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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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

Swaminathan P. Iyer1*, Auris Huen1, Weiyun Z. Ai2, Deepa Jagadeesh3, Mary J. Lechowicz4, Craig Okada5, Tatyana A. Feldman6, Paola Ghione7, Juan P. Alderuccio8, Rebecca Champion9, Seo-Hyun Kim10, Ann Mohrbacher11, Kasi V. Routhu12, Prajak Barde12, Ajit M. Nair12, Bradley M. Haverkos13

1The University of Texas MD Anderson Cancer Center, TX, USA
2Helen Diller Family Comprehensive Cancer Center, CA, USA
3Taussig Cancer Institute, OH, USA
4Winship Cancer Institute, GA, USA
5Oregon Health and Science University, OR, USA
6John Theurer Cancer Center at Hackensack University Medical Center, NJ, USA
7Roswell Park Comprehensive Cancer Center, NY, USA
8Sylvester Comprehensive Cancer Center, FL, USA
9Norton Cancer Institute, KY, USA
10Rush University Medical Center, IL, USA
11University of Southern California, CA, USA
12Rhizen Pharmaceuticals AG., Basel, Switzerland
13University of Colorado Cancer Center, CO, USA

Running Title: Tenalisib and romidepsin therapy for TCL

*Corresponding author
Dr. Swaminathan P Iyer,
Professor, Department of Lymphoma/Myeloma, Division of Cancer Medicine,
The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd,
Houston, TX, USA
Email: SPIyer@mdanderson.org
Ph: +1 (713) 792-5242

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Author contributions
SPI: Design, recruitment, data collection, result interpretation, critical review and approval of the manuscript
AH: Patient recruitment, data collection, review, and final approval of the manuscript
WZA: Patient recruitment, data collection, review, and final approval of the manuscript.
DJ: Recruitment, data collection, critical review and approval of the manuscript
MJL: Patient recruitment, data collection, critical review and final approval of the manuscript
CO: Patient recruitment, data collection, review, and final approval of the manuscript
TAF: Patient recruitment, data collection, review, and final approval of the manuscript
PG: Recruitment, data collection, review and approval of the manuscript
JPA: Recruitment, data collection, review and approval of the manuscript
RC: Patient recruitment, data collection, review, and final approval of the manuscript
SHK: Patient recruitment, data collection, review, and final approval of the manuscript.
AM: Patient recruitment, data collection, review, editing and final approval of the manuscript.
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BMH: Recruitment, data collection, result interpretation, critical review, editing and final approval of the manuscript

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Not applicable as the data related to the study findings are described in the manuscript and the related supplementary files.

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ABSTRACT (Word Count: 241 / 250 words)

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 (BID) and intravenous (IV) romidepsin administered on Days 1, 8 and 15 in 28-day cycles in adults with relapsed/refractory TCL. Phase I/dose-escalation determined the 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 (DLT) was identified. Hence, the recommended doses for dose-expansion were tenalisib 800 mg BID orally, and romidepsin 14 mg/m² IV. Overall treatment-emergent adverse events (TEAE) 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 TEAE. The overall objective response rate in evaluable patients was 63.0% (PTCL: 75% and CTCL: 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.

Keywords: Dose escalation, Drug combination, Histone deacetylase inhibitor, Phosphoinositide-3-kinase inhibitor, Romidepsin, Relapsed/refractory T-cell lymphoma, RP6530, Tenalisib
INTRODUCTION

T-cell lymphomas (TCLs) are a clinically and biologically heterogeneous group of lymphoid malignancies derived from mature T cells and comprise 15% of non-Hodgkin lymphomas (NHLs). TCLs are comprised of aggressive (Peripheral T cell lymphomas [PTCLs]) and indolent (Cutaneous T cell Lymphoma [CTCL]) subtypes. Most PTCL and advanced CTCL are characterized by poor outcomes. The five-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. Although seven drugs are currently approved for r/r TCL treatment, their activity remains modest. With the exception of brentuximab in anaplastic large cell lymphoma, ORR varies between 25% to 30%, 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. In recent years, PI3K inhibitors like idelalisib, duvelisib and copanlisib, have shown promising results as monotherapies in the treatment of r/r TCL. 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. The metabolite of tenalisib, IN0385, is an inhibitor of salt-inducible kinase 3 (SIK3). SIKs are known to play a key role in tumorigenesis in solid tumors by modulating several signaling pathways of tumor cells. 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. Romidepsin, is used to treat PTCL and CTCL in patients who have received at least one prior therapy. HDAC inhibitors combined with other agents have demonstrated enhanced activity in treatment-resistant tumors. 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. 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. 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, 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 (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/m². The study allowed adding or reducing the number of cohorts based on emerging safety and PK data. (Details in Supplementary Figure 1).

