Jakafi® (Ruxolitinib)

Myelofibrosis | Polycythemia Vera

MSL--RUX-US-0020 02/25

Notice

- Some information contained in this presentation may not be included in the approved Prescribing Information for Jakafi. This presentation is not intended to offer recommendations for any administration, indication, dosage, or other use for Jakafi in a manner inconsistent with the approved Prescribing Information

Indications and Usage

- Jakafi (ruxolitinib) is indicated for treatment of:
  - Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis in adults
  - Polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea
  - Steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older
  - Chronic graft-versus-host disease after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older

- **FOR MEDICAL INFORMATION PURPOSES ONLY. NOT FOR PROMOTIONAL USE. DO NOT COPY, DISTRIBUTE, OR OTHERWISE REPRODUCE**

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Summary of Warnings and Precautions

Thrombocytopenia, anemia, and neutropenia

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia
- Thrombocytopenia should be managed by reducing the dose or temporarily interrupting Jakafi, and platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5×10^9/L) was generally reversible by withholding Jakafi until recovery
- A pre-treatment CBC should be performed and CBCs should be monitored every 2 to 4 weeks until doses are stabilized, and then as clinically indicated

ANC, absolute neutrophil count; CBC, complete blood count.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Summary of Warnings and Precautions (cont)

Risk of infection

- Serious bacterial, mycobacterial, fungal, and viral infections have occurred with Jakafi
- Start of treatment with Jakafi should be delayed until active serious infections have resolved
- Patients receiving Jakafi should be observed for signs and symptoms of infection and managed promptly
- Active surveillance and prophylactic antibiotics should be used according to clinical guidelines
- Infections reported in patients receiving Jakafi include
  - Tuberculosis
  - PML
  - Herpes zoster and herpes simplex
  - Hepatitis B

PML, progressive multifocal leukoencephalopathy.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. .

Summary of Warnings and Precautions (cont)

Symptom exacerbation following interruption or discontinuation of treatment with Jakafi

- Following discontinuation of Jakafi, symptoms from MPNs may return to pretreatment levels over ~1 week

- Some patients with MF have experienced one or more of the following AEs:
  - Fever
  - Respiratory distress
  - Hypotension
  - DIC
  - Multi-organ failure

- If one or more of these AEs occur after discontinuation or while tapering Jakafi, any intercurrent illness should be evaluated and treated and restarting or increasing the dose of Jakafi should be considered

- If Jakafi is discontinued or interrupted for reasons other than thrombocytopenia or neutropenia, tapering the dose of Jakafi gradually should be considered instead of abrupt discontinuation

AE, adverse event; DIC, disseminated intravascular coagulation; MF, myelofibrosis; MPN, myeloproliferative neoplasm.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Summary of Warnings and Precautions (cont)

NMSC

- NMSC including basal cell, squamous cell, and MCC have occurred in patients treated with Jakafi
- Periodic skin examinations should be performed

Lipid elevations

- Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, LDL, and triglycerides
- The effect of these elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi
- Lipid parameters should be assessed ~8 to 12 weeks following initiation of Jakafi therapy
- Patients should be monitored and treated according to clinical guidelines for the management of hyperlipidemia

LDL, low-density lipoproteins; MCC, Merkel cell carcinoma; NMSC, non-melanoma skin cancer.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Summary of Warnings and Precautions (cont)

Major Adverse Cardiovascular Events (MACE)

- Another JAKi has increased the risk of MACE, including cardiovascular death, MI, and stroke (compared to those treated with TNF blockers), in patients with rheumatoid arthritis (RA), a condition for which Jakafi is not indicated

- Consider the benefit and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur

Thrombosis

- Another JAKi has increased the risk of thrombosis, including DVT, PE, and arterial thrombosis (compared to those treated with TNF blockers) in patients with RA, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, rates of thromboembolic events were similar in Jakafi and control treated patients

- Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately

DVT, deep vein thrombosis; JAKi, JAK inhibitor; MI, myocardial infarction; PE, pulmonary embolism.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Summary of Warnings and Precautions (cont)

Secondary malignancies

- Another JAKi has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with RA, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk

- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers

NMSC, non-melanoma skin cancer.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

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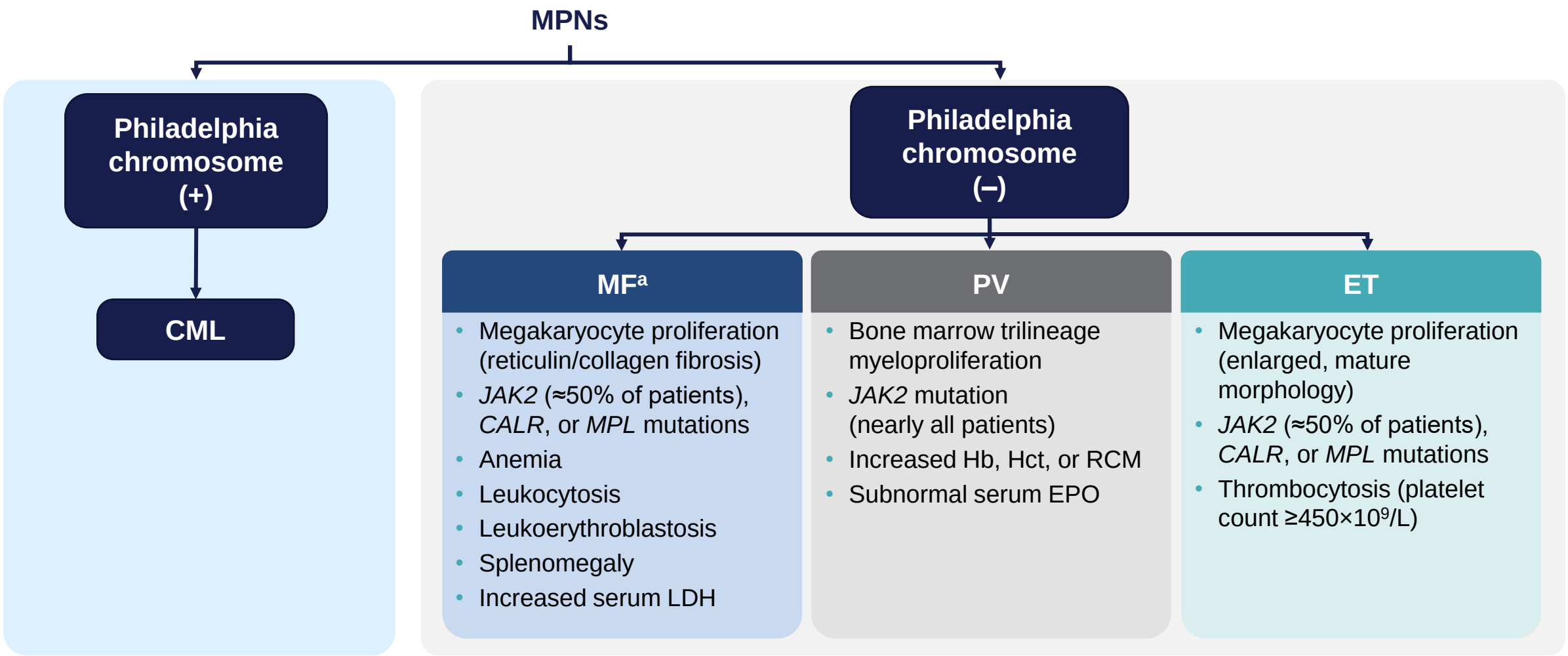
MPN Disease State Overview

MF, PV, and ET Are Philadelphia-Negative MPNs



[a] MF includes primary MF, post-PV MF, and post-ET MF.

CALR, calreticulin; CML, chronic myeloid leukemia; EPO, erythropoietin; ET, essential thrombocythemia; Hb, hemoglobin; Hct, hematocrit; JAK2, Janus kinase 2; LDH, lactate dehydrogenase; MF, myelofibrosis; MPL, MPL proto-oncogene thrombopoietin receptor; MPNs, myeloproliferative neoplasms; PV, polycythemia vera; RCM, red cell mass.

Arber DA, et al. *Blood*. 2016;127:2391-2405.

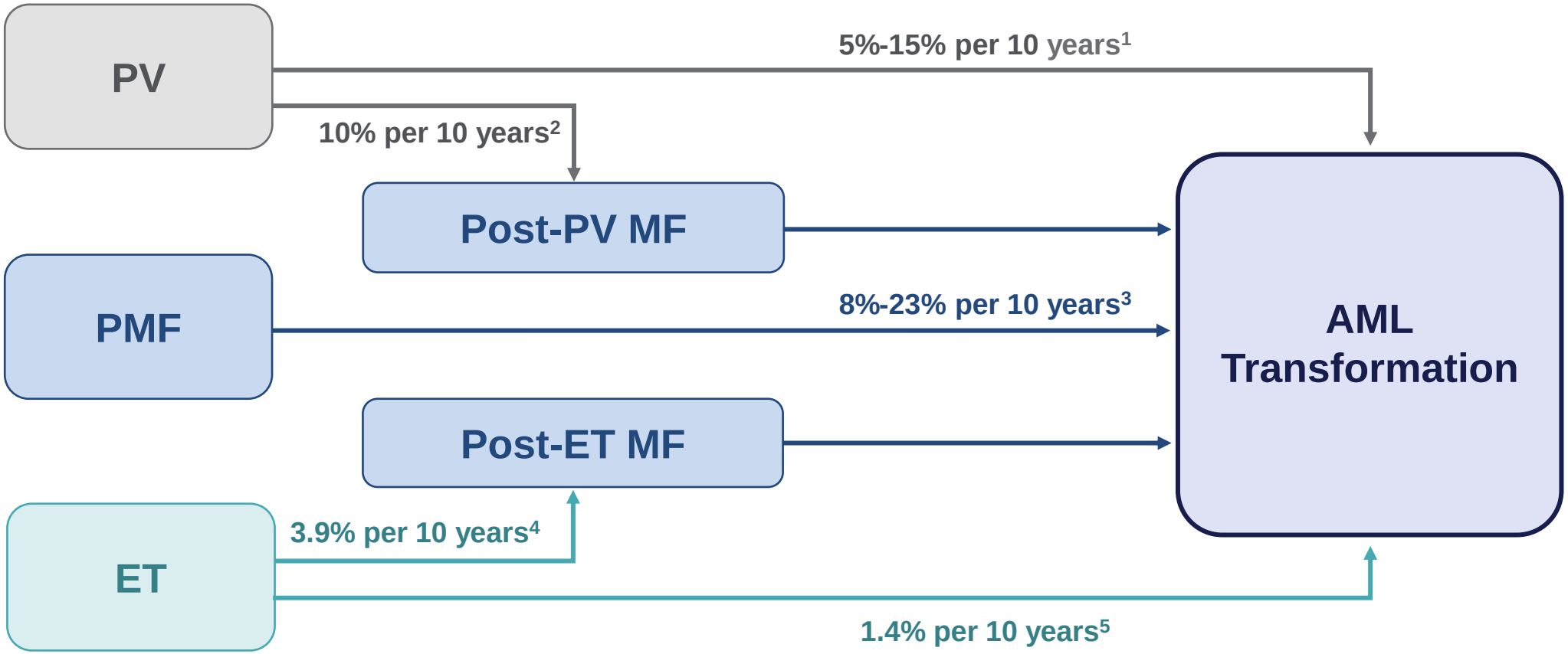
MPNs Are Rare and Usually Develop Later in Life

	MF	PV	ET
Prevalence	4-6 cases per 100,000[1,2]	44-57 cases per 100,000[1,3]	38-57 cases per 100,000[1]
Incidence	≈2-3 cases per 100,000 annually[1,2]	≈1-3 cases per 100,000 annually[4]	2.0-2.4 cases per 100,000[1,5]
Median age at diagnosis	>65 years and slightly more common in men than in women; ≈60% of affected patients are men[6]	60 years; similar frequency in men and women[7,8]	60 years[5]
Bone marrow abnormalities	Excess fibrous tissue and increase in megakaryocytes[9]	Trilineage myeloproliferation and pleomorphic megakaryocytes[10]	Increased megakaryocytes[9]
Blood cell abnormalities	Reduced RBCs;[9] variable/increased WBCs[9]	High Hct;[9] increased RCM[9]	Elevated platelets;[9] no or few WBCs or RBCs[9]
% with *JAK2* mutation	≈50% of patients[10]	>99%[11,a]	≈50% of patients[10]
Median survival	4.4-7.4 years[12,13]	14-15 years after diagnosis[8,13]	15-20 years[13,14]

[a] *JAK2* alterations include *JAK2* V617F mutations and *JAK2* exon 12 mutations.
RBCs, red blood cells; WBCs, white blood cells.

1. Mehta J, et al. *Leuk Lymphoma*. 2014;55:595-600. 2. Data on file, Incyte Corporation. 3. Stein B, et al. *J Clin Oncol*. 2015;33:3953-3960. 4. Johansson P. *Semin Thromb Hemost*. 2006;32:171-173. 5. Girodon F, et al. *Haematologica*. 2009;94:865-869. 6. Gangat N, et al. *J Clin Oncol*. 2010;29:392-397. 7. National Cancer Institute. Accessed Jan 2025. http://seer.cancer.gov/seertools/hemelymph/51f6cf57e3e27c3994bd538d/. 8. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. 9. Campbell PJ, Green AR. *N Engl J Med*. 2006;355:2452-2466. 10. Arber DA, et al. *Blood*. 2016;127:2391-2405. 11. Pardanani A, et al. *Leukemia*. 2007;21:1960-1963. 12. Cervantes F, et al. *J Clin Oncol*. 2012;30:2981-2987. 13. Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610. 14. Barbui T, et al. *J Clin Oncol*. 2011;29:761-770.

