Oncology Grand Rounds
Myeloproliferative Neoplasms

Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Friday, May 5, 2017
6:00 AM – 7:30 AM

Faculty

Jenny Dahl, PA-C
Aaron T Gerds, MD, MS
Emily A Knight, APRN, MSN, NP, OCN
Daniel A Pollyea, MD, MS
Sarah K Swanson, APN-BC

Moderator

Neil Love, MD

Research To Practice®

Oncology Grand Rounds Series

Wednesday	**Non-Small Cell Lung Cancer** 6:00 PM – 8:00 PM
Thursday	**Cancer Immunotherapy** 6:00 AM – 7:30 AM
	Breast Cancer 12:15 PM – 1:45 PM
	Lymphomas and CLL 6:00 PM – 8:00 PM
Friday	**Myeloproliferative Neoplasms** 6:00 AM – 7:30 AM
	Ovarian Cancer 12:15 PM – 1:45 PM
	Gastrointestinal Cancers 6:00 PM – 8:00 PM

Oncology Grand Rounds: Themes

Identifying and understanding oncology clinical scenarios

- Key determining factors; natural history and treatment
- Evaluating and managing clinical symptoms
- Patient and caregiver education

Integrating new agents and treatment strategies into practice

- Benefits and risks
- Prevention, identification and management of side effects/toxicity
- Identifying patients at high risk for toxicity

Psychosocial issues in clinical oncology

- Caring for family and loved ones, including minor children and grandchildren
- Job satisfaction and disappointment
- The bond that heals

Novel Agents Approved by the FDA in the Past 9 Weeks

Agent	Approval Date	FDA-Approved Use on Approval Date
Telotristat ethyl (tryptophan hydroxylase inhibitor)	February 28th	In combination with somatostatin analogue (SSA) therapy for the treatment of adults with carcinoid syndrome diarrhea inadequately controlled by SSA therapy alone
Ribociclib (CDK4/6 inhibitor)	March 13th	In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer
Avelumab (anti-PD-L1 antibody)	March 23rd	For the treatment of patients (≥12 years) with metastatic Merkel cell carcinoma, including those who have not received prior chemotherapy
Niraparib (PARP inhibitor)	March 27th	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer whose tumors have completely or partially shrunk in response to platinum-based chemotherapy
Brigatinib (ALK inhibitor)	April 28th	For the treatment of patients with ALK-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
Midostaurin (FLT3 inhibitor)	April 28th	For the treatment of adults with newly diagnosed FLT3-positive acute myeloid leukemia in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Durvalumab (anti-PD-L1 antibody)	May 1st	For the treatment of patients with PD-L1-positive inoperable or metastatic urothelial bladder cancer that has progressed during or after one standard platinum-based regimen

https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm537040.htm

- Newly diagnosed MF
- MF, anemia with ruxolitinib
- Newly diagnosed PV
- PV, resistance or intolerance to hydroxyurea
- Newly diagnosed ET
- ET, resistance or intolerance to hydroxyurea

About the Enduring Program

- The proceedings from this 7-part CNE series will be video recorded and used in a virtual meeting archive including a downloadable version of the slides.

- An email will be sent to all attendees when the web activity is available.
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Submit a challenging case or question for discussion during the program.

Email to **DrNeilLove@ResearchToPractice.com**

Text to **(786) 759-1458**

(Your phone number will remain confidential and will not be disclosed.)

If you are unable to text or email, please complete a question/comment card located on your conference table and drop it in one of the designated bins located throughout the meeting room.

Make the Meeting Even More Relevant to You

Join the conversation by sharing photos and videos using the hashtag #RTPLive

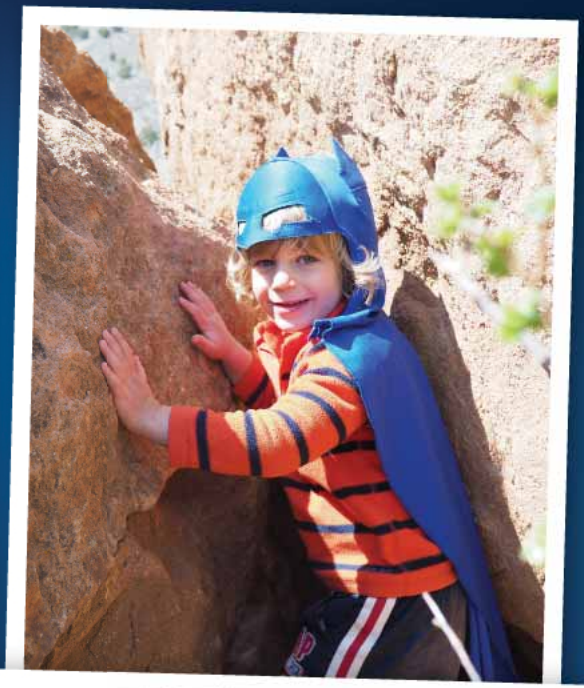
Facebook **@researchtopractice**

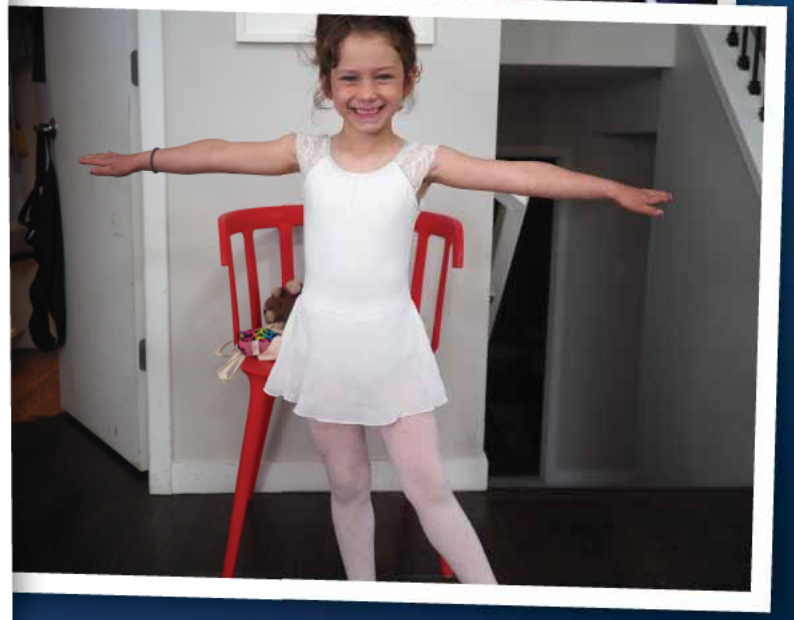
Twitter **@DrNeilLove**

Instagram **@researchtopractice**

And get here early to participate in a brief video interview, where you can tell us about your experiences with oncology nursing. You may even see your post on the big screen during the events!

Daniel A Pollyea, MD, MS
University of Colorado
School of Medicine
Aurora, Colorado





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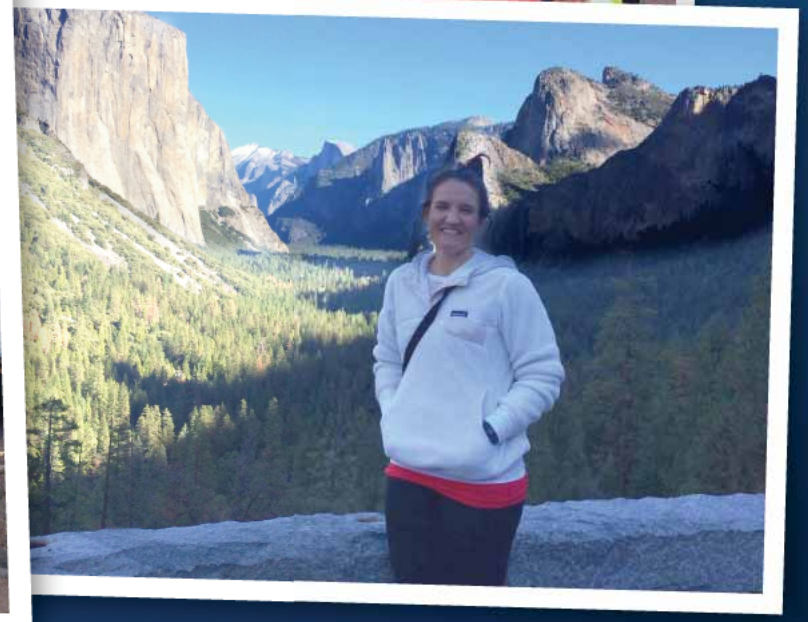
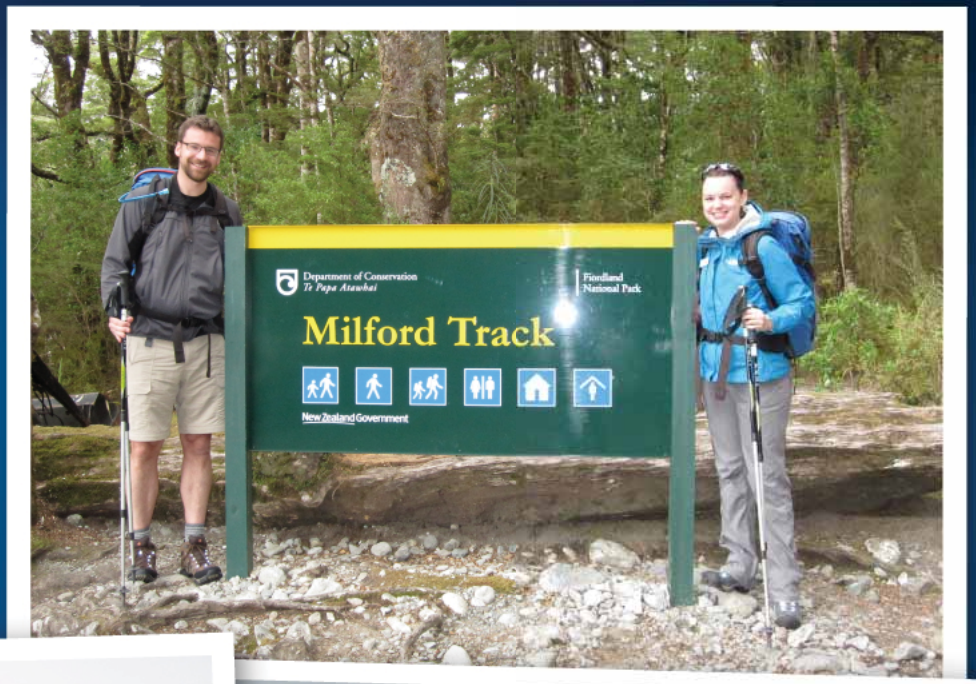
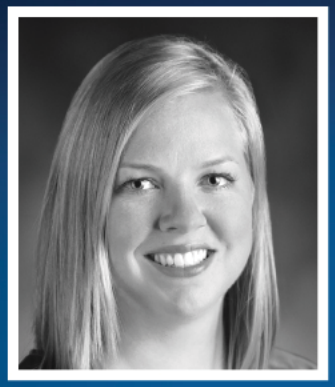


Sarah K Swanson, APN-BC
Rush University Medical Center
Chicago, Illinois





Jenny Dahl, PA-C
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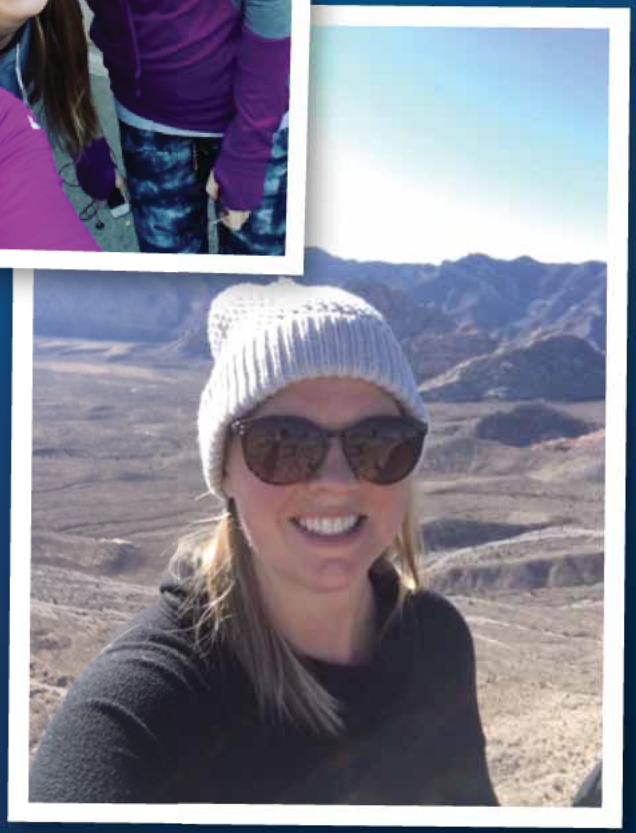

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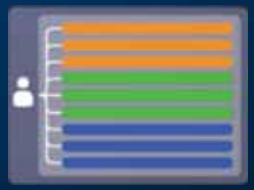
Module 1: Overview of Myeloproliferative Neoplasms

Key Clinical Considerations

- Disease characteristics and spectrum of clinical issues associated with myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET)
- Shared biology and clinical features of MPNs
- Progression from ET and PV to MF
- Risk of leukemic transformation in patients with MPNs
- Clinical significance of the JAK-STAT pathway and associated driver mutations in MPN development



MPNs: Overview of Disease Features

- **Myelofibrosis (MF)**
  - Prevalence in US: 13,000
  - Median survival: 6 years
  - May arise de novo (primary MF) or following PV or ET (post-PV MF or post-ET MF)
  - Variable clinical features (ie, splenomegaly, cytopenias, constitutional symptoms)
- **Polycythemia vera (PV)**
  - Prevalence in US: 148,000
  - Median survival: 14 years
  - Variable risk of vascular events and MPN-related symptoms
- **Essential thrombocythemia (ET)**
  - Prevalence in US: 134,000
  - Median survival: 20 years
  - Variable risk of vascular events and MPN-related symptoms

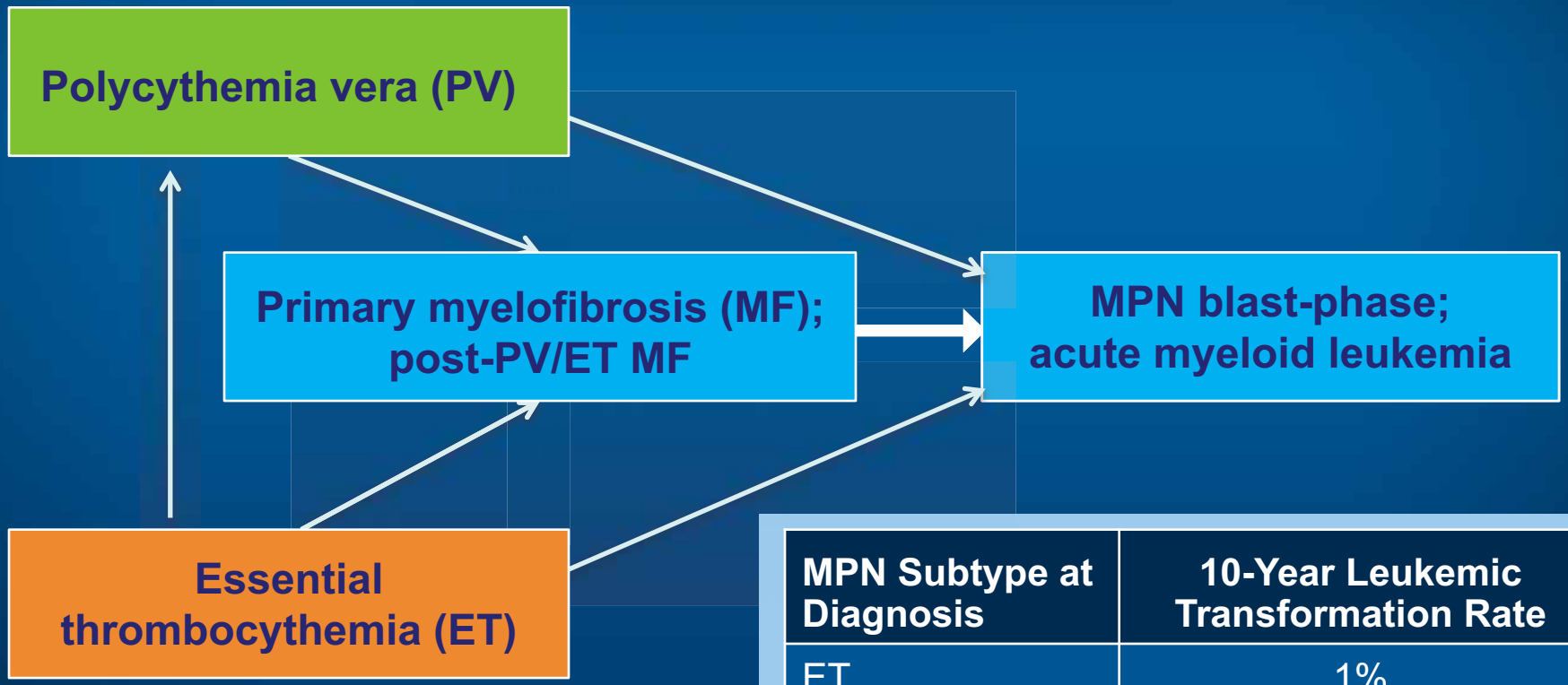
Courtesy of Srdan Verstovsek, MD, PhD; Mehta J et al. *Leuk Lymphoma* 2014;55(3):595-600. Tefferi A, Pardanani A. *JAMA Oncol* 2015;1(1):97-105; Tefferi A et al. *Blood* 2014;124(16):2507-13.