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. (Supplementary Figure 1). Details of the study participants are provided in Supplementary Table 1 and Supplementary Method 1.

Treatment and intervention
Eligible patients received tenalisib orally, BID, at the same time each day, one hour before their meals over a 28-day cycle (Day 1–28). Romidepsin was administered intravenously (IV) over four 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 Supplementary Method 2.

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 DLTs are provided in Supplementary Table 2)

The key secondary objectives: (a) the objective response rate (ORR: sum of complete response [CR] and partial response [PR] rates), evaluated in PTCL patients according to the Lugano Classification, and in CTCL patients as per the global response score, (b) the duration of response (DoR) calculated as the time from the initial response to documented disease progression; and (c) the PK of tenalisib and romidepsin. Additional PK assessment details are provided in Supplementary Method 3. The details of the study procedures are provided in Supplementary Method 4.

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 Supplementary Method 5.

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 and Supplementary Figure 2) No DLTs were reported for the combination doses ranging between 400 mg to 800 mg BID and romidepsin IV 12–14 mg/m². Hence, the highest dose of tenalisib (800 mg
BID) and romidepsin (14 mg/m²) 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 (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 (8-702 days). The median compliance in the study was 100% (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) (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 DLTs were reported. Twelve patients (36.4%) reported 19 serious TEAEs. Six TEAEs led to permanent study treatment discontinuation. Two patients (one PTCL and one 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/m²). This was an 81-year-old male with past medical history of asthma, chronic obstructive pulmonary disease, lung cancer, prostate cancer, diabetes mellitus, hypertension, and Stage IV 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 accentuated 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\text{max} and AUC\text{0-t} increasing with dose. Although the elimination kinetics of tenalisib were similar to its metabolite, IN0385, the exposure was higher for IN0385. (Supplementary Table 3) Romidepsin plasma levels were not significantly reduced on co-administration with tenalisib for C\text{max} and AUC\text{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 patients. 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 8 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. (Figures 2A and 2B)

**Duration of Response**

Overall, 17/27 patients were confirmed as a CR or PR, with a median DoR of 5.03 months (Range: 0.87-30.83 months). (Table 4 and 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 and Figure 2C)

**DISCUSSION**

In previous studies, single agent tenalisib and romidepsin have been well-tolerated with reasonable response rates in r/r TCL patients.\textsuperscript{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 pre-clinical 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 single agents. In line with these assumptions, the study revealed that the highest dose of tenalisib 800 mg BID and romidepsin IV14 mg/m\textsuperscript{2} was found to be tolerable with expected AEs.

In this study, no DLTs 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)\textsuperscript{37,38} where DLTs 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\%).\textsuperscript{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.\textsuperscript{41}

Romidepsin is primarily metabolized by cytochrome P450 3A4 (CYP3A4),\textsuperscript{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 AEs, 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%),\(^2\) suggesting synergism. The ORR rates for the combination seemed to be additive. The overall response rate 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 out 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+CHOP 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 $\geq$3 AEs.\(^4\) 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 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 demonstrates potential in patients with hematological malignancies (PTCL/CTCL). This supports further development of this combination for treating TCL.
REFERENCES


## TABLES

### Table 1: Study disposition - by indication

<table>
<thead>
<tr>
<th>Reason for discontinuation**</th>
<th>PTCL, n (%)</th>
<th>CTCL, n (%)</th>
<th>Overall, n (%)</th>
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<tr>
<td>Patients dosed</td>
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<td>17</td>
<td>33</td>
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<tr>
<td>Discontinued study</td>
<td>15 (93.7)</td>
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<td>Reason for discontinuation**</td>
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<tr>
<td>Adverse Event</td>
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<td>Investigator’s Decision</td>
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<td>1 (6.25)</td>
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<td>2 (6.06)</td>
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</table>

**Percentages for reason of discontinuation are based on the total number of patients discontinued.

### Drug interruptions due to AEs

<table>
<thead>
<tr>
<th>Drug interruptions due to AEs</th>
<th>PTCL, n (%)</th>
<th>CTCL, n (%)</th>
<th>Overall, n (%)</th>
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<tr>
<td>Non-related AE</td>
<td>3 (18.8)</td>
<td>3 (17.7)</td>
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<tr>
<td>Related AE</td>
<td>10 (62.5)</td>
<td>12 (70.6)</td>
<td>22 (66.7)</td>
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### Dose reduction due to AEs

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<th>Dose reduction due to AEs</th>
<th>PTCL, n (%)</th>
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<td>Non-related AE</td>
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<td>Related AE</td>
<td>7 (43.8)</td>
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### Drug withdrawn permanently due to AEs

