Clinical Trial Evaluation

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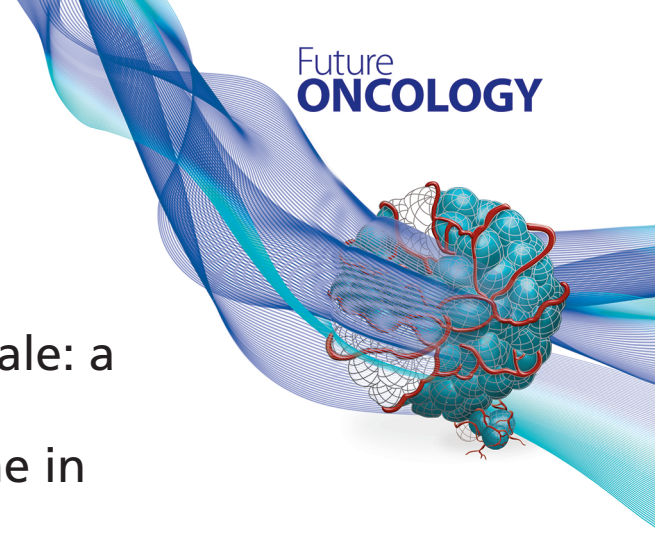

STIMULUS-MDS2 design and rationale: a phase III trial with the anti-TIM-3 sabatolimab (MBG453) + azacitidine in higher risk MDS and CMML-2

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Patients with higher-risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) unfit for hematopoietic stem cell transplantation have poor outcomes. Novel therapies that provide durable benefit with favorable tolerability and clinically meaningful improvement in survival are needed. T-cell immunoglobulin domain and mucin domain-3 (TIM-3) is an immuno-myeloid regulator expressed on immune and leukemic stem cells in myeloid malignancies. Sabatolimab is a novel immunotherapy targeting TIM-3 with a potential dual mechanism of reactivating the immune system and directly targeting TIM-3+ leukemic blasts suppressing the growth of cancer cells. Here, we describe the aims and design of the phase III STIMULUS-MDS2 trial, which aims to demonstrate the potential for sabatolimab plus azacitidine to improve survival for patients with higher-risk MDS and CMML-2 (NCT04266301).

Clinical Trial Registration: NCT04266301 (ClinicalTrials.gov)

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Myelodysplastic syndromes (MDS), also referred to as myelodysplastic neoplasms, include a complex group of hematopoietic stem cell (HSC) neoplasms characterized by ineffective hematopoiesis and progressive bone marrow (BM) failure resulting in blood cytopenias, cytogenetic and molecular abnormalities, and poor survival prognosis [1–3]. Chronic myelomonocytic leukemia (CMML) has features that overlap with MDS, including an inherent risk of progression to acute myeloid leukemia (AML) and short overall survival [4]. Patients with higher-risk MDS and CMML are often not eligible for allogeneic hematopoietic stem cell transplant (alloHSCT) and have poor survival when given available treatments including hypomethylating agent (HMA) monotherapy [4–7]. Patients with HMA failure have even fewer therapeutic options and worse survival (median overall survival <1 year) [4,6,8–10]. These outcomes demonstrate the importance of novel therapies that achieve durable benefits with favorable tolerability and clinically meaningful improvement in survival for patients with higher-risk MDS and CMML.

Prognosis and treatment options for patients with MDS vary according to their Revised International Prognostic Scoring System (IPSS-R) risk classification at diagnosis [2,3]. Patients with an IPSS-R score >3.5 are collectively referred to as 'higher-risk'; this group is composed of patients with the highest risk scores from the intermediate-risk

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group, and all patients in the high-risk and very high-risk groups [11]. As the risk classification score increases, the median duration of survival becomes shorter [3]. Patients with CMML are classified according to the presence of blasts (CMML-0, CMML-1 and CMML-2) which also holds prognostic significance [4,12].

In both MDS and CMML, patients with higher risk classifications, along with those with 'at-risk' disease subtypes, experience increased severity of symptoms stemming from BM failure [3,12]. Among patients with MDS, ~40% present with anemia and up to 80% will develop anemia over time. This leads to ~90% of patients requiring red blood cell (RBC) transfusions throughout the course of the disease [13]. Transfusion-requiring anemia is associated with inferior outcomes among MDS patients, and achieving transfusion-free intervals is associated with improved survival in patients with higher-risk MDS [13,14]. Fatigue, a severe symptom of anemia and often combined with pain and anxiety, is especially distressing for patients and greatly impacts their quality of life (QOL) [14,15]. Aside from prolonging patient survival, treatment options that lower transfusion frequency, minimize fatigue, and improve QOL are needed for these patients.

Available pharmacologic treatment options for patients with higher-risk MDS and CMML do not provide long-term survival benefit in most cases [6,16,17]. Many patients with MDS are of advanced age, frail, and present with comorbidities; more than 90% are not candidates for alloHSCT, the only potentially curative option [5,18]. HMAs, azacitidine and decitabine, are the only approved treatments for patients with higher-risk MDS who are not eligible for alloHSCT [10]. Additionally, patients with CMML-2 are often ineligible for alloHSCT and HMAs are the only treatment option for patients with a white blood cell count <12,000 [4,19]. The median overall survival for patients with higher-risk MDS after azacitidine treatment in the AZA-001 clinical trial was 24.5 months [6], although the reported survival in real-world and registry studies is substantially shorter at ~11–17 months [20,21]. Clinical trials with HMAs in patients with CMML are limited; prolonged overall survival has not been demonstrated in these patients [7]. Early-phase trials of combination strategies with HMAs have been reported to improve outcomes in patients with MDS, but improved survival has yet to be observed with combination therapy in large, randomized trials [22–24]. Despite the continued research efforts for more than a decade since the first approval of HMA therapy, there is still a significant unmet need for treatment options that provide durable benefit with favorable tolerability, better QOL, and clinically meaningful improvement in survival for patients with higher-risk MDS and CMML [25].

Trial

Sabatolimab is a novel immunotherapy that targets T-cell immunoglobulin domain and mucin domain-3 (TIM-3), an immuno-myeloid regulator that is expressed on immune cells and leukemic stem cells (LSCs) [26–30]. The STIMULUS Clinical Trial Program is evaluating the potential for sabatolimab to emerge as a therapeutic option for patients with myeloid malignancies. This broad program includes numerous trials evaluating the early and long-term efficacy and safety of sabatolimab combination therapy in patients with MDS, CMML and AML, with the potential for investigation of additional myeloid malignancies [31]. The ongoing STIMULUS-MDS1 phase II, randomized trial evaluating sabatolimab plus HMA therapy in higher-risk MDS (NCT03946670) has completed enrollment, and primary end points evaluate complete remission (CR) and progression-free survival (PFS) [31,32].

