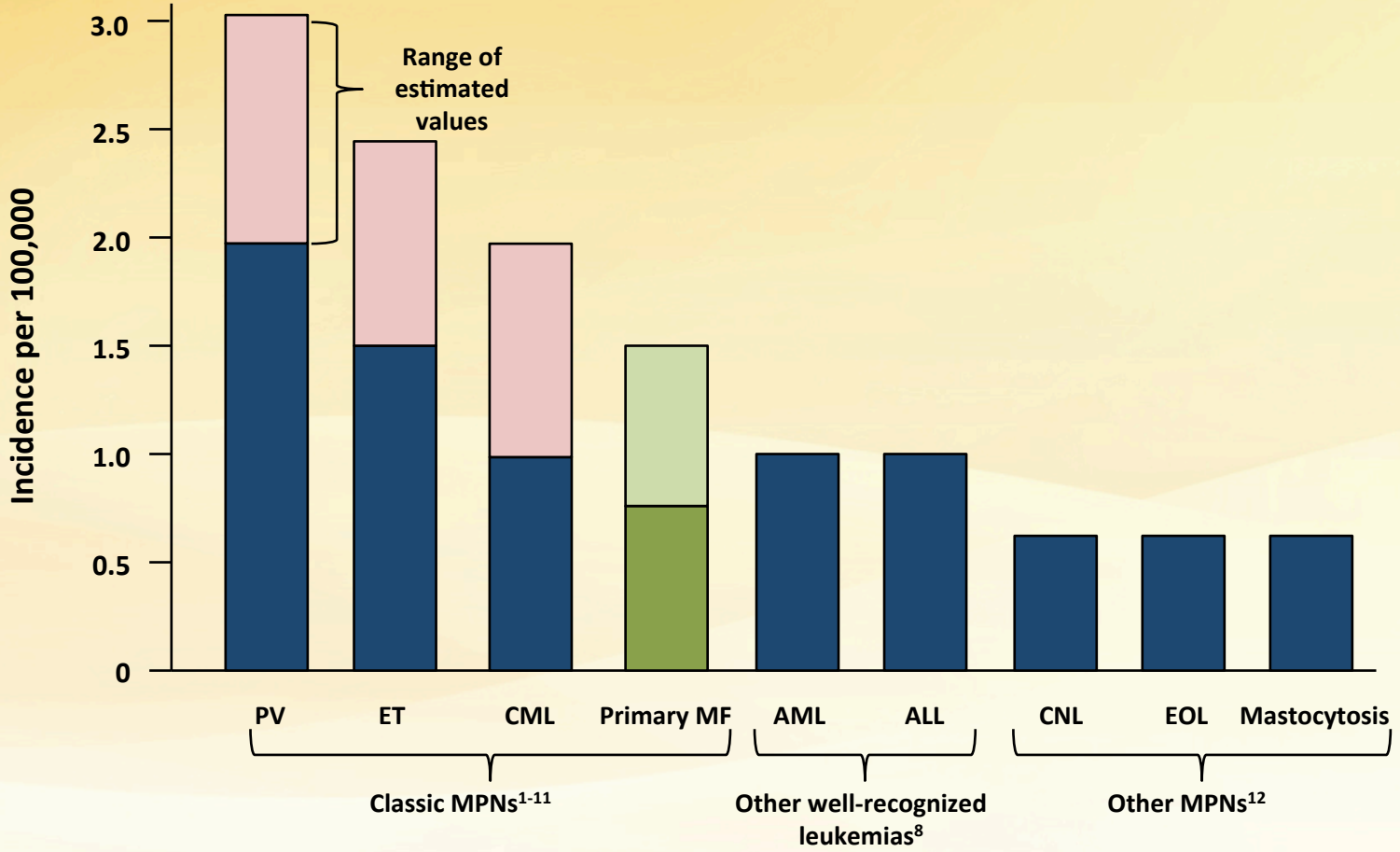
Management of myelofibrosis Updates ASH 2015

Ali Bazarbachi, MD, PhD

American University of Beirut

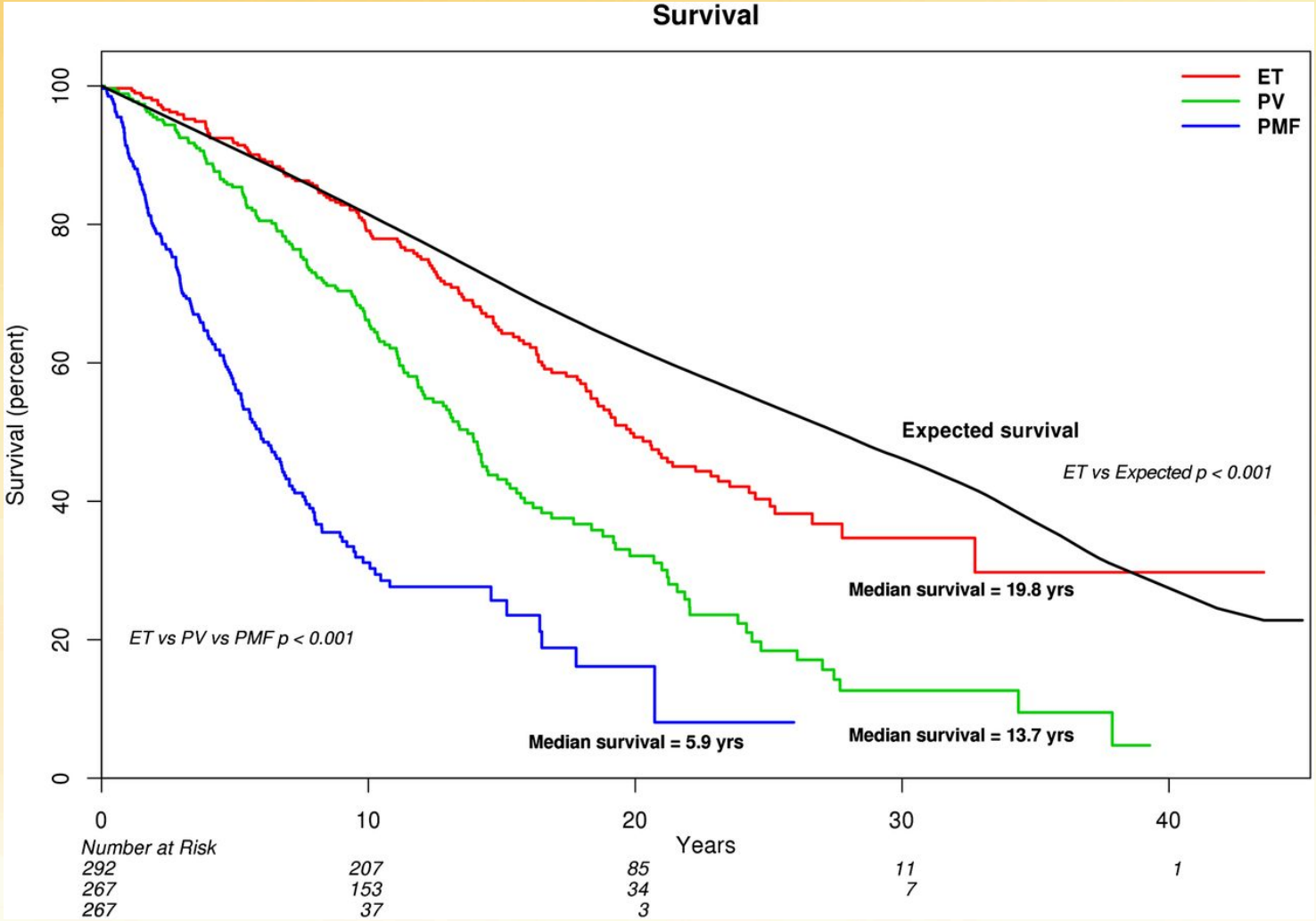
Beirut, Lebanon

The Incidence of MF Is Comparable to That of CML, ALL, and AML



1. Faderl S, et al. Ann Intern Med. 1999;131:207-219; 2. Mesa RA, et al. Am J Hematol. 1999;61:10-15; 3. Girodon F, et al. Haematologica. 2009;94:865-869; 4. Kutti J, Ridell B. Pathol Biol (Paris). 2001;49:164-166; 5. Johansson EH, et al. J Intern Med. 2004; 256:161-165; 6. Hemminki K, et al. Leuk Res. 2009;33:e14-16; 7. Dougan LE, et al. Cancer. 1981:48:866-872; 8. McNally RJ, et al. Hematol Oncol. 1997;15:173-189; 9. Phekoo KJ, et al. Haematologica. 2006;91:1400-1404; 10. Rohrbacher M, et al. Leukemia. 2009;23:602-604; 11. Ania B, et al. Am J Hematol. 1994;47:89-93; 12. Yamamoto J, et al. Cancer Causes Control. 2008;19:379-390.

Comparison of survival in 826 Mayo Clinic patients with ET vs PV vs PMF. Survival in ET was also compared with the age- and sex-matched US population.



Tefferi A et al. Blood 2014;124:2507-2513

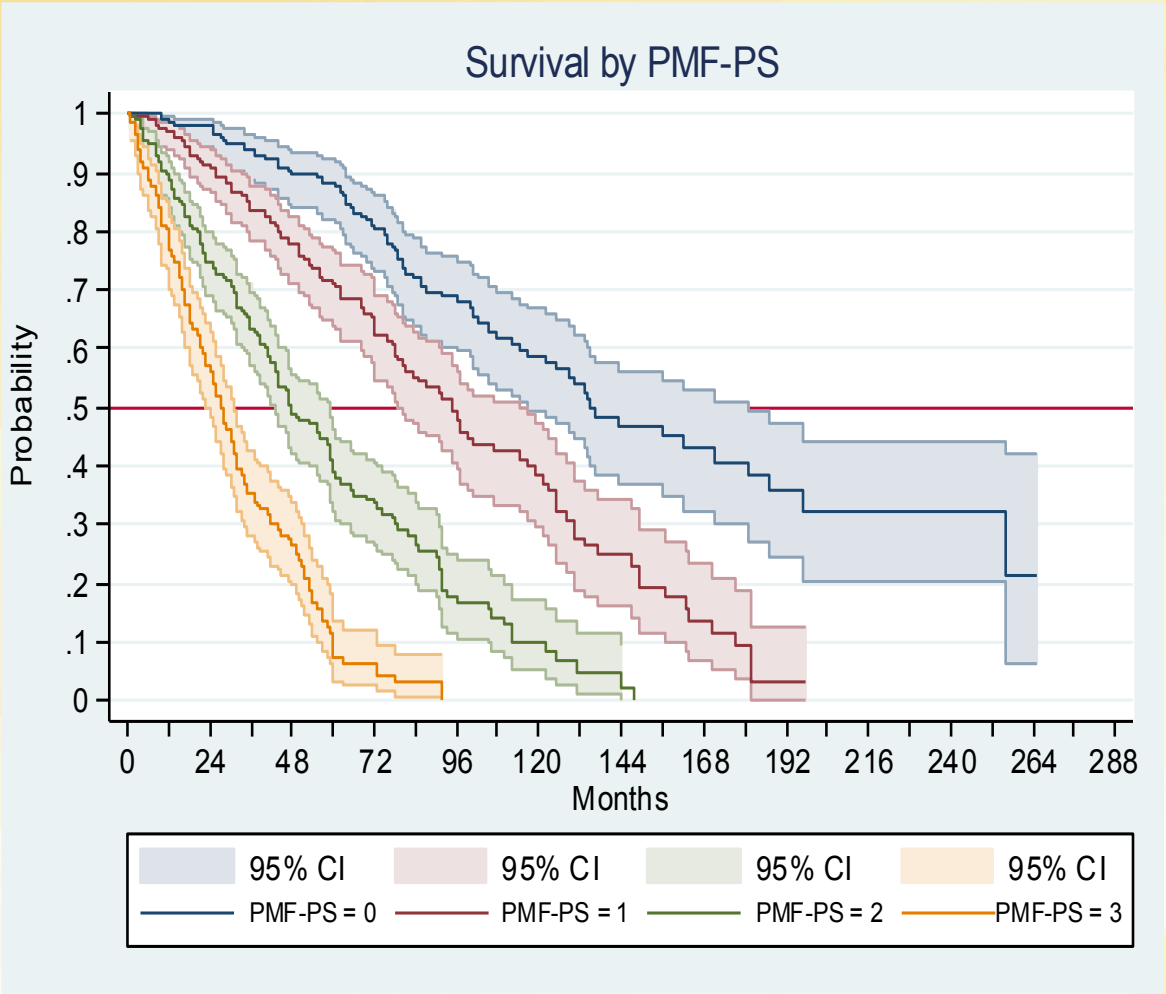
International Prognostic Scoring System (IPSS): Risk classification of PMF at presentation

Prognostic factors

- Age > 65 years
- Constitutional symptoms
- Hb < 10 g/dL
- Leukocytes > 25 x 10^9/L
- Blood blasts ≥ 1%

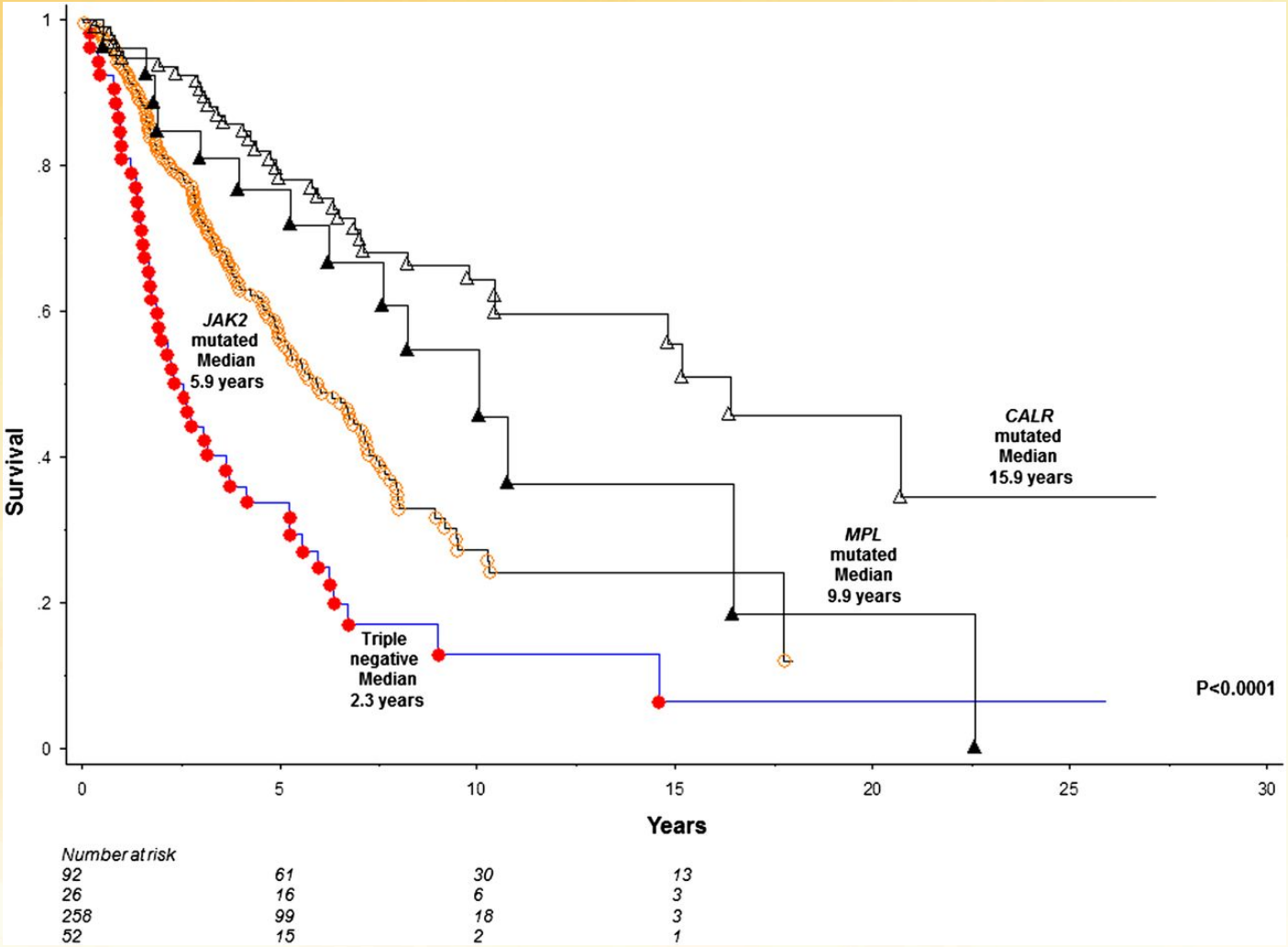
Risk groups

• Low	0
• Intermediate-1	1
• Intermediate-2	2
• High	≥ 3



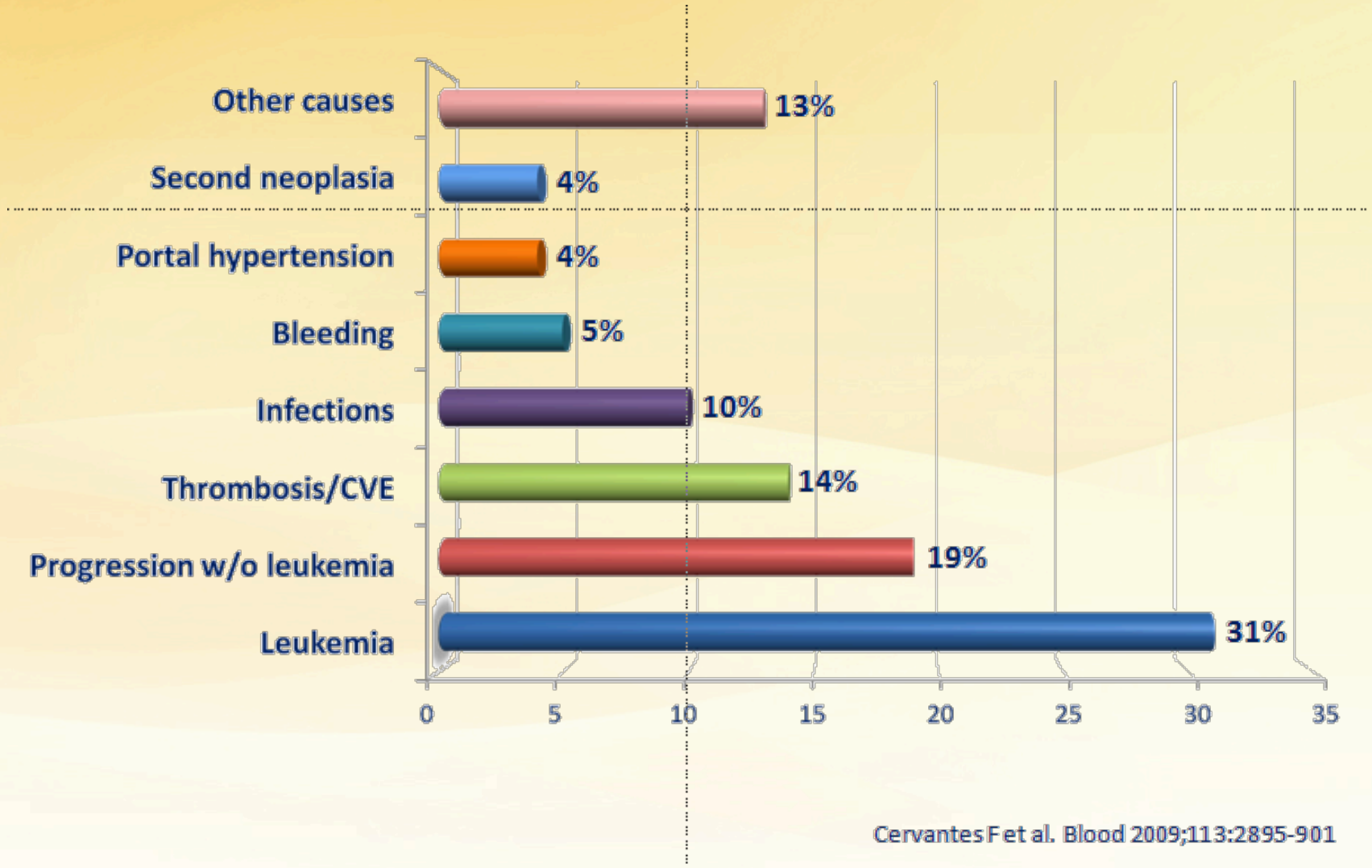
Cervantes et al., Blood 2009;113:2895-2901

Comparison of survival among 428 patients with PMF stratified by their mutational status.



