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Pooled Analysis of Pralatrexate Single-Agent Studies in Patients With Relapsed/Refractory Peripheral T-Cell Lymphoma

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Abstract:
Patients with relapsed or refractory (r/r) mature NK and T-cell lymphoma (MTCL) have limited treatment options. To evaluate pralatrexate's performance and factors influencing its safety and efficacy in r/r PTCL, we performed a pooled analysis of data from four similarly designed, regulatory-mandated prospective clinical trials. Of 221 patients (59 years median age; 67.0% male) in the study population, 48.9% had peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), 21.3% angioimmunoblastic T-cell lymphoma, and 11.8% ALK negative anaplastic large cell lymphoma (ALCL). Patients received pralatrexate for a median 2.56 months (range, 0.03-24.18) and had a 40.7% objective response rate with a median 9.1-month duration of response, 4.6-month progression-free survival, and 16.3-month overall survival. The most common treatment-related all grade adverse events were stomatitis, thrombocytopenia, white blood cell count decreased, pyrexia, and vomiting. Subgroup exploratory analyses suggest improved efficacy with 1 prior line of chemotherapy versus 2 or {greater than or equal to} 4 prior lines; PTCL NOS or ALCL versus transformed mycosis fungoides; chemotherapy and transplant before pralatrexate versus chemotherapy alone or chemotherapy with other non-transplant treatments. In conclusion, these pooled analysis results further support using pralatrexate in patients with r/r PTCL. Prospective studies are needed to confirm the findings of subgroups analyses.

Conflict of interest: COI declared - see note

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Pooled Analysis of Pralatrexate Single-Agent Studies in Patients With Relapsed/Refractory Peripheral T-Cell Lymphoma

Running title: Pooled Analysis of Pralatrexate Studies in PTCL

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Key Points

- Pooled analysis confirms pralatrexate clinical activity in heavily-pretreated patients with relapsed/refractory PTCL.
- Exploratory analyses suggest that certain populations of patients might derive more benefit from pralatrexate therapy.

Abstract

Patients with relapsed or refractory (r/r) mature NK and T-cell lymphoma (MTCL) have limited treatment options. To evaluate pralatrexate's performance and factors influencing its safety and efficacy in r/r PTCL, we performed a pooled analysis of data from four similarly designed, regulatory-mandated prospective clinical trials. Of 221 patients (59 years median age; 67.0% male) in the study population, 48.9% had peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), 21.3% angioimmunoblastic T-cell lymphoma, and 11.8% ALK negative anaplastic large cell lymphoma (ALCL). Patients received pralatrexate for a median 2.56 months (range, 0.03–24.18) and had a 40.7% objective response rate with a median 9.1-month duration of response, 4.6-month progression-free survival, and 16.3-month overall survival. The most common treatment-related all grade adverse events were stomatitis, thrombocytopenia, white blood cell count decreased, pyrexia, and vomiting. Subgroup exploratory analyses suggest improved efficacy with 1 prior line of chemotherapy versus 2 or ≥ 4 prior lines; PTCL NOS or ALCL versus transformed mycosis fungoides; chemotherapy and transplant before pralatrexate versus chemotherapy alone or chemotherapy with other non-transplant treatments. In conclusion, these pooled analysis results further support using pralatrexate in patients with r/r PTCL. Prospective studies are needed to confirm the findings of subgroups analyses.

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Introduction

Peripheral T-cell lymphomas (PTCLs), a category of rare non-Hodgkin lymphomas also referred to as mature NK and T-cell lymphoma (MTCL), include 29 subtypes.[1,2] The estimated US annual incidence of the 2 most common forms of PTCL is 2500 cases of PTCL not otherwise specified (PTCL-NOS) and 1800 cases of angioimmunoblastic T-cell lymphoma (AITL).[2] There is no widely-accepted standard of care for patients with these diseases due to limited and inconclusive data from mostly small noncomparative studies and a few randomized prospective trials. Anthracycline-eligible patients with PTCL-NOS, AITL, and other aggressive PTCLs often receive first-line chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone with or without etoposide.[3] Despite inconclusive data, many physicians in Western countries recommend consolidation therapy with autologous stem cell transplantation (SCT) for patients with PTCL who achieve first remission.[2] Patients with PTCL-NOS and AITL have a 32% estimated 5-year overall survival (OS).[4]

Patients with relapsed or refractory (r/r) PTCL marginally benefit from traditional chemotherapy.[5] A registry data analysis reported median OS of 29.1 months for relapsed disease and 12.3 months for refractory disease.[6] Another analysis from this registry noted longer OS and progression-free survival (PFS) with monotherapies (ie, pralatrexate, romidepsin, belinostat, brentuximab vedotin, bendamustine, alisertib, denileukin diftitox, lenalidomide) compared with combination chemotherapy in r/r PTCL.[7] A large cohort study reported median 4-month event-free survival, 9.1-month OS, and 34% 3-year OS in patients with r/r PTCL and disease progression.[8]

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There is no consensus on a standard of care for patients with r/r PTCL and a lack of comparative effectiveness data for monotherapies.[2] Studies in patients with r/r PTCL are difficult to perform and interpret because these diseases are rare with nearly 30 distinct sub-types. Patients who are not eligible for SCT or unable to participate in a clinical trial are candidates for palliative chemotherapy, typically as a monotherapy to reduce untoward toxicity and attempt to control disease related symptoms.[2] Combination chemotherapy is typically associated with more toxicity, which can limit the number of cycles that can be administered, and short duration of benefit. Chemotherapy agents such as gemcitabine and, to a lesser extent, bortezomib, bendamustine, lenalidomide, and etoposide have all been used off-label in r/r PTCL, despite limited data supporting their use.[2]

To date, four drugs have been approved by the US Food and Drug Administration (FDA) for patients with r/r PTCL. These include the antifolate pralatrexate, the histone deacetylase (HDAC) inhibitors belinostat and romidepsin (recently withdrawn secondary to a negative phase 4 clinical trial[9]), and the anti-CD30 monoclonal antibody brentuximab vedotin, which only approved in the r/r setting for patients with anaplastic large T-cell lymphoma.[2] The HDAC inhibitor chidamide (also called tucidinostat) was approved in China for the treatment of r/r PTCL.[10,11] Tucidinostat was approved in Japan for r/r PTCL[12] and for r/r adult T-cell leukemia-lymphoma (ATL).[13,14] The defucosylated anti-CCR4 monoclonal antibody mogamulizumab has approval in Japan for previously untreated and r/r ATL[15-17] and for r/r PTCL.[18] These approved monotherapies for r/r PTCL have distinct advantages and limitations. Without comparative studies, medical oncologists/hematologists must critically assess the limited available data to individualize treatment recommendations.

