

PHASE II STUDY OF ORAL RIGOSERTIB COMBINED WITH AZACITIDINE AS FIRST LINE THERAPY IN PATIENTS WITH HIGHER-RISK MYELODYSPLASTIC SYNDROMES (MDS)

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TREATMENT OF HIGHER-RISK MDS

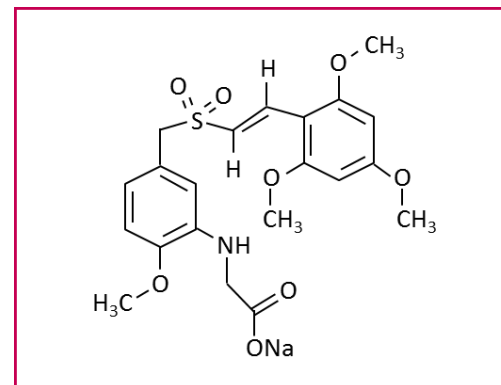
- Azacitidine is standard of care for HR-MDS patients
- Clinical responses in MDS 38-50%^a
 - CR rate 7-24%
 - Recent studies failed to demonstrate improved clinical benefit with combination therapies compared to single agent AZA
 - Aza + Valproic acid vs Daunorubicin + Cytarabine vs Aza (Ades L, et al., #467, ASH 2018)
 - Aza + Lenalidomide vs Aza + Vorinostat vs Aza (Sekeres M, et al., SWOG Intergroup JCO 2017)
 - Aza + Etenostat vs Azacitidine (Prebet T, et al., ECOG Intergroup JCO 2014)
- All patients ultimately relapse or fail to respond
- HMA failure is associated with a poor prognosis – Median OS 4-6 months^b
- Novel combinations should
 - Be well tolerated (Sekeres; Ades)
 - Mitigate potential negative interaction between agents (Prebet)

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.

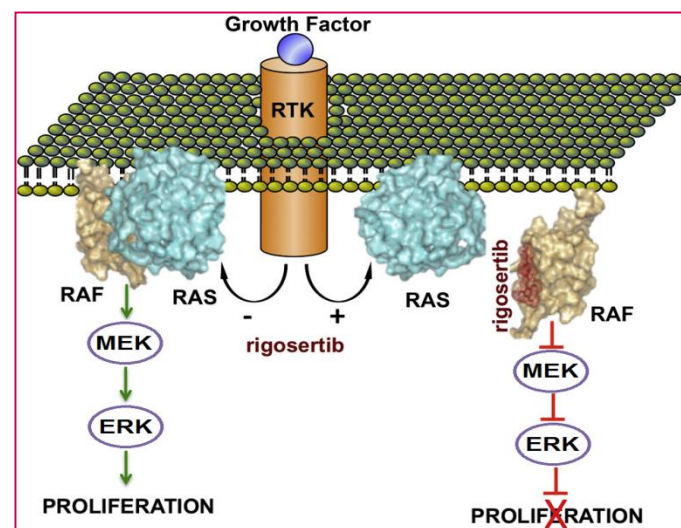
b Prebet T, Gore SD, Estemi B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 2011;29(24):33227

RIGOSERTIB MECHANISM OF ACTION

- Inhibits cellular signaling as a Ras mimetic by targeting the Ras-binding domain (RBD)^a
- Novel MOA blocks multiple cancer targets and downstream pathways PI3K/AKT and Raf/PLK
- Can ameliorate multiple dysregulated signaling transduction pathways in higher-risk MDS^b
- *In vitro*, sequential exposure to rigosertib followed by azacitidine achieves maximum synergy at clinically achievable concentrations^c



