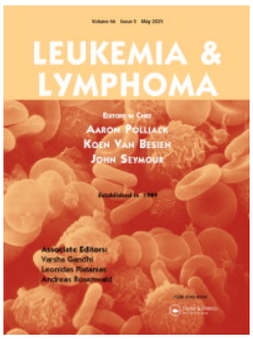

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ORIGINAL ARTICLE

Results from an open-label phase 2a study of cerdulatinib, a dual spleen tyrosine kinase/janus kinase inhibitor, in relapsed/refractory peripheral T-cell lymphoma

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ABSTRACT

In this phase-2a study (NCT01994382), patients aged ≥18 years with relapsed/refractory peripheral T-cell lymphoma (PTCL; angioimmunoblastic T-cell lymphoma/T follicular helper [AITL/TFH], $n=29$); PTCL-not otherwise specified [NOS], $n=11$; and Other, $n=25$) received 30 mg oral cerdulatinib, a reversible dual inhibitor of spleen tyrosine kinase and Janus kinase, twice daily in 28-day cycles until disease progression or unacceptable toxicity. Overall response rate (ORR) was 36.2% (12 complete responses [CR],9 partial responses [PR], and 14 stable disease); median time to response was 1.9 months. ORR was 51.9% for AITL/TFH (10 CR, 4 PR) and 31.8% for Other (2 CR, 5 PR); median duration of response was 12.9 and 5.3 months, respectively. The most common grade ≥3 treatment-emergent adverse events were asymptomatic amylase elevation (23.1%), anemia (20.0%), and asymptomatic lipase elevation (18.5%). These data suggest clinical activity and acceptable tolerability for cerdulatinib in patients with relapsed/refractory PTCL.

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Peripheral T-cell lymphoma; dual spleen tyrosine kinase/janus kinase inhibitor; phase-2 study; relapsed/refractory

Introduction

Peripheral T-cell lymphoma (PTCL) comprises a heterogeneous group of T-cell non-Hodgkin lymphoma subtypes characterized by chemoresistance and poor prognosis [1,2]. PTCL is uncommon in the USA, with 7000–10,000 new cases diagnosed annually [3,4]. The most common PTCL subtypes are PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL)/T follicular helper (TFH) subtypes, and anaplastic large-cell lymphoma (ALCL) [5]. In North America, PTCL-NOS and AITL account for approximately 30% and 20% of cases of PTCL with estimated 5-year overall survival (OS) rates of 32% and 44%, respectively [5–7].

Patients with PTCL frequently experience relapsed/refractory disease after front-line therapy with cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone (CHOP)/CHOP-like combination chemotherapy regimens, or brentuximab vedotin-CHOP [2,8]. Goals of subsequent therapy are deep or complete response for potentially curative successful allogeneic stem-cell transplantation or maintenance therapy to control disease [2]. Systemic treatment options include monotherapy (chemotherapy, immunomodulators, or targeted therapies), platinum-based or alternative chemotherapy combinations, or investigational drugs [2]. The Food and Drug Administration has approved four agents for relapsed/refractory PTCL since 2009, including pralatrexate (an antifolate) and two histone deacetylase inhibitors, romidepsin (subsequently withdrawn due to lack of observed benefit) and belinostat, and brentuximab vedotin (for relapsed/refractory ALCL andrelapsed/refractory CD30-positive PTCL [2,9,10]. However, none of these agents are curative, underscoring an urgent need for treatments with high efficacy [11–15]. Survival after relapse is poor with a median OS

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of 5.8 months and 3-year OS rates of 21% and 28% for refractory and relapsed patients, respectively [16].

The spleen tyrosine kinase (SYK) and Janus kinase (JAK) signaling pathways have been implicated in the pathogenesis of PTCL [17]. Interaction with pro-inflammatory cytokines and immune cells in the tumor microenvironment appears to be critical for the proliferation and survival of malignant T cells [18]. Gene expression profiling of PTCL suggests frequent dependency on cytokine-mediated JAK/STAT signaling for tumor cell survival [19]. Furthermore, activating mutations in components of the JAK/STAT signaling pathway and aberrant SYK expression frequently occur in malignant cells from some patients with PTCL [20–22]. Preclinical studies in mice show that expression of the SYK-inducible T-cell kinase fusion protein potentiates T-cell receptor signaling and induces lethal T-cell proliferative disease [20,23]. Silencing SYK induces apoptosis and blocks T-cell proliferation [24]. Collectively, these data implicate the SYK and JAK signaling pathways in T-cell proliferation and survival in PTCL.

Cerdulatinib (ALXN2075), an orally available, small-molecule, reversible ATP-competitive inhibitor of SYK, JAK1, JAK3, and TYK2, is under investigation for B- and T-cell malignancies [25]. A phase-1 dose-escalation and dose-expansion study of cerdulatinib (NCT01994382) confirmed concentration-dependent and reversible SYK/JAK pathway inhibition in peripheral whole blood at steady-state trough concentrations [26]. Doses of up to 35 mg twice daily were well tolerated with consistent anti-tumor activity in 43 patients with relapsed/refractory B-cell malignancies [27].

We report here the final efficacy and safety results from the dose-expansion cohort of patients with relapsed/refractory PTCL who received single-agent cerdulatinib.

Methods

Study design

This phase-2a, multicenter, open-label, single-arm, dose-expansion study (NCT01994382) conducted between May 2016 and March 2021 assessed the anti-tumor activity and safety of cerdulatinib in patients with relapsed/refractory T- and B-cell malignancies. The study was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. Institutional review boards and independent ethics committees reviewed and approved the protocols and trial documentation before study initiation. All patients provided written informed consent before participation.

Patients were enrolled across six cohorts according to malignancy and study treatment: PTCL, indolent B-cell lymphoma (predominantly follicular lymphoma) treated with monotherapy, follicular lymphoma treated with rituximab combination therapy, diffuse large B-cell and mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and cutaneous T-cell lymphoma. The study was conducted at 24 centers in the United States.

Patients attended a screening visit within 21 days before the first cerdulatinib dose. Study visits were scheduled on Days 1, 8, and 15 of Cycle 1; Days 1 and 15 of Cycle 2; Day 1 of every subsequent 28-day cycle; and 30 days after the last administered cerdulatinib dose.

