# Phase 2 Expansion Study of Oral Rigosertib Combined with Azacitidine (AZA) in Patients with Higher-Risk (HR) Myelodysplastic Syndromes: Efficacy and Safety Results in HMA Treatment Naive & Relapsed/Refractory Patients

Shyamala Navada, MD

Icahn School of Medicine at Mount Sinai

Guillermo Garcia-Manero, MD, Ehab L. Atallah, MD, M. Nabeel Rajeh, MD, Jamile M. Shammo, MD, Elizabeth A. Griffiths, MD, Samer K. Khaled, MD, Shaker R. Dakhil, MD, David E. Young, MD, Rosalie Odchimar-Reissig, RN, Yesid Alvarado Valero, MD, Maro N. Ohanian, DO, Naveen Pemmaraju, MD, Rosmy B. John, MSN, Patrick S. Zbyszewski, MBA, Manoj Maniar, PhD, Michael E. Petrone, MD, Steven M. Fruchtman, MD, Lewis R. Silverman, MD.

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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.
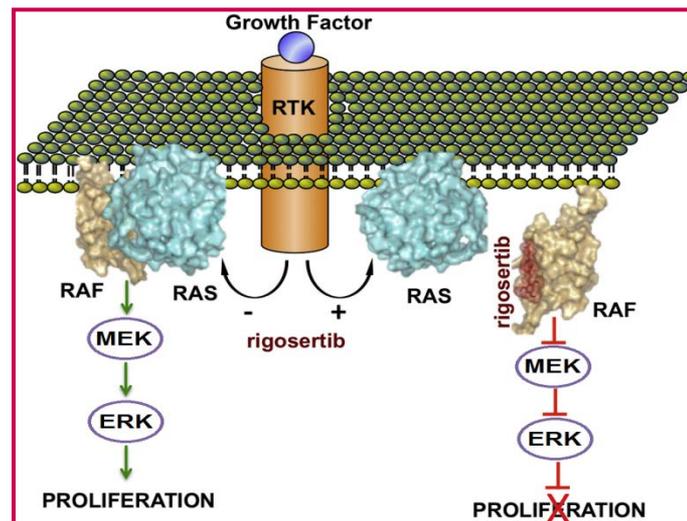
# RIGOSERTIB MECHANISM OF ACTION

- 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]

