Oral Rigosertib Combined with Azacitidine in Patients with Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS): Effects in Treatment Naïve and Relapsed-Refractory Patients

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Disclosure Slide

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Treatment of Higher-risk MDS

- Azacitidine is standard of care for higher-risk MDS patients
- Clinical responses (CR+PR+HI) occur in 45-50%[a]
- All responding patients ultimately relapse or progress
- Patients failing an HMA have a poor prognosis, with a median overall survival (OS) of only 4-6 months[b]
- There are no approved therapies after HMA failure

a Silverman LR et al. J Clin Oncol 2002; 20(10): 2429-40; Fenaux P et al. Lancet Oncol 2009; 10: 223-32.
b Prebet T et al. J Clin Oncol 2011;29(24):3322-7.

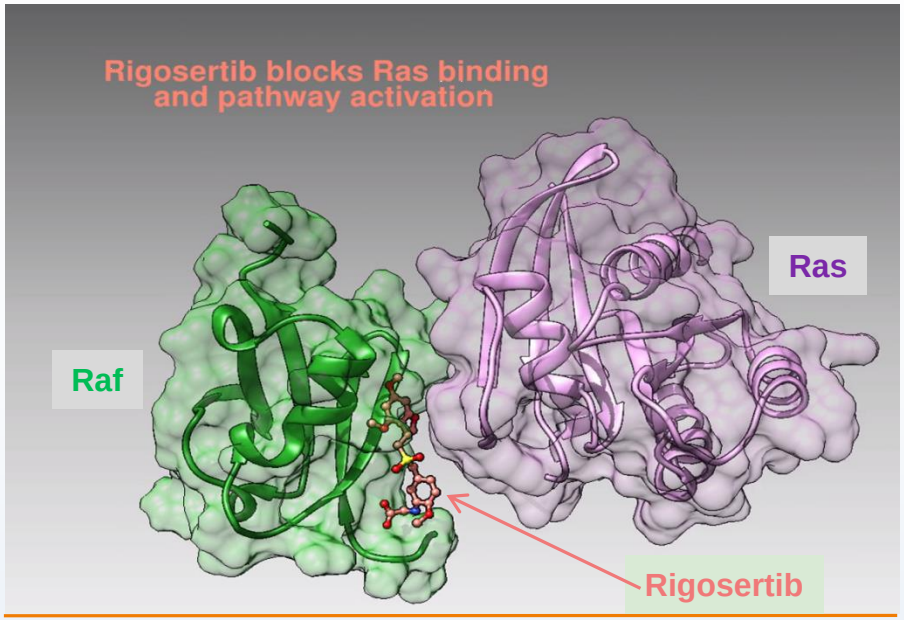
Background: AML

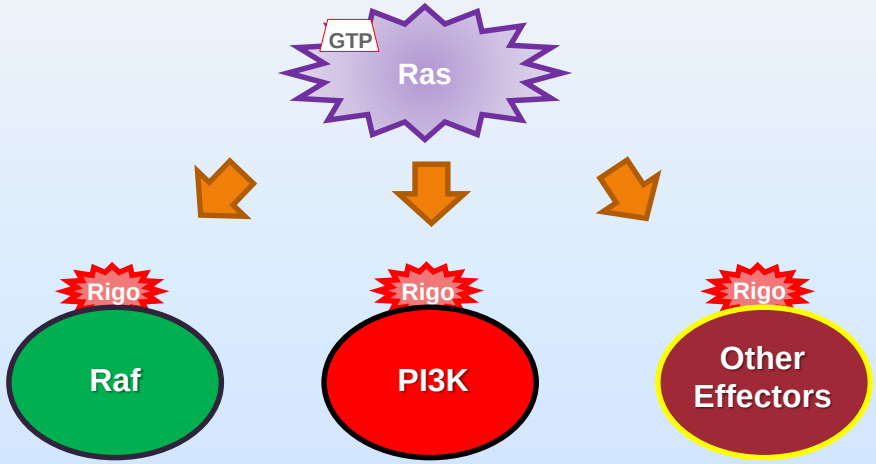
- Dismal prognosis in majority of older patients
- Azacitidine single agent – CR rate of 10-20% in phase 2 studies
- MDS 001 study[a] – low blast percentage WHO AML (20-30%) – Azacitidine significantly prolongs survival compared with conventional care regimens (CCR)
- Phase 3 in AML - azacitidine reduced risk of death by 31% compared to CCR[b]

a Fenaux P et al. Lancet Oncol 2009; 10: 223-32; Fenaux et al. J Clin Oncol 2009; 28: 562-9.
b Dombret H et al. Blood 2015; 126(3); 291-9.

