Abstract: S180

Title: PRIMARY RESULTS OF THE PHASE III STIMULUS-MDS2 STUDY OF SABATOLIMAB + AZACITIDINE VS PLACEBO + AZACITIDINE AS FRONTLINE THERAPY FOR PATIENTS WITH HIGHER-RISK MDS OR CMML-2

Abstract Type: Oral Presentation

Session Title: Immune and targeted therapies in MDS

Background:

Sabatolimab (MBG453, SABA) is an immunotherapy targeting TIM-3, an immuno-myeloid regulator expressed on immune and leukemic stem cells. In the randomized, placebo (PBO)-controlled, Phase (Ph) II STIMULUS-MDS1 (NCT03946670) study of SABA+hypomethylating agent (HMA) in patients (pts) with intermediate- (I; and ≥5% bone marrow [BM] blasts), high- (H), or very high (vH)-risk myelodysplastic syndromes (MDS) per Revised International Prognostic Scoring System (IPSS-R), the duration of complete response (CR) was prolonged with SABA+HMA and a trend for improvement in progression-free survival (PFS) was suggested, although the two primary endpoints (EP) were not met (CR rate + PFS) (Zeidan AM. *Lancet Haematol* 2024).

Aims:

STIMULUS-MDS2 (NCT04266301) is a randomized, double-blind, PBO-controlled, Ph III trial that evaluated SABA+azacitidine (AZA) as frontline therapy in pts with higher-risk (I-, H- or vH) MDS or chronic myelomonocytic leukemia (CMML)-2.

Methods:

Eligible pts were aged ≥18 years with I-, H- or vH-risk MDS per IPSS-R or non-proliferative CMML-2 and ineligible for allogeneic transplant at enrollment. Pts were randomized 1:1, stratified by MDS IPSS-R and CMML-2, to SABA 800 mg or PBO intravenously (IV) on Day (D) 8 of each 28D cycle and AZA 75 mg/m2/day (IV or subcutaneous) on D1–7 (or D1–5, 8, 9). Primary EP was overall survival (OS). Key secondary EPs were time to definitive deterioration (worsening with no subsequent improvement) of fatigue, RBC transfusion-free intervals, improvement of fatigue, physical and emotional functioning. Secondary EPs included PFS, leukemia-free survival (LFS) and response rates. Primary OS analysis was planned after 282 OS events.

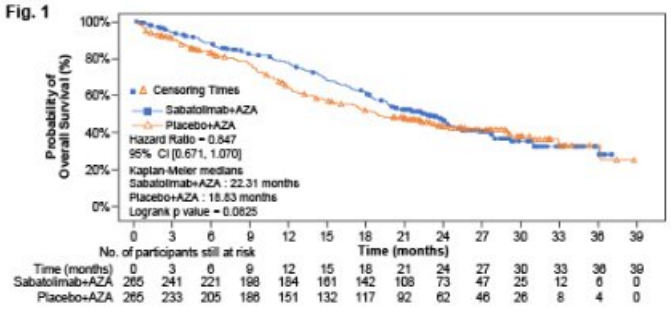
Results:

In total, 530 pts were randomized (265 in each arm). Median age was 71.0 years; 144 (27.2%), 177 (33.4%), 171 (32.3%) and 38 (7.2%) had I-, H-, vH-risk MDS and CMML-2, respectively. Baseline characteristics were well balanced between arms. In pts with MDS (N=492), 117 (23.8%), 169 (34.3%) and 206 (41.9%) had <5, 5–<10 and 10–<20% BM blasts, respectively. One randomized pt in each arm did not start therapy. At data cut-off (Sept 15, 2023), treatment was ongoing in 40 (15.1%) pts on SABA+AZA and 38 (14.3%) on PBO+AZA. In all pts in SABA and PBO arms, median exposure was 8.8 vs 6.8 months (mos). After end of treatment, 9.1% pts in SABA arm vs 11.3% in PBO arm went on to transplant. Median OS was 22.31 vs 18.83 mos for SABA+AZA and PBO+AZA (HR, 0.85 [95% CI, 0.67–1.07]; one-sided P-value 0.0825 [alpha-level 0.0246]) (**Fig. 1**). Subgroups with most favorable OS for SABA+AZA were vH-risk IPSS-R, vH-risk molecular IPSS, poor/v poor cytogenetics and ≥10% BM blasts (**Fig. 2**). Key secondary EPs were not statistically tested as the primary EP was not met. In SABA and PBO arms, median PFS and LFS were 13.6 vs 10.1 mos (HR, 0.70 [0.56–0.86]) and 19.4 vs 13.7 mos (HR, 0.78 [0.61–1.00]), respectively; CR was 19.6 vs 14.3%, marrow CR was 29.1 vs 26.0%, partial response (PR) was 1.5 vs 0.4% and CR+ PR+hematological improvement was 42.6 vs 34.7% (IWG 2006). Rates of any and most common grade ≥3 adverse events were (SABA+AZA [N=263] vs PBO+AZA [N=265]): any, 90.9 vs 88.3%; anemia, 36.9 vs 29.1%; neutropenia, 35.4 vs 27.9%; neutrophil count decreased, 24.0 vs 20.4%; febrile neutropenia, 22.8 vs 16.2%; and thrombocytopenia, 22.4 vs 17.4%.