Overview of Myeloproliferative Neoplasms

	Polycythemia vera (PV)	Essential thrombocythemia (ET)	Primary myelofibrosis (PMF)
Clinical features	Thrombosis Hemorrhage +/- SMG	Thrombosis Hemorrhage +/- SMG	Constitutional – fevers, chills, wt loss Painful, massive SMG
Labs	Erythrocytosis +/- leukocytosis/ thrombocytosis	Thrombocytosis +/- leukocytosis	Anemia Myeloid immaturity
Molecular	*JAK2* V617F (>95%)	*JAK2* V617F (~50%)	*JAK2* V617F (~50%)
Prognosis	Risk of conversion to MF/AML	Risk of conversion to MF/AML	Risk of conversion to AML
Treatment	ASA phlebotomy +/- cytoreductive agents JAK2 inhibitors	ASA +/- cytoreductive agents JAK2 inhibitors	Limited options – Thalidomide, lenalidomide, BMT JAK2 inhibitors

Courtesy of Daniel A Pollyea, MD, MS

MPN Disease Continuum: Shared Biology and Clinical Features

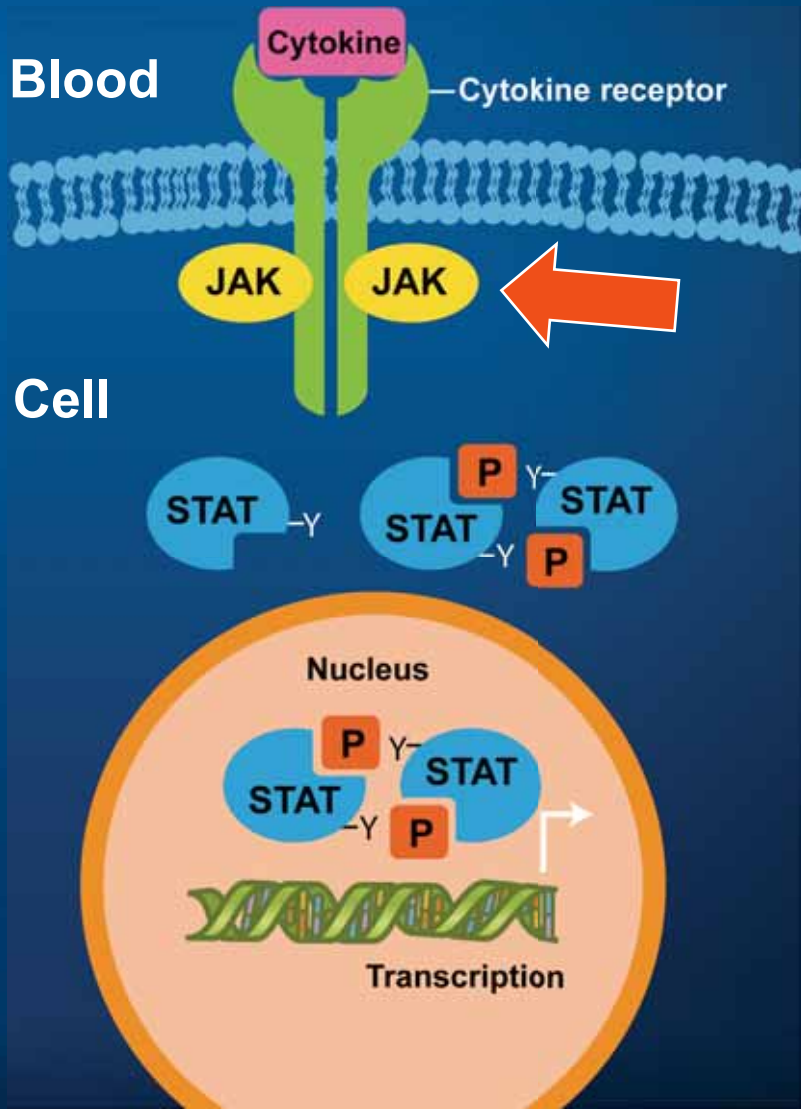


MPN Subtype at Diagnosis	10-Year Leukemic Transformation Rate
ET	1%
PV	4%
Primary PF	20%

Courtesy of Srdan Verstovsek, MD, PhD;
Tefferi A. *Am J Hematol* 2008;83:491-7; Rampal R, Mascarenhas J. *Curr Opin Hematol* 2014;21:65-71.

JAK-STAT Signaling

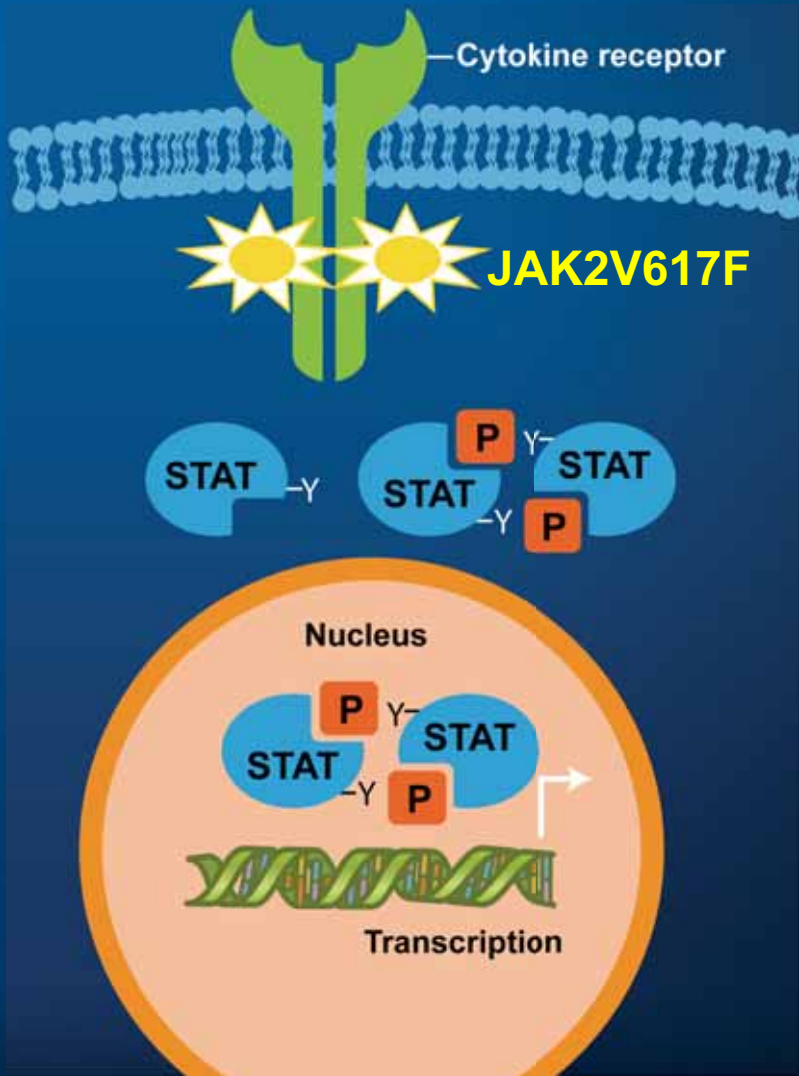
- A well-characterized signaling pathway involved in normal hematopoiesis (blood making), inflammation and immune function
- Four members of JAK family
  - JAK1, JAK2, JAK3 and Tyk2
  - Promiscuous signaling (!)
- JAK2 **specifically** mediates cytokine signaling for red blood cells and platelets (its inhibition causes anemia and low platelets)



Courtesy of Srdan Verstovsek, MD, PhD;
Shuai K, Liu B. Nat Rev Immunol 2003;3:900.

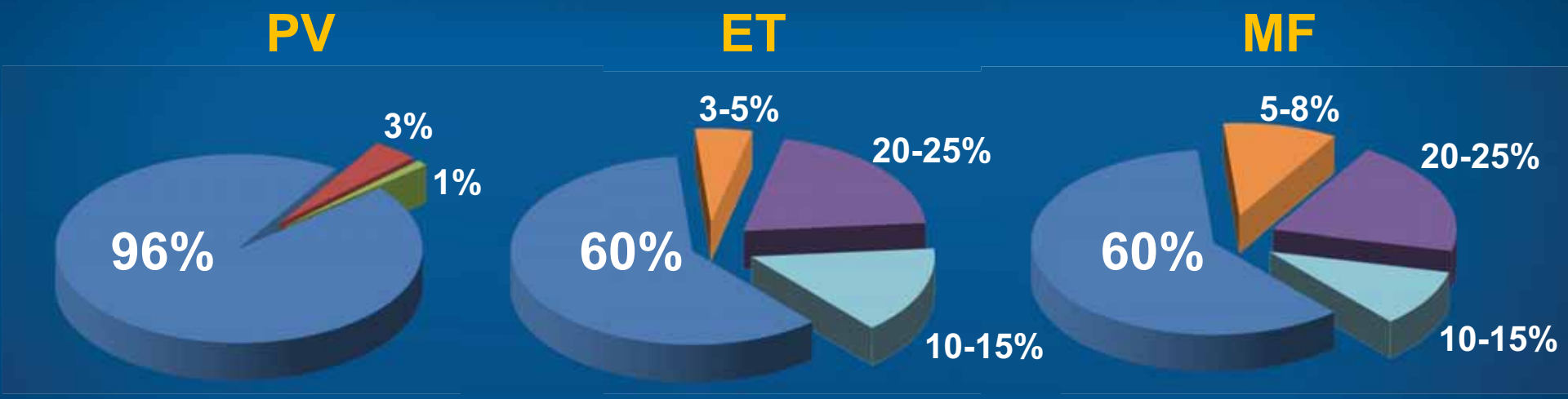
JAK2V617F Mutation in MPN

- Acquired; arises in multipotent progenitors
- Results in constitutively active JAK2 tyrosine kinase and always active JAK-STAT pathway
- Causes disease in mice (PV → MF)
- But not present in all patients
  - PV ~95%
  - ET ~50-60%
  - MF ~50-60%
  - And in other diseases



Courtesy of Srdan Verstovsek, MD, PhD;
Quintás-Cardama A. Nat Rev Drug Discov 2011;10(2):127-40.

Phenotypic Driver Mutations (they activate JAK-STAT pathway) in MPNs

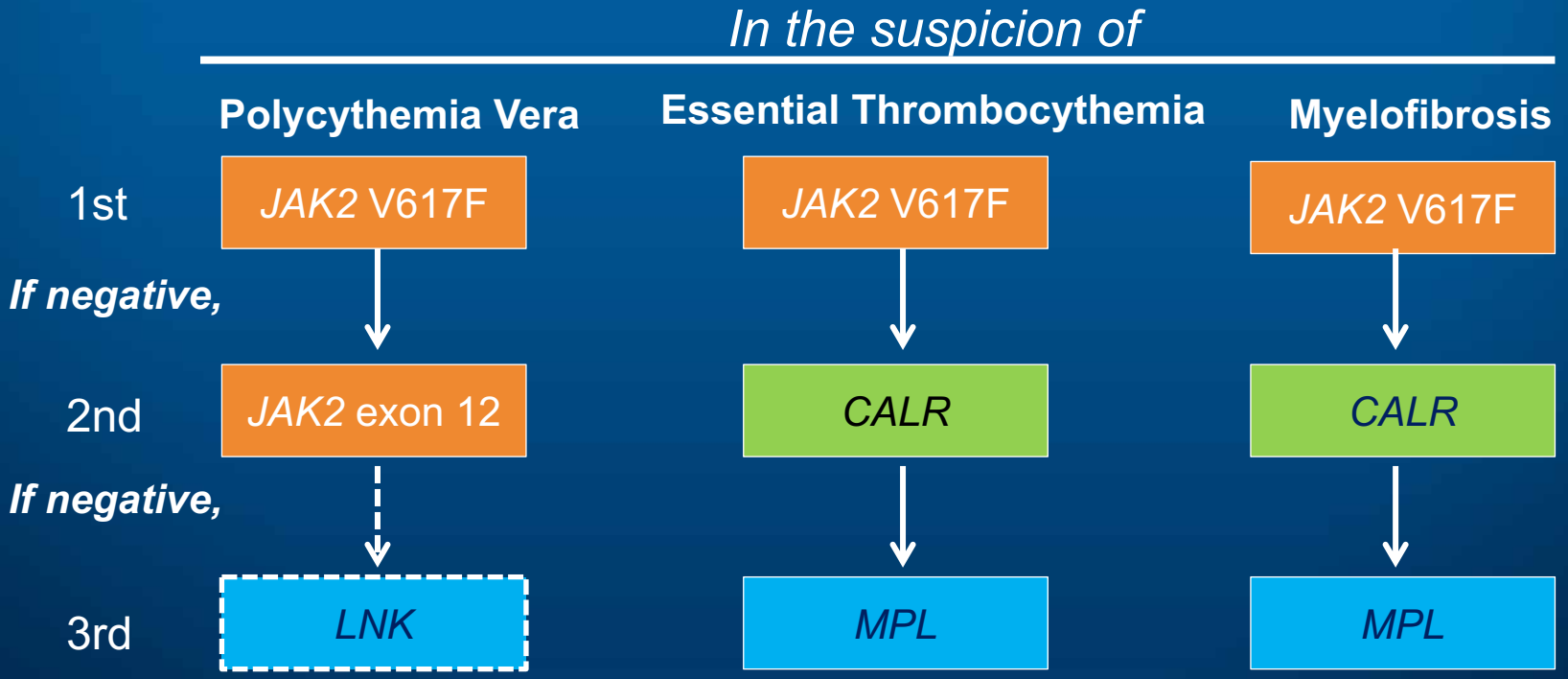


- *JAK2* V617F
- *JAK2* Exon12
- Others (*SH2B3*)
- *MPL* (W515x)
- *CALR* mut
  - Type1/Type1-like
  - Type2/Type2-like
- Unknown (Triple Negative)

Courtesy of Srdan Verstovsek, MD, PhD;
Klampfl T et al. *NEJM* 2013;369(25):2379-90; Nangalia J et al. *NEJM* 2013;369(25):2391-405.

