MDS-476

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Sabatolimab (MBG453) Combination Treatment Regimens for Patients With Higher-Risk Myelodysplastic Syndromes: The Myelodysplastic Syndromes Studies in the STIMULUS Immuno-MyeloidClinical Trial Program

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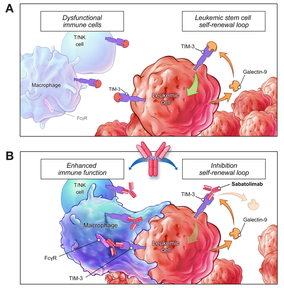
CONCLUSIONS

- The goal of the ongoing STIMULUS-MDS trials is to gain insight into the promising durable benefit of sabatolimab combination therapies in patients with higher-risk MDS
- As of May 13, 2022, there are 4 ongoing STIMULUS trials evaluating patients with MDS
- Additional exploration of the mechanism of action of sabatolimab and identification of potential biomarkers predictive of response is planned

INTRODUCTION

- Patients with very-high/high-risk myelodysplastic syndrome (vH/HR-MDS) generally have poor outcomes[1]
- For patients with vH/HR-MDS who are not eligible for hematopoietic stem cell transplant, treatment with single-agent hypomethylating agent (HMA) therapy shows minimal survival benefit[2]
- Novel treatments that provide durable responses and clinically meaningful survival benefit are needed
- T-cell immunoglobulin domain and mucin domain-3 (TIM-3) is an immuno-myeloid regulator as it is expressed on both immune cells and leukemic stem cells, making it a novel target in myeloid malignancies (**Figure 1A**)[3]
- Sabatolimab, a novel immunotherapy targeting TIM-3, is the first compound with immuno-myeloid activity. It therefore has a potential dual mechanism to combat acute myeloid leukemia and MDS (**Figure 1B**)[4]

Figure 1. Sabatolimab Targets TIM-3 on Immune and Leukemic Cells

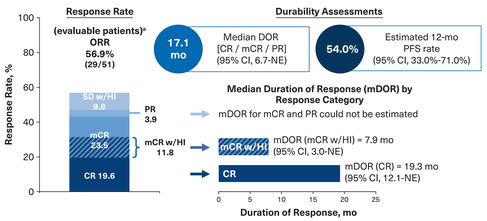


FcγR, Fc gamma receptor; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

SABATOLIMAB + HMA DEMONSTRATES DURABLE CLINICAL RESPONSES IN VH/HR-MDS

- Sabatolimab + HMA demonstrated promising efficacy and response durability in patients with vH/HR-MDS in a Phase Ib trial (**Figure 2**), with very few immunological adverse events[3]
- The STIMULUS immuno-myeloid clinical trial program is investigating the efficacy and safety profiles, as well as quality-of-life improvements, of multiple sabatolimab-based combination therapies in patients with myeloid malignancies
- Patients with adverse-risk disease were able to achieve durable responses
  - Patients with TP53 mutation (n=14), overall response rate (ORR): 71.4%, median duration of response (DOR): 21.5 months (95% confidence interval [CI], 6.7-not estimable [NE])
  - Patients with at least one of TP53/RUNX1/ASXL1 mutation (n=32), ORR: 65.6%, median DOR: 16.1 months (95% CI, 6.7-NE)

Figure 2. Sabatolimab + HMA Demonstrates Durable Responses in vH/HR-MDS



*Evaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.

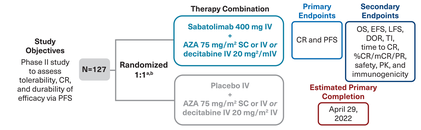
CR, complete remission; DOR, duration of response; HI, hematologic improvement; HMA, hypomethylating agent; mCR, bone marrow CR; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial remission; SD, stable disease; vH/HR-MDS, very high/high-risk myelodysplastic syndrome.

TRIALS IN PROGRESS

STIMULUS-MDS1 (NCT03946670)[5]

- STIMULUS-MDS1 is an international, randomized, double-blind, placebo-controlled, Phase II trial evaluating sabatolimab + HMA therapy
- STIMULUS-MDS1 is ongoing and has finished recruitment
- Study design is shown in **Figure 3**
- Eligibility criteria are described in **Table 1**

Figure 3. Study Design of STIMULUS-MDS1



[a]Stratified based on HMA therapy. [b]Stratified based on IPSS-R risk category.

AZA, azacitidine; CR, complete remission; DOR, duration of remission; EFS, event-free survival; HMA, hypomethylating agent; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; LFS, leukemia-free survival; mCR, bone marrow CR; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial remission; SC, subcutaneous; TI, transfusion independence.

Table 1. Highlighted Inclusion and Exclusion Criteria for STIMULUS-MDS1

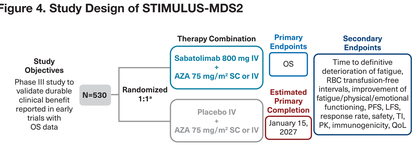
Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Prior TIM-3 therapy
vH/H/IR-MDS per IPSS-R risk assessment	Previous treatment for vH/H/IR-MDS
Not eligible for IC or HSCT	Active autoimmune disease
ECOG PS 0-2	Severe hypersensitivity to study treatment ingredients
AST and ALT ≤3 × ULN	Any uncontrolled medical condition, or condition requiring systemic steroid or immune suppressive treatment
Total bilirubin ≤1.5 × ULN	History of organ transplant or HSCT
Estimated glomerular filtration rate ≥30 mL/min/1.73 m²	AML, CMML, or primary/secondary MF

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; IPSS-R, Revised International Prognostic Scoring System; MF, myelofibrosis; TIM-3, T-cell immunoglobulin domain and mucin domain-3; ULN, upper limit of normal; vH/H/IR-MDS, very high/high/intermediate-risk myelodysplastic syndrome.

