A Phase II Study of the Combination of Oral Rigosertib and Azacitidine in Patients with Myelodysplastic Syndromes (MDS)

Shyamala C. Navada, MD[1], Lewis R. Silverman, MD[1], Katherine Hearn, RN[2], Rosalie Odchimar-Reissig, RN[1], Erin Demakos, RN[1], Yesid Alvarado, MD[2], Naval Daver, MD[2], Courtney DiNardo, MD[2], Marina Konopleva, MD[2], Gautam Borthakur, MD[2], Pierre Fenaux, MD[3], Steven Fruchtman, MD[4], Nozar Azarnia, PhD[4], Guillermo Garcia-Manero, MD[2]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [2]MD Anderson Cancer Center, Houston, TX; [3]Hôpital St Louis/Université Paris; [4]Onconova Therapeutics, Inc., Newtown, PA

Background: Treatment of Higher-risk MDS

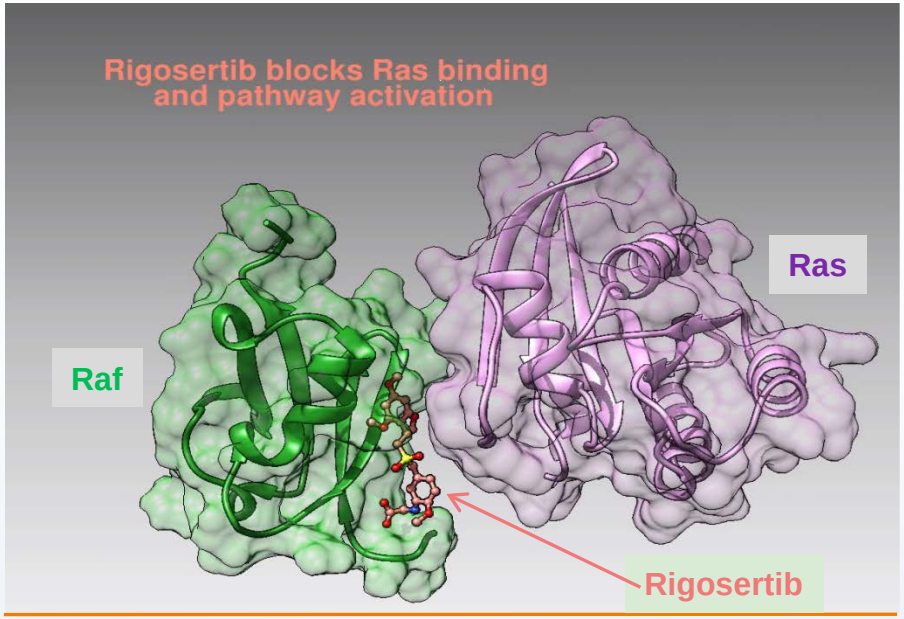
- Azacitidine is standard of care (SOC) for higher-risk MDS patients
- Clinical responses in MDS 45-50%[a]
  - CR rate 7-17%
  - Trilineage response rate of 24%
- All patients ultimately relapse or fail to respond; these patients have a poor prognosis, with a median overall survival (OS) of only 4-6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

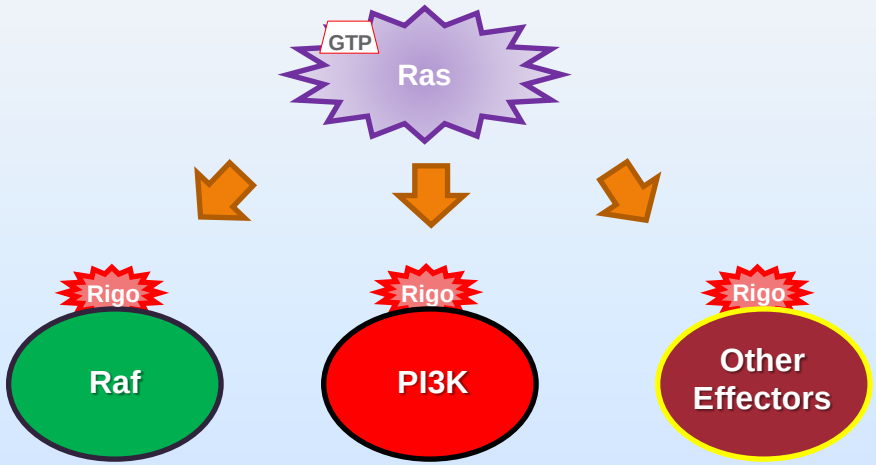
a Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24(24): 3895-3903.