For Diagnostic Purposes

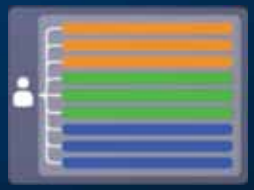
- The 3 phenotypic driver mutations should be searched for in any subjects suspected to have MPN



Courtesy of Srdan Verstovsek, MD, PhD

Approved and Commonly Used Systemic Treatments in MPNs

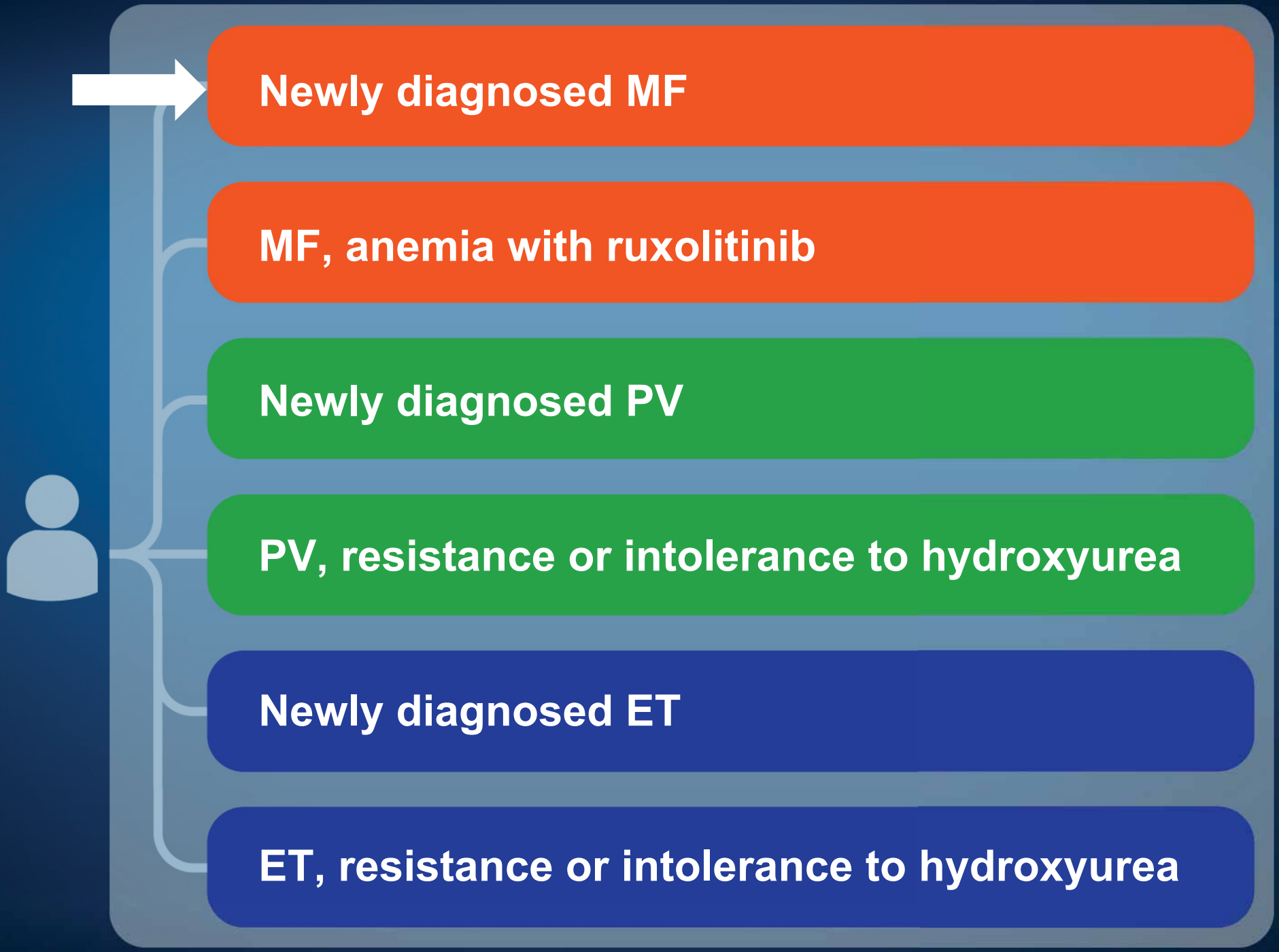
- JAK Inhibitors (Ruxolitinib)
- Hydroxyurea
- Anagrelide
- Peginterferon



71-Year-Old Man with Postpolycythemia Vera (PV) Myelofibrosis (Ms Knight)

- Diagnosed with PV in 2004
  - Hydroxyurea
- 2012: Increasing splenomegaly, fatigue and immature cells in peripheral blood, confirmed by bone marrow biopsy
  - Initiated on ruxolitinib with excellent response
  - Remains on therapy today with stable disease

Module 2: Myelofibrosis

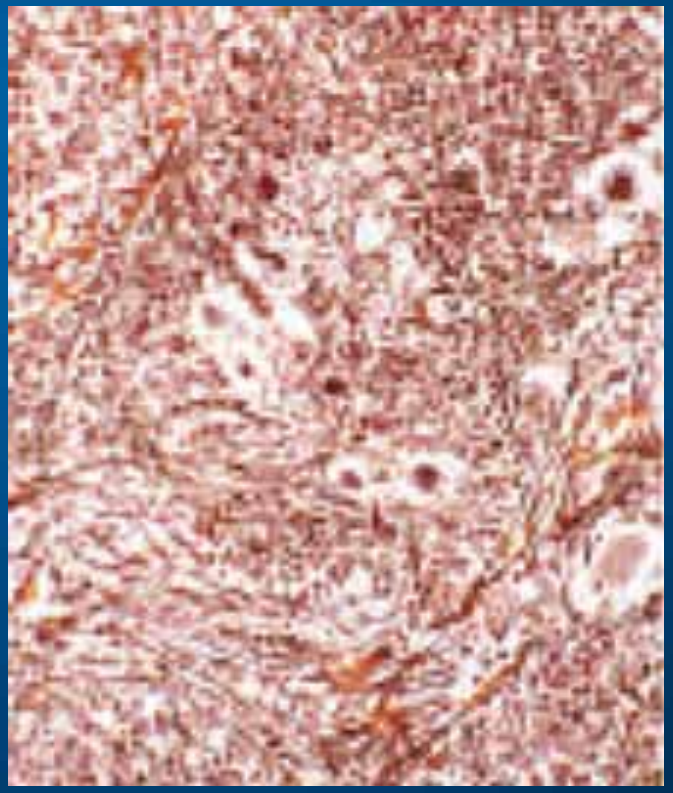

Newly diagnosed MF
MF, anemia with ruxolitinib
Newly diagnosed PV
PV, resistance or intolerance to hydroxyurea
Newly diagnosed ET
ET, resistance or intolerance to hydroxyurea

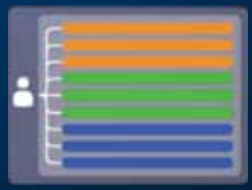
70-Year-Old Woman with Postpolycythemia Vera (PV) Myelofibrosis (Ms Swanson)

- Diagnosed with polycythemia vera
  - Anagrelide
  - Hydroxyurea
    - Transfusion dependent
- Bone marrow: Post-PV myelofibrosis
- Ruxolitinib initiated
  - Improvement in QOL including appetite, weight, diminished need for transfusion
- Recent increase in leukocytosis and splenomegaly
  - Discussed possibility of clinical trial of PI3 kinase inhibitor and ruxolitinib
  - Counts were stable at last visit so plan to continue with same dose of ruxolitinib

Clinical Features of Myelofibrosis (MF)

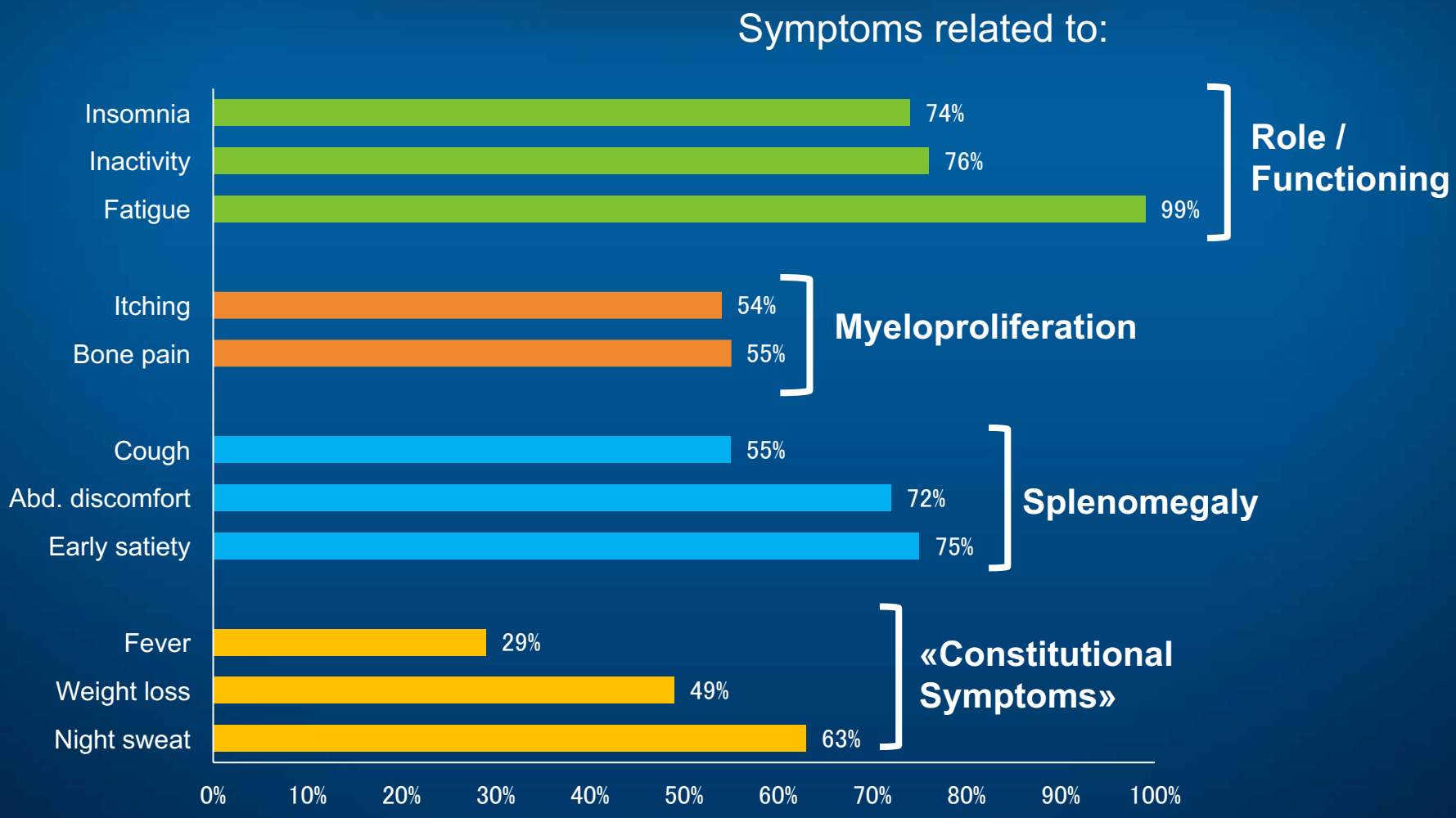
- **Bone marrow fibrosis**
- **Splenomegaly**
  - Splenomegaly-associated symptoms include abdominal pain/discomfort, early satiety
- **Cytopenias**
  - Anemia, thrombocytopenia, neutropenia
- **Constitutional symptoms**
  - Include fatigue, night sweats, pruritus (itching), bone aches, weight loss
- **Median survival: 6 years**





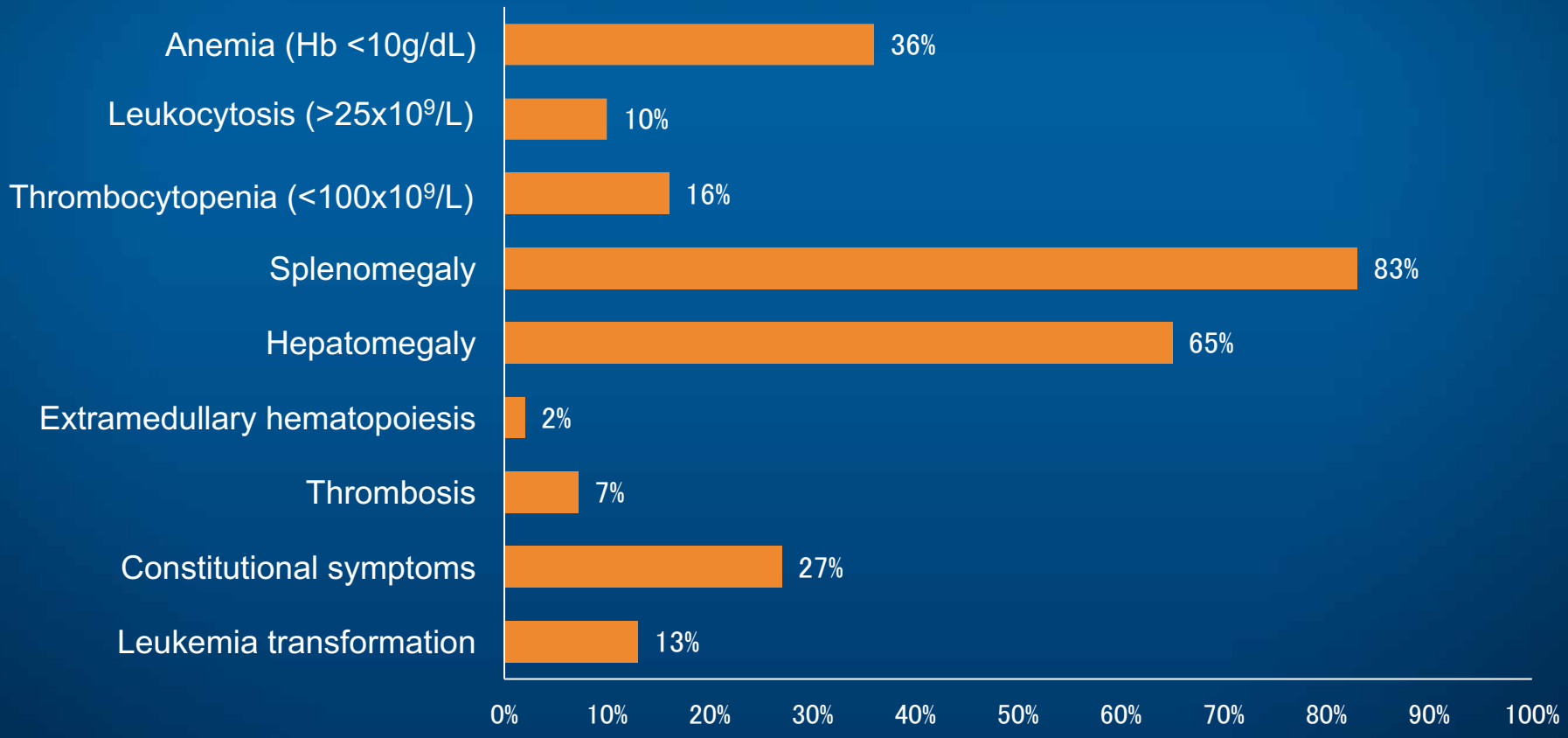
Courtesy of Srdan Verstovsek, MD, PhD

Symptomatic Burden in Myelofibrosis



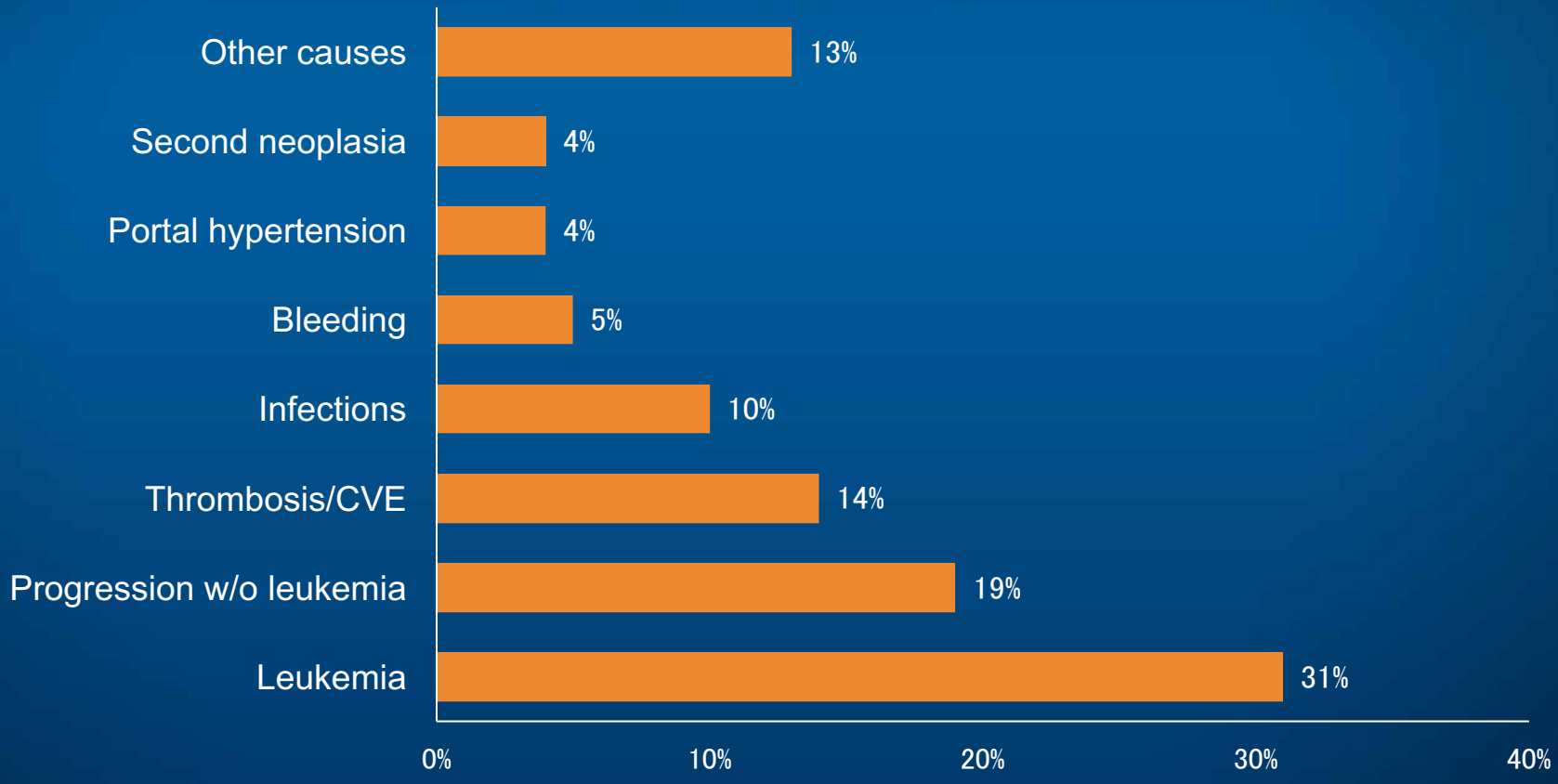
Courtesy of Srdan Verstovsek, MD, PhD; Scherber R et al. *Blood* 2011;118(2):401-8.

