Karyopharm® Therapeutics

# AACR 2023 – Update on Data in Treatment-Naïve Myelofibrosis

April 18, 2023

# On Today's Call

- **Welcome**
  Elhan Webb, CFA, *Senior Vice President, Investor Relations*
- **Opening Remarks**
  Richard Paulson, *President and Chief Executive Officer*
- **Review of Results from Ph 1 XPORT-MF-034 Study Evaluating Selinexor in Combination with Ruxolitinib in Treatment-Naïve Myelofibrosis**
  Dr. Reshma Rangwala*, Chief Medical Officer*
- **Myelofibrosis Treatment Landscape**
  Dr. John Mascarenhas, *Professor of Medicine at the Icahn School of Medicine at Mount Sinai and Director of the Center of Excellence for Blood Cancers and Myeloid Disorders*
- **Q&A Session**

# Forward-looking Statements and Other Important Information

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the ability of selinexor to treat patients with myelofibrosis; expectations related to the clinical development and potential regulatory submissions of selinexor, including the expected design of the Company's clinical trials, the Company's regulatory strategy, the anticipated availability of data to support such submissions, timing of such submissions and actions by regulatory authorities. Such statements are subject to numerous important factors, risks and uncertainties, many of which are beyond Karyopharm's control, that may cause actual events or results to differ materially from Karyopharm's current expectations. For example, there can be no guarantee that Karyopharm will successfully commercialize XPOVIO or that any of Karyopharm's drug candidates, including selinexor and eltanexor, will successfully complete necessary clinical development phases or that development of any of Karyopharm's drug candidates will continue. Further, there can be no guarantee that any positive developments in the development or commercialization of Karyopharm's drug candidate portfolio will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: the risk that the COVID-19 pandemic could disrupt Karyopharm's business more severely than it currently anticipates, including by negatively impacting sales of XPOVIO, interrupting or delaying research and development efforts, impacting the ability to procure sufficient supply for the development and commercialization of selinexor or other product candidates, delaying ongoing or planned clinical trials, impeding the execution of business plans, planned regulatory milestones and timelines, or inconveniencing patients; the adoption of XPOVIO in the commercial marketplace, the timing and costs involved in commercializing XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; the ability to obtain and retain regulatory approval of XPOVIO or any of Karyopharm's drug candidates that receive regulatory approval; Karyopharm's results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, including with respect to the need for additional clinical studies; the ability of Karyopharm or its third party collaborators or successors in interest to fully perform their respective obligations under the applicable agreement and the potential future financial implications of such agreement; Karyopharm's ability to enroll patients in its clinical trials; unplanned cash requirements and expenditures; development or regulatory approval of drug candidates by Karyopharm's competitors for products or product candidates in which Karyopharm is currently commercializing or developing; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any of its products or product candidates. These and other risks are described under the caption "Risk Factors" in Karyopharm's Annual Report on Form 10-K for the year ended December 31, 2022, which was filed with the Securities and Exchange Commission (SEC) on February 17, 2023, and in other filings that Karyopharm may make with the SEC in the future. Any forward-looking statements contained in this presentation speak only as of the date hereof, and, except as required by law, Karyopharm expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. Karyopharm regularly uses its website to post information regarding its business, drug development programs and governance. Karyopharm encourages investors to use www.karyopharm.com, particularly the information in the section entitled "Investors," as a source of information about Karyopharm. References to www.karyopharm.com in this presentation are not intended to, nor shall they be deemed to, incorporate information on www.karyopharm.com into this presentation by reference. Other than the currently approved indications of XPOVIO, selinexor and eltanexor are investigational drugs that have not been approved by the FDA or any other regulatory agency, and the safety and efficacy of these drugs has not been established by any agency.

**Richard Paulson**
*Chief Executive Officer*

# OPENING REMARKS

**Reshma Rangwala, MD, PhD**
*Chief Medical Officer*

# UPDATE FROM PHASE 1 XPORT-MF-034 Study

# XPO1, a Novel and Potentially Fundamental Mechanism in MF, has the Opportunity to Transform 1L Myelofibrosis

## Treatment Landscape and Unmet Need

**~20,000 living with MF in the U.S and ~ 17,000 in EU**[1]

**No other approved class of therapy other than JAK inhibitors, ruxolitinib generates > $2 billion revenues annually**

**Significant unmet need in 1L treatment with current standard of care, ruxolitinib:**

- <50% of patients achieve SVR35[2] and TSS50[2]
- ~25% of male patients achieve an SVR35 at week 24[3]
- ~23% patients who start on ruxolitinib 15 mg BID achieve an SVR35 at week 24[4]
  - ~70% patients in the real world start on ruxolitinib 15 mg BID or less[5]

**Leading causes of ruxolitinib discontinuation are thrombocytopenia and anemia, which is associated with shorter survival**[6,7,8]

## Selinexor has the Potential to Shift the Treatment Paradigm*

- **XPO1 inhibition is a novel and potentially fundamental mechanism in MF**
- **Synergism with ruxolitinib observed in preclinical data**[9]
- **Rapid, deep and sustained spleen response, and robust symptom improvement across all subgroups**
- **Generally tolerable and manageable side effect profile enabling sustained therapy**
- **Disease modifying with rapid normalization of platelets and maintenance of hemoglobin levels**

* Based on selinexor+ruxolitinib Ph 1 results using data cut as of February 24, 2023

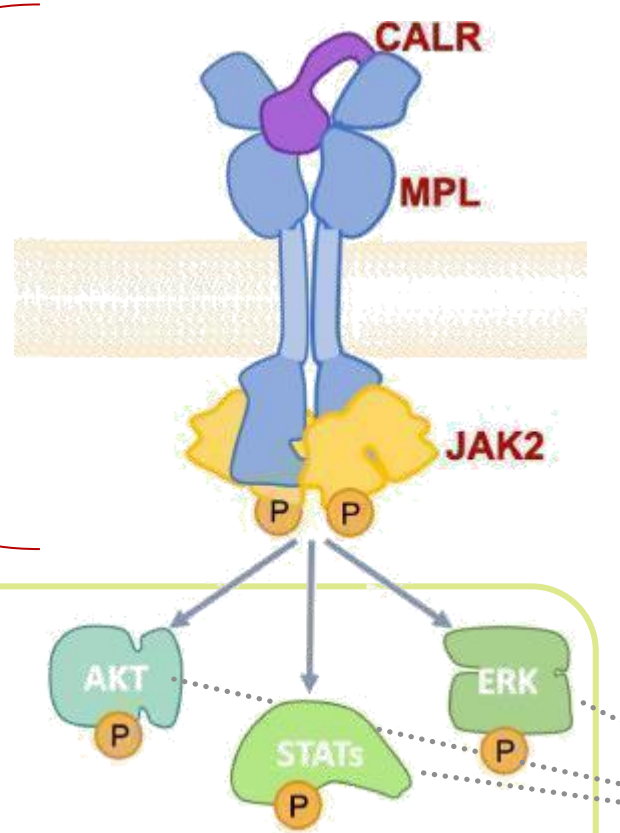
The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the U.S. FDA or any other regulatory authority.




**1.** Mehta el.al. Leuk Lyphoma 2014 Mar ;55(3):595-600 and US Census data; Clarivate/DRG Epidemiology Data (2022 figures, pub 2019). 2. Verstovsek S, et al. N Engl J Med. 2012;366(9)799-907 3. FDA multidisciplinary review of Jakafi in 2011; document no: 202192Orig1s000 4."Baseline factors associated with response to ruxolitinib: An independent study on 408 patients with myelofibrosis", Palandri et. al Oncotarget. 2017;8(45): 79073–79086.5. Passamonti et al. Future Oncology. 2022;18(18) 2217-2231. 6. Sastow D, et al. Clin Lymphoma, Myeloma Leuk. 2022;22(7):e507–20. 7. Masarova, et al. Eur J Haematol. 2018;100(3):257-263. 8. Al-Ali, et al. Hematologica. 2016;101(9):1065. 9. Yan et al. Clin Cancer Res. 2019;25(7): 2323–2335

# Selinexor Can Inhibit Multiple Targets of the JAK Pathway, Enabling Independent Suppression of MF cells and Potentially Complementing the Function of JAKi's[1,2,3,4,5]

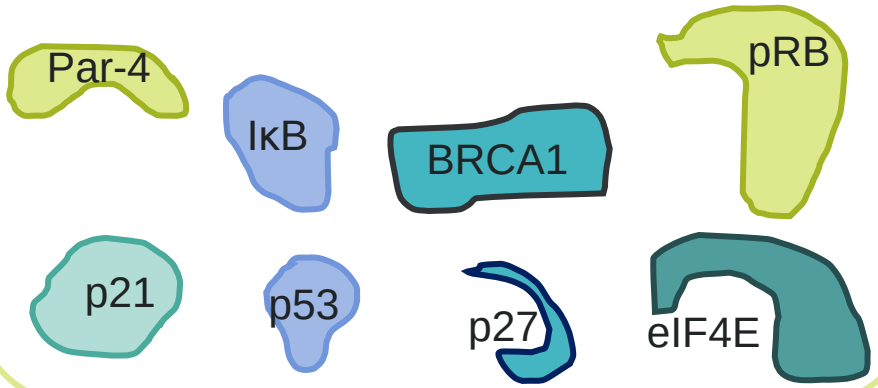
MF is driven by **upstream mutations** of *JAK2, CALR* or *MPL*




**Downstream pathways** are activated by the upstream mutations

**The AKT, STAT and ERK pathways contain XPO1 cargo proteins**

**Additional XPO1 cargos proteins** regulate cell growth and survival



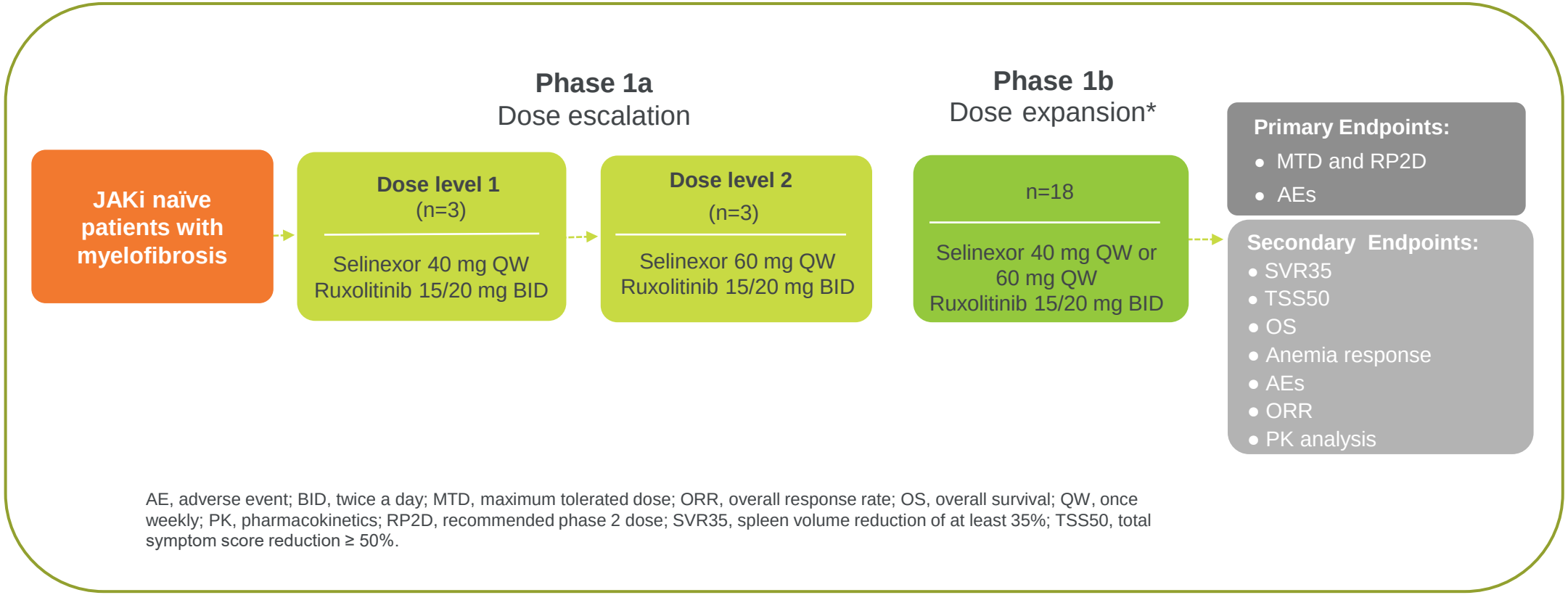

XPO1





1. Exp Hematol (105):2-9, Jan. 01, 2022
2. XPO1 Cargo references: https://doi.org/10.7554/eLife.11466; http://prodata.swmed.edu/LRNes/IndexFiles/namesGood.php
3. Zhong et al., Leukemia. 2014 May;28(5):1158-63 ; 4. Muqbil et al., Cancer Lett. 2016 Dec 28;383(2):309-317
5. Cheng et al., Mol Cancer Ther. 2014;13(3):675-686

# Phase 1 Study (XPORT-MF-034[1]) Evaluating Selinexor in Combination with Ruxolitinib in Treatment-naïve Myelofibrosis




AE, adverse event; BID, twice a day; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; QW, once weekly; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SVR35, spleen volume reduction of at least 35%; TSS50, total symptom score reduction ≥ 50%.

* Enrollment completed; 24 patients had been assigned to either a 40 mg (n=10) or 60 mg (n=14) once weekly dose of selinexor, in combination with ruxolitinib 15/20 mg BID (twice daily)

**1.** NCT04562389

# Definitions of Safety and Efficacy Populations

## Safety Population

- All patients who received at least one dose of selinexor.

## Efficacy Evaluable Population (EE)

- **Spleen assessment:** All patients who had at least one dose of selinexor and an evaluation at the timepoint (12 or 24 weeks).
- **Symptom assessment:** All patients who had at least one dose of selinexor, symptoms at baseline and a TSS evaluation at the timepoint (12 or 24 weeks).

## Intent-to-Treat (ITT) Population (primary analysis population)

- **Spleen assessment:** All patients who had at least one dose of selinexor.
- **Symptom assessment:** All patients who had at least one dose of Selinexor; excludes those patients who had no symptoms at baseline (TSS=0).

# Baseline Characteristics

| | Selinexor 40 mg + ruxolitinib (N=10) | Selinexor 60 mg + ruxolitinib (N=14) |
|---|---|---|
| **Age (years), median (range)** | 57.5 (44-71) | 64.5 (58-77) |
| **Female, n (%)** | 3 (30.0) | 5 (35.7) |
| **Baseline weight, median (range)** | 83.6 (53.0-94.4) | 77.5 (54.7-141.9) |
| **Transfusion Status, n (%)** | | |
| Transfusion-Dependent | 0 | 1 (7.1) |
| Transfusion-Independent | 10 (100.0) | 13 (92.9) |
| **MF type, n (%)** | | |
| Primary MF | 4 (40.0) | 7 (50.0) |
| Post-ET MF | 2 (20.0) | 4 (28.6) |
| Post-PV MF | 4 (40.0) | 3 (21.4) |
| **DIPSS risk, n (%)** | | |
| Int-1 | 4 (40.0) | 3 (21.4) |
| Int-2 | 3 (30.0) | 8 (57.1) |
| High | 3 (30.0) | 3 (21.4) |
| **Mutations, n (%)** | | |
| JAK2 | 7 (70.0) | 11 (78.6) |
| CALR | 3 (30.0) | 2 (14.3) |
| MPL | 0 | 1 (7.1) |
| High-risk mutation* | 6 (60) | 5 (35.7) |
| **Hemoglobin (g/dL), n (%)** | | |
| <10 | 4 (40) | 8 (57.1) |
| ≥10 | 6 (60) | 6 (42.9) |
| **Platelets ($10^9$/L), n (%)** | | |
| 100 - <150 | 1 (10.0) | 2 (14.3) |
| ≥150 | 9 (90.0) | 12 (85.7) |
| **Baseline spleen volume ($cm^3$), median (range)** | 1540.3 (660.0-2383.0) | 1961.6 (650.0-3657.0) |
| **Baseline TSS, median (range)** | 17.3 (7-29) | 12.0 (0-54) |
| **Median ruxolitinib starting dose** | 17.5 mg | 15.0 mg |

DIPSS, Dynamic International Prognostic Scoring System;
ET, essential thrombocythemia;
MF, myelofibrosis;
PV, polycythemia vera.

