-008. This was whilst having seemingly better prognostic factors than Study PDX-008 patients - UNMC patients had a shorter time from diagnosis to most recent therapy (median 7.8 versus 15.6 months) and were less heavily pre-treated (50% received only 1 therapy prior to the last, whereas in Study PDX-008 50% of patients had received 3 prior therapies). The majority of UNMC patients received combination chemotherapy as their most recent treatment – most commonly ICE (26%) and combination dexamethasone, cisplatin and cytarabine (DHAP; 14%).

- The Memorial Sloan-Kettering Cancer Center (MSKCC) database - comprising data from 171 patients with PTCL, diagnosed from June 1997 to July 2011.

  MSKCC provided the sponsor with access to demographic, treatment and outcome data for patients treated at the centre, including 100 patients who had received at least 2 prior systemic therapies for PTCL. A total of 70 patients were included in the comparison with Study PDX-008; the remaining 30 patients had received pralatrexate either in studies PDX-008, PDX-02-078 or PDX-009 or in the post-marketing setting.

  The PDX-008 patients were slightly older and more heavily pre-treated than the MSKCC controls. Also, the median time from initial diagnosis to initiation of the last therapy was longer in Study PDX-008 and a lower proportion of patients in Study PDX-008 had demonstrated a response to previous therapies and to the most recent therapy. The median survival, calculated from the initiation of last therapy to death or censoring in MSKCC patients was 6.1 months (95% CI 4.0-11.00 compared to 14.5 months (95% CI, 10.6- 22.5). The hazard ratio was 0.715 (95% CI: 0.486-1.053), in favour of pralatrexate.

Evaluator's comment:

The data available from the UNMC and MSKCC databases are the most relevant for use as historical controls because they allowed assessment of survival outcomes for patients with relapsed or refractory disease from the initiation of last therapy to death or censoring. This could be compared directly with the data from Study PDX-008. A full comparison of demographic and clinical characteristics, including most recent treatment of the patients from these databases and Study PDX-008 was provided in the submission. However, whilst the collection of data for these databases overlapped the conduct of the Study PDX-008, the timeframe for the historical controls was longer, particularly the UNMC database which included data from as early as 1984. Thus the controls are not entirely concurrent with that of Study PDX-008 which is a limitation of these analyses.

Also of note, patients were censored at 24.1 months, since that was the longest follow-up time of patients in the PDX-008 study. Interestingly, the Kaplan-Meier plots from these analyses (Figure 8, below) show that the survival curves cross in the UNMC analysis at approximately 15 months, whereby survival at 24 months is higher for the UNMC group; and that the curves converge in the MSKCC analysis at 24 months. It would be useful to have data beyond 24 months for both these groups to review against the data shown in Table 9, which provides survival rates (albeit with wide confidence intervals) for PDX out to 4 years.

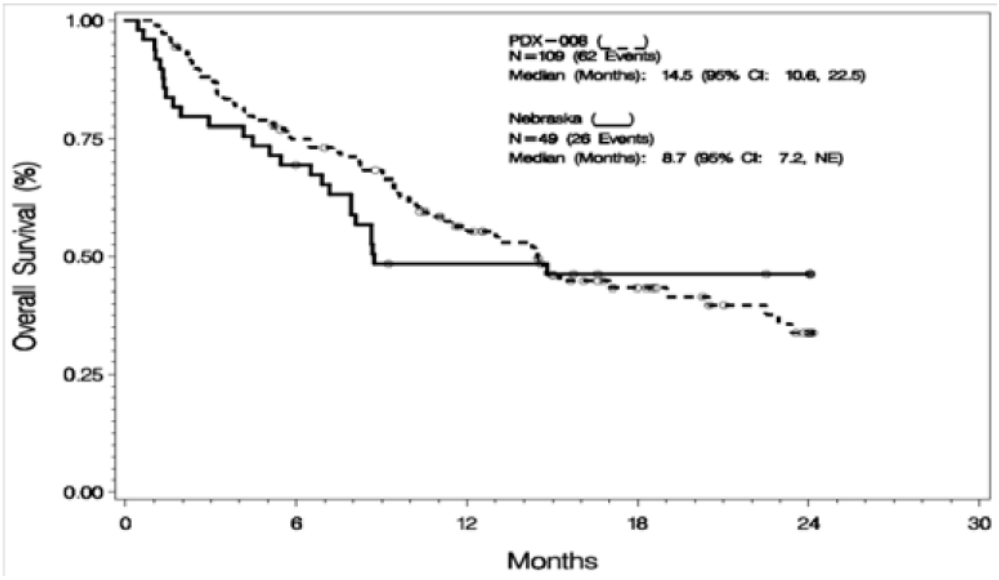
With respect to the survival curves shown above, it is evident there was a slowed decline with pralatrexate compared to other treatments but there is no real plateau, suggesting that the role of pralatrexate may be to provide a bridge to transplantation. However, it must be remembered this is a single agent being compared to what were essentially combinations of other agents, so the comparison provides proof of concept for the activity of pralatrexate in PTCL.

MSKCC was one of the highest enrolling investigational sites in the pivotal study. Seven controls from MSKCC received their last treatment during the period that Study PDX-008 was open at the centre, but were not included in the PDX-008 study. The sponsor noted this appeared to have been because the patients were considered to be candidates for aggressive multi-agent therapy, or because they were included in other clinical studies. The sponsor conducted a sensitivity analysis with these 7 patients excluded from the MSKCC cohort. This showed the survival for these 7 patients was similar to, or slightly better than, that of the other MSKCC patients, and thus would not have negatively impacted the analyses. It is also presumed that selection of patients for PDX-008 did not favour those likely to have better outcomes.

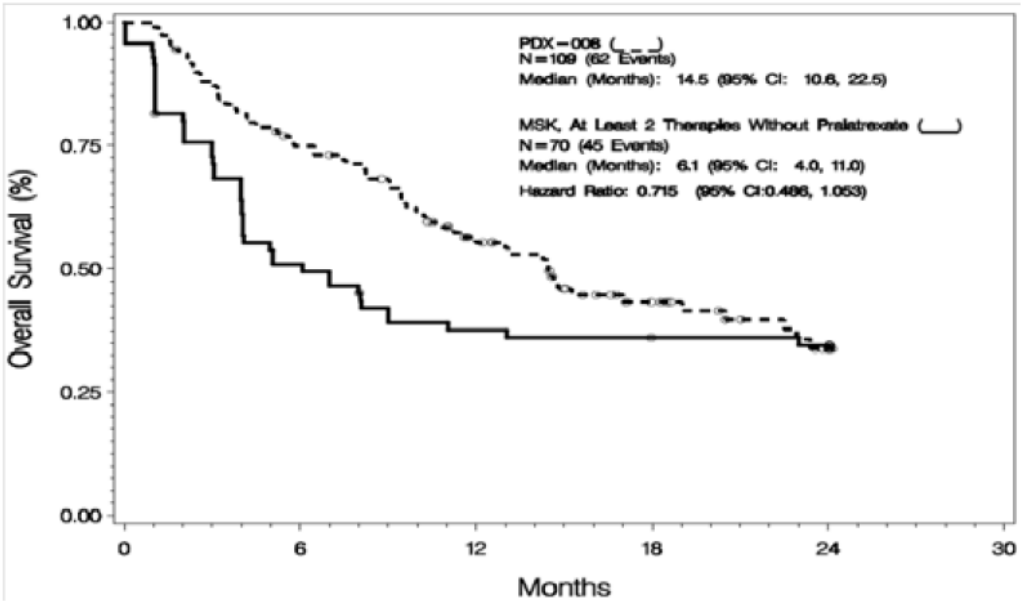
Despite the limitations associated with retrospective analyses and the use of historical controls, the survival data suggest that pralatrexate may have the efficacy to provide similar or improved clinical outcomes compared to those seen with available treatment options.

Figure 8. Survival from time of most recent treatment in patients with relapsed/refractory PTCL – pralatrexate (Study PDX-008) versus historical controls from UNMC (A) and MSKCC (B)

A



B



6.1.2. Other efficacy studies

6.1.2.1. Study PDX-02-078

This single arm, non-randomised, open-label study in patients aged 18+ years with relapsed or refractory aggressive NHL or Hodgkin's lymphoma (HL) was conducted at the MSKCC from September 2002 to May 2009 with the primary objectives of determining the efficacy of pralatrexate, determining the impact of PK on AEs and drug elimination, and to optimise a weekly schedule of pralatrexate with vitamin B12 and folic acid supplementation. Secondary objectives included the characterisation of adverse events in this patient population and evaluating the potential correlates of stomatitis.

Key entry criteria included: a requirement for patients to have measurable disease, defined as at least 1 lesion accurately measured in at least 1 dimension as ≥ 2cm on conventional techniques

or ≥ 1cm on spiral CT scan; Karnofsky performance status ≥ 60%; and adequate bone marrow and organ function, that is, ANC ≥ 1.0 x 10^9/L; PLT ≥ 50 x 10^9/L; total serum bilirubin ≤1.5 x ULN; serum ALT/AST ≤ 2.5 x ULN (4 x ULN if liver involvement); serum creatinine ≤ 1.5 mg/dL or creatinine clearance≥ 50 mL/min. Patients were allowed to have had any number of prior therapies.

The study was originally intended to be a Phase II study of efficacy and safety, where the starting dose of pralatrexate was 135 mg/m^2 administered every other week, with intra-patient dose escalation. However, the protocol was amended in 2004 (by which time 16 patients had received treatment) to include Phase I activities in the form of inter-patient dose escalation to determine the optimal dose and schedule of pralatrexate, using an initial dose of 30 mg/m^2 weekly for 3 weeks of a 4 week cycle, with subsequent increases in the number of consecutive doses (from 3 to 6 doses) and dose amount (15 mg/m^2 increments). These changes were in response to a higher than anticipated incidence of Grade 3 or 4 stomatitis in patients with Hcy and MMA concentrations > 10 µmol/L and > 200 nmol/L, respectively, and because many patients with palpable disease had responses that were suggestive of cytokine failure (that is, they experienced marked reductions in their disease by Day 7 but these grew back to baseline levels by Day 15). Of note, the study was amended to include a requirement for normalised Hcy and MMA levels or a 10-day course of folic acid/vitamin B12 repletion prior to study entry.

A total of 3-6 patients were to be enrolled at each dose level for the Phase I part of the study until the MTD was determined and a minimum of 17 patients and a maximum of 37 patients were to be enrolled for the Phase II component based on objective response. A 2-stage Simon design was to be employed for the Phase II whereby at least 4 out of 17 patients had to have experienced a response in Stage 1 for the study to proceed to Stage 2. In Stage 2, an additional 20 evaluable patients were to be enrolled. A patient was considered evaluable for efficacy per the protocol if he/she completed 2 cycles of therapy. Subsequently, the study was again amended in 2007 to have an emphasis on evaluating efficacy in B-cell lymphoma for the Phase II portion of the study and a higher dose of 270 mg/m^2 administered every 2 weeks (rather than every week) was used.

A total of 72 patients (61% male, 39% female; mean age 54.1 yrs (range 20-80); 63% Caucasian) were enrolled in the study, of whom 39 were evaluable. Thirty-six (50%) patients had T/natural killer (NK)-cell lymphoma; 25 (35%) had B-cell lymphoma; 8 (11%) had Hodgkin's lymphoma; 2 (3%) had composite T- and B-cell lymphoma; and 1 (1%) had Richter's transformation. Overall, 13 (33%) patients had a response (6 CR; 1 CRu; and 6 PR) based on investigator assessment according to guidelines for response criteria for lymphoma reported by Cheson *et al*., 1999, 2007. Twelve of the responses had occurred in patients with T-cell lymphoma and 1 in a patient with B-cell lymphoma. The treatment regimens received by patients with T-cell lymphoma are shown in Table 13, below. A total of 20 of 36 patients were evaluable per protocol and of these, 12 (60%) had a response (6 CR; 1 CRu; and 5 PR).

Table 13. Study PDX-02-078. Response by dosage schedule in patients with T-cell lymphoma (wks=weeks)

	Pralatrexate treatment group (dose/schedule)					Total
	135 mg/m² (1/2 wks)	30 mg/m² (3/4 wks)	30 mg/m² (6/7 wks)	45 mg/m² (6/7 wks)	270 mg/m² (2/4 wks)	
All patients	16	3	27	11	15	72
T-cell NHL	1	3	19	7	6	36
T-cell NHL & evaluable	0	3	13	3	1	20
Response in T-cell NHL						
CR		1	3	2		6
CRu		1				1
PR			5			5
CR + CRu + PR	0	2	8	2	0	12

The results for T-cell lymphoma patients who received the same dosage regimen as proposed in this application are highlighted in Table 13 by shading (Note: in this study dose reductions from 30 mg/m² to 15 mg/m² were made in this cohort in response to toxicities rather than 20 mg/m² as proposed). The duration of response in these patients ranged from <1 month (in a patient who had a PR but was discontinued the same day due to "investigator's decision") through to 8 months, with median of 4 months. The time to first response ranged from 44 to 308 days (median 90.5 days).

Evaluator's comment:

The responders in Study PDX-02-078 included one patient with mycosis fungoides (patients with this condition, apart from transformed mycosis fungoides were excluded from the pivotal study because of their indolent behaviour). Also, 2 patients had had no prior therapy for their disease which contravened the requirement for patients to have relapsed or refractory disease. The first patient achieved a PR at Day 93, with the duration of response of 5 months and the second patient achieved a CR at day 90, with the duration of response of 3 months.

In the Phase I part of the study, 5 dose-limiting toxicities and 2 patient deaths were experienced in the 45 mg/m² weekly for 6 doses/7-week cycle treatment group (n = 11 treated patients). The maximum tolerated dose was declared as the dose level below this, that is, 30 mg/m² weekly for 6 doses/7-week cycle, which was used in the Phase II part of the study and also used subsequently in Study PDX-008.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

6.2. Evaluator's conclusions on clinical efficacy for PTCL

The TGA-adopted EU *Guideline on the Evaluation of Anticancer Medicinal Products in Man* requires that the benefit-risk profile of new chemotherapeutic agents be established with data from well conducted Phase III randomised controlled trials (RCT). However, the guideline also recognises that for rare tumours or very narrow indications it may not be possible to recruit a sufficiently large number of patients to conduct an appropriately powered RCT, in which case the best options available are to either conduct a small randomised reference controlled study

and/or conduct a within-patient time-to-progression analysis in which the time-to-progression on last prior therapy is compared to time-to-progression on the new agent.

In this submission, the efficacy of pralatrexate was evaluated in a single non-randomised, open-label Phase II study comprising 109 evaluable patients with relapsed or refractory PTCL. The primary endpoint was based on objective response rate (an accepted marker of activity for cytotoxic agents) determined by independent, adjudicated central review using IWC criteria. The study used standardised treatment conditions and data collection; the study was compliant with GCP requirements; and data were collected prospectively. Key results from the study were:

- an overall response rate (CR+CRu+PR) of 29% (95% CI: 21 – 39%) by central review;
- 25% of pralatrexate responders had no evidence of response to their most recent prior therapy;
- 19% of pralatrexate responders had no evidence of response to any prior therapy;
- a median duration of response of 306 days (95% CI: 3.4 – NE) or 10.1 months by central review;
- a median progression-free survival of 106 days (95% CI: 51 – 146) or 3.5 months by central review; and
- a median overall survival of 14.5 months (95% CI: 10.6 – 22.5 months) by central review. The most recently available data indicates a survival rate of 56% (95% CI 46 – 65%) at 1 year; 35% (95% CI 26 – 44%) at 2 years; 29% (95% CI 19 – 39%) at 3 years; and 25% (95% CI 15 – 37%) at 4 years.

