Randomized Phase III Study of IV Rigosertib vs Best Supportive CARE (BSC) in Patients with Higher-risk MDS (HR-MDS) After Failure of Hypomethylating Agents (HMAs)

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INTRODUCTION

- After failure of HMAs, patients (pts) with HR-MDS have very poor prognosis, with a median survival of 6 months and no approved therapy options[1,2]
- Rigosertib is a novel dual PI3K/PLK pathway inhibitor that targets the RAS binding domain of signaling proteins.
- ONTIME was the first Phase III, randomized, controlled study in pts after failure of HMAs.

METHODS

- Pts with HR-MDS (<30% bone marrow blasts) were randomly assigned 2:1 to receive rigosertib or best supportive care (BSC).
- Rigosertib was administered at 1800 mg/24 hr for 72 hr as a continuous intravenous (CIV) ambulatory infusion, every 2 weeks for the first 16 weeks, and then every 4 weeks.
- Primary endpoint was overall survival (OS).
- Analysis based on 242 deaths (≥80% maturity) with median follow-up of >18 months.

RESULTS

Patient Characteristics

The study enrolled 299 HR-MDS pts who had failed to respond to (25%), progressed on (37%), or relapsed after (38%) HMA treatment. Overall, the 2 arms were balanced in terms of baseline characteristics, with the majority of pts being male (66%), and White (82%). Median age was 74 years. The majority of pts (85%) had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. The median duration of the last HMA therapy was 8.8 months (mo) for rigosertib and 10.3 mo for BSC.

Efficacy

The study did not show a statistically significant difference between rigosertib and BSC in overall survival (Figure 1). However, several subgroups were correlated with better OS, including pts classified as "primary HMA failure" (ie, they failed to respond to or progressed during HMA therapy, as defined by Prebet[1]), pts with duration of HMA treatment < 9 mo, pts < 75 years of age, and pts with very high risk per IPSS-R (Table 1).

Figure 1. ONTIME Trial: Primary Efficacy Results in Intention-to-Treat Population

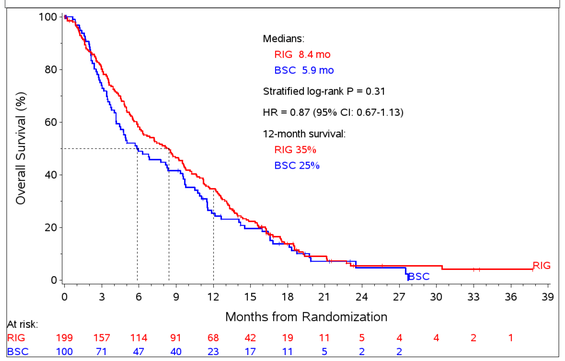

Table 1. ONTIME Trial: Subgroups Correlated with Better Survival

	Rigosertib		BSC		Hazard Ratio (95% CI)	p-value
	N	Median (mos)	N	Median (mos)		
Primary HMA failure	127	8.6	57	5.3	0.69 (0.49-0.98)	0.040
Duration of prior HMA < 9 mos	103	7.7	46	4.5	0.55 (0.37-0.81)	0.003
Age < 75 years	104	9.7	54	4.1	0.52 (0.35-0.75)	0.0004
Very high risk per IPSS-R	93	7.6	41	3.2	0.56 (0.37-0.84)	0.005

Safety

No obvious differences between rigosertib and BSC were found in the incidence of AEs or of ≥ Grade 3 AEs (Table 2). Median dose intensity was 92%. Protocol-defined dose reductions were reported in 5% of pts, with 24% experiencing dose delays of >7 days, mostly due to unrelated adverse events (AEs). Rigosertib had low myelotoxicity in ONTIME, which is consistent with previous clinical experience. There were no significant compliance or operations issues related to the ambulatory continuous infusion.

Table 2. ONTIME Trial: Most Common Treatment-emergent AEs and AEs ≥ Grade 3

	Percentage of Patients			
	Rigosertib (N = 184)		BSC (N = 91)	
	All Grades	≥Grade 3	All Grades	≥Grade 3
Patients with any TEAE	99%	79%	85%	68%
Nausea	35%	2%	18%	-
Diarrhea	33%	2%	20%	-
Constipation	31%	1%	11%	1%
Fatigue	30%	4%	18%	1%
Pyrexia	27%	1%	21%	-
Anemia	23%	18%	9%	8%
Edema peripheral	21%	1%	16%	-
Thrombocytopenia	21%	19%	8%	7%

CONCLUSION

The primary endpoint of OS was not statistically significant in the ITT population, but rigosertib-related improvement in OS was noted in several subgroups of MDS pts, including those with "primary HMA failure" and those with Very High Risk per IPSS-R. Continuous IV therapy with rigosertib had a favorable safety profile in this orphan population of elderly pts with MDS. These results suggest that rigosertib is most effective in, and can be safety administered to, patients who might be expected to have the worst prognosis.

REFERENCES

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2. Jabbour E, Garcia-Manero G, Batty N, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. Cancer 2010;116:3830-4.