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A Phase I Study of Romidepsin and Pralatrexate Reveals Marked Activity in Relapsed and Refractory T-cell Lymphoma

Running Title:
Phase I Study of Pralatrexate and Romidepsin

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Key Points

- The combination of romidepsin and pralatrexate is safe and well tolerated in patients with relapsed/refractory lymphoma.
- The combination led to an overall response rate of 71% (10/14) (4/14 CR) in patients with relapsed/refractory T-cell lymphoma.

Abstract

The peripheral T-cell lymphomas (PTCL) are a group of rare malignancies characterized by chemotherapy insensitivity and poor prognosis. Romidepsin and pralatrexate were approved by the U.S. FDA for patients with relapsed/refractory PTCL, exhibiting response rates of 25% and 29% respectively. Based on synergy of the combination in preclinical models of PTCL, we initiated a phase I study of pralatrexate plus romidepsin in patients with relapsed/refractory lymphoma (ClinicalTrials.gov (NCT01947140)). This was a single institution dose-escalation phase I study of pralatrexate plus romidepsin designed to determine the dose limiting toxicities (DLT), maximum tolerated dose (MTD), pharmacokinetic profile and response rates. Patients were treated with pralatrexate 10 mg/m^2 to 25 mg/m^2, and romidepsin 12mg/m^2 to 14 mg/m^2 on one of three schedules: (1) QWx3 Q28D; (2) QWx2 Q21D; (3) QOW Q28D. Treatment continued until progression, withdrawal of consent, or medical necessity. Response was assessed using the Lugano Classification. Twenty-nine patients were enrolled and evaluable for toxicity. Co-administration of pralatrexate and romidepsin was safe and well tolerated. There were 3 DLTs consisting of 2 Grade 3 oral mucositis and 1 Grade 4 sepsis. The RP2D was defined as pralatrexate 25 mg/m^2 and romidepsin 12 mg/m^2 QOW. Twenty-three patients were evaluable for response. The ORR across all patients was 57% (13/23); and in PTCL was 71% (10/14). The phase I study of pralatrexate plus romidepsin resulted in a high response rate in

patients with previously treated PTCL. A phase II study in PTCL will determine the efficacy of the combination on the QOW dose schedule.

Introduction

PTCL is a group of rare heterogeneous malignancies with an aggressive course, characterized by relative insensitivity to conventional chemotherapy, and an inferior prognosis compared to their B-cell counterparts(1, 2). Front-line therapy has been extrapolated from experiences treating B-cell lymphoma, and is predicated on a CHOP based backbone (cyclophosphamide, doxorubicin, vincristine, and prednisone)(3). Modest attempts to improve outcome have been made by adding agents like etoposide, and/or by consolidating responses with autologous stem cell transplantation (4, 5). The lack of randomized studies for these approaches makes it difficult to precisely quantitate the clinical benefit, though most believe the effect on survival is marginal.

Over the past 8 years, 3 new classes of drugs have been approved for the group of diseases recognized as peripheral T-cell lymphoma (PTCL). The novel anti-folate pralatrexate was the first drug approved for patients with relapsed or refractory PTCL in 2009(6). Four histone deacetylase (HDAC) inhibitors have been approved including vorinostat, romidepsin, belinostat, and chidamide (approved in China)(7-13). The antibody drug conjugate Brentuximab vedotin was approved in one subtype of PTCL, anaplastic large T-cell lymphoma (14). The HDAC inhibitors and pralatrexate exhibit near lineage-specific activity with limited-to-no activity in B-cell lymphomas. As single agents in the relapsed setting romidepsin and pralatrexate exhibit response rates of 25-38% and 29-54% respectively across published phase I and II studies(7-10, 15). While these studies are not identical in their patient composition, they included patients who are heavily pretreated from a diversity of PTCL subtypes. A recent case match control

analysis has demonstrated that patients treated with pralatrexate on PROPEL achieve a statistically significant survival advantage when compared to a matched historical population(16). In addition, sub-analysis of patients treated on PROPEL revealed that response and time-to-event metrics (duration of response (DOR) and progression free survival (PFS)) with pralatrexate improved as the therapy was used earlier in their treatment course, with a CR, PFS and DOR of 17%, 8 months and not reached (at two years) in second line(17). Patients achieving a response to romidepsin also exhibited a prolonged DOR of 28 months, with the median DOR not being reached in patients achieving complete response (CR)(18).

Rather than merely adding new agents to CHOP (19-22), our group pioneered the concept of creating novel platforms according to the following principles: (1) translating drugs uniquely approved in PTCL found to be synergistic in preclinical models of TCL; (2) exploring the merits of integrating drugs targeting the molecular derangements seen in PTCL; and (3) integrating complementary agents based on our evolving understanding of the mechanism of synergy (23-26). One example vetted in preclinical models was the combination of pralatrexate and romidepsin (24). These data established that the two drugs demonstrated potent synergy at dose levels 50% of their MTD. We translated these findings into a phase I clinical study of the combination of pralatrexate and romidepsin in patients with relapsed or refractory lymphoma. Herein we report these findings.

Methods

Study design and patients

This was a single institution, open-label, 3+3 dose-escalation Phase 1 study aimed to assess safety, tolerability, and early activity of response for the combination of pralatrexate and romidepsin. In addition, the trial was designed to explore schedule and pharmacokinetic profile. Patients were enrolled at the Center of Lymphoid Malignancies at Columbia University Medical

Center, New York, NY, USA under an institutional review board approved protocol. The study was conducted according to the provisions of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice, and was registered with ClinicalTrials.gov (NCT01947140). All patients were provided written informed consent. Eligible patients were required to have histologically confirmed relapsed or refractory lymphoma, of any subtype, or myeloma. There was no upper limit for the number of prior therapies. Patients may have relapsed after autologous or allogeneic stem cell transplant. Inclusion criteria were as follows: evaluable disease, age ≥ 18 years, Eastern Cooperative Group performance status ≤ 2, negative pregnancy test for females of childbearing potential; adequate contraception; and adequate organ and marrow function. Patients were ineligible if they had: central nervous system disease or lymphomatous meningitis; took concomitant CYP3A4 inhibitors; had a history of any severe cardiac abnormalities; were HIV positive, or had active hepatitis A, B, or C. Patients were eligible if that had received romidepsin or pralatrexate in the past.

Procedures

Patients were treated with pralatrexate (Spectrum Pharmaceuticals) and romidepsin (Celgene Corporation) administered intravenously on one of three treatment schedules including: (Cohort 1) days 1, 8 and 15 on a 28-day schedule (QW x 3 Q28D); (Schedule A) days 1 and 8 on a 21-day cycle (QWx2 Q21); and (Schedule B) days 1 and 15 on a 28-day treatment cycle (QOW Q28) (Figure 1a). All patients received 1 mg of folic acid orally daily starting 7 days prior to initiation of study drugs and 1000 mcg of vitamin B12 intramuscularly once every 8-10 weeks per FDA label. Cohorts of 3 patients were enrolled at pralatrexate doses starting at 10 mg/m^2 incrementally escalated to 25 mg/m^2, and romidepsin 12 mg/m^2 escalated to 14 mg/m^2. Dose escalations commenced for each schedule if less than 33% of patients experienced a dose limiting toxicity (DLT).

Treatment continued until disease progression, voluntary withdrawal of consent, or because of medical necessity. Once a DLT was identified, 3 additional patients were recruited to that cohort. If a second DLT was observed, this cohort was determined to be the maximum administrable dose (MAD) and the escalation was halted. No intra-patient dose escalations were allowed. The maximum tolerated dose (MTD) was defined as the dose level at which one-third or less patients experienced a DLT. Standard supportive treatment was allowed including antiemetics, antidiarrheal, antipyretics, anti-histamine, analgesics, antibiotics, and blood products. Leucovorin (15 mg orally twice a day on days 3-6) was permitted following cycle 1.

