Safety and Efficacy of Tenalisib Given in Combination with Romidepsin in Patients with Relapsed/ Refractory T-Cell Lymphoma: Final Results from a Phase I/II Open Label Multi-Center Study

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Introduction

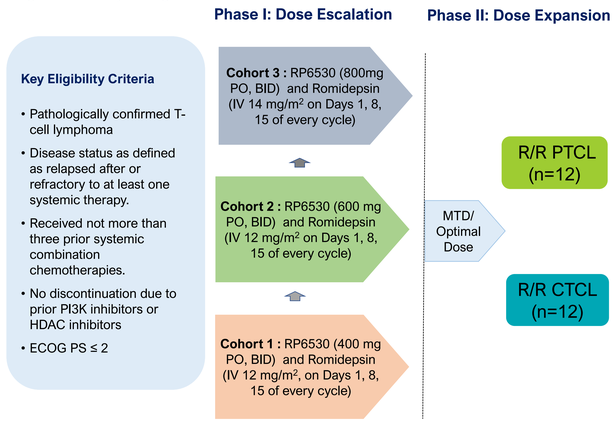
Tenalisib (RP6530), a highly selective PI3K δ/γ and SIK3 inhibitor, has shown promising activity as a single agent in patients with TCL, with a differentiated and favorable safety profile. *In vitro* studies in TCL cell lines showed synergistic potential of the combination of tenalisib and romidepsin. This combination was evaluated in patients with R/R T-cell lymphomas. The data presented is the final data set for the study.

Methods

Study Design:

- This was a multi-center, open label, Phase I/II study (Protocol ID: RP6530+Romidepsin-1805) in patients with T cell lymphoma (NCT03770000).
- The Phase I was a 3+3 dose escalation study to determine the MTD/optimal dose of the combination. The Phase II was an expansion cohort at the MTD/optimal dose.
- DLT assessment period was 28-days.
- Primary end points: Safety, tolerability and MTD. Secondary end points: PK, ORR and DoR
- Response assessed at C3D1, C5D1, C8D1. PTCL & CTCL patients were assessed as per Lugano classification (Cheson 2014) & Global assessment (Oslen 2011) respectively.

Figure 1: Study Design



Demographics

Table 1: Demographics of all subjects

Parameters	PTCL (n=16)	CTCL (N=17)	All (n=33)
Age, years Median (range)	61.85 (42-83)	66(48-80)	66(42-83)
Male/Female, n	9/7	8/9	17/16
Stage 3 or 4, n (%)	14 (87)	8 (47)	22 (66)
Prior Therapy, median (range)	3.0 (1-5)	6 (1-17)	3 (1-17)
• ≥ 3 Prior therapies, n (%)	10 (62.5)	15 (88.2)	25 (75.8)
Response to last therapy			
Relapse, n (%)	5 (31)	7 (41)	12 (36)
Refractory, n (%)	11 (69)	10 (59)	21 (64)
ECOG status, 0/1/2	8/8/0	6/10/1	14/18/1
Subtypes			
• MF	-	12	12
• Sezary syndrome	-	5	5
• PTCL-NOS	7	-	7
• AITL	7	-	7
• PTCL-ALCL	1	-	1
• PTCL-Cutaneous	1	-	1

Patient Disposition

Table 2: Patient disposition

	PTCL (n=16)	CTCL (n=17)	All (n=33)
Patients who completed the study (Completed 7 cycles), n(%)	6 (37.5)	3 (17.7)	9 (27.3)
• Moved to Compassionate study	3	3	6#
• Patient Bridged to transplant	1	-	1
• Disease Progression	2	-	2
Discontinued study, n (%)	10 (62.5)	14 (82.4)	24 (72.7)
Reason for discontinuation, n			
• Adverse Event	1	5	6
• Disease Progression	6	7	13
• Patient Bridged to Transplant	2	-	2
• Withdrew Consent	1	2	3
Drug interruptions due to related AEs, n(%)	10 (62.5)	12 (70.6)	22 (66.6)
Dose reduction due to related AEs, n(%)	7 (43.8)	8 (47.1)	15 (45.5)

#Two patients are ongoing

- None of the PTCL patients discontinued the study drug due to related AEs.
- AEs leading to dose reductions reported in 15 patients primarily related to romidepsin.

