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# Imetelstat in intermediate-2 or high-risk myelofibrosis refractory to JAK inhibitor: IMPactMF phase III study design

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Imetelstat, a first-in-class telomerase inhibitor, demonstrated meaningful clinical benefit including a robust symptom response rate and potential overall survival benefit in IMbark, a phase II study in intermediate-2 or high-risk myelofibrosis (MF) patients who have relapsed after or are refractory to JAK inhibitors. We describe the rationale and design for the phase III trial, IMPactMF (NCT04576156), an open-label evaluation of imetelstat versus best available therapy, excluding JAK inhibitors, in MF patients refractory to JAK inhibitor. Imetelstat 9.4 mg/kg is administered as an intravenous infusion every 21 days. Primary objective is to assess overall survival. Secondary objectives include symptom and spleen responses, progression-free survival, clinical response assessment, bone marrow fibrosis reduction, safety and pharmacokinetics. Biomarker, cytogenetics and mutation analyses will be performed.

**Plain language summary:** Imetelstat is a new type of treatment being studied in patients with myelofibrosis (MF). Encouraging clinical benefits were seen in a phase II clinical trial of imetelstat in higher risk MF. This article discusses the ongoing phase III trial, called IMPactMF. IMPactMF is comparing imetelstat to best available therapy (BAT) in MF patients not responding to a specific type of treatment, a JAK inhibitor. Imetelstat is an intravenous infusion, given every 21 days. This study will determine if patients who receive imetelstat live longer than patients who are given BAT. It will also collect information on additional outcomes, including safety.

Trial Registration Number: NCT04576156 (ClinicalTrials.gov)

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**Keywords:** biomarkers • fedratinib • imetelstat • JAK inhibitor • myelofibrosis • pacritinib • ruxolitinib • safety • survival • telomerase

## Background

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN), a clonal disease in the same group as polycythemia vera (PV) and essential thrombocythemia (ET). The manifestations of MF are broad, stemming from clonal myeloproliferation, ineffective erythropoiesis, bone marrow stromal changes, hepatosplenic extramedullary hematopoiesis and aberrant cytokine expression, resulting in splenomegaly, constitutional symptoms and hematologic abnormalities of moderate-to-severe anemia, thrombocytopenia and leukocytosis [1]. Survival post-MF diagnosis is strongly associated with the patient's Dynamic International Prognostic Scoring System (DIPSS) risk category. Approxi-

mately 70% of individuals with overt MF are categorized as intermediate-2 or high-risk disease [2]; whereas median overall survival (OS) from diagnosis is estimated at 14 years for patients with intermediate-1 risk disease, it falls to about 4 years for intermediate-2 disease and to 1.5 years for high-risk disease [3].

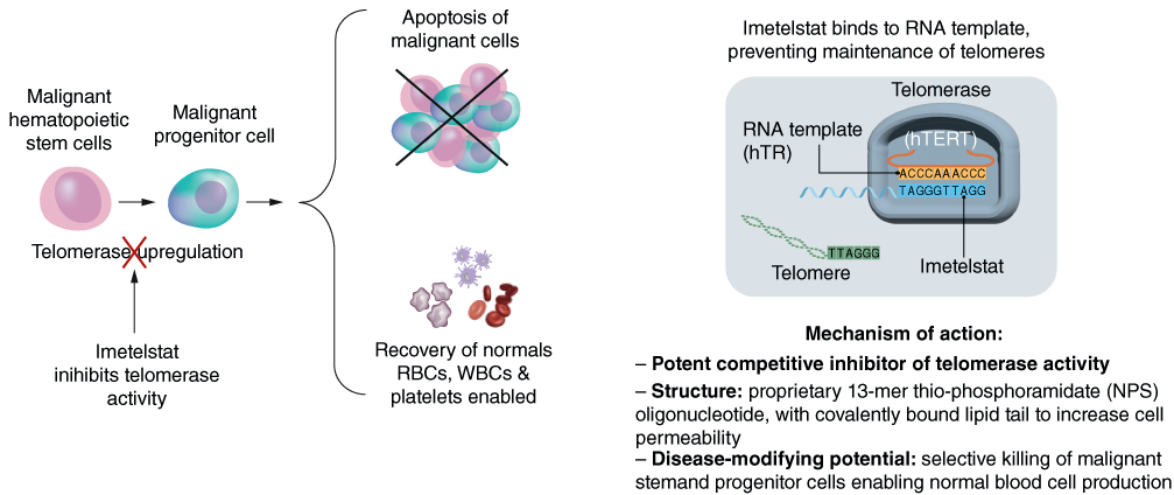
Allogeneic hematopoietic stem-cell transplantation (ASCT) is the only treatment that can induce long-term remissions in patients with MF. However, many patients are not considered candidates for transplant because of competing medical comorbidities and advanced age. For nearly a decade, the JAK1/JAK2 inhibitor ruxolitinib was the only approved treatment option for intermediate or high-risk MF [4]. In 2019, fedratinib, a selective JAK2 inhibitor, became the second approved treatment in the USA for MF, indicated for intermediate-2 or high-risk disease regardless of prior JAK inhibitor treatment [5]. The approval of pacritinib in February 2022 will allow access to JAK inhibition for a population of patients with thrombocytopenia ( $<50 \times 10^9/l$ ) who have historically been excluded from clinical trials with currently available JAK inhibitors [6]. In two phase III studies (PERSIST-1 and PERSIST-2), pacritinib has demonstrated both spleen and symptom benefit with limited myelosuppression and acceptable non-hematologic toxicity profile in patients with thrombocytopenia who would normally either receive suboptimal doses of ruxolitinib (i.e., 5 mg twice daily) or just supportive care only [7,8].