Blood samples for safety and pharmacokinetic analyses were taken on days 1, 8, 15 and 22 during cycle 1 and on days of study drug administration in subsequent cycles. The last study visit was 4 weeks after the last dose of study drug administration. All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Patients receiving 1 dose of drug were considered evaluable for toxicity and DLT determination. DLTs were determined in cycle 1 only. DLTs were defined as: any missed dose within cycle 1 and/or toxicity that is possibly related to drug, occurring up to 7 days after completion of cycle 1 that results in a delay of initiating cycle 2; Grade 4 neutropenia that does not resolve to ≤ Grade 2 within ≤ 7 days; Grade 3 febrile neutropenia (ANC<1000/mm^3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour); Grade ≥3 thrombocytopenia associated with clinically important bleeding or lasting ≥ 7 days, or Grade 4 thrombocytopenia that necessitates a platelet transfusion or does not resolve within 7 days;, Grade 5 (death) hematologic toxicity; any Grade ≥3 non-hematologic toxicity, with the specific exception of nausea, vomiting, diarrhea, or dehydration lasting > 48 hours in the setting of inadequate compliance with supportive care measures; acidosis or alkalosis that responds to medical intervention and returns to ≤ Grade 2 within 48 hours; elevation of liver function tests or amylase without clinical symptoms lasting ≤ 5 days; hypocalcemia, hypokalemia,

hypomagnesemia, hyponatremia, or hypophosphatemia that responds to medical intervention; and Grade 3 hypercholesterolemia, hypertriglyceridemia, constipation and fatigue. All adverse events, both drug-related and non-drug-related, were monitored for 4 weeks after discontinuation of study treatment. Staging with CT or PET-CT were performed as well as mSWAT (severity-weighted assessment tool) for patients with cutaneous involvement(27). Response assessments were performed every 2 cycles through the first 6 cycles, and then at the treating physician's discretion but no more than at 6 month intervals until progression. All patients were monitored after discontinuation of study treatment for both survival and subsequent lines of therapy, where possible.

Statistical analysis

The study employed a 3+3 dose-escalation design to assess safety, and tolerability of pralatrexate plus romidepsin. All patients were included in the safety analysis. The primary objective was to the determine MTD and DLT of the combination in patients with relapsed or refractory lymphoma and multiple myeloma. Secondary objectives included describing overall response rate (ORR) (complete remission [CR] plus partial remission [PR]), PFS and DOR. Response was determined using clinical parameters, CT or PET-CT, bone marrow biopsy and mSWAT as defined by the guidelines of the International Harmonization Project Group 2014 Revised Response Criteria(28). Patients considered evaluable for response were required to have received at least two cycles of therapy.

Descriptive statistics were used to summarize patient's demographic, baseline characteristics, prior therapies, safety and efficacy measures. Summary statistics for continuous variables included mean +/- standard deviation and/or median (inter-quartile range); categorical variables were reported as frequency counts and percentages. Time-to-event endpoints such as overall survival (OS) and PFS were estimated using Kaplan-Meier method and group comparison were

assessed using two-sided log-rank test and Cox regression for estimating the hazard ratios (95% CI). OS was defined as time from first treatment to death or last date of contact. PFS was measured from time of first treatment to progression/death or to the date of transitioning treatment. DOR was measured from time of first response to progression/death and summarized as medians (interquartile range). All the analyses were performed in SAS (v. 9.4, Cary, NC), using a type I error of 0.05

Pharmacokinetic Analysis

To define the pharmacokinetic profile of pralatrexate and romidepsin, plasma samples were collected during cycle 1 at the start of infusion, end of infusion, then at 0.5 hour (h), 1 h, 2 h, 24 h and 48 h. Non-compartmental analysis was performed using Phoenix Winnonlin software (Certara, Princeton, NJ) to define the maximum plasma concentration (Cmax), the time to maximum plasma concentration (Tmax), the terminal half-life (t½), the area under the plasma concentration time curve from t=0, to the last data point (AUC_{last}) and to infinity (AUC_{inf}) and the clearance (Cl). Paired t-tests were calculated using GraphPad Prism version 5.04 (GraphPad Soft-ware, Inc., San Diego, CA, USA).

For analytical pharmacology, romidepsin and pralatrexate were purchased from Selleck Chemicals (Houston, Texas), romidepsin-d7 from Clearsynth (Mumbai, India). All solvents and chemicals were Liquid Chromatography- Mass Spectrometry (LCMS) grade. Romidepsin and pralatrexate were extracted from blood plasma (EDTA) by mixing 50 ul of plasma with 500 ul acetonitrile/methanol. LC-MS/MS analysis was done using Agilent 6410 triple quad mass spectrometer connected to Agilent 1290 Infinity UHPLC (Santa Clara, CA). Data acquisition and peak integration was done using MassHunter software v 3.1. Quantitative measurements were done in Multiple Selected Reaction Monitoring mode using positive electrospray ionization. The assay performance was validated according to FDA guidelines(29).

Role of the funding source

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Results

Patients and treatment

As of March 1st 2017, 29 patients were enrolled on the Phase 1 study and all were evaluable for toxicity (Figure 1a). Table 1 details the demographic characteristics of the patients enrolled onto study. The median age was 54 years (23-73) and 18 (62%) were male. The median number of prior systemic therapies was 3 (range: 1-16). Histologies included Hodgkin's lymphoma (N=3), diffuse large B-cell lymphoma (N=1), Burkitt's lymphoma (N=1), indolent B-cell lymphoma (N=5), blastic plasmacytoid dendritic cell neoplasm (N=1), and T-cell lymphoma (N=18).

Initially, the protocol was designed to administer both drugs on days 1, 8 and 15 on a 28-day schedule (Figure 1). Although there were no DLTs in the initial cohort, two of the three patients enrolled did not meet the platelet threshold for treatment on cycle 1 day 15 and therefore their treatment was held that day (N=3) (Figure 1b). The protocol was subsequently revised to explore dosing on one of two schedules (A or B) through alternate assignment. On Schedule A, patients were treated on days 1 and 8 on a 21-day cycle (QWx2 Q21) (N=11), and on Schedule

B, patients were treated on day 1 and day 15 on a 28-day treatment cycle (QOW Q28) (N=15). For patients treated on Schedule A, at all dose levels, thrombocytopenia continued to result in held treatment doses (Figure 1c). This was not observed for patients treated on Schedule B with the exception of cohort 3B when the romidepsin dose was increased to 14 mg/m^2 (Figure 1d).

Safety

Most adverse events were Grade 1 or 2. The most common Grade 1-2 toxicities included nausea (66%), fatigue (52%), anorexia (24%), diarrhea (24%), and fever (24%). The most common Grade 3 toxicities included anemia (29%), oral mucositis (14%) thrombocytopenia (14%), and neutropenia (10%). Five Grade 4 toxicities were observed including thrombocytopenia (14%), neutropenia (10%), sepsis (7%), and fever and pneumonia (3%) (Table 2). Growth factor support was allowed beyond cycle 1 but no patients required or received growth factor support and there was no recurrence of grade 3-4 neutropenia in any patient treated beyond cycle 1. There were no effects seen on electrocardiogram or treatment-related deaths. All patients recovered from adverse events within 1-2 weeks of study drug administration. Dose reductions occurred in 5 patients in cohorts 3A and 4A. There were 2 patients in Cohort 3A who required dose reductions of romidepsin from 14 mg/m^2 to 12 mg/m^2, one for neutropenia and one for thrombocytopenia. There were 3 patients in Cohort 4A who required dose reductions of pralatrexate from 20 mg/m^2 to 15 mg/m^2 as follows: 2 patients experienced Grade 3 mucositis, the third patient did not experience any toxicity but was dose reduced per protocol as Cohort 4A was determined to be the maximum administered dose. As a result this last patient required a dose reduction to the MTD to continue on study. The median number of cycles completed was 4 (range 1-12).

