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ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

BMS-986158, a Potent BET Inhibitor, in Combination with Ruxolitinib or Fedratinib in Patients (pts) with Intermediate- or High-Risk Myelofibrosis (MF): Updated Results from a Phase 1/2 Study

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Introduction

Bromodomain and extra-terminal (BET) inhibitors in combination with Janus kinase inhibitors (JAKi) have demonstrated clinical benefits in pts with MF. BMS-986158 is an orally bioavailable, potent, and selective small molecule BET inhibitor with a dose-proportional pharmacokinetic profile with linear increases in exposure, which has shown time- and dose-dependent modulation of BET target gene expression. BMS-986158 in combination with JAKi ruxolitinib (RUX) or fedratinib (FED) is being evaluated in pts with MF in the CA011-023 study (NCT04817007). Previous analyses showed that BMS-986158+RUX in first-line (1L; RUX-naïve) MF and BMS-986158+FED in second-line (2L; relapsed, refractory, or intolerant to prior RUX treatment) MF

was well tolerated, with most pts remaining on treatment, and had promising preliminary efficacy (Ayala R et al. EHA 2023. S213). Updated results with longer follow-up will be presented.

Methods

Eligible pts had primary or secondary MF and were either RUX-naïve (1L) or relapsed, refractory, or intolerant to RUX (2L), with splenomegaly (spleen volume [SV] ≥ 450 cm ^{3}), ECOG PS ≤ 2, and Dynamic International Prognostic Scoring System risk scores of intermediate-1 with symptoms, intermediate-2, or high. In dose escalation, pts with 1L MF received BMS-986158 2.0, 3.0, or 3.75 mg QD 5d on/2d off + RUX 15 mg BID; pts with 2L MF received BMS-986158 0.5, 0.75, 1.0, or 1.25 mg QD 5d on/2d off (alternative schedule for 1.0-mg dose: 5d on/2d off, 3 wks on/1 wk off) + FED 400 mg QD. Primary objectives in dose escalation were safety, tolerability, and determination of the maximum tolerated dose and/or recommended phase 2 dose (RP2D) of BMS-986158+RUX and BMS-986158+FED. Secondary objectives included spleen volume reduction (SVR) from baseline and response rate (SVR35) at wk 24. Assessment of *JAK2* variant allele frequency (VAF) was an exploratory objective. *JAK2V617* VAF was measured longitudinally in peripheral blood CD34+ stem cells using next-generation sequencing.

Results

As of May 18, 2023, 16 pts with 1L MF received BMS-986158+RUX (median age 66 y [range, 36-81]) and 24 pts with 2L MF received BMS-986158+FED (median age 68 y [range, 34-81]). At baseline, median SV was 1504 cm ^{3} (range, 524-4379) in pts treated with BMS-986158+RUX and 2222 cm ^{3} (range, 581-6598) in pts treated with BMS-986158+FED. Any grade (G) treatment-related adverse events (TRAEs) were reported in 15 (94%) pts treated with BMS-986158+RUX; G 3/4 TRAEs were thrombocytopenia (n = 7, 44%), neutropenia (n = 2, 13%), anemia, leukopenia, herpes zoster, hyperbilirubinemia, and hypertension (n = 1 each, 6%). Any G TRAEs were reported in 18 (75%) pts treated with BMS-986158+FED; G 3/4 TRAEs were thrombocytopenia and anemia (n = 6 each, 25%), hyperbilirubinemia (n=2, 8%), leukocytosis, and diarrhea (n = 1 each, 4%). No TRAEs led to discontinuation of BMS-986158+RUX; 2 TRAEs (G4 thrombocytopenia and G3 hyperbilirubinemia) led to discontinuation of BMS-986158+FED. SVR was observed at wk 12 in all evaluable pts in both treatment regimens and continued to deepen at wk 24 (Figure). Median SV at wk 24 was 603 cm ^{3} (range, 170-2532) and 1826 cm ^{3} (range, 1079-5288) in evaluable pts with 1L MF and 2L MF, respectively. In pts with 1L MF, 8/11 (73%) treated with BMS-986158 (2.0, 3.0 or 3.75 mg)+RUX met SVR35 at wk 12; 9/10 (90%) pts met SVR35 at wk 24. In pts with 2L MF, 7/12 (58%) pts treated with BMS-986158 (0.5, 0.75, 1.0, or 1.25 mg)+FED met SVR35 at wk 12; 3/7 (43%) pts met SVR35 at wk 24. At the time of reporting, 32/40 (80%) pts remained on treatment: 14/16 (88%) receiving BMS-986158+RUX and 18/24 (75%) receiving BMS-986158+FED. Available analysis of *JAK2* VAF showed reductions in the frequency of *JAK2V617F* with BMS-986158+RUX (52% max. reduction by C10, n = 7) and BMS-986158+FED (29% max. reduction by C4, n = 4).