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<td>Non-related AE</td>
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<td>Related AE</td>
<td>0</td>
<td>5 (29.4)</td>
<td>5 (15.2)</td>
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</table>

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; CTCL, cutaneous T-cell lymphoma; n (%), number (percentage) of patients; PTCL, peripheral T-cell lymphoma
Table 2: Demographics and baseline characteristics – by indication (Safety Analyses Set)

<table>
<thead>
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<th></th>
<th>PTCL (N=16)</th>
<th>CTCL (N=17)</th>
<th>Overall (N=33)</th>
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<tr>
<td>Male</td>
<td>9 (56.3)</td>
<td>8 (47.1)</td>
<td>17 (51.5)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (43.8)</td>
<td>9 (52.9)</td>
<td>16 (48.5)</td>
</tr>
<tr>
<td>Race [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (81.3)</td>
<td>14 (82.4)</td>
<td>27 (81.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (12.5)</td>
<td>0</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Black/African/American</td>
<td>1 (6.3)</td>
<td>3 (17.7)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Time from initial diagnosis to treatment (days)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>583.5</td>
<td>1446</td>
<td>754</td>
</tr>
<tr>
<td>(Min-Max)</td>
<td>53-2643</td>
<td>253-5189</td>
<td>53-5189</td>
</tr>
<tr>
<td>PTCL subtype [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTCL, NOS</td>
<td>8 (50)</td>
<td>NA</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>ALCL</td>
<td>1 (6.3)</td>
<td>NA</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>T-cell follicular lymphoma (includingAITL)</td>
<td>7 (43.8)</td>
<td>NA</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>CTCL subtype [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF</td>
<td>NA</td>
<td>12 (70.6)</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>Sézary syndrome</td>
<td>NA</td>
<td>5 (29.4)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Staging at Screening [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5 (31.3)</td>
<td>1 (5.9)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>IV</td>
<td>9 (56.3)</td>
<td>7 (41.2)</td>
<td>16 (48.5)</td>
</tr>
<tr>
<td>Outcome of the last prior therapy [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>5 (31.3)</td>
<td>7 (41.2)</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>Refractory</td>
<td>11 (68.8)</td>
<td>10 (58.8)</td>
<td>21 (63.6)</td>
</tr>
<tr>
<td>Time from date of last prior therapy to study treatment (days)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>44</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>(Min-Max)</td>
<td>13-702</td>
<td>8-435</td>
<td>8-702</td>
</tr>
<tr>
<td>Prior therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>(Min-Max)</td>
<td>1-5</td>
<td>1-17</td>
<td>1-17</td>
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<tr>
<td>No. of prior therapies [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy ≥ 3</td>
<td>10 (62.5)</td>
<td>15 (88.2)</td>
<td>25 (75.8)</td>
</tr>
<tr>
<td>Therapy ≥ 5</td>
<td>2 (12.5)</td>
<td>10 (58.8)</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>ECOG Performance Status**[n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (50.0)</td>
<td>6 (35.3)</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>1</td>
<td>8 (50.0)</td>
<td>10 (58.8)</td>
<td>18 (54.6)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1 (5.9)</td>
<td>1 (3.0)</td>
</tr>
</tbody>
</table>

*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.

AITCL, 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; TCL, t-cell lymphoma.
Table 3: Overall related TEAEs of any grade reported in >15% patients and corresponding Grade ≥3 TEAEs reported – by indication (Safety Analysis Set)