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Pralatrexate was the first drug approved in the United States for r/r PTCL based on data from the single-arm, phase 2, multicenter PROPEL trial in patients from Canada, Europe, and the United States.[19] Subsequently, pralatrexate attained drug registration/regulatory approval in other countries based on results from PROPEL[19] and the following locally-mandated, single-arm regulatory studies: a confirmatory phase 3 trial (FOT12-CN-301) conducted in China;[20] a phase 4 trial (FOT14-TW-401) conducted in Taiwan;[21] and a phase 1/2 trial (PDX-JP1) conducted in Japan.[22] Here, we have performed a pooled analysis of the PROPEL, FOT12-CN-301, FOT14-TW-401, and PDX-JP1 (phase 2 part, only) trials to generate a more robust dataset for evaluating pralatrexate's performance and factors influencing its safety and efficacy in r/r PTCL.

Methods

Clinical trials

We analyzed pooled patient-level or summary-level data from the clinical study reports of 4 prospective clinical trials of pralatrexate monotherapy in patients with r/r PTCL (supplemental **Figure S1**).[19-22] Of 231 patients in the safety analysis set (defined as all patients who received ≥ 1 pralatrexate dose), 221 were deemed evaluable for efficacy.. Data were collected in accordance with the original protocol for each study and, where available, updated with longer survival follow-up. The institutional review boards (IRB) or ethics committees at the participating centers approved the respective studies, which were conducted in accordance with the Declaration of Helsinki and its relevant amendments, and with the International Conference on Harmonization Guidelines for Good Clinical Practice.

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Patients

The 4 pooled studies had very similar inclusion and exclusion criteria (supplemental Table 1).[19-22] In each study, the PTCL histologic subtypes were confirmed by central review. All participating patients provided written informed consent.

The PROPEL study[19] required that patients have a diagnosis of PTCL per the 2000 Revised European Lymphoma (REAL) and World Health Organization (WHO) classification of lymphoid neoplasm criteria;[23] with documented disease progression after ≥ 1 prior treatment. The FOT12-CN-301 study[20] required patients have a PTCL WHO 2008 diagnosis[24] with disease progression after ≥ 1 prior systemic therapy and with an enlarged lymph node or extranodal mass 1.5 cm. The FOT14-TW-401 study[21] required patients have a PTCL diagnosis per National Comprehensive Cancer Center diagnosis criteria, revised REAL, and WHO classification with documented disease progression after prior therapy. The PDX-JP1 study[22] required that patients have PTCL per 2008 WHO classification[24] after ≥ 1 prior antitumor therapy (not including systemic corticosteroid monotherapy).

Treatments and assessments

In all 4 trials, patients received pralatrexate at a dose of 30 mg/m^2 IV over 3-5 minutes, weekly for 6 weeks every 7 weeks (1 week off), and started vitamin B_{12} and folic acid supplementation ≥ 10 days before the first dose of pralatrexate.[19-22] All 4 studies assessed patients every 2 cycles. In the PROPEL[19] and FOT12-CN-301[20] studies, response assessments were performed within 7 days before the first dose of every even-numbered subsequent cycle. In the FOT14-TW-401

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study[21] response assessments were performed at the end of cycles 1 (week 7), 3 (week 21), 5 (week 35), and after the last dose of treatment beyond cycle 5. In the PDX-JP1 study[22] response assessments were performed at week 7 of odd-numbered cycles.

The PROPEL[19] and the PDX-JP1[22] studies graded adverse events (AEs) using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. The FOT12-CN-301[20] and FOT14-TW-401[21] studies used NCI CTCAE version 4.03.

Statistical analysis

The primary efficacy endpoint across all trials was objective response rate (ORR) assessed by central review using International Working Group criteria.[19-22,25,26] Secondary efficacy endpoints included duration of response (DoR), PFS, OS, and responses in patients who had undergone SCT after pralatrexate treatment. DOR was assessed from the first day of documented response until progressive disease (PD) or death and PFS and OS from the first treatment day until an event or censoring in the PROPEL study.[19]

Data from studies were combined and reported as observed. Assessments of the heterogeneity between the studies indicated that there was some variability in the observed treatment effects in the studies.

Objective response rate, PFS, and OS were analyzed for the following subgroups: relapse or refractory status at most recent treatment, number of lines of prior chemotherapy, type of prior chemotherapy, and histologic subtype. Relapse was defined as achieving a complete response (CR) or partial response (PR) on prior therapy lasting for ≥ 3 months. Refractory was

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defined as stable or progressive disease on prior therapy or relapsed disease < 3 months of achieving CR or PR. These analyses considered fixed and random effects models.

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Results

Patient characteristics

The pooled efficacy population (*n* = 221) had a median age of 59 years (range, 21–89) and was predominantly male (67.0%) (Table 1). Most patients (89%) had an Eastern Cooperative Oncology Group performance status of < 2. The 3 most common PTCL histologic subtypes were PTCL-NOS (48.9%), AITL (21.3%), and ALK negative anaplastic large cell lymphoma (ALCL; 11.8%). Patients had received a median of 2.0 (range, 1–14) prior systemic regimens and most patients had received 1 (34.4%) or 2 (27.1%) prior lines of systemic therapy. At the most recent prior therapy, 53.9% of patients had refractory disease and 24.4% had relapsed. Among types of prior treatment for PTCL, all patients had received chemotherapy, 22.2% radiation therapy, and 13.1% SCT. The most commonly used types of prior chemotherapy were anthracycline (89.6%), platinum agents (40.7%), and gemcitabine (30.3%). As the best response to their most recent prior regimen, 19.9% of patients had a complete response (CR) and 17.6% a partial response (PR). Baseline patient characteristics in the individual studies are shown in supplemental Table 2.

Exposure and safety

The median pralatrexate treatment duration was 2.56 months (range, 0.03–24.18), with a median dose intensity of 25.8 mg/m^2/week (range, 11.7–31.7). Table 2 lists treatment

emergent adverse events (TEAEs) reported in ≥ 10% of the total safety population from the 4 studies. The most frequently reported all grade TEAEs were stomatitis (65.8%), anemia (39.8%), nausea (33.8%), thrombocytopenia (32.9%), and pyrexia (30.3%).

The safety analyses by worst grade severity (grades 3-5; shown in Table 2) and by relationship to study treatment excluded patients in the PDX-JP1 study[21] due to a lack of accessible data from that study. Among the safety population of 209 patients from the PROPEL, FOT12-CN-301, and FOT14-TW-401 studies, the most common grade 3 and 4 TEAEs were thrombocytopenia (18.2% and 12.9%), stomatitis (17.7% and 1.9%), anemia (16.3% and 2.9%), and neutropenia (12.9% and 6.7%). The most frequently (ie, ≥ 10%) reported all grade TEAEs related to study treatment were stomatitis (35.4%), thrombocytopenia (26.3%), white blood cell count decreased (18.2%), pyrexia (17.2%), vomiting (16.3%), anemia (11.0%), nausea (11.0%), and epistaxis, fatigue, mucosal inflammation, and rash (10.0%, each). The 4 pooled studies were conducted before the implementation of leucovorin prophylaxis to mitigate stomatitis and oral mucositis.

