

MPNs: Current and Emerging Treatments

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Disclosures

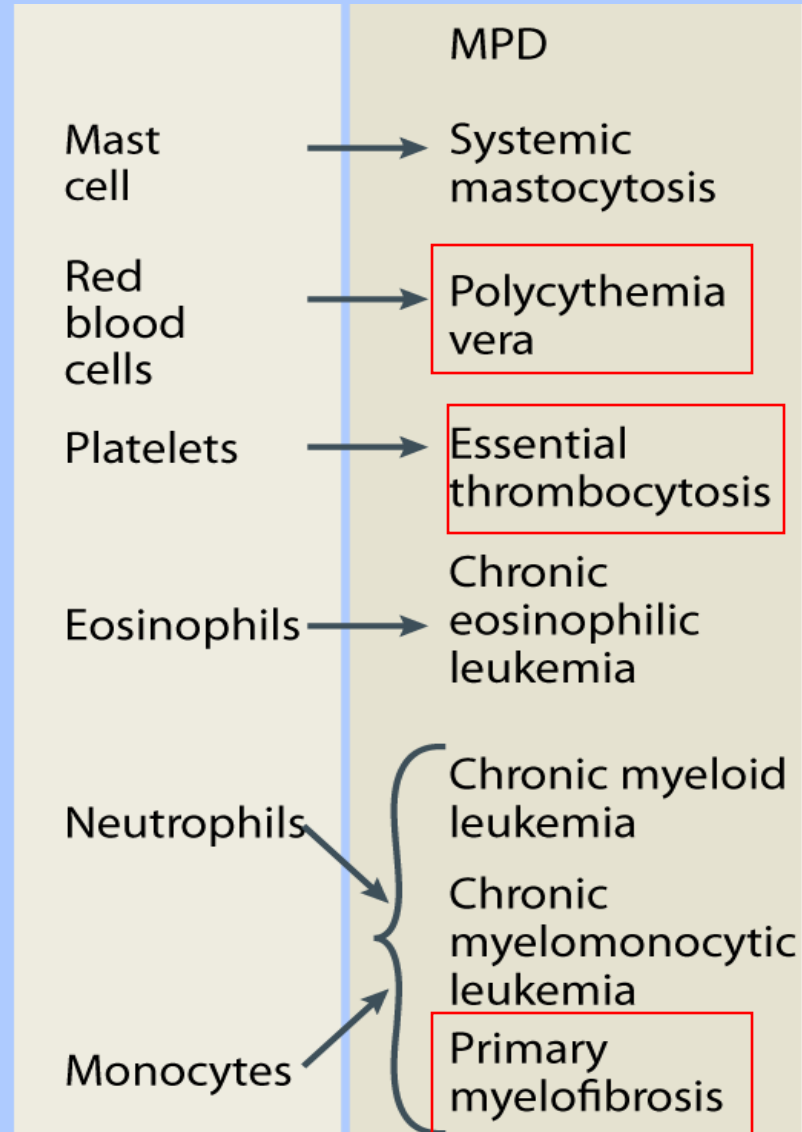
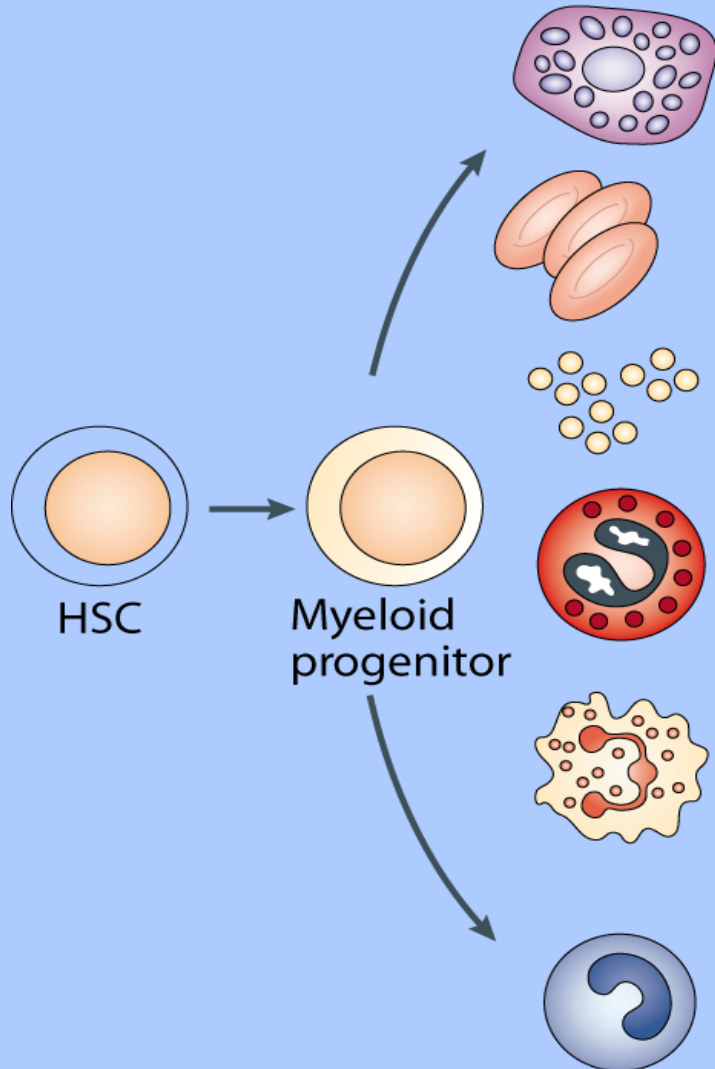
Consulting Fees: Incyte Corporation, Celgene/BMS, Blueprint, Abbvie, CTI, Stemline, Galecto, Pharmaessentia, Constellation/Morphosys, Sierra Oncology/GSK, Cogent, Sumitomo Pharma, Kartos, Servier, Zentalis, Opna, Karyopharm.

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Learning Objectives

- To Recognize the heterogeneity of disease phenotype and treatment in Myelofibrosis
- To Discuss the use of newer JAK inhibitors in Myelofibrosis
- To Explain the disease manifestations and diagnosis of Essential Thrombocytosis
- To Appraise the current treatment landscape for Polycythemia Vera