Rigosertib



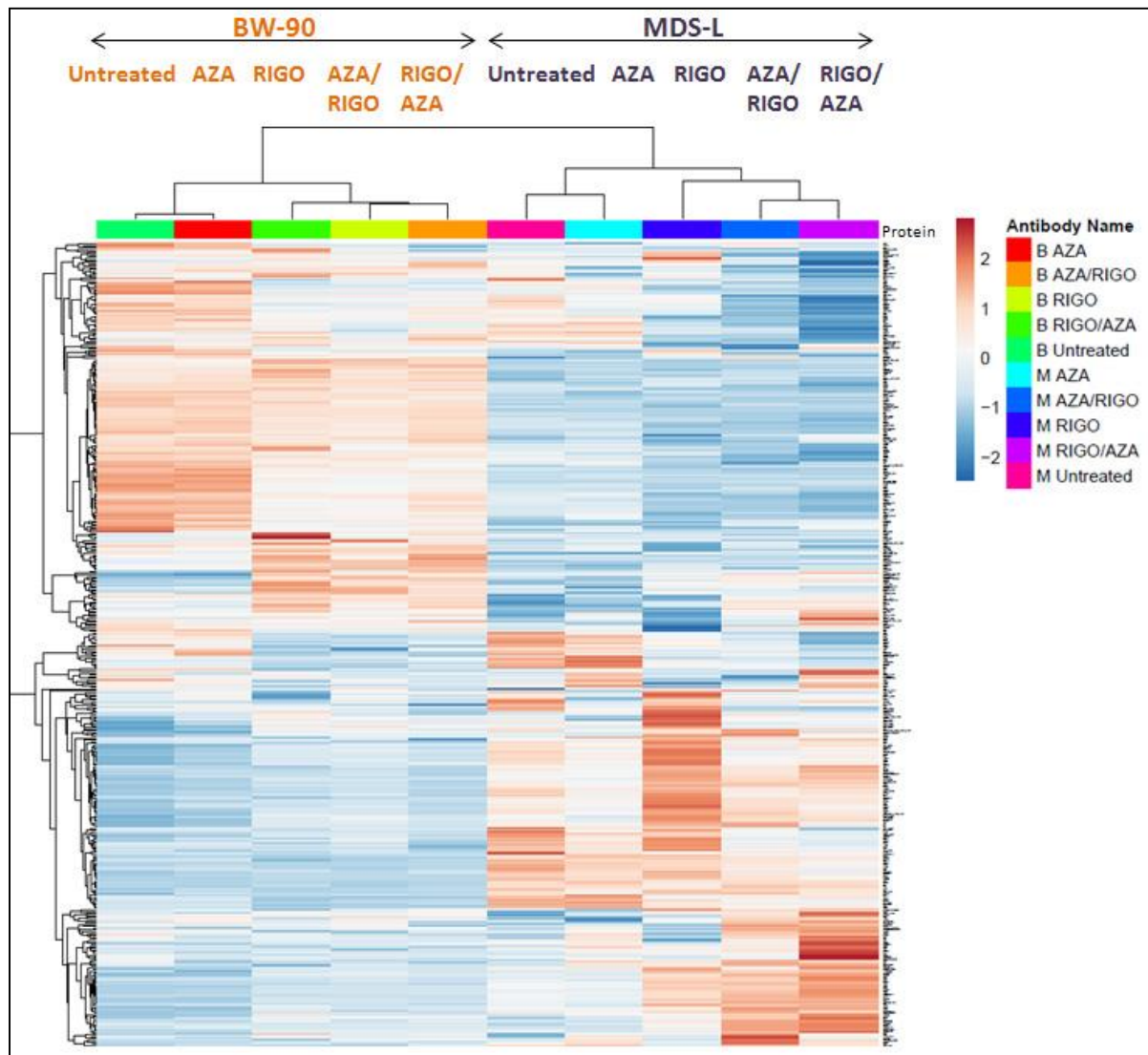
RAS targeted novel mode of action

^aDivikar, S.K., et al. (2016). "A Small Molecule RAS-Mimetic Disrupts Association with Effector Proteins to Block Signaling." *Cell* 165, 643-655

^bFeng Xu, Qi He, Xiao Li, Chun-Kang Chang, et al: *SCIENTIFIC REPORTS*; 4 : 7310; DOI: 10.1038/srep07310

^cSkiddan 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.

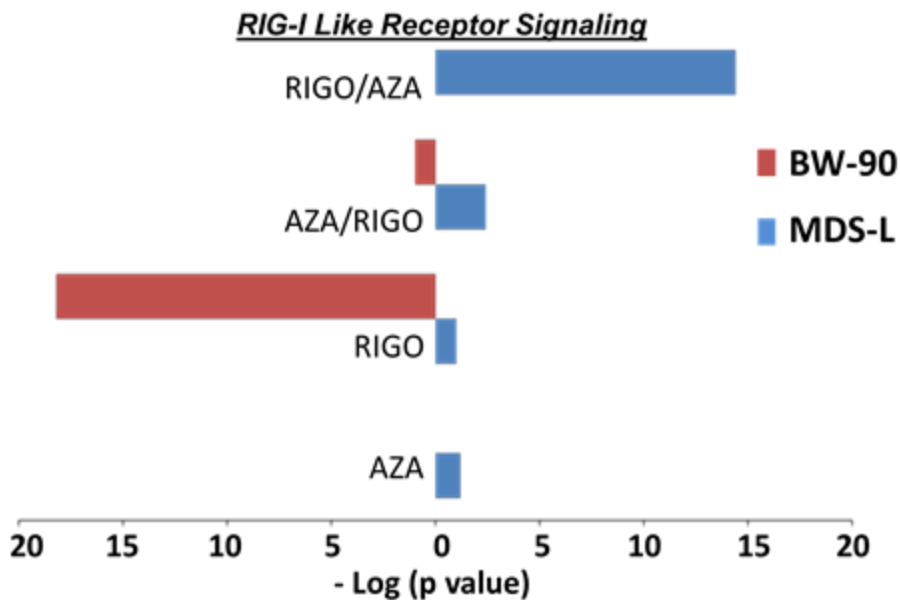
Heat map shows the differential protein expression on treatment with AZA and RIGO alone and their Sequential Combinations in MDS-L and BW-90 cell lines by Reverse Phase Protein Array Analysis



