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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Reclassification of Ascertain (ASTX727-02) Myelodysplastic Syndrome (MDS) Patients: Outcomes Including Clinical Response, Overall Survival (OS), and Leukemia Free Survival (LFS) Based on IPSS-R and IPSS-M Scoring Systems

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Background:
Oral decitabine/cedazuridine (ASTX727) is a fixed dose combination of decitabine (35 mg) and the cytidine deaminase inhibitor cedazuridine (100 mg) given once daily X 5 days on a 28-day cycle producing pharmacokinetic (PK) exposure equivalent to the standard intravenous (IV) decitabine regimen of 20 mg/m ^{2} daily X 5 days on a 28-day cycle. This was demonstrated in the pivotal ASCERTAIN study (Garcia-Manero, et al, ASH 2019) as it provided a PK bridge to existing decitabine data and demonstrated median OS was 31.7 mo. (Savona,et al. Intl. MDSF International Congress on MDS, 2021). Subjects were initially classified by the International Prognosis Scoring System (IPSS) for historical reasons, however IPSS-R and IPSS-M are enhancements to IPSS that provide dynamic risk assessment for predicting clinical outcomes in MDS. Here, the objective was to re-classify the MDS subjects enrolled on the ASCERTAIN study by IPSS-R and IPSS-M and measure the impact of informing patient outcomes based on re-calculated risk assessment.

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Methods:
One hundred thirty-three subjects with MDS/CMML (chronic myelomonocytic leukemia) were enrolled in ASCERTAIN and were randomly assigned either IV decitabine for cycle 1 and oral decitabine/cedazuridine for cycle 2 or the opposite treatment sequence. All subjects continuing beyond cycle 2 received oral decitabine/cedazuridine for all subsequent cycles until treatment discontinuation for disease progression, toxicity, patient's decision, or HSCT. Whole blood collected prior to treatment was used for DNA isolation and molecular abnormalities identified using next-generation sequencing (NGS) hematologic malignancy panel of 179 genes including all genes commonly mutated in MDS. In the initial analysis of clinical outcomes, subjects were classified by IPSS with response assessment by IWG 2006 IPSS low and Int-1 risk levels were categorized as lower-risk MDS (LR-MDS), whereas IPSS Int-2 and high-risk categories were categorized as higher-risk MDS (HR-MDS). Subjects with sufficient data based on (e.g., available heme parameters, cytogenetics, NGS etc.) were reclassified by IPSS-R and IPSS-M. Subjects with IPSS-R score of $\leq$3.5 or IPSS-M of either very low, low, or moderate low were categorized as LR-MDS. Similarly subjects with IPSS-R score of $>$3.5 or an IPSS-M categorization of either moderate high, high, or very high were categorized as HR-MDS. Reclassified subjects were reassessed for CR (Complete Response), OS, and LFS and Harrell's concordance index (c-index) was used to describe the level of agreement between each scale and outcomes.

Results:
Based on the available data, the number of MDS subjects in the different risk classifications were the following: IPSS: 117, IPSS-R: 104, and IPSS-M: 105. Thirteen and 12 subjects on the IPSS could not be reclassified in the IPSS-R and IPSS-M, respectively, including 5 Int-1 and 2 low-risk MDS cases. CMML subjects were excluded from these analyses. Re-classification generally resulted in the upgrade of the subjects from LR-MDS to HR-MDS (Fig. 1). Thirty-one (26.5%) subjects from IPSS were reallocated in the IPSS-R to different risk categories; 3 (9.7%) were downgraded and 28 (90.3%) were upgraded. Similarly on reclassification with IPSS-M 34 (32.4%) of the patients reclassified; 5 (14.8%) were downgraded and 29 (85.3%) were upgraded. For IPSS LR-MDS, 23.2% of patients achieved CR, and 22.9% in the IPSS HR-MDS. Similarly, 21.6% patients achieved CR in the IPSS-R LR-MDS, and 23.9% in the IPSS-R HR-MDS; 26.3% patients achieved CR in the IPSS-M LR-MDS, and 20.9% in the IPSS-M HR-MDS. The c-index for the IPSS was .64 (OS) and .67 (LFS), IPSS-R was .70 (OS) and .71 (LFS), and .75 (OS) and .78 (LFS) for the IPSS-M (Table1).

