Safety and Anti-Tumour Activity of Tenalisib (RP6530), a Dual PI3K δ/γ Inhibitor, in Relapsed/Refractory T-Cell Lymphoma: Updated Results from the Dose Expansion Cohort of an on-Going Phase I/Ib Study

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INTRODUCTION

Dual targeting of PI3K δ/γ is an attractive intervention strategy in patients with T-cell lymphoma. Tenalisib (RP6530) is a novel, highly specific dual equipotent PI3K δ/γ inhibitor with nanomolar inhibitory potency that effectively inhibits AKT phosphorylation and induces apoptosis in lymphoma/leukemic cell lines. Chemically, Tenalisib is an isoflavone substituted adenine.

Table 1: Enzyme, cell, and whole blood-based activity of Tenalisib for inhibition of PI3K isoforms.

Potency and Isoform selectivity of Tenalisib				
	PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ
Enzyme (IC_{50}, nM)	>10000	4023	**24.5**	**33.2**
Cell-based (EC_{50}, nM)	>10000	2067	**39.9**	**54.8**
Inhibition of anti-FcεR1 induced CD63 HWB Basophils (PI3Kδ Activity)				37.8 nM
Inhibition of fMLP induced CD63 in HWB Basophils (PI3Kγ Activity)				39.0 nM

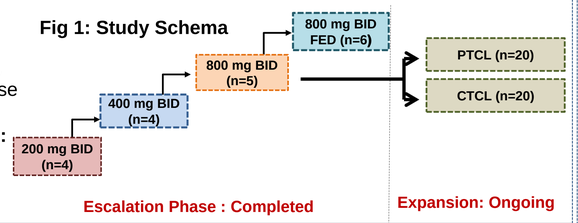
METHODS

STUDY DESIGN

- This is a Phase I/Ib, 3+3 design study in patients with relapsed or refractory T-cell lymphoma (Study protocol: RP6530-1401).
- Tenalisib is given orally twice a day in 28-Day cycles and Dose-limiting toxicities (DLTs) were assessed during the first cycle.
- Intra-patient dose escalation was allowed following safety of higher doses

- **Primary Objectives :**
- The Safety, Pharmacokinetics (PK), Maximum Tolerated Dose (MTD)
- **Secondary Objectives:** Pharmacodynamics, Overall response rate, Duration of response

Fig 1: Study Schema



KEY ELIGIBILTY CRITERIA

- Histologically confirmed T-cell Non-Hodgkin's lymphoma.
- Relapsed after, or refractory to ≥ 1 prior treatments, and not eligible for transplantation and or approved therapy; ECOG performance status ≤ 2; patient with measurable or evaluable disease; Adequate organ system function: ANC ≥ 750/μL; platelets ≥ 50 K/μL
- Prior therapy that inhibits PI3K/ BTK/ mTOR were part of exclusion criteria

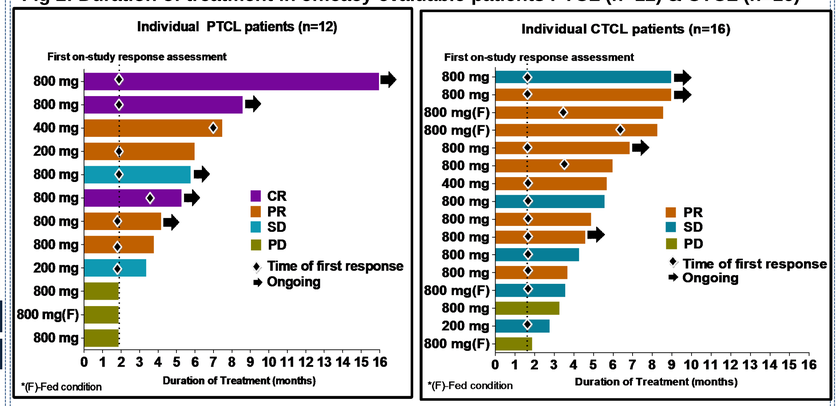
RESULTS

DEMOGRAPHICS	PTCL (n=24)	CTCL (n=26)	All (n=50)
Age (years), Median (Range)	63(40-89)	67 (37-84)	66.5 (37-89)
Gender			
Male, n (%)	16 (67)	12 (46)	28 (56)
Female, n (%)	8 (33)	14 (54)	22 (44)
Prior therapies, Median (Range)	3 (1-7)	5.5 (2-15)	4 (1-15)
Patients with ≥3 therapies, n (%)	17 (71)	25 (96)	42 (84)
Patients with ≥5 therapies, n (%)	7 (30)	16 (62)	23 (46)
Stage, 3 or 4, n, (%)	23 (96)	12 (46)	35 (70)
ECOG, 0/1/2	14/10/0	23/3/0	37/13/0
Disease status			
Relapse, n (%)	14 (58)	11 (42)	25 (50)
Refractory, n (%)	10 (42)	15 (58)	25 (50)

Data cut off is as of 10th November 2017

DURATION OF TREATMENT & INDIVIDUAL PATIENT RESPONSE

Fig 2: Duration of treatment in efficacy evaluable patients PTCL (n=12) & CTCL (n=16)



Adverse Event	Any grade, n (%)	Grade≥3, n (%)
Transaminitis	14 (28%)	11 (22%)
Rash	5 (10%)	3 (6%)
Diarrhea	6 (12%)	-
Fatigue	5 (10%)	-
Headache	5 (10%)	-

Table 2: Tenalisib related Adverse Events (Incidence ≥10%)

- Most of the AEs were mild/moderate in severity
- Related Grade ≥ 3 includes transaminitis (22%), rash (6%), neutropenia (6%), hypophosphatemia (2%), INR Increase (2%), Diplopia secondary to neuropathy (2%) and sepsis (2%).
- 7(50%) patients who had transaminitis treated with steroids.
- Treatment related serious adverse events (SAEs) were sepsis, increased INR, diplopia secondary to neuropathy and pyrexia.
- 5(10%) patients discontinued due to AEs.