Tefferi A et al. Blood 2014;124:2507-2513

Causes of Death in MF



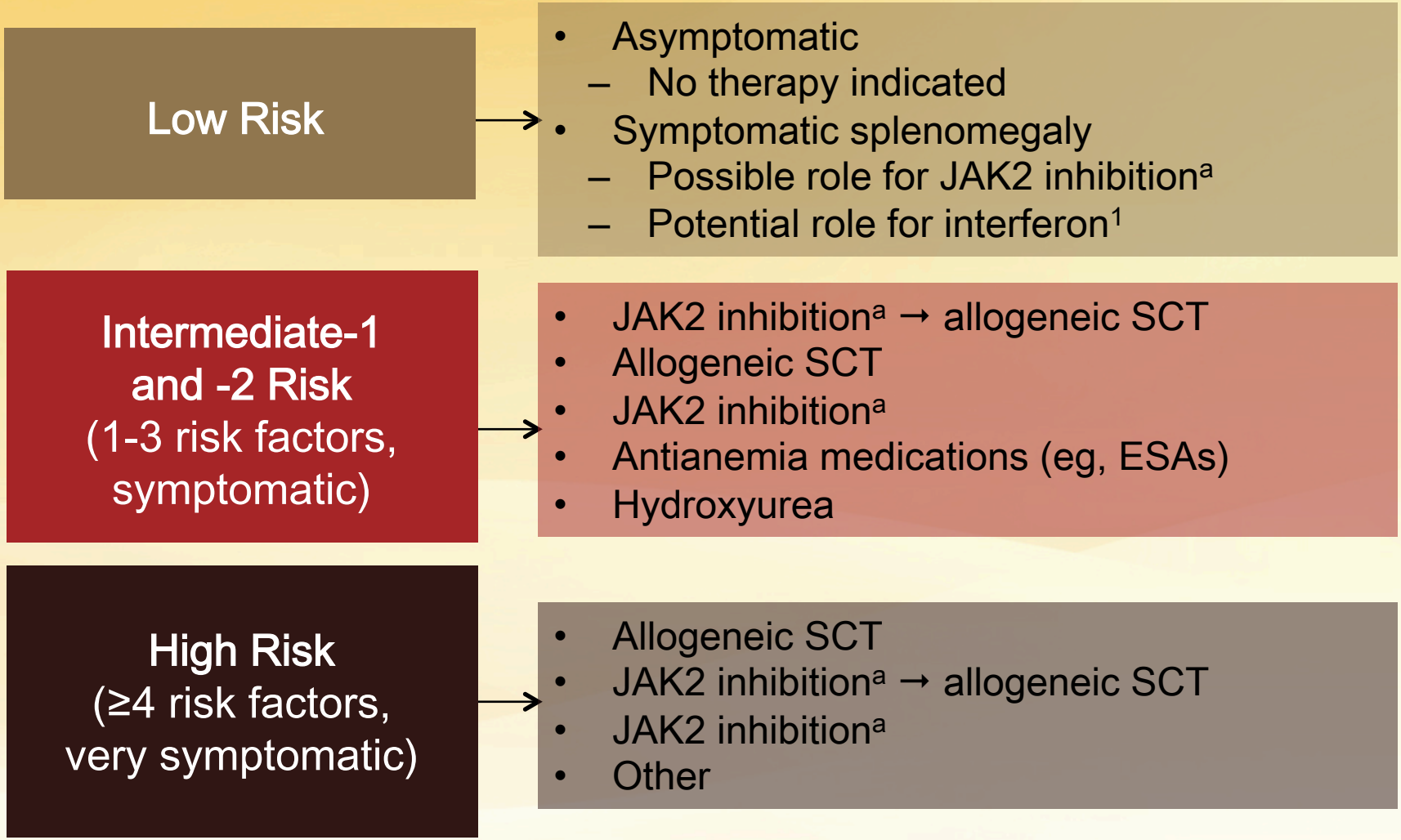
Cervantes F et al. Blood 2009;113:2895-901

Goals of therapy in PMF

- Cure if possible, which means allogeneic stem cell transplantation when indicated
- Treat anemia and other cytopenias when indicated
- Reduce symptomatic splenomegaly
- Reduce constitutional symptoms (weight loss, night sweats, fever, pruritus)
- Avoid first occurrence or recurrence of thrombotic and bleeding complications
- Manage risk situations (e.g. surgery)
- Minimize the risk of acute leukemia

Nordic guidelines on the diagnosis and treatment of patients with Myeloproliferative Neoplasms. www.nmpn.org

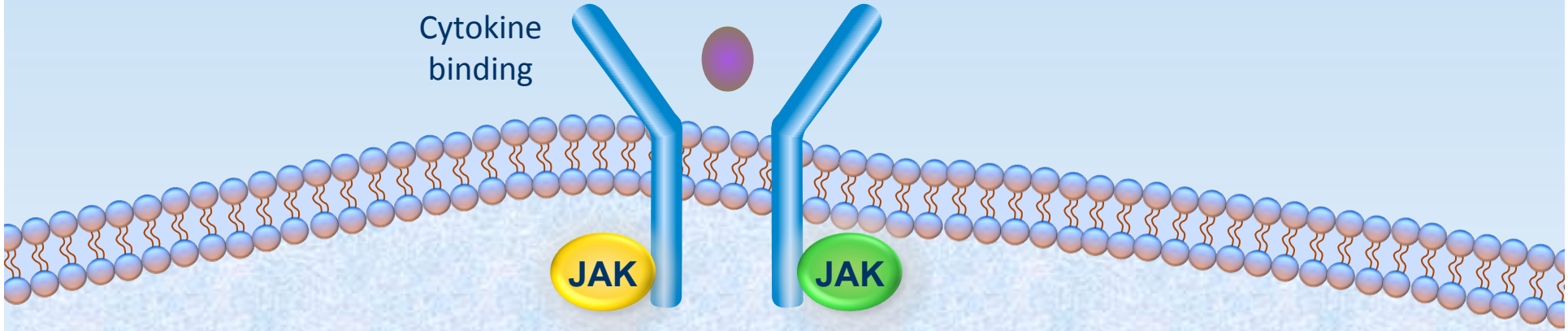
Suggested Risk Adapted Model for MF Management



ESAs: erythropoiesis-stimulating agents.

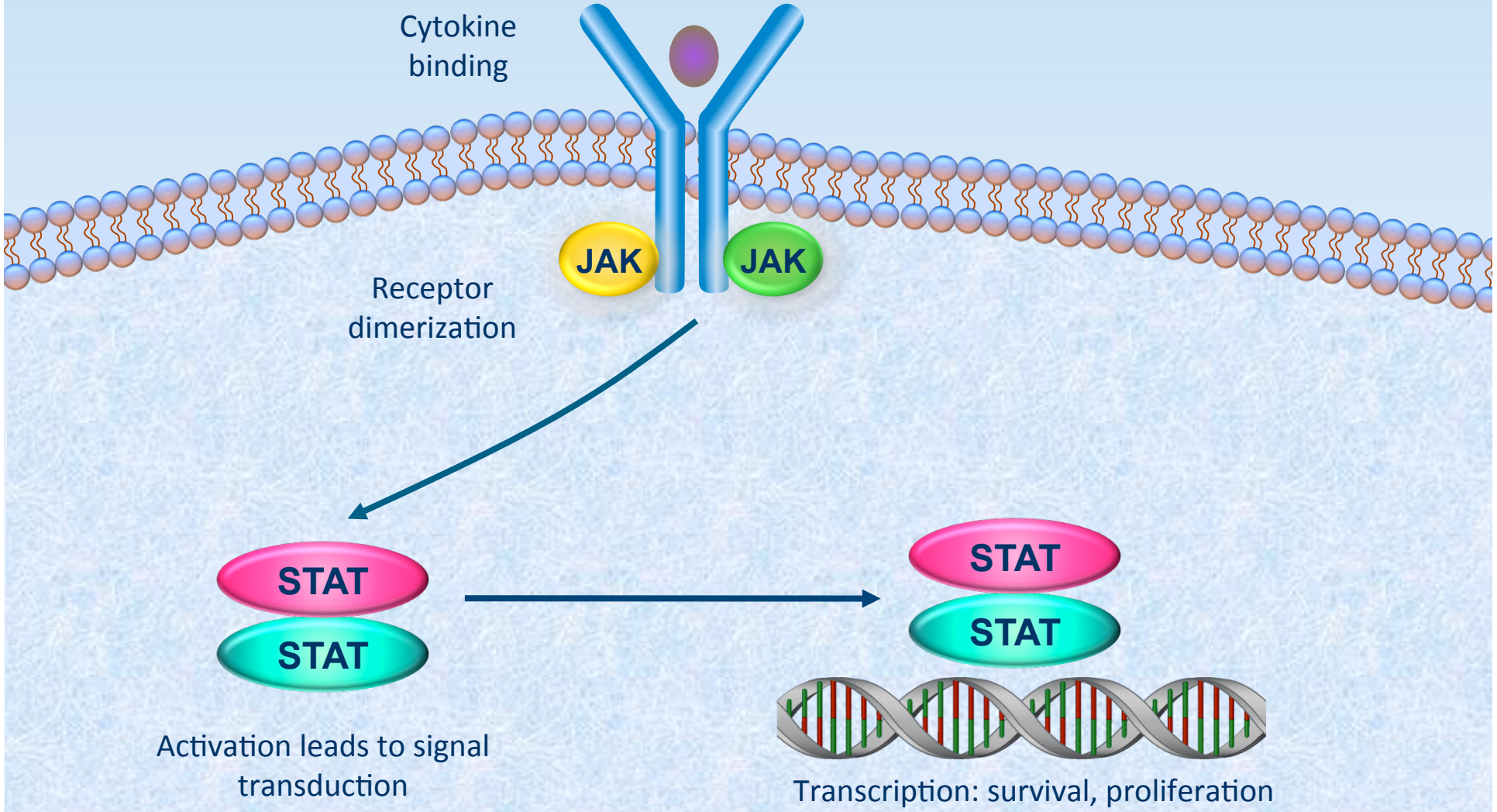
1. Silver R et al. *Blood*. 2011;117:6669-72.

Normal JAK/STAT Signaling Regulates Vital Cell Functions



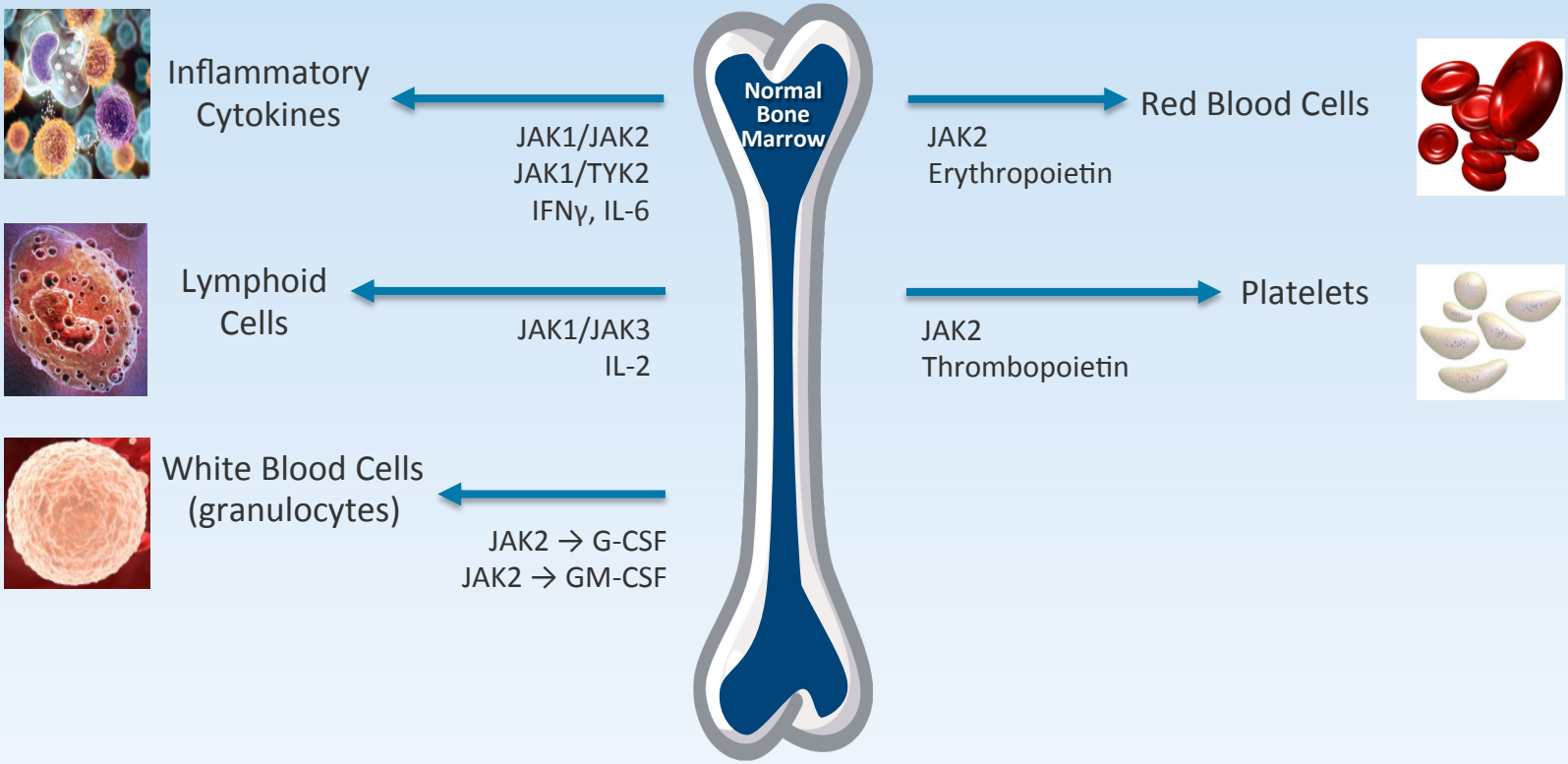
1. Vainchenker W, et al. *Semin Cell Dev Biol.* 2008;19:385-393; 2. Ghoreschi K, et al. *Immunol Rev*. 2009;228:273-287.

Normal JAK/STAT Signaling Regulates Vital Cell Functions



1. Vainchenker W, et al. *Semin Cell Dev Biol.* 2008;19:385-393; 2. Ghoreschi K, et al. *Immunol Rev*. 2009;228:273-287.

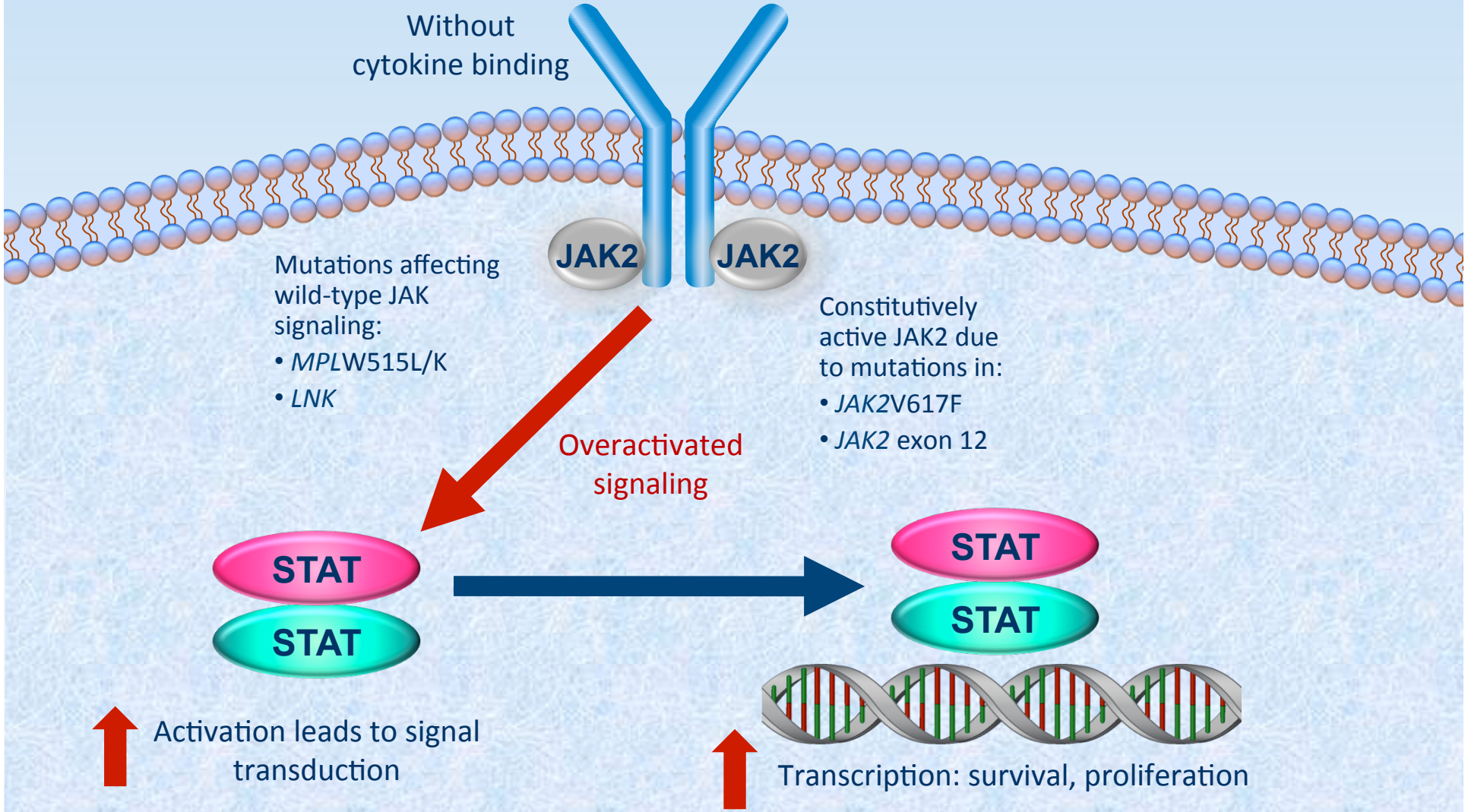
JAK (Janus Kinase) Is a Key Component of Hematopoietic Signaling



- The JAK family of nonreceptor tyrosine kinases has 4 members
  - JAK1, JAK2, and Tyk2 are ubiquitously expressed
  - JAK3 is expressed primarily in hematopoietic cells

1. Verma A, et al. *Cancer Metast* Rev. 2003;22:423-434; 2. Ghoreschi K, et al. *Immunol Rev*. 2009;228(1):273-287; 3. Vainchenker W, et al. *Semin Cell Dev Biol.* 2008;19:385-393.