Here we describe the trial design of STIMULUS-MDS2, a phase III, randomized trial evaluating the clinical effects of sabatolimab plus azacitidine versus placebo plus azacitidine in adults with higher-risk MDS and CMML-2 (NCT04266301). The primary end point is overall survival. Key secondary end points include improvement in transfusion-free intervals and QOL. The overall survival primary end point of STIMULUS-MDS2 aims to provide definitive evidence of the potential long-term benefits of sabatolimab plus HMA therapy in patients with higher-risk MDS. Additional clinical trials included in the STIMULUS program are planned or ongoing; findings from these studies may provide further support for the use of sabatolimab as a novel immunotherapy for patients with myeloid malignancies. Given the preliminary findings of sabatolimab plus HMA in early-phase trials and the need for treatment options that offer durable clinical survival benefit with favorable tolerability and better QOL, STIMULUS-MDS2 will investigate a new potential treatment approach using sabatolimab plus HMA for patients with a high unmet need.

Background & rationale

Several signaling pathways can transform preleukemic HSCs into LSCs, which can self-renew and further replicate. This leads to a shift from normal hematopoiesis to the production of leukemic clones, some gaining relapse-specific mutations that may, in part, contribute to the resistance to therapy and the short overall survival of patients with higher-risk MDS [33–36]. TIM-3 is reported to be expressed on LSCs, but not normal HSCs [26,27,35] and to promote

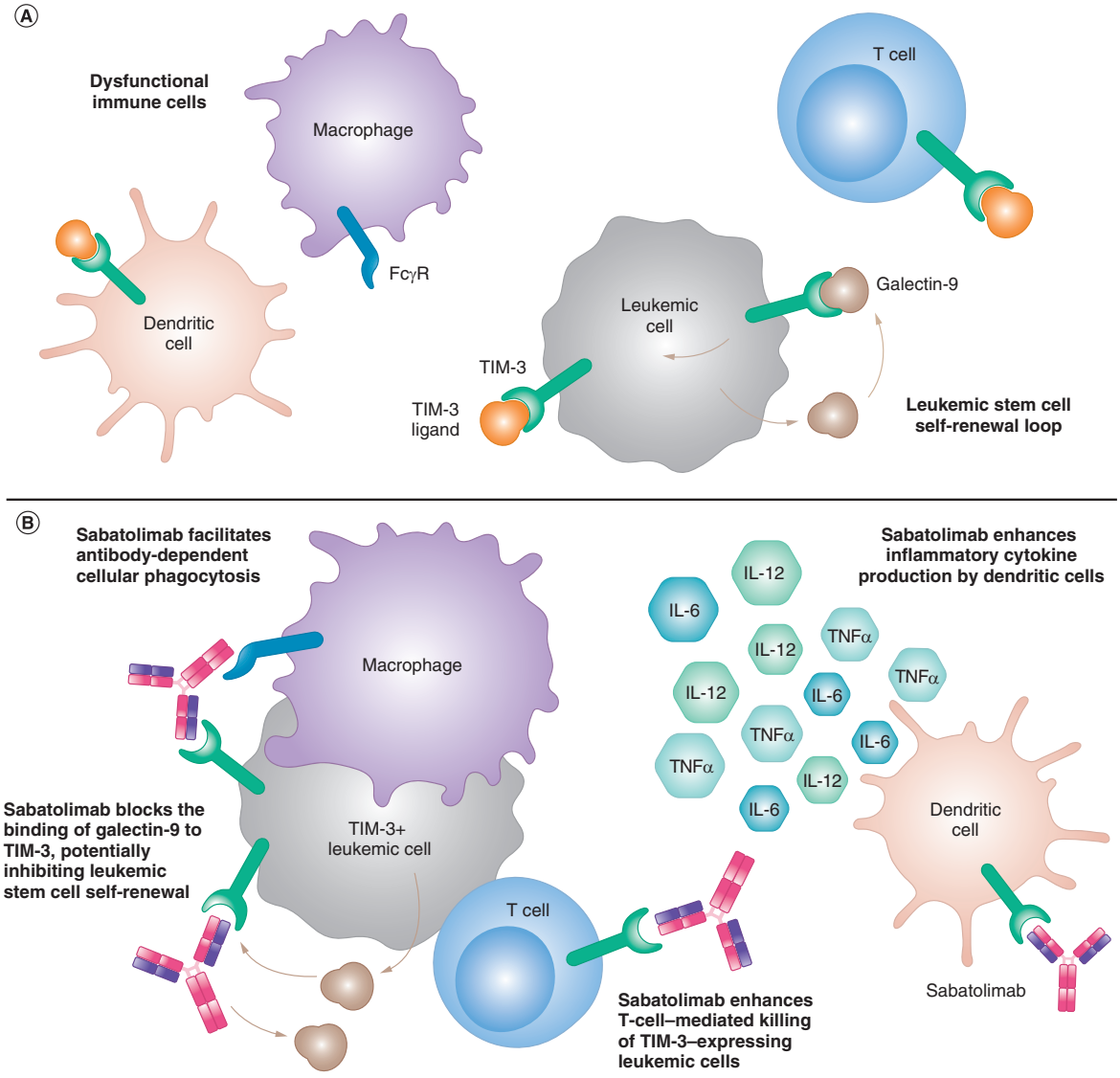

Figure 1. Sabatolimab putative mechanism of action on TIM-3, an immuno-myeloid regulator. (A) TIM-3 is an inhibitory receptor expressed on several immune cells including T cells, macrophages, and dendritic cells and regulates innate and adaptive immune responses. TIM-3 is also expressed on LSCs/blasts in myeloid malignancies. Interaction of TIM-3 with galectin-9 has been reported to form an autocrine stimulatory loop that drives leukemic stem cell self-renewal. **(B)** Sabatolimab has diverse effects on different cellular compartments via binding to TIM-3 and enhancing immune function. Sabatolimab induces phagocytic uptake of target cells by macrophages, potentially facilitating cell-mediated killing of TIM-3 expressing leukemic stem cells/blasts. Sabatolimab partially blocks the interaction of TIM-3 and galectin-9 and potentially inhibits TIM-3/galectin-9–pro-survival signaling pathways involved in self-renewal of LSCs. Sabatolimab increases dendritic cell activation as seen by enhanced secretion of pro-inflammatory cytokines, and also augments T-cell mediated killing of TIM-3+ leukemic cells.
FcγR: Fc gamma receptor; IL: Interleukin; LSC: Leukemic stem cell; MDS: Myelodysplastic syndrome; TIM-3: T-cell immunoglobulin domain and mucin domain-3.

an autocrine stimulatory loop via the TIM-3–galectin-9 interaction, which supports LSC self-renewal leading to disease progression and AML [26,28,29]. Production of TIM-3 ligands, such as galectin-9, is increased in patients with MDS, thereby contributing to disease progression [29].