Background: Rigosertib

- Novel agent that inhibits cellular signaling by targeting the Ras-binding domain (RBD)
- Proposed MOA blocks multiple cancer targets and has downstream effects on PI3K/AKT and Raf/PLK pathways
- Mechanism in MDS may be mediated in patients with aberrant signaling driven either by overexpression or genetic mutations of Ras
- Initial Phase 1/2 studies suggested clinical activity in patients with MDS and AML
- Oral formulation utilized in this study





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 et al. AACR Abstract 1310, April 2006; 47:309.

Combination Trial Design
Sequence Suggested by Preclinical Findings

Treatment regimen:

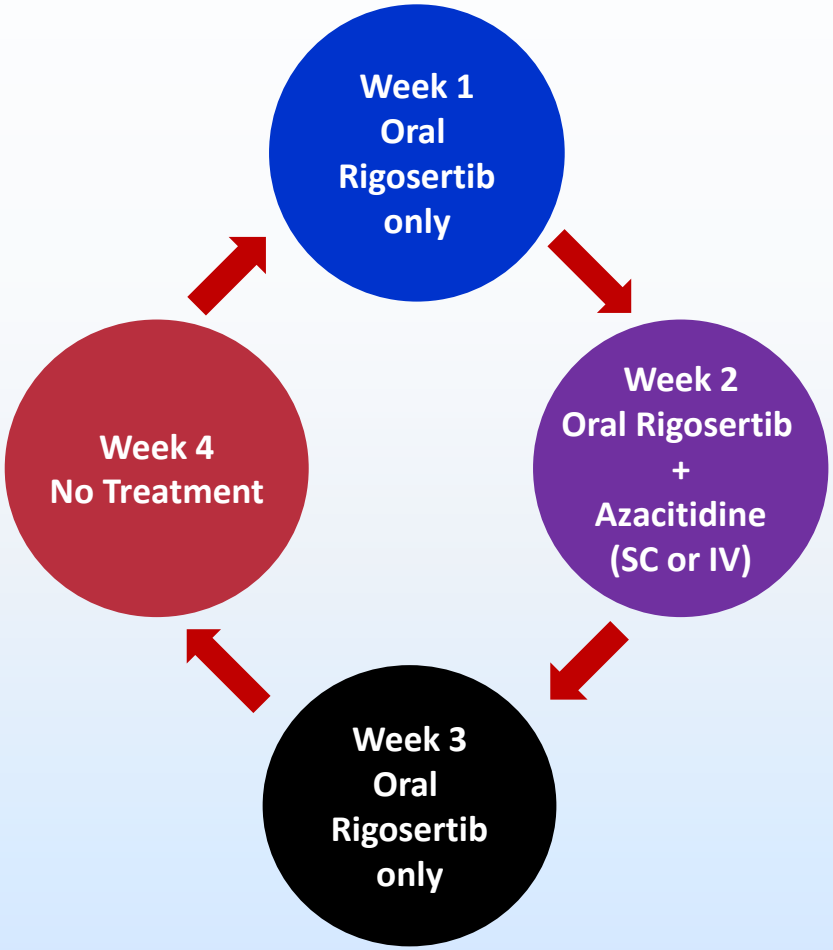
Week 1: Oral rigosertib BID[a]

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

Week 3: Oral rigosertib BID[a]