<table>
<thead>
<tr>
<th>System organ class/Preferred term</th>
<th>PTCL (N=16) n (%), E</th>
<th>CTCL (N=17) n (%), E</th>
<th>Overall (N=33) n (%), E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥3</td>
<td>Any grade</td>
</tr>
<tr>
<td>At least one TEAE</td>
<td>16 (100.0), 212</td>
<td>11 (68.8), 34</td>
<td>17 (100.0), 191</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>14 (87.5), 81</td>
<td>8 (50.0), 25</td>
<td>9 (52.9), 39</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (75.0), 48</td>
<td>6 (37.5), 13</td>
<td>7 (41.2), 14</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (37.5), 29</td>
<td>3 (18.8), 11</td>
<td>3 (17.6), 19</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (12.5), 4</td>
<td>1 (5.9), 1</td>
<td>5 (29.4), 6</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>12 (75.0), 29</td>
<td>-</td>
<td>13 (76.5), 34</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (68.8), 14</td>
<td>-</td>
<td>13 (76.5), 21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (18.8), 5</td>
<td>-</td>
<td>6 (35.3), 7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (25.0), 6</td>
<td>-</td>
<td>1 (5.9), 1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>8 (50.0), 13</td>
<td>1 (6.3), 1</td>
<td>12 (70.6), 19</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (50.0), 9</td>
<td>1 (6.3), 1</td>
<td>10 (58.8), 12</td>
</tr>
<tr>
<td>Investigations</td>
<td>9 (56.3), 34</td>
<td>2 (12.5), 4</td>
<td>9 (52.9), 65</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>3 (18.8), 5</td>
<td>-</td>
<td>7 (41.2), 21</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>2 (12.5), 7</td>
<td>2 (12.5), 2</td>
<td>6 (35.3), 19</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3 (18.8), 4</td>
<td>-</td>
<td>3 (17.6), 4</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>8 (50.0), 18</td>
<td>1 (6.3), 1</td>
<td>7 (41.2), 14</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (31.3), 5</td>
<td>-</td>
<td>4 (23.5), 8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (25.0), 4</td>
<td>-</td>
<td>1 (5.9), 1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>5 (31.3), 9</td>
<td>1 (6.3), 1</td>
<td>5 (29.4), 8</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4 (25.0), 4</td>
<td>-</td>
<td>3 (17.6), 3</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>4 (25.0), 8</td>
<td>-</td>
<td>2 (11.8), 5</td>
</tr>
</tbody>
</table>

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
Table 4: Objective Response Rate and Duration of Response – by indication (mITT Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>PTCL (N=12)</th>
<th></th>
<th>CTCL (N=15)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>(95% CI)</td>
<td>n (%)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>CR</td>
<td>6 (50.0)</td>
<td>(21.09, 78.91)</td>
<td>1 (6.7)</td>
<td>(0.17, 31.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(21.09, 78.91)</td>
<td></td>
<td>(0.17, 31.95)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (25.0)</td>
<td>(5.49, 57.19)</td>
<td>7 (46.7)</td>
<td>(21.27, 73.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.49, 57.19)</td>
<td></td>
<td>(21.27, 73.41)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (16.7)</td>
<td>(2.09, 48.41)</td>
<td>5 (33.3)</td>
<td>(11.82, 61.62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.09, 48.41)</td>
<td></td>
<td>(11.82, 61.62)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (8.3)</td>
<td>(0.21, 38.48)</td>
<td>2 (13.3)</td>
<td>(1.66, 40.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.21, 38.48)</td>
<td></td>
<td>(1.66, 40.46)</td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>9 (75.0)</td>
<td>(42.81, 94.15)</td>
<td>8 (53.3)</td>
<td>(26.59, 78.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(42.81, 94.15)</td>
<td></td>
<td>(26.59, 78.73)</td>
</tr>
<tr>
<td>DCR (CR+PR+SD)</td>
<td>11 (91.7)</td>
<td>(61.52, 99.79)</td>
<td>13 (86.7)</td>
<td>(59.54, 98.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(61.52, 99.79)</td>
<td></td>
<td>(59.54, 98.34)</td>
</tr>
</tbody>
</table>

Duration of Response

<table>
<thead>
<tr>
<th></th>
<th>Median duration of response (months)</th>
<th>(Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.87, 25.23+)</td>
</tr>
</tbody>
</table>

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; NE, non-estimable; ORR, overall response rate; PD, progression of disease; PR, partial response; PTCL, peripheral T-cell lymphoma; R, response; SD, stable disease
FIGURE LEGENDS

**Figure 1:** Mean plasma concentrations of Romidepsin
C1D1, Cycle 1 Day 1; C1D8, Cycle 1 Day 8; n, number of patients

**Figure 2:** Treatment duration and response in evaluable PTCL and CTCL patients

A) *, Disease progression due to new lesions; AITL, angioimmunoblastic T-cell lymphoma; CR, complete response; NOS, not otherwise specified; PD, progression of disease; PR, partial response; n, number of patients; SD, stable disease

B) CR, complete response; CTCL, cutaneous T-cell lymphoma; mSWAT, modified severity-weighted assessment tool; n, number of patients; PD, progression of disease; PR, partial response; SD, stable disease; MF, mycosis fungoides; SS, Sezary syndrome

C) AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CR, complete response; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; NOS, not otherwise specified; PD, progression of disease; PR, partial response; PTCL, peripheral T-cell lymphoma; SCT, stem cell transplant; SD, stable disease
Cohort 1:
Tenalisib (400 mg BID) and Romidepsin (12mg/m²)

- C1D8 (N=3)
- C1D1 (N=2)

Cohort 2:
Tenalisib (600 mg BID) and Romidepsin (12mg/m²)

- C1D8 (N=3)
- C1D1 (N=2)

