NCCN 11th Annual Congress:
Hematologic Malignancies™

Myeloproliferative Neoplasms and Myelofibrosis: Evolving Management

Ruben A. Mesa, MD
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Evolving Management of MPNs

- NCCN MPN Guidelines Panel
- Framework for MPN Guidelines
- Workup of an MPN
  - Diagnosis, risk stratification, symptom burden, and treatment goals
- NCCN Treatment Guidelines - Myelofibrosis
  - Low & intermediate 1 risk
  - Intermediate 2 & high risk
  - Progressive MF
  - Supportive care and management of MF-associated Anemia
- Future Directions

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NCCN Guidelines Version 1.2017 Panel Members
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NCCN Guidelines:
Myeloproliferative Neoplasms (MPNs) Inaugural

Diagnosis & Treatment Response
- Myelofibrosis
- Polycythemia Vera
- Essential Thrombocythemia

Disease Burden & Treatment Planning
- Myelofibrosis
- Polycythemia Vera
- Essential Thrombocythemia

Treatment Guidelines
- Myelofibrosis

Treatment Guidelines (Forthcoming 2017)
- Polycythemia Vera
- Essential Thrombocythemia

Diagnosis & Treatment (Forthcoming 2017)
- Atypical MPNs
  - HES, SMCD, etc.

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MPN Workup

- Diagnosis
  - Endorsement of WHO 2016
- Disease Burden
  - MPN SAF / MPN10
- Prognosis
  - IPSS at Dx; DIPSS subsequent. New Molecular Features

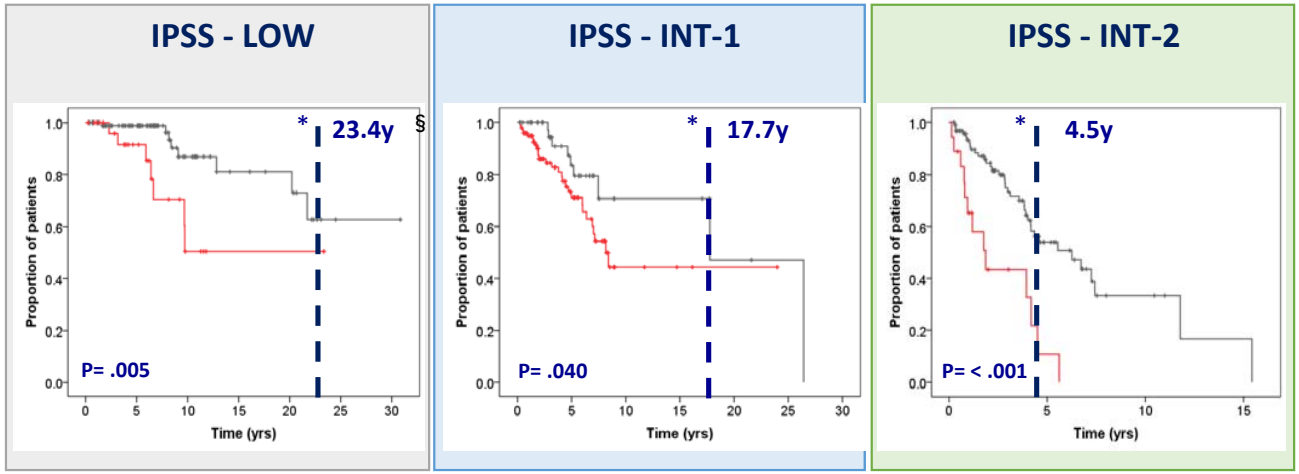
MIPSS: Molecular International Prognostic Score System

MULTIVARIATE ANALYSIS			Weighted Value
Variables	HR (95% CI)	P	
Age >60 years	3.8 (2.60-5.51)	<0.0001	1.5
Hb <100g/L	1.4 (1.01-1.99)	0.04	0.5
Constitutional Symptoms	1.5 .(1.13-2.16)	0.007	0.5
PLT <200x10^9/L	2.5 (1.77-3.42)	<0.0001	1.0
Triple Negativity	3.9 (2.20-6.80)	<0.0001	1.5
JAK2/MPL mutation	1.8 (1.11-2.90)	0.016	0.5
ASXL1 mutation	1.4 (1.06-1.99)	0.02	0.5
SRSF2 mutation	1.7 (1.08-2.58)	0.02	0.5

MIPSS: Mutation-Enhanced International Prognostic Scoring System

Vannucchi et. al. ASH 2014

MIPSS Permits to Refine Prognostic Stratification Within the IPSS Categories



Vannucchi et. al. ASH 2014

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Myeloproliferative Neoplasms

PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

Mutated Gene	Primary Myelofibrosis (PMF)
JAK2V617F	Intermediate prognosis and higher risk of thrombosis compared to patient with *CALR* mutation
MPLW515L/K	Intermediate prognosis and higher risk of thrombosis compared to patient with *CALR* mutation
CALR	Improved survival compared to *JAK2* mutation and "triple-negative" PMF Lower risk of thrombosis compared to *JAK2* mutation
CALR Type 1/ Type 1-like	Improved overall survival compared to *CALR* type 2/type 2-like and *JAK2* V617F mutation
"Triple Negative" (non-mutated *JAK2, MPL, and CALR)*	Inferior leukemia-free survival compared to patients with *JAK2*- and/or *CALR*-mutated PMF Inferior overall survival compared to patients with *CALR*-mutated PMF

MPN-D

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Myeloproliferative Neoplasms

PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

Mutated Gene	Primary Myelofibrosis (PMF)
ASXL1	Independently associated with inferior overall survival and leukemia-free survival
EZH2	Independently associated with inferior overall survival
IDH1/2	Independently associated with inferior leukemia-free survival
SRSF2	Independently associated with inferior overall survival and leukemia-free survival
Combined *CALR and ASXL1* status	Survival longest for *CALR*(+)*ASXL1*(-) patients (median 10.4 years) and shortest in *CALR*(-)*ASXL1*(+) patients (median 2.3 years) Intermediate survival (median 5.8 years) for *CALR*(+)*ASXL1*(+) or *CALR*(-)*ASXL1*(-) patients
TP53	Associated with leukemic transformation

MPN-D

Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story

Baseline Health
AGE/ Medicines
Comorbidities

Vascular Events
- PV/ET > MF
- Counts matter
- Can be unrecognized

Cytopenias
- MF> ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
- TPN 30%

Progression
- PV/ET to MF
- PV/ET to AML
- MF to AML
- ? 2nd MDS

Splenomegaly
- MF> ET/PV
- Pain not always a function of size

MPN Symptoms
- MF>PV>ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive rx frequently not effective

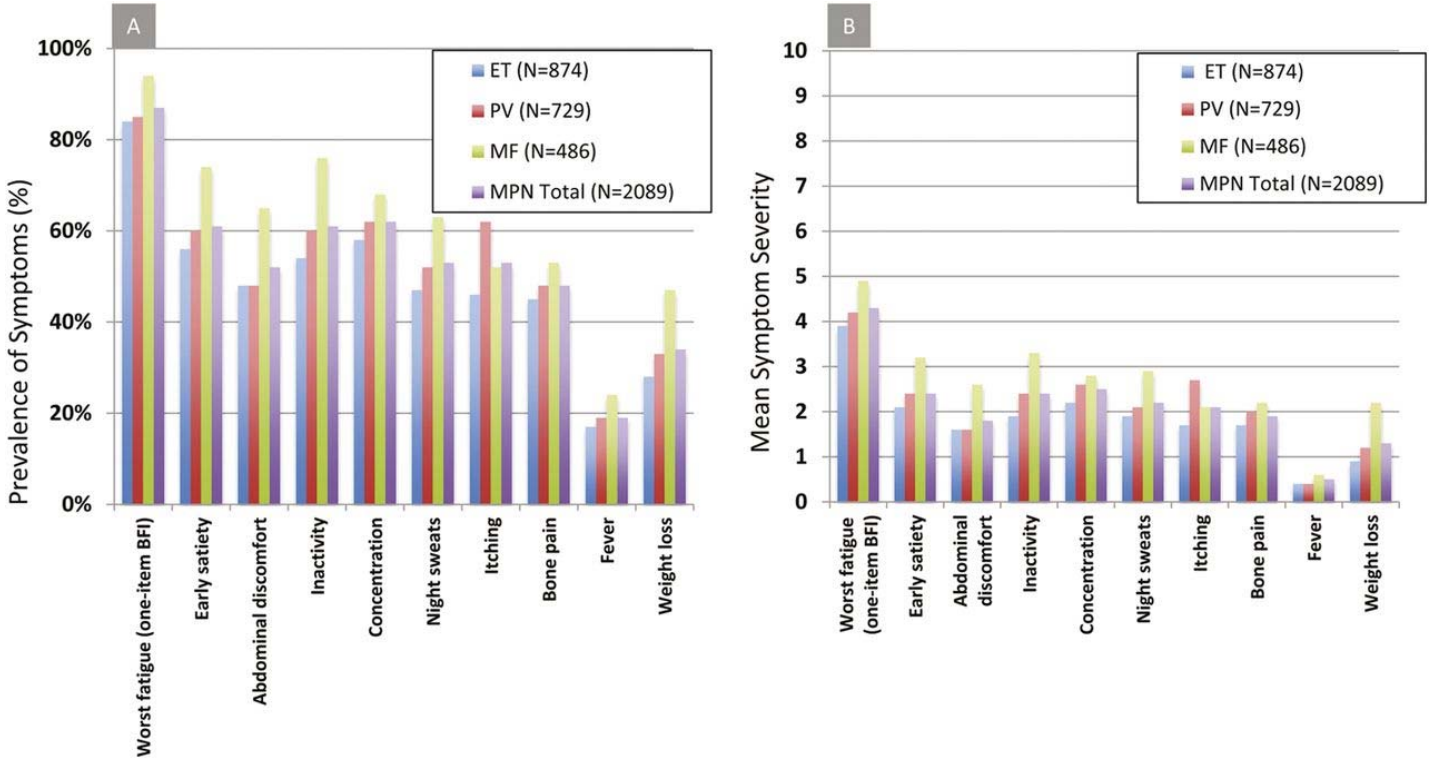
MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS-10 ITEMS)

