National Drug Monograph

Pralatrexate (Folotyn®)

June 2012

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:[1,2]

- Pralatrexate is a folate analog metabolic inhibitor that competitively inhibits dihydrofolate reductase. The inhibition results in depletion of thymidine and other biological molecules that depend on single carbon transfer.
- Pralatrexate has a high affinity for reduced folate carrier which leads to selective tumor cell accumulation. This results in higher tumor cell accumulation and disruption of DNA synthesis within these cells.
- Pralatrexate is indicated for treatment of refractory or relapsed Peripheral T-Cell Lymphoma (PTCL).
- The recommended dose of pralatrexate is 30mg/m2 IVP over 3-5 minutes weekly for 6 weeks in 7 week cycles.
- Supplementation with Vitamin B12 (cyanocobalamin) intramuscular injections every 8-10 weeks and folic acid 1-1.25mg orally on a daily basis is required to help prevent adverse events.
- The efficacy and safety of pralatrexate has been established in the PROPEL[2] trial.
- The primary endpoint of this study was ORR; secondary endpoints included Duration of Response, PFS and OS. The ORR was 29% (32 of 109 patients) and included 12 CR's (11%) and 20 PR's (18%) with a median DoR of 10.1 months. The median PFS was 3.5 months and the median OS was 14.5 months.
- An increase in overall survival was not shown.
- The most common AEs observed were mucositis, nausea, thrombocytopenia and fatigue. Common Grade 3 or 4 toxicities included thrombocytopenia, mucositis, neutropenia and anemia. Although the hematologic toxicities were rarely symptomatic, 15% of patients received platelet transfusions and 10% received filgrastim.
- Mucositis and thrombocytopenia were adverse effects that caused 23% of patients to discontinue therapy.
- Drug interactions include NSAIDs, probenecid, and sulfamethoxazole/trimethoprim. Renally excreted medications may increase the concentration of pralatrexate in the blood stream.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating pralatrexate for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1]

Mechanism of Action

Pralatrexate is a dihydrofolate reductase competitive inhibitor. Polyglutamylation is also competitively inhibited by pralatrexate by binding to folylpolyglutamyl synthetase. The result of inhibition is a loss of thymidine and other biological molecules that require single carbon transfer.

Pharmacokinetics

Absorption:
The pharmacokinetics of pralatrexate was evaluated in only 10 patients with PTCL at a dose of 30 mg/m^2. Area Under the Curve (AUC) and maximum concentration increased with increased dose. The terminal half life was 12-18 hours. Total clearance was 417 ml/min (S-diastereomer) and 191 ml/min (R-diastereomer). Over multiple cycles pralatrexate did not accumulate and kinetics did not seem to change.

Distribution:
In vitro pralatrexate is 67% bound to plasma proteins. It was shown to be a substrate for OATP1B3. It has weak inhibition of OATP1B1 and MRP2 and potent inhibition of MRP3. Pralatrexate's R- and S-diasterioisomers have a V_{dss} ~ 105 L and 37 L, respectively.

Metabolism:
Pralatrexate has not been shown to either induce or inhibit CYP450 enzymes.

Excretion:
It is estimated that ~ 34% of pralatrexate is excreted unchanged through the kidneys. This number is decreased in patients with decreased creatinine clearance.

FDA Approved Indication(s) and Off-label Uses[1]

Pralatrexate is a folate inhibitor indicated and approved by the FDA for treatment of patients who have relapsed or refractory peripheral T-cell lymphoma.