Preclinical studies show that sabatolimab functions as an immunotherapeutic agent with immuno-myeloid activity and with an immuno-modulatory mechanism to combat myeloid malignancies by reactivating the immune system, boosting its ability to eliminate leukemic stem cells (Figure 1 [27]). Although it remains unclear how these

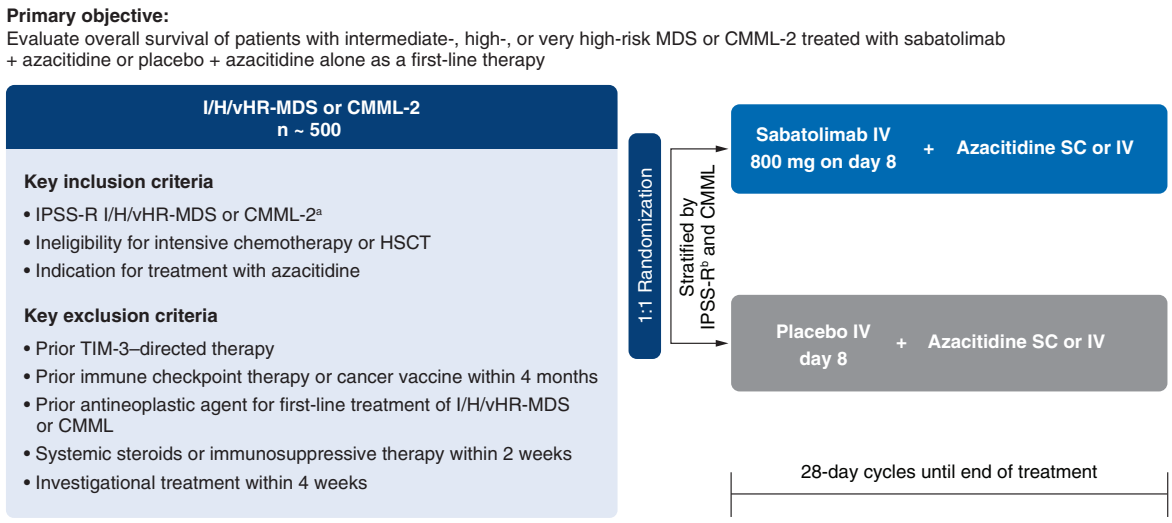

Figure 2. STIMULUS-MDS2 trial design.
[a]Defined according to the IPSS-R criteria: very high-risk (>6 points), high-risk (>4.5-6 points), or intermediate-risk (>3-4.5 points).
[b]IPSS-R prognostic risk score (intermediate-, high-, very high-risk).
CMML-2: Chronic myelomonocytic leukemia-2; CR: Complete remission; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5 L: EuroQol Five Dimensions Questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; H: High; HI: Hematologic improvement; HSCT: Hematopoietic stem cell transplant; I: Intermediate; IPSS-R: Revised International Prognostic Scoring System; IV: Intravenously; LFS: Leukemia-free survival; mCR: Bone marrow CR; MDS: Myelodysplastic syndrome; PFS: Progression-free survival; PK: Pharmacokinetics; PR: Partial remission; RBC: Red blood cell; SC: Subcutaneous; TIM-3: T-cell immunoglobulin domain and mucin domain-3; vHR: Very high-risk.

mechanisms may relate to clinical effects in patients, the potential dual mechanisms of sabatolimab provide a novel therapeutic approach for patients with myeloid malignancies.

Results from the phase I/Ib portion of the first-in-human study of sabatolimab, both as monotherapy and in combination with spartalizumab, demonstrated favorable tolerability in patients with advanced solid tumors [37]. Stable disease was observed in 25.6% (34/133) of patients who received sabatolimab monotherapy [37]. Final analysis from a phase Ib study of sabatolimab plus HMA therapy demonstrated clinical benefit with favorable tolerability [38]. Patients with high- and very high-risk MDS had an overall response rate of 56.9% in evaluable patients, a response duration of 17.1 months, and 12-month PFS of 54.0% [38]. Patients with newly diagnosed AML had an overall response rate of 42.5% in evaluable patients, a response duration of 12.6 months, and a 12-month PFS of 26.8% [38]. The most common adverse events (AEs) observed were similar to those AEs expected with single-agent HMA therapy, such as hematologic and gastrointestinal AEs [38]. Discontinuation from the trial due to an AE was infrequent; few possible immune-mediated AEs (imAEs) related to treatment were noted in patients with MDS, and all were grade 1/2 [38]. These preliminary results validate TIM-3 as a promising therapeutic target in myeloid malignancies and support further clinical development of sabatolimab in patients with higher-risk MDS.

Design

STIMULUS-MDS2 is an ongoing phase III, randomized, double-blind trial evaluating sabatolimab plus azacitidine versus placebo plus azacitidine in IPSS-R higher-risk MDS or CMML-2 (Figure 2). This trial is fully enrolled with 530 patients randomized at a 1:1 ratio to receive either sabatolimab plus azacitidine or placebo plus azacitidine, stratified according to IPSS-R: intermediate-risk MDS, high-risk MDS, very high-risk MDS or CMML-2.

The primary objective of the STIMULUS-MDS2 trial is to evaluate overall survival of patients with intermediate-, high- or very high-risk MDS or CMML-2 treated with sabatolimab plus azacitidine or placebo plus azacitidine as a first-line therapy. Key secondary objectives are between-arm comparisons of time to definitive deterioration of fatigue, RBC transfusion-free intervals, and improvement of fatigue and physical and emotional functioning. Other

