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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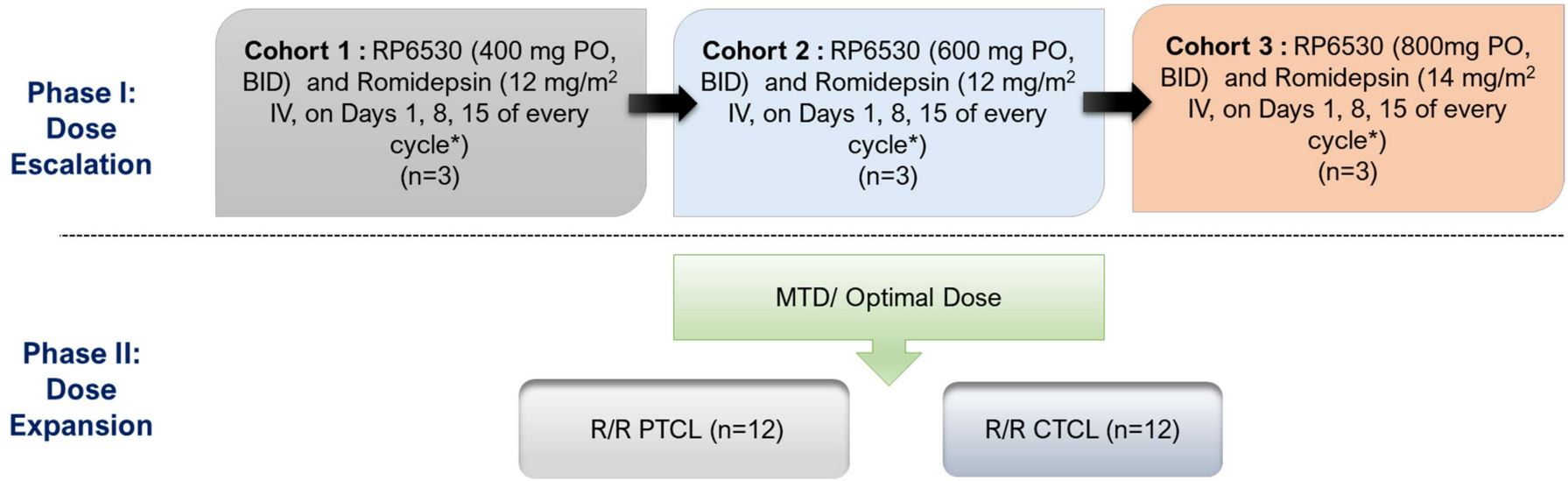
Supplementary File – Tenalisib and Romidepsin combination

