Safety and efficacy of tenalisib in combination with romidepsin in patients with relapsed/refractory T-cell lymphoma: results from a phase I/II open-label multicenter study

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Abstract

Tenalisib, a selective phosphoinositide-3-kinase δ/γ, and salt-inducible-kinase-3 inhibitor has shown efficacy and was well-tolerated in patients with T-cell lymphoma (TCL). *In vitro* studies suggest a synergistic anti-tumor potential for the combination of tenalisib with the histone-deacetylase inhibitor, romidepsin. This multicenter, open-label, phase I/II study was designed to characterize the safety, efficacy and pharmacokinetics of oral tenalisib twice-daily and intravenous romidepsin administered on days 1, 8 and 15 in 28-day cycles in adults with relapsed/refractory TCL. Phase I/dose escalation determined the maximum tolerated dose (MTD)/optimal doses of tenalisib and romidepsin. The phase II/dose expansion assessed the safety and anti-tumor activity of the combination at MTD/optimal dose. Overall, 33 patients were enrolled. In dose escalation, no dose-limiting toxicity was identified. Hence, the recommended doses for dose expansion were tenalisib 800 mg twice daily orally, and romidepsin 14 mg/m^2 intravenous. Overall treatment-emergent adverse events of any grade reported in >15% of patients were nausea, thrombocytopenia, increased aspartate aminotransferase, increased alanine aminotransferase, decreased appetite, neutropenia, vomiting, fatigue, anemia, dysgeusia, weight loss, diarrhea, and hypokalemia. Twenty-three patients (69.7%) had related grade ≥3 treatment-emergent adverse events. The overall objective response rate in evaluable patients was 63.0% (peripheral TCL: 75% and cutaneous TCL: 53.3%), with a complete response and partial response of 25.9% and 37.0% respectively. The median duration of response was 5.03 months. Co-administration of tenalisib and romidepsin did not significantly alter the pharmacokinetics of romidepsin. Overall, tenalisib and romidepsin combination demonstrated a favorable safety and efficacy profile supporting its further development for relapsed/refractory TCL (*clinicaltrials gov. Identifier: NCT03770000*).

Introduction

T-cell lymphomas (TCL) are a clinically and biologically heterogeneous group of lymphoid malignancies derived from mature T cells and comprise 15% of non-Hodgkin lymphomas (NHL).[1,2] TCL are comprised of aggressive (peripheral TCL [PTCL]) and indolent (cutaneous TCL [CTCL]) subtypes.[1,2] Most PTCL and advanced CTCL are characterized by poor outcomes. The 5-year overall survival in relapsed/refractory (r/r) cases of PTCL is reportedly <35%, which is further compounded by the lack of effective treatment options and treatment consensus.[3] Although seven drugs are currently approved for r/r TCL treatment,[4-10] their activity remains modest. With the exception of brentuximab in anaplastic large cell lymphoma, objective response rate (ORR) varies between 25% to 30%,[7-14] posing a challenge in effectively managing these patients. Hence, novel therapeutics are required to treat such patients.

Phosphatidylinositol 3-kinase (PI3K) pathway plays an

important role in cancer pathophysiology.[13,14] In recent years, PI3K inhibitors like idelalisib, duvelisib and copanlisib, have shown promising results as monotherapies in the treatment of r/r TCL.[15-18] Tenalisib, a highly specific dual equipotent PI3K δ/γ inhibitor, has shown an acceptable safety profile and showed consistent clinical responses in patients with r/r TCL.[19-21] The metabolite of tenalisib, IN0385, is an inhibitor of salt-inducible kinase 3 (SIK3).[22-24] SIK are known to play a key role in tumorigenesis in solid tumors by modulating several signaling pathways of tumor cells.[25] However, the role of SIK3 in lymphomas has not been evaluated.

Histone deacetylases (HDAC) pathways are involved in tumorigenesis. HDAC inhibitors like romidepsin, belinostat and vorinostat modulate epigenetic or non-epigenetic regulation, inducing death, apoptosis and cell cycle arrest in cancer cells.[26] Romidepsin, is used to treat PTCL and CTCL in patients who have received at least one prior therapy.[4,27]

HDAC inhibitors combined with other agents have demonstrated enhanced activity in treatment-resistant tumors.[28-30] Combining PI3K and HDAC inhibitors in TCL may result in a synergistic or additive response due to their different mechanisms of action. *In vitro* studies in TCL cell lines suggest that combining PI3K δ/γ and HDAC inhibitors is synergistic.[31] In a phase Ib/II clinical study, the response of the combination of romidepsin with duvelisib, a PI3K-δ/γ inhibitor was higher than observed responses as single agents.[32] These findings indicate that the combination of PI3K inhibitors with HDAC is promising.