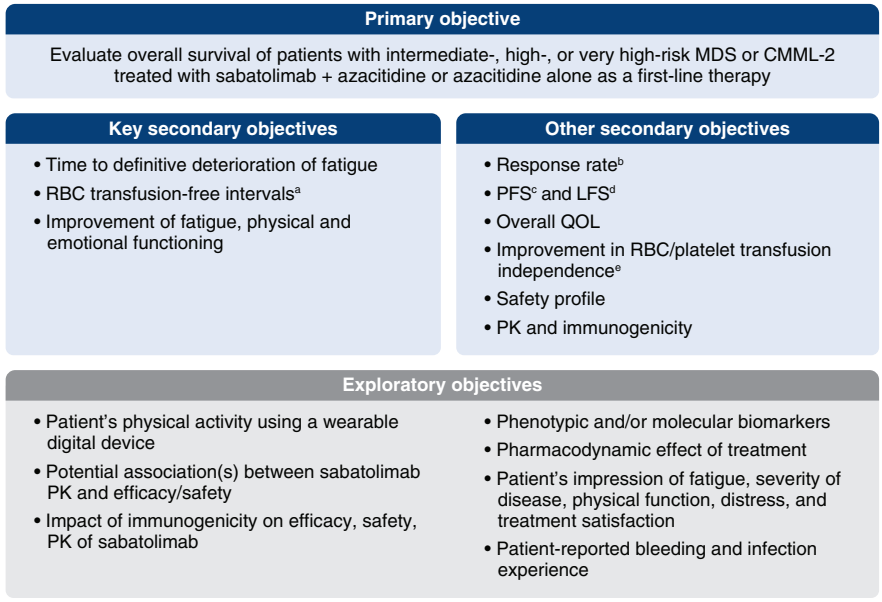

Figure 3. STIMULUS-MDS2 trial objectives.
[a]Transfusion-free intervals compose the cumulative time with no RBC transfusion for ≥8 weeks after randomization until death.
[b]Response rate is the proportion of patients with best overall response of either CR, mCR, PR, or HI according to the IWG response criteria in MDS at any time during the study.
[c]Progression-free survival is the time from randomization to disease progression, relapse from CR, or death.
[d]Leukemia-free survival refers to the time from randomization to evidence of ≥20% blasts in BM or peripheral blood, evidence of extramedullary leukemia, or death.
[e]Transfusion independence refers to the proportion of patients who received <3 units of RBCs/platelets for ≥16 consecutive weeks among transfusion-dependent patients at baseline or those who received ≥3 units within 8 consecutive weeks prior to screening.
BM: Bone marrow; CMML-2: Chronic myelomonocytic leukemia-2; CR: Complete remission; HI: Hematologic improvement; IWG: International Working Group; LFS: Leukemia-free survival; mCR: Bone marrow CR; MDS: Myelodysplastic syndrome; OS: Overall survival; PFS: Progression-free survival; QOL: Quality of life; PK: Pharmacokinetics; PR: Partial remission; RBC: Red blood cell.

secondary and exploratory objectives for efficacy and safety include response rates, PFS, leukemia-free survival, improvement in transfusion independence, pharmacokinetics (PK) and pharmacodynamics, and biomarker analyses (Figure 3).

This trial was designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations, and the Declaration of Helsinki. Investigators/institutions conducted the trial in accordance with their Institutional Review Boards/Independent Ethics Committees. Informed consent was obtained from all patients before inclusion in the trial.

At randomization, eligible patients must have morphologically confirmed MDS defined by >3 points per IPSS-R or morphologically confirmed CMML-2 with white blood cells $<13 \times 10^9$/l at diagnosis (2016 WHO classification [12]). Patients should be eligible for azacitidine treatment with no immediate plans for treatment with intensive chemotherapy or alloHSCT. Key exclusion criteria include previous TIM-3-directed therapy, immune checkpoint therapy or cancer vaccine ≤4 months before randomization, or first-line treatment for higher-risk MDS or CMML with any antineoplastic agent. Other eligibility criteria are shown in Table 1.

Patients are randomized to receive either sabatolimab 800 mg intravenously (iv.) on Day 8 plus azacitidine 75 mg/m^2 (iv. or subcutaneously [sc.]) on days 1–7 or days 1–5, 8, and 9, or placebo plus azacitidine at the same dose and frequency. Patients on placebo plus azacitidine are given placebo with the same dosing schedule and administration methods used for sabatolimab. The use of sabatolimab 800 mg iv. every 4 weeks was prompted by the results of earlier trials, which showed excellent safety and tolerability across all doses and schedules with high TIM-3 engagement at both the 400-mg every 2 weeks and 800-mg every 4 weeks sabatolimab doses [39]. Treatment

Table 1. Eligibility criteria for STIMULUS-MDS2.

Inclusion criteria
• Age ≥18 years old • Morphologically confirmed diagnosis of MDS (2016 WHO) classified as either intermediate- (>3 to ≤4.5 points), high- (>4.5 to ≤6 points) or very high-risk (>6 points) by IPSS-R or morphologically confirmed diagnosis of CMML-2 (2016 WHO) with WBC $<13 \times 10^9$/l • With an indication for azacitidine based on local standard medical practice • Not eligible for intensive chemotherapy or HSCT according to investigator based on local standard medical practice • ECOG performance status of 0, 1 or 2 • Adequate kidney and liver function: eGFR ≥30 mL/min/1.73 m^2, AST and ALT ≤3 × upper limit of normal, and total bilirubin ≤1.5 × upper limit of normal • With signed informed consent and able to communicate and able to comply with the study procedures
Exclusion criteria
• Any prior exposure to TIM-3-directed therapy • Prior immune checkpoint inhibitor therapy or cancer vaccines within 4 months prior to randomization • Previous first-line treatment for higher-risk MDS (IPSS-R) or CMML with any antineoplastic agent including chemotherapy, lenalidomide and HMAs • Investigational treatment within 4 weeks prior to randomization (except if checkpoint inhibitor, minimum interval of 4 months) • Any immunosuppressive therapy including systemic steroid therapy within 14 days prior to randomization • Live vaccine within 30 days prior to randomization • History of severe hypersensitivity reaction to any ingredient of the study treatment, or to monoclonal antibodies • Diagnosed with AML myelofibrosis or therapy-related myeloid neoplasms (2016 WHO) • History of organ transplant or HSCT • Prior malignancy except lower-risk MDS, those with history of adequately treated malignancy with no ongoing antineoplastic treatment during trial • Active autoimmune disease requiring systemic therapy or other severe and/or uncontrolled medical condition • Active HBV or HCV infection not controlled under antiviral therapy. HIV not controlled by standard therapy • At risk for pregnancy, whether sexually active male unwilling to use contraceptives or women of childbearing potential without contraceptive use. Pregnant or breastfeeding

ALT: Alanine aminotransferase; AML: Acute myeloid leukemia; AST: Aspartate aminotransferase; CMML-2: Chronic myelomonocytic leukemia-2; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HMA: Hypomethylating agent; HSCT: Hematopoietic stem cell transplant; IPSS-R: Revised International Prognostic Scoring System; MDS: Myelodysplastic syndrome; TIM-3: T-cell immunoglobulin domain and mucin domain-3; WBC: White blood cell count; WHO: World Health Organization.

is administered in 28-day cycles. Treatment doses may be modified or interrupted for patients who cannot tolerate the protocol-specified dosing schedule.

