Combination of Oral Rigosertib and Injectable Azacitidine in Patients with Myelodysplastic Syndromes (MDS)

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Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
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Will you be presenting or referencing off-label or investigational use of a therapeutic product?	
	No
X	Yes, please specify: Investigational use of rigosertib

Background: Treatment of Higher-risk MDS

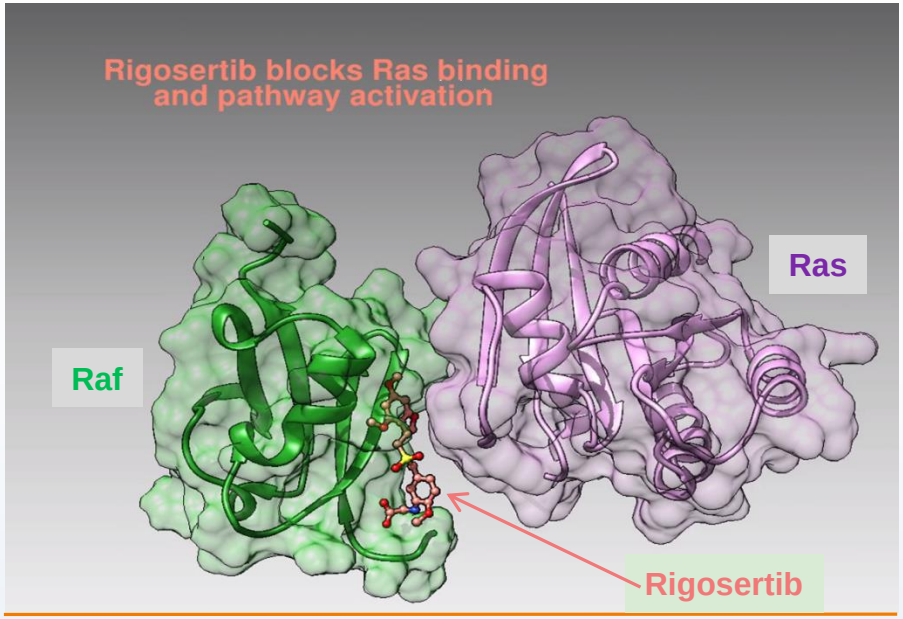
- Azacitidine is standard of care for higher-risk MDS patients
- Clinical responses in MDS 45-50%[a]
  - CR rate 7-17%
  - Trilineage response rate of 24%
- All patients ultimately relapse or fail to respond; these patients have a poor prognosis, with a median overall survival (OS) of only 4-6 months[b]
- Currently, there are no accepted standard therapies after HMA failure

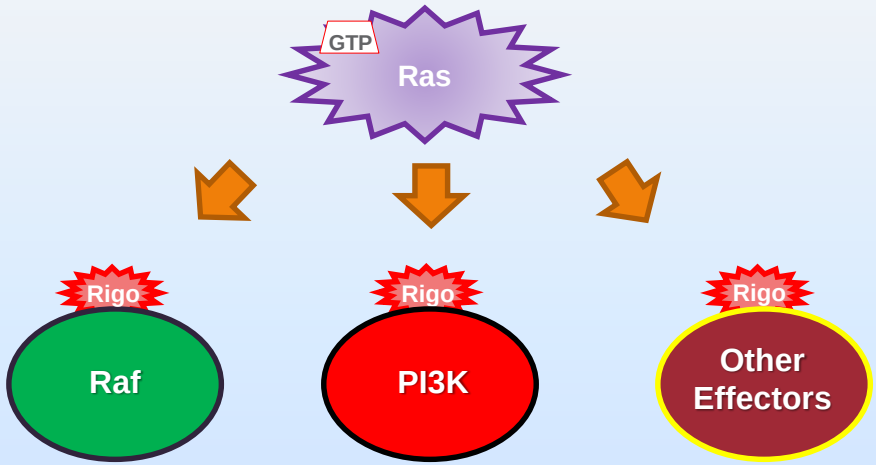
a Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24(24): 3895-3903.

b Prebet T, Gore SD, Estemi B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 2011;29(24):3322-7.

Background: Rigosertib

- Novel agent that inhibits cellular signaling acting as a Ras mimetic that targets the Ras-binding domain (RBD)
- Proposed MOA blocks multiple cancer targets and has downstream effects on PI3K/AKT and Raf/PLK pathways
- Mechanism may impact aberrant signaling in MDS
- Initial Phase I/II studies suggested clinical activity in patients with MDS and AML
- Both oral and IV rigosertib are available – this study used the oral formulation





Divakar et al, AACR Annual Meeting 2014; abstract LB-108; Olnes et al, Leuk Res 2012;36:964-5; Chapman et al, Clin Cancer Res 2012;18:1979-91.