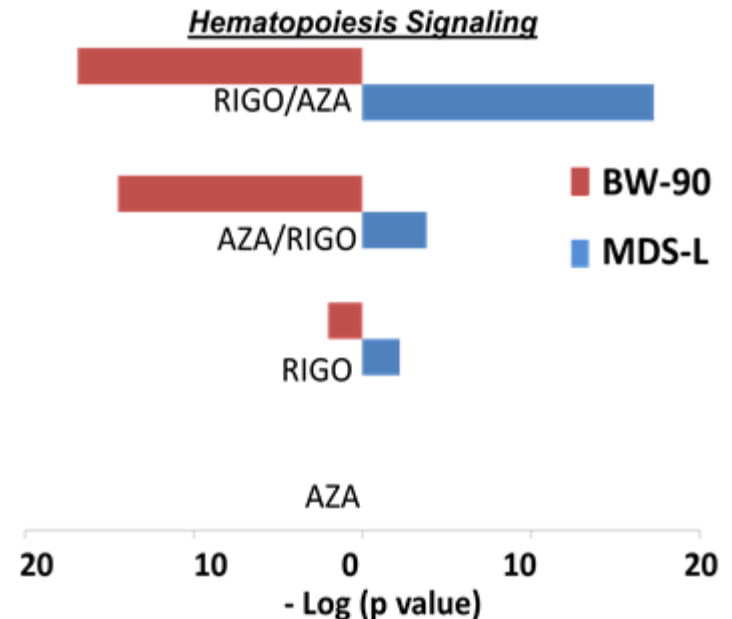
- Differences in protein expression are dependent on the sequence of Rigosertib and Azacitidine compared to either agent alone in MDS-L and BW90 (AML) cell lines.
- Wnt β catenin signaling, which affects hematopoiesis, was specifically upregulated with the Rigo/AZA combination compared to RIGO or AZA alone at both the mRNA and protein levels.

RIGOSERTIB MODULATES INNATE IMMUNE SIGNALING

The variation in RIG-I like receptor signaling in MDS-L and BW-90 cell lines upon treatment with AZA and RIGO either alone or in sequential combinations.



The variation in Hematopoiesis signaling in MDS-L and BW-90 cell line upon treatment with AZA and RIGO either alone or in sequential combinations.



- Antiviral response gene RIG-I is up-regulated by RIGO/AZA in an MDS cell line
- RIGO/AZA significantly up-regulates hematopoiesis signaling compared to either AZA or RIGO alone
- Supports the original observation regarding the significance of the sequence of RIGO/AZA

Rai R. et. al. (2019). The Sequenced Combination of Rigosertib and Azacitidine has Modulatory Effects on CXCL8, RIG-I like Receptor (RLR) and Wnt/ β -Catenin Signaling and Downstream Hematopoiesis Pathways in an in Vitro Model of the Myelodysplastic Syndrome. ASH Abstract # 4231.

