Published OnlineFirst August 21, 2013; DOI: 10.1158/1078-0432.CCR-12-2251

*CCR Drug Updates*

Clinical Cancer Research

# Pralatrexate Pharmacology and Clinical Development

Enrica Marchi[1], Michael Mangone[2], Kelly Zullo[1], and Owen A. O'Connor[1]

## Abstract

Folates are well known to be essential for many cellular processes, including cellular proliferation. As a consequence, antifolates, the fraudulent mimics of folic acid, have been shown to be potent therapeutic agents in many cancers. Over the past several decades, efforts to improve on this class of drugs have met with little success. Recently, one analog specifically designed to have high affinity for the reduced folate carrier, which efficiently internalizes natural folates and antifolates, has been shown to be very active in T-cell lymphoma. Pralatrexate, approved by the U.S. Food and Drug Administration in 2009, is highly active across many lymphoid malignancies, including chemotherapy-resistant T-cell lymphoma. Emerging combination studies have now shown that pralatrexate is highly synergistic with gemcitabine, histone deacetylase inhibitors like romidepsin and bortezomib. These insights are leading to a number of novel phase I and II combination studies which could challenge existing regimens like CHOP, and improve the outcome of patients with T-cell lymphoma *Clin Cancer Res; 19(24); 6657–61. ©2013 AACR.*

## Introduction

Mammalian cells lack the ability to synthesize folates. Consequently, these hydrophilic anionic molecules must be actively transported across the cellular membrane via sophisticated carrier-mediated transport systems, which include the reduced folate carrier (RFC), the folate receptors, and the recently discovered proton-coupled folate transporter, or the soluble carrier 46A1 (SLC46A1; ref. 1). Folate derivatives are essential one-carbon donors required for the synthesis of nucleic acid precursors and several amino acids, and are therefore critical to the *de novo* synthesis of DNA and proliferation of mammalian cells. After folates were discovered to be essential for many cellular processes, the development of fraudulent mimics of folic acid began to emerge, which initially included drugs like, aminopterin and methotrexate, which were synthesized in the early 1940s (2). In 1948, aminopterin was the first drug shown to induce temporary remissions in childhood leukemia (2, 3). Soon thereafter, methotrexate became the more commonly used antifolate in the treatment of many cancers, and is to this day still considered an important component of many chemotherapy regimens for solid tumors and hematologic malignancies, including: acute lymphoblastic leukemia, lymphoma, breast cancer, osteosarcoma, primary central nervous system, and head and neck cancer. A detailed understanding of the molecular pharmacology of antifolates has led to structural analogs with markedly improved activity, which includes the recently U.S. Food and Drug Administration (FDA)-approved agent, pralatrexate.

**Authors' Affiliations:** [1]Department of Medicine, Center for Lymphoid Malignancies, Columbia University Medical Center; and [2]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, New York

**Corresponding Author:** Owen A. O'Connor, Department of Medicine, Center for Lymphoid Malignancies, Columbia University Medical Center 51 West 51st Street, Suite 200, New York, N.Y. 10019. Phone: 212-326-5720; Fax: 212-326-5725; E-mail: oo2130@columbia.edu

**doi:** 10.1158/1078-0432.CCR-12-2251



## Pharmacology

Pralatrexate (10-propargyl-10-deazaaminopterin) is a novel antifolate belonging to a class of molecules known as 10-deazaaminopterins (4). Similar to other antifolates, pralatrexate inhibits the recycling of 5,10 methylene tetrahydrofolate, which is required for the synthesis of thymidylate, by inhibiting the conversion of dihydrofolate (DHF) to tetrahydrofolate (THF) through the inhibition of dihydrofolate reductase (DHFR). DHFR converts DHF to THF, a reduced form of folate, which is a cofactor required for the synthesis and catabolism of methionine, serine, and glycine, as well as the synthesis of purines, mediating the methylation of nucleic acids and synthesis of thymidine monophosphate (TMP). The metabolic inhibition of DHFR by pralatrexate results in depletion of TMP and other precursors essential for DNA and RNA synthesis, resulting in cell-cycle arrest and apoptosis (Fig. 1). Pralatrexate was rationally designed to have high affinity for the RFC and folylpolyglutamate synthase (FPGS), leading to enhanced and selective intracellular internalization and retention in tumor cells (5). RFC is an oncofetal protein known to be highly expressed in embryonic and malignant tissues (6, 7). A number of oncogenes are known to upregulate the transporter, including c-myc and ras, making RFC an ideal target for cancer drug development. Interestingly, in one study, a punch biopsy of the skin from a patient with human T-cell lymphotrophic virus (HTLV)-1 adult T-cell lymphoma/leukemia (ATLL) showed that pralatrexate induced apoptosis only in those T cells marking positive for TAX (i.e., those positive for the HTLV-1 virus), and not in those surrounding normal cells that were not ATLL. This simple observation