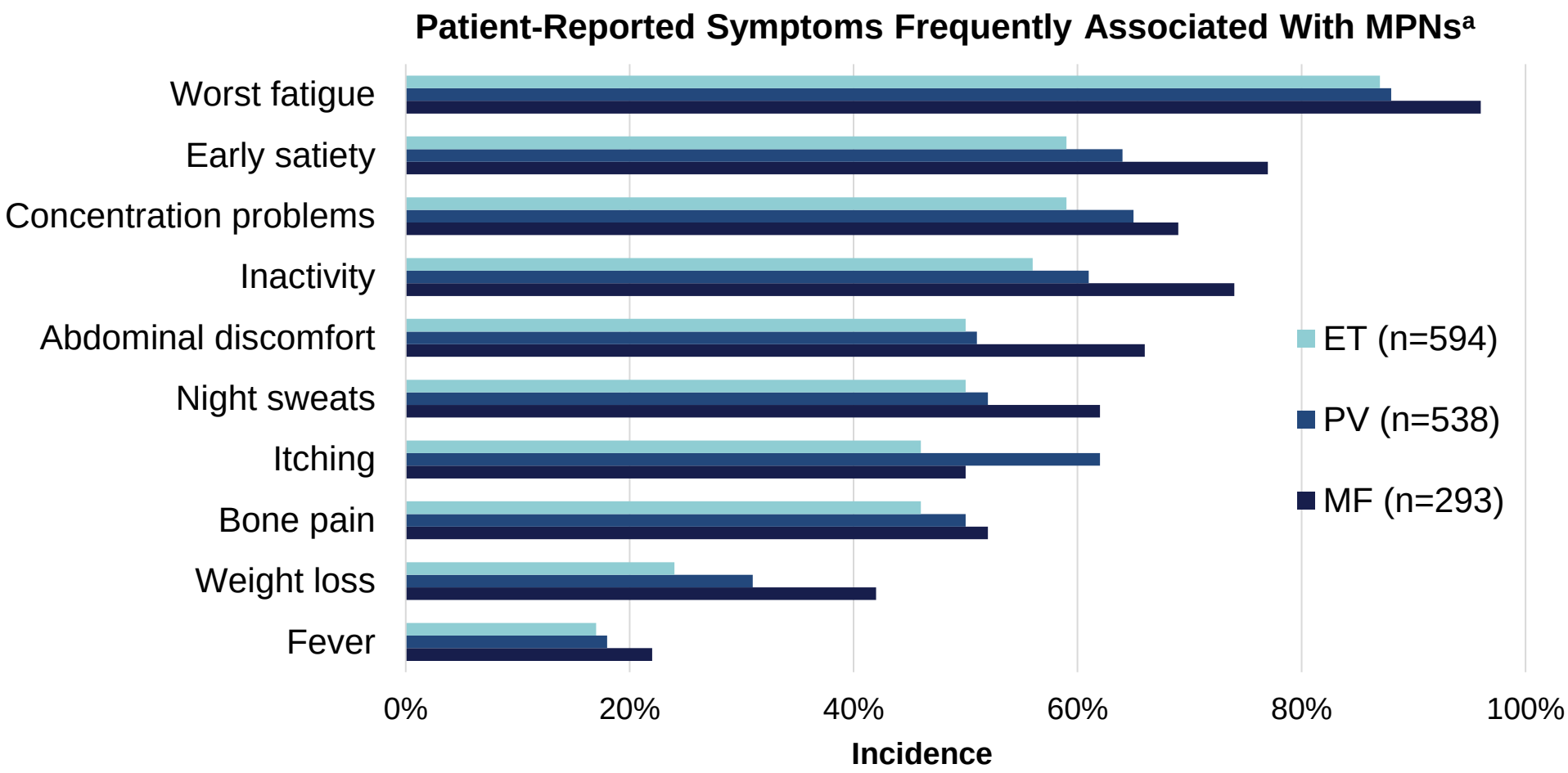
MPN Disease Progression and Transformation



AML, acute myeloid leukemia; PMF, primary myelofibrosis.

1. Finazzi G, et al. *Blood*. 2005;105:2664-2670. 2. Tefferi A. *Am J Hematol*. 2008;83:491-497. 3. Mesa RA, et al. *Blood*. 2005;105:973-977. 4. Cerquozzi S, Tefferi A. *Blood Cancer J*. 2015;5:e366. 5. Wolanskyj AP, et al. *Mayo Clin Proc*. 2006;81:159-166.

MPNs Are Associated With a Substantial Symptom Burden



[a] Symptom assessment was done using the BFI, MPN-SAF, and the EORTC QLQ-C30. MPN-SAF TSS was then constructed using the 10 items that were deemed most clinically relevant. Symptom severity was rated on a 0 (absent/as good as it can be) to 10 (worst-imaginable/as bad as it can be) scale. MPN-SAF TSS has a possible range of 0 to 100 with 100 representing the highest level of symptom severity.

BFI, Brief Fatigue Inventory; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, Total Symptom Score.

Emanuel RM, et al. *J Clin Oncol.* 2012;30(33):4098-4103.

Myelofibrosis

Diagnosis and Risk Stratification

2016 WHO Diagnostic Criteria: Overt Primary MF

MF WHO Criteria: ☑ Must meet all 3 major AND at least 1 minor[a]

Major

- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
- Not meeting WHO criteria for ET, PV, *BCR-ABL1*+ CML, myelodysplastic syndromes, or other myeloid neoplasms
- Presence of *JAK2*, *CALR*, or *MPL* mutation or, in the absence of these mutations, presence of another clonal marker,[b] or absence of reactive MF[c]

Minor

- Anemia not attributed to a comorbid condition
- Palpable splenomegaly
- LDH increased to above upper normal limit of institutional reference range
- Leukoerythroblastosis
- Leukocytosis ≥11×10^9/L

[a] Confirmed in 2 consecutive determinations. [b] In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations is of help in determining the clonal nature of the disease. [c] Bone marrow fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Arber DA, et al. *Blood*. 2016;127:2391-2405.

Various MF Prognostic Scales Are Available to Assess Risk and Median Survival

- Proper risk stratification of patients with MF is recommended for optimal disease treatment and management[1,2]
- Several prognostic scoring systems have been developed to appropriately stratify patients with MF[1,2]

	Prognostic Scale and Points per Risk Factor		
Risk Factor[1,2,a]	**IPSS (2009)[3,b]**	**DIPSS (2010)[4,c]**	**DIPSS-Plus (2011)[5,c,d]**
Age >65 years	1	1	1
Constitutional symptoms (weight loss, fever, night sweats)	1	1	1
Anemia (Hb <10 g/dL)	1	2	1
WBC count >25×10^9/L	1	1	1
Circulating blast ≥1%	1	1	1
Platelets <100×10^9/L	–	–	1
RBC transfusion need	–	–	1
Unfavorable karyotype (complex karyotype or a single or 2 abnormalities including +8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3), or 11q23)	–	–	1

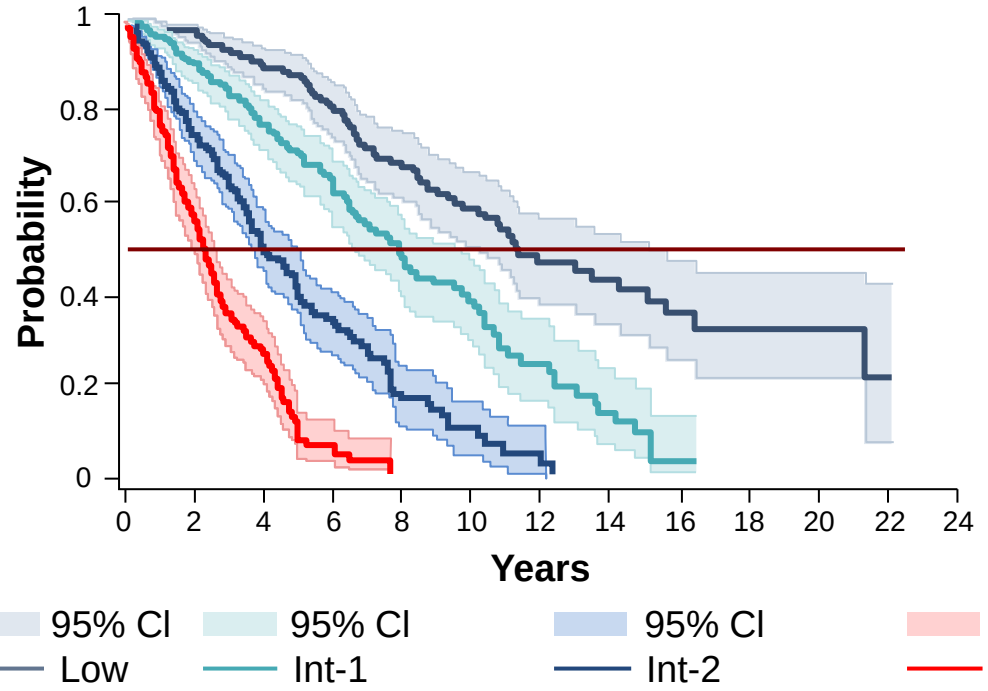
[a] Risk factors are related to underlying disease and not pharmacotherapy. [b] For use at diagnosis. [c] For use at follow-up. [d] Scoring system differs for DIPSS and DIPSS-Plus. DIPSS-Plus was more recently designed but less widely used than the other scoring systems.
DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System; RBC, red blood cell; WBC, white blood cell.
1. Vannucchi AM, et al. *Hematology Am Soc Hematol Educ Program*. 2011;2011:222-230. 2. Bose P, Verstovsek S. *Cancer*. 2016;122:681-692. 3. Cervantes F, et al. *Blood*. 2009;113:2895-2901. 4. Passamonti F, et al. *Blood*. 2010;116:2857-2858. 5. Gangat N, et al. *J Clin Oncol*. 2011;29:392-397.

MF Risk at Diagnosis Is Assigned Based on the Number of IPSS Risk Factors

IPSS Risk and Survival

Risk Category	Number of Risk Factors	Median Survival, y
High	≥3	2.3
Int-2	2	4.0
Int-1	1	7.9
Low	0	11.3

Survival Curves of Prognostic MF Risk Groups[a]



The number of risk factors present at diagnosis is prognostic for median survival

[a] Includes PMF, post-ET MF, and post-PV MF data points.
CI, confidence interval; Int-1, Internediate 1; Int-2, Intermediate 2.
Cervantes F, et al. *Blood*. 2009;113:2895-2901.

Polycythemia Vera

Diagnosis and Risk Stratification

2016 WHO Diagnostic Criteria: PV

2016 WHO Criteria: ☑ Must meet all 3 major OR the first 2 major and the minor[a]

Major

- ☐ Hb >16.5 g/dL in men, >16.0 g/dL in women; or Hct >49% in men, >48% in women; or increased RCM[b]
- ☐ Bone marrow biopsy showing trilineage myeloproliferation and pleomorphic megakaryocytes
- ☐ Presence of *JAK2* V617F or *JAK2* exon 12 mutation

Minor

- ☐ Subnormal sEPO level

[a] Bone marrow biopsy may not be required in cases with sustained absolute erythrocytosis: Hb levels >18.5 g/dL in men (Hct 55.5%) or >16.5 g/dL in women (Hct 49.5%) if major criterion 3 and minor criterion are present. However, initial MF (presented in ≤20% of patients) can be detected only by performing a bone marrow biopsy; this finding may predict a more rapid progression to overt MF (post-PV MF). [b] RCM >25% above mean normal predicted level.
sEPO, serum erythropoietin; WHO, World Health Organization.
Arber DA, et al. *Blood.* 2016;127:2391-2405.

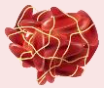
Risk Stratification With the Goal of Controlling Hct and Reducing the Risk of Thrombotic Events[1]

Traditional risk factors for thrombosis in PV include advanced age and a previous history of thrombosis[1]

Low Risk[1,2]
Median survival, 26 years

- NO HISTORY OF THROMBOSIS
- <60 YEARS OF AGE

High Risk[1,2]
Median survival, 8.3 years



HISTORY OF THROMBOSIS *OR* >60 YEARS OF AGE

Studies suggest that over 70% of patients diagnosed with PV may be considered high risk[5,6]

Additional Considerations[1,3,4]

- Leukocytosis
- Elevated Hct
- CV risk factors
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - BMI
  - Tobacco use

Failure to maintain an Hct <45% has been associated with a significantly increased risk of major thrombosis or CV-related death[4]

BMI, body mass index; CV, cardiovascular.

1. Tefferi A, Barbui. *Am J Hematol*. 2020;95:1599-1613. 2. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. 3. Tefferi A, et al. *Leukemia*. 2021;35:3339-3351. 4. Marchioli R, et al. *N Engl J Med*. 2013;368:22-33. 5. Lyons RM et al. *Clin Lymphoma Myeloma Leuk*. 2022;Suppl 2:S325. 6. Grunwald MR, et al. Clin Lymphoma Myeloma Leuk. 2020;20:219-225.