Serious TEAEs occurred in 110 patients (47.6%). Of the 6 patients (2.6%) who had TEAEs leading to death, 1 patient had infectious diarrhea, pneumonia, and sepsis, and 1 patient each had pneumonia, febrile neutropenia, lung infection, septic shock, or acute hepatic failure.

In the PROPEL study,[19] 23% of patients had a dose reduction for mucositis and 23% and withdrew from treatment due to AEs, primarily mucositis and thrombocytopenia. In FOT12-CN-301,[20] 46% of patients had dose reductions, primarily due to mucositis. In PDX-JP1,[22] 28% of patients had dose reductions, primarily due to mucositis, and 24% had AEs leading to treatment

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discontinuation. In FOT14-TW-401,[21] 22.2% of patients had dose reductions, primarily due to mucositis, neutropenia, and thrombocytopenia.

Efficacy

Among the pooled efficacy population of 221 patients, 10.0% had a CR, 3.6% had a CR unconfirmed (CRu), and 27.1% had a PR, as their best overall response determined by central review, leading to a 40.7% ORR (95% CI, 34.2–47.5) (Table 3). The 90 responders with a CR, CRu, or PR had a median DoR of 9.1 months (95% CI, 7.4–10.8). The median PFS was 4.6 months (95% CI, 3.2–5.6) and the median OS was 16.3 months (95% CI, 13.1–22.6) (Figure 1A-B).

Fourteen patients (6.3%) underwent autologous (*n* = 6) or allogeneic (*n* = 8) SCT after pralatrexate treatment. The best overall responses reported in these patients were 5 CRs (35.7%), 6 PRs (42.9%), 1 stable disease (SD; 7.1%), and 2 progressive disease (PD; 14.3%). This subgroup of patients had 78.6% ORR. The swimmer plot in Figure 2 illustrates the timeline of events for this group of patients.

Subgroup analyses

Exploratory subgroup analyses showed non-statically significant trends favoring certain subgroups (Table 4, Figure 3). In the subgroup analysis by relapse or refractory status at most recent treatment, the relapse subgroup had numerically higher ORR (48% vs 38%), median PFS (8.0 vs 3.2 months), and median OS (22.9 vs 14.7 months) than the refractory subgroup, respectively. In the subgroup analysis by prior chemotherapy lines, the 1 prior line subgroup had higher ORR (55%), PFS (6.7 months), and OS (24.2 months) than the 2 prior lines (ORR 32%;

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PFS 3.1 months; OS 12.0 months) and ≥4 prior lines (ORR 21%; PFS 3.0 months; OS 10.0 months) subgroups. The efficacy outcomes of the 1 prior line subgroup were similar to the 3 prior line subgroup (ORR 50%; PFS 4.6 months; OS 22.5 months). In the subgroup analysis by type of prior chemotherapy, the anthracycline-based chemotherapy only subgroup (ORR, 50%; PFS 4.8 months; OS 20.5 months) and the no anthracycline or platinum or gemcitabine-based chemotherapy subgroup (ORR 50%; PFS 7.8 months; OS 17.0 months) had numerically higher ORR, PFS, and OS than then other subgroups. In the histology subtype analysis, the PTCL NOS (ORR 41%; PFS 4.8 months; OS 15.4 months) and ALCL (ORR 46%; PFS 4.8 months; OS 19.3 months) subgroups had numerically higher efficacy outcomes than the transformed mycosis (tMF; ORR 25%; PFS 1.7 months; OS 13.6 months) subgroup. The AITL (ORR 43%; PFS 1.9 months; OS 18 months) subgroup had similar ORR than the PTCL NOS and ALCL subgroups but shorter PFS and OS.

Regarding therapies before initiation of pralatrexate (Table 4 and Figure 3**)**, the prior chemotherapy and transplant subgroup had higher ORR, median PFS and median OS (50%, 10.6 months, and 23.6 months, respectively) than the chemotherapy alone (43%, 4.7 months, and 18.2 months, respectively) or chemotherapy and other agents (31%, 1.6 months, and 10.0 months, respectively) subgroups.

Discussion

Prior to the availability of novel drugs, there had been little guidance on treatment for PTCL, and clinicians had to extrapolate treatments based on their experience treating patients with B-cell lymphomas, with minimal recognition that T-cell malignancies are different from B-cell neoplasms. PTCLs are very aggressive and heterogenous lymphoid malignancies recognized for

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their relative resistance to traditional chemotherapy. Extrapolation of treatments from B-cell lymphoma experiences often failed to recognize the paucity of data for a treatment in patients with PTCL, which has substantially greater unmet medical need. In fact, early phase experiences with pralatrexate demonstrated sharply greater activity in patients with PTCL compared to B-cell lymphomas, hence the basis for PROPEL. Our data provide insights into the activity of pralatrexate in this heterogeneous r/r population from the global clinical trial experience and provide substantially more data for pralatrexate across not only a more diverse population of patients, but also in some of the rarer PTCL subtypes.

The results of our pooled analysis confirm the marked clinical activity of pralatrexate in heavily-pretreated patients with r/r PTCL, with a 40.7% ORR and median 9.1 months DoR, 4.6 months PFS, and 16.3 months OS. Patients who received SCT after pralatrexate had a 78.6% ORR. The most frequently reported, treatment-related all-grade TEAEs were stomatitis, thrombocytopenia, white blood cell count decreased, pyrexia, and vomiting.

The 4 analyzed pralatrexate monotherapy studies reported variable ORRs of 29% (CR 10%, CRu 1%, PR 18%) in PROPEL,[19] 52% (CR 9%, CRu 11%, PR 32%) in FOT12-CN-31,[20] 71% (CR 14%m OR 57%) in FOT14-TW-401,[21] and 45% (CR 10%, PR 35%) in PDX-JP1.[22] Study sample size and differences in the number of lines of prior therapy are the most likely reasons for this wide variation in ORR. FOT14-TW-401[21] and PDX-JP1[22] only included 20 to 21 patients in contrast to the 109 patients in PROPEL[19] and 71 patients in FOT12-CN-31.[20]

Results of our pooled subgroup exploratory analyses suggest that certain populations of patients with r/r TCL may derive the most benefit from pralatrexate therapy. Numerically higher ORR, PFS, and OS were seen among patients with only 1 prior line of chemotherapy

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versus 2 and ≥ 4 prior lines, patients with PTCL NOS or ALCL versus tMF, and patients who had received chemotherapy and transplant before pralatrexate versus chemotherapy alone or chemotherapy with other non-transplant treatments. Interestingly, patients with AITL exhibited similar ORR to patients with PTCL-NOS and ALCL.

