SUBGROUP ANALYSES OF A PHASE 3 STUDY IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES FAILING HMA TREATMENT: IDENTIFICATION OF A HOMOGENEOUS POPULATION WHO BENEFIT FROM RIGOSERTIB THERAPY

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INTRODUCTION

- Myelodysplastic syndrome (MDS) is heterogeneous, with varying categories and prognosis as defined by the Revised International Prognostic Scoring System (IPSS-R; Greenberg 2012). Patients with higher IPSS-R scores have worse clinical outcomes; those with Very High Risk (VHR) IPSS-R have the worst prognosis, with most dying of bone marrow failure complications.
- ONTIME was the first randomized study in patients with MDS failing hypomethylating agents (HMAs), with overall survival (OS) as the primary endpoint. ONTIME enrolled RAEB-1, RAEB-2, RAEB-t and CMML patients previously treated with HMAs, with marrow blast count at entry of 5-30%. Thus, it included a heterogeneous population of MDS patients. When the study was designed, little information was available regarding the prognosis for patients with MDS failing HMAs. Subsequently, Prebet and others showed a short survival expectancy (<6 months) for these patients (Prebet, JCO 2011; Jabbour, Cancer 2010).
- ONTIME demonstrated a 2.3-month benefit in median OS (mOS) in the ITT population that was not statistically significant (8.2 mo rigosertib vs 5.9 mo BSC; p=0.33; HR=0.87; n=299). The study was well-balanced, permitting post-hoc analyses of OS in defined subgroups of patients, including those with the worst prognosis, based on the (i) types of failures of HMA therapy, (ii) duration of exposure to HMA therapy, (iii) prognostic risk categories per the IPSS-R, and (iv) cytogenetic aberrations.
- We sought to identify MDS subtypes who may benefit from rigosertib for a future clinical trial by defining a prospective patient population based on data from ONTIME and biological rationale.

Table 1. Survival analysis of ONTIME: ITT and selected subgroups

	Rigosertib		BSC			
	N	Median (months)	N	Median (months)	Log-rank *P*-value	Hazard Ratio (Rigosertib/BSC) (95% CI)
All patients (ITT)	199	8.2	100	5.9	0.33	0.87 (0.67–1.14)
AZA Response Classification						
Primary AZA Failure*	**94**	**8.6**	**43**	**4.6**	**0.032**	**0.65 (0.44–0.97)**
Secondary AZA Failure*	48	5.5	24	6.8	0.87	1.05 (0.58–1.89)
Duration of last HMA Therapy						
≤ 9 months	**103**	**7.7**	**46**	**4.5**	**0.0025**	**0.55 (0.37-0.81)**
> 9 months	96	9.2	52	8.1	0.42	1.18 (0.79-1.74)
IPSS-R Risk Category						
Intermediate	14	9.1	14	12.6	0.48	1.39 (0.56-3.47)
High	67	9.7	26	9.7	0.93	1.03 (0.61-1.74)
Very High	**93**	**7.6**	**41**	**3.2**	**0.005**	**0.56 (0.37-0.84)**
Unknown	24	8.2	19	6.3	0.79	0.90 (0.44-1.82)
Karyotype Aberration						
Normal	68	9.7	31	9.8	0.86	1.05 (0.64-1.72)
5q deletion	39	5	13	3.4	0.38	0.74 (0.37-1.46)
7q deletion	18	4.5	5	2.7	0.31	0.50 (0.13-1.93)
20q deletion	14	8.7	8	3.9	0.62	0.77 (0.27-2.19)
Monosomy 7	**16**	**5.6**	**13**	**2.8**	**0.0033**	**0.24 (0.09-0.66)**
Trisomy 8	**22**	**9.5**	**8**	**4.5**	**0.035**	**0.34 (0.12-0.95)**
Complex Karyotypes	39	4.9	21	3	0.96	0.99 (0.54-1.80)
Other Karyotypes	22	8.2	9	11.5	0.33	1.54 (0.64-3.69)

*Prebet (2011)

Figure 1. Overall survival in study ONTIME (ITT population)

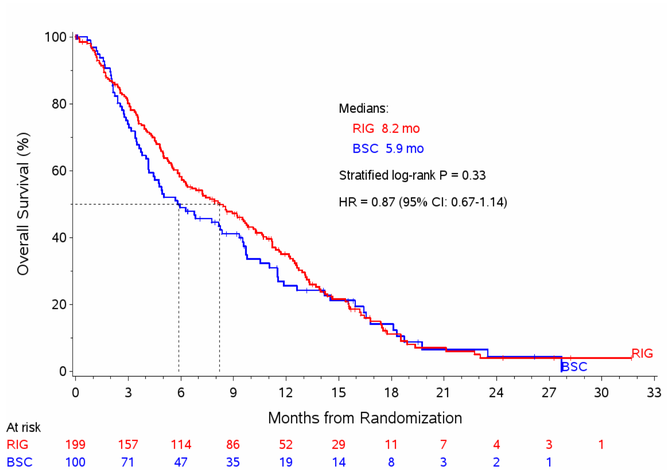


Figure 2. VENN diagram of VHR/IPSS-R, monosomy 7 and trisomy 8 populations of study ONTIME

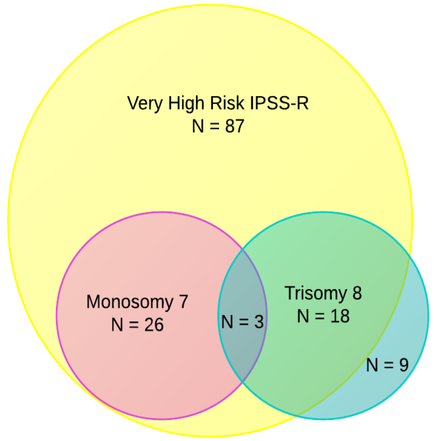
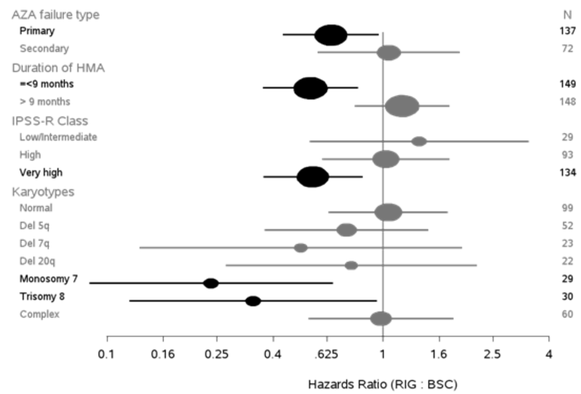


Figure 3. Forest plot of selected subgroups of study ONTIME



METHODS

Distribution of OS in each risk category and each arm was estimated by Kaplan-Meier method and log-rank test was used for treatment effect. Hazard ratio was estimated by Cox regression.

CONCLUSION

- We conducted in-depth analysis of ONTIME, and found that patients with the worst prognosis at entry, and thus with the greatest unmet medical need, appeared to benefit most from rigosertib treatment; namely, those with Primary AZA Failure, VHR- IPSS-R, and monosomy 7. The analyzed duration of prior HMA treatment inversely correlated with survival benefit.
- Based on these results, a new randomized prospective controlled study in this high-risk MDS patient population comparing rigosertib to physician's choice will be conducted to confirm these important observations.

REFERENCES

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