**Rigosertib**
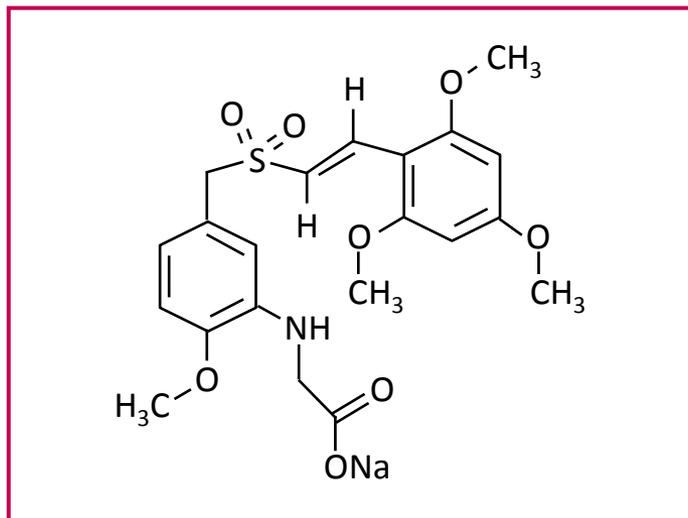


**RAS targeted novel mode of action**



[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

# RIGOSERTIB IS SYNERGISTIC WITH AZACITIDINE IN PRECLINICAL STUDIES

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

| 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 lines

*[a]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.*

# COMBINATION DOSE ADMINISTRATION

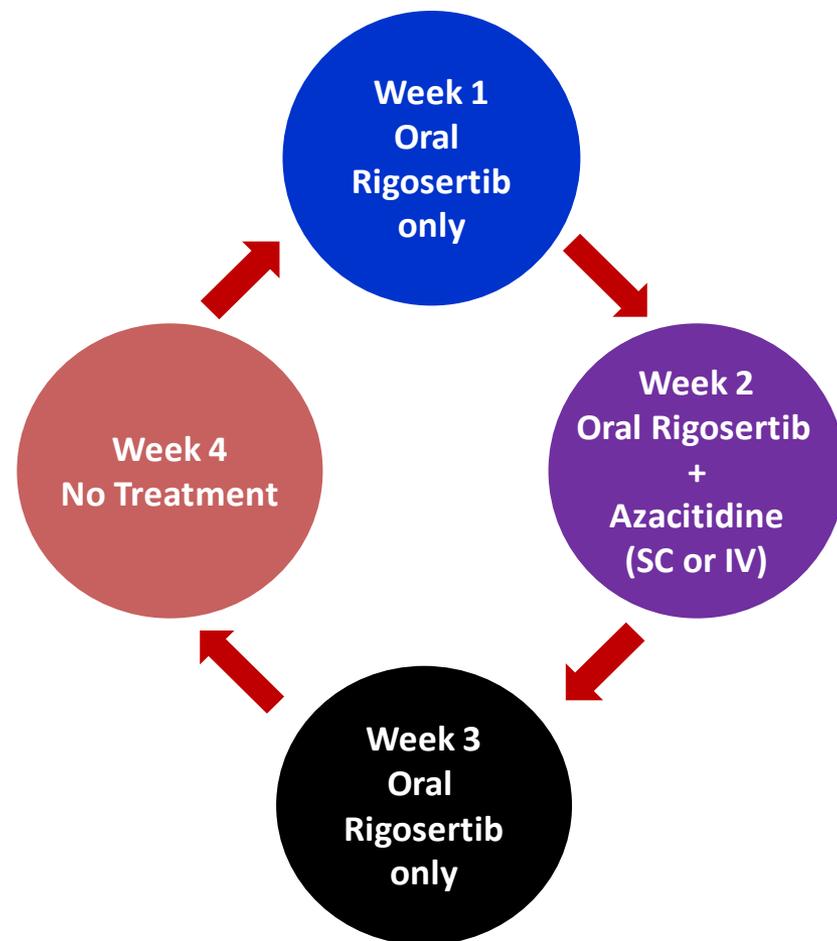*ORAL RIGOSERTIB 840 MG OR 1120 MG IN DIVIDED DOSES*

Week 1: Oral rigosertib twice daily*

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

Week 3: Oral rigosertib twice daily*

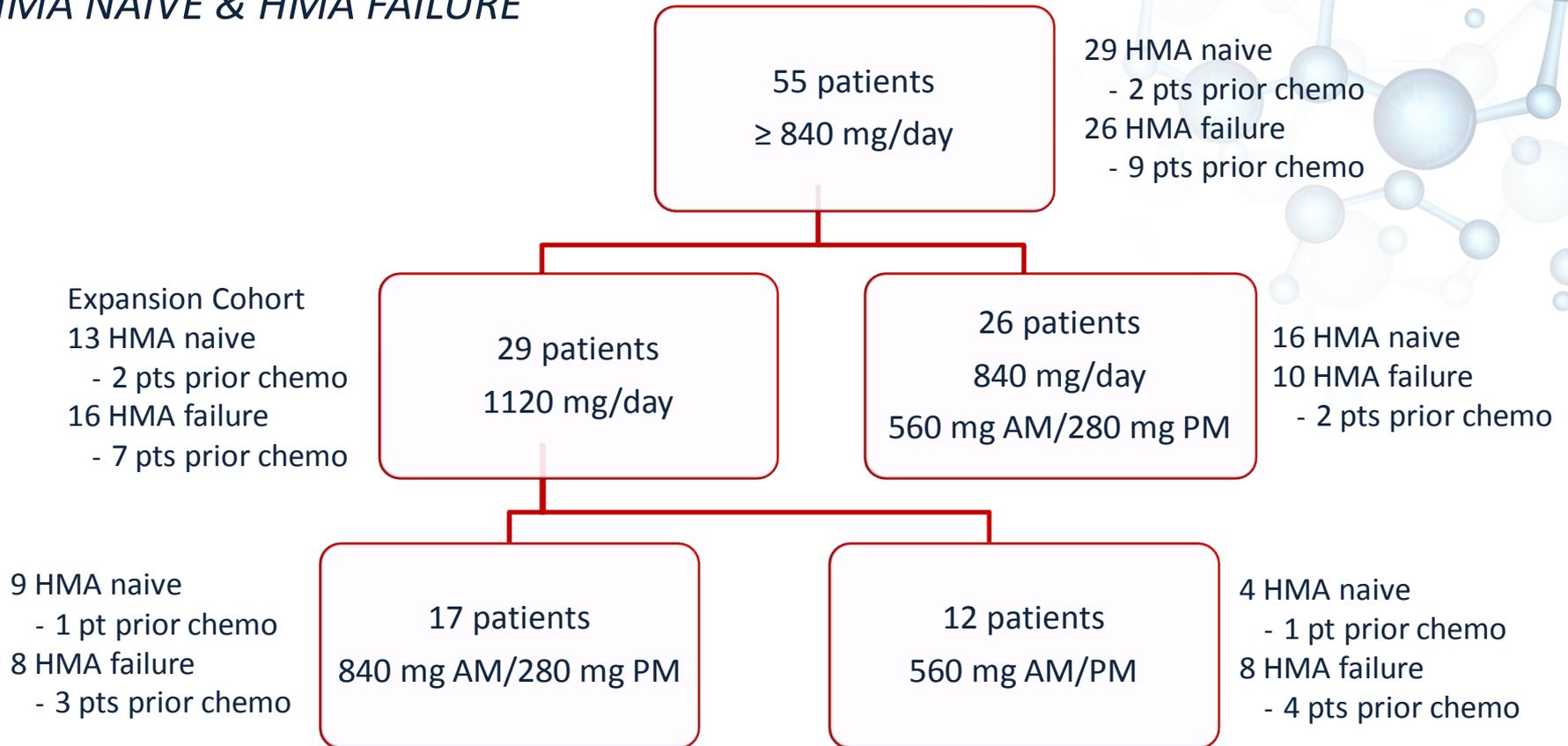Week 4: No treatment

*early AM/mid-afternoon PM

Week 1 Oral Rigosertib only

Week 2 Oral Rigosertib + Azacitidine (SC or IV)

Week 3 Oral Rigosertib only

Week 4 No Treatment

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*

**55 patients**
**≥ 840 mg/day**

29 HMA naive
- 2 pts prior chemo
26 HMA failure
- 9 pts prior chemo

Expansion Cohort
13 HMA naive
- 2 pts prior chemo
16 HMA failure
- 7 pts prior chemo