Conclusions

These updated analyses of study CA011-023 show that BMS-986158+RUX in 1L MF and BMS-986158+FED in 2L MF continue to be well tolerated, with most patients remaining on treatment. TRAEs were mostly low-grade and transient. Thrombocytopenia, an on-target effect, was manageable and did not result in clinically significant bleeding. Both treatment regimens produced early and deep SVR by wk 12, which continued and deepened at wk 24 and beyond. The reductions observed in *JAK2* VAF provide promising preliminary data of potential disease modification. Dose expansion with BMS-986158+RUX in 1L MF has opened and is actively enrolling patients.

Disclosures Lavie: *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Advisory Board and Travel/Accommodation expenses; *Roche:* Honoraria, Other: Advisory Board; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Lecture; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Lecture; *MSD:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel/Accommodation expenses, lecture; *Medisson:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Ribrag:** *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Incyte:* Consultancy; *NanoString:* Consultancy; *Roche:* Consultancy; *Argenx:* Research Funding; *Astex Pharmaceuticals:* Research Funding; *GSK:* Research Funding; *Gilead:* Consultancy. **Loschi:** *Alexion:* Honoraria; *AstraZeneca:* Honoraria; *BMS:* Honoraria; *Gilead:* Honoraria; *GSK:* Honoraria; *Jazz:* Honoraria; *Kartos:* Honoraria; *Medac:* Honoraria; *MSD:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *Sanofi:* Honoraria; *Sobi:* Honoraria; *Telios:* Honoraria. **Hernández-Rivas:** *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene/BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *GSK:* Consultancy, Honoraria, Speakers Bureau. **Fong:** *Servier:* Honoraria, Speakers Bureau; *Novartis:* Honoraria; *Otsuka:* Honoraria; *BMS:* Honoraria; *Jazz:* Honoraria; *Pfizer:* Honoraria, Speakers Bureau; *BeiGene:* Honoraria; *Astellas:* Honoraria; *Amgen:* Honoraria; *AbbVie:* Honoraria, Speakers Bureau. **Bonifacio:** *Clinigen:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Incyte:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Kiladjian:** *Incyte Corporation:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *AOP Orphan Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *AbbVie, AOP Health, Bristol-Myers Squibb, GlaxoSmithKline, Incyte, Novartis, Pharmaessentia.:* Consultancy. **García Gutiér-**

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Figure. Mean percentage changes in spleen volume from baseline per MRI/CT from blinded independent central review (BICR) in patients treated with (A) BMS-986158+RUX and (B) BMS-986158+FED

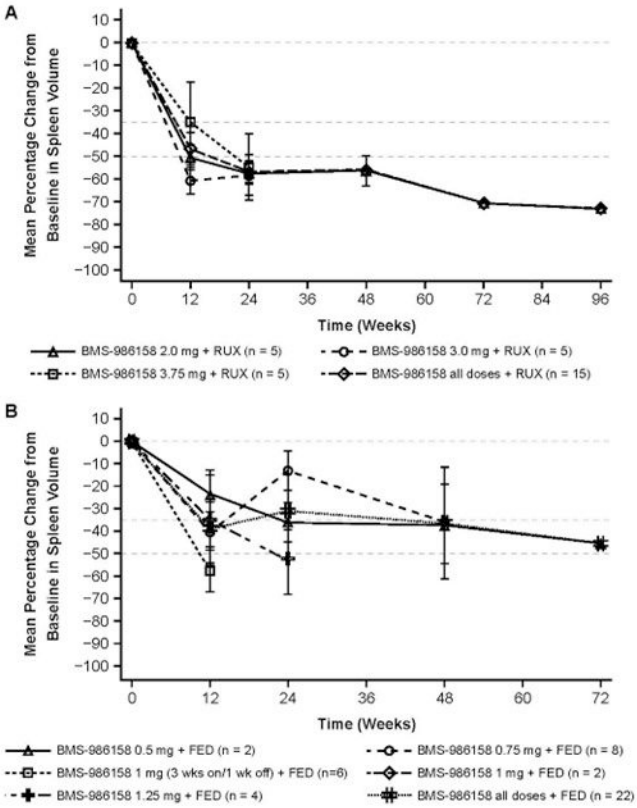

Figure 1

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