We hypothesized that combining tenalisib and romidepsin would improve responses in patients with r/r TCL with a better safety profile. We designed a study to investigate the safety, efficacy, and potential synergistic effects of tenalisib and romidepsin in these patients. Given the overlapping metabolic pathways of romidepsin and tenalisib,[33] extensive pharmacokinetic (PK) assessments were also planned to rule out any drug-drug interaction.

Methods

Study design and participants

This was a multicenter, open-label, non-randomized, two-stage phase I/II study of tenalisib combined with romidepsin in adult patients with r/r TCL (*clinicaltrails gov. Identifier: NCT03770000*). This TCL cohort represents patients with either PTCL or CTCL. The study, conducted from April 2019 to May 2021, included dose escalation and dose expansion phases. Each site's Institutional Review Board approved the study protocol. The study was conducted following the International Council for Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki.

Dose escalation phase

The phase I, 3+3 dose escalation study assessed the maximum tolerated dose (MTD)/optimal dose of the combination. Three dose escalation cohorts were planned. For cohort 1 to cohort 3, tenalisib doses were 400, 600, and 800 mg orally twice daily (BID). The corresponding doses of romidepsin were 12, 12, and 14 mg/m^2. The study allowed adding or reducing the number of cohorts based on emerging safety and PK data (details are provided in the *Online Supplementary Figure S1*).

Dose expansion phase

The phase II study assessed the safety and anti-tumor activity of tenalisib and romidepsin combination at the MTD/optimal dose. Twelve each of PTCL and CTCL patients were to be enrolled in the two patient groups (*Online Supplementary Figure S1*). Details of the study participants are provided in the *Online Supplementary Table S1* and the *Online Supplementary Method S1*.

Treatment and intervention

Eligible patients received tenalisib orally, BID, at the same time each day, 1 hour before their meals over a 28-day cycle (day 1–28). Romidepsin was administered intravenously (IV) over 4 hours on days 1, 8, and 15 during the 28-day cycle. Both tenalisib and romidepsin were given until disease progression or discontinuation from the study. Additional details on treatment and compliance are provided in the *Online Supplementary Method S2*.

Objectives and endpoints

Primary objective: to characterize the safety and tolerability and determine the MTD of the combination. Safety endpoints included assessments of adverse events (AE), treatment-emergent AE (TEAE), serious AE (SAE), and DLT (the definition and details of DLT are provided in the *Online Supplementary Table S2*).

The key secondary objectives: (i) ORR: sum of complete response [CR] and partial response [PR] rates), evaluated in PTCL patients according to the Lugano Classification,[34] and in CTCL patients as per the global response score,[35] (ii) the duration of response (DoR) calculated as the time from the initial response to documented disease progression; and (iii) the PK of tenalisib and romidepsin. Additional PK assessment details are provided in *Online Supplementary Method S3*. The details of the study procedures are provided in the *Online Supplementary Method S4*.

Statistical analysis

Dose escalation phase: three patients per cohort were appropriate for assessing MTD/optimal dose.

Dose expansion phase: 12 patients per group were considered appropriate for assessing the preliminary anti-tumor activity of tenalisib and romidepsin combination.

Data were summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables. Results from the study are presented by indication. All analyses were performed using SAS® software version 9.4 or higher.

All safety analyses were performed on the safety dataset that comprised all patients who received at least one dose of study medication. The efficacy analysis was performed on the modified intent-to-treat (mITT) population (evaluable patients). Further details are provided in the *Online Supplementary Method S5*.

Results

Patient demographics, baseline characteristics, and disposition

Overall, 56 patients were screened, of which 33 patients were enrolled and received the combination treatment. Of these, 16 PTCL and 17 CTCL patients received tenalisib and romidepsin. Twenty-three patients were screen failures. Of the PTCL patients, 93.7% and all CTCL patients discontinued the study. The most common reasons for study discontinuation were disease progression (57.57%) and AE (18.18%). Three PTCL patients (18.7%) were bridged to transplant and hence moved out from the study (Table 1; *Online Supplementary Figure S2*). No DLT were reported for the combination doses ranging between 400 mg to 800 mg BID and romidepsin IV 12–14 mg/m^2. Hence, the highest dose of tenalisib (800 mg BID) and romidepsin (14 mg/m^2) combination was considered the MTD/RP2D dose for the study.

