# BMS-986158, a potent BET inhibitor, in combination with ruxolitinib or fedratinib in intermediate- or high-risk myelofibrosis: results from a phase 1/2 study

MPN-381

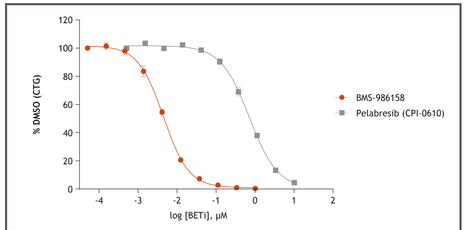
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## Introduction

- Bromodomain and extra-terminal domain inhibitors (BETi) alone and in combination with Janus kinase (JAK) inhibitors have shown clinical benefits for patients with myelofibrosis (MF)[1]
- BMS-986158 is an orally bioavailable, potent, and selective small-molecule BETi that has demonstrated:
  - A dose-proportional pharmacokinetic profile with linear increases in exposure[2,3]
  - Time- and dose-dependent modulation of BET target gene expression[2,3]
- BMS-986158 has shown more potent antitumor activity in JAK2 mutant cell lines compared with another BETi, pelabresib **(Figure 1)**[4]
- BMS-986158 is being evaluated in patients with 1L MF and 2L MF, in combination with the JAK inhibitors ruxolitinib (RUX) or fedratinib (FED), in the CA011-023 study (NCT04817007)

**Figure 1. BMS-986158 is more potent and cytotoxic than pelabresib in MF *JAK2* mutant cell line[a,4]**

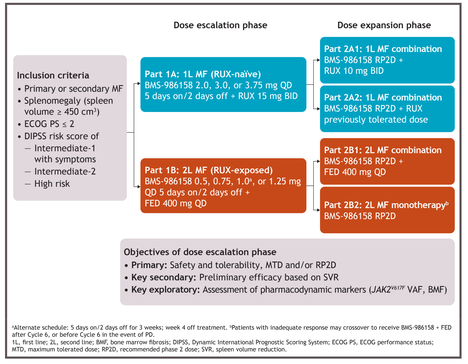



[a]HEL92.1.7 (homozygous JAK2 mutant).
CTG, CellTiter-Glo®; DMSO, dimethyl sulfoxide.

## Methods

- Study design, treatment schedules, and study endpoints for the open-label, phase 1/2 CA011-023 study are shown in **Figure 2**
- CA011-023 comprises a dose escalation phase with BMS-986158 + RUX in RUX-naïve patients (Part 1A) or BMS-986158 + FED in patients with inadequate response or intolerance to prior RUX treatment (Part 1B) and a dose expansion phase at the recommended phase 2 dose (RP2D) evaluating BMS-986158 + RUX (Part 2A) or BMS 986158 ± FED (Part 2B)
- *JAK2*$^{V617F}$ variant allele frequency (VAF) was measured in peripheral blood CD34+ stem cells using next-generation sequencing
- Data cutoff: February 27, 2023

**Figure 2. CA011-023 study design**




[a]Alternate schedule: 5 days on/2 days off for 3 weeks; week 4 off treatment. [b]Patients with inadequate response may crossover to receive BMS-986158 + FED after Cycle 6, or before Cycle 6 in the event of PD.
1L, first line; 2L, second line; BMF, bone marrow fibrosis; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, ECOG performance status; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; SVR, spleen volume reduction.

## Results

### Patients

- Patient disposition is described in **Table 1**. As of February 27, 2023, 31 patients were treated, 13 with BMS-986158 + RUX and 18 with BMS-986158 + FED **(Table 1)**

**Table 1. Patient disposition**

| Disposition | 1L MF BMS-986158 + RUX | 2L MF BMS-986158 + FED |
|---|---|---|
| **Treated, n** | 13 | 18 |
| **Discontinued treatment, n (%)** | 2 (15)[a] | 5 (28) |
| **Reason for discontinuation, n (%)** | | |
| Disease progression | 1 (8) | 1 (6) |
| Study drug toxicity | 0 | 2 (11) |
| Patient withdrawal | 0 | 1 (6) |
| AE unrelated to study drug | 1 (8) | 1 (6)[b] |
| **Ongoing treatment, n (%)** | 11 (85) | 13 (72) |
| **Median duration of treatment, weeks (range)** | 37 (1.6-97.7) | 10 (0.1-74.9) |

[a]One patient had AML transformation at C17, and 1 patient had atypical CML with *SETBP1* mutation. [b]One patient in the 1.25-mg group died from post-COVID community-acquired MRSA pneumonia.
AE, adverse event; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; MRSA, methicillin-resistant Staphylococcus aureus; SETBP1, SET binding protein 1.

