657 Efficacy and Safety of Sabatolimab (MBG453) in Combination with Hypomethylating Agents (HMAs) in Patients with Acute Myeloid Leukemia (AML) and High-Risk Myelodysplastic Syndrome (HR-MDS): Updated Results from a Phase 1b Study

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Background

Sabatolimab (MBG453) is a high-affinity, humanized, IgG4 (S228P) antibody targeting TIM-3, an inhibitory receptor that regulates adaptive and innate immune responses. TIM-3 is expressed on immune cells as well as leukemic stem cells (LSCs) and blasts, but not normal hematopoietic stem cells, making it a promising target in AML/MDS. Sabatolimab is a potential first-in-class immunotherapeutic agent that can target TIM-3 on immune and myeloid cells. Blockade of TIM-3 by sabatolimab may restore immune function while also directly targeting LSCs and blasts.

Study Design and Methods

This is a phase Ib, open-label, multicenter, dose-escalation study of sabatolimab + HMA (decitabine [Dec] or azacitidine [Aza]) in patients (pts) with AML or HR-MDS (NCT03066648). Pts were adults with newly diagnosed (ND) or relapsed/refractory (R/R; ≥1 prior therapy) AML or IPSS-R high- or very high-risk MDS; pts with chronic myelomonocytic leukemia (CMML) were also eligible. Pts were HMA naive and ineligible for intensive chemotherapy. Escalating dose cohorts of IV sabatolimab examined were: 240 or 400 mg Q2W (D8, D22) or 800 mg Q4W (D8) combined with Dec (20 mg/m^2; IV D1-5) or Aza (75 mg/m^2; IV/SC D1-7) per 28-day cycle. Primary objectives included safety/tolerability; secondary objectives included preliminary efficacy and pharmacokinetics.

Results

As of the data cutoff (25 Jun 2020), 48 pts with ND AML, 39 pts with HR-MDS, and 12 pts with CMML received sabatolimab + HMA. Data from 29 pts with R/R AML were previously reported. For a broader understanding of the effect of sabatolimab + HMA, results are reported here for the Dec and Aza arms both combined and separately (**Table**). Median (range) duration of sabatolimab exposure was 4.5 (0.3-28.3) mo for ND AML and 4.1 (0.7-33.6) mo for HR-MDS, with 17 and 11 pts ongoing, respectively.

With sabatolimab + HMA, the most common (>10% in either disease cohort) gr ≥3 treatment-emergent adverse events (TEAEs) in pts with ND AML and HR-MDS, respectively, were thrombocytopenia (45.8%, 51.2%), neutropenia (50%, 46.1%), febrile neutropenia (29.2%, 41%), anemia (27.1%, 28.2%), and pneumonia (10.4%, 5.1%). Discontinuation due to AE was infrequent among pts with ND AML (6.3% [3/48]; 1 each of fatigue, febrile neutropenia, and possible HLH); none occurred among pts with HR-MDS. One dose-limiting toxicity occurred with sabatolimab 240 mg Q2W + Dec (gr 3 ALT elevation); the maximum tolerated dose was not reached with either combination.

To comprehensively assess possible immune-mediated AEs (imAEs), events were evaluated across all disease cohorts. Seven gr 3 treatment-related possible imAEs were reported in 5 pts: arthritis, rash, possible HLH, and increased ALT in 1 pt each, and hypothyroidism, infusion-related reaction, and increased ALT in 1 pt. No gr 4 treatment-related possible imAEs occurred; however, there was a case of enterocolitis in a pt with HR-MDS who died of septic shock with neutropenic colitis. No other treatment-related deaths were reported.

Among 34 evaluable pts with ND AML, overall response rate (ORR) was 41.2%: 8 CR, 3 CRi, 3 PR. Median (range) time to response (TTR) was 2.1 (1.8-13.1) mo and estimated 6-mo duration of response (DOR) rate was 85.1% (95% CI: 68-100%). Estimated 12-mo progression-free survival (PFS) rate was 44% (95% CI: 28-69.3%). Among 35 evaluable pts with HR-MDS, ORR was 62.9%: 8 CR, 8 mCR (5 with hematologic improvement [HI]), 6 SD with HI. Median (range) TTR was 2.0 (1.7-9.6) mo and estimated 6-mo DOR rate for CR/mCR/PR was 90%

(95% CI: 73.2-100%). Encouraging response rates were achieved in both pts with high-risk MDS (ORR 50% [11/22]) and very high-risk MDS (ORR 84.6% [11/13]). Of pts with HR-MDS, 8 (5 high-risk, 3 very high-risk) proceeded to transplant. Estimated 12-mo PFS rate was 58.1% (95% CI: 39.9-84.6%).

Among 12 pts with CMML, the safety profile of sabatolimab + HMA was generally consistent with that for AML/HR-MDS (most common gr ≥3

TEAEs: thrombocytopenia, n=7; neutropenia, n=7; anemia, n=6). ORR among 11 evaluable pts was 63.6%: 2 CR, 3 mCR, 1 PR, 1 SD with HI.

Conclusions

Sabatolimab + HMA is well tolerated in pts with AML and HR-MDS and continues to show promising antileukemic activity and emerging durability. These results support TIM-3 as a potential therapeutic target and provide a basis for further development of sabatolimab + HMA in pts with AML or higher-risk MDS.

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	ND AML[a]		HR-MDS[a]		CMML[a,b]	
Parameter	+ Dec n=22	+ Aza n=26	+ Dec n=19	+ Aza n=20	+ Dec n=5	+ Aza n=7
Duration of sabatolimab exposure, median (range) mo	6.8 (0.7-28.3)	3.5 (0.3-15.2)	8.0 (0.7-33.6)	2.8 (0.8-14.3)	8.4 (5.6-12.6)	5.0 (1.6-15.8)
Efficacy evaluable pts[c], n	17	17	18	17	5	6
ORR[d], n (%)	8 (47.1)	6 (35.3)	11 (61.1)	11 (64.7)	3 (60)	4 (66.7)
CR	6 (35.3	2 (11.8)	6 (33.3)	2 (11.8)	0	2 (33.3)
CRi	1 (5.9)	2 (11.8)	NA	NA	NA	NA
mCR	NA	NA	3 (16.7)	5 (29.4)	1 (20)	2 (33.3)
mCR with HI	NA	NA	3 (16.7)	2 (11.8)	0	1 (16.7)
PR	1 (5.9)	2 (11.8)	0	0	1 (20)	0
SD with HI	NA	NA	2 (11.1)	4 (23.5)	1 (20)	0

[a] The + Dec and + Aza combination arms were initiated in August 2017 and February 2019, respectively.
[b] Response assessment for pts with CMML used IWG criteria (Cheson 2006).
[c] The first efficacy assessment was conducted at 2 months after the start of study treatment.
[d] ORR for pts with MDS was defined as CR + mCR + PR + SD with HI; ORR for pts with ND AML was defined as CR + CRi + PR.
CR, complete remission; CRi, CR with incomplete blood count recovery; mCR, marrow CR; PR, partial remission; SD, stable disease.