COMBINATION DOSE ADMINISTRATION

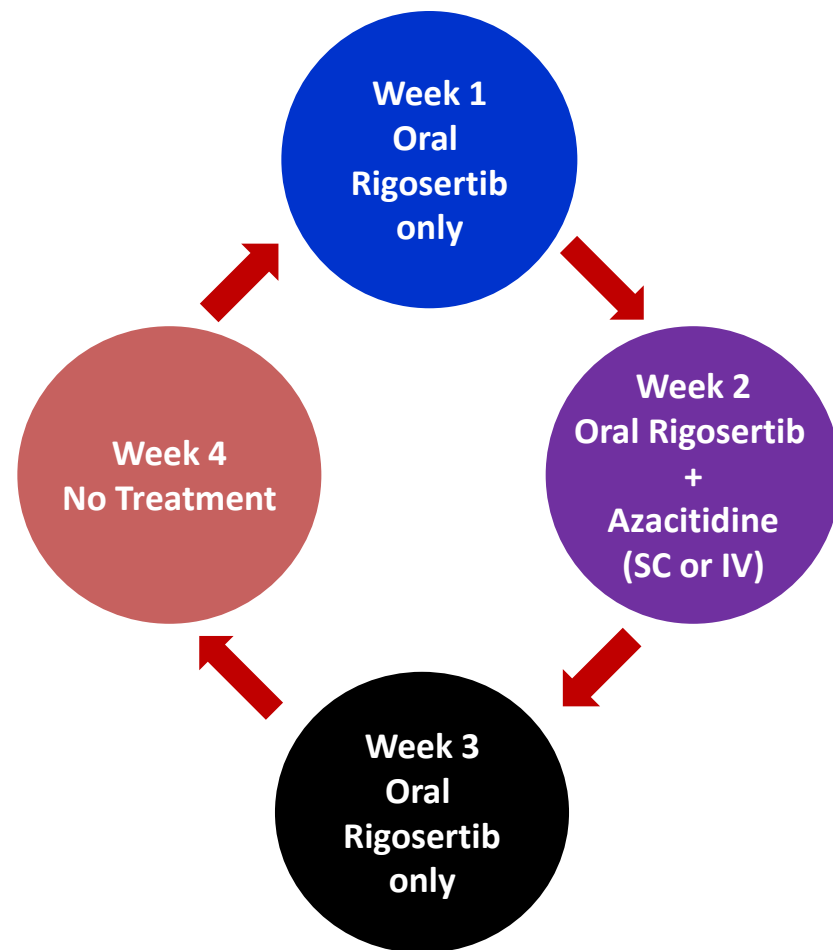
Week 1: Oral rigosertib
twice daily*

Week 2: Oral rigosertib
twice daily + azacitidine (75
mg/m²/day SC or IV)