ANTI-TUMOR ACTIVITY OF TENALISIB IN PTCL & CTCL

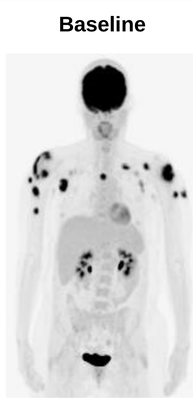


Fig 3: PET scan for a PTCL patient who showed partial response.

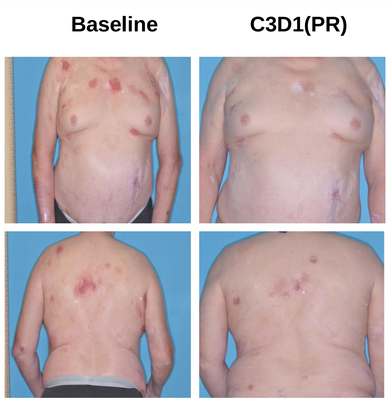
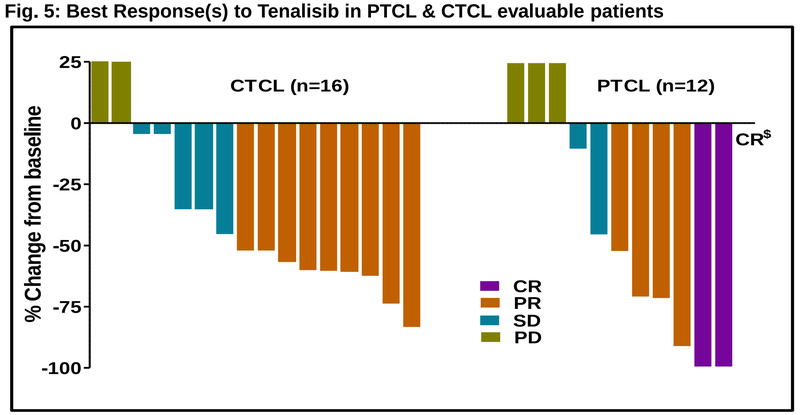


Fig 4: Skin photographs for a CTCL patient who showed partial response.

EFFICACY OF TENALISIB IN PTCL & CTCL

Fig. 5: Best Response(s) to Tenalisib in PTCL & CTCL evaluable patients



$Non-measurable disease; positive bone marrow became negative;

Population	Patients Treated/ Evaluable (n)	Best Observed Response n (%) ORR	CR	PR	SD	PD	DCR (CR+PR+SD)
All	50/28	16 (57)	3 (11)	13 (46)	7 (25)	5(18)	23 (82)
PTCL	24/12	7 (58)	3 (25)	4 (33)	2 (17)	3(25)	9 (75)
CTCL	26/16	9 (56)	-	9 (56)	5 (31)	2(12)	14 (87)

Table 3: Anti-tumor activity of Tenalisib

- 15 patients (8 PTCL; 7 CTCL) not considered for efficacy analysis due to rapid disease progression as per protocol.
- 7 patients (4 PTCL; 3 CTCL) have not yet reached the first efficacy assessment.
- Median duration of treatment: PTCL [2.0 months (0.4, 16.0+)], CTCL [3.4 months (0.7, 9.0+)]

PHARMACODYNAMIC MARKERS

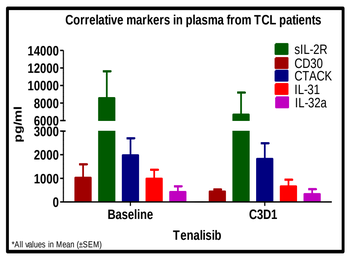


Fig 6: Correlative markers in plasma of patients treated with Tenalisib.

- Correlative markers were analysed in PTCL (sIL-2R and CD30) and CTCL (IL-31, IL-32α, and CTACK) in efficacy evaluable patients
- Reduction in CD30 (57%) and IL-31 (33%) were seen in patients who showed response

CONCLUSIONS

- ❑ Tenalisib demonstrated an acceptable safety profile which was devoid of colitis and pneumonitis shown by the first generation PI3K class of agents. Transaminitis was manageable with dose adjustments and steroids when required.
- ❑ Tenalisib showed promising objective response rates in heavily pretreated patients with PTCL & CTCL which correlated with reduction in disease biomarkers. In PTCL patients who responded, there was a median nodal reduction of ~70%.
- ❑ Further confirmatory studies in PTCL and other new indications are being evaluated.

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