Pathophysiology of MPNs and the Role of JAK Pathway Dysregulation

Pathogenesis of MPNs

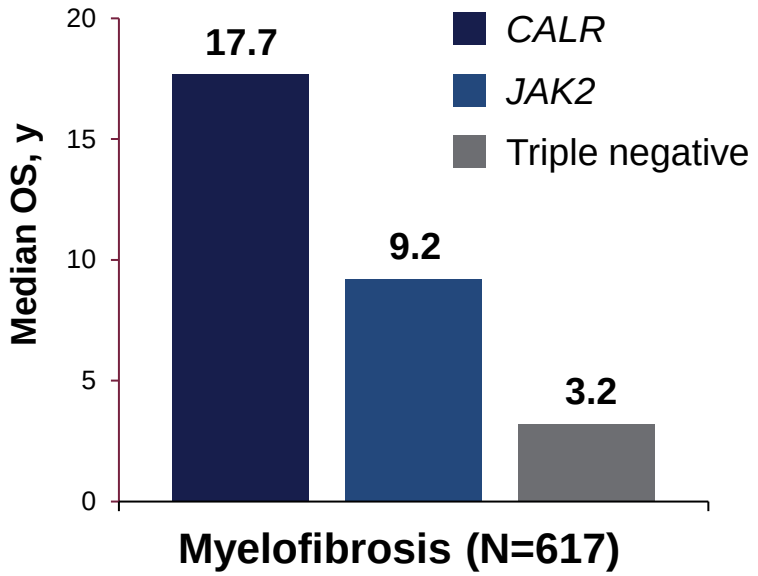
An overactive JAK pathway has been identified to play a key role in the pathogenesis of MPNs[1]

Mutations Associated With JAK Signaling Are the Most Common Among MPNs[2]

Polycythemia vera (N=382)

Myelofibrosis (N=203)

Driver Mutations Impact Survival Outcomes in MF[3]

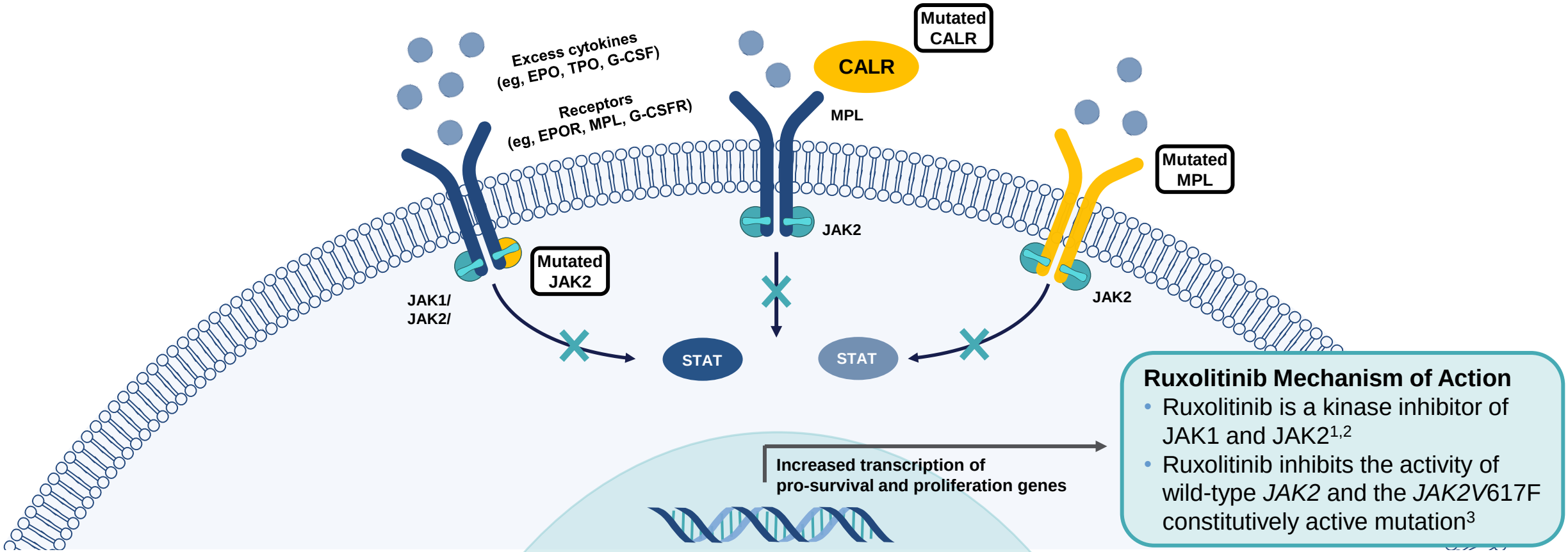


Myelofibrosis (N=617)

CALR, calreticulin; JAK, Janus kinase; MPL, myeloproliferative leukemia virus oncogene (thrombopoietin receptor); MPN, myeloproliferative neoplasm; OS, overall survival.

1. Kralovics R, et al. *N Engl J Med.* 2013;352:1779-1790. 2. Klampfl T, et al. *N Engl J Med.* 2013;369:2379-2390. 3. Rumi E, et al. *Blood.* 2014;124(7):1062-1069.

Ruxolitinib Targets Dysregulated JAK1 and JAK2 Signaling[1-6]



Ruxolitinib Mechanism of Action

- Ruxolitinib is a kinase inhibitor of JAK1 and JAK2[1,2]
- Ruxolitinib inhibits the activity of wild-type *JAK2* and the *JAK2V*617F constitutively active mutation[3]

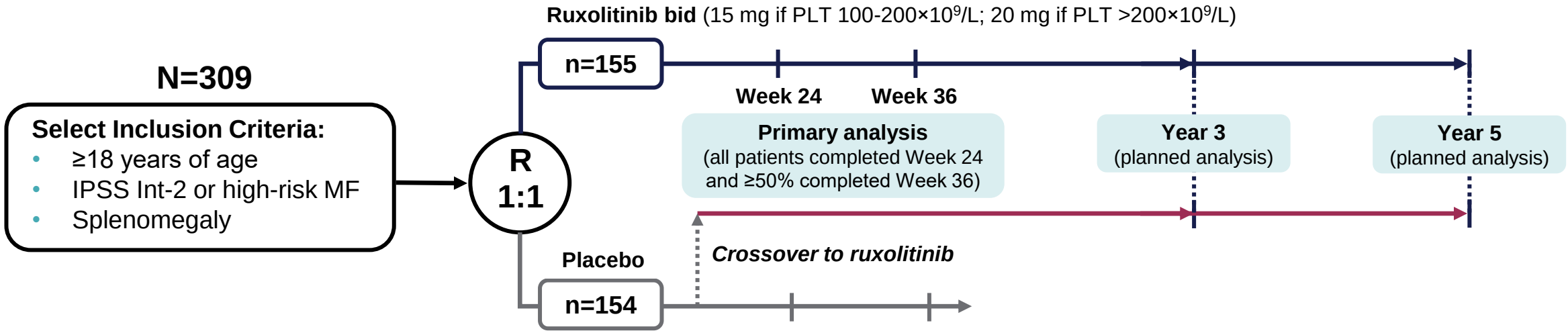
EPOR, erythropoietin receptor; G-CSFR, granulocyte-macrophage colony-stimulating factor receptor; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TYK2, non-receptor tyrosine protein kinase 2.

1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 2. Quintas-Cardama A, et al. *Nat Rev Drug Discov*. 2011;10(2):127-140. 3. Quintas-Cardama A, et al. *Blood*. 2010;115(15):3109-3117. 4. Barbui T, et al. *Haematologica*. 2011;96(2):315-318. 5. Van Rompaey L, et al. *J Immunol*. 2013;191(7):3568-3577. 6. Ghoreschi K, et al. *Immunol Rev.* 2009;228(1):273-287.

Ruxolitinib Clinical Efficacy and Safety in Myelofibrosis

COMFORT-I: Study Design

Study Design: Randomized, double-blind study (ClinicalTrials.gov, NCT00952289) comparing the efficacy and safety of ruxolitinib vs placebo in patients with MF (PMF, PPV-MF, or PET-MF)



Primary endpoint:
- ≥35% reduction from baseline in SV at Week 24[1]

Select secondary endpoints[1]:
- Duration of the reduction in SV
- Change from baseline in MFSAF TSS
- OS

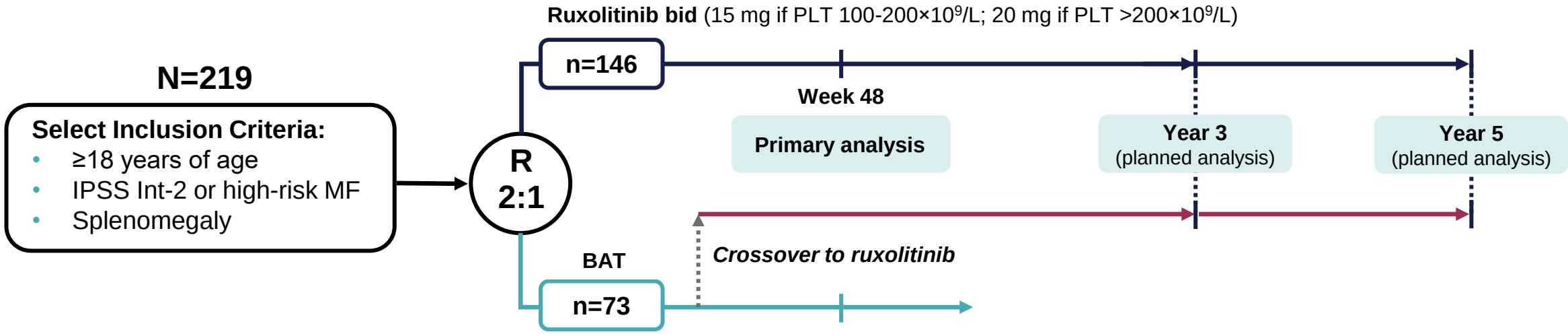
Parameters
- Crossover to ruxolitinib was permitted before Week 24 for protocol-defined increasing splenomegaly and after the primary analysis[1]
- Ruxolitinib dose could be increased for patients who did not achieve spleen response and had adequate PLT and neutrophil counts[2]
- Ruxolitinib dose reductions were required for protocol-defined decreases in PLT counts[2]

bid, twice daily; Int-2, intermediate-2; IPSS, International Prognostic Scoring System; MF, myelofibrosis; MFSAF TSS, Myelofibrosis Symptom Assessment Form v2.0 total symptom score; OS, overall survival; PET-MF, post–essential thrombocythemia myelofibrosis; PLT, platelet; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; R, randomized; SV, spleen volume.

1. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807. 2. Verstovsek S, et al. *Onco Targets Ther*. 2013;7:13-21.

COMFORT-II: Study Design

Study Design: Open-label, randomized study (ClinicalTrials.gov, NCT00934544) comparing the efficacy and safety of ruxolitinib vs BAT in patients with PMF, PPV-MF, or PET-MF



Primary endpoint:
- ≥35% reduction from baseline in SV at Week 48

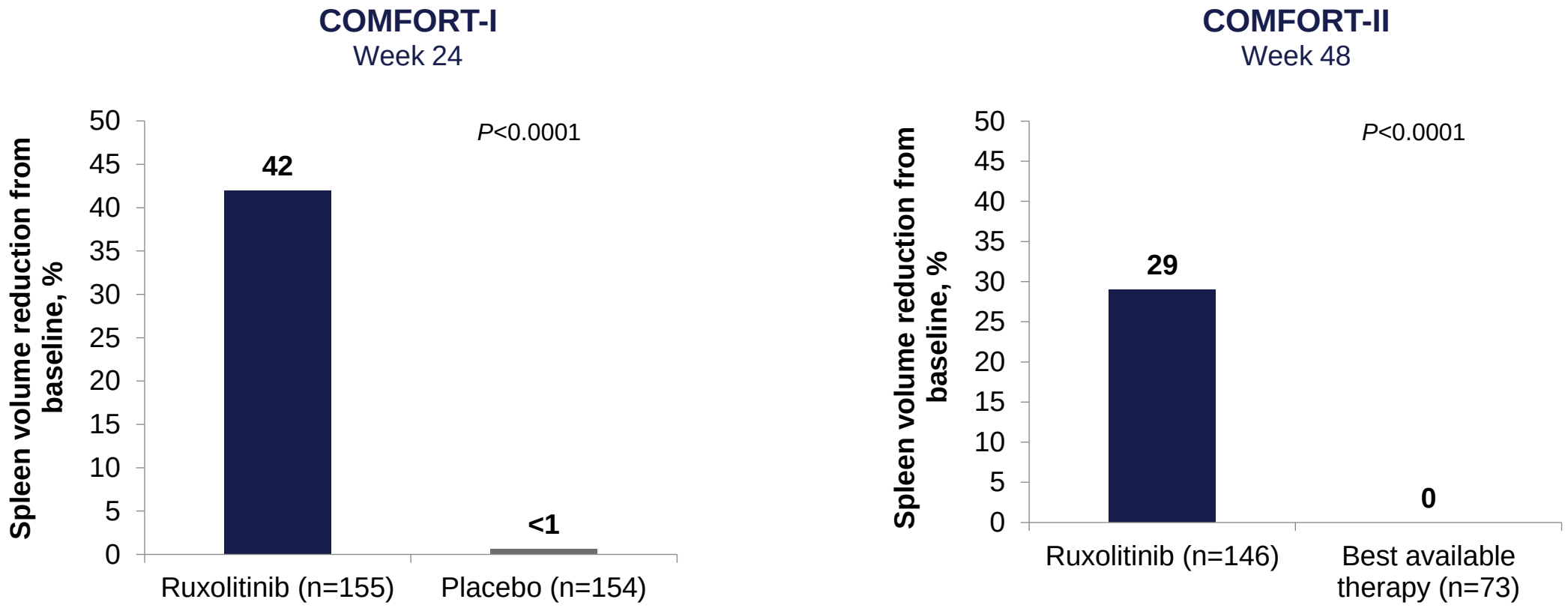
Select secondary endpoint:[1]
- ≥35% reduction from baseline in SV at Week 24

Parameters
- Crossover to ruxolitinib was permitted before Week 48 for protocol-defined increasing splenomegaly and after the primary analysis

BAT, best available therapy; bid, twice daily; Int-2, intermediate-2; IPSS, International Prognostic Scoring System; MF, myelofibrosis; PET-MF, post–essential thrombocythemia myelofibrosis; PLT, platelet; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; R, randomized; SV, spleen volume.

Harrison C, et al. *N Engl J Med*. 2012;366:787-798.