Week 3: Oral rigosertib
twice daily

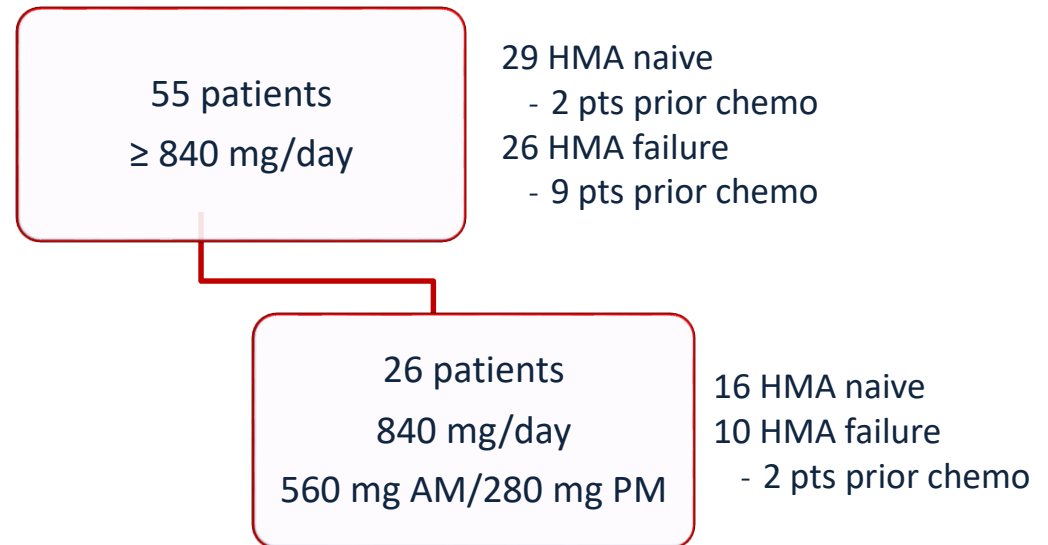
Week 4: No treatment

*early AM/mid-afternoon PM



PATIENTS WITH HR-MDS EVALUABLE FOR RESPONSE PER RIGOSERTIB DOSING COHORT

HMA NAIVE & HMA FAILURE

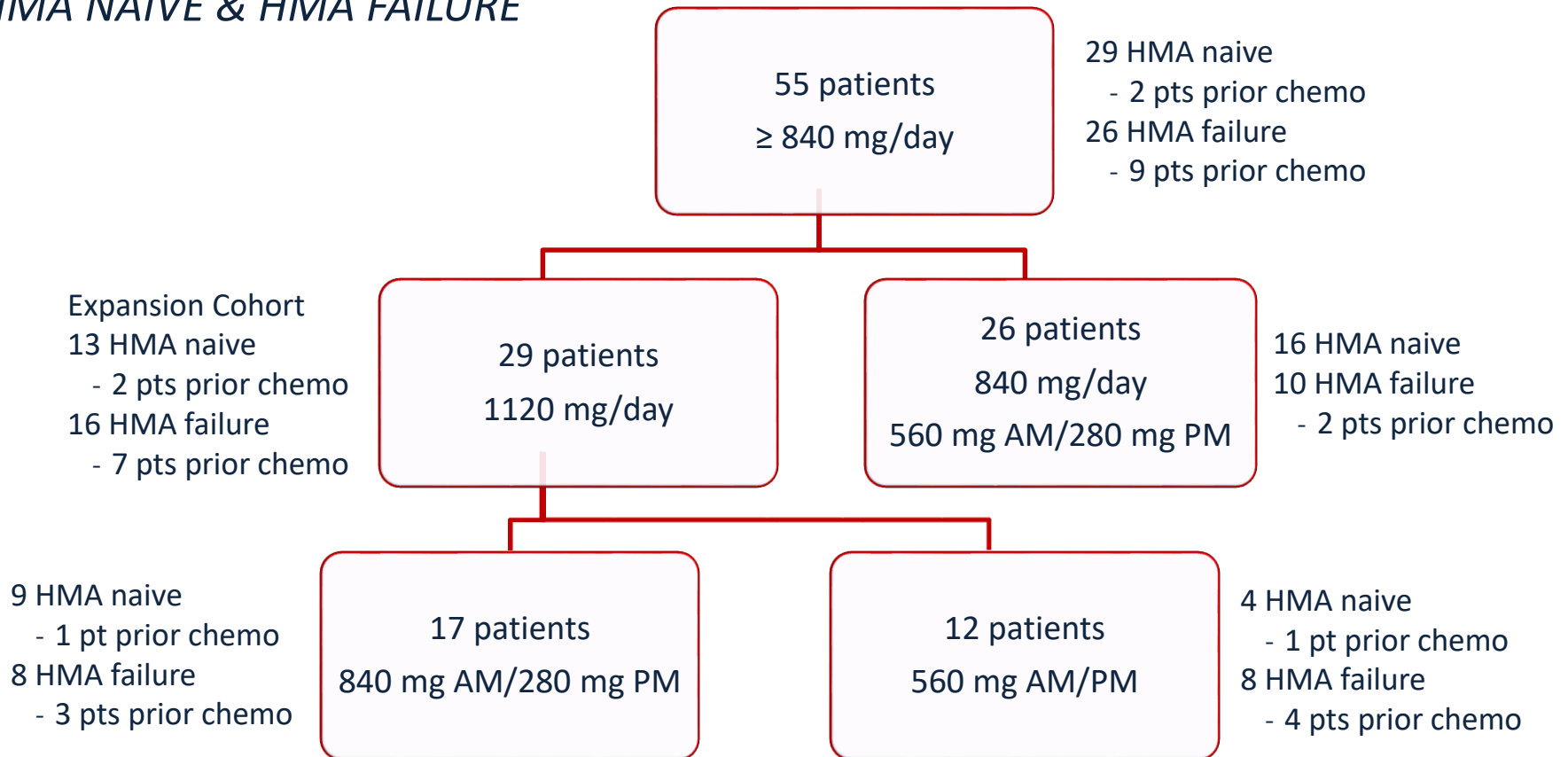


Rationale for Expansion Cohort at a dose of 1120mg/day:

- Rigosertib as a single agent administered orally at dose of 1120 mg/day yielded the highest response rate of transfusion independence (44%) in lower risk MDS (Raza A, et al., #1689 ASH 2017)
- Pursue Safety Optimization Strategies in additional patients at a higher daily dose

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PATIENT CHARACTERISTICS – RIGOSERTIB ≥ 840 MG/DAY

HMA NAIVE

Number of patients treated		39 (%)
Age	Median	64
	Range	42 – 90
Sex	Male	17 (44)
	Female	22 (56)
Race	Asian	3 (8)
	Black	6 (15)
	Hispanic	3 (8)
	White	26 (67)
	Unknown	1 (3)
IPSS-R classification	Low	3 (8)
	Intermediate	9 (23)
	High	8 (21)
	Very high	17 (44)
	Unknown	2 (5)
IPSS-R cytogenetics	Very poor	9 (23)
	Poor	7 (18)
	Intermediate	9 (23)
	Good	14 (36)

HMA NAIVE: RIGOSERTIB ≥ 840MG/DAY

EFFICACY

Evaluable for response	29* (%)
Overall response per IWG 2006	26 (90)
CR+PR	10 (34)
Complete remission (CR)	10 (34)
Partial remission (PR)	0
Marrow CR + Hematologic Improvement	5 (17)
Hematologic Improvement alone	3 (10)
Marrow CR alone	8 (28)
Stable disease	3 (10)
Progression	0
Median duration of response (months)	12.2 (range, 0.1-24.2+)
Median duration of treatment (months)	7.8 (range, 0.7-25.1+)
Median time to initial/best response (cycles)	1/4

** Includes 2 patients treated with non-HMA, chemotherapy*

RESPONSE BY IPSS-R CYTOGENETICS (N=29)

	Total Patients	Responders (%)
Very poor cytogenetics (n=9)	5	4 (80)
Poor cytogenetics (n=7)	4	4 (100)
Intermediate cytogenetics (n=9)	8	7 (88)
Good cytogenetics (n=14)	12	11 (92)

Baseline cytogenetics on study

RESPONSE BY IPSS-R RISK GROUP

Response per IWG 2006	Low/ Intermediate N=11 (%)	High N=6 (%)	Very high N=12 (%)
Complete remission	4 (36)	1 (17)	5 (42)
Marrow CR + HI	1 (9)	1 (17)	3 (25)
HI alone	3 (27)	0	0
Marrow CR alone	2 (18)	3 (50)	3 (25)
Stable disease	1 (9)	1 (17)	1 (8)