Main Clinical Problems in Myelofibrosis



Courtesy of Srdan Verstovsek, MD, PhD

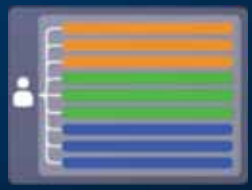
Causes of Death in Myelofibrosis



Courtesy of Srdan Verstovsek, MD, PhD; Cervantes F et al. *Blood* 2009;113:2895-901.

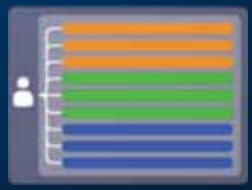
Key Clinical Considerations

- Risk stratification for patients with MF: IPSS, DIPSS and DIPSS Plus
- Potentially curative role of allogeneic stem cell transplant
  - Identification of appropriate patients
  - Risk of mortality
- Role of splenectomy in patients with MF
- Effectiveness of erythropoiesis-stimulating agents (ESAs) and growth factors in reversing MF-associated anemia and neutropenia



Primary Myelofibrosis: Treatment

- **Supportive care**
  - Transfusions
  - ESAs – not generally effective in PMF
- **Hydroxyurea**
  - Can control leukocytosis and/or thrombocytosis
  - Can ameliorate splenomegaly to some extent
  - Myelosuppression can be limiting
- **Thalidomide/lenalidomide/pomalidomide**
  - Low response rate
  - Myelosuppression
- **Splenectomy**
  - Indicated for severe symptoms related to splenomegaly
  - May be helpful for anemia and/or thrombocytopenia
- **Splenic irradiation**
  - Considered for poor surgical candidates
  - Benefits are transient (3-6 months)
- **BMT**
  - Eligibility issues



Courtesy of Daniel A Pollyea, MD, MS

Myelofibrosis: "Clinical needs"-oriented current therapy

Clinical need	Drugs/intervention	
Anemia	• Corticosteroids • Danazol • Erythropoietin	• Thalidomide • Lenalidomide
Symptomatic splenomegaly	• Ruxolitinib • Hydroxyurea	• Cladribine, IMIDs • Splenectomy
Extramedulary hematopoiesis	• Radiation therapy	
Hyperproliferative (early) disease	• Interferon	
Risk of thrombosis	• Low-dose ASA	
Constitutional symptoms/QoL	• Ruxolitinib • Corticosteroids	
Accelerated/blast phase	• Hypomethylating agents	
Improved survival	• Allo SCT • Ruxolitinib	

Courtesy of Srdan Verstovsek, MD, PhD

Allogeneic SCT in Myelofibrosis

- Consider in younger patients with higher-risk disease whose survival is expected to be <5 years

IPSS high risk	**Median survival: ~27 mo**
IPSS intermediate-2 risk	**Median survival: ~48 mo**

- Traditionally limited to patients aged <60 years and those with HLA-identical sibling match; now possible up to age 75!!!
- High transplant-related mortality and morbidity due to acute and chronic graft versus host disease (GVHD)
- Estimated 1-year treatment-related mortality: approximately 20-30%
  - Overall survival with alloSCT: approximately 50-70%

BOTTOM LINE: Less than 10% of patients undergo SCT

Courtesy of Srdan Verstovsek, MD, PhD

Splenectomy in Myelofibrosis

ASSOCIATED RISKS

- 40% morbidity
- 10% mortality
- Liver enlargement and failure
- Higher acute transformation rate?
- Average survival post splenectomy:
  - 18 months

CONTRAINDICATION

Thrombocytosis

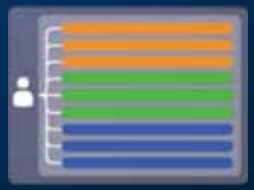
MAIN INDICATIONS

- Symptomatic splenomegaly unresponsive to treatment
- Severe refractory anemia and thrombocytopenia
- Unresponsive constitutional symptoms
- Uncontrollable hemolysis
- Portal hypertension

Courtesy of Srdan Verstovsek, MD, PhD

Key Clinical Considerations

- Mechanism of action of the JAK1/2 inhibitor ruxolitinib
  - Rapidity and durability of response
  - Role in symptom management
- Side effects and toxicities associated with ruxolitinib
  - Thrombocytopenia
  - Anemia
  - Neutropenia

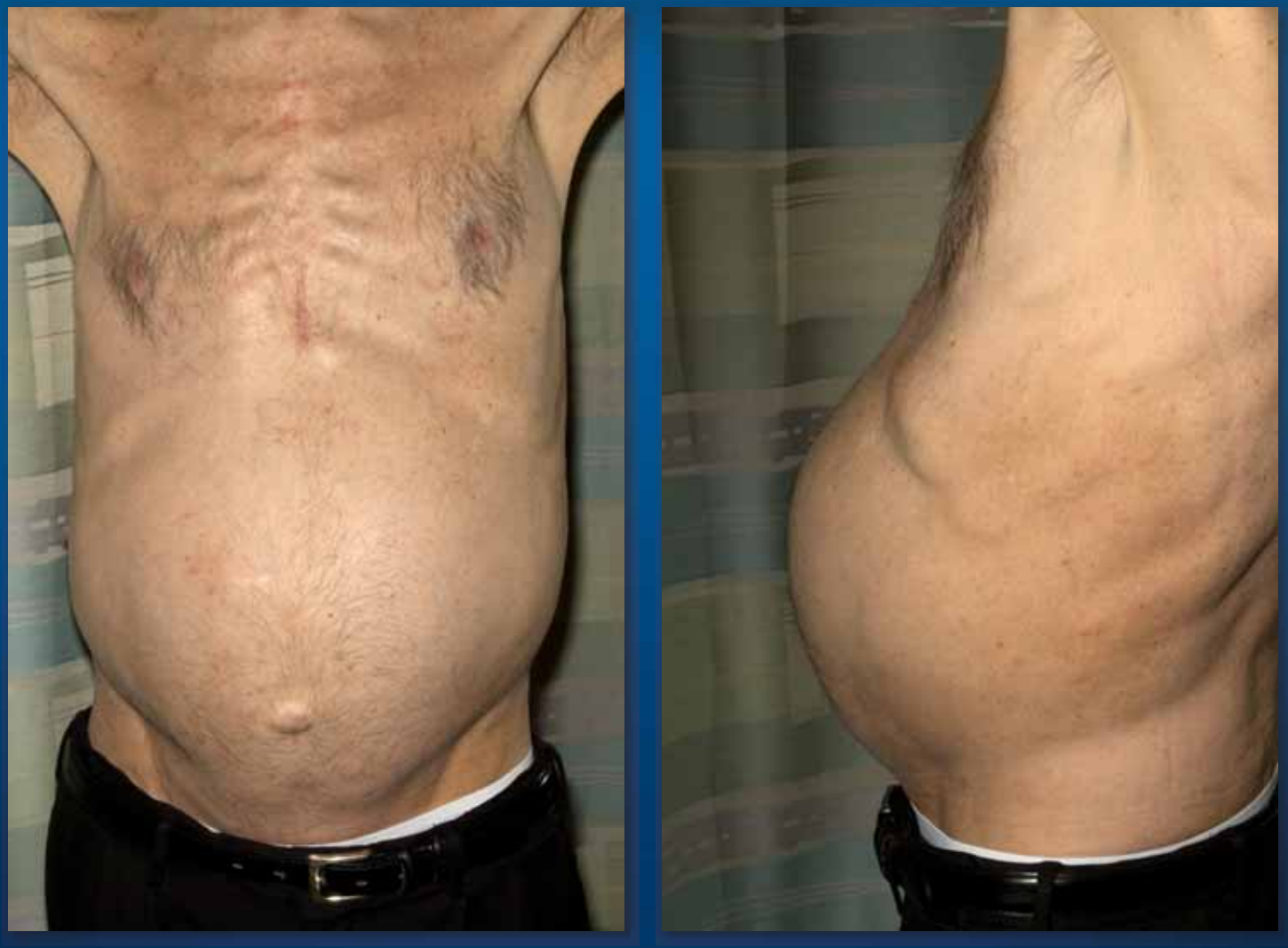


Janus Kinase (JAK)1/2 Inhibitor Ruxolitinib in Myelofibrosis (MF)

- First FDA-approved therapy for MF — November 16, 2011
- Indicated for the treatment of intermediate- and high-risk MF, including primary MF, postpolycythemia vera MF and postessential thrombocythemia MF
- COMFORT-I and COMFORT-II randomized, Phase III trials comparing ruxolitinib to placebo and best available therapy, respectively, demonstrated
  - Reduction in splenomegaly
  - Improvement in MF-related symptoms
  - Improvement in overall survival
- Key side effects: Anemia, thrombocytopenia, neutropenia
- Initial dosing based on platelet count
  - Greater than 200 x 10^9/L: 20 mg given orally twice daily
  - 100 - 200 x 10^9/L: 15 mg given orally twice daily
  - 50 - <100 x 10^9/L: 5 mg given orally twice daily

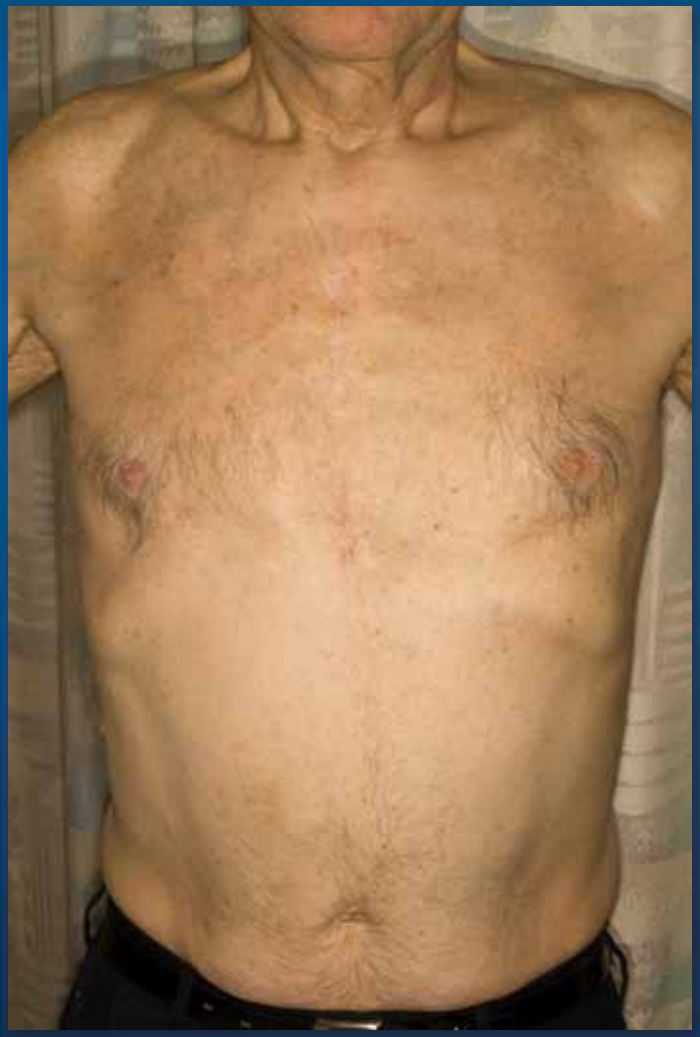
Mascarenhas J, Hoffman R. *Clin Cancer Res* 2012;18(11):3008-14. Ruxolitinib package insert

Patient with MF Before JAK Inhibitor Therapy



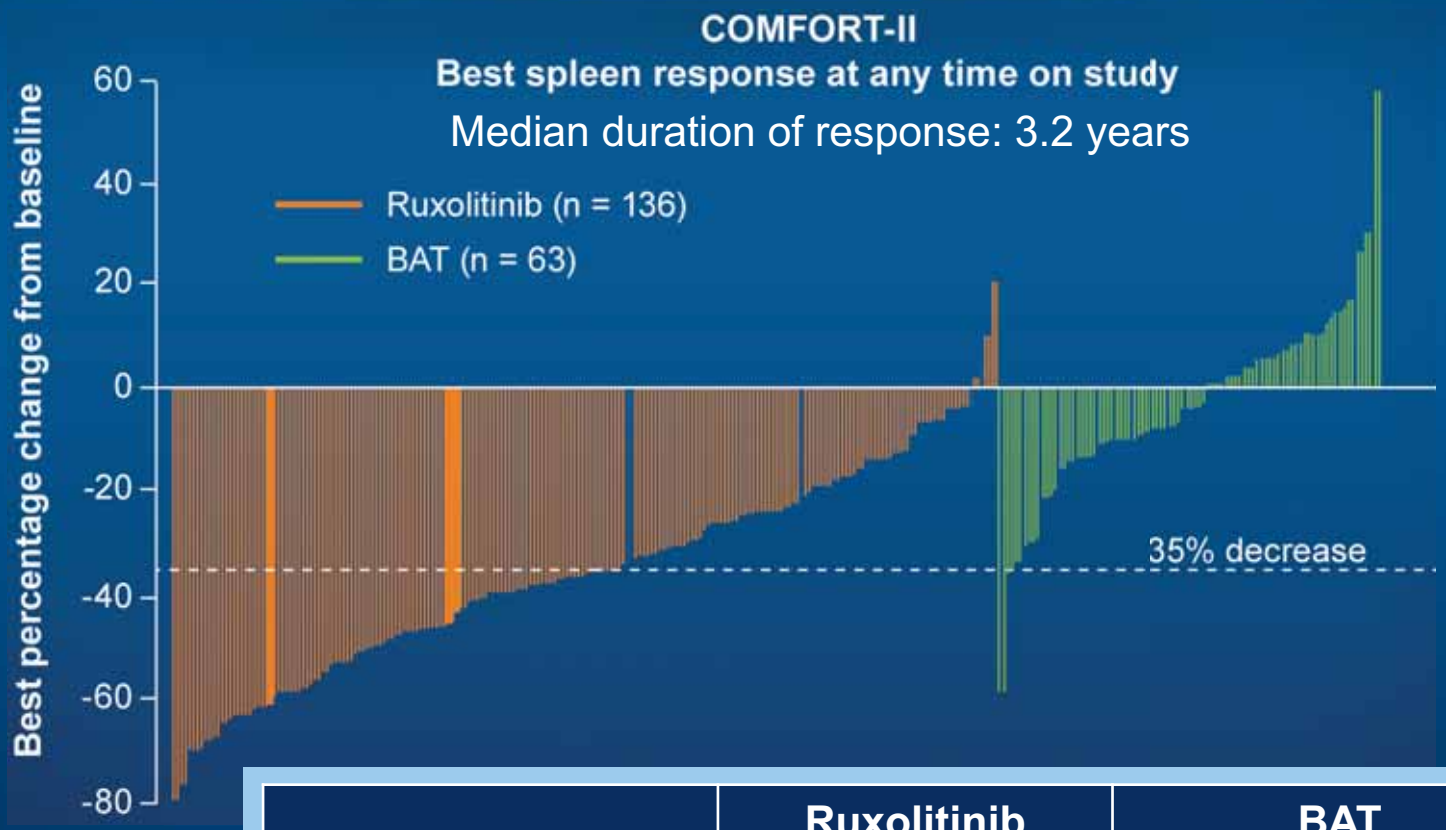
Courtesy of Srdan Verstovsek, MD, PhD

Patient with MF After 2 Months of Therapy



Courtesy of Srdan Verstovsek, MD, PhD

Phase III COMFORT-II Trial — Spleen Volume Response: Ruxolitinib vs BAT

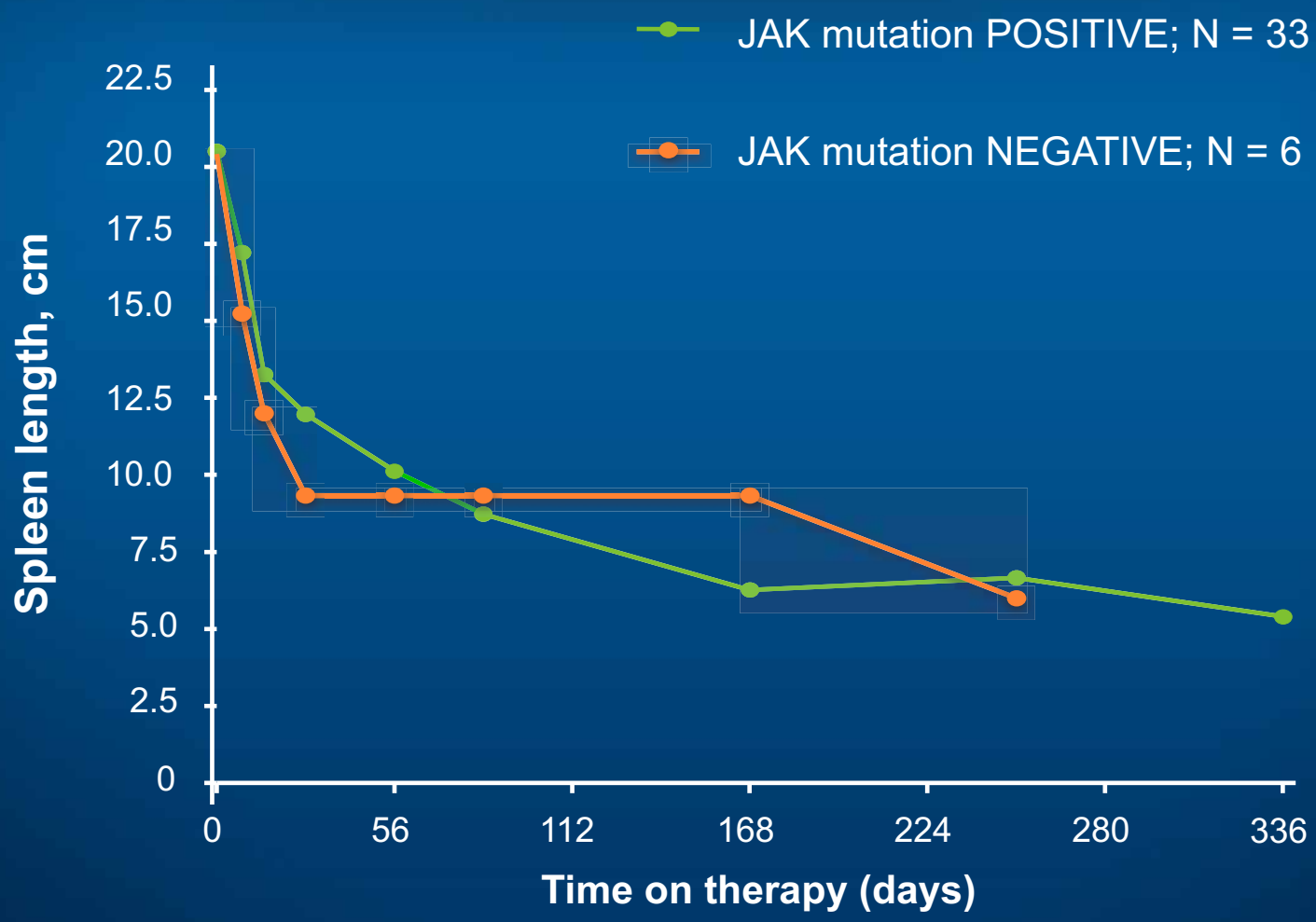


	Ruxolitinib	BAT
↓ Spleen volume	132 (97%)	35 (56%)
↑ Spleen volume	4 (3%)	28 (44%)