Despite the benefits reported with ruxolitinib in the front-line setting [9,10], a high proportion of patients discontinue treatment (1-, 2- and 3-year discontinuation rates are 49, 71 and 86%, respectively), primarily for loss of therapeutic effect and lack of response [11]. For patients who discontinue treatment with ruxolitinib, median OS is dismal and ranges from 11 to 16 months [12–17]. Subsequent lines of therapy have not proven to extend survival in this subset of MF patients. The more recently presented analyses of OS in the second-line setting with other agents such as JAK2 inhibitors have not always been uniform in design, baseline patient characteristics, and appropriate follow-up for OS analyses. For example, the SIMPLIFY-2 trial of momelotinib versus best available therapy (BAT) enrolled patients who were simply exposed to JAK inhibitor therapy and not relapsed/refractory to JAK inhibitor treatment [18,19]. Furthermore, the JAKARTA2 study with fedratinib was placed on clinical hold and therefore it is difficult to interpret the OS results, with median OS not reached [20,21]. As discussed herein, imetelstat offers a non-JAK inhibitor option to a subset of patients that have effectively failed JAK inhibition as a mechanism of action and in which the prospect of progressive disease and limited survival necessitates a different class of agent that has the potential to target the MF hematopoietic stem cell population. The IMPactMF phase III study is the first prospectively designed OS study in a strictly defined patient population which would offer appropriate assessment of potential benefit in the refractory MF setting.

## Imetelstat

The clonal myeloproliferation inherent to MF arises from malignant hematopoietic stem and progenitor cells (HSPCs) with shorter telomeres and multiple clonal genetic abnormalities [22]. In malignant progenitor clones, high activation and continual upregulation of telomerase allows for ongoing, uncontrolled proliferation [23]. Telomerase activity (TA) is generally undetectable in normal somatic cells; however, it is expressed in ~85% of human cancers, as well as in cancer progenitor cells that allow for dysregulated cell growth and tumor metastasis [24]. In patients with MPNs, TA (as measured in granulocytes) is high [25] whereas telomere length (TL) is short, regardless of *JAK2* mutational status – supporting the therapeutic potential for telomerase inhibition in both *JAK2V617F* and *JAK2* wild-type (including patients with a *CALR* or *MPL* mutation) MF [22,25,26].