(Recommended for monitoring symptoms during the course of treatment)

Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Classic Signs and Symptoms of MPNs



Geyer H L , and Mesa R A Blood 2014;124:3529-3537

2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS (MF)

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)	
CR	Bone marrow: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF and Peripheral blood: Hemoglobin ≥100 g/dL and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

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Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)	
PR	Peripheral blood: Hemoglobin ≥100 g/dL and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells OR Bone marrow: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF and Peripheral blood: Hemoglobin ≥85, but <100 g/dL and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥50, but <100 x 10^9/L and <UNL; <2% immature myeloid cells	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

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2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS (MF)

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
Progressive disease	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5–10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥20% or A peripheral blood blast content of ≥20% associated with an absolute blast count of $\geq 1 \times 10^9$/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least confidence interval (CI) after achieving complete response (CR), partial response (PR), or CI or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month

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Myeloproliferative Neoplasms

2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS (MF)

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
Clinical improvement (CI)	The achievement of anemia, spleen, or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia
Anemia response	Transfusion-independent patients: a ≥20 g/dL increase in hemoglobin level Transfusion-dependent patients: becoming transfusion-independent
Spleen response	A baseline splenomegaly that is palpable at 5–10 cm, below the LCM, becomes not palpable or A baseline splenomegaly that is palpable at >10 cm below the LCM, decreases by ≥50% A baseline splenomegaly that is palpable at <5 cm below the LCM, not eligible for spleen response A spleen response requires confirmation by MRI or CT showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS

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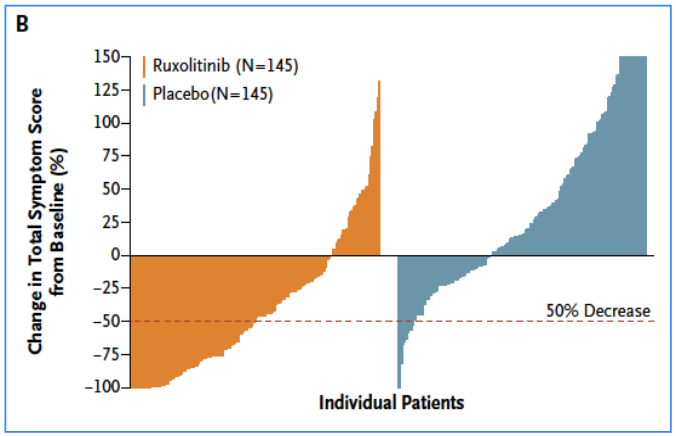
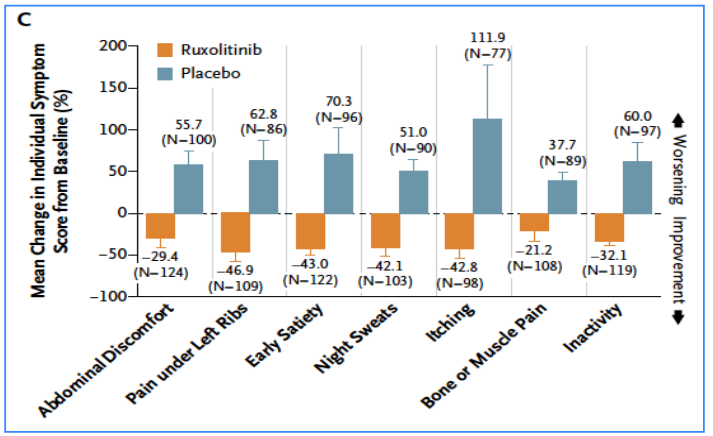
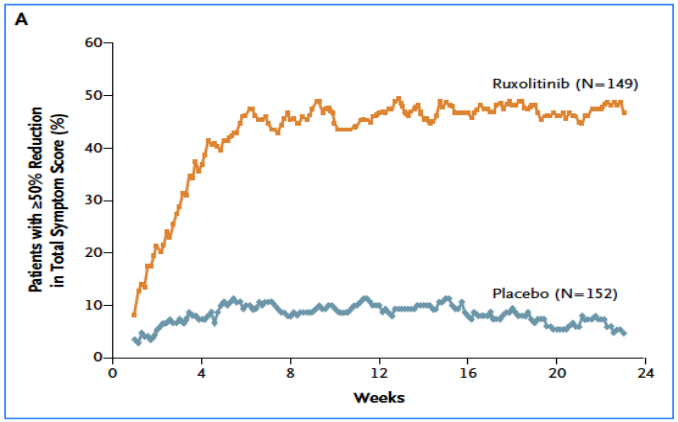
Ruxolitinib Phase III MF

(COMFORT I – *Symptom Response*)







Verstovsek, Mesa, Gotlib et. al. NEJM 2012;366(9):799-807

Gupta et. al. ASCO 2016

Long-Term Outcomes of Ruxolitinib Therapy in Patients With Myelofibrosis: 5-Year Update From COMFORT-I

Vikas Gupta,[1] Srdan Verstovsek,[2] Ruben A. Mesa,[3,*] Jason Gotlib,[4] John F. DiPersio,[5] John V. Catalano,[6] Michael W. N. Deininger,[7] Carole B. Miller,[8] Richard T. Silver,[9] Moshe Talpaz,[10] Elliott F. Winton,[11] Jimmie H. Harvey, Jr,[12] Murat O. Arcasoy,[13] Elizabeth O. Hexner,[14] Roger M. Lyons,[15] Ronald Paquette,[16] Azra Raza,[17] Deanna Kornacki,[18] Kang Sun,[18] Hagop Kantarjian[2]

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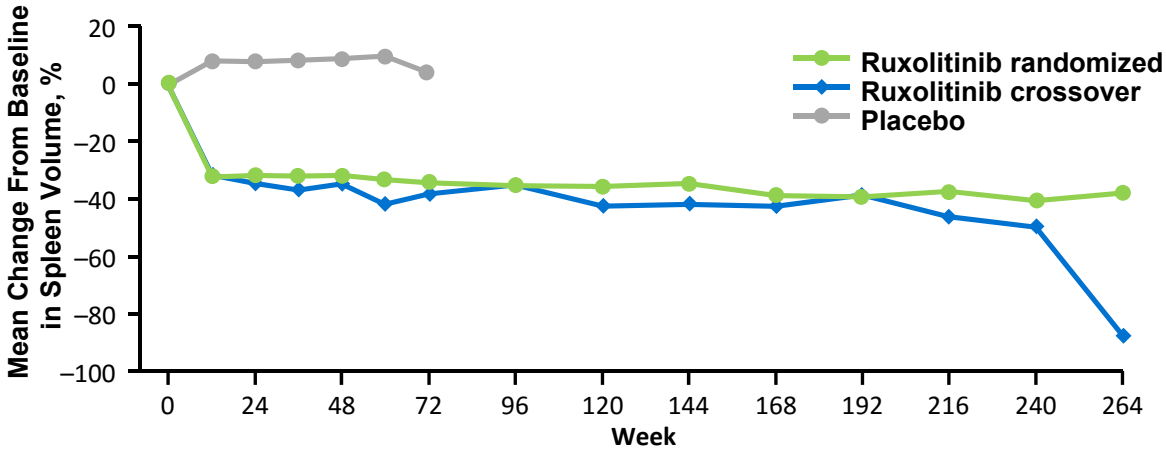
*Presenting author (mesa.ruben@mayo.edu)