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Potential off label uses include: Cutaneous T-Cell Lymphoma, refractory or non-refractory; Non-Small Cell Lung Cancer, recurrent or refractory non-Hodgkins or Hodgkins Lymphoma

Current VA National Formulary Alternatives[3]

Currently there are no standard treatments for relapsed/refractory PTCL. Those who relapse are typically treated with a second-line combination regimen in an attempt to achieve a complete remission. Those who respond should be offered autologous or allogeneic hematopoietic cell transplantation. Those who are not transplant candidates, who fail to respond to second-line therapy or relapse after transplant are treated with a palliative intent. Second-line therapies can include the following:

- ICE (ifosfamide, carboplatin, etoposide) for transplant candidates
- DHAP (dexamethasone, high dose cytarabine, cisplatin) for transplant candidates
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) for transplant candidates
- GDP: (Gemcitabine, cisplatin, dexamethasone) for transplant candidates
- GemOx: (gemcitabine; oxaliplatin) for transplant candidates
- Single agent gemcitabine;
- Single agent denileukin – not on VA National Formulary (VANF)
- Single agent romidepsin – not on VANF
- Single agent pralatrexate – not on VANF

All of the above listed are formulary items, unless otherwise noted.

Dosage and Administration[1,2,4]

- 30 mg/m^2 injected intravenous push over 3 to 5 minutes once weekly for 6 weeks
- Each cycle consists of 7 weeks, which includes 6 weeks of therapy and 1 week of rest prior to initiating next cycle
- The injection must be administered intravenously as undiluted solution
- Do not administer intramuscularly or subcutaneously
- Pre-medications are not required immediately before administration
- Patients receiving pralatrexate should receive folic acid and cyanocobalamin supplementation throughout duration of treatment
    - Folic acid 1.0-1.25 mg PO every day; start during the 10-day period prior to initiating pralatrexate therapy, and continue for 30 days after last dose
    - Cyanocobalamin 1 mg IM every 8-10 weeks; start no more than 10 weeks prior to initiating pralatrexate therapy

Administration

- Products do not need to be diluted, and should be used immediately due to lack of preservatives in solution.
- As with all other intravenous medications, products should be made using aseptic technique and inspected for any discoloration, particulates, or other abnormalities prior to use.
- Pralatrexate should be handled and treated appropriately, according to hazardous/cytotoxic drug storage policies.
- Gloves and protective clothing necessary for preparation and administration of cytotoxic medications should be used when handling pralatrexate.

Monitoring

- Recommended monitoring parameters include:
    - Weekly complete blood count

- Weekly monitoring for mucositis and its severity
- Serum chemistry tests should be monitored prior to doses 1 and 4 of each cycle, which includes renal and hepatic function

Dose Modifications

- Dose and treatment modifications may be necessary based on adverse events and treatment-related toxicities
  - Adjustments due to mucositis:
    - Mucositis grades are established by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)
      - Grade 1: Asymptomatic or mild symptoms; intervention not indicated
      - Grade 2: Moderate pain; not interfering with oral intake; modified diet indicated
      - Grade 3: Severe pain; interfering with oral intake
      - Grade 4: Life-threatening consequences; urgent intervention indicated
    - Degree of mucositis should be ≤ Grade 1 prior to administration
    - If Grade 2 on day of treatment, dose should be omitted; continue prior dose once returning to Grade 1
    - If recurring Grade 2, dose should be omitted; upon recovery to ≤ grade 1 toxicity, decrease to 20 mg/m^2 for subsequent doses
    - If Grade 3, dose should be omitted; upon recovery to ≤ grade 1 toxicity, decrease to 20 mg/m^2 for subsequent doses
    - If Grade 4, discontinue treatment
  - Adjustments due to thrombocytopenia:
    - Platelets should be ≥ 100,000/µL prior to initial dose, and ≥ 50,000/µL for subsequent doses
    - If < 50,000/µL on day of treatment and the duration of toxicity persists for one week, omit dose; continue prior dose for subsequent doses once platelets recover
    - If < 50,000/µL on day of treatment and the duration of toxicity persists for two weeks, omit dose; decrease dose to 20 mg/m^2 for subsequent doses once platelets recover
    - If < 50,000/µL on day of treatment and the duration of toxicity persists for three weeks, discontinue treatment
  - Adjustments due to neutropenia:
    - Absolute neutrophil count (ANC) should be ≥ 1,000/µL prior to administration
    - If ANC 500-1,000/µL with no fever on day of treatment and the duration of toxicity persists for one week, omit dose; continue prior dose for subsequent doses once ANC recovers
    - If ANC 500-1,000/µL with fever or < 500/µL for 1 week, omit dose and give G-CSF or GM-CSF; continue prior dose with G-CSF or GM-CSF treatment for subsequent doses once resolved
    - If ANC 500-1,000/µL with fever or < 500/µL that persists for 2 weeks or recurs, omit dose and give G-CSF or GM-CSF; decrease dose to 20 mg/m^2 with G-CSF or GM-CSF support for subsequent doses once ANC recovers
    - If ANC 500-1,000/µL with fever or < 500/µL and persists for 3 weeks or for a 2nd occurrence, discontinue treatment
  - Adjustments for all other treatment-related toxicities:

- For Grade 3 toxicity on day of treatment, omit dose. When toxicity recovers to ≤ Grade 2 toxicity, dose at 20 mg/m^2.
- For Grade 4 toxicity on day of treatment, stop therapy.

o Doses omitted should not be made up at the end of each cycle
o If a dose reduction is necessary, do not re-escalate to initial dosing

Dosage Form/Strength/Storage

Pralatrexate is clear, yellow solution available as preservative-free, sterile, single-dose vials. It is available in two package sizes, each with a concentration of 20 mg/mL: 20mg in 1 mL of solution, and 40 mg in 2 mL of solution.

Pralatrexate vials should be stored in the refrigerator at 36-46°F until necessary for use. Each vial is stable for 72 hours at room temperature and should be protected from light and stored in original container. Pralatrexate should be stored appropriately, according to hazardous/cytotoxic drug storage policies.

Efficacy[2]

Efficacy Measures

Primary Endpoints:
- Overall Response Rate (ORR) includes Complete Responses (CR), CR unconfirmed (CRu) and Partial Responses (PR).

Secondary Endpoints:
- Duration of response (DoR)
- Progression-free survival (PFS)
- Overall Survival (OS)

Summary of efficacy findings[2]

Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma: Results from the Pivotal PROPEL Study. J Clin Onc 2011; 29: 1182-1189.

- PROPEL was a phase II, single-arm, open-label study designed to evaluate the safety and efficacy of pralatrexate in patients with PTCL with documented disease progression after receipt of ≥ 1 prior therapy.
- The primary endpoint of this study was ORR; secondary endpoints included Duration of Response, PFS and OS. The ORR was 29% (32 of 109 patients) and included 12 CR's (11%) and 20 PR's (18%) with a median DoR of 10.1 months. The median PFS was 3.5 months and the median OS was 14.5 months.
- The most common AEs observed were mucositis, nausea, thrombocytopenia and fatigue. Common Grade 3 or 4 toxicities included thrombocytopenia, mucositis, neutropenia and anemia. Although the hematologic toxicities were rarely symptomatic, 15% of patients received a platelet transfusion and 10% received filgrastim.
- A total of 23% of patients withdrew from treatment due to AEs. The most frequent causes were mucositis (6%) and thrombocytopenia (5%).

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 11).

Adverse Events (Safety Data)[1,2]

Table 1 – Adverse Events in > or = 10% of patients with PTCL (n=111)