Week 4: No treatment

[a] in escalating dose cohorts



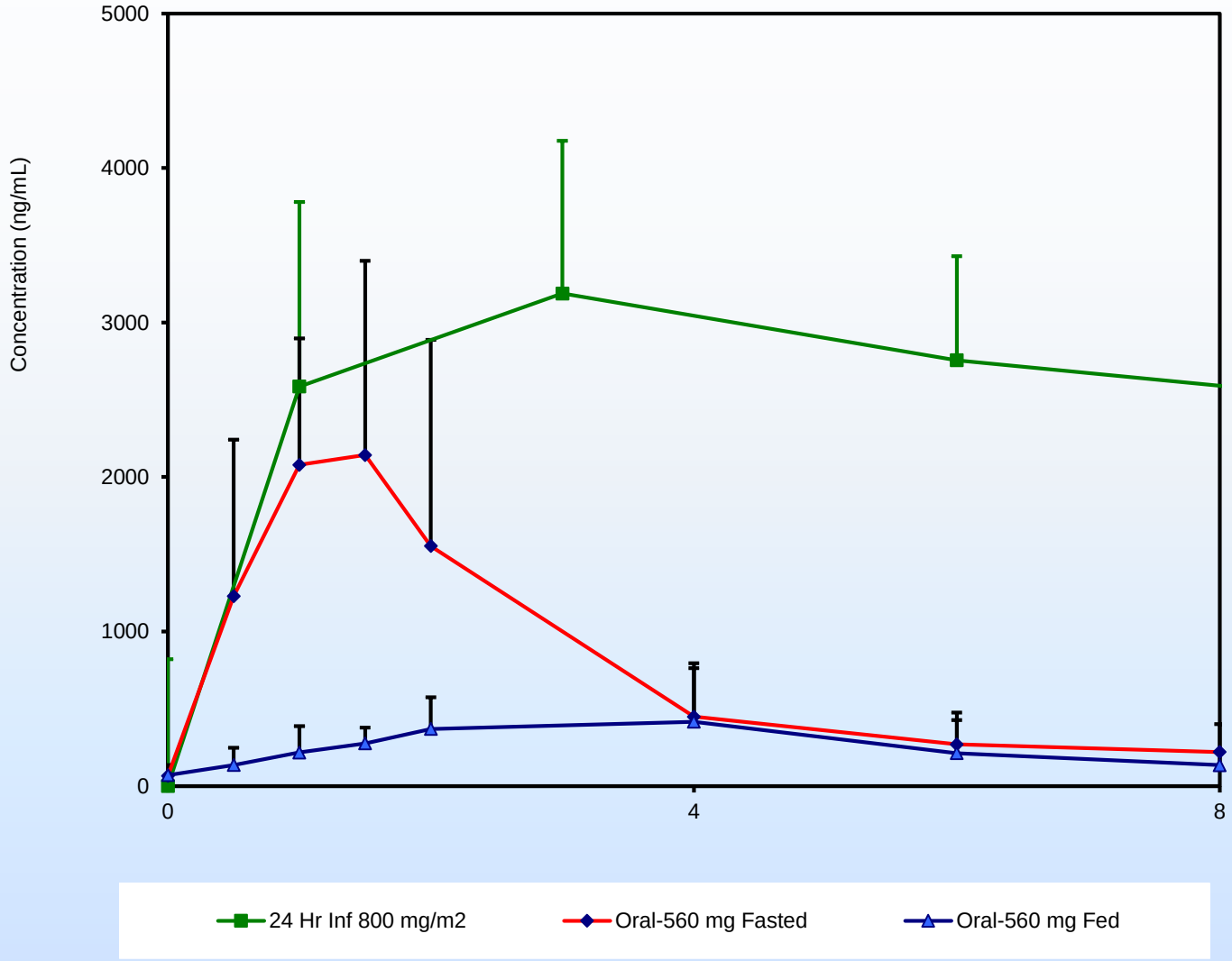
Navada S et al. ASH 2014; Abstract 3252.

Phase I Rigosertib and Azacitidine Combination

- Included patients with MDS and AML, both de novo and failing primary therapy in classic 3+3 design
- AML inclusion limited to: wbc < 25 x 10^9/L, and absence of rapidly rising blast percentage
- Rigosertib was administered in dose escalating cohorts
  - 140 mg/140 mg
  - 280 mg/280 mg
  - 560 mg/280 mg

** Navada S et al. ASH 2014; Abstract 3252.*

Plasma Levels of Rigosertib from a Bioavailablity Study



Eligibility Criteria for Phase 2

- Included patients with MDS (IPSS Int-1, Int-2, or High risk) and CMML
- AML (blasts 20-30%)
- Prior HMAs permitted; No prior rigosertib
- ECOG PS ≤ 2; Age ≥ 18 years
- Creatinine ≤ 2.0 mg/dL;
  Total bilirubin ≤ 2.0 mg/dL;
- ALT/AST ≤ 2.5 x ULN