Mean Percentage Change From Baseline in Spleen Volume Over Time*

- Mean percentage reductions from Baseline in spleen volume were rapid and durable in the ruxolitinib randomized and crossover arms



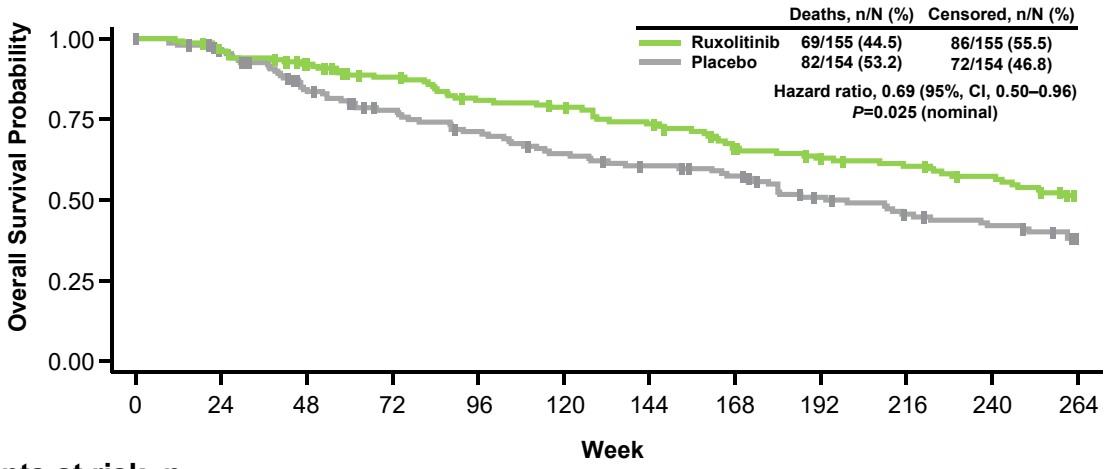
Patients, n												
Ruxolitinib randomized	155	139	120	107	100	85	76	57	55	53	50	42
Ruxolitinib crossover	111	85	44	55	63	46	41	35	33	25	9	1
Placebo	153	107	35	1								

*For patients in the ruxolitinib crossover arm, Baseline represents the date of crossover to ruxolitinib

Gupta et. al. ASCO 2016

Overall Survival as Assessed by the Kaplan-Meier Method

- Median follow-up was 268.4 weeks for ruxolitinib and 269.0 weeks for placebo
- Median OS was not reached for patients randomized to ruxolitinib and was 200 weeks for patients in the placebo arm
  - A sensitivity analysis censoring patients at crossover showed a median OS of 108 weeks for patients randomized to placebo



Patients at risk, n

Ruxolitinib	155	148	137	124	112	108	100	86	80	75	69	57
Placebo	154	144	119	105	95	85	78	72	59	51	46	38

Gupta et. al. ASCO 2016

Nonhematologic Treatment-Emergent Adverse Events (All Grades)

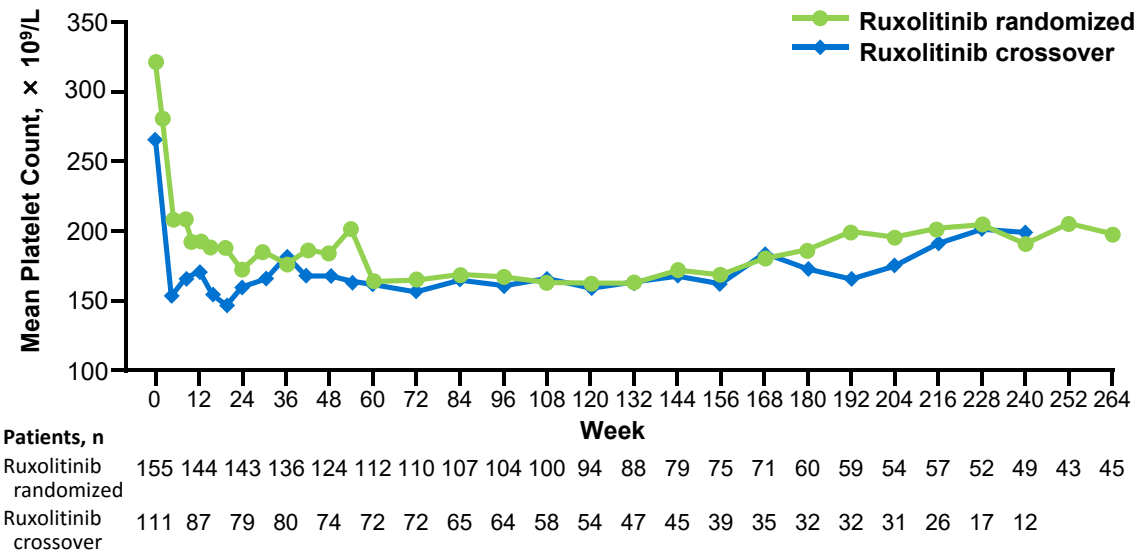
	Ruxolitinib Randomized (n=155)	Ruxolitinib Crossover (n=111)	Placebo (n=151)
Median Duration of Exposure, d	**1045.0**	**777.0**	**260.0**
Number of patients/patient-years exposure (rate per 100 patient-years of exposure)*			
Fatigue	79/325.2 (24.3)	36/199.0 (18.1)	54/79.8 (67.6)
Diarrhea	62/335.8 (18.5)	28/220.4 (12.7)	34/85.0 (40.0)
Ecchymosis	47/377.1 (12.5)	25/210.2 (11.9)	13/98.8 (13.2)
Constipation	47/392.2 (12.0)	16/248.2 (6.4)	19/94.8 (20.1)
Peripheral edema	46/381.2 (12.1)	23/228.1 (10.1)	35/89.3 (39.2)
Dyspnea	45/375.5 (12.0)	20/236.3 (8.5)	28/93.5 (30.0)
Cough	44/400.1 (11.0)	21/238.1 (8.8)	13/98.7 (13.2)
Nausea	44/408.0 (10.8)	21/234.7 (8.9)	29/89.9 (32.3)
Dizziness	40/365.2 (11.0)	18/232.4 (7.7)	10/99.6 (10.0)
Headache	40/392.4 (10.2)	17/230.6 (7.4)	10/100.7 (9.9)
Pyrexia	40/425.6 (9.4)	20/245.6 (8.1)	12/100.3 (12.0)
Pain in extremity	38/376.1 (10.1)	18/229.6 (7.8)	16/96.9 (16.5)

*Occuring at a rate of ≥10 per 100 patient-years of exposure in ruxolitinib-treated patients

- No new or unexpected adverse events occurred with long-term ruxolitinib treatment

Mean Platelet Counts Over Time in the Ruxolitinib Randomized and Crossover Arms*

- Mean platelet counts decreased during the first 12 weeks of ruxolitinib treatment for both randomized and crossover groups but remained stable thereafter

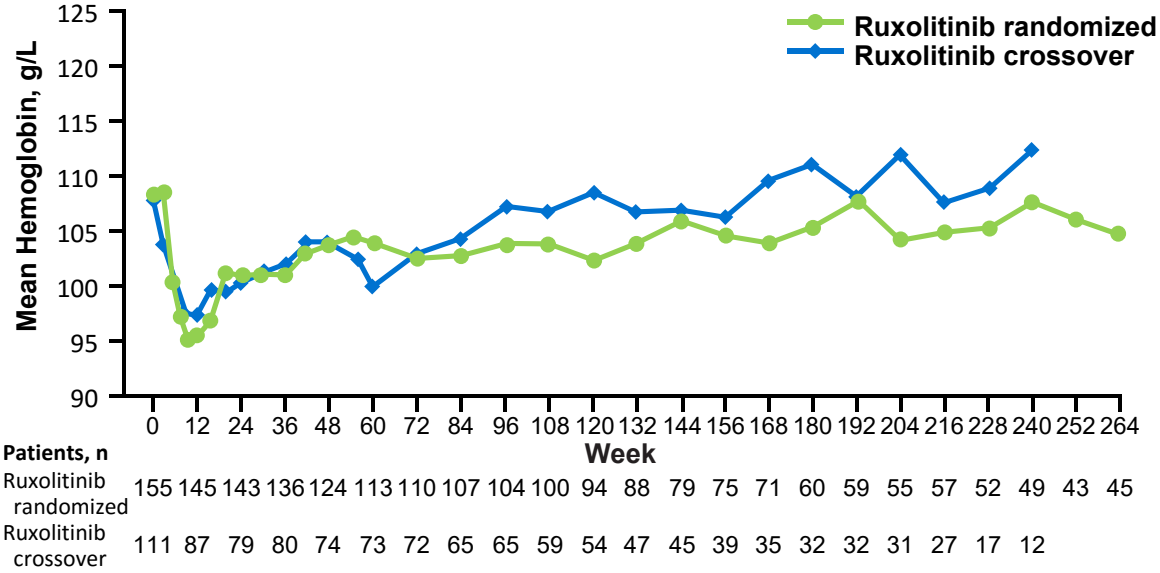


*For patients in the ruxolitinib crossover arm, Baseline represents the date of crossover to ruxolitinib