- Baseline demographic and clinical characteristics are described in **Table 2**

**Table 2. Baseline demographics and clinical characteristics**

| | 1L MF BMS-986158 + RUX (n = 13) | 2L MF BMS-986158 + FED (n = 18) |
|---|---|---|
| **Median age, years (range)** | 67 (36-81) | 69 (37-77) |
| ≥ 65 years, n (%) | 8 (62) | 10 (56) |
| **Sex, n (%)** | | |
| Male | 11 (85) | 11 (61) |
| Female | 2 (15) | 7 (39) |
| **Race, n (%)** | | |
| White | 13 (100) | 16 (89) |
| Other | 0 | 2 (11) |
| **DIPSS score** | | |
| Intermediate risk-1 | 5 (39) | 7 (39) |
| Intermediate risk-2 | 7 (54) | 9 (50) |
| High risk | 1 (8) | 2 (11) |
| ***JAK2* mutation,[a] n (%)** | | |
| Positive | 8 (62) | 9 (50) |
| Negative | 3 (23) | 7 (39) |
| **Median spleen volume, cm³ (range)** | 2056 (524-4379) | 2350 (1176-6202)[b] |
| **Median platelet count, ×10⁹/L (range)** | 290 (121-583) | 182 (18[c]-604) |
| **Median hemoglobin, g/L (range)** | 111 (82-155) | 95 (71-131)[d] |

[a]JAK2 mutation status not reported for 2 patients each in the 1L MF and 2L MF groups. [b]n = 16 for baseline spleen volume in 2L MF group. [c]Patient with platelet count of 18 × 10⁹/L predose C1D1 was enrolled without meeting eligibility criteria. [d]n = 17 for baseline hemoglobin in 2L MF group.
C, cycle; D, day.

### Safety

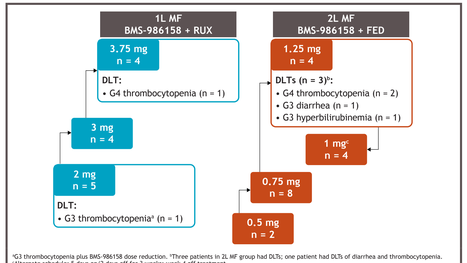
- Any-grade treatment-related adverse events (TRAEs) were reported in 12 (92%) patients treated with BMS-986158 + RUX and in 14 (78%) patients treated with BMS-986158 + FED **(Table 3)**
- No grade 5 TRAEs were reported for either combination
- Dose-limiting toxicities (DLTs) were reported in 2 patients treated with BMS-986158 + RUX (both thrombocytopenia in the 2-mg and 3.75-mg groups) and in 3 patients treated with BMS-986158 + FED (diarrhea, thrombocytopenia, and elevated bilirubin; all in the 1.25-mg group; **Figure 3**)
- Two serious TRAEs were reported: grade 3 herpes zoster (BMS-986158 + RUX) and grade 4 thrombocytopenia (BMS-986158 + FED)
- Two TRAEs led to treatment discontinuation: grade 3 blood bilirubin increase (BMS-986158 + FED) and grade 4 thrombocytopenia (BMS-986158 + FED)

