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

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TREATMENT OF HIGHER-RISK MDS

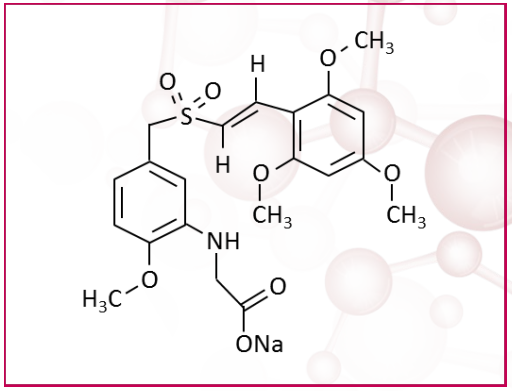
- Azacitidine is standard of care for HR-MDS patients
- Clinical responses in MDS 38-50%[a]
  - CR rate 7-24%
  - Recent studies failed to demonstrate improved clinical benefit with combination therapies compared to single agent AZA
    - (Ades L, et al., #467, ASH 2018)
    - (Sekeres M, et al., Intergroup JCO 2017)
- 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]
- Novel better tolerated combination strategies for patients with MDS are required to improve the clinical outcome

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.

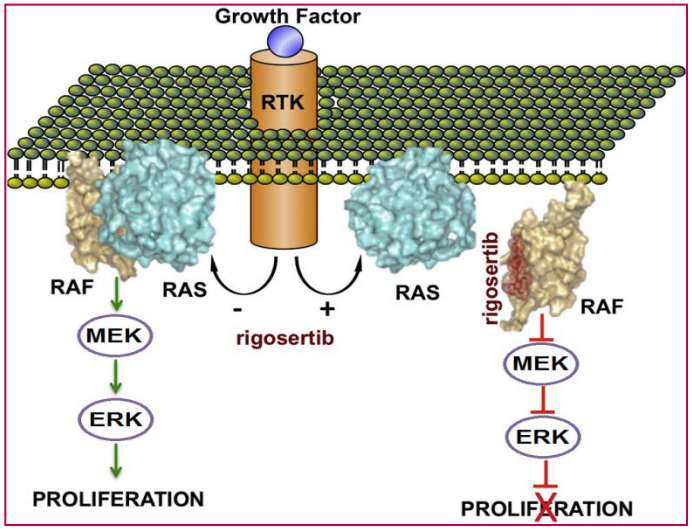
b Prebet T, Gore SD, Estemi B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 2011;29(24):3322-7.

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]
- Sequential exposure with rigosertib followed by azacitidine achieved maximum synergy with clinically achievable concentrations[c]



Rigosertib



RAS targeted novel mode of action

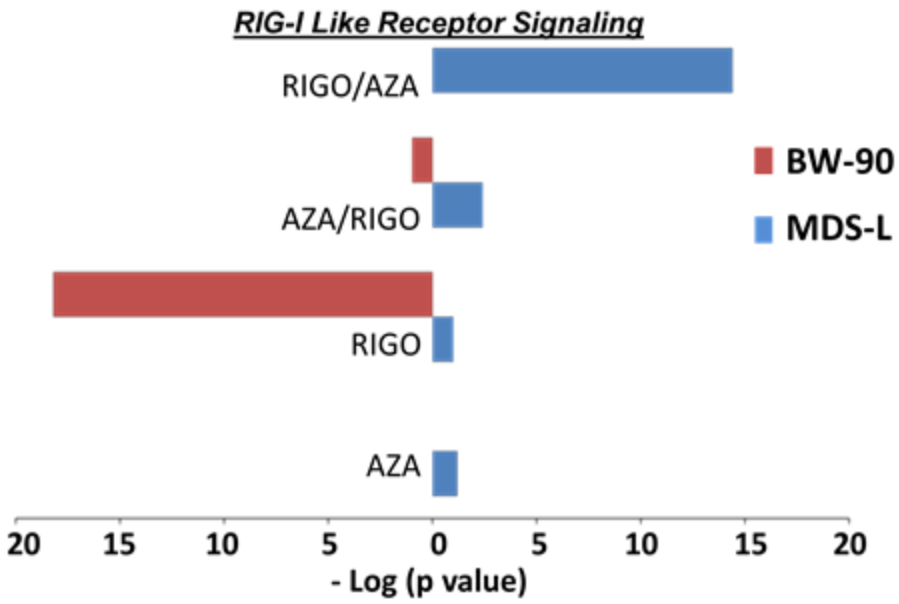
[a]*Divikar, S.K.,et al. (2016). "A Small Molecule RAS-Mimetic Disrupts Association with Effector Proteins to Block Signaling." Cell 165, 643-655*