Cohort 3:
Tenalisib (800 mg BID) and Romidepsin (14mg/m²)

- C1D8 (N=3)
- C1D1 (N=2)
Supplementary File – Tenalisib and Romidepsin combination

**FILES**

**Supplementary Figure 1 – Study Design**

**Phase I: Dose Escalation**

**Cohort 1:** RP6530 (400 mg PO, BID) and Romidepsin (12 mg/m² IV, on Days 1, 8, 15 of every cycle*) (n=3)

**Cohort 2:** RP6530 (600 mg PO, BID) and Romidepsin (12 mg/m² IV, on Days 1, 8, 15 of every cycle*) (n=3)

**Cohort 3:** RP6530 (800 mg PO, BID) and Romidepsin (14 mg/m² IV, on Days 1, 8, 15 of every cycle*) (n=3)

**Phase II: Dose Expansion**

MTD/ Optimal Dose

R/R PTCL (n=12)  
R/R CTCL (n=12)

*Each cycle consists of 28 days; BID, twice daily; IV, intravenous; MTD, maximum tolerated dose; n, number of patients; PO, per oral; RP6530, code name of tenalisib; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory; CTCL, cutaneous T-cell lymphoma
Supplementary Figure 2: Study disposition

Number of screen failures (N=23)
- Lab abnormalities (n=7)
- Lack of measurable disease (n=3)
- Systemic infections (n=3)
- CNS involvement (n=2)
- Others (n=8).

Number of patients screened (N=56)
- Number of patients discontinued the study (N=15)
  - Adverse Events (N=1)
  - Disease progression (N=10)
  - Consent withdrawal (N=1)
  - Patient bridged to transplant (N=3)

Number of patients dosed (N=33)
- PTCL (N=16)
- CTCL (N=17)

Number of patients who are ongoing (N=1)

Number of patients discontinued the study (N=17)
- Adverse Events (N=5)
- Disease progression (N=9)
- Consent withdrawal (N=1)
- Investigator’s decision (N=1)
- Study drug intolerance (N=1)

*Number of patients with either tenalisib/romidepsin/both; AEs, adverse events; CTCL, cutaneous T-cell lymphoma; N, number of patients; PTCL, peripheral T-cell lymphoma
### Supplementary Table 1: Inclusion and exclusion criteria

#### Inclusion criteria

- Patient must be ≥18 years of age on the day of signing informed consent.
- Patient must have pathologically confirmed T-cell lymphoma at the enrolling institution.
- Patient must have disease status as defined as relapsed after or refractory to at least one systemic therapy.
- Patients should not have received more than three prior systemic combination chemotherapies.
- Patient must have eastern cooperative oncology group performance status ≤ 2.
- Peripheral T-cell lymphoma (PTCL) patients must have measurable disease defined as at least one bi-dimensional measurable lesion with minimum measurement of >1.5 cm in the longest diameter.
- Patients with life expectancy of at least 3 months
- Toxicities in patients related to prior therapy must have returned to Grade 1 or less, except for alopecia.
- Patient must have adequate bone marrow, liver, and renal function in line with below mentioned laboratory parameters. Hemoglobin and platelet levels should not be met by use of recent transfusion or growth factor support (granulocyte colony-stimulating factor or erythropoietin) within 3 weeks prior to treatment initiation.
  - Hemoglobin ≥8.0 g/dL
  - Absolute neutrophil count (ANC) ≥1,000/μL
  - Platelet count ≥75,000/μL
  - Total bilirubin ≤1.5 times the upper limit of normal (ULN) (or ≤3 x ULN, if patient has Gilbert syndrome)
  - Aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) ≤ 3 x ULN; ≤ 5 ULN in case of liver involvement
  - Calculated creatinine clearance >50 ml/min by Cockcroft-Gault formula.
- Females of childbearing potential and men with partners of childbearing potential must use an effective means of contraception.
- Female patients of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or not confirmed as negative, a serum pregnancy test will be required.
- Patient must provide written informed consent prior to any study-specific screening procedures.
- Patient must be willing and capable to comply with the requirements of the study.

*Note: The European Organization for Research and Treatment of Cancer classification of cutaneous T-cell lymphomas (CTCLs) will be used to classify patients. CTCL includes variants other than mycosis fungoides (e.g., Gamma delta cutaneous T-cell lymphoma or subcutaneous or panniculitis like T-cell lymphoma and CD8 positive T-cell lymphoma). PTCL include patients with predominantly nodal disease (systemic involvement) but some patients (e.g., angioimmunoblastic t-cell lymphoma or anaplastic large cell lymphoma) may have skin lesions. Patient having both skin and node lesions will be placed into one of the groups (CTCL or PTCL) as approved by investigator.