Table 3 presents the DLTs per dose cohort and disease sub-type. There were 5 DLTs in total in cohort 3 on both schedule A and B (pralatrexate 15mg/m^2 and romidepsin 14mg/m^2), consisting of 3 Grade 4 thrombocytopenia, one Grade 4 pancytopenia and one Grade 4 neutropenia attributed to the romidepsin. Based on the cytopenias attributed to romidepsin, the romidepsin dose was reduced to 12 mg/m^2 for all cohorts while the pralatrexate dose was escalated per protocol which eliminated the recurrence of thrombocytopenia. There were 3 DLTs in cohort 4A (pralatrexate 20mg/m^2 and romidepsin 12mg/m^2, QWx2 Q21D) consisting of two Grade 3 oral mucositis and one Grade 4 sepsis. Schedule A was closed to enrollment and the MTD on this schedule was determined to be pralatrexate 15 mg/m^2 and romidepsin 12 mg/m^2 QWx2, Q21D. Schedule B continued with dose escalation of pralatrexate with no DLTs in cohorts 4B and 5B. The MTD for Schedule B was not reached and the recommended phase 2 dose was determined to be pralatrexate 25 mg/m^2 and romidepsin 12 mg/m^2 on QOW Q28.

Efficacy

Twenty-three patients were evaluable for response (Figure 2b). Four patients achieved a CR (17%, all with PTCL), seven patients achieved a PR (30%), four had stable disease (17%) and 6 had progression of disease (26%). Among the T-cell lymphoma patients, 10 of 14 (71%) achieved a response with 4 of the 14 achieving a complete response (29%). An additional 2 patients with T-cell lymphoma exhibited stabilization of their disease. Figure 2B depicts the waterfall plot for all patients on study. Three of four follicular lymphoma patients achieved a response (all PR). The median time to response was 2 cycles or 1.6 months, and responses were observed across all treatment schedules (Table 3).

The PFS, OS and DOR were calculated for all patients enrolled onto the study and further analyzed as a function of the histologic subtype (Figure 3). The median PFS for the entire population was 3.7 months (1.4-10.8), while the PFS for patients with non-T-cell and T-cell

lymphoma were 1.8 (95% CI: 3.5 – N/A) and 4.4 months (95% CI: 1.2 – N/A) respectively. The median OS for the T-cell lymphoma and non-TCL patients was 12.4 months (95% CI: 8.1- N/A) 34.0 months (95% CI: 9.7 – N/A) respectively. Figure 3D depicts the duration of treatment, DOR, and time to first response for all evaluable T-cell lymphoma patients. The median DOR was 4.29 months (IQR 2.97-6.98). Five of the 14 (36%) patients had a durable response lasting 6 months or greater.

Pharmacokinetic Analysis

First dose pharmacokinetic analysis for pralatrexate and romidpesin was evaluated in 27 patients. Figure 4 summarizes the pharmacokinetic (PK) parameters and average serum concentrations for pralatrexate and romidepsin. The mean C_{max} for patients receiving pralatrexate 25 mg/m^2 was 8373.8 ng/mL or 17.5 μM (IC_{50} in lymphoma cell lines = 2.0-23 nM)(30). Romidepsin 14 mg/m^2 demonstrated a mean C_{max} of 591.2 ng/mL or 1.1μM (IC_{50} in T-cell lymphoma cell lines = 1.2-1.6 nM)(31) .

Pharmacokinetic profiles from patients who received pralatrexate 15 mg/m^2 in conjunction with romidepsin at 12 mg/m^2 were compared to those treated with romidepsin 14 mg/m^2. No difference was detected when the effects of romidepsin were tested against pralatrexate. When comparing the influence of pralatrexate on romidepsin, PK parameters were compared among patients who received romidepsin 12 mg/m^2 with varying doses of pralatrexate. Notably, a statistically significant difference was noted in C_{max}, $t_{1/2}$ and plasma levels of romidepsin at 4h between patients receiving pralatrexate 10 mg/m^2 (n=3) vs. pralatrexate 25 mg/m^2 (n=5), with patients receiving pralatrexate 25 mg/m^2 having slightly higher concentration of romidepsin (p=0.045, 0.044, and 0.045, respectively). Additionally, $AUC_{0\rightarrow\infty}$ and C_{max} of pralatrexate and romidepsin were compared to historical PK data from single agent studies of each drug. In this study, patients who received pralatrexate 25 mg/m^2 had a mean C_{max} and $AUC_{0\rightarrow\infty}$ of 8373.8 ng/mL and 6646.6 ng*h/mL, while patients who were exposed to single agent pralatrexate at 30

mg/m^2 had values of 5815 ng/mL and 4464.2 ng*h/mL, respectively(6). Comparing the same PK parameters for romidepsin 14 mg/m^2 cohort to the single agent romidepsin PK data available from the NCI 1312 study, romidepsin values were higher in our population (C_{max} and $AUC_{0\rightarrow\infty}$ 591.2 ng/mL and 2459.6 ng*h/mL vs. 427.0 ng/mL and 1899 ng*h/mL)(9). It is possible that the co-administration leads to an increase in the relative exposure of each drug compared to what has been seen by the single agents, explaining in part the benefit seen at lower doses.

Discussion

The prospect of creating novel platforms to treat T-cell lymphoma predicated on principles we outlined above offers promise in developing strategies that are not CHOP predicated. The challenge lies in identifying the doses and schedules of drugs that do not exacerbate the toxicities of the single agent, while retaining the synergy demonstrated in preclinical models. Both pralatrexate and romidepsin produce thrombocytopenia, which creates pause in thinking about how these drugs should be combined. Fortunately, the thrombocytopenia seen with these agents is short-lived and reversible, owing to the fact they are likely not toxic to megakaryocytes as is seen with conventional chemotherapy drugs. Patients who completed therapy and required additional treatment were able to do so without any lasting sequelae from the combination. Interestingly, thrombocytopenia emerged with only a relatively small increase in romidepsin from 12 mg/m^2 to 14 mg/m^2. Grade 1-3 mucositis was appreciated on the weekly schedule, albeit at levels that appeared substantially lower compared to the PROPEL study (32). A modest schedule adjustment from weekly to every other week abrogated mucositis as a DLT. Schedule A (QWx2 Q21) was associated with DLTs of mucositis and sepsis but no DLTs were observed for Schedule B (QOW Q28) when the romidepsin dose was maintained at 12 m/m^2 or less. The MTD was not reached on Schedule B and the recommended phase 2 dose (RP2D) was determined to be pralatrexate 25 mg/m^2 and romidepsin 12 mg/m^2 on QOW Q28. This dose and schedule was very well tolerated.

As predicted by the preclinical data, the combination of these two agents produced a high level of activity in patients with T-cell lymphoma. Despite a very heavily treated patient population, which included patients who had previously been treated with these agents in the past, and many who were treated at early dose cohorts, the combination exhibited an overall response rate of 71% (10/14), compared to an ORR of 33% (3/9) among the non-T-cell lymphoma patients. Six of the 14 evaluable PTCL patients had received either an autologous (N = 6) or allogeneic (N= 1) stem cell transplantation. The median time to response was rapid, the median DOR, PFS and OS were 4.29, 4.4 months and 12.4 months respectively, with one of these patients being successfully bridged to an allogeneic transplant. Interestingly, responses were observed across all dose levels, perhaps underscoring the synergistic activity of romidepsin in combination with pralatrexate.

The pharmacokinetic data provide important insights into the disposition of these drugs when given in combination in this population. These data suggest that the plasma concentrations achieved in the combination were slightly higher compared to historical single agent exposure and warrants further investigation. Slight increases in doses correlated with increased toxicity which was most pronounced when romidepsin was increased from 12 to 14 mg/m2 leading to thrombocytopenia. The conspicuous lack of mucositis especially on the QOW schedule, raises interesting questions regarding mechanism. This study (beyond Cycle 1) provided provisions for leucovorin on Days 3-6 (15 mg orally twice daily), which appears to substantially reduce the risk of pralatrexate associated mucositis with no impact on its efficacy(33).