Published OnlineFirst August 21, 2013; DOI: 10.1158/1078-0432.CCR-12-2251



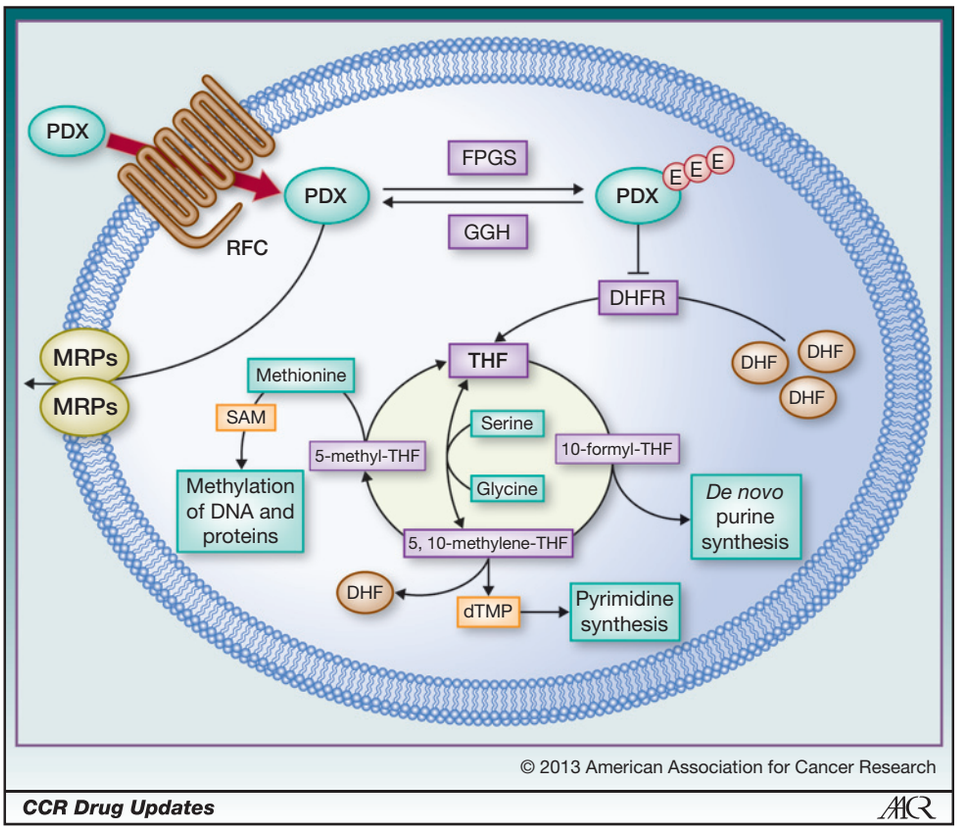


Figure 1. Pralatrexate (PDX) inhibits folate-mediated one-carbon metabolism. Pralatrexate is actively transported across the cellular membrane through the RFC, a member of the solute carrier transmembrane protein family. Retention in the cytoplasm depends upon polyglutamylation (PDX-E) of the antifolate compound, which is catalyzed by FPGS. Conversely γ-glutamyl hydrolase (GGH) removes glutamate groups from the antifolate causing the efflux of pralatrexate into the extracellular space via multidrug resistance-related protein (MRP)-like ATPase. Intracellular pralatrexate competitively inhibits DHFR. The reduction of DHF molecules via DHFR into THF is an essential prerequisite to folate-mediated one-carbon metabolism in the cell. THF and its family of cofactors (10-formyl-THF; 5,10 methylene-THF; 5-mthyl-THF) contribute to the biosynthesis of nucleic acid precursors (purines, pyrimidines), amino acids (methionine, serine, and glycine), and maintenance of methylated DNA and proteins (SAM). Pralatrexate disrupts several necessary metabolic cellular processes by targeting the upstream folate interconverting enzyme - DHFR.