[b]*Feng Xu, Qi He, Xiao Li, Chun-Kang Chang, et al: SCIENTIFIC REPORTS; 4 : 7310; DOI: 10.1038/srep07310*

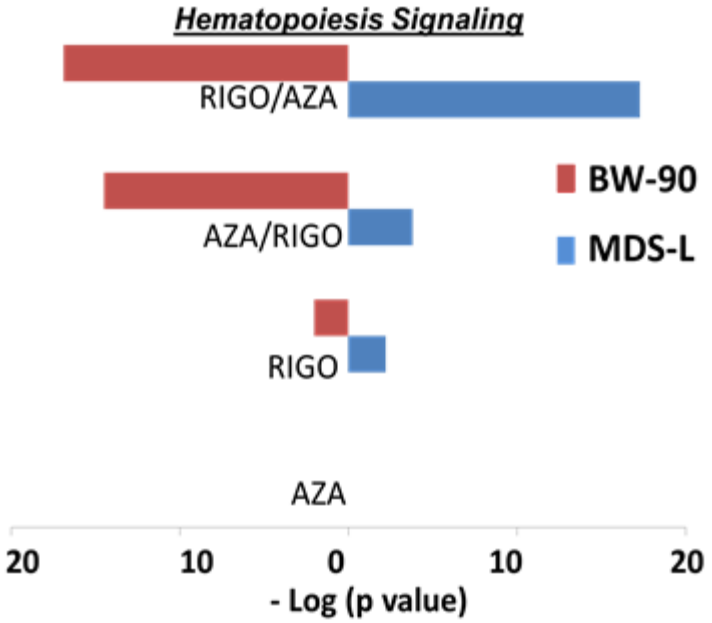
[c]*Skiddan I, Zinzar S, Holland JF, et al. Toxicology of a novel small molecule ON1910Na on human bone marrow and leukemic cells in vitro. AACR Abstract 1310, April 2006; 47:309.*

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

Silverman, L. et. al. (2019). RIGOSERTIB MODULATES HEMATOPOIESIS GENE SIGNALING PATHWAYS ALONE OR IN SEQUENCED COMBINATION WITH AZACTIDINE ON MDS CELLS IN VITRO. EHA Abstract # PS1332. Presenting Sat Jun 15 2019 17:30-19:00

