Correlation of Overall Survival (OS) with of Bone Marrow Blast (BMBL) Response in Patients (pts) with Myelodysplastic Syndrome (MDS)

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INTRODUCTION

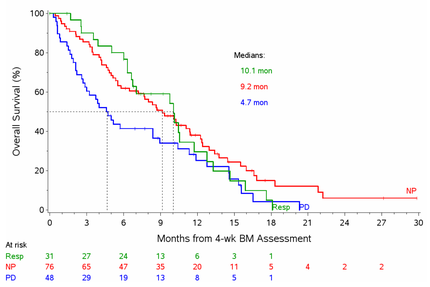
- **Percentage of BMBL is the prognostic variable with the greatest impact on outcome in MDS at diagnosis and subsequent time points.**
- **Current composite response criteria (2006 IWG)[1] do not consistently correlate with OS.**
- **Treatment impact of BMBL as an independent response criterion has not been adequately evaluated.**

METHODS

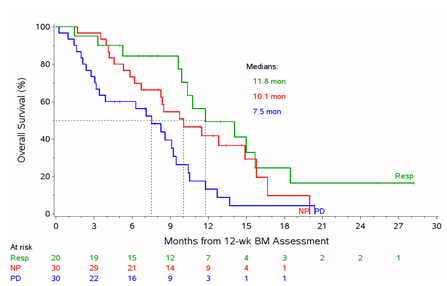
- **Evaluated correlation between OS and BMBL in pts with higher-risk MDS from 4 datasets from 7 studies with 887 pts total:**
  - **ONTIME – a Phase III randomized study of second-line rigosertib (RIG, N=199) vs best supportive care (BSC, N=100)[2]**
  - **4 Phase I/II studies of RIG in pts with MDS/AML[3]**
  - **AZA-001, a Phase III study of azacitidine (AZA) vs 3 conventional care regimens (N=358)[4,5]**
  - **Cancer & Leukemia Group B (CALGB) Study 9221, a Phase II, randomized trial of 1st-line AZA vs BSC (N=191)[6]**
- **Change in blasts was defined similarly: BM complete response is BMBL ≤5% and ≥50% decrease from baseline; BM partial response is ≥50% decrease from baseline, but BMBL still >5%; stable disease is <50% decrease or increase from baseline.**

RESULTS

<u>ONTIME</u>: Landmark time-dependent analyses showed correlation of BMBL response/stabilization with OS at 4 weeks (P=0.011) and 12 weeks (p<0.001).

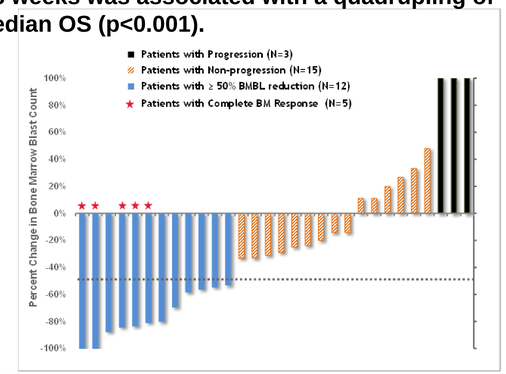


Overall Survival by 4-week BMBL response



Overall Survival by 12-week BMBL response

<u>4 Phase I/II studies</u>: BMBL response/stabilization at 4-8 weeks was associated with a quadrupling of median OS (p<0.001).



<u>Study AZA-001:</u> Time-dependent analysis of BMBL stabilization was associated with a significantly reduced risk of death in both treatment cohorts (p<0.001).

Overall Survival: Multivariate Cox Regression Analysis with Response as a Time-varying Covariate in Study AZA-001

Final Model	Hazard Ratio (95% CI)	P-value for Factor in Model*
Overall response (HI, PR, CR) as time-varying covariate	0.16 (0.07, 0.37)	<0.0001
Interaction term of overall response with treatment group (AZA vs. CCR)	0.05 (0.01, 0.43)	0.006
Stable disease (no HI, PR or CR) as time-varying covariate	0.09 (0.06, 0.15)	<0.0001
Treatment group (AZA vs. CCR)	1.19 (0.88, 1.61)	0.26

HI = hematologic improvement; PR = partial response; CR = complete response; AZA = azacitidine; CCR = conventional care regimen
*From the Cox regression model stratified by FAB and IPSS.

<u>Study 9221</u>: Landmark analysis of BMBL response/ stabilization showed a 6-fold improvement in OS (p<0.001).

Analysis of Response in Study 9221

	Aza C	Supportive Care	Cross-over
	N (%)	N (%)	N (%)
No. pts evaluated	99	92	49
Complete response (CR)	7 (7%)*	0	5 (10%)
Partial response (PR)	16 (16%)*	0	2 (4%)
Improved	37 (37%)*	5 (5%)	16 (33%)
Total	60 (60%)*	5 (5%)	23 (47%)
Landmark analysis alive at 12 mo treatment or not	Transformed to AML	No AML	
Additional survival (median) beyond 12 months	3	18	P <0.001

* Significant difference between the arms in CR rate (p=0.01), CR + PR rate (p<0.0001), and CR + PR + improvement rate (p<0.0001)

CONCLUSION

These studies, spanning more than a decade with different therapeutic agents and settings, demonstrate a consistent positive correlation between BMBL response and OS in pts with HR-MDS, including pts on supportive care. This suggests that use of reduction/stabilization in BMBL can serve as

- **a new early response parameter**
- **an intermediate clinical endpoint for evaluation of new agents**
- **a biomarker for disease progression in HR-MDS itself.**

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