* High-risk genes include: ASXL1, EZH2, IDH1, IDH2, SRSF2 or U2AF1

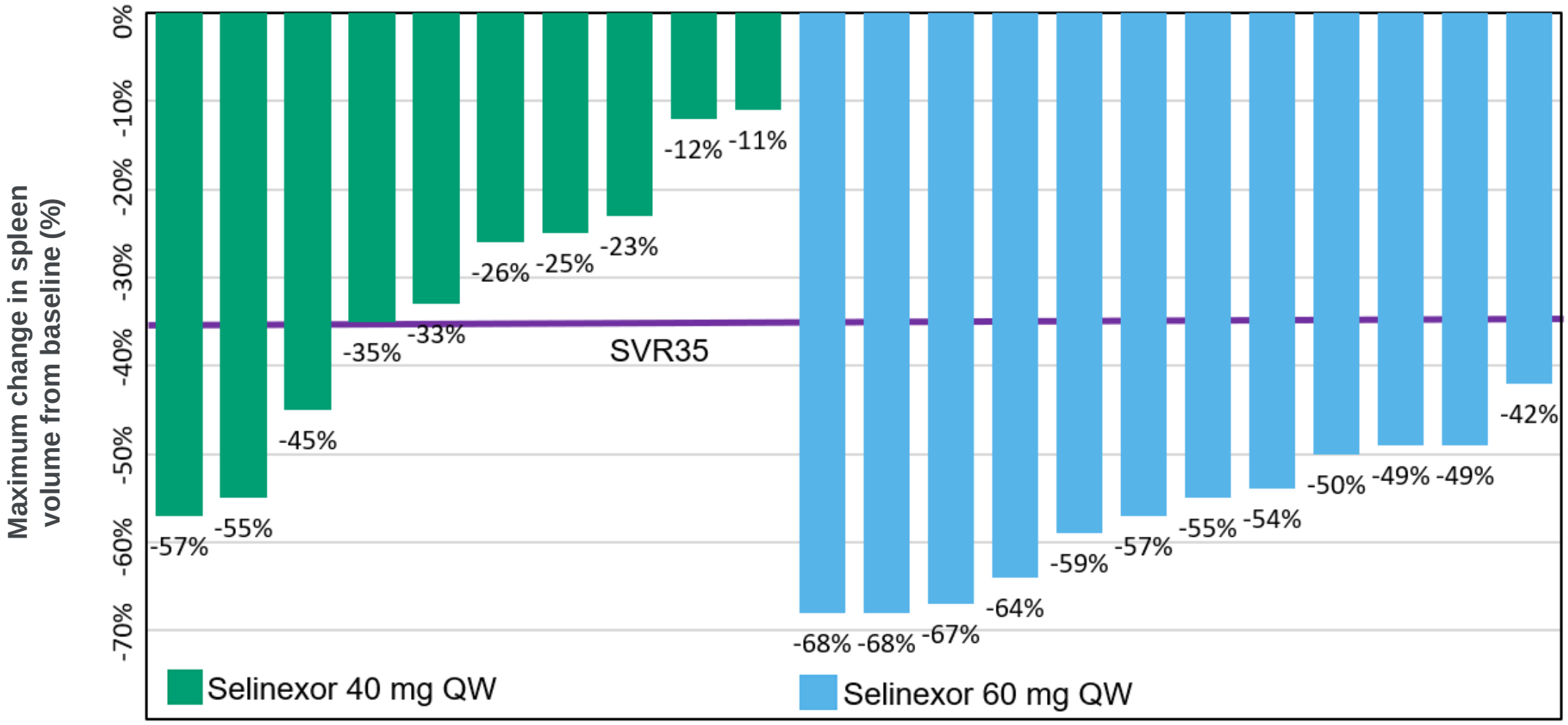
# Rapid and Deep SVR35 Achieved with Selinexor 60 mg at Weeks 12 and 24

| Population | Timepoint | Selinexor 40 mg +ruxolitinib n (%) | Selinexor 60 mg +ruxolitinib n (%) |
|---|---|---|---|
| Efficacy Evaluable | SVR35 at Week 12 | 3/10 (30.0) | 10/12** (83.3) |
| | **SVR35 at Week 24** | **4/8* (50.0)** | **11/12 (91.7)** |
| | SVR35 at anytime | 4/10 (40.0) | 12/12 (100.0) |
| Intent-to-Treat | SVR35 at Week 12 | 3/10 (30.0) | 10/14 (71.4) |
| | **SVR35 at Week 24** | **4/10 (40.0)** | **11/14 (78.6)** |
| | SVR35 at anytime | 4/10 (40.0) | 12/14 (85.7) |

* Two patients discontinued prior to Week 24.
** One patient discontinued prior to week 12; one patient with missing data at week 12 who subsequently discontinued prior to week 24.

SVR35, spleen reduction volume ≥35%

# All Evaluable Patients* Treated with Selinexor 60 mg Achieved an SVR35 at Anytime

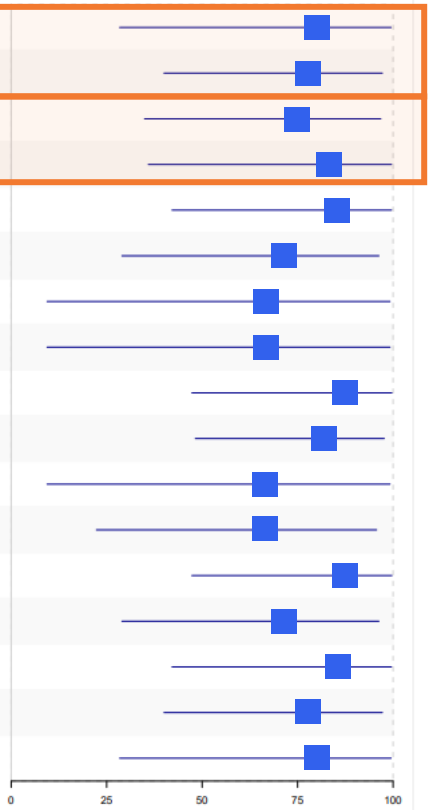



* n=12; one patient discontinued prior to week 12; one patient with missing data at week 12 who subsequently discontinued prior to week 24.

# Selinexor + Ruxolitinib Treatment Effective for All JAKi Naïve Patients, Across All Subgroups Including Males and Patients Who Start at Low Ruxolitinib Doses

## SVR35* (selinexor 60 mg)

| Subgroup | Total | Responder | Response Rate |
|---|---|---|---|
| Gender: Female | 5 | 4 | 80 (28.4, 99.5) |
| Gender: Male | 9 | 7 | 77.8 (40, 97.2) |
| Rux: 15/20 BID | 8 | 6 | 75 (34.9, 96.8) |
| Rux: 5/10 BID | 6 | 5 | 83.3 (35.9, 99.6) |
| MF type: Primary | 7 | 6 | 85.7 (42.1, 99.6) |
| MF type: Secondary | 7 | 5 | 71.4 (29, 96.3) |
| DIPSS: High Risk | 3 | 2 | 66.7 (9.4, 99.2) |
| DIPSS: Intermediate 1 | 3 | 2 | 66.7 (9.4, 99.2) |
| DIPSS: Intermediate 2 | 8 | 7 | 87.5 (47.3, 99.7) |
| JAK2 Mutation: Mutated | 11 | 9 | 81.8 (48.2, 97.7) |
| JAK2 Mutation: Not mutated | 3 | 2 | 66.7 (9.4, 99.2) |
| Baseline Platelet: Platelet <= 200K | 6 | 4 | 66.7 (22.3, 95.7) |
| Baseline Platelet: Platelet > 200K | 8 | 7 | 87.5 (47.3, 99.7) |
| Baseline Spleen Volume: < 1800 | 7 | 5 | 71.4 (29, 96.3) |
| Baseline Spleen Volume: >= 1800 | 7 | 6 | 85.7 (42.1, 99.6) |
| Baseline TSS: < 20 | 9 | 7 | 77.8 (40, 97.2) |
| Baseline TSS: >= 20 | 5 | 4 | 80 (28.4, 99.5) |




* Intent To Treat (ITT) population

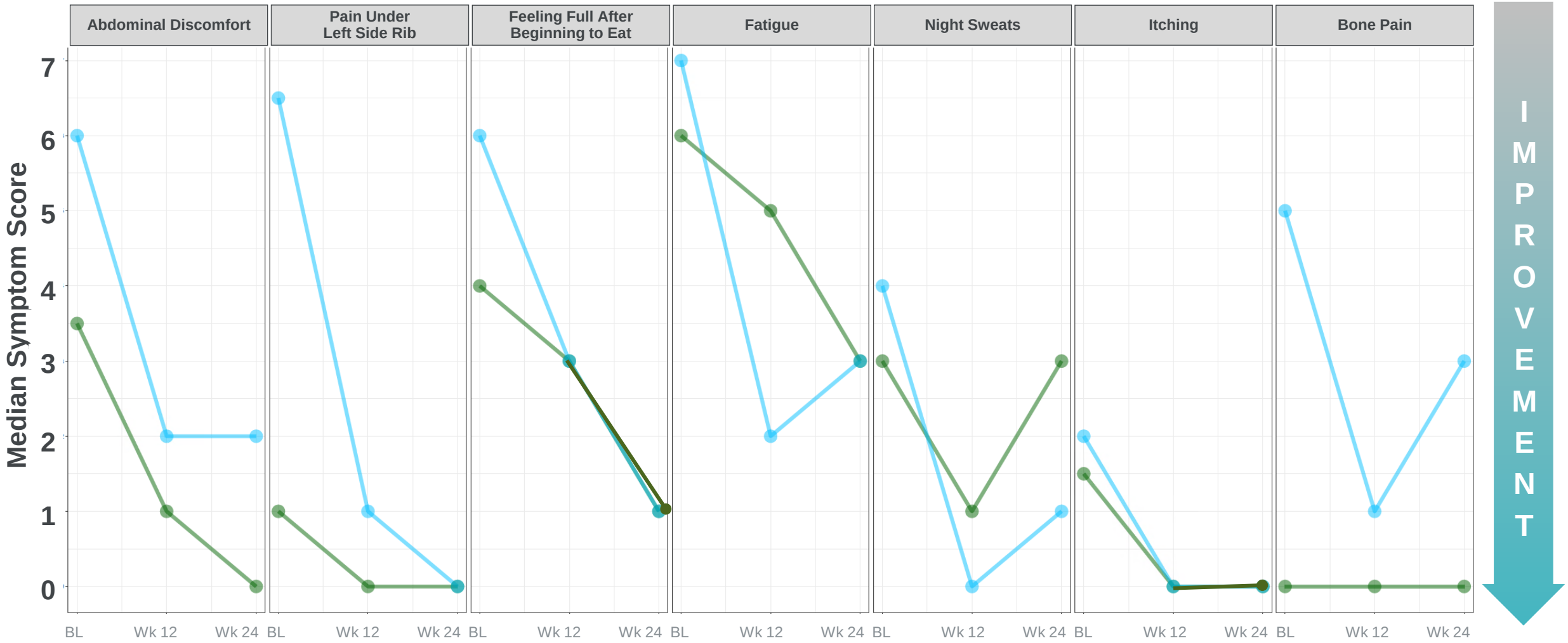
# Robust TSS50 Achieved with Selinexor 60 mg at Weeks 12 and 24

| Population | Timepoint | Selinexor 40 mg +ruxolitinib n (%) | Selinexor 60 mg +ruxolitinib n (%) |
|---|---|---|---|
| Efficacy Evaluable | TSS50 at Week 12 | 6/9* (66.7) | 8/10*** (80.0) |
| | **TSS50 at Week 24** | **4/7** (57.1)** | **7/9**** (77.8)** |
| | TSS50 at anytime | 8/10 (80.0) | 9/10 (90.0) |
| Intent-to-Treat | TSS50 at Week 12 | 6/10 (60.0) | 8/12 (66.7) |
| | **TSS50 at Week 24** | **4/10 (40.0)** | **7/12 (58.3)** |
| | TSS50 at anytime | 8/10 (80.0) | 9/12 (75.0) |

Note: Median TSS was calculated for each cycle, regardless of number of scores collected per cycle.
* One patient with missing data
** Two patients discontinued prior to Week 24 and one had missing data.
*** One patient discontinued prior to week 12; one patient with missing data at week 12, who subsequently discontinued prior to week 24.
**** Two patients discontinued prior to Week 24 and one had missing data.

TSS50, total symptom score ≥ 50. Note: Median TSS was calculated for each cycle, regardless of number of scores collected per cycle

# Improvement In Major Spleen and Cytokine Related Symptoms Across the MFSAF* Domains with Selinexor 60mg



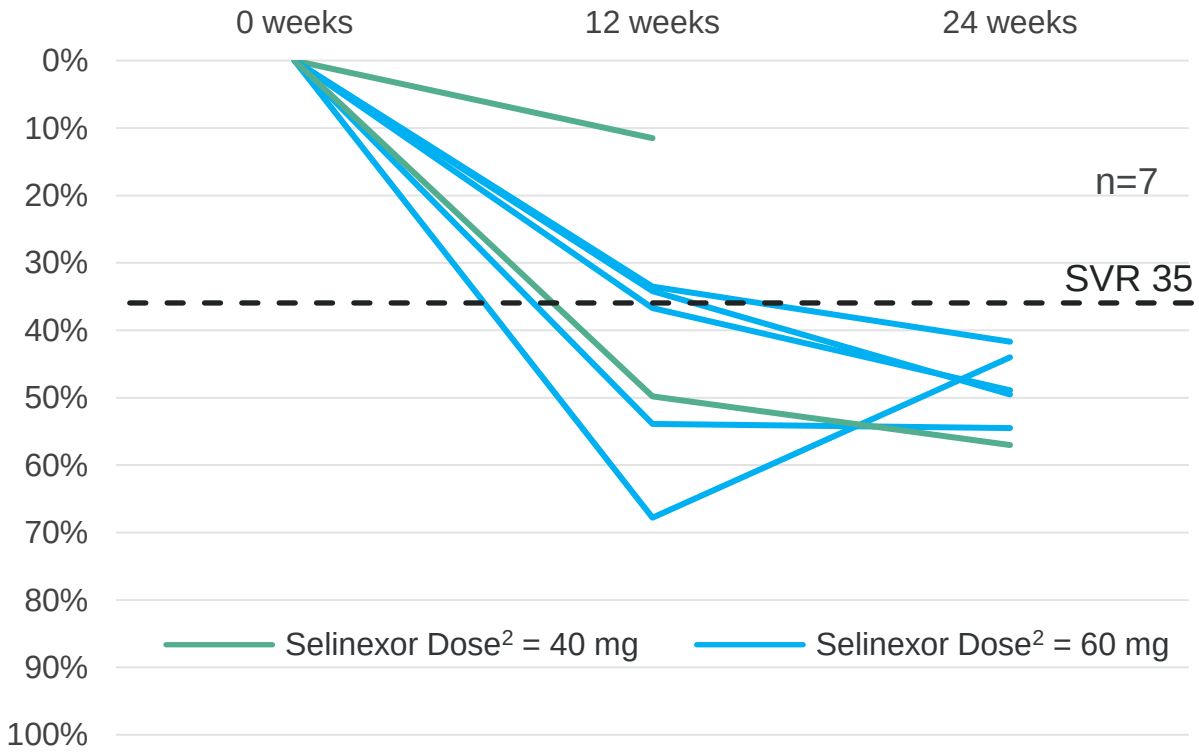

* Myelofibrosis Symptom Assessment Form

Data cut February 24, 2023

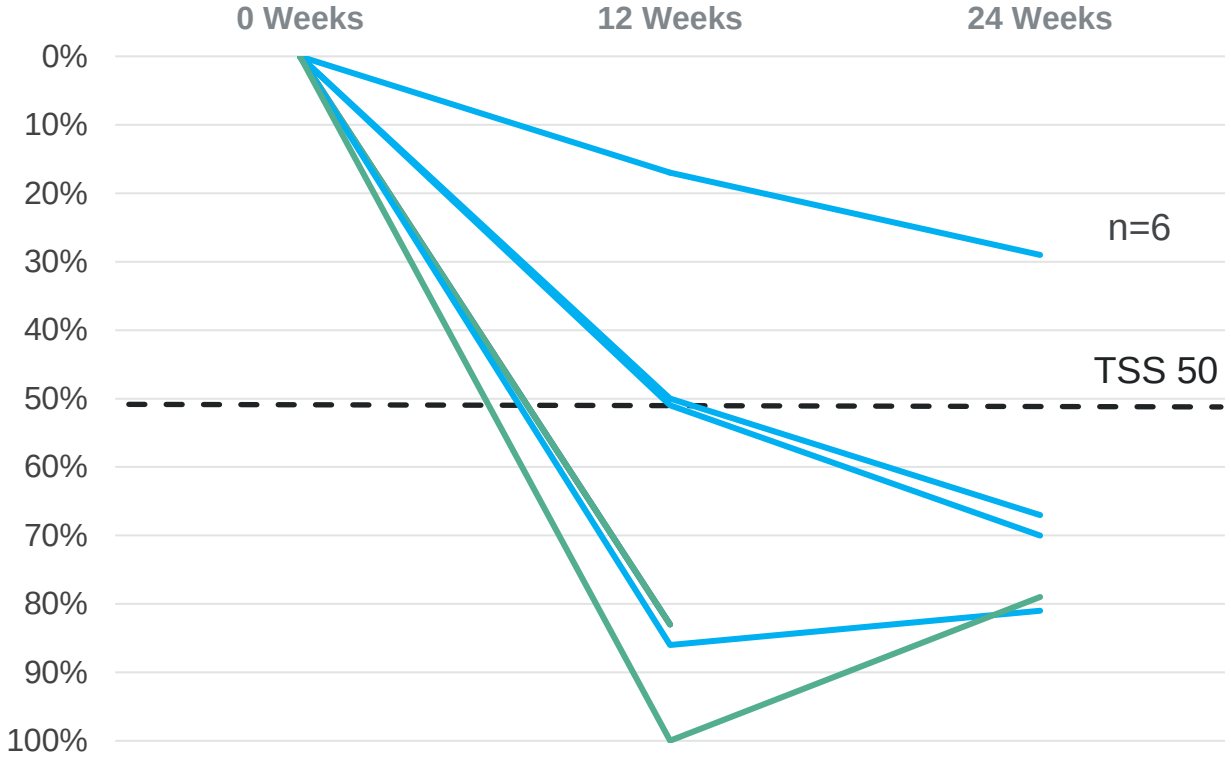
# Efficacy with Selinexor in Combination with Suboptimal Dose of Ruxolitinib (5 mg) Further Supports XPO1 as a Fundamental MoA in MF

**Retrospective, Exploratory Analysis from Phase 1 Selinexor + Ruxolitinib Study (034)**

## Spleen Volume Reduction




## Total Symptom Score Reduction[1]




**"Based on limited clinical data, long-term maintenance at a 5 mg twice daily dose has not shown responses and continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks." Jakafi (ruxolitinib) U.S. Package Insert, January 2023**

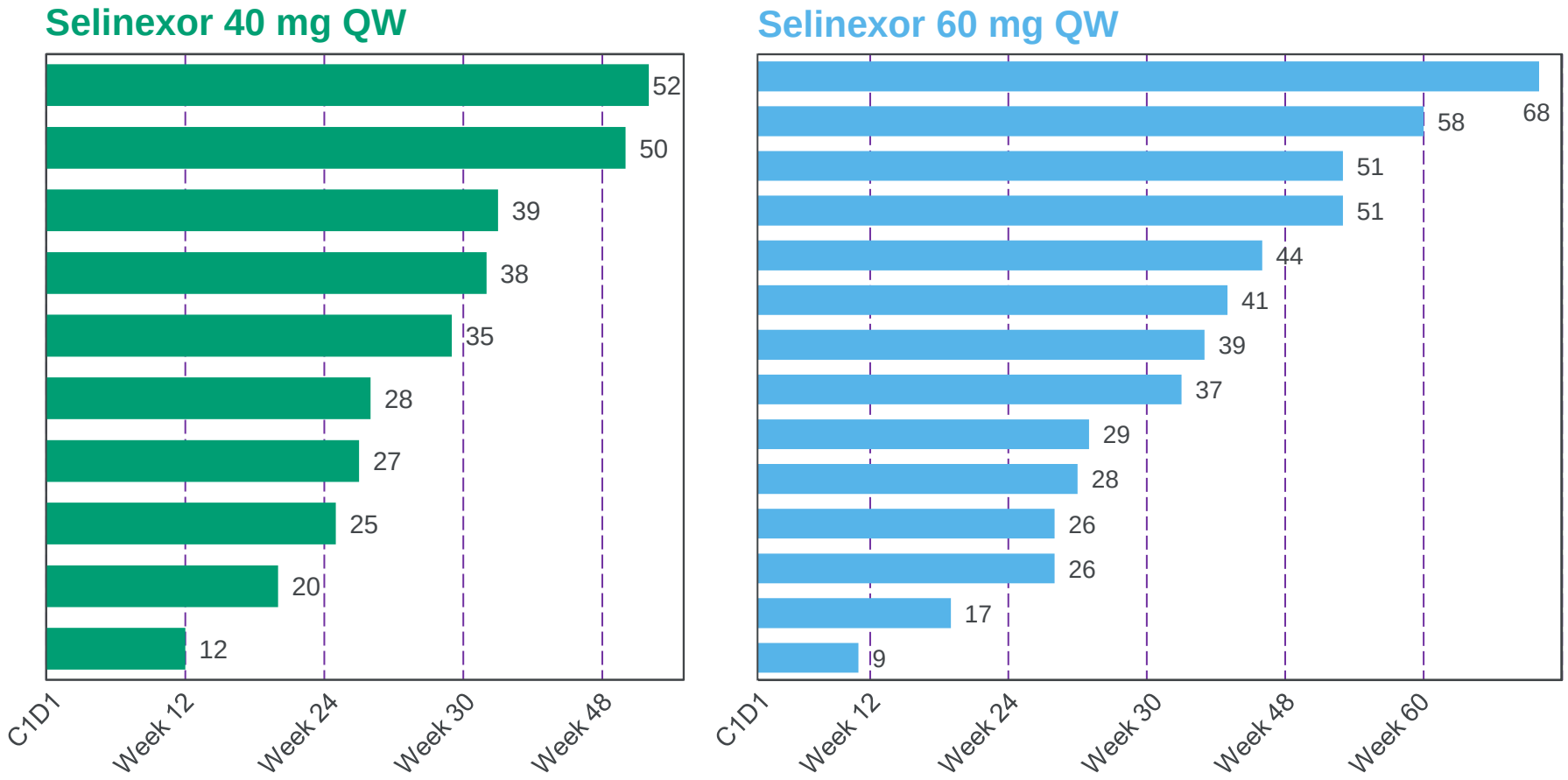
**The safety and efficacy of selinexor in myelofibrosis has not been established and has not been approved by the U.S. FDA or any other regulatory authority.**