Whilst the absence of a randomised controlled design is understandable in the context of PTCL being a rare disease for which there are no standard treatment protocols, there are consequential limitations of the data:

- The absence of blinding

  This introduces the potential for investigator bias and reader bias in radiographic evaluation which impacts on the reliability and reproducibility of results. Furthermore, diagnosis of PTCL and subtype can be difficult and not always readily reproducible. However, this bias was mitigated as far as possible by requiring that tumour diagnosis, eligibility for study entry and tumour responses be assessed and adjudicated centrally and independently using International Workshop Criteria (IWC), with blinding to the investigator's assessment.

- The absence of a comparator

  The most obvious consequence of the lack of a comparator is that it is difficult to determine whether the magnitude and duration of responses observed in this study will confer a meaningful clinical benefit in the target population. This compromises the reliability of the study and is particularly important given that the response rate was driven largely by partial responses (20/32; 62.5% of responders) and the fact that 9/20 (45%) of partial responders subsequently experienced either disease progression and/or death within 100 days of achieving the response. The revised IWC response criteria for malignant lymphoma recognises that response rates do not necessarily influence other outcomes (especially survival) in lymphoma, but the presence of durable complete responses may be important (Cheson *et al* 2007). In this regard, it is evident from the data that enduring complete responses were seen amongst a subset of patients who achieved a response, including patients with extranodal disease at the time of enrolment in the study. In addition, treatment with pralatrexate allowed bridging to transplant and subsequent ongoing prolonged response in a number of patients.

Other issues of note in the pivotal study were:

- Heterogeneity of the study population

  There were more than 8 tumour subtypes among patients enrolled in the study. At face value this limits to some extent the internal validity of the study, for different subtypes may have different prognoses and different natural histories following diagnosis. However, it must be remembered that this was a heavily pre-treated, relapsed and refractory population (with a median number of systemic treatments of 3; range 1 to 12). The fact that these patients had experienced disease progression following use of other available treatments would have largely offset the heterogeneity in tumour subtype. For example, it is known that anaplastic large cell lymphoma (ALCL) has a higher chance of cure with initial therapy than other subtypes, especially if it is ALK +ve. However, once this tumour subtype relapses it behaves like the other aggressive PTCL subtypes, with a poor prognosis. Also, where heterogeneity in a study population exists, it is desirable to see similar benefits in all subgroups – in this regard the response amongst patients with angioimmunoblastic subtype was notably lower than with other subtypes. However, the study was not designed to study specific subgroups and the number of patients with angioimmunoblastic PTCL was quite small, so caution is needed in interpreting this result. With regard to the external validity of the study, the proportions of the different subtypes and the demographics of the patients were generally representative of the target population. The prevalence of the various histopathological subtypes reflects that previously reported for patients with PTCL, (Evens and Gartenhaus, 2004; Rodriguez-Abreu *et al*., 2008) with the majority in the safety analysis set (n = 59, 53%) having PTCL-unspecified according to central review assessment. Furthermore, there were no centre effects evident, so the results can be readily extrapolated to the target population. It is also of some note that the sample size of 100+ patients represents a substantial study in this indication.

- Use of PET

  The incorporation of PET in the central assessment of response decreased overall response rate (from 29 to 26%) but increased the complete response rate (from 10% to 14%). At the time the study was initiated PET assessment was included as an exploratory analysis. Issues with the use of PET include variability amongst readers and equipment; the potential for false-positive findings due to rebound thymic hyperplasia, infection, inflammation; the potential for false negative findings as a consequence of variable FDG avidity among tumour subtypes and/or variable resolution of PET equipment; and confounding by concomitant administration of haemopoietic growth factors that can cause diffusely increased bone marrow uptake (Cheson *et al* 2007). Thus, the PET based response data should be treated with some caution.

The analysis of efficacy was supplemented by the sponsor with a series of retrospective analyses of data from the pivotal study that employed patients as their own controls, as well as historical controls. Notwithstanding the well-known limitations of retrospective analyses and use of historical controls, the results suggest (but are not conclusive) that pralatrexate may:

- stabilise or reverse an observed trend toward poorer outcomes with progressive lines of treatment in PTCL;
- yield response rates and PFS as good as or better than the immediate prior therapy; and
- alter the natural course of the disease and provide improved survival compared with the currently available treatment options for patients with relapsed/refractory PTCL.

Overall, although the data are less than ideal (which was openly acknowledged by the sponsor), this evaluator is satisfied that the data from the study and its associated retrospective analyses show that pralatrexate has activity against PTCL and that the results are sufficiently compelling to conclude that an acceptable level of efficacy has been demonstrated.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal efficacy study in PTCL – PDX-008

In the pivotal efficacy study of pralatrexate in PTCL (PDX-008), the following safety data were collected:

- General adverse events (AEs) were assessed by asking patients to report all problems, complaints, or symptoms at each study visit during treatment with pralatrexate, as well as at the early termination visit (if applicable), the safety follow-up visit 35 (± 5) days after the last dose of pralatrexate, and each routine follow up visit (every 3 months ± 2 weeks) thereafter. AEs regardless of causality were recorded for all patients on-study and events considered possibly, probably, or definitely related to pralatrexate therapy were recorded during the post-treatment period. AEs were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.
- Selected AEs of interest included mucosal inflammation, neutropaenia, leucopaenia, thrombocytopenia, anaemia, abnormalities of liver function (increases in AST and ALT), oedema, dry mouth, dyspepsia, odynophagia, pruritus, anorexia and hypokalaemia. These events were summarised and presented separately using the single lowest-level preferred term in order to present each event uniformly. Haematological and mucosal toxicities were closely monitored and formed the basis for pralatrexate dosage reductions.
- Laboratory assessments were performed at screening, during the treatment phase of the study (Weeks 2-6 of each cycle), at the early termination visit (if applicable), and at the post-treatment safety follow-up visit. All results were converted to standard international (SI) units and flagged as low or high compared to reference normal ranges, markedly low or high (≥ Grade 2 per NCI CTCAE Version 3.0), or clinically significant (≥ Grade 2 per NCI CTCAE Version 3.0, and a shift of ≥ 1 grade from the baseline value). Haematology parameters comprised haemoglobin, haematocrit, white blood cells (WBCs), neutrophils, and platelets. Clinical chemistry assessments comprised total bilirubin, creatinine, ALT, AST, and LDH levels. Of note, alkaline phosphatase and electrolyte levels were <u>not</u> routinely measured.
- Physical examinations were performed at baseline and changes recorded on Week 3 of cycle 1, within 7 days of the first dose of each subsequent cycle, at the early termination visit (if applicable), and at the post-treatment safety follow-up visit. An ECG was performed within 21 days prior to the projected start of pralatrexate administration and thereafter if clinically indicated at anytime during the study.

7.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.1.3. Supporting efficacy study for PTCL – PDX-02-078

In the supporting study of single agent pralatrexate in haematological malignancies, including patients with PTCL (PDX-02-078), the following safety data were collected:

- General adverse event data were obtained at every study visit in Cycle 1, during Week 1 of subsequent cycles, and when the patient went off treatment with pralatrexate. The data were elicited, recorded and assessed in the same manner as used in the pivotal study. Haematological and mucosal toxicities were closely monitored and formed the basis for pralatrexate dosage reductions.

- Laboratory assessments were performed at screening, during the treatment phase of the study, and once the patient went off study treatment. Standard haematology parameters were collected at the screening visit; Cycle 1, Dose 1, Cycle 1, Dose 2 (Week 3); subsequent cycles (both Weeks 1 and 3); and once the patient went off study treatment. A broader range of clinical chemistry was assessed in this study compared to the pivotal efficacy study. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, creatinine, glucose, LDH, potassium, total protein, AST/SGOT, ALT/SGPT, and sodium levels were assessed at the screening visit and once the patient went off study treatment. Also, a "basal" metabolic panel and hepatic function panel, including tests for sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST/ALT, and total bilirubin, were collected at the screening visit; Cycle 1, Dose 1 and Dose 2; subsequent cycles Dose 1 only; and once the patient went off study treatment. The laboratory results were analysed and presented in the same manner as used in the pivotal study.
- A physical examination was performed at the same time as for general adverse events.

This study was initiated in 2002 at MSKCC under an investigator-sponsored IND application. The IND for pralatrexate was transferred to Allos Therapeutics, Inc. from MSKCC in early February 2003. Prior to the transfer of the IND to Allos, MSKCC established a process of entering the patient data for PDX 02-078 directly into the MSKCC's research database without the use of CRFs. After the IND transfer, prospective monitoring of the study was undertaken in accordance with ICH GCP requirements by a contract research organisation on behalf of Allos. An intensive monitoring activity was undertaken in 2008 whereby baseline and safety data collected by the MSKCC were entered on CRFs, reviewed, and entered into the Allos database. These data included (but were not limited to) pralatrexate administration/adjustments, AEs and laboratory results. Laboratory values were not recollected and monitored as part of this process because laboratory data collection in the MSKCC's research database was automated. Overall, it can be accepted that the baseline and the safety information presented in the study report were based on rigorously collected and audited data, with the exception of laboratory values.

7.1.4. Other studies evaluated for safety but not efficacy

The studies undertaken in malignancies other than PTCL were of two general types:

- 8 studies (PDX-007, PDX-009, PDX-010, PDX-011, PDX-012, PDX-014, PDX-015 and PDX-016) were initiated by the sponsor and conducted in accordance with GCP requirements. These studies can be considered to provide high quality supportive safety information.

  The various elements of monitoring of safety (that is, AEs, laboratory parameters and physical examination) appeared to be standardised across all the Allos-initiated studies, although the timing was tailored to suit the treatment regimen of each particular study. Therefore, the broad information outlined for the pivotal study (PDX-008) also applies to this group of studies. In Study PDX-007 a subset of patients underwent more intensive ECG monitoring as part of the sub-study that examined the effect of pralatrexate on QT interval.

- 5 studies were initiated by the MSKCC prior to in-licensing of pralatrexate by Allos (PDX-97-006, PDX-99-053, PDX-99-083, PDX-01-014 and PDX-01-076). The data from these studies have not been subjective to rigorous, extensive auditing by the sponsor. Consequently, the quality of the data could not be assured, but the sponsor considered they still provided relevant "contributive" information. This has been accepted by this evaluator.

  Somewhat scant descriptions of the monitoring of safety (that is, AEs, laboratory parameters and physical examination) were provided in the abbreviated clinical study reports and protocols submitted for this group of studies. The timing of assessments was tailored to the treatment regimen of the study. Haematology and clinical chemistry testing, physical examination and AE assessments were monitored closely in patients (usually on a weekly basis) following the initiation of treatment, with the frequency reduced during latter

doses and cycles. AEs were graded using the NCI Common Toxicity criteria (CTC), Version 2.0. However it was not clear from the information provided as to how the AEs were elicited (that is, whether by direct questioning of patients or reported spontaneously by patients). Also, the laboratory parameters measured across these studies were not standardised. For example, haemoglobin levels were measured across all 5 studies, but leucocyte counts were measured in only 3 studies and platelet counts in 2 studies.

Patient safety populations

The sponsor provided a comprehensive analysis of the safety data for pralatrexate in its *Summary of Clinical Safety* and presented the results for 6 separate patient population categories according to the treatment indication, whether pralatrexate was administered as a single agent or in combination and whether the study provided pivotal, supportive or contributive safety data. These populations are defined below.

Population 1 pivotal study (PDX-008) in patients with PTCL; pralatrexate administered at a dose of 30 mg/m^2 weekly for the first 6 weeks of a 7 week cycle (that is, identical to the proposed dosage regimen).

Population 2 supportive studies in patients with lymphoproliferative malignancies; pralatrexate administered as a single agent (PDX-02-078, PDX-010 and PDX-015). Twenty seven (38%) patients in this population received the same dose and schedule for pralatrexate as the pivotal study, including 19 patients with PTCL (Note: a total of 36 patients from Study PDX-02-078 had PTCL). The remaining patients from these studies received doses of pralatrexate ranging from 15 to 270 mg/m^2, with the schedule of doses ranging from once every 2 weeks to weekly doses for the first 6 weeks of a 7 week cycle.

Population 3 supportive studies in patients with solid tumours; pralatrexate administered as a single agent at doses ranging from 150-325 mg/m^2 on a second weekly basis (PDX-007, PDX-011, PDX-012 and PDX-014).

Population 4 supportive, dose-finding study (PDX-009) in patients with lymphoproliferative malignancies; pralatrexate administered in combination with gemcitabine. This population included 24 patients with PTCL. Pralatrexate doses ranged from 10 to 30 mg/m^2 with either sequential or same day dosing with gemcitabine.

Population 5 contributive studies in patients with various solid tumours; pralatrexate 15 to 170 mg/m^2 administered in various dosage regimens (PDX-97-006, PDX-99-053, PDX-99-083, PDX-01-014, and PDX-01-076).

Population 6 - mass balance study (PDX-016); 2 patients with solid tumours who received 150 mg/m^2 pralatrexate for the mass balance assessment, escalated to 190 mg/m^2 for 5 and 3 subsequent cycles, respectively (2 weekly doses/cycle).

Evaluator's note:

The sponsor's *Summary of Clinical Safety* was based on an analysis of data available from 574 patients as at 17 February 2010. The sponsor did not include Studies PDX-014 and PDX-015 in their analysis because each of these studies had recruited only 1 patient at the time of data cut-off. Also, tabulations in the sponsor's *Summary of Clinical Safety* only included results for Populations 1 to 5. Population 6 was not included in the tabulations because it comprised only 2 patients.

The sponsor also submitted a document titled *Updated Safety Tables, Listings and Narratives* that presented updated and supplemental tables and listings of adverse event data, generated in response to the European Day 120 List of Questions. These tables presented safety data from 689 patients across all clinical studies as of a cut-off date of 31 January 2011. The updated tables

included data from an additional 115 patients enrolled in ongoing studies since the original data cut-off as follows: in Population 2, an additional 16 patients with lymphoproliferative disorders who received pralatrexate as a single agent (PDX-010: 6 patients; PDX-015: 10 patients); in Population 3, an additional 52 patients with solid tumours who received pralatrexate as a single agent (PDX-011: 13 patients; PDX-012: 24 patients; PDX-014: 15 patients); and in Population 4, an additional 45 patients with haematologic malignancies who received pralatrexate in combination with gemcitabine in Study PDX-009. Of note, data from the pivotal study were unchanged.

However, the discussion within the *Summary of Clinical Safety* was not updated to reflect these additional data. Similarly, a number of seminal tables within the *Summary of Clinical Safety* were not updated. Consequently, the main analysis and discussion of safety in this CER is based on the seminal tables provided within the *Summary of Clinical Safety*. Where relevant, additional comment has been provided by this evaluator to indicate whether the updated information available as of 31 January 2011 has fundamentally changed the nature of the data presented or the conclusions that can be drawn from the data.

Patient demographics for each of the safety populations and the safety population overall are shown in Table 14, below. From this table it can be appreciated that there was a predominance of males in Population 1 (in accord with a higher incidence of the disease in males) and across the development program as a whole; and the majority of patients were Caucasian and over the age of 65 years.