**29 patients**
**1120 mg/day**

**26 patients**
**840 mg/day**
**560 mg AM/280 mg PM**

16 HMA naive
10 HMA failure
- 2 pts prior chemo

9 HMA naive
- 1 pt prior chemo
8 HMA failure
- 3 pts prior chemo

**17 patients**
**840 mg AM/280 mg PM**

**12 patients**
**560 mg AM/PM**

4 HMA naive
- 1 pt prior chemo
8 HMA failure
- 4 pts prior chemo

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

# HMA NAIVE OR FAILURE 1120 MG/DAY

## *EFFICACY*

| | HMA Naive | HMA Failure |
|---|---|---|
| Evaluable for response | 13* | 16** |
| Overall response per IWG 2006 | 12 (92%) | 8 (50%) |
| CR+PR | 4 (31%) | 2 (12%) |
|     Complete remission (CR) | 4 (31%) | 1 (6%) |
|     Partial remission (PR) | 0 | 1 (6%) |
|     Marrow CR + Hematologic Improvement | 2 (15%) | 3 (19%) |
|     Hematologic Improvement alone | 2 (15%) | 2 (12%) |
|     Marrow CR alone | 4 (31%) | 1 (6%) |
|     Stable disease | 1 (8%) | 3 (19%) |
|     Progression | 0 | 5 (31%) |
| Median duration of response (months) | 13.5 (range, 1.6-13.5+) | 9.2 (range, 0.1-10.2+) |
| Median duration of treatment (months) | 6.7 (range, 3.0-17.1+) | 3.6 (range, 1.1-13.7+) |
| Median time to initial/best response (cycles) | 1/4 | 3/3 |