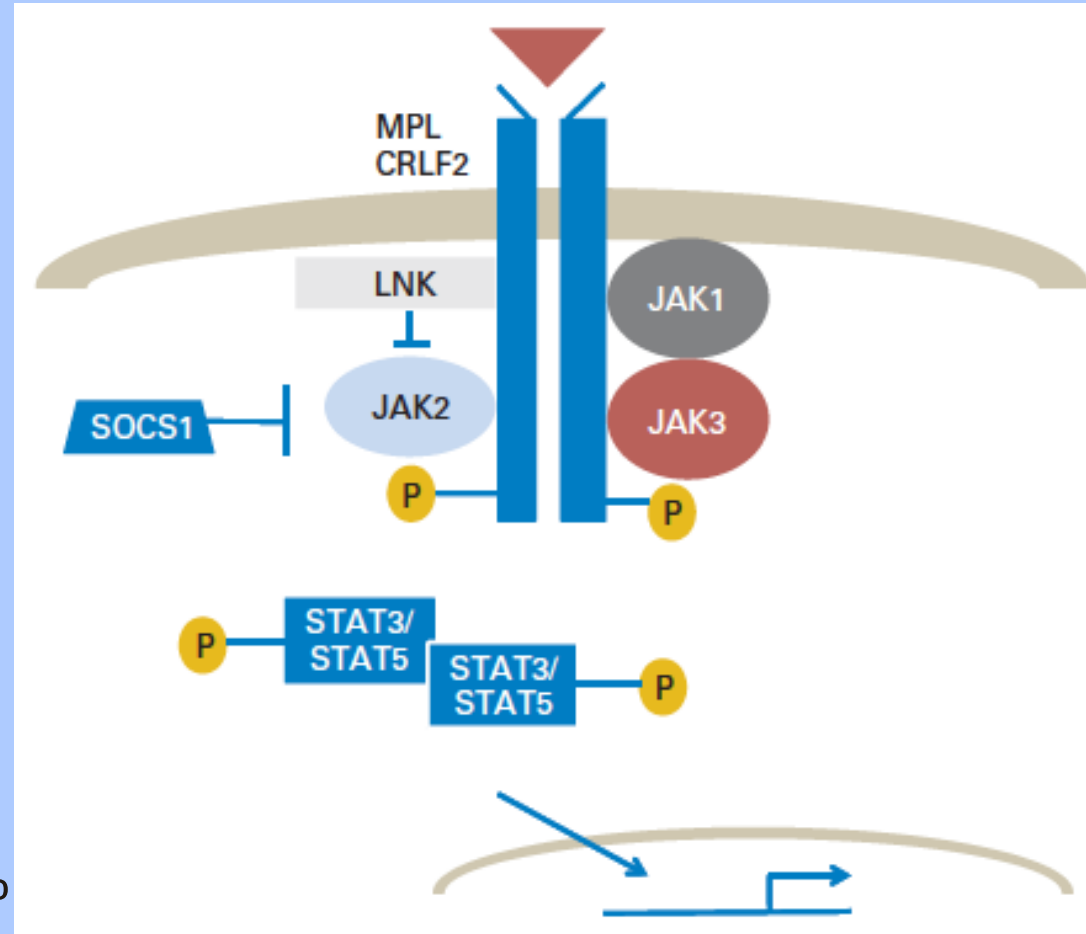
Myeloproliferative Neoplasms



JAK-STAT Activation is the Hallmark of MPNs

- **LNK** :
- ET/MF:<5%

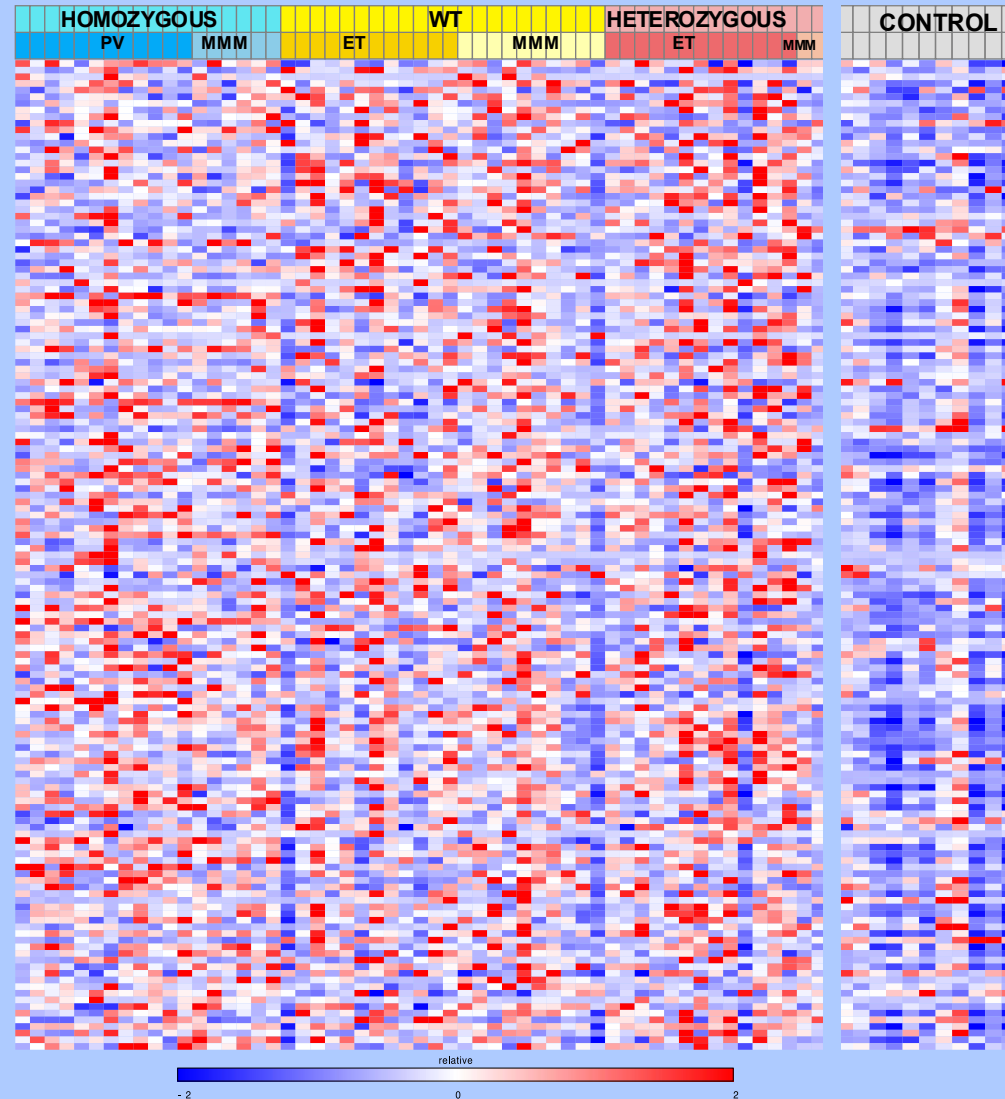
- **CALR** :
- ET/MF:30-40%



- **MPL** :
- ET/MF: 10%

- **JAK2** :
- PV: 95%
- ET: 45-50%
- MF: 45-50%

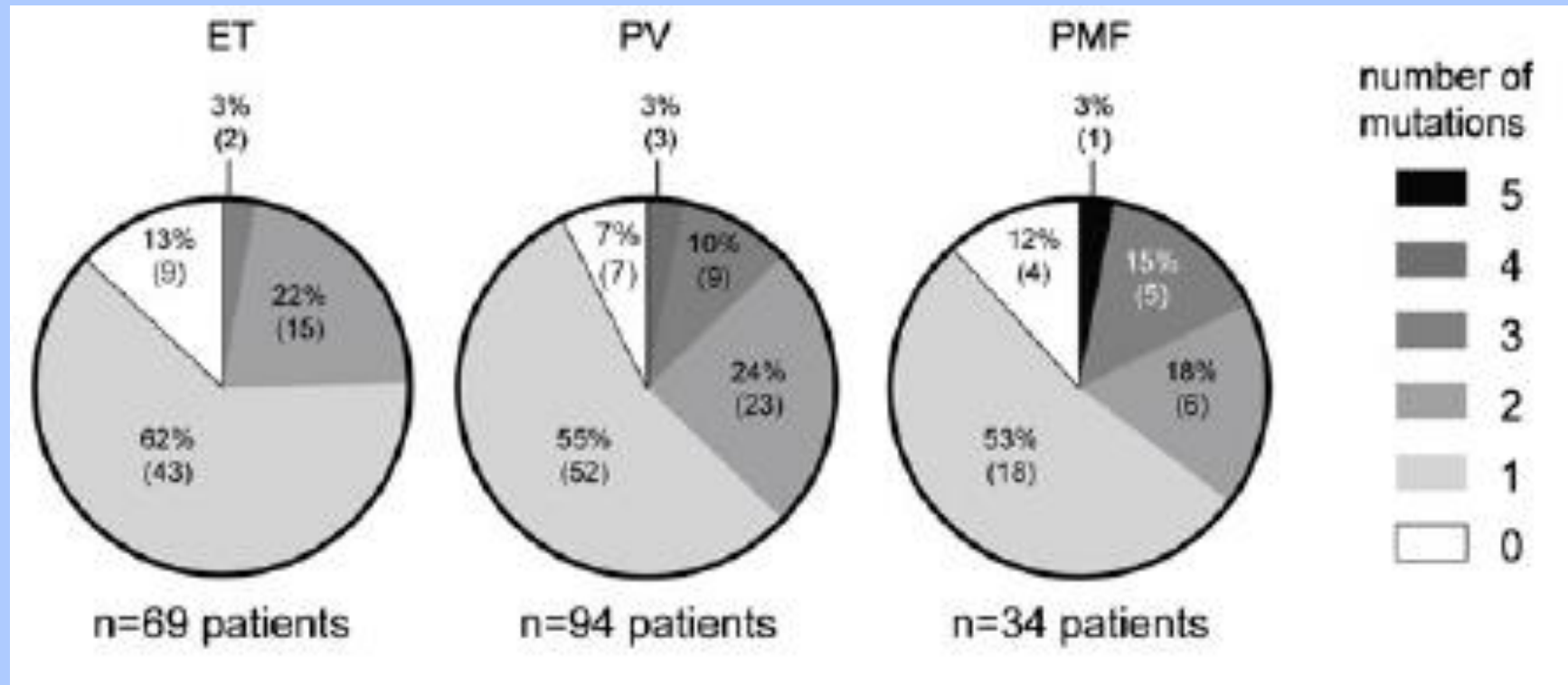
JAK2 signature in MPN and control samples