Participants

Patients with relapsed/refractory PTCL aged ≥18 years, and who had received ≥1 prior systemic treatment for PTCL for ≥2 cycles were eligible for this study [28]. Patients with CD30-expressing PTCL were required to have received prior treatment with a CD30-directed antibody (e.g. brentuximab vedotin). Relapsed/refractory disease was defined as having achieved less than partial response (PR), or having relapsed within 6 months on prior therapy, as determined by the investigator. Patients were required to have ≥1 lesion (excluding skin) that measured ≥1.5 cm in a single dimension by computed tomography (CT) or CT/positron emission tomography, an Eastern Cooperative Oncology Group performance status score of 0–1, absolute neutrophil count (ANC) ≥1000/μL, platelet count ≥75,000/μL, and adequate renal and hepatic function. Full details of study inclusion and exclusion criteria are given in the Supplemental Information.

Treatment

Patients received oral cerdulatinib (Alexion, AstraZeneca Rare Disease, Boston, MA, USA) monotherapy at a starting dose of 30 mg twice daily (recommended phase-2 dose) in 28-day cycles until disease progression or unacceptable toxicity. Dose interruptions and reductions to 25 mg, 20 mg, then 15 mg twice daily, and subsequent dose escalation back to 30 mg were permitted at the investigator's discretion depending on the severity of adverse events (AEs). Patients with dose interruption of >28 days, and those who experienced grade ≥3 AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 at the 15 mg dose level were permanently

discontinued from the study. Following Epstein–Barr virus (EBV) reactivation in one patient, the protocol was revised to allow investigators to interrupt cerdulatinib dosing for patients with EBV reactivation confirmed by a positive peripheral blood quantitative EBV polymerase chain reaction (PCR) assay. An EBV PCR assay was conducted postbaseline where there was clinical suspicion of EBV reactivation because of unexplained fever. Cerdulatinib dosing was resumed after symptomatic treatment for EBV (optional rituximab 375 mg/m^2 until EBV PCR assay negative) and normalization of viral load. Following a protocol amendment, investigators were permitted to continue cerdulatinib without dose modification or interruption for patients with asymptomatic elevations of amylase or lipase. Patients were required to receive antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia, nocardia, and herpes simplex virus. Vaccination (e.g., influenza, pneumonia) was encouraged before study entry (see Supplemental Information for further details). Patients could also receive prophylaxis for tumor lysis syndrome at the investigator's discretion.

Assessments and outcomes

Tumor response for nodal/extranodal/cutaneous PTCL was based on investigator assessment of CT or CT/positron emission tomography scans conducted at the end of Cycle 2, and every three cycles thereafter, and was categorized using the Lugano classification criteria [29]. For patients with leukemic forms of PTCL, disease-appropriate classification criteria were used [2].

The primary endpoint was investigator-assessed overall response rate (ORR), defined as a sum of best overall response including complete response [CR] and PR. Predefined secondary endpoints included ORR by histologic subtype, time to response (TTR; time from the start of cerdulatinib treatment to the first documented CR or PR), duration of response (DoR; time from first documented CR or PR to the earliest of disease progression or death from any cause), clinical benefit rate (CBR; stable disease or better as the best overall response per Lugano criteria as assessed by the investigator), and progression-free survival (PFS; time from the start of cerdulatinib treatment to the earliest of disease progression or death from any cause) [29].

Safety was assessed based on AEs graded according to NCI-CTCAE, version 4.03 or 5.0.

Statistical analyses

The safety analysis set included all patients who received ≥1 dose of cerdulatinib. Efficacy was evaluated in the efficacy-evaluable analysis set, which included all patients who received ≥1 dose of cerdulatinib and had a baseline and ≥1 postbaseline scan. A sensitivity analysis of efficacy in the safety analysis population was also conducted.

Demographics and baseline disease characteristics were summarized descriptively. ORR and CBR were summarized along with two-sided 95% confidence intervals (CI) estimated by the Clopper-Pearson method. The Kaplan–Meier method was used to analyze time to events, except for TTR, which was summarized descriptively. DoR was analyzed in patients with CR or PR. DoR and PFS were censored if patients had no baseline disease assessment, started a new cancer therapy before disease progression or death, had disease progression or death >6 months after the last disease assessment, or were alive without disease progression at their last follow-up visit. The 95% CI and quartiles for median DoR and PFS were estimated using the Brookmeyer method [30]. No imputation for missing data was performed.

Statistical analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA). Data were analyzed by the sponsor, Alexion, AstraZeneca Rare Disease. All authors had access to the primary clinical trial data on request.

Results

Participants

The study enrolled and treated 220 patients, including 65 with PTCL (Figure 1). The PTCL cohort included patients with the AITL/TFH subtype ($n=29$), PTCL-NOS ($n=11$), and Other subtypes ($n=25$; gamma-delta T-cell lymphoma [$n=5$: cutaneous, $n=4$; cutaneous+lymph node, $n=1$], adult T-cell leukemia/lymphoma [$n=5$], ALK-negative ALCL [$n=3$], hepatosplenic T-cell lymphoma [$n=4$: gamma-delta, $n=3$; unknown subtype, $n=1$], CD4-positive PTCL [$n=2$], T-cell prolymphocytic leukemia [$n=2$], large granular lymphocytic leukemia [$n=1$], aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma [$n=1$], NK T-cell lymphoma [$n=1$], and monomorphic epitheliotropic intestinal T-cell lymphoma [$n=1$]).

All patients with PTCL have discontinued from the study. Disease progression was the most common reason for treatment discontinuation in the total PTCL cohort (44/62; 71.0%) and across subtypes (Figure 1). Six patients discontinued treatment because of AEs of EBV reactivation ($n=2$) and West Nile viral infection, sepsis, infection, and colitis (each $n=1$). Two patients (AITL/TFH [$n=1$], primary cutaneous gamma-delta T-cell lymphoma [$n=1$]) discontinued treatment to undergo stem-cell transplant.