The demographic and baseline characteristics for all patients are shown in Table 2. Among the 33 patients enrolled, 51.5% were male, the majority (81.8%) being Caucasian. The median age of patients was 66.2 years (range, 42.9-83.4 years). The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42.4%) or 1 (54.6%). Twenty-two (66.6%) patients (87.6% in PTCL, 47.1% in CTCL) had stage 3/stage 4 diseases. Overall, 36.4% of patients had relapsed following the last prior therapy (31.3% in PTCL, 41.2% in CTCL). Twenty-one (63.6%) patients (68.8% in PTCL, 58.8% in CTCL) were refractory to their last prior therapy. The median duration from the date of the last prior therapy to treatment was 46 days (range, 8-702 days). The median compliance in the study was 100% (range, 99.1-105.3) and was within the acceptable range of 80-120%.

Safety

Overall, at least one related TEAE of grade 1 or 2 severity was reported in all enrolled patients. In 69.7% of patients, grade ≥3 were reported (68.8% of PTCL patients, and 70.6% of CTCL patients).

The related TEAE reported in >15% of patients were nausea (72.7%); thrombocytopenia (57.6%); fatigue (54.5%); increased aspartate aminotransferase (AST) (30.3%); increased alanine aminotransferase (ALT)

Table 1. Study disposition by indication.

	PTCL, N (%)	CTCL, N (%)	Overall, N (%)
Patients dosed	16	17	33
Discontinued study	15 (93.7)	17 (100)	32 (96.9)
Reason for discontinuation**			
Adverse event	1 (6.25)	5 (29.4)	6 (18.18)
Disease progression	10 (62.5)	9 (52.9)	19 (57.57)
Investigator's decision	0	1 (5.8)	1 (3.03)
Intolerance of study drug	0	1 (5.8)	1 (3.03)
Patient bridged to yransplant	3 (18.7)	0	3 (9.09)
Withdrawal of consent	1 (6.25)	1 (5.8)	2 (6.06)
Drug interruptions due to AE	12 (75.0)	12 (70.6)	24 (72.7)
Non-related AE	3 (18.8)	3 (17.7)	6 (18.2)
Related AE	10 (62.5)	12 (70.6)	22 (66.7)
Dose reduction due to AE	7 (43.8)	8 (47.1)	15 (45.5)
Non-related AE	0	1 (5.9)	1 (3.0)
Related AE	7 (43.8)	8 (47.1)	15 (45.5)
Drug withdrawn permanently due to AE	1 (6.3)	5 (29.4)	6 (18.2)
Non-related AE	1 (6.3)	0	1 (3.0)
Related AE	0	5 (29.4)	5 (15.2)

Cutaneous T-cell lymphoma (CTCL) percentages are based on the total number of patients dosed in the study. **Percentages for reason of discontinuation are based on the total number of patients discontinued. AE: adverse events; N (%): number (percentage) of patients; PTCL: peripheral T-cell lymphoma.

(24.2%); decreased appetite, neutropenia, and vomiting (27.3% each); anemia and dysgeusia (21.2% each); weight decrease (18.2%); and diarrhea and hypokalemia (15.2% each) (Table 3). No DLT were reported. Twelve patients (36.4%) reported 19 serious TEAE. Six TEAE led to permanent study treatment discontinuation. Two patients (1 PTCL and 1 CTCL) died due to sepsis; of these, an event of sepsis in the CTCL patient was considered possibly related to the combination (at tenalisib 800 mg BID and romidepsin 14 mg/m^2). This was an 81-year-old male with a past medical history of asthma, chronic obstructive pulmonary disease, lung cancer, prostate cancer, diabetes mellitus, hypertension, and stage 4 CTCL. The patient had multiple underlying comorbidities and risk factors. Disease progression could not be completely ruled out based on CT findings. Given this patient's underlying comorbidities and risk factors, there seemed to be no conclusive evidence that the combination ac-

Table 2. Demographics and baseline characteristics – by indication (safety analyses set).