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

- Inhibits cellular signaling as a Ras mimetic by targeting the Ras-binding domain (RBD)
- Novel MOA blocks multiple cancer targets and downstream pathways PI3K/AKT and Raf/PLK
- Mechanism may impact aberrant signaling in MDS
- Initial studies indicate 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

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

- Rigosertib is active in azacitidine-resistant cell line

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 1 combination was well tolerated with evidence of efficacy in patients with MDS*

- The adverse event profile of combining azacitidine with oral rigosertib 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 per IWG 2006*

- Complete response, partial response or bone marrow response
- Hematologic improvement in neutrophil, platelet, and erythroid response
- 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

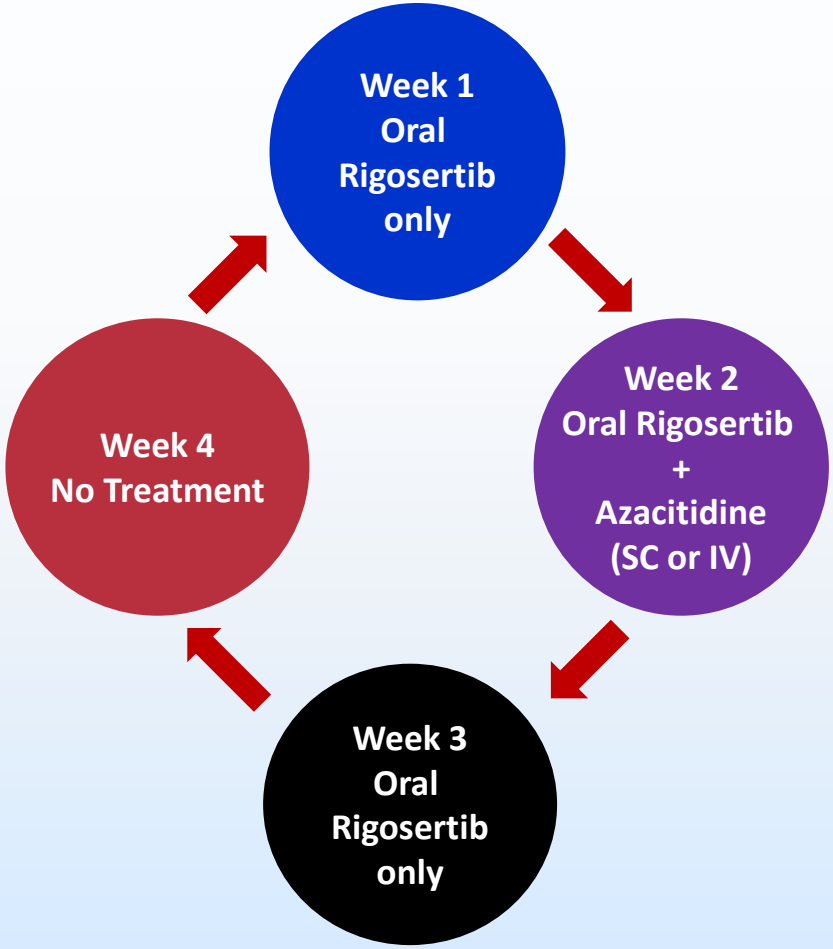
Treatment regimen:

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
- Recommended rigosertib Phase 2 Dose - 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		37
Age	Median	64
	Range	25-85
Sex	Male	27 (73%)
	Female	10 (27%)
ECOG performance status	0	9 (24%)
	1	27 (73%)
	2	1 (3%)
IPSS classification	Intermediate-1	10 (27%)
	Intermediate-2	15 (41%)
	High	12 (32%)
IPSS cytogenetic risk	Good	8 (22%)
	Intermediate	14 (38%)
	Poor	9 (24%)
	Unknown	6 (16%)
Prior HMA therapy	Azacitidine	10 (27%)
	Decitabine	3 (8%)
	Both	1 (3%)

Efficacy Results

Number of MDS patients treated		37
Evaluable for response (8 Ph1, 22 Ph2)		30
Overall response		23 (77%)
Hematologic response*	Complete remission	6 (20%)
	Partial remission	0
	Marrow CR	16 (53%)
	Stable disease	6 (20%)
	Progressive disease	1 (3%)
Hematologic improvement*		1 (3%)
Not evaluable		3 (10%)
Too early to evaluate		4 (13%)
Median duration of treatment (months)		4 (1-27+)