Gupta et. al. ASCO 2016

Mean Hemoglobin Levels Over Time in the Ruxolitinib Randomized and Crossover Arms*

- Mean hemoglobin levels decreased during the first 12 weeks of ruxolitinib treatment for both randomized and crossover groups but increased toward Baseline levels and stabilized thereafter



*For patients in the ruxolitinib crossover arm, Baseline represents the date of crossover to ruxolitinib

Treatment-Emergent Adverse Events of Interest (All Grades)

	Ruxolitinib Randomized (n=155)	Ruxolitinib Crossover (n=111)	Placebo (n=151)
Median duration of exposure, d	**1045.0**	**777.0**	**260.0**
Number of patients/patient-years exposure (rate per 100 patient-years of exposure)			
Herpes zoster	16/452.5 (3.5)	14/241.2 (5.8)	1/104.1 (1.0)
Basal cell carcinoma	12/450.9 (2.7)	10/252.7 (4.0)	4/103.7 (3.9)
AML	5/483.8 (1.0)	5/270.1 (1.9)	0

- Exposure-adjusted rates of herpes zoster infection were higher in the ruxolitinib randomized and crossover arms, but no patient experienced a serious event
- Of the 26 patients who developed basal cell carcinoma, 2 in the ruxolitinib crossover arm had severe cases; both had a history of skin cancer
- Rates of transformation to AML were consistent with those published for similar patient populations with MF[1,2]

AML, acute myeloid leukemia; MF, myelofibrosis

1. Gangat N, et al. *J Clin Oncol*. 2011;29(4):392-397
2. Quintas-Cardama A, et al. *Clin Lymphoma Myeloma Leuk*. 2013;13(3):315-318

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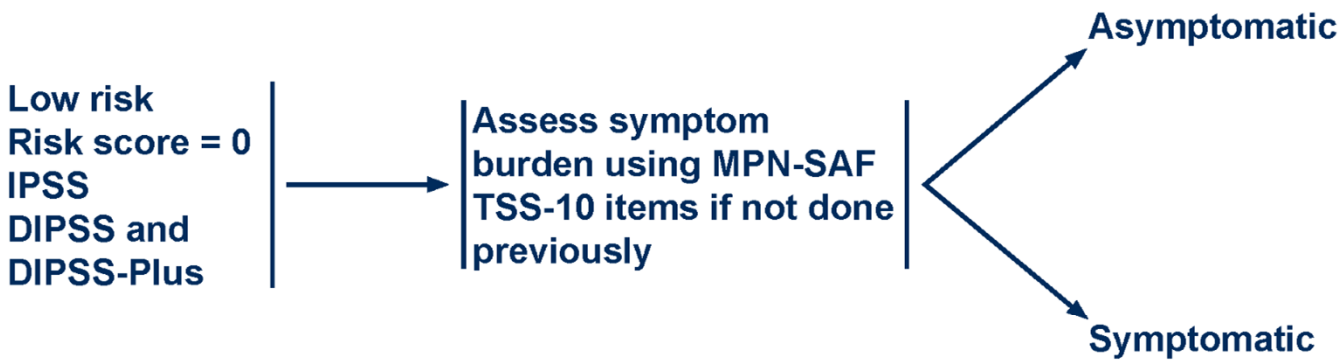
Myeloproliferative Neoplasms

TREATMENT FOR LOW-RISK MYELOFIBROSIS



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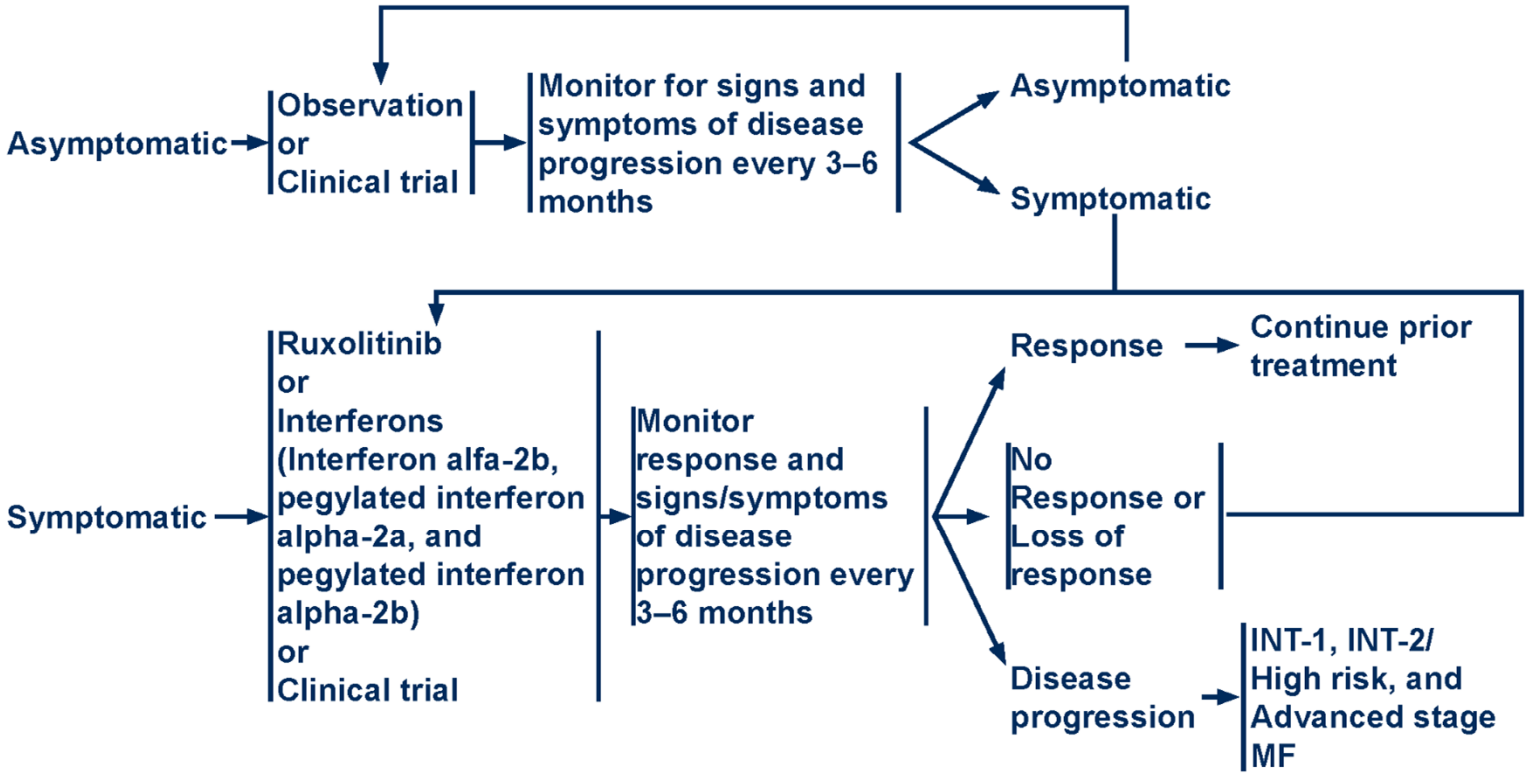
TREATMENT FOR LOW-RISK MYELOFIBROSIS