*2 patients received prior chemotherapy     **7 patients received prior chemotherapy

# 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*

# DURATION OF COMPLETE AND PARTIAL REMISSION
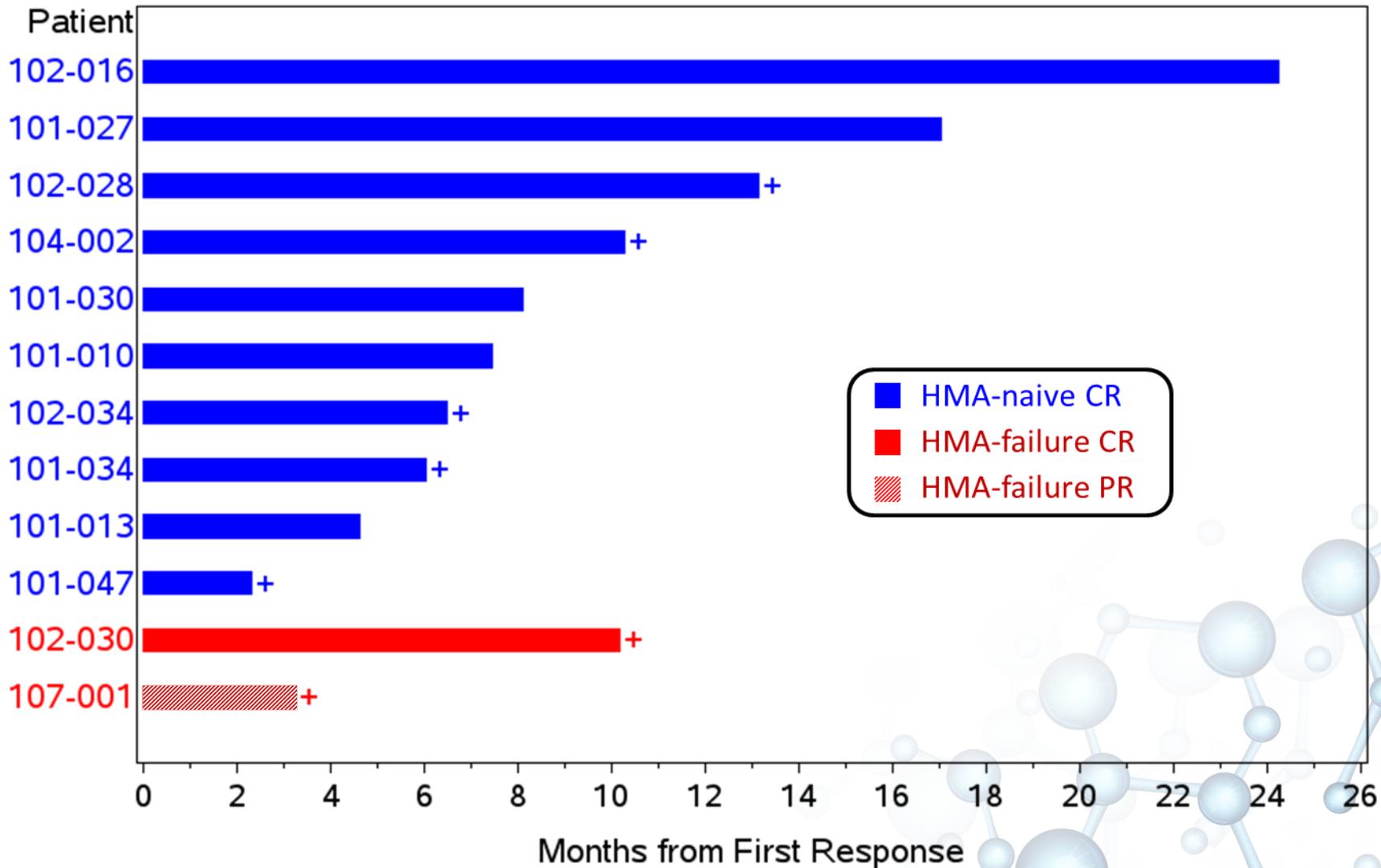