supports the contention that pralatrexate has selectivity not just for T cells, but also for malignant T cells in a patient (8). Like other folate derivatives and antifolates, pralatrexate enters cells via the RFC, after which it is polyglutamated by FPGS in the cytosol. The polyglutamylated forms of pralatrexate are then retained in the cytoplasm. The polyglutamylated derivatives of pralatrexate more potently inhibit DHFR. In virtually every enzymatic kinetic metric studied, consistently showed that pralatrexate is superior to methotrexate and other antifolates by at least one log. For example, the $K_m$ of pralatrexate and methotrexate for RFC are 0.3 and 4.8 mol/L, respectively, whereas the $V_{max}/K_m$ values (rate of intracellular transport) are 12.6 (pralatexate) and 0.9 (methotrexate; ref. 9). These data establish that the rate of pralatrexate influx is nearly 14-fold more than that of methotrexate. Following a similar pattern, the $K_m$ of pralatrexate and methotrexate for FPGS are 5.9 and 32.3 mol/L, respectively, whereas the $V_{max}/K_m$ for FPGS is 23.2 (pralatrexate) and 2.2 (methotrexate; Table 1; ref. 9). These biochemical data similarly support a greater potential for pralatrexate to be polyglutamylated compared with other traditional antifolates. The favorable results from the enzyme kinetic experiments established the rationale for further study across malignant disease.

## Preclinical Data

### Pralatrexate used as single agent

Initial *in vitro* studies in the NCI cancer cell panel showed that pralatrexate was potently cytotoxic across a broad panel of cancer cell types, including solid tumors and hematologic malignancies. The activity of pralatrexate was subsequently compared with methotrexate against five lymphoma cell lines including: RL (transformed follicular lymphoma), HT, SKI-DLBCL-1 (diffuse large B cell), Raji (Burkitt), and Hs445 (Hodgkin disease). Pralatrexate showed more than 10-fold greater cytotoxicity than methotrexate in all cell lines as predicted by the RFC-binding assay results ($IC_{50}$ pralatrexate = 3–5 nmol/L, $IC_{50}$ methotrexate = 30–50 nmol/L). The activities of pralatrexate and methotrexate were also compared *in vivo* against three established NHL

Published OnlineFirst August 21, 2013; DOI: 10.1158/1078-0432.CCR-12-2251



**Table 1.** $V_{max}$ and $K_m$ of antifolates for RFC, FPGS, and DHFR

| Antifolate | DHFR Inhibition $K_i$ (pmol/L) | Influx $K_m$ (mmol/L) | Influx $V_{max}$ | $V_{max}/K_m$ | FPGS $K_m$ (mmol/L) | FPGS ($V_{max}$) | $V_{max}/K_m$ | Reference |
|---|---|---|---|---|---|---|---|---|
| Aminopterin | 4.9 ± 1 | 1.2 ± 0.2 | 3.6 ± 1.0 | 3 | 5.8 ± 1 | 117 | 20.2 | Sirotnak and colleagues (9) |
| Methotrexate | 5.4 ± 2 | 4.8 ± 1.0 | 4.1 ± 1.2 | 0.9 | 32.2 ±5 | 70 | 2.2 | Sirotnak and colleagues (9) |
| Edatrexate | 5.8 ± 1 | 1.1 ± 0.1 | 3.9 ± 0.9 | 3.5 | 6.3 ± 1 | 65 | 10.3 | Sirotnak and colleagues (9) |
| Pralatrexate | 13.4 ± 1 | 0.3 ± 0.1 | 3.8 ± 1.3 | 12.6 | 5.9 ± 1 | 137 | 23.2 | Sirotnak and colleagues (9) |

xenograft mouse models (HT, RL, and SKI cells injected subcutaneously). Pralatrexate consistently exhibited statistically superior inhibition of tumor growth compared with methotrexate (10). Recently, the activity of pralatrexate has been investigated in multiple myeloma. Pralatrexate induced concentration-dependent apoptotic cell death in a subset of human myeloma cell lines (HMCL) via induction of the intrinsic pathway, exhibiting a 10-fold greater potency compared with methotrexate. The sensitivity to pralatrexate correlated with higher relative levels of RFC mRNA expression in the sensitive HMCLs compared with resistant HMCLs. In addition, pralatrexate was also effective *in vivo* in an HMCL xenograft mouse model (11). From the *in vitro* assays to preclinical mouse models, the activity of pralatrexate has been noted to be consistently superior to all antifolates against which it was compared.

