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

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INTRODUCTION

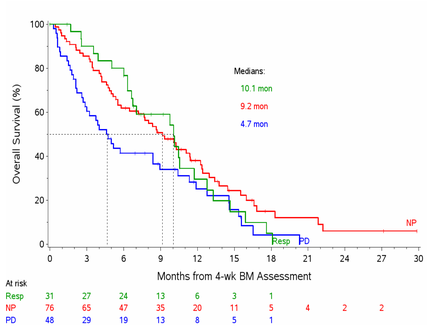
- **Percentage of BMBL is the prognostic variable with the greatest impact on outcome in MDS at diagnosis and subsequent time points.**
- **Current composite response criteria (2006 IWG)[1] do not consistently correlate with OS.**
- **Treatment impact of BMBL as an ndependent response criterion has not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

METHODS

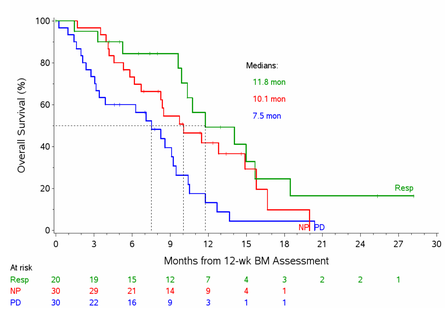
- **Evaluated correlation between OS and BMBL in pts with higher-risk MDS from 4 datasets from 7 studies with 887 pts total:**
  - **ONTIME – a Phase III randomized study of second-line rigosertib (RIG, N=199) vs best supportive care (BSC, N=100)[2]**
  - **4 Phase I/II studies of RIG in pts with MDS/AML[3]**
  - **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).

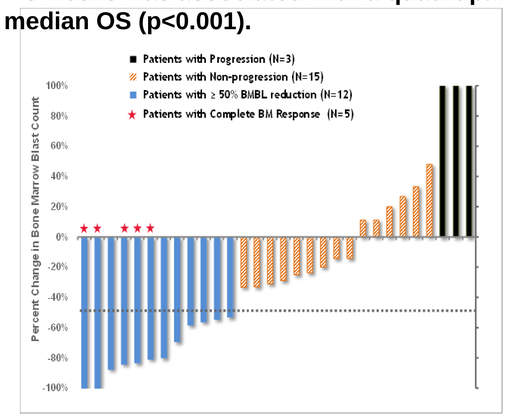


Overall Survival by 4-week BMBL response



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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