The subgroup of 47 patients with r/r AITL had an ORR of 43% (95% CI, 28%–58%) which may be lower than the ORR of 52% (95% CI, 34%–70%) reported in a pooled subset analysis[27] of data from 29 patients with r/r AITL treated with single-agent pralatrexate in the FOT12-CN-301 and PDX-JP1. This discrepancy is likely attributed to smaller patients numbers and may be influenced by the lower 8% (95% CI, 0%–36%) ORR in the 13 patients with r/r AITL in PROPEL.[19] Interestingly, the ORR was 55% (95%, CI 32%–77%) among 20 patients with r/r AITL in FOT12-CN-301,[20] 71% among 5 patients with r/R AITL in FOT14-TW-401,[21] and 44% (90% CI, 17%–75%) among 9 patients with r/r AITL in PDX-JP1.[22] Given the rarity of AITL and the need to conduct subset analysis to tease out these effects, results of individual trials are not powered to adequately define the 'real' ORR in AITL, or any other PTCL subtype. Studies that include real-world data provide some further evidence of pralatrexates' activity in AITL. For example, a retrospective real-world analysis that reported a 41% ORR (95% CI, 21%–64%) among 27 patients with r/r PTCL-NOS or AITL treated with pralatrexate, noted no significant differences in ORR between the two small subgroups, albeit there was 1 CR among patients with AITL and 4 among patients with PTCL-NOS.[28] A propensity score case-matched analysis reported median OS of 9.8 months (95% CI, 2.2–10.2) for 12 patients with r/r AITL treated with pralatrexate in the PROPEL study and 5.5 months (95% CI, 0.4–8.2) for 12 patients with r/r AITL treated with

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other therapies.[29] In contrast, the 47 patients with r/r AITL included in our pooled analysis had a median OS of 18 months (95% CI, 11.9–28.2).

The fact that the 4 pooled studies shared a very similar design and patient inclusion/exclusion circumvented some common limitations of pooled analyses such as heterogeneity in study methodology and patient populations. However, there were some differences in included histologic subtypes. For example, the PROPEL study[19] allowed inclusion of patients with extranodal NK/T-cell lymphoma (ENKTL) unspecified whereas the 3 other studies[20-22] allowed inclusion only of patients with ENKTL nasal type. Interpretation of our analysis is limited by the fact that pralatrexate clinical trials were designed before the availability of other novel single agents for r/r PTCL. Despite this, our pooled analysis provides clinically applicable insights considering the current lack of consistency in the use of monotherapies for patients with most types of r/r PTCL. After the clinical development and approval of pralatrexate, researchers have tried to limit their study populations to include fewer PTCL subtypes, reducing heterogeneity at the expense of limiting availability of data for underrepresented subtypes. Despite the small numbers in individual studies, our pooled analysis captures the broader r/r PTCL population and provides some insights on pralatrexate activity in this difficult-to-treat population.

Pralatrexate is being studied in combination regimens in patients with PTCL. A phase 1 trial of romidepsin plus pralatrexate reported a 71% ORR (including 4 CRs) and 4.4 months (95% CI, 1.2–not achieved) median PFS in 14 patients with PTCL.[30] The ongoing NCT03240211 phase 1b study is testing pembrolizumab with decitabine and/or pralatrexate in patients with PTCL or

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cutaneous T-cell lymphoma. The ongoing NCT03598998 phase 1/2 trial is studying the combination of pembrolizumab and pralatrexate in patients with r/r PTCL.

In conclusion, data from 3 additional regulatory-mandated clinical studies meaningfully augment the US registration PROPEL data supporting the use of pralatrexate in patients with r/r PTCL. Furthermore, results from pooled subgroup exploratory analyses suggest that certain populations of patients with r/r PTCL might derive more benefit from pralatrexate therapy. Prospective studies in these subgroups are needed to confirm these findings.

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Author contributors

Owen A. O'Connor and Ee-Min Yeoh designed and planned the study. Owen A. O'Connor, Bor-Sheng Ko, Ming-Chung Wang, Dai Maruyama, Yuqin Song and Kensei Tobinai who were also investigators of the individual country studies acquired and analyzed the data. Owen A. O'Connor and Ee-Min Yeoh interpreted the data. All authors wrote, reviewed, and/or revised the manuscript. All authors read and approved the final manuscript.

Disclosures of conflict of interest

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Table 1. Baseline demographic and disease characteristics

Characteristic	*N* = 221
Age, median years (range)	59.0 (21–89)
Age group, n (%)	
< 65 years	145 (65.6)
≥ 65 years	76 (34.4)
Gender, n (%)	
Female	73 (33.0)
Male	148 (67.0)
Histologic subtype, n (%)	
PTCL-NOS	108 (48.9)
AITL	47 (21.3)
ALCL, ALK negative	26 (11.8)
tMF	12 (5.4)
ENKTL nasal type	7 (3.2)
Blastic NK lymphoma	4 (1.8)
Adult TCL/leukemia HTLV1+	2 (0.9)
Subcutaneous panniculitis-like TCL	2 (0.9)
Enteropathy-associated TCL	1 (0.5)
Extranodal peripheral NK/T-cell lymphoma unspecified	1 (0.5)
Missing	11 (5.0)
Time from most recent therapy for MTCL, median months (range)	2.0 (0.03–89.2)
Lines of prior systemic regimens, median (range)	2.0 (1, 14)

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Characteristic	*N* = 221
Number of lines of prior systemic regimens, n (%)	
1	76 (34.4)
2	60 (27.1)
3	38 (17.2)
4	20 (9.0)
≥5	27 (12.2)
Relapsed or refractory at most recent prior therapy,[a] n (%)	
Relapsed	54 (24.4)
Refractory	119 (53.8)
Missing	48 (21.7)
Prior treatment for MTCL, n (%)	
Chemotherapy	221 (100.0)
Stem cell transplantation	29 (13.1)
Radiation therapy	49 (22.2)
Systemic investigational agents	7 (3.2)
Monoclonal antibody therapy	3 (1.4)
Resection	2 (0.9)
Other therapy	22 (10.0)
Type of prior chemotherapy for MTCL, n (%)	
Anthracycline	198 (89.6)
Platinum agents	90 (40.7)
Gemcitabine	67 (30.3)

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Characteristic	*N* = 221
Methotrexate	37 (16.7)
Novel agents	27 (12.2)
Others	99 (44.8)
Best response to most recent prior regimen, n (%)	
CR	44 (19.9)
CRu	1 (0.5)
PR	39 (17.6)
SD	23 (10.4)
PD	66 (29.9)
Not available/not evaluable	48 (21.7)
ECOG performance status, n (%)	
0	79 (35.7)
1	118 (53.4)
2	24 (10.9)

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ENKTCL, extranodal NK/T cell lymphoma; HTLV, human T-cell leukemia virus; MTCL, mature NK and T-cell lymphoma; PD, progressive disease; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; SD, stable disease; tMF, transformed mycosis fungoides; u, unconfirmed.