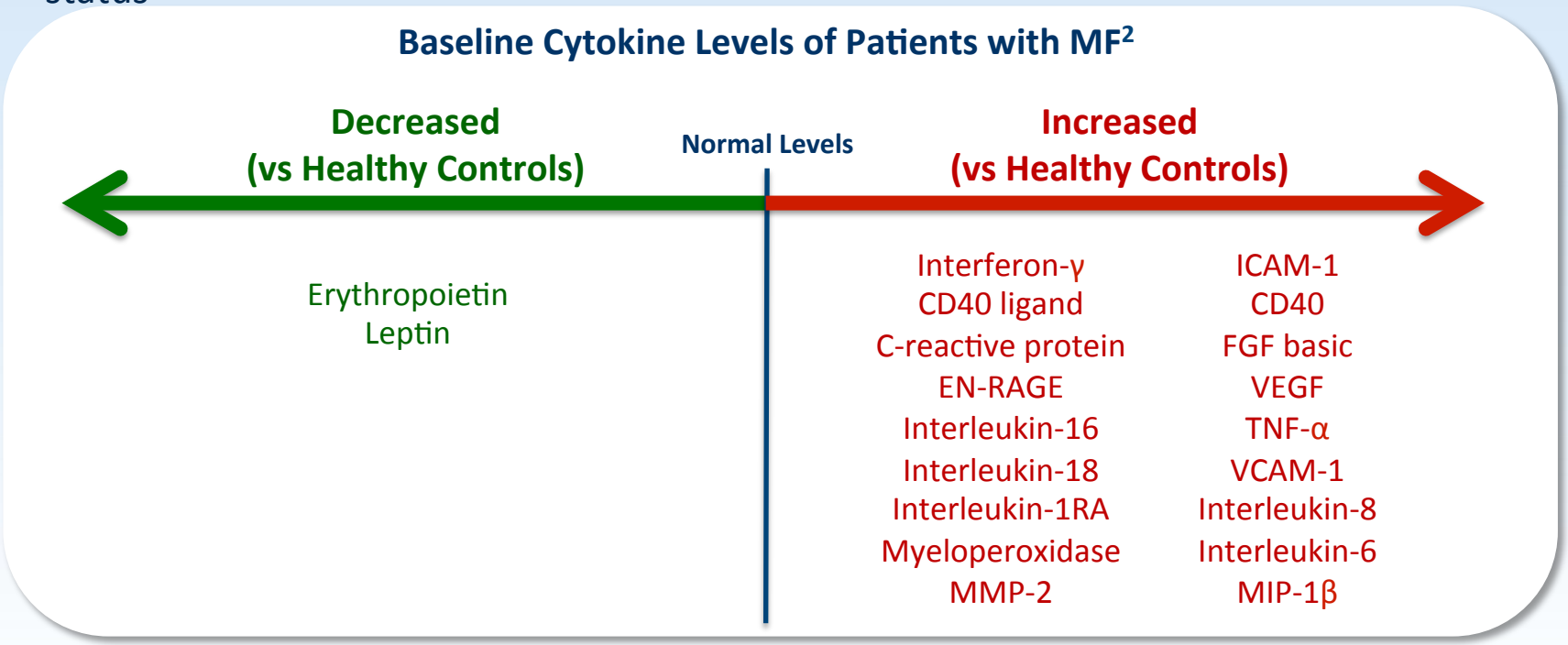
Dysregulated JAK2 Signaling Is Characteristic of MF



1. Vainchenker W, et al. *Semin Cell Dev Biol.* 2008;19:385-393; 2. Ghoreschi K, et al. *Immunol Rev*. 2009;228:273-287.

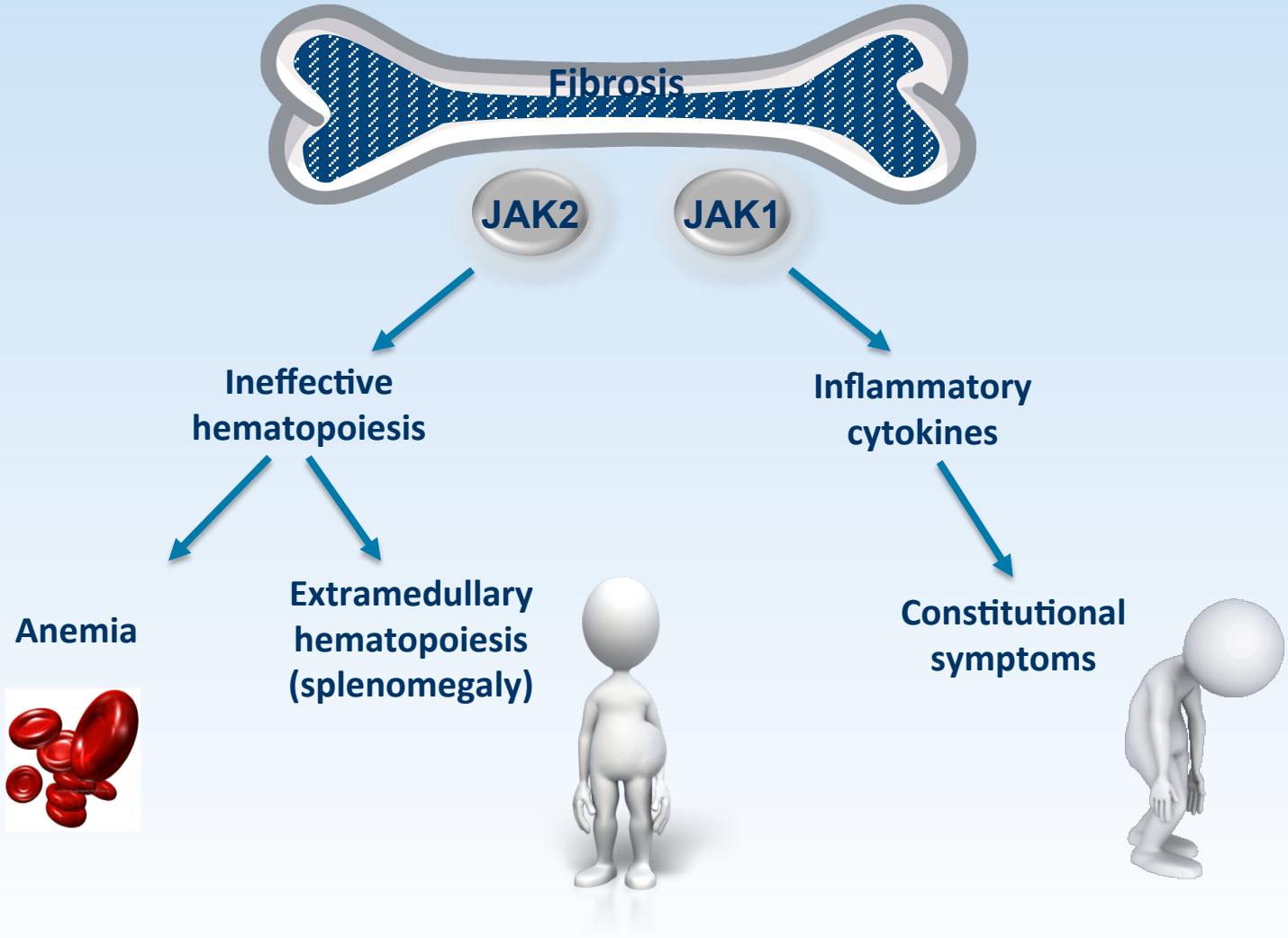
Increased Levels of Inflammatory Cytokines and JAK1 Activation Are Common in MF

- In patients with MF, abnormal levels of circulating cytokines are commonly detected[1,2]
- Many proinflammatory cytokines signal via **JAK1**-dependent cytokine receptors[2]
- Increased cytokines and **JAK1** activation are independent of *JAK2V617F* mutation status[2]



1. Quintás-Cardama A, et al. *Blood*. 2010;115:3109-3117; 2. Verstovsek S, et al. *N Engl J Med*. 2010;363:1117-1127.

Abnormal JAK1 and JAK2 Signaling Lead to Clinical Manifestations of MF



1. Verma A, et al. *Cancer Metast Rev.* 2003;22:423-434; 2. Tefferi A, et al. *Am J Hematol*. 2011;86:1018-1026.

Dysregulation of the JAK Pathway Is Present in All MF Patients

- **No single hallmark mutation has been identified**[1]
- Numerous recurrent somatic mutations have been found in MF[1,2]
- Multiple mutations may coexist within a single patient[2]
- At the time of its discovery, *JAK2*V617F was hypothesized to be a disease marker of MF (analogous to *BCR-ABL* in CML), but this did not turn out to be the case[2]

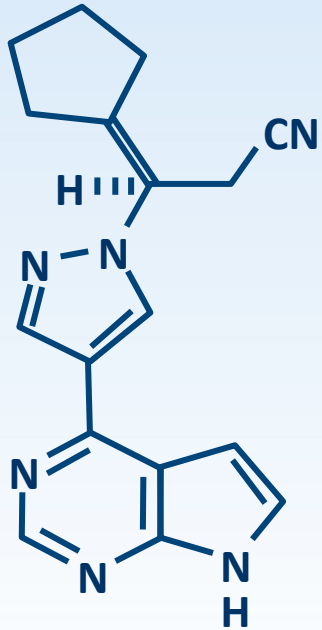
Mutation[3]	Proportion of MF Patients
JAK pathway-related	
*JAK2*V617F	60%
JAK2 exon 12	Rare
*MPL*W515L/K (TpoR)	5% to 10%
CBL	5% to 10%
SH2B3 (LNK)	3% to 6%

1. Abdel-Wahab O. *Curr Opin Hematol.* 2011;18:117-123; 2. Levine RL, et al. *Nat Rev Cancer.* 2007;7(9):673-683; 3. Cross NCP. *Hematology Am Soc Hematol Educ Program*. 2011;2011:208-214.

Ruxolitinib* Is the First Targeted Therapy for MF

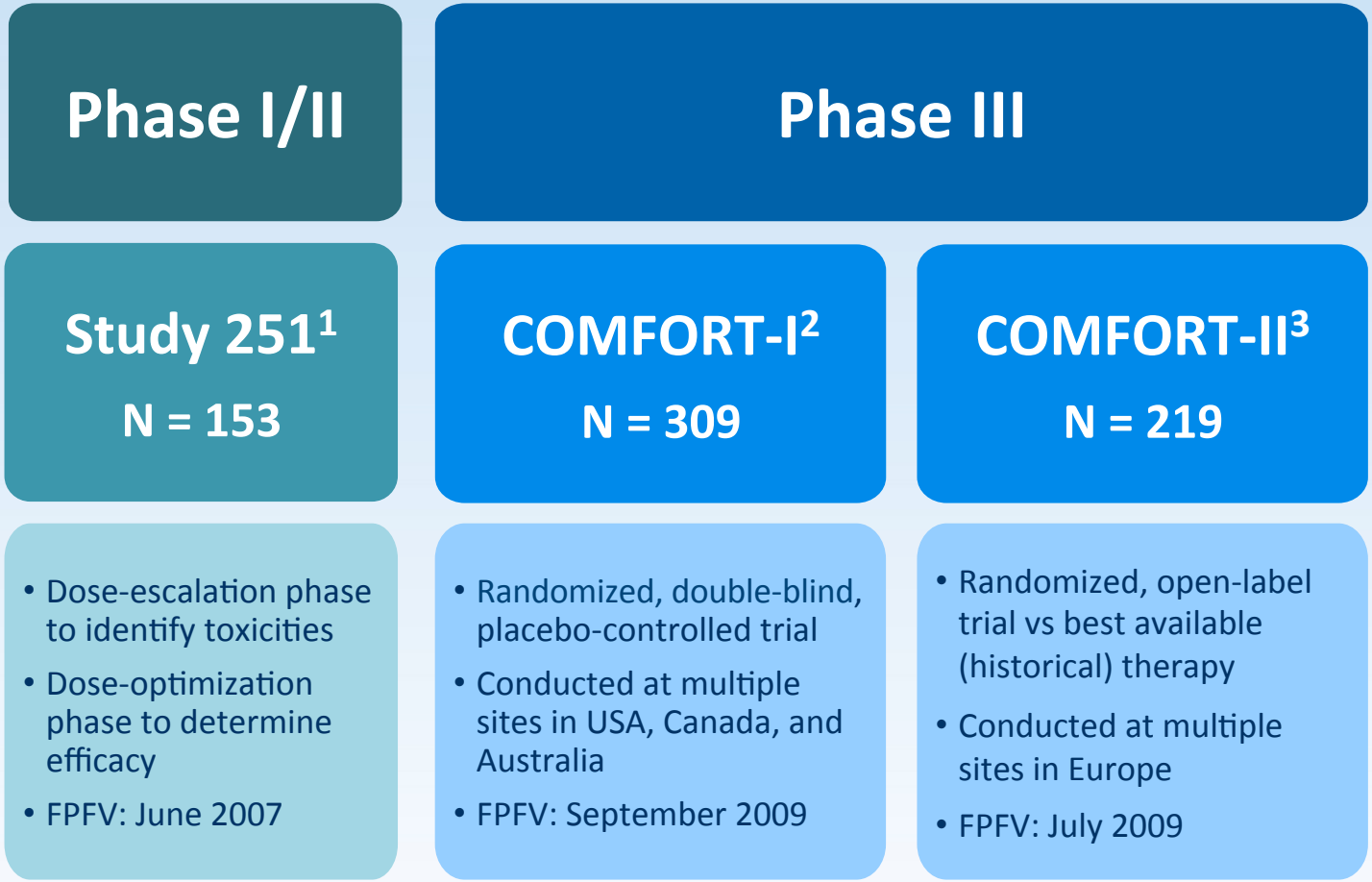
- A potent, selective JAK1 and JAK2 inhibitor[1]
  - More than 100-fold selectivity against a broad panel of kinases, for minimal off-target effects[1]
- Addresses key dysregulated JAK signaling pathways[1]
  - JAK1 overactivity increases cytokines and MF symptoms[1,2]
  - JAK2 overactivity affects hematopoiesis, splenomegaly, and symptoms[1,2]

Enzyme[1]	Ruxolitinib IC_{50} Mean ± SD (nM), at 1 mM ATP
JAK1	3.3 ± 1.2
JAK2	2.8 ± 1.2
JAK3	428 ± 243
TYK2	19 ± 3.2



1. Quintás-Cardama A, et al. *Blood*. 2010;115(15):3109-3117; 2. Vainchenker W, et al. *Semin Cell Dev Biol.* 2008;19(4):385-393; 3. JAKAVI, Summary of Product Characteristics.

Ruxolitinib Clinical Trial Program in MF



FPFV, First Patient First Visit

1. Verstovsek S, et al. *N Engl J Med*. 2010;363(12):1117-1127; 2. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807; 3. Harrison CN, et al. *N Engl J Med*. 2012;366:787-798.

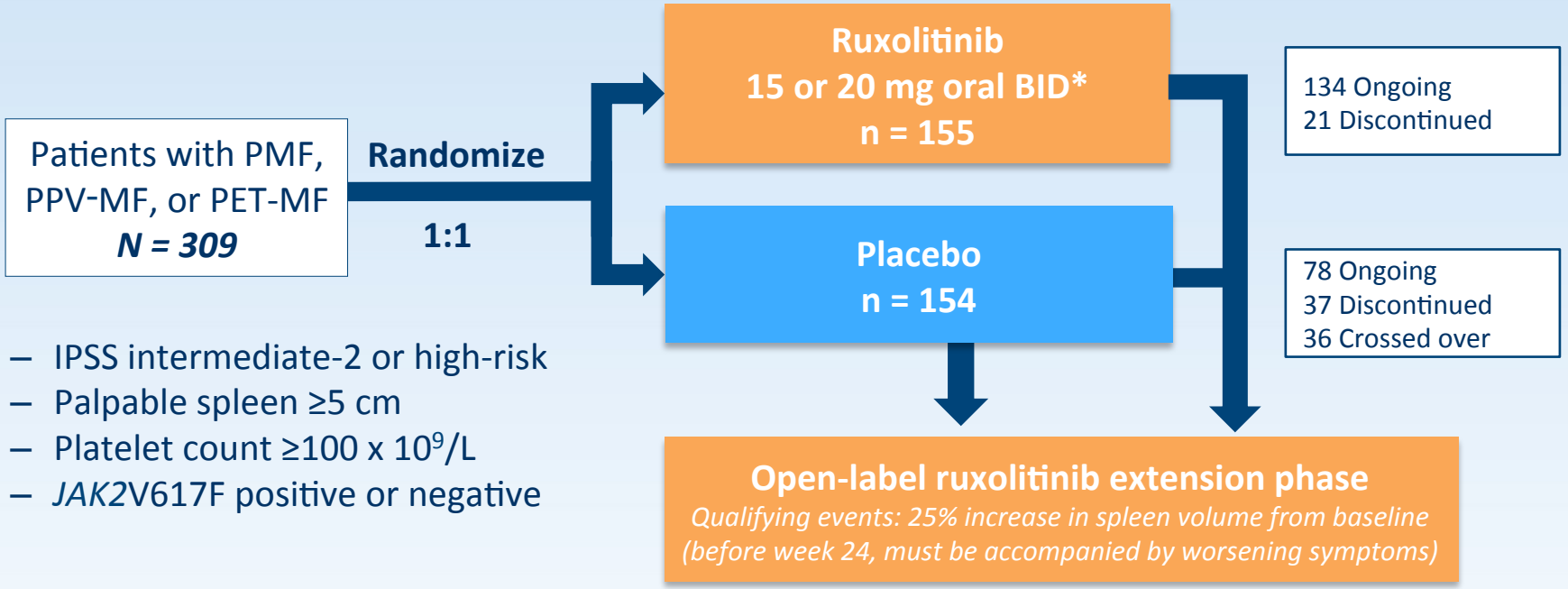
Rationale for Phase III COMFORT Studies

- Based on phase I/II findings, ruxolitinib was determined to have clinical benefit warranting further exploration
- 15 or 20 mg BID (based on platelet count) provides an optimal starting dose for safety and efficacy
  - Favorable safety profile
  - Rapid and sustainable reduction of splenomegaly
  - Significant improvement in symptoms and QoL
  - Overall survival benefit when compared with historical controls
- 35% reduction in volume (assessed by MRI) reliably correlates to 50% reduction in palpable spleen length
  - MRI may be used as a more precise and reliable measurement of spleen response than the typical clinical practice of palpation

Verstovsek S, et al. *N Engl J Med*. 2010;363(12):1117-1127.

COMFORT-I Trial Design

- COMFORT: **CO**ntrolled **M**yelo**F**ibrosis study with **OR**al JAK inhibitor **T**reatment
- Randomized, double-blind, multicenter phase III study conducted in USA, Canada, and Australia



- IPSS intermediate-2 or high-risk
- Palpable spleen ≥5 cm
- Platelet count ≥100 x 10^9/L
- *JAK2*V617F positive or negative

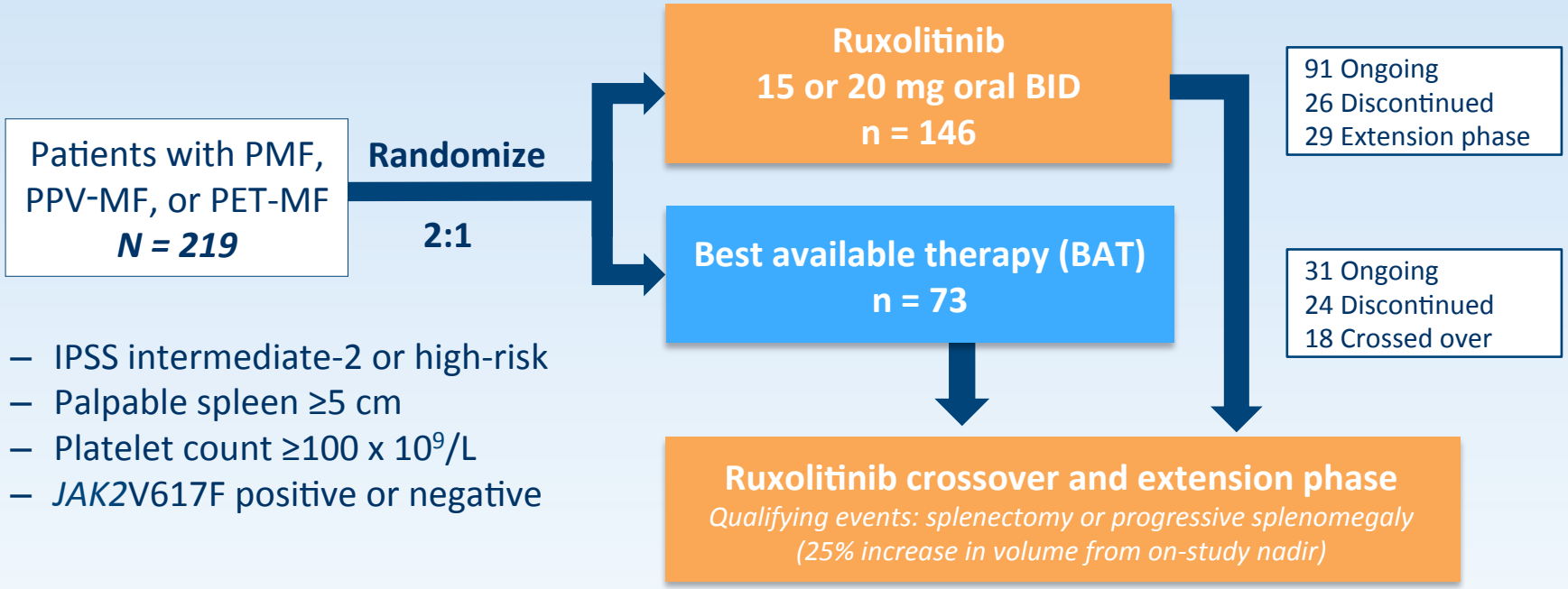
- Primary endpoint: ≥35% reduction of spleen volume from baseline to week 24
- Secondary endpoints: Symptom score, overall survival, duration of spleen response, QoL

*3 patients not evaluable for safety – included in ITT analysis of efficacy.
IPSS, International Prognostic Scoring System

1. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807; 2. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807 (supplemental appendix).