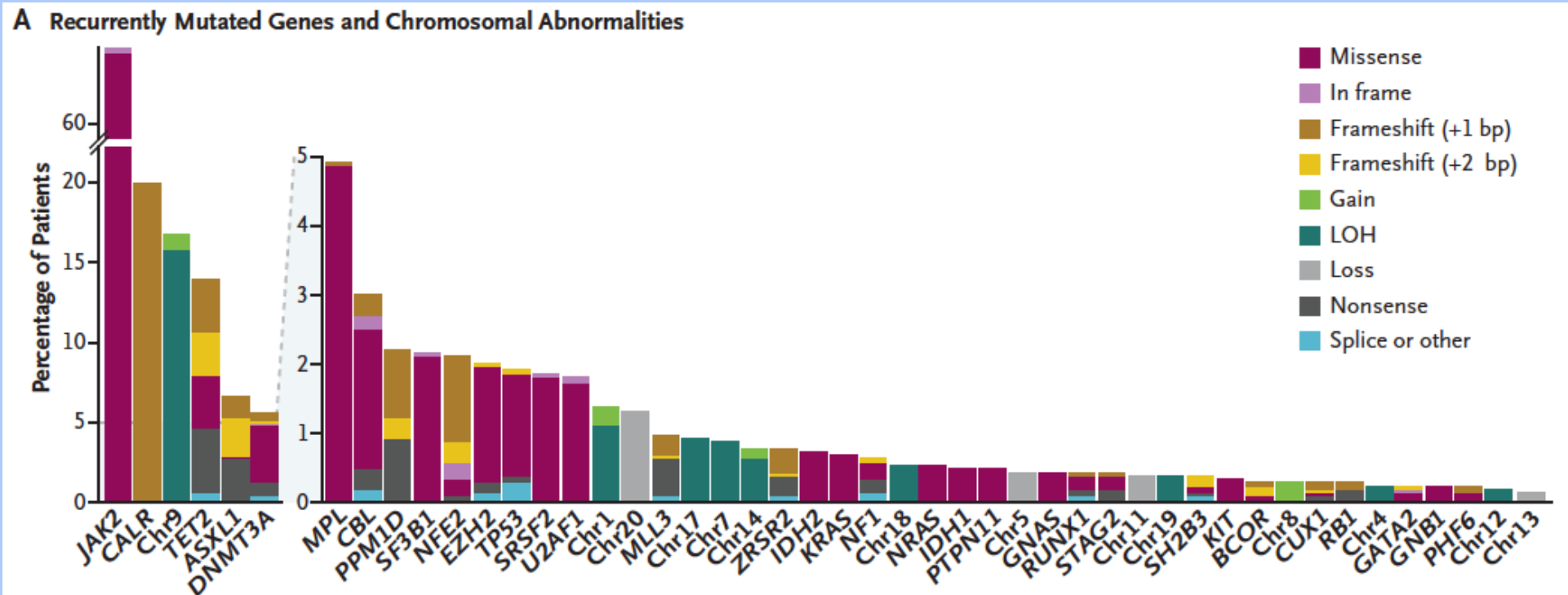
Seen in all MPN patients, not in controls