[a]Relapsed was defined as on prior therapy achieving a CR or PR lasting for ≥ 3 months, and refractory was defined as stable disease or progressive disease on prior therapy or relapsed disease < 3 months of achieving CR or PR.

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Table 2. TEAEs by preferred term reported in ≥ 10% of patients

TEAE, n (%)	All grades (*N* = 231)	Grade 3 (*n* = 209),[a]	Grade 4 (*n* = 209),[a]	Grade 5 (*n* = 209),[a]
Any TEAE	230 (99.6)	156 (74.6)	73 (34.9)	11 (5.3)
Hematologic				
Anemia	92 (39.8)	34 (16.3)	6 (2.9)	0
Thrombocytopenia	76 (32.9)	38 (18.2)	27 (12.9)	0
Neutropenia	56 (24.2)	27 (12.9)	14 (6.7)	0
Leukopenia	35 (15.2)	11 (5.3)	10 (4.8)	0
White blood cell count decreased	41 (17.8)	16 (7.7)	6 (2.9)	0
Neutrophil count decreased	35 (15.2)	13 (6.2)	11 (5.3)	0
Non-hematologic				
Stomatitis	152 (65.8)	37 (17.7)	4 (1.9)	0
Nausea	78 (33.8)	4 (1.9)	0	0
Pyrexia	70 (30.3)	4 (1.9)	0	1 (0.5)
Vomiting	56 (24.2)	2 (1.0)	0	0
Constipation	55 (23.8)	0	0	0
Fatigue	52 (22.5)	9 (4.3)	2 (1.0)	0
Rash	48 (20.8)	4 (1.9)	0	0
Cough	47 (20.4)	2 (1.0)	0	0
Oedema peripheral	47 (20.4)	0	0	0

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TEAE, n (%)	All grades (*N* = 231)	Grade 3 (*n* = 209),[a]	Grade 4 (*n* = 209),[a]	Grade 5 (*n* = 209),[a]
Diarrhea	45 (19.5)	3 (1.4)	0	0
Hypokalemia	41 (17.8)	13 (6.2)	4 (1.9)	0
Alanine aminotransferase increased	40 (17.3)	7 (3.4)	0	0
Epistaxis	39 (16.9)	0	0	0
Upper respiratory tract infection	35 (15.2)	5 (2.4)	0	0
Mucosal inflammation	30 (13.0)	6 (2.9)	1 (0.5)	0
Aspartate aminotransferase increased	27 (11.7)	3 (1.4)	0	0
Pruritus	25 (10.8)	4 (1.9)	0	0
Decreased appetite	24 (10.4)	0	0	0

TEAE, treatment-emergent adverse event.

[a]Excludes study PDX-JP1[21] due to lack of accessible data.

Patients could have > 1 TEAE in any category.

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Table 3. Anti-tumor activity in evaluable patients

Characteristic	Total (*N* = 221)
Best overall response by central review, n (%)	
Complete response (CR)	22 (10.0)
Complete response unconfirmed (CRu)	8 (3.6)
Partial response (PR)	60 (27.1)
Stable disease	38 (17.2)
Progressive disease	64 (29.0)
Not evaluable	2 (0.9)
Not available	9 (4.1)
Unknown (missing or no response assessment)	18 (8.1)
Objective response rate (CR + CRu + PR) by central review, n (%)	90 (40.7) (95% CI, 34.2–47.5)
Duration of response, median months (95% CI)	9.1 (7.4–10.8)
Progression-free survival, median months (95% CI)	4.6 (3.2–5.6)
Overall survival (OS), median months (95% CI)	16.3 (13.1–22.6)
Kaplan-Meier OS estimates at 12 months (95% CI)	0.58 (0.51–0.64)
Kaplan-Meier OS estimates at 24 months (95% CI)	0.39 (0.32–0.46)

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Table 4. Efficacy by subgroup

Subgroup	ORR (CR + CRu + PR), % (95% CI)	PFS, median months (95% CI)	OS, median months (95% CI)
Overall (*N* = 221)	40.7 (34.2–47.5)	4.6 (3.2–5.6)	16.3 (13.1–22.6)
Relapse or refractory status at most recent treatment			
Relapse (*n* = 54)	48.1 (34.3–62.2)	8.0 (4.6–11.1)	22.9 (14.6–NE)
Refractory (*n* = 119)	37.8 (29.1–47.2)	3.2 (2.5–4.6)	14.6 (10.3–23.6)
Number of prior chemotherapy lines			
1 (*n* = 76)	55.3 (43.4–66.7)	6.7 (4.4–10.7)	24.2 (17.0–NE)
2 (*n* = 60)	31.7 (20.3–45.0)	3.1 (1.7–7.7)	12.0 (9.0–22.9)
3 (*n* = 38)	50.0 (33.4–66.6)	4.6 (1.6–8.5)	22.5 (9.6–28.2)
≥4 (*n* = 47)	21.3 (10.7–35.7)	3.0 (1.4–4.9)	10.0 (6.1–15.2)
Type of prior chemotherapy			
Anthracycline-based only (*n* = 102)	50.0 (39.9–60.1)	4.8 (3.2–7.8)	20.5 (14.4–26.7)
Anthracycline, platinum, gemcitabine-based (*n* = 53)	32.1 (19.9–46.3)	4.2 (1.6–7.7)	11.2 (6.8–23.4)
Anthracycline, platinum-based (*n* = 33)	27.3 (13.3–45.5)	3.0 (1.4–10.6)	10.4 (3.8–23.6)
Not anthracycline or platinum or gemcitabine-based (*n* = 18)	50.0 (26.0–74.0)	7.8 (3.9–14.1)	17.0 (10.6–NE)
PTCL histological subtype by central review			
PTCL NOS (*n* = 108)	40.7 (31.4–50.6)	4.8 (3.3–6.7)	15.4 (10.5–24.2)
AITL (*n* = 47)	42.6 (28.3–57.8)	1.9 (1.5–6.0)	18 (11.9–28.2)
ALCL, ALK negative (*n* = 26)	46.2 (26.6–66.6)	4.8 (1.4–NE)	19.3 (4.2–NE)
tMF (*n* = 12)	25.0 (5.5–57.2)	1.7 (1.4–8.1)	13.6 (1.7–NE)
Type of prior systemic therapy			

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Subgroup	ORR (CR + CRu + PR), % (95% CI)	PFS, median months (95% CI)	OS, median months (95% CI)
Chemotherapy only (*n* = 162)	42.6 (34.9–50.6)	4.7 (3.3–6.6)	18.3 (14.4–24.2)
Chemotherapy and transplant (*n* = 26)	50.0 (29.9–70.1)	10.6 (1.4–NE)	23.6 (8.2–NE)
Chemotherapy and other (*n* = 16)	31.3 (11.0–58.7)	1.6 (0.6–3.5)	10.0 (3.2–13.1)

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CR, complete response; NE, not estimable; NOS, not otherwise specified; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; tMF, transformed mycosis fungoides; u, unconfirmed.