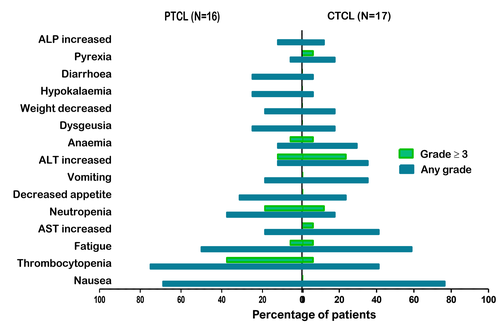
Results: Safety

- No DLTs were reported in the dose escalation phase and Tenalisib 800 mg BID plus Romidepsin 14 mg/m^2 on Days 1, 8, 15 of every cycle was considered as the optimal dose for expansion cohorts.
- No unexpected AEs or increased frequency of exiting AEs for individual agents.

Table 3: Incidence of Related Adverse Events (AEs ≥ 10% of patients)

Related AEs ≥ 10%	Tenalisib		Romidepsin		Combination		All related	
	All, %	≥G3,%	All, %	≥G3,%	All, %	≥G3, %	All, %	≥G3,%
Nausea	3.0	-	45.5	-	33.3	-	72.7	-
Thrombocytopenia	-	-	24.2	9.1	36.4	12.1	57.6	21.6
Fatigue	3.0	-	36.4	6.1	18.2	-	54.5	6.1
AST increased	18.2	-	-	-	15.2	3.0	30.3	3.0
Neutropenia	-	-	18.2	12.1	18.2	12.1	27.3	15.2
Decreased appetite	-	-	21.2	-	6.1	-	27.3	-
Vomiting	6.1	-	18.2	-	9.1	-	27.3	-
ALT increased	15.2	9.1	-	-	12.1	12.1	24.2	18.2
Anaemia	-	-	6.1	-	15.2	6.1	21.2	6.1
Dysgeusia	-	-	15.2	-	6.1	-	21.2	-
Weight decreased	-	-	18.2	-	-	-	18.2	-
Hypokalemia	-	-	6.1	-	9.1	-	15.2	-
Diarrhoea	-	-	3.0	-	12.1	-	15.2	-
Pyrexia	6.1	-	3.0	3.0	6.1	-	12.1	3.0
ALP increased	9.1	-	-	-	3.0	-	12.1	-

Figure 2: Incidence of Related Adverse Events (AEs ≥ 10%) in PTCL and CTCL



Pharmacokinetics

- Co-administration of romidepsin along with tenalisib did not significantly alter the PK of either agents.

Figure 3a: Plasma concentrations of Romidepsin

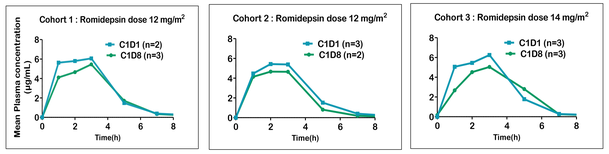
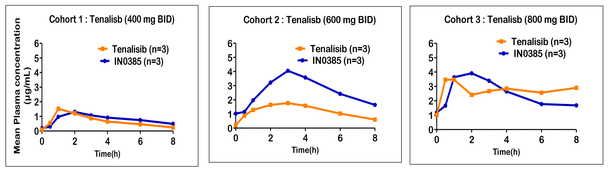
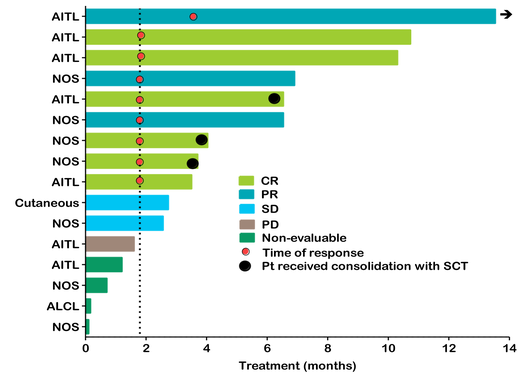


