Results from Phase I/II Study of the Combination of Oral Rigosertib and Azacitidine in Patients with Myelodysplastic Syndromes (MDS)

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BACKGROUND

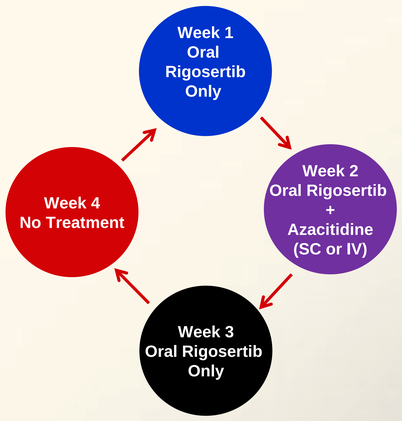
- Azacitidine (AZA) is first-line therapy for patients (pts) with higher-risk MDS.
- Rigosertib is a Ras-mimetic that inhibits the PI3K and PLK cellular signaling pathways by binding directly to the RAS-binding domain found in Ras effector proteins.
- In vitro, the combination of rigosertib with AZA synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence–dependent manner (rigosertib administered prior to AZA) (Skidan, AACR 2006).
- Phase I results of this study in pts with MDS or AML showed the combination of oral rigosertib and standard-dose AZA to be well-tolerated with evidence of efficacy (Navada, Blood 2014).

OBJECTIVES

- To investigate the safety and toxicity of the combination of oral rigosertib and AZA in pts with MDS
- To evaluate the activity of the combination of oral rigosertib and AZA with respect to IWG response and hematologic improvement

METHODS

- Oral rigosertib was administered twice daily on Day 1-21 of a 28-day cycle.
- Dose was escalated to the recommended Phase II dose (RPTD: 560 mg qAM, 280 mg qPM).
- Azacitidine 75 mg/m^2/day SC or IV was administered for 7 days starting on Day 8.
- A CBC was performed weekly and a bone marrow aspirate and/or biopsy was done at baseline, on Day 29, and every 8 weeks thereafter.



RESULTS

Demographics

- The combination of oral rigosertib and AZA has been administered to 40 pts with MDS.
- Pts were classified into the following MDS risk categories per the IPSS (Greenberg et al, Blood 1997): intermediate-1 (12 pts), intermediate-2 (15 pts), high-risk (13 pts).
- Median age was 66 years; 73% of pts were male; and ECOG performance status was 0 or 1 in 95% of pts (Table 1).
- Prior HMA treatment consisted of azacitidine (12 pts), decitabine (4 pts), and both (1 pt).

Efficacy

- The 30 MDS pts who were evaluable for response have received 1-27+ months of study treatment (median, 4 months).
- Hematologic responses according to IWG criteria (Cheson, Blood 2006) were observed in 23 (77%) of the 30 evaluable pts with MDS (Table 2).
- Among the 13 evaluable pts with mCR, hematologic improvement per IWG 2006 criteria was seen in 6 (46%) (Table 3).
- Response was seen in 5 of 9 (55.5%) evaluable pts with high risk and 9 of 10 pts (90%) with very high risk per IPSS-R (Table 4).
- Response was seen in 7 of 11 (64%) evaluable pts who had failed to respond to an HMA or had relapsed following HMA treatment (data not shown). In pts who had not previously been treated with an HMA (N=19), response was seen in 16 (84%).

Safety

- The most common treatment-emergent adverse events were nausea , constipation, and fatigue (Table 5); the most common serious AEs were febrile neutropenia, pneumonia, pneumonia fungal, and urinary tract infection (Table 6).

Table 1: Patient Characteristics

Number of MDS pts with data		40
Age (years)	Median Range	66 25-85
Sex	Male Female	29 (73%) 11 (27%)
ECOG performance status	0 1 2	9 (23%) 29 (73%) 2 (5%)
IPSS-R * classification	Low/Intermediate High Very high Unknown	8 (20%) 12 (30%) 14 (35%) 6 (15%)
Prior HMA therapy	Azacitidine Decitabine Both	12 (30%) 4 (10%) 1 (3%)

*International Prognostic Scoring System – Revised (Greenberg, Blood 2012)

Table 2: Responses for Pts with MDS

Number of MDS pts evaluable for response	30	
Overall response	**23 (77%)**	
Hematologic response per IWG 2006 criteria	Complete remission	6 (20%)
	Partial remission	0
	Marrow CR	16 (53%)
	Stable disease	6 (20%)
	Progressive disease	1 (3%)
Hematologic improvement per IWG 2006	1 (3%)	
Not evaluable	3	
Too early to evaluate	7	
Median duration of trt (months)	4 (1-27+)	

Table 3: Lineage Responses per IWG 2006 Criteria (Cheson, Blood 2006)

Marrow CR (N=16)	Evaluable	13
	HI Platelet / Erythroid / Neutrophil	**3 (23%)**
	HI Platelet / Erythroid	**3 (23%)**
	HI – None	7 (58%)
	HI – Too early to evaluate	3
Hematologic improvement* (N=26)	Any lineage	13 (50%)*
	Erythroid	11
	Platelet	12
	Neutrophil	7

*Includes pts with CR, HI and mCR lineage responses among evaluable pts

Table 4: Overall Response per IPSS-R* Subgroup

	Low/Inter N=7	High N=12	Very High N=13	Unknown N=5
Evaluable per IWG 2006	6 (86)	9 (75)	10 (77)	5 (100)
CR	2 (33)	1 (11)	**3 (30)**	0
mCR	3 (50)	4 (44)	**6 (60)**	3 (60)
SD	1 (17)	3 (33)	1 (10)	1 (20)
PD	0	1 (8)	0	0
NE	0	0	0	1 (20)

*International Prognostics Scoring System-Revised (Greenberg, Blood 2012)

Table 5: Most Common Treatment-emergent AEs Among Pts with MDS, All Grades (N = 40)

MedDRA Preferred Term	Number (%) of Patients	
	All Grades	Grade ≥3
Any TEAE	40 (100)	34 (85)
Nausea	17 (43)	-
Constipation	16 (40)	-
Fatigue	15 (38)	-
Diarrhoea	13 (33)	1 (3)
Dysuria	13 (33)	1 (3)
Pyrexia	12 (30)	-
Thrombocytopenia	11 (28)	11 (28)
Decreased appetite	11 (28)	-
Cough	10 (25)	-
Haematuria	10 (25)	3 (8)
Neutropenia	10 (25)	10 (25)

MedDRA = Medical Dictionary of Regulatory Activities

Table 6: Most Common Serious AEs Among Pts with MDS (N = 40)

MedDRA Preferred Term	Number (%) of Patients	
	All Causes	Study-drug-related
Any SAE	27 (68)	3 (8)
Febrile neutropenia	4 (10)	-
Pneumonia	3 (8)	-
Pneumonia fungal	3 (8)	-
Urinary tract infection	3 (8)	-
Atrial fibrillation	2 (5)	-
Bacteraemia	2 (5)	-
Haematuria	2 (5)	2 (5)
Hypotension	2 (5)	-
Renal failure acute	2 (5)	-

CONCLUSIONS

- A novel and important observation is that oral rigosertib in combination with AZA showed an overall response rate of 77% in pts with MDS, including an 84% response rate among pts who had not previously been treated with an HMA, and a 64% response rate among pts with prior HMA failure.
- Importantly, 90% of pts with very high risk per IPSS-R showed a response to the combination.
- The combination was well-tolerated in pts with MDS; repetitive cycles of the combination can be safely administered without evidence of cumulative toxicity.
- Further exploration of this combination is warranted in defined MDS populations.

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