Abstract: #3211

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)

Joseph M Scandura,[1] Aaron T Gerds,[2] Ellen Ritchie,[1] Xulong Wang,[3] Steve Kye,[3] Raajit Rampal[4]

[1]Weill Cornell Medicine, New York, NY, USA; [2]Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH, USA;
[3]Karyopharm Therapeutics, Newton, MA, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA

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.[1,2]

Thrombocytopenia is common in patients with MF and associated with poor outcomes.[3]

- ~25% of Janus kinase inhibitor (JAKi)-naïve patients have thrombocytopenia (platelets less than 100×10^9/L).[3]
- Thrombocytopenia is an on-target side effect of many JAKi leading to use of suboptimal doses.[4]
- Suboptimal dosing of JAKi in patients with thrombocytopenia leads to suboptimal symptom and/or spleen volume reduction.[4]

Unmet need for effective non-JAKi treatments for patients with MF and moderate thrombocytopenia.

RATIONALE

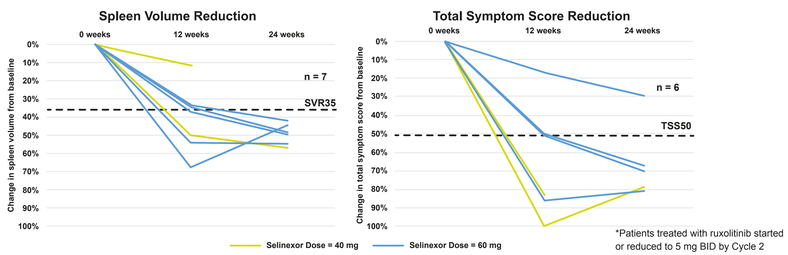
Selinexor: Oral exportin 1 (XPO1) inhibitor with pro-apoptotic and anti-inflammatory properties that may impact both Janus kinase (JAK) and non-JAK pathways, undergoing investigation for treatment of MF.[5,6]

Findings from the Phase 1 analysis[7,8]:

- Spleen volume reduction (SVR) and total symptom score (TSS) improvement with selinexor 60 mg plus ruxolitinib in JAKi-naïve patients with MF was observed.
- 79% (11/14) of patients treated with 60 mg selinexor plus ruxolitinib achieved spleen volume reduction of 35% from baseline (SVR35) and 58% (7/12) achieved total symptom score reduction of 50% from baseline (TSS50) at Week 24 in the intent-to-treat population.
- 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.

Efficacy With Selinexor in Combination With Suboptimal Dose of Ruxolitinib* (5 mg)[7,8]

Retrospective, Exploratory Analysis From Phase 1 Selinexor + Ruxolitinib Study



*Patients treated with ruxolitinib started or reduced to 5 mg BID by Cycle 2

Selinexor Single-Agent Activity in Patients With MF Refractory or Intolerant to JAKi (ESSENTIAL; NCT03627403)[9]

STUDY DESIGN

XPORT-MF-044 (NCT05980806)

A two-arm, sequential, multicenter, open-label, Phase 2 study with optional expansion arms

ENROLLMENT
JAKi-naïve MF (N = 58–118)

- Spleen volume ≥450 cm^3
- DIPSS Int-1 with symptoms, Int-2, or high risk
- ECOG 0–2
- Platelets 50 to $<100\times10^9$/L

Week 12 Week 24
Selinexor **60 mg** QW (n = 29) → (n = 30)

Week 12 Week 24
Selinexor **40 mg** QW (n = 29) → (n = 30)

Futility analysis[b] at n = 12 Week 24. Enrollment will pause during futility analysis.

Optional add-on medication[a]

- SVR <10% **Week 12** ■ SVR <35% **Week 24**
- Add **ruxolitinib** if platelets ≥50×10^9/L and hemoglobin level is ≥10 g/dL
- Add **pacritinib** if platelets <50×10^9/L
- Add **momelotinib** if platelets ≥50×10^9/L and hemoglobin level is <10 g/dL

Optional expansion arms

Supportive care requirement: Dual antiemetics for nausea prophylaxis required for first two selinexor cycles.

[a]Optional add-on medication use is to the respective label, optional add-on pacritinib and momelotinib for US sites only[10-12]; [b]SVR35 assumptions: 15% "poor" vs 31% "good" responses at 70% power, 1-sided alpha.

Primary Objective:

To evaluate the efficacy and safety of selinexor monotherapy for patients with JAKi-naïve MF and moderate thrombocytopenia

ENDPOINTS

Primary Endpoint:

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

Secondary Endpoints:

- Safety
- TSS50 at Week 24
- Anemia response at Week 24
- Overall survival
- Overall response rate
- SVR35 and TSS50 at any time
- SVR35 and TSS50 by pre-specified subgroups
- SVR35, TSS50, and safety with add-on treatment
- Pharmacokinetics/pharmacodynamics (PK/PD)
- Bone marrow fibrosis (BMF)

Exploratory Endpoints:

- Duration of response
- Progression-free survival
- Platelet counts
- Changes in variant allele frequency (VAF)
- Patient-reported outcomes: Patient global impression of change (PGIC)
- Selected biomarker changes
- Transfusion independence

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 50 to $<100\times10^9$/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-044 Phase 2 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 3 part of the XPORT-MF-034: Study design poster

Maher K, Rampal RK, Bose P, et al. 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) [abstract]. *Blood.* 2023. Abstract 3209

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; 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/PD, pharmacokinetics/pharmacodynamics; PPV, post-polycythemia vera; QW, once-weekly dosing; SVR, spleen volume reduction; SVR35, spleen volume reduction of 35% from baseline; TSS, total symptom score; TSS50, total symptom score reduction of 50% from baseline; VAF, variant allele frequency; 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.** Sastow D, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22(7):e507-e520. **4.** Levavi H, et al. *Clin Adv Hematol Oncol*. 2022;20(7):456-467. **5.** Kashyap T, et al. *Oncotarget*. 2016;7(48):78883-78895. **6.** Maloof M, et al. Poster presented at: the 15th International Congress for Myeloproliferative Neoplasms (MPN); November 2–3, 2023, Brooklyn, NY. **7.** Ali H, et al. *Cancer Res*. 2023;83(Suppl 8):CT261. **8.** Ali H, et al. Poster presented at: 2023 American Society of Clinical Oncology Annual Meeting; June 2–6, 2023; Chicago, IL. **9.** Tantravahi SK, et al. Oral presentation presented at: 63rd ASH Annual Meeting and Exposition; December 11–14, 2021; Atalanta, GA. **10.** JAKAFI® (ruxolitinib) [prescribing Information]. Wilmington, DE: Incyte Corporation; 2021. **11.** VONJO™ (pacritinib) [prescribing Information]. Seattle, WA: CTI BioPharma Corp; 2022. **12.** OJJAARA (momelotinib) [prescribing information]. Durham, NC: GlaxoSmithKline; 2023.

Acknowledgments

Medical writing support for this poster was provided by dna Communications and funded by Karyopharm Therapeutics. This study is funded by Karyopharm Therapeutics.

65th ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY
December 9–12, 2023. San Diego, California, USA