COMBINATION DOSE ADMINISTRATION

ORAL RIGOSERTIB 840 MG OR 1120 MG IN DIVIDED DOSES

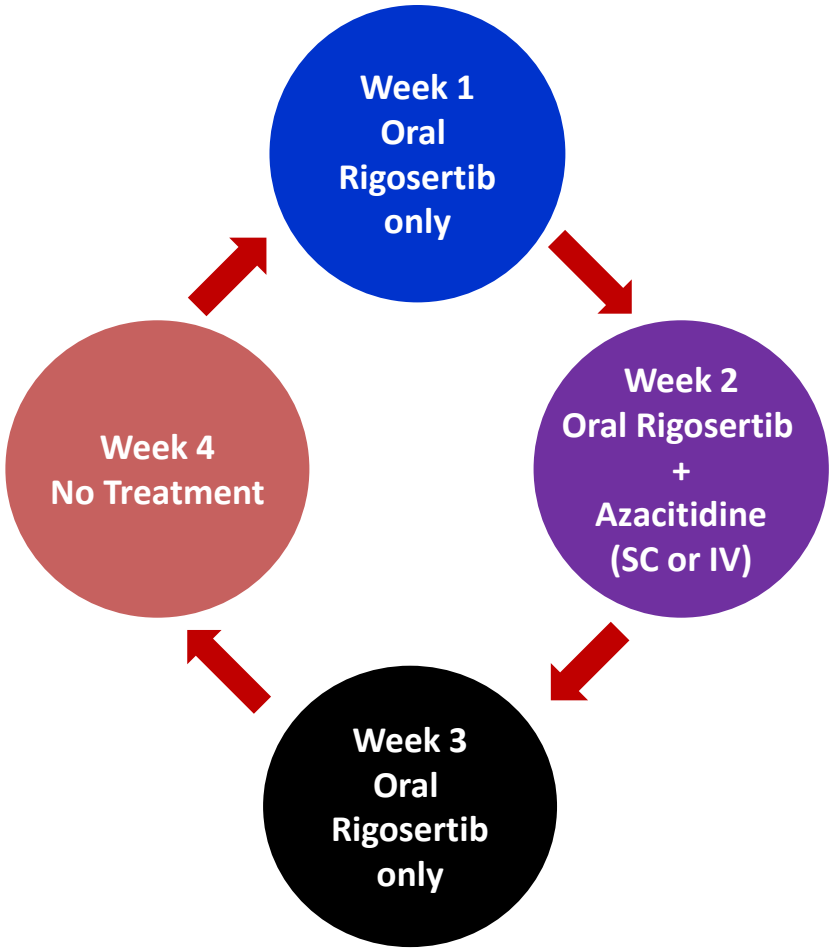
Week 1: Oral rigosertib twice daily*

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

Week 3: Oral rigosertib twice daily*

Week 4: No treatment

*early AM/mid-afternoon PM



Navada S, EHA 2017 Abstract #S488

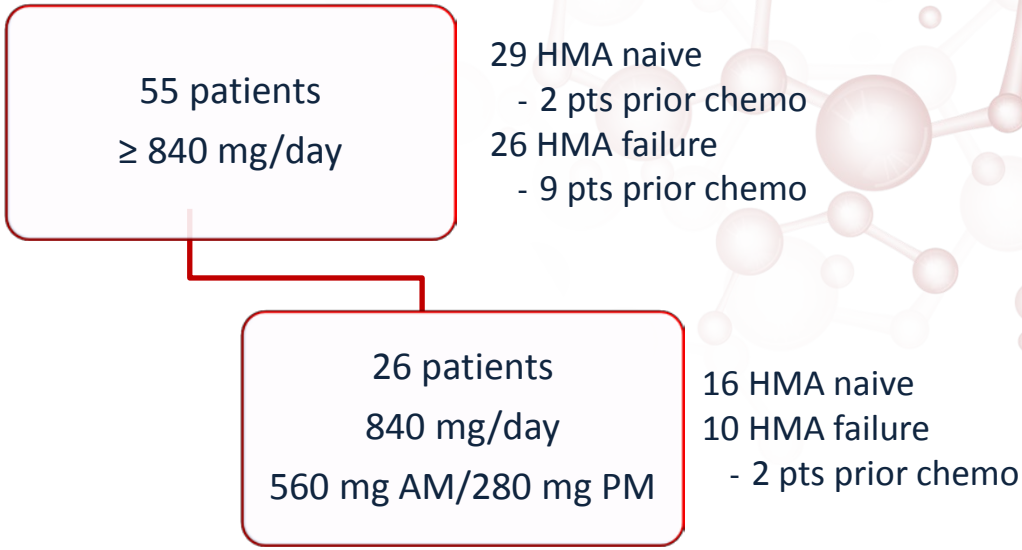
PATIENT CHARACTERISTICS – HR-MDS ≥ 840 MG/DAY

HMA NAIVE & HMA FAILURE

Number of patients treated		74 (%)
Age	Median	69
	Range	42-90
Sex	Male	44 (59)
	Female	30 (41)
IPSS classification	Intermediate-1	24 (32)
	Intermediate-2	26 (35)
	High	21 (28)
	Unknown	3 (4)
IPSS-R classification	Low	3 (4)
	Intermediate	14 (19)
	High	23 (31)
	Very high	33 (45)
	Unknown	1 (1)
Prior HMA therapy	Azacitidine	26 (35)
	Decitabine	6 (8)
	Both	3 (4)

