A Phase I/II Study of the Combination of Oral Rigosertib and Azacitidine (AZA) in Patients with Myelodysplastic Syndromes (MDS) or Acute Myeloid Leukemia (AML)

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BACKGROUND

- Azacitidine (AZA) is first-line therapy for patients with higher-risk MDS.
- Rigosertib is a small molecule anti-cancer agent targeting PI3/polo-like kinase pathways that promotes G2/M arrest and has effects on the B-Raf and Ras pathways.
- Rigosertib is currently being tested as a single agent with the IV formulation in patients who have relapsed or are refractory to hypomethylating agents (HMAs) as well as with the oral formulation in lower-risk, red-cell transfusion dependent MDS patients.
- In vitro, the combination of rigosertib with AZA acts synergistically. Skidan et al., 2006 used a human leukemia cell line to show that the combination of these agents resulted in a 1.7- to 2.9- fold increase in cytotoxicity ($p<0.05$) [US patent # 8,664, 272 B2 (2014)]. Furthermore, the interaction of the 2 compounds resulted in a synergistic median effect (combination indices between 0.3 and 0.75).
- Anti-proliferative activity was observed in both sensitive and resistant cell lines, suggesting a unique mechanism of action for rigosertib that is complementary to that of AZA. This effect appears to be sequence dependent, requiring exposure to rigosertib first, followed by AZA.

OBJECTIVES

- To investigate the safety and toxicity of the combination of AZA and oral rigosertib at increasing doses in a Phase 1 study in patients with MDS or AML.
- To evaluate the activity of the combination of AZA and oral rigosertib with respect to IWG response and hematologic improvement.

METHODS

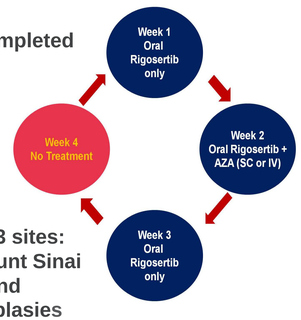
Study Design

Phase 1 stage; 18 patients

- Ascending dose 3 cohorts
- Phase 1 cohorts successfully completed
- Phase 2 dose selected
  - 560/280 mg BID
  - Rigosertib 3/4 weeks;
  - AZA 1/4 weeks

Phase 2 stage active in US/EU

- Simon Minimax two-stage design
- Can be expanded based on data
- Phase 2 is currently enrolling at 3 sites:
  1) Icahn School of Medicine at Mount Sinai
  2) MD Anderson Cancer Center, and
  3) Groupe Français des Myélodysplasies



- Patients with MDS and non-proliferative AML, who were previously untreated, failed or progressed on an HMA, were included in the phase I component of the study. Patients were treated with the agents according to cohorts (Table 1).
- Oral rigosertib was administered twice daily from day 1 through day 21 of a 28-day cycle. AZA 75 mg/m^2/day was administered for 7 days starting on day 8 of the 28-day cycle.

Table 1: Dosing Regimen (SC or IV Aza) + Oral Rigosertib During Dose Escalation

Cohort	# Pts	Oral Rigosertib Dose (mg)	AZA dose (mg/m^2)
1	3-6	140 mg BID	75
2	3-6	280 mg BID	75
3	3-6	560 mg qAM, 280 mg qPM	75

RESULTS

Table 2: Patient Characteristics

Diagnosis	Intermediate -1 MDS	3
	Intermediate -2 MDS	6
	Chronic Myelomonocytic Leukemia	1
	Acute Myeloid Leukemia	8
Number of Patients		18
Sex	11 Male and 7 Female	
Number of cycles	1-14	
Cytogenetic profiles	Good	8
	Intermediate	2
	Poor	8
Transfusion dependent (Baseline)	Red blood cells	11
	Platelets	6
Prior treatment with HMA	AZA	6
	Decitabine	4

Adverse Events

- The most frequent adverse events in Cycle 1 included constipation, diarrhea, nausea, fatigue, hypotension, and pneumonia (Table 3).
- The adverse events did not differ significantly among the 3 cohorts. The only AEs ≥ Grade 3 that occurred in more than 1 patient were pneumonia (4) , neutropenia, (3), febrile neutropenia (2) and thrombocytopenia (2). Only pneumonia occurred in more than 1 pt in any cohort (1 in Cohort 1, 2 in Cohort 2, and 1 in Cohort 3).
- Elevation in creatinine in 1 patient in cohort 1 was a possibly related grade 3 dose-limiting toxicity that required subsequent expansion of the cohort.

Response to Treatment

- Responses according to IWG criteria were observed in the bone marrow and peripheral blood: marrow complete remission (mCR) (5 pts), complete remission with incomplete blood count recovery (CRi) (4 pts), stable disease (2 pts) (Table 4).
- Two evaluable patients have responded to the combination after progression or failure on hypomethylating agents alone.

Table 3: Treatment Emergent Adverse Events (>10%) in Cycle 1

Symptoms	Cohort 1	Cohort 2	Cohort 3	Total
	N=7	N=5	N=6	N=18
Constipation	2 (29)	1 (20)	2 (33)	5 (28)
Diarrhea	1 (14)	-	3 (50)	4 (22)
Ecchymosis	2 (29)	-	-	2 (11)
Fatigue	-	-	3 (50)	3 (17)
Nausea	3 (43)	-	3 (50)	6 (33)
Pneumonia	1 (14)	-	1 (17)	2 (11)
Pollakiuria	-	-	2 (33)	2 (11)
Pyrexia	1 (14)	-	1 (17)	2 (11)

Table 4: Response To Treatment

Pt ID	Diagnosis	Prior HMA	%BM blasts baseline	% BM blasts after treatment	Response	
					BM	Peripheral
1	MDS	No	2	1	CRi	Platelet
2	AML	No	40	0	mCR	
3	AML	No	22	N/A	NE	
4	MDS	AZA	0	0	SD	
5	AML	No	59	N/A	NE	
6	AML	No	21	<5	CRi	Platelet
7	MDS	No	2	1	mCR	
8	MDS	No	2.5	2	NE	
9	AML	Decitabine	25	N/A	NE	
10*	MDS	Decitabine	12	1	CRi	Erythroid, Neutrophil
11	CMML	AZA	2	3	SD	
12*	MDS	AZA	4	1	CRi	Platelet, Erythroid, Neutrophil
13	AML	Decitabine	47	40	NE	
14	MDS	Decitabine	7	24	PD	
15	MDS	No	9	<5	mCR	
16	AML	AZA	25	4	mCR	
17	MDS	AZA	15	5	mCR	
18	AML	AZA	64	45	NE	

Legend: mCR = marrow complete remission; Cri = complete remission with incomplete blood count recovery; NE = not evaluable; SD = stable disease PD = progression of disease *Response after progression on a hypomethylating agent (HMA)

CONCLUSIONS

- The combination of oral rigosertib at 560/280 mg BID (recommended phase II dose) and standard-dose AZA can be safely administered and appears to be well tolerated in repetitive cycles in patients with MDS and non-proliferative AML.
- The adverse event profile does not differ significantly from that of AZA alone.
- Data from the phase I study suggests activity in patients with MDS after HMA failure.
- The Phase II segment of the study is underway to further assess the response of the combination.

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Disclosures: Wilhelm: *Onconova Therapeutics, Inc:* Employment, Equity Ownership. **Demakos:** *Onconova:* Consultancy. **Azarnia:** *Onconova Therapeutics, Inc:* Employment. **Silverman:** *Onconova:* with Icahn School of Medicine at Mount Sinai Patents & Royalties.