Courtesy of Srdan Verstovsek, MD, PhD

Harrison CN et al. *Leukemia* 2016;30:1701-7.

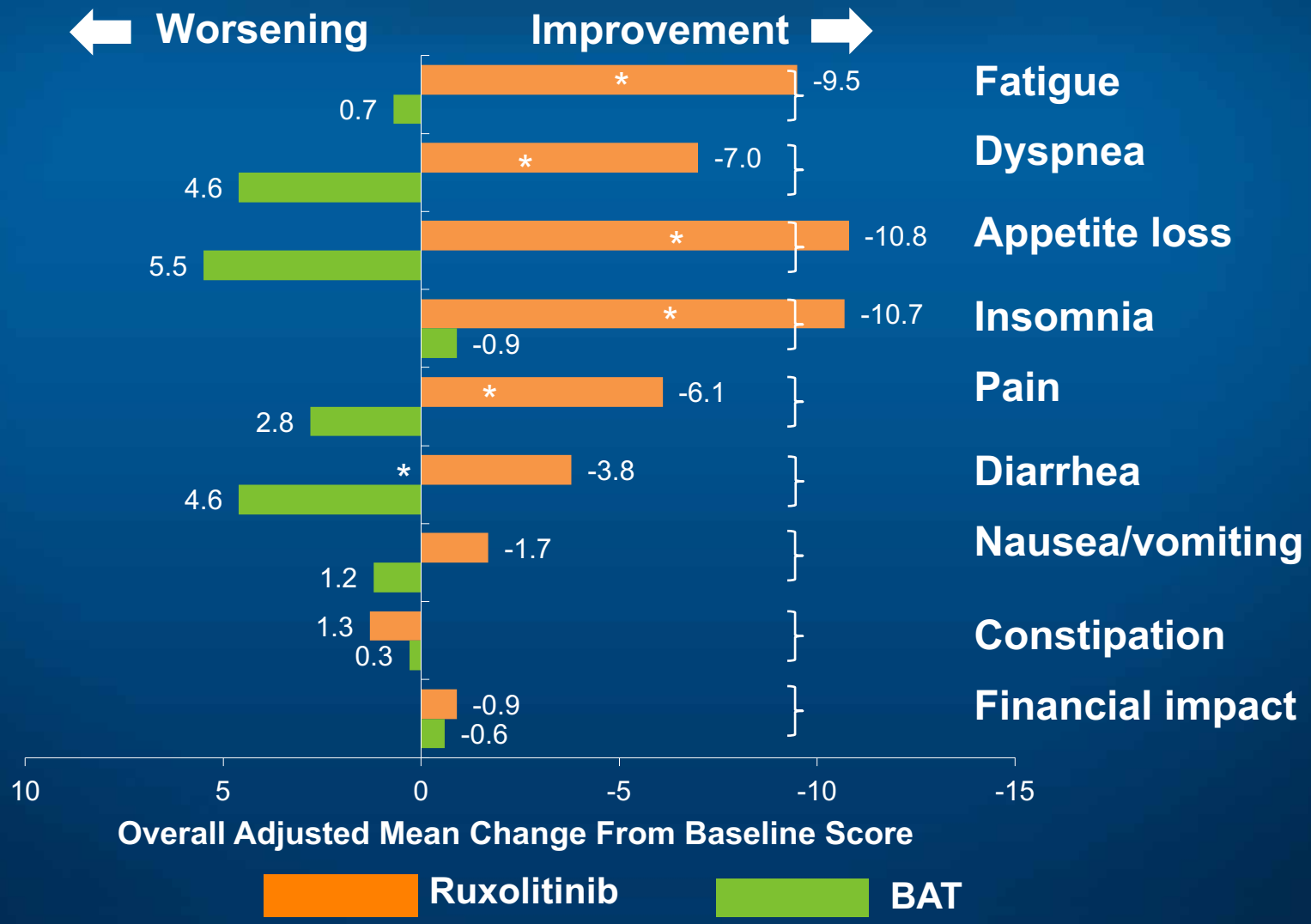
Rapid and Durable Impact on Spleen Size in Patients With and Without JAK2V617F Mutation



Courtesy of Srdan Verstovsek, MD, PhD

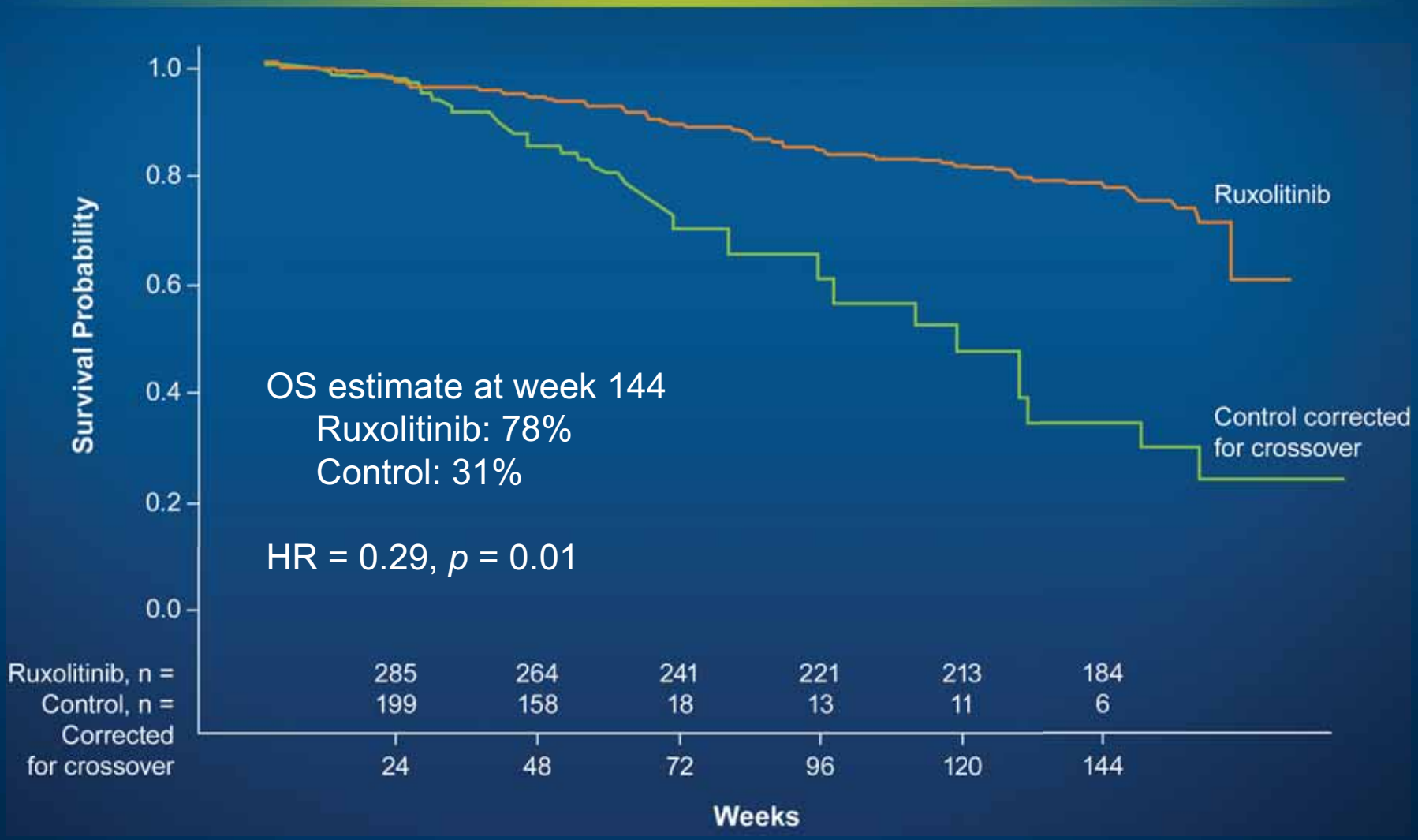
Ruxolitinib phase I/II

Improvement in Symptoms

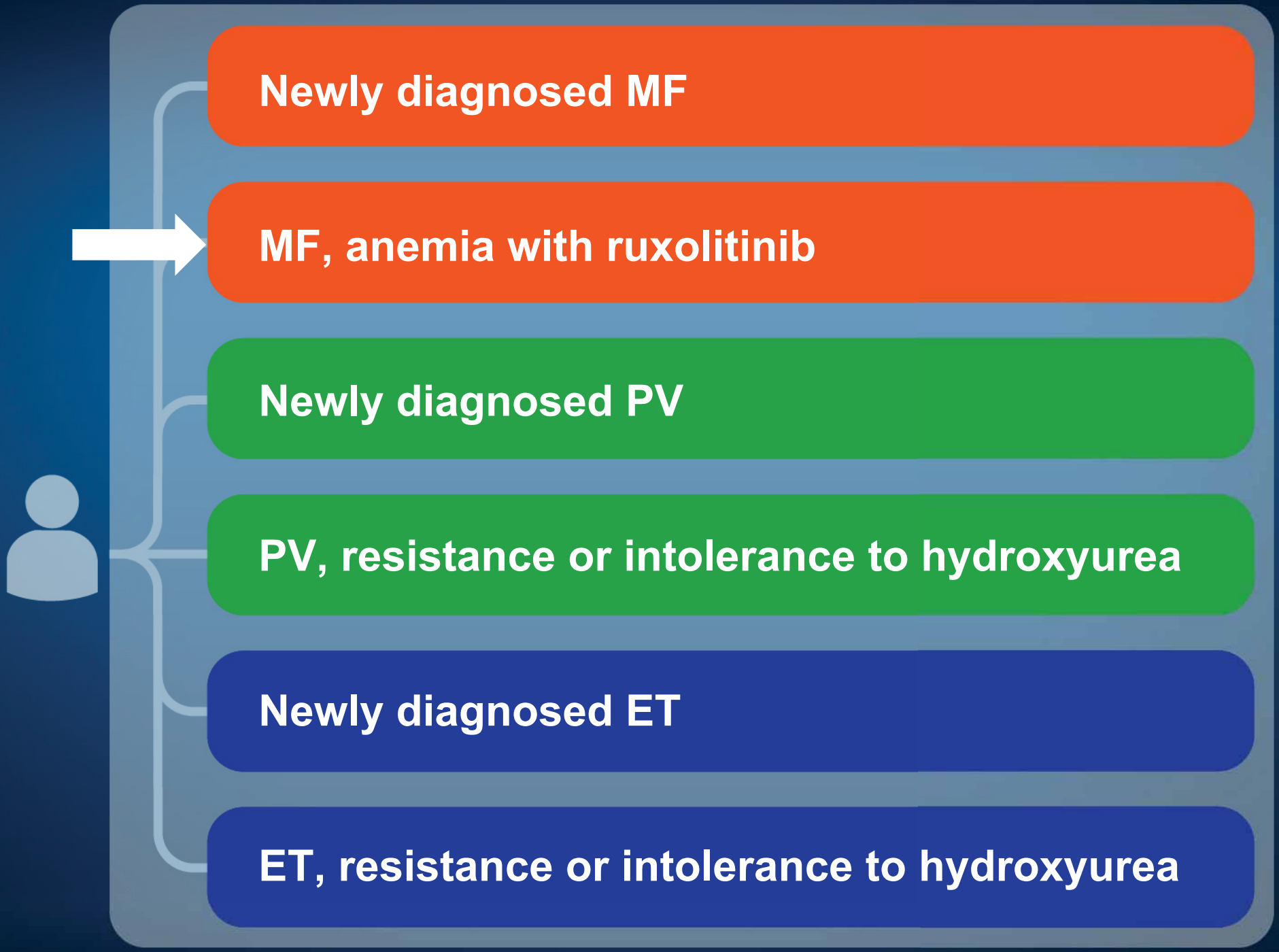


Courtesy of Srdan Verstovsek, MD, PhD

Pooled Survival Analysis of COMFORT-I and -II with Control Corrected for Crossover

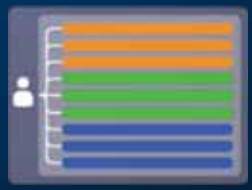


Vannucchi AM et al. *Haematologica* 2015;100(9):1139-45.


Newly diagnosed MF
MF, anemia with ruxolitinib
Newly diagnosed PV
PV, resistance or intolerance to hydroxyurea
Newly diagnosed ET
ET, resistance or intolerance to hydroxyurea

Key Clinical Considerations

- Monitoring of blood counts in patients receiving ruxolitinib
  - Dosing strategies in patients with dropping platelet or red blood cell counts
- Incidence of infections and importance of assessing risk factors for tuberculosis prior to initiating therapy with ruxolitinib
- Continuation of JAK1/2 inhibitor therapy in patients with minimal response in the spleen but stable disease and resolution of symptoms
  - Dose escalation in patients with no or suboptimal response
- Importance of gradual tapering versus abrupt discontinuation when stopping ruxolitinib



Anemia

Ruxolitinib-associated: Any grade: 96%, Grade 3/4: 45%

- **Prior to starting and during therapy, educate about the possible signs and symptoms of anemia:**
  - Shortness of breath or fatigue
  - Chest discomfort, headache or dizziness
  - Cold extremities or pale skin
- **Reinforce education during therapy and instruct patients to report any of these symptoms to their provider**
- **Dose interruption or modification**
  - Dose modification or interruption for treatment-induced anemia is at the provider's discretion.
  - Transfusion of blood products is based on patient symptoms and institution-based guidelines and protocols.
- **Laboratory monitoring**
  - Monitor complete blood count with differential prior to therapy initiation, every 2 to 4 weeks and as needed based on symptoms.

Lowery EW et al. *Clin J Oncol Nurs* 2013;17(3):312-8.

Thrombocytopenia

Ruxolitinib-associated: Any grade: 70%, Grade 3/4: 13%

- **Prior to starting and during therapy, assess for and educate patients about the possible signs and symptoms of thrombocytopenia, such as unusual bleeding, easy bruising and petechiae**
- **Educate patients about safety precautions to prevent bleeding events during thrombocytopenia**
  - Avoid straining, heavy lifting or valsalva maneuver.
  - Avoid bending at the waist (keep head above heart).
  - Use soft toothbrush and avoid dental floss or dental procedures if platelets are 50 x 10^9/L or less.
  - Avoid sexual intercourse if platelets are 50 x 10^9/L or less.
  - Consider a stool softener for constipation.
- **Reinforce education during therapy and instruct patients to report any of these symptoms to their provider**
- **Dose interruption or modification**
  - Thrombocytopenia (Grades 3/4) typically resolves after 2 weeks of dose interruption.
- **Laboratory monitoring**
  - Monitor complete blood count with differential prior to therapy initiation, every 2 to 4 weeks and as needed based on symptoms.