PATIENTS WITH HR-MDS EVALUABLE FOR RESPONSE PER RIGOSERTIB TREATMENT GROUP

HMA NAIVE & HMA FAILURE

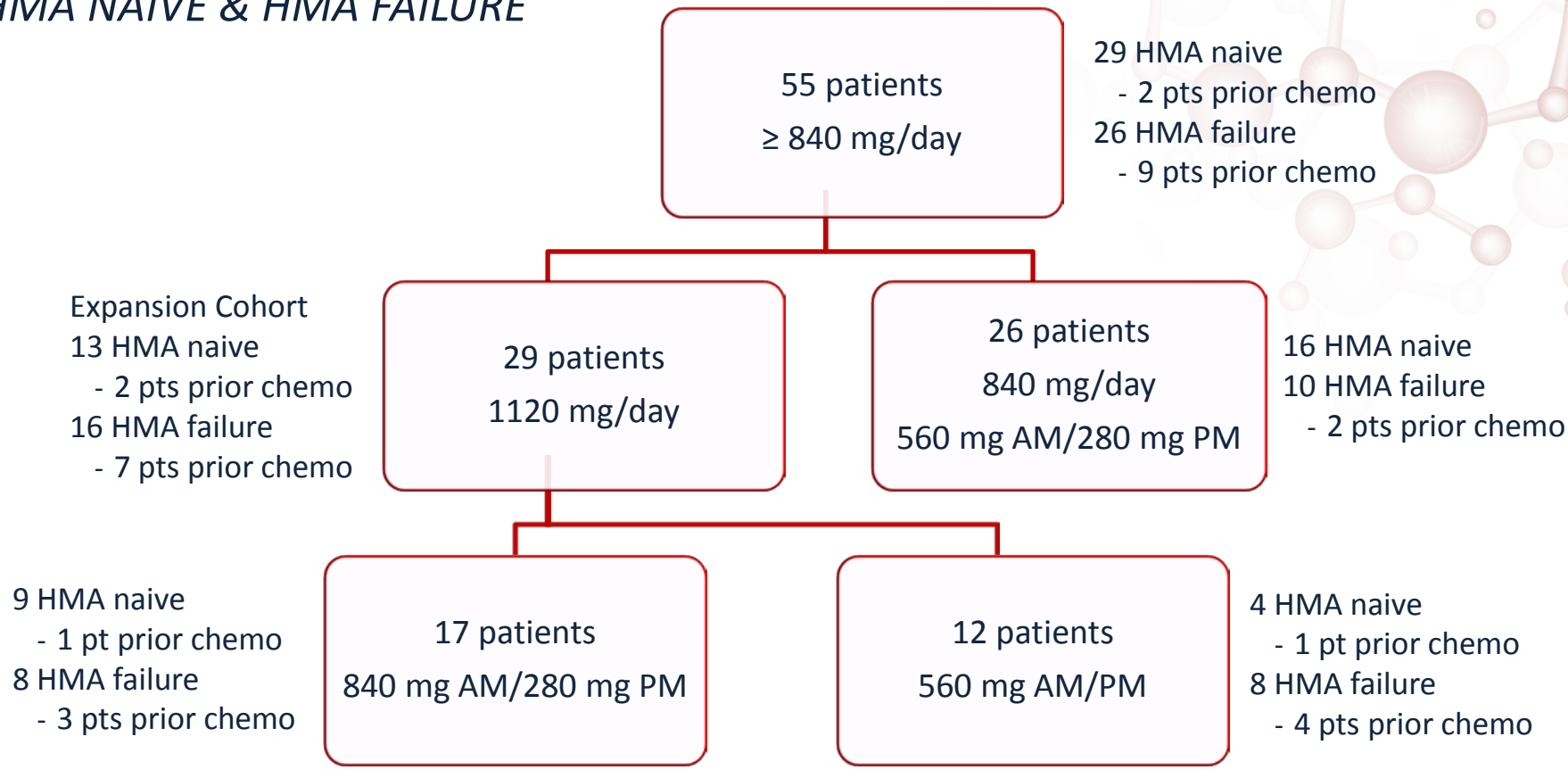


Rationale for Expansion Cohort at a dose of 1120mg/day:

- 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

PATIENTS WITH HR-MDS EVALUABLE FOR RESPONSE PER RIGOSERTIB TREATMENT GROUP

HMA NAIVE & HMA FAILURE



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- Confirm effectiveness of the GU toxicity safety guidelines in additional MDS patients

HMA NAIVE ≥ 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***

HMA FAILURE ≥ 840MG/DAY

EFFICACY

Evaluable for response	26* (%)
Overall response per IWG 2006	14 (54)
CR+PR	2 (8)
Complete remission (CR)	1 (4)
Partial remission (PR)	1 (4)
Marrow CR + Hematologic Improvement	5 (19)
Hematologic Improvement alone	2 (8)
Marrow CR alone	5 (19)
Stable disease	7 (27)
Progression	5 (19)
Median duration of response (months)	10.8 (range, 0.1-11.8+)
Median duration of treatment (months)	4.9 (range, 1.1-20.9+)
Median time to initial/best response (cycles)	2/5

**** Includes 9 patients treated with non-HMA, chemotherapy in addition to HMA***

CYTOGENETICS ≥ 840MG/DAY

	Total Evaluable	Total Responders (%)	HMA naive Responders/ Evaluable (%)	HMA failure Responders/ Evaluable (%)
Very poor cytogenetics (n=17)	11	8 (73)	4/5 (80)	4/6 (67)
Poor cytogenetics (n=9)	5	4 (80)	4/4 (100)	0/1
Intermediate cytogenetics (n=17)	14	9 (64)	7/8 (88)	2/6 (33)
Good cytogenetics (n=29)	25	19 (76)	11/12 (92)	8/13 (62)
Very good cytogenetics (n=0)	-	-	-	-

Baseline cytogenetics on study

TRANSFUSION INDEPENDENCE ≥ 840MG/DAY

	Total evaluable*	Total TI (%)	HMA naive TI/ Evaluable (%)	HMA failure TI/ Evaluable (%)
Low transfusion burden: 1-4 units RBC	33	9 (27)	6/17 (35)	3/16 (19)
High transfusion burden: >4 units RBC	13	1 (8)	0/3	1/10 (10)
All transfusion dependent pts	46	10 (22)	6/20 (30)	4/26 (15)