COMFORT-II Trial Design

- COMFORT: **CO**ntrolled **M**yelo**F**ibrosis study with **OR**al JAK inhibitor **T**reatment
- Randomized, open-label, multicenter phase III study conducted in Europe



- IPSS intermediate-2 or high-risk
- Palpable spleen ≥5 cm
- Platelet count ≥100 x 10^9/L
- *JAK2*V617F positive or negative

- Primary endpoint: ≥35% reduction of spleen volume from baseline to week 48
- Secondary endpoints: Spleen response at week 24, duration of spleen response
- Exploratory endpoint: QoL

*Best available therapy as selected by investigator, including possibility of combination therapy, no therapy, or changing therapy over the course of the trial.

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

Treatments on BAT Arm

Standardized treatment name	BAT, n = 73 No. (%)
Any BAT medication*	**49 (67.1)**
No BAT medication	**24 (32.9)**
Other antineoplastic agents	37 (50.7)
Hydroxyurea	34 (46.6)
Anagrelide	4 (5.4)
Glucocorticoids	12 (16.4)
Prednisone/prednisolone	9 (12.3)
Methylprednisolone	3 (4.1)
Other anti-anemia preparations	5 (6.8)
Epoetin-alpha	5 (6.8)
Other immunomodulatory agents	5 (6.8)
Thalidomide	3 (4.1)
Lenalidomide	2 (2.7)

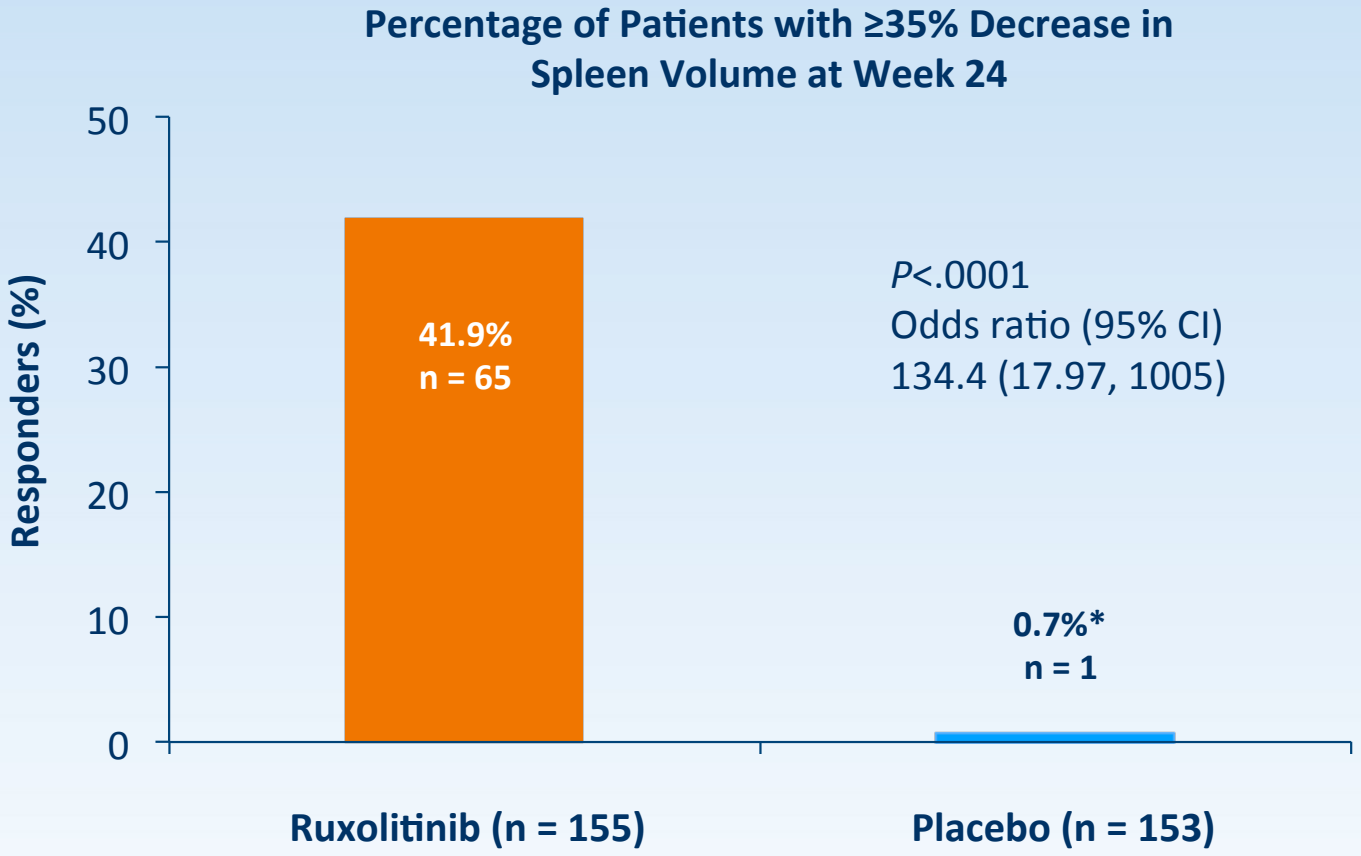
Standardized treatment name	BAT, n = 73 No. (%)
Purine analogs	4 (5.5)
Mercaptopurine	3 (4.1)
Thioguanine	1 (1.4)
Antigonadotropins and similar agents	3 (4.1)
Danazol	3 (4.1)
Interferons	3 (4.1)
PEG-interferon-alpha-2a	2 (2.7)
Interferon-alpha	1 (1.4)
Nitrogen mustard analogs	2 (2.7)
Melphalan	2 (2.7)
Pyrimidine analogs	2 (2.7)
Cytarabine	2 (2.7)

*Patients may have received more than one treatment as BAT.

Harrison CN, et al. *N Engl J Med.* 2012;366:787-798 (supplemental appendix).

COMFORT-I

Ruxolitinib Significantly Decreased Spleen Volume From Baseline to Week 24

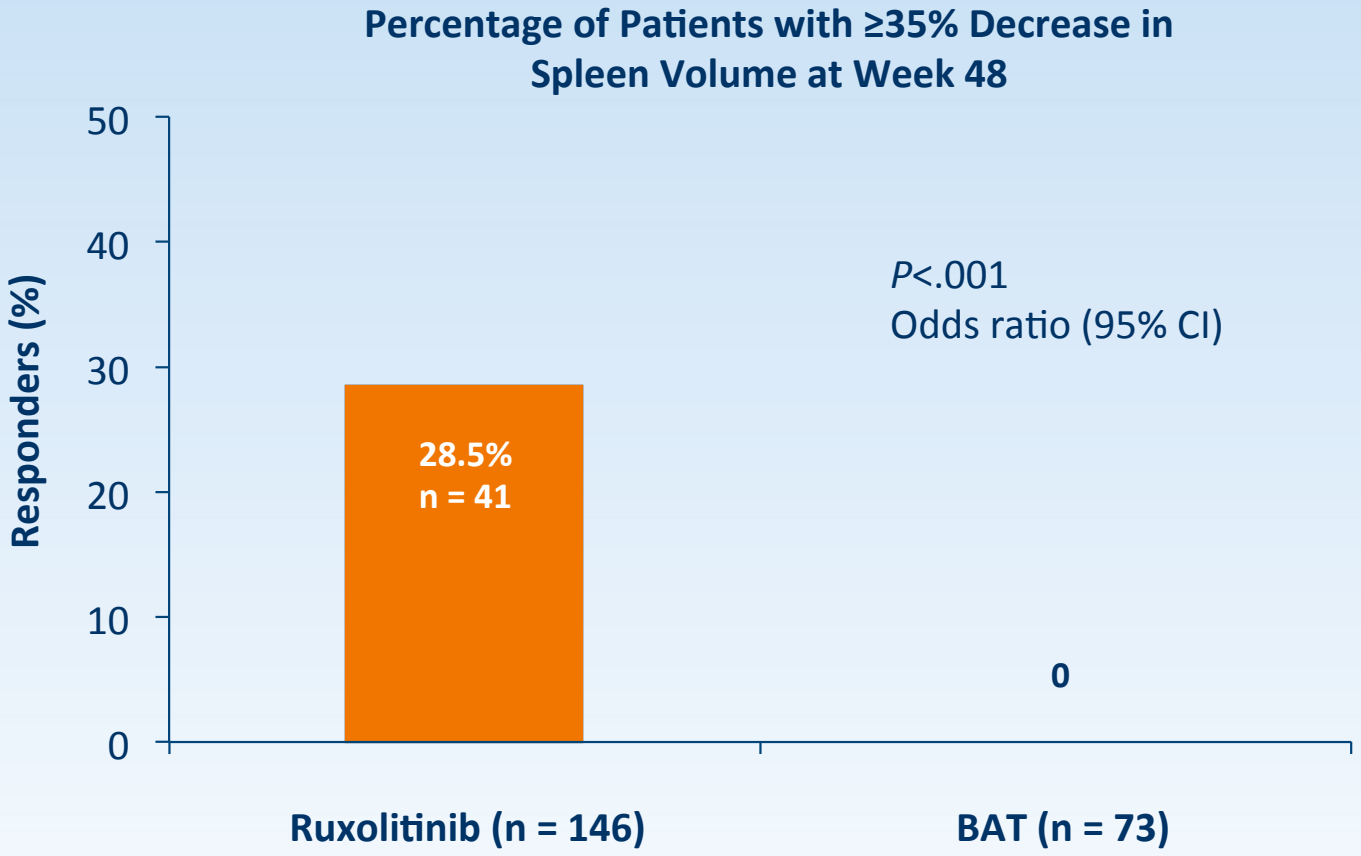


- Median spleen reduction was 33.0% in the ruxolitinib arm vs median 8.5% increase in spleen volume in the placebo arm

*Response was due to a splenic infarction which led to death.
Patients who discontinued prior to week 24 or crossed over prior to week 24 were counted as nonresponders.
Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807.

COMFORT-II

Ruxolitinib Significantly Decreased Spleen Volume From Baseline to Week 48

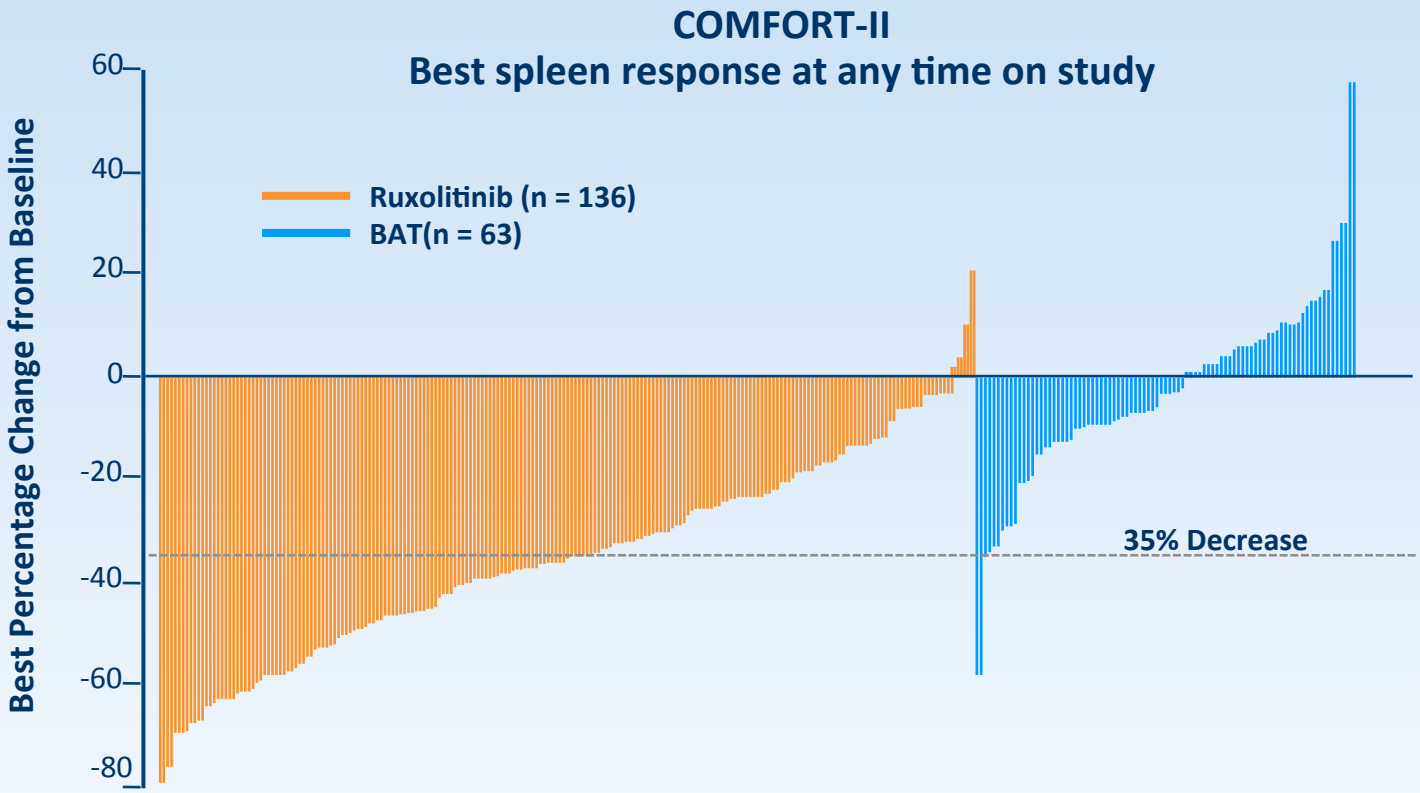


- Median time to response, 12.29 weeks
- Of the 69 patients who achieved ≥35% reduction in spleen volume at any time during the study, 44 (64%) did so at the first assessment (at 12 weeks)

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

COMFORT-II

97% of Ruxolitinib-Treated Patients Experienced Spleen Reduction

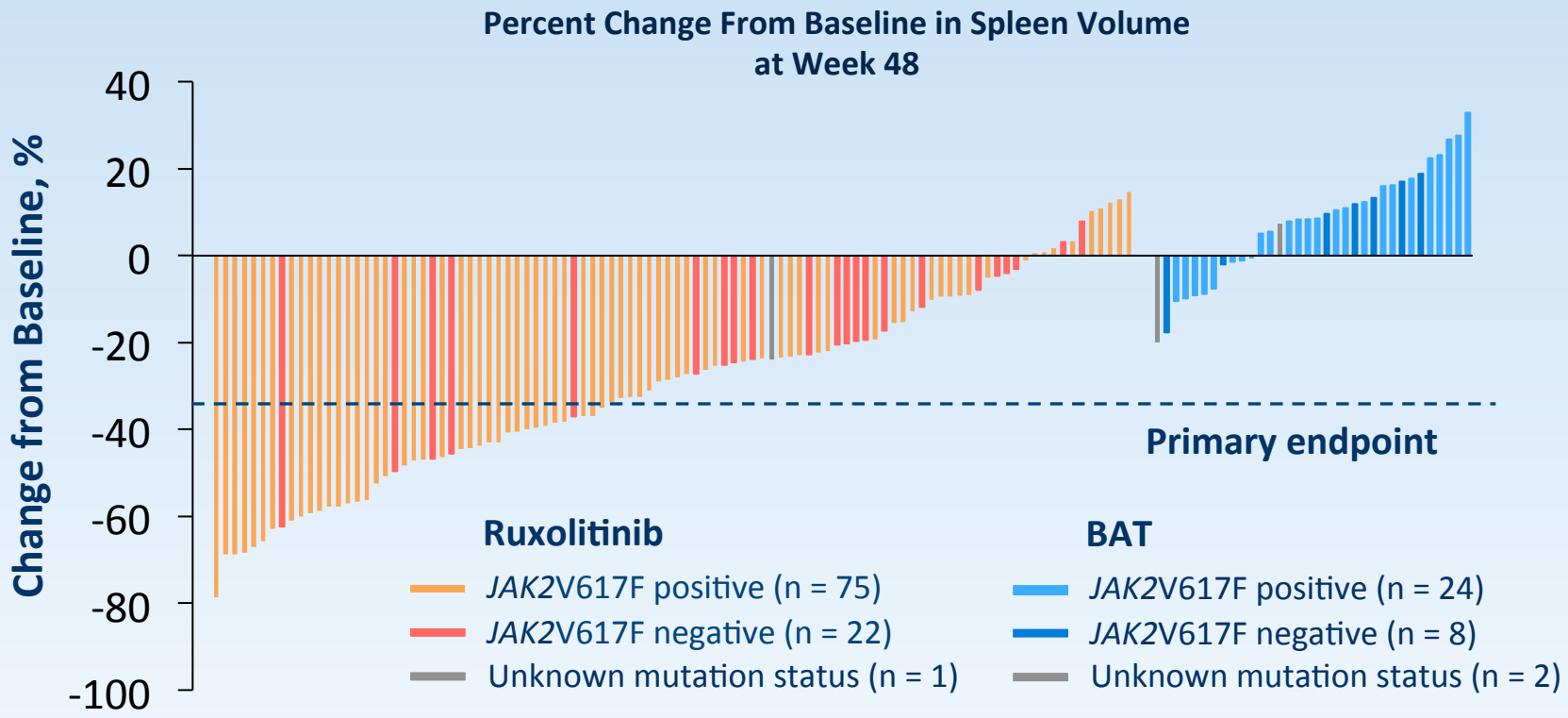


	Ruxolitinib	BAT
↓ Spleen volume	132 (97%)	35 (56%)
↑ Spleen volume	4 (3%)	28 (44%)

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

COMFORT-II

Vast Majority of Patients Receiving Ruxolitinib Experienced Spleen Reduction, Regardless of *JAK2*V617F Mutation Status

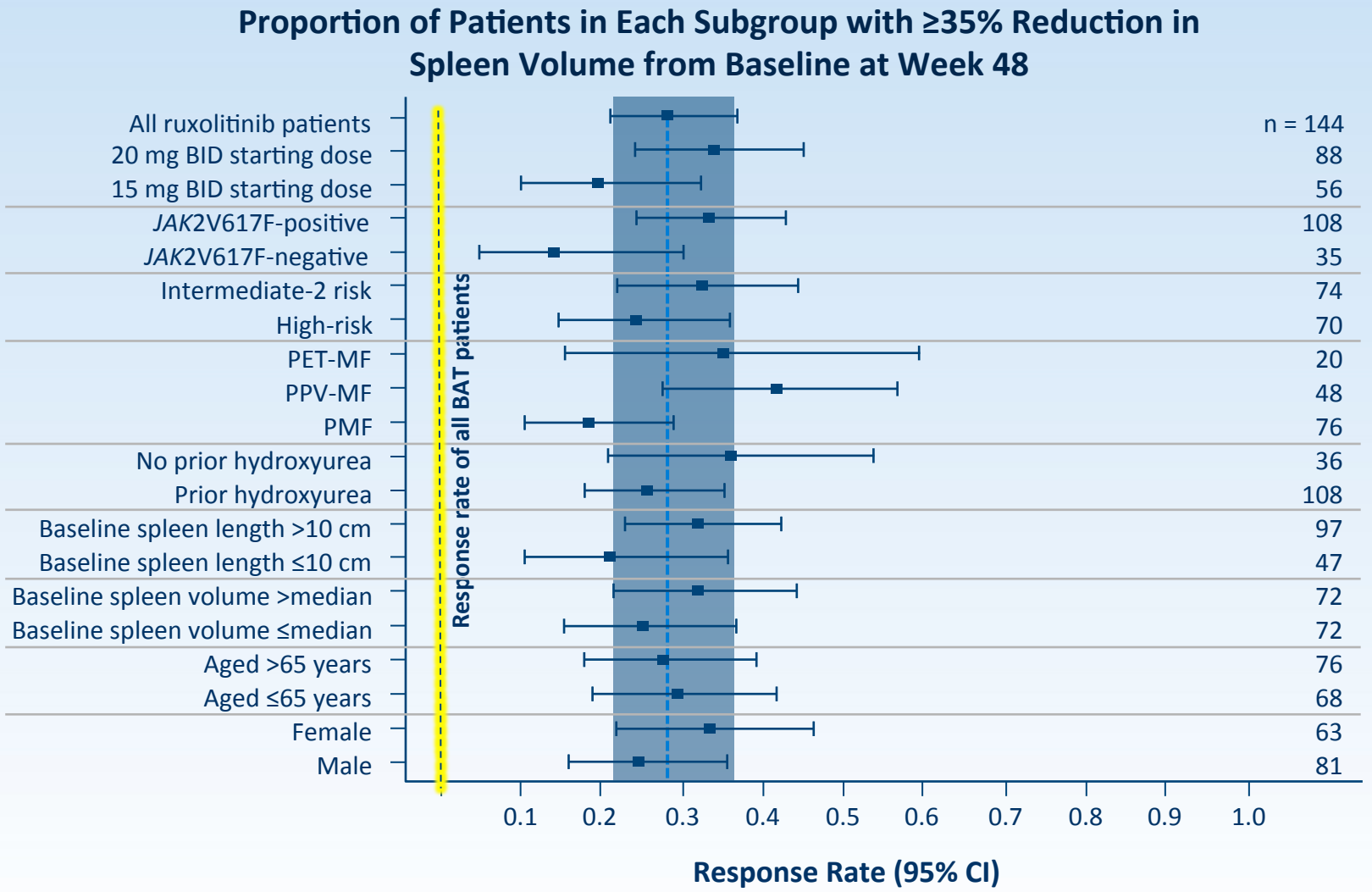


- At week 48, most patients receiving ruxolitinib experienced spleen volume reductions, including *JAK2*V617F-positive (88% [66/75]) and *JAK2*V617F-negative (91% [20/22]) patients

Harrison CN, et al. Oral presentation at ASH Annual Meeting; December 10-13, 2011. Abstract 279.