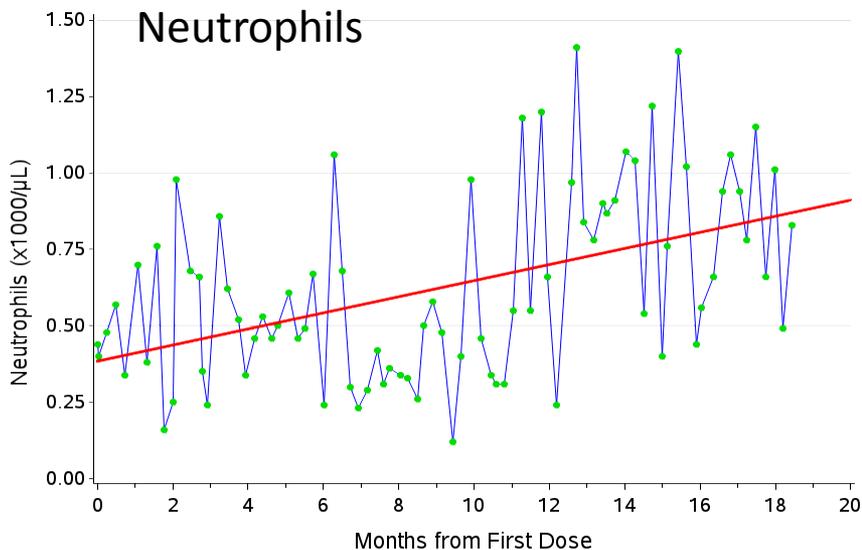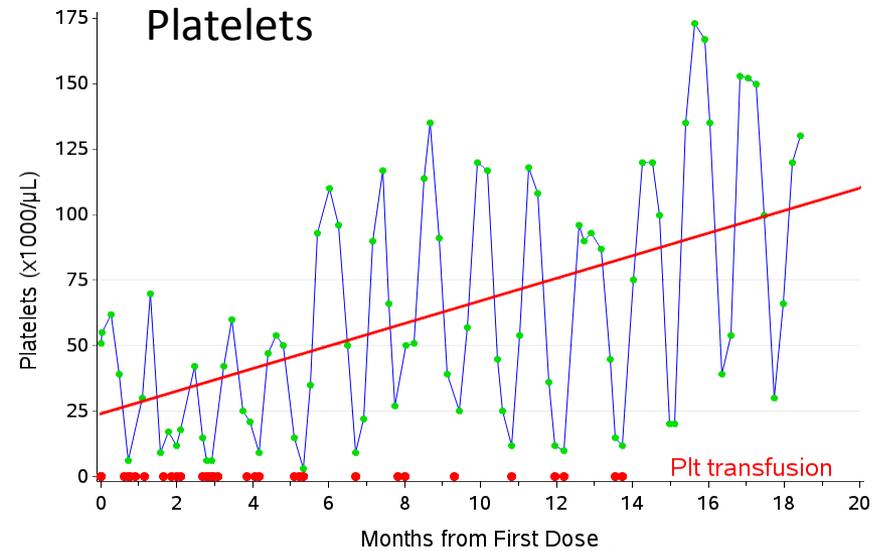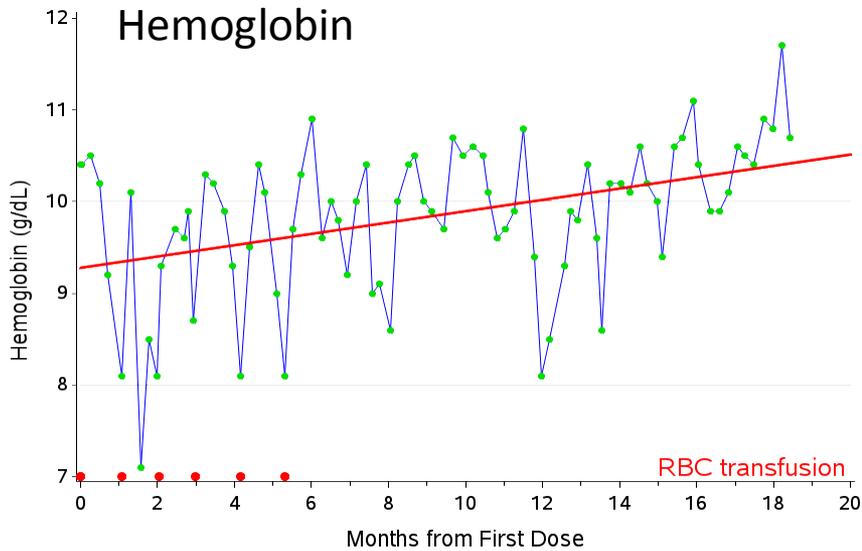*(+) continuing in response or in response at time of censoring*