* Per IWG 2006

Lineage Response per IWG 2006

Marrow CR (N=16)	Evaluable HI P/E/N HI P/E HI – none HI – TETE	12 3 (25%) 3 (25%) 6 (50%) 4
Hematologic improvement* (N=26)	Any lineage Erythroid (E) Platelet (P) Neutrophil (N)	13 (50%)* 11 12 7

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

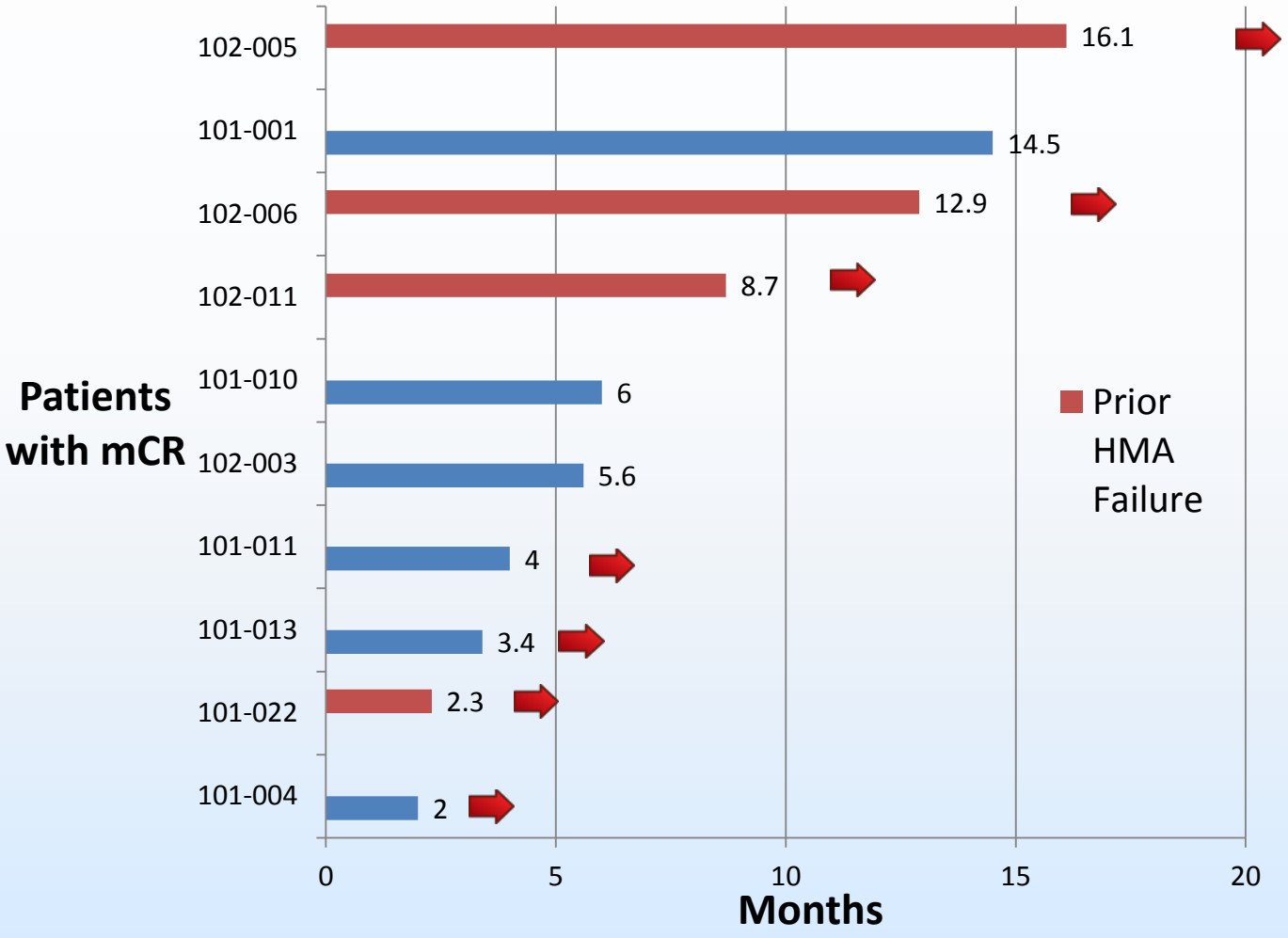
TETE = too early to evaluate

Overall Response per IPSS Subgroup

IPSS	# Pts	CR	PR	mCR	HI	SD	PD	NE	RR
Int-1	10	3	0	2	1	2	0	2	75%
Int-2	15	2	0	6	3*	4	1	2	62%
High	12	1	0	8	3*	0	0	3	100%