STIMULUS-MDS2 (NCT04266301)[6]

- STIMULUS-MDS2 is an international, randomized, double-blind, placebo-controlled, Phase III trial of sabatolimab + azacitidine (AZA)
- STIMULUS-MDS2 is ongoing and has finished recruitment
- Study design is shown in **Figure 4**
- Eligibility criteria are described in **Table 2**

Figure 4. Study Design of STIMULUS-MDS2



*Stratified based on IPSS-R risk category and CMML-2.

AZA, azacitidine; CMML, chronic myelomonocytic leukemia; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; LFS, leukemia-free survival; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QoL, quality of life; RBC, red blood cell; SC, subcutaneous; TI, transfusion independence.

Table 2. Highlighted Inclusion and Exclusion Criteria for STIMULUS-MDS2

Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Prior TIM-3 therapy
vH/H/IR-MDS per IPSS-R risk assessment or CMML-2	Previous treatment for vH/H/IR-MDS or CMML-2
Not eligible for IC or HSCT	Active autoimmune disease
ECOG PS 0-2	Severe hypersensitivity to study treatment ingredients
AST and ALT ≤3 × ULN	Any uncontrolled medical condition or condition requiring systemic steroid or immune suppressive treatment
Total bilirubin ≤1.5 × ULN	History of organ transplant or HSCT
Estimated glomerular filtration rate ≥30 mL/min/1.73 m²	AML or primary/secondary MF, therapy-related myeloid neoplasms

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; IPSS-R, Revised International Prognostic Scoring System; MF, myelofibrosis; TIM-3, T-cell immunoglobulin domain and mucin domain-3; ULN, upper limit of normal; vH/H/IR-MDS, very high/high/intermediate-risk myelodysplastic syndrome.

STIMULUS-MDS3 (NCT04812548)[7]

- STIMULUS-MDS3 is an international, open-label, single-arm, Phase II trial that explores triplet therapy of sabatolimab combined with AZA and the BCL-2 inhibitor venetoclax
- STIMULUS-MDS3 is ongoing and recruiting as of March 8, 2022
- Study design is shown in **Figure 5**
- Eligibility criteria are described in **Table 3**

Figure 5. Study Design of STIMULUS-MDS3

*Duration of response for patients who achieved hematologic improvement or better.

AZA, azacitidine; CR, complete remission; DLT, dose-limiting toxicity; EFS, event-free survival; HMA, hypomethylating agent; IV, intravenous; LFS, leukemia-free survival; mCR, bone marrow CR; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; SC, subcutaneous;TI, transfusion independence; VEN, venetoclax.

Table 3. Highlighted Inclusion and Exclusion Criteria for STIMULUS-MDS3

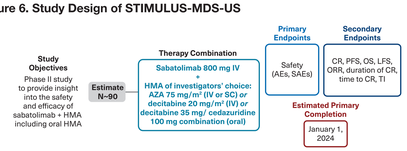
Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Prior TIM-3 therapy or any BCL-2 inhibitors
vH/H/IR-MDS per IPSS-R risk assessment	Previous treatment for vH/H/IR-MDS
Not eligible for IC or HSCT at time of screening	Active autoimmune disease
ECOG PS 0-2	Severe hypersensitivity to study treatment ingredients
AST and ALT ≤3 × ULN	Any uncontrolled medical condition or condition requiring systemic steroid or immune suppressive treatment
Total bilirubin ≤1.5 × ULN	History of organ transplant or HSCT
Estimated glomerular filtration rate ≥30 mL/min/1.73 m²	AML, therapy-related MDS, CMML, MDS/MPN, or primary/secondary MF

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; MF, myelofibrosis; TIM-3, T-cell immunoglobulin domain and mucin domain-3; ULN, upper limit of normal; vH/H/IR-MDS, very high/high-risk myelodysplastic syndrome.

STIMULUS-MDS-US (NCT04878432)[8]

- STIMULUS-MDS-US is a US-based, open-label, single-arm, Phase II trial investigating sabatolimab + HMAs of investigators' choice (AZA intravenous [IV] or SC, decitabine IV or oral decitabine)
- STIMULUS-MDS-US is ongoing and recruiting as of March 8, 2022
- Study design is shown in **Figure 6**
- Eligibility criteria are described in **Table 4**

Figure 6. Study Design of STIMULUS-MDS-US



AE, adverse event; AZA, azacitidine; CR, complete remission; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IV, intravenous; mCR, marrow CR; ORR, overall response rate; OS, overall survival; PR, partial remission; SAE, serious AE; SC, subcutaneous; TI, transfusion independence.

Table 4. Highlighted Inclusion and Exclusion Criteria for STIMULUS-MDS-US

Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Prior TIM-3 therapy
vH/H/IR-MDS per IPSS-R risk assessment	Previous treatment for vH/H/IR-MDS
Not eligible for immediate myeloablative/ chemotherapy or HSCT	Active autoimmune disease
ECOG PS 0-2	Severe hypersensitivity to study treatment ingredients
AST and ALT ≤3 × ULN	Any uncontrolled medical condition or condition requiring systemic steroid or immune suppressive treatment
Total bilirubin ≤2 × ULN	History of organ transplant or HSCT
Estimated glomerular filtration rate ≥30 mL/min/1.73 m²	AML, CMML, or current diagnosis of MDS with IPSS-R ≤3

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; IPSS-R, Revised International Prognostic Scoring System; MF, myelofibrosis; TIM-3, T-cell immunoglobulin domain and mucin domain-3; ULN, upper limit of normal; vH/H/IR-MDS, very high/high-risk myelodysplastic syndrome.

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