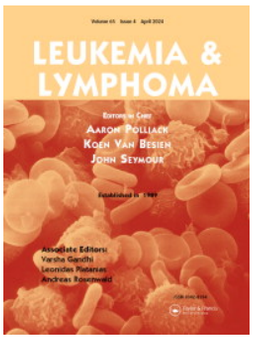

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Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ilal20

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To cite this article: Yun Kyoung Ryu Tiger, Salvia Jain, Stefan K. Barta, Seda Tolu, Brian Estrella, Ahmed Sawas, Jennifer K. Lue, Mark M. Francescone, Barbara Pro & Jennifer E. Amengual (22 Mar 2024): Phase II study of the novel antifolate agent pralatrexate in combination with the histone deacetylase inhibitor romidepsin for the treatment of patients with mature T-cell lymphoma, Leukemia & Lymphoma, DOI: 10.1080/10428194.2024.2329996

To link to this article: https://doi.org/10.1080/10428194.2024.2329996

Published online: 22 Mar 2024.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2024.2329996

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ORIGINAL ARTICLE

Phase II study of the novel antifolate agent pralatrexate in combination with the histone deacetylase inhibitor romidepsin for the treatment of patients with mature T-cell lymphoma

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ABSTRACT

Previously, we conducted a Phase I study of the combination of pralatrexate and romidepsin in patients with relapsed/refractory (R/R) lymphomas and subsequently conducted a multicenter Phase II study in patients with untreated or R/R mature T cell lymphomas (MTCL). Patients received pralatrexate 25 mg/m^2 and romidepsin 12 mg/m^2 every 2 weeks. Fourteen patients were evaluable for efficacy. Overall response rate was 35.7% with CR in 14.3% and disease control in 50%. The mDOR was 8.2 months, mPFS was 3.6 months, and mOS was 20.2 months. Gastrointestinal side effects were most common in up to 33%; there was only one hematologic toxicity of grade 3 anemia. Combining results of MTCL patients from the Phase I and II studies ($N = 28$), the ORR was 53.5% with CR in 21.4%, disease control in67.8%, and DOR of 7.2 months. The combination was safe however does not out-perform other combination strategies.

Trial Registration: www.clinicaltrials.gov (NCT 01947140).

ARTICLE HISTORY
Received 15 November 2023
Revised 28 February 2024
Accepted 8 March 2024

KEYWORDS
Chemotherapeutic approaches; lymphoma and Hodgkin disease; clinical results; T-cell lymphoma; epigenetics; antifolate

Introduction

Mature T-cell lymphomas (MTCLs) comprise a heterogeneous group of rare non-Hodgkin lymphomas (NHL) making up approximately 5–10% of all NHL [1]. More than 30 established and provisional entities of MTCL are recognized by the World Health Organization [2]. The most common subtypes are PTCL-not otherwise specified (PTCL-NOS, accounting for 30% of MTCLs), angioimmunoblastic TCL (AITL, 15–30%), anaplastic large-cell lymphoma (ALCL, 15%), and extranodal natural killer TCL (ENKTCL, 10%) [3,4]. One of the more rare subtypes, adult T-cell leukemia/lymphoma (ATLL), makes up 7% of all T cell lymphoma. ATLL is an extremely aggressive disease with 5-year OS of 23.4% and median survival of 11 months [3,5].

Over the past 15 years, novel targeted therapies have made a significant impact in the care of patients with MTCL [6–10]. The antifolate pralatrexate, was approved for relapsed or refractory (R/R) PTCL in 2009. Theoverall response rate(ORR)with pralatrexate was reported as 29% and a complete response (CR) rate of 11% in R/RPTCL [11]. These responses translate to a progression free survival (PFS) of only 3.5 m and overall survival (OS) of 14.5 months. In a case match control analysis evaluating patients treated on the PROPEL study, pralatrexate was associated with significantly longer OS compared to matched control population treated with other approved agents(median OS 16.6 months [95% CI 11.99–25.56] vs 4.04 months [95% CI 2.83f5.78], respectively). Hazard ratio was 0.426 with pralatrexate (95% CI 0.29–0.61) [12]. One speculative explanation for why pralatrexate has enriched efficacy in TCL versus other lymphomas could be that its antifolate properties affect the 1-carbon transfer pathway thereby influencing DNA methylation, which is

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significant given the many derangements altering DNA methylation in TCL.

Epigenetic mutations are frequently found in MTCL such in TET2 and DNMT3A, which are early events in lymphomagenesis [3]. Mutated IDH2, EP300 and CREBBP, are also found in MTCL. These observations likely explain why epigenetic therapies have been successful for this disease entity [13]. HDAC inhibitors are FDA approved for R/R CTCL (vorinostat and romidepsin), and R/R MTCL (belinostat). HDAC inhibitors are pleiotropic drugs affecting multiple signaling pathways that are critical for tumor survival through post-translational modification of histone and non-histone proteins [14–17]. Single-agent romidepsin has shown to be effective in patients with R/R MTCL (ORR 25–38%, CR 5–15%), with a median duration of response (DOR) of8.9–17 months. Similar to pralatrexate, the median PFS with romidepsin is only3.5 months, with median OS ranging from7.1–14.5 months [18–22]. Romidepsin received accelerated approval in MTCL patients based on these findings but the drug was voluntarily withdrawn by the manufacturer in 2021, when a study of romidepsin in combination with CHOP as first-line therapy showed no added benefit compared to CHOP alone [23]. Nevertheless, clinicians continue to use romidepsin for challenging MTCL cases and the combination of romidepsin with many other novel therapies has proven beneficial in TCL [24,25].