MPN-2

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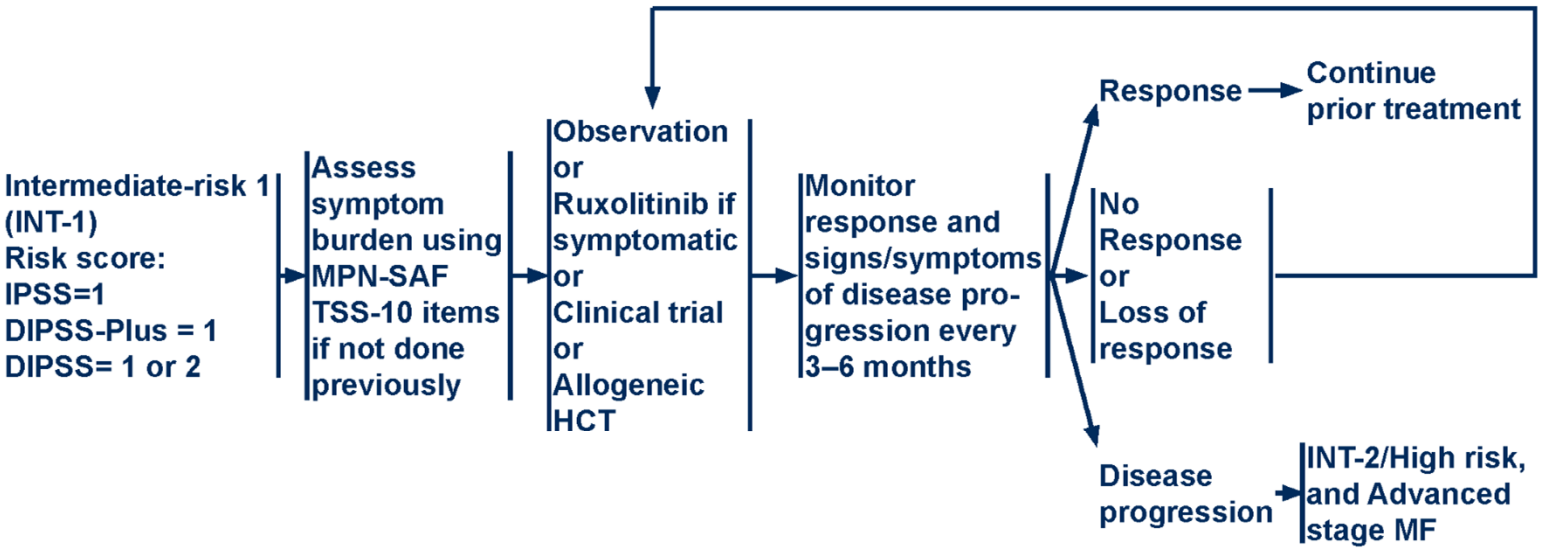
Myeloproliferative Neoplasms

TREATMENT FOR INTERMEDIATE-RISK 1 (INT-1) MYELOFIBROSIS



Intermediate-1 myelofibrosis

- 63-year-old gentleman had PV for 12 years; progressive fatigue, cachexia, loss of need for phlebotomy
  - MPN 10: 40 (out of 100)
  - Spleen: 10 cm BLCM
  - Hb: 11.8 g/dL
  - WBC: 18 x 10(9)/L
  - Platelets: 240 x 10(9)/L
  - Peripheral smear = 2% myelocytes
- Bone marrow
  - 3+ reticulin fibrosis. Karyotype 20q-
- Diagnosis of post-PV myelofibrosis

Intermediate-1 myelofibrosis

DIPSS risks	Present
Age >65 years	
Symptoms	X
Hemoglobin <10 g/dL	
Leukocytes >25 x 10(9)/L	
Blasts >1% in Blood	

Intermediate-1 risk myelofibrosis

MF patient burden	Present
Symptoms (MPN 10 – Score 40)	X
Splenomegaly	X
Anemia	
Movement towards AML	

Begins ruxolitinib 20 mg – twice daily

Monitor:
- Blood counts
- Spleen size
- MPN 10

Intermediate-1 myelofibrosis (follow-up)

- 4 months later
  - (IWG-MRT Response Spleen and Symptoms)

  - Spleen originally: 10 cm BLCM – Now: 2 cm BLCM
  - Hb original: 11.8 g/dL – Now: 10.4 g/dL
  - WBC original: 18 x 10(9)/L – Now: 13.4 x 10(9)/L
  - Platelets original: 240 x 10(9)/L – Now: 135 x 10(9)/L

  - MPN 10 – original: 40 (out of 100) – Now: 14

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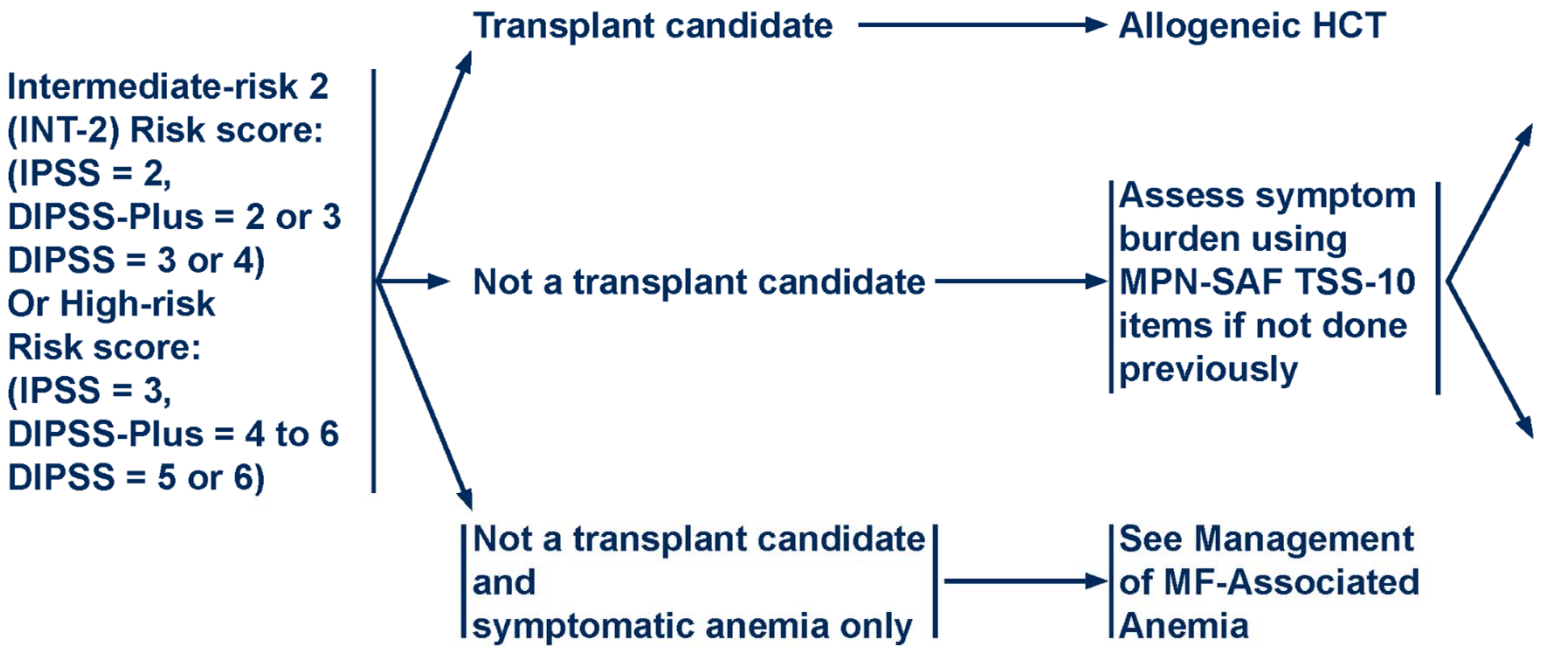
Myeloproliferative Neoplasms