Albeit early, these data coupled with compelling preclinical data, support the contention that novel combinations of drugs highly active in PTCL can be combined safely with a meaningful signal of activity. This combination is now being explored in a multicenter Phase 2 study. The strategy of defining unique doublets active in PTCL, and leveraging the recent promising advances in experimental drug development, offers an opportunity to reconfigure the paradigm

of care for patients in both the upfront and relapsed or refractory setting. Creating novel doublet platforms opens the prospect for the creation of novel triplet based combinations, exploiting novel biological agents deemed active in T-cell lymphoma.

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Authorship Contributions

JEA, AS and OAO conceived and designed the study. JEA, OAO, RL, JL, EL, KK, LA, HK, SC, CD, MF, LS, LF, EM, MK, AR and AS acquired the data. JEA, RL, JL, CC, SC and OAO analyzed and interpreted the data. JEA, RL, JL and OAO wrote the paper.CC performed the statistical analysis.

Disclosure of Conflicts of Interest

All authors have no disclosures.

References

1. Abouyabis AN, Shenoy PJ, Lechowicz MJ, Flowers CR. Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. Leukemia & lymphoma. 2008;49(11):2099-107.
2. Abouyabis AN, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A Systematic Review and Meta-Analysis of Front-line Anthracycline-Based Chemotherapy Regimens for Peripheral T-Cell Lymphoma. ISRN hematology. 2011;2011:623924.
3. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma. New England Journal of Medicine. 1993;328(14):1002-6.
4. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093-9.
5. Schmitz N, Trumper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418-25.
6. 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. Journal of Clinical Oncology. 2011;29(9):1182-9.
7. Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol. 2009;27(32):5410-7.
8. Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol. 2010;28(29):4485-91.
9. Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood. 2011;117(22):5827-34.
10. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol. 2012;30(6):631-6.
11. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25(21):3109-15.
12. O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, et al. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol. 2015;33(23):2492-9.
13. Ning Z-Q, Li Z-B, Newman MJ, Shan S, Wang X-H, Pan D-S, et al. Chidamide (CS055/HBI-8000): a new histone deacetylase inhibitor of the benzamide class with antitumor activity and the ability to enhance immune cell-mediated tumor cell cytotoxicity. Cancer Chemotherapy and Pharmacology. 2012;69(4):901-9.
14. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol. 2012;30(18):2190-6.
15. 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(26):4357-64.

16. O'Connor OA, Marchi E, Volinn W, Kim WS. Case Match Control Analysis of Propel Reveals Survival Advantage for Patients with Relapsed/Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL) Treated with Pralatrexate. Blood. 2016;128(22):4149-.
17. O'Connor OA, Marchi E, Kim WS. CASE MATCH CONTROL ANALYSIS OF PROPEL REVEALS A SURVIVAL ADVANTAGE FOR PATIENTS WITH RELAPSED PTCL RECEIVING PRALATREXATE: A NOVEL APPROACH TO BENCHMARK DRUGS IN RARE DISEASES. Hematological Oncology. 2017;35:250-.
18. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. Journal of Hematology & Oncology. 2014;7(1):11.
19. Gallamini A, Zaja F, Patti C, Billio A, Specchia MR, Tucci A, et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood. 2007;110(7):2316-23.
20. Johnston PB, Cashen AF, Nikolinakos PG, Beaven AW, Barta SK, Bhat G, et al. Safe and Effective Treatment of Patients with Peripheral T-Cell Lymphoma (PTCL) with the Novel HDAC Inhibitor, Belinostat, in Combination with CHOP: Results of the Bel-CHOP Phase 1 Trial. Blood. 2015;126(23):253-.
21. Dupuis J, Morschhauser F, Ghesquieres H, Tilly H, Casasnovas O, Thieblemont C, et al. Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: a non-randomised, phase 1b/2 study. The Lancet Haematology. 2015;2(4):e160-5.
22. Advani RH, Ansell SM, Lechowicz MJ, Beaven AW, Loberiza F, Carson KR, et al. A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial. British journal of haematology. 2016;172(4):535-44.
23. Zullo K, Scotto L, Amengual JE, O'Connor OA. The Aurora A Kinase Inhibitor, Alisertib, Has Broad Activity In Nonclinical Models Of T-Cell Lymphoma and Is Highly Synergistic With Romidepsin, But Not With Pralatrexate Or The Proteasome Inhibitor, Ixazomib2013. 5141- p.
24. Jain S, Jirau-Serrano X, Zullo KM, Scotto L, Palermo CF, Sastra SA, et al. Preclinical Pharmacologic Evaluation of Pralatrexate and Romidepsin Confirms Potent Synergy of the Combination in a Murine Model of Human T-cell Lymphoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2015.
25. 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. Clinical cancer research : an official journal of the American Association for Cancer Research. 2010;16(14):3648-58.
26. Marchi E, Zullo KM, Amengual JE, Kalac M, Bongero D, McIntosh CM, et al. The combination of hypomethylating agents and histone deacetylase inhibitors produce marked synergy in preclinical models of T-cell lymphoma. British journal of haematology. 2015.
27. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. Journal of Clinical Oncology. 2011;29(18):2598-607.
28. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

29. Abbas E, Abelev B, Adam J, Adamova D, Adare AM, Aggarwal MM, et al. J/psi elliptic flow in Pb-Pb collisions at radical(s(NN))=2.76 TeV. Physical review letters. 2013;111(16):162301.
30. 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. Leukemia & lymphoma. 2003;44(6):1027-35.
31. Piekarz RL, Robey RW, Zhan Z, Kayastha G, Sayah A, Abdeldaim AH, et al. T-cell lymphoma as a model for the use of histone deacetylase inhibitors in cancer therapy: impact of depsipeptide on molecular markers, therapeutic targets, and mechanisms of resistance. Blood. 2004;103(12):4636-43.
32. 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.
33. Tedeschi PM, Kathari YK, Farooqi IN, Bertino JR. Leucovorin rescue allows effective high-dose pralatrexate treatment and an increase in therapeutic index in mesothelioma xenografts. Cancer Chemotherapy and Pharmacology. 2014;74(5):1029-32.

Tables

Table 1: Demographic Features of Study Populations

Table 2: Toxicities Occurring in >5% of Study Population

Table 3: Patient Characteristics, Toxicity and Outcomes as a Function of Cohort

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Figure 1: Schematic of Study Design, Patient Disposition and Thrombocytopenia as a Function of Schedule Dose. A) Screening and enrollment data for all patients. B-D) Platelet trend over time. Platelet re-treated parameter is 50,000/uL. B) Cohort 1 patients treated with pralatrexate 10 mg/m^2 and romidepsin 12 mg/m^2 on days 1, 8, 15 Q28 days. C) Cohorts treated on schedule A: pralatrexate 15-20 mg/m^2 and romidepsin 12-14 mg/m^2 days 1, 8 q 21 days. D) Cohorts treated on schedule B: pralatrexate 15-25 mg/m^2 and romidepsin 12-14 mg/m^2 days 1, 15 q 28 days.

Figure 2: Summary of Response Rates Across Study Population for Patients Treated with Romidepsin and Pralatrexate. A) Response rates by disease sub-type. B) Waterfall plot representing percent change of tumor growth following treatment depicted by disease sub-type.

Figure 3: Progression Free and Overall Survival as a Function of Treatment in Study Population. Curves on the left represent all patients who received study drug (N=29) and confidence intervals, curves on the right are subdivided between non-T-cell (N=11) and T-cell patients (N=18). A) Median progression free survival (PFS) for All patients is 3.7 months (95% CI 1.4, 10.8); for TCL patients is 4.4 months (95% CI 3.5) and for non-TCL is 1.8 months (95% CI 1.2). B) Median overall survival (OS) for all patients is 13.8 months (95% CI 8.8, NA); for TCL

patients is 12.4 months (95% CI 8.1) and non-TCL 34 months (95% CI 9.7). C) Swimmer's Plot detailing the progression free survival of all TCL patients enrolled onto study. Start time denotes the first dose of study drugs. Stop time denotes progression of disease, change in treatment (including transplant), or death.