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Figure 1

Figure 1. Kaplan-Meier plots of progression-free survival (panel A) and overall survival (panel B)

A.

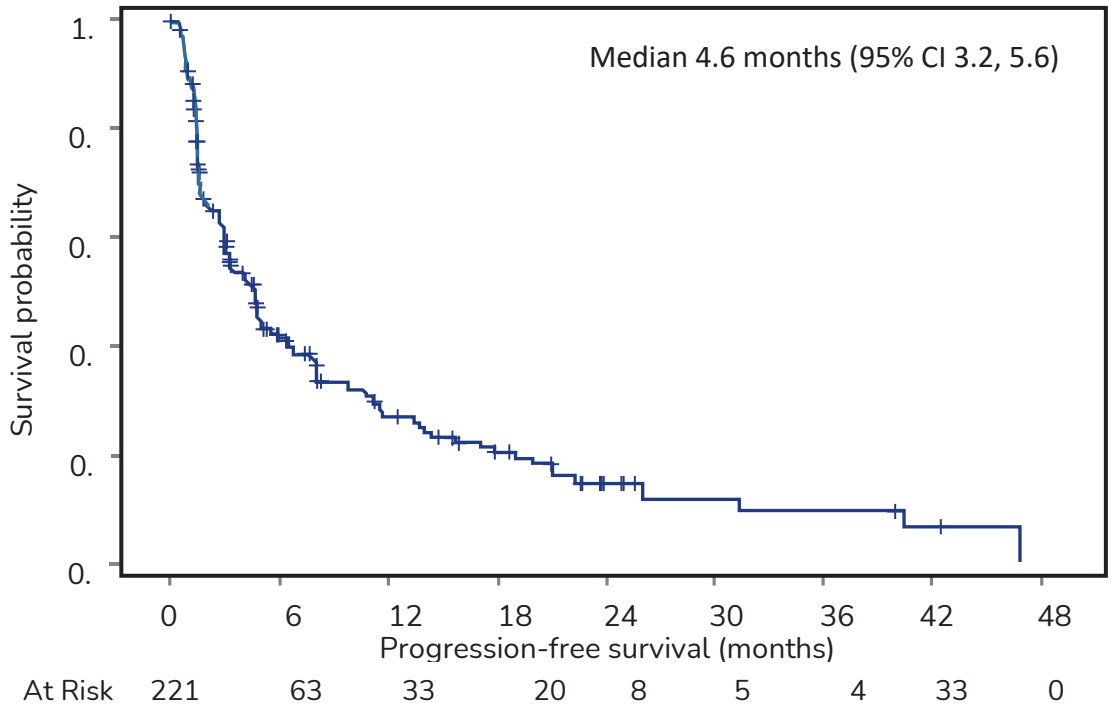

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Figure 1

B.

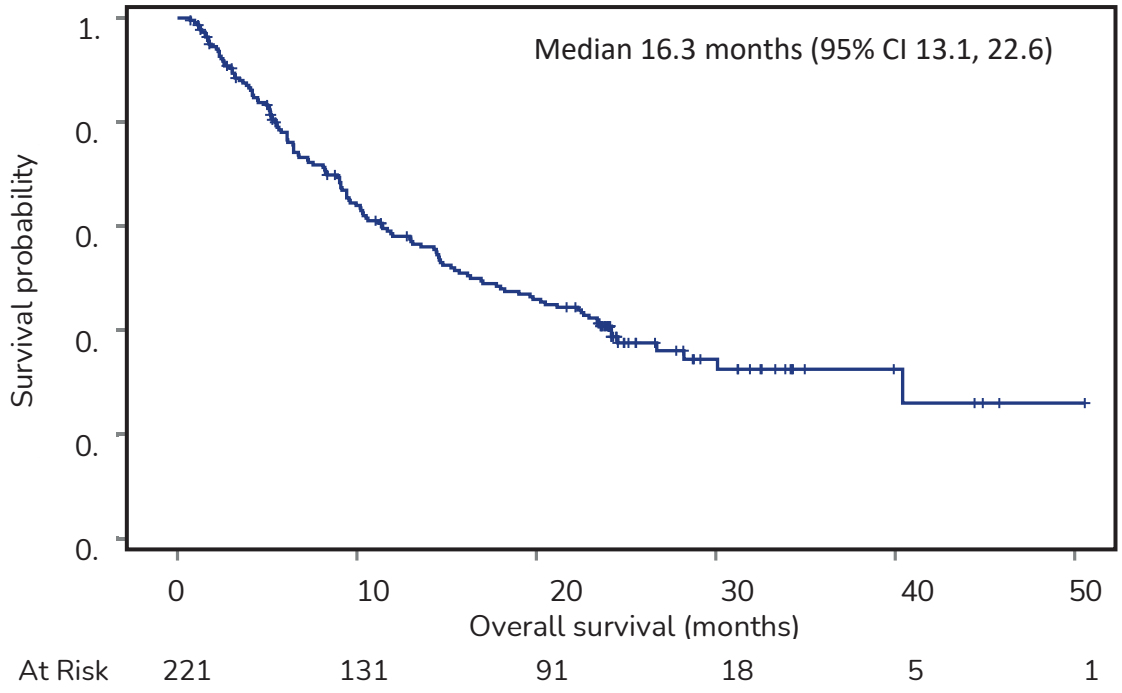

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Figure 2. Response in patients with SCT post-pralatrexate treatment