TREATMENT FOR INTERMEDIATE-RISK 2 (INT-2) OR HIGH-RISK MYELOFIBROSIS



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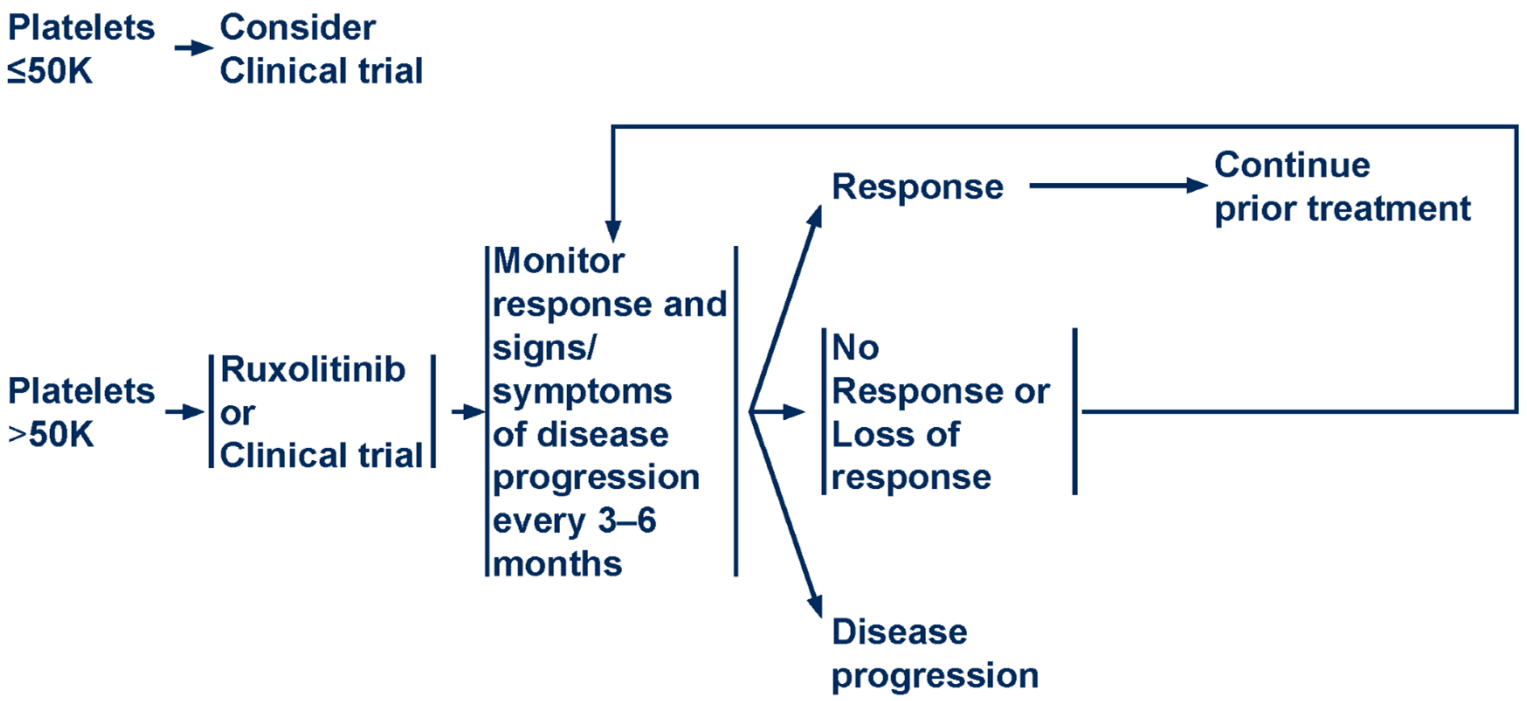
Myeloproliferative Neoplasms

TREATMENT FOR INTERMEDIATE-RISK 2 (INT-2) OR HIGH-RISK MYELOFIBROSIS



MPN-4

Evolving Management of MPNs

- NCCN MPN Guidelines Panel
- Framework for MPN Guidelines
- Workup of an MPN
  - Diagnosis, risk stratification, symptom burden, and treatment goals
- NCCN Treatment Guidelines - Myelofibrosis
  - Low & intermediate 1 risk
  - Intermediate 2 & high risk
  - Progressive MF
  - Supportive care and management of MF-associated Anemia
- Future Directions

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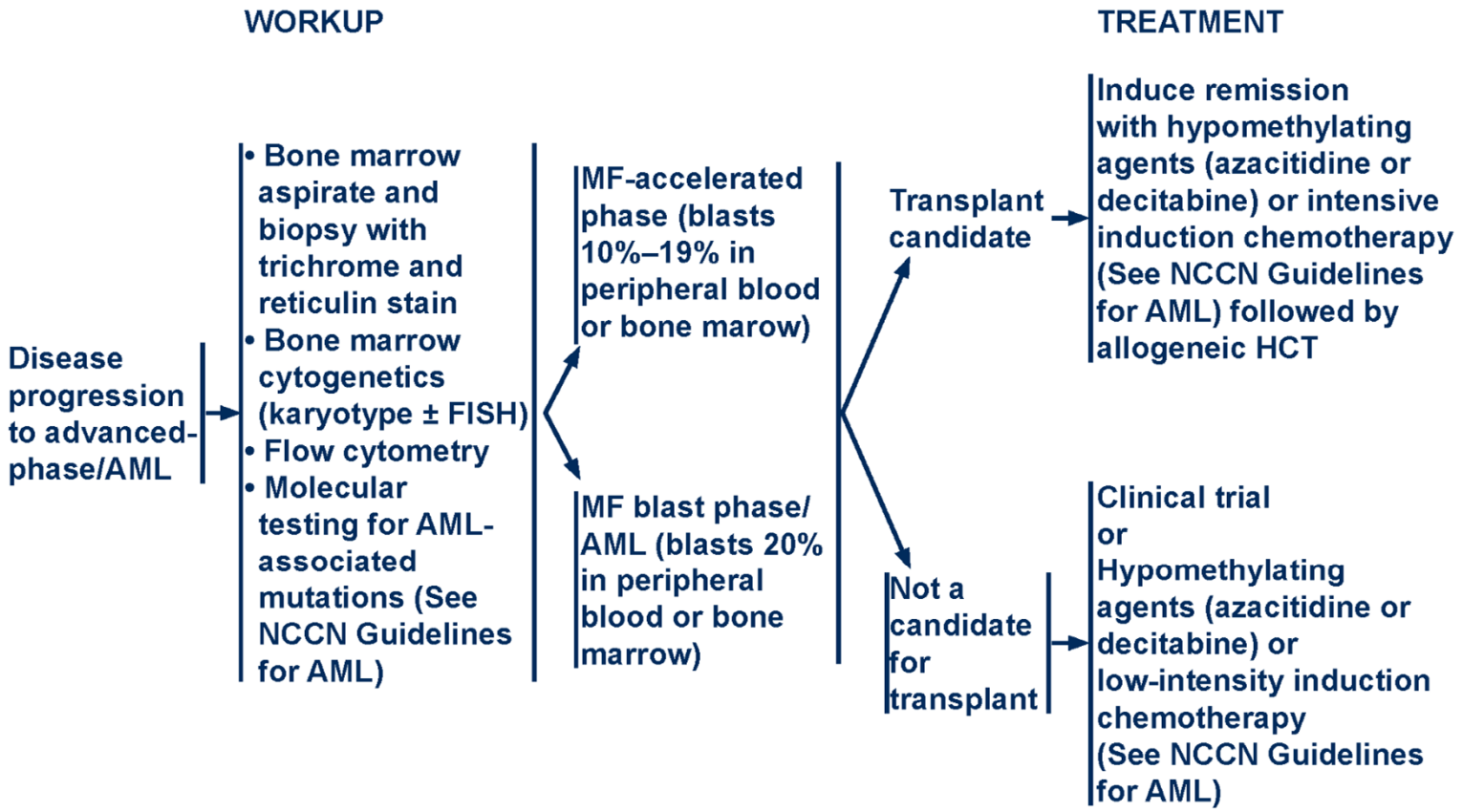
Myeloproliferative Neoplasms



MPN-6

Evolving Management of MPNs

- NCCN MPN Guidelines Panel
- Framework for MPN Guidelines
- Workup of an MPN
  - Diagnosis, risk stratification, symptom burden, and treatment goals
- NCCN Treatment Guidelines - Myelofibrosis
  - Low & intermediate 1 risk
  - Intermediate 2 & high risk
  - Progressive MF
  - Supportive care and management of MF-associated Anemia
- Future Directions

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Myeloproliferative Neoplasms

MANAGEMENT OF MF-ASSOCIATED ANEMIA

- H&P
- CBC with differential
- Examination of blood smear
- Bone marrow aspirate and biopsy with trichrome and reticulin stain
- Bone marrow cytogenetics (karyotype ± FISH)
- Serum EPO level
- Rule out coexisting causes (eg, bleeding, iron, B12 or folate deficiency, hemolysis)

→

- Treat coexisting causes
  - Replace iron, folate, B12, if needed
  - Treat hemolysis if clinically indicated
  - Red blood cell (RBC) transfusions (leuko-reduced)
- Supportive care