	PTCL, N=16	CTCL, N=17	Overall, N=33
Age in years			
Median	61.85	66.53	66.21
Min-Max	42.89-83.44	48.76-80.55	42.89-83.44
Sex, N (%)			
Male	9 (56.3)	8 (47.1)	17 (51.5)
Female	7 (43.8)	9 (52.9)	16 (48.5)
Race, N (%)			
White	13 (81.3)	14 (82.4)	27 (81.8)
Asian	2 (12.5)	0	2 (6.1)
Black/African/American	1 (6.3)	3 (17.7)	4 (12.1)
Time in days from initial diagnosis to treatment*			
Median	583.5	1,446	754
Min-Max	53-2,643	253-5,189	53-5,189
PTCL subtype, N (%)			
PTCL, NOS	8 (50)	NA	8 (24.2)
ALCL	1 (6.3)	NA	1 (3.0)
T-cell follicular lymphoma (including AITL)	7 (43.8)	NA	7 (21.2)
CTCL subtype, N (%)			
MF	NA	12 (70.6)	12 (36.4)
Sézary syndrome	NA	5 (29.4)	5 (15.2)
Staging at Screening, N (%)			
III	5 (31.3)	1 (5.9)	6 (18.2)
IV	9 (56.3)	7 (41.2)	16 (48.5)
Outcome of the last prior therapy, N (%)			
Relapse	5 (31.3)	7 (41.2)	12 (36.4)
Refractory	11 (68.8)	10 (58.8)	21 (63.6)
Time from date of last prior therapy to study treatment in days*			
Median	44	46	46
Min-Max	13-702	8-435	8-702
Prior therapies, N			
Median	3	6	3
Min-Max	1-5	1-17	1-17
Prior therapies, N (%)			
≥3	10 (62.5)	15 (88.2)	25 (75.8)
≥5	2 (12.5)	10 (58.8)	12 (36.4)
ECOG Performance Status**, N (%)			
0	8 (50.0)	6 (35.3)	14 (42.4)
1	8 (50.0)	10 (58.8)	18 (54.6)
2	0	1 (5.9)	1 (3.0)

*Partial dates are imputed using the missing data conventions as mentioned in the statistical analysis plan. **The baseline measurement is the last pretreatment measurement taken on or before cycle 1 day 1. AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large-cell lymphoma; CTCL: cutaneous T-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; MF: mycosis fungoides; N (%): number (percentage) of patients; NA: not applicable; N: number of evaluable patients; NOS: not otherwise specified; PTCL: peripheral T-cell lymphoma; SD: standard deviation.

centuated or worsened the known adverse effect of individual agents.

Overall, in both PTCL and CTCL groups, drug interruptions were observed in 60.6%, 63.6%, and 45.5% of patients for tenalisib, romidepsin, and the combination, respectively. Three or more drug interruptions occurred in 12.1% of patients for tenalisib and 24.2% of patients for romidepsin during the combination treatment. Dose reductions occurred in 27.3%, 33.3%, and 15.2% of patients for tenalisib, romidepsin, and the combination respectively.

Pharmacokinetics

Tenalisib was rapidly absorbed in all three cohorts, with the C_{max} and AUC_{0-t} increasing with dose. Although the elimination kinetics of tenalisib were similar to its metabolite, IN0385, the exposure was higher for IN0385 (*Online Supplementary Table S3*). Romidepsin plasma levels were not significantly reduced on co-administration with tenalisib for C_{max} and AUC_{0-t} (Figure 1).

Efficacy

A total of 27 patients (12 PTCL and 15 CTCL) were considered evaluable for efficacy. Six patients (4 PTCL and 2 CTCL) discontinued early in the first cycle, due to disease progression, drug toxicity, and consent withdrawal (2 patients each) and were considered non-evaluable.

Objective response rate

In evaluable patients, ORR was 75% in PTCL group and 53.3% in CTCL patients. The disease control rate (DCR) was 91.7% in the PTCL patients and 86.7% in the CTCL pa-

Table 3. Overall related treatment-emergent adverse events of any grade reported in >15% patients and corresponding grade ≥3 treatment-emergent adverse events reported - by indication (safety analysis set).