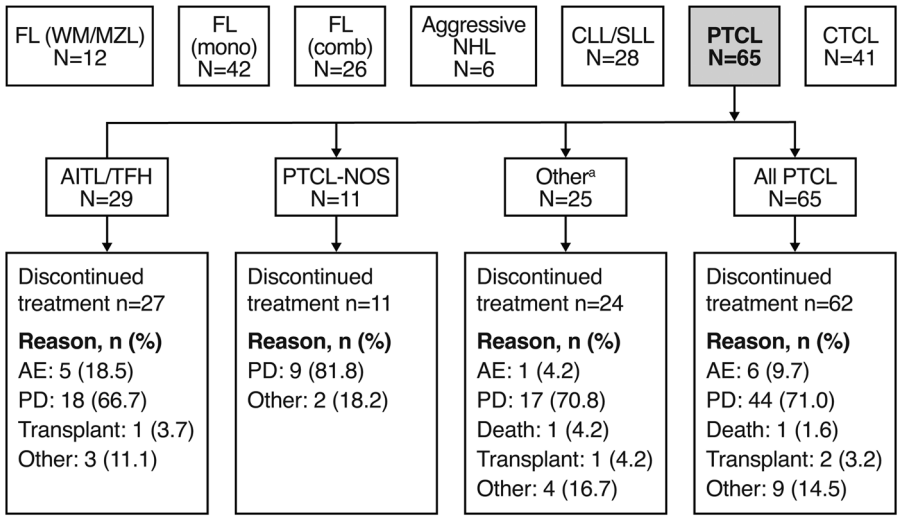

Figure 1. Patient disposition for the total PTCL cohort and by histologic subtypes.
[a]Other subtypes included gamma-delta T-cell lymphoma (n=5: cutaneous, n=4; cutaneous + lymph node, n=1); adult T-cell leukemia/lymphoma (n=5); ALK-negative anaplastic large-cell lymphoma (n=3); hepatosplenic T-cell lymphoma (n=4: gamma-delta, n=3; unknown subtype, n=1); CD4-positive PTCL (n=2); T-cell prolymphocytic leukemia (n=2); large granular lymphocytic leukemia (n=1); aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma (n=1); natural killer T-cell lymphoma (n=1); and monomorphic epitheliotropic intestinal T-cell lymphoma (n=1).
Abbreviations: AE, adverse event; AITL, angioimmunoblastic T-cell lymphoma; CLL, chronic lymphocytic leukemia; comb: combination; CTCL, cutaneous T-cell lymphoma; FL, follicular lymphoma; mono, monotherapy; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; PD, progressive disease; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic leukemia; TFH, T follicular helper; WM, Waldenström macroglobulinemia.

The majority of patients in the PTCL cohort were male, and median age was 65 years (Table 1). Median time since diagnosis was 22.3 months. Patients had received a median (range) of 2 (1–10) prior regimens. The majority of patients (70.8%) had received CHOP/CHOP-like or cyclophosphamide-combination regimens. Previous therapies included brentuximab vedotin, pralatrexate, and romidepsin, received by 23.1%, 15.4%, and 30.8% of patients, respectively, in the PTCL cohort. Overall, 27.7% of patients with PTCL had prior stem-cell transplant and 23.1% had prior radiotherapy. In the total PTCL cohort, 50.8% of patients had relapsed and 49.2% were refractory to their last therapy. Median time since last regimen was 1.8 months for the total PTCL cohort (Table 1).

Efficacy

Seven patients discontinued before their first assessment for reasons other than disease progression (physician decision, $n=3$; withdrawal by patient, $n=2$; AE, $n=1$; sudden death, $n=1$).

Among the 58 efficacy-evaluable patients, ORR was 36.2% for all PTCL, 51.9% for AITL/TFH, 0% for PTCL-NOS, and 31.8% for Other subtypes (Table 2). In a sensitivity analysis of those who received ≥1 dose of cerdulatinib (safety analysis set), ORR was 32.3% (Online Supplementary Table S1). Twelve patients had a best overall response of CR, including patients with the AITL/TFH subtype ($n=10$), ALK-negative ALCL ($n=1$), and cutaneous gamma-delta T-cell lymphoma ($n=1$). PRs ($n=9$) were observed for AITL/TFH ($n=4$) and Other subtypes ($n=5$): NK/T-cell lymphoma ($n=1$), adult T-cell leukemia/lymphoma ($n=2$), large granular lymphocytic leukemia ($n=1$), and aggressive epidermotropic CD8-positive lymphoma ($n=1$). Twenty-three patients had progressive disease as best response, including patients with AITL/TFH ($n=10$), PTCL-NOS ($n=7$), and Other subtypes ($n=6$). Overall CBR was 60.3% (Figure 2(A)).

Median (range) TTR was 1.9 (1.5–16.5) months for the total PTCL cohort, 1.9 (1.5–16.5) months for AITL/TFH, 1.9 (1.7–4.4) months for Other subtypes, and not assessed for PTCL-NOS. Median (range) time on cerdulatinib treatment for the efficacy-evaluable analysis set was 2.9 (0.2–37.9) months for all PTCL and 3.3 (0.5–37.9) months for AITL/TFH (Figure 2(B)). The median time on last prior therapy was 2.2 months and 3.0 months for all PTCL and AITL/TFH, respectively.

Median (range) DoR based on Kaplan–Meier analysis was 12.9 (<0.1–35.5) months for AITL/TFH and 5.3 (1.0–26.2) months for Other subtypes, with median (range) follow-up of 16.4 (<0.1–35.5) months and 26.2 (1.0–26.2) months, respectively (Figure 3(A)). Based on Kaplan–Meier analysis, the median (range) PFS for the total PTCL cohort was 3.3 (0.3–37.4) months with median (range) follow-up of 22.4 (0.3–37.4) months (Figure 3(B)). Median PFS was reached for all subtypes:

Table 1. Demographics and baseline disease characteristics for the total PTCL cohort and by histologic subtype (safety analysis set).