Figure 3b: Plasma concentrations of Tenalisib and its metabolite (IN0385)



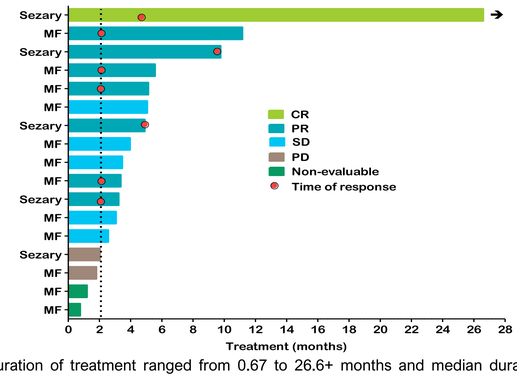
Efficacy assessment

Figure 4a: Clinical response in PTCL patients



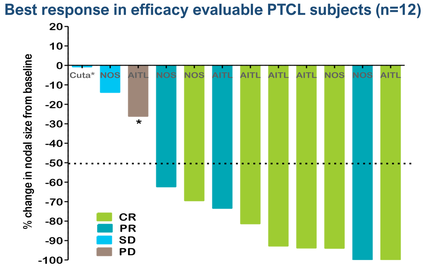
- Duration of treatment ranged from 0.03 to 13.5+ months and median duration of response was 5.03 months (range 1.87-8.47+)

Figure 4b: Clinical response in CTCL patients



- Duration of treatment ranged from 0.67 to 26.6+ months and median duration of response was 3.8 months (range 0.87-22.2+).

Figure 5a: Best response in efficacy evaluable PTCL subjects (n=12)



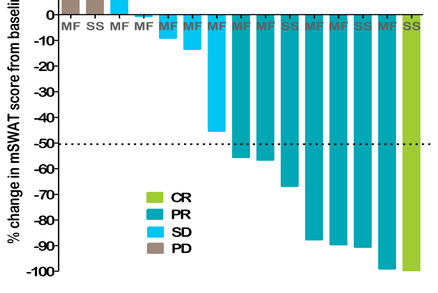
*Disease progression due to new lesion

Outcome	PTCL-NOS	PTCL-AITL	All PTCL
# of patients considered for efficacy evaluation$	5	6	12
Overall Response Rate (ORR), (%)			75
Complete Response (CR) n (%)	2	4	6 (50)
Partial Response (PR) n (%)	2	1	3 (25)
Stable disease (SD) n (%)*	1	-	2 (16.6)
Progressive disease (PD) n (%)	-	1	1 (8.3)
Disease Control Rate (DCR), (CR+PR+SD) (%)			91.7

**One cutaneous PTCL subject had stable disease (not shown in the table)*

$Four patients not considered for evaluation due to rapid disease progression before reaching C3D1 as per protocol

Figure 5b: Best response in efficacy evaluable CTCL subjects (n=15)



Outcome	Mycosis fungoides	Sezary syndrome	All CTCL
# of patients considered for efficacy evaluation$	10	5	15
Overall Response Rate (ORR), (%)			53.3
Complete Response (CR) n (%)	-	1	1 (6.7)
Partial Response (PR) n (%)	4	3	7 (46.7)
Stable disease (SD) n (%)	5	-	5 (33.3)
Progressive disease (PD) n (%)	1	1	2 (13.3)
Disease Control Rate (DCR), (CR+PR+SD) (%)			86.7

$Two patients not considered for evaluation due to rapid disease progression before reaching C3D1.

Conclusion

- The combination of tenalisib and romidepsin demonstrated a favorable safety profile and promising anti-tumor activity in patients with R/R TCL.
- No DLT was reported with the combination at any dose level in the dose escalation.
- Co-administration of romidepsin along with tenalisib did not significantly alter the PK of either agents.
- Overall efficacy response in both PTCL & CTCL continues to be encouraging and supports further development of Tenalisib in patients with T-cell lymphoma.

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