Imetelstat is a 13-mer thiophosphoramidate (NPS) oligonucleotide, with a covalently bound lipid tail to increase permeability, that acts as a potent competitive inhibitor of telomerase activity (Figure 1) [27,28]. Imetelstat specifically binds to the RNA template of human telomerase and acts as a competitive inhibitor of telomerase enzymatic activity. Telomerase inhibition leads to loss of a cancer cell's ability to maintain TL, resulting in cell-cycle arrest, apoptosis, or senescence [27,28]. Treatment of various cancer cells with imetelstat *in vitro* increases their sensitivity to radiation, decreases their clonogenic potential, and results in altered expression of stem cell-related genes [29–31]. The selective killing of malignant HSPCs enables normal blood cell production and suggests disease-modifying potential. *In vitro* studies have demonstrated that imetelstat selectively inhibits spontaneous megakaryocytic colony-forming unit growth from the blood of patients with MPNs such as ET, but not from healthy individuals [32]. Inhibition of neoplastic progenitor cell growth was observed *ex vivo* [33]. Furthermore, imetelstat demonstrated the ability to selectively reduce the malignant megakaryocyte colony-forming unit from patients with MF and ET, but had a minimal effect on clonogenicity of normal megakaryocyte progenitors [34]. The first proof-of-concept study of imetelstat in hematological malignancies was a phase II study that enrolled patients with ET who were resistant to, intolerant of, or had refused conventional therapies, with a hematologic response rate of 100% and a complete



**Figure 1. Mechanism of action of imetelstat.**

hTERT: Human telomerase reverse transcriptase; RBC: Red blood cell; WBC: White blood cell.

| Clinical benefit   | Imetelstat<br>4.7 mg/kg<br>(n = 48) | Imetelstat<br>9.4 mg/kg<br>(n = 59) |
|--|-------------------------------------|-------------------------------------|
| Median overall survival, months (95% CI)                                   | 19.9 (17.1, 33.9)                   | 28.1 (22.8, 31.6)                   |
| Bone marrow fibrosis improvement, n/N (%)                                  | 4/20 (20.0%)                        | 15/37 (40.5%)                       |
| ≥25% reduction in VAF of <i>JAK2</i> , <i>CALR</i> or <i>MPL</i> , n/N (%) | 1/18 (5.6%)                         | 8/19 (42.1%)                        |
| Symptom response at week 24 (TSS reduction ≥50%), n (%)                    | 3 (6.3%)                            | 19 (32.2%)                          |
| Spleen response at week 24 (SVR ≥35% by IRC), n (%)                        | 0                                   | 6 (10.2%)                           |
| Median progression-free survival, months (95% CI)                          | 16.7 (8.5, 19.5)                    | 23.2 (16.8, 28.3)                   |
| Clinical improvement, per IWG-MRT, n (%)                                   | 8 (16.7%)                           | 15 (25.4%)                          |
| Transfusion independence of 12 weeks, n/N (%)                              | 2/14 (14.3%)                        | 3/12 (25.0%)                        |

IRC: Independent review committee; IWG-MRT: International Working Group-Myeloproliferative Neoplasms Research and Treatment; SVR: Spleen volume reduction; TSS: Total symptom score; VAF: Variant allele frequency.

remission rate of 89% (16/18) [35]. Importantly, seven of eight patients with the *JAK2V617F* mutation achieved partial molecular response, with 72–96% reduction in allele burden. Subsequently, an open-label, pilot study was conducted to evaluate single-agent imetelstat in patients with MF [36]. Among 33 patients, the overall response rate was 21%, including four complete responses and three partial responses, and median duration of response was 18 months. Reversal of bone marrow fibrosis was observed in the four patients with complete responses and three of these patients also attained a molecular response.

To further explore the role of imetelstat in MF, IMbark/MYF2001 a randomized (1:1), single-blind, multicenter, phase II study was initiated. This study tested two doses of single-agent imetelstat (9.4 mg/kg and 4.7 mg/kg iv. once every 3 weeks) in 107 patients with intermediate-2 or high-risk MF per DIPSS who were relapsed after or refractory to JAK inhibitor treatment [37]. The co-primary end points were the spleen response (≥35% reduction in spleen volume reduction [SVR]) and symptom response (total symptom score [TSS] reduction of ≥50% as determined by the modified Myelofibrosis Symptom Assessment Form [MFSAF] version 2) rates at week 24. Key efficacy results are summarized in Table 1 [37–39]. The 9.4 mg/kg arm had a higher symptom response rate at week 24 (32.2 vs 6.3%), at which time the spleen response rate was 10.2 versus 0% in the 4.7 mg/kg arm. As of the final database lock (April 2020), with an overall follow-up of 42 months, median OS was 28.1 months for the 9.4 mg/kg arm (95% CI: 22.8, 31.6) and 19.9 months for the 4.7 mg/kg arm (95% CI: 17.1, 33.9) [38]. Overall, imetelstat treatment at 9.4 mg/kg every 21 days demonstrated dose-related improvement in OS in patients who are relapsed/refractory to JAK inhibitor treatment and other clinical benefits, including symptom response and improvement in bone marrow fibrosis, with a correlation between fibrosis improvement and OS [37,38]. Biomarker