Pralatrexate and romidepsin have shown encouraging efficacy in combination in preclinical models of MTCL, where mice treated with combination therapy resulted in statistically significant reduction in tumor volume compared to control or romidepsin and pralatrexate monotherapy [26]. Based on this promising result, a Phase I study examining the safety and tolerability of this combination was performed in patients with R/R lymphoma, yielding a 71% ORR PFS of 4.4 m and OS of 34 m in the TCL patients [27]. The Phase II study of this combination, was performed using the recommended phase II dose and schedule defined in the phase I study: pralatrexate 25 mg/m^{2}and romidepsin 12 mg/m^2 every other week [27]. This manuscript presents the results from the Phase II study and the results of all evaluable MTCL patients across the Phase I and II studies.

Methods

Study design

This was a multi-center, single-arm Phase II study of pralatrexate combined with romidepsin for patients diagnosed with untreated or R/R MTCL. The primary objective was efficacy. The primary endpoint was to estimate ORR, CR, and partial response rate (PR). Secondary objectives were to estimate DOR, PFS, and OS. Patients were enrolled at Columbia University Medical Center (New York, NY), Fox Chase Cancer Center (Philadelphia, PA), and Beth Israel Deaconess Medical Center (Boston, MA) 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 at www.clinicaltrials.gov (NCT01947140). All patients provided written informed consent to participate.

Study population

The inclusion criteria allowed for patients with histologically confirmed MTCL by local hematopathology review according to the WHO criteria, untreated, relapsed or refractory. There was no upper limit for the number of prior therapies. Patients who relapsed after autologous or allogeneic stem cell transplant were eligible, as were patients who had received prior treatment with either of the study drugs. Patients must have had measurable disease; age ≥ 18 years; Eastern Cooperative Group (ECOG) performance status ≤2; adequate contraception in females of childbearing age; and adequate organ and marrow function.

Exclusion criteria included known allergic reaction to the study drugs; recent chemotherapy or radiotherapy (<2 weeks; <6 weeks for nitrosureas or mitomycin C); ongoing adverse effects from prior therapy; use of other investigational agents; use of systemic corticosteroids not stabilized to equivalent of ≤10 mg/d prednisone; pregnancy or breastfeeding; concomitant use of CYP3A4 inhibitors; serious cardiac abnormalities or other serious illness; CNS involvement including lymphomatous meningitis; untreated anaplastic lymphoma kinase (ALK)-positive ALCL; untreated CTCL with the exception of untreated tumor stage mycosis fungoides; HIV-positivity; and active hepatitis B or C.

Treatment regimen

Patients were treated with pralatrexate 25 mg/m^2 and romidepsin 12 mg/m^2 administered intravenously on days 1 and 15 of a 28-day cycle (4-h infusion of romidepsin followed by pralatrexate IV push) as established in the Phase I study. As per US Food and Drug Administration guidelines, all patients also received 1 mg folic acid orally once daily starting 7 days prior to initiation of study drugs, and 1000 µg of vitamin B12 intramuscularly every 8–10 weeks during treatment. Use

of the folate analog leucovorin (15 mg orally twice daily on days 3–13 and 17–27) was permitted as prophylaxis or treatment of pralatrexate-induced mucositis. Serum potassium had to be maintained ≥3.8 mmol/L and magnesium ≥1.8 mg/dL. Ondansetron 16 mg and dexamethasone 12 mg were given intravenously prior to administration of romidepsin, which is moderately emetogenic. Standard supportive treatment was allowed, including antiemetics, antidiarrheals, antipyretics, antihistamines, analgesics, antibiotics, blood products, and colony-stimulating factors including G-CSF.

Patients were treated until disease progression, unacceptable side effects, voluntary withdrawal of consent, or investigator's decision based on adverse events or changes in patient's condition.

Evaluations

Baseline disease assessment was performed using computerized tomography (CT) or positron emission tomography (PET)/CT during the screening period prior to initiation of study drugs. For patients with cutaneous disease, a modified Severity-Weighted Assessment Tool (mSWAT) score was determined at screening [28]. Electrocardiogram was performed during the screening period.

Response was assessed by physical examination, PET/CT or CT, and tissue biopsy as per guidelines of the International Harmonization Project Group 2007 Revised Response Criteria, and mSWAT score for patients with cutaneous disease. Efficacy was assessed following cycles 3 and 6 and then at the investigator's discretion (at intervals no greater than 6 months) until disease progression was noted.CR and PR were reported using standard definitions; ORR was computed as CR + PR (best outcome in each patient).