	AITL/TFH	PTCL-NOS	Other[a]	Total PTCL
	(*N* = 29)	(*N* = 11)	(*N* = 25)	(*N* = 65)
Age				
Median (range), years	70 (45-84)	67 (51-79)	59 (21-85)	65.0 (21-85)
>65 years, n (%)	17 (58.6)	6 (54.5)	9 (36.0)	32 (49.2)
Male, n (%)	20 (69.0)	7 (63.6)	14 (56.0)	41 (63.1)
Stage,[b] n (%)				
II/IIE	0/2 (6.9)	1 (9.1)/0	0/0	1 (1.5)/2 (3.1)
III	6 (20.7)	5 (45.5)	2 (8.0)	13 (20.0)
IV	20 (69.0)	5 (45.5)	18 (72.0)	43 (66.2)
ECOG PS, n (%)				
0 or 1	28 (96.6)	11 (100.0)	25 (100.0)	64 (98.5)
2	1 (3.4)[c]	0 (0.0)	0 (0.00)	1 (1.5)[c]
Time since diagnosis, months, median (range)	27.7 (0.9-258.2)	9.1 (2.4-101.2)	16.6 (1.5-68.4)	22.3 (0.9-258.2)
Number of prior regimens, median (range)	2 (1-10)	2 (1-8)	2 (1-9)	2 (1-10)
Prior therapies, n (%)				
CHOP/CHOP-like or cyclophosphamide combinations	23 (79.3)	11 (100.0)	12 (48.0)	46 (70.8)
Cisplatin-containing combinations	5 (17.2)	4 (36.4)	7 (28.0)	16 (24.6)
Brentuximab vedotin monotherapy/combination	9 (31.0)	0 (0.0)	6 (24.0)	15 (23.1)
Pralatrexate (dihydrofolate reductase)	3 (10.3)	1 (9.1)	6 (24.0)	10 (15.4)
Romidepsin	11 (37.9)	3 (27.3)	6 (24.0)	20 (30.8)
Lenalidomide	4 (13.8)	2 (18.2)	1 (4.0)	7 (10.8)
Prior radiotherapy, n (%)	2 (6.9)	2 (18.2)	11 (44.0)	15 (23.1)
Prior stem-cell transplant, n (%)	11 (37.9)	3 (27.3)	4 (16.0)	18 (27.7)
Relapsed, n (%)	19 (65.5)	4 (36.4)	10 (40.0)	33 (50.8)
Refractory to last therapy, n (%)	10 (34.5)	7 (63.6)	15 (60.0)	32 (49.2)
Time since last regimen, median (range)	4.4 (0.5-134.2)	2.0 (0.9-59.8)	1.0 (0.1-41.3)	1.8 (0.1-134.2)
LDH > ULN, n (%)[d]	11 (37.9)	6 (54.5)	13 (52.0)	30 (46.2)
CRP and/or ESR > ULN, n (%)[d]	18 (62.1%)	8 (72.2%)	10 (40.0%)	36 (55.4%)
Beta-2 microglobulin > LLN, n (%)[d]	29 (100.0)	11 (100.0)	24 (96.0)	64 (98.5)
Serum albumin <4.0 g/dL, n (%)[d]	13 (44.8)	6 (54.5)	14 (56.0)	33 (50.8)
ANC, n (%)		0		
<1000/mm^3	3 (10.3)	0	2 (8.0)	5 (7.7)
<1500/mm^3	4 (13.8)		5 (20.0)	9 (13.8)

[a]Other subtypes included gamma-delta T-cell lymphoma (*n* = 5: cutaneous, *n* = 4; cutaneous + lymph node, *n* = 1); adult T-cell leukemia/lymphoma (*n* = 5); ALK-negative anaplastic large-cell lymphoma (*n* = 3); hepatosplenic T-cell lymphoma (*n* = 4: gamma-delta, *n* = 3; unknown subtype, *n* = 1); CD4-positive PTCL (*n* = 2); T-cell prolymphocytic leukemia (*n* = 2); large granular lymphocytic leukemia (*n* = 1); aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma (*n* = 1); natural killer T-cell lymphoma (*n* = 1); and monomorphic epitheliotropic intestinal T-cell lymphoma (*n* = 1).
[b]Ann Arbor stage, assessed by investigator.
[c]One patient with ECOG PS 2 was recruited at the investigator's discretion with the sponsor's approval.
[d]Last non-missing value prior to initiating study drug.
Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ANC, absolute neutrophil count; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; LLN, lower limit of normal range; NOS, not otherwise specified; PS, performance status; PTCL, peripheral T-cell lymphoma; TFH, T follicular helper; ULN, upper limit of normal range.

4.6 (0.6–37.4) months for AITL/TFH, 1.2 (0.3–3.9) months for PTCL-NOS, and 3.5 (0.8–30.6) months for Other subtypes (Figure 3(C)).

Safety

Median (range) cerdulatinib treatment duration for all patients with PTCL in the safety analysis set was 2.8 (0.2–36.7) months. All patients in the PTCL cohort experienced treatment-emergent AEs (TEAEs; Table 3), of which 92.3% were considered by the investigator to be cerdulatinib-related. The most common TEAEs were gastrointestinal disorders, reported for 73.8% of patients. The most common TEAEs by preferred term were amylase increased (43.1%), diarrhea (43.1%), nausea (33.8%), anemia (32.3%), lipase increased (29.2%), fatigue (27.7%), and abdominal pain (26.2%). The most common cerdulatinib-related TEAEs were amylase increased (41.5%), diarrhea (38.5%), nausea (27.7%), lipase increased (27.7%), and fatigue (18.5%). The majority of patients (89.2%) experienced grade ≥3 TEAEs, including disease progression as an AE; the most common grade ≥3 TEAEs were amylase increased (23.1%), anemia (20.0%), lipase increased (18.5%), neutrophil count decreased (13.8%), and/or neutropenia (12.3%) (Table 3). Elevations in amylase and lipase were transient and reversible and were not associated with clinical pancreatitis. Eight patients (12.3%) had

Table 2. Tumor response for the total PTCL cohort and by histologic subtype (efficacy-evaluable analysis set).

	AITL/TFH	PTCL-NOS	Other[a]	Total PTCL
	(*N* = 27)	(*N* = 9)	(*N* = 22)	(*N* = 58)
Best overall response, n				
CR	10	0	2	12
PR	4	0	5	9
SD	3	2	9	14
PD	10	7	6	23
Missing	0	0	0	0
Overall response rate,[b] n (%) (95% CI)	14 (51.9) (31.9–71.3)	0 (0.0) (0–33.6)	7 (31.8) (13.9–54.9)	21 (36.2) (24.0–49.9)
Clinical benefit rate,[c] n (%) (95% CI)	17 (63.0) (42.4–80.6)	2 (22.2) (2.8–60.0)	16 (72.7) (49.8–89.3)	35 (60.3) (46.6–73.0)

Efficacy-evaluable patients had baseline and ≥1 follow-up assessment. Tumor responses were investigator-assessed based on Lugano classification.