HEMATOLOGIC IMPROVEMENT BY IPSS-R RISK GROUP

Per IWG 2006	Low/ Intermediate N=11 (%)	High N=6 (%)	Very high N=12 (%)
Hematologic improvement	8 (73)	2 (33)	8 (67)
Erythroid response	1 (9)	1 (17)	8 (67)
Platelet response	6 (55)	1 (17)	7 (58)
Neutrophil response	4 (36)	1 (17)	4 (33)

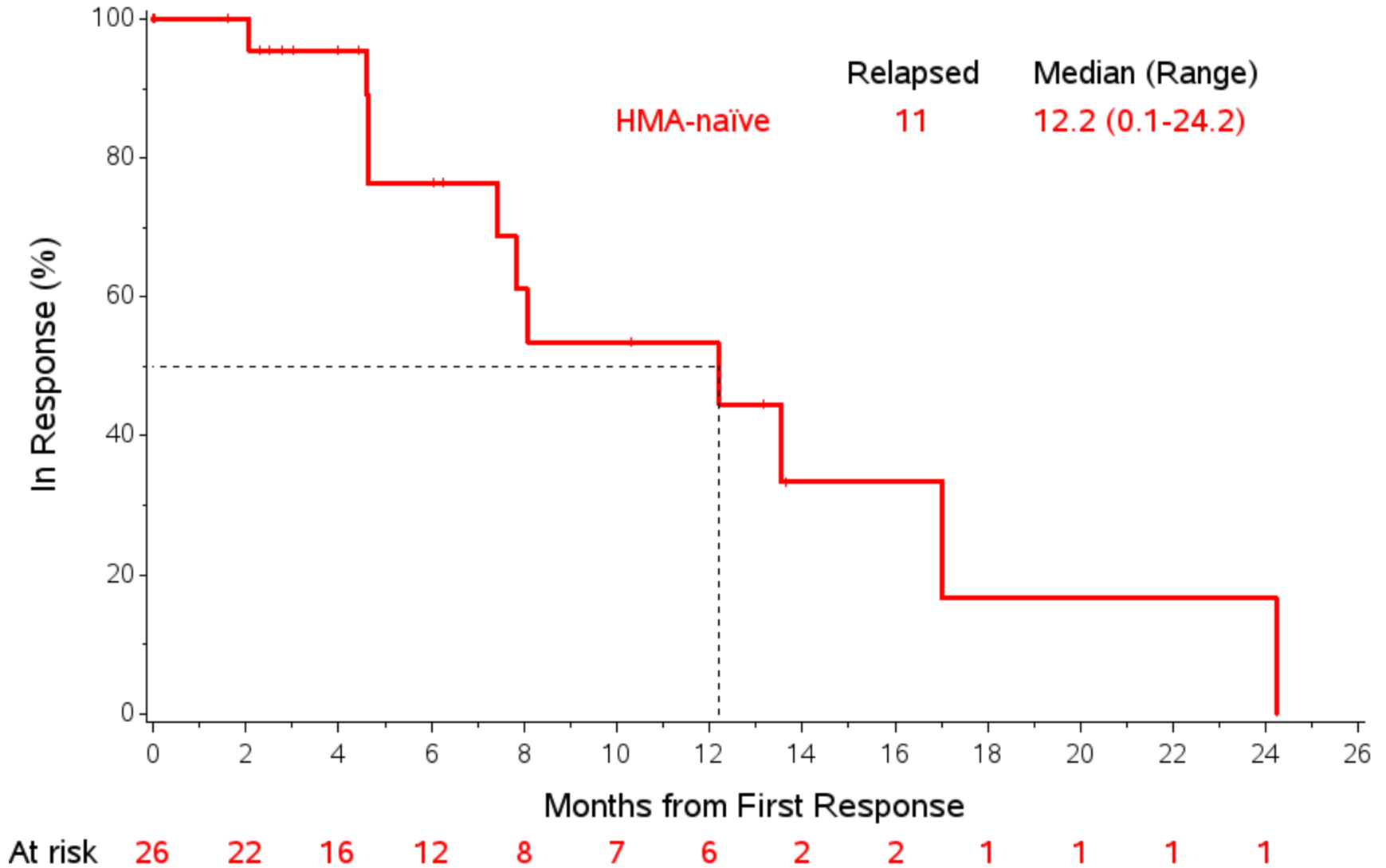
OVERALL HEMATOLOGIC RESPONSE BY DOSING COHORT

Response per IWG 2006	560/280 N=16 (%)	560/560 N=4 (%)	840/280 N=9 (%)
Complete remission	6 (38)	2 (50)	2 (22)
Marrow CR + Hematologic improvement	3 (19)	0	2 (22)
Hematologic improvement alone	1 (6)	0	2 (22)
Marrow CR alone	4 (25)	1 (25)	3 (33)
Stable disease	2 (13)	1 (25)	0