End-of-study visit was 4 weeks after the last administered dose of study drug, with follow-up every three months for one year or until new treatment was initiated. Patients removed from study for unacceptable adverse events were followed until resolution or stabilization of the adverse event. All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Statistical analysis

For analysis of the primary endpoint (ORR), the study used a Simon's 2-stage design with the null hypothesis (ORR 25%) tested at a 5% type-1 error rate on a cohort of 24 patients. In the first stage, if less than 2 patients of 9 accrued obtained a response, the study would have been stopped for futility. The study was designed to yield a power of 80% when the true ORR is 50%. Safety analysis included all patients who received at least 1 dose of study medication.

Descriptive statistics were used to summarize patients' demographic, baseline characteristics, prior therapies, and safety and efficacy measures. Summary statistics for continuous variables including mean ± standard deviation and/or median including the interquartile range (IQR). Categorical variables were reported as frequency counts and percentages. Overall disease control rate was defined as the percentage of patients who achieved CR, PR and stable disease to intervention. Time-to-event end points (OS, PFS) were estimated using the Kaplan-Meier method. PFS was defined as the time from first treatment to progression/death or to the date of transitioning treatment. OS was defined as the time from first treatment to death from any cause. DOR was measured from the time of first response to progression/death and summarized as median (range, or IQR if specified). All analyses were performed on GraphPad (version 9.4.1) using 0.05 type-1 error.

Results

Study population

In this multicenter trial, patients were enrolled from 9/2016 to 10/2020 at three study centers. Of the planned accrual of 24 patients, 20 were screened (Figure 1), and 18 were enrolled. Two were excluded (one for ineligibility, one withdrew consent). Table 1 details the demographic characteristics of the patients enrolled in the study. The study was halted prematurely due to discontinuation of funding from the sponsoring pharmaceutical company due to change in acquisition and slow accrual during the COVID pandemic, and therefore did not reach its target enrollment. The median age was 58 years (range, 30–93 years); 12 (66.7%) were male;2 (11.1%) were black and 3 (16.7%) were Hispanic. Histologically determined TCL subtypes included PTCL-NOS ($n = 8$), nodal PTCL with T-Follicular helper phenotype or AITL ($n = 4$), ATLL ($n = 2$), subcutaneous panniculitis PTCL ($n = 2$), CTCL ($n = 1$), and ENKTCL ($n = 1$). The median number of prior systemic therapies was 2 (range, 0–7); 3 patients (16.7%) were treatment-naive. The most common prior therapies were CHOP or CHOP-like regimen with etoposide ($n = 11$) and4 patients had prior ASCT. Three patients had previously received a HDAC inhibitor (in one case, romidepsin) and one patient had previously received pralatrexate.

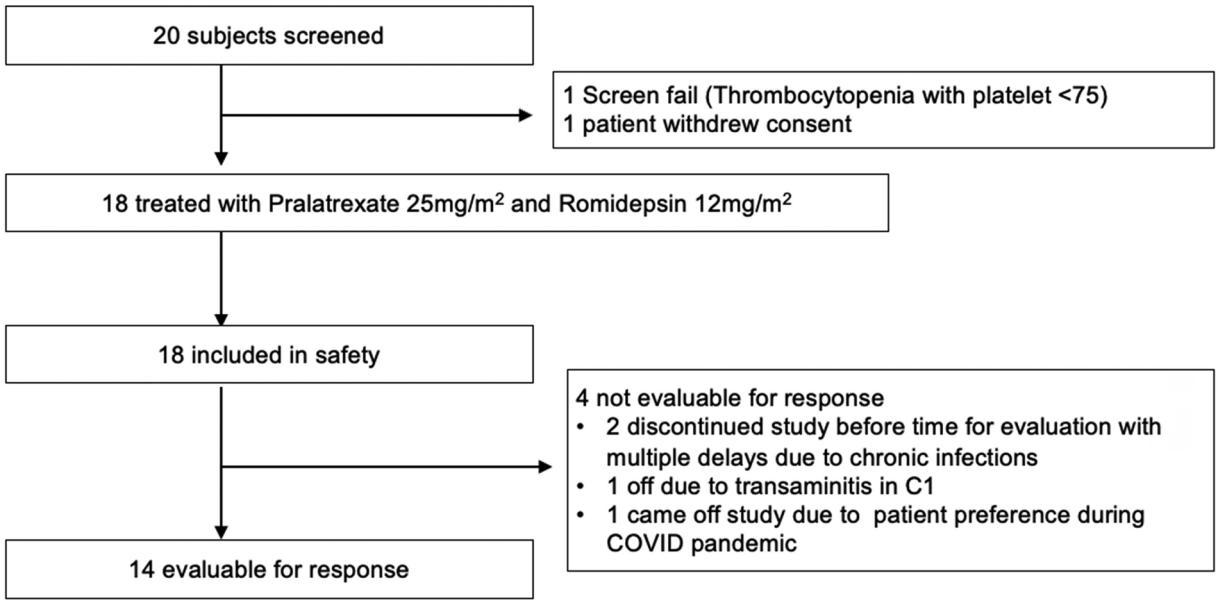

Figure 1. CONSORT diagram.

Efficacy

Fourteen of the 18 enrolled patients were evaluable for response. Four patients were excluded from evaluation, having discontinued participation prior to the first response assessment (2patients with preexisting chronic infections did not adhere to protocol-defined treatment; 1 patient was discontinued per protocol due to asymptomatic grade 1 liver toxicity that did not resolve per protocol requirements; and 1 patient chose to discontinue during the COVID pandemic).