analyses showed significant, dose-dependent reductions in the variant allele frequencies (VAFs) of key MF driver mutations [39], correlating with clinical benefits (spleen and symptom response, fibrosis improvement and OS), and there were documented cytogenetic responses – collectively suggesting disease-modifying activity of imetelstat via selective targeting of the malignant clone [37,39]. The adverse event profile was as expected and primarily consisted of cytopenias, the majority of which were manageable and reversible within 4 weeks and led to limited clinical consequences, such as infection or bleeding [37].

The promising IMbark phase II data were further supported by additional analyses in which the OS results were compared with those for a closely matched real world population of patients who discontinued ruxolitinib and were treated with BAT at the Moffitt Cancer Center. In this analysis, treatment with imetelstat was associated with longer OS compared with BAT (30 vs 12 months, respectively) in closely matched patients with MF after JAK inhibitor failure [40]. Taken together, these compelling findings supported continued study of imetelstat in a well-designed phase III randomized controlled trial in patients with refractory MF, using OS as the primary end point.

### IMPactMF/MYF3001 phase III trial

We describe the design of the randomized, open-blind, phase III trial (NCT04576156) comparing imetelstat versus BAT placebo in with intermediate-2 or high-risk MF who are refractory to JAK inhibitor treatment [41].

#### Objectives

The primary objective of this study is to compare the OS of patients treated with imetelstat versus BAT (excluding JAK inhibitors). Secondary objectives include the evaluation of symptom and spleen response rates at Week 24, progression-free survival, responses per 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria, time to and duration of responses, reduction in degree of bone marrow fibrosis, safety, pharmacokinetics and immunogenicity of imetelstat and patient-reported outcomes. As exploratory objectives, biomarkers relevant to the mechanism of action of imetelstat will be assessed to demonstrate their correlation with OS, symptom response, or spleen response, the association between baseline cytogenetic and mutational status and clinical responses will be characterized, and change in driver VAF will be evaluated in the assessment of molecular responses.

#### Key eligibility criteria

To be eligible, participants must have MF (DIPSS intermediate-2 or high-risk) that is refractory to JAK inhibitor (1 or more agent) treatment and show active symptoms of MF and measurable splenomegaly. Refractory was defined as 1) treatment with JAK inhibitor for  $\geq 6$  months, including  $\geq 2$  months at an optimal dose and no decrease in spleen volume, spleen size or symptoms from the start of JAK inhibitor treatment or a TSS score  $\geq 15$  at study entry, or 2) treatment with JAK inhibitor for  $\geq 3$  months with maximal doses and no decrease in spleen volume/size or symptoms. Participants may not have received prior imetelstat or have elevated blasts ( $> 10\%$ ) in the peripheral blood or marrow. Other eligibility criteria are listed in [Box 1](#).

Of note, the phase III study has carefully defined a patient population of refractory MF who have had an adequate trial of treatment with a JAK inhibitor with respect to duration and dose optimization without achieving clinically meaningful benefit in terms of reduction in spleen size/volume or disease-related symptoms and, therefore, would not be considered an appropriate candidate for further treatment with a JAK inhibitor. Given that patients in this study would have failed to respond and have discontinued JAK inhibitor treatments after they have had adequate challenge and exposure to a JAK inhibitor without achieving meaningful clinical benefit, JAK inhibitors are not included in the BAT arm.