MPN-5

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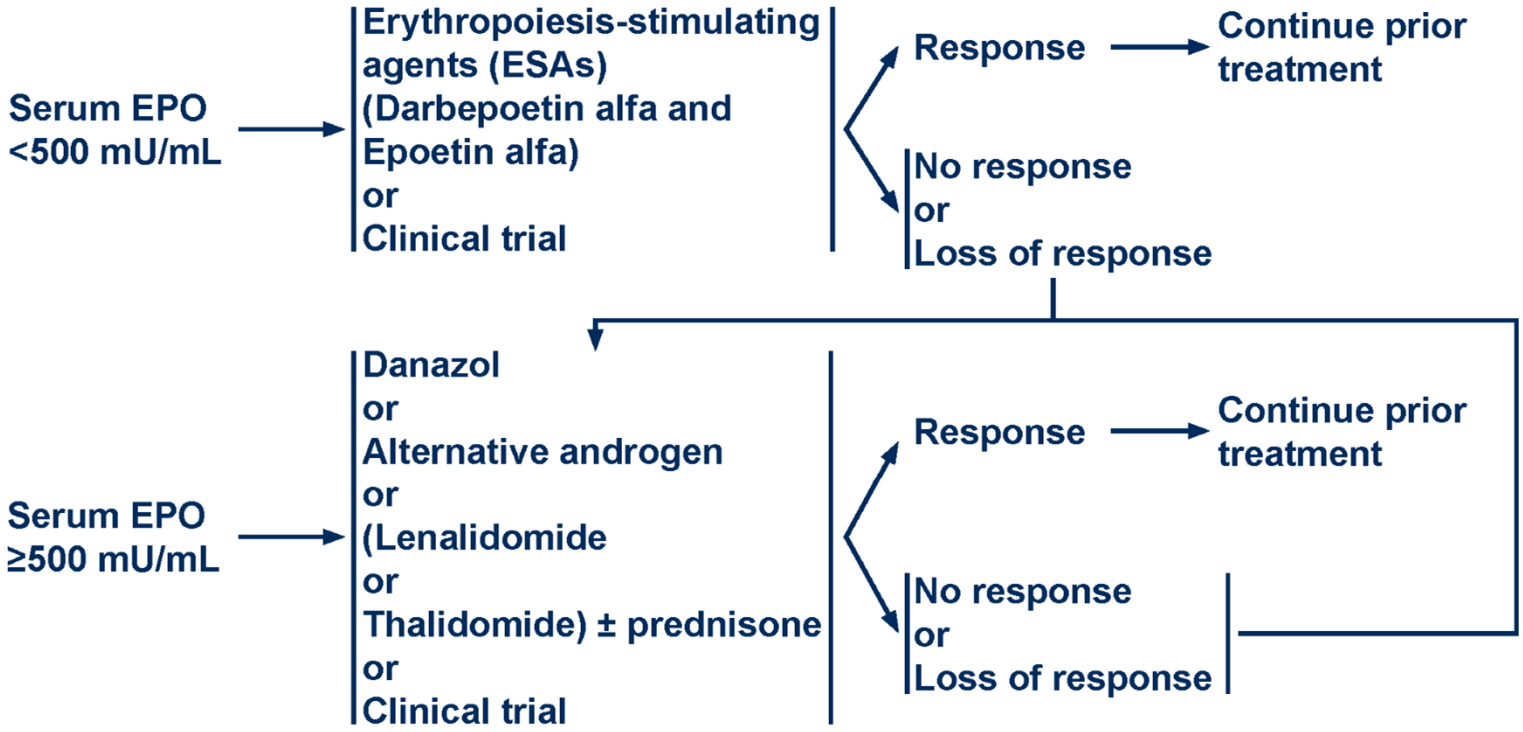
Myeloproliferative Neoplasms

MANAGEMENT OF MF-ASSOCIATED ANEMIA



MPN-5

Evolving Management of MPNs

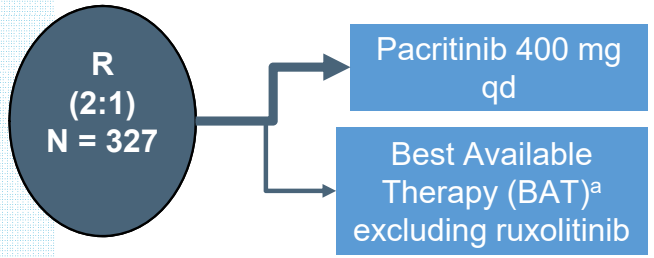
- NCCN MPN Guidelines Panel
- Framework for MPN Guidelines
- Workup of an MPN
  - Diagnosis, risk stratification, symptom burden, and treatment goals
- NCCN Treatment Guidelines - Myelofibrosis
  - Low & intermediate 1 risk
  - Intermediate 2 & high risk
  - Progressive MF
  - Supportive care and management of MF-associated Anemia
- Future Directions

PERSIST-1 (Pacritinib – JAK2/FLT3 Inhibitor)

Study Design

Mesa et. al. ASCO 201

Key Eligibility Criteria
PMF, PET-MF, or PPV-MF
Intermediate- or high-risk disease
Palpable spleen ≥5 cm
No exclusion for baseline platelet levels; stratified for platelet counts <100,000/µL and <50,000/µL
No exclusion for baseline Hgb levels
No prior treatment with JAK2 inhibitors



[a] Cross-over from BAT allowed after progression or after Week 24 assessment

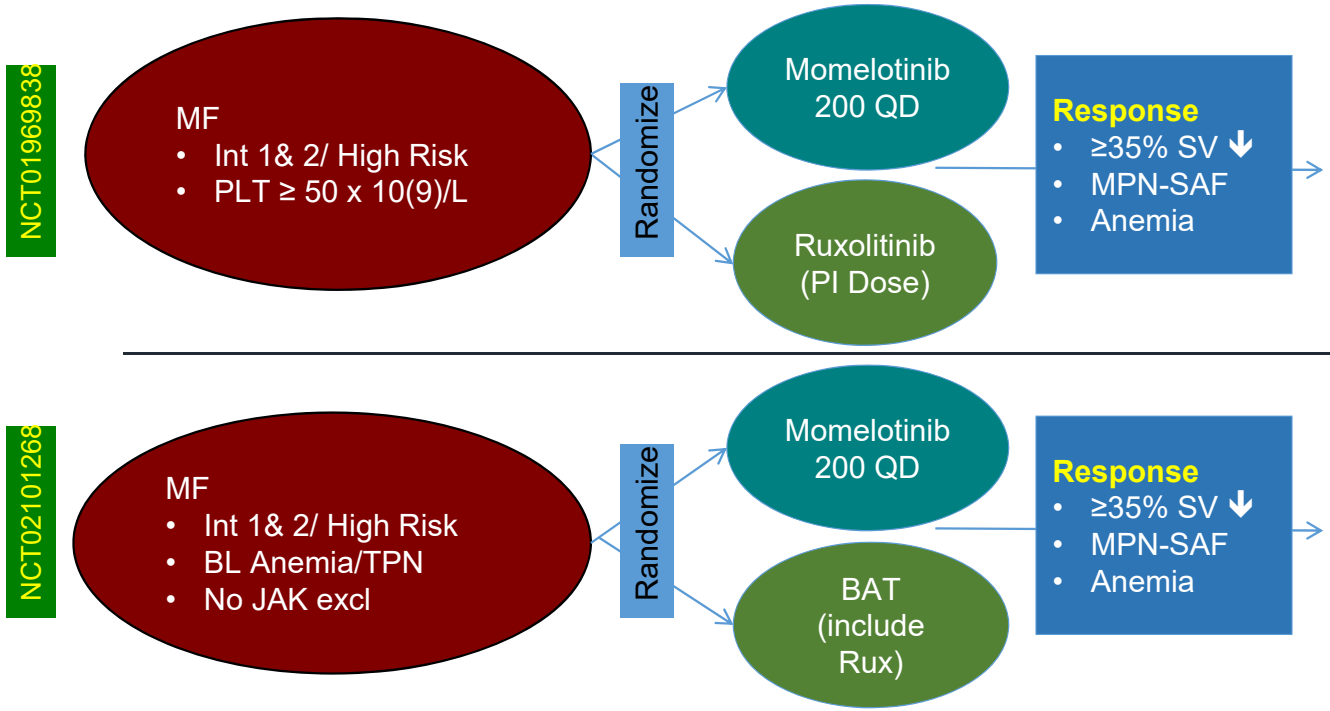
- Stratification at randomization: platelet count, risk category, and region
- Study endpoints
  - **Primary**: proportion of patients achieving a ≥35% reduction in spleen volume (by MRI/CT) from baseline to Week 24
  - **Secondary**: proportion of patients with ≥50% reduction in TSS from baseline to Week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form

CT, computed tomography; Hgb, hemoglobin JAK, Janus kinase; MRI, magnetic resonance imaging; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; R, randomized; TSS, total symptom score.