COMFORT-II

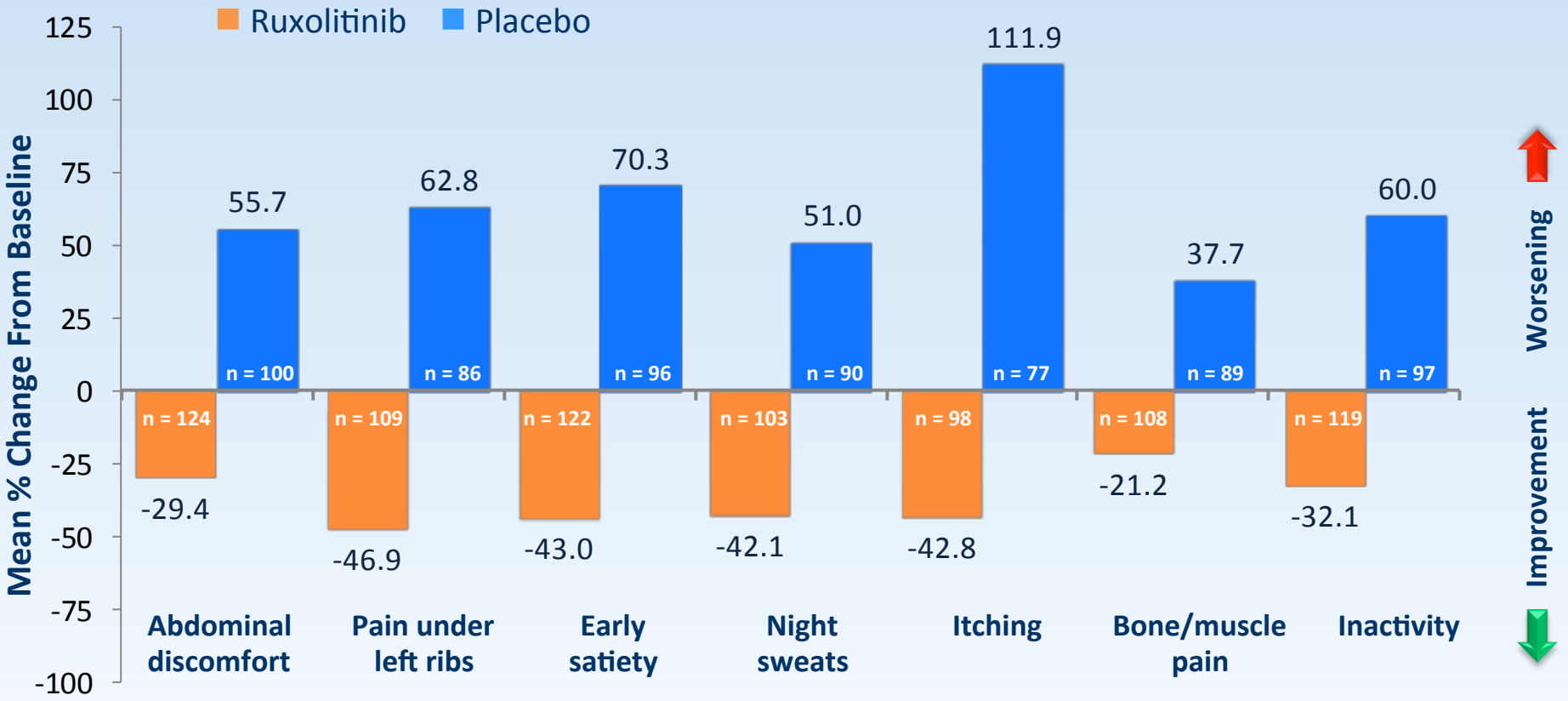
All Patient Subgroups Exhibited Significant Rates of Response to Ruxolitinib Treatment



Harrison CN, et al. Oral presentation at ASH Annual Meeting; December 10-13, 2011. Abstract 279.

COMFORT-I

All Individual Symptoms Assessed Were Significantly Improved by Ruxolitinib Treatment



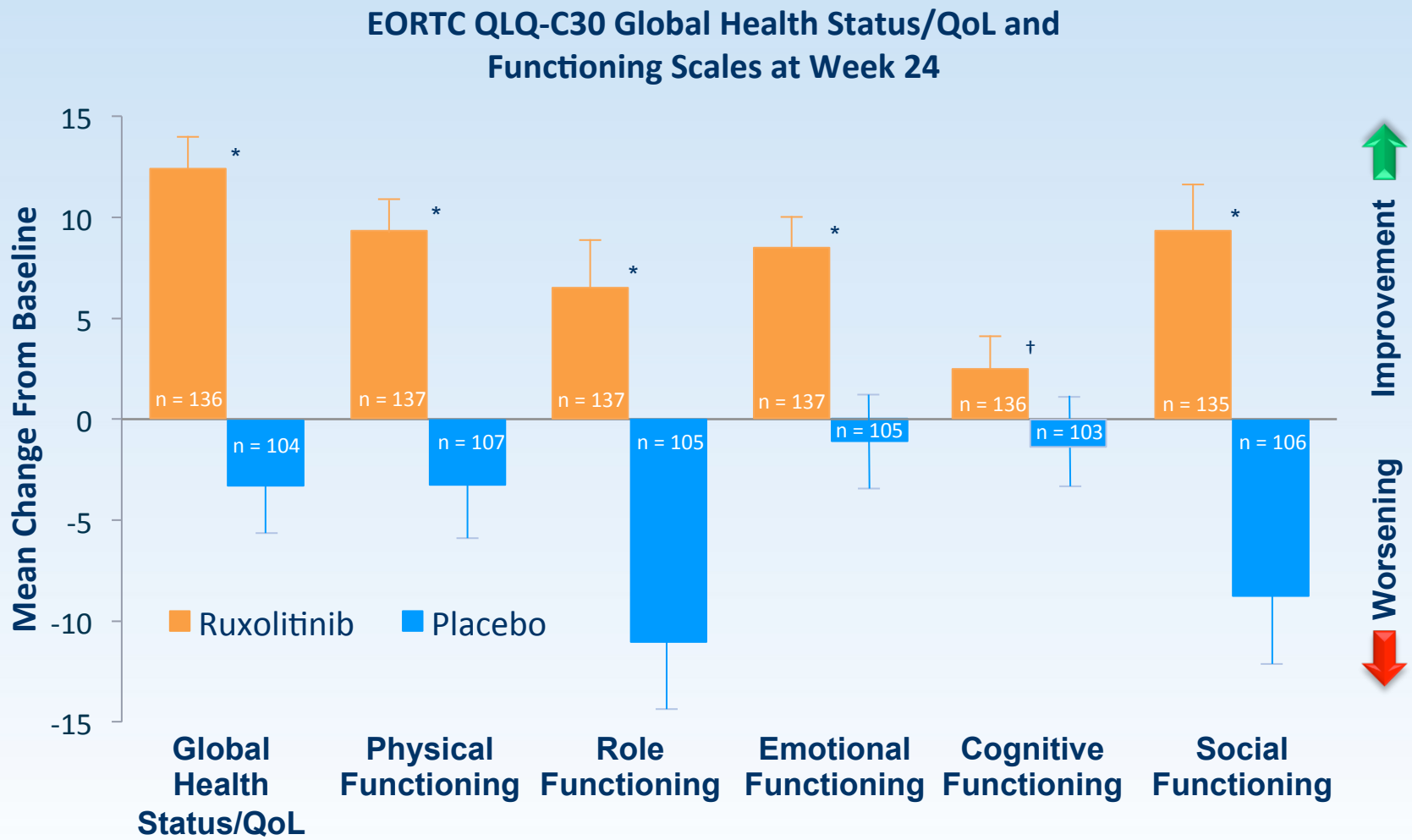
- For all individual symptoms above, comparisons between ruxolitinib- and placebo-treated groups were highly statistically significant (*P*<.01)

*As measured by the Myelofibrosis Symptom Assessment Form (MFSAF) on a scale of 0 to 10.

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

COMFORT-I

Global Health Status and Functioning Scales Were Significantly Improved by Ruxolitinib Treatment

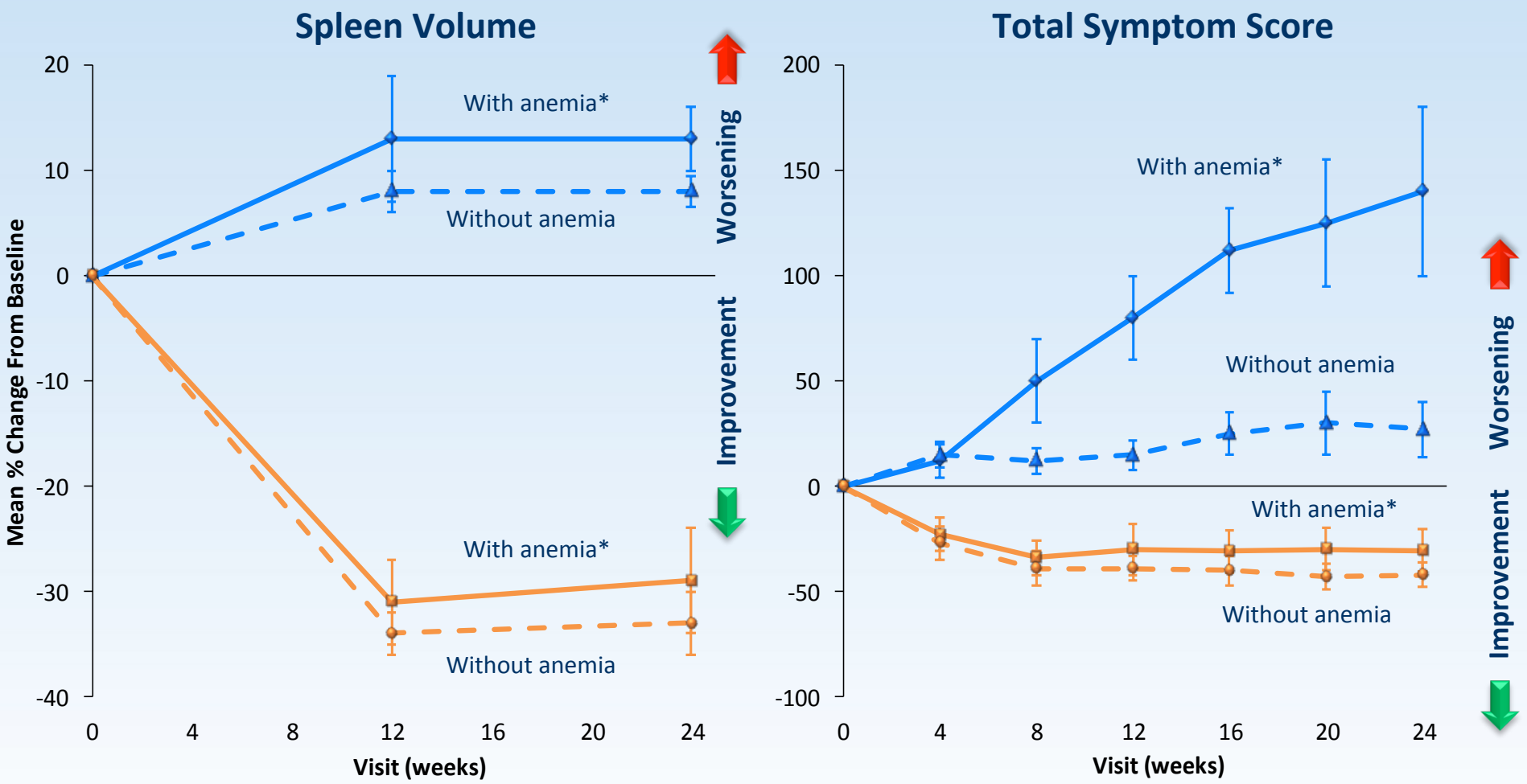


* $P < .001$.
† $P = .06$.

Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807 (supplemental appendix).

COMFORT-I

Ruxolitinib Efficacy Was Maintained Despite Presence of Anemia



*New-onset, grade 3/4 anemia

Verstovsek S, et al. Oral presentation at ASCO Annual Meeting; June 3-7, 2011. Abstract 6500.

Abstract #59
Presented at the 57th American Society of Hematology Annual Meeting
Orlando, Florida, USA, Dec 05−08, 2015

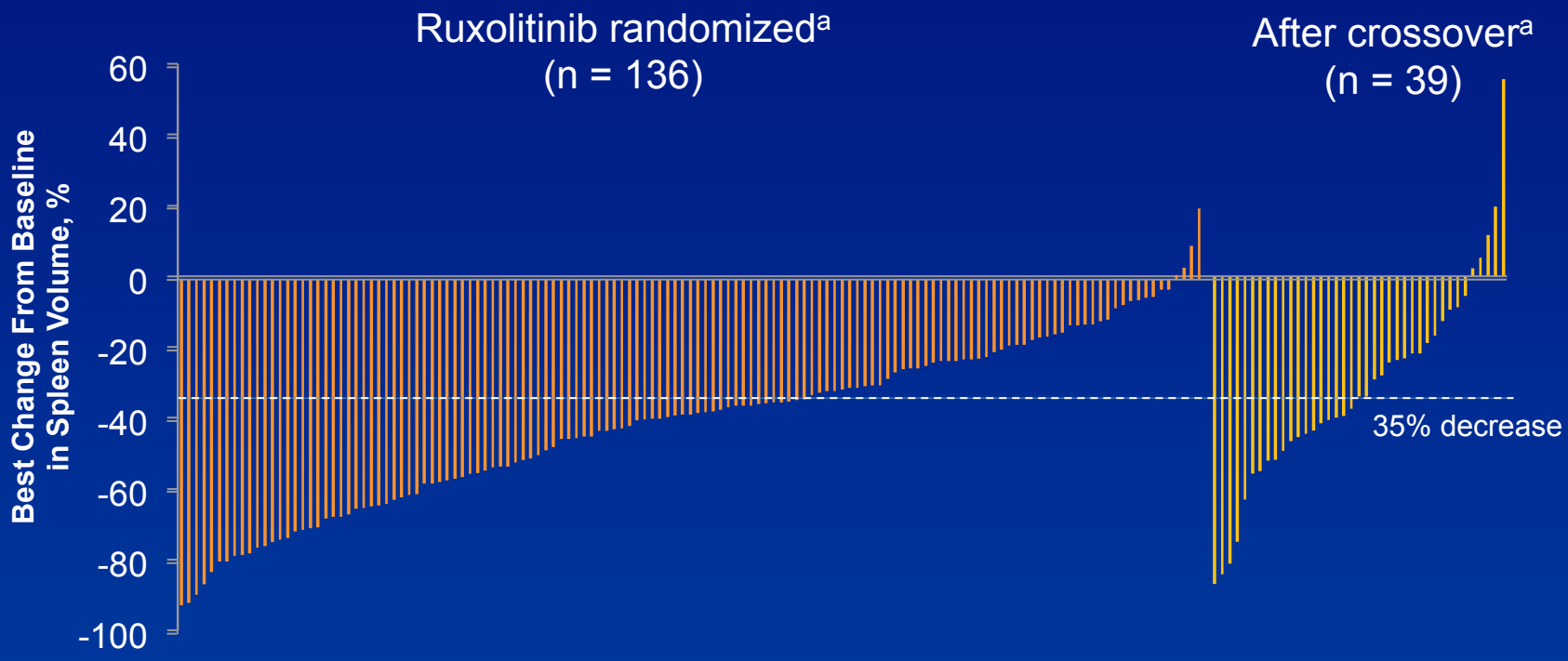
Long-Term Efficacy and Safety in COMFORT-II, a Phase 3 Study Comparing Ruxolitinib With Best Available Therapy for the Treatment of Myelofibrosis: 5-Year Final Study Results

Claire N. Harrison,[1] Alessandro M. Vannucchi,[2] Jean-Jacques Kiladjian,[3] Haifa Kathrin Al-Ali,[4] Heinz Gisslinger,[5] Laurent Knoops,[6] Francisco Cervantes,[7] Mark M Jones,[8] Kang Sun,[8] Laurence Descamps,[9] Viktoriya Stalbovskaya,[10] Prashanth Gopalakrishna,[10] Tiziano Barbui[11]

On Behalf of the COMFORT-II Investigators

[1]Guy's and St. Thomas' NHS Foundation Trust, Guy's Hospital, London, UK; [2]University of Florence, Florence, Italy; [3]Hôpital Saint-Louis et Université Paris Diderot, Paris, France; [4]University of Leipzig, Leipzig, Germany; [5]Medical University of Vienna, Vienna, Austria; [6]Cliniques universitaires Saint-Luc and de Duve Institute, Université catholique de Louvain, Brussels, Belgium; [7]Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [8]Incyte Corporation, Wilmington, DE; [9]Novartis Pharma S.A.S., Rueil-Malmaison, France; [10]Novartis Pharma AG, Basel, Switzerland; [11]Hospital Papa Giovanni XXIII, Research Foundation, Bergamo, Italy

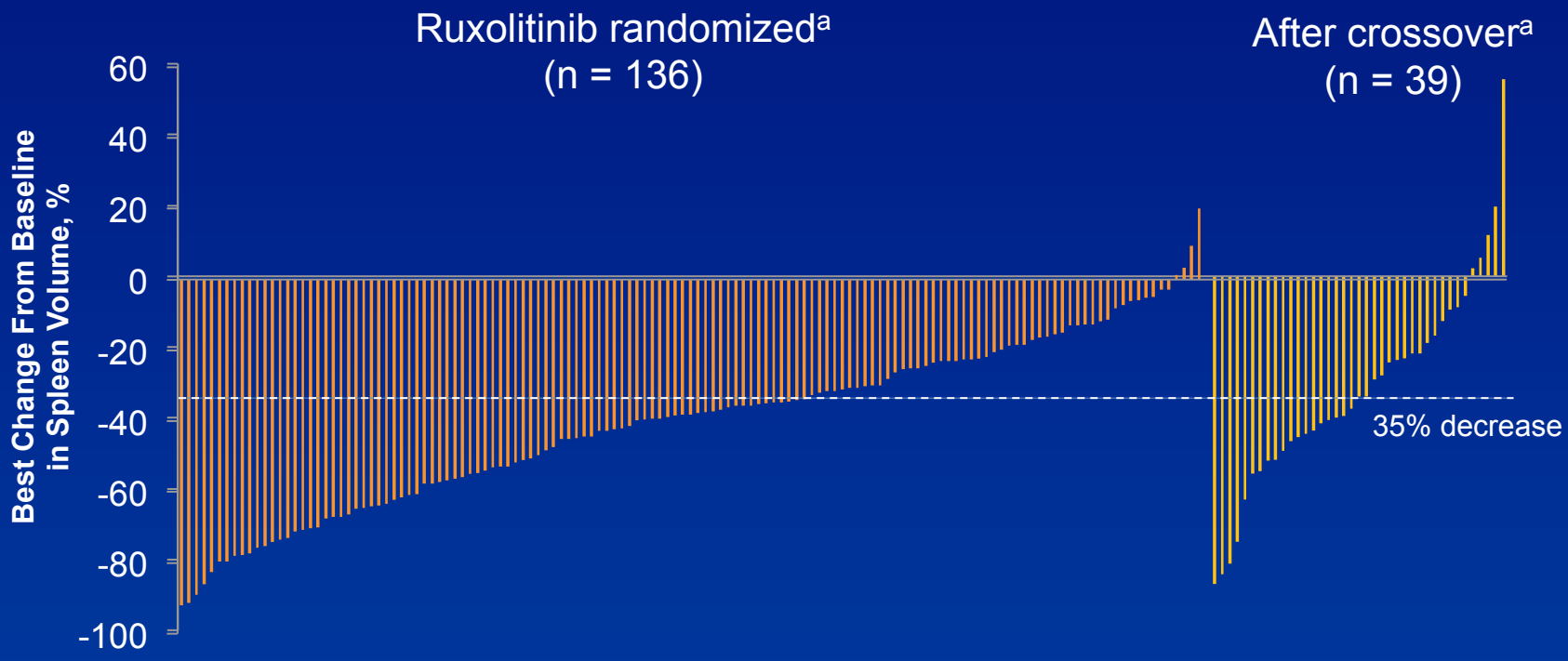
Best Percentage Change in Spleen Volume for Individual Patients



- 97.1% of patients (132/136) experienced some degree of spleen volume reduction
- 78 patients (53.4%) in the ruxolitinib arm achieved a ≥ 35% reduction in spleen volume at any time on treatment

[a] Only patients with baseline and postbaseline spleen volume assessments are included; for crossover patients, the spleen volume at the time of crossover was used as the new baseline value.