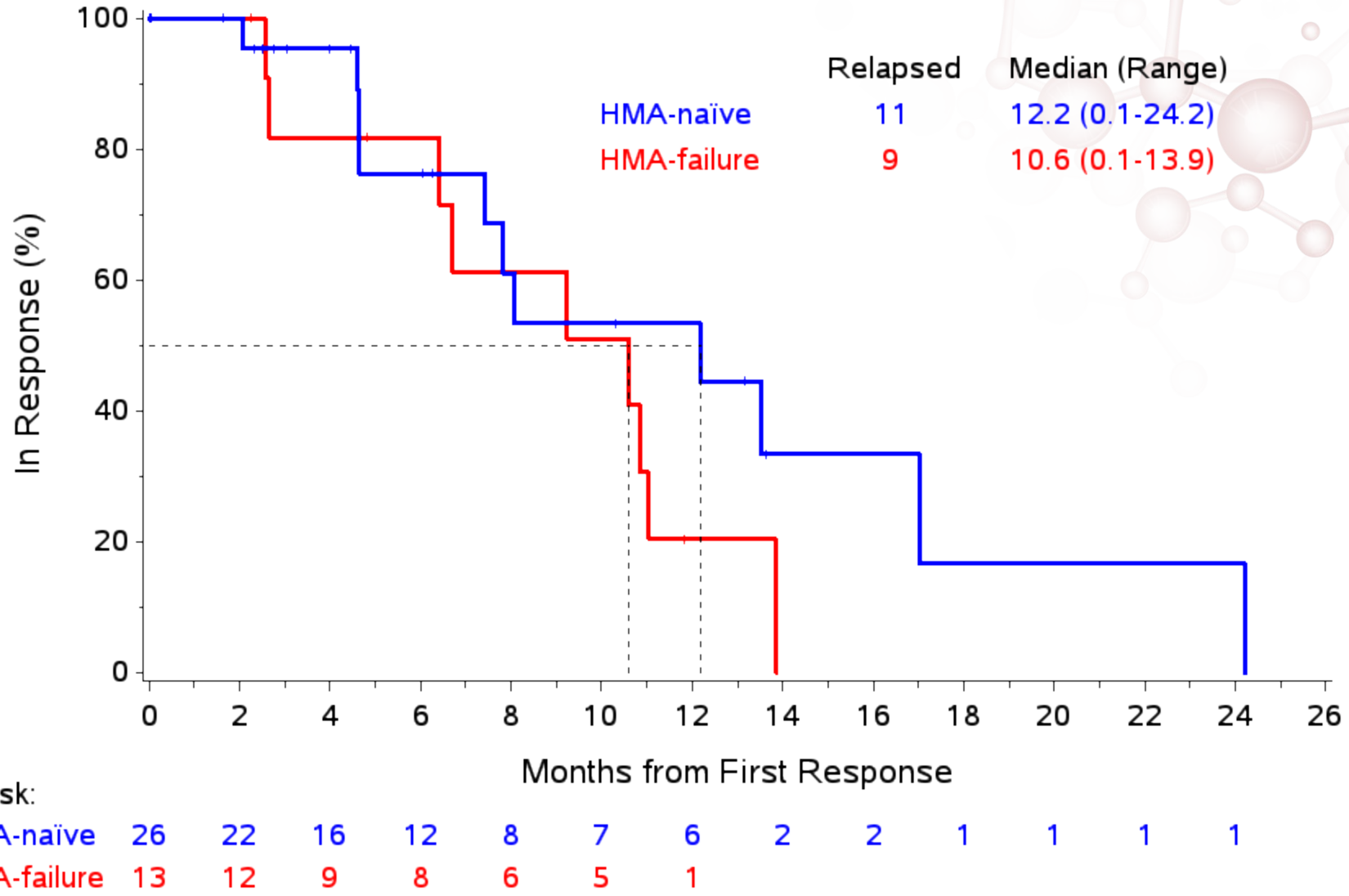
*Patients with RBC transfusions within 8 weeks prior to screening

- Of the 74 treated MDS patients (HMA naive and failure)
  - 28 (38%) were not RBC transfusion dependent
  - 46 (62%) received at least 1 RBC transfusion in the 8 weeks prior to treatment

RESPONSE PER IWG 2006 AMONG MDS IPSS-R SUBGROUPS IN ≥ 840MG/DAY

Response per IWG 2006	Low/Intermediate N=17 (%)	High N=23 (%)	Very high N=33 (%)	Unknown N=1 (%)
Complete remission	4 (24)	2 (9)	5 (15)	0
Partial remission	0	1 (4)	0	0
Marrow CR	5 (29)	8 (35)	10 (30)	0
Stable disease	2 (12)	6 (26)	2 (6)	0
Progression	0	1 (4)	4 (12)	0
Not evaluable	3 (18)	4 (17)	11 (33)	1 (100)
Hematologic improvement	9 (53)	7 (30)	11 (33)	0
Erythroid response	2 (12)	3 (13)	11 (33)	0
Platelet response	6 (35)	6 (26)	10 (30)	0
Neutrophil response	4 (24)	3 (13)	6 (18)	0

