# Combination of Oral Rigosertib and Injectable Azacitidine in Patients with Myelodysplastic Syndromes (MDS): Results from a Phase II Study

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## BACKGROUND

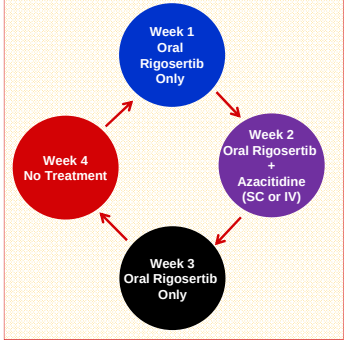
- Azacitidine (AZA) is first-line therapy for patients (pts) with higher-risk MDS.
- Rigosertib interferes with the RAS-binding domains of RAF kinases and inhibits the RAS-RAF-MEK and the PI3Ks pathways.
- In vitro, the combination of rigosertib with AZA synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence–dependent manner (rigosertib administered prior to AZA) (Skidan, AACR 2006).
- Phase I results of this study in pts with MDS or AML showed the combination of oral rigosertib and standard-dose AZA to be well-tolerated with evidence of efficacy (Navada, Blood 2014).

## OBJECTIVES

- To investigate the safety and toxicity of the combination of oral rigosertib and AZA in pts with MDS
- To evaluate the activity of the combination of oral rigosertib and AZA with respect to IWG response and hematologic improvement

## METHODS

- Oral rigosertib was administered twice daily on Day 1-21 of a 28-day cycle.
- Dose was escalated to the recommended Phase II dose (RPTD: 560 mg qAM, 280 mg qPM).
- Azacitidine 75 mg/m$^2$/day SC or IV was administered for 7 days starting on Day 8.
- A CBC was performed weekly and a bone marrow aspirate and/or biopsy was done at baseline, on Day 29, and every 8 weeks thereafter.




## RESULTS

**Demographics**
- The combination of oral rigosertib and AZA has been administered to 40 pts with MDS.
- Pts were classified into the following MDS risk categories per the IPSS (Greenberg et al, Blood 1997): intermediate-1 (12 pts), intermediate-2 (15 pts), high-risk (13 pts).
- Median age was 66 years; 73% of pts were male; and ECOG performance status was 0 or 1 in 95% of pts.
- Prior HMA treatment consisted of azacitidine (12 pts), decitabine (4 pts), and both (1 pt).

**Efficacy**
- The 33 MDS pts who were evaluable for response have received 1-37+ cycles of study treatment (median, 6 cycles).
- Overall responses according to IWG criteria (Cheson, Blood 2006) were observed in 25 (76%) of the 33 evaluable pts with MDS (Table 1).
- When overall response is defined as CR plus PR plus HI, defined here as Clinical Benefit Response, 58% of all evaluable pts and 70% of the evaluable HMA-treatment-naïve pts demonstrated responses.
- Median duration of response was 7.4 months for erythroid response, 8 months for platelet response, and 6.2 months for neutrophil response·
- Median duration of remission (CR, PR) was 8 months for the combination compared to the 3.2 months reported for AZA alone (Fenaux et al for the international Vidaza High risk MDS survival study group, Lancet Oncology 2009, 10:223-232)

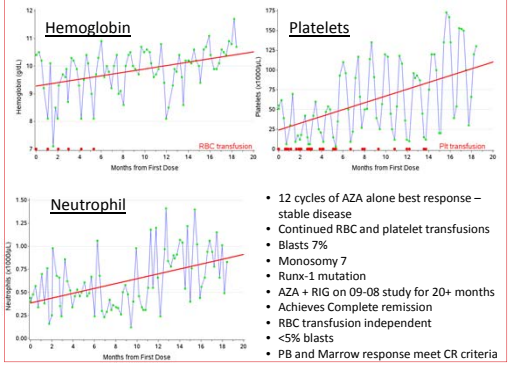
**Safety**
- The most common treatment-emergent adverse events were constipation, diarrhea, nausea, haematuria, dysuria, and fatigue (Table 3); the most common serious AEs were febrile neutropenia (10%), urinary tract infection (10%), pneumonia (8%), pneumonia fungal (8%), and acute renal failure (8%).

