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# Novel agents and evolving strategies in myelofibrotive neoplasm: an update from 2022 ASH annual conference

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**Abstract**

Myelofibrosis (MF) is a disorder characterized by the proliferation of myeloid precursors, commonly due to overactive JAK signaling. The discovery of the JAK2$^{V617F}$ mutation and subsequent development of JAK inhibitors (JAKi) results in reduced spleen size, improved symptom, and enhanced survival in MF patients. However, there are unmet needs of additional novel targeted therapies for this incurable disease due to the limited utility of first-generation JAKis, which are associated with dose-limiting cytopenia and disease recurrence. New targeted treatment strategies for MF are on the horizon. We are here to discuss the latest clinical research findings presented in the 2022 ASH Annual Meeting.

**Keywords** Myelofibrotive neoplasm, Targeted therapy, Clinical research

## To the editor

Myelofibrosis research has dramatically advanced in the last several years [1]. In this article, we summarized some of the most exciting developments and innovations in investigational targeted therapeutic agents and novel regimens in treating MF from the 2022 ASH Annual Meeting.

## Targeted therapeutics of myelofibrosis

JAK2$^{V617F}$ is the most common mutation, leading to the overactivation of JAK/STAT signaling linked with clonal expansion in myeloproliferative neoplasms (MPNs) [2]. JAK/STAT pathway inhibition has become the cornerstone therapeutic strategy for patients with symptomatic MF. Ruxolitinib (RUX), Fedratinib and Pacritinib are FDA approved JAK1/2 inhibitors for treatment of intermediate and high-risk MF [2]. Even though these drugs change the landscape of MF management and provide significant clinical benefits, approximately 1/3 of MF patients either cannot tolerate the treatment, developing cytopenias during treatment, or do not respond to the therapy well [2]. In abstract 627 and 3028, the phase III MOMENTUM data demonstrate that Momelotinib (MMB), the first JAK1/2/ACVR1 inhibitor, reduced symptoms and spleen volumes, improved transfusion independence (TI), and prolonged survival in a group of symptomatic and anemic MF patients who failed JAKi treatment (Table 1) [3]. Additional analysis also shows that transfusion independence response (TI-R) at W24 is a potential surrogate for improved overall survival (OS) (Table 1). In abstract 628, MF patients treated with Pacritinib, another FDA approved JAK2 inhibitor, achieved greater TI in comparing the ones with best-available therapy (BAT) (24% vs. 5%, based on SIMPLIFY criteria; 37% vs. 7%, based on Gale criteria) in a phase III PERSIST-2 trial, which enrolled MF patients with severe thrombocytopenia. The possible mechanisms of erythropoietic

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**Table 1** Selected studies on the novel single agent targeted therapeutic on myelofibrosis from the 2022 ASH annual meeting

| Name | Target | Route | Trial phase | Inclusion criteria (prior treatments; subject age; spleen size) | Subjects Baseline Characteristics | Study duration (current / planned) | Accrual (current accrual #/ target accrual #) | Efficacy | Adverse Events | Clinicaltrials.gov Registration | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MMB | JAK1/2/ACVR1 | PO | III | One prior JAKi for ≥ 90 days; ≥ 18 years; palpable spleen ≥ 5 cm | N/A | 27/96 months | 195/195 | TI-R (31%); SVR (100%) at W24 | Thrombocytopenia Anemia Infection Peripheral neuropathy | NCT04173494 | [3] |
| Pacritinib | JAK2/ACVR1 | PO | III | JAKi-naïve patients; ≥ 18 years; palpable spleen ≥ 5 cm | All patients had platelet counts $\leq 100 \times 10^9$/L | 40/40 months | 327/327 | TL-R (24% on SIMPLIFY criteria, 37% on Gale criteria) at W24 | Not reported | NCT01773187 | [4] |
| TP-3654 | PIM1 | PO | I/II | At least one prior JAKi; ≥ 18 years; palpable spleen ≥ 5 cm or SV ≥ 450 $cm^3$ | Median age of 70 years; median spleen volume of 2370 $cm^3$ | 32/55 months | 8/60 | SVR (83%); TSS50 (66%); at W12 | Nausea Vomiting Diarrhea | NCT04176198 | [5] |
| IMG-7289 | LSD1 | PO | II | Prior JAKi or JAKi-naïve patients; ≥ 18 years; | Median age of 68 years; median spleen volume of 1354 $cm^3$ | 56/56 months | 89/89 | SVR (66%); TSS50 (19%); TI-R (90%); BMF (53%) at W24 | Dysgeusia Diarrhea | NCT03136185 | [6] |