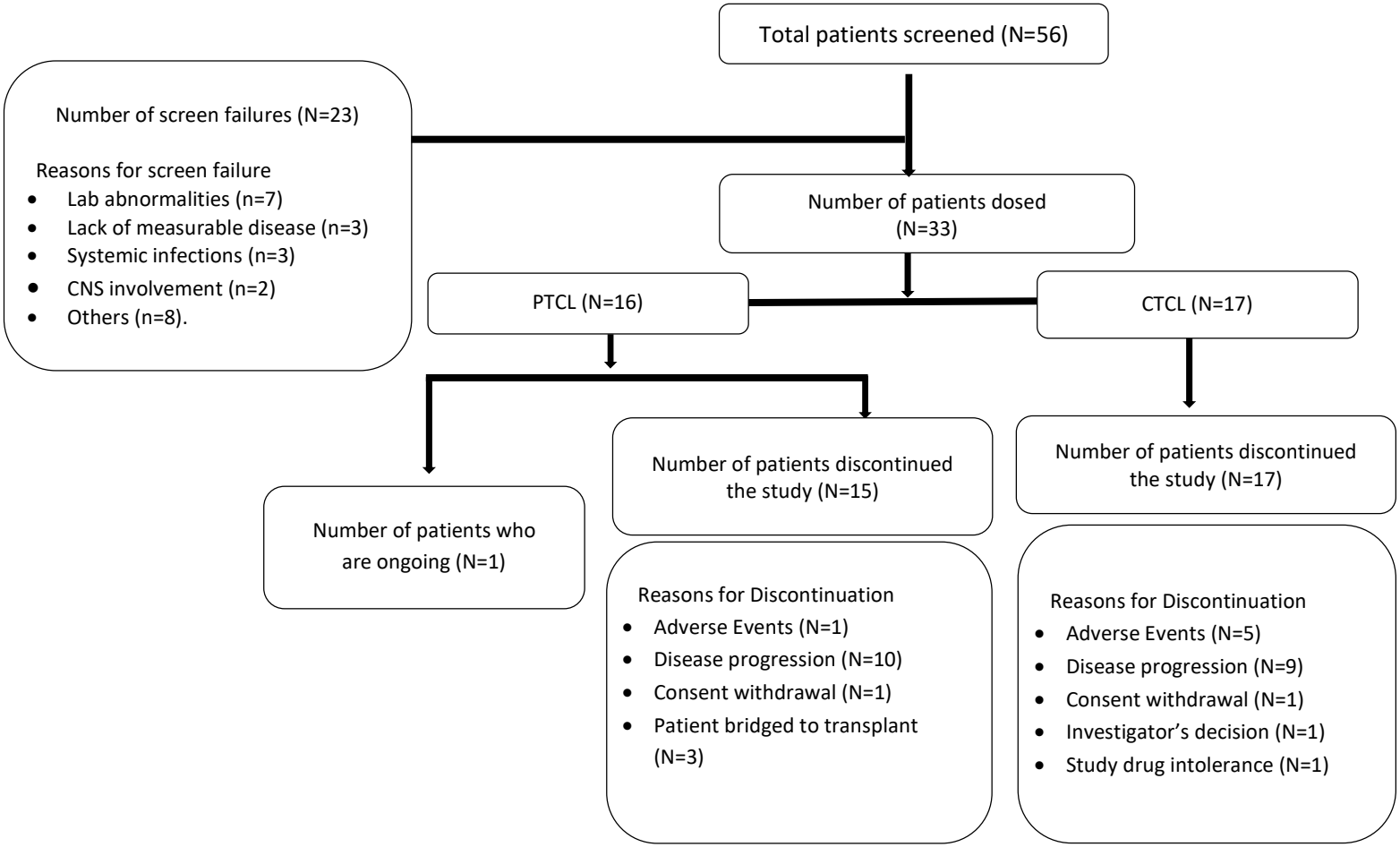
FILES

Supplementary Figure 1 – Study Design



*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 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:

Hematological DLTs	**Non-Hematological DLTs**
• 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 <1000/μL with fever >38.5ºC [101ºF]) and thrombocytopenia of Grade ≥3 that did not resolve to Grade ≤2 within 14 days with supportive treatment.	• 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.

Supplementary Table 3: Mean plasma concentration of Tenalisib and its metabolite (IN0385)

Parameters (Units)	Cohort-1 (Tenalisib 400 mg BID + Romidepsin 12 mg/m^2)		Cohort-2 (Tenalisib 600 mg BID + Romidepsin 12 mg/m^2)		Cohort-3 (Tenalisib 800 mg BID + Romidepsin 14 mg/m^2)	
	Tenalisib	IN0385	Tenalisib	IN0385	Tenalisib	IN0385
C_{max} (ng/mL)	1544.42 ± 1609.44	1369.28 ± 622.37	2152.17 ± 748.83	4852.08 ± 4238.77	5791.11 ± 2426.44	4900.92 ± 2469.65
AUC_{0-t} (ng.hr/mL)	5767.14 ± 5999.89	6948.76 ± 4536.46	11311.28 ± 2260.53	25654.24 ± 18498.26	31678.21 ± 24000.34	26881.26 ± 10326.27
$AUC_{0-\infty}$ (ng.hr/mL)	8048.65 ± 7277.07	9801.81 ± 5268.94	13388.55 ± 1175.88	32880.02 ± 21925.04	98951.37 ± 121673.18	45059.211 (NE)
T_{max} (hr) [Median (Min-Max)]	1.00 (1.00, 2.00)	2.00 (1.00, 2.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	1.00 (0.50, 8.00)	2.00 (1.00, 10.00)
K_{el} (1/hr)	0.352 ± 0.0367	0.249 ± 0.0098	0.200 ± 0.0807	0.149 ± 0.0284	0.099 ± 0.1142	0.160 (NE)
$t_{1/2}$ (hr)	1.979 ± 0.2064	2.785 ± 0.1094	3.802 ± 1.2874	4.765 ± 0.8311	20.953 ± 24.1760	4.335 (NE)

All values are expressed in Mean ± SD. AUC, area under curve; BID, twice daily; C_{max}, peak drug concentration; hr, hour; K_{el}, elimination constant; m^2, 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_{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,[1] 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.[2] For romidepsin, one dose below the approved dose of a single agent was considered appropriate as the starting dose (12 mg/m^2). 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/m^2), 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 ($AUC_{0-\infty}$ and AUC_{0-t}), peak drug concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination constant (K_{el}), and plasma half-life ($t_{½}$) 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 $t_{½}$) 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).[3] 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

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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).