JAK2 is activated in all MPN patients regardless of specific mutation

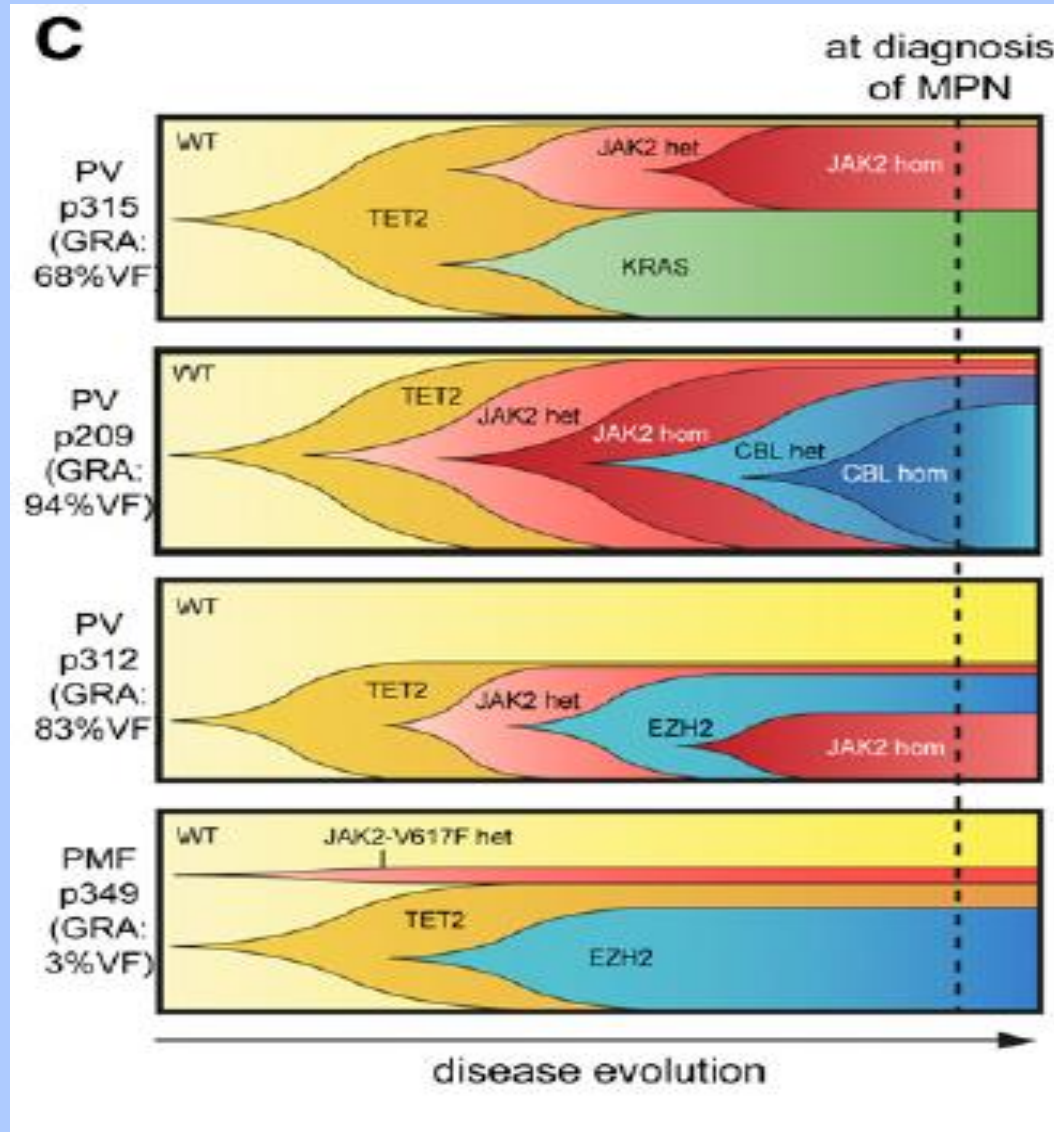
Additional Genetic Events Occur in MPNs



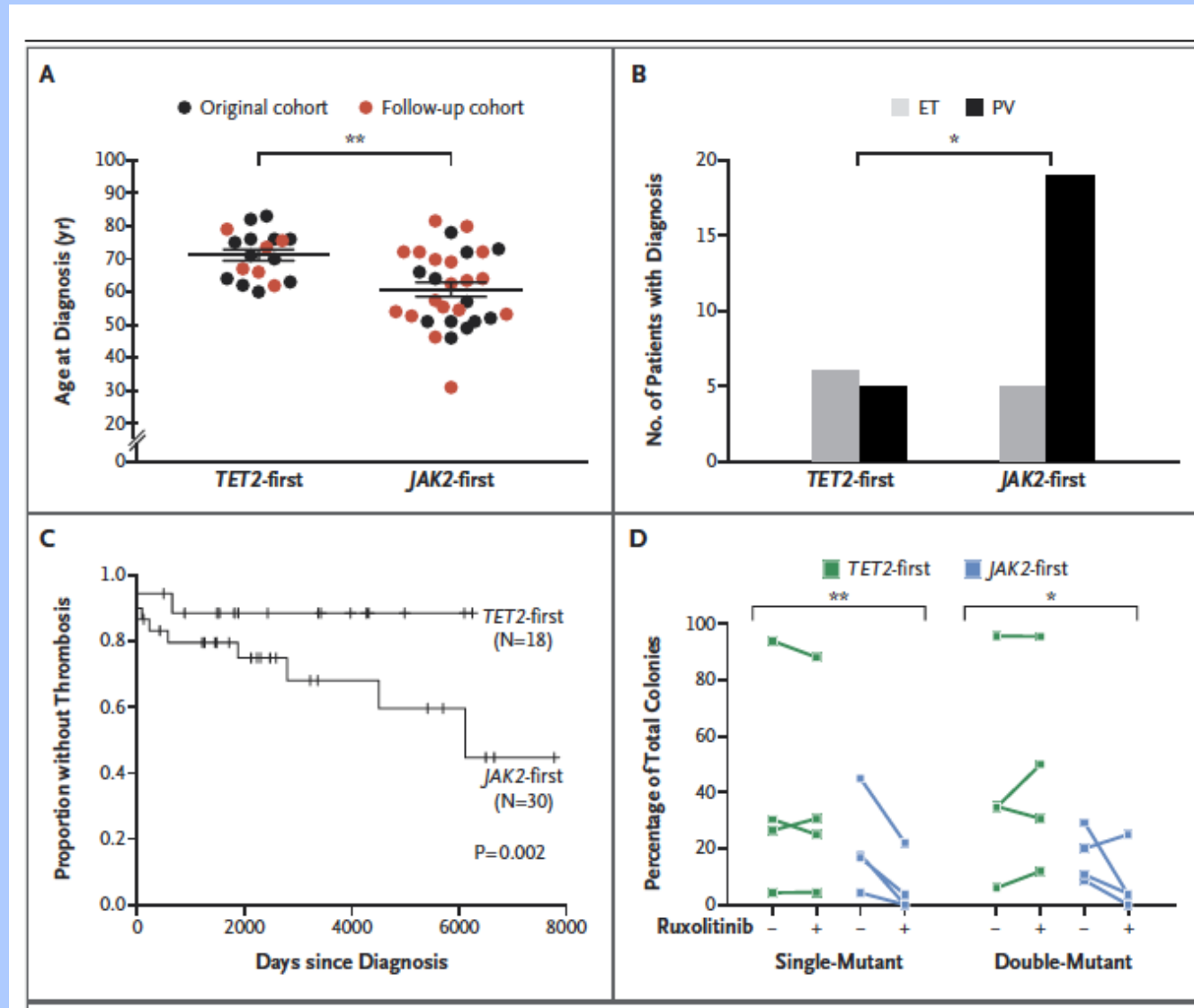
The Mutation Profile of Chronic-Phase MPNs



Mutations may evolve over time

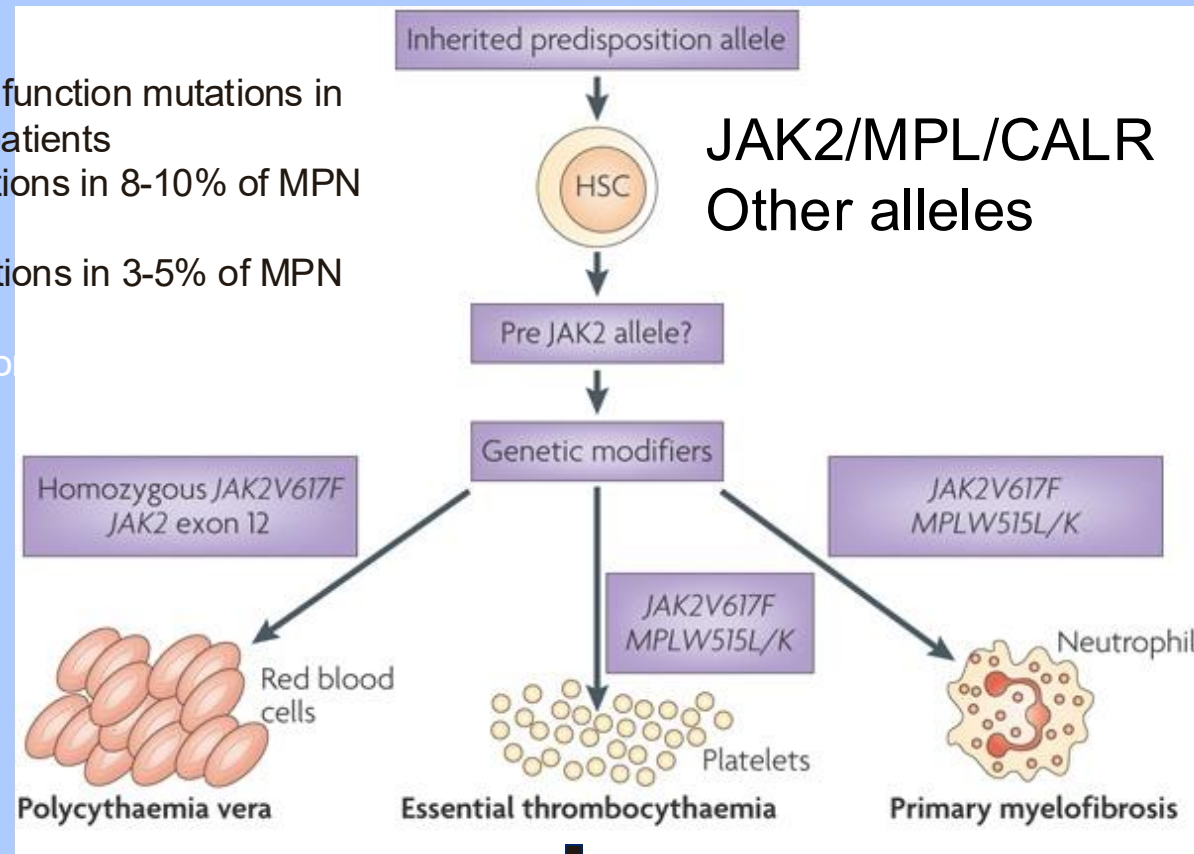


Mutation order may impact clinical phenotype



Model of MPN Pathogenesis

- TET2 loss of function mutations in 10% of MPN patients
- ASXL1 mutations in 8-10% of MPN patients
- IDH1/2 mutations in 3-5% of MPN patients
- EZH2 mutations