**Table 2** Selected studies on the novel targeted therapeutic in combination with RUX on myelofibrosis from the 2022 ASH annual meeting

| Name | Target | Route | Trial Phase | Inclusion Criteria (prior treatments; subject age; spleen size) | Subject Baseline Characteristics | Study Duration (current / planned) | Accrual (current accrual #/target accrual #) | Efficacy | Adverse Events | Clinicaltrials.gov Registration | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SIR | HDM2 | PO | Ib | One prior JAKi; ≥ 18 years; palpable spleen ≥ 5 cm or SV ≥ 450 $cm^3$ | Median spleen volume of 1162 $cm^3$ | 30/45 months | 23/45 | SVR35 (100%) at W24 | Fatigue<br>GI toxicity<br>Anemia<br>Leukopenia<br>Thrombocytopenia | NCT04097821 | [8] |
| PELA | BET | PO | II | One prior JAKi; ≥ 18 years; SV ≥ 450 $cm^3$ | Median age of 68 years | 96/123 months | 84/341 | SVR35 (80%); MF-SAF-TSS50 (81%); BMF (40% ≥ 1 grade improvement) at any time | Thrombocytopenia<br>Anemia | NCT02158858 | [9] |
| Navitoclax | BCL-2 family | PO | II | One Prior IAKi or JAKi-naïve patients; ≥ 18 years; splenomegaly | JAKi-naïve pts; median age of 69 years; median SV of 1889 $cm^3$ | 51/131 months | 32/191 | SVR35(59%) in high DIPSS score pts, BMF (35%) at W24 | Not reported | NCT03222609 | [10] |
| Parsaclisib | PI3K | PO | II | Pts with existing stable regimen of RUX; ≥ 18 years; palpable spleen ≥ 10 cm | Median age of 68 years; 47% of pts male; median SV of 2415 $cm^3$ in QD/QW, 1878 $cm^3$ in QD | 63/63 months | 74/74 | SVR35 (7.1%); MPN-SAF-TSS50 (48.6%); BMF (33%) all daily dosing at W24 | Pneumonia<br>Fatigue<br>Hypoxia<br>Dyspnea<br>Elevation of liver enzymes<br>Hypocalcemia<br>Thrombocytopenia | NCT02718300 | [11] |
| SEL | XPO1 | PO | I/II | JAKi-naïve pts; ≥ 18 years; SV ≥ 450 $cm^3$ | Median age of 64 years | 17/44 months | 19/237 | SVR35 (84%) at any time; TSS50 (69%) at W12 | Nausea<br>Anemia<br>Vomiting<br>Thrombocytopenia | NCT04562389 | [12] |

benefit of Pacritinib were inhibition of activin A receptor, type I (ACVR1) (Table 1) [4]. In abstract 240, TP-3654, a selective oral PIM1 Kinase Inhibitor, was utilized in an ongoing Phase I/II study showing encouraging signs of clinical activity in spleen volume reduction (SVR), symptom improvement, and cytokine reduction in MF patients previously treated with JAKi. TP-3654 is well tolerated with limited myelosuppressive adverse events (Table 1) [5]. ASXL1 mutations confer poor prognosis in MF patients with low $JAK2^{V617F}$ allele burden. Abstract 4368 reports a Lysine-specific demethylase-1 (LSD1) inhibitor, IMG-7289, as an oral monotherapy, which reduced symptoms, SVR, BMF, TSS50 and selectively inhibited ASXL1 mutation clones with acceptable tolerability in a phase II study (Table 1) [6].

