Phase I study of ON 01910.Na (rigosertib), a multikinase PI3K inhibitor in relapsed/refractory B-cell malignancies

Mark Roschewski[1], Mohammed Farooqui[2], Georg Aue[2], Clifton Mo[3], Janet Valdez[2], Susan Soto[2], Patricia Perez-Galan[4], Francois Wilhelm[5], and Adrian Wiestner[2]

[1]Metabolism Branch, NCI, NIH; [2]Hematology Branch, NHLBI, NIH; [3]Hematology-Oncology, Walter Reed National Military Medical Center; [4]Department of Hemato-Oncology, Institut d'Investigacions Biomediques August Pi L Sunyer (IDIBAPS), Barcelona, Spain; [5]Onconova Therapeutics Inc, Newton, PA

Background

• B-cell malignancies such as CLL and MCL universally relapse after initial therapy and effective salvage therapies are needed

• Myelosuppression is a common barrier to salvage therapy in these relapsed B-cell malignancies

• Rigosertib is a multikinase inhibitor that inhibits PI3 kinase and PLK-1 kinase pathways and induces apoptosis in CLL and MCL cells, in vitro

• Pre-clinical testing of rigosertib demonstrated selectivity for CLL and MCL cell lines with minimal effect on normal B and T cells

• Minimal myelosuppression with rigosertib which is undergoing phase III testing in refractory myelodysplastic syndrome at a 1800 mg/day for 3 days every other week dosing

Materials and Methods

• Phase 1, dose-escalation study in patients with relapsed/refractory CLL, MCL, and related B-cell malignancies

• Primary endpoint was toxicity after 2 cycles

• Baseline cytopenias permitted if ANC ≥ 500 and PLT ≥ 10K

• Infusion cycles every 14 days; responding patients allowed to continue until disease progression or unacceptable toxicity

• Dosing via ambulatory infusion pump at following schedules:

Cohort 1: 1200mg/m2 IV over 48 hours
Cohort 2: 1500mg/m2 IV over 48 hours
Cohort 3: 1800mg/m2 IV over 48 hours
*Cohort 4: 1800mg FLAT dose over 72 hours
*Cohort 5: 2100mg FLAT dose over 72 hours

*Dosing schedule changed to 72 hours based on efficacy observed in MDS

Patient characteristics

Characteristic	Patients	%
Study population	**16**	
Age , years		
Median	**61**	
Range	**52-67**	
Male to Female ratio		
Male	**10**	**63**
Female	**6**	**37**
Histology		
CLL	**10**	**63**
MCL	**2**	**12**
MM	**2**	**12**
HCL	**2**	**12**
Number of prior regimens		
2	**3**	**19**
3	**1**	**6**
4	**5**	**31**
≥5	**7**	**44**
Baseline neutrophil count (cells/μL)		
≥1500	**7**	**44**
1000-1500	**4**	**25**
≤1000	**5**	**31**

Results - Toxicity

Adverse Events	Cohort 1 (n=3)		Cohort 2 (n=4)		Cohort 3 (n=3)		Cohort 4 (n=3)		Cohort 5 (n=3)		Total	
	G2	G3/4	G2	G3/4	G2	G3/4	G2	G3/4	G2	G3/4	G2	G3/4
Hematologic												
Neutropenia	-	-	-	-	-	1	-	-	-	6	-	7
Anemia	-	-	-	-	-	-	-	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	-	-	-	-	-	-	-
Non-Hematologic												
Syncope	-	-	-	-	-	-	1	"	-	-	-	1
Constipation	-	-	-	-	-	-	-	"	1	-	1	-
Musculoskeletal pain	-	-	-	-	-	-	-	"	1	-	1	-
Infection	-	-	1	-	1	-	-	"	-	-	2	-
Catheter-related thrombosis	-	-	2	-	-	-	-	"	-	-	2	-
ALT increased	-	-	-	-	-	-	-	"	-	1	-	1

2 events of G4 neutropenia observed in cohort 5 in patient with pre-existing G3 neutropenia

4 events of G3 neutropenia observed in cohort 5 in patient with pre-existing G2 neutropenia

All events felt possibly due to drug and possibly due to disease

Results - Response

Pt number	Gender/ Age (y)	# prior regimens	Disease	Cohort	# of cycles	Response
1	M/58	4	HCL	1200mg/m2 over 48 h	4	SD
2	M/52	6	CLL	1200mg/m2 over 48 h	4	SD
3	M/64	9	MM	1200mg/m2 over 48 h	2	NE
4	M/66	6	HCL	1500mg/m2 over 48 h	4	SD
5	M/55	5	CLL	1500mg/m2 over 48 h	4	PD
6	M/67	4	MCL	1500mg/m2 over 48 h	1	NE
7	F/65	2	CLL	1500mg/m2 over 48 h	3	PD
8	F/65	4	CLL	1800mg/m2 over 48 h	4	SD
9	F/61	6	MM	1800mg/m2 over 48 h	1	PD
10	F/65	2	CLL	1800mg/m2 over 48 h	1	PD
11	M/60	7	MCL	1800mg over 72 h	3	PD
12	F/65	4	CLL	1800mg over 72 h	4	SD
13	M/52	2	CLL	1800mg over 72 h	4	SD
14	M/58	6	CLL	2100mg over 72 h	4	PD
15	F/61	4	CLL	2100mg over 72 h	4	SD
16	M/57	3	CLL	2100mg over 72 h	4	PD

Conclusions

• Rigosertib is well-tolerated in patients with relapsed/refractory B-cell lymphoid malignancies – no MTD identified

• Hematologic toxicity is limited and rigosertib can be safely administered to patients with pre-existing cytopenias

•As a single agent, rigosertib did not induce objective responses even at doses higher than currently being investigated in MDS

• Rigosertib's relative lack of myelosuppressive activity may allow for combination strategies in B-cell lymphoid malignancies

Disclaimer/Disclosure

This work was supported by the intramural Research Program of the NHLBI of the NIH. None of the authors have significant disclosures of conflict of interest.

Correspondence: roschewskimj@mail.nih.gov