[a]Other subtypes included gamma-delta T-cell lymphoma (*n* = 5: cutaneous, *n* = 4; cutaneous + lymph node, *n* = 1); adult T-cell leukemia/lymphoma (*n* = 4); ALK-negative anaplastic large-cell lymphoma (*n* = 3); hepatosplenic T-cell lymphoma (*n* = 3: gamma-delta, *n* = 2; unknown subtype, *n* = 1); CD4-positive PTCL (*n* = 2); T-cell prolymphocytic leukemia (*n* = 1); large granular lymphocytic leukemia (*n* = 1); aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma (*n* = 1); natural killer T-cell lymphoma (*n* = 1); and monomorphic epitheliotropic intestinal T-cell lymphoma (*n* = 1).

[b]PR or better.

[c]SD or better.

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; CI, confidence interval; CR, complete response; NOS, not otherwise specified; PD, progressive disease; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease; TFH, T follicular helper.

EBV viral load changes, for which five patients received rituximab; three reactivations were considered cerdulatinib related. Two patients had *P. jirovecii* pneumonia (3.1%) and one had nocardiosis (1.5%). Serious TEAEs were reported for 64.6% of patients and included neoplasm progression (20.0%), sepsis (9.2%), pyrexia (7.7%), pneumonia (4.6%), and diarrhea (4.6%). Two deaths not associated with disease progression were considered to be related to cerdulatinib by the investigator: one each due to infection and sepsis.

Six patients (9.2%) discontinued cerdulatinib during the study because of TEAEs unrelated to disease progression: EBV reactivation (*n* = 2), and infection, West Nile virus, colitis, and sepsis (each *n* = 1). Dose interruptions and modification because of TEAEs were most frequently associated with gastrointestinal (18.5% and 9.2%, respectively) and infections and infestations (27.7% and 6.2%, respectively) toxicities.

Discussion

The results of our phase-2a study evaluating monotherapy with cerdulatinib, an oral inhibitor of SYK/JAK signaling, in heavily pretreated patients with relapsed/refractory PTCL are encouraging with a favorable benefit-risk profile. The ORR for cerdulatinib was 36.2% for the total PTCL efficacy cohort and generally consistent with those for the approved agents pralatrexate (29.4%, including 11.0% CR) and belinostat (25.8%, including 10.8% CR) [12,13]. However, in our study, there were marked differences in the responses between subtypes ranging from 51.9% for patients with AITL/TFH and 31.8% for patients with Other histologic subtypes to 0% for patients with PTCL-NOS. By comparison, the ORRs for patients with AITL and PTCL-NOS subtypes were 7.7% and 32.2%, respectively among patients treated with pralatrexate and 45.5% and 23.3%, respectively among patients treated with belinostat [12,13]. In contrast to the oral delivery of cerdulatinib, these approved agents are infused. These data suggest that cerdulatinib may be more effective in patients with some subtypes, for example, AITL than others, for example, PTCL-NOS. The differences in responses to cerdulatinib observed across PTCL subtypes highlights the importance of disease classification and suggests the need for more subtype-specific treatment investigations.

In our study, 10/27 (37.0%) evaluable patients with the AITL/TFH achieved CR and four (14.8%) achieved PR. Most of these responses were maintained for >6 months with five patients maintaining response for >12 months. Notably, the median age of patients in this subgroup was 70 years, with 58.6% of these patients being >65 years of age and with limited treatment options. Furthermore, median DoR in this subgroup was approximately 1 year. This subtype has a complex tumor microenvironment with extensive infiltration by nontumor leukocytes generating a pro-inflammatory microenvironment that may contribute to tumor cell survival [31]. Hence, the efficacy observed in patients with AITL/TFH may be a consequence of dual SYK/JAK blockade with cerdulatinib impacting intrinsic tumor signals and disrupting the supportive tumor microenvironment.

The lack of therapeutic response in the PTCL-NOS subgroup was unexpected. PTCL-NOS encompasses a heterogenous patient population, including subtypes with diverse underlying pathogenetic mechanisms and treatment outcomes. In one study of the selective JAK1/2 inhibitor ruxolitinib, ORRs across different patient subgroups ranged from 13% to 53% [32]. The lack of observed objective clinical response in our patients suggests lack of sensitivity to the SYK/JAK mechanism. However, resistance mechanisms and molecular typing/mutation analysis of the PTCL-NOS subtypes were not assessed as part of our study. Further understanding of resistance mechanisms and response predictors in PTCL subpopulations could guide subsequent studies of cerdulatinib to focus on those most likely to benefit. Of note,