Figure 4: Pharmacokinetic Parameters for Pralatrexate and Romidepsin in Study Population. Concentration over time for each dose cohort of A) pralatrexate and B) romidepsin. C) Cmax, Tmax, T1/2, AUC, CI and Vobs for pralatrexate and romidepsin at each dose cohort.

Table 1. Demographic Features of Study Populations

Demographics	N=29
Age (years)	54 (23-73)
Sex	
Male	18 (62%)
Female	11 (38%)
Race	
Black	8 (29%)
White	17 (59%)
Asian	3 (10%)
Other	1 (3%)
Ethnicity	
Hispanic	7 (24%)
Non-Hispanic	22 (76%)
Disease Type	
B Cell Lymphomas	**7 (24%)**
Burkitt's	1 (3%)
DLBCL	1 (3%)
Follicular	5 (17%)
T Cell Lymphomas	**18 (62%)**
ATLL	6 (21%)
ALCL ALK (-)	3 (10%)
Sezary Syndrome	2 (7%)
CTCL	1 (3%)
CD4+ T-Cell	1 (3%)
Hepatosplenic T-Cell	1 (3%)
Intestinal T-Cell	1 (3%)
NK T-cell	1 (3%)
PTCL	1 (3%)
SPTL-AB	1 (3%)
Other	**4 (14%)**
Blastic plasmacytoid dendritic cell neoplasm (BPDCN)	1 (3%)
Hodgkin's Lymphomas	3 (10%)
Prior Therapies	3 (1-16)
CHOP/RCHOP/CHOEP/EPOCH/HYPERCVAD	24 (83%)
Experimental Therapies - Clinical Trials	11 (38%)
Gemcitabine Based - GEM/GemiFOX/GemOX/GVD	9 (31%)
HDAC Inhibitors	9 (31%)
Alkylator Based - Benda/CTX/CVP	8 (28%)
Platinum Based - RICE/ICE/DHAP/ESHAP	7 (24%)
Radiation	7 (24%)
Biologics - Bexarotene/Ublituximab/Rituxan	7 (24%)
Autologous Stem Cell Transplant	6 (21%)
MTX/SMILE	5 (17%)
ABVD/ABV-COPP/MOPP	4 (14%)
Brentuximab Vedotin	4 (14%)
Lenalidomide Based	4 (14%)
Phototherapy - light/PUVA	3 (10%)
Pralatrexate	2 (7%)
Allogeneic Transplant	1 (3%)

Values are presented as frequency (%) or median (min-max)

Table 2. Toxicities Occurring in > 5% of Study Population

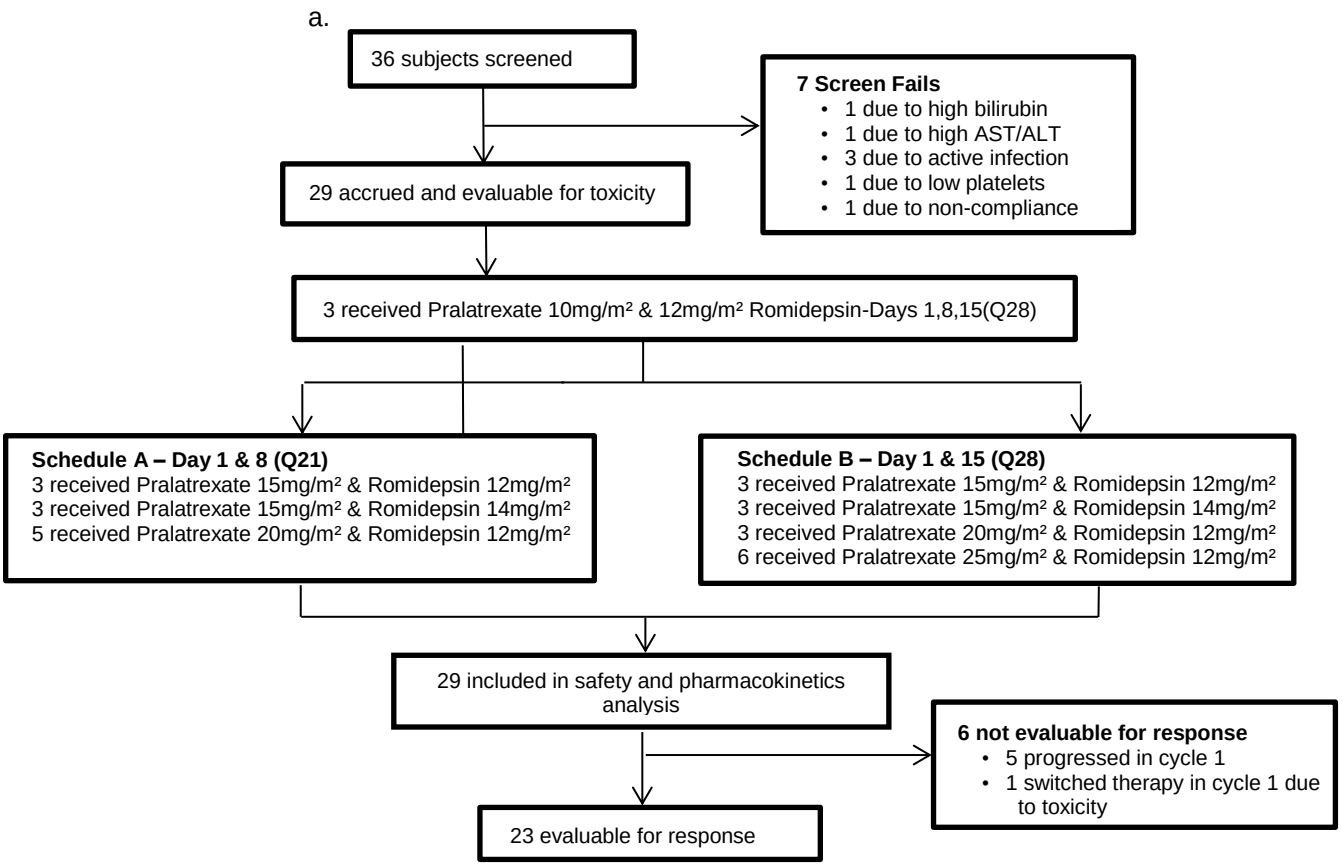
Adverse Event	Grade 1-2	Grade 3	Grade 4
Abdominal Pain	5 (19%)	1 (3%)	
Allergic Rhinitis	3 (10%)		
Anemia		7 (29%)	
Anorexia	7 (24%)		
Anxiety	3 (10%)		
Back Pain	3 (10%)		
Constipation	5 (19%)		
Cough	6 (21%)		
Dehydration	2 (7%)	1 (3%)	
Diarrhea	7 (24%)	1 (3%)	
Dizziness	2 (7%)		
Dysgeusia	2 (7%)		
Dyspnea	2 (7%)		
Edema	4 (14%)		
Epistaxis	3 (10%)		
Fatigue	15 (52%)		
Febrile Neutropenia		2 (7%)	2 (7%)
Fever	7 (24%)		1 (3%)
Gastroesophageal reflux disease	2 (7%)		
Gastrointestinal disorders	1 (3%)	1 (3%)	
Headache	3 (10%)		
Hyponatremia		2 (7%)	
Laryngitis	2 (7%)		
Mucositis oral	5 (19%)	4 (14%)	
Nasal congestion	3 (10%)		
Nausea	19 (66%)		
Neutropenia		1 (3%)	1 (3%)
Pain	6 (21%)		
Pain in extremity	2 (7%)		
Pneumonia		1 (3%)	1 (3%)
Pruritus	2 (7%)		
Rash maculo-papular	2 (7%)		
Sepsis			2 (7%)
Sore throat	2 (7%)		
Stomach pain	2 (7%)		
Thrombocytopenia	2 (7%)	4 (14%)	4 (14%)
Upper respiratory infection	2 (7%)		
Urinary tract infection	2 (7%)		
Vomiting	6 (21%)	1 (3%)	