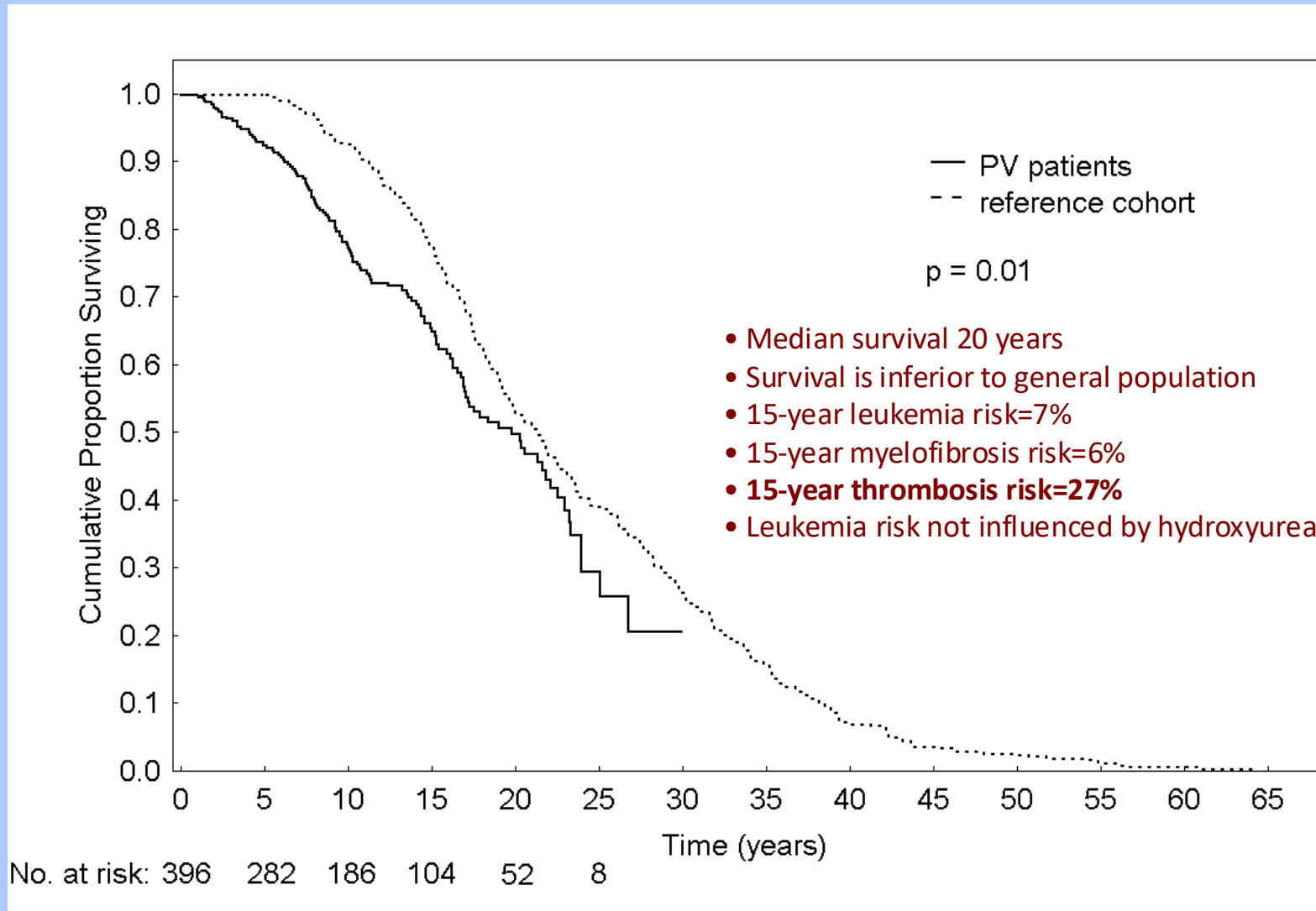
Polycythemia Vera

Evolution of WHO PV Diagnostic Criteria

2008 WHO ^[1]	2016 WHO ^[2]
Requirement for diagnosis	
<ul style="list-style-type: none">2 major and 1 minor criteria OR 1 major and 2 minor criteria	<ul style="list-style-type: none">All 3 major criteria OR first 2 major criteria and the minor criterion
Major criteria	
<ol style="list-style-type: none">Hb > 18.5 g/dL (men); > 16.5 g/dL (women)<i>JAK2</i> V617F mutation or similar (<i>JAK2</i> exon 12)	<ol style="list-style-type: none">Hb > 16.5 g/dL or Hct > 49% (men); or Hb > 16.0 g/dL or Hct > 48% (women); or increased red cell massBM biopsy showing hypercellularity, trilineage growth (panmyelosis) with erythroid, granulocytic, and pleomorphic, mature megakaryocytic proliferation<i>JAK2</i> V617F or <i>JAK2</i> exon 12 mutation
Minor criteria	
<ol style="list-style-type: none">Subnormal serum EPO levelBM trilineage proliferationEndogenous erythroid colony growth	<ol style="list-style-type: none">Subnormal serum EPO level

1. Thiele J, et al. *Curr Hematol Malig Rep.* 2009;4:33-40. 2. Arber DA, et al. *Blood.* 2016;127:2391-2405.

MODERN NATURAL HISTORY OF PV



Therapy and goals in PV

Goals of therapy

- Reduce symptoms burden
- Decrease risk of thrombotic events

Therapeutic modalities

- Therapeutic phlebotomy
- Cytoreductive therapies: hydroxycarbamide (HU), Interferon
- JAK inhibitors: ruxolitinib
- Antithrombotic modalities: Aspirin, lifestyle modification

STRATIFICATION FOR THROMBOHEMORRHAGIC COMPLICATIONS IN ET AND PV

Low-risk	Age < 60 years <i>and</i> No history of thrombosis <i>and</i> Platelet count < 1.5 million <i>and</i> No cardiovascular risk factors	Thrombosis risk is not significantly increased compared to controls
High-risk	Age ≥ 60 years <i>or</i> Previous thrombosis	Thrombosis risk is significantly increased
Indeterminate risk	Neither low nor high risk	Thrombosis risk is not well studied