The primary end point of the STIMULUS-MDS2 trial is overall survival, defined as the time from randomization until death due to any cause, regardless of start of new therapies, alloHSCT, or discontinued treatment. Information regarding patients' survival status is gathered either through visits or through phone calls, and if a patient is not known to have died, overall survival is analyzed using the latest date the patient was known to be alive. Analysis of overall survival will be based on the full analysis set (FAS) and will be estimated using the Kaplan–Meier method. To compare the overall survival between treatment arms, a stratified log-rank test (overall 1-sided 2.5% level of significance) is planned to be used. The hazard ratio and 95% CI will be calculated from a stratified Cox model.

For the key secondary end points, time to definitive deterioration of fatigue is measured through the use of the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue [40]). Other patient-reported outcomes (PROs) will be assessed using the European Organization for Research and Treatment of Cancer's core QOL questionnaire (EORTC-QLQ-C30) and the EuroQol Five Dimensions Questionnaire (EQ-5D-5L) [41,42]. RBC transfusion-free intervals correspond to the cumulative number of intervals that the patient is transfusion free for at least 8 weeks.

The related clinical question for the key secondary QOL end points refers to the well-being of patients after randomization status and covers the entire patient journey. A complete focus on response rate in clinical trials may not be clinically meaningful if not accompanied by improvement in QOL and ideally prolongation of survival [43]. As a consequence, in this trial QOL data will continue to be collected beyond end of study treatment, beyond disease progression or relapse from CR, and also after start of new therapies (including HSCT). Disease-modifying therapies might result in benefits when study treatment is terminated, and patients might enter a treatment-free period with absence of therapy-related toxicities and disease-related symptoms. The study treatment might enable patients to receive HSCT which may have further impact on QOL. QOL assessments covering the whole patient journey will address the key questions of patients and doctors regarding overall outcome when deciding on a treatment option. This approach follows similar considerations as the primary end point, overall survival. Overall survival is considered to be the most robust efficacy end point and is a gold standard as it reflects the overall outcome of a therapy regardless of treatment discontinuation, disease progression, or start of new therapies.

Exploratory biomarker evaluations are conducted at baseline and during the course of the trial to improve understanding of the treatment effect of sabatolimab, to measure minimal residual disease levels, to identify

potential molecular subgroups that may benefit from sabatolimab, and to evaluate patterns of clonal evolution and mutational clearance. A correlative analysis of TIM-3 expression is evaluated in cellular subpopulations of interest. Additional correlative analyses include assessment of immune changes induced by TIM-3 blockade and the potential impact of galectin-9 levels on disease progression and response to treatment. No pre-specified subgroup analyses of efficacy data are planned based on expression cut-off of TIM-3 or galectin-9, but these analyses will be considered. Subgroup analyses based on molecular groups of interest (e.g., IPSS-Molecular [IPSS-M] and *TP53* mutation status) are planned.

The safety of sabatolimab plus azacitidine therapy will be evaluated based on the incidence and severity of AEs and serious AEs (SAEs) as reported according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5).The occurrence of imAEs will be evaluated based on the consistency of the AE with an immune-mediated mechanism and ruling out of alternative explanations through serologic, histologic, and immunological assessments, as well as treatment with corticosteroids when appropriate. Changes in baseline laboratory tests and vital signs are monitored, sabatolimab serum concentrations and PK parameters are collected, and immunogenicity is assessed by testing antidrug antibody at baseline and on treatment. Sabatolimab PK, immunogenicity, and pharmacodynamics, including the measurement of pharmacodynamic markers such as soluble TIM-3, are evaluated in all patients during the course of the trial.

BM assessments are conducted at screening and pre-dose on cycle 7 Day 1 and cycle 13 Day 1 and subsequently every 12 cycles until the end of treatment. The schedule of BM assessments was designed to minimize patient burden, while allowing for sufficient data collection to support relevant secondary trial objectives. Additional BM assessments can be performed if clinically indicated (eg, if progression or relapse is suspected). Hematologic assessments were conducted at screening and pre-dose on Day 1 and 8 and thereafter on Day 1 of every cycle. Patients who end study treatment for any reason other than progressive disease, death, lost to follow-up, or withdrawal will enter the posttreatment follow-up period. During posttreatment follow-up, patients receive hematology and PRO assessments every 3 months, response assessments every 12 months, with blood transfusion information collected throughout the period. Patients who discontinue the study due to progression or who have disease progression during the posttreatment follow-up period enter the survival follow-up period. Survival follow-up includes overall survival and PRO assessments every 3 months. Patients who become eligible for alloHSCT following treatment are included in both posttreatment and survival follow-up periods. If end of treatment was brought about by progressive disease, patients will directly enter the survival follow-up period. Overall survival and other efficacy data, including PROs, are planned to be collected for up to 5 years after the last patient is randomized.

PK, immunogenicity, soluble TIM-3, and biomarker samples are collected at specific time points before, during, and/or at end of treatment, and during follow-up (except for biomarkers). An unscheduled PK sample is obtained when an AE or SAE leading to discontinuation is experienced, an unscheduled immunogenicity sample is obtained when an imAE is suspected, and both a PK and immunogenicity sample are taken if disease progression is confirmed.

Efficacy analyses will include all randomized patients; each patient will be analyzed according to the treatment and strata to which they were assigned (FAS). Safety analyses will be performed in all patients who received at least one dose of any study treatment. The study follows a group-sequential design with a futility interim and an efficacy interim analysis, which will be reviewed by an independent Data Monitoring Committee prior to the primary analysis.

Discussion

Currently available options for the treatment of patients with higher-risk MDS and CMML provide limited survival benefit for most patients [4–6]. A novel treatment that could offer durable responses with clinically meaningful survival with no added toxicity and enhanced QOL is needed. Sabatolimab is a novel immunotherapy that reactivates the immune system, boosting its ability to potentially eliminate LSCs, and directly targets TIM-3+ leukemic blasts, suppressing the growth of cancer cells [27]. Final analysis of sabatolimab plus HMA therapy in an early-phase study shows potential efficacy and durability in patients with high- and very high-risk MDS [38]. In this study, sabatolimab did not add clinically significant toxicity to HMA therapy [38].

Given the number of combination approaches with HMAs in clinical trials, the apparent lack of added safety concerns with sabatolimab plus HMAs may offer advantages for older and more frail patients who might not be able to tolerate severe myelosuppression. Additionally, sabatolimab could be administered in the outpatient or inpatient setting depending on institutional considerations. Further, sabatolimab is administered only once every 28 days. As such, patients may perceive sabatolimab as a manageable treatment option.