Lowery EW et al. *Clin J Oncol Nurs* 2013;17(3):312-8.

Neutropenia and Infection

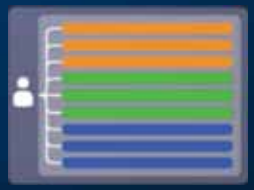
Ruxolitinib-associated: Any grade: 19%, Grade 3/4: 7%

- **Prior to starting and during therapy, assess for and educate patients about the possible signs and symptoms of infection, including fever**
- **Prior to starting therapy, instruct the patient to:**
  - Buy a digital thermometer.
  - Check temperature if suspect fever and peripheral neuropathy.
  - Report any temperature of 100.5˚ F (38˚ C) or greater to provider.
- **Reinforce education throughout therapy**
- **Dose interruption or modification**
  - Dose interruption or modification for treatment-induced neutropenia is at the provider's discretion.
  - Only 1% of patients in clinical trials stopped treatment for neutropenia.
- **Laboratory monitoring**
  - Monitor complete blood count with differential prior to therapy initiation, every 2 to 4 weeks and as needed based on symptoms.
  - If a patient develops neutropenic fever, obtain blood cultures (and other cultures depending on symptoms) and begin antibiotics per institution guidelines and protocols.

Lowery EW et al. *Clin J Oncol Nurs* 2013;17(3):312-8.

Key Clinical Considerations

- Commonly used approaches in the management of progressive MF
- Promising investigational agents and regimens

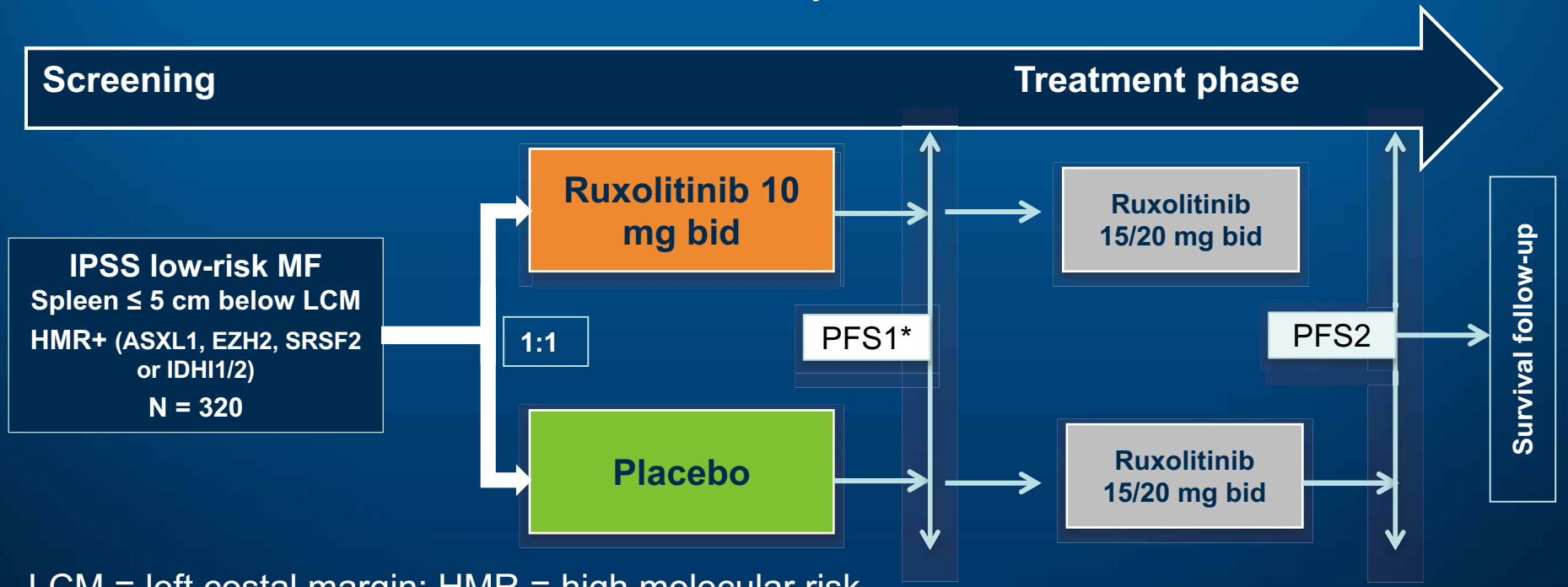


Phase III ReTHINK trial: Prevention study in early MF

Objectives & study design

Primary Objective: Progression-free survival

Secondary Objectives: Time to progression in spleen/symptoms, safety, overall survival



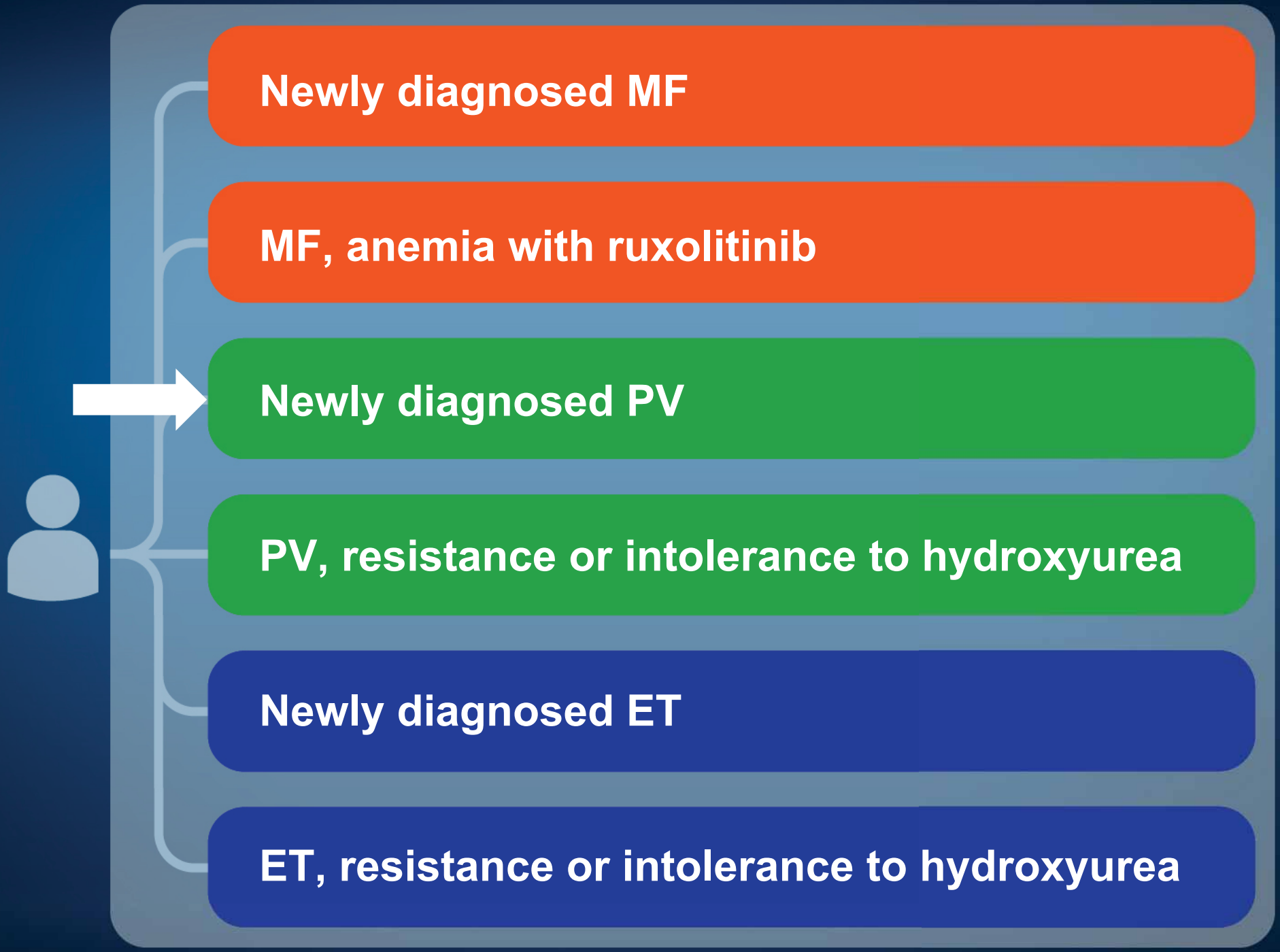
LCM = left costal margin; HMR = high molecular risk

Passamonti F et al. *Proc ASCO* 2016;Abstract TPS7080; www.clinicaltrials.gov (NCT02598297).

54-Year-Old Man with JAK-Mutant Myelofibrosis (Ms Knight)

- 2009: Presents with fatigue, weight loss and night sweats
  - Diagnosed with JAK2-mutant primary myelofibrosis
- Dec 2011: Treated on trial with JAK inhibitor NS-018
  - Oct 2013: Completed 25 cycles and discontinued due to increasing splenomegaly
- Nov 2013: Initiated on clinical trial of antifibrotic investigational agent PRM-151
  - Currently on study cycle 41 and doing well

Module 3: Polycythemia Vera (PV)

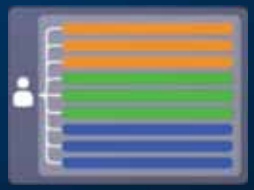

Newly diagnosed MF
MF, anemia with ruxolitinib
Newly diagnosed PV
PV, resistance or intolerance to hydroxyurea
Newly diagnosed ET
ET, resistance or intolerance to hydroxyurea

47-Year-Old Woman with Polycythemia Vera (Ms Dahl)

- 2001: Diagnosis of PV after delivery of her first child
- 2002–2005: Initial treatment with phlebotomies, imatinib on clinical trial
- May 2006–Sept 2006: Interferon
- Sept 2006: Transient ischemic attack
  - Treatment switched to hydroxyurea
- Phlebotomies no longer required, platelet counts normalized
- Patient has concurrent diagnosis of cervical cancer

Key Clinical Considerations

- Typical presentation, symptoms and clinical course of PV
- Incidence of venous and arterial thrombosis among patients with PV



Polycythemia Vera Clinical Features

- Often incidental finding of high Hgb/HCT
- Nonspecific complaints: HA, weakness, dizziness, excessive sweating
- Pruritus
  - Typically after hot bath/shower or rubbing of skin
  - Presumed 2/2 mast cell degranulation – histamine, prostaglandins, etc...(unproven)
  - ASA often effective in reducing symptoms; can be debilitating
- Thrombosis (venous or arterial)
  - Risk factors include age, h/o thrombosis, leukocytosis
  - Suspect PV in patients with unusual sites of thrombosis, eg, Budd-Chiari, portal, splenic or mesenteric vein thrombosis, particularly in women younger than 45
- Splenomegaly +/- hepatomegaly

Courtesy of Daniel A Pollyea, MD, MS

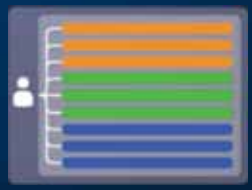
Course and Prognosis

- Median survival is ~ 14 years
- Chronic phase may last for years
- Progression to:
  - Myelofibrosis (~10% at 10 years)
  - AML (1-5% at 10 years)
- Thrombosis is major source of morbidity and mortality

Courtesy of Daniel A Pollyea, MD, MS

Key Clinical Considerations

- Primary treatment approaches in PV
  - Phlebotomy
  - Antiplatelet/anticoagulation therapy
  - Cytoreductive therapy (ie, hydroxyurea or interferon alpha)
- Management of common hydroxyurea-associated side effects
- Time course to and development of hydroxyurea resistance



PV Treatment

- Modification of cardiovascular risk factors
  - Smoking, weight loss, blood pressure control, glucose control if diabetic, etc
- Low-dose aspirin indicated for all patients
- Phlebotomy: Goal to hematocrit < 45% (<42% in females)
- Cytoreductive therapy (usually hydroxyurea)
  - Indicated for patients at high risk for thrombosis
    - Age > 60 or h/o thrombosis
- Alpha-interferon (younger patients with high-risk disease)

Courtesy of Daniel A Pollyea, MD, MS

Hydroxyurea (HU) in PV Management

- HU is often used as a first-line cytoreductive treatment for patients with PV who are at high risk for vascular complications
- Clinical activities
  - Controls myeloproliferation
  - Reduces splenomegaly
  - May reduce risk of major thrombosis (limited evidence in PV)
- Side effects
  - Myelosuppression, leg ulcers, hyperpigmentation, fever, alopecia, increased risk of squamous cell carcinoma

Courtesy of Srdan Verstovsek, MD, PhD

Sever M et al. *Leuk Lymphoma* 2014;55(12):2685-90; Mascarenhas J et al. *Haematologica* 2014;99(6):945-49; Fruchtman SM et al. *Semin Hematol* 1997;34(1):17-23.

Phlebotomy and Aspirin in PV Management

Phlebotomy

- Reduces hematocrit (HCT) (hyperviscosity); goal is HCT < 45%
- Does not control systemic symptoms or progressive symptomatic splenomegaly well
- Iron deficiency is common with repeated phlebotomies
  - Associated with fatigue, cognitive impairment, increased pulmonary artery pressure

Low-dose aspirin

- Persistently enhanced platelet activation contributes to the higher risk of thrombosis in patients with PV
- Placebo-controlled ECLAP trial (N= 518): Low-dose aspirin can safely prevent thrombotic complications in patients with PV who have no contraindications to aspirin
- Screening for acquired von Willebrand syndrome is recommended before administrating aspirin in the presence of extreme thrombocytosis

Courtesy of Srdan Verstovsek, MD, PhD

Marchioli R et al. *N Engl J Med* 2013;368(1):22-33; Mascarenhas J et al. *Haematologica* 2014;99(6):945-49; Patrono C et al. *Blood* 2013;121(10):1701-11; Landolfi R et al. *N Engl J Med* 2004;350:114-24; Tefferi A, Barbui T. *Am J Hematol* 2015;90:163-73.

- Newly diagnosed MF
- MF, anemia with ruxolitinib
- Newly diagnosed PV
- PV, resistance or intolerance to hydroxyurea
- Newly diagnosed ET
- ET, resistance or intolerance to hydroxyurea

Resistance/Intolerance to Hydroxyurea in PV

Need for phlebotomies
after 3 months of ≥2 g/day of HU

Uncontrolled myeloproliferation
after 3 months of ≥2g/day of HU

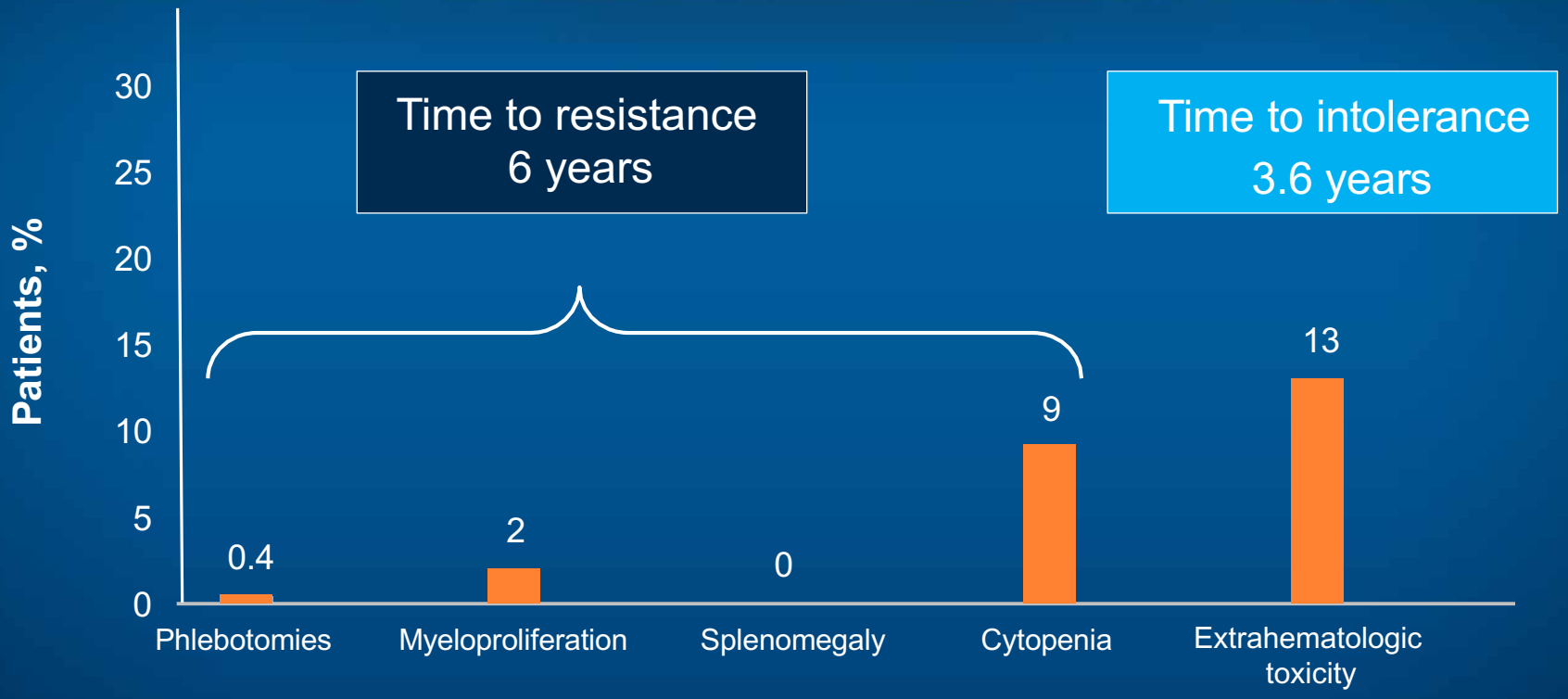
Splenomegaly
after 3 months of ≥2 g/day of HU

Cytopenia
at the lowest dose of HU required to achieve a CR or a PR

Nonhematologic toxicity
at any HU dose

Courtesy of Srdan Verstovsek, MD, PhD; Barosi G et al. *Blood* 2013;121:4778-81.