Table 14. Patient demographics - all safety populations

Parameter	Value	Population 1 (N=111) n	(%)	Population 2 (N=120) n	(%)	Population 3 (N=128) n	(%)	Population 4 (N=62) n	(%)	Population 5 (N=153) n	(%)	Total (N=574) n	(%)
Gender n (%)	Male	76	(68)	72	(60)	83	(65)	42	(68)	76	(50)	349	(61)
	Female	35	(32)	48	(40)	45	(35)	20	(32)	77	(50)	225	(39)
Race n (%)	White	80	(72)	79	(66)	109	(85)	48	(77)	131	(86)	447	(78)
	Black	14	(13)	22	(18)	9	(7)	2	(3)	9	(6)	56	(10)
	Hispanic	9	(8)	9	(8)	2	(2)	7	(11)	5	(3)	32	(6)
	Asian	6	(5)	6	(5)	7	(5)	2	(3)	8	(5)	29	(5)
	Chinese, african, scottis	0	(0)	0	(0)	0	(0)	1	(2)	0	(0)	1	(<1)
	Guyanese	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	1	(<1)
	Indian	0	(0)	0	(0)	0	(0)	1	(2)	0	(0)	1	(<1)
	Lebanese middle-east	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	1	(<1)
	Middle eastern	1	(<1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(<1)
	Native American	0	(0)	0	(0)	1	(<1)	0	(0)	0	(0)	1	(<1)
	Pacific island	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	1	(<1)
	Pakistani	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	1	(<1)
	Philippine	0	(0)	0	(0)	0	(0)	1	(2)	0	(0)	1	(<1)
	Unknown	1	(<1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(<1)
Age (years) n (%)	< 65	71	(64)	79	(66)	74	(58)	37	(60)	96	(63)	357	(62)
	>=65	40	(36)	41	(34)	54	(42)	25	(40)	57	(37)	217	(38)
	Median	59.0		58.5		63.0		60.0		59.0		60.0	
	Min - Max	21 - 85		20 - 81		40 - 85		19 - 81		33 - 86		19 - 86	

Note: Patient from Study PDX-015 (n=1) is not included in population 2; patient from Study PDX-014 (n=1) is not included in population 3; and population 6 (2 patients from Study PDX-016) is not shown.

Data available as at 31 January 2011 showed similar demographic profile.

7.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.3. Patient exposure

This evaluator has summarised the study types, indications and treatment combinations under which patients received pralatrexate in Table 15, below. The data are presented by each safety population (1 to 6) and include studies PDX-014 and PDX-015 as at 17 February 2010. As noted above, patients with PTCL were in 3 the populations and these are highlighted by shading. It can be appreciated that:

- As at 17 February 2010, 578 cancer patients had received treatment with pralatrexate;
- 451 patients received pralatrexate as a single agent and 127 patients received pralatrexate in combination with other chemotherapeutic agents that included taxanes (docetaxel and paclitaxel), gemcitabine and probenecid.
- 294 patients had a lymphoproliferative malignancy and, of these, 232 received pralatrexate as a single agent and 62 had received pralatrexate in combination with gemcitabine.
- Specifically with regard to patients with PTCL, 171 patients had been treated and of these 147 received pralatrexate as a single agent (111 patients in Study PDX-008 and 36 in Study PDX-02-078) and 24 received pralatrexate in combination with gemcitabine as part of a study involving patients with relapsed or refractory lymphoproliferative malignancies (PDX-009).

Table15. Exposure to pralatrexate (PDX) in clinical studies as at 17 February 2010. Table continued across two pages..

Safety population/study/ indication		Controlled	Uncontrolled						Total PDX
		PDX only	PDX only	PDX in combination					
				PDX + DOC	PDX + PAC	PDX + GEM	PDX + PRO	Total	
Population 1									
PDX-008	*PTCL*		111						111
Subtotal			***111***						***111***
Population 2									
PDX-02-078	*PTCL*		32 4*						32 4*
	HL, BCNHL		29 7*						29 7*
PDX-010	*CTCL*		48						48
PDX-015	*BCNHL*		1						1
Subtotal			***121***						***121***
Population 3									
PDX-007	*NSCLC*		39						39
PDX-011	*TCC*		16						16
PDX-012	*NSCLC*	73^							73
PDX-014	*Breast cancer*		1						1
Subtotal		***73***	***56***						***129***
Population 4									
PDX-009	*PTCL*					24		24	24
	HL, BCNHL					38		38	38
Subtotal						***62***		***62***	***62***
Population 5									
PDX-97-006	*NSCLC*		33*						33*
PDX-99-053	*NSCLC*		39#						39#
PDX-99-083	*Mostly lung cancer*			34 8*,$	 6*,$			34 14*,$	34 14*,$
PDX-01-014	*Mostly lung and colon cancer*						17*	17*	17*
PDX-01-076	*Malignant pleural mesothelioma*		16						16
Subtotal			***88***	***42***	***6***		***17***	***17***	***153***
Population 6									
PDX-01	*Mass balance@*		2						2
Subtotal			***2***						***2***

Safety population/study/ indication	Controlled	Uncontrolled					Total PDX
	PDX only	PDX only	PDX in combination				
			PDX + DOC	PDX + PAC	PDX + GEM	PDX + PRO	Total
TOTAL	**73**	**378**	**42**	**6**	**62**	**17**	**127**	**578**

* denotes patients who did not receive vitamin B12/folate supplementation; # patients only received folate supplementation for significant stomatitis;$vitamin B12/folate supplementation was implemented part way through study. 14/48 patients did not receive vitamins; @ patients with solid tumour or NHL (to date only solid tumour patients enrolled); ^ the comparator in Study PDX-012 is erlotinib PTCL = peripheral T-cell lymphoma; BCNHL = B-cell non Hodgkin's lymphoma; HL = Hodgkin's lymphoma; CTCL = cutaneous T-cell lymphoma; NSCLC = non-small cell lung cancer; TCC = transitional cell carcinoma; PDX = pralatrexate; DOC = docetaxel; PAC = paclitaxel; GEM = gemcitabine; PRO = probenecid

- 75 patients received pralatrexate without any vitamin supplementation (in PDX-97-006 and the early stages of Studies PDX-99-083 and PDX-02-078) and a further 39 received folate supplementation only in the event of "significant" stomatitis (PDX-99-053). With regard to Study PDX-02-078, in the first 2 versions of the protocol no patients received vitamin supplementation as part of the study procedures; however, with the second amendment of the protocol (early 2003), patients with ≥ Grade 2 stomatitis received vitamin supplementation. After the third amendment of the protocol (mid 2004), all patients received vitamin supplementation. Consequently, 4 patients with PTCL in that study did not receive any vitamin supplementation.

As at 31 January 2011, 519 patients had received pralatrexate as a single agent and 172 patients received pralatrexate in combination with other chemotherapeutic agents. A total of 355 patients had a lymphoproliferative malignancy and, of these, 248 received pralatrexate as a single agent and 107 had received pralatrexate in combination with gemcitabine. It was not reported how many of the additional 45 patients enrolled in Study PDX-009 had PTCL.

Exposure according to dose and duration

The dose of pralatrexate administered to patients across all studies ranged from 10-325 mg/m^2. A variety of administration schedules were also used, ranging from a dose every 2 weeks to weekly doses for 2 of 3 weeks, 3 of 4 weeks, and 6 of 7 weeks (each with 1 week of rest).

In the pivotal study, all 111 patients with PTCL initially received pralatrexate 30 mg/m^2 weekly for 6 weeks in a 7-week cycle. The majority of patients (n = 76; 68%) remained at this dose for the duration of their treatment. The pralatrexate dose was reduced from 30 mg/m^2 to 20 mg/m^2 in the remaining 35 (32%) patients. Dose reduction below 20 mg/m^2 was not allowed. The median duration of treatment was 70 days (mean 121; range: 1-696). The median number of cycles administered to patients (based on cycles initiated) was 2.0 (mean 3.0; range: 1-14). Nineteen (17%) patients were treated with pralatrexate for ≥ 6 months and 10 (9%) patients were treated for ≥ 1 year, including 13 (12%) patients treated for ≥ 6 months and 5 (4.5%) patients treated for ≥ 1 year without a dose reduction at any time. The criteria for treatment modifications used in the study were summarised in the study report. A total of 76 (38%) patients required at least one dose omission mainly due to mucositis (n=46; 41%), thrombocytopaenia (n=28; 25%) and neutropaenia (n=14; 13%). Thirty five (32%) patients required a dose reduction and, once again, the most common cause was mucositis (n=25; 23%). Other reasons for dose reduction occurring in 2 or more patients were liver function abnormality, thrombocytopaenia and fatigue (all n=2; 2%). The median total dose of pralatrexate administered over the course of treatment was 208 mg/m^2 (mean: 384; range: 27-2109).

Twenty seven patients in Study PDX-02-078 were treated with the same dose and schedule as in PDX-008, although doses were reduced to 15 mg/m^2 rather than 20 mg/m^2 in the event of specified toxicities. These patients received a median of 11 doses (range 1-45), with a median duration of treatment of 85 days (mean: 135; range: 1-715). The numbers of doses received by patients in PDX-02-078 were higher than for PDX-008 because the study had been ongoing for significantly longer, with some patients remaining on treatment for long periods. Nineteen of these patients had PTCL. The dose and regimen for patients in the other lymphoproliferative malignancy studies (PDX-010, and the subset of PDX-02-078 patients who did not receive the same dose/schedule as PDX-008) varied by cohort. Treatment doses ranged from 10-270 mg/m^2, and the schedule ranged from once every 2 weeks to weekly for 6 weeks of treatment followed by 1 week of rest. The median number of doses received was 4 for PDX-02-078 and 8 for PDX-010 and the median total dose received was 543 mg/m^2 (range 45-2804) in Study PDX-02-078 and 96 mg/m^2 (range 20-1306) in PDX-010. The median duration of treatment range was 36 days (range 1-567) in PDX-02-078 and 71 days (range 7-708) in PDX-010.

The doses in the solid tumour studies (PDX-007, PDX-011, PDX-012) were higher (up to 325 mg/m^2) and given less frequently (every 2 weeks) than those in the lymphoproliferative studies. The range of the median number of doses received was 3-6. The range of the median duration of treatment was 36-44 days. Overall, the cumulative doses were higher and the duration of treatment shorter in these solid tumour studies compared with the lymphoproliferative malignancies studies.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal study

All 111 patients in Study PDX-008 experienced at least 1 treatment emergent AE. The most commonly affected system organ classes were: Gastrointestinal System (N=98; 88%), General Disorders and Application Site Conditions (N=85; 77%), Respiratory System (N=75; 68%), Skin And Connective Tissue Disorders (N=71; 64%), Infection (n=62; 56%) and Blood And Lymphatic System (n=57; 51%). Individual AEs occurring in ≥ 10% patients are summarised according to grade of severity in Table 16.

Table 16. Study PDX-008 - Adverse events occurring in ≥10% patients, by severity

	PDX-008 (N=111)									
	Grade 1		Grade 2		Grade 3		Grade 4		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AE	5	(5)	24	(22)	47	(42)	35	(32)	111	(100)
Mucosal inflammation (grouped)	23	(21)	32	(29)	20	(18)	4	(4)	79	(71)
Nausea	28	(25)	14	(13)	4	(4)	0	(0)	46	(41)
Thrombocytopenia (grouped)	1	(1)	8	(7)	15	(14)	21	(19)	45	(41)
Fatigue	19	(17)	13	(12)	6	(5)	2	(2)	40	(36)
Anaemia (grouped)	3	(3)	15	(14)	18	(16)	2	(2)	38	(34)
Constipation	28	(25)	10	(9)	0	(0)	0	(0)	38	(34)
Pyrexia	27	(24)	9	(8)	1	(1)	1	(1)	38	(34)
Oedema (grouped)	21	(19)	12	(11)	1	(1)	0	(0)	34	(31)
Cough	27	(24)	4	(4)	1	(1)	0	(0)	32	(29)
Epistaxis	27	(24)	2	(2)	0	(0)	0	(0)	29	(26)
Neutropenia (grouped)	0	(0)	4	(4)	15	(14)	9	(8)	28	(25)
Vomiting	18	(16)	8	(7)	2	(2)	0	(0)	28	(25)
Diarrhoea	13	(12)	10	(9)	2	(2)	0	(0)	25	(23)
Dyspnoea	10	(9)	3	(3)	8	(7)	0	(0)	21	(19)
Anorexia (grouped)	14	(13)	1	(1)	3	(3)	0	(0)	18	(16)
Hypokalaemia (grouped)	10	(9)	3	(3)	4	(4)	1	(1)	18	(16)
Rash	11	(10)	6	(5)	0	(0)	0	(0)	17	(15)
Pruritus (grouped)	7	(6)	7	(6)	2	(2)	0	(0)	16	(14)
Pharyngolaryngeal pain	13	(12)	1	(1)	1	(1)	0	(0)	15	(14)
Back pain	5	(5)	6	(5)	3	(3)	0	(0)	14	(13)
Liver function test abnormal (grouped)	3	(3)	5	(5)	6	(5)	0	(0)	14	(13)
Abdominal pain	5	(5)	4	(4)	4	(4)	0	(0)	13	(12)
Headache	11	(10)	2	(2)	0	(0)	0	(0)	13	(12)
Pain in extremity	9	(8)	4	(4)	0	(0)	0	(0)	13	(12)
Asthenia	5	(5)	5	(5)	2	(2)	0	(0)	12	(11)
Leukopenia (grouped)	2	(2)	2	(2)	4	(4)	4	(4)	12	(11)
Night sweats	9	(8)	3	(3)	0	(0)	0	(0)	12	(11)
Upper respiratory tract infection	7	(6)	4	(4)	1	(1)	0	(0)	12	(11)
Dyspepsia (grouped)	8	(7)	3	(3)	0	(0)	0	(0)	11	(10)
Sinusitis	3	(3)	7	(6)	1	(1)	0	(0)	11	(10)
Tachycardia	10	(9)	1	(1)	0	(0)	0	(0)	11	(10)

The most common individual AEs were mucosal inflammation (n = 79; 71%), nausea (n = 46; 41%), thrombocytopenia (n = 45; 41%), and fatigue (n = 40, 36%). Overall, most events were of Grade 1 or 2 severity. The most commonly reported Grade 3 or 4 events were thrombocytopenia (n = 36; 32%), mucosal inflammation (n = 24; 22%), neutropaenia (n = 24; 22%) and anaemia (n = 20; 18%). The median time to onset of thrombocytopenia ≥ Grade 3 was 15 days, with a median duration of 16 days. The median time to onset of ≥ Grade 3 neutropaenia was slightly longer at 22 days but the median duration was only 8 days. This is likely due to the fact that use of granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor (GM-CSF) was allowed according to institutional standards and

investigator judgment. Finally, the median time to onset for ≥ Grade 3 mucosal inflammation was 19 days, with a median duration of 13 days.

Other haematological AEs included febrile neutropaenia (n= 5; 5% - all cases Grade 3), pancytopaenia (n=2; 2% - 1 Grade 3 and 1 Grade 4) and haemolytic anaemia (n=1; 1% - Grade 2).

Other AEs of particular note, but occurring in smaller numbers of patients were skin AEs including (but not limited to) 17 reports of rash (all ≤ Grade 2); 9 reports of skin ulceration (2 Grade 3, 3 Grade 2 and 4 Grade 1); 6 reports of skin blistering (all ≤ Grade 2); 2 reports of penile ulceration (both ≤ Grade 2); and 1 report each of skin exfoliation (Grade 2), skin toxicity (Grade 2), genital rash (Grade 1) and genital ulceration (Grade 2).