Rigosertib is Synergistic with Azacitidine in Preclinical Studies

- Sequential exposure with rigosertib followed by azacitidine achieved maximum synergy at concentrations achievable in the clinical setting

Combination Drug	CI	Ratio	Description
Rigosertib* (125 nM) + 5AzaC (2 uM)	0.44	1:62.5	Synergism
Rigosertib (125 nM) + 5AzaC (4 uM)	**0.30**	**1:31.25**	**Strong synergism**
Rigosertib (250 nM) + 5AzaC (2 uM)	0.68	1:125	Synergism
Rigosertib (250 nM) + 5AzaC (4 uM)	0.57	1:62.5	Synergism
Rigosertib (500 nM) + 5 AzaC (2 uM)	0.63	1:250	Synergism
Rigosertib (500 nM) + 5AzaC (4 uM)	0.75	1:125	Moderate synergism

Skiddan I, Zinzar S, Holland JF, et al. Toxicology of a novel small molecule ON1910Na on human bone marrow and leukemic cells in vitro. AACR Abstract 1310, April 2006; 47:309.

Background
Phase I Rigosertib and Azacitidine

- Combination was well tolerated with evidence of efficacy in patients with MDS*

- The adverse event profile of the combination was similar to single-agent azacitidine

** Navada S, Garcia-Manero G, Wilhelm F, et al. A phase I/II study of the combination of oral rigosertib and azacitidine in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). ASH 2014; Abstract 3252.*

Eligibility Criteria for Phase 2

Diagnosis

- MDS, CMML
- IPSS Int-1, Int-2, or High risk

Prior Treatment

- Prior HMAs permitted
- No prior rigosertib

Demographics

ECOG PS ≤ 2

Age ≥ 18 years

Organ Function

- Creatinine ≤ 2.0 mg/dL
- Total bilirubin ≤ 2.0 mg/dL
- ALT/AST ≤ 2.5 x ULN

Study Endpoints
Response Criteria Assessed per IWG 2006*

- Complete remission, partial remission or marrow CR
- Hematologic improvement in neutrophil, platelet, and erythroid lineages was assessed
- Safety and tolerability of combination

* *Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108: 419-25*.

Combination Trial Design
Sequence Suggested by Preclinical Findings

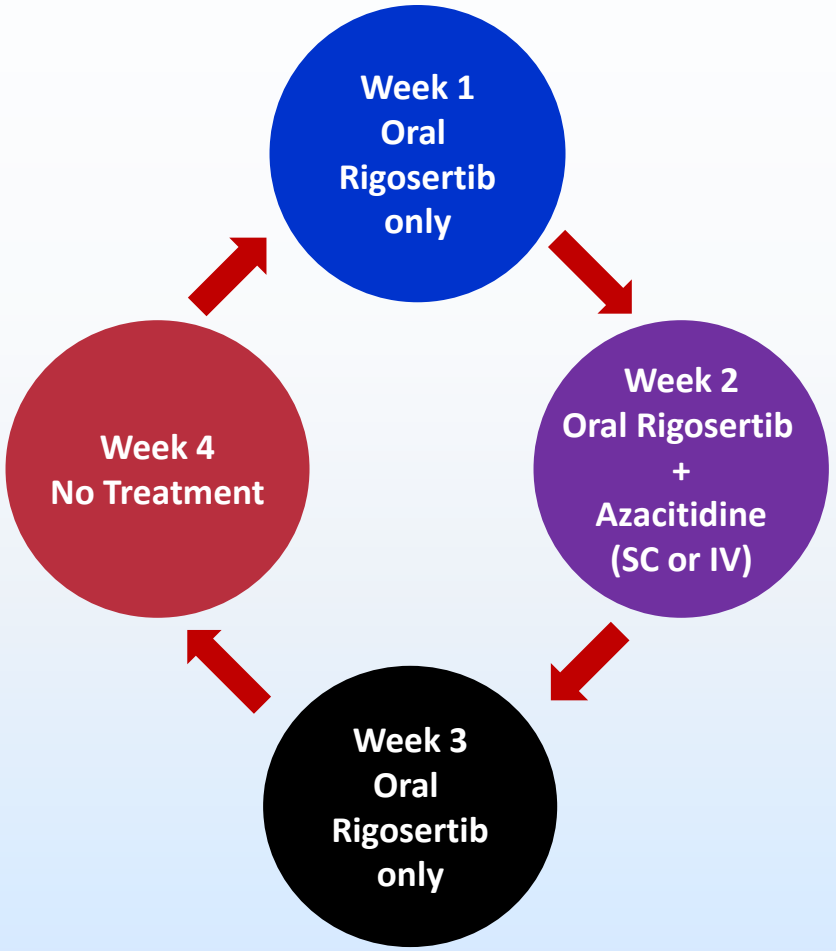
Treatment regimen:

Week 1: Oral rigosertib BID (560 mg AM/280 mg PM)

Week 2: Oral rigosertib + azacitidine (75 mg/m^2/day SC or IV)

Week 3: Oral rigosertib BID

Week 4: No treatment



Navada S, Garcia-Manero G, Wilhelm F, et al. A phase I/II study of the combination of oral rigosertib and azacitidine in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). ASH 2014; Abstract 3252.

Methods

- **Phase 1** - Escalating-dose cohorts of oral rigosertib with standard-dose azacitidine in a classic 3+3 design in patients with MDS, CMML, or AML
- Initial recommendation for dosing of rigosertib in the Phase 2 - 560 mg in AM and 280 mg in PM
- **Phase 2** - Patients with MDS and CMML, previously untreated, or had failed or progressed on a prior HMA
- Bone marrow aspirate/biopsy at Baseline, Week 4, and every 8 weeks after
- This analysis includes only the MDS patients from phase 1 and phase 2

Patient Characteristics

Number of MDS patients treated		40
Age	Median	66
	Range	25-85
Sex	Male	29 (73%)
	Female	11 (27%)
ECOG performance status	0	9 (22%)
	1	29 (73%)
	2	2 (5%)
IPSS classification	Intermediate-1	12 (30%)
	Intermediate-2	15 (37%)
	High	13 (33%)
IPSS-R cytogenetic risk	Very Good/Good	14 (35%)
	Intermediate	12 (30%)
	Poor/Very Poor	10 (25%)
	Unknown	4 (10%)
Prior HMA therapy	Azacitidine	12 (30%)
	Decitabine	4 (10%)
	Both	1 (3%)

Efficacy Results

Number of MDS patients treated	40
Evaluable for response (8 Ph1, 25 Ph2)	33
Overall response	25 (76%)
Complete remission (CR)	8 (24%)
Partial remission	0
Marrow CR + Hematologic Improvement	10 (30%)
Marrow CR alone	6 (18%)
Hematologic Improvement alone	1 (3%)
Stable disease	8 (24%)
Progression	0
Not evaluable for response (per protocol)	7 (18%)
Median duration of treatment (months)	6 (1-37+)
Median time to initial/best response (cycles)	2/3