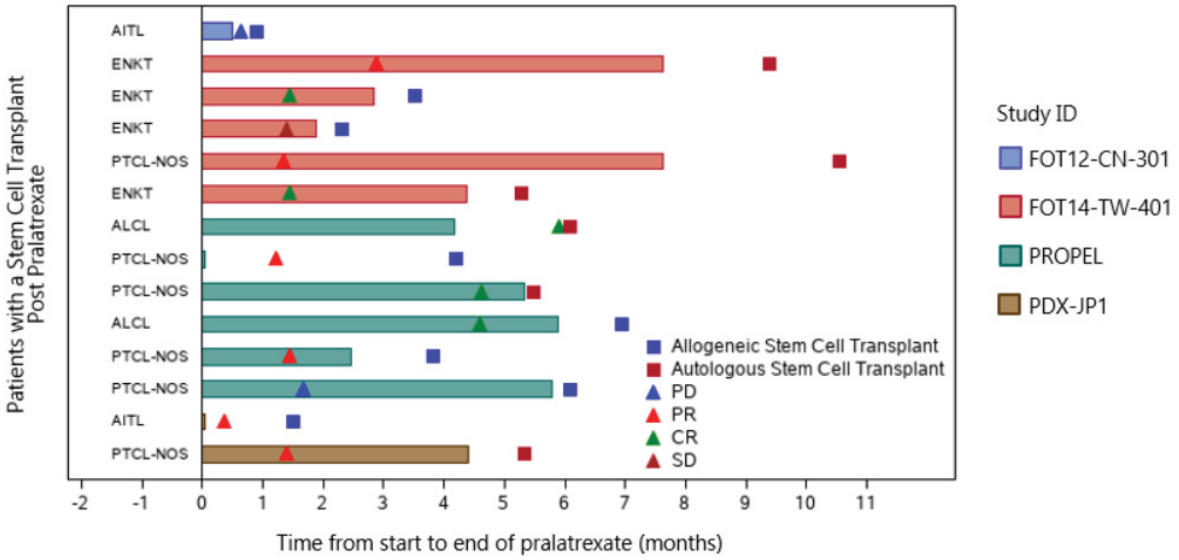

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Figure 3

Figure 3: Forest plots for subgroup analyses of objective response rate (A), progression-free survival (B), and overall survival (C)

A

Category by subgroup	N	Responder (%)	95% CI
Overall			
Objective response (CR+CRu+PR)	221	90 (40.7%)	(34.2, 47.5)
Relapsed/Refractory			
Relapsed	54	26 (48.1%)	(34.3, 62.2)
Refractory	119	45 (37.8%)	(29.1, 47.2)
PTCL histological subtype by central review*			
Peripheral T cell lymphoma not otherwise specified (NOS)	108	44 (40.7%)	(31.4, 50.6)
Angioimmunoblastic T cell lymphoma	47	20 (42.6%)	(28.3, 57.8)
Anaplastic large cell lymphoma, ALK negative	26	12 (46.2%)	(26.6, 66.6)
Transformed mycosis fungoides	12	3 (25.0%)	(5.5, 57.2)
Number of prior chemotherapy lines			
1	76	42 (55.3%)	(43.4, 66.7)
2	60	19 (31.7%)	(20.3, 45.0)
3	38	19 (50.0%)	(33.4, 66.6)
≥4	47	10 (21.3%)	(10.7, 35.7)
Response to the most recent prior therapy			
Responder (CR+CRu+PR)	84	42 (50.0%)	(38.9, 61.1)
Non-responder	137	48 (35.0%)	(27.1, 43.6)
Type of prior systemic therapy*			
Chemotherapy only	162	69 (42.6%)	(34.9, 50.6)
Chemotherapy, transplant	26	13 (50.0%)	(29.9, 70.1)
Chemotherapy, other	16	5 (31.3%)	(11.0, 58.7)
Type of prior chemotherapy*			
Anthracycline-based only	102	51 (50.0%)	(39.9, 60.1)
Anthracycline, platinum, gemcitabine-based	53	17 (32.1%)	(19.9, 46.3)
Anthracycline, platinum-based	33	9 (27.3%)	(13.3, 45.5)
Not anthracycline or platinum or gemcitabine-based	18	9 (50.0%)	(26.0, 74.0)

*Only categories with N>10 are displayed.

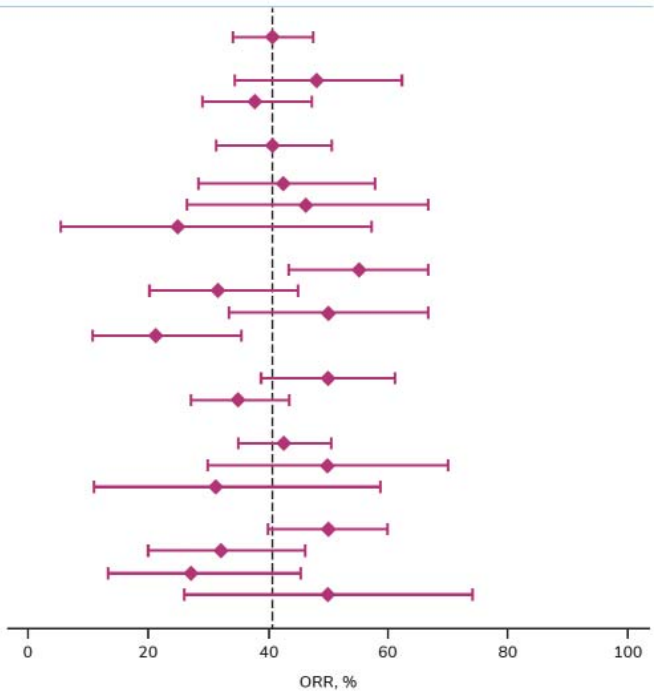

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Figure 3

B

Category by subgroup	N	Event (%)	Censor (%)	Median (95% CI)
Overall				
Progression-free survival (months)	221	146 (66.1%)	75 (33.9%)	4.63 (3.15, 5.55)
Relapsed/Refractory				
Relapsed	54	33 (61.1%)	21 (38.9%)	8.02 (4.63, 11.07)
Refractory	119	82 (68.9%)	37 (31.1%)	3.15 (2.53, 4.63)
PTCL histological subtype by central review*				
Peripheral T cell lymphoma not otherwise specified (NOS)	108	69 (63.9%)	39 (36.1%)	4.76 (3.29, 6.74)
Angioimmunoblastic T cell lymphoma	47	35 (74.5%)	12 (25.5%)	1.87 (1.48, 6.01)
Anaplastic large cell lymphoma, ALK negative	26	15 (57.7%)	11 (42.3%)	4.80 (1.41, NE)
Transformed mycosis fungoides	12	9 (75.0%)	3 (25.0%)	1.74 (1.35, 8.08)
Number of prior chemotherapy lines				
1	76	51 (67.1%)	25 (32.9%)	6.74 (4.40, 10.74)
2	60	37 (61.7%)	23 (38.3%)	3.06 (1.68, 7.72)
3	38	25 (65.8%)	13 (34.2%)	4.63 (1.61, 8.51)
≥4	47	33 (70.2%)	14 (29.8%)	3.02 (1.41, 4.90)
Response to the most recent prior therapy				
Responder (CR+CRu+PR)	84	53 (63.1%)	31 (36.9%)	7.72 (4.63, 11.07)
Non-responder	137	93 (67.9%)	44 (32.1%)	3.15 (2.53, 4.57)
Type of prior systemic therapy*				
Chemotherapy only	162	107 (66.0%)	55 (34.0%)	4.70 (3.29, 6.64)
Chemotherapy, transplant	26	14 (53.8%)	12 (46.2%)	10.64 (1.45, NE)
Chemotherapy, other	16	12 (75.0%)	4 (25.0%)	1.61 (0.59, 3.52)
Type of prior chemotherapy*				
Anthracycline-based only	102	66 (64.7%)	36 (35.3%)	4.76 (3.19, 7.85)
Anthracycline, platinum, gemcitabine-based	53	34 (64.2%)	19 (35.8%)	4.17 (1.64, 7.72)
Anthracycline, platinum-based	33	20 (60.6%)	13 (39.4%)	2.96 (1.41, 10.64)
Not anthracycline or platinum or gemcitabine-based	18	14 (77.8%)	4 (22.2%)	7.79 (3.94, 14.09)

*Only categories with N>10 are displayed..