7.4.1.2. Other studies

From a table of the AEs reported for ≥ 10% patients in any of the safety populations it can be appreciated that, on the whole, despite variable dosage regimens similar patterns of AEs were observed for each population, with the most frequently occurring AEs being mucosal inflammation, fatigue, nausea, and epistaxis. However, there were some exceptions:

- haematological AEs (anaemia, thrombocytopenia, neutropaenia) and pyrexia were more common in Populations 1, 2, and 4 (that is, patients with lymphoproliferative malignancies) than in Populations 3 and 5 (patients with solid tumours), which is not an unexpected finding.
- mucositis had a much lower frequency in Population 4, that is, patients who received pralatrexate (10-30 mg/m^2) in combination with gemcitabine (200-1000 mg/m^2). However, this study was conducted as 2 distinct phases; comprising a Phase I (dose escalation/dose finding) component and a Phase IIa (confirmation of tolerability and assessment of efficacy) component. During the Phase IIa component, the much lower MTD of pralatrexate 10 mg/m^2 + gemcitabine 400 mg/m^2 on sequential days every 2 weeks was used. Fewer patients in the Phase IIa component of the study experienced AEs, and there was a lower incidence of most AE terms, including mucositis (Phase IIa n=2; 7% versus Phase I n=16; 46%, giving an overall frequency of 29%).
- there was an increased frequency of the respiratory AEs (cough, dyspnoea) in Population 5, which may reflect a predominance of NSCLC and lung cancer patients.
- peripheral neuropathy was more frequently reported as an AE in Population 5. These patients were heavily pre-treated with known neurotoxic agents such as taxanes, cisplatin, carboplatin and vinorelbine, such that a substantial proportion of patients entered these studies with evidence of sensory neuropathies. Furthermore in Study 99-083, which contributed almost half of the reports of neuropathy, patients received pralatrexate in combination with a taxane.

The sponsor reported that assessments were conducted on the association of thrombocytopenia and the occurrence of bleeding complication and on the association of neutropaenia and the occurrence of infections. Bleeding complications in patients who had thrombocytopenia were generally mild in severity and predominantly presented clinically as epistaxis. Across all pralatrexate studies (excluding PDX-016), none of the thrombocytopenic events reported as AEs were associated with Grade 4 bleeding events. Unsurprisingly, bleeding AEs were also observed in patients for whom thrombocytopenia was not reported as an AE. Also, across all pralatrexate studies (excluding PDX-016), no Grade 4 infectious AEs were reported in patients who had neutropaenia. Infectious AEs were also observed in patients for whom neutropaenia was not reported as an AE.

A total of 40 (7%) patients across the clinical development program were reported to have experienced an exfoliative rash; 45 (8%) had a rash and 38 (7%) had a 'dermatosis'. There were also 2 reports of erythema multiforme.

Updated data available as at 31 January 2011 showed a similar profile of the most common AEs.

7.4.2. Treatment-related adverse events (adverse drug reactions (ADRs))

7.4.2.1. Pivotal study

Adverse drug reactions (that is, those AEs considered by the investigator to be possibly, probably or definitely related to pralatrexate) occurred in 106/111 (95%) patients. The most commonly affected system organ classes were: Gastrointestinal System (N=90; 81%), General Disorders and Application Site Conditions (N=59; 77%), Respiratory System (N=53; 48%), Blood and Lymphatic System (N=52; 47%), Skin and Connective Tissue Disorders (N=40; 36%) and Infection (n=39; 35%). Individual ADRs occurring in ≥ 10% patients are summarised in Table 17.

Table 17. Study PDX-008 - ADRs occurring in ≥ 10% patients

	Severity				Total
	Grade 1	Grade 2	Grade 3	Grade 4	
General disorders					
Mucosal inflammation**	20 (18%)	32 (29%)	20 (18%)	4 (4%)	76 (68%)
Fatigue	16 (14%)	11 (10%)	5 (5%)	1 (1%)	33 (30%)
Pyrexia	17 (15%)	4 (4%)	0	0	21 (19%)
Oedema*	13 (12%)	7 (6%)	0	0	20 (18%)
Blood and lymphatic system					
Thrombocytopaenia*	9 (8%)		16 (14%)	19 (17%)	44 (40%)
Anaemia*	19 (17%)		15 (14%)	2 (2%)	36 (32%)
Neutropaenia *	3 (3%)		16 (14%)	8 (7%)	27 (24%)
Leucopaenia*	4 (4%)		4 (4%)	4 (4%)	12 (11%)
Gastrointestinal disorders					
Nausea	21 (19%)	12 (11%)	4 (4%)	0	37 (33%)
Constipation	17 (15%)	6 (5%)	0	0	23 (21%)
Vomiting	15 (14%)	6 (5%)	2 (2%)	0	23 (21%)
Diarrhoea	12 (11%)	6 (5%)	1 (1%)	0	19 (17%)
Respiratory disorders					
Epistaxis	24 (22%)	2 (2%)	0	0	26 (23%)
Dyspnoea	8 (7%)	0	3 (3%)	0	11 (10%)
Metabolic and nutritional disorders					
Anorexia*	10 (%)	1 (1%)	2 (2%)	0	13 (12%)
Hypokalaemia*	9 (8%)	2 (2%)	0	0	11 (10%)
Investigations					
Liver function abnormal*					13 (12%)
Skin and subcutaneous tissue disorders					
Rash	10 (9%)	2 (2%)	0	0	12 (11%)

* includes grouping of similar preferred terms, ** includes grouping of similar preferred terms across SOCs

The most common individual ADRs were mucosal inflammation (n = 76; 68%), thrombocytopenia (n = 44; 40%), nausea (n = 37; 33%), anaemia (n=36; 32%) and fatigue (n = 33, 30%). Comparing Tables 16 and 17, it is evident that most mucosal inflammation AEs and haematological AEs were considered treatment related, which is consistent with the expected profile for a cytotoxic agent.

With the exception of the haematological ADRs, the majority of ADRs were Grade 2 or less in severity. A total of 76 (68%) patients experienced an ADR under the grouped term of mucosal inflammation. Of these, 20 (18%) had Grade 3 reaction and 4 (4%) had a Grade 4 reaction. Under the collective term of thrombocytopenia, 44 (40%) patients had a pralatrexate-related event, with Grade 3 severity occurring in 16 (14%) patients and Grade 4 in 19 (17%) patients. Neutropaenia was recorded as an ADR in 27 (24%) patients, of whom 16 (14%) had Grade 3 severity and 8 (7%) had Grade 4 severity. Grade 4 haematological ADRs were otherwise observed as follows: anaemia (n=2); leucopenia (n=4); and pancytopaenia (n=1).

Most of the skin AEs were also considered to be pralatrexate treatment-related: 12 cases of rash (all ≤ Grade 2); 6 reports of skin ulceration (2 Grade 3, 1 Grade 2 and 3 Grade 1); 4 reports of skin blistering (all ≤ Grade 2); and 1 report each of penile ulceration (Grade 2), skin exfoliation (Grade 2), skin toxicity (Grade 2), genital rash (Grade 1) and genital ulceration (Grade 2).

7.4.2.2. Other studies

The most frequently occurring ADRs across all studies were mucosal inflammation, fatigue, nausea, and epistaxis.

As with AEs, more haematological ADRs occurred in the lymphoproliferative malignancies compared to solid tumours, although most haematological AEs were considered pralatrexate-related in all populations. Many of the non-haematological AEs were also considered treatment-related, except for most respiratory AEs which occurred more frequently in the solid tumour studies and were likely considered a manifestation of the underlying disease (predominantly NSCLC). Most skin events were also considered to be ADRs.

Updated data available as at 31 January 2011 showed a similar profile of the most common ADRs and no new clinically important ADRs.

7.4.3. Deaths and other serious adverse events (SAEs)

7.4.3.1. Pivotal study

7.4.3.1.1. Deaths

Seven patients from Study PDX-008 died while still on treatment with pralatrexate due to progression of their PTCL. Vignettes were provided for each death and this evaluator is satisfied that these patients had clear evidence of disease progression and that death was due to this and not concomitant pralatrexate toxicity.

Another patient died within 30 days of his last dose of pralatrexate due to cardiopulmonary arrest that was considered to be possibly related to pralatrexate. This patient, a 64M with PTCL-unspecified, received pralatrexate at a dose of 30 mg/m^2 for 5 doses in Cycle 1 before having a dose omitted because of mucositis. He received a further 2 doses at 30 mg/m^2 in Cycle 2 before the dose was omitted because of the mucositis and pancytopaenia. Two doses were then given at 20 mg/m^2, with the last dose administered on Day 78. Pralatrexate was subsequently discontinued because of Grade 3 mucosal inflammation and pancytopaenia/febrile neutropaenia (both of which were considered related to pralatrexate treatment). He was hospitalised but these events never resolved despite treatment with broad spectrum intravenous (IV) antibiotics, IV fluids, and granulocyte colony-stimulating factor. He died approximately 3 weeks after his last dose of pralatrexate, having been on study for 96 days.

7.4.3.1.2. Other SAEs

Fifty patients (45%) experienced an SAE while on study or within 30 days after their last dose of pralatrexate. SAEs that occurred in ≥ 2% of patients in Study PDX-008 are shown below in Table 18.

Table 18. Study PDX-008 - serious adverse events occurring in ≥2% patients

	All SAEs		Treatment-related SAEs	
	All grades	≥ Grade 3	All grades	≥ Grade 3
Any SAE	50 (45%)	42 (38%)	28 (25%)	21 (19%)
Pyrexia	8 (7%)	1 (1%)	5 (5%)	0
Mucosal inflammation (grouped)	6 (5%)	6 (5%)	6 (5%)	6 (5%)
Febrile neutropaenia	5 (5%)	5 (5%)	4 (4%)	4 (4%)
Sepsis	5 (5%)	4 (4%)	2 (2%)	2 (2%)
Dehydration	4 (4%)	2 (2%)	0	0
Dyspnoea	4 (4%)	4 (4%)	1 (1%)	1 (1%)
Herpes zoster	3 (3%)	3 (3%)	2 (2%)	2 (2%)
Neutropaenia (grouped)	3 (3%)	2 (2%)	2 (2%)	1 (1%)
Pneumonia	3 (3%)	2 (2%)	2 (2%)	1 (1%)
Thrombocytopaenia (grouped)	3 (3%)	3 (3%)	3 (3%)	3 (3%)
Abdominal pain	2 (2%)	1 (1%)	0	0
Cerebral infarction	2 (2%)	2 (2%)	0	0
Fatigue	2 (2%)	2 (2%)	1 (1%)	1 (1%)
Hypotension	2 (2%)	2 (2%)	0	0
Acute renal failure	2 (2%)	2 (2%)	0	0
Skin ulcer	2 (2%)	0	1 (1%)	0
Urinary tract infection	2 (2%)	2 (2%)	1 (1%)	1 (1%)

Regardless of causality, SAEs most frequently manifested as infections and infestations (n = 18, 16%); blood and lymphatic system disorders (n = 13, 12%); and general disorders and administration site conditions (n = 11, 10%). The most common individual SAEs were pyrexia, mucosal inflammation, febrile neutropaenia, sepsis, dehydration, and dyspnoea. Most of these SAEs could be expected from the cytotoxic activity of pralatrexate or the patient's underlying tumour and immuno-compromised status. It can be appreciated from the table that most SAEs manifesting as mucosal or haematological toxicity were of Grade 3 or higher severity and almost all were considered to be treatment-related by the investigators. Grade 4 treatment-related haematological SAEs included 3 cases of thrombocytopaenia, 1 case of neutropaenia and 1 case of pancytopaenia.

SAEs of particular note were:

- One patient (095) developed tumour lysis syndrome 2 days after beginning Cycle 2, manifesting with elevated BUN (49 mg/dL; normal reference range 7-23 mg/dL), hyperphosphataemia (6.7 mg/dL; normal reference range 2.2-4.7 mg/dL) and hyperuricaemia (23.5 mg/dL; normal reference range 2.9-7.9 mg/dL). Hypocalcaemia was also recorded as an AE around that time. The event resolved approximately a week later, but the next 2 doses were omitted due to thrombocytopaenia. The patient ultimately discontinued treatment due to thrombocytopaenia and disease progression.

- Two patients were reported to have experienced SAEs of renal failure, both considered causally unrelated to pralatrexate. The first patient, a 65 year old man, developed Grade 3 acute renal failure 28 days after initiating study treatment with pralatrexate and approximately a week after discontinuing pralatrexate due to disease progression. Two days prior to the onset of renal failure the patient had been treated with antibiotics for tumour-associated fever. His serum creatinine was 2.7 mg/dL (baseline value not provided, normal reference range 0.3-1.5 mg/dL) at presentation and peaked at 4.3 mg/dL 2 days later. Treatment included IV hydration and event resolved approximately 2 weeks later. This patient was receiving multiple concomitant medications at the time of SAE onset, including acyclovir, vancomycin and allopurinol. The second patient developed Grade 4 renal failure (serum creatinine 6.5 mg/dL; NR 0.8-1.5 mg/dL) secondary to bilateral ureteric obstruction and hydronephrosis caused by disease progression after the third dose of Cycle 1.

  Evaluator's comment:

  Interestingly, the first patient also had hyperuricaemia and hyperphosphataemia recorded as adverse events around the same time as the renal failure (Note: actual serum values for these parameters were not documented). These events were thought to be possibly related to pralatrexate treatment. These metabolic derangements in combination with acute renal failure are suggestive of possible tumour lysis syndrome.

- Four patients required investigation and hospital treatment of dyspnoea. In most cases the dyspnoea was considered to be a manifestation of either the underlying disease/disease progression (such pulmonary infiltration, pleural effusion and compression) or pneumonia. One patient was found to have pneumonitis which was considered to be an acute hypersensitivity to pralatrexate.

- Five patients had a serious thromboembolic event. Three of these occurred more than 2 weeks after the most recent dose of pralatrexate. The first of these patients, developed right subclavian vein thrombosis 2 days after the peripheral insertion of a central catheter (site not stated) and 3 weeks after the most recent dose of pralatrexate. The event was considered causally unrelated to pralatrexate. The second patient had also had his most recent (and final) dose of pralatrexate some three weeks prior to developing frontal lobe infarction (MRI proven) that presented as a series of seizures. In the period between the last dose of pralatrexate and the onset seizures the patient had experienced disease progression and had discontinued pralatrexate and commenced gemcitabine. Five days before the onset of seizures the patient was hospitalised with dehydration (no electrolyte data were recorded). The event was considered causally unrelated to pralatrexate. The third patient developed an ischaemic stroke involving the left posterior cerebral artery, non sustained ventricular tachycardia and atrial fibrillation 491 days after starting treatment with pralatrexate and 2 weeks after the most recent dose. This 74 year old man had a past history of vascular disease including coronary artery disease and bypass grafting, atherosclerosis, deep vein thrombosis and intermittent atrial fibrillation. Brain MRI also revealed the presence of right vertebral artery stenosis and there was evidence of irregularity of the carotid bifurcation (side not stated) on angiography. The event was considered causally unrelated to pralatrexate. Of the remaining 2 patients, one patient developed what was reported to be a cerebral infarction (diagnostic results not provided), manifesting with aphasia, lateral hemianopia and facial paralysis 236 days after commencing treatment with pralatrexate and 5 days after the most recent dose. The symptoms resolved after 2 days of treatment with acetylsalicylic acid. Platelet count was normal at the time. The event was considered by the investigator to be causally unrelated to pralatrexate. The final patient developed a pulmonary embolus 649 days after commencing pralatrexate and 1 day after her most recent dose. At the time she had concurrent Grade 2 pneumonitis that was considered by the investigator to be treatment-related but not serious. Her past history

included bilateral DVT and bilateral pulmonary embolism. The pulmonary embolus was considered to be possibly causally related to pralatrexate.