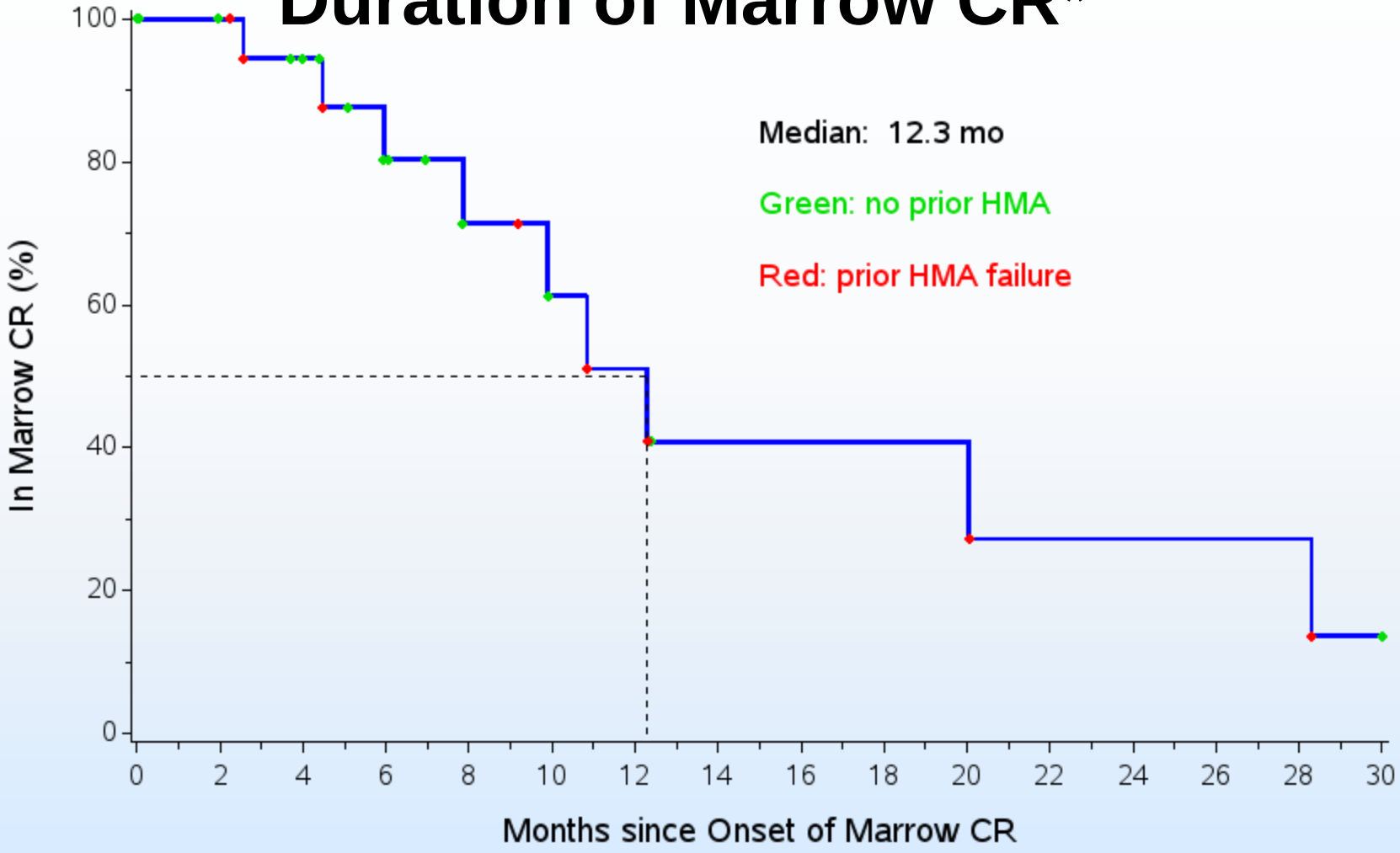
* Per IWG 2006

Response per IWG 2006 Among IPSS-R Subgroups

Response per IWG 2006	Low/Intermediate N=8	High N=15	Very High N=13	Unknown N=4
CR	3 (38)	2 (13)	3 (23)	0
mCR	2 (25)	6 (40)	6 (46)	2 (50)
SD	2 (25)	4 (27)	1 (8)	1 (25)
PD	0	0	0	0
NE	0	3 (20)	3 (23)	1 (25)
Erythroid Response	2 (25)	5 (33)	6 (46)	0
Platelet Response	3 (38)	5 (33)	6 (46)	1 (25)
Neutrophil Response	4 (50)	5 (33)	4 (31)	0
Overall Response	6 (75)	8 (53)	9 (69)	2 (50)