Study Endpoints

Response Assessed per IWG 2006 MDS and modified IWG 2003 AML Criteria *

- Complete remission, partial remission or marrow CR (MDS and AML); morphologic CR, morphologic leukemia free state
- Hematologic improvement in any lineage and stable disease were categorized
- Safety and tolerability of combination

** Cheson BD et al. J Clin Oncol 2003: 21(24): 4642-9; Cheson BD et al. Blood 2006; 108(2): 419-25.*

Patient Characteristics (MDS)

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 in MDS

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

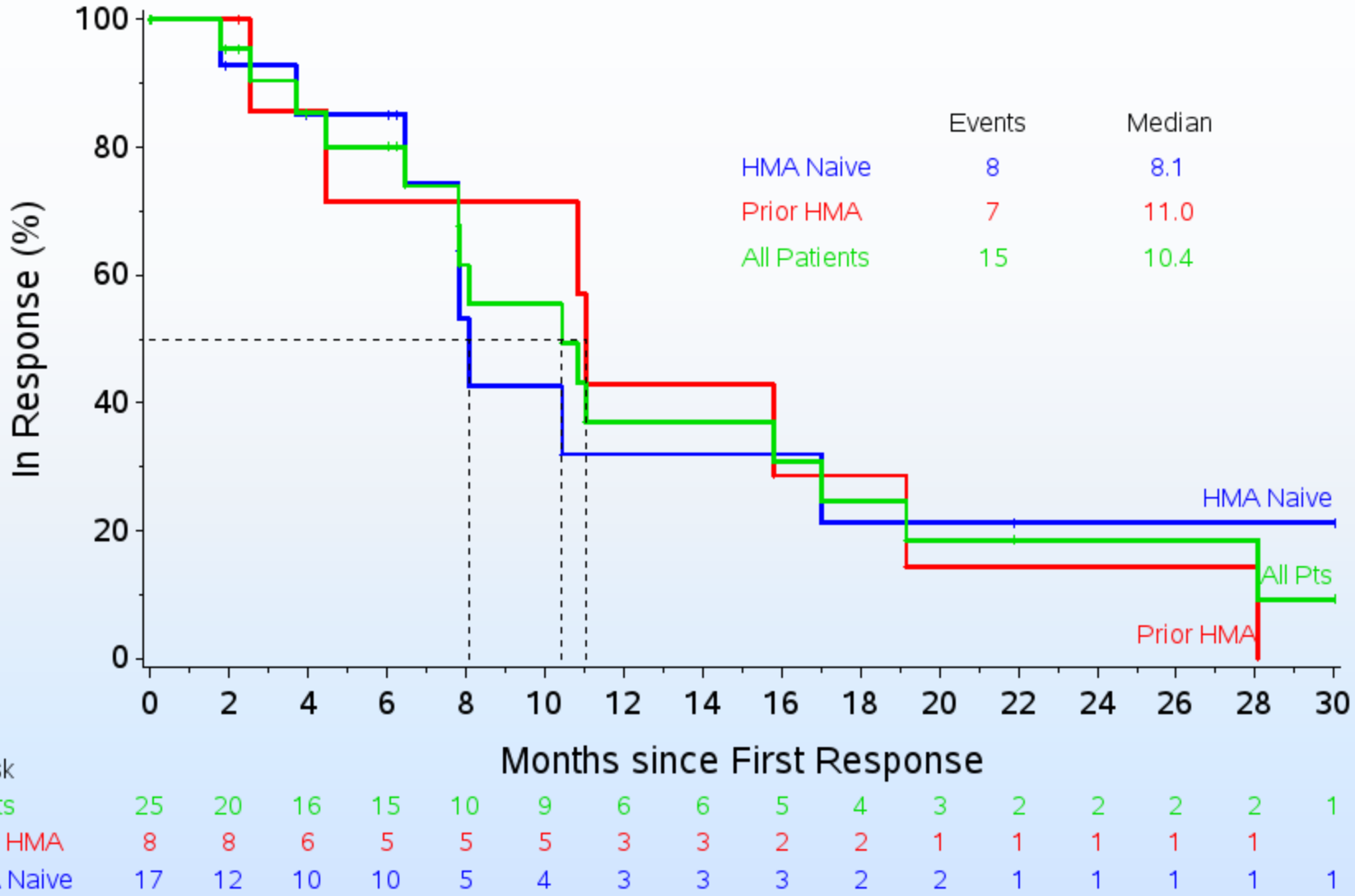
Response per IWG 2006 Among MDS IPSS-R Subgroups