7.4.3.2. Other studies

7.4.3.2.1. Deaths

A total of 43 (7%) patients in the overall clinical development program either died while still on treatment with pralatrexate or died within 30 days of stopping treatment. The majority of these deaths (33/43; 77%) were due to either disease progression or events that could be reasonably attributed to complications of the underlying tumour (for example, respiratory failure in patients with lung cancer). Six deaths (16%) were considered by the investigator to be causally related to treatment with pralatrexate, including the case from the pivotal study.

Evaluator's comment:

This evaluator compiled a table of information from narratives within the individual study reports and synopses and includes studies PDX-014, PDX-015 and PDX-016. This was used in preference to Table 2.7.4.14 of the *Summary of Clinical Safety*, because it was difficult to readily reconcile the information provided in the text against the categories of the causes of death used in Table 2.7.4.14. This evaluator's table also draws a sharper distinction between deaths that were considered by the investigator to be causally related to treatment with pralatrexate (that is, due to ADRs) and those that were not (that is, due to AEs). The total number of deaths captured in the evaluator's table differs from the *Summary of Clinical Safety* because some of the interim study reports post-dated the cut off for the Allos safety database. No additional information about deaths was available from the *Updated Safety Tables*.

In the non-pivotal studies, the deaths considered to be causally related to pralatrexate administration were:

- One patient from Study PDX-02-078 (Population 2) - a 48F with T/NK-cell lymphoma (adult T-cell lymphoma/leukaemia (HTLV1+)) and extensive skin/subcutaneous involvement died 6 days after being hospitalised for febrile neutropaenia (probably related to pralatrexate) and infection (probably related to pralatrexate) and a desquamating rash (possibly related to pralatrexate). This patient received only 2 doses of pralatrexate 45 mg/m^2. Four days after the first dose she was admitted to hospital with febrile neutropaenia, hypotension, and anuria. At that time the patient's skin was noted to be erythematous with some breakdown beneath her breasts and anterior abdominal wall. She was treated with antibiotics and intravenous (IV) fluids and later discharged at which time she was given her second dose of pralatrexate. Four days after the second dose the patient re-presented with chills and new marked desquamation of her skin. Despite treatment she developed haemodynamic compromise and later died. Skin desquamation was considered to be the major contributor to her death.
- One patient from Study PDX-012 (Population 3) - a 70M with NSCLC who was hospitalised with pancytopaenia 10 days after receiving his first and only dose of pralatrexate 190 mg/m^2. He subsequently also developed stomatitis and chest pain and died the following morning. A post mortem examination confirmed the cause of death as pancytopaenia. Concomitant medications included tiotropium bromide, megestrol acetate, fluconazole, methylprednisolone, glycerin borax, and filgrastim. The investigator considered the pancytopaenia to be probably related to pralatrexate.
- Another patient from Study PDX-012 (Population 3) - a 65F with NSCLC who died from sepsis 21 days after receiving her first and only dose of pralatrexate (190 mg/m^2). Other ADRs present at the time of her death were stomatitis, mucositis, leucopenia, thrombocytopenia and respiratory distress. She was hospitalised 6 days after administration of pralatrexate with Grade 4 mucositis and an inability to eat or drink, as

well as a marked, severe erythematous and bullous rash of her trunk and proximal extremities. The patient was treated with hydrocortisone in a desensitisation regimen due to concurrent corticosteroid allergy. Leucopaenia and thrombocytopaenia developed 12 days after receiving pralatrexate and this was followed a day later by respiratory distress that required intubation. She then developed sepsis with profound metabolic acidosis and required treatment with vasopressors. The rash improved but the mucositis and marrow suppression persisted despite leucovorin therapy. She died 3 weeks after the dose of pralatrexate. The investigator assessed all events as probably related to pralatrexate.

> Evaluator's comment:
>
> The investigator thought this reaction was out of proportion to what would be expected from a single dose of pralatrexate and considered the reaction to be 'idiosyncratic'. Skin reactions were examined in detail by the sponsor during post-marketing surveillance and were the subject of a *Summary of Clinical Safety Addendum*. The sponsor identified 6 dermatological reactions resulting in death and the analysis highlighted that all but one of the reactions that resulted in death occurred after only one dose of pralatrexate and in the remaining case the reaction occurred after only 2 doses. Although this particular death was not included amongst those considered in the sponsor's analysis of dermatological deaths, the patient also presented with a severe bullous rash which could have compromised the integrity of the skin and pre-disposed the patient to infection and subsequent sepsis in the setting of leucopaenia.

- One patient from Study PDX-011 (Population 3) - a 73M with TCC of the bladder who died 10 days after receiving a single dose of pralatrexate (190 mg/m^2). A narrative was not provided in the brief study synopsis but it appears from IPD listings that 6 days post dosing the patient developed anorexia; fatigue; Grade 3 mucositis, leucopaenia and neutropaenia (which all progressed to Grade 4 on day 7); and Grade 1 thrombocytopaenia (which subsequently increased to Grade 2). Renal failure ensued on Day 7 and by Day 9 the patient had a depressed level of consciousness and a right hemiparesis. The anorexia, fatigue, mucositis, leucopaenia, neutropaenia and thrombocytopaenia were all considered definitely related to treatment with pralatrexate.
- One patient from Study PDX-009 (population 4) - a 49F with transformed mycosis fungoides and extensive skin involvement who died 15 days after her first and only dose of pralatrexate (10 mg/m^2) and 14 days after gemcitabine (400 mg/m^2). She was hospitalised 4 days after the administration of pralatrexate because of severe almost full body desquamation, cutaneous lymphoma lesions on her right arm, knees and buttocks, and multiple bullous lesions throughout. Despite wound care and prophylactic antibiotics, wound cultures subsequently yielded gram positive cocci, moderate enterococcus, few pseudomonas aeruginosa, and gram positive rods. The patient became increasingly nonresponsive over several days and later died. Relevant medical history included the completion of a course of liposomal doxorubicin and gemcitabine approximately 8 months earlier, complicated by "total skin breakdown."

Four deaths were due to events that were not considered by the investigator to be causally related to pralatrexate. Amongst these were 2 reports of cardiac arrest. The first of these was in a 60M with stage IV NSCLC who developed respiratory distress and died while being transported to hospital 7 days after receiving his first and only dose of pralatrexate (190 mg/m^2). No other details (for example, autopsy) were provided. The second report was for a 58F with metastatic NSCLC who died after the second dose of pralatrexate (150 mg/m^2). She had developed bilateral pulmonary emboli 11 days after her first dose and remained dalteparin and warfarin at the time of her death. She received her second dose of pralatrexate and 15 days later developed severe shortness of breath and died from cardiac arrest en route to the hospital. The investigator suspected that a possible recurrence of the pulmonary emboli led to the cardiac arrest. However, no autopsy was reported.

7.4.3.2.2. Other SAEs

The patterns of SAEs in patients enrolled in the supporting and contributive studies were generally consistent with that observed in the pivotal study. The most frequently occurring SAEs were mucosal inflammation, pyrexia, dyspnoea, febrile neutropaenia, pneumonia and dehydration. However, the populations comprising patients with lymphoproliferative malignancies (Populations 1, 2 and 4) included all of the SAEs of febrile neutropaenia and dehydration and a higher proportion of the SAEs of pyrexia. This is not an unexpected finding given the greater degree of immuno-compromise in patients with lymphoproliferative malignancies.

The most frequently occurring SAEs by single preferred term across all studies were stomatitis, febrile neutropaenia, mucosal inflammation, pyrexia, and thrombocytopenia. Other SAEs of note were:

- Tumour lysis syndrome was recorded as a SAE in 4 patients with lymphoproliferative disorders - with 1 patient each from studies PDX-02-078, PDX-008, PDX-009 and PDX-010. Three of these patients had PTCL - 1 with anaplastic large cell lymphoma [ALCL]; 1 with subcutaneous PTCL; and one with adult T-cell leukaemia/lymphoma [ATLL] human T-lymphotropic virus [HTLV-1] associated. The remaining patient had CTCL (mycosis fungoides and Sezary Syndrome). All cases of tumour lysis syndrome were of Grade 3-4 severity, with onset between 3-51 days following initial administration of pralatrexate and duration ranging from 7-14 days. All 4 cases were considered to be related to the administration of pralatrexate.
- Renal failure (acute) and renal failure were recorded as SAEs in 8 patients across the clinical development program, including 2 from the pivotal study. Of the 6 cases from the supportive studies, 5 cases of renal failure were considered to be casually unrelated to pralatrexate as they were either a manifestation of underlying disease complications or a consequence of other side effects, as follows: sepsis; diarrhoea; concomitant drug administration (vancomycin); infected skin ulcers and hypotension; and sepsis/pneumonia. The case considered to be possibly causally related to pralatrexate occurred in a 48 F with DLBCL who developed pulmonary embolism, hypotension and renal failure the same day as she received her first and only dose of pralatrexate 45 mg/m^2. The event resolved after treatment that included anticoagulants, IV fluids and furosemide.
- Pneumonitis was reported as an SAE in 5 patients (4 with a lymphoproliferative malignancy), including one from the pivotal study. Three cases were considered to be related to treatment with pralatrexate.
- Eight cases of pulmonary embolism (5 of which were considered by the investigator to be treatment-related, including the case from the pivotal study), 3 cases of DVT (one of which was considered to be treatment-related) and 3 cases of myocardial infarction (none considered to be treatment-related).

The updated safety information as of 31 January 2011 identified in addition 2 SAE reports of acute renal failure, 1 case of renal insufficiency and 1 report of pneumonitis. The reports of acute renal failure were both from Study PDX-009 (Population 4), which used combination therapy with gemcitabine. In the first case the patient had discontinued the combination therapy 3 weeks prior to the onset of renal failure and had commenced a new chemotherapy regimen 9 days earlier. In the second case the acute renal failure occurred in the context of symptomatic congestive cardiac failure (ejection fraction 19%) in a patient previously treated with CHOP. Neither of these cases was considered to be causally related to pralatrexate. The additional case of renal insufficiency (PDX-011; Population 3) was considered by the investigator to be probably causally related to pralatrexate. In this patient, the renal insufficiency (urea 11.6 mmol/L; NR 3.0-7.5 mmol/L and creatinine 2.28 mg/dL; NR 1.05-1.64 mg/dL) occurred after a single dose of pralatrexate in the setting of a severe bullous eruption

(with biopsy results consistent with toxiderma) and mucositis. The additional report of pneumonitis occurred in a patient with lymphoproliferative disorders (Population 4) and considered to be causally related to pralatrexate treatment. Pneumonitis is discussed in further detail below.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal study

Twenty-six patients (23%) withdrew from pralatrexate treatment due to an AE in Study PDX-008. The AEs reported most frequently as the reason for withdrawal of treatment were mucosal inflammation (n = 7; 6%), thrombocytopenia (n = 4; 4%) and neutropaenia (n=2; 2%), with all these events considered by the investigator to be causally related to pralatrexate treatment. Other ADRs leading to withdrawal were single cases of CMV colitis, pyrexia, abnormal liver function (elevated ALT), cardiopulmonary arrest, nausea, pain, pulmonary embolism, pneumonitis and urticaria. Additional reasons for withdrawal that were not considered to be causally related to pralatrexate were single cases of renal failure, metastatic cholangiocarcinoma, pneumonia and thrombosis.

7.4.4.2. Other studies

A tabulation of the ADRs that led to treatment withdrawal in at least 2 patients across the clinical development program shows that the discontinuation profiles of the other populations were similar to the pivotal study, in that the majority of withdrawals were due to stomatitis/mucositis and haematological reactions. However, it is also evident that withdrawals due to skin and appendage reactions were much more prominent in the other treatment populations, with 7 patients withdrawing due to a variety of rashes (including one case of an exfoliative rash), 3 with skin ulceration and 2 due to alopecia. Also, not shown in the table is a single case of whole body desquamation in a patient from population 4 (this is discussed under *Deaths* below).

No additional information about withdrawals due to ADRs was available from the *Updated Safety Tables*.

7.5. Laboratory tests

7.5.1. Liver function

7.5.1.1. Pivotal study

A total of 29 (26%) patients had at least one clinically significant abnormality of liver function testing during treatment with pralatrexate.

Shifts in transaminase levels during treatment with pralatrexate are shown in Table 19, below. Clinically significant changes (that is, ≥ Grade 2 toxicity and a shift of ≥ 1 grade from the baseline value, where Grade 2 toxicity is a value >2.5 – 5.0 x ULN) are highlighted by shading. From these tables it can be appreciated that the vast majority of patients entered the study with normal transaminase levels and most of these patients had either no deterioration in levels or Grade 1 toxicity. Most patients who had an increase in transaminase levels had an increase in both AST and ALT. Clinically significant increases in AST and ALT levels were recorded in 19 (17%) and 18 (16%) patients, respectively. Eight patients had Grade 3 AST levels and 7 patients (6%) had Grade 3 ALT values. No patients developed Grade 4 AST or ALT abnormalities.

Most patients also entered the study with normal total bilirubin levels and the vast majority of these patients also had either no deterioration in levels or Grade 1 toxicity. Clinically significant increased total bilirubin was reported in 10 patients (9%). Five patients had a bilirubin value of > 2.5 mg/dL during pralatrexate treatment.

Abnormal liver function tests were responsible for dose omission in 3 patients, dose reduction in 2 patients and withdrawal of pralatrexate therapy in 1 patient. One of these patients discontinued study treatment specifically because of increased ALT levels. His ALT level increased to a maximum level of 277 IU/L in cycle 1 (with a corresponding AST of 101 IU/L) and his pralatrexate dose was reduced to 20 mg/m^2. However, the elevated transaminase levels did not resolve and he discontinued treatment after Cycle 3. His maximum on-study ALT and AST levels were 358 IU/L and 187 IU/L, respectively. Approximately 3 weeks after discontinuing pralatrexate treatment his ALT was 89 IU/L and AST was 37 IU/L. This patient's total bilirubin levels remained normal throughout and after the study.

Four patients experienced clinically significant increases in all 3 parameters measured on–study (AST, ALT and total bilirubin):

- One patient had concurrent clinically significant elevations in all 3 parameters. This patient had entered the study with normal values for all three parameters. Clinically significant abnormalities were first detected at Dose 3 of Cycle 1 (total bilirubin 2.76 mg/dL; ALT 313 IU/L; AST 310 IU/L). Doses 2 and 3 of Cycle 1 were not administered and Dose 4 was reduced to 20 mg/m^2 because of mucositis. Following investigation of the abnormal liver function, the patient was diagnosed with metastatic cholangiocarcinoma (considered unrelated to pralatrexate treatment) and discontinued from the study.

Table 19. Study PDX-008 - shifts in transaminase and total bilirubin levels during treatment. Table continued across two pages.