Aspirin

Double-blind placebo controlled trial of ASA (100mg) in PV patients

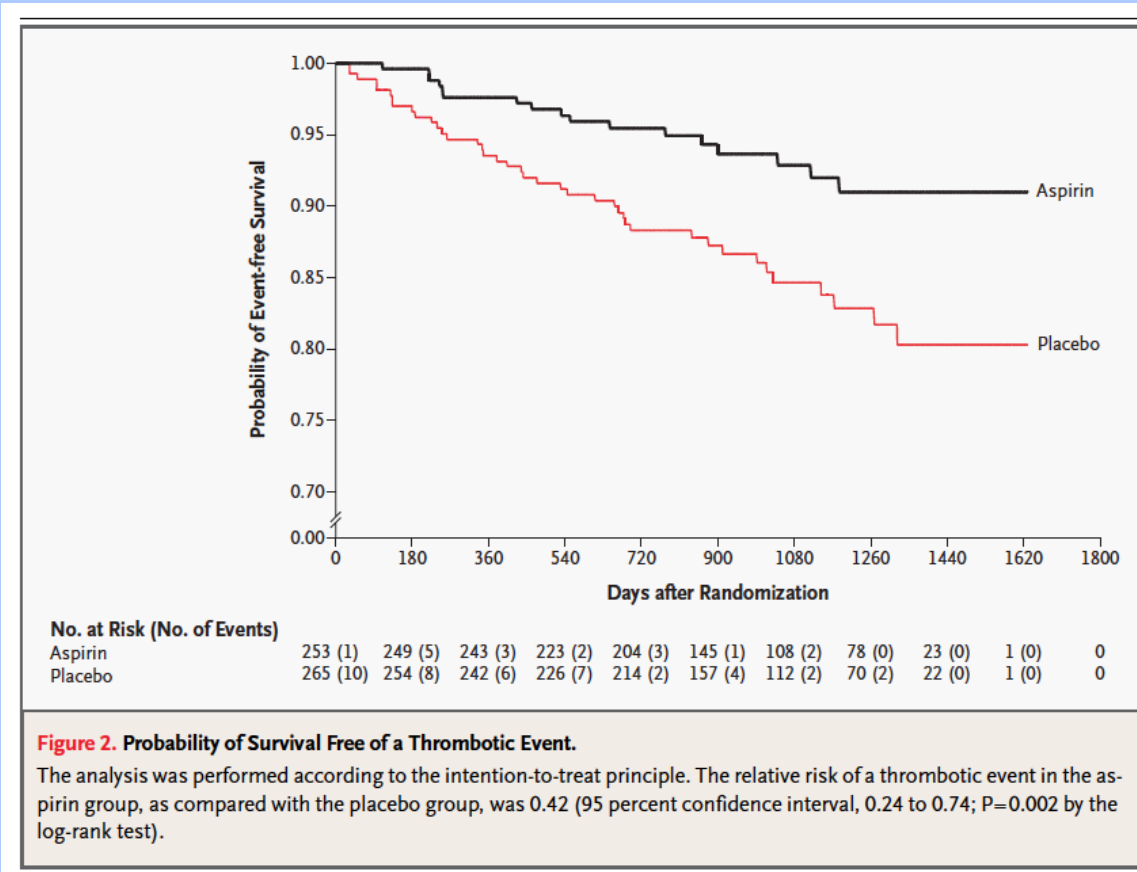
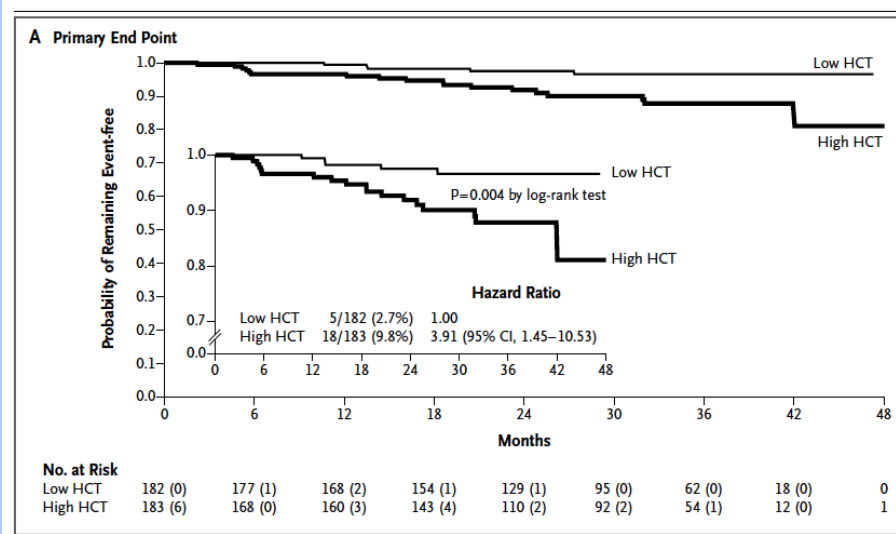


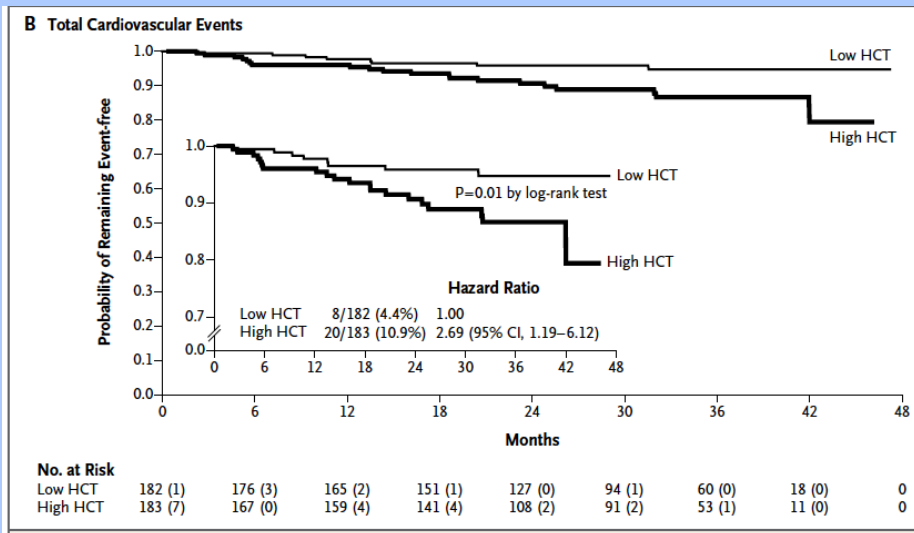
Table 3. Rates and Relative Risks of Bleeding Episodes in the Two Groups.*

Type of Bleeding Episode	Aspirin Group (N=253)	Placebo Group (N=265)	Relative Risk (95% CI)	P Value
	<i>no. (%)</i>			
Any bleeding	23 (9.1)	14 (5.3)	1.82 (0.94–3.53)	0.08
Major bleeding	3 (1.2)	2 (0.8)	1.62 (0.27–9.71)	0.60
Gastrointestinal	2 (0.8)	0		
Intracranial	1 (0.4)	2 (0.8)		
Minor bleeding	20 (7.9)	12 (4.5)	1.83 (0.90–3.75)	0.10
Hematoma	2 (0.8)	2 (0.8)		
Gastrointestinal	7 (2.8)	3 (1.1)		
Hematuria	1 (0.4)	3 (1.1)		
Epistaxis	9 (3.6)	1 (0.4)		
Other	2 (0.8)	4 (1.5)		

Therapeutic Phlebotomy: what is the optimal goal?



Low hematocrit group (<45%)
Versus
high hematocrit group (45-50%)



Is this the optimal HCT goal
for women?
Is <42% more appropriate?

Additional Studies of HU for Frontline Cytoreduction in Pts With PV

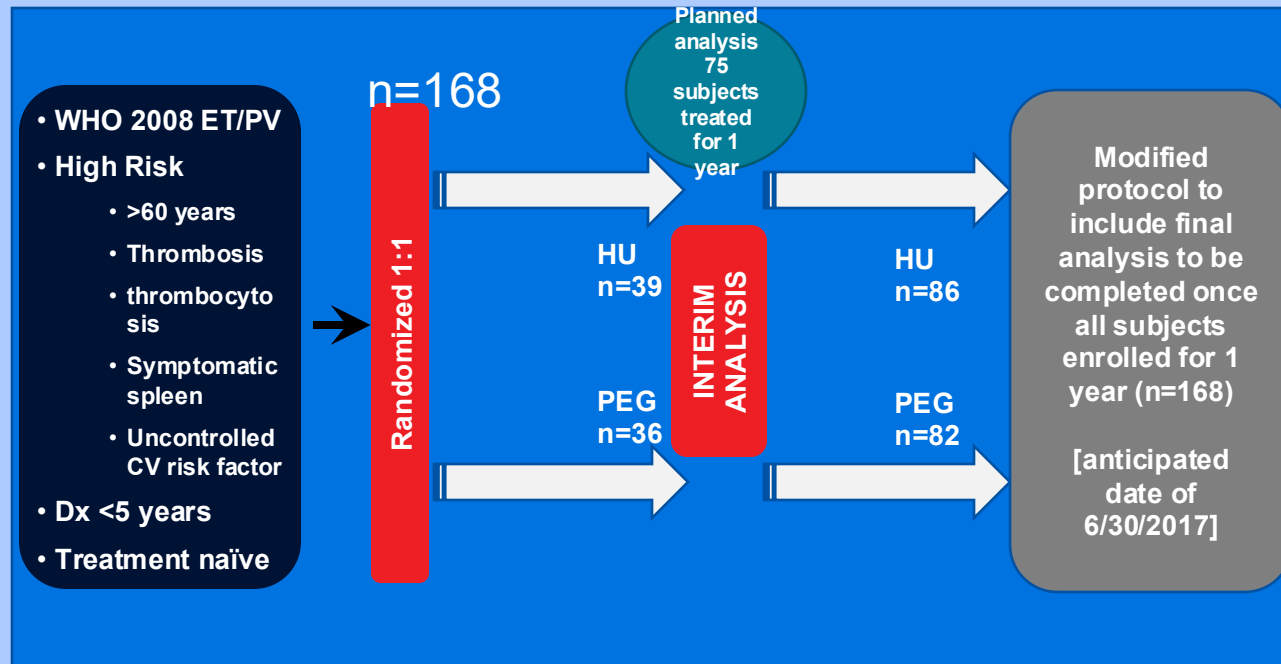
Study/Organization	Pts, N	Intervention	Comparator	Thrombosis
French PV Study Group ^[1]	292 < 65 yrs (median FU: 7 yrs)	HU (randomized)	Pipobroman	No significant difference
French PV Study Group ^[2]	285 (median FU: 16 yrs)	HU (randomized)	Pipobroman	No significant difference
PV cohort of ECLAP study ^[3]	1042 (median FU: ~ 30-35 mos)	HU (propensity matching)	Phlebotomy	CV events/100 PY: HU: 3.0 Phlebotomy: 5.8
Retrospective study ^[4]	235 with thrombosis history	Cytoreduction; 77% received HU	None	Cytoreduction reduced recurrence rates

