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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

Guillermo Garcia-Manero[1], James K McCloskey[2], Elizabeth A. Griffiths[3], Amer M. Zeidan[4], Karen W.L. Yee[5], Aref Al-Kali[6], H. Joachim Deeg[7], Prapti A. Patel[8], Mitchell Sabloff[9], Mary-Margaret Keating[10], Nancy Zhu[11], Nashat Y. Gabrail[12], Salman Fazal[13], Joseph J. Maly[14], Olatoyosi Odenike[15], Hagop Kantarjian[1], Amy E. Dezern[16], Casey L. O'Connell[17], Gail J. Roboz[18], Lambert Busque[19], Rena Buckstein[20], Harshad Amin[21], Jasleen K. Randhawa[22], Brian Leber[23], Shannon Lee[24], Winny Chan[24], Sonia Souza[24], Yuri Sano[24], Harold N. Keer[24], and Michael R. Savona[25]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]John Theurer Cancer Center, Hackensack Medical Center, Hackensack, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Yale University and Yale Cancer Center, New Haven, CT; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Mayo Clinic, Rochester, Rochester, MN; [7]Fred Hutchinson Cancer Center, Seattle, WA; [8]University of Texas Southwestern Medical Center, Dallas, TX; [9]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; [10]Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [11]University of Alberta, Edmonton, AB, Canada; [12]Gabrail Cancer Center, Canton, OH; [13]West Penn Hospital, Allegheny Health Network, Pittsburgh, PA; [14]Norton Cancer Institute, Louisville, KY; [15]University of Chicago, Chicago, IL; [16]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; [17]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [18]Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY; [19]Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; [20]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [21]Boca Raton Clinical Research, Boca Raton, FL; [22]Houston Methodist Research Institute, Houston, TX; [23]Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; [24]Astex Pharmaceuticals, Inc., Pleasanton, CA; [25]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

BACKGROUND

Oral decitabine/cedazuridine (ASTX727) is a fixed-dose combination of the hypomethylating agent (HMA) decitabine (DEC) and the cytidine deaminase (CDA) inhibitor cedazuridine. ASTX727 has been developed as monotherapy treatment for MDS/CMML and AML (NCT03306264).

- Oral DEC has poor oral bioavailability, but when co-administered with cytidine deaminase inhibitor cedazuridine (CED) has increased oral bioavailability
- Results of the Phase III ASCERTAIN (ASTX727-02) study demonstrated a fixed dose combination of DEC (35 mg) and CED (100 mg) given once daily X 5 days on a 28-day cycle is pharmacokinetic (PK) exposure equivalent to the standard intravenous (IV) DEC regimen of 20 mg/m^2 daily X 5 days on a 28-day cycle[1]
- To facilitate PK-bridging with existing historical efficacy data, ASCERTAIN study subjects were classified using the International Prognostic Scoring System (IPSS)
- IPSS considers three main prognostic indicators (marrow blasts, cytogentics, and cytopenias) in determining risk level[2]
- Many of the relevant hematologic parameters were collected as part of ASCERTAIN allowing reclassification of many patients by more recently developed prognostic criteria (IPSS-R, IPSS-M)
- Here we present additional analyses which characterize the ASCERTAIN population as possible using IPSS-R and IPSS-M

Table 1. IPSS-R Scoring

IPSS-R defines five IPSS-R risk groups: very low, low, intermediate, high, and very high

- IPSS-R enhances the prognostic model with more detailed cytogenetic subgroups (five vs three risk groups), separate subgroups within the "marrow blasts <5%" group, and a depth of cytopenias measurement defined with cut-offs for hemoglobin counts, platelet counts, and neutrophil counts[3]

	Prognostic score value						
	0	0.5	1	1.5	2	3	4
Prognostic category							
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
BM blasts, %	≤ 2		> 2 to < 5		5–10	> 10	
Hgb, g/dL	≥ 10		8 to < 10	< 8			
Platelets, x 10^9/L	≥ 100	50 to < 100	< 50				
ANC, x 10^9/L	≥ 0.8	< 0.8					
Cytogenetic group	**Characteristics**						
Very good	−Y, del(11q)						
Good	Normal, del(5q), del(12p), del(20q), del(5q) + 1 additional abnormality						
Intermediate	del(7q), +8, +19, i(17q), other abnormalities not in other groups						
Poor	−7, inv(3)/t(3q), −7/del(7q) + 1 additional abnormality, complex (3 abnormalities)						
Very poor	Complex (> 3 abnormalities)						