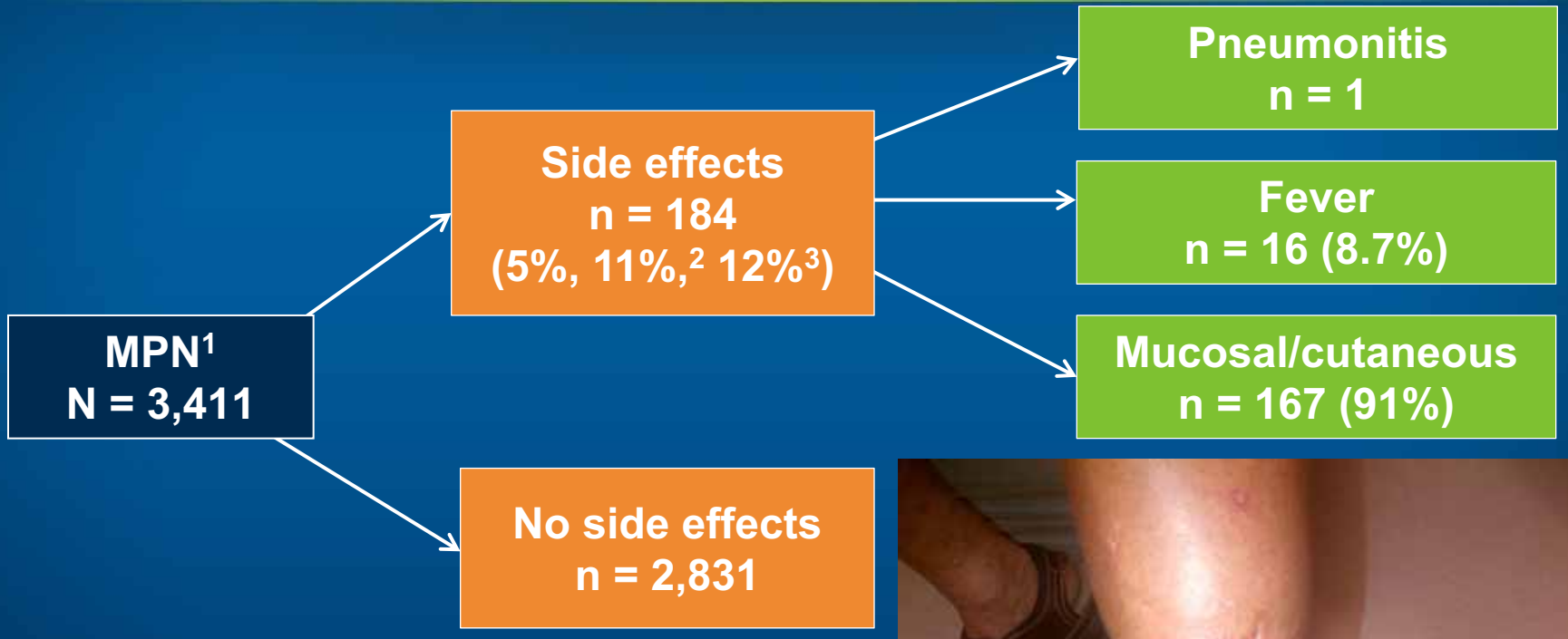
Frequency of Resistance or Intolerance to Hydroxyurea in 261 Patients with PV

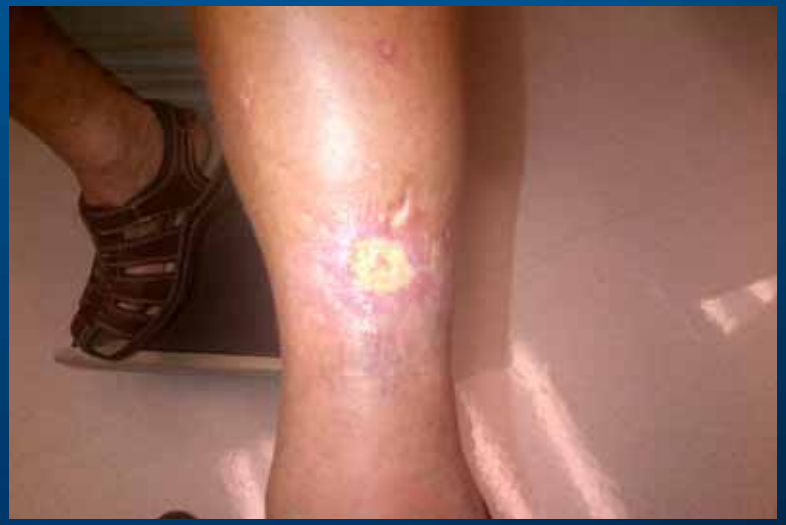


Median follow-up: 7.2 years
Median duration of HU: 4.4 years
Median age: resistance 75 years, intolerance 73 years

Courtesy of Srdan Verstovsek, MD, PhD; Alvarez-Larrán A et al. *Blood* 2012;119:1363-9.

Intolerance of Hydroxyurea in the PV Setting



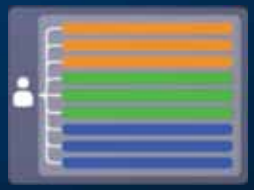


Courtesy of Srdan Verstovsek, MD, PhD;

1. Antonioli E et al. *Am J Hematol* 2012;87:552-4.
2. Harrison CN et al. *N Engl J Med* 2005;353:33-45.
3. Hernández-Boluda JC et al. *Br J Haematol* 2011;152:81-8.

Key Clinical Considerations

- Biologic rationale for JAK1/2 inhibitor activity in PV
- Integration of ruxolitinib into the treatment algorithm for patients who are hydroxyurea refractory or intolerant
- Rationale for differences in approach to ruxolitinib dosing for patients with PV versus MF



Recommendations of Second-Line Therapy in PV: Current Drug Options

- **Interferon-α**, *if hydroxyurea resistant/intolerant*
- **Hydroxyurea**, *if interferon-α resistant/intolerant*
- **Busulfan**, for patients with short life expectancy
- **Ruxolitinib**, in patients with inadequate response or intolerant to hydroxyurea (in the USA)

Courtesy of Srdan Verstovsek, MD, PhD; Barbui T et al. *J Clin Oncol* 2011;29:761-70.

Ruxolitinib (JAK1/JAK2 Inhibitor) for Patients with HU-Refractory or Intolerant PV

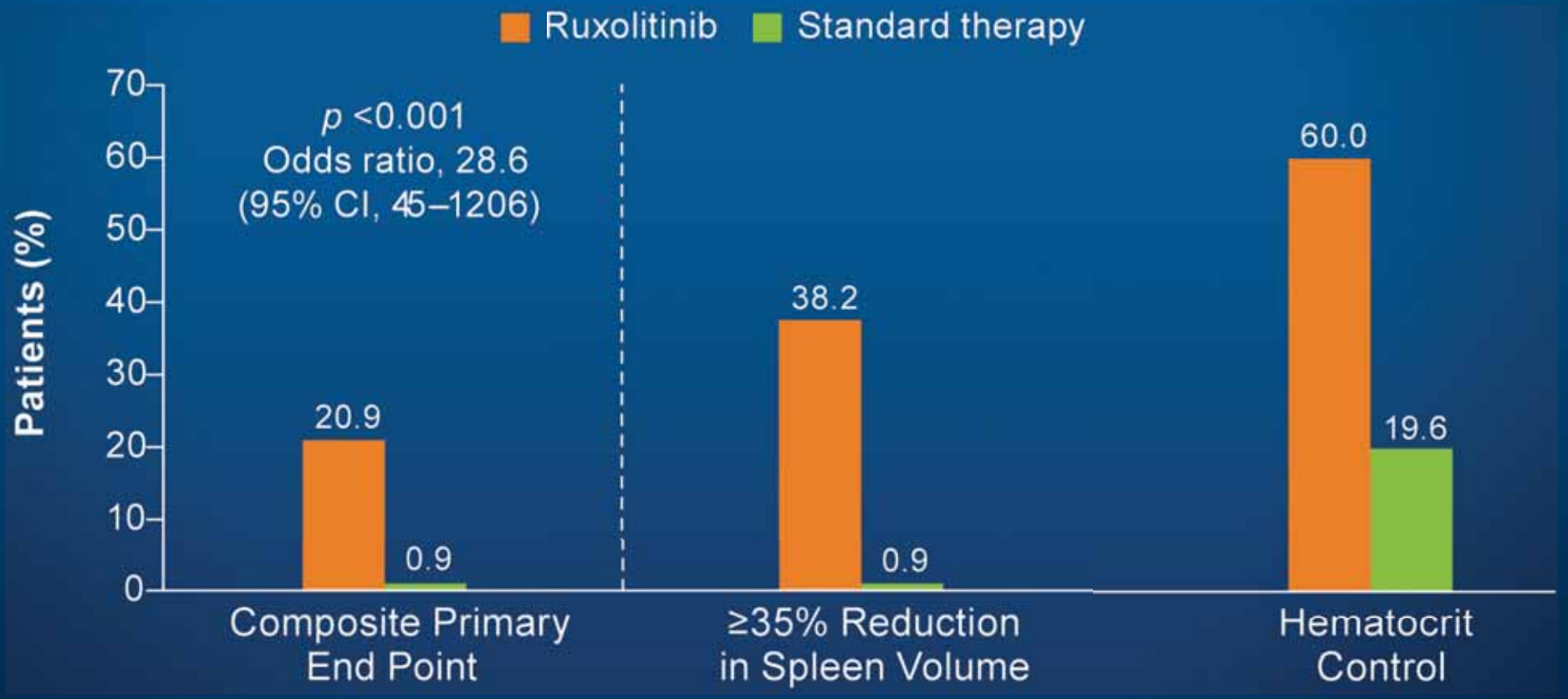
Approved Indication	US Approval Date
Patients with intermediate or high-risk MF, including primary MF, post-PV MF and post-ET MF	Nov 2011
Patients with PV who have had an inadequate response to or are intolerant of hydroxyurea*	Dec 2014

* Compared to best available therapy, ruxolitinib led to:
  - Superior control of hematocrit
  - Superior control of CBC (incl. WBC and platelets)
  - Superior reduction in splenomegaly
  - Superior reduction in PV-related symptoms
  - Trend for less thrombotic events

For PV, the approved starting dose is **10 mg** orally twice daily.

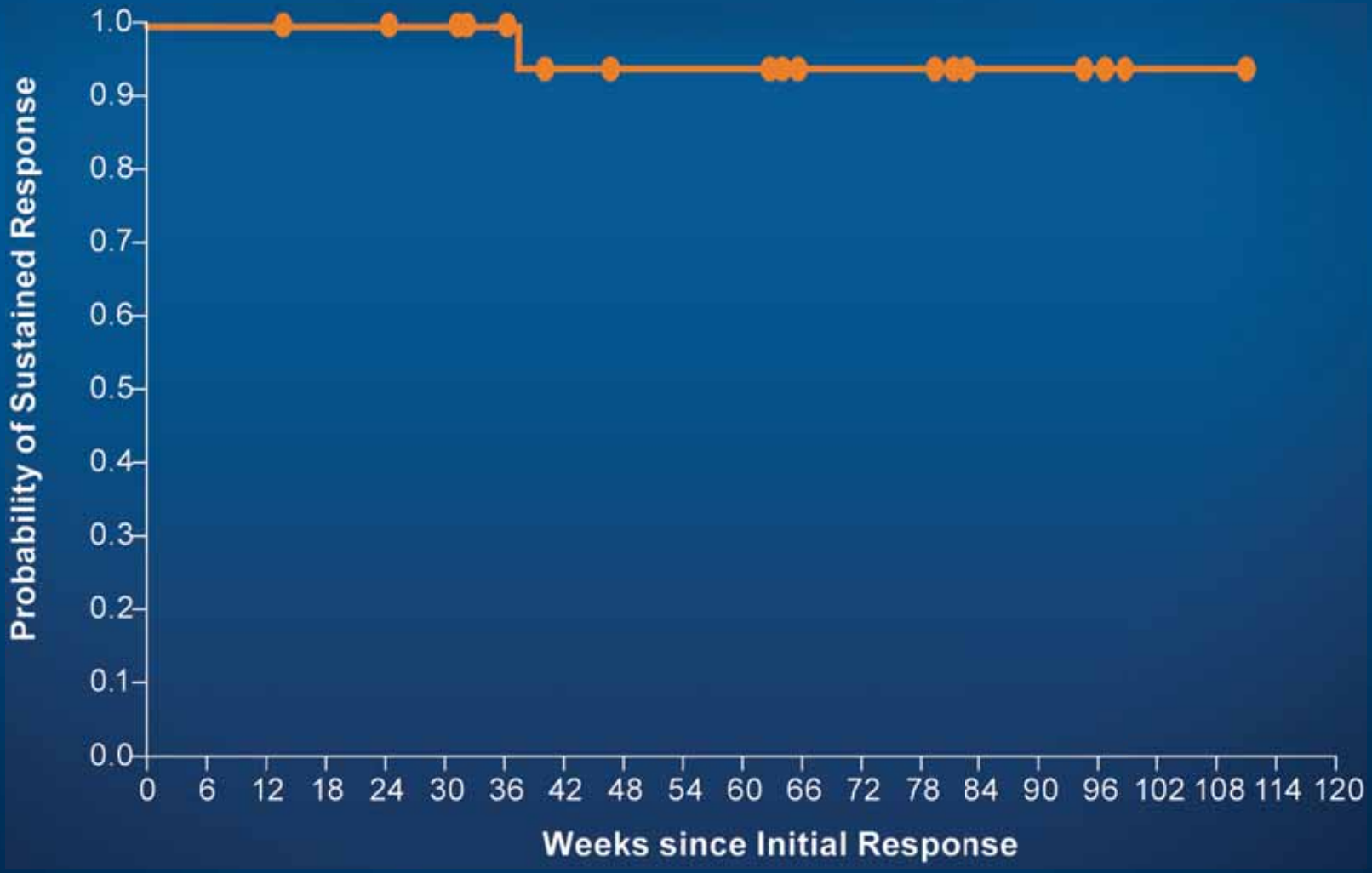
Courtesy of Srdan Verstovsek, MD, PhD; Ruxolitinib package insert.