## Frontline "Add-on" targeted therapeutics of myelofibrosis

In the front-line setting, some novel targeted therapeutics are used in combination with RUX to improve the depth of response seen upfront with single agent RUX. In a preclinical study, Lu et al. shows that Siremadlin (SIR), an HDM2 inhibitor, was able to restore p53-mediated apoptosis in MF via combining with other pharmacological agents that disrupted the interplay between HDM2/p53, HIF1α and nuclear factor kappa B (NFκB) pathways [7]. Furthermore, abstract 239 reports an phase I/II ADORE study Part 1 (phase Ib), where the recommended phase 2 dose (RP2D) of SIR was established as 30 mg orally once daily on days 1–5/28-day cycle when added to the existing stable dose of RUX in patients who presented either persistent splenomegaly (spleen size ≥ 5 cm from the left costal margin or spleen volume ≥ 450 $cm^2$ by MRI/CT scan) or continuous anemia (HgB < 11 g/dL) after at least 12 weeks of RUX monotherapy [8]. Good tolerability at 30 mg daily allowed patients to remain on SIR + RUX and to achieve robust SVR at W24 (Table 2). Pelabresib (PELA) is a selective Bromodomain and Extraterminal (BET) inhibitor to modify NFκB signaling related genes' expression. In the MANIFEST phase II study, PELA combining with RUX (Arm 3) showed improved spleen volume reduction of 35% (SVR35) and total symptom score reduction of ≥ 50% (TSS50) and BMF improvement at any time (Table 2) in JAKi-naïve MF patients with intermediate-1/2 or high risks [9]. Navitoclax inhibits the anti-apoptotic BCL-2 family proteins (primarily BCL-XL). In the REFINE phase II study (Cohort 3; Abstract 237), navitoclax combining with RUX achieved SVR35 at W24 in all subgroups known to confer poor prognosis [10]. The paralleled reduction of both driver mutation $JAK^{V617F}$'s VAF (36% patients achieved > 50% VAF reduction from baseline) and BMF indicates that this combination therapy regimen is promising (Table 2). In abstract 236, Parsaclisib, a potent and highly selective inhibitor of PI3 kinase, was assessed as an "add-on" agent to RUX among MF patients with suboptimal response to RUX in a phase II trial. The trial data show improvement in both symptoms and spleen size [11]. Responder efficacy variables analysis (SV, MF-SAF, and MPN-SAF-TSS) indicates that the continuous daily dosing regimen was more efficacious than daily dosing for 8 weeks then following with weekly dosing. This combination therapy was associated with limited grade 3/4 AEs and TEAE-related discontinuations (Table 2). Selinexor (SEL) is a Selective Inhibitor of Nuclear Export (SINE) compound that inhibits XPO1, which leads to nuclear retention and activation of tumor suppressor proteins. Abstract 1734 presents a phase I/II study evaluating the impact of SEL + RUX combination in treating JAKi-naïve MF. The preliminary data from this study demonstrate a manageable safety profile and encouraging preliminary data on SV, symptoms and TI-R (Table 2) [12].

## Conclusion

The next-generation JAKi have been evaluated in clinical trials, some even being FDA approved, to manage RUX intolerant or resistant MF. Other non-JAK/STAT therapeutic molecules, such as epigenetic modifiers, apoptotic machinery, and intracellular signaling pathway inhibitors, are also being investigated in clinical settings as both a single agent and in combination with RUX. The future of MF management is bright and promising.

### Abbreviations

| | |
|---|---|
| ACVR1 | Activin A receptor, type I |
| ASH | American Society of Hematology |
| BAT | Best Available Therapy |
| BET | Bromodomain and Extraterminal |
| BMF | Bone Marrow Fibrosis |
| HDM2 | Human Double Minute-2 |
| Hgb | Hemoglobin |
| JAK | Janus Kinase |
| JAKi | JAK inhibitor |
| LSD1 | Lysine-specific demethylase-1 |
| MF | Myelofibrosis |
| MMB | Momelotinib |
| MPN | Myeloproliferative Neoplasms |
| NA | Not available |
| NFκB | Nuclear Factor Kappa B |
| OS | Overall Survival |
| PELA | Pelabresib |
| PI3K | Phosphoinositide 3-kinase |
| PIM1 | Proto-oncogene serine/threonine-protein kinase 1 |
| PO | Per os (oral administration) |
| QD | Once Daily |
| QoL | Quality of Life |
| QW | Once Weekly |
| RP2D | Recommended Phase 2 Dose |
| R/R | Relapsed/refractory |
| RUX | Ruxolitinib |
| SIR | Siremadlin |
| STAT | Signal transducer and activator of transcription |
| SV | Spleen Volume |

| | |
|---|---|
| SVR | Spleen Volume Reduction |
| SAF | Symptom Assessment Form |
| SINE | Selective Inhibitor of Nuclear Export |
| SL | Spleen Length |
| SQ | Subcutaneous |
| TEAE | Treatment-Emergent Adverse Event |
| TI | Transfusion Independence |
| TI-R | Transfusion Independence Response |
| TSS | Total Symptom Score |
| VAF | Variant Allele Frequency |
| W12 | Week 12 |
| W24 | Week 24 |
| XPO1 | Exportin-1 |

**Author contributions**
JJP designed this study. JJP, AW, and JL participated in manuscript writing. AW and JL contribute equally to this study. All authors read and approved the final manuscript.

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**Availability of data and materials**
The material supporting the conclusion of this study has been included within the article.

## Declarations

**Ethics approval and consent to participate**
This is not applicable for this summary.

**Consent for publication**
This is not applicable for this summary.

**Competing interests**
The authors declare that they have no competing interests.

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