#### Exclusion criteria

- Patient who are on anticancer therapy including any investigational therapy (e.g., chemotherapy, biologic therapy, hormonal therapy, radiotherapy (except limited field palliative radiation), surgery and/or tumor embolization) ≤3 weeks or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1 (C1D1).
- Patient who discontinued prior therapy with phosphatidylinositol 3-kinase inhibitors or histone deacetylase inhibitors due to drug toxicity.
- PTCL patients with allogeneic hematopoietic stem cell transplantation (Allo-SCT) or active graft versus host disease or immunosuppression therapy within 3 months prior to C1D1 and CTCL patients with the history of Allo-SCT will be excluded.
- Patient with medical conditions who require usage of systemic immunosuppressive medications (>20 mg/day of prednisone or equivalent).
- Patients with severe bacterial, viral, or mycotic infection requiring systemic treatment.
- Female patients who are pregnant or lactating.
- Patients with history of chronic liver disease, hepatic veno-occlusive disease, or current alcohol abuse.
- Patients with known clinically active central nervous system (CNS) or meningeal involvement. (Note: In the absence of symptoms, investigation into CNS involvement is not required. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable for at least 4 weeks prior to C1D1).
- Patients who are known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection.
- Patients who are known seropositive requiring anti-viral therapy for hepatitis B virus infection OR evidence of active hepatitis B infection as defined by detectable viral load if the antibody tests are positive. [Note: A positive hepatitis B core antibody subject with an undetectable/negative hepatitis B deoxyribonucleic acid test (e.g., polymerase chain reaction [PCR] test) can be enrolled].
- Patients who are known seropositive requiring anti-viral therapy for hepatitis c virus infection OR patients with positive hepatitis C virus antibody.
- Patients with active Epstein-Barr virus (EBV) not related to underlying lymphoma (positive serology for anti-EBV viral capsid antigen immunoglobulin M (IgM) antibody and negative for anti-EBV Epstein-Barr nuclear antigen immunoglobulin G (IgG) antibody, or clinical manifestations and positive EBV PCR consistent with active EBV infection).
- Patient with active cytomegalovirus (CMV) (positive serology for anti-CMV IgM antibody and negative for anti-CMV IgG antibody and positive CMV PCR with clinical manifestations consistent with active CMV infection) and requiring therapy.
- Patients are excluded if they have concomitant second malignancies (except adequately treated non-melanomatous skin cancers, ductal carcinoma in situ, superficial bladder cancer, prostate cancer or in situ cervical cancers) unless a complete remission is achieved at least 2 years prior to study entry and no additional therapy (except adjuvant or maintenance therapy to reduce the risk of recurrence) is required or anticipated to be required during the study period.
- Patients who have taken any of the following within 1 week prior to C1D1:
  - Strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) including but not limited to grapefruit products, herbal supplements and drugs
  - Strong inhibitors or inducers of cytochrome P450 family 2 subfamily C member 9 including but not limited to herbal supplements and drugs
  - Substrates of CYP3A4 enzyme with a narrow therapeutic range.
- Patients with history of Grade 4 anaphylactic reaction.
- Patients who have taken live vaccines within 6 weeks of C1D1.
- Patients with history of prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy)
• Patients with recent history of a serious uncontrolled medical disorder, metabolic dysfunction, physical examination findings, or clinical laboratory findings indicating disease or condition that contraindicates use of an investigational drugs or put subject at high risk from treatment complications.

Supplementary Table 2: Evaluation of toxicity

All toxicities were related to either tenalisib and romidepsin combination or to the individual unless there was a clear alternative explanation. Toxicity was considered dose limiting if it occurred during the first cycle (28 days) treatment and was considered related to the combination. Toxicity was assessed utilizing the NCI CTCAE v5.0. The period of dose limiting toxicity (DLT) assessment was 28 days unless extended by the medical monitor.

DLTs were defined as follows:

<table>
<thead>
<tr>
<th>Hematological DLTs</th>
<th>Non-Hematological DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neutropenia and thrombocytopenia of Grade 4 that did not resolve to Grade ≤3 within 14 days with supportive treatment (e.g., growth factors) OR febrile neutropenia (absolute neutrophil count &lt;1000/μL with fever &gt;38.5°C [101°F]) and thrombocytopenia of Grade ≥3 that did not resolve to Grade ≤2 within 14 days with supportive treatment.</td>
<td>• Grade ≥3 non-hematologic toxicity that could not be controlled or prevented by supportive care including corticosteroids with exception of: o Grade ≥3 alanine aminotransferase/aspartate aminotransferase elevation that resolved to Grade ≤2 within 14 days. o Grade ≥3 diarrhea that improved Grade ≤2 within 48 hours or Grade ≥3 diarrhea in patients who had not received optimal treatment with anti-diarrheal drugs. o Grade ≥3 vomiting in patients who had not received the highest therapeutic dose of antiemetics (e.g., steroids, 5-hydroxytryptamine antagonists, prochlorperazine, lorazepam). o Single episode of Grade ≥3 infusion reaction. o Grade 3 nausea, Grade 3 asthenia or Grade 2 alopecia. • Treatment delays of ≥14 days due to unresolved toxicity.</td>
</tr>
</tbody>
</table>
### Supplementary Table 3: Mean plasma concentration of Tenalisib and its metabolite (IN0385)

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Cohort-1 (Tenalisib 400 mg BID + Romidepsin 12 mg/m²)</th>
<th>Cohort-2 (Tenalisib 600 mg BID + Romidepsin 12 mg/m²)</th>
<th>Cohort-3 (Tenalisib 800 mg BID + Romidepsin 14 mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tenalisib</td>
<td>IN0385</td>
<td>Tenalisib</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1544.42 ± 1609.44</td>
<td>1369.28 ± 622.37</td>
<td>2152.17 ± 748.83</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.hr/mL)</td>
<td>5767.14 ± 5999.89</td>
<td>6948.76 ± 4536.46</td>
<td>11311.28 ± 2260.53</td>
</tr>
<tr>
<td>AUC_{0-\infty} (ng.hr/mL)</td>
<td>8048.65 ± 7277.07</td>
<td>9801.81 ± 5268.94</td>
<td>13388.55 ± 1175.88</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr) [Median (Min-Max)]</td>
<td>1.00 (1.00, 2.00)</td>
<td>2.00 (1.00, 2.00)</td>
<td>3.00 (2.00, 4.00)</td>
</tr>
<tr>
<td>$K_{\text{el}}$ (1/hr)</td>
<td>0.352 ± 0.0367</td>
<td>0.249 ± 0.0098</td>
<td>0.200 ± 0.0807</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>1.979 ± 0.2064</td>
<td>2.785 ± 0.1094</td>
<td>3.802 ± 1.2874</td>
</tr>
</tbody>
</table>

All values are expressed in Mean ± SD. AUC, area under curve; BID, twice daily; $C_{\text{max}}$, peak drug concentration; hr, hour; $K_{\text{el}}$, elimination constant; m², meter square; mL, milliliter; Max, maximum; Min, minimum; mg, milligram; ng, nanogram; NE, Not Estimable since the presence of only one patient in the summary and hence could not estimate SD; SD, standard deviation; $T_{\text{max}}$, time to maximum plasma concentration; $t_{1/2}$, plasma half-life
Supplementary Method 1: Study design and participants

A minimum of three patients were to be enrolled at each dose level. Escalation to the next cohorts was to occur if no patient within the three-patient cohort or one in six patients experienced a dose limiting toxicity (DLT).

Adult patients with pathologically confirmed PTCL or CTCL, who relapsed after or refractory to at least one systemic therapy, were enrolled after providing written informed consent. Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤2, the life expectancy of at least three months, measurable disease, and with adequate bone marrow, liver, and renal function were enrolled. Patients were excluded from the study if they had discontinued prior treatment with PI3K inhibitors or HDAC inhibitors due to drug toxicity, had a history of allogeneic hematopoietic stem cell transplantation or were taking immunosuppressive therapy. Supplementary Table 1 provides a complete list of inclusion and exclusion criteria.

Supplementary Method 2: Treatment and intervention

Even though tenalisib and romidepsin have non-overlapping toxicity profiles, the starting dose of tenalisib which was considered (i.e., 400 mg BID) was half of the single agent tenalisib dose that was established to be safe and well tolerated in the previous single-agent study. For romidepsin, one dose below the approved dose of a single agent was considered appropriate as the starting dose (12 mg/m²). During dose escalation, the doses of tenalisib and romidepsin were increased simultaneously to achieve the highest doses of both tenalisib (800 mg BID) and romidepsin (IV 14 mg/m²), under close monitoring, with the flexibility of dose reduction in case of any safety concerns or DLT. The study was monitored for adherence to the dosing regimen and overall treatment compliance.

Only during Cycle 1 in dose escalation, tenalisib administration was initiated from Day 3 onwards to permit PK assessment of romidepsin alone, before the initiation of combination treatment.

On the day of romidepsin administration (except on Cycle 1), patients received the morning dose of tenalisib in the clinic one hour before romidepsin infusion.