Phase III RESPONSE Study: Compositive Endpoints — Splenic Reduction and Hematocrit Control



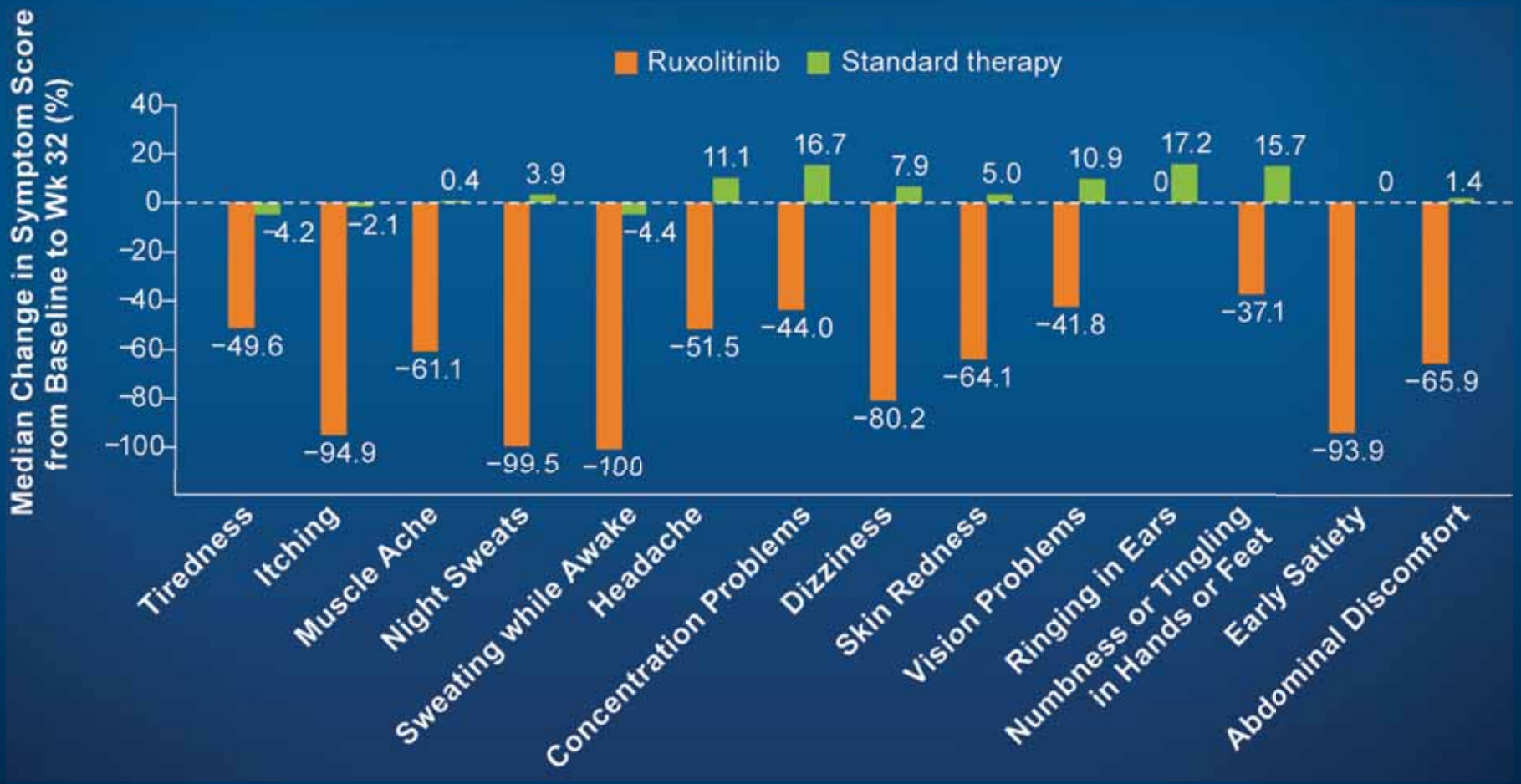
Vannucchi AM et al. *N Engl J Med* 2015;372:426-35.

RESPONSE Study: Duration of the Primary Response



Vannucchi AM et al. *N Engl J Med* 2015;372:426-35.

RESPONSE Study: Median Percentage Change from Baseline to Week 32 of 14 Symptoms on the MPN-SAF



Vannucchi AM et al. *N Engl J Med* 2015;372:426-35.

Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study

Francesco Passamonti, Martin Griesshammer, Francesca Palandri, Miklos Egyed, Giulia Benevolo, Timothy Devos, Jeannie Callum, Alessandro M Vannucchi, Serdar Sivgin, Caroline Bensasson, Mahmudul Khan, Nadjat Mounedji, Guray Saydam

Lancet Oncol 2017;18(1):88-99.

72-Year-Old Woman with Polycythemia Vera (Ms Swanson)

- Initially treated with phlebotomy followed by hydroxyurea but developed severe rash
- Transitioned to low-dose aspirin, anagrelide and phlebotomy with poor response
- April 2015: Ruxolitinib
- Dec 2016: Presented to ED with symptoms of stroke
  - Patient was noncompliant with therapy at time of stroke, so she was continued on same dose of ruxolitinib and phlebotomized
  - Has been compliant since recovering from stroke with stable counts and was able to attend her daughter's wedding

Module 4: Essential Thrombocythemia (ET)

Newly diagnosed MF

MF, anemia with ruxolitinib

Newly diagnosed PV

PV, resistance or intolerance to hydroxyurea

Newly diagnosed ET

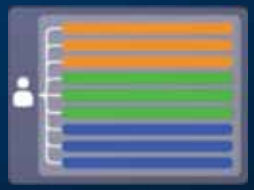
ET, resistance or intolerance to hydroxyurea

50-Year-Old Man with Essential Thrombocythemia (Ms Dahl)

- Thrombocytosis discovered on annual exam
  - Patient reports occasional night sweats
- Feb 2017: Diagnosis of essential thrombocythemia with CALR mutation
  - Hydroxyurea and aspirin
  - Platelet counts improved
- Family history of AML (grandfather)
- Patient continues to work in his career in sales

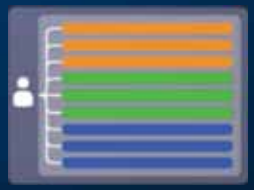
Key Clinical Considerations

- Systemic therapy for low-risk, asymptomatic versus high-risk ET
- Treatment options for patients with high-risk ET who are resistant or intolerant to hydroxyurea
  - Anagrelide
  - Interferon alpha
- Available data with and current role, if any, of ruxolitinib in the management of ET



ET Clinical Features

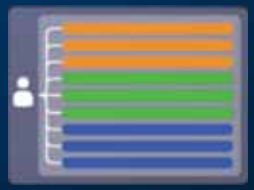
- Chronic thrombocytosis (often extreme, >1 x 10^6/μL)
- Many patients are asymptomatic
- Vasomotor symptoms: headaches, syncope, visual disturbances, atypical chest pain, erythromelalgia (typically ASA responsive)
- Thrombosis is a major cause of morbidity and mortality
  - Both arterial and venous; unusual sites
  - No clear association with platelet count
- Paradoxical increase in bleeding complications
  - Risk factors/associations:
    - Extreme thrombocytosis > 1 million (controversial)
    - Use of ASA > 325 mg/day or other NSAIDs
    - Acquired von Willebrand disease
- Splenomegaly



Courtesy of Daniel A Pollyea, MD, MS

ET Clinical Course

- Survival curves near age-matched controls
  - Thrombosis major cause of morbidity and mortality
  - Progression to myelofibrosis in ~5% and AML in ~1-5%



Courtesy of Daniel A Pollyea, MD, MS

Key Issues in ET Management

  - Normalization of platelet count (cytoreduction) to decrease thrombotic risk in high-risk disease
  - Stroke and heart attack are the main concerns
- Correction of other CV risk factors
  - Weight reduction, blood pressure control, glucose control in diabetic patients, smoking cessation
- Improvement in disease-related symptoms

Courtesy of Srdan Verstovsek, MD, PhD

ET Treatment

Low-risk asymptomatic ET

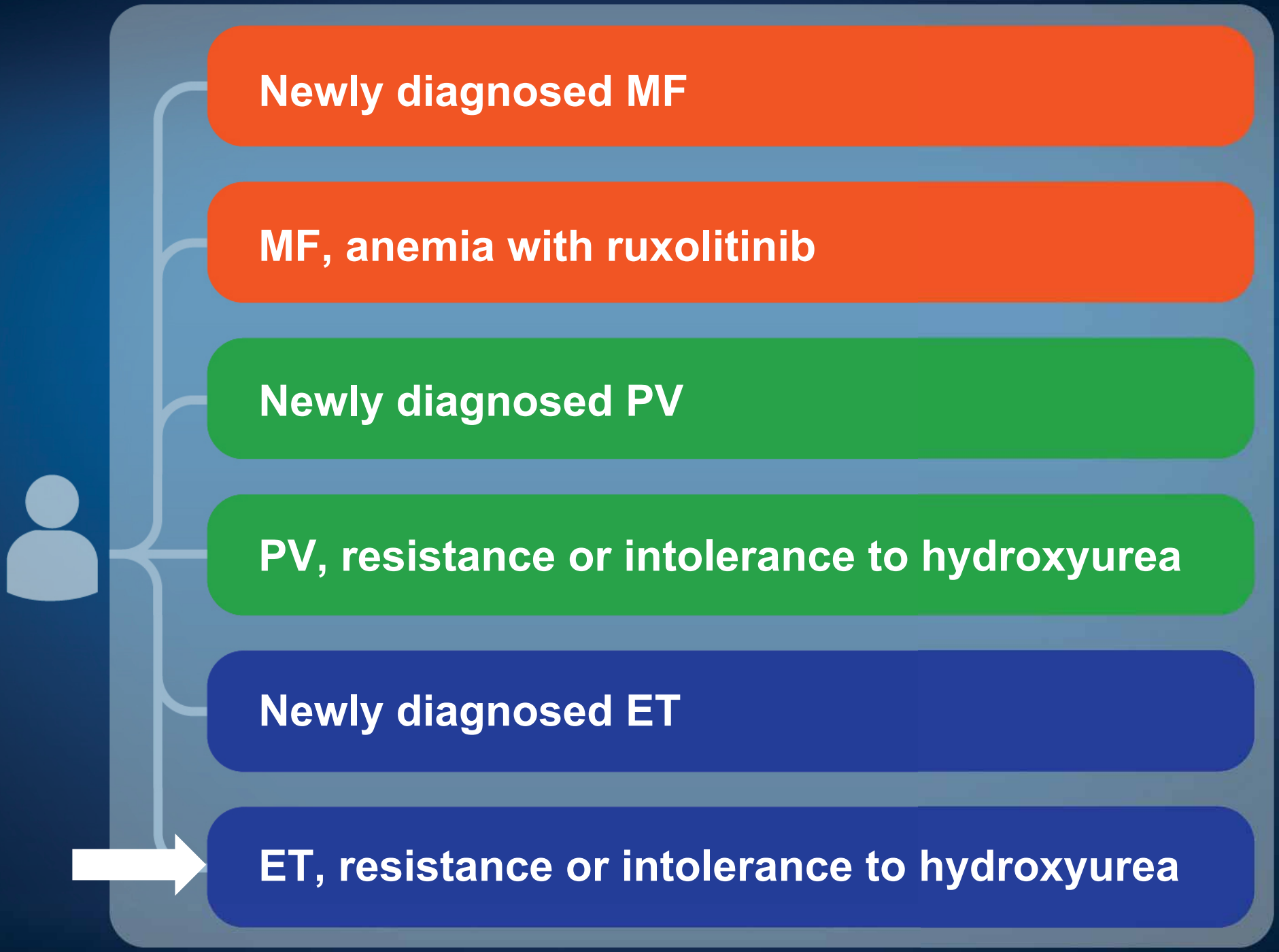
- Observation is appropriate
- Daily low-dose aspirin is standard practice for most patients, if not contraindicated*
  - Due to high risk of *bleeding* in patients with platelet counts >1,500 x 10^9/L, cytoreduction may be considered prior to aspirin initiation

High-risk ET also includes

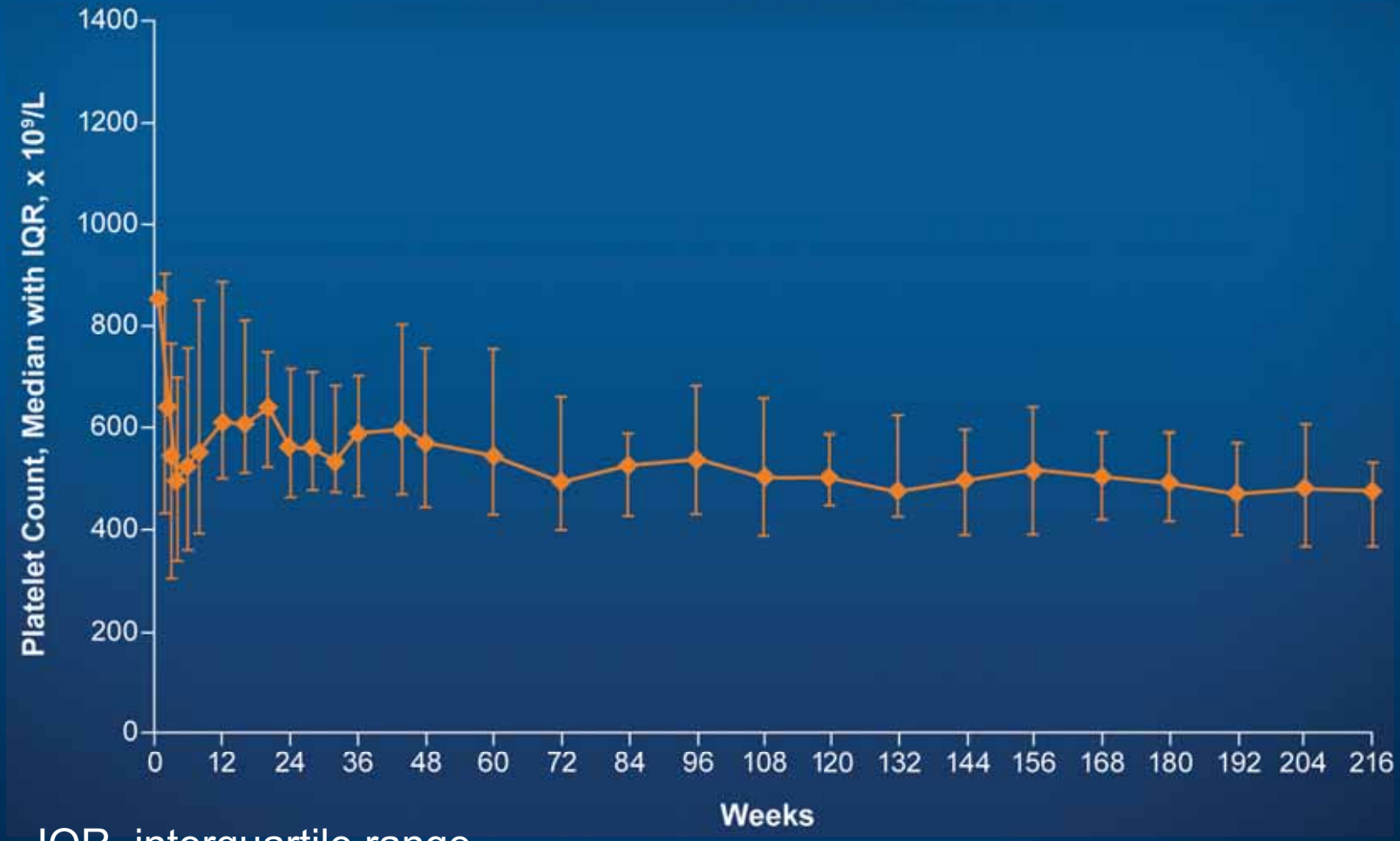
- **Cytoreductive therapy**
  - Hydroxyurea (HU): First-line treatment of choice
  - Anagrelide: Generally 2nd-line therapy if resistant or intolerant to HU
  - IFN-alpha: Young patients, pregnant women or patients who are refractory/intolerant to HU
  - Consider clinical trials for patients who are intolerant to or have progressed on all 3 agents

* Aspirin is not universally recommended - typically for those with *JAK2* positive ET, CV risk factors or microvascular symptoms

Gowin K, Mesa R. *F1000Res* 2014;3:227-37.


Newly diagnosed MF
MF, anemia with ruxolitinib
Newly diagnosed PV
PV, resistance or intolerance to hydroxyurea
Newly diagnosed ET
ET, resistance or intolerance to hydroxyurea

Phase II Open-Label Study of Ruxolitinib in Patients with Essential Thrombocythemia Refractory to or Intolerant of Hydroxyurea: Platelet Count



IQR, interquartile range

Verstovsek S et al. *Blood* 2014;124(21):1847.

53-Year-Old Woman with Essential Thrombocythemia (Ms Knight)

- 2006: Diagnosed with ET, with platelets over 1 million
- 2010: Hydroxyurea, with poor tolerance
- April 2014: Peginterferon-alfa-2a, with poor tolerance and worsening depression and anxiety
- Feb 2015: Clinical trial with momelotinib discontinued due to inadequate platelet response
- Feb 2015 - present: Ruxolitinib off label
  - Good control of counts
  - Ongoing debilitating fatigue likely multifactorial

Reminder

Please turn in your CNE course evaluation for credit as you exit the activity.

Thank you for joining us.

66-Year-Old Man with Newly Diagnosed Myelofibrosis (Ms Dahl)

- Dec 2016: Presents with kidney stone and splenomegaly (10 cm) noted on exam
  - Lab results within normal limits
  - Diagnosed with JAK-mutant primary myelofibrosis
- Jan 2017: Ruxolitinib 15 mg BID
  - No night sweats, fever chills, weight loss
- May 2017: Patient reports feeling better, increased energy
- Patient is a very active, retired social worker

59-Year-Old Woman with Polycythemia Vera (Ms Knight)

- Diagnosed with JAK2 mutation-positive PV at age 50 (H/H 19.7/59%)
  - Phlebotomy and ASA
- Over the years became more symptomatic with pruritus and fatigue; phlebotomy every 2 months
- 2013: initiated hydroxyurea 1,000 mg daily while awaiting approval for peginterferon-alfa-2a
  - Hydroxyura tapered off and patient was maintained on peginterferon and ASA with no need for phlebotomy
- July 2015: Hemolytic anemia thought to be related to peginterferon
  - Peginterferon discontinued
- Initated ruxolitinib, which continues to date