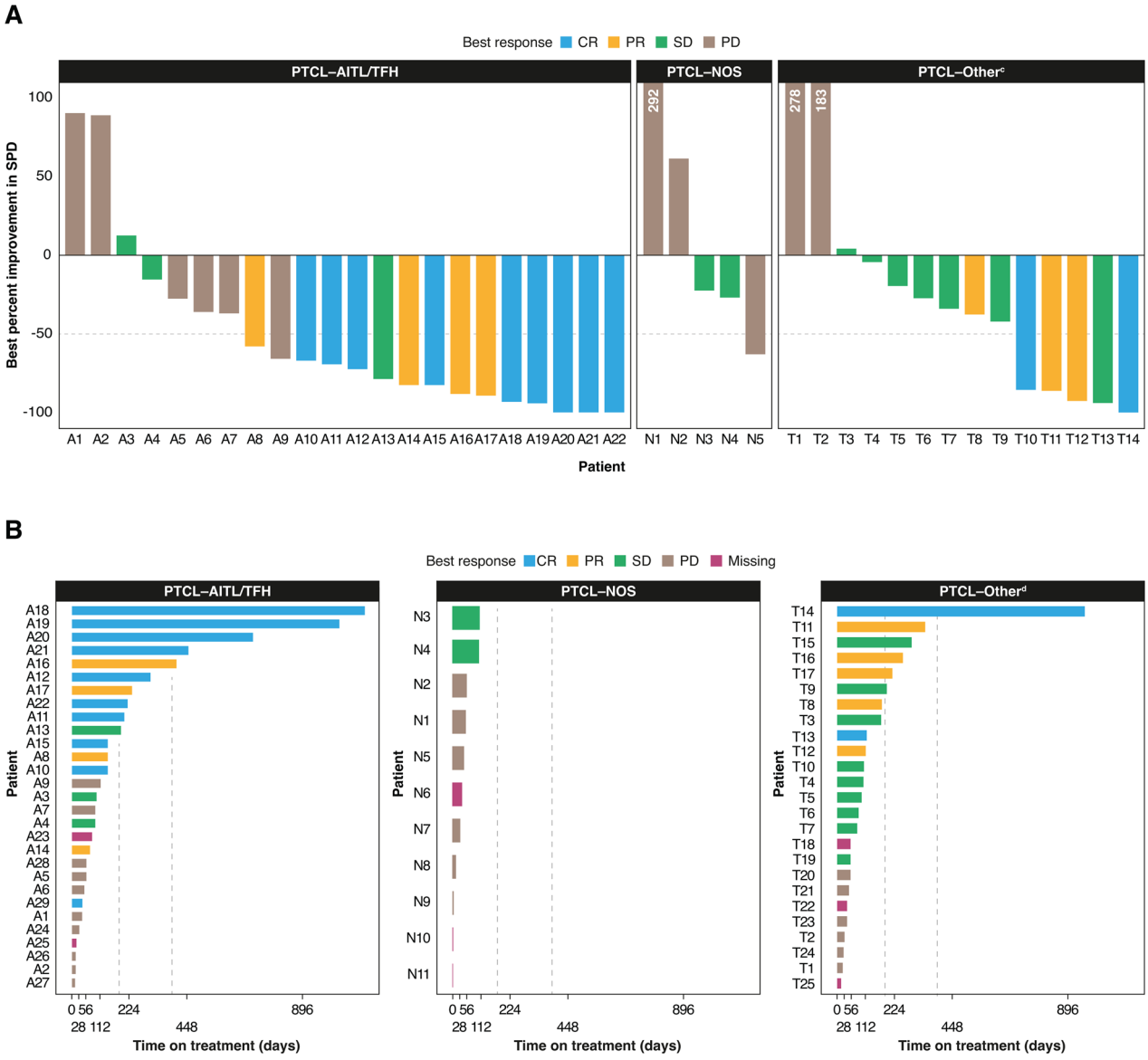

Figure 2. Response characteristics in patients with relapsed/refractory PTCL treated with cerdulatinib. (A) Best change in tumor volume[a] (efficacy-evaluable analysis set) and (B) time on treatment[b] for target lesions by histologic subtype of PTCL (safety analysis set).

[a]Includes only those patients who had ≥1 follow-up assessment. Five additional patients in the efficacy-evaluable analysis set for the AITL/TFH subtype had missing SPD assessments; one of these five patients had CR confirmed by PET scan. [b]Includes patients who did not have a post-baseline assessment. [c]Other subtypes included gamma-delta T-cell lymphoma (n=5: cutaneous, n=4; cutaneous + lymph node, n=1); adult T-cell leukemia/lymphoma (n=4); ALK-negative ALCL (n=3); hepatosplenic T-cell lymphoma (n=3: gamma-delta, n=2; unknown subtype, n=1); CD4-positive PTCL (n=2); T-cell prolymphocytic leukemia (n=1); large granular lymphocytic leukemia (n=1); aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma (n=1); natural killer T-cell lymphoma (n=1); and monomorphic epitheliotropic intestinal T-cell lymphoma (n=1). [d]Other subtypes included gamma-delta T-cell lymphoma (n=5: cutaneous, n=4; cutaneous + lymph node, n=1); adult T-cell leukemia/lymphoma (n=5); ALK-negative ALCL (n=3); hepatosplenic T-cell lymphoma (n=4: gamma-delta, n=3; unknown subtype, n= 1); CD4-positive PTCL (n=2); T-cell prolymphocytic leukemia (n=2); large granular lymphocytic leukemia (n=1); aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma (n=1); natural killer T-cell lymphoma (n=1); and monomorphic epitheliotropic intestinal T-cell lymphoma (n=1).

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; CR, complete response; NOS, not otherwise specified; PD, progressive disease; PET, positron emission tomography; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease; SPD, sum of the products of the greatest perpendicular diameters of the target nodal and extranodal lesions; TFH, T follicular helper.

the PTCL-NOS subgroup was very high risk compared with the other subtypes with more refractory disease at baseline, shorter time since last treatment, and high frequency of relapse despite autologous stem cell transplantation, which may have contributed to the lack of response.

In the subgroup with Other PTCL subtypes, ORR was 31.8% and median DoR was approximately 5 months. CRs were observed in a patient with ALK-negative ALCL and another with cutaneous gamma-delta T-cell lymphoma, a particularly aggressive and chemoresistant subtype of PTCL [33]. Aberrant