A. AST

		Worst on-study grade					
		Missing	**0**	**1**	**2**	**3**	**4**
Baseline grade	Missing n=2	2	0	0	0	0	0
	Grade 0 n=89	0	51	27	5	6	0
	Grade 1 n=17	0	0	10	6	1	0
	Grade 2 n=3	0	0	1	1	1	0

Grade 1 = >1 – 2.5 x ULN Grade 2 = >2.5 – 5.0 x ULN Grade 3 = >5.0 – 20.0 x ULN Grade 4 = >20.0 x ULN

B. ALT

		Worst on-study grade					
		Missing	**0**	**1**	**2**	**3**	**4**
Baseline grade	Missing n=2	2	0	0	0	0	0
	Grade 0 n=98	0	54	31	9	4	0
	Grade 1 n=7	0	0	2	2	3	0
	Grade 2 n=4	0	0	1	3	0	0

Grade 1 = >1 – 2.5 x ULN Grade 2 = >2.5 – 5.0 x ULN Grade 3 = >5.0 – 20.0 x ULN Grade 4 = >20.0 x ULN

C. Total bilirubin

		Worst on-study grade					
		Missing	0	1	2	3	4
Baseline grade	Missing n=2	2	1	0	0	0	0
	Grade 0 n=103	0	80	14	7	1	1
	Grade 1 n=4	0	3	0	0	1	0
	Grade 2 n=0	0	0	0	0	0	0
	Grade 3 n=1	0	0	0	0	1	0

Grade 1 = >1 – 1.5 x ULN Grade 2 = >1.5 – 3.0 x ULN Grade 3 = >3.0 – 10.0 x ULN Grade 4 = >10.0 x ULN

- One patient entered the study with elevated AST (42 IU/L) and ALT (88 IU/l) levels. ALT levels remained elevated throughout the study (with clinically significant increases on 3 occasions), whilst the AST level normalised. AST and bilirubin levels became clinically significantly elevated around the time of treatment withdrawal due to disease progression. This patient received pralatrexate 30 mg/m^2 up to the time of withdrawal.
- One patient entered the study with normal liver function. ALT values first became elevated (58 IU/L) at the time of the first dose of pralatrexate. By Dose 3 of Cycle 1 both ALT (282 IU/L) and AST (106 IU/L) were significantly elevated, with a concurrent mild elevation of total bilirubin (1.2 mg/dL). The dose was omitted, with subsequent normalisation of AST (29 IU/L) and reduction in ALT (77 IU/L). However, the total bilirubin level increased significantly to 2.1mg/dL and the dose was consequently reduced to 20 mg/m^2. By the time of the next dose the only abnormality was an elevated ALT (91 IU/L). The patient withdrew from treatment a week later because of disease progression. At the follow up visit liver function was normal.
- The final patient also entered the study with normal hepatic function and first developed a very mild elevation in AST (39 IU/L) at Dose 2, Cycle 1. By Dose 3 the patient's AST and ALT were both significantly increased (217 IU/L and 249 IU/L, respectively), with a normal total bilirubin level. The dose was omitted because of thrombocytopenia. A week later the transaminase levels had returned to normal but the total bilirubin level had risen significantly from 0.4 mg/dL to 1.6 mg/dL. The dose was again omitted because of persisting thrombocytopaenia and the total bilirubin level subsequently returned to normal. Treatment was resumed at a reduced dose of 20 mg/m^2 and the patient's liver function remained normal thereafter.

A further 9 patients had concurrent clinically significant elevations in both AST and ALT during treatment with pralatrexate. Most of the clinically significant elevations occurred on a background of repeated elevations in either one or both transaminases throughout treatment on study. Most of these patients did not develop abnormalities of total bilirubin levels. Two of these patients required either dose omission and/or reduction because of the abnormal liver function (patients mentioned above). Four of the patients remained on a dose of 30 mg/m^2 throughout treatment, including one patient whose liver function tests completely normalised – one patient developed significantly elevated AST (80 IU/L) and ALT (213 IU/L) levels at Dose 4 of Cycle 1, which remained elevated through to Dose 6 of Cycle 1 but then subsequently decreased and remained normal until last measured at Dose 4, Cycle 3. The remaining 3 patients underwent dose reductions at some stage during treatment because of toxicities other than abnormal liver function. In one patient the abnormality in liver function coincided with the development of mucositis after Dose 3 of Cycle 1 and essentially normalised after the dose was reduced to 20 mg/m^2. The second patient also first developed abnormal transaminases (AST 79 IU/L; ALT 190 IU/L) coincident with the development of mucositis at Dose 4 of Cycle 1 at which

time the dose was omitted. This patient had had a slightly elevated total bilirubin level but otherwise normal liver function at screening. ALT (303 IU/L) and AST (96 IU/L) became clinically significantly elevated at Dose 1 Cycle 2, whilst total bilirubin levels remained at baseline levels. The derangement in liver function persisted throughout Cycle 2 despite the omission of Doses 3 and 4 because of concurrent mucositis and a dose reduction to 20 mg/m2 for Dose 5. The patient discontinued because of persisting mucositis. The final patient experienced a derangement of liver transaminases from Dose 4 to 6 of Cycle 7, with concurrent clinically significant increases in AST (118 IU/L) and ALT (209 IU/L) at Dose 6 of Cycle 7. Apart from the single occurrence of mildly elevated AST (65 IU/L) and ALT (57 IU/L) in Cycle 3, this patient had no derangement of liver function until Cycle 7. Of note, the liver function had returned to normal by Dose 1 of Cycle 8 and remained normal apart from elevations of both AST and ALT at Dose 3 of Cycle 8. The patient had been receiving 20 mg/m^2 since mid way through cycle 4 when the dose was reduced on account of mucositis.

7.5.1.2. Other studies

The proportion of patients with clinically significant laboratory abnormalities by safety population was tabulated in the study report. The denominators in the table are based on the number of patients who had a baseline measurement and at least one measurement performed while receiving pralatrexate. The denominators for some of the parameters vary considerably, especially for Population 5. This is because some studies did not routinely measure all laboratory parameters and in some studies, even though parameters were measured they were not measured in all patients. The shaded columns represent those patients who received pralatrexate 30 mg/m^2 every 6 of 7 weeks (Population 1 and a subset of patients in Study PDX-02-078).

Clinically significantly high values of serum transaminases were reported in 2-17% of patients, depending on the study population, with numerically higher rates amongst patients with lymphomas. Clinically significantly high bilirubin levels were observed in 2-16% of patients.

A total of 27 patients in Study PDX-02-078 were treated at the same dose/frequency of pralatrexate as administered in PDX-008. Of these patients, 11 (44%) had at least one clinically significant abnormality on liver function testing. Clinically significant abnormalities of ALT, AST and bilirubin were each observed in 5 (19%) patients, which is similar to the rates observed in Study PDX-008. Additionally, 4 (15%) patients had clinically significant elevations in alkaline phosphatase (which was not measured in the pivotal study). Of particular note with this study, all 11 patients who developed clinically significant abnormalities of liver function had at least one abnormal liver function parameter at baseline, suggesting a possible contribution of the underlying disease and/or prior therapy. Only one patient had a dose of pralatrexate omitted because of derangement in liver function. This patient with composite B/T cell NHL entered the study with elevated alkaline phosphatase (207 IU/L; NR 0-115 IU/L) and ALT (62 IU/L; NR 5-37 IU/L) levels, both of which became significantly elevated by Dose 6 of Cycle 2 (Alkaline phosphatase 950; ALT 234) during treatment with a 15 mg/m^2 dose (reduced in Cycle 1 because of thrombocytopaenia). The dose was omitted and the patient was subsequently withdrawn as a result of “investigator decision”.

7.5.2. Kidney function

7.5.2.1. Pivotal study

All but 2 patients entered the study with normal serum creatinine levels. The vast majority of these patients had no deterioration in renal function (Table 20). Clinically significant increases in creatinine were reported for 3 patients, with maximum levels of 2.2 mg/dL; ULN 1.3mg/dL (patient 025), 6.5 mg/dL; ULN 1.5 mg/dL (patient 077) and 4.5 mg/dL; ULN 1.3mg/dL (patient 106), respectively. For two of these patients, the underlying disease process played a key role in the development of elevated creatinine levels. One patient developed renal failure as a consequence of ureteric obstruction associated with disease progression, whilst the recent

medical history of another patient included bilateral hydronephrosis and a recent hospitalisation for acute renal failure secondary to ureteric obstruction requiring bilateral nephrostomy tube placement. One patient was withdrawn from pralatrexate treatment when he developed renal failure. Both patients had sudden marked increases in serum creatinine levels. On the other hand, another patient, had an elevated creatine level at the time of the first dose, which persisted throughout dosing (at 30 mg/m^2) until treatment was withdrawn after Dose 6 of Cycle 3, on account of a concomitant steroid injection. The maximum creatinine level of 2.2 mg/dL occurred at Dose 2 of Cycle 2.

Table 20. Study PDX-008 - shifts in serum creatinine levels during treatment with pralatrexate

		Worst on-study grade					
		Missing	0	1	2	3	4
Baseline grade	Missing (n=1)	1	0	0	0	0	0
	Grade 0 (n=98)	0	79	17	0	2	0
	Grade 1 (n=11)	0	2	8	1	0	0
	Grade 2 (n=1)	0	0	0	1	0	0

7.5.2.2. Other studies

Clinically significant decreases in renal function, as measured by increases in serum creatinine levels to >1.5 x ULN, occurred in 1%-6% of patients across the development program, depending on study population.

Clinically significant renal impairment occurred in 1 (4%) of 27 patients in Study PDX-02-078 who received the proposed regimen (30 mg/m^2 once every 6 of 7 weeks). This patient had angioimmunoblastic T-cell lymphoma and developed clinically significant renal impairment (serum creatinine 2.3 mg/dL; NR 0.6 – 1.3 mg/dL) approximately 2 weeks after discontinuing pralatrexate because of disease progression. Earlier, whilst on treatment, the patient was found to have elevated serum creatinine (1.9 mg/dL) and BUN (40 mg/dL; NR 6-20 mg/dL) levels during investigation of an acute episode of confusion. Other metabolic abnormalities identified at that time were hyperphosphataemia (5.2 mg/dL; NR2.5 – 4.2 mg/dL) and hypercalcaemia (12.3 mg/dL; NR 8.5 – 10.5 mg/dL).

7.5.3. Other clinical chemistry

7.5.3.1. Pivotal study

There was no routine monitoring of other clinical chemistry parameters in the pivotal study.

7.5.3.2. Other studies

Other serum chemistry abnormalities that were observed in at least 1 clinical study with pralatrexate included low serum albumin, low and high serum calcium, low and high blood glucose, low serum magnesium, low serum phosphorus, low and high serum potassium, and low and high serum sodium. Of particular note, hypoalbuminaemia, hyperglycaemia and hypocalcaemia were frequently recorded as clinically significant abnormalities across the various safety populations.

7.5.4. Haematology

7.5.4.1. Pivotal study

Clinically significant myelotoxicity occurred in approximately 40-50% patients depending on the parameter measured:

- decreased platelet counts were the predominant laboratory abnormality of clinical significance, occurring in 53 (48%) patients. Overall, 17 patients (15%) had Grade 3 platelet counts and 25 patients (23%) had Grade 4 severity at some time during the study and 4 patients had treatment discontinued because of thrombocytopaenia. The shifts in platelet levels are shown in Table 21, below (clinically significant changes are highlighted by shading).

Table 21. Study PDX-008 - shifts in platelet counts during treatment with pralatrexate

		Worst on-study grade				
		0	1	2	3	4
Baseline grade	Grade 0 (n=80)	30	25	6	7	12
	Grade 1 (n=29)	0	3	5	10	11
	Grade 2 (n=2)	0	0	0	0	2

A total of 5 (5%) patients had a platelet count at some point on study of < 10,000/μL and all received platelet transfusions. Three patients discontinued study treatment because of the thrombocytopaenia, 2 of whom had persisting Grade 3-4 thrombocytopaenia despite dose reductions to 20 mg/m^2. Another patient had his dose reduced to 20 mg/m^2 and never experienced > Grade 2 thrombocytopaenia with subsequent dosing. The final patient discontinued study treatment due to disease progression at the time of the thrombocytopenia.

- clinically significant low neutrophil counts were reported for 49 (44%) patients, with 21 developing Grade 3 and 10 developing Grade 4 neutropaenia (Table 22, below). Two patients had treatment withdrawn primarily because of neutropaenia;

Table 22. Study PDX-008 - shifts in neutrophil counts during treatment with pralatrexate

		Worst on-study grade				
		0	1	2	3	4
Baseline grade	Missing (n=2)	2	0	0	0	0
	Grade 0 (n=97)	50	7	16	17	7
	Grade 1 (n=4)	1	0	2	1	0
	Grade 2 (n=7)	0	0	2	3	2
	Grade 3 (n=1)	0	0	0	0	1

- low WBC counts were reported for 47 patients (42%);
- Most patients (n=58; 52%) entered the study with Grade 1 anaemia. Overall 46 (41%) patients experienced clinically significant low haemoglobin; 16 patients developed Grade 3 anaemia and 1 developed Grade 4 anaemia (Table 23, below).

Table 23. Study PDX-008 - in haemoglobin levels during treatment with pralatrexate

		Worst on-study grade				
		0	1	2	3	4
Baseline grade	Grade 0 (n=37)	7	19	8	3	0
	Grade 1 (n=58)	0	30	21	6	1
	Grade 2 (n=16)	0	0	9	7	0

7.5.4.2. Other studies

The frequency of clinically significant abnormalities across each of the safety populations was summarised in a table in the study report. From this table it can be appreciated that there was generally a higher frequency of clinically significant low haemoglobin values, and neutrophil, leucocyte and platelet counts in patients with lymphoproliferative disorders (Populations 1, 2 and 4) who received pralatrexate compared with patients with solid tumours. This is likely to be due to bone marrow involvement with lymphoproliferative malignancies and possible myelotoxic effects of prior chemotherapies for these indications.

7.5.5. Electrocardiograph

7.5.5.1. Pivotal study

All patients had an electrocardiogram (ECG) within 21 days prior to the projected start of pralatrexate administration. Thereafter, ECGs could be obtained at anytime during the study if clinically indicated but the results were not recorded on the CRFs and therefore, no useful information was available for evaluation. In particular, none of the reports of death or serious adverse events had any ECG recordings/reports available.

Two patients had an abnormal ECG at screening considered by the investigator to be a significant abnormality. One patient had sinus tachycardia with probable left atrial abnormality but did not experience any cardiac-related AEs while on study. The second patient had sinus tachycardia with left anterior fascicular block at screening and experienced syncope, tachycardia, carotid sinus syndrome, hypotension, and orthostatic hypotension while on study.

7.5.5.2. Other studies

Screening ECGs were performed as a clinical safety measure prior to dosing with pralatrexate in all but 4 of the studies (PDX-01-076, PDX-99-053, PDX-99-083 and PDX-015) in the clinical development program. However, other than in the completed Study PDX-007 and the recently commenced Study PDX-014 (where it is proposed that 12-lead ECGs will be obtained prior to and within 30 minutes post end of the pralatrexate infusion) no ECGs were performed post-dose in the studies unless clinically indicated. Consequently, the only presentation of ECG data from these studies occurred in the context of the discussion of deaths and adverse events. The most comprehensive data are those from Study PDX-007, which were the subject of a separate, dedicated company report summarised under Pharmacodynamics above.

7.6. Post-marketing experience

Seven PSURs covering the period 24 September 2009 to 23 June 2011, and written in accordance with the 2001 Draft *Food and Drug Administration (FDA) Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines*, were submitted by the sponsor.