1. One patient with missing TSS50 score
2. Assigned selinexor starting dose




Data cut February 24, 2023

# Treatment Durations Up to 68 Weeks in Selinexor 60 mg, as of Data Cut-Off




Median duration of selinexor treatment:

- 40 mg cohort: 31.5 weeks (range 12-52 weeks)
- 60 mg cohort: 38 weeks (range 9-68 weeks)

# Generally Tolerable and Manageable Side Effect Profile Support 60mg Selinexor as the Recommended Dose in Combination with Ruxolitinib

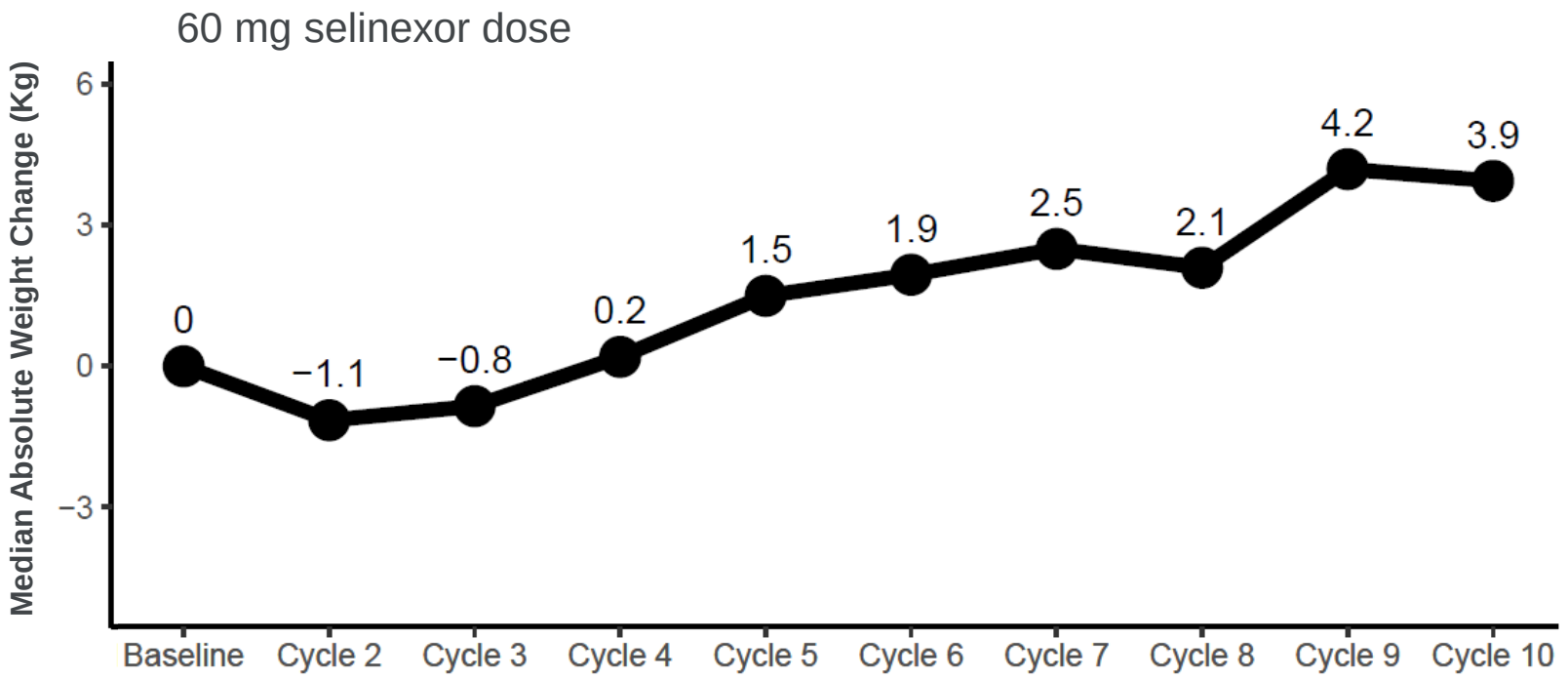
| Treatment Emergent Adverse Events | Selinexor 40 mg + ruxolitinib (N=10) | Selinexor 60 mg + ruxolitinib (N=14) |
|---|---|---|
| **Any grade, >25% overall** | | |
| Nausea | 7 (70.0) | 11 (78.6) |
| Anemia | 4 (40.0) | 9 (64.3) |
| Fatigue | 6 (60.0) | 8 (57.1) |
| Thrombocytopenia | 4 (40.0) | 9 (64.3) |
| Constipation | 2 (20.0) | 7 (50.0) |
| Headache | 4 (40.0) | 5 (35.7) |
| Vomiting | 2 (20.0) | 7 (50.0) |
| Neutropenia | 2 (20.0) | 5 (35.7) |
| Dyspnea | 2 (20.0) | 5 (35.7) |
| Decreased appetite | 2 (20.0) | 4 (28.6) |
| Dysgeusia | 2 (20.0) | 4 (28.6) |
| Hyponatremia | 1 (10.0) | 5 (35.7) |
| **Grade 3+, >5% overall** | | |
| Anemia | 3 (30.0) | 6 (42.9) |
| Thrombocytopenia | 1 (10.0) | 4 (28.6) |
| Neutropenia | 2 (20.0) | 1 (7.1) |
| Atrial fibrillation | 2 (20.0) | 1 (7.1) |
| Back pain | 0 | 2 (14.3) |
| **Treatment-related adverse events leading to treatment discontinuations** | | |
| Thrombocytopenia, Grade 3 | 0 | 1 (7.1) |
| Peripheral Neuropathy | 0 | 1 (7.1) |

- Treatment related discontinuations due to cytopenias were low (n=1)
- 75% of nausea events were Grade 1
  - One patient experienced Grade 3 nausea (no antiemetic prophylaxis)
- In the 60 mg cohort, 64% of pts received one prophylactic antiemetic
  - Amongst the subgroup who received one prophylactic antiemetic, 67% of pts experienced nausea (Grade 1 only) compared to 100% of those who did not receive prophylactic antiemetics (Grades 1-3)
- Despite nausea and vomiting incidence, patients generally did not experience weight loss



Data cut February 24, 2023

# Patients Experienced Improved Weight with Selinexor in Combination with Ruxolitinib

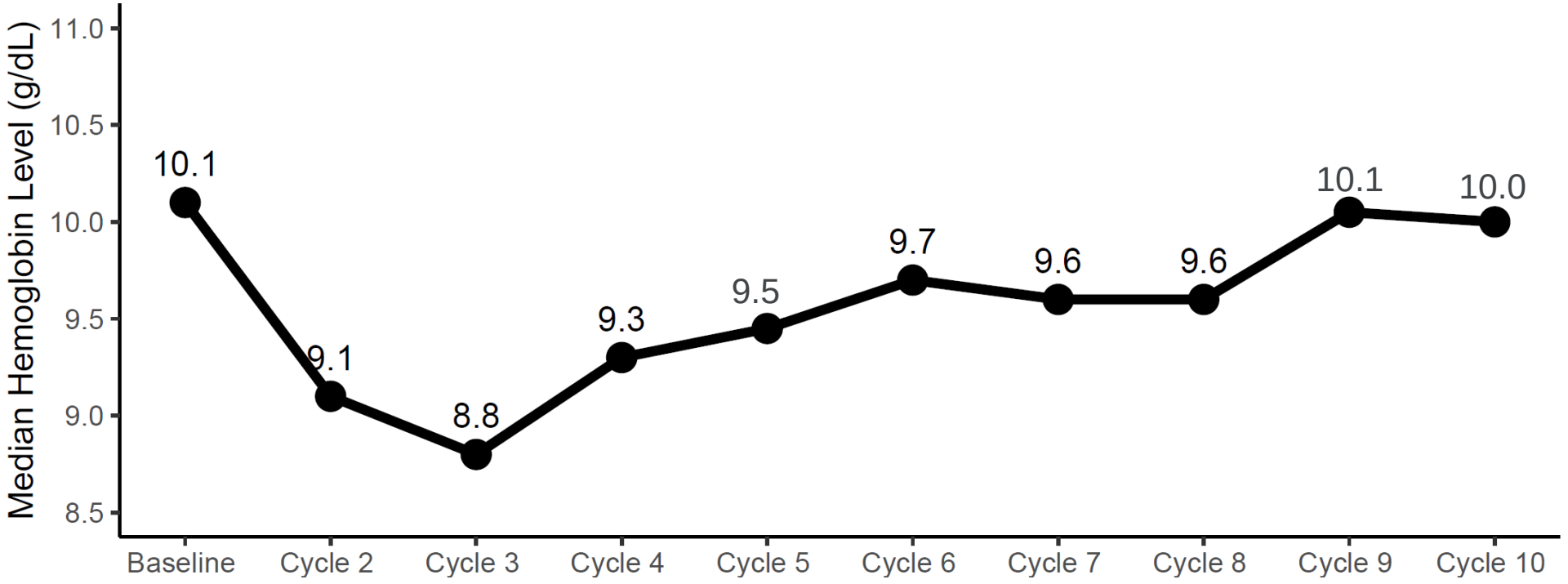



- Patients' median weight increase at Week 24 was 3 kg in the 40mg cohort and 2.5 kg in the 60mg cohort
- Despite nausea and vomiting incidence, patients generally did not experience weight loss



Data cut February 24, 2023

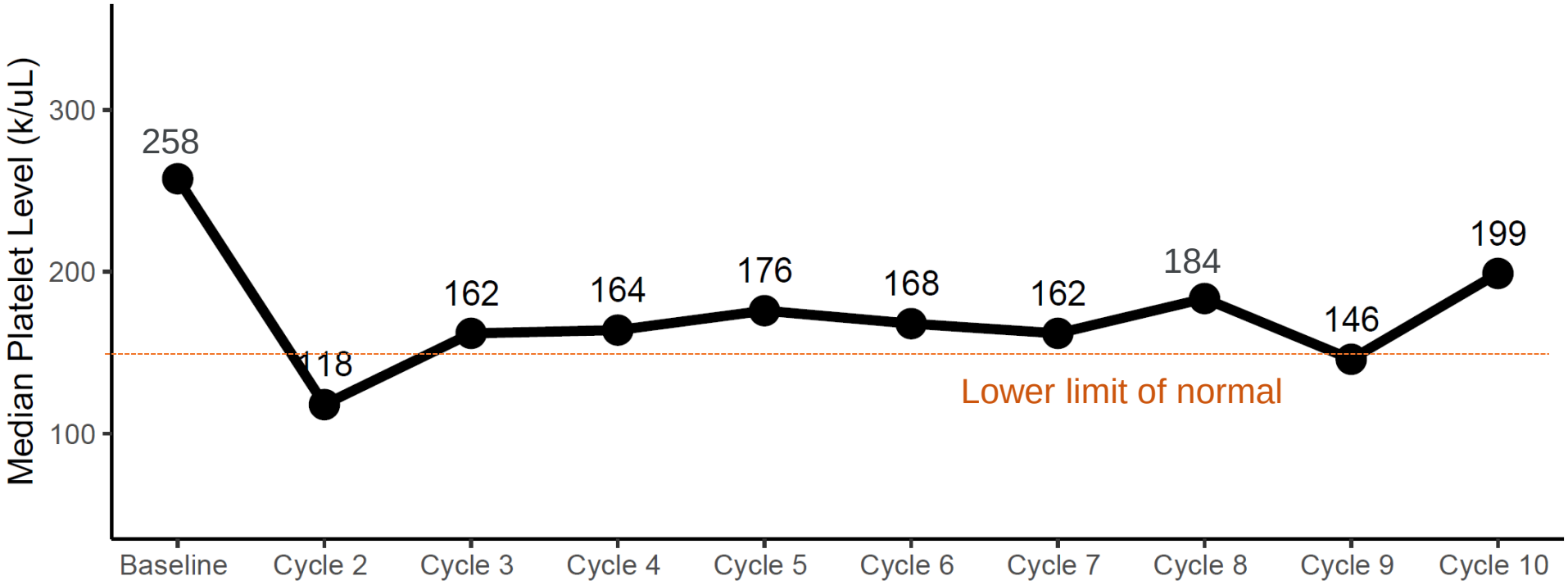
# Potential Disease Modification Given Hemoglobin Levels Increased back to Baseline






Data cut February 24, 2023

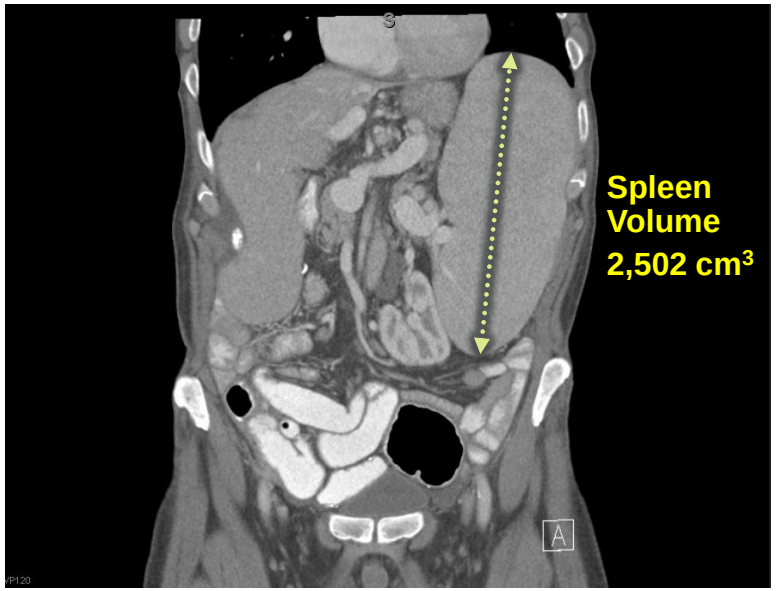
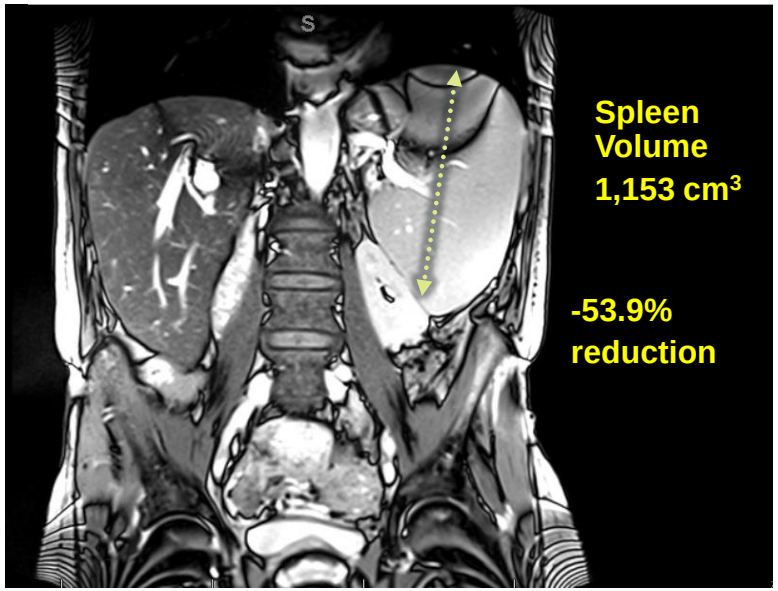
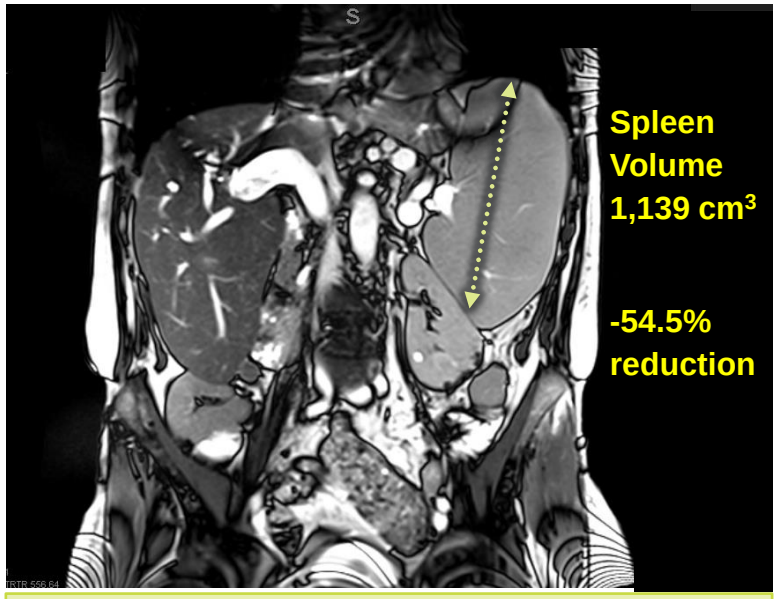
# Normalization of Platelet Levels Also Indicative of Disease Modification