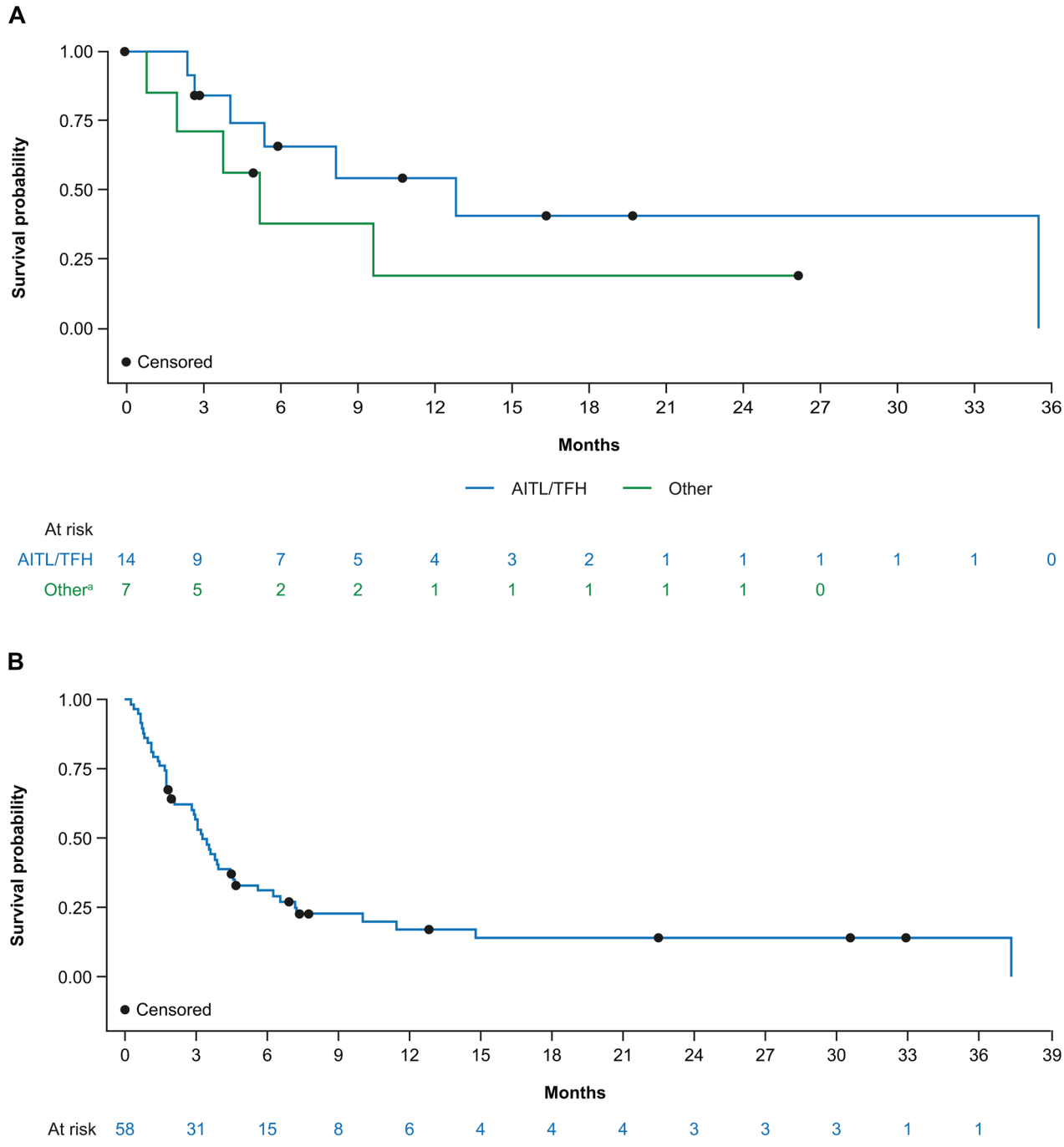

Figure 3. Kaplan-Meier analysis of (A) duration of response for PTCL AITL/TFH and other histologic subtypes (efficacy-evaluable analysis set with objective response), (B) the total PTCL cohort, and (C) AITL/TFH, PTCL-NOS, and other histologic subtypes (efficacy-evaluable analysis set).

In A, Other subtypes with objective response included cutaneous gamma-delta T-cell lymphoma (n=1); adult T-cell leukemia/lymphoma (n=2); ALK-negative anaplastic large-cell lymphoma (n=1); large granular lymphocytic leukemia (n=1); aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma (n=1); and natural killer T-cell lymphoma (n=1).

In B and C, Other subtypes included gamma-delta T-cell lymphoma (n=5: cutaneous, n=4; cutaneous + lymph node, n=1); adult T-cell leukemia/lymphoma (n=4); ALK-negative anaplastic large-cell lymphoma (n=3); hepatosplenic T-cell lymphoma (n=3: gamma-delta, n=2; unknown subtype, n=1); CD4-positive PTCL (n=2); T-cell prolymphocytic leukemia (n=1); large granular lymphocytic leukemia (n=1); aggressive CD8-positive epidermotropic cytotoxic T-cell lymphoma (n=1); natural killer T-cell lymphoma (n=1); and monomorphic epitheliotropic intestinal T-cell lymphoma (n=1).

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; TFH, T follicular helper.

expression of SYK appears almost universally high and JAK/STAT mutations are common in gamma-delta-expressing subtypes of PTCL and thus represent important therapeutic targets [20,22,34]. Although the decreases in tumor volume elicited by cerdulatinib were not durable (<6 months), 1 of 6 patients

