Pooled Safety Analysis and Efficacy of Tenalisib (RP6530), a PI3Kδ/γ Inhibitor in Patients with Relapsed/Refractory Lymphoid Malignancies

Swami P . Iyer [1], Auris Huen[1], Andrés J M Ferreri[2], Bradley M. Haverkos[3], Jasmine M. Zain[4], Radhakrishnan Ramchandren[5], Mary Jo Lechowicz[6], Sumana Devata[7], Neil Korman[8], Lauren C.Pinter-Brown[9], Richard Delarue[10], Kasi V Routhu[11], Prajak Barde[11], Ajit M Nair[11] and Carmelo Carlo-Stella[12]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]IRCCS San Raffaele Scientific Institute, Milano, Italy; [3]University of Colorado School of Medicine, Aurora, CO; [4]City of Hope, Duarte, CA; [5]Karmanos Cancer Institute, Detroit, MI; [6]Emory University , Atlanta, GA; [7]University of Michigan, Ann Arbor , MI; [8]University Hospitals Cleveland Medical Center, Cleveland, OH; [9]University of California, Irvine, CA; [10]Necker University Hospital, AP-HP , Paris, France; [11]Rhizen Pharmaceuticals S.A., Switzerland; [12]Humanitas Cancer Center , Milano, Italy

Introduction

- PI3K inhibitors on the market or in clinical development have shown good activity in indolent and difficult to treat lymphoid malignancies, however their safety profiles have always been a major point of discussion, especially their long term use. Immune-mediated adverse events like transaminitis, colitis and pneumonitis have been major reasons for treatment discontinuation in addition to other toxicities like cytopenias, and infections.
- Tenalisib (RP6530) is a next generation, oral, selective, PI3Kδ/γ inhibitor with nanomolar inhibitory potency and has demonstrated activity in patients with relapsed/refractory lymphoid malignancies (Carmelo, ASH 2016 and Oki, ASCO 2018).
- A pooled safety analysis across two Phase I/Ib studies in patients treated with Tenalisib was to assess the short and long term adverse events of Tenalisib.

Methods

- Safety data was pooled from two Phase I/Ib Tenalisib monotherapy trials NCT02017613 (EU study) and NCT02567656 (US study)
- Patients had R/R lymphoid malignancies with ≥1 prior therapy. Both studies shared similar key eligibility criteria
- Patients were refractory to or relapsed after ≥ 1 prior treatment lines and patients with a measurable or evaluable disease and ECOG performance status ≤2 enrolled in the study.
- Responses were evaluated in lymphoid malignancies using IWG criteria (Cheson et al., 2007) and in CTCL using the modified Severity Weighted Assessment Tool (mSWAT). Adverse events were graded according to CTCAE v4.03.

Results

- In EU study, a total of 35 patients were enrolled across 11 dose levels (25mg-1200 mg BID & 600mg-800 mg TID in patients with B & T cell malignancies.
- In US study, a total of 58 patients were treated at 200 mg-800 mg BID in patients with T-cell malignancies.
- Overall, 93 patients are considered for pooled safety analysis.

Table 1: Patient characteristics

DEMOGRAPHICS	All (n=93)
Disease Sub type, n (%)	
T- cell Malignancies, PTCL (32); CTCL (30)	62 (67)
B-cell Malignancies, HL (15); DLBCL (6); MCL (4); CLL/SLL (2); MM (1); WM (1); MZL (1); FL(1)	31 (33)
Prior therapies, Median (Range)	5(1-15)
≥3 therapies, n (%)	75 (81)
≥5 therapies, n (%)	49 (53)
Stage, 3 or 4, n, (%)	66 (71)
ECOG, 0/1/2	51/38/4
Disease status	
Relapse, n (%)/ Refractory, n (%)	47(51)/46 (49)

Safety

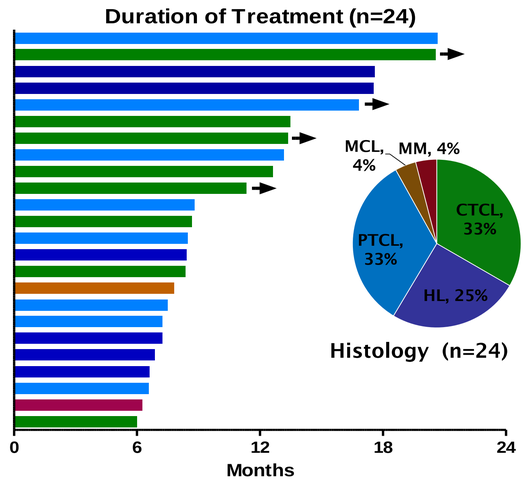
Table 2: AE in Patients Treated with Tenalisib