COMFORT-I and II: Primary Endpoint (≥35% Reduction in Spleen Volume)

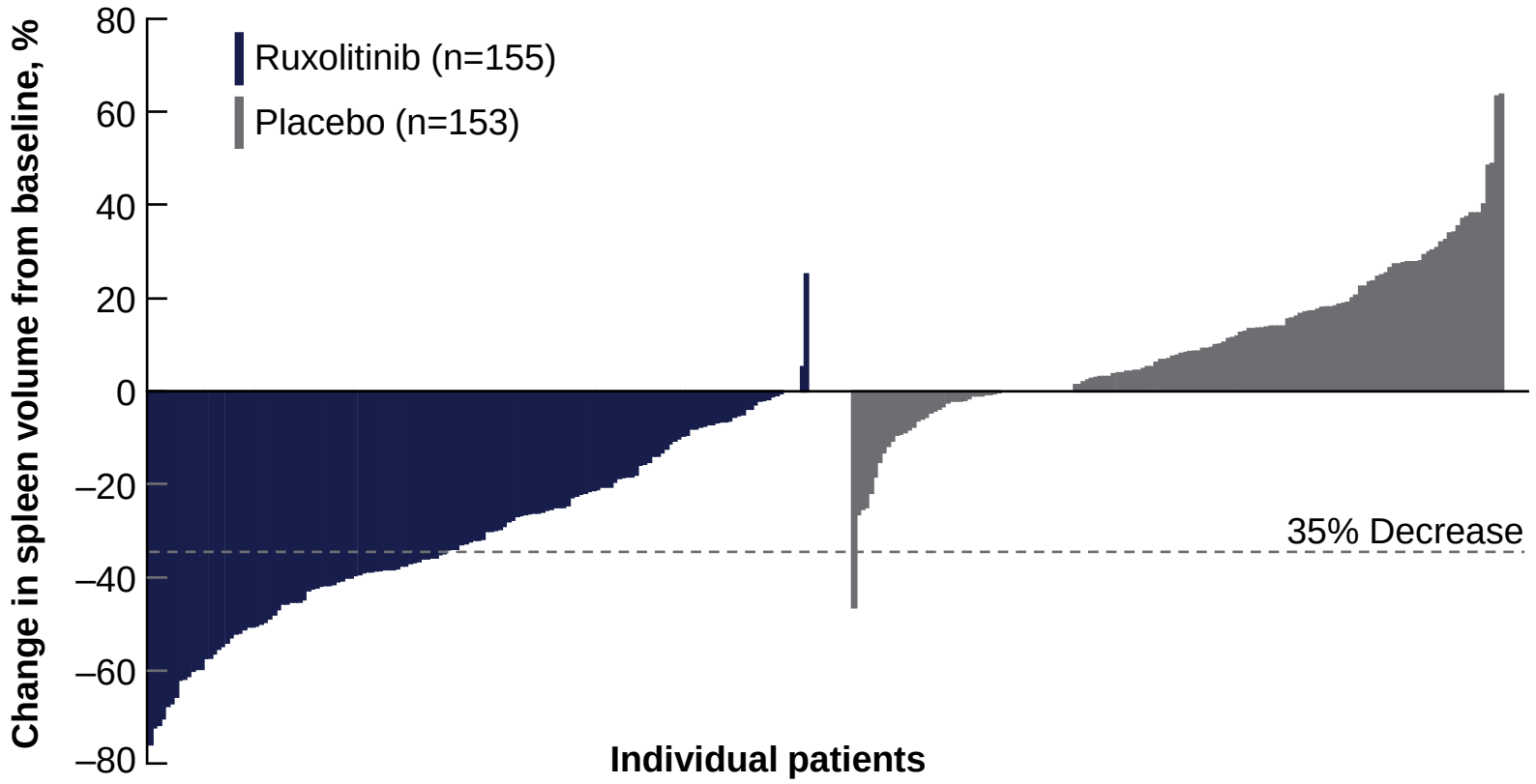


A significantly larger proportion of patients in the ruxolitinib group achieved a 35% or greater reduction from baseline in spleen volume across both studies

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

COMFORT-I: Primary Endpoint (≥35% Reduction in Spleen Volume)

Percent Change From Baseline in Spleen Volume at Week 24 or Last Observation

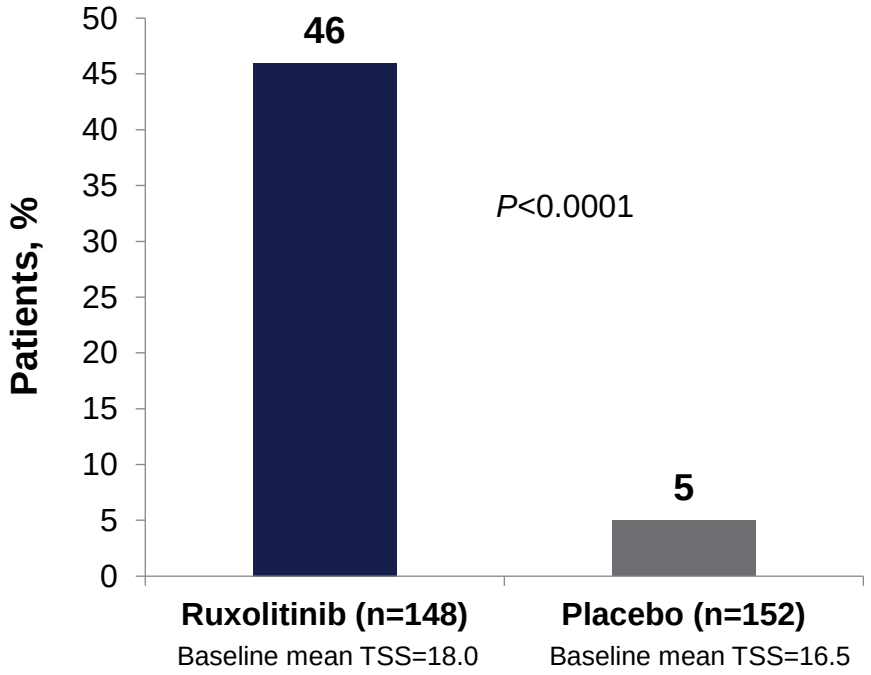


Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

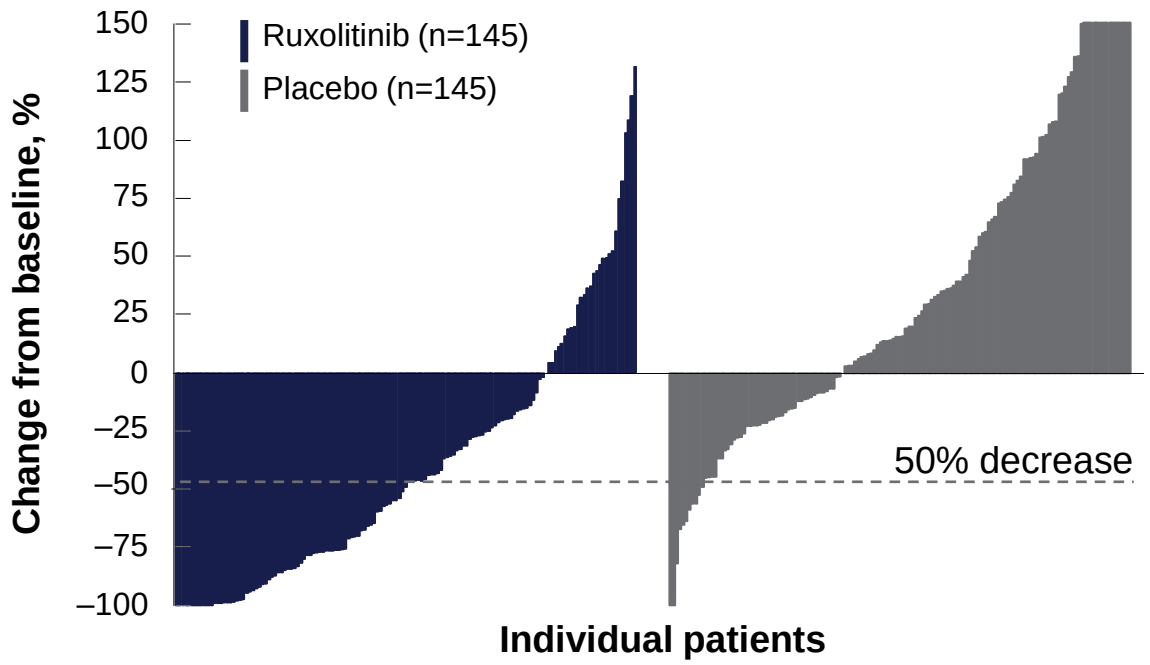
COMFORT-I: Improvement in Total Symptom Score

Median time to response (≥50% reduction in TSS[a]) was <4 weeks

Patients With ≥50% Improvement in TSS at Week 24



Percent Change From Baseline in TSS at Week 24 or Last Observation for Each Patient[b]



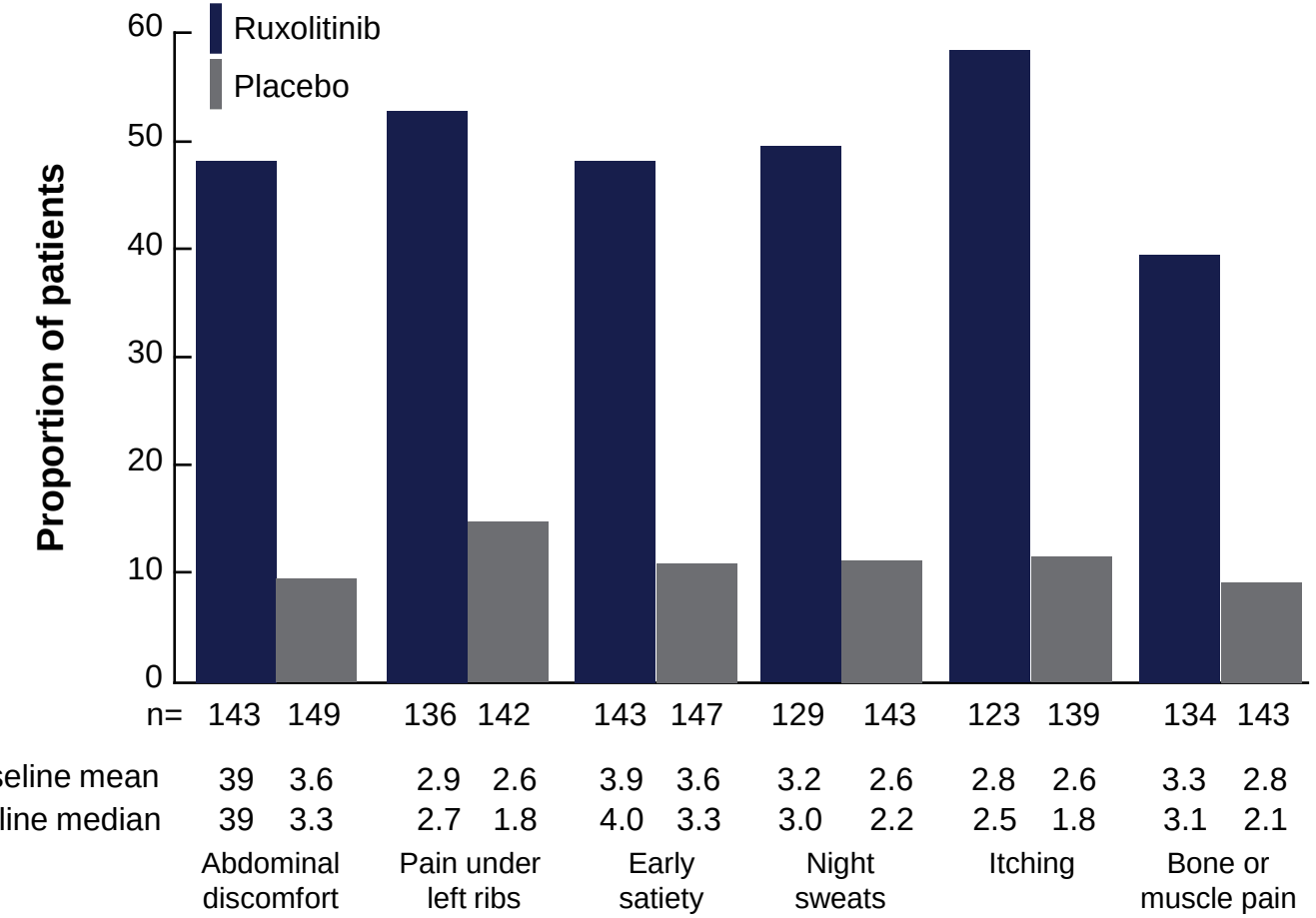
Worsening of total symptom score is truncated at 150%.

[a] TSS was derived from the modified MFSAF, a daily diary capturing the core symptoms of myelofibrosis (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety). Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60. [b] Results are excluded for 5 patients with a baseline total symptom score of 0, 8 patients with missing baseline, and 6 patients with insufficient postbaseline data.