### Pralatrexate used in combination

The cytotoxicity of pralatrexate has been investigated in combination with classic chemotherapeutic agents in preclinical studies. It has been well established that methotrexate synergizes with cytarabine [1-h-D-arabinofuranosylcytosine (cytarabine)] in a schedule-dependent manner. The activity of pralatrexate plus gemcitabine was compared with the standard combination of methotrexate plus cytarabine (12). *In vitro* and *in vivo* models showed that the sequenced combination of pralatrexate followed by gemcitabine was superior to sequenced methotrexate followed by cytarabine. In addition, the sequenced pralatrexate–gemcitabine combination was significantly more potent at inducing apoptosis in diffuse large B-cell lymphoma. To further evaluate the activity of pralatrexate in combination with other active drugs, our group investigated the effects of combining pralatrexate with the proteasome inhibitor, bortezomib (13, 14). *In vitro*, pralatrexate and bortezomib independently exhibited concentration- and time-dependent cytotoxicity against a broad panel of T-cell lymphoma cell lines. However, the combination of pralatrexate and bortezomib synergistically induced apoptosis and caspase activation across the panel of T-cell lymphoma lines studied. Studies on healthy donor peripheral blood mononuclear cells showed that the combination of pralatrexate and bortezomib was not more toxic than the single agents, suggesting a highly favorable therapeutic index for the combination. Western blot assays for proteins involved in growth and survival pathways showed that p27, NOXA, histone 3 (H3), and RFC were all significantly modulated by the combination. In a transformed cutaneous T-cell lymphoma (CTCL) mouse model, the cohort that received pralatrexate along with bortezomib exhibited a significantly greater reduction in tumor volume compared with cohorts that received either drug alone and the control. These data suggest that pralatrexate in combination with bortezomib represents a novel and potentially important platform for the treatment of T-cell malignancies. As a result of these preclinical studies, a phase I/II clinical trial is currently planned.

## Clinical Development

As described above, preclinical data indicate that pralatrexate is significantly more potent than methotrexate in a wide array of tumor cell types, and especially across all lymphoid cell lines studied. These data led the investigators to study the activity of pralatrexate in patients with lymphoma (Table 2). The initial phase I trial was opened using pralatrexate at a dose of 135 mg/m$^2$, which was the maximum tolerated dose (MTD), previously defined in patients with lung cancer (15). Pralatrexate was given at this dose every other week in patients with relapsed/refractory Hodgkin and non-Hodgkin lymphoma (NHL). All 16 patients treated experienced stomatitis on this dose and schedule, with a majority of patients exhibiting grade 3 or higher (54%) toxicity. Analysis of various nutritional covariates and pharmacokinetic parameters revealed that the essentiality of the stomatitis observed was associated with elevated levels of homocysteine (Hcy) and methylmalonic acid (MMA), or an elevated area under the curve of drug exposure. Correction of the elevated Hcy and MMA with the supplementation of folic acid and vitamin B12 prevented or substantially reduced the stomatitis/mucositis in the majority of patients (16). Because of the incidence of stomatitis along with laboratory data suggesting that lower more frequent dosing was associated with a more favorable treatment outcome, the trial was amended to a weekly phase I dose-escalation regimen (every week) accompanied with vitamin B12 and folic acid supplementation. A total of 17 patients with both NHL and Hodgkin lymphoma were enrolled in this weekly study, and the MTD was determined to be 30 mg/m$^2$ given weekly for 6 out of 7 weeks. This dosing schedule was examined further in another 24 patients in the phase II portion of the study, with a substantially improved tolerance and interesting clues into its activity. Overall, 48 patients were treated on this trial with a