DURATION OF THE OVERALL RESPONSE IN ≥ 840MG/DAY



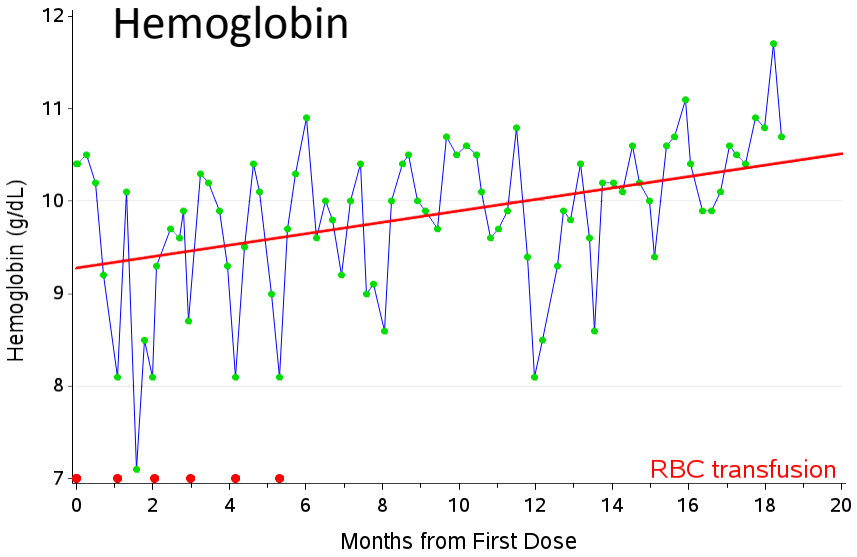
ALL MDS PATIENTS: HMA NAIVE & FAILURE*

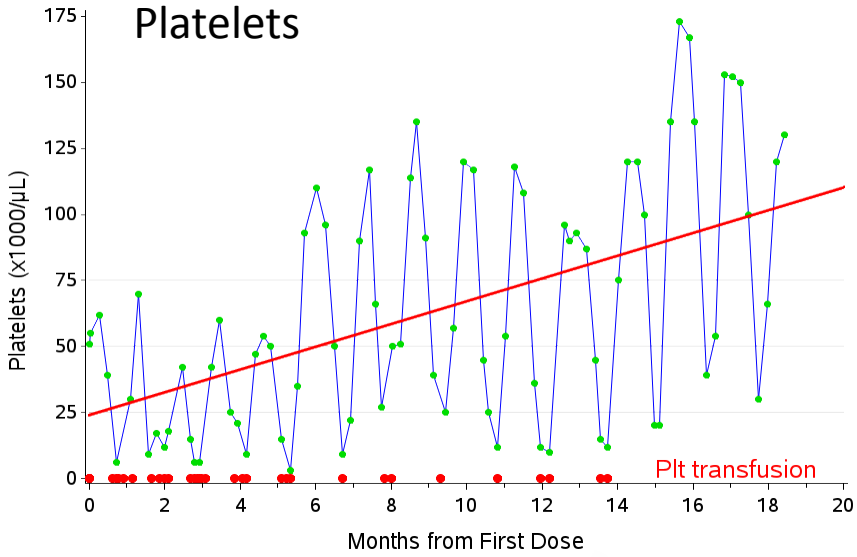
EFFICACY

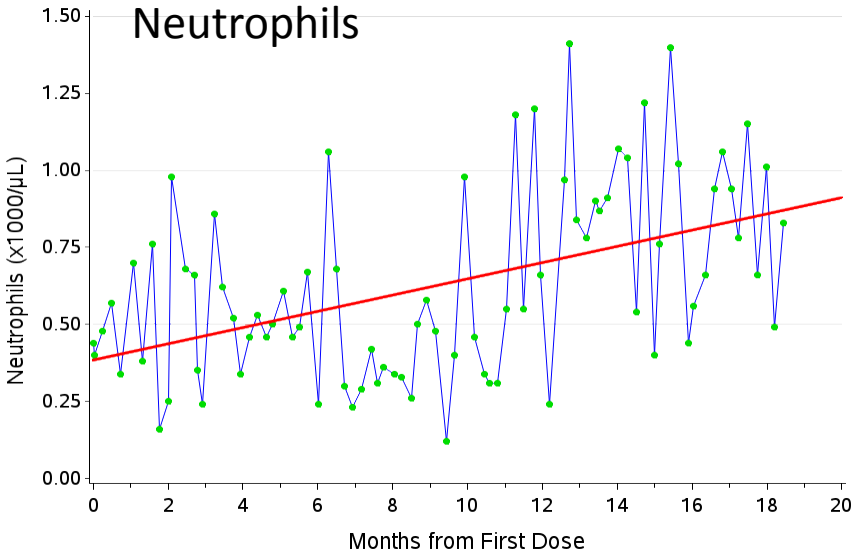
	HMA Naive (%)	HMA Failure (%)
Evaluable for response	33	28
Overall response per IWG 2006	29 (88)	16 (57)
CR+PR	11(33)	3 (11)
Complete remission (CR)	11 (33)	2 (7)
Partial remission (PR)	0	1 (4)
Marrow CR + Hematologic Improvement	6 (18)	6 (21)
Hematologic Improvement alone	3 (9)	2 (7)
Marrow CR alone	9 (27)	5 (18)
Stable disease	4 (12)	8 (29)
Progression	0	4 (14)
Median duration of response (months)	12.2 (range, 0.1-42.2+)	10.8 (range, 0.1-27.9)
Median duration of treatment (months)	7.8 (range, 2.2-40.9)	4.9 (range, 1.1-27.6)
Median time to initial/best response (cycles)	1/4	2/6