# DURATION OF THE OVERALL RESPONSE
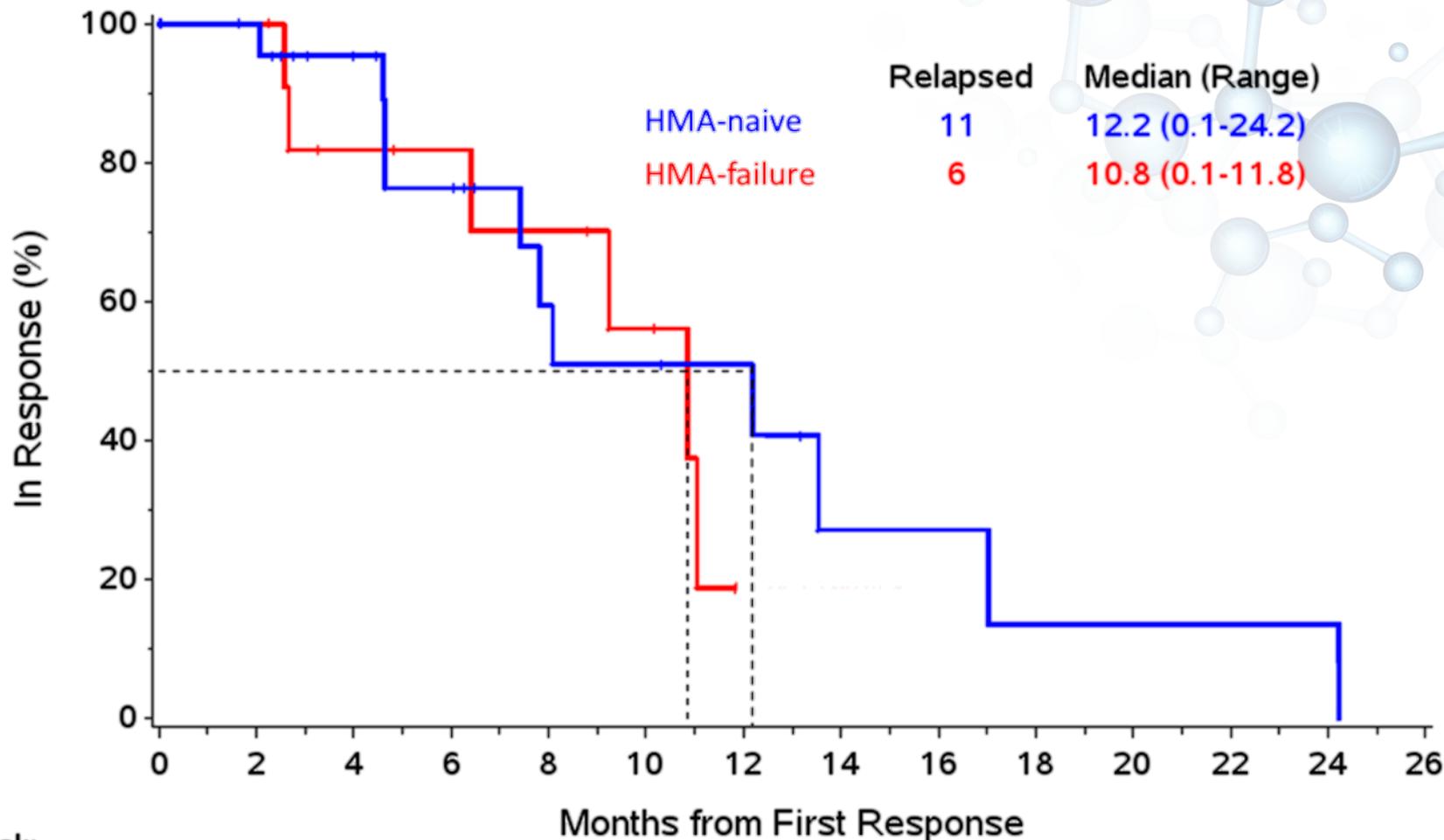
# HEMATOPOIETIC RESPONSE TO RIGOSERTIB COMBINATION AFTER HMA FAILURE