[1]Greenberg PL, et al Blood 2012;12 (12)

Table 2. IPSS-M Scoring

IPSS-M incorporates molecular data into its risk assessment

- IPSS-M considers the effects of molecular profiling on adverse patient outcome, in particular the impact of variations in the TP53^{multihit}, MLL^{ptd}, and FLT3 mutations[4]

Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
ML1^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD>TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{HI}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1^{a}	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

*Bernard et al, NEJM Evid 2022;1(7)

Figure 1. Risk Classifications By IPSS Version

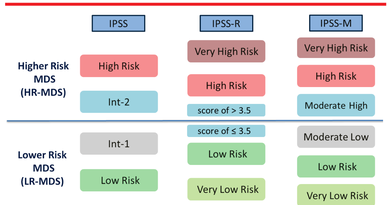
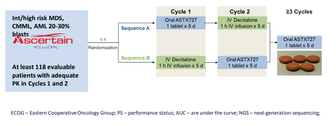


Figure 2. Phase 3 Study Design



ECOG – Eastern Cooperative Oncology Group; PS – performance status; AUC – are under the curve; NGS – next-generation sequencing;

Major Entry Criteria:
- Candidates for IV decitabine
- ECOG PS 0-1
- Life expectancy of ≥3 months
- Adequate organ function
- One prior cycle of HMA is allowed

Previously Presented:
- Demonstrated PK AUC equivalence to IV DEC at 20 mg/m^2
- Oral safety profile consistent with IV, no marked GI toxicity[1]
- Clinical activity (CR rate 22%, mOS ~32 months)[5]

Current Analyses:
- 133 subjects enrolled and whole blood collected for NGS analyses
- NGS (179 genes) analyses available for 125 subjects
- Focus on genes from 2022 MDS NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[6] (30 genes)

ASCERTAIN STUDY PATIENT CHARACTERISTICS

Table 3. Patient Characteristics

		Total Treated N=133 (%)
CMML		16 (12%)
MDS, IPSS classification	High	21 (16%)
	Int-2	27 (20%)
	Int-1	64 (48%)
	Low	5 (4%)

- Of the 117 MDS subjects treated, 104 and 105 had the necessary data for reclassification by IPSS-R and IPSS-M, respectively

		Total Treated N=117 (%)
IPSS-R Classification N/A		13 (11%)
MDS, IPSS-R classification	Very High Risk	23 (20%)
	High Risk	24 (21%)
	Intermediate	31 (26%)
	Low Risk	23 (20%)
	Very Low	3 (2%)

- As a result of re-classification from IPSS to IPSS-R, 28 subjects upgraded to HR-MDS, 3 downgraded to LR-MDS

		Total Treated N=117 (%)
IPSS-R Classification N/A		12 (10%)
MDS, IPSS-M classification	Very High	25 (21%)
	High	24 (21%)
	Moderate High	18 (15.5%)
	Moderate Low	13 (11%)
	Low	21 (18%)
	Very Low	4 (3.5%)

- As a result of re-classification from IPSS to IPSS-M, 29 subjects upgraded to HR-MDS, 5 downgraded to LR-MDS

RECLASSIFICATION RESULTS

Figure 3. Reclassification Results: Sankey Diagram

- IPSS reclassification results in majority upgraded to HR-MDS

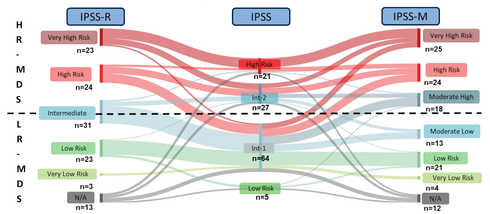


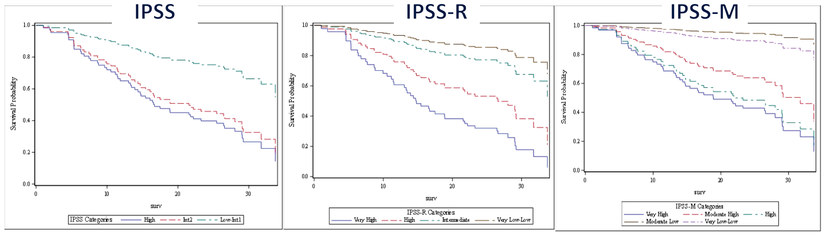
Table 4. Reclassification Results: OS and LFS