Figure 2 depicts duration of treatment and response for all evaluable patients. The ORR in the intention-to-treat (ITT) population ($N=18$) was 27.8% ORR in the evaluable population ($N=14$) was 35.7% with overall disease control in 50% of evaluable patients. Two patients (14.3%) achieved CR (1 patient with PTLD/AITL, 1 patient with ATLL); 3 patients (21.4%) achieved PR; 2 patients (14.3%) had stable disease (SD); and 7 patients (50.0%) had disease progression. One patient who experienced a CR went on to receive an allogeneic transplant. The median number of treatment cycles was 3 (range 3–8) and the median time to response was 3 months. Four patients (28.6%) had a durable response lasting ≥6 months. In the intention-to-treat (ITT) population (18 patients), median PFS was 3.1 months (IQR 2.5–4.8 months) and median OS was 18.6 months (IQR 3.1–27.3 months) (Figure 3). In the evaluable population the median DOR was 8.2 months (IQR, 5.4–50.7); median PFS was 3.6 months (IQR2.8–5.3 months); and median OS was 20.2 months (IQR5.6–43.7 months) (Figure 3). Two of the 3 treatment naïve patients were evaluable for response with ORR of 50% (1 patient with PR, 1 patient with POD).

To better understand the efficacy of this combination in MTCL, evaluation of MTCL patients from both the Phase I and II portions of the study were evaluated together. In total, there were 36 ITT patients: 18 from Phase I (representing all dose levels) and 18 from Phase II, of whom 28 were evaluable for response assessment: 14 from each the Phase I and Phase II (Table 2). In the evaluable population, ORR was 53.5% with CR in 6 patients (21.4%), PR in 9 patients (32.1%), SD in 4 patients (14.3%) and disease progression in 9 patients (32.1%); the overall disease control rate was 67.8%. Among the responders, DOR was 7.2 months (IQR 3.6–19.1 months). In the ITT ($N=36$) population, median PFS was 3.8 months (range 0.3–67 months) and median OS was 13.8 months (range 1.1–90 months) (Figure 3).

There was an enrichment of patients with ATLL enrolled to this study. Despite this disease entity typically having a poor prognosis, ATLL patients responded as well as other TCL in the combined Phase I and Phase II population. Among 7 evaluable patients with ATLL (6 with lymphomatous subtype and 1 with acute form of ATLL), ORR was 57.1% (4 of 7) and disease control rate was 71.4% (5 of 7 patients). Two patients obtained a CR, 2 patients obtained aPR, and 1 patient with acute form of ATLL had SD. One of the patients who obtained a CR went on to receive and allogeneic stem cell transplant. The median DOR was 6.2 months (IQR4.6–18.1 months). Among all 8 ITT ATLL patients, median PFS was4.4 months (IQR2.2–7.6 months), and median OS was 12.4 months (IQR7.4–12.6 months) (Figure 4).

Table 1. Patient demographics and clinical characteristics at baseline (intention-to-treat population $N = 18$).

Demographic feature	N (%)
Age (y), median (range)	58 (30–93)
Sex	
Male	12 (66.6)
Female	6 (33.3)
Race	
Black	2 (11.1%)
White	14 (77.8%)
Other/unknown	2 (11.1%)
Ethnicity	
Hispanic	3 (16.7 %)
Non-Hispanic	14 (77.8%)
Unknown	1 (5.6%)
Disease type	
PTCL–NOS	8(44.4%)
PTCL-NOS (PTLD subtype)	1 (5.6%)
PTCL with TFH phenotype/AITL	4 (22.2%)
AITL (PTLD subtype)	1 (5.6%)
ATLL	2 (11.1%)
Subcutaneous Panniculitis PTCL	2 (5.6%)
CTCL	1 (5.6%)
NK T cell	1 (5.6%)
Number of Prior Therapies	
0	3 (16.7%)
1	4 (22.2%)
2	5 (27.8%)
3	1 (5.6%)
≥4	5 (27.8%)
Median prior therapies (range)	2 (0–7)
Prior Therapies	**N**
CHOP/CHOEP/DA-EPOCH/EPOCH	11
ASCT	4
HDAC inhibitor: Romidepsin/Belinostat/ Vorinostat	4
Pralatrexate	1
Radiation	2
Phototherapy: Light/PUVA	1
ICE	2
SMILE	1
Rituximab	1
Brentuximab	2
Bortezomib	1
Pembrolizumab	1
Other clinical trials	2
Gemcitabine based: GND/Gem-Ox-Asp/ Gem-Busulfan-Melphalan	3
IFN	1
Methotrexate	2

N = number, Y = year, PTCL-NOS = peripheral T cell lymphoma not otherwise specified; PTLD = posttransplant lymphoproliferative disorder, TFH = T follicular helper, AITL = angioimmunoblastic t call lymphoma, ATLL = adult T cell leukemia lymphoma, CTCL = cutaneous T cell lymphoma, NK = natural killer, CHOP = cyclophosphamide, hydroxydoxorubicin, oncovin, prednisone, CHOEP = cyclophosphamide, hydroxydoxorubicin, oncovin, etoposide, prednisone, DA-EPOCH = dose adjusted etoposide, prednisone, oncovin, cyclophosphamide, hydroxydoxorubicin, ASCT = autologous stem cell transplant, HDAC = histone deacetylase, PUVA = psoralen and ultraviolet radation, ICE = ifosfamide, carboplatin, etoposide, SMILE = dexamethasone, methotrexate, ifosfamide, l-asparaginase, etoposide, GND = gemcitabine, nalelbine, doxorubicin, Gem = gemcitabine, Ox = oxaliplatin, Asp = l-asparaginase, IFN = interferon.

