Bone Marrow Blast (BMBL) Response Correlates with Overall Survival in Rigosertib-Treated Patients with Higher-risk Myelodysplastic Syndrome After Failure of Hypomethylating Agents (HMAs): A New Response Criterion?

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INTRODUCTION

- **Patients (pts) with HR-MDS have a median OS of 4 to 6 months (mo) after HMA failure[1] and no accepted salvage therapy.**
- **Surrogate endpoints and markers that can serve as an intermediate clinical endpoint (ICE) and predict survival will be an aid in drug development for this population.**
- **Response to azacitidine in first-line therapy for HR-MDS has been shown to be a surrogate to predict survival.[2]**
- **Rigosertib, a novel dual PI3K/PLK pathway inhibitor, has been shown to reduce bone marrow blasts (BMBL) in these pts.[3]**
- **Silverman et al described complete or partial bone marrow (BM) response, or stabilization after 4-8 weeks (wks) of treatment with rigosertib as a potential ICE for predicting survival in pts with HR-MDS after failure of primary HMA therapy.[4]**

METHODS

- **After signing informed consent, Pts with HR-MDS were randomly assigned 2:1 to rigosertib or best supportive care (BSC) after progressing on, failing to respond to, or relapsing after HMA treatment.**
- **BM aspirates were assessed pretreatment, at 4 wks and at 8-week intervals thereafter.**
- **The BMBL response at each time point was assessed using the following definitions: bone marrow complete response (mCR) = BMBL ≤ 5% and decrease of ≥ 50% from baseline; bone marrow partial response (mPR) = BMBL decrease from baseline of ≥ 50%, but BMBL still > 5%; stable disease (SD) = BMBL decrease or increase from baseline of < 50%; progressive disease (PD) = BMBL increase from baseline of ≥ 50% by an absolute minimum of 5%; Not evaluable (NE).**

RESULTS

- **Bone marrow assessment was carried out in 156 patients (pts) on the rigosertib arm and 24 pts on the BSC arm at 4 wks after enrollment, and in 86 and 20 pts, respectively, at 12 wks.**
- **The invasive BM procedure was optional on the BSC arm, which accounts for the low number of assessments in this group.**
- **A landmark analysis was conducted that separated pts who were alive at the 4- and 12-wk landmark time into response categories: BM response + SD vs PD (Table 1).**
- **Results of this analysis in rigosertib-treated patients were statistically significant at p = 0.011, with a hazard ratio (HR) of 0.62 and a median OS (from 4 wks onward) of 9.8 months in the mCR+mPR+SD group vs 4.6 months in the PD group (Figure 1).**
- **Another landmark analysis was conducted at 12 wks. Results of this analysis were also significant (p < 0.001) in rigosertib-treated patients, with an HR of 0.39 and a median OS (from 12 wks onward) of 10.4 months in the mCR + mPR + SD group vs 7.5 months in the PD group.**
- **A time-dependent Cox regression of OS by 4-wk BMBL response reinforced the validity of the 4-wk and 12-wk BM assessments as surrogate biomarkers for survival (Table 2).**
- **A landmark analysis of Primary HMA failures demonstrated that rigosertib-treated patients with mCR+mPR+SD had significantly greater OS compared to the PD group, at both 4 and 12 weeks, median 10.1 vs 4.2 months (p=0.025, HR = 0.58 and median 10.7 vs 7.5 month, P= 0.013, HR 0.44, respectively (Figure 2).**

Table 1
Number (%) of Rigosertib Patients with 4- and 12-week Bone Marrow Blast Response: Intention-to-treat Population and Patients with Primary HMA Failure

	4-wk BMBL Response		12-wk BMBL Response	
	ITT N = 199	Primary HMA Failure N = 127	ITT N = 199	Primary HMA Failure N = 127
Pts with BMBL assessment*	156 (78)	103 (81)*	86 (43)	57 (45)*
BM complete response (mCR)	22	14	11	7
BM partial response (mPR)	8	8	9	7
Stable disease (SD)	77	51	32	25
Progressive disease	49	30	34	18

* Bone marrow assessment was optional for BSC patients

Table 2
Time-dependent Cox Regression of Overall Survival by Bone Marrow Blast Response

	Rigosertib		BSC	
Analysis	Wald P-value	Hazard Ratio (95% CI)	Wald P-value	Hazard Ratio (95% CI)
By 4-wk BMBL response	0.051	0.72 (0.51-1.00)	0.56	0.83 (0.45-1.54)
By 12-wk BMBL response	0.0005	0.55 (0.39-0.77)	0.16	0.68 (0.39-1.17)

*Stratified by pretreatment BMBL: 5%-19% vs 20%-30%

Figure 1
Overall Survival by 4-week and 12-week BM Blast Response Among Rigosertib-treated Patients

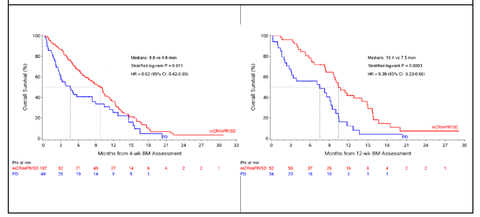
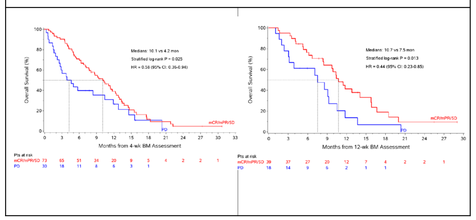


Figure 2
Overall Survival by 4-week and 12-week BM Blast Response Among Patients with Primary HMA Failure



CONCLUSION

Consistent with previous observations in Phase II studies, BMBL response at 4 or 12 weeks was correlated with OS in this population. These data suggest that BMBL response at 4 or 12 weeks may serve as a biomarker as an intermediate clinical endpoint (ICE) in rigosertib trials. Further analyses are underway to determine whether BMBL response can be considered a broader response biomarker in MDS.

REFERENCES

1. Prebet T, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 2011;29:3322-27.
2. Gore SD, et al. A multivariate analysis of the relationship between response and survival among patients with higher-risk myelodysplastic syndromes treated with azacitidine or conventional care regimens in the randomized AZA-001 trial. Haematol 2013 98(7):1067–72.
3. Seetharam M, et al. Treatment of higher risk myelodysplastic syndrome patients unresponsive to hypomethylating agents with ON 01910.Na. Leuk Res 2012;36(1):989-103.
4. Silverman L, et al. Clinical activity and safety of the dual pathway inhibitor rigosertib for higher risk myelodysplastic syndromes following DNA methyltransferase inhibitor therapy, Hematol Oncol 2014 (published online).

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