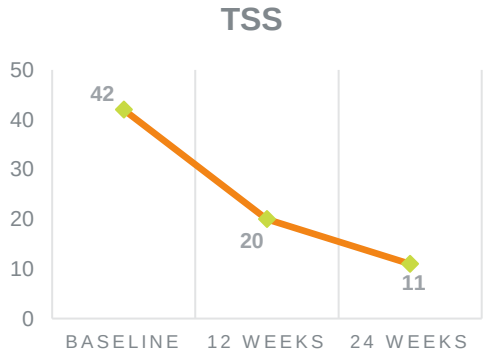


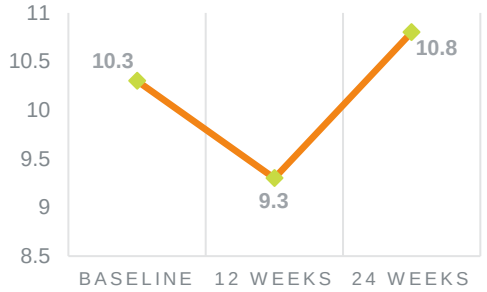

Data cut February 24, 2023

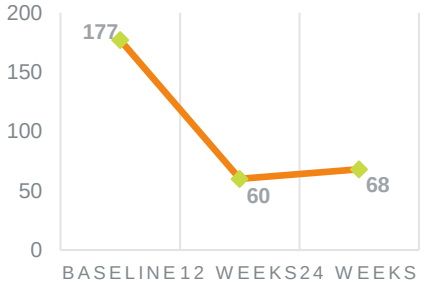
# Case Study of 76 y/o Male Patient with Primary MF, DIPSS Int-1 and JAK2+

| Baseline | 12 Weeks | 24 Weeks |
|---|---|---|
|  |  |  |
| Spleen Volume 2,502 $cm^3$ | Spleen Volume 1,153 $cm^3$<br>-53.9% reduction | Spleen Volume 1,139 $cm^3$<br>-54.5% reduction |
| Selinexor = 60 mg / Ruxolitinib = 15 mg | Selinexor = 60 mg / Ruxolitinib = 5 mg | Selinexor = 60 mg / Ruxolitinib = 5 mg |

- Ruxolitinib dose reduced from 15 mg to 5 mg at cycle 2 due to Grade 2 thrombocytopenia which remained stable; selinexor maintained at 60 mg
- SVR35 and TSS50 at 12W deepening at 24W
- Antiemetic started at C1D1, with no nausea AE
- 4 kg weight gain at Week 24 compared to baseline
- Remains on selinexor 60 mg and ruxolitinib 5 mg treatment for >62 weeks






Data cut February 24, 2023

# Selinexor 60 mg is Synergistic with Ruxolitinib and Has the Potential to Transform 1L Myelofibrosis Treatment Paradigms

- **Selinexor 40 mg and 60 mg dose levels generally well tolerated and manageable allowing most patients to remain on therapy (up to 68 weeks as of data cutoff)**
  - **Only two treatment related discontinuations observed (peripheral neuropathy and thrombocytopenia)**
- **Rapid, deep, and sustained spleen response and robust symptom improvement in patients treated with 60 mg selinexor: SVR35: 78.6% ITT (91.7%, EE) and TSS50: 58.3% ITT (77.8%, EE) at week 24**
  - **SVR35: Observed in 100% of evaluable patients at anytime; rates consistent by gender and ruxolitinib starting dose**
  - **SVR35 and TSS50 observed amongst patients treated with suboptimal doses of ruxolitinib 5 mg**
  - **TSS50: Improvement seen across all major spleen and cytokine related MFSAF Domains**
- **Disease modification observed as evidenced by rapid normalization of platelets and stabilization of hemoglobin levels**
- **Efficacy and safety data support 60 mg dose of selinexor as the recommended dose for Phase 3 study in combination with ruxolitinib**

# Key Opinion Leader Guest Speaker

## JOHN MASCARENHAS, MD

**Professor of Medicine at the Icahn School of Medicine at Mount Sinai**

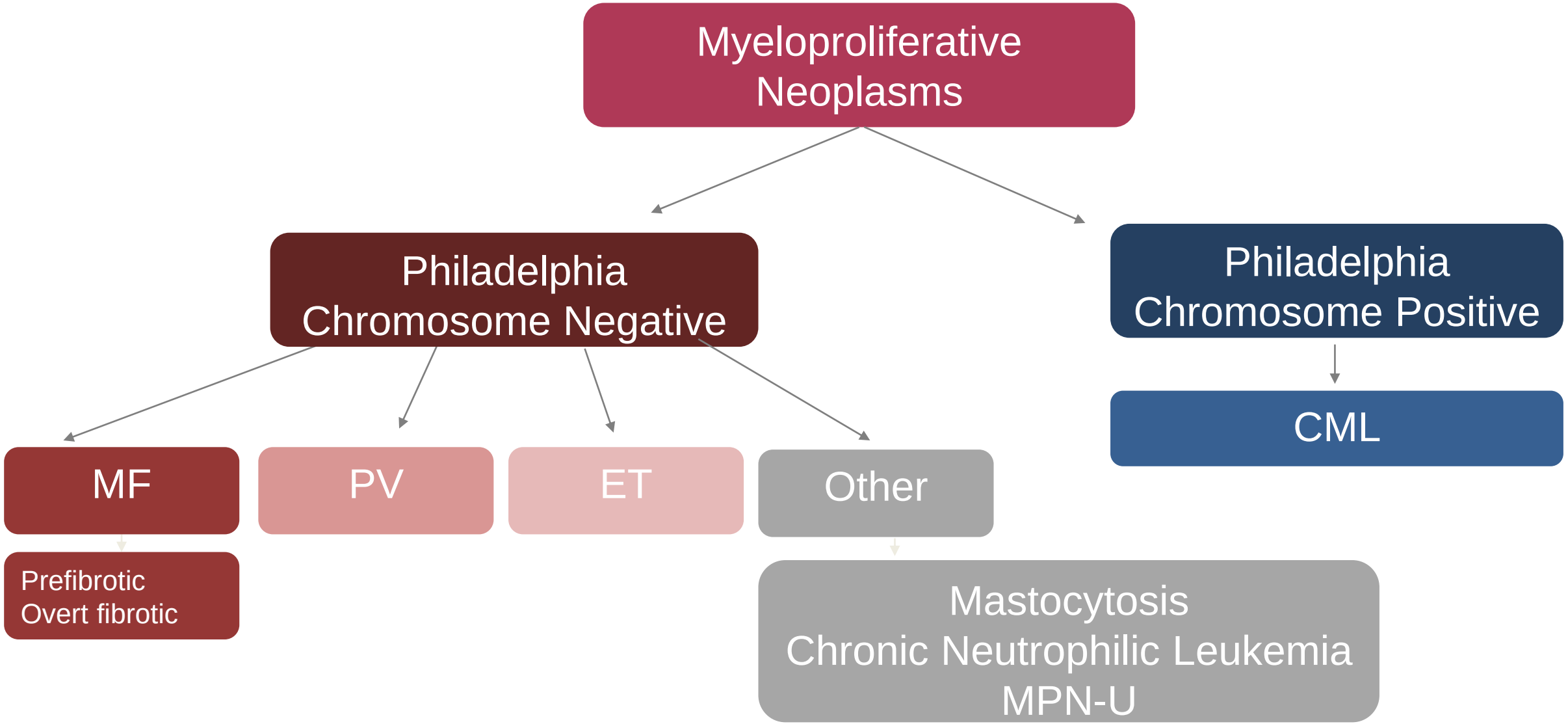
*Director of the Center of Excellence for Blood Cancers and Myeloid Disorders*

# Myelofibrosis: Disease Background and Treatment Approach

Icahn School of Medicine at Mount Sinai

John Mascarenhas, MD
Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, NY

# The Myeloproliferative Neoplasms

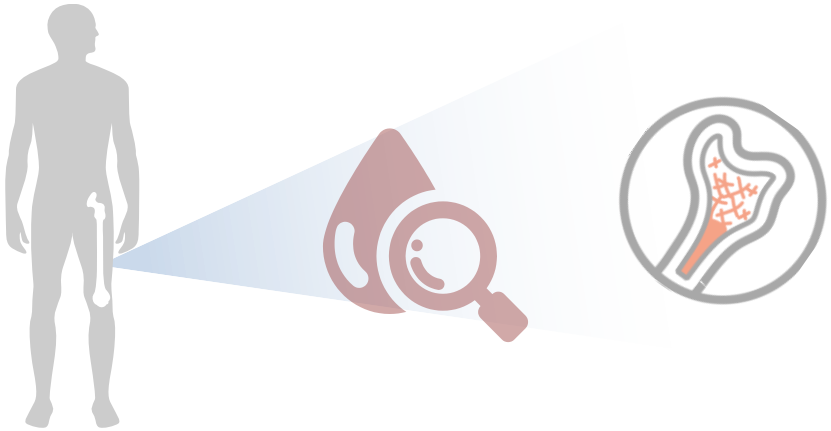



Thapa B, et al. Myeloproliferative Neoplasms. StatPearls Publishing; May 8, 2022.

# Myelofibrosis – Disease Background

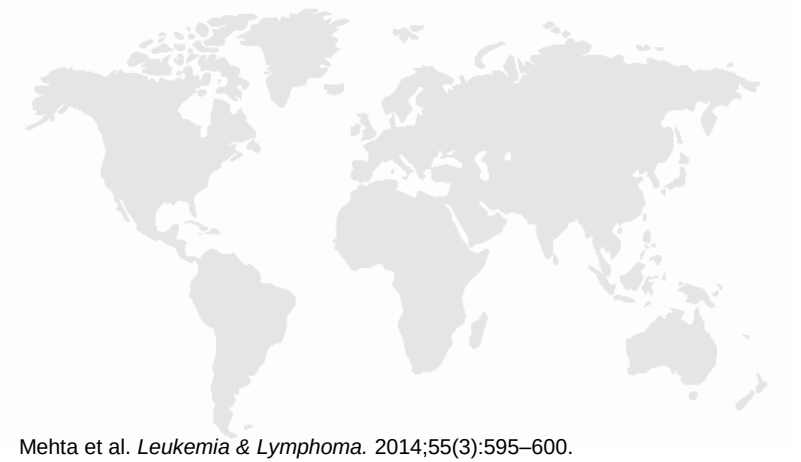
## Types of Myelofibrosis[1]

| | |
|---|---|
| **Primary** | **Primary myelofibrosis (PMF)** |
| **Secondary** | **Post-essential thrombocythemia (post-ET) Myelofibrosis** |
| | **Post-polycythemia vera (post-PV) Myelofibrosis** |



## Epidemiology, Demographics and Etiology

- Myelofibrosis is uncommon[1,2]
  - Estimated **prevalence** in the US is 3.6 – 5.7 per 100,000
  - Estimated **incidence** in the US is 1.7 to 2.4 per 100,000
- Slightly more **men** are diagnosed with myelofibrosis, 62%[3]
- Median age at diagnosis is approximately **65 years**[3]
- Most MF patients have **driver mutations** in the *JAK2*, *CALR* or *MPL* genes[4]
- Specific **etiology is unknown**, but certain risk factors have been linked to MF[1]




1. Mehta et al. *Leukemia & Lymphoma.* 2014;55(3):595–600.
2. Tefferi et al. *Leukemia*. 2018;23:1189-1199
3. Tefferi et al. *Am J Hematol*. 2018;93:348-355
4. Mughal et al. *Int. Journal of Gen Medicine.* 2014:89–101.

# Myelofibrosis – Prognosis and Mortality

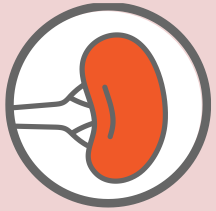
## Prognosis and Mortality

- **Prognosis can vary** significantly dependent on MF patient risk factors
- **~40%** of MF patients have **anemia**[1]
- **~25%** require **RBC transfusions**[1]
- Patients with intermediate- to high-risk MF have poor **median overall survival** compared to those at low-risk[2]
  - **High-risk**: 1.8 years
  - **Intermediate – 2 risk:** 3.6 years
  - **Intermediate – 1 risk**: 7.8 years
  - **Low-risk**: 17.5 years
- Causes of death include:
  - **Leukemic transformation** with reported 10-year estimates of incidence range from **10% – 20% in PMF**[3]
  - **Comorbid conditions** including cardiovascular events and consequences of cytopenias including infection or bleeding[4]




1. Naymagon and Mascarenhas, *HemaSphere* 2017 1:1
2. Tefferi A. *Am J Hematol*. 2018;93:1551–1560
3. Vallapureddy et al. *Blood Cancer Journal* 2019;9:12
4. Tefferi A. *Am J Hematol*. 2021;96:145–162.

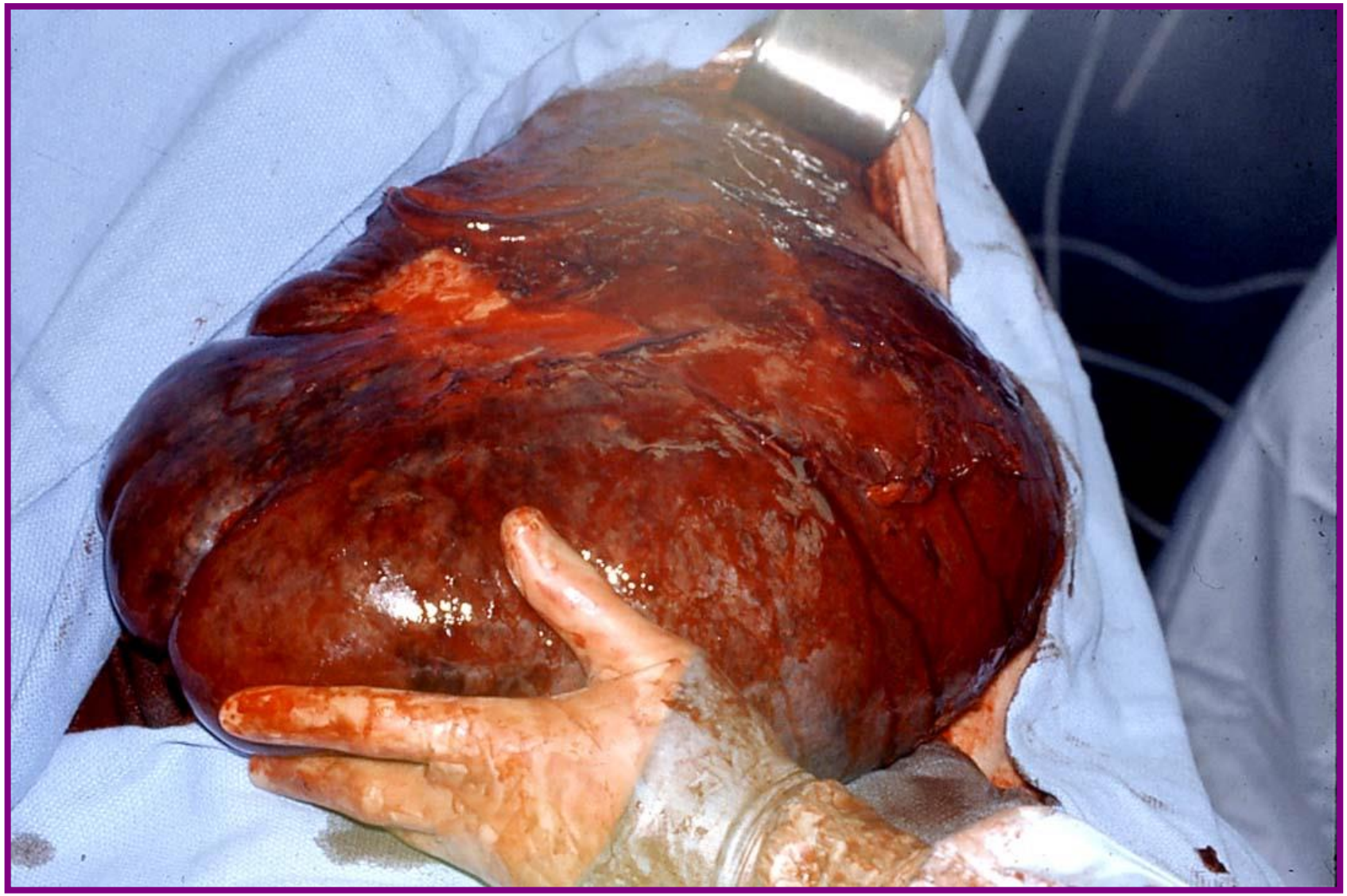
# Presentation – Four Key Hallmarks of Myelofibrosis

| The 4 hallmarks of myelofibrosis | | | | |
|---|---|---|---|---|
| **Hallmark** |  **Spleen volume** |  **Constitutional symptoms** |  **Anemia and transfusion dependence** |  **Bone marrow fibrosis** |
| **Features and Symptoms** | • Abdominal pain<br>• Early satiety | • Weight loss<br>• Pruritis<br>• Anorexia<br>• Fever<br>• Night sweats<br>• Inactivity<br>• Concentration problems | • Fatigue<br>• Bleeding<br>• Anemia<br>• Thrombocytopenia<br>• Leucopenia | • Thrombocytosis<br>• Leukocytosis<br>• Acute leukemia<br>• Bone pain |

- **25% of MF patients are asymptomatic[1]**
  - Diagnosis made detection of splenomegaly or low blood counts from unrelated cause

1. Lal et la., Medscape 2021. https://emedicine.medscape.com/article/197954

# Long Term Complications of MPNs
## *Surgical Therapy of Splenomegaly*



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# Other Risk Stratification Tools for Primary MF
# DIPSS Plus

## Use DIPSS-Plus if cytogenetic data are available

### Dynamic IPSS-Plus (DIPSS-Plus)

| Prognostic Variable | Points |
|---|---|
| DIPSS low risk | 0 |
| DIPSS INT-1 | 1 |
| DIPSS INT-2 | 2 |
| DIPSS high risk | 3 |
| Platelets < 100 × $10^9$/L | 1 |
| Transfusion need | 1 |
| Unfavorable karyotype* | 1 |

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q−, i(17q), 5/5q−, 12p−, inv(3), or 11q23 rearrangement.