Conclusion:

Despite a favorable trend in OS, CR rate, PFS, and LFS, STIMULUS-MDS2, to our knowledge the largest randomized trial conducted in higher-risk MDS, did not meet its primary EP of OS. The safety profile of SABA+HMA was consistent with Ph Ib/II trials. Additional analyses will be provided at the meeting.

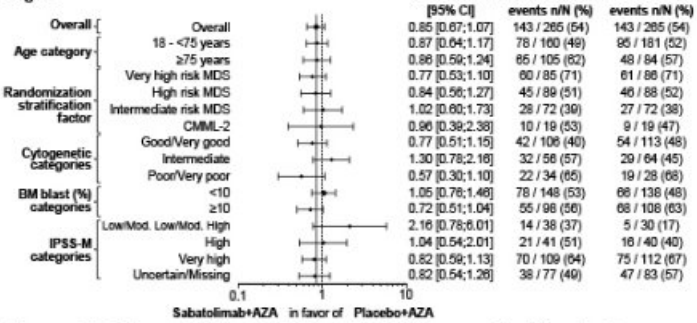
Fig. 1



No. of participants still at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Sabatolimab+AZA	265	241	221	198	184	161	142	108	73	47	25	12	6	0
Placebo+AZA	265	233	205	186	151	132	117	92	62	46	26	8	4	0

Fig. 2



		Hazard Ratio [95% CI]	Sabatolimab+AZA events n/N (%)	Placebo+AZA events n/N (%)
Overall	Overall	0.85 [0.67;1.07]	143 / 265 (54)	143 / 265 (54)
Age category	18 - <75 years	0.87 [0.64;1.17]	78 / 160 (49)	95 / 181 (52)
	≥75 years	0.86 [0.59;1.24]	65 / 105 (62)	48 / 84 (57)
Randomization stratification factor	Very high risk MDS	0.77 [0.53;1.10]	60 / 85 (71)	61 / 86 (71)
	High risk MDS	0.84 [0.56;1.27]	45 / 89 (51)	46 / 88 (52)
	Intermediate risk MDS	1.02 [0.60;1.73]	28 / 72 (39)	27 / 72 (38)
	CMML-2	0.96 [0.39;2.38]	10 / 19 (53)	9 / 19 (47)
Cytogenetic categories	Good/Very good	0.77 [0.51;1.15]	42 / 106 (40)	54 / 113 (48)
	Intermediate	1.30 [0.78;2.16]	32 / 56 (57)	29 / 64 (45)
	Poor/Very poor	0.57 [0.30;1.10]	22 / 34 (65)	19 / 28 (68)
BM blast (%) categories	<10	1.05 [0.76;1.46]	78 / 148 (53)	66 / 138 (48)
	≥10	0.72 [0.51;1.04]	55 / 98 (56)	68 / 108 (63)
IPSS-M categories	Low/Mod. Low/Mod. High	2.16 [0.78;6.01]	14 / 38 (37)	5 / 30 (17)
	High	1.04 [0.54;2.01]	21 / 41 (51)	16 / 40 (40)
	Very high	0.82 [0.59;1.13]	70 / 109 (64)	75 / 112 (67)
	Uncertain/Missing	0.82 [0.54;1.26]	38 / 77 (49)	47 / 83 (57)

Primary analysis of OS was a stratified log-rank test. AZA, azacitidine; BM, bone marrow; CI, confidence interval; IPSS-M, Molecular International Prognostic Scoring System; NE, not evaluable. Dotted line shows no effect point. Bold line shows overall treatment effect point (for all subjects).

Keywords: Survival, Myelodysplastic syndrome, Phase III, Clinical trial