#### Study design

IMPactMF phase III is a multicenter, randomized (2:1), open-label trial ([Figure 2](#)). Approximately 320 patients will be randomized to receive imetelstat and BAT, respectively. Eligible participants will be stratified based on intermediate-2 or high-risk per DIPSS and platelet count at study entry. Participants randomized to imetelstat will receive a starting dose of 9.4 mg/kg administered by intravenous infusion once every 21 days. Those randomized to BAT will receive investigator-selected non-JAK inhibitor treatment per local standard of care and investigator decision, including but not limited to hydroxyurea, thalidomide or an analog of thalidomide, interferon, danazol, hypomethylating agents, chemotherapy or a combination of treatments as appropriate in this setting. Of note,



**Box 1. Patient eligibility criteria in the IMpactMF phase III trial.**

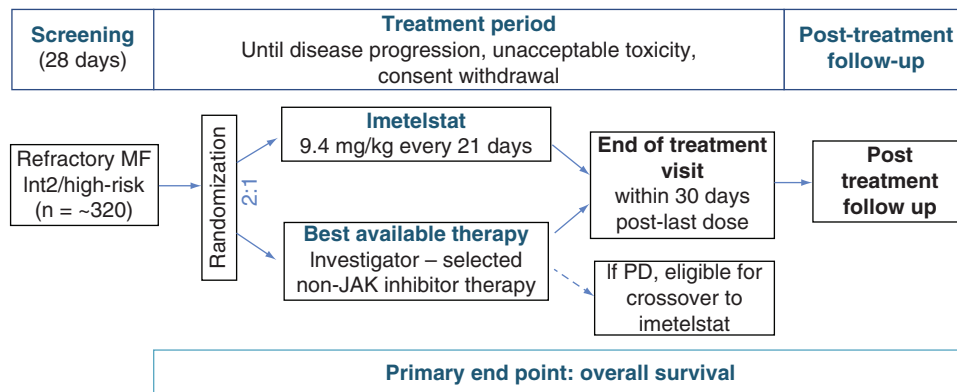
**Inclusion criteria**

- Man or woman ≥ 18 years of age
- DIPSS intermediate-2 or high-risk MF
- Diagnosis of primary MF by WHO or PET-MF or PPV-MF by IWG-MRT
- Refractory to JAK inhibitor (1 or more agent):
  - Treated for at least 6 months including 2 at an optimal dose (as assessed by the investigator) with no decrease in spleen volume (<10% by MRI or CT), spleen size (<30% by palpation or length by imaging), or symptoms (<20% by MFSAF or myeloproliferative neoplasm SAF) from start of JAK inhibitor treatment. Or TSS ≥15 on MFSAF v4.0 at study entry
  - Treated for at least 3 months at maximal dose (e.g., 20–25 mg twice daily ruxolitinib) and no decrease in spleen volume, size or symptoms per definitions above
- Measurable splenomegaly with palpable spleen ≥ 5 cm or spleen volume ≥ 450 cm<sup>3</sup>
- Active symptoms of MF by MFSAF v4.0.
- Absolute neutrophil count ≥ 1.5 × 10<sup>9</sup>/l independent of growth factor support
- Platelets ≥ 75 × 10<sup>9</sup>/l independent of platelet support
- ECOG performance status 0–2

**Exclusion Criteria**

- Peripheral blood blast count ≥ 10% or bone marrow blast count ≥ 10%.
- Any chemotherapy or MF directed therapy, including investigational drug, immunomodulatory or immunosuppressive therapy, corticosteroids >30 mg/day prednisone or equivalent, and JAK inhibitor treatment ≤ 14 days prior to randomization.
- Major surgery within 28 days
- Prior treatment with imetelstat

CT: Computed tomography; DIPSS: Dynamic International Prognostic Scoring System; ECOG: Eastern Cooperative Oncology Group; IWG-MRT: International Working Group-Myeloproliferative Neoplasms Research and Treatment; MF: Myelofibrosis; MFSAF: Myelofibrosis Symptom Assessment Form; PET: Primary essential thrombocythemia; PPV: Primary polycythemia vera; SAF: Symptom assessment form; TSS: Total symptom score.



**Figure 2. Phase III IMpactMF study design schema.**  
Int2: Intermediate-2; MF: Myelofibrosis; PD: Progressive disease.

