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ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence (RBC-TI) across Different Risk Subgroups in Patients with Lower-Risk Myelodysplastic Syndromes (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis-Stimulating Agents (ESAs) in IMerge Phase 3 Study

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BACKGROUND IMerge (NCT02598661) is a phase 2/3 global study of imetelstat, a first-in-class telomerase inhibitor, for patients with RBC transfusion-dependent non-del(5q) LR-MDS R/R to or ineligible for ESAs, a population with unmet needs. Phase 3 results showed that the rate of ≥8-week, ≥24-week and 1-year RBC-TI was higher with imetelstat than placebo (Zeidan et al. ASCO 2023. Abstr 7004; Platzbecker et al. EHA 2023. Abstr S165).

METHODS Toevaluate clinical efficacy of imetelstat across different International Prognostic Scoring System (IPSS), revised IPSS (IPSS-R), IPSS-R cytogenetic, or IPSS-molecular (IPSS-M) risk categories,cytogenetic analysis was performed centrally on bone marrow aspirates by karyotyping, and mutation profile was analyzed using peripheral blood samples by next-generation sequencing on a panel of 36 genes commonly mutated in MDS. Baseline IPSS, IPSS-R, IPSS-R cytogenetic, or IPSS-M risk categories were derived for patients in the phase 3 portion of IMerge based on specific classification criteria, and rates of RBC-TI ≥8-week, ≥24-week, ≥1-year were assessed for each risk subgroup.

RESULTS In 105 IPSS-low patients, 95 (90.5%) remained IPSS-M very low/low/moderate low, and 10 patients (9.5%) upstaged to IPSS-M moderate high and high. In 50 IPSS-intermediate-1 patients, 39 (78%) remained IPSS-M very low/low/moderate low, and 11 patients (22%) upstaged to IPSS-M moderate high/high. Among 129 IPSS-R low/very low patients, 118 (91.5%) remained IPSS-M very low/low/moderate low, and 11 (8.5%) patients upstaged to IPSS-moderate high/high. In 25 IPSS-R-intermediate patients, 16 (64%) remained IPSS-M low/moderate low, and 9 patients (36%) upstaged to IPSS-M moderate high/high/very high. One IPSS-R high-risk patient remained IPSS-M high.
Overall, significantly higher rates of ≥8-week, ≥24-week, and ≥1-year RBC-TI were achieved in patients receiving imetelstat (39.8%, 28%, and 13.6%) vs those receiving placebo (15%, 3.3%, and 1.7%). Further subgroup analysis demonstrated that imetelstat consistently had higher TI response rates than placebo across different risk subgroups, irrespective of classification system.
For IPSS risk groups, the TI rates of ≥8-week, ≥24-week, and ≥1-year with imetelstat vs placebo were 40.0% vs 20.5% ($P = 0.034$), 28.8% vs 5.1% ($P = 0.003$), and 12.5% vs 2.6% ($P = 0.082$), respectively, in patients with low risk and 39.5% vs 4.8% ($P = 0.004$), 26.3% vs 0% ($P = 0.009$), and 15.8% vs 0% ($P = 0.048$), respectively, in patients with intermediate-1 risk.
For IPSS-R risk groups, the TI rates of ≥8-week, ≥24-week, and ≥1-year with imetelstat vs placebo were 42.5% vs 19.6%, 29.9% vs 4.3%, and 11.5% vs 2.2%, respectively, in the low-risk subgroup. The TI rates of ≥8-week, ≥24-week, ≥1-year TI with imetelstat were 35%, 25%, and 20%, respectively, in the intermediate-risk subgroup, whereas placebo treatment had no

response. The number of patients was too low in both arms of the very low or high IPSS-R subgroups to assess difference in TI response.
For IPSS-R cytogenetic risk groups, the TI rates of ≥8-week, ≥24-week, and ≥1-year with imetelstat vs placebo were 37.1% vs 17.0%, 24.7% vs 4.3%, and 10.1% vs 2.1%, respectively, in very good/good risk groups and 54.5% vs 11.1%, 40.9% vs 0%, and 22.7% vs 0%, respectively, in the intermediate-risk group.
For IPSS-M risk groups, the TI rates of ≥8-week, ≥24-week, and ≥1-year with imetelstat vs placebo were 47.8% vs 21.2%, 34.8% vs 3%, and 14.5% vs 0%, respectively, in patients with very low/low risk and 20.7% vs 6.3%, 10.3% vs 0%, and 6.9% vs 0%, respectively, in patients with moderate low/moderate high risk. In patients with high/very high risk, ≥8-week TI rates were 40% vs 0% with imetelstat vs placebo, with no ≥24-week or ≥1-year TI observed in either arm. All results are summarized in the Table.