System organ class/ preferred term	PTCL, N=16 N (%), E		CTCL, N=17 N (%), E		Overall, N=33 N (%), E	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
At least one TEAE	16 (100.0), 212	11 (68.8), 34	17 (100.0), 191	12 (70.6), 32	33 (100.0), 403	23 (69.7), 66
Blood and lymphatic system disorders	14 (87.5), 81	8 (50.0), 25	9 (52.9), 39	3 (17.6), 11	23 (69.7), 120	11 (33.3), 36
Thrombocytopenia	12 (75.0), 48	6 (37.5), 13	7 (41.2), 14	1 (5.9), 3	19 (57.6), 62	7 (21.2), 16
Neutropenia	6 (37.5), 29	3 (18.8), 11	3 (17.6), 19	2 (11.8), 7	9 (27.3), 48	5 (15.2), 18
Anemia	2 (12.5), 4	1 (5.9), 1	5 (29.4), 6	1 (5.9), 1	7 (21.2), 10	2 (6.1), 2
Gastrointestinal disorders	12 (75.0), 29	-	13 (76.5), 34	-	25 (75.8), 63	-
Nausea	11 (68.8), 14	-	13 (76.5), 21	-	24 (72.7), 35	-
Vomiting	3 (18.8), 5	-	6 (35.3), 7	-	9 (27.3), 12	-
Diarrhea	4 (25.0), 6	-	1 (5.9), 1	-	5 (15.2), 7	-
General disorders and administration site conditions	8 (50.0), 13	1 (6.3), 1	12 (70.6), 19	2 (11.8), 2	20 (60.6), 32	3 (9.1), 3
Fatigue	8 (50.0), 9	1 (6.3), 1	10 (58.8), 12	1 (5.9), 1	18 (54.5), 21	2 (6.1), 2
Investigations	9 (56.3), 34	2 (12.5), 4	9 (52.9), 65	6 (35.3), 12	18 (54.5), 99	8 (24.2), 16
Aspartate aminotransferase increased	3 (18.8), 5	-	7 (41.2), 21	1 (5.9), 1	10 (30.3), 26	1 (3.0), 1
Alanine aminotransferase increased	2 (12.5), 7	2 (12.5), 2	6 (35.3), 19	4 (23.5), 6	8 (24.2), 26	6 (18.2), 8
Weight decreased	3 (18.8), 4	-	3 (17.6), 4	-	6 (18.2), 8	-
Metabolism and nutrition disorders	8 (50.0), 18	1 (6.3), 1	7 (41.2), 14	1 (5.9), 1	15 (45.5), 32	2 (6.1), 2
Decreased appetite	5 (31.3), 5	-	4 (23.5), 8	-	9 (27.3), 13	-
Hypokalemia	4 (25.0), 4	-	1 (5.9), 1	-	5 (15.2), 5	-
Nervous system disorders	5 (31.3), 9	1 (6.3), 1	5 (29.4), 8	-	10 (30.3), 17	1 (3.0), 1
Dysgeusia	4 (25.0), 4	-	3 (17.6), 3	-	7 (21.2), 7	-
Skin and subcutaneous tissue disorders	4 (25.0), 8	-	2 (11.8), 5	2 (11.8), 4	6 (18.2), 13	2 (6.1), 4

CTCL: cutaneous T-cell lymphoma; E: events; N (%): number (percentage) of patients; N: number of evaluable patients; PTCL: peripheral T-cell lymphoma; TEAE: treatment-emergent adverse events.

tients. CR was observed in 50% of PTCL patients (2 patients with PTCL not otherwise specified [NOS] and 4 of angioimmunoblastic T-cell lymphoma [AITL]) and 6.7% of CTCL patients (1 with Sezary syndrome [SS]). PR was observed in 25% of PTCL patients (2 patients with PTCL NOS and 1 with AITL) and 46.7% of CTCL patients (4 patients with mycosis fungoides [MF] and 3 with SS) (Table 4). Nine PTCL patients (CR: 6 patients, PR: 3 patients) and eight CTCL patients (CR: 1 patient, PR: 7 patients) had at least 50% improvement in the nodal lesions and modified severity weighted assessment tool (mSWAT) score respectively (Figure 2A, B).

Duration of response

Overall, 17 of 27 patients were confirmed as a CR or PR, with a median DoR of 5.03 months (range, 0.87-30.83 months) (Table 4; Figure 2C). Of the 12 patients with PTCL, nine patients were confirmed as a CR or PR, with a median DoR of 5.03 months (range, 1.87-25.23+ months). Of the 15 patients with CTCL, eight patients were confirmed as a CR or PR, with a median DoR of 3.80 months (range, 0.87-30.83 months) (Table 4; Figure 2C).

Discussion

In previous studies, single agent tenalisib and romidepsin have been well-tolerated with reasonable response rates in r/r TCL patients.[19,21,36] Thus, combining these two agents were expected to improve responses in these patients, considering the synergistic anti-tumor activity of the combination seen in preclinical studies and with similar class combinations in the clinic. The safety profile was unlikely to be affected due to the non-overlapping toxicities of the