Published OnlineFirst August 21, 2013; DOI: 10.1158/1078-0432.CCR-12-2251



**Table 2.** Clinical trial results using pralatrexate as a single agent in hematologic malignancies

| | | | Response rates | | | |
|---|---|---|---|---|---|---|
| **Reference** | **Description** | **Patients (*n*)** | **ORR%** | **CR%** | **MDR (mo)** | **CI** |
| O'Connor and colleagues (17) | Ph II-I-II: NHLs | 48 | 31 | 17 | 6 | 18–46 |
| | B-cell lymphoma subset | 20 | 5 | 0 | 1.5 | 0.1–25 |
| | T-cell lymphoma subset | 26 | 54 | 31 | 6.5 | 33–74 |
| PROPEL study | Ph II: relapsed or refractory PTCL | 109 | [a]29 | 11 | 10.1 | 21–39 |
| Horwitz and colleagues (21) | Ph I: relapsed or refractory CTCL | 54 | 41 | 5.5 | N/A | 27.6–55 |

Abbreviations: MDR, median duration of response; mo, months.

[a]This ORR is based upon rigorous independent response review. The investigator-assessed response rate was 39%.

wide range of lymphoma diagnoses. The overall response rate (ORR) was 31% with a complete remission (CR) rate of 17% and a 95% confidence interval (CI) 18% to 46%. The majority of the responses were seen in patients with a T-cell lymphoma, including: peripheral T-cell lymphoma (PTCL) nitric oxide synthase, anaplastic large cell lymphoma, and angioimmunoblastic T-cell lymphoma. Of particular interest was the ORR seen in patients with T-cell lymphoma, which was 54% with a 95% CI of 33% to 74%, which when compared with the ORR of 5% observed among patients with B-cell lymphoma, suggested a possible selectivity of the T-cell malignanicies (17). Interestingly, 4 of the first 5 patients had T-cell lymphoma and achieved a CR within the first cycle of treatment. This trial established the specific activity of pralatrexate in T-cell lymphomas at the dose level of 30 mg/m$^2$ given as a single agent on a 6 out of 7-week schedule (18). The success of this treatment schedule among the subset of patients with T-cell lymphoma led to an expanded, confirmatory phase II study.

The registration directed multicenter study PROPEL (Pralatrexate in Relapsed or Refractory Peripheral T-cell Lymphoma) enrolled 115 patients with T-cell lymphoma. In general, the patient population was heavily pretreated with a median of 3 prior treatment regimens (range of 1–12) including 18 patients with a prior autologous transplant (19). Interestingly, 20% of the patients had received more than 5 lines of prior therapy. The majority of the patients exhibited aggressive, refractory disease (53%), whereas 25% of the patients never experienced a response to any therapy, consistent with primary refractory PTCL. In addition, 10% of these patients were diagnosed with mycosis fungoides, a rare and challenging subtype of NHL typically from studies in T-cell lymphoma (20). The treatment schedule consisted of administering pralatrexate at 30 mg/m$^2$/week for 6 out of 7 weeks. All patients received folic acid and vitamin B12 supplementation as well. On the basis of an independent response review, an ORR of 29% was noted, with 9 patients (11%) achieving a CR or a CR unconfirmed. A 95% CI of 29 to 39 was also achieved during this study. Remarkably, the heavily pretreated group consisting of patients receiving two or more prior therapies including prior autologous stem cell transplantation experienced a favorable response rate of 30%. Four responding patients went on to definitive therapy with stem cell transplant. Also of interest was the investigator-assessed response of 39%, which included a CR rate of 18%. At the time, this was the largest prospective study ever conducted in patients with relapsed or refractory PTCL. The PROPEL trial led to the FDA approval of pralatrexate for the treatment of relapsed and refractory T-cell lymphoma in October 2009.

