Abstract: #3209

A Global, Phase 3, Randomized, Double-blind Study to Evaluate Safety and Efficacy of Selinexor, an XPO1 Inhibitor, in Combination With Ruxolitinib in JAK-Inhibitor-Naïve Myelofibrosis (XPORT-MF-034)

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INTRODUCTION

Myelofibrosis (MF) is a heterogenous, progressive, and fatal disease.[1]

- Underlying biological hallmarks include aberrant blood and bone marrow differentiation, cytokine production and inflammation, bone marrow fibrosis, and extramedullary hematopoiesis.

An urgent need for therapies, beyond Janus kinase inhibitors (JAKi; e.g., ruxolitinib), with rapid, effective, and durable response that address underlying drivers of MF persists, due to:

Limited responses:

- <50% of patients achieve Week 24 spleen volume reduction ≥35% from baseline (SVR35) and total symptoms score reduction of ≥50% from baseline (TSS50) with ruxolitinib.[2]
- Probability of maintaining SVR35 decreases as early as Week 12 response in patients who achieved SVR35 with ruxolitinib.[3]

Lack of evidence of disease modification[3]:

- JAKi have limited ability to alter inflammation, bone marrow fibrosis, or prevent disease progression.

Treatments for patients with cytopenic MF[3]:

- Patients with anemia and thrombocytopenia have limited treatment options and may require suboptimal doses of ruxolitinib.

Improved outcomes[3]:

- MF continues to be a disease of decreased survival and significant morbidity.

RATIONALE

Selinexor: Oral exportin 1 (XPO1) inhibitor with pro-apoptotic and anti-inflammatory properties that may impact both Janus kinase (JAK) and non-JAK pathways, undergoing investigation for treatment of MF.[4,5]

Findings from the Phase 1 analysis[6,7]:

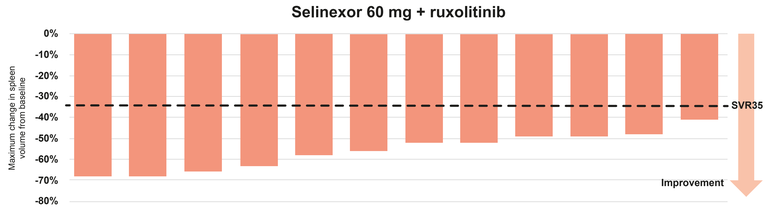
- Spleen volume reduction (SVR) and total symptom score (TSS) improvement was observed in patients treated with 60 mg selinexor plus ruxolitinib at Week 12 and sustained to Week 24.
- The most common adverse events were nausea (75%), fatigue (58%), anemia (54%), and thrombocytopenia (54%), the majority of which were Grades 1–2.
- Treatment-related adverse events leading to treatment discontinuation were reported in two patients; thrombocytopenia in one patient and neuropathy in one patient.

SVR35 and TSS50 Outcomes of the Phase 1 Trial Component

		SVR35	TSS50
Population	**Timepoint**	**Selinexor 60 mg + ruxolitinib n (%)**	**Selinexor 60 mg + ruxolitinib n (%)**
Efficacy evaluable	Week 12	10/12 (83)*	8/10 (80)†
	Week 24	11/12 (92)	7/9 (78)‡
Intent-to-treat	Week 12	10/14 (71)	8/12 (67)
	Week 24	11/14 (79)	7/12 (58)

*Two patients discontinued prior to Week 24; †One patient discontinued prior to Week 12; one patient had missing data at Week 12 and discontinued prior to Week 24; ‡Two patients discontinued prior to Week 24 and one had missing data.

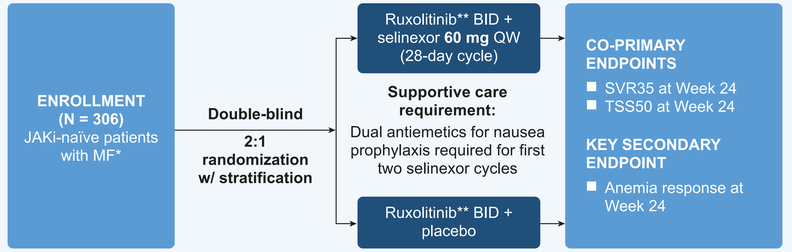
All Patients in the Efficacy Evaluable Population Treated With Selinexor 60 mg Plus Ruxolitinib Achieved an SVR35 at Anytime



STUDY DESIGN

XPORT-MF-034 (NCT04562389)

A multicenter, randomized, double-blind, placebo-controlled, global Phase 3 study (Phase 3 component)



Randomization stratified by:

- DIPSS risk category: Int-1 vs Int-2 or high risk
- Spleen volume: <1800 cm^3 vs >1800 cm^3
- Baseline platelet counts: 100–200×10^9/L vs >200×10^9/L

*Sample size per protocol is N = 300–450.