* Concurrent marrow CR and hematologic improvement

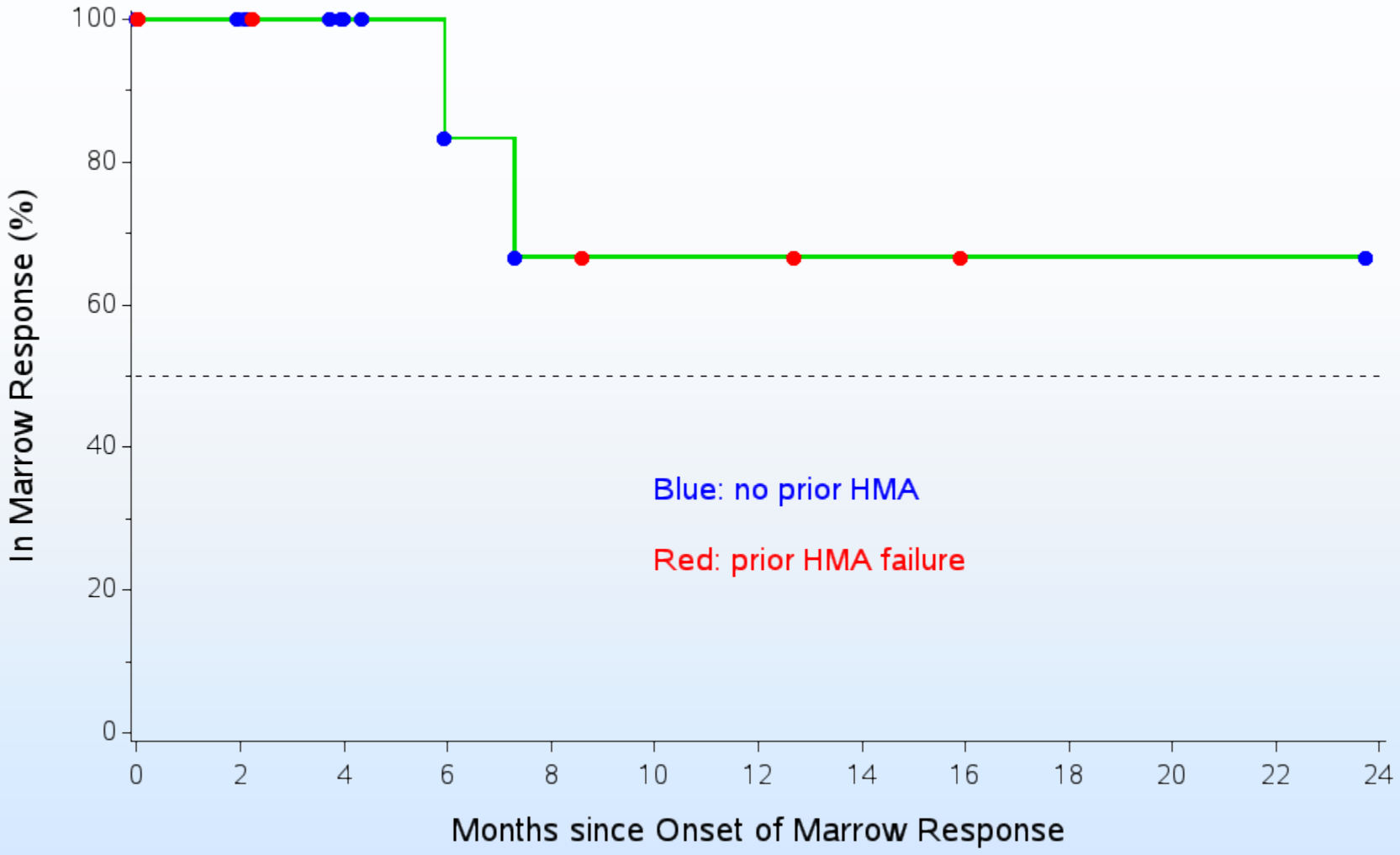
Duration of Marrow CR



Marrow response was ongoing at the time of the last assessment

Not shown are 12 patients who are pending marrow assessment after achieving mCR

Duration of Marrow Response



Efficacy: MDS Patients with Prior HMA Failure

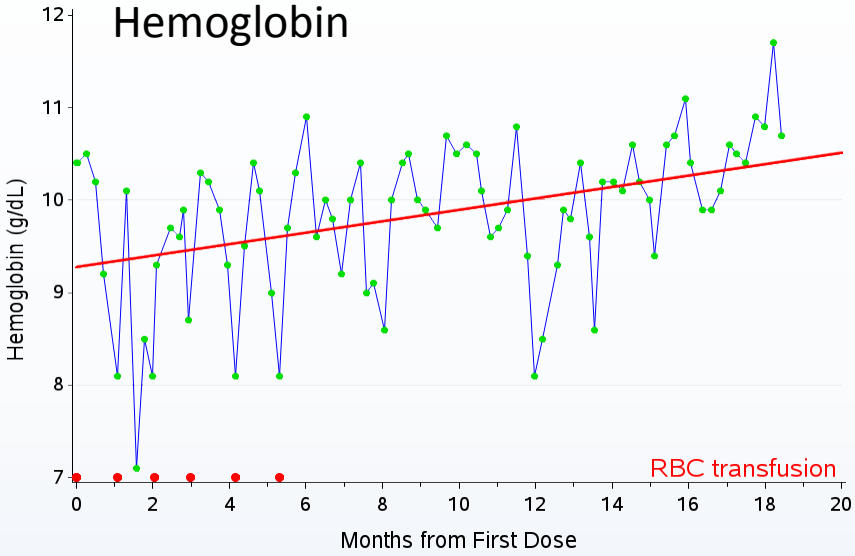
Number of patients evaluable for response (3 Ph1, 8 Ph2)	11 (8 AZA, 2 DAC, 1 both)