Table 3. Patient Characteristics, Toxicity and Outcome as a Function of Cohort

Cohort	Patient	Disease Subtype	Prior Lines of Therapies/Past Romidepsin or Pralatrexate	Toxicities	Best Response
1 10mg/m2 Pralatrexate 12mg/m2 Romidepsin Days 1,8,15(Q28)	1	ALCL Alk (-), Multiple Myeloma, MF	6 (asct)	No DLT	CR
	2	Hodgkin's Lymphoma	14 (asct)	No DLT	SD
	3	Intestinal T-Cell Lymphoma	1/Romidepsin	No DLT	PR
2a 15mg/m2 Pralatrexate 12mg/m2 Romidepsin Days 1 & 8(Q21)	1	T-Cell Lymphoma	2	No DLT	PR
	2	ATLL	2	No DLT	CR
	3	Follicular Lymphoma	4/Pralatexate	No DLT	PR
2b 15mg/m2 Pralatrexate 12mg/m2 Romidepsin Days 1 & 15(Q28)	1	CD4+ T-Cell Lymphoma	1	No DLT	PR
	2	Follicular Lymphoma	9	No DLT	NE
	3	Follicular Lymphoma	3	No DLT	PR
3a 15mg/m2 Pralatrexate 14mg/m2 Romidepsin Days 1 & 8(Q21)	1	SPTL-AB	2	DLT - (Pancytopenia, Plts=4)	PR (PET neg)
	2	Burkitt's Lymphoma	3	DLT - (Neutropenia, ANC=0.244)	POD
	3	Follicular Lymphoma	5	DLT - Thrombocytopenia, Plts=17)	PR
3b 15mg/m2 Pralatrexate 14mg/m2 Romidepsin Days 1 & 15(Q28)	1	PTCL	2	No DLT	CR
	2	DLBCL, CML	3	DLT - (Thrombocytopenia, Plts=10)	NE
	3	ALCL, ALK (-)	2	DLT - (Thrombocytopenia, Plts=3)	NE
4a 20mg/m2 Pralatrexate 12mg/m2 Romidepsin Days 1 & 8(Q21)	1	Hodgkin's Lymphoma	16 (asct)/ Romidepsin and Pralatrexate	No DLT	POD
	2	Sezary Syndrome	5/Romidepsin	DLT - (Grade 3 Oral Mucositis)	POD
	3	ATLL	3	DLT - (Grade 4 Sepsis)	NE
	4	ATLL	3	DLT - (Grade 3 Oral Mucositis)	PR
	5	CD30+ ALK(-) ALCL	2 (asct)	No DLT	CR
4b 20mg/m2 Pralatrexate 12mg/m2 Romidepsin Days 1 & 15(Q28)	1	Hodgkin's Lymphoma	12 (asct & allo)/ Romidepsin	No DLT	POD
	2	BPDCN	1	No DLT	SD
	3	ATLL	3 (asct)	No DLT	POD
5b 25mg/m2 Pralatrexate 12mg/m2 Romidepsin Days 1 & 15(Q28)	1	ATLL	2	No DLT	PR
	2	Follicular Lymphoma	2/Romidepsin	No DLT	POD
	3	CTCL	2/Romidepsin	No DLT	SD
5b Safety Expansion	4	NK T cell	2	No DLT	NE
	5	Sezary Syndrome	5	No DLT	NE
	6	ATLL	1	No DLT	SD

Figure 1. Schematic of Study Design, Patient Disposition and Thrombocytopenia as a Function of Schedule Dose

a.



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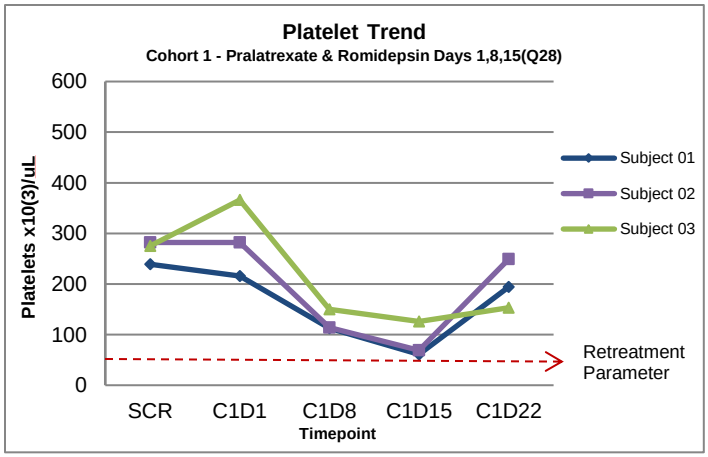

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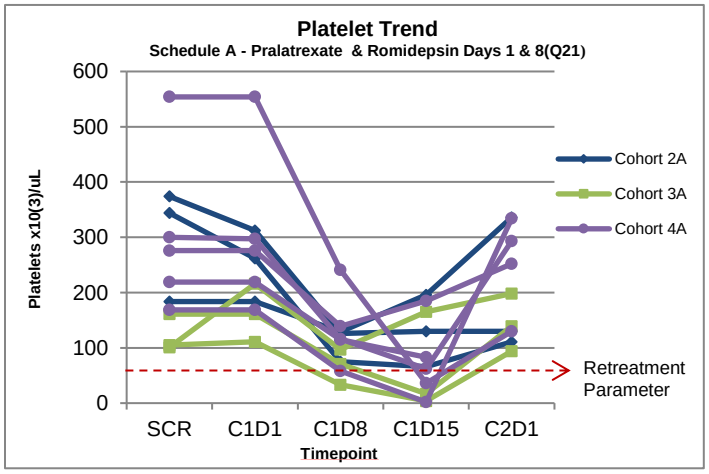


d.

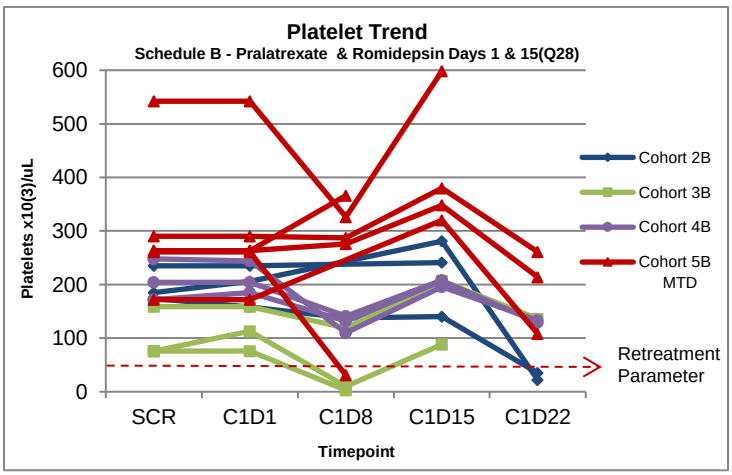


Figure 2. Summary of Response Rates Across Study Population for Patients Treated with Romidepsin and Pralatrexate

a.

Parameter	Number
Total # of Patients (evaluable)	29 (23)
All patients ORR	13/23 (57%)
All patients ORR CR	4/23 (17%)
All patients ORR PR	9/23 (39%)
non-TCL ORR	3/9 (33%)
non-TCL CR	0/9 (0%)
non-TCL PR	3/9 (33%)
T-Cell ORR	10/14 (71%)
T-Cell CR	4/10 (40%)
T-Cell PR	6/10 (60%)

b.