**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) | - |
| Diarrhoea | 17 (43) | 1 (3) |
| Nausea | 17 (43) | - |
| Haematuria | 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

**Hematology Trends for Patient 101-006**




- 12 cycles of AZA alone best response – stable disease
- Continued RBC and platelet transfusions
- Blasts 7%
- Monosomy 7
- Runx-1 mutation
- AZA + RIG on 09-08 study for 20+ months
- Achieves Complete remission
- RBC transfusion independent
- <5% blasts
- PB and Marrow response meet CR criteria

**Table 1: Response per IWG 2006**

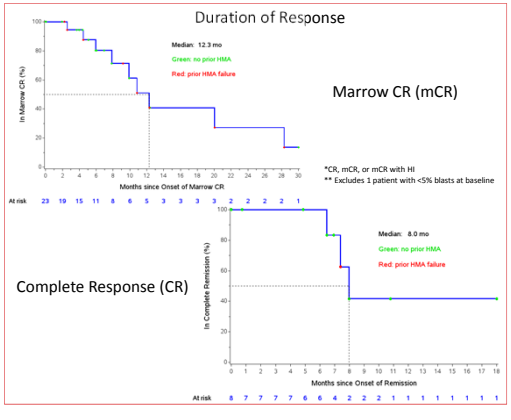
| | Overall evaluable (N=33) | No prior HMA (N=20) | HMA resistant (N=13) |
|---|---|---|---|
| Complete Remission | 8 (24%) | 7 (35%) | 1 (8%) |
| Partial Remission | 0 | 0 | 0 |
| Marrow CR + Hematologic Improvement (HI) | 10 (30%) | 6 (30%) | 4 (31%) |
| Marrow CR alone | 6 (18%) | 3 (15%) | 3 (23%) |
| Hematologic Improvement alone | 1 (3%) | 1 (5%) | 0 |
| Stable Disease | 8 (24%) | 3 (15%) | 5 (38%) |
| Overall IWG Response | 25 (76%) | 17 (85%) | 8 (62%) |
| Clinical Benefit Response | 19 (58%) | 14 (70%) | 5 (38%) |

HMA resistant = Primary refractory or relapsed after treatment with hypomethylating agents

**Table 2: Response per IWG 2006 Criteria by IPSS-R* Subgroup**

| | Low N=3 | Intermediate N=5 | High N=15 | Very High N=13 | Unknown N=4 |
|---|---|---|---|---|---|
| Response per IWG 2006 | | | | | |
| CR | 1 (33) | 2 (40) | 2(13) | 3(23) | 0 |
| mCR | 1 (33) | 1(20) | 6 (40) | 6 (46) | 2(50) |
| SD | 1 (33) | 1 (20) | 4 (27) | 1 (8) | 1(25) |
| PD | 0 | 0 | 0 | 0 | 0 |
| NE | 0 | 0 | 3(20) | 3 (23) | 1(25) |
| Hematologic Improvement | | | | | |
| Erythroid Response | 0 | 2(40) | 5(33) | 6(46) | 0 |
| Platelet Response | 1(33) | 2(40) | 5(33) | 6(46) | 1(25) |
| Neutrophil Response | 1(33) | 3(60) | 5(33) | 4(31) | 0 |
| Overall Response | 2(66) | 4(80) | 8(53) | 9(69) | 2(50) |

*International Prognostics Scoring System-Revised (Greenberg, Blood 2012)




## CONCLUSIONS

- Oral rigosertib in combination with AZA demonstrates an overall response rate of 76% in pts with MDS, including an 85% response rate among pts who had not previously been treated with an HMA, and a 62% response rate among pts with prior HMA failure.
- The combination was well-tolerated in pts with MDS. Repetitive cycles of the combination can be safely administered without evidence of cumulative toxicity. Addition of rigosertib does not substantially change the adverse event profile of single agent azacitidine and thus may overcome the limitations identified in other HMA based combination studies.
- The CR rate in HMA naïve patients is higher and responses occur more rapidly with the combination than with single agent AZA
- Further exploration of this combination is warranted in a randomized trial in defined MDS populations.

## REFERENCES

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