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)

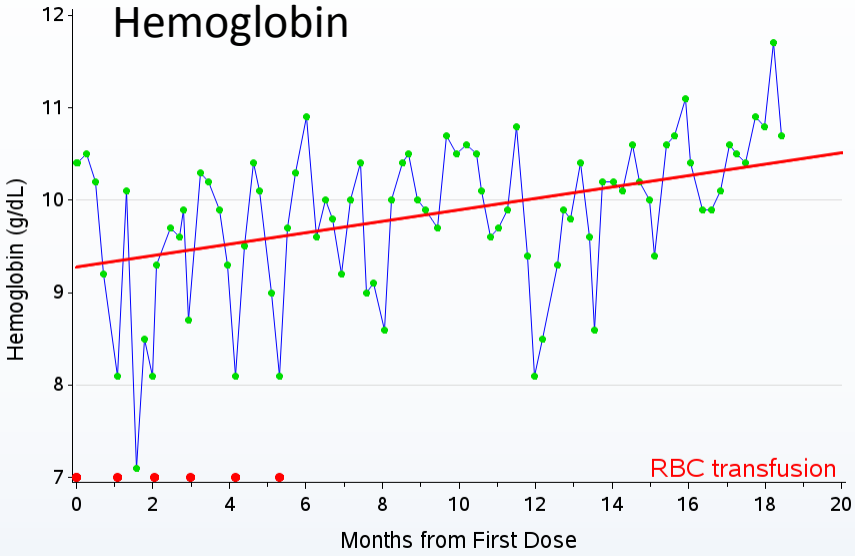
Efficacy: MDS Patients with Prior HMA Failure

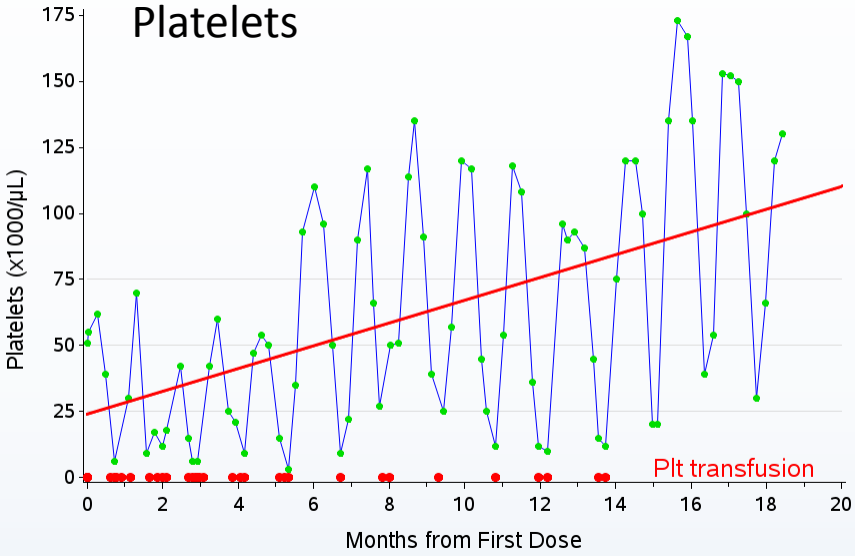
Number of patients evaluable for response (3 Ph1, 10 Ph2)	13 (10 AZA, 2 DAC, 1 both)
Number of prior HMA cycles	4-20
Hematologic response per IWG 2006	8 (62%)
Complete remission (CR)	1 (8%)
Partial remission	0
Marrow CR with concurrent HI	4 (31%)
Marrow CR alone	3 (23%)
Stable disease	5 (38%)
Progressive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