Best Percentage Change in Spleen Volume for Individual Patients

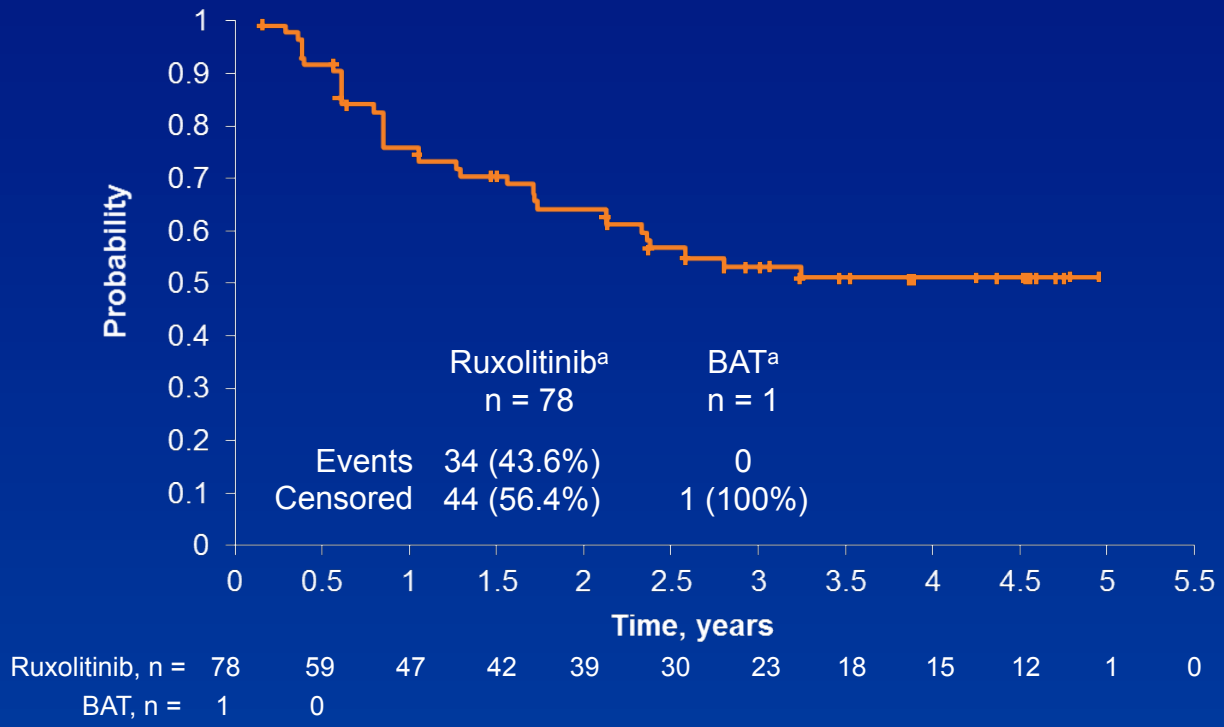


- 75.6% (34/45) of patients who crossed over experienced spleen volume reductions from the time of crossover, and 42.2% (19/45) had a ≥ 35% reduction
- At ≈ 5 years, 88% of patients (45/51) who remained on treatment had improvements from baseline in spleen volume, and 67% (34/51) achieved ≥ 35% reductions

[a] Only patients with baseline and postbaseline spleen volume assessments are included; for crossover patients, the spleen volume at the time of crossover was used as the new baseline value.

Duration of Spleen Response

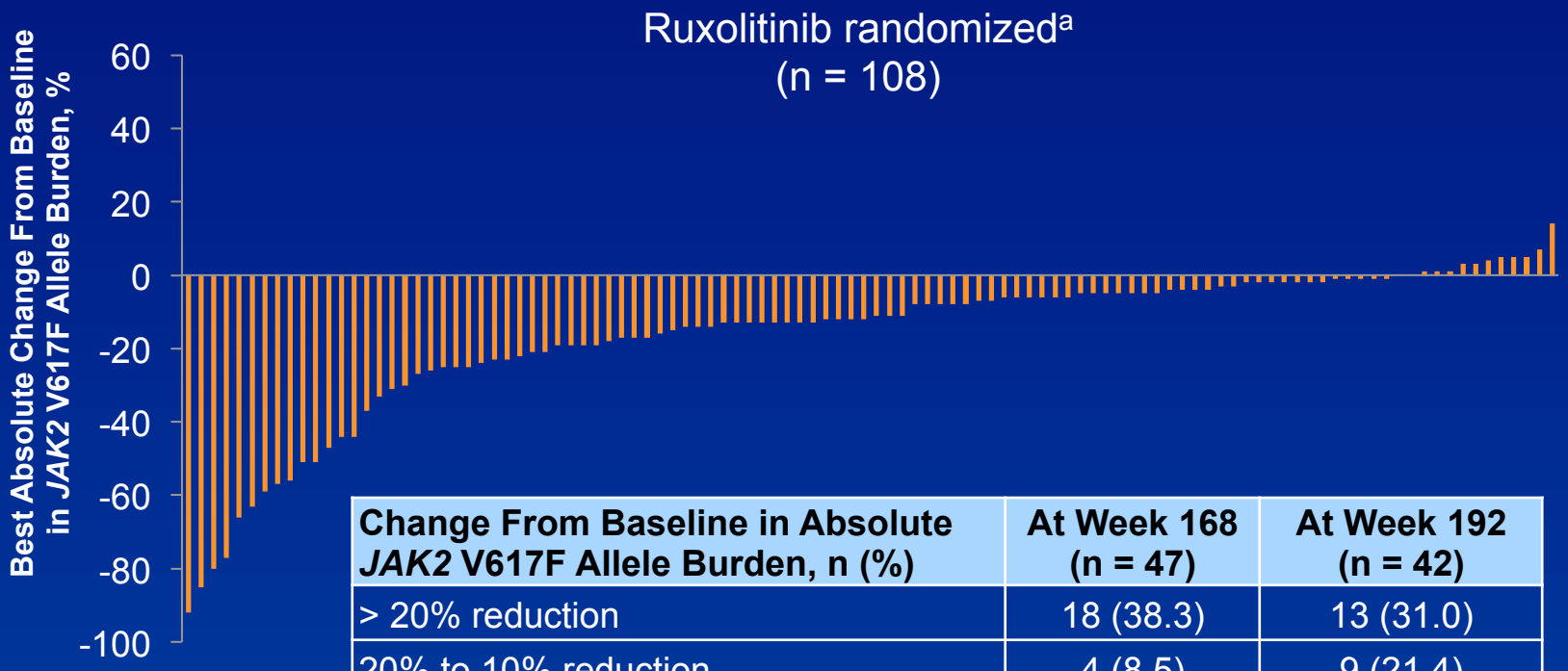
Loss of response: no longer a ≥ 35% reduction that is also a > 25% increase over nadir



- Median duration of response: ruxolitinib, 3.2 years
- The Kaplan-Meier estimated probability of maintaining response
  - 3 years, 0.51 (95% CI, 0.38-0.62)
  - 5 years, 0.48 (95% CI, 0.35-0.60)

[a] For patients who achieved a ≥ 35% reduction at any time during randomized treatment; crossover patients are not summarized.

JAK2 V617F Allele Burden



Change From Baseline in Absolute *JAK2* V617F Allele Burden, n (%)	At Week 168 (n = 47)	At Week 192 (n = 42)
> 20% reduction	18 (38.3)	13 (31.0)
20% to 10% reduction	4 (8.5)	9 (21.4)
0% to 10% reduction	13 (27.7)	13 (31.0)
No change or increase	12 (25.5)	7 (16.7)

- The majority of patients had a reduction in allele burden over the course of ruxolitinib treatment

[a] Only ruxolitinib-randomized patients with positive *JAK2* V617F mutation status at baseline and ≥ 1 postbaseline assessment are included.

Bone Marrow Fibrosis

Shift Table For Fibrosis Grade by Treatment

Last available postbaseline fibrosis grade	Ruxolitinib (n = 146)					BAT[a] (n = 73)				
	Baseline Fibrosis Grade, n (%)					Baseline Fibrosis Grade, n (%)				
	0	1	2	3	Missing	0	1	2	3	Missing
0	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	2 (1.4)	0	0	0	0	0
1	0	10 (6.8)	9 (6.2)	2 (1.4)	0	0	1 (1.4)	0	1 (1.4)	0
2	0	2 (1.4)	8 (5.5)	8 (5.5)	1 (0.7)	0	0	4 (5.5)	1 (1.4)	0
3	0	6 (4.1)	19 (13.0)	28 (19.2)	2 (1.4)	0	0	4 (5.5)	8 (11.0)	3 (4.1)
Missing	2 (1.4)	2 (1.4)	17 (11.6)	20 (13.7)	3 (2.1)	2 (2.7)	2 (2.7)	19 (26.0)	24 (32.9)	4 (5.5)

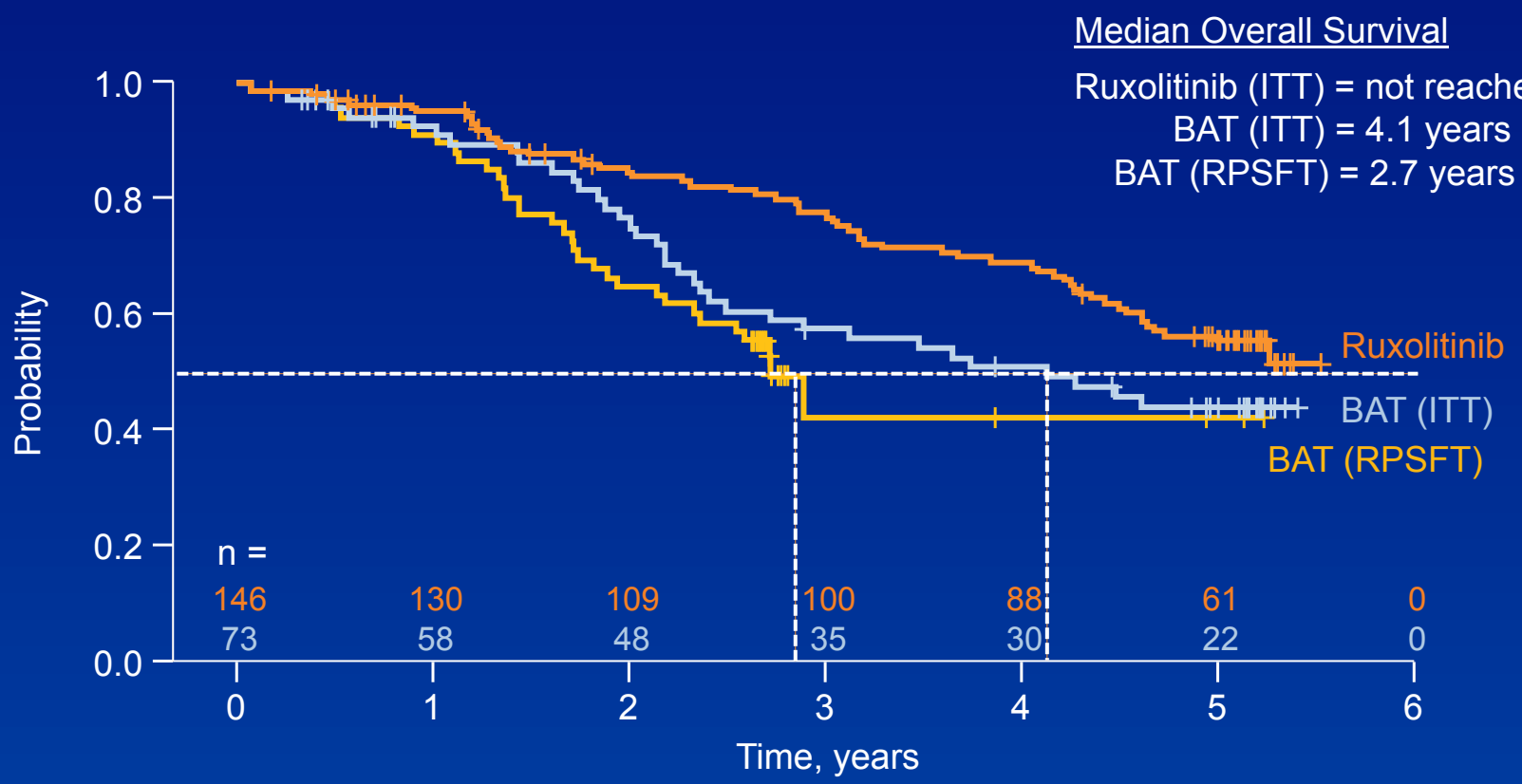
Improvement No change Worsening

With ruxolitinib treatment

- 23 patients (15.8%) had improved fibrosis
  - Including 4 who improved to grade 0 from baseline grades of 1 [n = 1], 2 [n = 2], and 3 [n = 1])
- 47 patients (32.2%) had stable fibrosis
- 27 patients (18.5%) had a worsening at their last assessment

[a] Assessments after crossover from BAT to ruxolitinib are excluded.

Overall Survival



- Median OS was not yet reached in the ruxolitinib arm (ie, > 5 years)
  - ITT: HR, 0.67 (95% CI, 0.44-1.02); *P* = .06
  - RPSFT: HR, 0.44 (95% CI, 0.18-1.04) in favor of ruxolitinib vs BAT

HR, hazard ratio; ITT, intent-to-treat; RPSFT, Rank-Preserving Structural Failure Time.

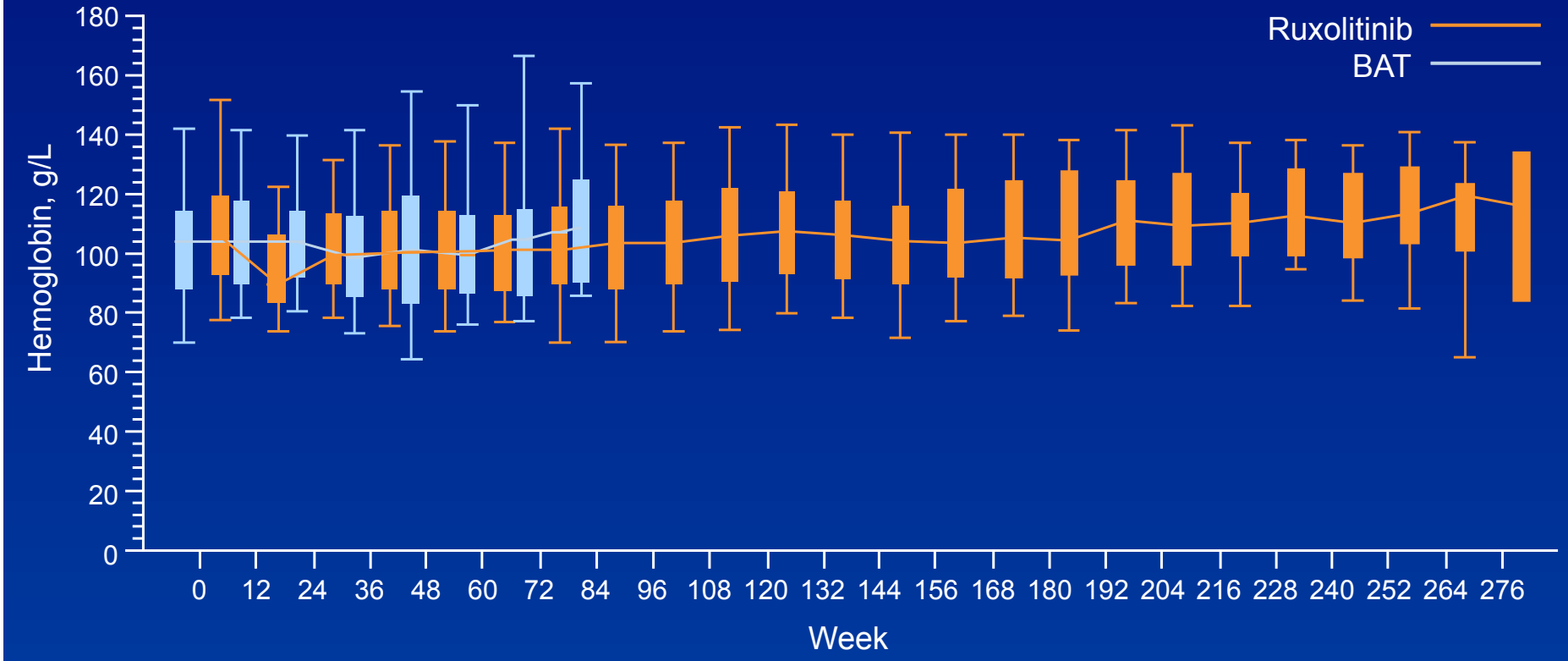
Nonhematologic Adverse Events (exposure adjusted)

Preferred Term, n (exposure-adjusted rate)[a]	Ruxolitinib Randomized (n = 146)	Ruxolitinib Randomized + Extension (n = 146)	BAT Randomized (n = 73)	Ruxolitinib Crossover (n = 45)	Total Ruxolitinib (n = 191)
Patient-year exposure	170.12	409.52	66.98	79.70	489.22
Diarrhea	38 (22.3)	56 (13.7)	13 (19.4)	12 (15.1)	68 (13.9)
Peripheral edema	33 (19.4)	55 (13.4)	21 (31.4)	8 (10.0)	63 (12.9)
Dyspnea	24 (14.1)	37 (9.0)	15 (22.4)	12 (15.1)	49 (10.0)
Asthenia	28 (16.5)	38 (9.3)	9 (13.4)	10 (12.5)	48 (9.8)
Cough	22 (12.9)	38 (9.3)	12 (17.9)	10 (12.5)	48 (9.8)
Pyrexia	22 (12.9)	39 (9.5)	7 (10.5)	8 (10.0)	47 (9.6)
Bronchitis	18 (10.6)	41 (10.0)	6 (9.0)	3 (3.8)	44 (9.0)
Fatigue	23 (13.5)	36 (8.8)	8 (11.9)	8 (10.0)	44 (9.0)
Nasopharyngitis	27 (15.9)	40 (9.8)	9 (13.4)	4 (5.0)	44 (9.0)
Arthralgia	19 (11.2)	30 (7.3)	8 (11.9)	7 (8.8)	37 (7.6)
Nausea	21 (12.3)	30 (7.3)	7 (10.5)	5 (6.3)	35 (7.2)
Pain in extremity	18 (10.6)	24 (5.9)	4 (6.0)	11 (13.8)	35 (7.2)
Weight increase	23 (13.5)	29 (7.1)	1 (1.5)	5 (6.3)	34 (6.9)
Headache	18 (10.6)	23 (5.6)	4 (6.0)	8 (10.0)	31 (6.3)
Abdominal pain	17 (10.0)	26 (6.3)	13 (19.4)	4 (5.0)	30 (6.1)
Back pain	18 (10.6)	24 (5.9)	10 (14.9)	4 (5.0)	28 (5.7)

- After adjusting for exposure, the rates of nonhematologic AEs were generally lower with longer-term ruxolitinib treatment and when compared with those in the BAT arm

[a] Occurring at a rate of ≥ 10 per 100 patient-years of exposure in any group.