Safety

All 18 enrolled patients received at least 1 dose of study medication and were evaluated for safety and tolerability. The study regimen was generally well tolerated, with no reports of unanticipated toxicity. Among the 18 patients, 14 experienced adverse events of any grade and only 4 patients experienced grade 3/4 toxicities (Table 3). The most common adverse events were nausea (33%), diarrhea (22%), abdominal pain (17%), and vomiting (17%), all of which were grade 1 or 2. Mucositis, a common side effect of pralatrexate was observed in only one patient (grade 2). Leucovorin was given to only 1 patient. Two patients (11%) experienced electrolyte abnormalities (grade 1 hypokalemia and grade 3 hyponatremia), and 3 patients (17%) experience darrhythmia (1 patient with grade 3;1 with grade 2 sinus tachycardias; 1 with grade 1 atrial fibrillation). There was only one hematologic adverse event of grade 3 anemia.

Serious adverse events (SAE), occurred in 4 patients, included grade 2 fever, lymph node infection, stroke, sinus tachycardia, and abdominal pain. Grade 3 SAE included appendicitis and small bowel obstruction, and grade 4 included staphylococcal bacteremia and sepsis. Of4 patients with SAEs, only 2 had SAEs at least possibly related to study drugs. The first patient was a 44-year-old man who experienced 2 SAEs including a grade 4 infection of a necrotic lymph node and palatine tonsillar abscess following cycle 2, requiring hospitalization for intravenous broad-spectrum antibiotics. Following discharge, he was readmitted for possible treatment-related sinus tachycardia. The second patient was an 89-year-old woman who developed sepsis requiring hospitalization for broad-spectrum antibiotics after the third cycle of treatment.

Discussion

MTCL is an aggressive disease that remains challenging to study due to its rarity and heterogeneous presentation. Most treatment strategies result in short disease-free intervals, especially in those who are refractory to initial chemotherapy. Newly diagnosed MTCL patients were included in the study because of the poor prognosis observed with standard frontline therapy and the promising results generated in the Phase I study. The pralatrexate plus romidepsin combination enrolled patients from a racially diverse population with a variety of MCTL subtypes at three different cancer centers. With an ORR of 53.5%, CR of 21.4%, and DOR of 7.2 months the results from the Phase I and II indicate modest efficacy. When comparing these results to the efficacy of each pralatrexate and romidepsin as single agents, there is an observed difference in ORR and CR rates (romidepsin 25–38% and 17–25%, and pralatrexate 29% and 11% respectively), however there is no improvement in the PFS with the combination. The results from the Phase II study are not as strong as that observed among the MTCL patients

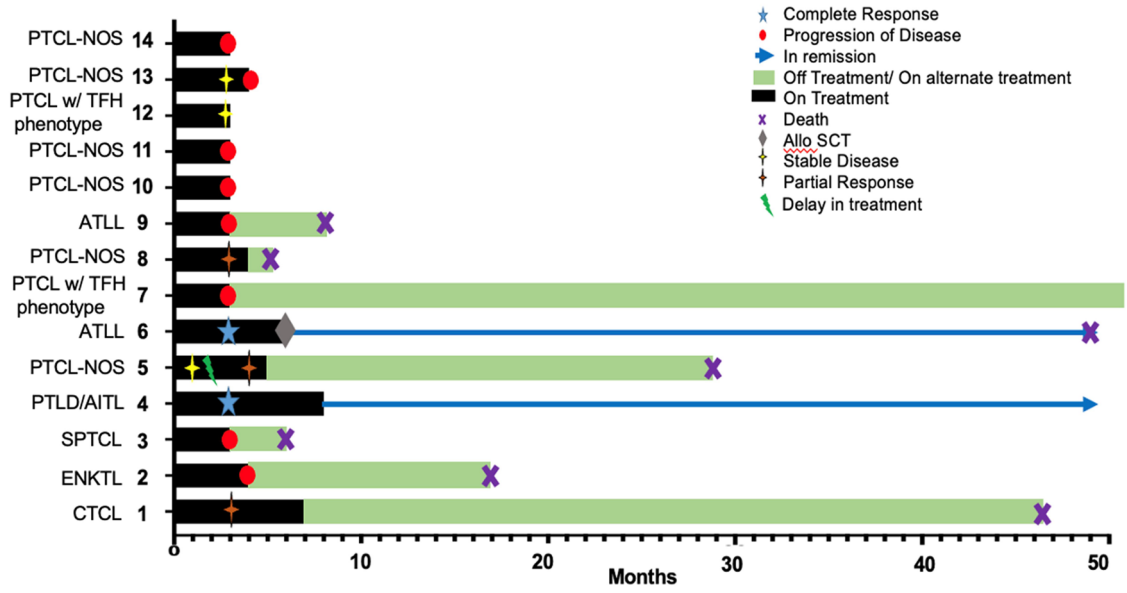

Figure 2. Swimmers Plot and Survival responses of all evaluable patients. Swimmer plot representing the duration of treatment. 14 patients were evaluable and each bar is an individual patient. Timing of first response, death and discontinuation are noted. 2 patients had complete response and 3 patients had partial response.