Several therapies beyond traditional HMAs are currently under development for this patient population. Oral HMAs offer the advantage of administration in the outpatient setting; however, no clinically meaningful survival benefit has been observed relative to traditional HMAs [6,44]. Venetoclax, a BCL2 inhibitor, is currently being investigated in higher-risk MDS [45]. Findings from a phase I trial of venetoclax plus azacitidine in patients with higher-risk MDS showed a favorable overall response rate with a manageable safety profile; however, there was no difference in durability of responses compared with previous trials on HMAs [6,45,46]. Magrolimab, another agent in development for higher-risk MDS, is an anti-CD47 monoclonal antibody that increases phagocytosis of tumor cells. Patients who were given magrolimab plus azacitidine have shown improved responses, with AEs similar to those given placebo plus azacitidine [47]. Additionally, patients with wild-type tumor protein 53 (*TP53*) have shown similar responses than those with *TP53* mutations when treated with magrolimab plus azacitidine [48]. Potential concerns related to on-target anemia resulted in a temporary clinical hold that was placed and subsequently lifted on magrolimab in combination with azacitidine treatment [49]. Emavusertib is being investigated as a monotherapy and in combination with azacitidine or venetoclax in MDS and AML. Emavusertib is an IRAK inhibitor and has shown preliminary efficacy in relapsed/refractory AML; however, no patients with MDS achieved a CR [50]. CPX-351 is under development for the treatment of patients with MDS following HMA failure. CPX-351 is a liposomal formulation of cytarabine and daunomycin that may improve tolerability and efficacy of intensive chemotherapy; however, it is only approved in patients with AML post MDS [51]. Moreover, the phase III study of pevonedistat in combination with azacitidine failed to meet its primary end point of event-free survival [52]. These results highlight the need for long-term outcomes from large, randomized, phase III data sets.

Recent updates to World Health Organization guidelines for Haematolymphoid Tumours, International Consensus Classification of Myeloid Neoplasms and Acute Leukemia, and 2022 European LeukemiaNet recommendations for AML [53–55] may inform future patient eligibility in trials and modify treatment decisions as some patients may be differently categorized into the new MDS/AML category for patients with 10% to 19% blasts. Additionally, the newly developed clinical-molecular prognostic model (IPSS-M) improves the risk stratification of patients with MDS by combining genomic profiling with hematologic and cytogenetic parameters [56]. These updates to existing, and development of new classification systems may help develop and validate novel risk-tailored treatment strategies and may subsequently identify patient populations that are not benefiting from current treatment options, which will collectively reshape the prognostic and therapeutic landscapes for MDS and CMML-2.

The STIMULUS Clinical Trial Program includes multiple trials evaluating sabatolimab as a potential first-in-class immuno-myeloid therapy for patients with myeloid malignancies, including MDS and CMML. STIMULUS-MDS1 was initiated before STIMULUS-MDS2 and the findings from both trials aim to demonstrate efficacy of sabatolimab in the treatment of patients with higher-risk MDS and CMML-2. STIMULUS-MDS2 will evaluate overall survival, aiming to confirm any benefits seen in STIMULUS-MDS1 [31]. In addition to the studies focusing on higher-risk MDS, the program includes studies evaluating sabatolimab doublet or triplet therapy in patients with lower-risk MDS, which are currently recruiting (NCT04810611), AML unfit for intensive chemotherapy (STIMULUS-AML1, NCT04150029), and AML post-transplant with measurable residual disease, which is also recruiting (STIMULUS-AML2, NCT04623216). Overall, the STIMULUS trial program was designed to evaluate sabatolimab for patients with myeloid malignancies. STIMULUS-MDS2 focuses on survival and aims to confirm the durability and long-term clinical benefit of sabatolimab plus azacitidine and to demonstrate benefits in QOL for patients with higher-risk MDS and CMML-2.

Conclusion

Patients with higher-risk MDS and CMML have a substantial unmet need for treatment options that can provide durable clinically meaningful survival benefit with acceptable safety and improved QOL. Sabatolimab is a novel immuno-myeloid therapy that targets TIM-3. Sabatolimab in combination with HMA, in an early-phase study, has shown potential durable clinical benefit in patients with high- and very high-risk MDS. The safety profile of sabatolimab in combination with HMA was consistent with that reported for HMA alone. As part of the STIMULUS Clinical Trial broad program, STIMULUS-MDS2 evaluates the combination of sabatolimab and azacitidine in patients with higher-risk MDS and CMML-2. Findings from STIMULUS-MDS2, particularly overall survival and QOL end points, aim to support the potential of sabatolimab for improved and more durable outcomes in patients who currently have very limited treatment options.

Executive summary

- Patients with higher risk myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) who are not candidates for intensive chemotherapy or allogeneic hematopoietic stem cell transplant (alloHSCT) have poor outcomes when given single-agent hypomethylating agents (HMAs).
- Novel therapies that provide durable responses with clinically meaningful survival benefit with improved quality of life (QOL) are needed.
- T-cell immunoglobulin domain and mucin domain-3 (TIM-3) is an immuno-myeloid target and cell surface receptor that is expressed on immune cells as well as leukemic stem cells (LSCs), but not on hematopoietic stem cells, and is associated with proliferation of LSCs and progression of MDS.

Background & rationale

- Sabatolimab is a novel immunotherapy targeting TIM-3. Sabatolimab has immuno-modulatory potential by reactivating the immune system and potentially increasing the killing of LSCs and blasts.
- Final results from a phase Ib trial in high- and very-high risk MDS treated with sabatolimab in combination with HMAs showed durable clinical benefit with favorable tolerability.

STIMULUS-MDS2

- STIMULUS-MDS2 is a phase III, randomized, double-blind, multicenter trial evaluating sabatolimab in combination with azacitidine compared with placebo and azacitidine in Revised International Prognostic Scoring System higher risk MDS or CMML-2.
- The primary end point is overall survival; key secondary end points include time to deterioration of fatigue, transfusion-free intervals, and improvement in QOL.

Discussion/conclusion

- The STIMULUS Clinical Trial Program includes multiple trials evaluating sabatolimab as a potential first-in-class immuno-myeloid therapy for patients with myeloid malignancies.
- The findings from STIMULUS-MDS2 aim to confirm the potential of sabatolimab plus azacitidine to deliver a clinically meaningful benefit, and establish sabatolimab as an option for patients with higher-risk MDS and CMML-2.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: https://www.futuremedicine.com/doi/suppl/10.2217/fon-2022-1237

Author contributions

All authors met the criteria for authorship set forth by the International Committee of Medical Journal Editors, and were involved in conception, preparation, and approval of the manuscript. AM Zeidan serves as the primary author and V Santini is the senior author for this manuscript

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Ethical conduct of research

This trial was designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, applicable local regulations, and the Declaration of Helsinki. Investigators/institutions conducted the trial in accordance with their Institutional Review Boards/Independent Ethics Committees. Informed consent was obtained from all patients before inclusion in the trial.