HEMATOLOGIC IMPROVEMENT BY DOSING COHORT

Per IWG 2006	560/280 N=16 (%)	560/560 N=4 (%)	840/280 N=9 (%)
Hematologic improvement	10 (63)	2 (50)	6 (67)
Erythroid response	7 (44)	1 (25)	2 (22)
Platelet response	8 (50)	2 (50)	4 (44)
Neutrophil response	5 (31)	1 (25)	3 (33)

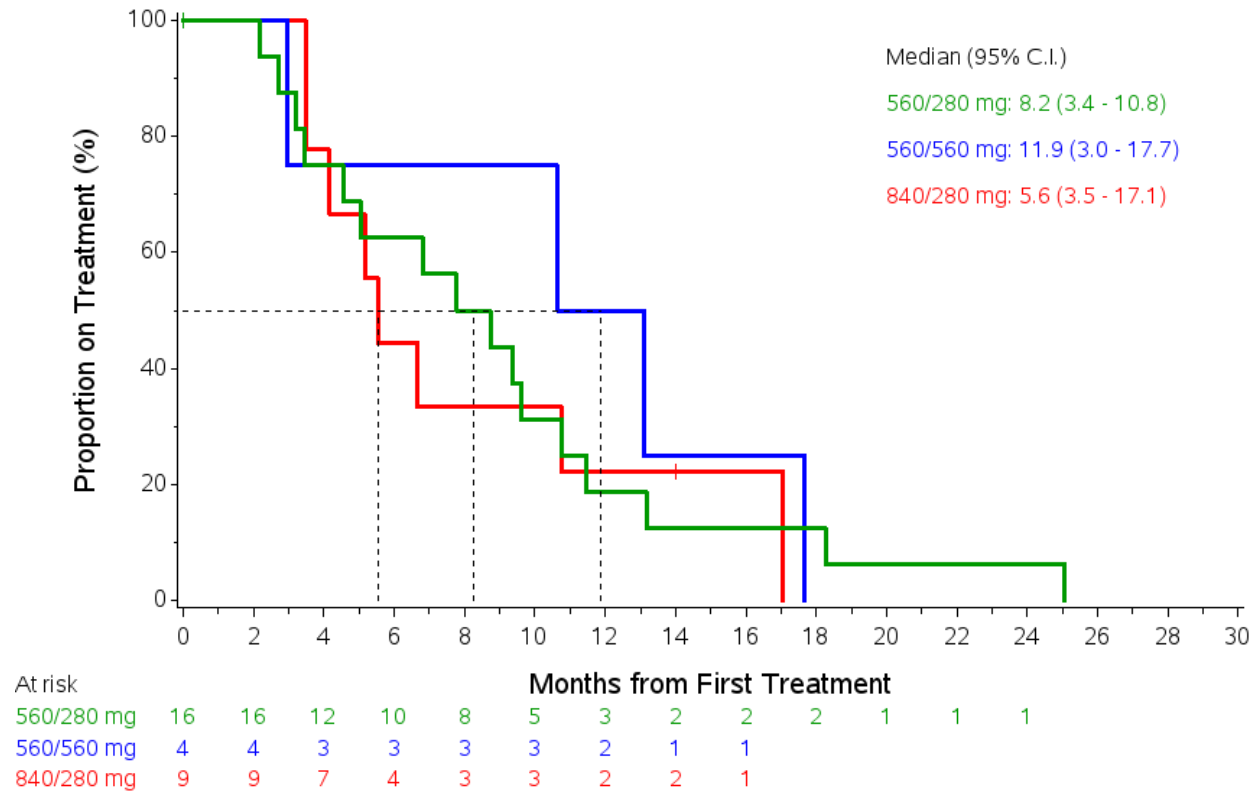
DURATION OF THE OVERALL RESPONSE



DURATION OF TREATMENT IN HMA-NAIVE PATIENTS

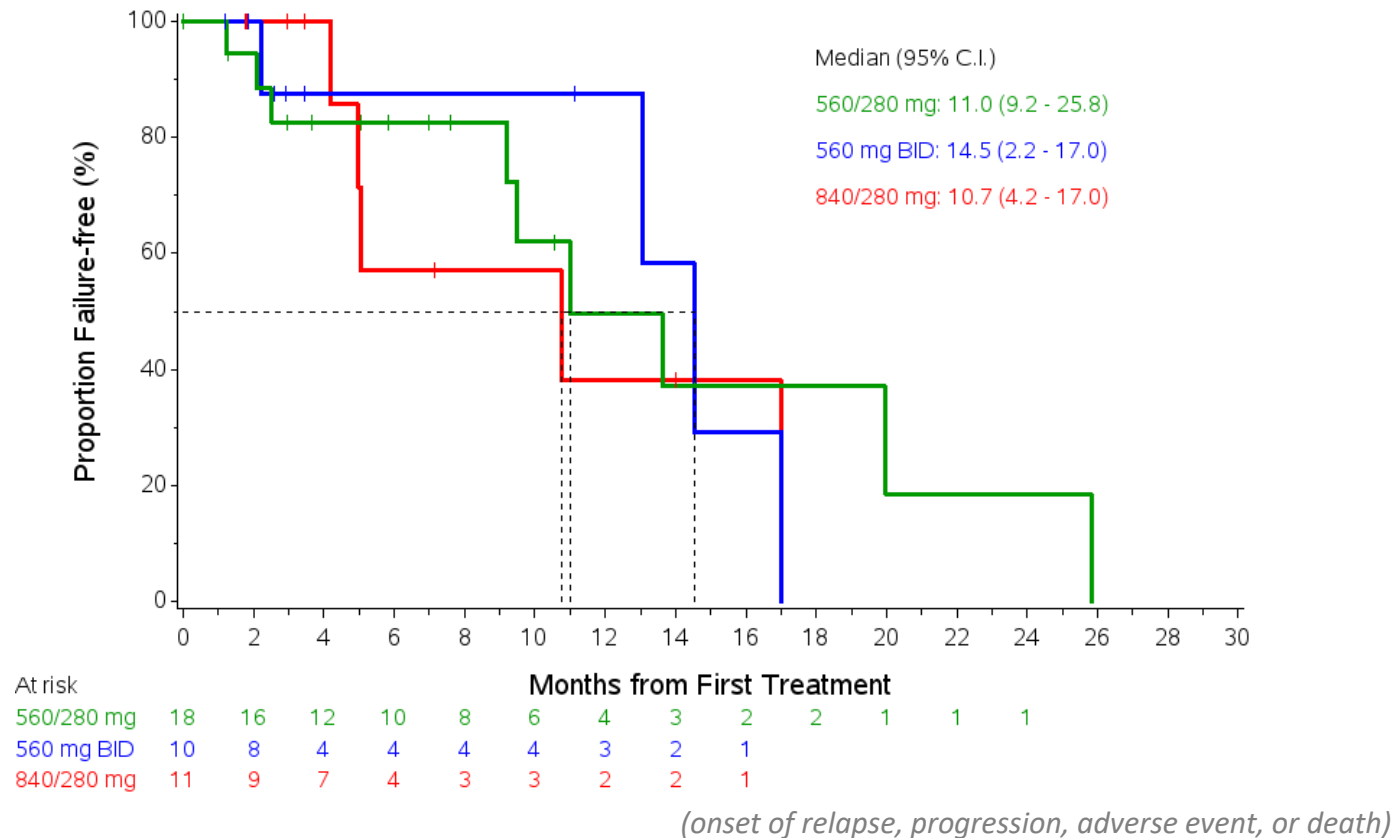
Cohort	Evaluable patients	Off-treatment	On-treatment
560/280 mg	16	16 (100%)	0
560/560 mg	4	4 (100%)	0
840/280 mg	9	8 (89%)	1 (9%)

Time on treatment of the continuing patient was censored at the last study treatment.



TIME TO TREATMENT FAILURE IN HMA-NAIVE PATIENTS

Cohort	Patients	Treatment failure	No failure
560/280 mg	18	9 (50%)	9 (50%)
560 mg BID	10	4 (40%)	6 (60%)
840/280 mg	11	5 (45%)	6 (55%)



ADVERSE EVENTS

Most Common Treatment Emergent Adverse Events		
N = 39	Patients (%)	
MedDRA Preferred Term	All grades	Grade ≥3
Any Event	39 (100)	35 (90)
Haematuria	20 (51)	6 (15)
Fatigue	19 (49)	2 (5)
Pyrexia	17 (44)	1 (3)
Diarrhoea	16 (41)	4 (10)
Nausea	15 (38)	-
Constipation	14 (36)	-
Dysuria	14 (36)	5 (13)
Neutropenia	14 (36)	13 (33)
Thrombocytopenia	14 (36)	12 (31)
Anaemia	11 (28)	11 (28)
Febrile neutropenia	10 (26)	9 (23)

CONCLUSIONS

- Oral rigosertib in combination with AZA demonstrated efficacy in HMA-naive patients
- In HMA-naive MDS patients oral rigosertib at doses ≥ 840 mg/day administered with AZA is associated with an ORR of 90% and a CR rate of 34%
- Oral rigosertib in combination with AZA was well tolerated and administered in repetitive cycles for more than two years
- Based on the efficacy data and favorable safety profile, a pivotal Phase II/III adaptive design trial in higher-risk HMA naive MDS population is planned

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