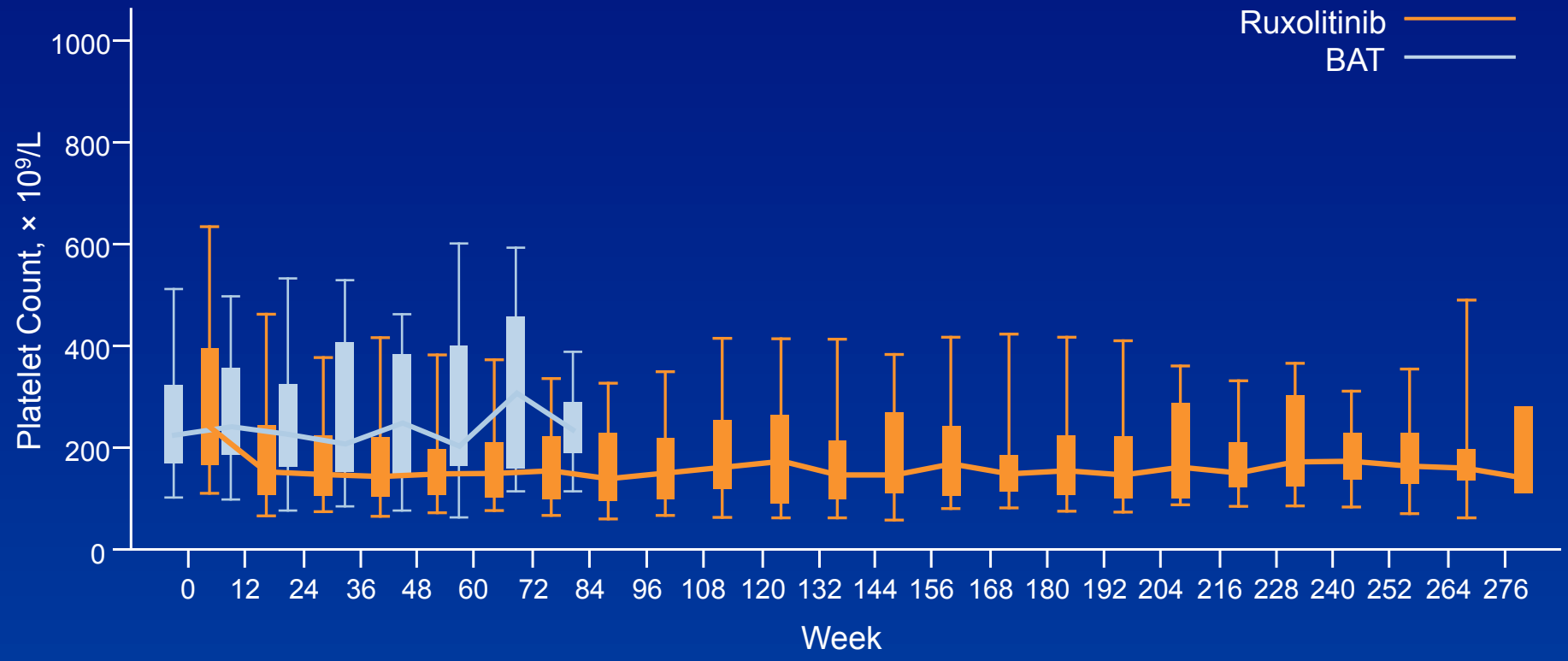
Laboratory Data: Hemoglobin



Ruxolitinib, n =	146	123	104	103	99	93	79	71	65	62	60	49	51	46	43	38	34	31	29	27	30	30	17	3
BAT, n =	73	53	42	32	29	19	10	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- In the ruxolitinib arm, mean hemoglobin levels decreased over the first 12 weeks of treatment and then recovered to levels similar to those in the BAT arm and remained > 10 g/dL from week 24 onward (> 151 weeks)

Laboratory Data: Platelets



Ruxolitinib, n =	146	118	102	96	93	90	76	68	63	60	58	48	49	46	41	37	34	31	28	27	28	29	17	3
BAT, n =	73	51	40	28	27	19	10	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- Thrombocytopenia was primarily grade 1 or 2, with 19% of patients experiencing grade 3 or 4 thrombocytopenia at any time with ruxolitinib treatment

Conclusions

- These 5-year findings demonstrate that the immediate benefits of ruxolitinib treatment, such as improvements in spleen size, were maintained with long-term therapy
- Reductions in *JAK2* V617F allele burden were apparent with longer-term treatment; improvement or stabilization of bone marrow fibrosis was seen in 48% of ruxolitinib-treated patients (18.5% worsening; 34% missing)
- Long-term safety and tolerability were consistent with previous findings
- Patients randomized to ruxolitinib treatment in the study had a relatively lower risk of death compared with patients on the BAT arm, most of whom switched to receive ruxolitinib at a later date
  - In the ITT analysis, reduction in the risk of death with ruxolitinib was 33%
- This hypothetical benefit with earlier treatment with ruxolitinib is being evaluated through a phase 3 study in patients with early MF

Abstract # 825
Presented at the 57th American Society of Hematology Annual Meeting
Orlando, Florida, USA, Dec 05−08, 2015

Phase 1b/2 Study of the Efficacy and Safety of Sonidegib (LDE225) in Combination With Ruxolitinib (INC424) in Patients With Myelofibrosis

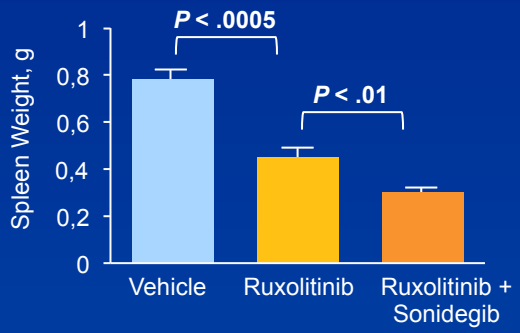
Vikas Gupta,[1] Claire Harrison,[2] Hans Hasselbalch,[3] Lisa Pieri,[4] Steffen Koschmieder,[5] Francisco Cervantes,[6] Weichao Bao,[7] Stacey Kalambakas,[7] Edric Atienza,[7] Prashanth Gopalakrishna,[8] Florian Heidel[9]

[1]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [2]Guy's and St Thomas' Hospital, London, UK; [3]Roskilde University Hospital, Roskilde, Denmark; [4]Azienda Ospedaliera-Universitaria Careggi, University of Florence, Florence, Italy; [5]RWTH Aachen University Hospital, Aachen, Germany; [6]Hospital Clínic de Barcelona, Barcelona, Spain; [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [8]Novartis AG, Basel, Switzerland; [9]Otto-von-Guericke-University Magdeburg, Magdeburg, Germany

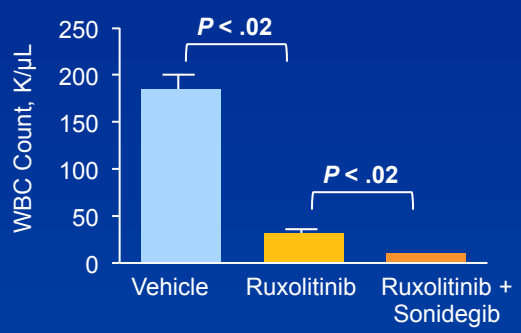
Study Rationale

- The Hh pathway is involved in hematopoietic stem cell proliferation and is active in hematologic malignancies[1]
  - In a murine model of MF, ruxolitinib in combination with the Hh pathway inhibitor sonidegib (selectively inhibits SMO[2]) improved splenomegaly and bone marrow fibrosis better than ruxolitinib alone[3]

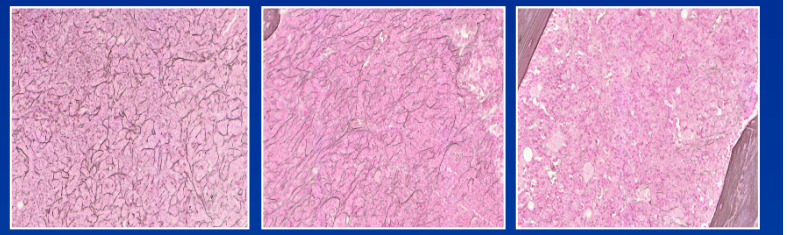
Spleen Weight



WBC Count



Bone Marrow Fibrosis



1. Tibes R, Mesa RA. *J Hematol Oncol.* 2014;7:18.
2. Pan S, et al. *ACS Med Chem Lett*. 2010;1:130-134.
3. Bhagwat N, et al. *Blood*. 2013;122(21) [abstract 666].

Study Design

- This phase 1b/2 study is evaluating sonidegib + ruxolitinib for the treatment of patients with intermediate- or high-risk MF
  - Data from 24 weeks after the last patient enrollment (cutoff, May 8, 2015) are presented for patients treated at the RP2D

- Primary or PPV/PET MF
- Intermediate or high IPSS risk[1]
- Palpable splenomegaly
- JAK and SMO inhibitor naive

Dose-escalation phase

- **Determine MTD/RP2D**

Dose-expansion phase

- **Enroll additional patients for treatment with the MTD/RP2D**

Dose Level	Sonidegib	Ruxolitinib
1	400 mg QD	10 mg BID
2	400 mg QD	15 mg BID
3	**400 mg QD**	**20 mg BID**

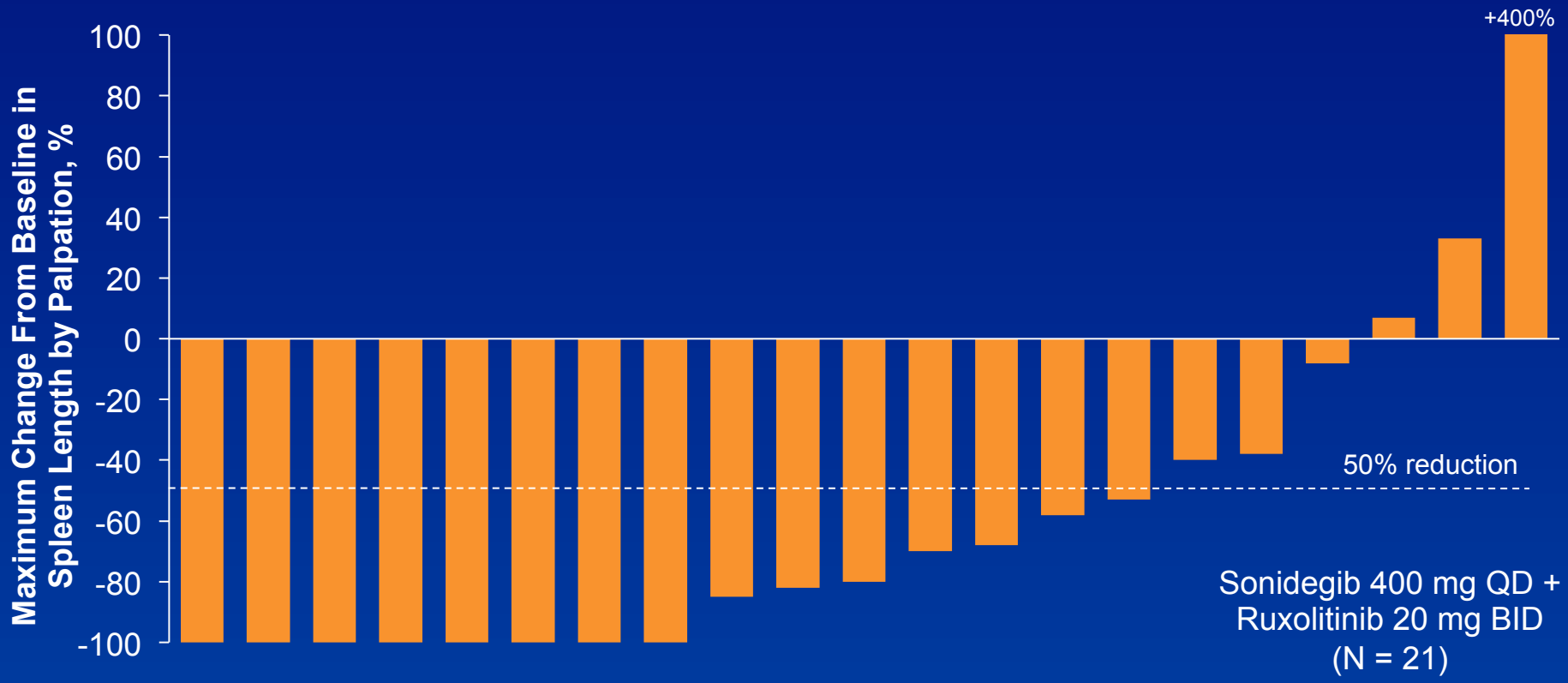
Objectives:

- Determine MTD/RP2D
- Assess safety and tolerability
- Characterize PK
- Preliminary efficacy
  - Spleen responses
  - Bone marrow changes
  - *JAK2* V617F

BID, twice daily; IPSS, International Prognostic Scoring System; MTD, maximum tolerated dose; PET, post–essential thrombocythemia; PK, pharmacokinetics; PPV, post–polycythemia vera; QD once daily.

1. Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.

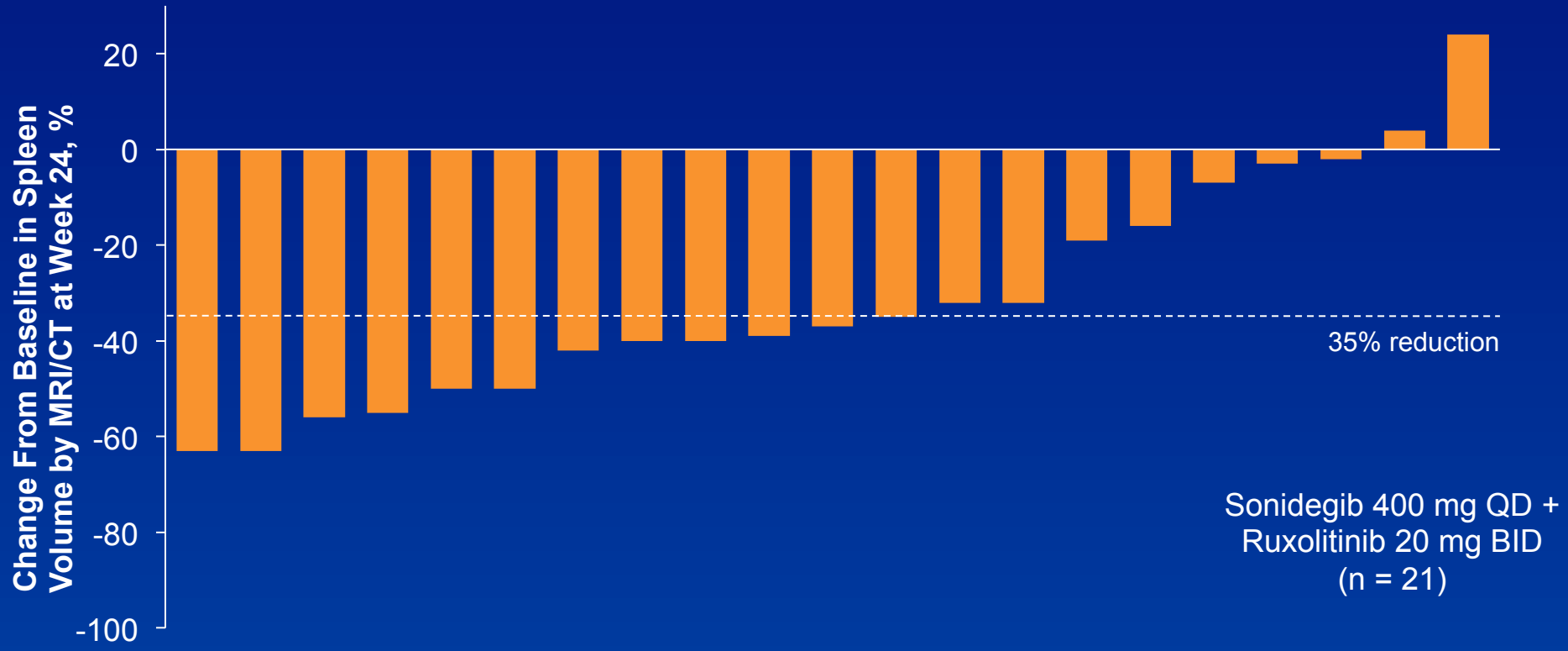
Spleen Length Response at Week 24



- At the end of week 24, 55.6% of patients (15/27) achieved a ≥ 50% reduction in palpable spleen length
- 25 patients (92.6%) had a ≥ 50% reduction in spleen length at any time on treatment; 15 patients (55.6%) achieved a nonpalpable spleen

Data cutoff: May 8, 2015

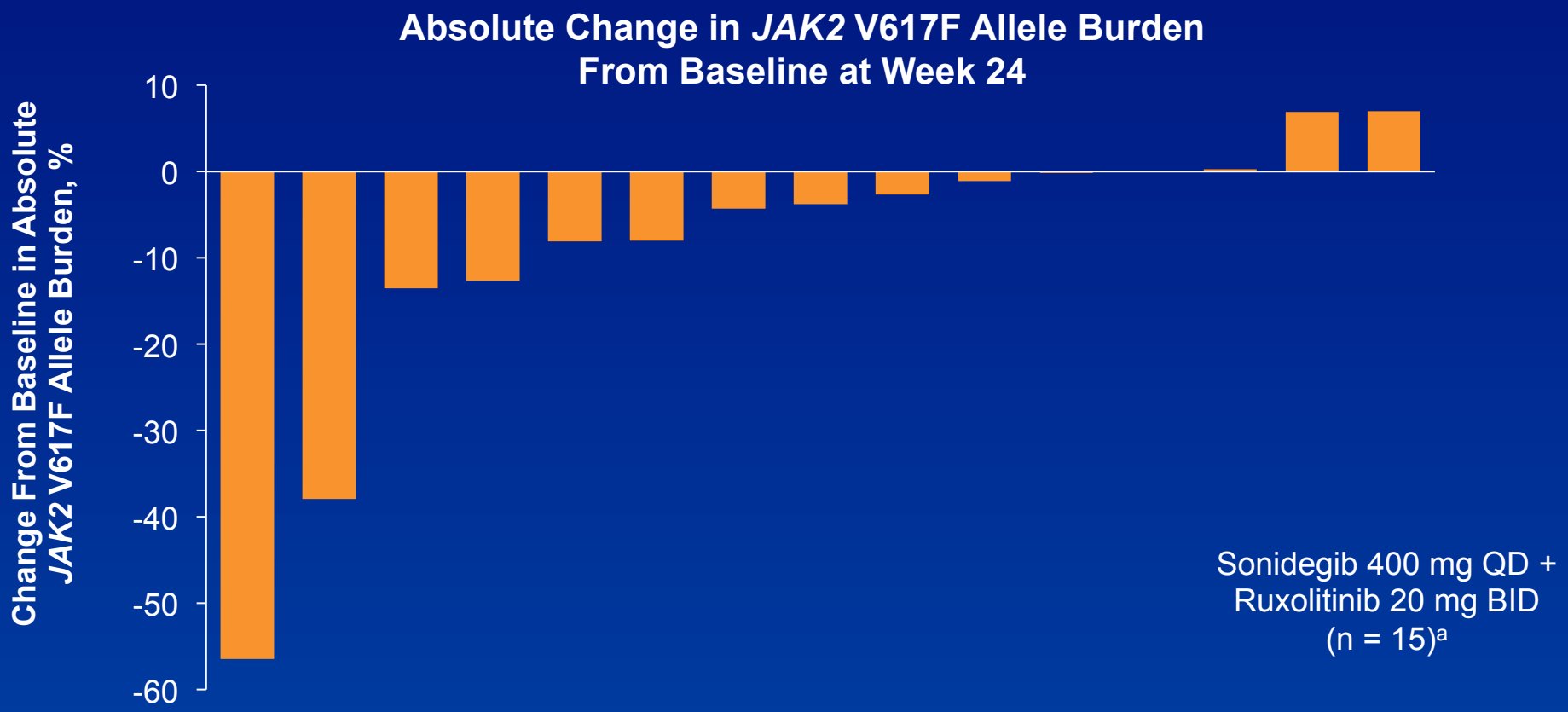
Spleen Volume Response at Week 24



- At the end of week 24, 12 patients (44.4%) had a ≥ 35% reduction in spleen volume as measured by MRI/CT
- 15 patients (55.6%) achieved a ≥ 35% reduction in spleen volume at any time on treatment

Data cutoff: May 8, 2015

JAK2 V617F Allele Burden



- The mean absolute change in *JAK2* V617F allele burden was −9.0 percentage points (range, −56.5% to 7.0%) from baseline to the end of week 24

[a] *JAK2* V617F–positive patients with assessments at baseline and week 24.