Number of prior HMA cycles	4-20
Hematologic response per IWG 2006	7 (64%)
CR	1
PR	0
mCR	4
mCR with concurrent HI	2
Stable disease	3
Progressive disease	1
Hematologic improvement (trilineage)	3
HMA-naïve patients (N=19) response per IWG	16 (84%)

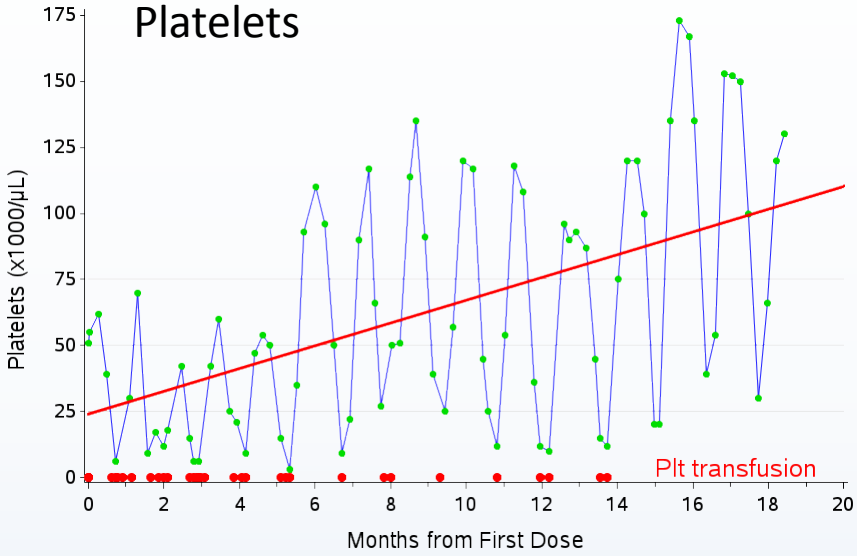
Response per IPSS Subgroup with Prior HMA Failure

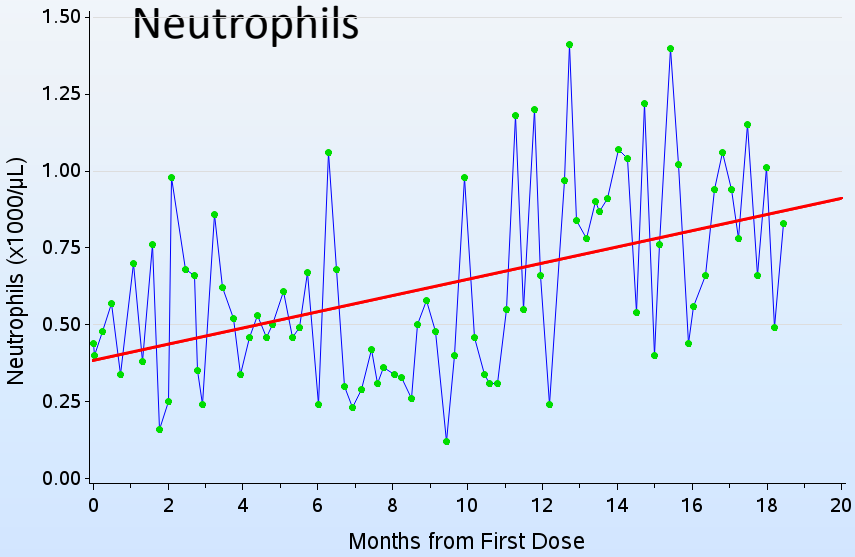
IPSS	# Pts	CR	PR	mCR	HI	SD	PD	NE	RR
Int-1	3	0	0	2	0	1	0	0	67%
Int-2	7	0	0	2	1*	2	1	2	40%
High	4	1	0	2	1*	0	0	1	75%