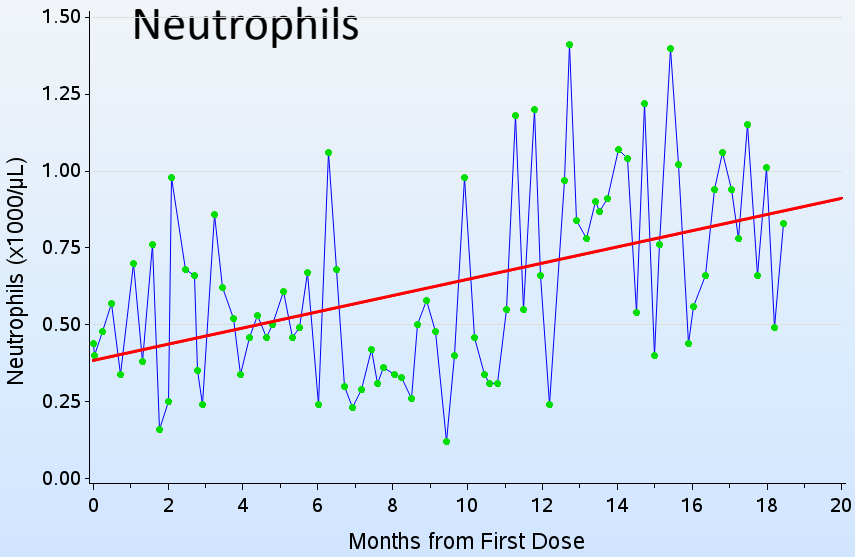
Duration of Overall Response



Hematology Trends for Patient 101-006 with MDS







- 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

Patient Characteristics (AML)

Number of AML patients treated		10
Age (years)	Median	66
	Range	57–80
Sex	Male	5 (50%)
	Female	5 (50%)
ECOG performance status	0	1 (10%)
	1	7 (70%)
	2	2 (20%)
Prior therapy	Cytarabine	6 (60%)
	Clofarabine/Cladarabine	4 (40%)
	Anthracyclines	5 (50%)
	Azacitidine	2 (20%)
	Decitabine	2 (20%)

Treatment Related Characteristics & Response - AML

UPN	Age (yrs)	Cohort*	Previous Therapy	DoT (months)	AML Status at Study Entry	IWG Response (D0R) – weeks)
101-033	61	140 bid	1. Induction 2. Investigational	4.0	Refractory	NE
101-002	70	140 bid	Growth Factors	29.6	Secondary	MoCR (25.3)
102-001	76	140 bid	Growth Factors	4.0	MDS/AML	NE
102-003	78	140 bid	Growth Factors	55.1	MDS/AML	MoCR (43)
101-005	73	280 bid	1. Induction 2. DEC x 5	4.0	1st Relapse	TF/I
102-009	71	560/280	1. Induction x 2 2. AZA x 25	12.9	Relapsed	TF/R
102-007	80	560/280	AZA x 5	32.0	Secondary	TF/R
101-008	57	560/280	Induction	8.1	Refractory	MLFS (4.1)
101-009	60	560/280	Induction	24.4	Relapsed	SD
101-007	77	560/280	1. Induction 2. DEC x 5	16.0	Relapsed	SD

MDS/AML – 20 to <30% blasts
NE – patients off study prior to 12 weeks of combination
MoCR – morphologic complete remission
TF/I – treatment failure/indeterminate
TF/R – treatment failure/resistant
MLFS – morphologic leukemia-free state
SD – stable disease