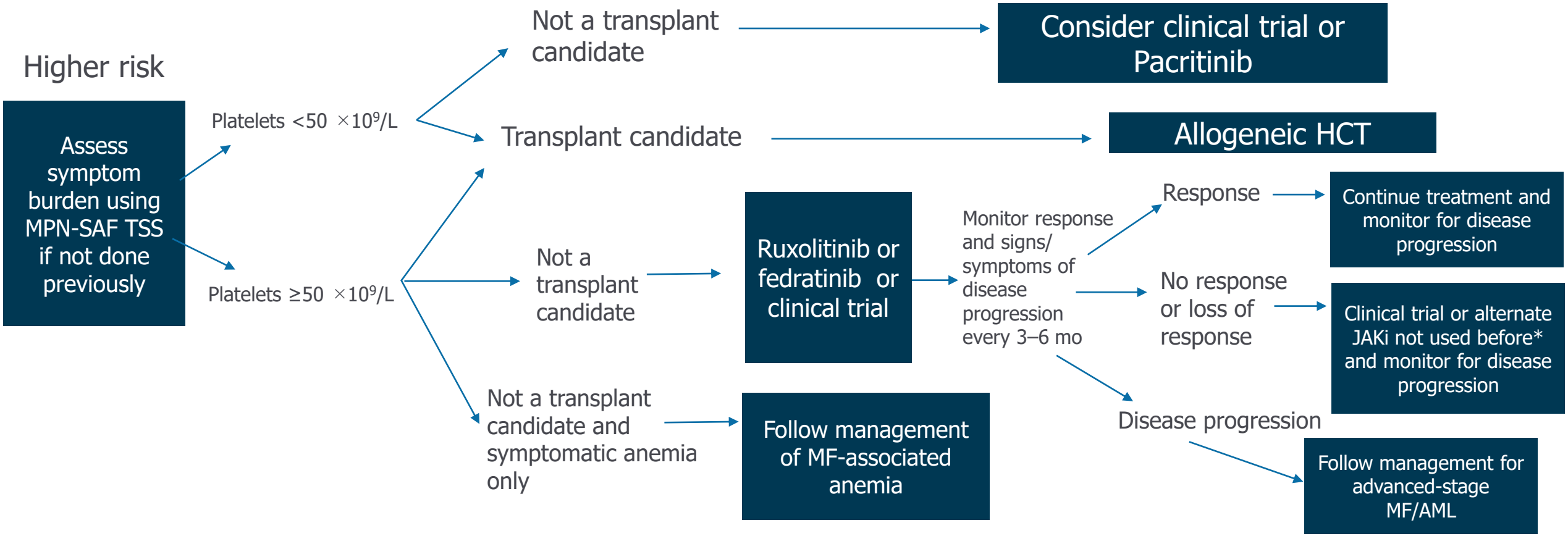
| Risk Group | Points |
|---|---|
| Low | 0 |
| INT-1 | 1 |
| INT-2 | 2 or 3 |
| High | 4 to 6 |

Online calculator for DIPSS-Plus score can be found at https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis

INT-1, intermediate-1; INT-2, intermediate-2.

NCCN Guidelines. Myeloproliferative neoplasms (v3.2022). 2022.

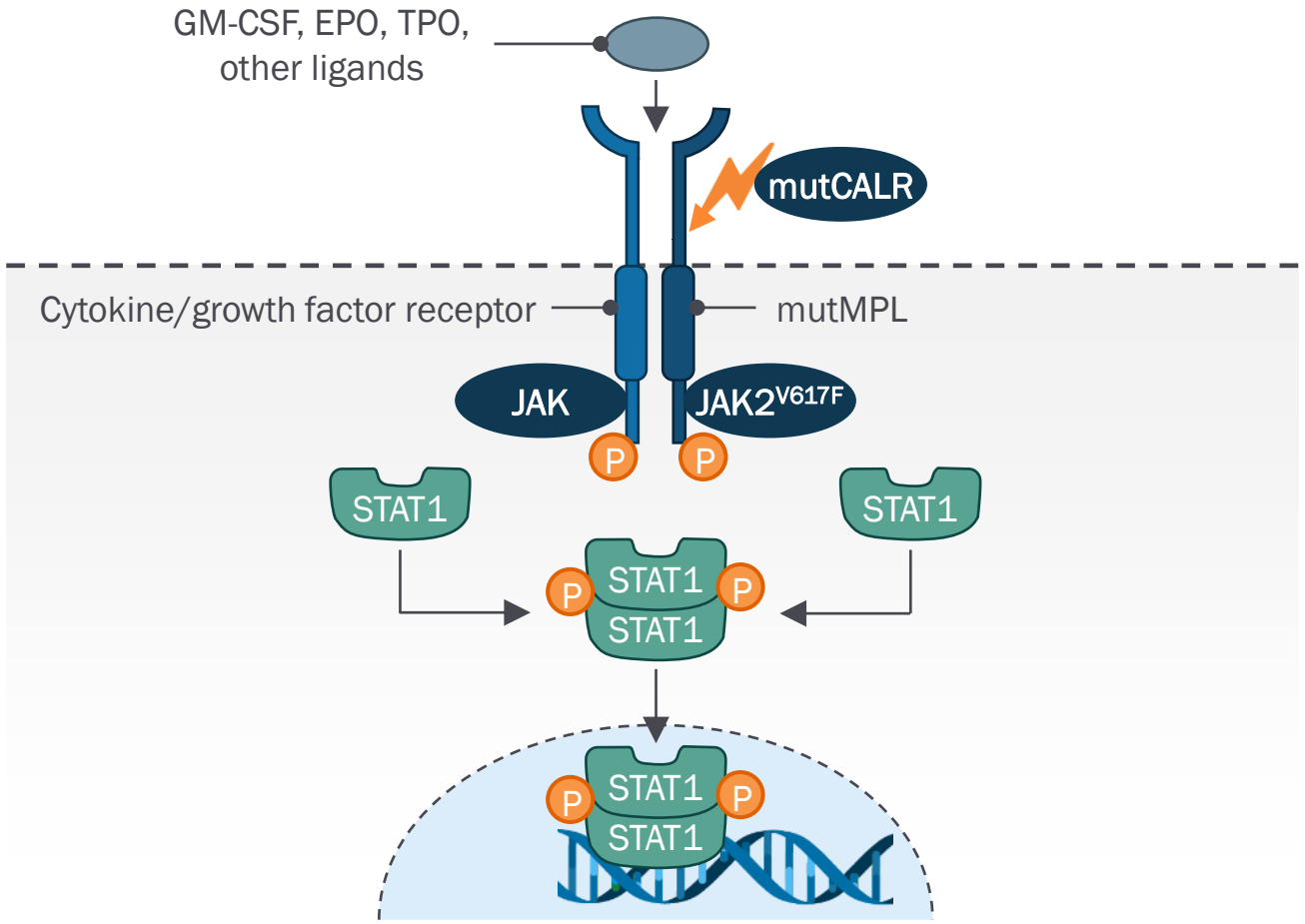
# NCCN Guidelines: Treatment for Higher-Risk MF




*Consider pacritinib for patients with platelet counts ≥50,000 × 109/L with one prior JAK inhibitor.
HCT, hematopoietic stem cell transplant; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form.
NCCN. Myeloproliferative neoplasms (Version 2.2022). 2022. Accessed August 8, 2022. https://www.nccn.org/guidelines.

# JAK/STAT Signaling Pathway in MF

Dysregulated JAK/STAT signaling in MF drives inflammatory cytokine overproduction, bone marrow fibrosis, constitutional symptoms, extramedullary hematopoiesis, and splenomegaly[a]




EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; JAK/STAT, Janus kinase/signal transducers and activators of transcription; TPO, thrombopoietin.

a. Mesa RA, et al. J Clin Oncol. 2022;40(16 suppl): Abstract 7002; b. Mascarenhas J. Expert Rev Hematol. 2022;15:671-684.

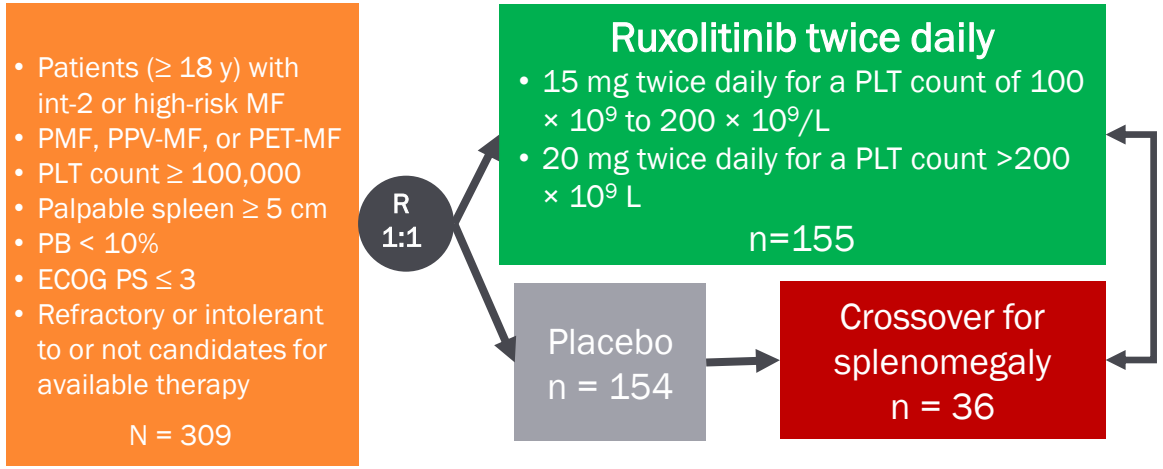
# The JAK Inhibitor Landscape in MF

| APPROVED | IN DEVELOPMENT | INACTIVE |
| --- | --- | --- |
| Ruxolitinib (PLT > 50) | Momelotinib (Second-line for symptoms and anemia) | XL-019 |
| Fedratinib (PLT > 50) | Ilginatinib (NS-018) (Low PLT, for spleen and symptoms) | BMS-911543 |
| Pacritinib (PLT < 50) | | AZD-1480 |
| | | LY2784544 |

Mascarenhas JO, et al. Blood Rev. 2014;28:189-96.

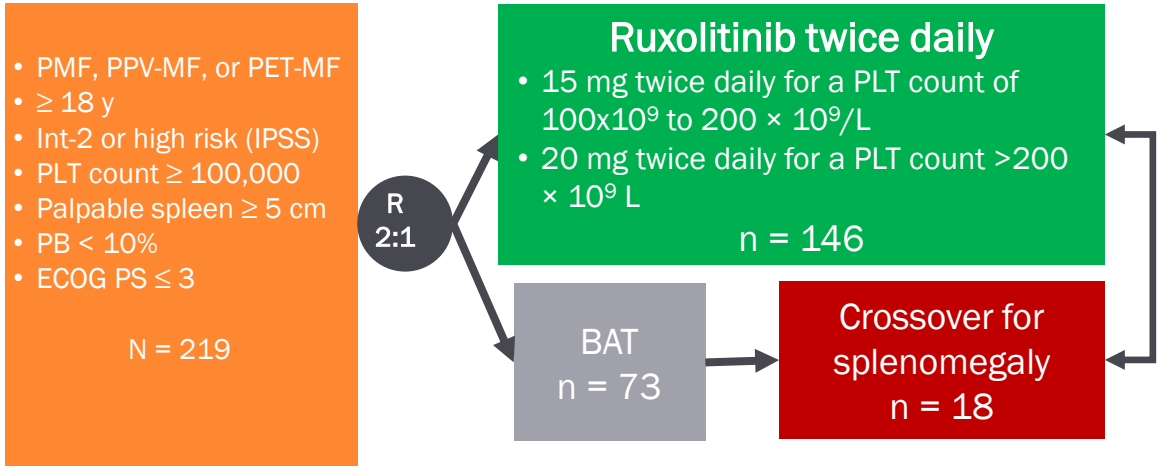
# Ruxolitinib Phase 3 Trials *COMFORT-I and COMFORT-II*

## COMFORT-I: Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial[a]




- **Primary endpoint:** Number of patients in whom ≥ 35% SVR was achieved from baseline to week 24 as measured by MRI (or CT scan in applicable patients)
- **Secondary endpoints:** Proportion of patients with ≥ 50% reduction in TSS from baseline to week 24 as measured by the MFSAF 2.0, OS, duration of SVR

## COMFORT-II: Randomized, open-label, phase 3 trial[b]

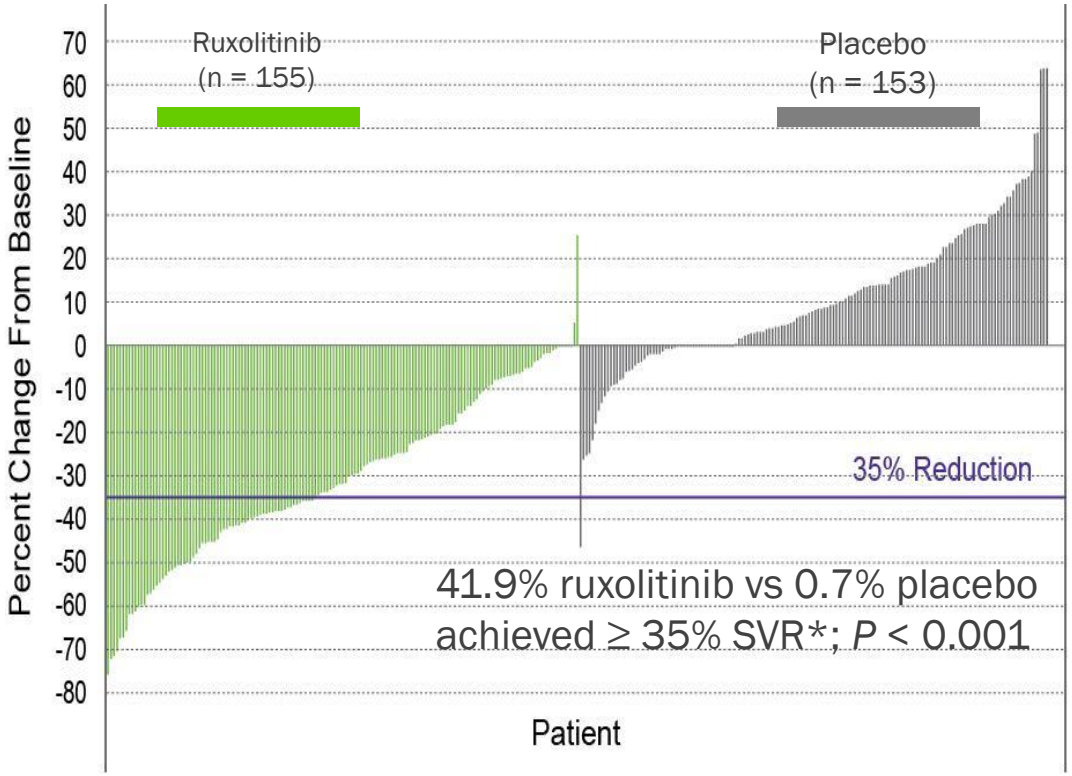



- **Primary endpoint:** Number of patients with ≥ 35% SVR from baseline to week 48 as measured by MRI (or CT scan in applicable patients)
- **Key secondary endpoint:** ≥ 35% SVR from baseline to week 24, length of response, PFS, OS, and change in marrow morphology

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Int, intermediate; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PET-MF, postessential thrombocythemia MF; PFS, progression-free survival; PMF, primary MF; PPV-MF, postpolycythemia vera MF; SVR, spleen volume reduction; TSS, total symptom score.
a. Verstovsek S, et al. N Engl J Med. 2012;366:799-807; b. Harrison CN, et al. N Engl J Med. 2012;366:787-798.