1. Najean Y, et al. Blood. 1997;90:3370-3377. 2. Kiladjian JJ, et al. J Clin Oncol. 2011;29:3907-3913.
3. Barbui T, et al. Am J Hematol. 2017;92:1131-1136. 4. De Stefano V, et al. Haematologica. 2008;93:372-380.

PegIFN for Pts With PV

Study	Population	Findings
PVN ^[1,2] <ul style="list-style-type: none"> ▪ PegIFN α-2a 	<ul style="list-style-type: none"> ▪ N = 37 ▪ Newly diagnosed pts 	<ul style="list-style-type: none"> ▪ CHR: 95%; CR: 82% in extended FU <ul style="list-style-type: none"> – 0 thromboembolic events in 6 yrs ▪ CMR: 8 (28%); sustained improvements after d/c of treatment ▪ Grade 1/2 AEs: 89%; d/c for toxicity (1 yr): 24% ▪ Median response duration: hematologic: 65 mos; molecular: 58 mos <ul style="list-style-type: none"> – Failure to achieve CMR: more likely to have/acquire nondriver mutations ▪ Thrombosis and progression can occur ▪ Toxicity continued over time (new grade 3/4 events in 10% to 17% of PY); d/c for AEs: 22%
MDACC ^[3,4] <ul style="list-style-type: none"> ▪ PegIFN α-2a 	<ul style="list-style-type: none"> ▪ N = 43 ▪ ~ 50% previous cytoreductives ▪ Median FU: 83 mos 	<ul style="list-style-type: none"> ▪ CR: 43% to 57%; PR: 43%; CMR: 21% ▪ 1 TIA, 1 DVT during study period ▪ AEs (any): 88%; d/c for AEs: 20%
PEGINVERA ^[5,6] <ul style="list-style-type: none"> ▪ RopegIFN α-2b 	<ul style="list-style-type: none"> ▪ N = 51 ▪ HU pretreated: 33% ▪ Median FU: 80 wks 	<ul style="list-style-type: none"> ▪ CR: 43% to 57%; PR: 43%; CMR: 21% ▪ 1 TIA, 1 DVT during study period ▪ AEs (any): 88%; d/c for AEs: 20%

MPD-RC 112 Study



MPD-RC 112: First-line PegIFN α -2a vs HU for High-Risk PV and Essential Thrombocythemia

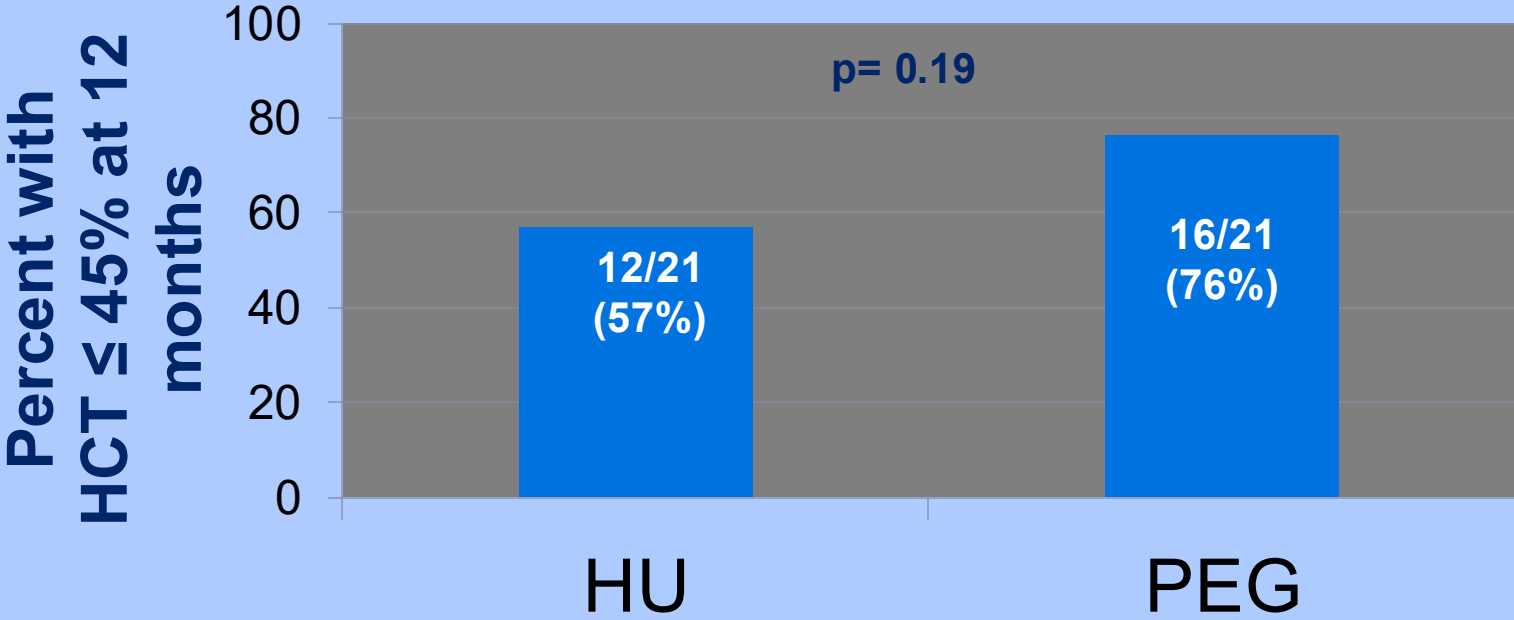
Interim Analysis: Overall Response Rates at 12 Months

	Hydroxyurea (n = 39)			PegIFN α -2a (n = 36)			P value
	PR n (%)	CR n (%)	ORR n (%)	PR n (%)	CR n (%)	ORR n (%)	
Entire cohort (n = 75)	14 (36)	13 (33)	27 (69)	19 (53)	10 (28)	29 (81)	0.6*
PV (n = 44)	10/23 (44)	6/23 (26)	16/23 (70)	13/21 (62)	4/21 (19)	17/21 (81)	0.6
ET (n = 31)	4/16 (25)	7/16 (44)	11/16 (69)	6/15 (40)	6/15 (40)	12/15 (80)	0.8