Event	Number (%)	Grade 3/4
General events and administration conditions		
Mucositis	79 (71)	20/4
Fatigue	40 (36)	6/2
Pyrexia	38 (34)	1/1
Edema	34 (31)	1/0
Hematologic Events		
Thrombocytopenia	45 (41)	15/21
Anemia	38 (34)	18/2
Neutropenia	28 (25)	15/9
Leukopenia	12 (11)	4/4
GI Events		
Nausea	46 (41)	4/0
Constipation	38 (34)	0/0
Vomiting	28 (25)	2/0
Diarrhea	25 (23)	2/0
Dyspepsia	11 (10)	0/0
Respiratory, thoracic, and mediastinal events		
Cough	32 (29)	1/0
Epistaxis	29 (26)	0/0
Dyspnea	21 (19)	8/0
Skin and subcutaneous tissue events		
Rash	17 (15)	0/0
Pruritus	16 (14)	2/0
Night sweats	12 (11)	0/0
Infections		
Upper respiratory tract	12 (11)	1/0
Sinusitis	11 (10)	1/0
Other Conditions		
Hypokalemia	18 (16)	4/1
Anorexia	18 (16)	3/0
Pharyngolaryngeal pain	15 (14)	1/0
Liver function test abnormal	14 (13)	6/0
Back pain	14 (13)	3/0
Abdominal pain	13 (12)	4/0
Headache	13 (12)	0/0
Pain in extremity	13 (12)	0/0
Asthenia	12 (11)	2/0
Tachycardia	11 (10)	0/0

Adapted from Table 4 – O'Connor et al. J Clin Oncol 2011; 29(9): 1182-1189

Common Adverse Events

Most common adverse events were thrombocytopenia, mucositis, nausea and fatigue. The most common serious adverse events were mucositis (23%), pyrexia (7%), febrile neutropenia (5%), sepsis (5%), dehydration (4%), dyspnea (4%) and thrombocytopenia.

Deaths and Other Serious Adverse Events (SAE) (Sentinel Events)

Eight patients died within 30 days of the last dose of pralatrexate in the PROPEL trial by O'Connor et al. Seven due to progression of disease and one due to cardiopulmonary arrest

which may be attributed to pralatrexate. Within this clinical trial setting, 44% of patients (n=49) experienced a SAE while taking pralatrexate. SAEs included pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

Other Adverse Events
Other adverse events included abnormal liver function tests, fatigue, leucopenia, neutropenia, and pruritic rash.

Tolerability
Forty five percent of patients receiving pralatrexate experienced serious adverse events. Twenty three percent withdrew from the study due to adverse events, most due to mucositis or thrombocytopenia. The majority of patients (69%; n=77) received the target dose of 30 mg/m^2 given once weekly for 6 doses, every 7 weeks. A total of 85% of scheduled doses were administered.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 11).

Precautions/Contraindications[1]

Precautions
- Pralatrexate has been shown to suppress bone marrow function, resulting in thrombocytopenia, neutropenia, and anemia. ANC and platelet counts should be evaluated prior to each dose as low counts require changes in dosing, as shown in "Dosage and Administration" above.
- Mucositis is a dose-limiting adverse effect. Its occurrence may necessitate omitting and/or adjusting doses (see "Dosage and Administration").
- Severe skin reactions have also been shown with pralatrexate administration, and can be potentially fatal. Studies have shown occurrences of skin exfoliation, formation of ulcers, and toxic epidermal necrolysis. Occurrences may become more severe with continued treatment. If skin reactions do occur, the patient should be carefully monitored with possible cessation of therapy if too severe.
- Pralatrexate can cause tumor lysis syndrome, which requires careful monitoring and treatment if occurring.
- Folic acid and cyanocobalamin should be supplemented while receiving pralatrexate to help prevent or reduce hematological toxicity and mucositis (see "Dosage and Administration" section).
- Pralatrexate is pregnancy category D and can cause harm to the fetus if administered. It was shown to be toxic to both the fetus and embryo in animal studies.
- Pralatrexate has not been officially studied in patients with renal impairment, and is therefore recommended to not use in end stage renal disease or patients on dialysis. Caution should be used in patients with moderate to severe renal dysfunction. Renally compromised patients should be closely monitored for drug toxicity.
- Pralatrexate has been shown to cause elevated liver enzymes. If liver enzymes continue to be elevated throughout treatment, dose adjustments may be necessary.