Study 09-08
Duration of Complete Remission

Study 09-08
Duration of Marrow CR*



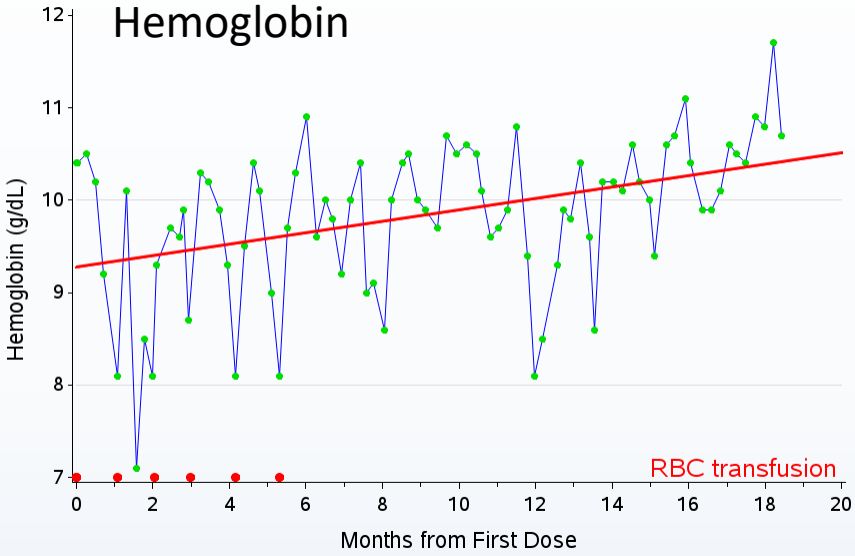
*CR, mCR, or mCR with HI

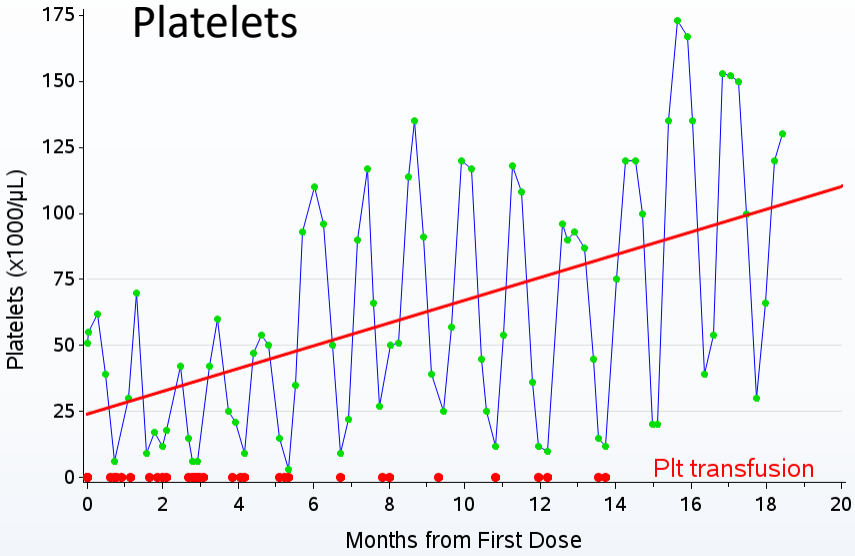
** Excludes 1 patient with <5% blasts at baseline

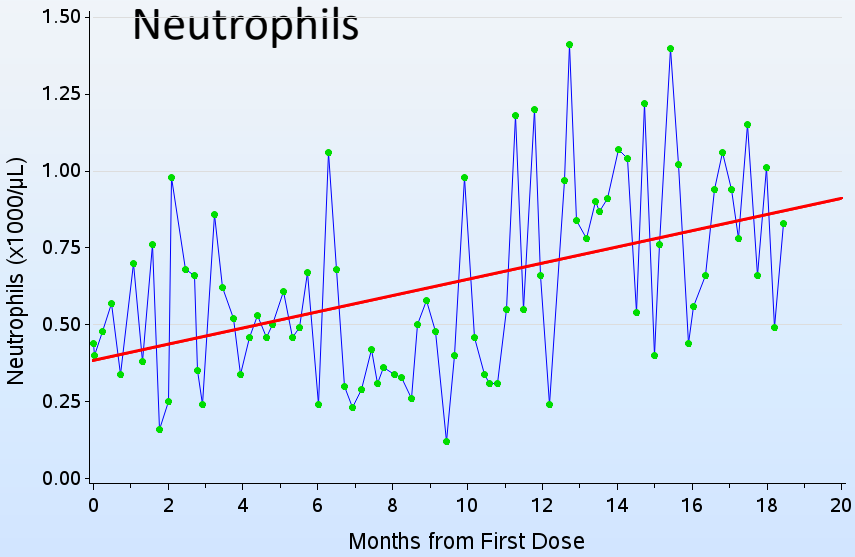
Efficacy: MDS Patients with Prior HMA Failure

Number of patients evaluable for response (3 Ph1, 10 Ph2)	13 (10 AZA, 2 DAC, 1 both)
Number of prior HMA cycles	4-20
Hematologic response per IWG 2006	8 (62%)
Complete remission (CR)	1 (8%)
Partial remission	0
Marrow CR with concurrent HI	4 (31%)
Marrow CR alone	3 (23%)
Stable disease	5 (38%)
Progressive disease	0
Hematologic improvement (trilineage)	4
HMA-naïve patients (N=20) response per IWG	17 (85%)