Includes 6 patients who received lower doses 280 mg/day - 560 mg/day

HEMATOPOIETIC RESPONSE TO RIGOSERTIB COMBINATION AFTER HMA FAILURE







- 12 cycles of AZA – stable disease
- RBC and platelet transfusion
- Baseline blasts 7%
- Monosomy 7
- Runx-1
- AZA + RIG for 20+ months
- RBC & platelet transfusion independent
- Blasts < 5% - CR achieved following addition of Rigosertib

ADVERSE EVENTS

Treatment Emergent Adverse Events (≥30%) in MDS Patients				
	All MDS (N=79) (%)		≥840mg (N=71) (%)	
MedDRA Preferred Term	All grades	Grade ≥3	All grades	Grade ≥3
Any Event	79 (100)	71 (90)	71 (100)	63 (89)
Constipation	36 (46)	-	31 (44)	-
Hematuria	32 (41)	7 (9)	32 (45)	7 (10)
Diarrhea	32 (41)	4 (5)	29 (41)	4 (6)
Fatigue	32 (41)	2 (3)	29 (41)	2 (3)
Dysuria	28 (35)	7 (9)	27 (38)	7 (10)
Pyrexia	28 (35)	1 (1)	25 (35)	1 (1)
Nausea	27 (34)	-	24 (34)	-

SAFETY MANAGEMENT GUIDELINES FOR GU TOXICITY

COMPARISON OF RIGOSERTIB DOSING GROUPS

	Rigosertib 840mg	Rigosertib 1120mg*
	42 (%)	43 (%)
Patients with hematuria	19 (45)	17 (40)
Patients with grade 1 or 2 hematuria only	14 (33)	15 (35)
Patients with grade 3 hematuria	5 (12)	2 (5)
Patients with dysuria	18 (43)	13 (30)
Patients with grade 1 or 2 dysuria only	13 (31)	10 (23)
Patients with grade 3 dysuria	5 (12)	3 (7)

- **No Gr 4 reported**
- **16 of 23 (70%) patients who experienced ≥ Gr 2 hematuria were successfully managed & continued to receive the doublet on study**

***Safety Management Guidelines for GU toxicity**

2nd RIGO dose must be administered at 3 PM (±1 hour) at least 2 hours after lunch to avoid a nocturnal bladder dwell time	**Oral hydration of at least two liters of fluid per day is encouraged**	**Mandatory bladder emptying prior to bedtime**	**Urine pH approximately 2 hrs after AM dose. Sodium bicarbonate suggested administration of 650 TID if pH tests < 7.5**

CONCLUSIONS

- Oral rigosertib in combination with AZA demonstrated efficacy in both HMA-naive and HMA-refractory MDS 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
- GU toxicity management guidelines are effective and allow patients to continue on combination therapy
- Based on the efficacy data and favorable safety profile, a pivotal Phase III trial in higher-risk HMA naive MDS population is planned

THANKS TO PARTICIPATING PATIENTS AND THEIR FAMILIES, INVESTIGATORS AND RESEARCH STAFF

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