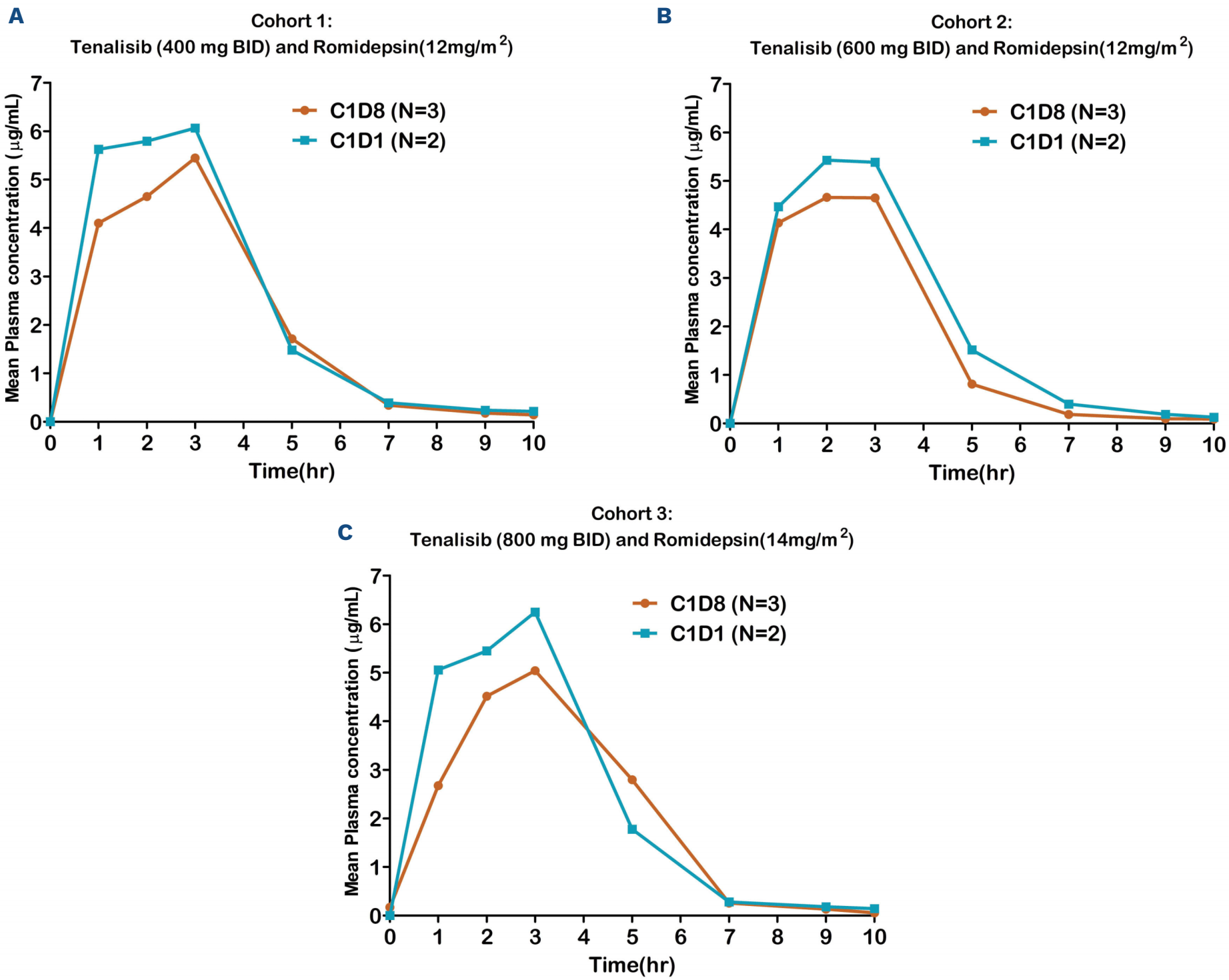

Figure 1. Mean plasma concentrations of romidepsin. (A) Cohort 1. (B) Cohort 2. (C) Cohort 3. C1D1: cycle 1 day 1; C1D8: cycle 1 day 8; N: number of patients.

single agents. In line with these assumptions, the study revealed that the highest dose of tenalisib 800 mg BID and romidepsin IV 14 mg/m^2 was found to be tolerable with expected AE.

In this study, no DLT were reported with the combination even at the highest dose. This finding is in contrast to studies evaluating other drug combinations with romidepsin (e.g., with pralatrexate or oral 5-azacytidine combination)[37,38] where DLT such as thrombocytopenia, neutropenia, and sepsis were reported. Discontinuation rates due to adverse events were around 18% in our study, which is in line with other single agent studies of romidepsin (19-28%).[39,40]

Despite the high number of dose interruptions/dose reductions reported with the combination, it was in line with other single agent studies of romidepsin. Thus, discontinuation rates or dose modifications did not increase with the combination as compared to single agent romidepsin.[41]

Romidepsin is primarily metabolized by cytochrome P450 3A4 (CYP3A4),[41] while tenalisib and its metabolite IN0385 are moderate inhibitors and substrates for CYP3A4. Due to the CYP3A4 inhibitory potential of tenalisib, there could have been an increase in plasma concentrations of romidepsin leading to increased severity and frequency of romidepsin-induced toxicities. However, analyses in our study revealed that the co-administration of romidepsin and tenalisib did not significantly alter the pharmacokinetic profiles of romidepsin.

The study revealed that there were no unexpected AE, or increased incidence of existing AE observed for individual regimens. This was validated by the pharmacokinetic data which showed no drug-drug interaction. Thus, the PK data findings suggest that in a clinical setting, romidepsin and tenalisib do not interact and can be administered as a combination devoid of drug-drug interactions.