Conclusion:
Reclassification from IPSS to IPSS-R or IPSS-M upgraded multiple subjects from a LR to a HR category, describing the ASCERTAIN patient population as a majority higher risk population with worse prognosis than previously assumed based on the IPSS. The efficacy as measured by the CR rates did not change when the LR and HR categories were defined by the different risk stratification systems. In contrast, the c-index improves with migration from IPSS to IPSS-R to IPSS-M, indicating an increased discriminatory ability of IPSS-M score in comparison to IPSS and IPSS-R, to predict patient outcomes.

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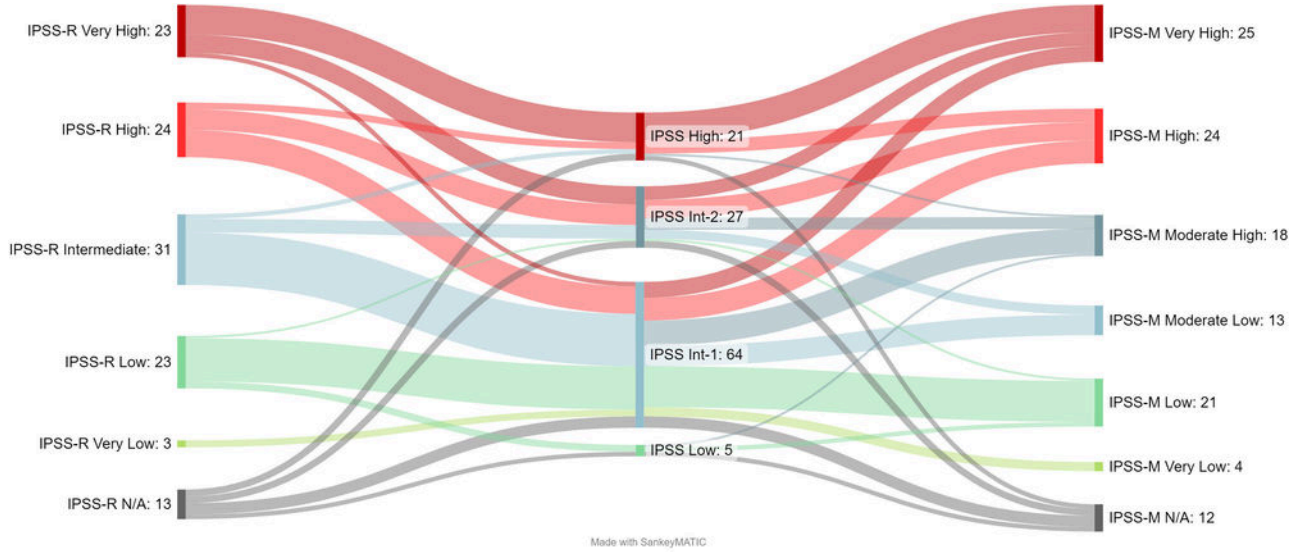

Table 1: CR Rates and OS/LFS Median Months for IPSS, IPSS-R, and IPSS-M

	Risk Category			CR (%)	OS Median Estimate (Months)		LFS Median Estimate (Months)	
IPSS (n=117)	HR-MDS	High		11/48(22.9)	15.44		10.87	
		Int-2			23.26		16.66	
	LR-MDS	Low/Int-1		16/69(23.2)	33.74		33.74	
IPSS-R (n=104)	HR-MDS	Very High	Risk Level >3.5	16/67(23.9)	26.58	14.69	18.86	11.70
		High				28.02		18.09
		Intermediate				33.74		33.74
	LR-MDS	Intermediate	Risk Level ≤3.5	8/37(21.6)	NE	33.74	NE	33.74
		Very Low/Low				NE		NE
IPSS-M (n=105)	HR-MDS	Very High		10/38 (26.3%)	13.44		9.95	
		High			21.78		17.20	
		Mod High			29.21		29.21	
	LR-MDS	Mod Low		14/67(20.9%)	NE		NE	
		Very Low/Low			NE		NE	

Figure 1

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