Hematology Trends for Patient 101-006



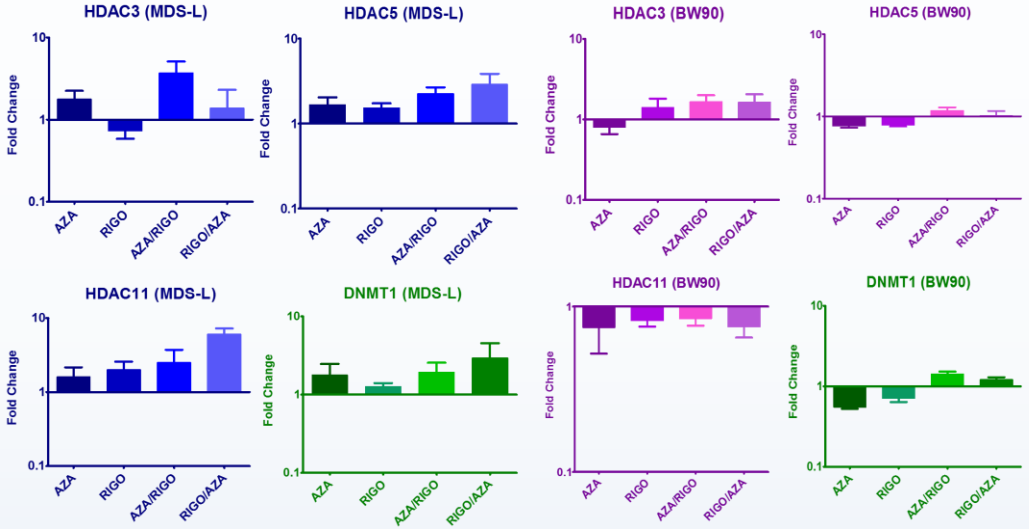




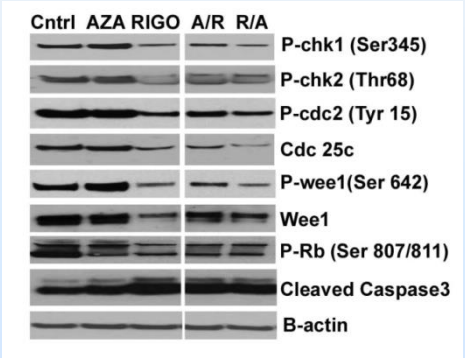
- 12 cycles of AZA – stable disease
- RBC and platelet transfusions
- Blasts 7%
- Monosomy 7
- RUNX-1
- AZA + RIG in 09-08 for 20+ months
- Complete remission
- RBC transfusion independent
- <5% blasts
- PB CR criteria

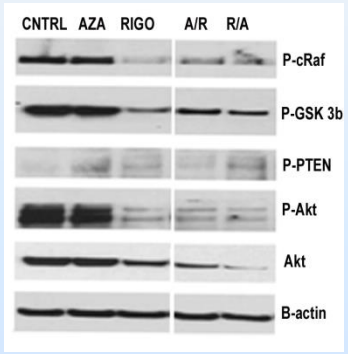
Rigosertib alone and in combination with azacitidine has Epigenetic effects in vitro and in vivo

- Rigosertib modulates HDACs (class I, II and IV) and DNMT1 in MDS and AML cells in vitro
- Rigosertib alone or in combination with AZA leads to different levels of histone methylation and acetylation altering activator/repressor marks
- Rigosertib alone or in combination with Azacitidine down regulated the AKT pathway and reduced cell cycle check point protein levels; an increase in apoptosis was demonstrated only with the combination.
- Similar effects on chromatin were seen in preliminary data from patients before and after the first cycle of treatment



Effects of rigosertib on HDACs (class I, II and IV) and DNMT1





Effect of RIGO alone or in combination with AZA on cell cycle check proteins, apoptosis and AKT cell signaling pathway

Chaurasia et al MDS Symposium Valencia Spain 2017

Adverse Events

Table 3: 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)	38 (95)
Constipation	18 (45)	-
Diarrhea	17 (43)	1 (3)
Nausea	17 (43)	-
Hematuria	16 (40)	5 (13)
Dysuria	16 (40)	3 (8)
Fatigue	16 (40)	-
Decreased appetite	15 (38)	-
Thrombocytopenia	13 (33)	13 (33)
Pyrexia	13 (33)	-
Neutropenia	12 (30)	12 (30)
Arthralgia	11 (28)	1 (3)
MedDRA = Medical Dictionary of Regulatory Activities		

Conclusions

- Oral rigosertib and azacitidine demonstrated an overall response rate of 76% in patients with MDS.
- 62% of patients who had previously received an HMA and either did not respond or relapsed, responded to the combination; this represents a novel and important observation.
- The combination is well tolerated in patients with MDS and has a safety profile similar to single-agent azacitidine.
- 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.

Acknowledgments

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