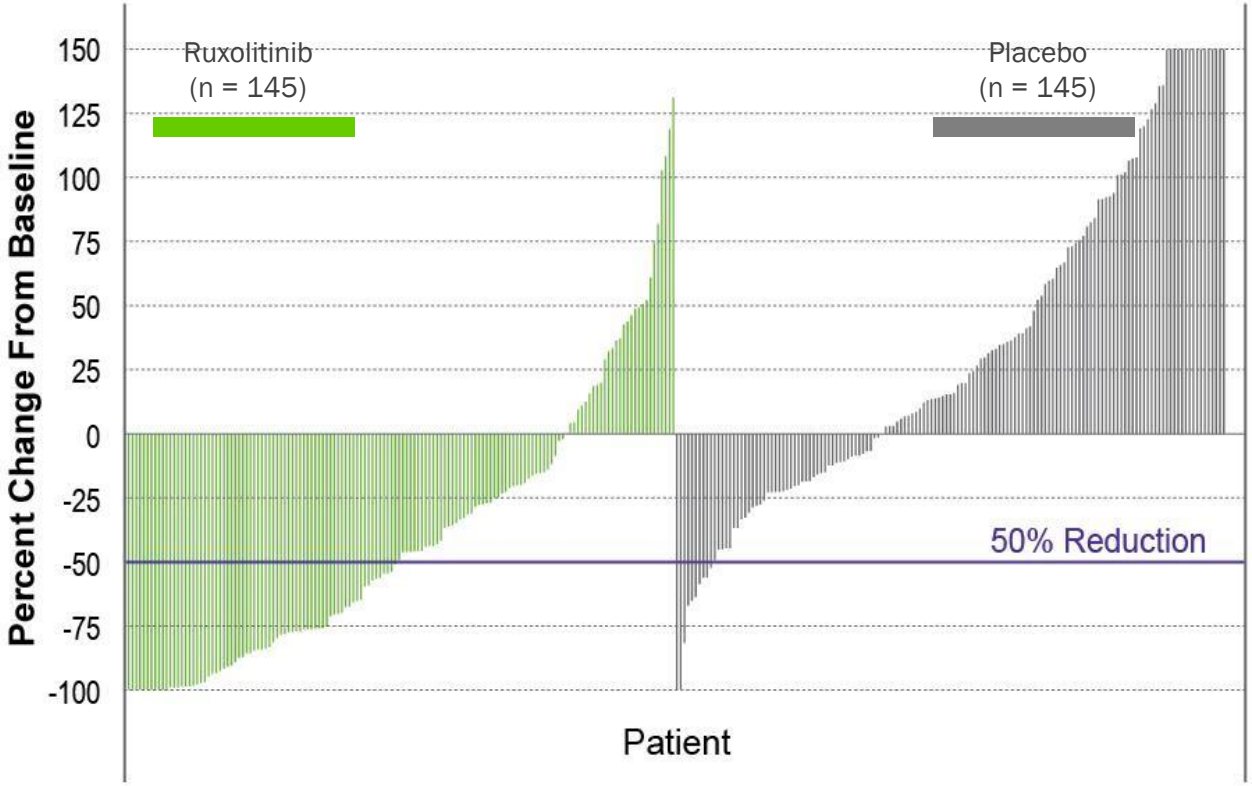
# COMFORT-I
## *Key Efficacy Endpoints*

### Primary Endpoint: ≥ 35% SVR at 24 Weeks




OR = 134.4 (95% CI: 18, 1004.9); *P* < .001

### TSS at 24 Weeks



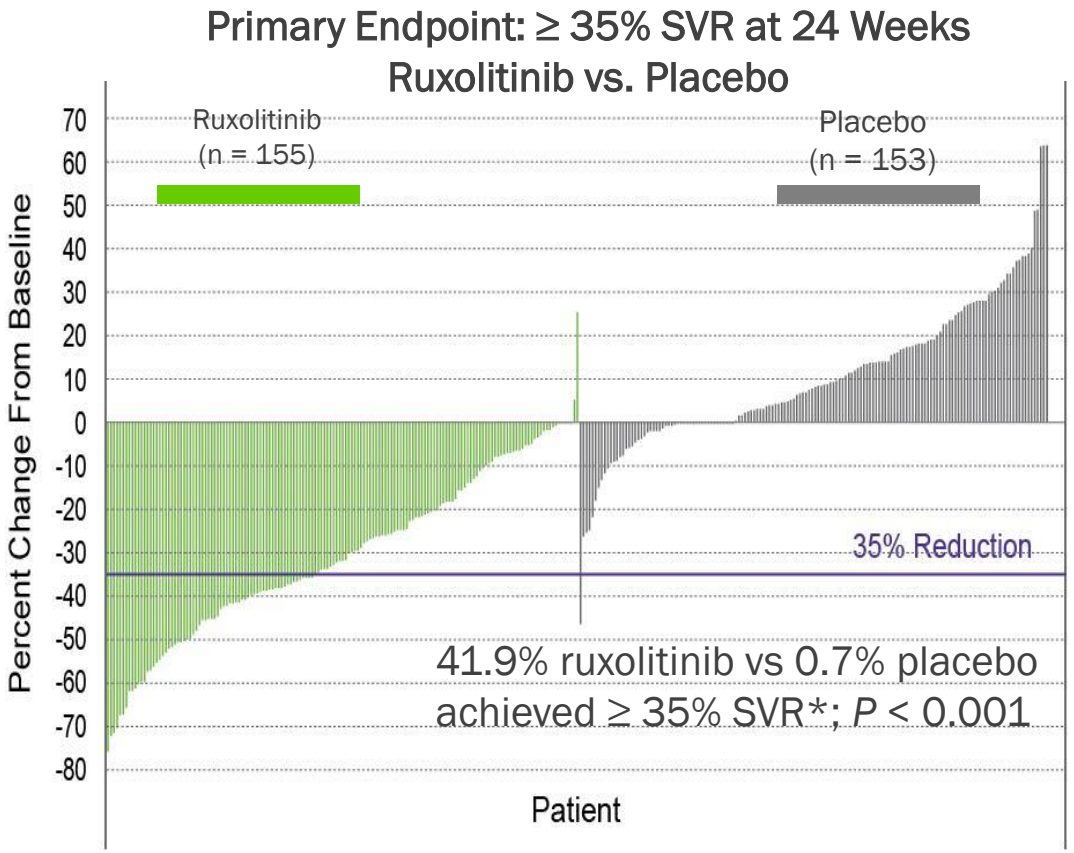

OR = 15.3 (95% CI: 6.9, 33.7); *P* < .001

**SVR responses were seen with ruxolitinib in *JAK2*$^{V617F}$-positive and *JAK2*$^{V617F}$-negative patients, relative to placebo**

*Changes in palpable spleen length in the ruxolitinib and placebo groups mirrored the changes in spleen volume.

Verstovsek S, et al. N Engl J Med. 2012;366:799-807.

# COMFORT-I Phase 3

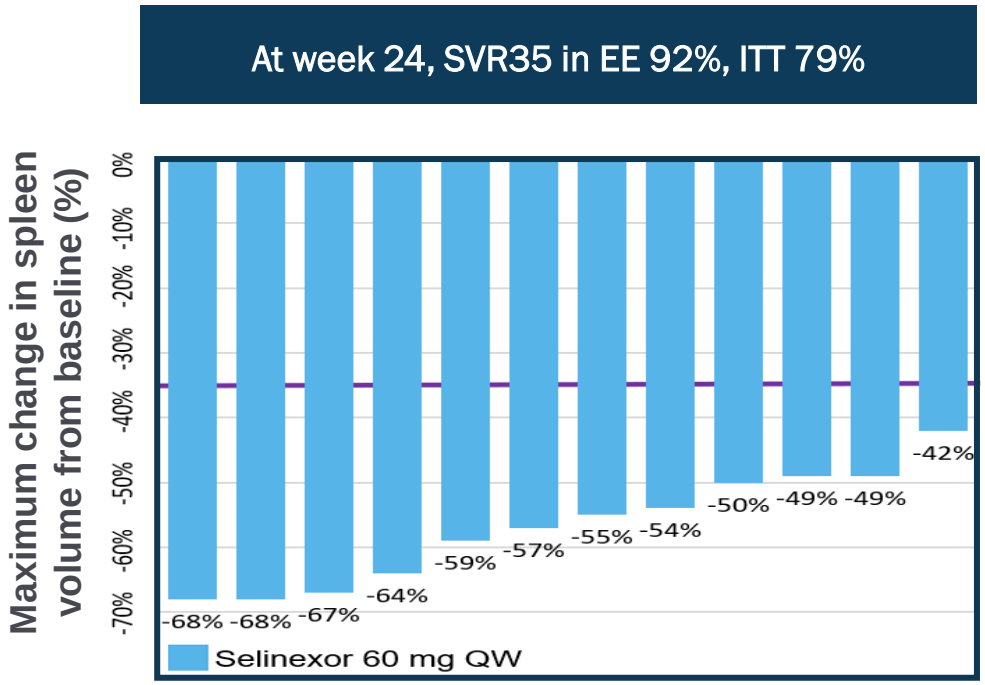



OR = 134.4 (95% CI: 18, 1004.9); *P* < .001

* Changes in palpable spleen length in the ruxolitinib and placebo groups mirrored the changes in spleen volume. (Verstovsek S, et al. N Engl J Med. 2012;366:799-807)

# XPORT-MF-034 Phase 1

SVR35 at Anytime
Selinexor (60 mg) + Ruxolitinib**




** Data from the XPORT-MF-034 study, efficacy evaluable (EE) population. (Ali et. al. AACR 2023)

# COMFORT-I
# Worst Hematologic Laboratory Test Abnormalities

| Hematologic Adverse Reactions[a] | Ruxolitinib n = 155 | | Placebo n = 151 | |
|---|---|---|---|---|
| | All Grades, % | Grade 3/4, % | All Grades, % | Grade 3/4, % |
| Thrombocytopenia | 69.7 | 12.9 | 30.5 | 1.3 |
| Anemia | 96.1 | 45.2 | 86.8 | 19.2 |
| Neutropenia | 18.7 | 7.1 | 4.0 | 2.0 |

Hematologic adverse reactions rarely led to treatment discontinuation. The following percentages are from both phase 3 studies: anemia (0.3%), thrombocytopenia (0.7%), neutropenia (1.0%)

Management of hematologic abnormalities[b]

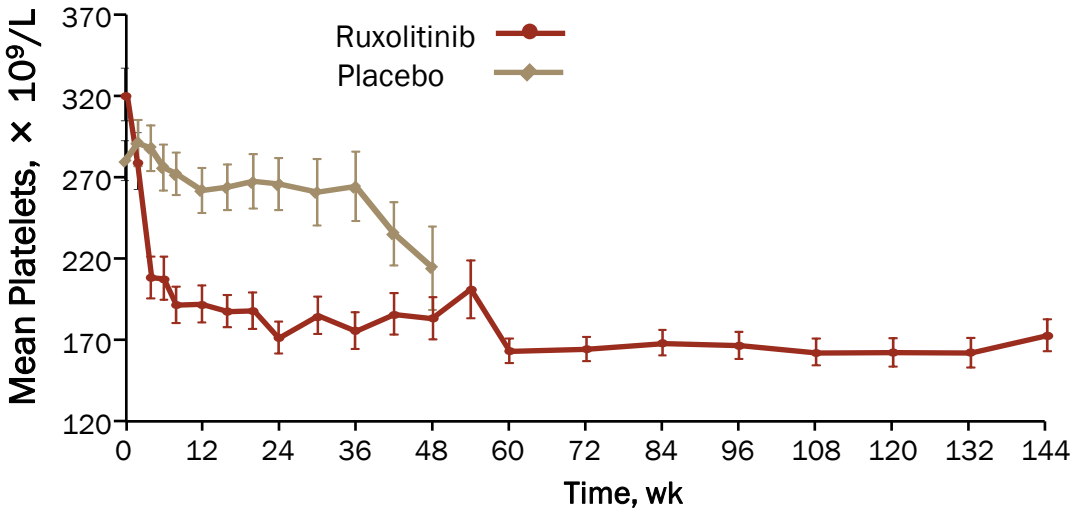
- ***Thrombocytopenia:*** Generally reversible; usually managed by reducing the dose or temporarily withholding ruxolitinib; if clinically indicated, platelet transfusions may be administered
- ***Anemia:*** Some patients may require blood transfusions; dose modifications may also be considered
- ***Neutropenia (ANC < 0.5 × $10^9$/L)*:** Generally reversible; managed by temporarily withholding ruxolitinib

ANC, absolute neutrophil count.

a. Verstovsek S, et al. N Engl J Med. 2012;366:799-807; b. Talpaz M, et al. J Hematol Oncol. 2013;6:81-91.

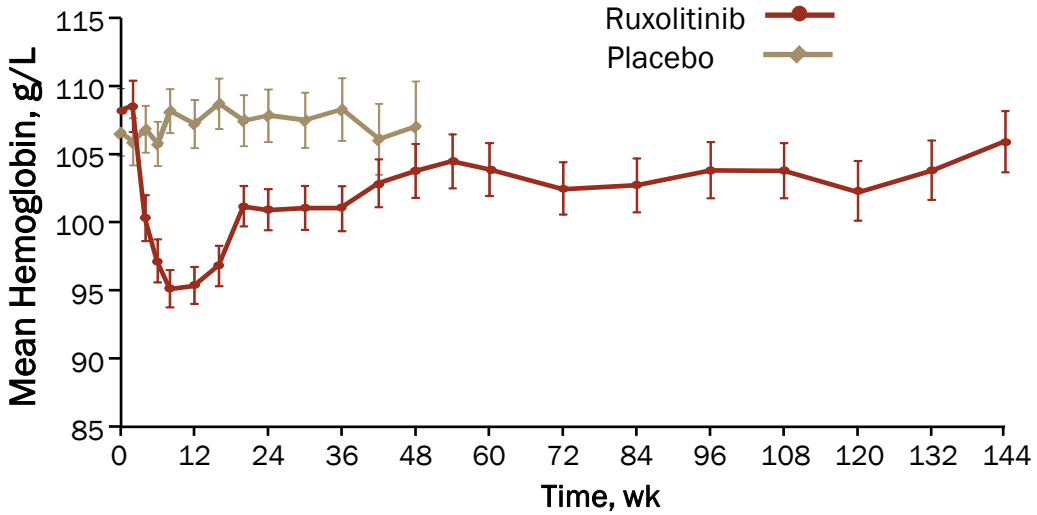
# COMFORT-I

## *Mean Platelet Count and Hemoglobin Over Time*




No. of Patients

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RUX | 155 | 144 | 143 | 136 | 124 | 112 | 110 | 107 | 104 | 100 | 94 | 88 | 79 |
| Placebo | 151 | 128 | 112 | 82 | 37 | | | | | | | | |




No. of Patients

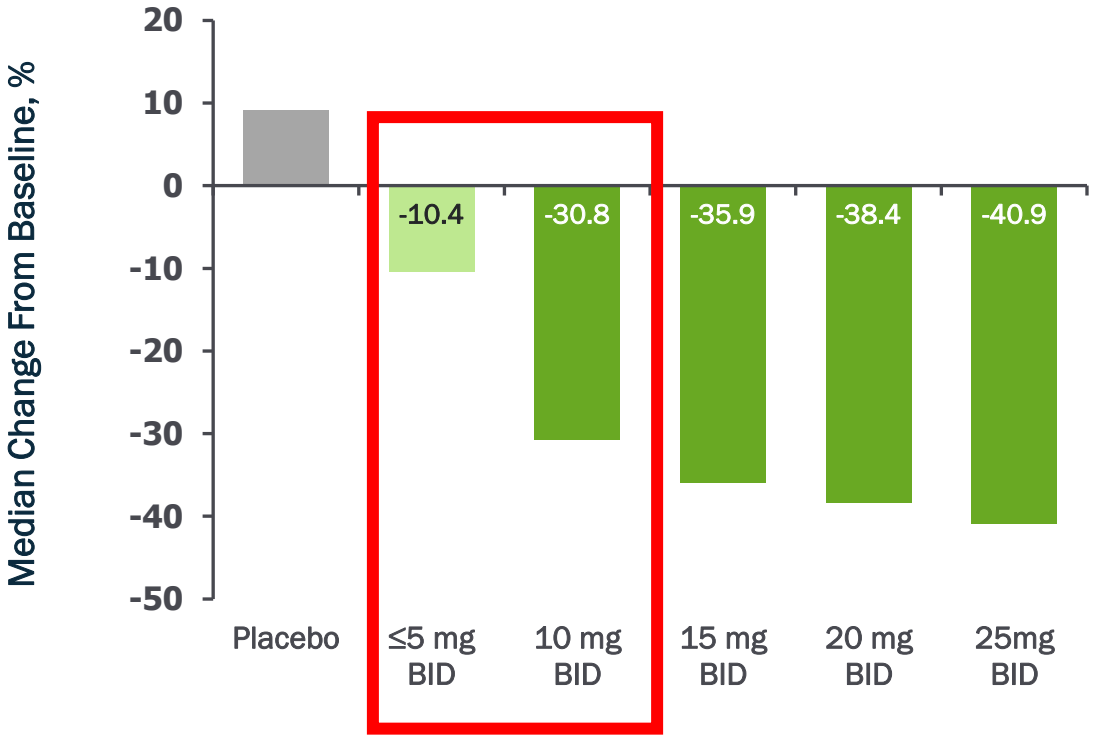
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 155 | 145 | 143 | 136 | 124 | 113 | 110 | 107 | 104 | 100 | 94 | 88 | 79 | |
| 151 | 132 | 113 | 83 | 37 | | | | | | | | | |

Verstovsek S, et al. Haematologica. 2015;100:479-488.

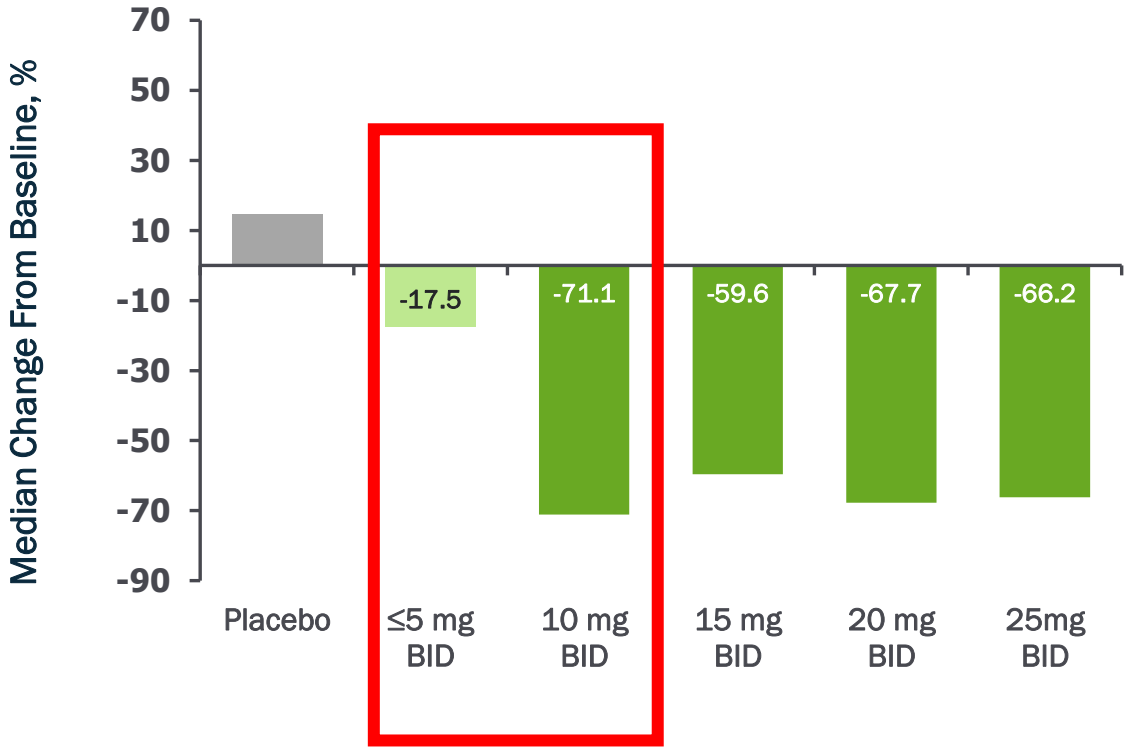
# COMFORT-I
## *Spleen Volume and Symptom Scores*

- Limited change from baseline in spleen volume and TSS with low-dose ruxolitinib[a]*
- Long-term maintenance with low-dose ruxolitinib has not shown responses in patients with myelofibrosis[b]