The most common events spontaneously reported to the sponsor have been mucosal inflammation; stomatitis and neutropaenia. Other events reported in 3 or more patients include erythema, rash, febrile neutropaenia, pancytopaenia, absolute neutrophil count decreased, pain in extremity, skin ulcer and toxic epidermal necrolysis (TEN). The majority of these events were assessed as being serious. Most of these types of events had been identified as clinically significant adverse reactions during the clinical development program. However, the identification of 4 spontaneous post marketing reports of severe dermatological reactions with a fatal outcome, including the 3 cases of TEN, a reaction not observed during the clinical development program, prompted a review of the dermatological safety of pralatrexate by the sponsor. Other dermatological reactions reported during the post marketing phase included skin exfoliation; skin ulceration; Steven's Johnson Syndrome; bullous dermatitis and skin necrosis. The sponsor implemented a labelling change in the US in May 2010 to include warning statements about dermatological reactions. Dermatological safety is appraised further below.

7.7. Safety issues with the potential for major regulatory impact

7.7.1. Liver toxicity

See below.

7.7.2. Haematological toxicity

See below.

7.7.3. Serious skin reactions

The sponsor provided a comprehensive and detailed compilation and review of all severe dermatological reactions reported with pralatrexate during the clinical development program as well as those reported spontaneously in the post marketing phase. This additional analysis post dated the labelling change in the US (see below) and captured all data obtained up to 31 January 2011, at which time, a total of 689 patients had received at least 1 dose of pralatrexate across all clinical studies. The key findings of the analysis presented in the *Summary of Clinical Safety Addendum* were:

- A total of 346 patients (50%) had experienced at least one dermatological AE regardless of causality, with the most common events being alopecia (12%), pruritus (7%), and rash (7%). Most patients who reported a dermatological AE experienced mild to moderate (that is, Grade 1-2) events;
- 245 (36%) patients in the clinical development program had experienced treatment-related dermatological AEs. Grade 3-5 treatment-related dermatological events occurred in 23 (3%) patients overall, with the most common ADRs being pain of skin, pruritus and skin ulcer (all n=3); and exfoliative rash, palmar-plantar erythrodysaesthesia syndrome, skin lesion, and toxic skin eruption (n=2); see **Table 24**, below.

Table 24. Grade 3-5 dermatological ADRs

	Population 1 (N=111)		Population 2 (N=137)		Population 3 (N=181)		Population 4 (N=107)		Population 5 (N=153)		All (N=689)	
System Organ Class MedDRA Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	6	(5)	10	(7)	5	(3)	1	(<1)	1	(<1)	23	(3)
Pain of skin	0	(0)	2	(1)	1	(<1)	0	(0)	0	(0)	3	(<1)
Pruritus	1	(<1)	2	(1)	0	(0)	0	(0)	0	(0)	3	(<1)
Skin ulcer	2	(2)	1	(<1)	0	(0)	0	(0)	0	(0)	3	(<1)
Exfoliative rash	0	(0)	2	(1)	0	(0)	0	(0)	0	(0)	2	(<1)
Palmar-plantar erythrodysaesthesia syndrome	0	(0)	0	(0)	2	(1)	0	(0)	0	(0)	2	(<1)
Skin lesion	1	(<1)	1	(<1)	0	(0)	0	(0)	0	(0)	2	(<1)
Toxic skin eruption	0	(0)	0	(0)	2	(1)	0	(0)	0	(0)	2	(<1)
Dermatitis exfoliative	0	(0)	0	(0)	1	(<1)	0	(0)	0	(0)	1	(<1)
Dermatosis	0	(0)	0	(0)	0	(0)	0	(0)	1	(<1)	1	(<1)
Erythema	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	1	(<1)
Erythema multiforme	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	1	(<1)
Rash	0	(0)	1	(<1)	0	(0)	0	(0)	0	(0)	1	(<1)
Rash erythematous	1	(<1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(<1)
Rash pruritic	1	(<1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(<1)
Skin exfoliation	0	(0)	0	(0)	0	(0)	1	(<1)	0	(0)	1	(<1)
Urticaria	1	(<1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(<1)

- Across the clinical studies there were 17 clinically significant dermatological reactions reported, 2 of which were associated with a fatal outcome. The 2 fatalities occurring during the clinical development program have been discussed in Section 8.4.3.21.2 of this CER. A further 7 clinically significant reactions had been reported in the post marketing setting and of these 4 had a fatal outcome. A complete tabulation of all the clinically significant reactions was included in the study report. From this table it can be appreciated that the clinically important dermatological reactions included skin necrosis, exfoliation and ulceration, TEN

and bullous eruptions. The onset of these reactions was generally within 1 to 2 weeks of the first dose of pralatrexate. In the clinical trials the clinically significant skin reactions were distributed evenly between males and females (n=10; 2.4% versus n=7; 2.5%). The rate of important skin reactions were higher in patients aged ≥65 years compared to <65 years and (n=8; 3.1% versus n=9; 2.1%).

- The 4 post marketing dermatological fatalities were as follows:
  - Case MCN 1; a 59F with transformed mycosis fungoides and extensive skin disease (80% of skin involved with lymphoma) was hospitalised with extensive desquamation 5 days after administration of a single 60 mg dose of pralatrexate. It was difficult to determine whether the desquamation was occurring at the sites of lymphoma because she was dark-skinned and had undergone extensive prior total skin electron beam therapy. Although the investigator diagnosed the event as radiation recall, there was no localisation or regionalisation of the skin reaction to establish a definitive diagnosis of a radiation recall dermatological reaction. Furthermore, the skin lesions in this patient had been biopsied and showed evidence of TEN. The patient also had Grade 4 mucositis and neutropaenia and continued to decline. The patient died, but the date of death was unknown. Prior treatments included PUVA and extracorporeal photopheresis.
  - Case MCN 2: a 49F with T-cell lymphoma developed TEN and stomatitis, remained hospitalised, and subsequently died two weeks after receiving her first dose of pralatrexate 30 mg/m^2. She had been previously treatment with CHOP and EPOCH.
  - Case MCN 3: a 45F with PTCL (with subcutaneous involvement) and end-stage renal disease developed an erythematous, bullous skin eruption 6 days after receiving her first dose of pralatrexate 15 mg/m^2 (a lower dose was used on account of the ESRD). She initially had a diffuse and erythematous rash with bullae on her hands and feet and severe oral mucositis. The rash subsequently evolved into TEN (biopsy confirmed) and she became hypotensive and pancytopaenic. She died 3 weeks after the one and only dose of pralatrexate, with TEN as the stated cause of death.
  - Case MCN 4: a 83F with Stage IVA Sézary syndrome died 15 days after receiving a single 15 mg/m^2 dose of pralatrexate for disease progression. Following administration of pralatrexate she developed (time to onset not stated) a severe skin reaction, pancytopaenia, bacterial wound infections (worsening of previously existing infections), subsequent mucositis and then sepsis with ultimate complications of multi-organ failure (pneumonia, respiratory failure, acute renal failure due to acute tubular necrosis, and multiple metabolic, electrolyte and haematological abnormalities). The patient's recent prior history included significant wound infection (pseudomonas, methicillin-resistant Staphylococcus aureus [MRSA]) and low white blood cell (WBC) count with ongoing antibiotic therapy.

Evaluator's comment:

None of the vignettes submitted by the sponsor for these 4 cases contained information about the level of compliance of the patient with the rescue therapy regimens for folate and vitamin B12 recommended in the US prescribing information (these regimens are identical to those proposed for the Australian PI). Of note, the patient in case MCN 4 had a known history of vitamin B12 deficiency and prior therapy had included methotrexate (although the proximity to the use of pralatrexate was not reported).

With regard to the 2 dermatological deaths in the clinical trials details of compliance with rescue therapy was only available for a patient from Study PDX-02-078 (which had a full study report plus IPD listings). This patient was enrolled after the final protocol amendment, which means she was required to have a Hcy level of ≤ 10 µmol/L and a MMA level of ≤ 200 nmol/L at baseline, or the patient must have been on a regimen of folic acid 1 mg PO daily for at least 7 days prior to planned start of pralatrexate and had to receive vitamin B12 1 mg intramuscularly within 10 weeks of the

planned start of pralatrexate.

This patient was recorded as having an elevated Hcy level of 13 µmol/L and normal MMA at screening and having commenced folate and vitamin B12 supplementation 14 days prior to the first dose of pralatrexate. A repeat Hcy level 7 days after commencement of vitamin supplementation (7 days prior to pralatrexate) was normal (8 µmol/L). Incidentally this patient had completed treatment with methotrexate + EPOCH some 2 months earlier.

- With regard to important dermatological reactions more generally, the sponsor noted that skin or subcutaneous sites of known lymphoma were frequently involved and this may represent a manifestation of response to the underlying disease rather than a purely toxic effect of the drug. For example, in many cases, patients had received previous therapy for their skin lesions including both local and total body radiation exposure, as well as phototherapy and/or experienced adverse skin reactions with prior chemotherapy. The sponsor pointed to a case of skin erosions in one patient from Study PDX-02-078, which appeared 3 days after the first dose of pralatrexate and were limited to the areas of a pre-existing papular rash associated with the lymphoma and spared unaffected skin. This case was published in the scientific literature and the authors hypothesised that the effect was a manifestation of apoptosis of tumour cells and not the result of cytotoxicity of pralatrexate on keratinocytes.
- It was also noted by the sponsor that patients in early pralatrexate clinical studies (where higher doses were used) had apparent exaggerated cutaneous responses to minor trauma and impaired cutaneous wound healing.

7.7.4. Cardiovascular safety

No specific cardiovascular safety issues have been identified. Pralatrexate is unlikely to markedly delay cardiac repolarisation in PTCL patients treated with pralatrexate doses ≤ 30 mg/m^2.

7.7.5. Unwanted immunological events

No issue has been identified to date.

7.8. Other safety issues

7.8.1. Safety in special populations

No formal covariate analysis has been undertaken to assess the impacts of age, gender, race or pralatrexate dose on the frequency or severity of AEs or laboratory parameter abnormalities. Tabulations of age and gender specific data (using the single lowest-level preferred term) for the 13 selected AEs of interest identified in *Studies providing Safety data*. The table is limited to data from patients who received the proposed dose of 30 mg/m^2 for 6 of every 7 weeks, that is, patients from the pivotal Study PDX-008 and the subset of 27 patients in Study PDX-02-078, as these are most relevant to the intended use of the product.

There were no differences in the overall AE rates for patients aged <65 years versus ≥ 65 years or for males versus females. However, in the pivotal study there were numerically higher rates in patients aged ≥ 65 years than in those <65 years of a number of events including, most notably, mucosal inflammation, thrombocytopaenia, neutropaenia, oedema and pruritus. Only mucosal inflammation (85% versus 63%), and thrombocytopenia (48% versus 37%) had between subgroup differences of > 10%. The results for Study PDX-02-078 were not consistent with those of the pivotal study in that most of the events actually occurred more frequently in younger patients. However, the results of this study are much less reliable because of the very small patient numbers.

No formal statistical analysis of the differences was performed but it appears from this evaluator's own calculations that only the difference in mucosal inflammation rate would reach statistical significance at the 5% level.

Overall, although there does not seem to be a difference in overall AEs between older and younger patients, greater sensitivity of some older individuals to pralatrexate cannot be ruled out, especially with regard to the development to mucosal inflammation and thrombocytopaenia. Any propensity to increased frequency for these events in older patients can be mitigated by careful monitoring and dosage adjustment during treatment.

With regard to gender differences, the largest differences observed in the frequencies in male versus female patients in the pivotal study were thrombocytopaenia (33% versus 57%) and anaemia (29% versus 46). By this evaluator's calculations, only the result for thrombocytopaenia would reach statistical significance at the 5% level. There were occasional differences between the occurrences of AEs overall and by individual terms between males and females in the other populations in various indications and dose regimens but there was not a consistent trend in these differences.

7.8.2. Safety related to drug-drug interactions and other interactions

There are limited safety data about drug-drug and other interactions. Co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure to pralatrexate (Study PDX-01-014). However, there were too few patients enrolled in the study to discern if the higher exposure appreciably altered the safety profile of pralatrexate by way of either a higher incidence or severity of ADRs.

A POPPK analysis based on the pivotal study and 2 supporting efficacy/safety studies did not detect any clinically relevant PK interactions with NSAIDs, sulfonamides or diuretics. However, once again, limited conclusions can be drawn because the studies only analysed single dose pharmacokinetics; there was relatively low co-administration of these medications; and there were deficiencies in the quality and quantity of available information about the dose and duration of the concomitant medicines.

Thus, the possibility of clinically significant drug-drug interactions has not been excluded. Given the significant contribution of renal excretion to the overall clearance of pralatrexate, concomitant administration of nephrotoxic drugs or those that affect glomerular filtration and/or renal tubular secretion could potentially result in a greater risk of ADRs. The proposed PI contains appropriate relevant warnings in this regard.

7.8.3. Pulmonary toxicity

Pulmonary toxicity is a known class effect of antifolate therapies, particularly methotrexate. It can manifest as acute or chronic pneumonitis, pulmonary infiltrates and pulmonary fibrosis. It often presents with non-productive cough and dyspnoea and can occur at low doses and at any time during treatment. In addition, pemetrexed (approved for the treatment of NSCLC and malignant pleural mesothelioma) has been associated with cases of radiation pneumonitis in patients treated with radiation prior to their pemetrexed therapy. Pulmonary toxicity is important clinically because it can have a major impact on oxygen saturation, activities of daily living and quality of life. Furthermore, this particular target population is likely to have undergone previous treatment with regimens that are known to cause pulmonary toxicity.

As of 31 January 2011, a total of 9 (1.3%) patients in the clinical development program for pralatrexate had experienced pneumonitis, (see details in Table 25, below). Eight of the patients with pneumonitis were receiving pralatrexate for the treatment of a lymphoproliferative disorder (7 PTCL; 1 Hodgkin's disease) and one was being treated for NSCLC. Time to onset ranged from 7 to 362 days and the dose of pralatrexate ranged from 10 to 230 mg/m^2. Most cases were considered to be causally related to pralatrexate treatment. Two of the patients came from the pivotal study and experienced Grade 2 events that were considered to be

treatment-related by the investigator. Of note, 2 patients were from Study PDX-009 in which pralatrexate was given in combination with gemcitabine. Interestingly, one of the cases in that study was considered to be related to gemcitabine but not pralatrexate. Gemcitabine is known to be associated with pneumonitis and this may have biased the attribution of causality in this case since it was an open label study. Cases of Grade 3 severity have been reported only in associated with combination therapy involving gemcitabine.

Table 25. Reports of pneumonitis in pralatrexate clinical studies

Study/p't	Indication	Dose (mg/m²)	Onset (study day)	Grade	Serious (Y/N)	Treatment-related (Y/N)	Concurrent AEs	Outcome
PDX-008								
060	PTCL-U	30	141	2→3	Y	Y (probable)	Cough	PDX stopped
057	PTCL-U	30	NR^	2	N	Y	Pulmonary embolus	PDX stopped
PDX-02-078								
022	Adult T-cell lymphoma (HTLV1+)	30	7	2	N	N	Chest pain Dyspnoea	No action
036	ALCL	45	11	2	Y	Y (possible)	Atelectasis Pleural effusion	PDX not given
118	Blastic NK lymphoma	45	362	2	N	Y (probable)	Pulmonary infiltrates Honeycomb appearance on lung CT scan	PDX not given
PDX-012								
1460	NSCLC	230 →190	52	2	Y	Y (possible)	Chronic cough Bilateral pulmonary infiltrates on CT	PDX stopped
PDX-009								
020	PTCL-U	10 + GEM400	43	3	Y	Y (GEM only - possible)	Cough Dyspnoea Hypoxia	PDX delayed
026	Hodgkin's lymphoma	10 + GEM400	125	3	Y	N	Pleural effusion	No action
NA*	NA	NA	NA	≥3	Y	NA	NA	NA

* Not available - this case was identified from the Updated Safety Tables and no patient-specific information was available to the evaluator.