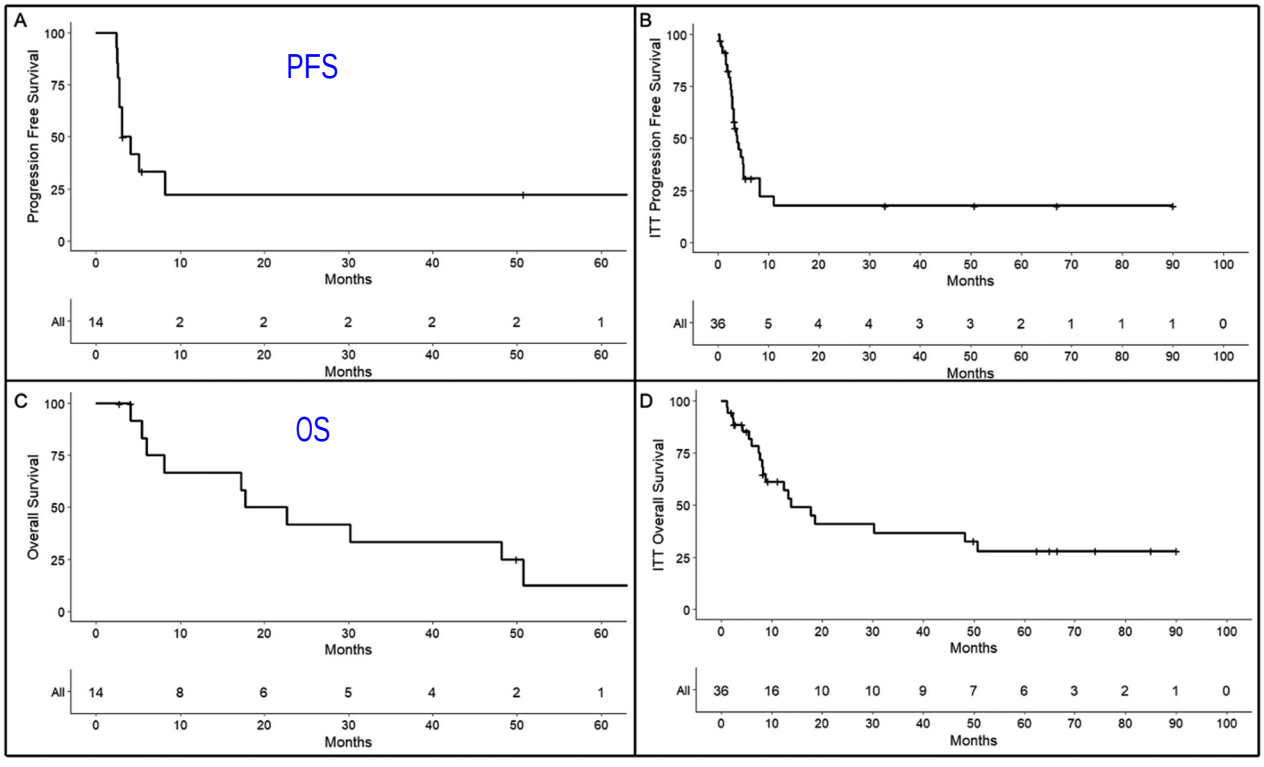

Figure 3. PFS and OS. Kaplan-Meier analysis of treatment outcomes. (A) PFS of evaluable patients from phase II (14 patients, median PFS of 3.56 months). (B) PFS of all T cell patients from phase I and phase II in an intention to treat population (36 patients, median PFS of 3.8 months). (C) OS of evaluable patients from phase II (14patients, median OS of 20.2 months). (D) OS of all T cell patients from phase I and phase II in an intention to treat population (total 36 patients, median OS of 13.8 months).

treated on the Phase I and that is likely owing to increased selection bias during the Phase I study where patients who were less of a risk to trigger a dose limiting toxicity were enrolled.

Interestingly, there was no maximum tolerated dose identified in the every 2 week dosing schedule during the Phase I portion of the study suggesting that perhaps the recommended Phase II dose could have been

Table 2. Characteristics and best response of all MTCL patients from Phase I and Phase II in an intention to treat population (*N* = 36).