TSS, total symptom score.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

COMFORT-I: Patients Achieving ≥50% Reduction in Improvement in Individual Symptom Scores[a] at Week 24

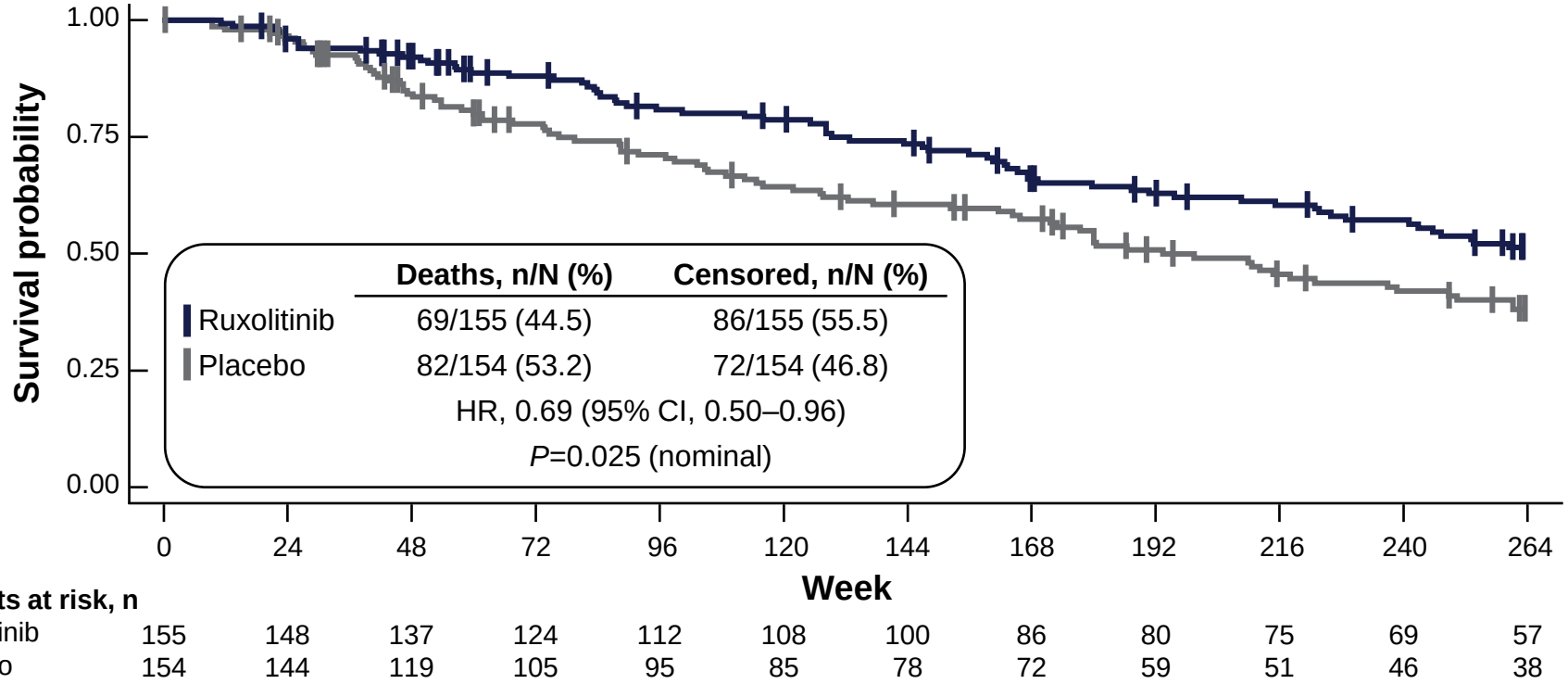


- Additionally, fatigue response[b] was reported in 35% of patients in the ruxolitinib group versus 14% of the patients in the placebo group

[a] Symptom scores were derived from the modified MFSAF, a daily diary capturing the core symptoms of myelofibrosis (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety). Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60. [b] Fatigue response defined as patients who achieved a reduction of ≥4.5 points from baseline to week 24 in the PROMIS Fatigue total score.
PROMIS, Patient-Reported Outcomes Measurement Information System.
Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

COMFORT-I: 5-Year Overall Survival by Treatment Group[1,a]

- Patients were eligible for crossover from placebo prior to week 24 if criteria were met[1,2,b]; median time to crossover was 39.9 weeks[2]
- By 80 weeks, all patients originally randomized to placebo discontinued or crossed over to ruxolitinib therapy[3]
- At 3 years, survival probability was 70% for patients originally randomized to ruxolitinib and 61% for those originally randomized to placebo[2]
- At 5 years, survival probability was 51% for patients originally randomized to ruxolitinib and 40% for those originally randomized to placebo[4]

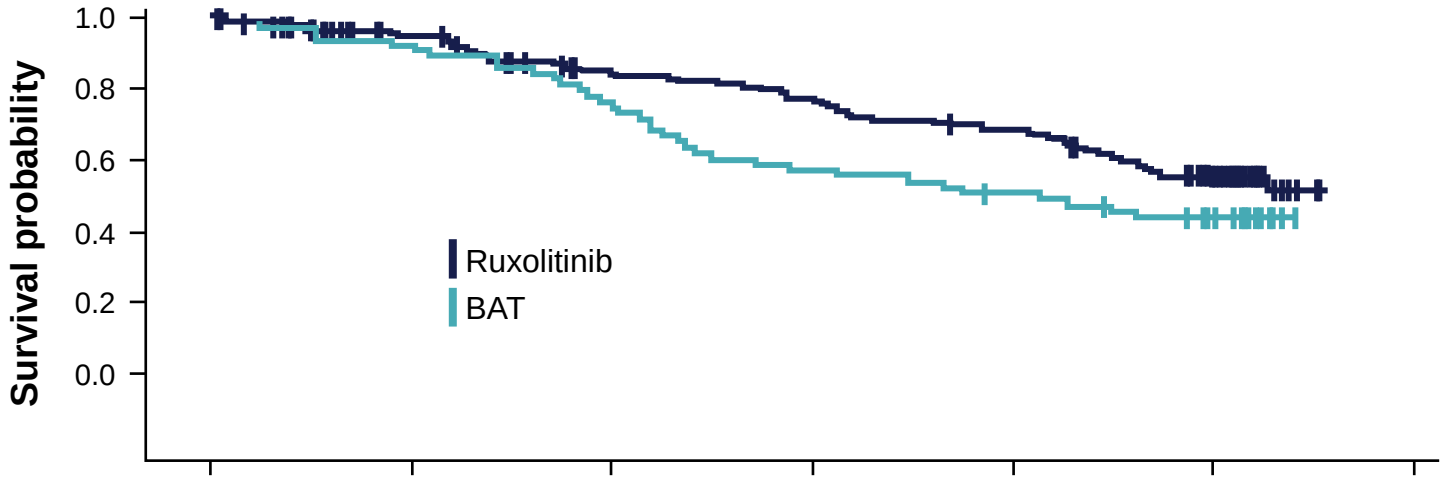


[a] Kaplan-Meier curves of overall survival by ITT analysis. [b] Crossover was allowed based on defined criteria for worsening splenomegaly.

Figure reproduced with permission from Verstovsek S, et al. *J Hematol Oncol.* 2017;10(1):55. 1. Verstovsek S, et al. *J Hematol Oncol.* 2017;10(1):55. 2. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 3. Verstovsek S, et al. *N Engl J Med.* 2012;366(9):799-807. 4. Data on file, Incyte Corporation.

COMFORT-II: 5-Year Overall Survival by Treatment Group[1,a]

- Patients were eligible for crossover from BAT prior to 48 weeks if criteria were met[1,2,b]
  - After 48 weeks, all patients were allowed to cross over[1]
  - Median time to crossover from BAT to ruxolitinib was 75 weeks[1]
- Patients randomized to ruxolitinib had longer OS compared with those randomized to BAT, with a 33% reduction in risk of death with ruxolitinib treatment compared to BAT (HR, 0.67; 95% CI, 0.44-1.02; *P*=0.06)
- At 3 years, survival probability was 79% for patients originally randomized to ruxolitinib and 59% for those originally randomized to BAT[2]
- At 5 years, survival probability was 56% for patients originally randomized to ruxolitinib and 44% for those originally randomized to BAT[3]



Patients, n							
Ruxolitinib	146	130	109	100	88	61	0
BAT (ITT)	73	58	48	35	30	22	0

[a] Kaplan-Meier curves of overall survival by ITT analysis. [b] Crossover criteria included protocol defined progressive splenomegaly, defined as a ≥25% increase in spleen volume from on-study nadir.
ITT, intention-to-treat.

1. Reproduced with permission from Harrison CN, et al. *Leukemia*. 2017;31(3):775. 2. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.
3. Harrison CN, et al. *Leukemia*. 2017;31(3):775.

COMFORT-I: Nonhematologic Adverse Reactions[1-3]

	Ruxolitinib, % (n=155)			Placebo, % (n=151)		
Adverse reactions	**All grades[a]**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary tract infections[d]	9	0	0	5	<1	<1
Weight gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes zoster[f]	2	0	0	<1	0	0
	Grade 1	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
ALT elevations	25	2	1	7	NR	NR
AST elevations	17	<1	0	6	NR	0
Cholesterol elevations	17	<1	0	<1	NR	0

- Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with ruxolitinib and 11% of patients treated with placebo
- Following interruption or discontinuation of ruxolitinib, symptoms of MF generally returned to pretreatment levels over a period of ≈1 week
- In the 5-year analysis, all AEs were consistent with the 3-year analysis[2,3]

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. [b] Includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, and purpura. [c] Includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's disease, and labyrinthitis. [d] Includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, and nitrite urine present. [e] Includes weight increased and abnormal weight gain. [f] Includes herpes zoster and postherpetic neuralgia.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; NR, not reported.
1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 2. Verstovsek S, et al. *Hematologica*. 2015;100(4):479-488.
3. Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55.

COMFORT-I: Worst Hematology Laboratory Abnormalities[1-3,a]

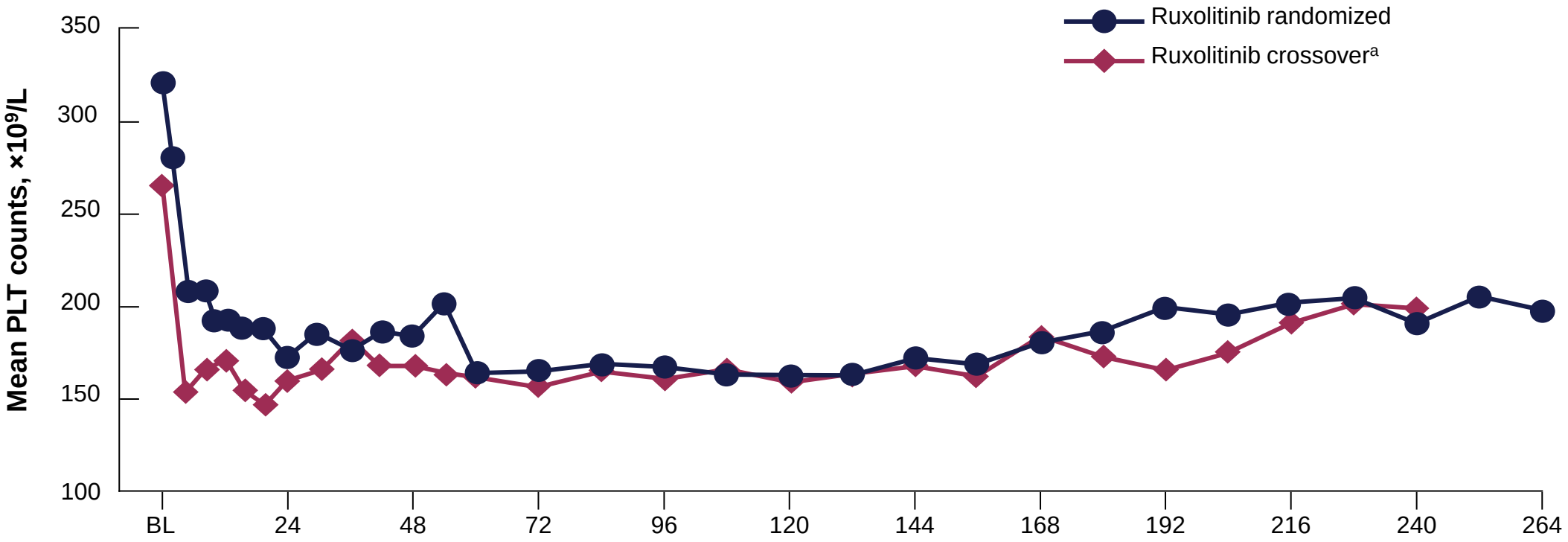
	Ruxolitinib, % (n=155)			Placebo, % (n=151)		
Laboratory parameter	**All grades[b]**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

In the 5-year analysis, all AEs were consistent with the 3-year analysis[2,3]

[a] Presented values are worst-grade values regardless of baseline. [b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 2. Verstovsek S, et al. *Hematologica*. 2015;100(4):479-488.
3. Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55.