^ Not reported – details of this case were available from the narrative for the SAE pulmonary embolus included in the response to day 120 questions raised in Europe. There was no mention of pneumonitis in the original narrative included in the CSR for PDX-008.

One additional patient with NSCLC from Study PDX-007 experienced radiation pneumonitis (with associated dyspnoea) of Grade 2 severity, occurring 92 days after commencing treatment with pralatrexate 270 mg/m^2 every 3/4 weeks. The patient had completed a 1 month course of radiotherapy 5 weeks prior to commencing treatment with pralatrexate.

Other potential but not necessarily specific indicators of pulmonary toxicity were:

- dyspnoea in 163 (24%) patients across the clinical development program; 80 (23%) patients with lymphoproliferative disorders (that is, Populations 1, 2 and 4); and 21 (19%) patients from the pivotal study;
- hypoxia in 19 (2.7%) patients across the clinical development program; 17 (5%) patients with lymphoproliferative disorders; and 3 (3%) patients from the pivotal study; and
- non productive cough in 157 (23%) patients across the clinical development program; 17 (22%) patients with lymphoproliferative disorders; and 32 (29%) patients from the pivotal study.

7.9. Evaluator's overall conclusions on clinical safety

The safety profile and risks of pralatrexate have been well elucidated and the main identified risks of pralatrexate can be considered to be related a pharmacological class effect. Although a relatively small proportion of the patients in the pralatrexate clinical development program were from the target population (PTCL) and received pralatrexate as a single agent administered via the proposed regimen, it is clear that the safety profile seen in those patients was generally consistent with that observed across a number of patient populations studied to date. These data have been supplemented by post marketing data generated over a 21 month period during which an estimated additional 985 to 1725 patients with PTCL were exposed to the drug.

The toxicities identified in the clinical development program include:

Mucositis Mucosal inflammation was observed in 71% patients with PTCL in the pivotal study, with the majority of cases being oral. Serious reactions occurred in 6% patients. In this study 18% patients had Grade 3 toxicity and 4% had Grade 4 toxicity and the median time to onset of ≥ Grade 3 mucosal inflammation was 19 days. Mucosal inflammation/ stomatitis was the most common reason for dose reduction and treatment withdrawal in the pivotal study and across the clinical development program.

Myelotoxicity Thrombocytopaenia, neutropaenia and anaemia were very common toxicities which, along with mucositis, accounted for the majority of treatment-related withdrawals of pralatrexate therapy, dose omissions and dose-reductions. In the pivotal study the median time to onset of thrombocytopenia ≥ Grade 3 was 15 days, with a median duration of 16 days. The median time to onset of ≥ Grade 3 neutropaenia was slightly longer at 22 days but the median duration was only 8 days which possibly reflects the use of the colony stimulating factors G-CSF and GM-CSF.

Dermatological toxicity 36% patients with PTCL in the pivotal study and 36% patients across the clinical development program experienced treatment-related dermatological AEs. Grade 3-5 treatment-related dermatological events occurred in 5% PTCL patients in the pivotal study and 3% patients overall. There have been 24 clinically significant dermatological reactions reported in clinical trials and post marketing usage. Severe dermatological reactions occur early in treatment and generally after the first dose. The majority of the important dermatological reactions resolved with supportive therapy and

some patients were able to continue pralatrexate therapy. However, of most concern were 6 reactions (skin necrosis, skin exfoliation; skin ulceration; TEN; and bullous eruptions) that occurred after only one or two doses and were associated with a fatal outcome. The fatal and/or life-threatening reactions occurred in patients with extensive skin disease and were generally associated with mucositis, neutropaenia, and/or infection and included extensive skin involvement of the underlying lymphoma. Compromise in the integrity of the skin may also pre-dispose patients to infection and subsequent sepsis in the setting of myelosuppression.

Abnormal liver function Pralatrexate appears to have a mild potential for hepatotoxicity. In the pivotal study clinically significant abnormalities of AST and ALT were reported in 17% and 16% patients with PTCL, respectively. 9% of patients had clinically significant derangements in total bilirubin levels. Most abnormalities of hepatic function were managed successfully with dose reduction, although in almost all cases the dose reduction was undertaken primarily for other concomitant toxicities such as thrombocytopaenia, neutropaenia or mucositis. Overall, very few patients had pralatrexate doses omitted or reduced, or therapy withdrawn primarily as a result of adverse effects on liver function.

Infection Susceptibility to infections such as pneumonia, sepsis and herpes zoster in patients receiving pralatrexate may be increased as the result of myelosuppression (neutropaenia, pancytopaenia), previous chemotherapies and the underlying disease process. In the pivotal study 6% PTCL patients experienced ≥ Grade 3 sepsis; 3% had ≥ Grade 3 herpes zoster infection; and 5% had ≥ Grade 3 pneumonia.

Tumour lysis syndrome Tumour lysis syndrome was observed in 4 patients with lymphoproliferative disorders across the clinical development program, including 3 patients with PTCL. All cases of tumour lysis syndrome were of Grade 3-4 severity, with onset between 3-51 days following initial administration of pralatrexate and duration ranging from 7-14 days. Two patients discontinued pralatrexate because of this ADR. Patients with bulky disease and those responding to pralatrexate may be at higher risk of developing tumour lysis syndrome. Patients experiencing tumour lysis may develop metabolic complications including hyperuricaemia and acute renal failure. The risk of tumour lysis syndrome can be managed through the prophylactic use of allopurinol and ensuring patients are adequately hydrated.

Pulmonary toxicity Pulmonary toxicity is a known class effect of antifolate therapies. There have been 9 reports of pneumonitis (including 3 Grade 3 cases when pralatrexate was used in combination with gemcitabine) and 1 report of radiation pneumonitis. All but one case of pneumonitis occurred in patients with a lymphoproliferative malignancy (mainly PTCL). Two cases occurred in the pivotal study and were both considered to be treatment-related.

Personal communication between this evaluator and 2 medical officers at the TGA who have haematological expertise confirmed the safety profile for pralatrexate, including dermatological safety, is consistent with the experience of other antifolate cytotoxics available in Australia.

The safety of pralatrexate has not been evaluated in patients with moderate to severe renal impairment or patients with hepatic impairment. Renal toxicity has been identified as a Potential risk in the Risk Management Plan.

Also, although there does not seem to be a difference in the overall frequency of AEs between older and younger patients, greater sensitivity of some older individuals cannot be ruled out, especially for the development of mucosal inflammation and thrombocytopaenia. Any propensity for increased frequency of these events in older patients can be mitigated by careful monitoring and dosage adjustment during treatment. Creatinine clearance was found to be a clinically important predictor (representing both renal function and age dependencies) of pralatrexate exposure and therefore potential for adverse effect in population pharmacokinetic modelling. Whilst no dosage adjustments are recommended for age *per se*, age-related decline in renal function is highlighted appropriately in the proposed PI.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of pralatrexate in the proposed usage are:

- an overall response rate (CR+CRu+PR) of 29% (95% CI: 21 – 39%) by independent adjudicated (central) review;
- 25% of pralatrexate responders had no evidence of response to their most recent prior therapy;
- 19% of pralatrexate responders had no evidence of response to any prior therapy;
- a median duration of response of 306 days (95% CI: 3.4 – NE) or 10.1 months by central review;
- a median progression-free survival of 106 days (95% CI: 51 – 146) or 3.5 months by central review; and
- a median overall survival of 14.5 months (95% CI: 10.6 – 22.5 months) by central review. The most recently available data indicates a survival rate of 56% (95% CI 46 – 65%) at 1 year; 35% (95% CI 26 – 44%) at 2 years; 29% (95% CI 19 – 39%) at 3 years; and 25% (95% CI 15 – 37%) at 4 years.

There is evidence that suggests that pralatrexate may also:

- stabilise or reverse an observed trend toward poorer outcomes with progressive lines of treatment in PTCL;
- yield response rates and PFS as good as or better than the immediate prior therapy; and
- alter the natural course of the disease and provide improved survival compared with the currently available treatment options for patients with relapsed/refractory PTCL.

However, these latter benefits have been identified from underpowered retrospective analyses.

8.2. First round assessment of risks

The risks of pralatrexate in the proposed usage are typical of those associated with antifolate cytotoxic agents and include:

- Mucositis;
- Myelotoxicity;
- Serious skin reactions, including fatal reactions;
- Pulmonary toxicity;

- Infection;
- Abnormal liver function; and
- Tumour lysis syndrome.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of pralatrexate, given the proposed usage, is favourable.

In reaching this conclusion this evaluator notes the limitations of the single pivotal study and the difficulty in reaching firm conclusions about the clinical benefit of pralatrexate in the target population. However, it appears that pralatrexate offers durable responses and meaningful survival benefits in a subset of patients with relapsed or refractory PTCL who otherwise have a dismal prognosis from an aggressive disease that has no approved or standard care. On balance, these benefits outweigh the risks associated with the adverse effects of pralatrexate on folate metabolism in that the toxicities are by and large manageable with careful monitoring, vitamin supplementation and dose modification, all of which are emphasised in the proposed product information.

9. First round recommendation regarding authorisation

The application for the registration of pralatrexate (Folotyn®) for *the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and leukaemic/disseminated) who have progressed after at least one prior therapy* should be approved.

10. Clinical questions

10.1. Efficacy

Please provide a justification for the censoring of patients [information redacted] from the Kaplan-Meier analysis of duration of response in Study PDX-008 on the basis of "*other cancer treatment*". It appears that for these two patients the commencement of another cancer treatment occurred after documentation of the event of interest that is, progression of disease, as follows:

- Patient [information redacted] (duration of response censored at 306 days) - according to the data this patient received pralatrexate for 442 days, having first achieved a response of CR on 1 October 2007. Pralatrexate was last administered on 25 July 2008. On 8 August 2008 treatment was permanently discontinued and the primary reason was documented to be "*Other, Progression of Disease*". According to the data, the therapy received subsequent to pralatrexate was combination liposomal doxorubicin and gemcitabine, commenced on 22 August 2008 that is, after the documented date of disease progression;
- Patient [information redacted] (duration of response censored at 1 day) - according to the data this patient received pralatrexate for 246 days and the patient first achieved a response of PR on 4 March 2008. Pralatrexate was last administered on 4 March 2008. On 11 March 2008 treatment was permanently discontinued and the primary reason was documented to be "*Other, Progression of Disease*". According to the data, the therapy received subsequent to pralatrexate was methotrexate, aracytine and hydrocortisone, commenced on 13 August 2008 that is, after the documented date of disease progression.

11. References

Aherne GW, Piall E, Marks V *et al*. Prolongation and enhancement of serum methotrexate concentrations by probenecid. *Br Med J* 1978; **1**: 1097-9.

Armitage JO, Weisenberger DD. New approach to classifying Non-Hodgkin's lymphoma: Clinical features of the major histologic subtypes. *J Clin Oncol* 1998; **16**: 2780-2795.

Brunton L (ed). Goodman and Gilman's The Pharmacological basis of Therapeutics, 12th edition (on-line) The McGraw-Hill Companies Inc.

Cheson BD, Horning SJ, Coiffier B, *et al*. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999; **17(4)**: 1244-53.

Cheson BD, Pfistner B, Juweid ME, *et al*. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25(5)**: 579-86.

Dang NH, Hagemeister FB, Duvic M, *et al*. Pentostatin in T-non-Hodgkin's lymphomas: Efficacy and effect on CD26+ T lymphocytes. *Oncol Rep* 2003; **10**: 1513-1528.

Dang NH, Pro B, Hagemeister FB, *et al*. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non Hodgkin lymphoma. *Br J Haematol* 2006; **136**: 439-447.

Dearden C, Matutes E & Catovsky D. Deoxycoformycin in the treatment of mature T-cell leukaemias. *Br J Cancer* 1991; **64**: 903-906.

Dueck GS, Chua N, Prasad A, *et al*. Activity of lenalidomide in a Phase II trial for T-cell lymphoma; Report on the first 24 cases. *J Clin Oncol* 2009; **27(15S)**: 8524 (abstract).

Evens AM & Gartenhaus RB. Treatment of T-cell Non-Hodgkin's Lymphoma. *Curr Treat Options Oncol* 2004; **5**: 289-303.

Fisher RI, Gaynor ER, Dahlberg S, *et al*. Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma. *NEJM* 1993; **328**: 1002-1006.

International Conference on Harmonisation (ICH) E14 Guidance: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

Lopez-Guillermo A, Cid J, Salar A, *et al*. Peripheral T-cell lymphomas: Initial features, natural history and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. classification. *Ann Oncol* 1998; **9**: 849-855.

Mercieca J, Matutes E, Deardon C, *et al*. The Role of Pentostatin in the treatment of T-Cell Malignancies: Analysis of response Rates in 154 Patients According to Disease Subtype. *J Clin Oncol* 1994; **12**: 2588-2593.

Mould DR, Sweeney K, Duffull SB, *et al*. A population pharmacokinetic and pharmacodynamic evaluation of pralatrexate in patients with relapsed or refractory non-Hodgkin's or Hodgkin's lymphoma. *Clin Pharmacol Ther* 2009; **86**(2): 190-6.

Rodriguez-Abreu D, Filho VB & Zucca E. Peripheral T-cell lymphomas, unspecified (or not otherwise specified): a review. *Haematol Oncol* 2008; **26**: 8-20.

Rudiger T, Weisenberger DD, Anderson JR, *et al*. Peripheral T-cell lymphoma (excluding anaplastic large cell lymphoma): results from the Non-Hodgkin's: Lymphoma Classification Project. *Ann Oncol* 2002; **12**: 140-149.

Sallah S, Wan JY & Nguyen NP. Treatment of refractory T-cell malignancies using gemcitabine. *Br J Haematol* 2001; **113**: 185-187.

Savage DG, Lindenbaum J. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. *Am J Med* 1994; **96**: 239-246.

Savage KJ. Peripheral T-cell lymphomas. *Blood Reviews* 2007; **21**: 201-216.

Serova M, Bieche I, Sabin MP, *et al*. Single agent and combination studies of pralatrexate and molecular correlates of sensitivity. *British Journal of Cancer* 2011; **104(2)**: 272-80.

Shipp MA. Prognostic Factors in Aggressive Non-Hodgkin's Lymphoma: Who has "High-Risk" Disease. *Blood* 1994; **83(5)**: 1165-1173.

Sirotnak FM, DeGraw JI, Calwell WJ & Piper JR. A new analogue of 10-deazaaminopterin with markedly enhanced curative effects against human tumor xenografts in mice. *Cancer Chemother Pharmacol* 1998; **42**: 313-318.

Sonnen R, Schmidt W-P, Muller-Hermelink HK & Schmitz N. The International Prognostic Index determines the outcome of patients with nodal mature T-cell lymphomas. *Br J Haematol* 2005; **129**: 366-372.

Suzuki K, Doki K, Homma M, *et al*. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high dose methotrexate therapy. *Br J Clin Pharmacol* 2008; **67**(1): 44-49.

Vose J, Harris NM, Harris ME *et al*. International Peripheral T-cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes. *J Clin Oncol* 2008; **26**: 4124 – 4130.

Walling J. From methotrexate to pemetrexed and beyond. A review of the pharmacodynamic and clinical properties of antifolates. *Invest New Drugs* 2006; **24**: 37-77.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au