Contraindications
- Per manufacturer and prescribing information, there are no contraindications for use

Use in Specific Populations
- *Pregnancy:*
    - Pregnancy category D

    - Patients who are pregnant or become pregnant during treatment with pralatrexate should be cautioned on potential risk of harm to the fetus
- *Nursing:*
    - It is unknown if pralatrexate is excreted into milk
    - A risk vs. benefit analysis should be considered based on need for treatment and potential harm to infant
- *Pediatrics* (for inclusion only):
    - Data regarding use in pediatrics has not been studied
- *Geriatrics:*
    - Dose modifications are not required in elderly patients unless required due to renal or hepatic dysfunction, or other dose-limiting factors outlined above
    - Studies show no differences in efficacy and safety based on age
- *Hepatic impairment:*
    - As mentioned, pralatrexate has been associated with elevated liver enzymes
    - Patients with hepatic dysfunction with the following values were not included in studies:
        - Total bilirubin > 1.5 mg/dL
        - AST/ALT > 2.5x upper limit of normal
        - AST/ALT > 5x upper limit of normal with documentation of hepatic involvement from lymphoma

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for pralatrexate:
- Pemetrexed (Lexi-Comp, ISMP)
- Methotrexate (Lexi-Comp)
- Raltitrexed (Lexi-Comp)

LA/SA for Folotyn:
- Focalin

Drug Interactions[1,5]

Drug-Drug Interactions
Approximately 34% of pralatrexate was eliminated unchanged into the urine following a single 30 mg/m^2 dose, therefore medications which are eliminated renally such as probenacid, NSAIDs, and trimethoprim/sulfamethoxazole can decrease the elimination time and increase blood concentration of pralatrexate.

In vitro studies show that pralatrexate is not a substrate, inducer, or inhibitor of CYP450 isoenzymes. There have been no formal assessments of drug-drug interactions between pralatrexate and other drugs.

Drug-Lab Interactions
There have been no studies done or reports to identify any Drug-Lab interactions.

Acquisition Costs[3,6]

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

Currently, no pharmacoeconomic analysis of pralatrexate has been published.

Conclusions[2]

Pralatrexate is a folate analog metabolic inhibitor and the first medication to be approved for treatment of relapsed or refractory PTCL, which is considered a rare condition. The prognosis for patients with newly diagnosed PTCL is poor with the lowest 5-year survival rates among NHL subtypes.

The trial by O'Connor et al. evaluated pralatrexate in the relapsed or refractory population PTCL population. Results indicate an ORR (total responders) of 29% (95% CI, 21% to 39%), and duration of response of 10.1 months. The median PFS was 3.5 months with a median OS of 14.5 months.

Adverse events of mucositis and thrombocytopenia can limit its use in patients. Both ADEs can cause doses to be modified or therapy discontinued altogether. Platelet transfusions were required in 15% of the study population and 10% received a WBC growth factor. Pralatrexate has a low emetogenic risk, antiemetic prophylaxis can be easily managed with oral premedication.

Pralatrexate therapy requires supplementation with cyanocobalamin intramuscular injections given every 8-10 weeks as well as oral folic acid taken on a daily basis. It is important to ensure that patients are able to comply with this supplementation as it is necessary to prevent adverse events.

Pralatrexate received FDA-approval for treatment of patients with relapsed/refractory PTCL. It was approved based on an improvement in overall response rate. Clinical benefit such as improvement in progression-free survival and overall survival has not been shown. The effect of pralatrexate on Patient-Related Outcomes has not been evaluated to date.