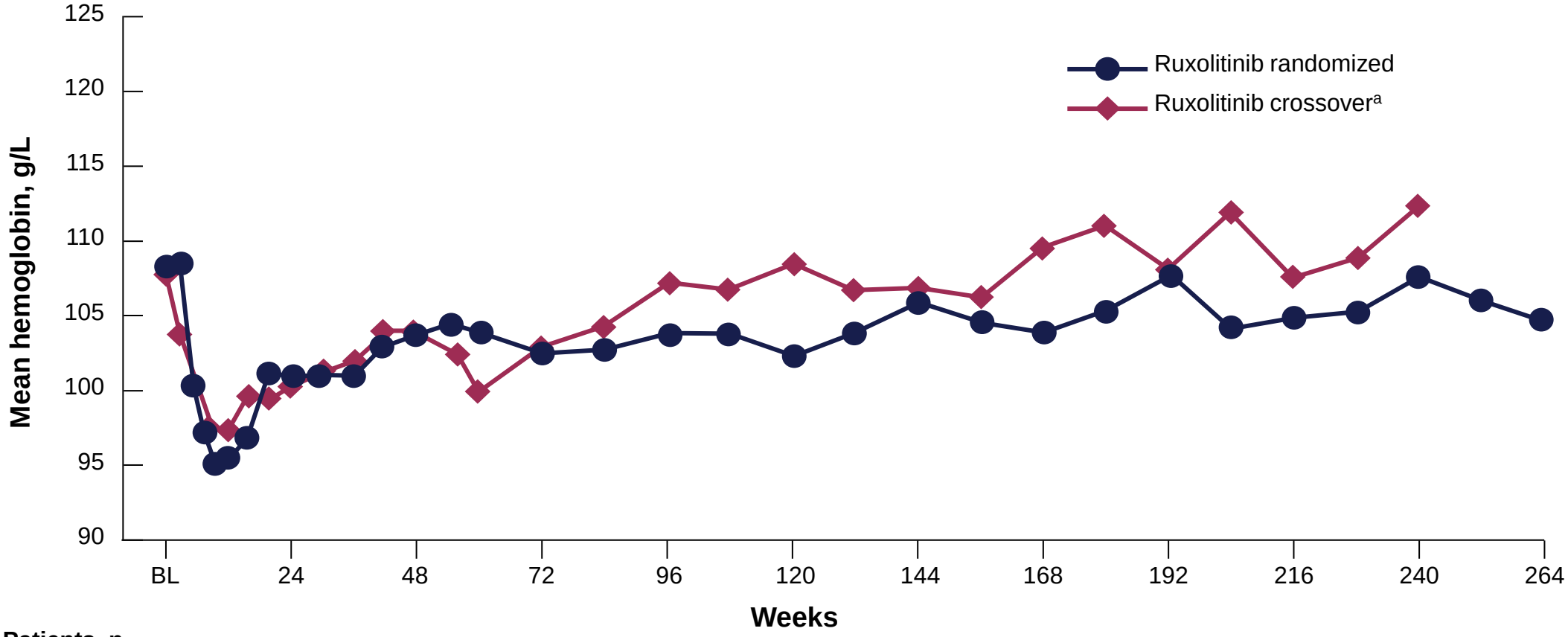
COMFORT-I: Platelet Counts Over Time



Patients, n	BL	24	48	72	96	120	144	168	192	216	240	264
Ruxolitinib randomized	155	143	124	110	104	94	79	71	59	57	49	45
Ruxolitinib crossover	111	79	74	72	64	54	45	35	32	26	12	

[a] For patients in the ruxolitinib crossover group, baseline represents the date of crossover to ruxolitinib.
BL, baseline.
Reproduced with permission from Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55.

COMFORT-I: Hemoglobin Levels Over Time

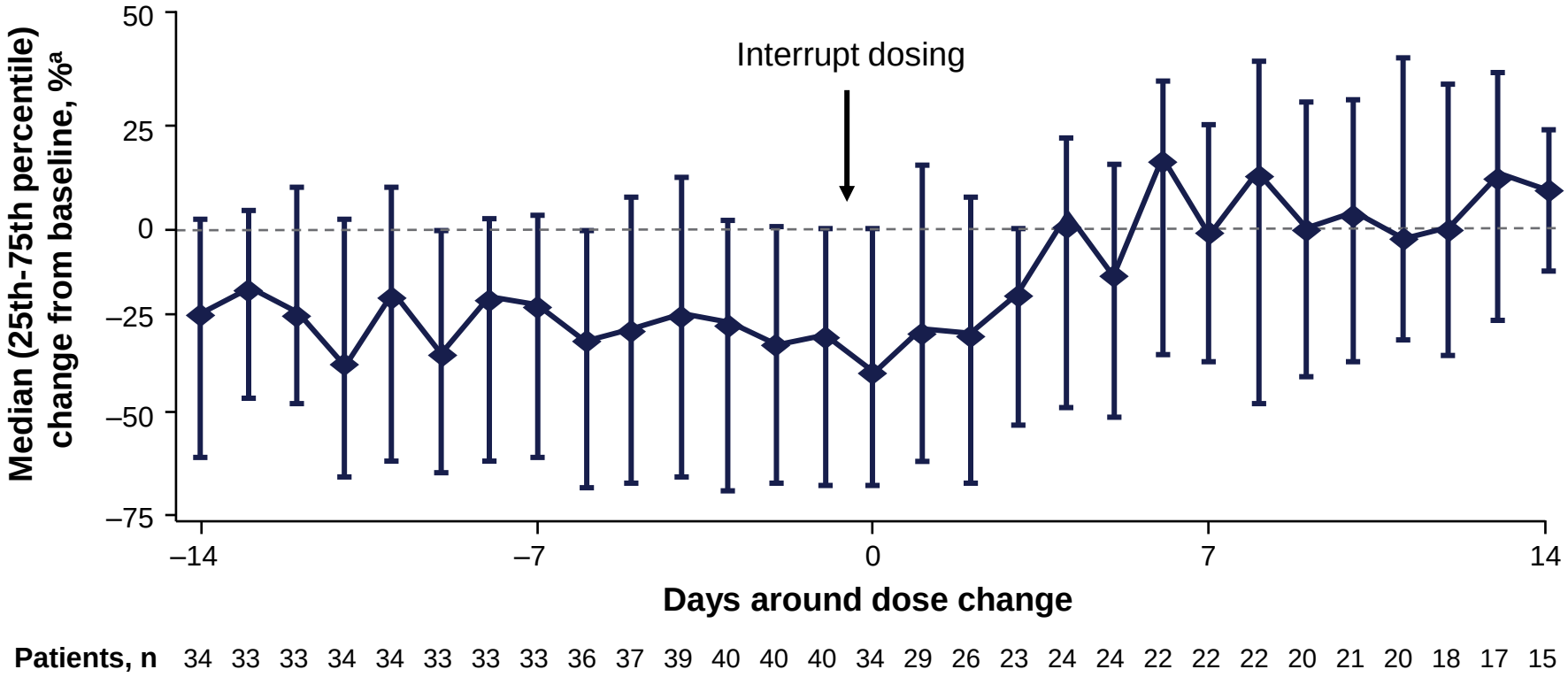


Patients, n												
Ruxolitinib randomized	155	143	124	110	104	94	79	71	59	57	49	45
Ruxolitinib crossover	111	79	74	72	64	54	45	35	32	26	12	

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

COMFORT-I: TSS Before and During Interruption[1]

- When discontinuing or interrupting therapy with ruxolitinib for reasons other than thrombocytopenia or neutropenia, consider tapering the dose gradually rather than discontinuing abruptly[2]



[a] Median TSS for the 14 days before and after the first dose interruption; baseline is the 7-day moving average before day 1. The graph represents the median percentage change from baseline plus and minus 14 days around the first ruxolitinib dose interruption. Patients were counted only for those days around dose interruption for which data were available.

1. Verstovsek S, et al. *N Engl J Med*. 2012;366(9)(suppl):799-807. 2. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

COMFORT-I and COMFORT-II Data Summary

- Ruxolitinib was compared with placebo and best available therapy in the COMFORT-I and COMFORT-II trials, respectively

- Primary endpoint
  - In the pivotal phase 3 COMFORT-I and COMFORT-II trials, 42% and 29% of patients receiving ruxolitinib achieved ≥35% reduction in spleen volume, respectively

- Key secondary endpoints
  - 46% of patients receiving ruxolitinib vs 5% of patients receiving placebo achieved a ≥50% improvement in TSS in COMFORT-I
  - 5-year survival probability was 56% (ruxolitinib) and 47% (placebo) in COMFORT-I, and 56% (ruxolitinib) and 44% (BAT) in COMFORT-II

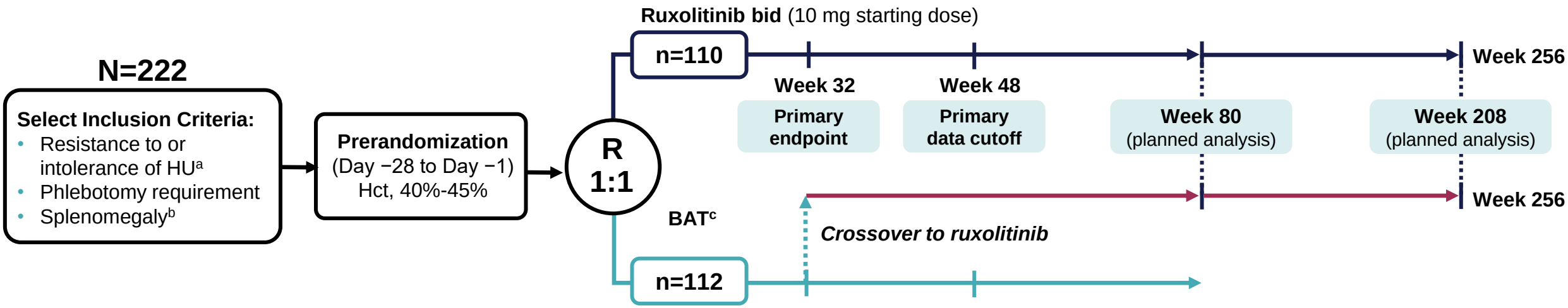
- Safety
  - Nonhematologic adverse reactions were generally grade 1/2 in severity
  - Hematologic abnormalities included thrombocytopenia, anemia, and neutropenia
  - Hematologic adverse events should be managed by dose reduction, dose interruption, or transfusion
  - Discontinuation rates were similar with ruxolitinib and placebo

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Ruxolitinib Clinical Efficacy and Safety in Polycythemia Vera

RESPONSE: Study Design

Study Design: Randomized, open label, phase 3 study (ClinicalTrials.gov, NCT01243944) comparing the efficacy and safety of ruxolitinib with BAT in patients with PV who are resistant to or intolerant of HU



Primary endpoint:
- Hct control and ≥35% reduction from baseline in SV at Week 32[d]

Secondary endpoints:
- Duration of response, symptom reduction

Parameters
- Patients were stratified by HU intolerance/resistance and randomized to open-label
- Patients receiving BAT could crossover to ruxolitinib at Week 32 if they failed to meet the primary endpoint or later in case of progression[e]
- Dose increases to ≤25 mg bid were allowed
- Dose reductions or interruptions were mandated for specific cytopenias of grade ≥2
- All patients received low-dose aspirin unless medically contraindicated

[a] Modified ELN criteria. [b]SV ≥450 cm^3. [c] BATwas selected by the investigator and could include HU (at a dose that did not cause unacceptable side effects), IFN or pegylated IFN, pipobroman, anagrelide, IMIDs such as lenalidomide or thalidomide, or no medication. BAT could be changed owing to a lack of response or toxic effects requiring drug discontinuation. [d]Assessed by centrally reviewed MRI or CT. [e]Progression defined as phlebotomy eligibility and/or progression of splenomegaly.
bid, twice daily; CT, computed tomography; ELN, European LeukemiaNet; Hct, hematocrit; HU, hydroxyurea; IFN, interferon; IMID, immunomodulatory drug; MRI, magnetic resonance imaging; PV, polycythemia vera; R, randomized; SV, spleen volume.
Vannucchi AM, et al. *N Engl J Med*. 2015;372(5):426-435.

Primary Analysis Efficacy Measures and Endpoints

- **Primary Composite Endpoint:[1]**
  - Percentage of patients who achieved both Hct control and spleen response at Week 32
    - Hct control
      - Ineligibility for phlebotomy from Weeks 8 to 32, with no more than 1 postrandomization phlebotomy eligibility between randomization and Week 8
      - Phlebotomy eligibility was defined as Hct >45% and ≥3 percentage points higher than baseline or >48%, whichever was lower
    - Spleen response
      - ≥35% reduction from baseline in spleen volume by MRI or CT studies
- **Key Secondary Endpoints (Type-I Error Controlled):[1]**
  - Proportion of patients who maintained primary response at Week 32 that was maintained until at Week 48
  - Proportion of patients who achieved CHR at Week 32
    - CHR=Hct control, platelet count ≤400×10^9/L, and WBC count ≤10×10^9/L
- **Exploratory Endpoints:[2]**
  - Duration of primary response
  - Symptom reduction and patient-reported outcomes measured using the MPN-SAF, EORTC QLQ-C30, Pruritus Symptom Impact Scale, and Patient Global Impression of Change
  - Safety

CHR, complete hematologic remission; CT, computed tomography; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire−Core 30; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; MRI, magnetic resonance imaging; WBC, white blood cell.

1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 2. Vannucchi AM, et al. *N Engl J Med*. 2015;372(5):426-435.

Baseline Characteristics

Parameter	Ruxolitinib (n=110)	BAT (n=112)
Median (range) age, years	62.0 (34-90)	60.0 (33-84)
Sex, n (%)		
Male	66 (60.0)	80 (71.4)
Female	44 (40.0)	32 (28.6)
Median (range) time since diagnosis of PV, years	8.2 (0.5-36)	9.3 (0.5-23)
Median (range) duration of previous HU therapy, years	3.1 (<0.1-20.9)	2.8 (<0.1-20.9)
ECOG performance status, n (%)[a]		
0	76 (69.1)	77 (68.8)
1	31 (28.2)	34 (30.4)
2	3 (2.7)	1 (0.9)
Status with regard to previous HU therapy, n (%)		
Unacceptable side effects	59 (53.6)	61 (54.5)
Inadequate response	51 (46.4)	51 (45.5)
Previous thromboembolic event, n (%)	39 (35.5)	33 (29.5)
Positive status for *JAK2*V617F mutation, n (%)	104 (94.5)	107 (95.5)
Allele burden, % (SD)	76.2 (±17.8)	75.0 (±22.6)

[a] The ECOG performance status ranges from 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing disability.
ECOG, Eastern Cooperative Oncology Group.
Vannucchi AM, et al. *N Engl J Med*. 2015;372:426-435.