Phase	Subtype of MTCL (*N* = 36)	Prior lines of therapies/Past Romidepsin or pralatrexate/Past HDACi	Best Response (ORR in evaluable patients)
	PTCL-NOSn = 10		**ORR = 50%**
I	PTCL-NOS	2	CR
I	PTCL-NOS	2	PR
II	PTCL-NOS	3 (vorinostat, ASCT)	PR
II	PTCL-NOS	0	PR
II	PTCL-NOS	7 (romidepsin, ASCT)	SD
II	PTCL-NOS	2	POD
II	PTCL-NOS	2	POD
II	PTCL-NOS	4 (belinostat, ASCT)	POD
II	PTCL-NOS	1	NE
II	PTCL-NOS (PTLD)	0	NE
	ATLL *n* = 8		**ORR = 57%**
I	ATLL (lymphomatous)	2	CR
II	ATLL (lymphomatous)	1	CR
I	ATLL (lymphomatous)	3	PR
I	ATLL (lymphomatous)	2	PR
I	ATLL (acute)	1	SD
I	ATLL (lymphomatous)	3 (ASCT)	POD
II	ATLL (lymphomatous)	2	POD
I	ATLL (lymphomatous)	3	NE
	PTCL with TFH phenotype/AITL *n* = 4		**ORR = 33%**
II	AITL (PTLD)	1	CR
II	PTCL with TFH phenotype	0	POD
II	PTCL with TFH phenotype	1 (ASCT)	SD
II	AITL	2	NE
	CTCL/Sezary *n* = 4		**ORR = 33%**
II	CTCL	4	PR
I	CTCL	2 (romidepsin)	SD
I	Sezary syndrome	5 (romidepsin)	POD
I	Sezary Syndrome	5	NE
	ALCL *n* = 3		**ORR = 100%**
I	ALCL ALK-, MF	6 (ASCT)	CR
I	CD30+ ALK (-) ALCL	2 (ASCT)	CR
I	ALCL ALK-	2	NE
	SPTL *n* = 3		**ORR = 50%**
I	SPTL-AB	2	PR (PET neg)
II	SPTCL	2	POD
II	SPTCL	4 (pralatrexate)	NE
	NK T cell *n* = 2		**ORR = 0%**
II	NKT cell	4	POD
I	NK T cell	2	NE
	Other *n* = 2		**ORR = 100%**
I	CD4+ TCL	1	PR
I	Intestinal T cell Lymphoma	1 (romidepsin)	PR

PTCL-NOS = peripheral T cell lymphoma not otherwise specified, ATLL = adult T cell leukemia lymphoma, TFH = T follicular helper, AITL = angioimmunoblastic t call lymphoma, CTCL = cutaneous T cell lymphoma, ALCL = anaplastic large cell lymphoma, SPTL = subpanniculitis T cell lymphoma, NK = natural killer, TCL = T cell lymphoma, ASCT = autologous stem cell transplant, MTCL = mature T cell lymphoma, HDACi = histone deacetylase inhibitor, ORR = overall response rate, CR = complete response, PR = partial response, SD = stable disease, NE = not evaluable, POD = progression of disease, PET neg = positron emission tomography negative

at higher doses for both romidepsin and pralatrexate. The approved doses for pralatrexate and romidepsin are 30 mg/m^2 and 14 mg/m^2, respectively, however were dosed at 25 mg/m^2 and 12 mg/m^2 for the clinical study. The combination was very well tolerated, which is a strength of this combination. In fact, there was only 1 case of mucositis and leucovorin was only used in 1 patient. In addition, there only 1grade 3 hematologic toxicity (anemia) observed. However, this may have translated into decrease depth of response as the ORR with the combination was improved over that which has been observed with the single agents but the CR and PFS rates were not.

To allow the results of the pralatrexate plus romidepsin study to be put in context, it should be recognized that many attempts to improve outcomes through targeting biological drivers have been explored [6]. Brentuximab vedotin, has been transformative in the frontline treatment of CD30 + MTCL, however, in relapsed disease, the ORR was only 41% [8–10, 24]. The PI3K-δ,γ inhibitor duvelisib led to an ORR of 50% and CR rate of 32%in the PRIMO study [29]. It is combination with romidepsin improved theORRto58% with a CR rate of 42%, with a median PFS of 6.9 months [30]. Romidepsin in combination with 5-azacytidinehas also shown favorable results with an ORR of 61% and CR of 43% [31,32].

Among all types of MTCL, HTLV-1 associated ATLL represents a particularly difficult clinical challenge, with the most common subtypes of ATLL (acute and lymphomatous) having median survival less than 1 year [33–37]. Treatment ranges from interferon-α plus zidovudine to multiagent chemotherapy in the frontline [38]. A recent advance for the treatment of R/R ATLL is the dual EZH1/2 inhibitor valemetostat tosilate, which achieved a 48% ORR and a 20% CR in a Phase II trial in 25 patients [39]. These results have led to the approval of this drug in Japan. Though only 7 evaluable patients with ATLL were treated on the pralatrexate plus romidepsin study,5 of 7 patients (71.4%) had disease control with an ORR of 57.1% and 2 CRs leading to a median DOR of 6.2 months. Though the numbers are small, they suggest further study in this disease entity is warranted.

