Relationship of bone marrow blast (BMBL) response to overall survival in a multi-center study of rigosertib in patients with myelodysplastic syndrome with excess blasts progressing on or after treatment with a hypomethylating agent

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BACKGROUND

No therapies are approved for MDS after HMA failure. Study 04-24 was a single-arm study to evaluate best BMBL response as a potential surrogate for overall survival (OS) in higher-risk (HR) MDS patients who progressed on or after an HMA. Rigosertib is a small molecule that inhibits RAS-Mediated Transformation and Tumor Growth.[1]

METHODS

Eligible MDS patients had 5-30% BMBL confirmed within 6 wks pre-study and progression per International Working Group (IWG) 2006 criteria on or after HMAs within 2 yrs. Rigosertib 1800 mg/24 hrs was continuously infused over 72 hrs q 2 wks × 8 cycles, then q 4 wks until progression or unacceptable toxicity. Primary endpoint was relationship of best BMBL IWG response to OS by Kaplan Meier method. Bone Marrow Blast Response as a predictor for survival from the 04-24 Study was combined with the prior 04-21 study for a more robust analysis.

PATIENT CHARACTERISTICS

Sixty-four (64) patients were treated (median 5 cycles, range 1-32+), with 61% male, median age 73 (range 47-87) (Table 1), median prior HMA duration 10.8 mos (range 1.2-70.2). The majority (59%) of patients (38) had an ECOG performance status of 1, the remaining 19 patients or 30% 0, and 7 patients or 11%.[2]

Table 1. Patient characteristics

	N=64
Sex	
Female	25(39)
Male	39(61)
Median Age (range)	73 (47-87)
Revised International Prognostic Scoring System	
Low	1(2%)
Intermediate	7(11%)
High	17(27%)
Very high	34(53%)
Unknown	5(8%)

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Figure 1. Study 04-24 – Survival by Best Bone Marrow Blast Response

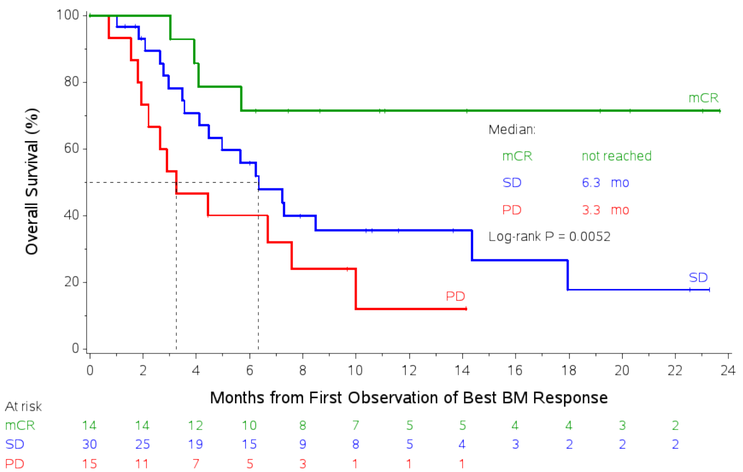
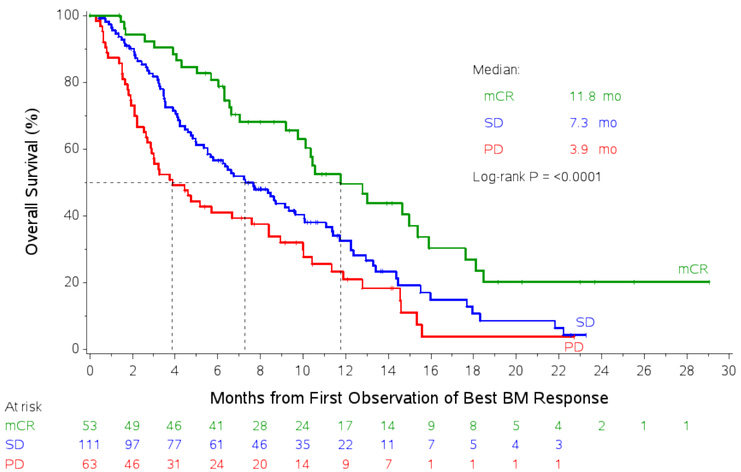


Figure 2. Studies 04-21 and 04-24 – Survival by Best Bone Marrow Blast Response



RESULTS

At the time of analysis 40 patients (63%) had died *(Table 2).* Best BMBL IWG response was marrow complete response (mCR) 14 patients (22%), stable disease (SD) 30 (47%), progressive disease (PD) 15 (23%), and failure (early death/withdrawal) 5 (8%); 2 mCR patients proceeded to transplant. Median overall survival was 7.0 mos (95% confidence interval 4.8-10.8). Landmark median overall survival (from day of best BMBL response) was mCR not reached; SD 6.3 mos; PD 3.3 mos. Median overall survival of mCR+SD was 8.5 mos, with log-rank p = 0.011 (mCR+SD OS compared to PD OS).

Table 2. Overall survival

	N=64
Number of deaths	40(63%)
Median duration of follow-up (mos)	14.1
Median survival time (mos)	7.0
95% confidence interval	4.8-10.8
The primary cause of death	
Progressive disease	15(23%)
Acute myeloid leukemia	9(14%)
Respiratory failure	4 (6%)
Sepsis	4 (6%)
Liver failure	1 (2%)
Unknown	7(11%)

SAFETY

Adverse events in study 04-24 were similar to those observed in the preceding Phase 3 Study 04-21.[2]

CONCLUSION

BMBL response is a SURROGATE predictor of survival for MDS patients receiving rigosertib after HMA failure, confirming findings in earlier Phase 1/2 studies.[3] Bone marrow blast response predicted prolonged survival in the Study 04-24 (Figure 1) and when results combined with Study 04-21 (Figures 2). Based on earlier results identifying an MDS subset benefitting from Rigosertib,[2] a randomized Phase 3 trial of rigosertib vs physician's choice (INSPIRE) is ongoing to determine if rigosertib improves survival after HMA failure within 9 cycles.[4]

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American Society of Clinical Oncology 53rd Annual Meeting, June 2-6, 2017, Chicago, Illinois, USA.