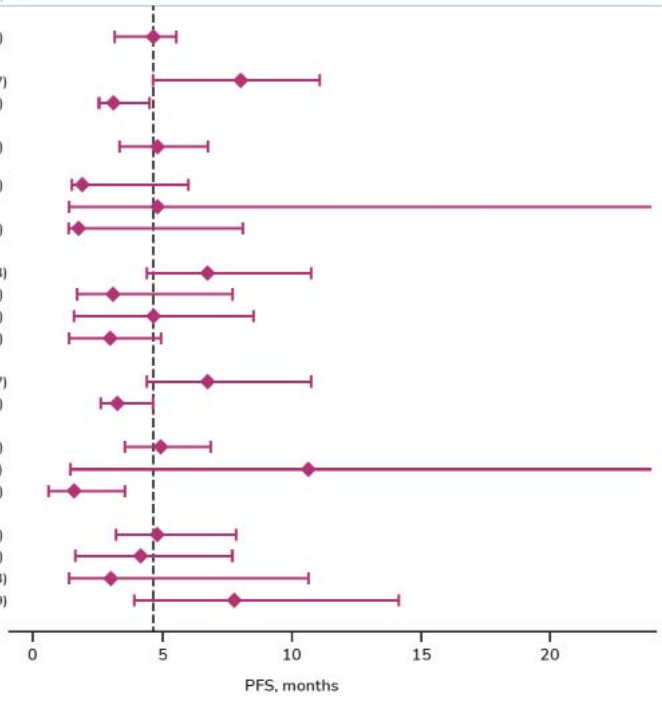

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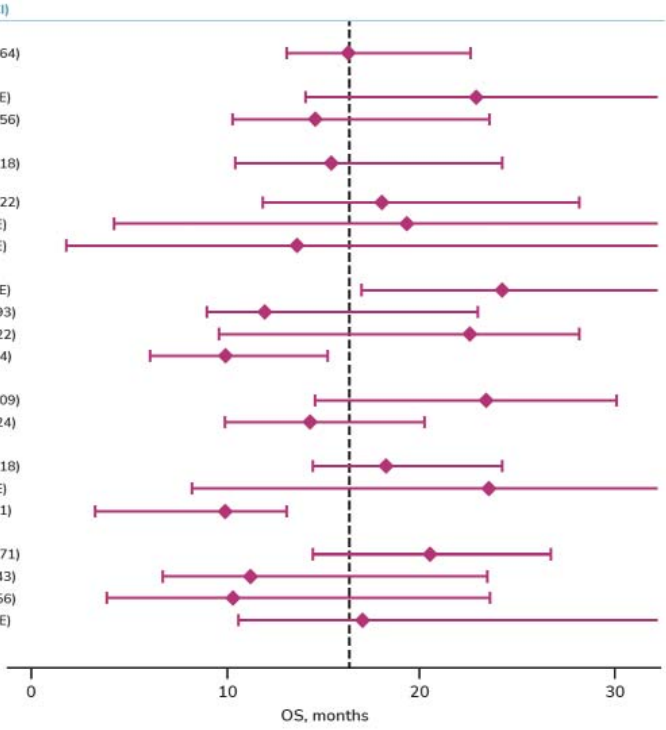
Figure 3

C

Category by subgroup	N	Event (%)	Censor (%)	Median (95% CI)
Overall				
Overall survival (months)	221	129 (58.4%)	92 (41.6%)	16.33 (13.11, 22.64)
Relapsed/Refractory				
Relapsed	54	29 (53.7%)	25 (46.3%)	22.93 (14.59, NE)
Refractory	119	70 (58.8%)	49 (41.2%)	14.65 (10.32, 23.56)
PTCL histological subtype by central review*				
Peripheral T cell lymphoma not otherwise specified (NOS)	108	63 (58.3%)	45 (41.7%)	15.44 (10.51, 24.18)
Angioimmunoblastic T cell lymphoma	47	28 (59.6%)	19 (40.4%)	18.00 (11.89, 28.22)
Anaplastic large cell lymphoma, ALK negative	26	14 (53.8%)	12 (46.2%)	19.32 (4.24, NE)
Transformed mycosis fungoides	12	9 (75.0%)	3 (25.0%)	13.65 (1.74, NE)
Number of prior chemotherapy lines				
1	76	38 (50.0%)	38 (50.0%)	24.18 (17.02, NE)
2	60	38 (63.3%)	22 (36.7%)	11.99 (9.03, 22.93)
3	38	21 (55.3%)	17 (44.7%)	22.51 (9.63, 28.22)
≥4	47	32 (68.1%)	15 (31.9%)	9.95 (6.14, 15.24)
Response to the most recent prior therapy				
Responder (CR+CRu+PR)	84	45 (53.6%)	39 (46.4%)	23.39 (14.59, 30.09)
Non-responder	137	84 (61.3%)	53 (38.7%)	14.29 (9.95, 20.24)
Type of prior systemic therapy*				
Chemotherapy only	162	93 (57.4%)	69 (42.6%)	18.23 (14.42, 24.18)
Chemotherapy, transplant	26	13 (50.0%)	13 (50.0%)	23.56 (8.21, NE)
Chemotherapy, other	16	13 (81.3%)	3 (18.8%)	9.95 (3.19, 13.11)
Type of prior chemotherapy*				
Anthracycline-based only	102	56 (54.9%)	46 (45.1%)	20.50 (14.42, 26.71)
Anthracycline, platinum, gemcitabine-based	53	33 (62.3%)	20 (37.7%)	11.24 (6.77, 23.43)
Anthracycline, platinum-based	33	21 (63.6%)	12 (36.4%)	10.35 (3.84, 23.56)
Not anthracycline or platinum or gemcitabine-based	18	11 (61.1%)	7 (38.9%)	17.02 (10.61, NE)

*Only categories with N>10 are displayed.



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