Given the specific T-cell activity of pralatrexate, a phase I clinical dose-reduction trial was initiated for patients with relapsed or refractory CTCL (21). The primary objective of the study was to identify the optimal dose and schedule of pralatrexate for patients with this disease subtype. Because of the indolent nature of CTCL, a dose-deescalation study was designed with the intent of finding the least toxic-effective dose for this population. In the dose-finding cohort, 31 patients with CTCL received various dosages and schedules of pralatrexate. Similar to the previous trials, the most common treatment-related adverse event (all grades) was mucositis (58%), which was dose limiting (grade 2) in 8 patients (26%). A total of 11 responses were observed, including 2 CRs and 9 partial responses. Among the 18 patients who received pralatrexate at a dose intensity of at least 15 mg/m$^2$/week for 3 out of 4 weeks, the ORR was 61% (11/18 patients). The results of this trial showed that pralatrexate has high activity with acceptable toxicity in patients with relapsed or refractory CTCL at the identified optimal dose and schedule of 15 mg/m$^2$ weekly for 3/4 weeks. The lack of significant hematologic toxicity or cumulative toxicity suggested that pralatrexate should be further evaluated as continuous or maintenance therapy for patients with CTCL. The positive response despite the dose reduction suggests that altering the schedule of pralatrexate administration may allow for treatment in patient populations that would be otherwise restricted.

## Advantages Over Other Agents

Pralatrexate, a compound rationally designed to be efficiently internalized in tumor cells, has been shown to be superior to methotrexate in preclinical models, and highly active in drug-resistant PTCL. As discussed previously, the

Published OnlineFirst August 21, 2013; DOI: 10.1158/1078-0432.CCR-12-2251



increased affinity of pralatrexate for RFC and FPGS allows for rapid internalization and intracellular retention. It is believed the pharmacologic features of pralatrexate over other antimetabolites, coupled with it almost selective activity in PTCL, makes it worthy of future study with other T-cell lymphoma active drugs like romidepsin and bortezomib. Combination studies in both the preclinical and clinical setting have begun to establish that pralatrexate synergizes with a number of such agents including gemcitabine (12), bortezomib (14), and HDAC inhibitors in general (22). These observations are now being translated into phase I/II clinical trials, with the hope that the successful development of drugs with selective activity in PTCL will lead to new treatment platforms for this challenging disease.

## Disclosure of Potential Conflicts of Interest

O.A. O'Connor is a consultant/advisory board member of Allos Therapeutics, which previously marketed pralatrexate, and Millennium Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

## Authors' Contributions

**Conception and design:** M. Mangone, O.A. O'Connor
**Development of methodology:** O.A. O'Connor
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** M. Mangone, O.A. O'Connor
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** O.A. O'Connor
**Writing, review, and/or revision of the manuscript:** E. Marchi, M. Mangone, K. Zullo, O.A. O'Connor
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** M. Mangone, O.A. O'Connor

Received September 6, 2012; revised July 12, 2013; accepted July 28, 2013; published OnlineFirst August 21, 2013.