- 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 (N = 74) | | | | |
|---|---|---|---|---|
| | Number (%) of Patients | | | |
| MedDRA Preferred Term | All grades | Grade 1 | Grade 2 | Grade ≥3 |
| Any Event | 74 (100) | 74 (100) | 70 (95) | 65 (88) |
| Hematuria | 33 (45) | 12 (16) | 14 (19) | 7 ( 9) |
| Constipation | 32 (43) | 19 (26) | 13 (18) | - |
| Diarrhea | 31 (42) | 22 (30) | 5 ( 7) | 4 ( 5) |
| Fatigue | 31 (42) | 6 ( 8) | 22 (30) | 3 ( 4) |
| Dysuria | 28 (38) | 15 (20) | 6 ( 8) | 7 ( 9) |
| Pyrexia | 27 (36) | 22 (30) | 4 ( 5) | 1 ( 1) |
| Nausea | 26 (35) | 21 (28) | 5 ( 7) | - |
| Neutropenia | 23 (31) | 2 ( 3) | 1 ( 1) | 20 (27) |
| Thrombocytopenia | 22 (30) | - | 3 ( 4) | 19 (26) |

# SAFETY OPTIMIZATION STRATEGIES
## *COMPARISON OF RIGOSERTIB DOSING GROUPS*

**Safety Optimization Strategies**

| | | | |
|---|---|---|---|
| 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 |

| | Rigosertib 840mg 42 | Safety Optimization Strategies Applied Rigosertib 1120mg 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

# REASONS FOR DISCONTINUATION

| Reason for discontinuation | | N=68* |
|---|---|---|
| | HMA Naive | HMA Failure |
| Progressive Disease | 7 | 12 |
| Toxicity / Adverse Event | 8 | 5 |
| Investigator Decision | 5 | 4 |
| Patient Request | 7 | 2 |
| Bone Marrow Transplant | 5 | 3 |
| No hematological response | 3 | 3 |
| Death | 0 | 2 |
| Disease relapse | 1 | 1 |

*6 patients still on treatment

# 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

- Safety optimization strategies mitigated urinary AEs in the expansion cohort

- Based on the safety and efficacy profile of the combination in MDS, a pivotal Phase III trial is planned in an HMA naive population

# THANKS TO OUR PATIENTS AND THEIR FAMILIES, INVESTIGATORS AND RESEARCH STAFF

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University of Texas MD Anderson Cancer Center, Houston

**Ehab L. Atallah, MD**
Froedtert Hospital & the Medical College of Wisconsin, Milwaukee

**M. Nabeel Rajeh, MD**
Saint Louis University, St. Louis

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Rush University Medical Center, Chicago

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