**Table 3. All grade and grade 3/4 TRAEs[a,b]**

| TRAEs[a,b] | 1L MF BMS-986158 + RUX (n = 13) | | | 2L MF BMS-986158 + FED (n = 18) | | |
|---|---|---|---|---|---|---|
| | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 |
| **Patients with ≥ 1 TRAE, n (%)** | 12 (92) | 6 (46) | 1 (8) | 14 (78) | 5 (28) | 2 (11) |
| Thrombocytopenia[c] | 8 (62) | 4 (31) | 1 (8) | 8 (44) | 4 (22) | 2 (11) |
| Diarrhea | 9 (69) | 0 | 0 | 9 (50) | 1 (6) | 0 |
| Anemia | 3 (23) | 1 (8) | 0 | 8 (44) | 6 (33) | 0 |
| Herpes zoster | 2 (15) | 1 (8) | 0 | 0 | 0 | 0 |
| Hyperbilirubinemia | 1 (8) | 1 (8) | 0 | 2 (11) | 2 (11) | 0 |
| Nausea | 0 | 0 | 0 | 5 (28) | 0 | 0 |
| Dry mouth | 0 | 0 | 0 | 2 (11) | 0 | 0 |
| Vomiting | 0 | 0 | 0 | 2 (11) | 0 | 0 |
| Fatigue | 0 | 0 | 0 | 2 (11) | 0 | 0 |
| Blood creatinine increased | 0 | 0 | 0 | 2 (11) | 0 | 0 |

[a]TRAEs shown occurred in > 10% of patients in either treatment group. [b]Data in top row summarize highest grade TRAEs per patient; data for individual TRAEs summarize the highest grade within the specific TRAE. [c]Thrombocytopenia is an on-target toxicity of BMS-986158 that is managed by dose reduction and/or dose interruption.

**Figure 3. Dose escalation and dose-limiting toxicities**

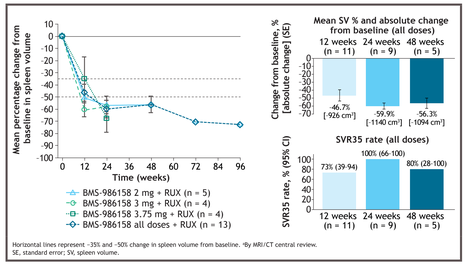



[a]G3 thrombocytopenia plus BMS-986158 dose reduction. [b]Three patients in 2L MF group had DLTs; one patient had DLTs of diarrhea and thrombocytopenia. [c]Alternate schedule: 5 days on/2 days off for 3 weeks; week 4 off treatment.
G, grade.

### Spleen volume reduction

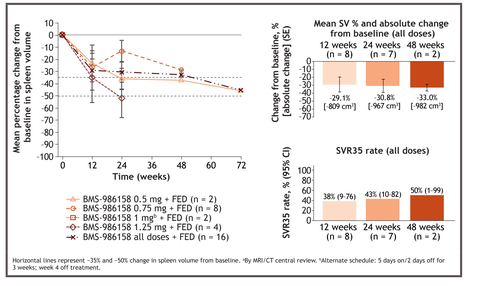
- SVR was observed at week 12 in all evaluable patients treated with BMS-986158 + RUX **(Figure 4)** and BMS-986158 + FED **(Figure 5)**
  - Responses continued to deepen beyond week 24 under ongoing treatment with BMS-986158 + RUX **(Figure 4)**
- In the BMS-986158 + RUX group, 8/11 (73%) patients met spleen volume reduction ≥ 35% (SVR35) at week 12, 9/9 (100%) met SVR35 at week 24, and 4/5 (80%) met SVR35 at week 48 **(Figure 4)**
- In the BMS-986158 + FED group, 3/8 (38%) patients met SVR35 at week 12, 3/7 (43%) met SVR35 at week 24, and 1/2 (50%) met SVR35 at week 48 **(Figure 5)**

**Figure 4. Spleen volume reduction[a]: BMS-986158 + RUX (1L MF)**




Horizontal lines represent –35% and –50% change in spleen volume from baseline. [a]By MRI/CT central review.
SE, standard error; SV, spleen volume.

**Figure 5. Spleen volume reduction[a]: BMS-986158 + FED (2L MF)**

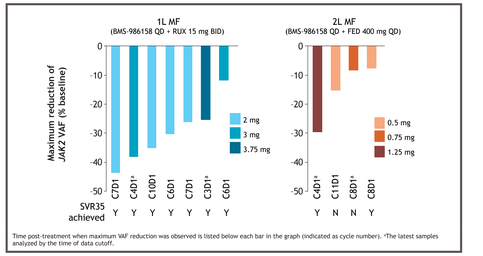



Horizontal lines represent –35% and –50% change in spleen volume from baseline. [a]By MRI/CT central review. [b]Alternate schedule: 5 days on/2 days off for 3 weeks; week 4 off treatment.