## References


1. Zhao R, Matherly LH, Goldman ID. Membrane transporters and folate homeostasis: intestinal absorption and transport into systemic compartments and tissues. Expert Rev Mol Med 2009;11:e4.
2. Farber S, Cutler EC, Hawkins JW, Harrison JH, Peirce EC II, Lenz GG. The action of pteroylglutamic conjugates on man. Science 1947;106: 619–21.
3. Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. N Engl J Med 1948;238:787–93.
4. Sirotnak FM, DeGraw JI, Chello PL, Moccio DM, Dorick DM. Biochemical and pharmacologic properties of a new folate analog, 10-deazaaminopterin, in mice. Cancer Treat Rep 1982;66:351–8.
5. DeGraw JI, Colwell WT, Piper JR, Sirotnak FM. Synthesis and antitumor activity of 10-propargyl-10-deazaaminopterin. J Med Chem 1993;36:2228–31.
6. Sweiry JH, Yudilevich DL. Transport of folates at maternal and fetal sides of the placenta: lack of inhibition by methotrexate. Biochim Biophys Acta 1985;821:497–501.
7. Goldman ID, Zhao R. Molecular, biochemical, and cellular pharmacology of pemetrexed. Semin Oncol 2002;29(6 Suppl 18):3–17.
8. Marneros AG, Grossman ME, Silvers DN, Husain S, Nuovo GJ, MacGregor-Cortelli B, et al. Pralatrexate-induced tumor cell apoptosis in the epidermis of a patient with HTLV-1 adult T-cell lymphoma/leukemia causing skin erosions. Blood 2009;113:6338–41.
9. Sirotnak FM, DeGraw JI, Moccio DM, Samuels LL, Goutas LJ. New folate analogs of the 10-deaza-aminopterin series. Basis for structural design and biochemical and pharmacologic properties. Cancer Chemother Pharmacol 1984;12:18–25.
10. Wang ES, O'Connor O, She Y, Zelenetz AD, Sirotnak FM, Moore MA. Activity of a novel anti-folate (PDX, 10-propargyl 10-deazaaminopterin) against human lymphoma is superior to methotrexate and correlates with tumor RFC-1 gene expression. Leuk Lymphoma 2003;44:1027–35.
11. Mangone M, Scotto L, Marchi E, O'Connor OA, Cho HJ. Pralatrexate has potent activity against multiple myeloma *in vitro* and *in vivo*, and activity correlates with tumor RFC-1 and DHFR expression [abstract]. In: Proceedings of the 53rd ASH Annual Meeting and Exposition; 2011 Dec 10–13; San Antonio, TX. Washington, DC: ASH; 2011. Abstract nr 1831.
12. Toner LE, Vrhovac R, Smith EA, Gardner J, Heaney M, Gonen M, et al. The schedule-dependent effects of the novel antifolate pralatrexate and gemcitabine are superior to methotrexate and cytarabine in models of human non-Hodgkin's lymphoma. Clin Cancer Res 2006; 12(3 Pt 1):924–32.
13. Zinzani PL, Musuraca G, Tani M, Stefoni V, Marchi E, Fina M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293–7.
14. Marchi E, Paoluzzi L, Scotto L, Seshan VE, Zain JM, Zinzani PL, et al. Pralatrexate is synergistic with the proteasome inhibitor bortezomib in *in vitro* and *in vivo* models of T-cell lymphoid malignancies. Clin Cancer Res 2010;16:3648–58.
15. Krug LM, Heelan RT, Kris MG, Venkatraman E, Sirotnak FM. Phase II trial of pralatrexate (10-propargyl-10-deazaaminopterin, PDX) in patients with unresectable malignant pleural mesothelioma. J Thorac Oncol 2007;2:317–20.
16. Mould DR, Sweeney K, Duffull SB, Neylon E, Hamlin P, Horwitz S, 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;86:190–6.
17. O'Connor OA, Horwitz S, Hamlin P, Portlock C, Moskowitz CH, Sarasohn D, et al. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol 2009; 27:4357–64.
18. O'Connor OA, Hamlin PA, Portlock C, Moskowitz CH, Noy A, Straus DJ, et al. Pralatrexate, a novel class of antifol with high affinity for the reduced folate carrier-type 1, produces marked complete and durable remissions in a diversity of chemotherapy refractory cases of T-cell lymphoma. Br J Haematol 2007;139:425–8.
19. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 2011;29:1182–9.
20. Foss F, Horwitz SM, Coiffier B, Bartlett N, Popplewell L, Pro B, et al. Pralatrexate is an effective treatment for relapsed or refractory transformed mycosis fungoides: a subgroup efficacy analysis from the PROPEL study. Clin Lymphoma Myeloma Leuk 2012;12:238–43.
21. Horwitz SM, Kim Y, Foss F, Zain JM, Myskowski P, Lechowicz MJ, et al. Identification of an active, well tolerated dose of pralatrexate in patients with relasped or refractory cutaneous T-cell lymphoma (CTCL). Blood 2012;119:4115–22.
22. Jain S, Scotto L, Marchi E, Kalac M, Amengual J, Buitrago JB, et al. Validation of a novel bioluminescent mouse model of sezary syndrome for preclinical drug screening [abstract]. In: Proceedings of the 53rd ASH Annual Meeting and Exposition; 2011 Dec 10–13; San Antonio, TX. Washington, DC: ASH; 2011. Abstract nr 2725.

Published OnlineFirst August 21, 2013; DOI: 10.1158/1078-0432.CCR-12-2251

AACR American Association for Cancer Research

Clinical Cancer Research

# Pralatrexate Pharmacology and Clinical Development

Enrica Marchi, Michael Mangone, Kelly Zullo, et al.

*Clin Cancer Res* 2013;19:6657-6661. Published OnlineFirst August 21, 2013.