Adverse events (≥10% all grades & causality)	Safety population (n=93)			
	All Grades (%)		Grade ≥ 3 Events (%)	
	Related	All Causality	Related	All Causality
Fatigue	9	28	-	3
Pyrexia	4	26	2	4
AST Increase	17	22	10	11
ALT Increase	17	20	11	11
Nausea	9	20	-	1
Anemia	5	18	1	8
Diarrhea	10	18	1	2
Abdominal Pain	3	17	-	4
Asthenia	2	17	-	2
Dyspnea	2	16	-	2
Cough	2	14	-	1
Decreased Appetite	4	14	-	1
Pruritus	4	14	1	1
Thrombocytopenia	2	14	1	10
Vomiting	5	14	-	-
Headache	6	13	-	
Neutropenia	4	13	2	11
Oropharyngeal Pain	-	12	-	-
Constipation	3	11	-	-
Dizziness	5	11	-	1
Rash	6	11	3	3
Dehydration	3	10	-	1

- Majority of AEs included transaminitis, diarrhea, fatigue and nausea
- Related Grade ≥ 3 AE was mainly transaminitis.
- Six (12%) patients discontinued therapy due to a drug related AEs, like transaminitis, rash, diarrhea, sepsis, diplopia secondary to neuropathy and drug reaction
- Analysis of immune mediated adverse events revealed that transaminitis was seen primarily in the T- cell lymphoma population and occurred in the early part of therapy during the first two cycles. The event was manageable and resolved/stabilised in a median of 14 days with or without intervention.
- Diarrhea was seen in few patients with only one Grade 3 event.
- No related events of pneumonia/ pneumonitis were reported in either of the studies

Long term safety analysis

- Duration of treatment in patients who were on Tenalisib for more than 6 months (n=24)



- Median duration of treatment: 8.6 months (Range 6.0 – 20.67 months); with 37% patients on 1+ years of therapy

Table 3: AE Occurring after 6 months on Tenalisib

(AEs≥10% of Causality-All)	Safety population (n=24)			
	All Grades (%)		Grade ≥ 3 Events (%)	
	Related	All Causality	Related	All Causality
Cough	-	21	-	-
Anemia	4	17	4	8
Diarrhea	4	17	4	4
Abdominal pain	4	13	-	4
Asthenia	-	13	-	-
Blood creatinine increased	-	13	-	-
Fatigue	4	13	-	-
Hypokalaemia	4	13	-	-

- AEs≥3 were observed in 7/24 (29%) patients; only two of them had related Grade 3 AEs (diarrhea and anemia).
- Only one Grade 1 event of transaminitis observed in one patient
- There were no events of colitis reported in patients even after > 1 year of therapy
- Four (17%) patients still continuing therapy.

Efficacy

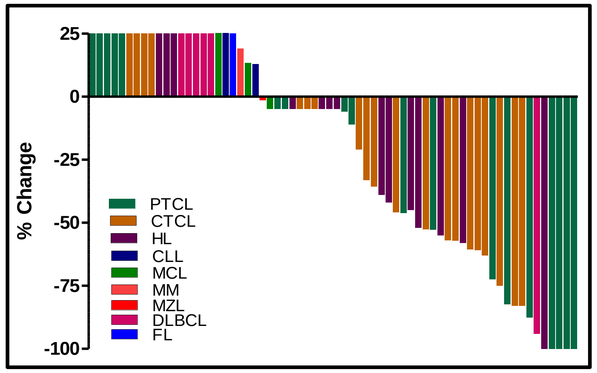


Table 4: Anti-tumor activity of Tenalisib

Response	PTCL	CTCL	HL	DLBCL
Treated Patients	32	30	15	6
Response Evaluable patients	18	20	14	6
Complete Response, n (%)	4(22)	-	1 (7)	-
Partial Response, n (%)	4(22)	9(45)	3(21)	1(17)
Stable Disease, n (%)	5(28)	7(35)	7(50)	-
Progressive Disease, n (%)	5(28)	4(20)	3(22)	5(83)
Objective Response Rate (ORR)	**44%**	**45%**	**29%**	**17%**
Disease Control Rate (DCR) (CR+PR+SD)	**72%**	**80%**	**79%**	**17%**

- Median duration of response: PTCL [4.7 months (0.9, 18.37], CTCL 3.8 months (1.63, 16.10+]

Discussion & Conclusion

- Pooled safety analysis with long term follow-up showed acceptable safety profile of Tenalisib with no late onset toxicities like colitis or pneumonitis. Transaminitis was seen relatively early during therapy and did not occur during long term exposure.
- Transaminitis was seen primarily in the T cell lymphoma patient population.
- Tenalisib shows promising response as monotherapy in PTCL, CTCL and HL populations.
- Tenalisib is currently being studied in combination with Pembrolizumab and Romidepsin and as monotherapy in a Phase II trial in indolent NHL.

Abstract #2925

60th American Society of Hematology Annual Meeting (2018)

For more information please contact Dr. Ajit Nair at an@rhizen.com