References

Papers of special note have been highlighted as: • of interest; • • of considerable interest

1. Cogle CR. Incidence and burden of the myelodysplastic syndromes. *Curr. Hematol. Malig. Rep.* 10(3), 272–281 (2015).
2. Fenaux P, Haase D, Sanz GF, Santini V, Buske C. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 25(Suppl. 3), iii57–69 (2014).
3. Greenberg PL, Tuechler H, Schanz J *et al.* Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 120(12), 2454–2465 (2012).
4. Itzykson R, Fenaux P, Bowen D *et al.* Diagnosis and treatment of chronic myelomonocytic leukemias in adults: recommendations from the European Hematology Association and the European LeukemiaNet. *Hemasphere* 2(6), e150 (2018).
5. Steensma DP. Myelodysplastic syndromes: diagnosis and treatment. *Mayo Clin. Proc.* 90(7), 969–983 (2015).
6. Fenaux P, Mufti GJ, Hellstrom-Lindberg E *et al.* Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* 10(3), 223–232 (2009).

• **Pivotal trial that established azacitidine as the standard-of-care treatment for patients with higher risk myelodysplastic syndrome (MDS), with an observed median overall survival of 24.5 months.**

7. Xu R, Li M, Wu P *et al.* Hypomethylating agents in the treatment of chronic myelomonocytic leukemia: a meta-analysis and systematic review. *Hematology* 26(1), 312–320 (2021).
8. Jabbour E, Garcia-Manero G, Batty N *et al.* Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. *Cancer* 116(16), 3830–3834 (2010).
9. Prébet T, Gore SD, Esterni B *et al.* Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J. Clin. Oncol.* 29(24), 3322–3327 (2011).
10. National Comprehensive Cancer Network. National Comprehensive Cancer Network: Myelodysplastic Syndromes (Version 1.2022) (2021). www.nccn.org/professionals/physician_gls/pdf/mds.pdf
11. Pfeilstöcker M, Tuechler H, Sanz G *et al.* Time-dependent changes in mortality and transformation risk in MDS. *Blood* 128(7), 902–910 (2016).
12. Arber DA, Orazi A, Hasserjian R *et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 127(20), 2391–2405 (2016).
13. Bell JA, Galaznik A, Blazer M *et al.* Transfusion-free interval is associated with improved survival in patients with higher-risk myelodysplastic syndromes engaged in routine care. *Leuk. Lymphoma* 60(1), 49–59 (2019).
14. Chan LSA, Shapiro R, Buckstein R *et al.* Initial transfusion intensity predicts survival in myelodysplastic syndrome. *Leuk. Lymphoma* 55(10), 2296–2300 (2014).
15. Escalante CP, Chisolm S, Song J *et al.* Fatigue, symptom burden, and health-related quality of life in patients with myelodysplastic syndrome, aplastic anemia, and paroxysmal nocturnal hemoglobinuria. *Cancer Med.* 8(2), 543–553 (2019).
16. Coston T, Pophali P, Vallapureddy R *et al.* Suboptimal response rates to hypomethylating agent therapy in chronic myelomonocytic leukemia; a single institutional study of 121 patients. *Am. J. Hematol.* 94(7), 767–779 (2019).
17. Lachowiez C, Cook RJ, Hayes-Lattin B *et al.* Allogeneic transplantation outcomes amongst a contemporary cohort of high-risk myelodysplastic syndrome and acute myeloid leukemia patients aged ≥70 years. *Hematol. Oncol. Stem Cell Ther.* 12(2), 105–109 (2019).
18. Niscola P, Palombi M, Trawinska MM *et al.* Managing myelodysplastic syndromes in very old patients: a teaching case report. *Clin. Interv. Aging* 8, 391–394 (2013).

19. Santini V, Allione B, Zini G *et al.* A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia. *Leukemia* 32(2), 413–418 (2018).

20. Zeidan AM, Stahl M, Sekeres MA, Steensma DP, Komrokji RS, Gore SD. A call for action: increasing enrollment of untreated patients with higher-risk myelodysplastic syndromes in first-line clinical trials. *Cancer* 123(19), 3662–3672 (2017).

•• **Critical review of the accumulating data suggesting that the actual survival impact of azacitidine, in patients with higher-risk MDS is significantly lower than what was observed in the AZA-001 trial and discussion of the potential explanations for this discrepancy.**

21. Dinmohamed AG, Van Norden Y, Visser O *et al.* Effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes in daily practice: results from the Dutch population-based PHAROS MDS registry. *Leukemia* 29(12), 2449–2451 (2015).

22. Daver N, Boddu P, Garcia-Manero G *et al.* Hypomethylating agents in combination with immune checkpoint inhibitors in acute myeloid leukemia and myelodysplastic syndromes. *Leukemia* 32(5), 1094–1105 (2018).

23. Garcia JS, Wei AH, Borate U *et al.* Safety, efficacy, and patient-reported outcomes of venetoclax in combination with azacitidine for the treatment of patients with higher-risk myelodysplastic syndrome: a phase 1b study. Presented at: *American Society of Hematology Virtual Congress.* 5–8 December 2020 (Abstract 656).

24. Chandhok NS, Lewis R, Prebet T. Hypomethylating agent based combinations in higher risk myelodysplastic syndrome. *Leuk. Lymphoma* 61(5), 1012–1027 (2020).

25. Kaminskas E, Farrell AT, Wang YC, Sridhara R, Pazdur R. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist* 10(3), 176–182 (2005).

26. Acharya N, Sabatos-Peyton C, Anderson AC. Tim-3 finds its place in the cancer immunotherapy landscape. *J. Immunother. Cancer* 8(1), e000911 (2020).

27. Schwartz S, Patel N, Longmire T *et al.* Characterization of sabatolimab, a novel immunotherapy with immuno-myeloid activity directed against TIM-3 receptor. *Immunotherapy Advances* 2, ltac019 (2022).

•• **Preclinical data describing sabatolimab's mechanism of action as a novel immunotherapy targeting T-cell immunoglobulin domain and mucin domain-3 (TIM-3).**

28. Wolf Y, Anderson AC, Kuchroo VK. TIM3 comes of age as an inhibitory receptor. *Nat. Rev. Immunol.* 20(3), 173–185 (2020).

29. Asayama T, Tamura H, Ishibashi M *et al.* Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. *Oncotarget* 8(51), 88904–88917 (2017).