### Reduction of *JAK2*$^{V617F}$ VAF

- BMS-986158 + RUX and BMS-986158 + FED led to reduction of *JAK2*$^{V617F}$ VAF in 1L MF and 2L MF, respectively **(Figure 6)**
- 7/9 patients with SVR35 had > 25% VAF reduction

**Figure 6. Maximum *JAK2*$^{V617F}$ VAF reduction observed in 1L MF and 2L MF**

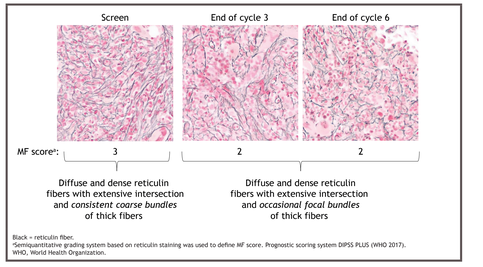



Time post-treatment when maximum VAF reduction was observed is listed below each bar in the graph (indicated as cycle number). [a]The latest samples analyzed by the time of data cutoff.

### Reduction of bone marrow fibrosis

- BMS-986158 + RUX and BMS-986158 + FED led to reduction of bone marrow fibrosis in some patients **(Figure 7)**
- ≥ 1 grade reduction of fibrosis post-treatment was observed in 60% (n = 10) of evaluable bone marrow biopsies

**Figure 7. Representative image of bone marrow biopsy showing reduction in fibrosis**

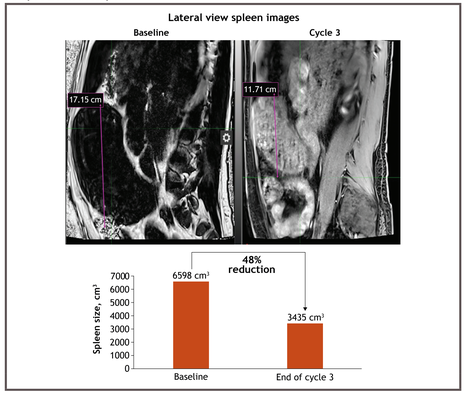



Black = reticulin fiber.
[a]Semiquantitative grading system based on reticulin staining was used to define MF score. Prognostic scoring system DIPPS PLUS (WHO 2017).
WHO, World Health Organization.

### Case study: BMS-986158 + FED in a patient with relapsed/refractory MF

- Following discontinuation of RUX, patients have a poor prognosis and reduced survival[5]
- Patient characteristics:
  - 46-year-old male
  - History of DIPSS intermediate risk-2, *JAK2*$^{V617F}$ MF with grade 2 bone marrow fibrosis
  - Baseline spleen volume 6598 cm³
  - Inadequate response to RUX after ~7 years of treatment
- Treated with BMS-986158 1 mg (alternate schedule: 5 days on/2 days off for 3 weeks; week 4 off treatment) + FED 400 mg QD in Part 1B
- At end of cycle 3, spleen volume was reduced to 3435 cm³ (48% reduction); reduction was ongoing at cycle 5, with continued improvement in spleen size by palpation **(Figure 8)**

**Figure 8. Case study: spleen reduction with BMS-986158 + FED in a patient with relapsed/refractory MF**




## Conclusions

- BMS-986158 + RUX in patients with 1L MF and BMS-986158 + FED in patients with 2L MF was tolerable and had manageable safety
  - Most TRAEs were low grade and transient
  - Thrombocytopenia, an on-target effect, was manageable and did not result in clinically significant bleeding
  - Most patients (85% with BMS-986158 + RUX; 72% with BMS-986158 + FED) have remained on treatment
- BMS-986158 + RUX produced early and deep SVR in RUX-naïve patients with 1L MF; responses continued to deepen beyond week 24 under ongoing treatment
- Early and deep SVR was also observed with BMS-986158 + FED in RUX-exposed patients with 2L MF
- Reduction of *JAK2* VAF and reduction of bone marrow fibrosis was observed in patients with 1L MF and 2L MF, providing evidence of early disease modifying potential of these drug combinations
- The dose expansion phase in 1L MF has been opened and is actively enrolling patients

### References

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