Baseline Characteristics (cont)

Parameter	Ruxolitinib (n=110)	BAT (n=112)
Spleen length		
Median (range) spleen length below costal margin, cm	7.0 (0-24.0)	7.0 (0-25.0)
<10 cm, n (%)	71 (64.5)	67 (59.8)
>20 cm, n (%)	2 (1.8)	4 (3.6)
Spleen volume, median (range), cm^3	1195 (396-4631)	1322 (254-5147)
Hct, mean (SD), %[a]	43.6 (±2.2)	43.9 (±2.2)
Median (range)	43.3 (39.2-50.5)	44.0 (37.6-50.5)
Hct category, n (%)		
40-45%	79 (71.8)	83 (74.1)
>45%	28 (25.5)	25 (22.3)
Mean (SD) WBC count $\times 10^9$/L	17.6 (±9.6)	19.0 (±12.2)
Mean (SD) platelet count $\times 10^9$/L	484.5 (±323.3)	499.4 (±318.6)
Median (range) number of phlebotomies within 24 weeks before screening	2.0 (1-8)	2.0 (0-16)

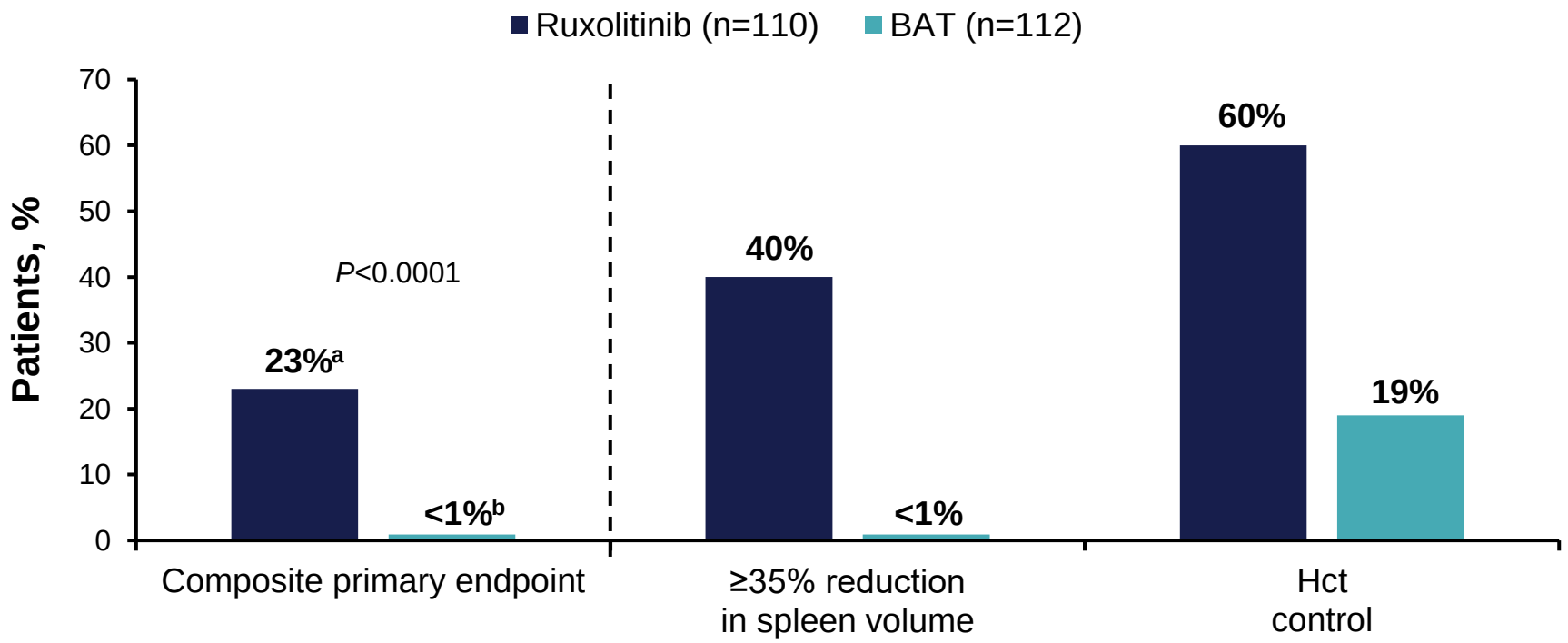
BAT options included HU (58.9%), IFN/pegylated-IFN (11.6%), anagrelide (7.1%), pipobroman (1.8%), and immunomodulator drugs (4.5%)[2]

[a] Shown is the value at the end of the Hct control period before randomization; patients who had a Hct of 40% to 45% within 14 days before their day 1 visit could proceed to randomization; however, the Hct at baseline may have been higher or lower.

1. Reproduced with permission from Vannucchi AM, et al. *N Engl J Med*. 2015;372(5):426-435,. Copyright Massachusetts Medical Society. 2. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023..

Primary Response at Week 32

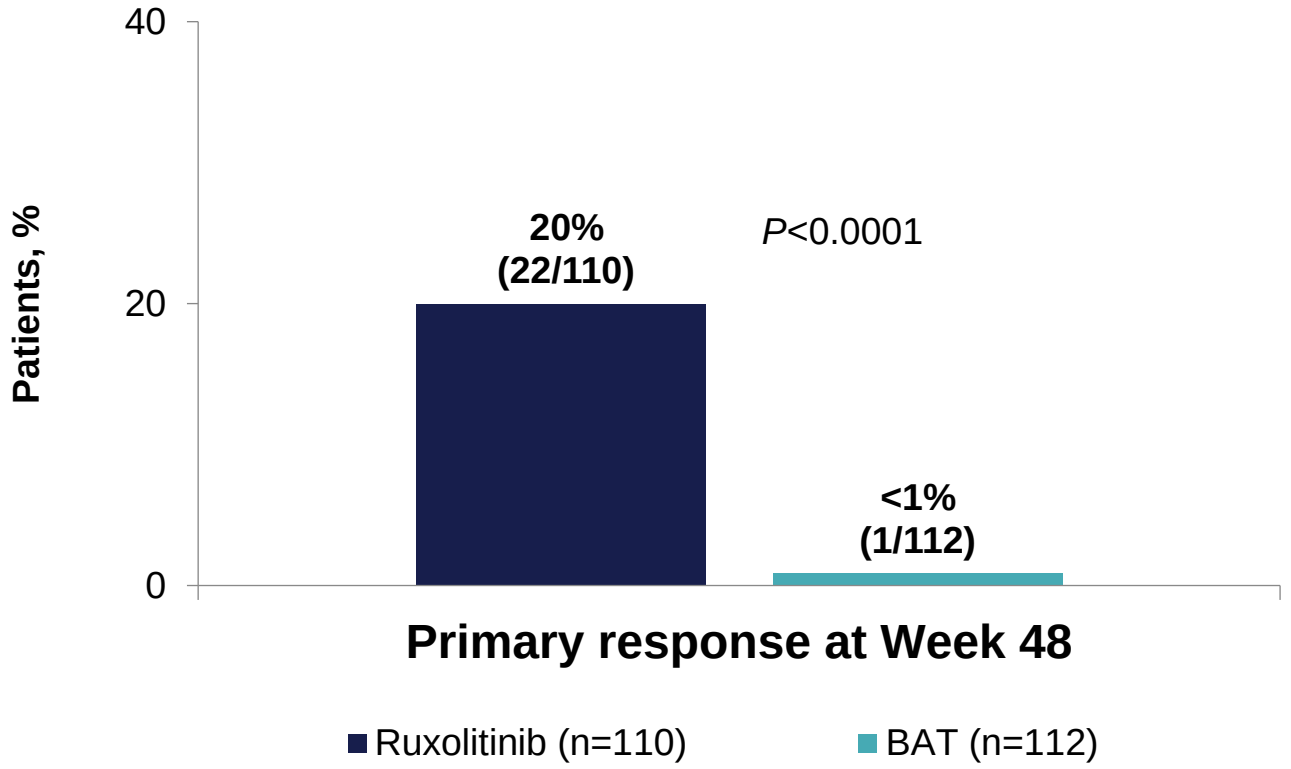
- A significantly greater proportion of patients in the ruxolitinib group achieved a response for the primary endpoint at week 32 compared with BAT



- 98% (43/44) of patients-maintained SVR through week 80
- 77% (51/66) of patients-maintained hematocrit control through week 80

[a] 95% CI, 15%-32%. [b] 95% CI, 0%-5%.
Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Duration of Primary Response at Weeks 48 and 80

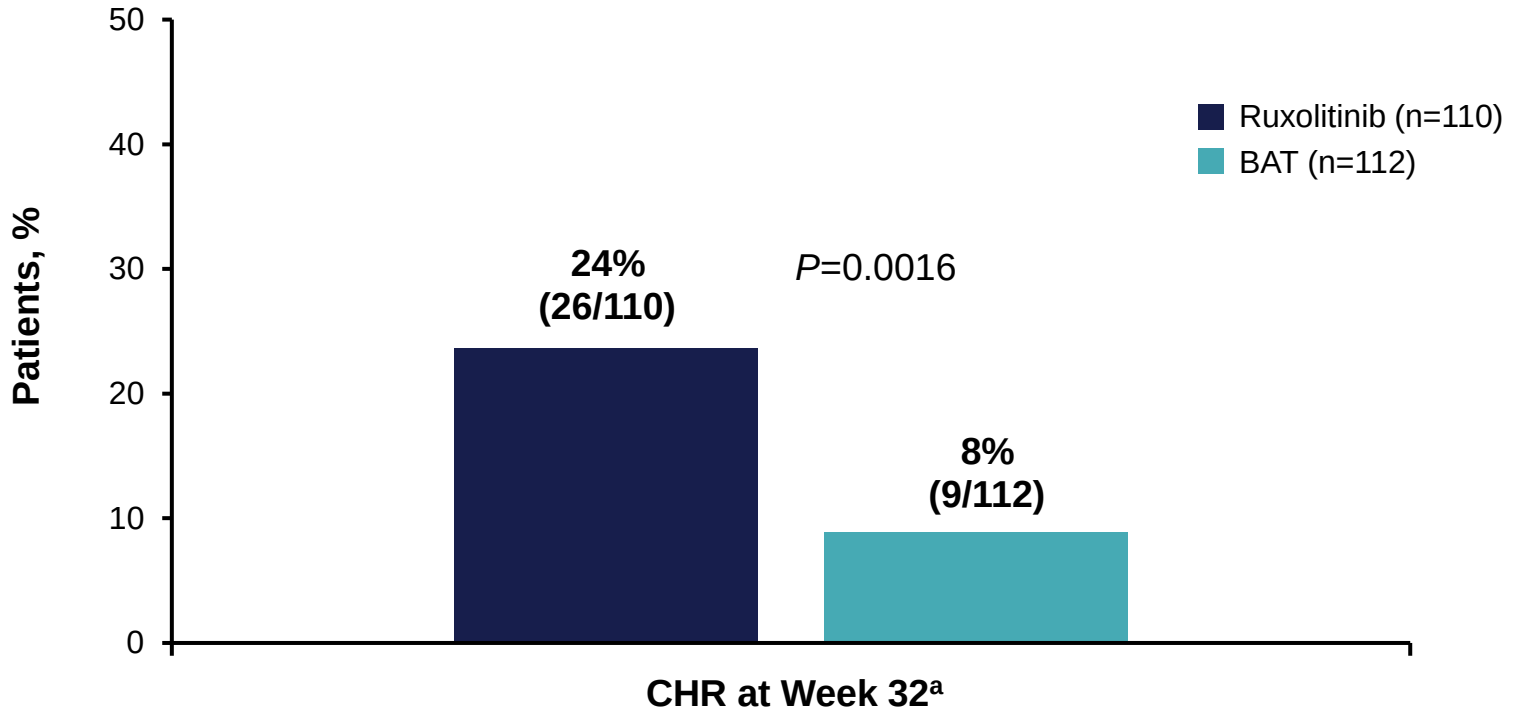


- 76% (19/25) maintained their response through week 80

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Complete Hematologic Remission at Week 32

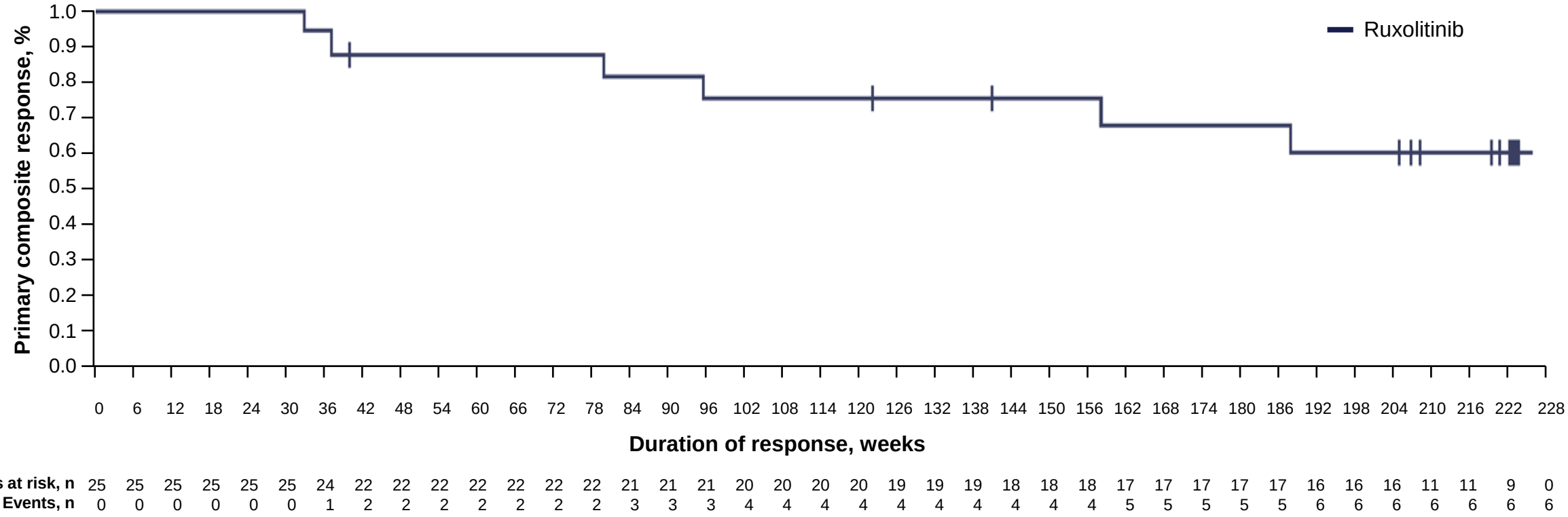
- A significantly greater proportion of patients in the ruxolitinib group achieved a CHR at week 32 compared with BAT