Supplementary Method 3: Pharmacokinetic evaluations

PK parameters included assessment of the area under the curve (AUCₐ₋ₓ and AUC₀₋ₜ), peak drug concentration (Cₘₐₓ), time to maximum plasma concentration (tₘₐₓ), elimination constant (Kₑ), and plasma half-life (t½) of the combination.
Blood samples were collected for the PK analysis (AUC$_{0-\infty}$ and AUC$_{0-t}$, C$_{max}$, t$_{max}$, K$_{el}$, and t$_{1/2}$) of tenalisib, its metabolite (IN0385), and romidepsin in the dose-escalation part of the study. The blood samples collected on Cycle 1 Day 1 (C1D1, Pre-infusion (0), 1, 2, 3, 5, 7, 9, 10 h post-infusion) were analyzed to estimate romidepsin levels, and samples collected on C1D8 (Pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 11 post-dose) and on C2D1, C3D1, and C4D1 were analyzed for tenalisib, its metabolite (IN0385), and romidepsin. PK analysis was performed using a validated software Phoenix® WinNonlin® version 8.1. Non-Compartmental Analysis was conducted on the final audited data sets in Cohort 1, Cohort 2, Cohort 3. PK parameters (C$_{max}$, T$_{max}$, AUC$_{s}$, CL/F, V$_{z}$/F, λ$_{z}$, t$_{1/2}$) were calculated for individual patients and summarized for each Cohort for Cycle 1 Day 1 and Cycle 1 Day 8. Assessment of dose proportionality of tenalisib and its metabolite (IN0385) using a power model was conducted. Mean (sorted by Cohort and Visit Day) and individual (for each patient) concentration versus time plots were generated on linear and semi-log scales. The dose proportionality of tenalisib and its metabolite (IN0385) was assessed using a power model.

**Supplementary Method 4: Study Procedures**

All patients were treated with tenalisib and romidepsin and followed up until disease progression or discontinuation from the study. Patients who continued treatment for 7 cycles and who derived benefit (patients with stable disease [SD] or patients with partial response [PR]/complete response [CR]) were rolled over to compassionate use protocol and continued to receive the tenalisib and romidepsin until disease progression. These patients were followed up at every 3 monthly intervals.

All AEs/SAEs regardless of relationship to tenalisib/romidepsin were recorded from the time of informed consent until 30 calendar days after the last dose of the study drugs. The severity of AEs/SAEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v 5.0). All toxicities were considered related to either the combination or to tenalisib or romidepsin individually unless there was a clear alternative explanation. Toxicity was considered dose-limiting if it occurred during the first cycle and was considered related to the combination. Supplementary Table 2 presents the assessment and criteria of DLTs.

Vitals and laboratory tests were done at every visit and other safety evaluations (including physical examinations, pregnancy tests, and ECGs) were done at the scheduled time points till the completion of Cycle 7. Post Cycle 7, laboratory tests and other evaluations were done as part of the SOC.
Dose interruption/modification/drug discontinuation was based on AEs and their relationship with the individual drugs and were done as per the pre-defined criteria for both tenalisib and romidepsin. Tenalisib was resumed at one dose level if the event resolved to ≤Grade 2 or baseline. Instructions based on prescribing information was referred for resuming romidepsin.4

Blood samples were collected for PK analysis of tenalisib, its metabolite (IN0385), and romidepsin in the dose-escalation part of the study. The blood samples collected at Cycle 1 Day 1 were analyzed to estimate romidepsin levels, and samples collected on C1D8 and on C2D1, C3D1, and C4D1 were analyzed for tenalisib, IN0385, and romidepsin. Supplementary Method 3 presents the assessment of PK evaluations. Analysis of human plasma for levels of romidepsin and tenalisib was done by LC/MS/MS method.

The efficacy responses were assessed approximately at 8 weekly intervals for the first 2 assessments and then at the end of Cycle 7 and/or as clinically indicated. Post Cycle 7, efficacy evaluations were performed as part of the standard of care (SOC) and the date of disease progression was recorded. Supplementary Table 2 and Supplementary Method 3 presents the assessment of DLTs and PK evaluations, respectively.

References


Supplementary Method 5: Statistical analysis

The endpoints were presented as percentages and its 95% confidence intervals (CIs). DoR was assessed as time from the initial response to documented disease progression. Compliance with
study treatment measured as <80%, 80-120%, and >120 %, was calculated by the total planned
dose of tenalisib dispensed at each cycle and the total dose consumed at that cycle.

The efficacy analysis included all patients who received at least one dose of the study medication
and had at least one post-baseline efficacy assessment. The efficacy endpoints CR, CR+PR
(ORR), and disease control rate (DCR) were defined as CR+PR+stable disease (SD).