- Overall Survival (OS) and Leukemia Free Survival (LFS)

	Risk Category			OS Median Estimate (Months)		LFS Median Estimate (Months)	
IPSS (n=117)	HR-MDS	High		15.44		10.87	
		Int-2		23.26		16.66	
	LR-MDS	Low/Int-1		33.74		33.74	
IPSS-R (n=104)	HR-MDS	Very High	Risk Level >3.5	26.58	14.69	18.86	11.70
		High			28.02		18.09
	LR-MDS	Intermediate	Risk Level ≤3.5	NE	33.74	NE	33.74
		Very Low/Low			NE		NE
IPSS-M (n=105)	HR-MDS	Very High		13.44		9.95	
		High		21.78		17.20	
		Mod High		29.21		29.21	
	LR-MDS	Mod Low		NE		NE	
		Very Low/Low		NE		NE	

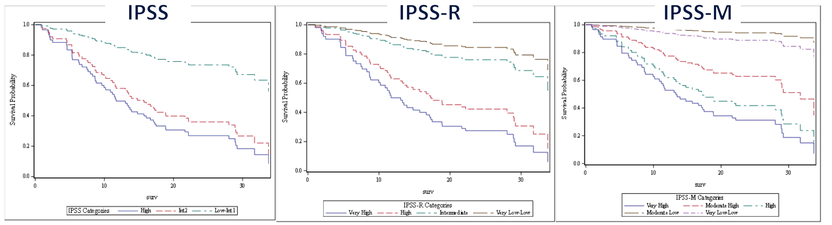
RECLASSIFICATION RESULTS

Figure 4. Kaplan-Meier Plot: Overall Survival



- IPSS, IPSS-R, and IPSS-M showed a clear separation of the different risk categories for OS

Figure 5. Kaplan-Meier Plot: Leukemia Free Survival



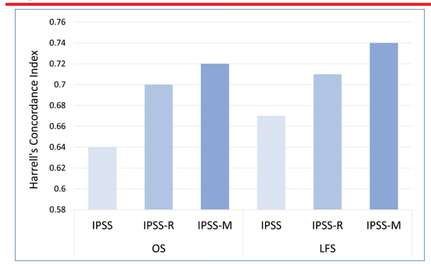
- IPSS, IPSS-R, and IPSS-M showed a clear separation of the different risk categories for LFS

Table 5. Clinical Response

	Risk Category			CR (%)
IPSS (n=117)	HR-MDS	High		11/48 (22.9)
		Int-2		
	LR-MDS	Low/Int-1		16/69 (23.2)
IPSS-R (n=104)	HR-MDS	Very High	Risk Level >3.5	16/67 (23.9)
		High		
	LR-MDS	Intermediate	Risk Level ≤3.5	8/37 (21.6)
		Very Low/Low		
IPSS-M (n=105)	HR-MDS	Very High		14/67 (20.9%)
		High		
		Mod High		
	LR-MDS	Mod Low		10/38 (26.3%)
		Very Low/Low		

- No significant difference in CR rates was observed from redefining HR and LR risk categories after migration from IPSS to IPSS-R and IPSS-M

Figure 6. c-index for OS and LFS



- Harrell's concordance index (c-index) for both OS and LFS improves with migration from IPSS to IPSS-R to IPSS-M
- IPSS-M has the highest c-index for both OS and LFS, indicating better ability to predict patient outcome compared to IPSS and IPSS-R

CONCLUSIONS

Impact of risk stratification by IPSS-R and IPSS-M on the IPSS-defined ASCERTAIN patient population

- 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 from 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
- The c-index improves with migration from IPSS to IPSS-R to IPSS-M, suggests that the IPSS-M score is more effective in predicting patient outcomes compared to IPSS and IPSS-R

REFERENCES

1. Garcia-Manero, et al. [ASH Abstract 846] Blood. 2019;134 (suppl 1)
2. Greenberg PL et al, Blood 1997;89(6)
3. Greenberg PL, et al Blood 2012;12 (12)
4. Bernard et al, NEJM Evid 2022;1(7)
5. Savona, et al. MDS symposium 2021.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes 3.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed [Nov 8, 2022]. To view the most recent and complete version of the guideline, go online to NCCN.org.