JAK Inhibitor Monotherapy (Phase 3 Programs - MF)

Momelotinib (Gilead, USA)

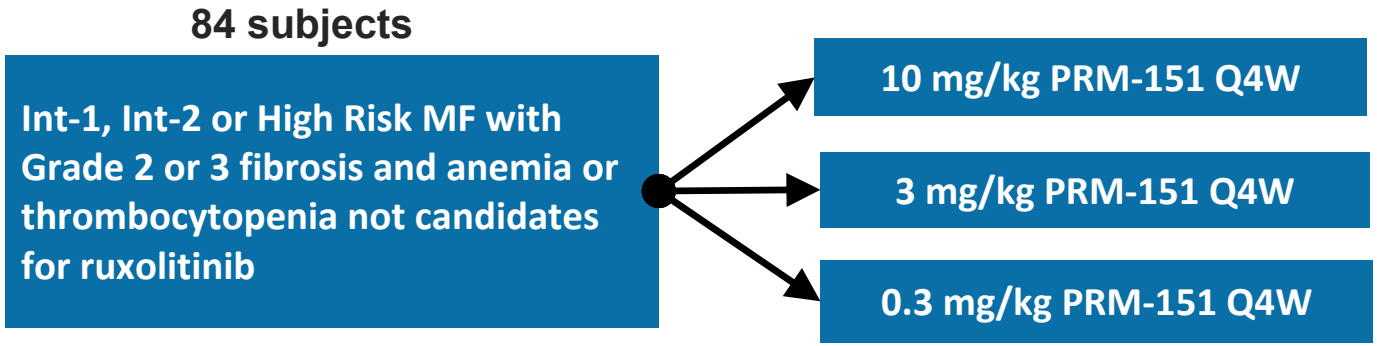
JAK1/ JAK2 Inhibitor: Phase II Program ↓ Spleen, ↓ MPN Sx, ↑ Hemoglobin



Combination + Ruxolitinib	Authors	Spleen Response	Symptom Response	PLT Impact	HB Impact	Fibrosis Response	Other
Danazol	Gowin Mascarenhas Mesa						
Pomalidomide	Stegelman Dohner						
PEG IFN a2a	Mikkelson Hasselbalch						
5-AZA	Daver Verstovsek						
Panobinostat (HDAC)	Harrison Ribrag						
BKM-120 (PI3-K)	Durrant Martinez-Lopez						
LDE-225 (HH)	Gupta Heidel						

PRM-151 MF Stage 2
Enrolling

- A Phase 2, Prospective Study Of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), Or Post-Essential Thrombocythemia MF (post-ET MF)

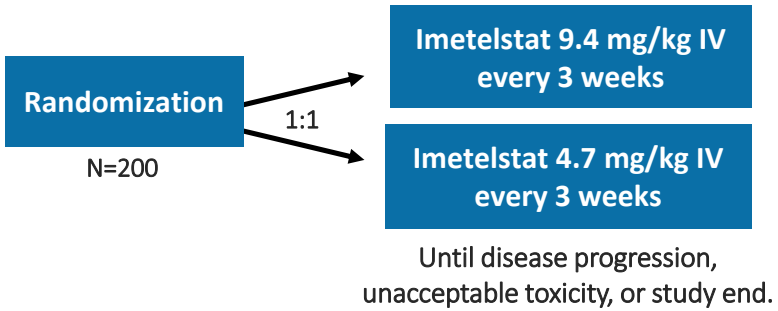


Key Eligibility:

- Int-1, Int-2, High Risk MF: Primary, Post-ET, or Post-PV
- WHO Grade 2 or 3 MF
- Not a candidate for ruxolitinib based on
- EITHER Hgb <100 g/L, requiring transfusions, and intolerant of or inadequate response to RUX
- OR Platelets <50 x 10^9/L

Imetelstat Phase 2 MF Study – Opened for Enrollment

A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects With Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor



Co - Primary End Points

To evaluate the spleen response rate at Week 24
- The percentage of participants who achieve ≥ 35% reduction in spleen volume from baseline as measured by MRI

▪ To evaluate the symptom response rate at Week 24
- The percentage of subjects who have ≥50% reduction in total symptom score as measured by modified MFSAF v2.0.

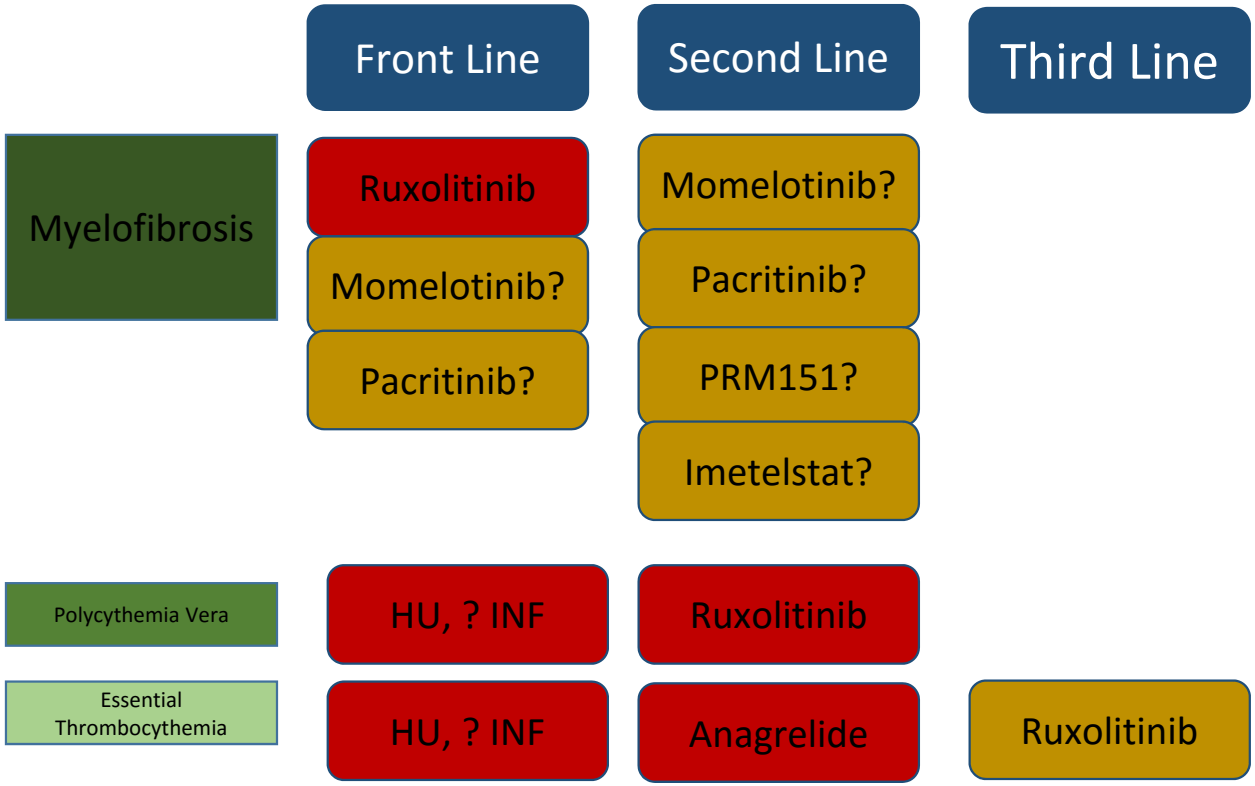
Secondary End Points
- To measure complete remission (CR) or partial remission (PR) per modified 2013 IWG-MRT criteria
- To measure clinical improvement (CI) per modified 2013 IWG-MRT criteria
- PK profile
- Safety profile
- Overall Survival

Key Eligibility Criteria*
- 18 years of age and older
- Diagnosis of PMF; or PET-MF or PPV-MF
- DIPSS intermediate-2 or high risk MF
- Measurable splenomegaly
- Active symptoms of MF prior to study entry
- Documented progressive disease during or after JAK inhibitor
- ANC ≥ 1,500/ul
- Platelets ≥ 75,000/ mm^3
- Peripheral blood and bone marrow blast count of <10%

NCT02426086 – clinicaltrials.gov

*Not a complete list of inclusion and exclusion criteria

New MPN Therapies – Possible Positioning



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