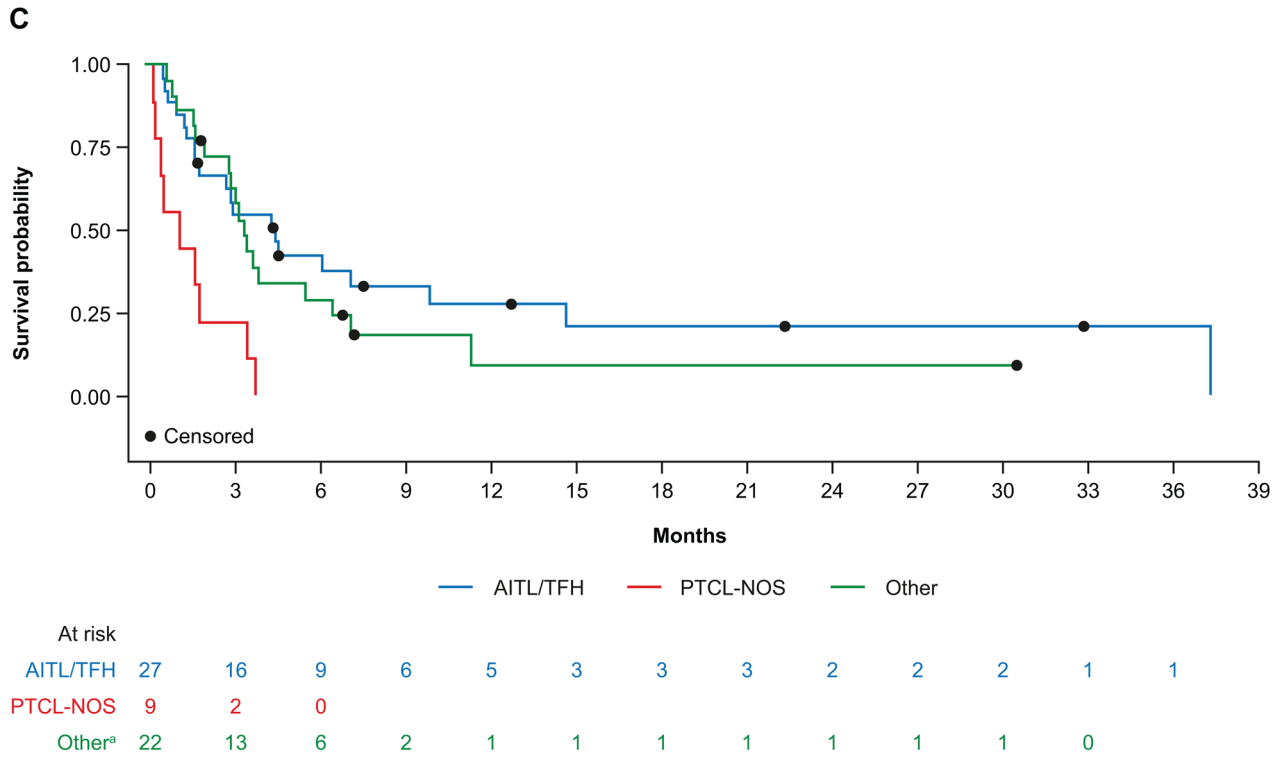

Figure 3. Continued.

Table 3. Overview of TEAEs for the PTCL cohort (safety analysis set).

AE, n (%)	PTCL (*N* = 65)
≥1 TEAE	65 (100.0)
≥1 treatment-related TEAE	60 (92.3)
Serious AE	42 (64.6)
Deaths within 30 days of last dose due to AEs	14 (21.5)
Dose reductions due to TEAEs	19 (29.2)
Dose interruptions	41 (63.1)
Discontinuations due to TEAEs	21 (32.3)
Grade ≥3 TEAEs	58 (89.2)
Grade ≥3 TEAEs in ≥5% of patients in the PTCL cohort[a]	
Amylase increased	15 (23.1)
Anemia	13 (20.0)
Lipase increased	12 (18.5)
Neutrophil count decreased	9 (13.8)
Neutropenia	8 (12.3)
Sepsis	6 (9.2)
Diarrhea	5 (7.7)

[a]Excludes Grade ≥3 TEAEs of disease progression in 13 (20.0%) patients.
Abbreviations: AE, adverse event; PTCL, peripheral T-cell lymphoma; TEAE, treatment-emergent adverse event.

experienced a CR and another had marked tumor reduction, suggesting that cerdulatinib may be useful as part of a combination regimen for patients with this subtype. These subtypes of PTCL represent another patient population with a significant need for new therapies where further exploration of cerdulatinib is of interest. Our results support careful consideration of treatment benefit by histologic subtype in future investigations.

Treatment with cerdulatinib had side effects which were manageable, with transient and reversible elevations of asymptomatic amylase and lipase being most common. These elevations were generally without concurrent acute pancreatic inflammation (chemical pancreatitis), even in those asymptomatic patients who underwent CT scans of the pancreas (data not shown). Initially, amylase/lipase elevations were managed by interruption of cerdulatinib and did not recur upon re-challenge with cerdulatinib (data not shown). The elevations in amylase and lipase concentrations typically occurred within days of treatment initiation and were self-limiting irrespective of treatment interruptions. Consequently, guidance was introduced to continue dosing through this laboratory-observed phenomenon. The mechanism underlying these pancreatic-enzyme elevations is unclear. Gastrointestinal toxicities were the most common reason for dose modifications/interruptions. Although a gastrointestinal toxicity management algorithm was developed and introduced, uniform implementation may have reduced the need for modification of cerdulatinib dosing.

There were several viral and opportunistic infections observed in this trial. This includes eight instances of EBV reactivation, two cases of *P. jirovecii* infection, and one instance of nocardiosis. These numbers are somewhat higher than might be expected with other agents used in the treatment of PTCL and warrant strong

consideration of antimicrobial prophylaxis in any future investigations. The rationale for increased opportunistic infections likely lies in the combination of off-target effects of cerdulatinib in a heavily pretreated patient population. Antimicrobial prophylaxis for pneumocystis and nocardia was required in the study and was administered to 75% of patients. No patients in the study experienced serious SARS-CoV-2 infection, a concern with any immunosuppressive therapy.

With the exception of thrombocytopenia, the safety findings are comparable with other agents used in PTCL treatment. In the romidepsin trial, the most frequent grade ≥3 TEAEs were thrombocytopenia (24.4%), neutropenia (19.8%), and infections (19.1%) [14]. In the pralatrexate study, the most frequent grade ≥3 TEAEs were thrombocytopenia (32.4%), mucositis (21.6%), neutropenia (21.6%), and anemia (18.0%) [12]. In the duvelisib trial, the most frequently observed grade ≥3 TEAEs in a combined population of patients with PTCL and cutaneous T-cell lymphoma were transaminase elevations (40.0% alanine/aspartate aminotransferase), maculopapular rash (17.1%), pneumonia (17.1%), and neutropenia (17.1%) [35].

Limitations of this study include the single-arm design, small sample size, and the inherent heterogeneity of this disease. The inclusion of disease progression events as AEs and the insufficient duration of follow-up for death or disease progression also limit interpretation of the study findings. In addition, data on dose reductions and discontinuations because of AEs are impacted by the lack of consistent antimicrobial prophylaxis throughout the duration of the study and failure to implement a uniform gastrointestinal toxicity management algorithm.

There remains significant unmet therapeutic need for patients with relapsed/refractory PTCL. In this context, there is encouraging efficacy and an acceptable safety signal with the convenience of oral cerdulatinib in this population. The clinical outcomes reported here support a critical role for SYK and JAK in the pathogenesis of PTCL. Further clinical evaluation of cerdulatinib in PTCL, including biomarker analysis, is warranted, and will enhance our understanding of the relationship between SYK expression, JAK/STAT mutations, and subtype-specific therapeutic responses to cerdulatinib.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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