ASCT, splenectomy or JAK inhibitor will not be permitted as BAT. Investigators will determine and record the BAT treatment(s) prior to randomization in the event that the participant is randomized to BAT. Treatment is given until disease progression, unacceptable toxicity or withdrawal of consent. Study participants receiving BAT who have discontinued treatment and meet criteria for progressive disease (worsening splenomegaly or leukemic transformation) may crossover to receive imetelstat treatment. The primary efficacy end point of this study is OS. Secondary and exploratory end points are summarized in Box 2.

**Evaluations**

Efficacy evaluations include daily symptoms collected by the MFSAF version 4.0 e-dairy, MRI or CT assessment of spleen volume, laboratory testing, limited physical examinations, bone marrow biopsy and aspirate for disease

**Box 2. IMpactMF phase study end points.****Primary end point**

- Overall survival

**Secondary end points**

- Symptom response rate at week 24 ( $\geq 50\%$  reduction in TSS measured by MFSAF v4.0)
- Progression-free survival
- Spleen response rate at week 24 ( $\geq 35\%$  spleen volume reduction by MRI or CT)
- Complete remission, partial remission, clinical improvement, spleen response, symptom response and anemia response per 2013 IWG-MRT
- Time to and duration of responses
- Reduction in degree of bone marrow fibrosis
- Safety
- Pharmacokinetics and immunogenicity
- Patient-reported outcomes as measured by the European Organization for Research and treatment of Cancer QLQ-C30 and EuroQol-EQ-5D questionnaires

**Exploratory end points**

- Biomarkers: telomerase activity, telomere length, hTERT and correlation with overall survival, symptom response or spleen response
- Baseline cytogenetic profile
- Baseline mutation status and change of mutation burden

CT: Computed tomography; hTERT: Human telomerase reverse transcriptase; IWG-MRT: International Working Group-Myeloproliferative Neoplasms Research and Treatment; MFSAF: Myelofibrosis Symptom Assessment Form; TSS: Total symptom score.

assessment, peripheral blood smears, and limited patient-reported outcome symptom assessment. All participants will be followed for OS according to randomized treatment arm until the end of the study.

Safety will be assessed by adverse events, physical examinations, clinical laboratory parameters, electrocardiograms, vital sign measurements, Eastern Cooperative Oncology Group performance status, and concomitant medication usage. The sponsor will review the safety data on an ongoing basis. Additionally, an Independent Data Monitoring Committee (IDMC) was commissioned to monitor safety and efficacy data during the study.

Blood samples to assess both the pharmacokinetics and immunogenicity of imetelstat will be obtained from a subset of imetelstat-randomized patients. Bone marrow samples will be collected from all participants during screening to evaluate the baseline cytogenetic status by karyotyping and to evaluate the association with clinical responses. Blood samples will be collected to evaluate the baseline mutational status. The baseline mutation status and the change in mutant allele burden will be evaluated for the association with clinical responses. Additional blood samples will be collected at baseline from all participants to evaluate TA, TL and hTERT expression level to assess correlation with clinical outcomes.

**Statistical analysis methods**

The study is designed to enroll approximately 320 participants, randomly assigned in an approximately 2:1 ratio to receive treatment with either imetelstat or BAT. Assuming a hazard ratio of 0.6 for the imetelstat arm relative to BAT arm, the study has approximately 88% power to achieve a statistical significance level of 0.025 (one-sided) using a group sequential design. One interim analysis is planned, whereby the IDMC will review the results and make recommendations regarding study continuation following the pre-specified statistical guidelines. The interim analysis is expected to happen when approximately 35% of the patients planned to be enrolled have died.

Primary and secondary efficacy data will be compared between the imetelstat group and the BAT group based on the intention-to-treat (ITT) population. OS distribution will be compared between the treatment arms using stratified log-rank test adjusting for the stratification factors in the ITT population. The Kaplan–Meier method will be used to estimate the distribution for each treatment. The treatment effect (hazard ratio) and its two-sided 95% CIs will be estimated using a stratified Cox regression model. Safety variables are to be analyzed for the treated population by descriptive statistics.