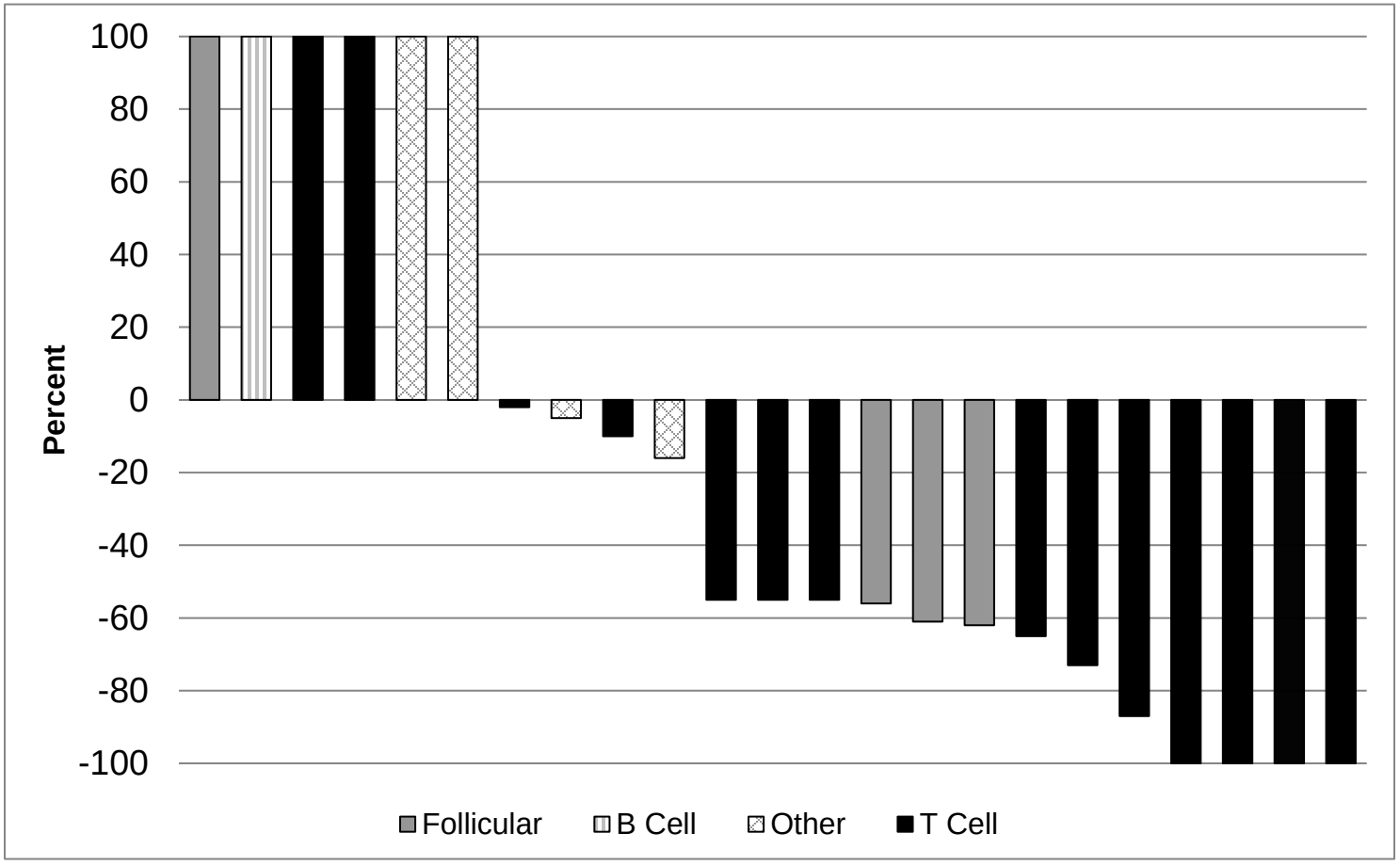
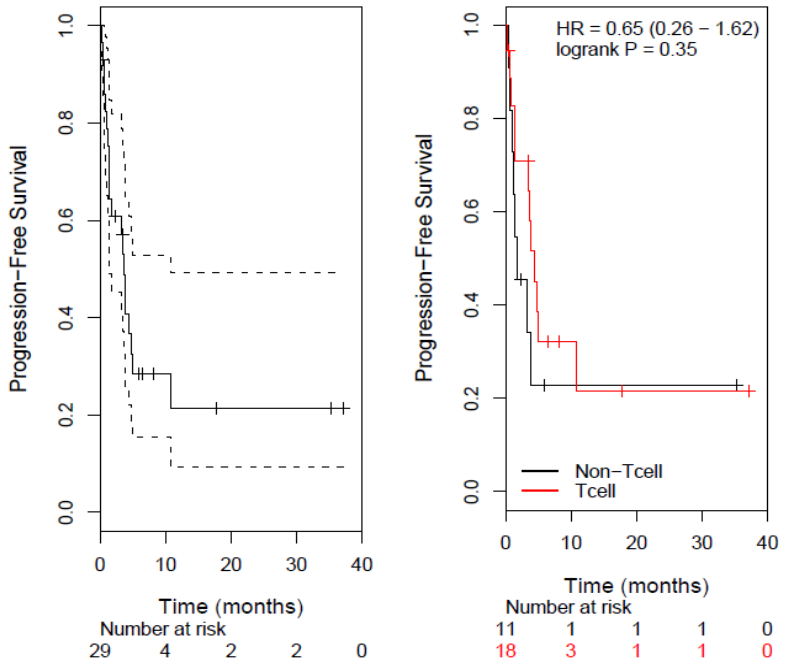


Figure 3. Progression Free and Overall Survival Curves as a Function of Treatment in Study Population

a.



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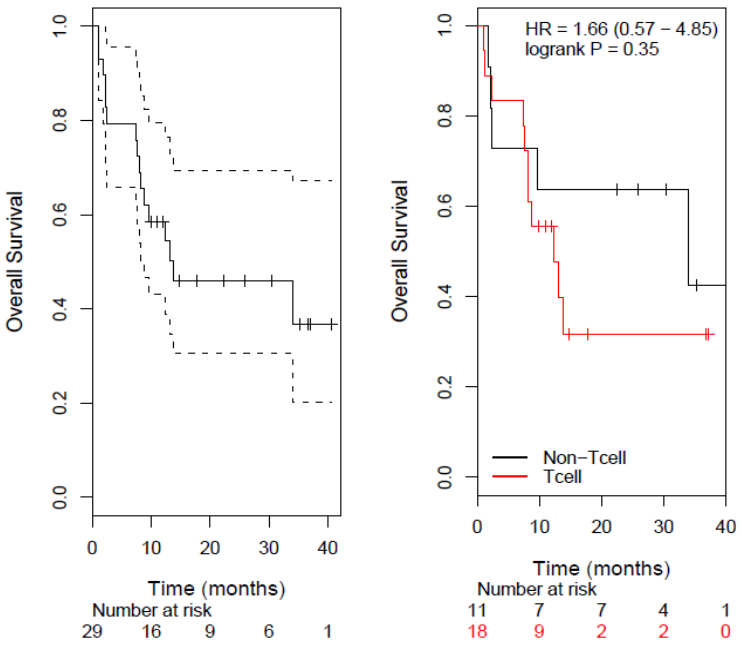