- 58% (15/26) of patients who achieved CHR at week 32 maintained their response through week 80

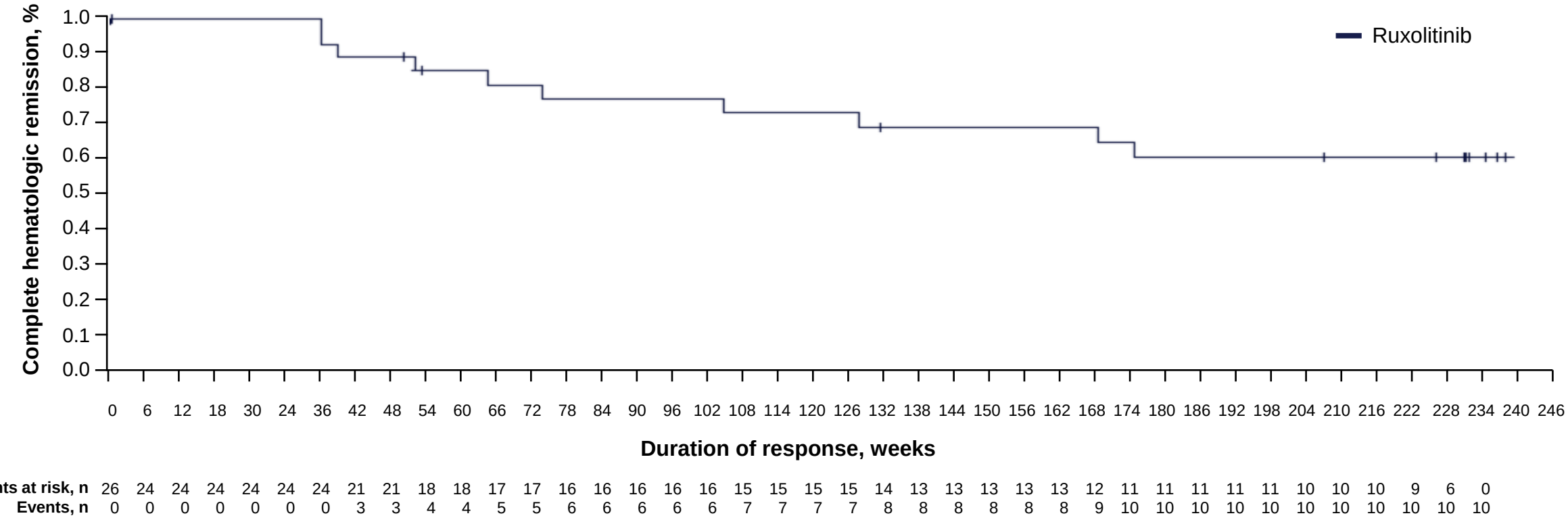
[a] CHR is defined as Hct control, platelet count ≤400×10^9/L, and WBC count ≤10×10^9/L.
Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

5-Year Kaplan Meier Estimate of Primary Response



- In the 5-year analysis, 24% of primary responders at week 32 had progressed, and 74% maintained primary response at 224 weeks (from week 32)

5-Year Kaplan Meier Estimate of Complete Hematologic Remission

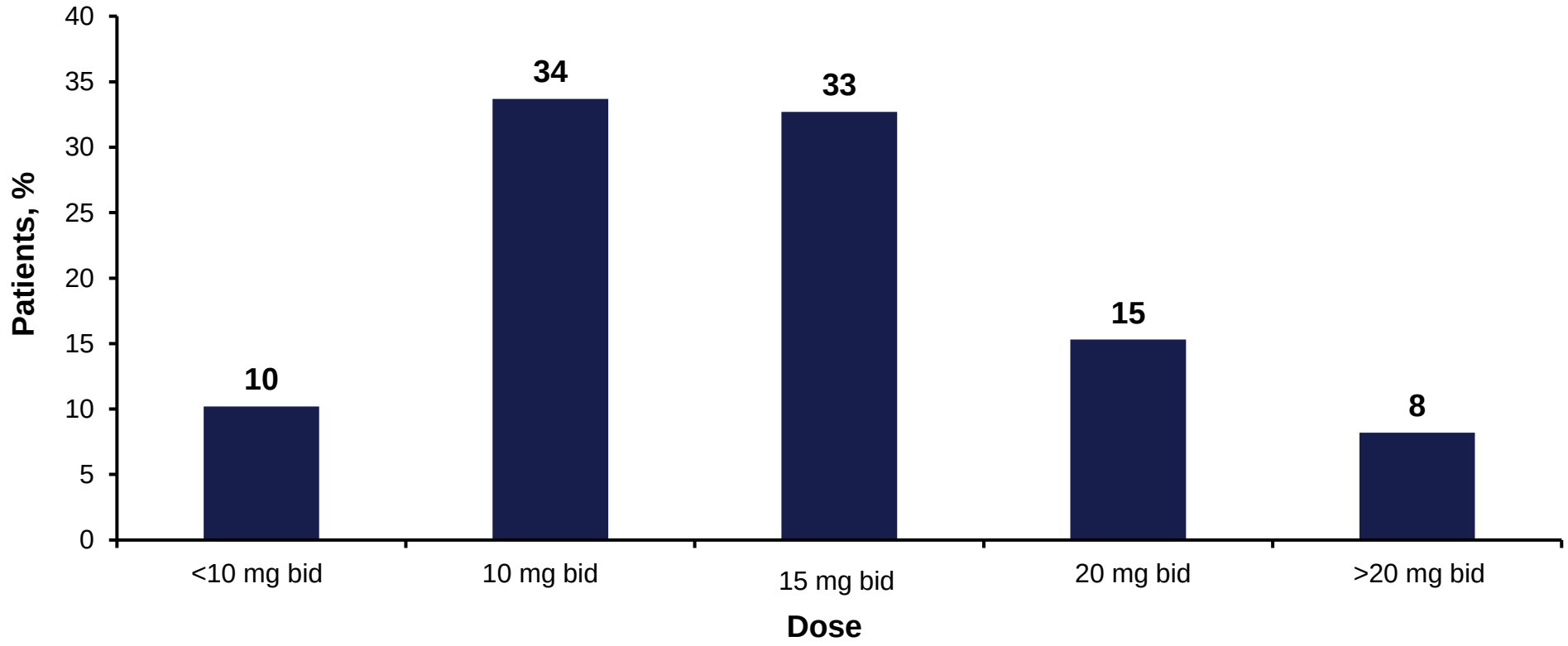


- In the 5-year analysis, 38% of patients achieving CHR at week 32 had progressed, and 55% maintained CHR at 224 weeks (from week 32)

Ruxolitinib Dosing

- The ruxolitinib starting dose was 10 mg bid, which is the FDA-recommended starting dose for PV[1]
  - Most dose adjustments occurred within the first 8 weeks of treatment[2]

Ruxolitinib Dose at Week 32 (n=98)[1]



FDA, United States Food and Drug Administration.

1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 2. Vannucchi AM, et al. *N Engl J Med*. 2015;372(5):426-435.

Treatment-Emergent Nonhematologic Adverse Events (AEs) From Start of Study Drug to Week 32

- Most patients in the standard therapy group crossed over to receive ruxolitinib immediately after Week 32; therefore, AE rates were evaluated through Week 32, when the duration of exposure to therapy was similar in the 2 study groups

AE, n (%)[a]	Ruxolitinib (n=110)		BAT (n=111)[b]	
	All grades	Grade 3/4	All grades	Grade 3/4
Dizziness[d]	15	0	13	0
Diarrhea	15	0	7	<1
Dyspnea[e]	13	3	4	0
Muscle spasms	12	<1	5	0
Constipation	8	0	3	0
Herpes zoster[f]	6	<1	0	0
Nausea	6	0	4	0
Weight gain[g]	6	0	<1	0
Urinary tract infections[h]	6	0	3	0
Hypertension	5	<1	3	<1

[a] AEs that occurred in ≥5% of patients in the ruxolitinib group. [b] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. [c] One patient withdrew consent and did not receive study treatment. [d] Includes dizziness and vertigo. [e] Includes dyspnea and dyspnea exertional. [f] Includes herpes zoster and postherpetic neuralgia. [g] Includes weight increased and abnormal weight gain. [h] Includes urinary tract infection and cystitis.
AE, adverse event.
Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Selected Laboratory Abnormalities From Start of Study Drug to Week 32[1]

Laboratory parameter, %[a]	Ruxolitinib (n=110)			BAT (n=111)[c]		
	All grades[b]	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst grade values regardless of baseline. [b] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. [c] One patient withdrew consent and did not receive study treatment.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

RESPONSE Data Summary

- **Primary endpoint[1,2]**
  - At week 32, 23% and <1% of patients from the ruxolitinib and BAT groups, respectively, achieved the primary endpoint (Hct control and reduction in spleen volume)
  - A greater proportion of patients from the ruxolitinib group achieved each individual component of the primary endpoint compared with the BAT group
  - 76% of primary responders at week 32 maintained response through the 5-year cutoff
  - Similarly, 62% of patients achieving CHR at week 32 maintained remission through the 5-year cutoff

- **Key secondary endpoints[1,3]**
  - Patients randomized to receive ruxolitinib were more likely to achieve durable primary response at week 48 compared with the BAT group
  - A greater proportion of patients in the ruxolitinib group achieved CHR compared with the BAT group

- **Safety[1]**
  - Most AEs were primarily grades 1 or 2
  - The most common hematologic AE observed was anemia; there was a low incidence of grade 3 or 4 cytopenias
  - The AEs observed were consistent with the overall safety profile of ruxolitinib

1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 2. Kiladjian JJ, et al. Lancet Haematol. 2020;7(3):e226-e237. 3. Vannucchi AM, et al. N Engl J Med. 2015;372(5):426-435.

FOR MEDICAL INFORMATION PURPOSES ONLY.

APPENDIX

MF: Recommended Starting Dose

- The recommended starting dose of ruxolitinib is based on platelet count

Platelet count	Proposed starting dose
>200×10^9/L	20 mg bid
100-200×10^9/L	15 mg bid
≥100×10^9/L or patients taking strong CYP3A4 inhibitors or fluconazole	10 mg bid
100-150×10^9/L and either of the following: moderate or severe renal impairment[a] or any hepatic impairment	10 mg bid
50×10^9/L to <100×10^9/L	5 mg bid
50×10^9/L to <100×10^9/L and any 1 of the following: moderate or severe renal impairment,[a] any hepatic impairment, or patients taking strong CYP3A4 inhibitors or fluconazole	5 mg qd

- A CBC and platelet count should be performed before initiating ruxolitinib, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Ruxolitinib should be avoided in specific patient populations who have platelets less than 50×10^9/L or end-stage renal disease not requiring dialysis
- Avoid the use of fluconazole doses of greater than 200 mg daily concomitantly with ruxolitinib

[a] Renal impairment defined as: moderate=CrCl 30-59 mL/min; or severe=CrCl 15-29 mL/min.
bid, twice daily; CBC, complete blood count; CrCl, creatinine clearance; MF, myelofibrosis; qd, once daily.
Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

PV: Recommended Starting Dose

Recommended starting dose for patients with PV who have had an inadequate response to or are intolerant of HU[1]

Standard Starting Dose	10 mg bid

- The starting dose for patients with PV and concomitant use with strong CYP3A4 inhibitors or fluconazole (doses ≤200 mg) is 5 mg bid[1]
- Perform a pretreatment CBC, and monitor CBCs every 2 to 4 weeks until doses are stabilized, then as clinically indicated[1]
- Doses may be titrated based on safety and efficacy[1]
- Most dose adjustments occurred within the first 8 weeks of treatment[2]

PV, polycythemia vera.

1. Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023. 2. Vannucchi AM, et al. N Engl J Med. 2015;372(5):426-435.

General Dose-Modification Guidelines

- Dose adjustments may be necessary due to changes in platelets, hemoglobin, or ANC, or due to renal or hepatic impairment
- Dosing may be decreased or increased based on safety and efficacy
- Interrupt treatment for bleeding requiring intervention regardless of current platelet count
- When discontinuing or interrupting therapy with ruxolitinib for reasons other than thrombocytopenia or neutropenia, consider tapering the dose gradually rather than discontinuing abruptly
- Based on limited clinical data, long-term maintenance at a 5 mg bid dose has not shown responses, and continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks
- Please see the Prescribing Information for detailed guidelines regarding dose titration and restarts based on patients' baseline platelet counts

Consult the US PI for details related to dosing modification

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.

Additional Hematologic Safety Considerations

Hematologic abnormality	Discontinuation rate[a]	Management
Thrombocytopenia	<1%	Manage by reducing the dose or temporarily interrupting ruxolitinib; platelet transfusions may be necessary
Anemia	<1%	Patients may require blood transfusions and/or dose modification of ruxolitinib
Neutropenia	1%[b]	Generally reversible by withholding ruxolitinib until recovery

Perform a pretreatment CBC, and monitor every 2 to 4 weeks until doses are stabilized, then as clinically indicated

[a] Percentages are from both phase 3 studies. [b] Includes patients who had a dose reduction.

Jakafi (ruxolitinib). Prescribing information. Incyte Corporation; January 2023.