***Oral rigosertib dose**

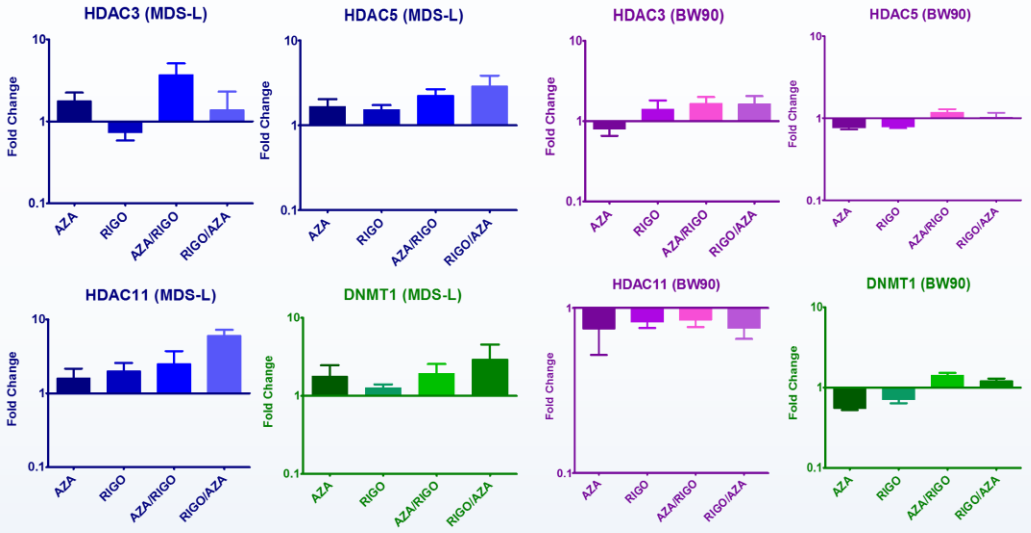
Efficacy Results in AML

Number of AML patients treated Evaluable for response	10 8
Overall response	3 (37.5%)
Morphologic complete remission Morphologic leukemia free state Treatment failure Stable disease	2 (25%) 1 (12.5%) 3 (37.5%) 2 (25%)
Not evaluable for response (per protocol)	2
Median duration of treatment (months)	14.5

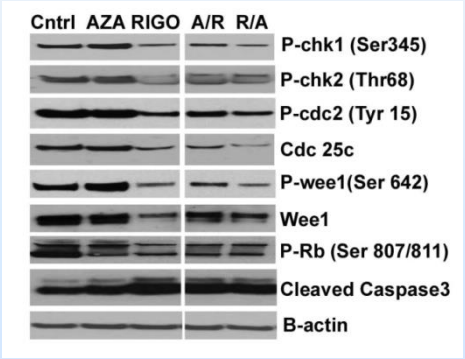
* Per IWG 2006

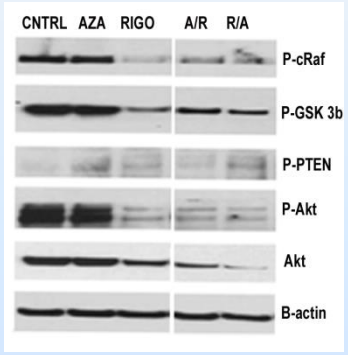
Rigosertib alone and in combination with azacitidine has Epigenetic effects in vitro and in vivo

- 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 EHA, 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

AML

- ORR 37.5% in secondary and refractory AML patients with an additional 25% with stable disease
- The combination is well tolerated in patients with MDS & AML and has a safety profile similar to single-agent azacitidine.
- The combination should be explored as a novel therapeutic approach in older patients with AML

MDS

- Oral rigosertib and azacitidine demonstrated an overall response rate of 76% in patients with MDS
- 85% and 62% of patients with MDS who where either HMA naïve or HMA failures, respectively, responded to the combination
- The combination will be explored further in a future Phase 3 study; discussions underway for dose optimization

Future Directions

- Rationale for Phase 2 Expansion
  - High response rate in HMA naïve and HMA failure, respectively
  - Planning a randomized Phase 3 of the combination compared to single agent azacitidine in HMA naïve patients
  - 40 patients to refine the CR + PR response rate with greater precision – reduce the Confidence Interval by 30%

Future Directions *(cont.)*

- Phase 2 Expansion
  - Reduce the incidence of bladder AEs and further optimize dose and schedule of rigosertib
    - Phase 2 in LR MDS had best results in 560/560 group (compared to 560/280 group)
      - Transfusion independence: 39 vs 24%
      - Hematologic improvement: 46 vs 21%
    - 2 cohorts – 560 mg/560 mg and 840 mg/280 mg
      - Enhance bladder emptying and reduce exposure to rigosertib metabolite overnight
  - Randomized Phase 3 Study of Azacitidine + oral Rigosertib vs Azacitidine
    - Primary Endpoint: CR + PR
    - Anticipated start 1H 2018

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