### Spleen Volume at Week 24 by Ruxolitinib Dose[a]

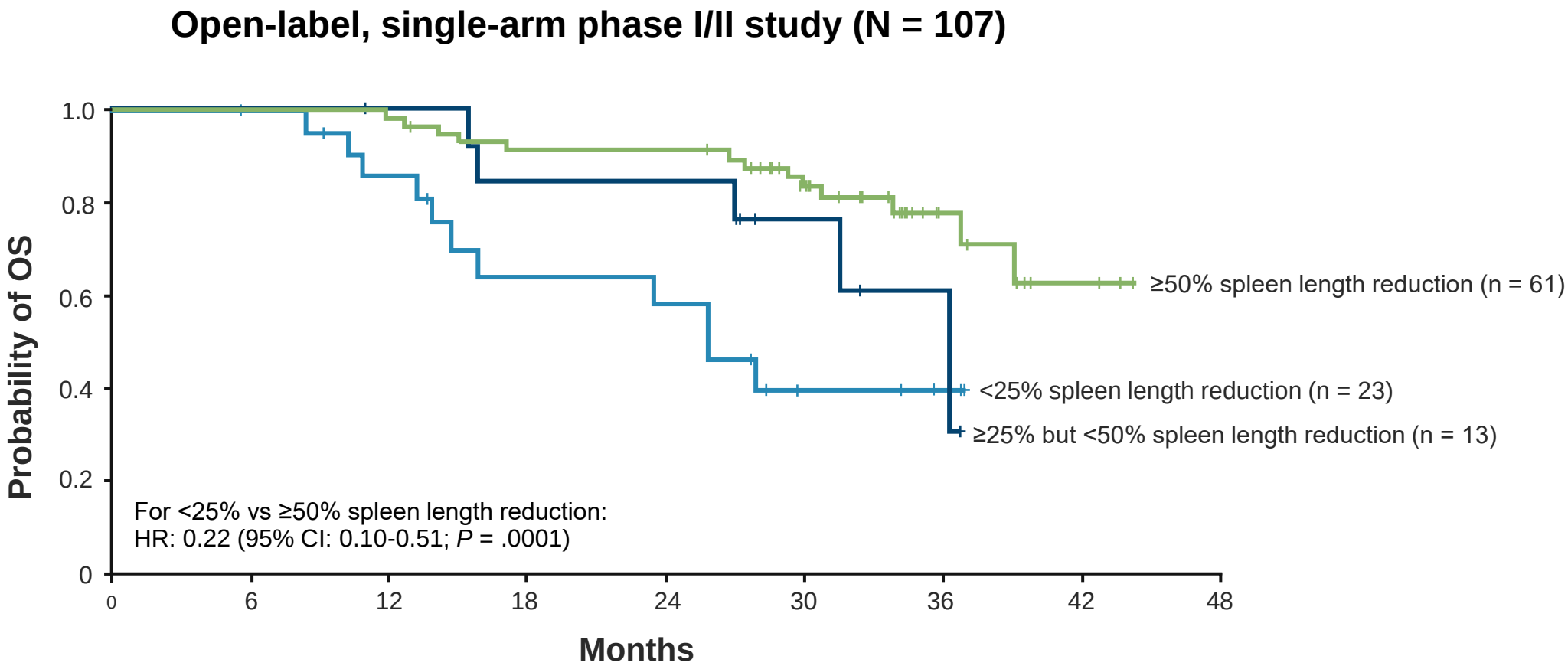



### TSS at Week 24 by Ruxolitinib Dose[b]



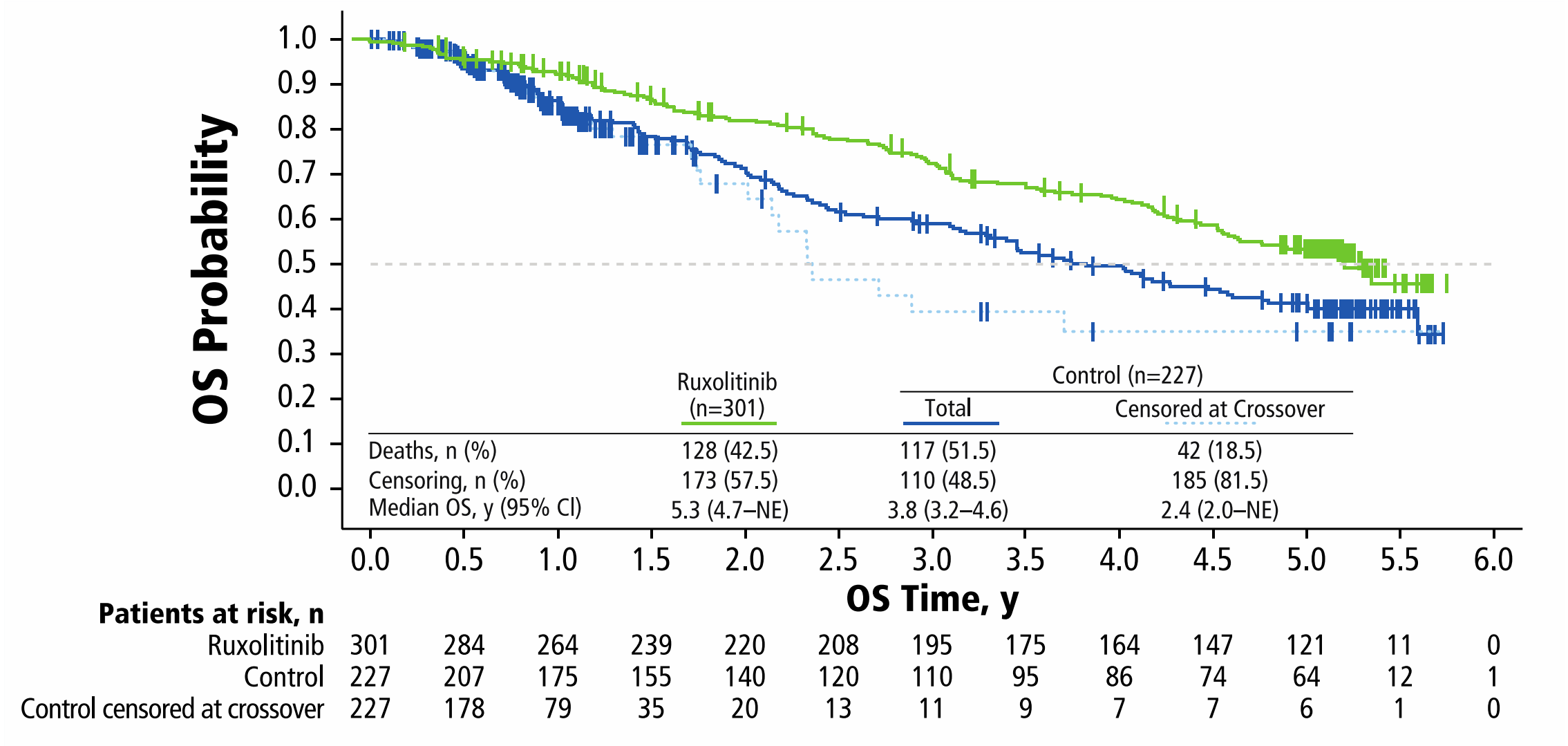

* ≤ 5 mg twice daily.
BID, twice daily.
a. Verstovsek S, et al. OncoTargets Ther. 2014;7:13-21; b. Ruxolitinib [PI]. Approved 2011. Updated 2021.

# Survival Improves With Spleen Length Reduction in Patients Receiving Ruxolitinib



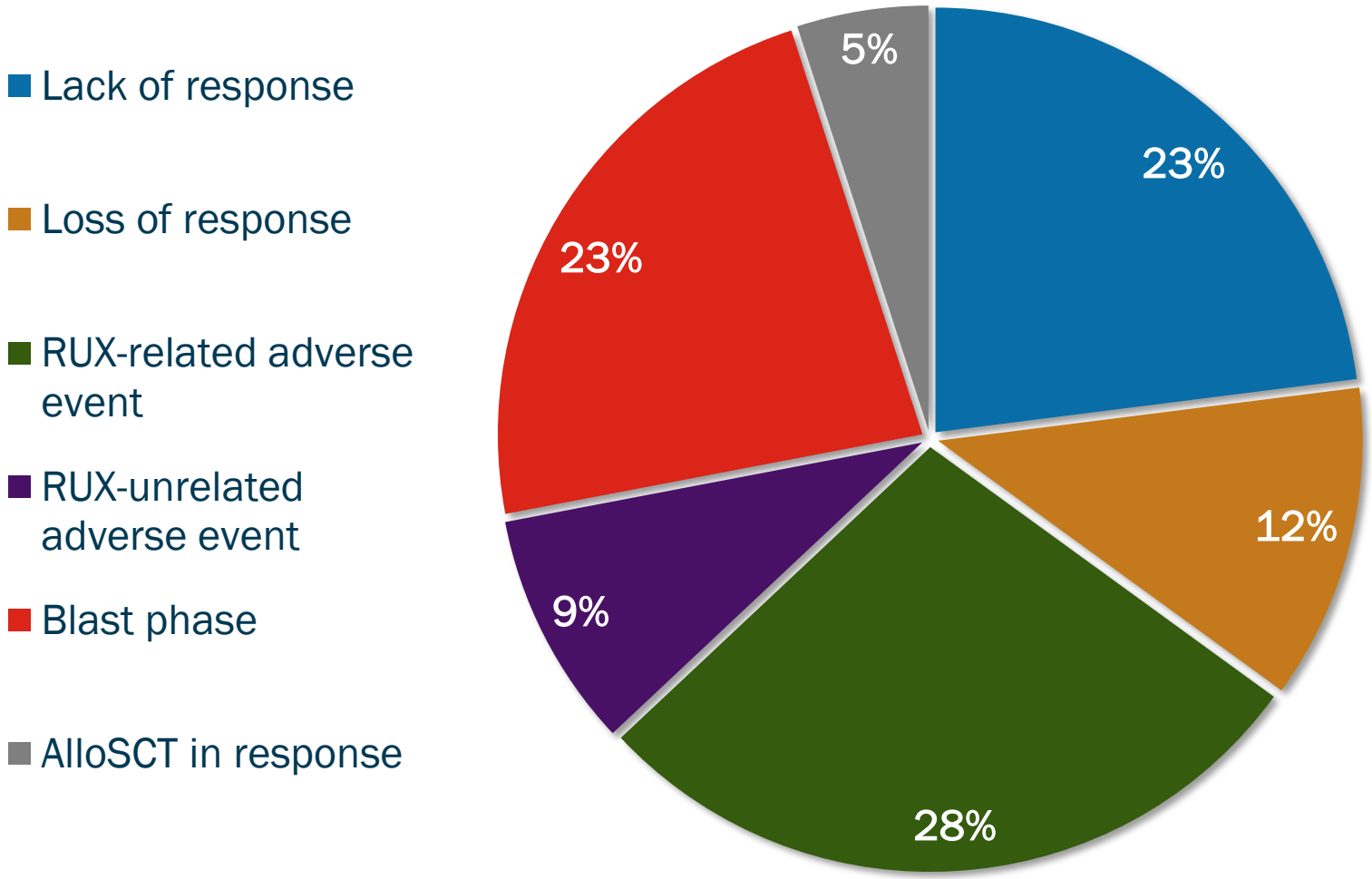

**HR, hazard ratio; OS, overall survival.**
**Verstovsek S, et al. *Blood.* 2012;120:1202-1209.**

# Pooled Analysis of COMFORT Studies
## *Survival Benefit*




Verstovsek S, et al. J Hematol Oncol. 2017;10:156.

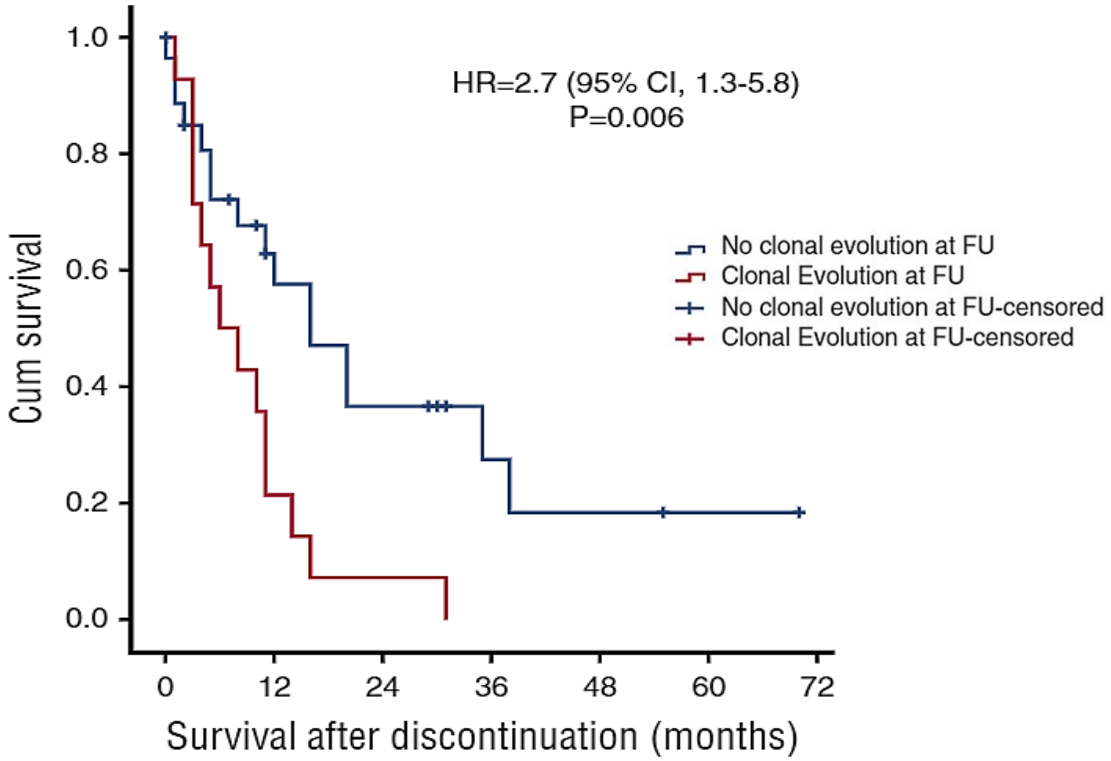
# Lack/Loss of Response and Ruxolitinib-Related AEs Drive Majority of Discontinuations




**Palandri. *Cancer* March 15, 2020; N=218.**

# Outcomes After Ruxolitinib Discontinuation

**Retrospective analysis of clonal evolution and outcomes after ruxolitinib discontinuation in an open-label phase 1/2 study (N = 56)**



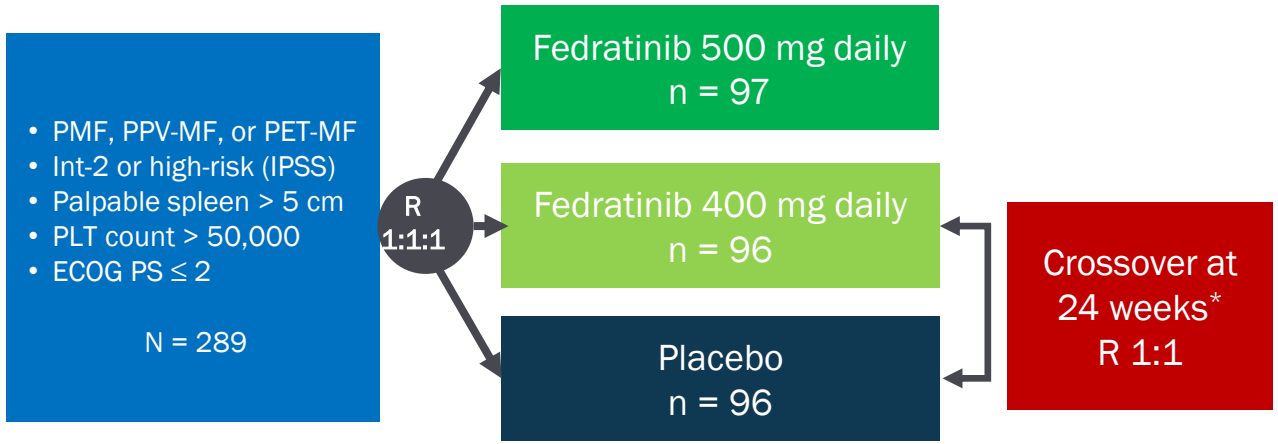

- Median OS = 14 mo
- Survival improved if baseline platelets ≥ 260 vs < 260 × $10^9$/L (HR = 2.7; *P* = .006)
- Survival improved if follow-up platelets ≥ 100 vs < 100 × $10^9$/L (HR = 4.1; *P* = .001)
- 35% of patients acquired a new mutation while on ruxolitinib, most commonly *ASXL1*

Hashed lines = censored.

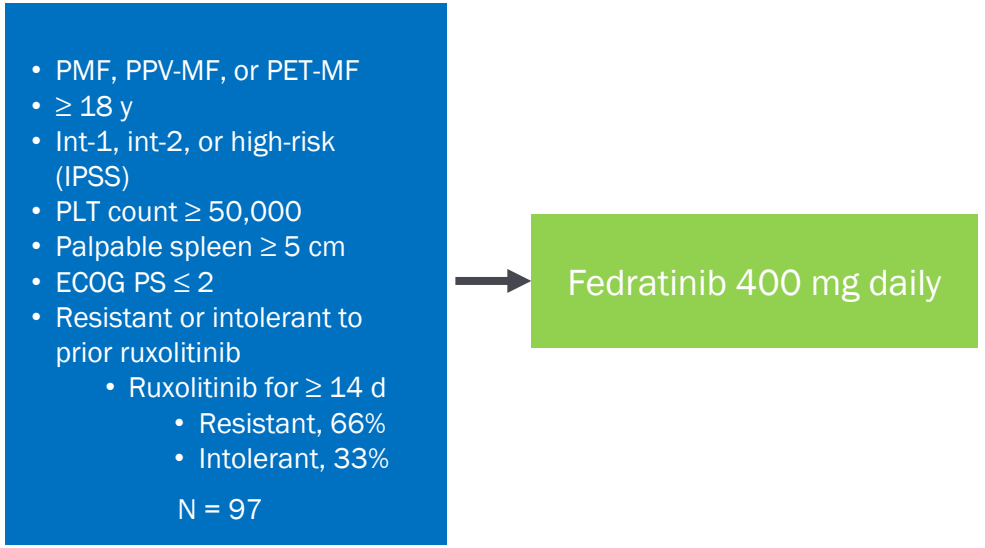
Newberry KJ, et al. Blood. 2017;130:1125-1131.

