# Overall Survival (OS) and Baseline Disease Characteristics in MDS Patients with Primary HMA Failure in a Randomized, Controlled, Phase III study of Rigosertib

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## INTRODUCTION

**ONTIME was a randomized (2:1) study of rigosertib (RIG) vs best supportive care (BSC, including optional low-dose ARA-C) in 299 pts with HR-MDS who had relapsed after, failed to respond to, or progressed during hypomethylating agents (HMAs). For pts who fail HMAs, there are no approved therapies. Thus, an unmet medical need exists for effective second-line therapies. ONTIME showed a significant treatment effect with RIG in the subgroup of patients with "primary HMA failure."** (Prebet et al, Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 2011; 29:3322-27)

## AIMS

**To describe differences in OS after primary or secondary HMA failure in 299 pts treated with RIG (N=199) or BSC (N=100) in this Phase III study.**

## METHODS

**We evaluated the correlation between baseline disease characteristics and OS in pts with primary HMA failure (RIG N=117; BSC N=52) as ascertained by a centralized, blinded reader.**

## RESULTS

**Pts with primary HMA failure were generally male, age 50-86 years, at high or very high risk per IPSS-R, with 5-19% bone marrow blast count, and duration of last HMA 0.2-42.1 months (Table 1). A meaningful difference in median OS between RIG and BSC was observed not only in the overall population of pts with primary HMA failure (Figure) but also in several subgroups (Table 2).**

**Overall, adverse events (AEs) were reported in 99% of RIG pts and 88% of BSC pts. The following AEs >=Grade 3 were reported by ≥ 10% of pts: anaemia, thrombocytopenia, neutropenia, febrile neutropenia, pneumonia, febrile neutropenia, and MDS (Table3).**

**Table 1: Pretreatment Patient Characteristics for Patients with Primary HMA Failure**

| | Rigosertib N = 117 | BSC N = 52 |
|---|---|---|
| Gender | | |
| Female | 37 (32) | 15 (29) |
| Male | 80 (68) | 37 (71) |
| Age (yr) | | |
| Median | 73 | 74 |
| Range | 50 - 86 | 55 - 86 |
| Revised IPSS score | N=105 | N=43 |
| Low | 1 (1) | 0 |
| Intermediate | 7 (6) | 5 (10) |
| High | 42 (36) | 17 (33) |
| Very High | 55 (47) | 21 (40) |
| Bone marrow blasts | N-117 | N-51 |
| 5% -10% | 39 (33%) | 13 (25%) |
| 11% -19% | 54 (46%) | 23 (44%) |
| 20% - 30% | 24 (21%) | 15 (29%) |
| Duration of last HMA | | |
| Median (months) | 6.7 | 6.0 |
| Range | 0.2 – 38.9 | 0.8 – 42.1 |

**Overall Survival pf Patients with Primary HMA Failure**

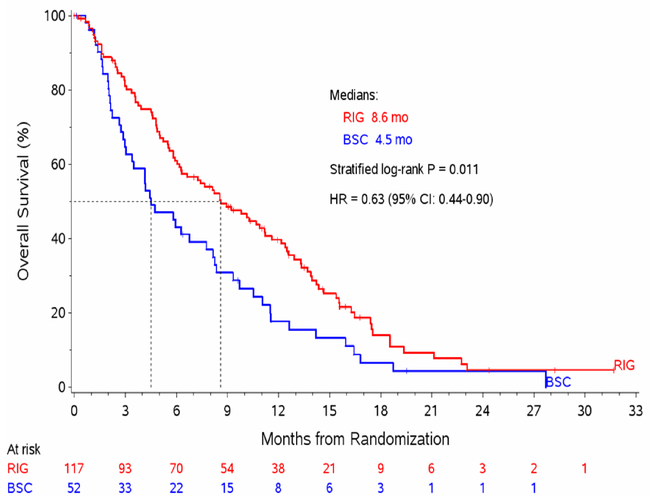


**Table 2: Median (months) Overall Survival by Baseline Disease Characteristics in Pts with Primary HMA Failure**

| Characteristic | Rigosertib N | Rigosertib OS | BSC N | BSC OS | Log-rank p-value | Hazard ratio (RIG/BSC) (95% CI) |
|---|---|---|---|---|---|---|
| All patients with Primary HMA Failure | 117 | 8.6 | 52 | 4.5 | 0.011 | 0.63 (0.44-0.90) |
| IPSS-R category of high or very high risk | 97 | 8.6 | 38 | 4.1 | 0.0015 | 0.52 (0.35-0.79) |
| Bone marrow blast 5%-19% | 93 | 10.1 | 36 | 4.7 | 0.0079 | 0.58 (0.39-0.87) |
| Duration of prior HMA treatment < 9 months | 79 | 8.6 | 37 | 4.5 | 0.0014 | 0.49 (0.31-0.76) |

**Table 3: Adverse Events ≥ Grade 3 Reported for ≥ 5% of Pts in Either Treatment Group**

| | Rigosertib N=184 | | BSC N=91 | |
|---|---|---|---|---|
| | All Grades | ≥Grade 3 | All Grades | ≥Grade 3 |
| **Patients with any TEAE*** | 183 (99) | 145 (79) | 77 (85) | 62 (68) |
| Anaemia | 42 (23) | 34 (18) | 8 (9) | 7 (8) |
| Thrombocytopenia | 38 (21) | 35 (19) | 7 (8) | 6 (7) |
| Neutropenia | 32 (17) | 30 (16) | 7 (8) | 7 (8) |
| Pneumonia | 27 (15) | 22 (12) | 13 (14) | 10 (11) |
| Febrile neutropenia | 22 (12) | 22 (12) | 10 (11) | 10 (11) |
| Myelodysplastic syndrome | 20 (11) | 20 (11) | 19 (21) | 18 (20) |

*AEs that occur or worsen on or after first study treatment or first visit

## CONCLUSION

**Patients with primary HMA treatment failure and certain subgroups identifiable on the basis of baseline disease characteristics randomized to RIG showed an improvement in OS compared to BSC. Such characteristics should be considered in the design of future trials in second-line in primary HMA failure patients.**

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