Although in the study, the efficacy evaluable analysis population considered only patients who had had at least one post baseline assessment (C3D1) when compared with pivotal studies which considers all patients who had one dose of the drug, the combination showed encouraging anti-tumor activity in patients with TCL in our study. For PTCL, 75% of evaluable patients achieved ORR with a CR of 50%. The CR rates observed using this combination were higher than that reported individually with tenalisib and romidepsin monotherapy in PTCL patients (tenalisib CR: 20.0%, romidepsin CR: 14%),[21] suggesting synergism. The ORR for the combination seemed to be additive. The ORR in CTCL patients was numerically higher compared to individual single agents tenalisib and romidepsin but not as high as observed in the PTCL population.

In the PTCL patients, the median duration of treatment was 3.6 months (range, 0.1-28.96+ months) (Figure 2C). Nine of 16 patients completed seven cycles of treatment and one patient continues to be on combination therapy for more than 1.5 years. However, the DoR was impacted by three patients who were bridged to transplant and thus taken off the study.

In the CTCL patients, the median duration of treatment was 3.46 months (range, 0.76-34.53 months) (Figure 2C). Three patients were treated for seven cycles. Out of these three patients, one patient with Sezary syndrome (SS) was in remission for more than 30 months. Long-term treatment in these patients indicates that tenalisib has been well tolerated without any long-term immune-mediated toxicities associated with PI3K inhibitors, such as colitis or pneumonitis.

When the study was conceptualized and began enrolling, romidepsin was approved for both PTCL and CTCL in patients who had received one prior therapy. In a pivotal phase III study of romidepsin plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in previously untreated PTCL, the addition of romidepsin to CHOP did not improve the responses (progression-free survival, response rates, or overall survival) over CHOP alone but led to increased frequency of grade ≥3 AE.[42] As a result, the label for the use of romidepsin in PTCL was withdrawn. However, romidepsin is still approved for CTCL. Given the results seen with tenalisib being combined with romidepsin, the authors believe that the development of the combination should still be explored in both patients with PTCL and CTCL in a larger clinical

Table 4. Objective response rate and duration of response – by indication (mITT analysis set).

	PTCL, N=12 N (%) 95% CI	CTCL, N=15 N (%) 95% CI
CR	6 (50.0) 21.09-78.91	1 (6.7) 0.17-31.95
PR	3 (25.0) 5.49-57.19	7 (46.7) 21.27-73.41
SD	2 (16.7) 2.09-48.41	5 (33.3) 11.82-61.62
PD	1 (8.3) 0.21-38.48	2 (13.3) 1.66-40.46
ORR (CR+PR)	9 (75.0) 42.81-94.51	8 (53.3) 26.59-78.73
DCR (CR+PR+SD)	11 (91.7) 61.52-99.79	13 (86.7) 59.54-98.34
Duration of response		
Median duration of response in months (range)	5.03 (1.87-25.3+)	3.80 (087-30.83)

CR: complete response; CTCL: cutaneous T-cell lymphoma; DCR: disease control rate; mITT: modified intent-to-treat; N: number of evaluable patients for efficacy; N (%): number (percentage) of patients; ORR: overall response rate; PD: progression of disease; PR: partial response; PTCL: peripheral T-cell lymphoma; SD: stable disease.

study. In addition, given the favorable results seen in PTCL, the combinations of tenalisib with other approved HDAC inhibitors in PTCL can also be explored.

Our study had several strengths. We evaluated drug-drug interaction to establish the safety of the combination. The study classified the patient population separately into PTCL and CTCL groups in the dose expansion part, allowing for the differential investigation of the safety and efficacy of the drug combination in these populations. Our study was limited by sample size as is seen in the early phase of the drug development.