CONCLUSIONS Improvement in RBC-TI rates was observed in patients treated with imetelstat vs placebo across different risk subgroups as defined by IPSS, IPSS-R, IPSS-R cytogenetic, or IPSS-M risk profiles. Notably, placebo had not achieved durable (≥24-week and ≥1-year) TI response in the higher-risk groups irrespective of the risk classification assessment model used, while TI response rates with imetelstat in higher-risk subgroups with poor prognosis were similar to TI response rates in lower-risk subgroups of heavily transfused R/R ESA LR-MDS, indicating that clinical efficacy of imetelstat is independent of risk categories.

Disclosures Komrokji: *AbbVie, CTI biopharma, Jazz, Pharma Essentia, Servio:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Geron:* Consultancy; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Rigel, Taiho, DSI:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Santini:** *Syros:* Other: Advisory boards; *Janssen:* Other: travel grant; *CTI:* Other: Advisory boards; *Geron:* Other: Advisory boards; *Gilead:* Other: Advisory boards; *BMS/Celgene:* Other: Advisory boards; *Novartis:* Other: Advisory boards; *Otsuka:* Other: Advisory boards; *Servier:* Other: Advisory boards; *AbbVie:* Other: Advisory boards. **Fenaux:** *Janssen:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; 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OffLabel Disclosure: Imetelstat to treat lower-risk myelodysplastic syndromes relapsed/refractory to or ineligible for erythropoiesis-stimulating agents

Table. Risk subgroup analysis of RBC-TI rates.

	Imetelstat (n = 118)	Placebo (n = 60)	*P* value[a]
All patients, n	118	60	
8-week RBC-TI, n (%)	47 (39.8)	9 (15.0)	<.001
24-week RBC-TI, n (%)	33 (28.0)	2 (3.3)	<.001
1-year RBC-TI, n (%)	16 (13.6)	1 (1.7)	.012
IPSS			
Low, n	80	39	
8-week RBC-TI, n (%)	32 (40.0)	8 (20.5)	.034
24-week RBC-TI, n (%)	23 (28.8)	2 (5.1)	.003
1-year RBC-TI, n (%)	10 (12.5)	1 (2.6)	.082
Intermediate-1, n	38	21	
8-week RBC-TI, n (%)	15 (39.5)	1 (4.8)	.004
24-week RBC-TI, n (%)	10 (26.3)	0	.009
1-year RBC-TI, n (%)	6 (15.8)	0	.048
IPSS-R cytogenetic risk			
Good/very good, n	89	47	
8-week RBC-TI, n (%)	33 (37.1)	8 (17.0)	.014
24-week RBC-TI, n (%)	22 (24.7)	2 (4.3)	.002
1-year RBC-TI, n (%)	9 (10.1)	1 (2.2)	.071
Intermediate, n	22	9	
8-week RBC-TI, n (%)	12 (54.5)	1 (11.1)	.029
24-week RBC-TI, n (%)	9 (40.9)	0	.024
1-year RBC-TI, n (%)	5 (22.7)	0	.152
IPSS-R			
Very low, n	3	2	
8-week RBC-TI, n (%)	0	0	NE
24-week RBC-TI, n (%)	0	0	NE
1-year RBC-TI, n (%)	0	0	NE
Low, n	87	46	
8-week RBC-TI, n (%)	37 (42.5)	9 (19.6)	.008
24-week RBC-TI, n (%)	26 (29.9)	2 (4.3)	<.001
1-year RBC-TI, n (%)	10 (11.5)	1 (2.2)	.064
Intermediate, n	20	8	
8-week RBC-TI, n (%)	7 (35.0)	0	.055
24-week RBC-TI, n (%)	5 (25.0)	0	.091
1-year RBC-TI, n (%)	4 (20.0)	0	.131
High, n	1	0	
8-week RBC-TI, n (%)	1 (100.0)	0	NE
24-week RBC-TI, n (%)	0	0	NE
1-year RBC-TI, n (%)	0	0	NE
IPSS-M			
Very low/low, n	69	33	
8-week RBC-TI, n (%)	33 (47.8)	7 (21.2)	.017
24-week RBC-TI, n (%)	24 (34.8)	1 (3.0)	<.001
1-year RBC-TI, n (%)	10 (14.5)	0	.025
Moderate low/moderate high, n	29	16	
8-week RBC-TI, n (%)	6 (20.7)	1 (6.3)	.167
24-week RBC-TI, n (%)	3 (10.3)	0	.154
1-year RBC-TI, n (%)	2 (6.9)	0	.248
High/very high, n	5	3	
8-week RBC-TI, n (%)	2 (40.0)	0	.157
24-week RBC-TI, n (%)	0	0	NE
1-year RBC-TI, n (%)	0	0	NE

[a]P value based on Cochran-Mantel-Haenszel controlling for prior RBC transfusion burden (≤6 vs >6 U of RBCs) and IPSS risk group (low vs intermediate-1) applied to randomization, for comparison between treatment arms (imetelstat vs placebo) within each specific risk group.

Figure 1

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