30. Haubner S, Perna F, Köhnke T *et al.* Coexpression profile of leukemic stem cell markers for combinatorial targeted therapy in AML. *Leukemia* 33(1), 64–74 (2019).

31. Zeidan AM, Al-Kali A, Borate U *et al.* P787: sabatolimab (MBG453) combination therapy regimen for patients with higher-risk myelodysplastic syndromes: the myelodysplastic syndromes studies in the STIMULUS immuno-myeloid clinical trial program. *HemaSphere* 6, 682–683 (2022).

• **Trials in progress presentation decribing the four studies in the STIMULUS Clinical Trials Program in MDS.**

32. Zeidan AM, Ando K, Rauzy O *et al.* Primary Results of STIMULUS-MDS1: a randomized, double-blind, placebo-controlled phase II study of TIM-3 inhibition with sabatolimab added to hypomethylating agents (HMAs) in adult patients with higher-risk myelodysplastic syndromes (MDS) [oral]. Presented at: *2022 American Society of Hematology (ASH) Annual Meeting and Exposition.* New Orleans, LA, USA 12 December 2022 (Abstract 853).

33. Bencomo-Alvarez AE, Rubio AJ, Gonzalez MA, Eiring AM. Energy metabolism and drug response in myeloid leukaemic stem cells. *Br. J. Haematol.* 186(4), 524–537 (2019).

34. Riether C, Schürch CM, Ochsenbein AF. Regulation of hematopoietic and leukemic stem cells by the immune system. *Cell Death Differ* 22(2), 187–198 (2015).

35. Kikushige Y, Miyamoto T, Yuda J *et al.* A TIM-3/Gal-9 autocrine stimulatory loop drives self-renewal of human myeloid leukemia stem cells and leukemic progression. *Cell Stem Cell* 17(3), 341–352 (2015).

36. Ding L, Ley TJ, Larson DE *et al.* Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. *Nature* 481(7382), 506–510 (2012).

37. Curigliano G, Gelderblom H, Mach N *et al.* Phase I/Ib clinical trial of sabatolimab, an anti-TIM-3 antibody, alone and in combination with spartalizumab, an anti-PD-1 antibody, in advanced solid tumors. *Clin. Cancer Res.* 27(13), 3620–3629 (2021).

38. Brunner AM, Esteve J, Porkka K *et al.* Efficacy and safety of sabatolimab in combination with hypomethylating agents in patients with very high/high-risk myelodysplastic syndrome and acute myeloid leukemia: final analysis from a phase Ib study. Presented at: *2021 American Society of Hematology (ASH) Annual Meeting and Exposition.* Atlanta, GA, USA, 10–14 December 2021.

•• **Phase Ib data of sabatolimab plus hypomethylating agents in patients with high and very-high risk MDS presented at ASH 2021.**

39. Wei AH, Esteve J, Porkka K *et al.* Sabatolimab (MBG453) dose selection and dose-response analysis in myelodysplastic syndrome/acute myeloid leukemia: population pharmacokinetics modeling and evaluation of clinical efficacy/safety by dose.. Presented at: *2020 American Society of Hematology Virtual Congress.* 5–8 December 2020.

40. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J. Pain Symptom Manage.* 13(2), 63–74 (1997).
41. Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J. Natl Cancer Inst.* 85(5), 365–376 (1993).
42. Herdman M, Gudex C, Lloyd A *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual. Life Res.* 20(10), 1727–1736 (2011).
43. Sekeres MA, Steensma DP. Rethinking clinical trial endpoints in myelodysplastic syndromes. *Leukemia* 33(3), 570–575 (2019).

•• **Reviews challenges in drug development in MDS with respect to aligning trial end points with treatment goals meaningful to patients.**

44. Thota S, Oganesian A, Azab M, Griffiths EA. Role of cedazuridine/decitabine in the management of myelodysplastic syndrome and chronic myelomonocytic leukemia. *Future Oncol.* 17(16), 2077–2087 (2021).
45. Wei A, Garcia J, Borate U *et al.* Updated safety and efficacy of venetoclax in combination with azacitidine for the treatment of patients with treatment-naive higher-risk myelodysplastic syndromes: phase Ib results. Presented at: *European Hematology Association Virtual Congress.* 9–17 June 2021 (Abstract EP917).
46. Uy N, Singh A, Gore SD, Prebet T. Hypomethylating agents (HMA) treatment for myelodysplastic syndromes: alternatives in the frontline and relapse settings. *Expert Opin Pharmacother* 18(12), 1213–1224 (2017).
47. Sallman D, Malki MA, Asch A *et al.* The first-in-class anti-CD47 antibody magrolimab combined with azacitidine is well-tolerated and effective in MDS patients: phase 1b results. Presented at: *European Hematology Association Virtual Congress.* 11–14 June 2020 (Abstract S187).
48. Sallman DA, Al Malki MM, Asch AS *et al.* Magrolimab in combination with azacitidine for patients with untreated higher-risk myelodysplastic syndromes (HR MDS): 5F9005 phase 1B study results. Presented at: *European Hematology Association Annual Congress.* Vienna, Austria, 9–12 June 2022 (Abstract S166).
49. Gilead Sciences Inc. Gilead Sciences Inc: FDA lifts partial clinical hold on MDS and AML magrolimab studies (2022). www.gilead.com/news-and-press/press-room/press-releases/2022/4/fda-lifts-partial-clinical-hold-on-mds-and-aml-magrolimab-studies
50. Garcia-Manero G, Winer ES, Deangelo DJ *et al.* S129: TAKEAIM LEUKEMIA- a phase 1/2A study of the IRAK4 inhibitor emavusertib (CA-4948) as monotherapy or in combination with azacitidine or venetoclax in relapsed/refractory AML or MDS. *HemaSphere* 6, 30–31 (2022).
51. Santini V. How I treat MDS after hypomethylating agent failure. *Blood* 133(6), 521–529 (2019).
52. Ades L, Girshova L, Doronin VA *et al.* Pevonedistat plus azacitidine vs azacitidine alone in higher-risk MDS/chronic myelomonocytic leukemia or low-blast percentage AML. *Blood Adv.* 6(17), 5132–5145 (2022).
53. Khoury JD, Solary E, Abla O *et al.* The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* 36(7), 1703–1719 (2022).
54. Dohner H, Wei AH, Appelbaum FR *et al.* Diagnosis and Management of AML in Adults: 2022 ELN Recommendations from an International Expert Panel. *Blood* 140(12), 1345–1377 (2022).
55. Arber DA, Orazi A, Hasserjian RP *et al.* International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. *Blood* (2022).
56. Bernard E, Tuechler H, Greenberg PL *et al.* Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *NEJM Evidence* 1(7), EVIDoa2200008 (2022).