# Fedratinib Clinical Trials
## *JAKARTA (Phase 3) and JAKARTA-2 (Phase 2)*

### JAKARTA-1: Phase 3, randomized, double-blind, placebo-controlled trial[a]




### JAKARTA-2: Phase 2, single-arm, open-label, nonrandomized, multicenter study[b]



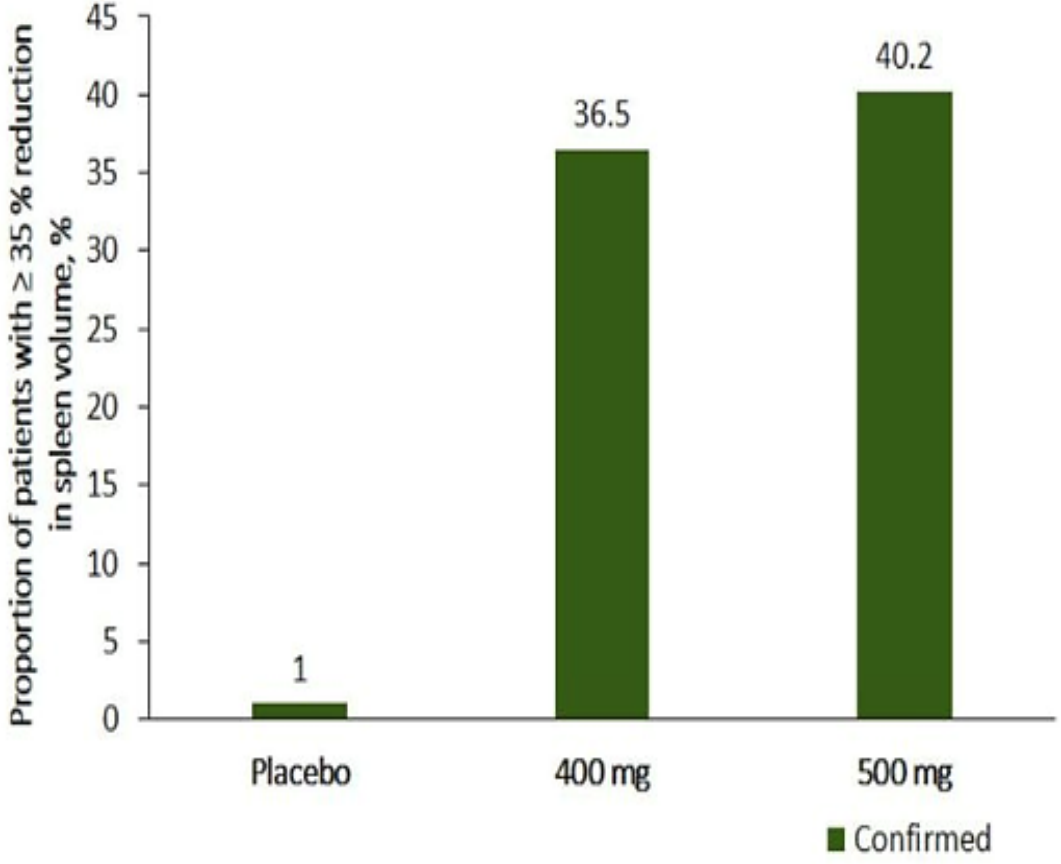

- **Primary endpoint:** Number of patients with ≥ 35% SVR from baseline to week 24 as measured by MRI (or CT in applicable patients)
- **Key secondary endpoint:** Proportion of patients with ≥ 50% reduction in TSS from baseline to week 24 as measured by the MFSAF 2.0

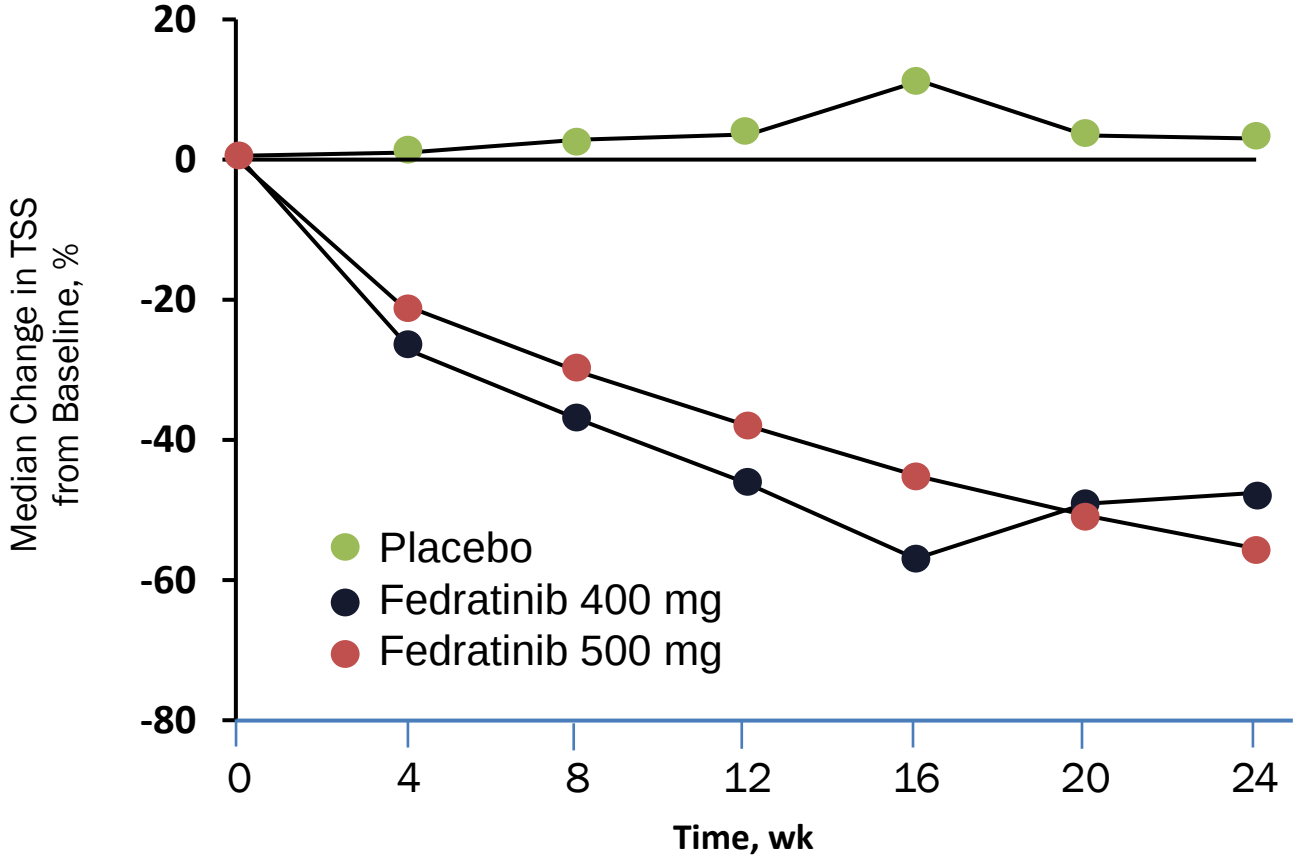
*Crossover prior to 24 weeks was permitted if patients experienced progressive disease as defined in the study protocol.

a. Pardanani A, et al. JAMA Oncol. 2015;1:643-651; b. Harrison CN, et al. Lancet Haematol. 2017;4:e317-e324.

# JAKARTA: First-Line Fedratinib
## *Spleen Volume and Symptom Response*

### ITT Population




Pardanani A, et al. JAMA Oncol. 2015;1:643-651.

# JAKARTA-1: First-Line Fedratinib
## *Adverse Events*[a]

| Adverse Event, % | Fedratinib 400 mg (n = 96) | | Fedratinib 500 mg (n = 97) | | Placebo (n = 95) | |
|---|---|---|---|---|---|---|
| | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 |
| **Nonhematologic** | | | | | | |
| Diarrhea | 66 | 5 | 56 | 5 | 16 | 0 |
| Vomiting | 42 | 3 | 55 | 9 | 5 | 0 |
| Nausea | 64 | 0 | 51 | 6 | 15 | 0 |
| Constipation | 10 | 2 | 18 | 0 | 7 | 0 |
| Asthenia | 9 | 2 | 16 | 4 | 6 | 1 |
| Abdominal pain | 15 | 0 | 12 | 1 | 16 | 1 |
| Fatigue | 16 | 6 | 10 | 5 | 1 | 0 |
| **Hematologic** | | | | | | |
| Anemia | 99 | 43 | 98 | 60 | 91 | 25 |
| Thrombocytopenia | 63 | 17 | 57 | 27 | 51 | 9 |
| Lymphopenia | 57 | 21 | 66 | 27 | 54 | 21 |
| Leukopenia | 47 | 6 | 53 | 16 | 19 | 3 |
| Neutropenia | 28 | 8 | 44 | 18 | 15 | 4 |

**Black box warning**[b]

- Wernicke encephalopathy (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

**Considerations**

- Measure and address thiamine levels prior to treatment initiation
- Do not start fedratinib in patients with thiamine deficiency

a. Pardanani A, et al. JAMA Oncol. 2015;1(5):643-651; b. Fedratinib [PI]. Revised December 2021.

# Phase 3 Pacritinib Trials
## *PERSIST-1 and PERSIST-2*

### PERSIST-1[a]

**Key eligibility criteria:**
- Primary MF/ secondary MF
- No exclusion for baseline platelets
- No prior JAK2 inhibitors allowed

2:1 R (n = 327)

- Pacritinib *400 mg daily*
- BAT (excluding ruxolitinib)

**Primary endpoint (week 24):**

Percentage of patients with ≥ 35% SVR

**Secondary endpoint:**

Percentage of patients with ≥ 50% reduction in TSS

### PERSIST-2[b]

**Key eligibility criteria:**
- Primary MF/ secondary MF
- Platelets ≤ 100 × $10^9$/L
- Prior JAK2 inhibitors allowed

1:1:1 R (n = 311)

- Pacritinib *400 mg daily*
- Pacritinib *200 mg twice daily*
- BAT (including ruxolitinib)

**Co-primary endpoints (week 24):**

Percentage of patients with ≥ 35% SVR

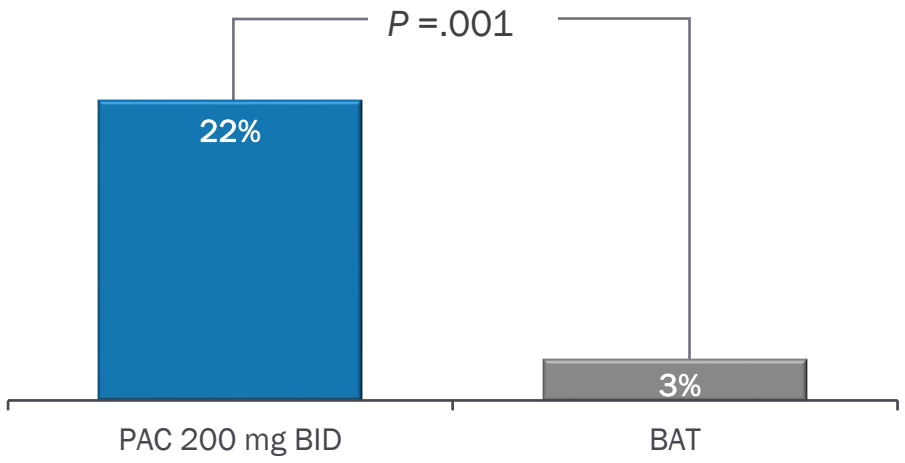
**and**

Percentage of patients with ≥ 50% reduction in TSS

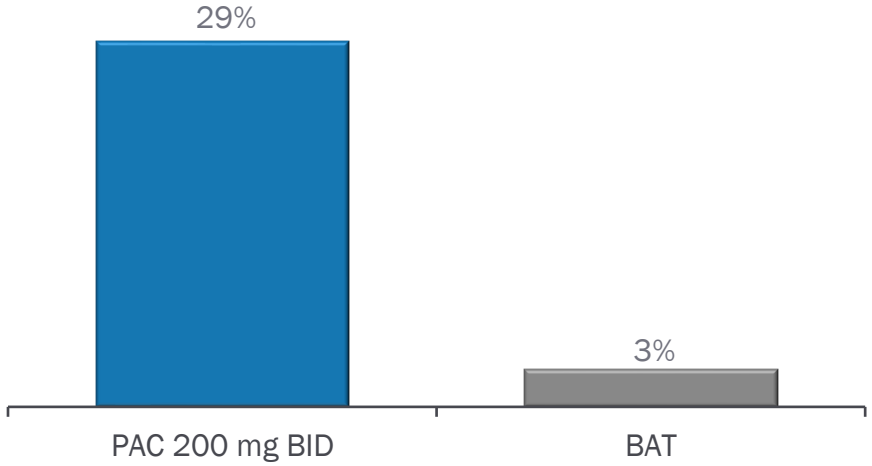
a. Mesa RA, et al. Lancet Haematol. 2017;4:e225-e236; b. Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

# PERSIST-2
## *Spleen Volume Responses ≥ 35% at Week 24*

### ITT Population




### Patients With Platelets < 50 × $10^9$/L




Additional subgroup analyses demonstrated patients receiving pacritinib achieved SVR ≥ 35% regardless of subgroup (eg, sex, age, *JAK2* V617F mutation status, prior treatment with JAK2 inhibitors, and baseline cytopenias)

PAC, pacritinib.

Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

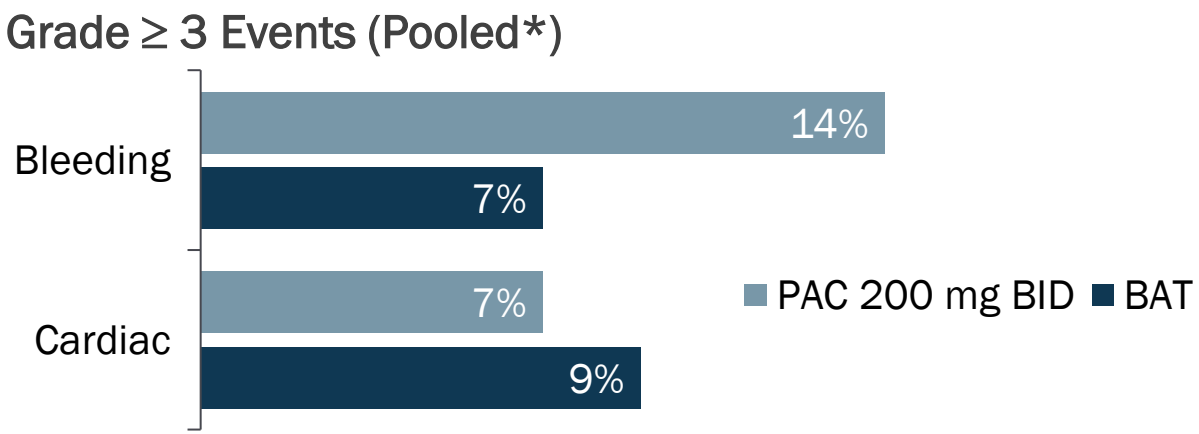
# PERSIST-2
## *Adverse Events*

| Adverse Reactions | PAC 200 mg BID (n = 106) | BAT (n = 98) |
|---|---|---|
| Any-grade AEs in > 15% of patients in either arm, % | | |
| Diarrhea | 48 | 15 |
| Thrombocytopenia | 34 | 24 |
| Nausea | 32 | 11 |
| Anemia | 24 | 15 |
| Peripheral edema | 20 | 15 |
| Vomiting | 19 | 5 |
| Fatigue | 17 | 16 |
| Grade ≥ 3 AEs in > 5% of patients in either arm, % | | |
| Thrombocytopenia | 32 | 18 |
| Anemia | 22 | 14 |
| Neutropenia | 7 | 5 |
| Pneumonia | 7 | 3 |
| Serious AEs in > 3% of patients in either arm, % | | |
| Anemia | 8 | 3 |
| Thrombocytopenia | 6 | 2 |
| Pneumonia | 6 | 4 |
| Congestive heart failure | 4 | 2 |

*Pooled, per standardized MedDRA queries.

Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659..

- Diarrhea with pacritinib most often occurred during weeks 1 through 8, was manageable, and resolved within 1 to 2 weeks
- Neurologic AEs and opportunistic infections rarely reported with pacritinib
- **Safety outcomes with pacritinib were similar for those with < 50 × $10^9$/L vs 50 to 100 × $10^9$/L platelets at baseline**



# Evolving MF Treatment Landscape – Beyond JAK Inhibitors

## Emerging First Line MF Therapies

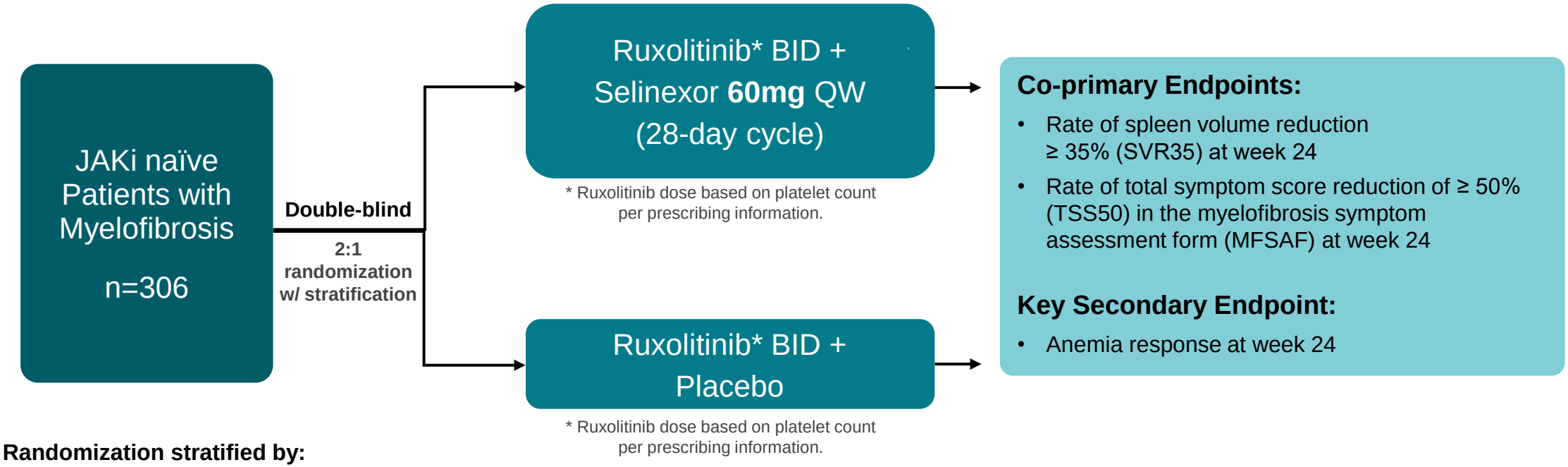
| Drug | Company | MOA | Latest Phase in MF |
|---|---|---|---|
| Pelabresib | MorphoSys | BET inhibitor | Phase III |
| Navitoclax | AbbVie | BCL-2 inhibitor | Phase III |
| Parsaclisib | Incyte | Pi3Kd inhibitor | Phase III |
| Selinexor | Karyopharm | XPO1 inhibitor | Phase I →III |

ONCrg Pipeline Strategies. Myeloproliferative Neoplasms. Q4 2020. Oncology Resource Group. https://clinicaltrials.gov/. Accessed February 23, 2021

# CONCLUSIONS

- MF is an aggressive hematologic malignancy involving HSCs and intimately linked to inflammation
- Unmet need exists to improve upon depth of initial response and extend benefit and ultimately survival
- JAK inhibitors afford our patients benefit but not cure and outcome is dismal when dose reduced or stopped
- Over the next 3 years, a likely paradigm shift to upfront combination therapy, given novel agents in late stage development, non-JAK2 inhibitor sequencing, and increase in survival
- Given the encouraging selinexor data in JAKi naïve patients, selinexor has the potential to improve on existing and future first line treatment options

# XPORT-MF-034- Phase 3 Design*




**Randomization stratified by:**

- Dynamic International Prognostic Scoring System (DIPSS) risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 $cm^3$ vs. >1800 $cm^3$ by MRI/CT scan
- Baseline platelet counts 100-200 x $10^9$/ L vs. >200 x $10^9$/L

BID, twice a day; MFSAF, myelofibrosis symptom assessment form; QW, once weekly.

*Planning to be initiated in 1H 2023


Q&A