Overall, the combination of tenalisib and romidepsin dem-

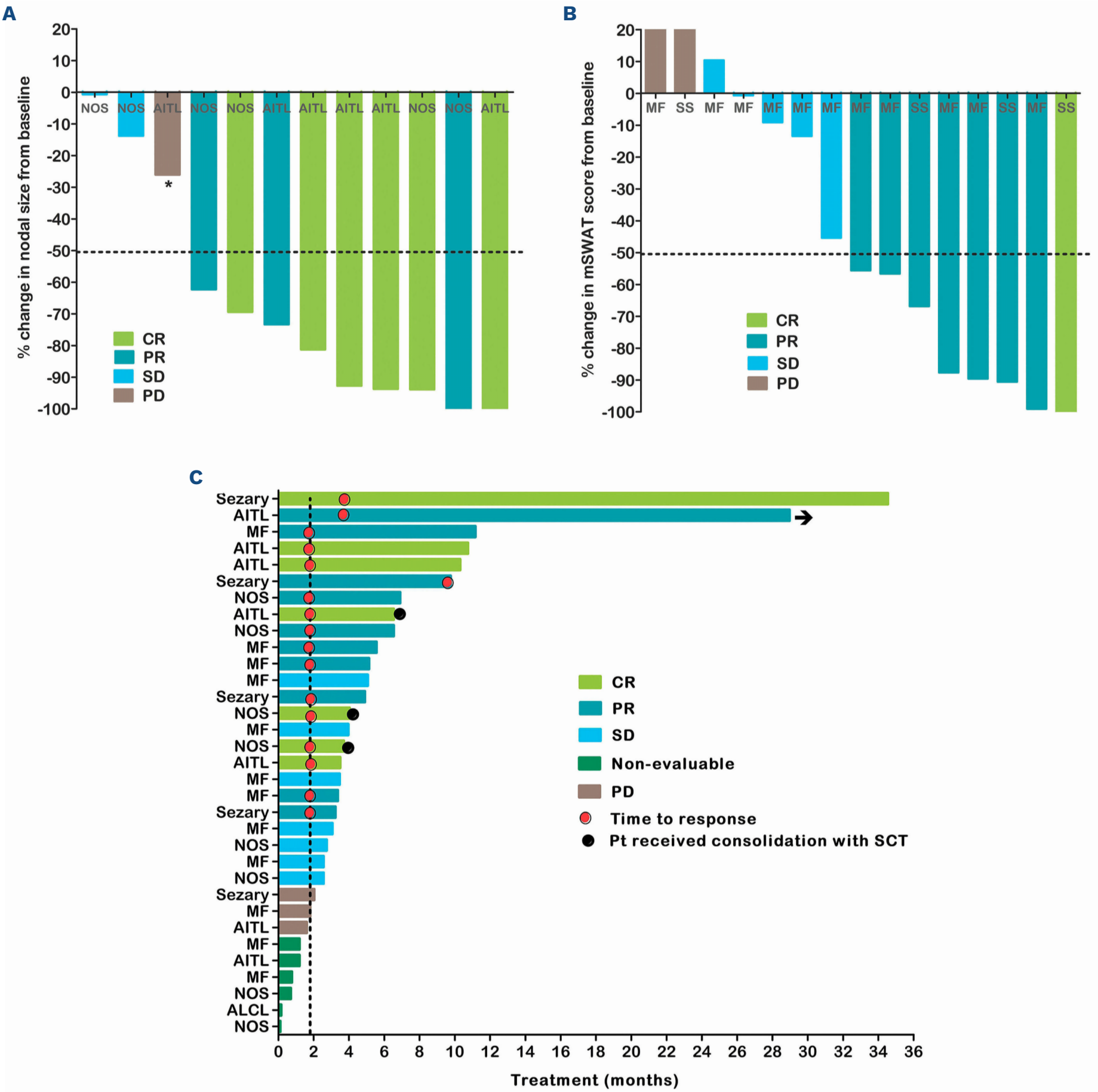

Figure 2. Treatment duration and response in evaluable peripheral T-cell lymphoma and cutaneous T-cell lymphoma patients. (A) Percentage change in nodal size from baseline. *Disease progression due to new lesions. (B) Percentage change in modified severity-weighted assessment tool (SWAT) score from baseline. (C) Treatment duration in peripheral T-cell lymphoma (PTLC) and cutaneous T-cell lymphoma (CTCL) patients. AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; SS: Sezary syndrome; CR: complete response; MF: mycosis fungoides; NOS: not otherwise specified; PD: progression of disease; PR: partial response; SCT: stem cell transplant; SD: stable disease.

onstrates potential in patients with hematological malignancies (PTCL/CTCL). This supports further development of this combination for treating TCL.

Disclosures

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Contributions

SPI contributed to design, recruitment, data collection, result interpretation, critical review and approval of the manuscript. AH and WZA contributed to patient recruitment, data collection, review, and final approval of the manuscript. DJ contributed to recruitment, data collection, critical review and approval of the manuscript. MJL contributed to patient recruitment, data collection, critical review and final approval of the manuscript. CO, TAF, RC and SHK contributed to patient recruitment, data collection, review, and final approval of the manuscript. PG and JPA contributed to recruitment, data collection, review and approval of the manuscript. AM contributed to patient recruitment, data collection, review, editing and final approval of the manuscript. KVR contributed to conception, design, analysis, result interpretation, critical review and approval of the manuscript. PB and AMN contributed to conception, design, result interpretation, critical review and approval of the manuscript. BMH contributed to recruitment, data collection, result interpretation, critical review, editing and final approval of the manuscript.

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Data-sharing statement

All data related to the study findings are described in the manuscript and the related Online Supplementary Appendix.

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