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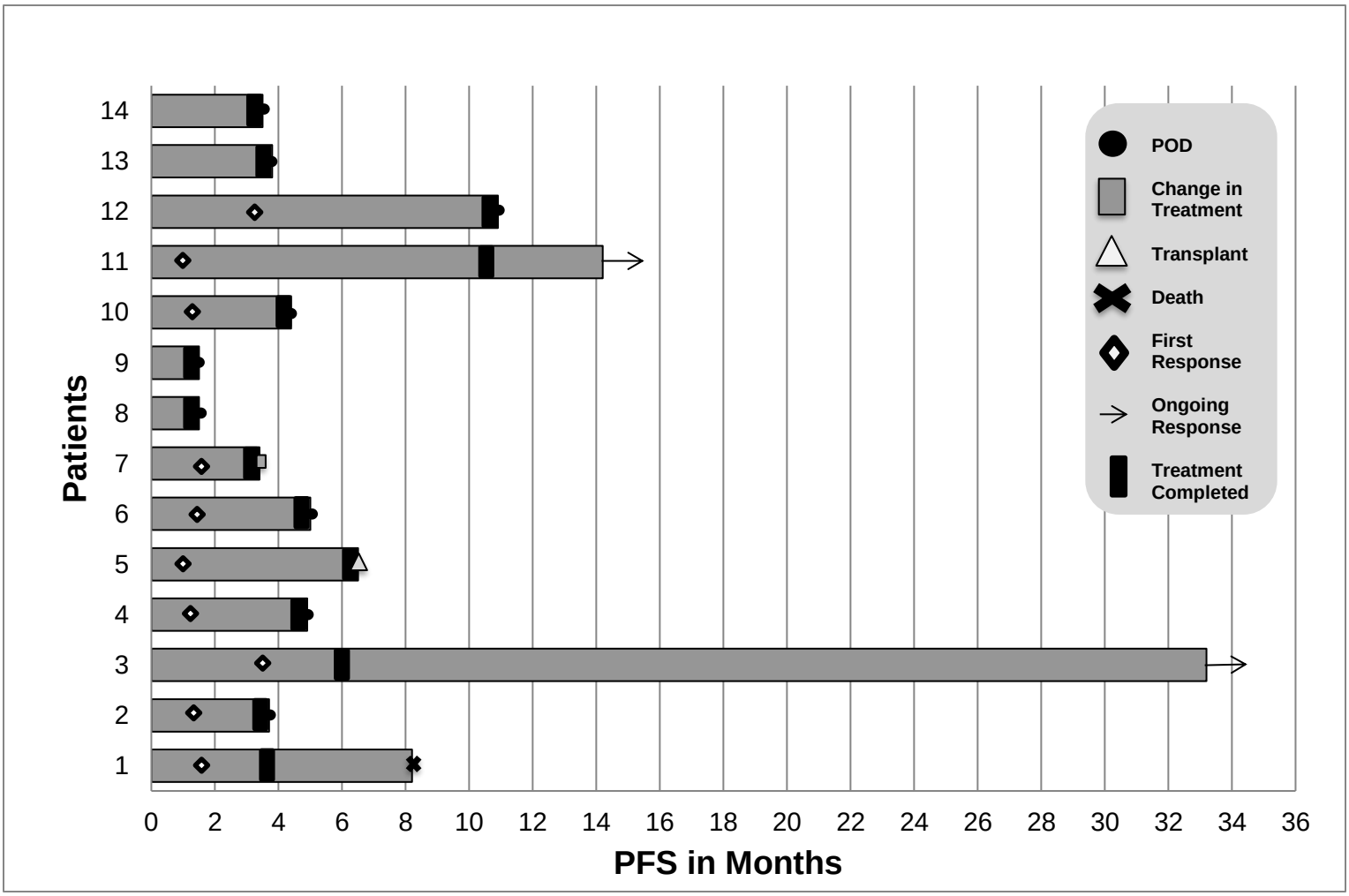

Figure 4. Pharmacokinetic Parameters for Pralatrexate and Romidepsin in Study Population

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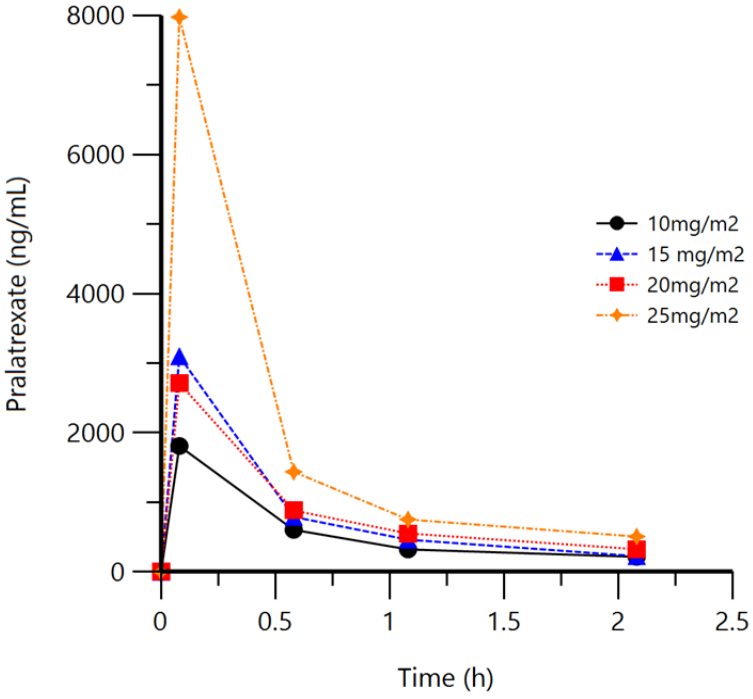

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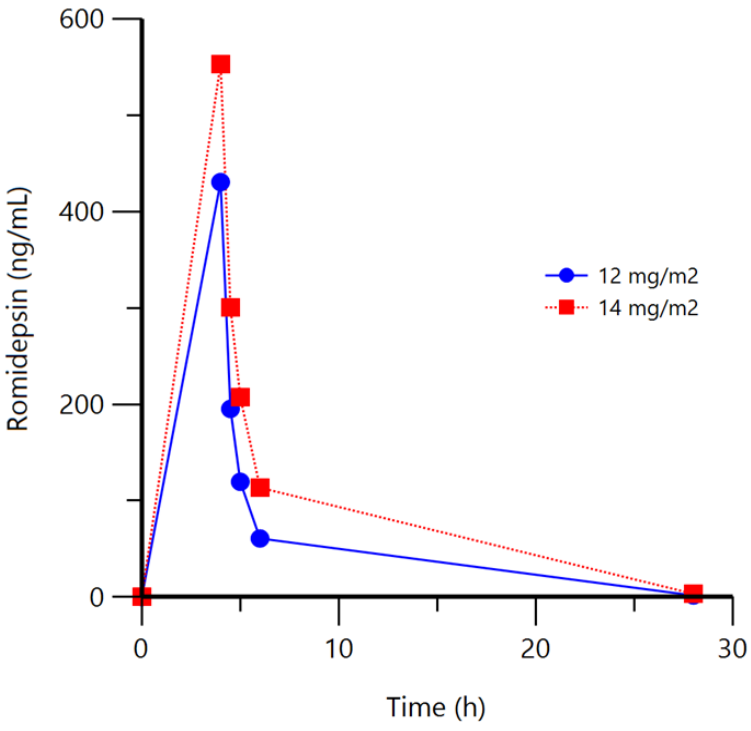

c.

	n	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\rightarrow\infty}$ (h*ng/mL)	Cl (mL/h)	V_{obs} (mL)
Pralatrexate 10 mg/m^2	3	1809.5 +/- 1302.2	0.08	4.0 +/- 0.03	2488.4 +/- 1315.5	10052.11 +/- 7387.6	46956.6 +/- 1302.2
Pralatrexate 15 mg/m^2	11	2876.0 +/- 1088.6	0.12 +/- 0.1	3.2 +/- 1.0	2872.6 +/ - 1450.8	12854.7 +/- 7734.5	34866.1 +/- 19642.3
Pralatrexate 20 mg/m^2	8	2713.0 +/- 1338.0	0.08	3.2 +/- 0.2	3374.4 +/- 1927.2	13261.5 +/- 4714.4	43385.7 +/- 17985.6
Pralatrexate 25 mg/m^2	5	8373.8 +/- 1964.5	0.08	3.6 +/- 0.6	6646.6 +/- 1788.2	7790.7 +/- 1629.6	25803.9 +/- 8016.6
Romidepsin 12 mg/m^2	22	419.0 +/- 259.0	4	1.7 +/ - 1.7	1378.2 +/- 1134.8	26647.8 +/- 23877.19	72003.14 +/- 57221.6
Romidepsin 14 mg/m^2	5	591.2 +/ - 332.0	4	3.6 +/- 2.7	2459.6 +/- 1856.4	21538.5 +/- 19065.2	123853.70 +/- 179019

Values are presented as mean +/- standard deviation

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A phase I study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma

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