One strength of the current study is that our population was demographically diverse and included a relatively large proportion of Hispanic and African-American patients, who have often been underrepresented in clinical studies. The main limitation of the current study is the small number of patients due to the rarity of the disease, discontinuation due to withdrawal of support from the study-drug manufacturers, and, in part, the COVID pandemic. The histological diversity in MTCL further reduces the number of patients with each subtype. Response rates reflecting evaluable patients from both the Phase I and Phase II studies, are similar to those obtained only from the

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Phase	Prior lines of therapies/Past Romidepsin or pralatrexate	Best Response	Duration of response (months)
II	1	CR Consolidated with allo	50.7
I	2	CR	5.1
I	3	PR	2.9
I	2	PR	7.2
I	1	SD	N/A
I	3 (ASCT)	POD	N/A
II	2	POD	N/A
I	3	NE	N/A

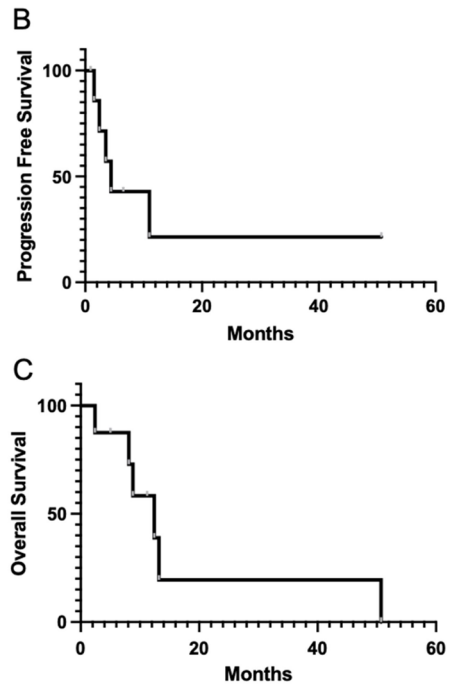

Figure 4. ATLL patient characteristics and their responses. (A) All patients with ATLL from Phase I and II clinical trial and their patient characteristics. (B) PFS of all ATLL patients from phase I and II in an intention to treat population (8 patients, median PFS of 4.4 months). (C) OS of all ATLL patients from phase I and II in an intention to treat population (8 patients, median OS of 12.4 months).

Table 3. Summary of adverse events in the safety population.

		Grade 1	Grade 2	Grade 3	Grade 4
	Number of events (percent) in 18 patients				
Adverse event	13 (72)	9 (50)	5 (28)	3 (17)	2 (11)
Nausea	6 (33)	3 (17)	3 (17)		
Diarrhea	4 (22)	3 (17)	1 (6)		
Abdominal pain	3 (17)		3 (17)		
Fatigue*	3 (17)	2 (11)	1 (6)		
Vomiting	3 (17)	2 (11)	1 (6)		
Sore throat	2 (11)	2 (11)			
Anorexia	2 (11)		2 (11)		
Sinus tachycardia	2 (11)		1 (6)	1 (6)	
Dizziness	2 (11)	1 (6)		1 (6)	
Electrolyte Abnormalities**	2 (11)	1 (6)		1 (6)	
Atrial fibrillation	1 (6)	1 (6)			
Headache	1 (6)	1 (6)			
Nasal congestion	1 (6)	1 (6)			
Fever	1 (6)	1 (6)	1 (6)		
URI	1 (6)		1 (6)		
Mucositis oral	1 (6)		1 (6)		
Otitis media	1 (6)		1 (6)		
Stroke	1 (6)		1 (6)		
Pain	1 (6)		1 (6)		
Constipation	1 (6)		1 (6)		
Anemia	1 (6)			1 (6)	
Appendicitis	1 (6)			1 (6)	
Dysphagia	1 (6)			1 (6)	
Small bowel obstruction	1 (6)			1 (6)	
Staph infection	1 (6)				1 (6)
Heart failure	1 (6)				1 (6)
Sepsis	1 (6)				1 (6)
Lymph node infection	1 (6)				1 (6)

*Fatigue includes Grade 1 somnolence.
**Electrolyte abnormalities includes Grade 1 hypokalemia and Grade 3 hyponatremia.
URI = upper respiratory infection

Phase II evaluable population, supporting the validity of the Phase II data.

Progress continues to be made since the first trials of targeted drugs in MTCL, however survival continues to be inferior to other lymphoma subtypes. Though the pralatrexate plus romidepsin does not out-perform other combination studies, given its safety and enrichment of results in ATLL, further study in this disease entity could be considered.

Authors' contributions

YKRT: Analysis, interpretation of results, draft manuscript preparation. SJ, SKB, AS, JKL, MMF: Data collection. ST: Analysis and draft manuscript preparation. BE: Analysis. BP: Supervision. JEA: Conceptualization, design, methodology and project administration, funding acquisition, data collection and analysis, manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

Disclosure statement

SJ: SRA with Acrotech; SKB: Consulting for Acrotech, Affimed, Daiichi Sankyo, Janssen, Kyowa Kirin, Research Support from Calgene, Seagen; JKL: Consulting for Epizyme and Merck; AS: Honorarium and Speaker: Acrotech, Daiichi Sankyo, Kite, Seagen; Employment; Flatiron Health; Stock: Roche; BP: Honoraria Takeda, Seagen; JEA: Advisory Board: AstraZeneca, Incyte; Honorarium: Epizyme.

Funding

The authors acknowledge support from the Herbert Irving Scholar Program UL1 TR001873 (JEA) and The Esther and Oded Aboodi Lymphoma Research Fund (JEA), American Society of Hematology Research Training for Fellow Award (YKRT and ST) and Conquer Cancer American Society of Clinical Oncology Young Investigator Award (YKRT).

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