## Discussion & future perspective

JAK inhibitors are currently the only approved therapy for patients with MF, and there is a high unmet need for patients with MF who experience primary or secondary response failure and have discontinued JAK inhibitor treatment. Acknowledging the limits of cross-study comparisons, the median OS of approximately 30 months for imetelstat 9.4 mg/kg in the IMbark phase II trial [37,40] was nearly double the 11–16 months that has been reported in the literature for MF patients who have discontinued JAK inhibitor treatment [12–17]. Based on this potential OS improvement, OS was selected as the primary end point in the IMpactMF phase III study, representing the first study in the MF setting to have survival as a primary end point. Approximately 180 sites are planned across North America, South America, Europe, the Middle East, Australia and Asia. IMpactMF is currently open for screening and enrollment.

## Conclusion

The phase III IMpactMF trial will elucidate the impact of imetelstat, a first-in-class telomerase inhibitor, on OS in patients with intermediate-2 or high-risk MF refractory to JAK inhibitor treatment. The study has the potential to change the treatment landscape in refractory MF and address a critical unmet need for disease-modifying therapies that will improve survival in this poor-prognosis patient population.

### Executive summary

#### Background

- Myelofibrosis (MF), a myeloproliferative neoplasm (MPN), leads to splenomegaly, constitutional symptoms, moderate to severe anemia, thrombocytopenia and leukocytosis.
- Most patients with MF have intermediate-2 or high-risk disease, with median overall survival (OS) of about 4 and 1.5 years from diagnosis, respectively.
- Allogeneic hematopoietic stem-cell transplantation (ASCT) is required to achieve long-term remission in MF, but its use is limited by patient ineligibility and high rates of mortality and severe morbidity.
- Two JAK inhibitors, ruxolitinib and fedratinib, are approved for the treatment of intermediate-2 or high-risk MF in the USA; however, discontinuation rates for loss or lack of response are high and subsequent prognosis is poor, with median survival ranging from 11 to 16 months post-ruxolitinib discontinuation.

#### Imetelstat

- Imetelstat, a 13-mer thiophosphoramidate (NPS) oligonucleotide, acts as a potent competitive inhibitor of telomerase activity (TA) by binding to the RNA template of human telomerase. Elevated TA has been detected in approximately 85% of human cancers and in cancer progenitor cells.
- Data from the phase II IMbark/MYF2001 trial of two doses imetelstat demonstrated dose-related improvement in OS (supporting the higher dose of 9.4 mg/kg), other clinical benefits, and manageable toxicities in patients with intermediate-2 or high-risk MF who were relapsed/refractory to JAK inhibitor treatment.
- In a subsequent analysis, the median OS of 30 months observed with imetelstat 9.4 mg/kg in IMbark compared favorably to that of 12 months for a closely matched real-world population of patients who received best available therapy after ruxolitinib discontinuation.
- Based on these findings, a phase III randomized controlled trial of imetelstat in patients with refractory MF with overall survival as a primary end point was warranted.

#### IMpactMF/MYF3001

- IMpactMF/MYF3001 is a global randomized, open-blind, phase III trial comparing imetelstat versus BAT placebo in patients with intermediate-2 or high-risk MF who are refractory to JAK inhibitor treatment (NCT04576156).
- Eligible patients are adults with MF (DIPSS intermediate-2 or high-risk) that is refractory to JAK inhibitor treatment and who show active symptoms of MF and measurable splenomegaly. Participants may not have received prior imetelstat or have elevated blasts (>10%) in the peripheral blood or marrow.
- Patients will be randomized (2:1; stratified based on DIPSS risk and platelet count at study entry) to receive imetelstat at a starting dose of 9.4 mg/kg administered by intravenous infusion once every 21 days or BAT (investigator-selected treatment per local standard-of-care and investigator decision, with ASCT, splenectomy or JAK inhibitor not be permitted).
- Patients receiving BAT who have discontinued treatment and meet criteria for progressive disease (worsening splenomegaly or leukemic transformation) may crossover to imetelstat.
- The primary end point is OS; secondary end points include symptom and spleen responses, progression-free survival, clinical response assessment, bone marrow fibrosis reduction, safety and pharmacokinetics.
- A total of 320 patients are anticipated to be enrolled.



### 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.

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### Ethical conduct of research

This study will be undertaken only after the Independent Ethics Committee or Institutional Review Board has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative), the informed consent form (ICF), applicable recruitment materials, and participants compensation programs, and the sponsor has received a copy of this approval. Each participant (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity.

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