* Concurrent marrow CR and hematologic improvement

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

Fatal Serious Adverse Events

Number of MDS pts treated	37
Number (%) of deaths*	3 (8%)
Multi-organ failure	1
Worsening of AML	1
Sepsis	1
* No death was considered to be treatment-related	

Most Common (≥ 10%) Treatment-emergent Adverse Events (N = 37)

MedDRA Preferred Term	Cycle 1		Cycles ≥2	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Constipation	7 (19%)	-	8 (22%)	-
Cough	6 (16%)	-	5 (14%)	-
Decreased appetite	6 (16%)	-	6 (16%)	-
Diarrhoea	7 (19%)	-	7 (19%)	1 (3%)
Dizziness	5 (14%)	-	4 (11%)	-
Dysuria	6 (16%)	-	7 (19%)	-
Fatigue	10 (27%)	-	7 (19%)	-
Haematuria	5 (14%)	1 (3%)	5 (14%)	2 (5%)
Hypokalaemia	5 (14%)	1 (3%)	3 (8%)	1 (3%)
Injection site pain	4 (11%)	-	1 (3%)	-
Nausea	10 (27%)	-	6 (16%)	-
Neutropenia	4 (11%)	4 (11%)	8 (22%)	8 (22%)
Pyrexia	9 (24%)	-	3 (8%)	-
Tachycardia	4 (11%)	-	2 (5%)	-
Thrombocytopenia	9 (24%)	9 (24%)	5 (14%)	5 (14%)

Conclusions

- Oral rigosertib and azacitidine demonstrated an overall response rate of 77% in patients with MDS.
- 64% 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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- Research Coordinators
- Icahn School of Medicine at Mount Sinai
- MD Anderson Cancer Center
- Hôpital St Louis/Université Paris
- Onconova Therapeutics, Inc.

2006 IWG Response Criteria for MDS*

Category	Hematologic Response Criteria (responses must last at least 4 weeks)[a]

Complete remission (CR)	• Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines.
	• Persistent dysplasia will be noted (dysplastic changes should consider the normal range of dysplastic changes)
	• Peripheral blood:
	  • Hemoglobin (Hgb) ≥ 11 g/dL (untransfused, patient not on erythropoietin)
	  • Neutrophils ≥ 1.0 x 10^9/L (not on myeloid growth factor)
	  • Platelets ≥ 100 x 10^9/L (not on a thrombopoietic agent)
	  • Blasts 0%

Partial remission (PR)	• All CR criteria (if abnormal prior to treatment), except: • Bone marrow blasts decreased by ≥ 50% compared with pretreatment but still > 5% • Cellularity and morphology not relevant
Marrow CR	• Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment • Peripheral blood: if hematologic improvement (HI) responses, they will be noted in addition to the marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks

a For a designated response (CR, PR), relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period following therapy (eg, 1 month or longer).

** 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.*

2006 IWG Response Criteria for MDS*

Hematologic Improvement[a]	Response Criteria (responses must last at least 8 weeks)[b]
Erythroid response (pretreatment, < 11 g/dL)	• Hgb increase by ≥ 1.5 g/dL • Relevant reduction of units of red blood cell (RBC) transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet response (pretreatment, < 100 x 10^9/L)	• Absolute increase of ≥ 30 x 10^9/L for patients starting with >20 x 10^9/L • Increase from < 20 x 10^9/L to >20 x 10^9/L and by at least 100%
Neutrophil response (pretreatment, < 1.0 x 10^9/L)	At least 100% increase and an absolute increase > 0.5 x 10^9/L
Progression or relapse after HI	At least 1 of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥ 1.5 g/dL • Transfusion dependence

a Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification)

b For a designated response (CR, PR), relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period following therapy (eg, 1 month or longer).

** 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.*