References:

1. Package Insert- FOLOTYN® (pralatrexate injection). Allos Therapeutics, Inc. Westminster, CO 80020. January 2012.
2. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma: Results From the Pivotal PROPEL Study. Journal of Clinical Oncology 2011;29 (9): 1182-1189.
3. Jacobson, E; Arnold, SE. Treatment of relapsed or refractory peripheral T-cell Lymphoma. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2012.
4. Common Terminology Criteria for Adverse Events (CTCAE): v4.03 - NIH Publication No. 09-5410. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 14 June 2012.
5. Gold Standard, Inc. Pralatrexate Monograph. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed: May 5, 2012.
6. Denileukin Diftitox. Lexi-Drugs Online. Lexi-Comp Online. Lexi-Comp, Inc. Hudson, OH. Available at: http://online.lexi.com/crlonline Accessed April 11, 2012.
7. Horwitz SM, Kim Y, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma(CTCL): final results of a multicenter dosefinding study. Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 2800.
8. Krug LM, Azzoli CG, Kris MG, et al. 10-propargyl-10-deazaaminopterin: an antifolate with activity in patients with previously treated non-small cell lung cancer. Clin Cancer Res. 2003;9:2072-8.

9. Azzoli CG, Patel J, Krug LM, et al. Pralatrexate plus vitamin B12 and folic acid supplementation in patients with previously treated, advanced, non-small cell lung cancer: safety and efficacy in a Phase 1 trial [P-9086]. Poster presented at European Society of Medical Oncology (ESMO) 2009; Berlin, Germany. September 20-24.
10. Patel JD, Azzoli CG, Weems G, et al. Results of a randomized phase 2B study estimating overall survival of pralatrexate vs. erlotinib in platinum-treated NSCLC. Poster presented at American Society of Clinical Oncology (ASCO) 2011; Chicago, Illinois. June 3-7.
11. Malik SM, Liu K, Qiang X, et al. Folotyn (pralatrexate injection) for the Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma: U.S. Food and Drug Administration Drug Approval Summary. Clinical Cancer Research 2010: 16: 4921-4927.

Prepared April 2012 by Sarah Clay, Pharm.D, PGY1 Pharmacy Resident; Derek Cole, Pharm.D, PGY1 Pharmacy Resident
Contact person: Berni Heron, Pharm.D., BCOP Pharmacy Benefits Management Service

Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to April 2012) using the search terms pralatrexate and Folotyn ®. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Study	Eligibility Criteria	Interventions	Results
PROPEL Study[2] - Single arm - Open label - Multicenter n_R = 115 6 weeks duration Location: US, Europe, Canada	Inclusion: - Patients ≥18 yrs - PTCL - > 1 prior tx and recovered from toxicities - > 4 weeks since prior therapy - Eastern coop oncology group performance status ≤ 2 - ANC ≥ 1,000 - Platelet ≥ 100,000 - Tot bili < 1.5mg/dL - ALT/AST < 2.5x ULN - Cr < 1.5mg/dL Exclusion: - Prespecified T/NL-cell neoplasms - Prior allogenic stem cell transplant - Relapse <75 days after ASCT - Major surgery within 2 weeks of study entry - Investigational drugs, biologics, or devices as only prior therapy - Any conventional chemotherapy or radiation <4 weeks before study treatment	Pralatrexate 30mg/m2/wk over 3-5 minutes for 6 weeks; followed by 1 week of rest	

Response to Time to Event	IWC	IWC + PET	Local Investigator
Best response			
CR +Cru +PR	29% (N=32)	26% (N=28)	39% (N=43)
CR	10% (N=11)	14% (N=15)	16% (N=17)
CRu	1% (n=1)	0	3% (n=3)
PR	18% (N=20)	12% (N=13)	21% (N=23)
SD	19% (N=21)	17% (N=18)	19% (N=21)
PD	37% (N=40)	28% (N=31)	37% (N=40)
UE	2% (N=2)	17% (N=18)	0
Missing, off treatment in cycle 1	13% (n=14)	13% (n=14)	5% (n=5)
Time to Event	32	28	43
Median time to Response, days			
First response	46	48	50
Range	37-349	37-248	38-358
Best Response	141	136	51
Range	37-726	37-542	38-542
Median duration of response, months	10.1	12.7	8.1
Median duration of response, days	306	386	246

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

AE Withdrawals: 23% (mucositis and thrombocytopenia)
Adverse effects: >10% see Adverse Effects section