Adverse Events

AEs of any cause in ≥ 15% of patients, n (%)	RP2D (N = 27)	
	All Grade	Grade 3/4
Hematologic AEs		
Anemia[a]	14 (52)	9 (33)
Thrombocytopenia[a]	7 (26)	3 (11)
Nonhematologic AEs		
Muscle spasms[a]	13 (48)	1 (4)
Increased creatine phosphokinase[a]	10 (37)	5 (19)
Myalgia[a]	8 (30)	2 (7)
Dysgeusia[b]	8 (30)	—
Diarrhea[a]	7 (26)	1 (4)
Fatigue	7 (26)	0
Pyrexia	6 (22)	1 (4)
Alopecia[b]	6 (22)	—
Constipation	5 (19)	0
Nausea	5 (19)	0
Abdominal pain	4 (15)	0
Dizziness	4 (15)	0
Headache	4 (15)	0

[a] Led to dose adjustment or interruption in ≥ 2 patients each.
[b] Led to dose adjustment or interruption in 1 patient each.

AEs not typically observed with ruxolitinib

Data cutoff: May 8, 2015

Conclusions

- Sonidegib 400 mg QD + ruxolitinib 20 mg BID was generally well tolerated, with no unexpected safety concerns
- Combining sonidegib and ruxolitinib did not appear to affect the PK of either agent
- Preliminary efficacy data were consistent with the known effects of ruxolitinib monotherapy, with clinically relevant responses in JAK inhibitor–naive patients
  - Most patients (92.6%) had ≥ 50% reduction in spleen length; 55.6% achieved complete resolution of palpable splenomegaly
  - The majority of patients (55.6%) achieved a ≥ 35% reduction in spleen volume at any time on treatment, and 44.4% achieved this response at week 24
  - Some patients achieved reductions in *JAK2* V617F allele burden and improvements in bone marrow fibrosis with combination therapy
- Observed efficacy at week 24 did not reach the pre-specified threshold for further enrollment of patients in the trial; the study is ongoing and intends to continue longer-term follow-up of existing patients

EXPAND: A Phase 1b, Open-Label, Dose-Finding Study of Ruxolitinib in Patients With Myelofibrosis and Low Platelets

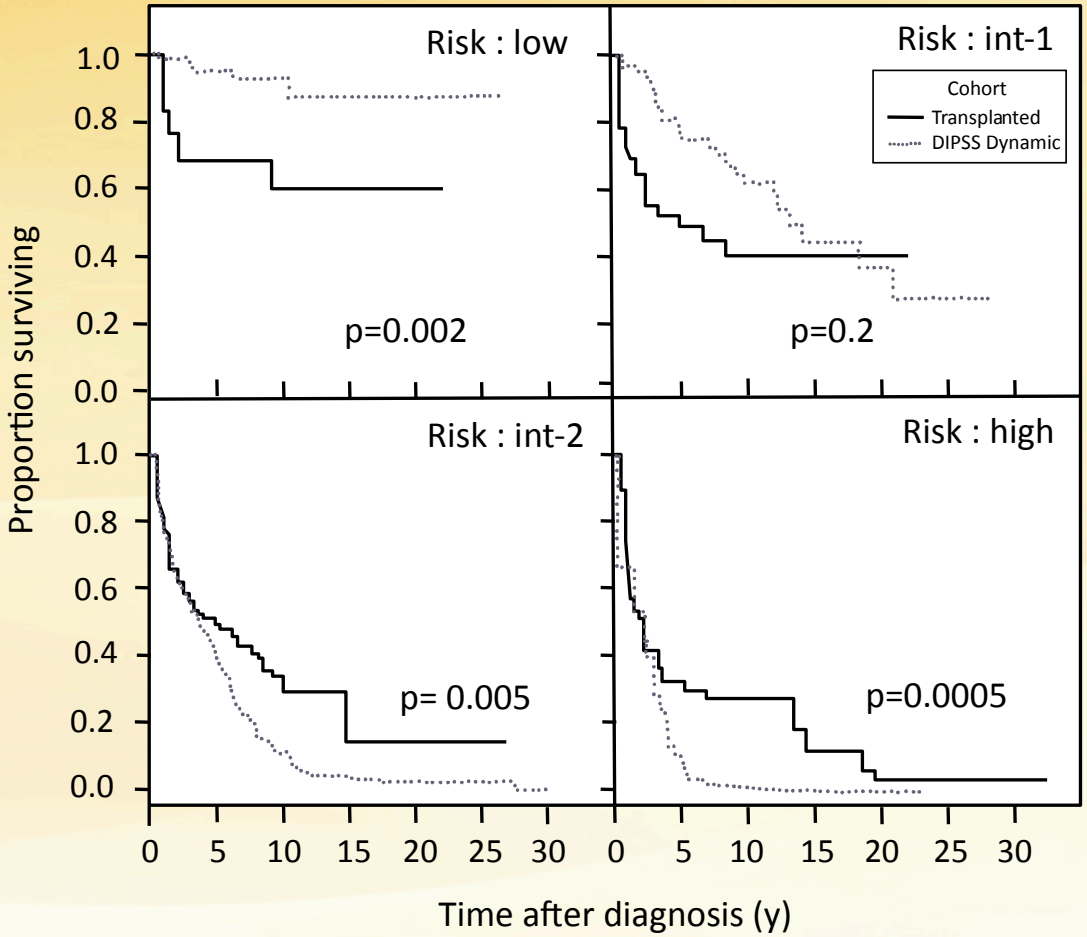
- Ruxolitinib was safely administered in patients with MF and low PLT counts at starting doses of up to 15 mg bid (stratum 1, PLT count 75-99 . 109/L) or 10 mg bid (stratum 2, PLT count 50-74 . 109/L)
- AEs were consistent with the known safety profile of ruxolitinib and the studied population, with no new or unexpected adverse findings
- Spleen length reductions were observed across all groups, including the MSSDs, and were consistent with those observed in patients with higher platelet counts
- Based on these findings, the study has been revised to administer ruxolitinib at a starting dose of 10 mg bid in both strata and thus focus on an optimal dosing strategy for patients with a PLT count of 50 to 99 . 109/L
- The study is ongoing and is currently open for enrollment

Vannucchi et al. ASH 2015

Transplantation for MF in 2016

- Patients in the transplant age group
  - Usually <70 yrs old, reasonable performance status and no prohibitive co-morbidities
- MF related features
  - DIPSS-Intermediate-2/high-risk
  - ? DIPSS-Intermediate - 1
    - High risk cytogenetics
    - Severely cytopenic patients
      - Transfusion dependent (non-responders to conservative options)
      - Severe thrombocytopenia
      - ?? High-risk mutations (ASLX1 + patients)

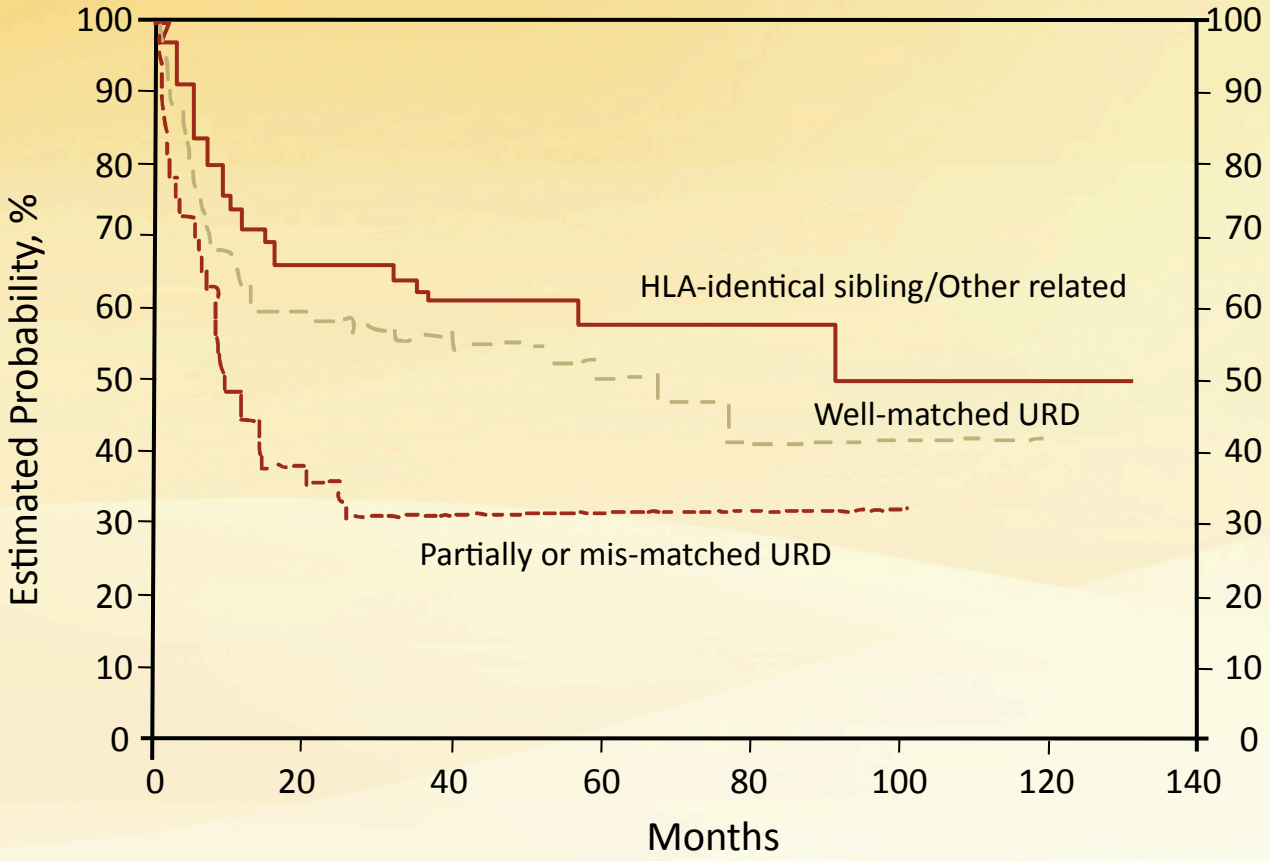
Comparison of HCT vs non-transplant according to DIPSS in pts. <65



HCT, hematopoietic cell transplantation; DIPSS, dynamic international prognostic scoring system

Kroger et al. ASH 2014; abstract 320

Outcomes of HCT in Myelofibrosis (CIBMTR data)



Cohort 12% low, 49% intermediate-1, 37% intermediate-2, and 1% high-risk MF patients

CIBMTR, Center for International Blood and Marrow Transplant Research; HLA, human leukocyte antigen; URD, unrelated donor.

Gupta V, et al. BBMT, 2014;20:89-97

Various Time Points of using HCT in MF Management

- **Model 1:** Clinical improvement or stable disease on JAK inhibitor therapy
- **Model 2:** Delay the HCT as long as benefiting from JAK inhibitor therapy, and consider HCT if
  - Intolerant to JAK inhibitors due to toxicities
  - Worsening of anaemia transfusion dependence
  - Increased blast count (10-19%)
  - Sub-optimal/loss of response requiring change in therapy
- **Model 3:** Progressed on JAK inhibitor (progression of splenomegaly/splenectomy/blasts>20%)

Adapted from Shavanas & gupta, Best Pract Res Clin Hematol.204; 27:165-74

HCT: Hematopoietic cell transplantation

Graft failure in prospective studies in Myelofibrosis

	EBMT N= 103 *(Kroger et al,Blood,2009)*	MPD-RC N=66 *(Rondelli et al,Blood, 2014)*
Low-risk pts	17%	5%
% URD tx	70/103 (68%)	34/66 (52%)
Survival	68% @5-yrs	78% at 2-yrs (MRD) 44% at 1-yr (MUD)
LFS	40% @5-yrs	NR
Primary graft failure	2%*,11% needed stem cell boost	24% URD Tx

EBMT, European group for blood and marrow transplantation; MPD-RC, myeloproliferative disorders research consortium; URD, unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; LFS , Leukamia-free survival

Kroger N et al. Blood 2009;114:5264-70.;Rondelli D et al. Blood 2014;124:1183-91.

Facing the difficulties associated with HCT for Myelofibrosis

- **Graft failure ?**
  - Bone marrow fibrosis-poor environment for the stem cell
  - Significant Splenomegaly
  - Cytokines?
- **GVHD?**
  - Decreased cytokine levels may reduce the risk of severe GVHD
- **TRM?**
  - Better perfomance status prior to HCT may yield improved outcomes

GVHD,graft versus host disease; TRM, tansplant-related mortality

Combined approach of JAK inhibitors in transplant protocols

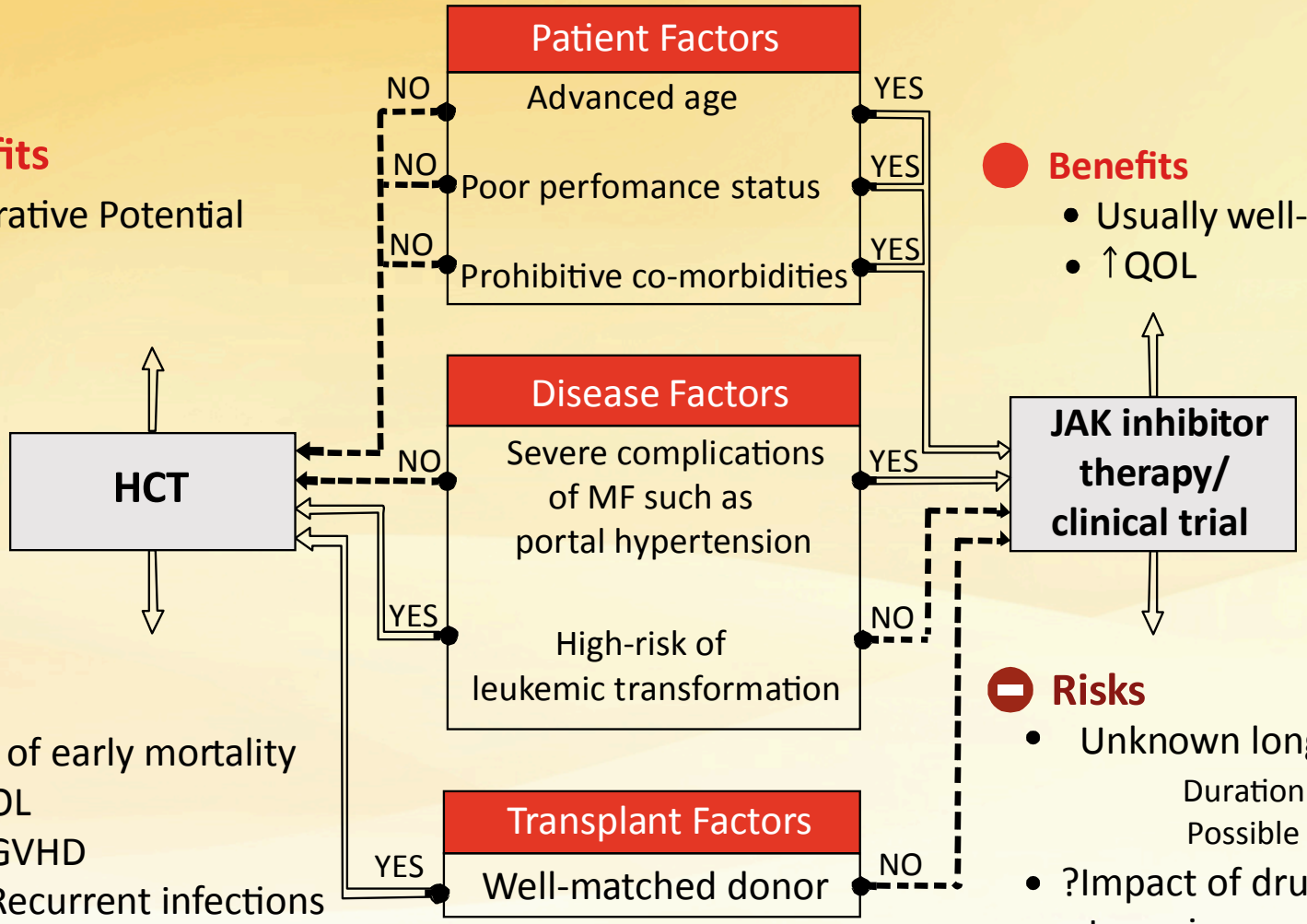
Study	No	Study Design	Results	Conclusions
Jaekel et al BMT 2014	14	Retrospective	GF 1/14 Treatment related sepsis, 1/14	Tapering Rux. Until conditioning did not result in unexpected SAE
Shanavas,et,al,BMT 2014	6	Retrospective	No adverse impact on early post HCT outcomes	As above
Stubig et al,Leukemia,2014	22	Retrospective	1- year OS of 100% in those good resp. to Rux.Vs. 60% others	Continuing Rux. Until conditioning without taper - No unexpected SAEs
Lebon et al,ASH abstract 2013	11	Retrospective	Good engraftment rates	Differing schedules of tapering

Jaekel N et al. BMT 2014;49:179-84.; Shanavas M et al. BMT 2014;49:1162-69.; Stubig T et al. Leukemia 2014;28:1736-38.;Lebon Det al. ASH 2013, Abstract 2111

Conclusions

- HCT is an appropriate option for selected patients with Myelofibrosis
  - Int-2/high-risk disease
  - Int-1 with transfusion dependency or unfavourable cytogenetics
- The selection of patients should be individualized based on patient wishes and other patient-, disease-, and transplant-related factors
- Combination of JAK inhibitor therapy in the transplant setting may help in overcoming some of the current issues with the transplantation in myelofibrosis

Selection of upfront therapy for patients with Myelofibrosis



Benefits

- Curative Potential

Risks

- Risk of early mortality
- ↓QOL
  - GVHD
  - Recurrent infections

Benefits

- Usually well-tolerated
- ↑QOL

Risks

- Unknown long-term effects
  - Duration of response
  - Possible resistance
- ?Impact of drug-induced cytopenias on survival / LT

HCT, hematopoietic cell transplantation; GvHD, graft versus host disease; JAK, Janus Kinase; LT, leukemic transformation; MF, myelofibrosis; QOL, quality of life.

Gupta V, et al. *Blood* 2012;120:1367-1379.