Relationship of Bone Marrow Blast (BMBL) Response to Overall Survival (OS) in Patients with Higher-risk Myelodysplastic Syndrome (HR-MDS) Treated with Rigosertib After Failure of Hypomethylating Agents (HMAs)

Lewis R. Silverman, MD[1], Pierre Fenaux, MD[2], Aref Al-Kali, MD[3], Maria R. Baer, MD[4], Mikkael Sekeres, MD[5], Gail Roboz, MD[6], Gianluca Gaidano, MD[7], Bart Scott, MD[8], Peter Greenberg, MD[9], Uwe Platzbecker, MD[10], David P. Steensma, MD[11], Suman Kambhampati, MD[12], Karl-Anton Kreuzer, MD[13], Lucy Godley, MD[14], Robert Collins, Jr, MD[15], Ehab Atallah, MD[16], Shyamala C Navada, MD[1], Francois Wilhelm, MD, PhD[17], Nozar Azarnia, PhD[17], Guillermo Garcia-Manero, MD[18]

[1]Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Hospital St Louis, Paris, France; [3]Mayo Clinic, Rochester, MN; [4]University of Maryland, Baltimore, MD; [5]Cleveland Clinic, Cleveland, OH; [6]Weill Cornell Medical College, New York, NY;[7]Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; [8]Fred Hutchinson Cancer Research Center, Seattle, WA; [9]Stanford Medical School, Stanford, CA; [10]Universitätsklinikum Dresden, Dresden, Germany; [11]Dana-Farber Cancer Institute, Boston, MA; [12]University of Kansas Medical Center, Westwood, KS; [13]Universitätsklinikum Köln, Köln, Germany; [14]University of Chicago Medical Center, Chicago, IL; [15]Univ of Texas, Southwestern Medical Center at Dallas, Dallas, TX; [16]Froedtert Hospital and Medical College of Wisconsin, Milwaukee, WI [17]Onconova Therapeutics, Inc., Newtown, PA; [18]MD Anderson Cancer Center, Houston, TX

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 surrogate for predicting survival in pts with HR-MDS after failure of primary HMA therapy.[4]**

METHODS

- **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. BM responses at the 2 time points are presented in Table 1.**
- **A landmark analysis was conducted that separated pts who were alive at the 4-wk landmark time into two 4-wk response categories: BM response + SD vs PD.**
- **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 (Figure 2).**
- **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 11.1 vs 3.9 months (p=0.025, HR = 0.57 and median 11.8 vs 7.5 month, P= 0.0042, HR 0.39, respectively (Fig 3).**

Table 1
4 – week Bone Marrow Blast Response (Intention-to-treat Population)

	Number (%) of Patients			
	4-wk BMBL Response		12-wk BMBL Response	
	Rigosertib N = 199	BSC* N = 100	Rigosertib N = 199	BSC* N = 100
Pts with BMBL assessment*	156 (78)	24 (24)	86 (43)	20 (20)
BM complete response (mCR)	22	4	11	5
BM partial response (mPR)	8	2	9	2
Stable disease (SD)	77	9	32	8
Progressive disease	49	9	34	5
* Bone marrow assessment was not required on the BSC arm				

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
4-Week Landmark Analysis of Overall Survival of Patients with Bone Marrow Response Assessment

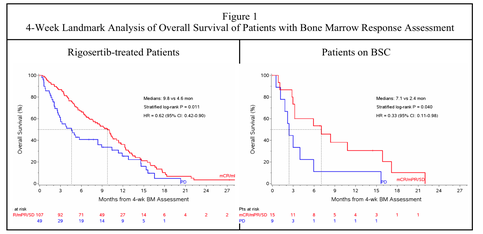


Figure 2
12-week Landmark Analysis of Overall Survival of Patients with Bone Marrow Response Assessment

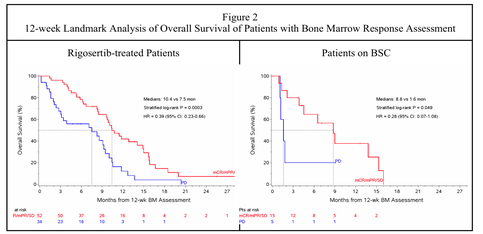
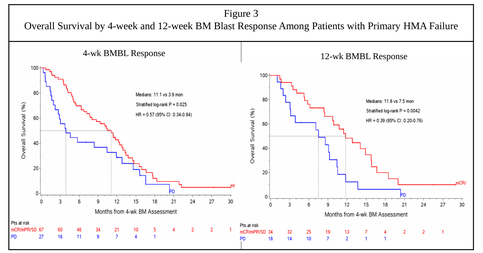


Figure 3
Overall Survival by 4-week and 12-week BM Blast Response Among Patients with Primary HMA Failure



CONCLUSION

These data suggest that BMBL response at 4 or 12 weeks was correlated with OS in this population of pts with HR-MDS treated with rigosertib after HMA failure and are consistent with previous observations in Phase II studies. BMBL response may serve as an intermediate clinical endpoint for drug development.

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