**Ruxolitinib dose based on platelet count per prescribing information.

Primary Objective:

To evaluate the efficacy of selinexor plus ruxolitinib in patients with JAKi-naïve MF

ENDPOINTS

Co-primary Endpoints:

Spleen volume reduction ≥35% (SVR35) at Week 24

Total symptom score reduction ≥50% (TSS50) at Week 24

Key Secondary Endpoint:

Anemia response at Week 24

Secondary Endpoints:

- Safety
- Overall survival
- Overall response rate
- SVR35 and TSS50 at any time
- SVR35 and TSS50 by pre-specified subgroups
- Pharmacokinetics (PK)
- Bone marrow fibrosis (BMF)

Exploratory Endpoints:

- Duration of response
- Progression-free survival
- Changes in variant allele frequency (VAF)
- Patient-reported outcomes: Patient Global Impression of Change (PGIC) and EuroQoL five-dimensional instrument 5 levels (ED-5D-5L)
- Selected biomarker changes
- Transfusion independence
- Ruxolitinib PK

ELIGIBILITY CRITERIA

Select Inclusion Criteria:

- Diagnosis of primary MF, post-essential thrombocythemia (PET) MF, or post-polycythemia vera (PPV) MF
- ≥18 years of age
- Measurable splenomegaly as demonstrated by spleen volume of ≥450 cm^3 by magnetic resonance imaging (MRI) or computed tomography (CT) scan
- Active symptoms of MF as determined by presence of at least two symptoms with a score of ≥3 or total score of ≥10 at screening using the Myelofibrosis Symptom Assessment Form Version 4.0 (MF-SAF v4.0)
- Dynamic international prognostic scoring system (DIPSS) of intermediate-1 with symptoms, intermediate-2, or high-risk
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- Platelet count of ≥100×10^9/L without platelet transfusion
- Not a candidate for stem-cell transplantation

Select Exclusion Criteria:

- >10% blast in peripheral blood or bone marrow
- Previous treatment with JAKi for MF
- Previous treatment with selinexor or other XPO1 inhibitors
- Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of selinexor
- Major surgery <28 days prior to Cycle 1, Day 1 (C1D1)
- Prior splenectomy, or splenic radiation within 6 months prior to C1D1
- Unable to tolerate two forms of antiemetics

STUDY INFORMATION

Participating locations

- Belgium
- Bulgaria
- Canada
- Czech Republic
- Denmark
- France
- Germany
- Greece
- Hungary
- Israel
- Italy
- Netherlands
- Poland
- Romania
- South Korea
- Spain
- Taiwan
- United Kingdom
- USA

- The XPORT-MF-034 Phase 3 study is currently open for enrollment.
- Study contact: clinicaltrials@karyopharm.com.
- Thank you to the patients, caregivers, study sites, and study investigators.

Study details on clinicaltrials.gov

To learn more about other ongoing clinical studies of selinexor in MF:

Phase 2 selinexor monotherapy for patients with MF and moderate thrombocytopenia: Study design poster

Scandura JM, Gerds AT, Ritchie EK, el al. A Phase 2 Study to Evaluate the Efficacy and Safety of Selinexor Monotherapy in Patients With JAK-Inhibitor-Naïve Myelofibrosis and Moderate Thrombocytopenia (XPORT-MF-044). [abstract]. *Blood*. 2023. Abstract 3211

Abbreviations

BID, twice-daily dosing; BMF, bone marrow fibrosis; C1D1, Cycle 1, Day 1; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQoL five-dimensional instrument 5 levels; GI, gastrointestinal; Int-1, intermediate-1; Int-2, intermediate-2; JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MF-SAF v4.0, Myelofibrosis Symptom Assessment Form version 4.0; MRI, magnetic resonance imaging; PET, post-essential thrombocythemia; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; PPV, post-polycythemia vera; QW, once-weekly dosing; SVR35, spleen volume reduction of 35% from baseline; TSS50, total symptom score reduction of 50% from baseline; VAF, variant allele frequency; w/, with; XPO1, exportin 1.

References

1. Tefferi A. *Am J Hematol*. 2023;98(5):801-821. **2.** O'Sullivan JM, Harrison CN. *Clin Adv Hematol Oncol*. 2018;16(2):121-131. **3.** Levavi H, et al. *Clin Adv Hematol Oncol*. 2022;20(7):456-467. **4.** Kashyap T, et al. *Oncotarget*. 2016;7(48):78883-78895. **5.** Maloof M, et al. Poster presented at: the 15th International Congress for Myeloproliferative Neoplasms (MPN); November 2–3, 2023; Brooklyn, NY. **6.** Ali H, et al. *Cancer Res*. 2023;83(Suppl 8):CT261. **7.** Ali H, et al. Poster presented at: 2023 American Society of Clinical Oncology Annual Meeting; June 2–6, 2023; Chicago, IL.

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