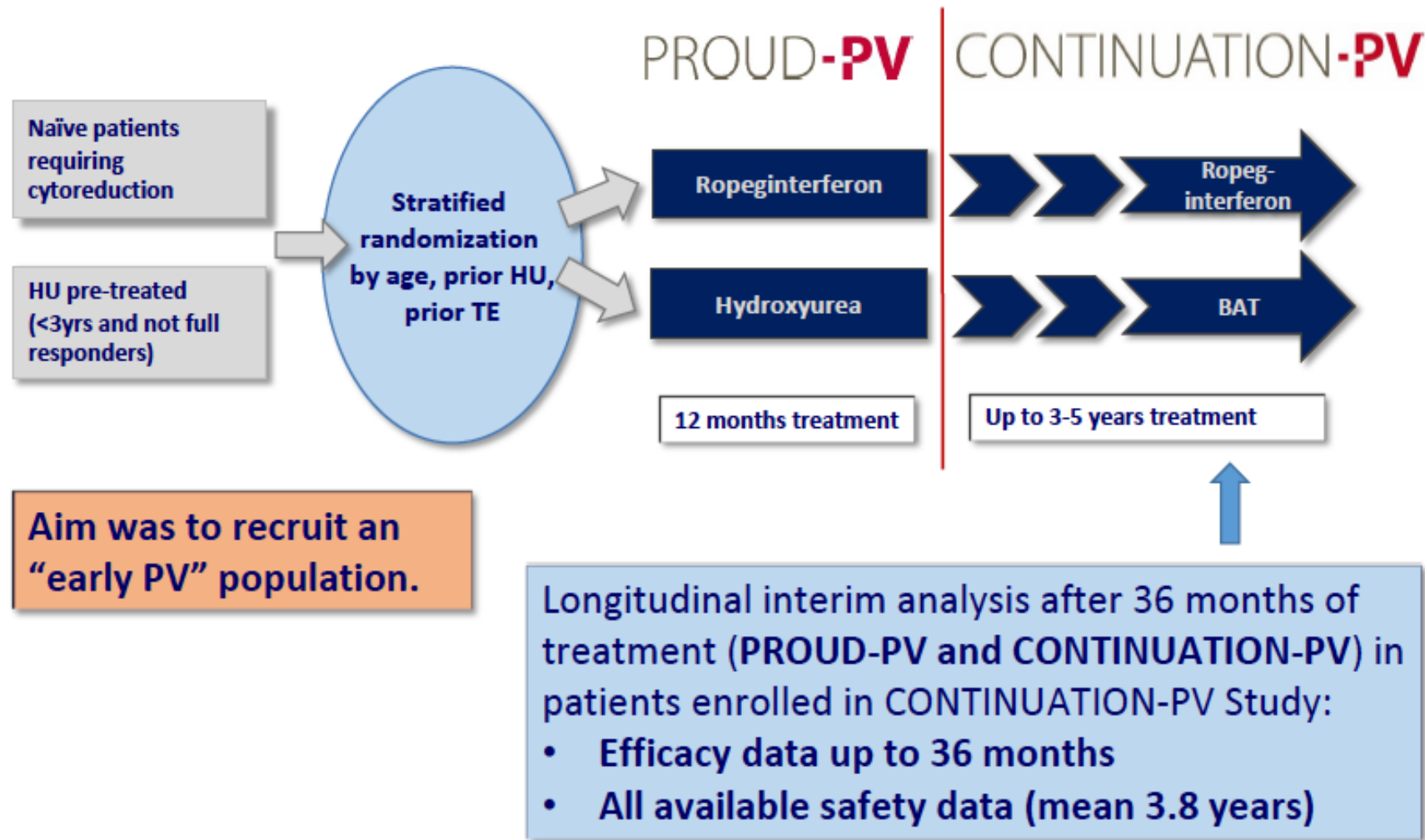
*CR comparison based on z-test; did not cross stopping boundary. CR, complete response; PR, partial response; ORR, overall response rate

AE, [†] n (%)	Hydroxyurea (n = 36)	PegIFN α -2a (n = 36)	P Value
AE grade \geq 3	5 (14)	17 (47)	.002
Depression	0	10 (28)	< .001
Dyspnea	1 (3)	7 (19)	.02
Fatigue	10 (28)	18 (50)	.05
Flulike symptoms	1 (3)	12 (33)	< .001
Injection-site reaction	0	9 (25)	.001
Pruritus	3 (8)	10 (28)	.03

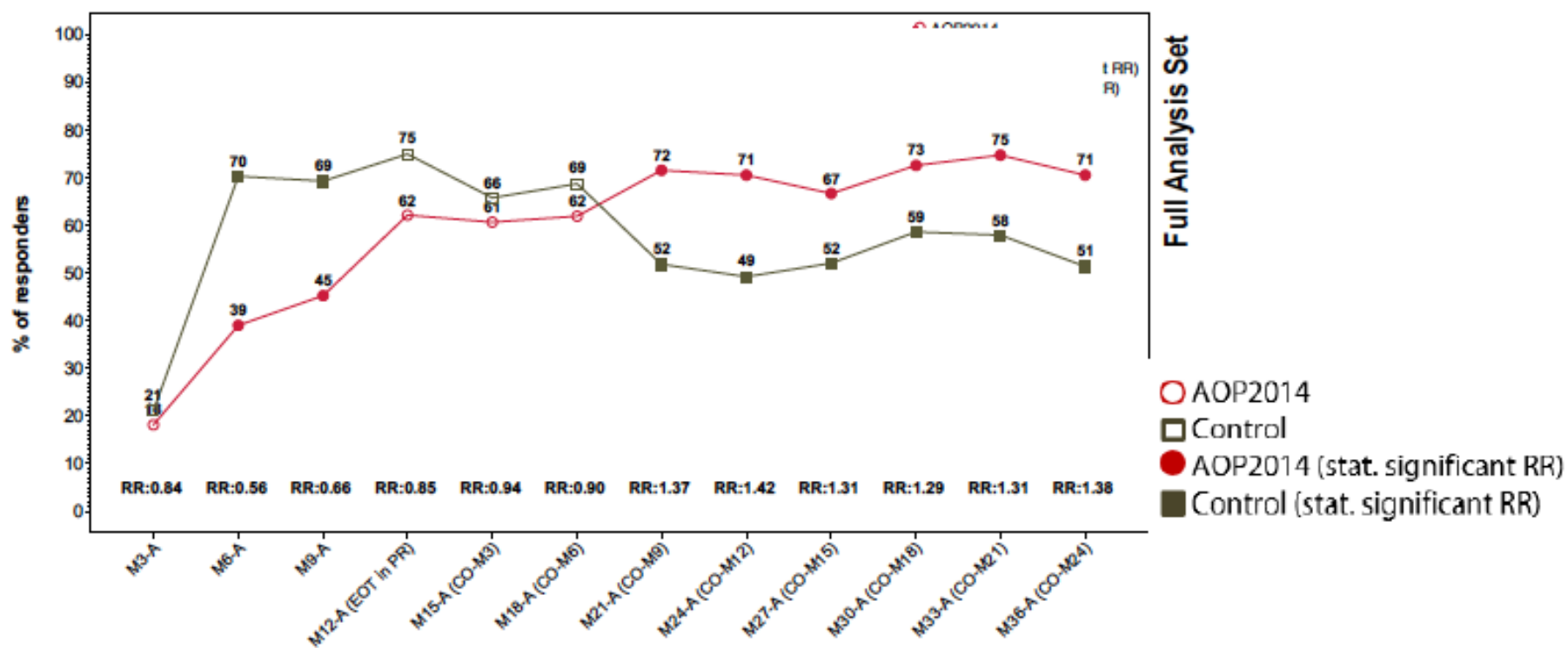
HCT Control in PV Patients by Treatment Arm (at 12 months or last visit)



Ropeginterferon alfa-2b phase III development in PV: PROUD-PV and CONTINUATION-PV Studies



Complete hematologic response (CHR)



Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1201	0.85 [0.70-1.04]
MONTH 24	67/95	70.5	33/67	49.3	0.0111	1.42 [1.08-1.87]
MONTH 36	67/95	70.5	38/74	51.4	0.0122	1.38 [1.07-1.79]

PROUD-PV and CONTINUATION-PV: Safety

Most Common Grade 3/4 TRAEs w/ Ropeg:

- ↑ γ -glutamyltransferase (6%, n=7)
- ↑ alanine aminotransferase (3%, n=4)

Treatment-related serious AEs:

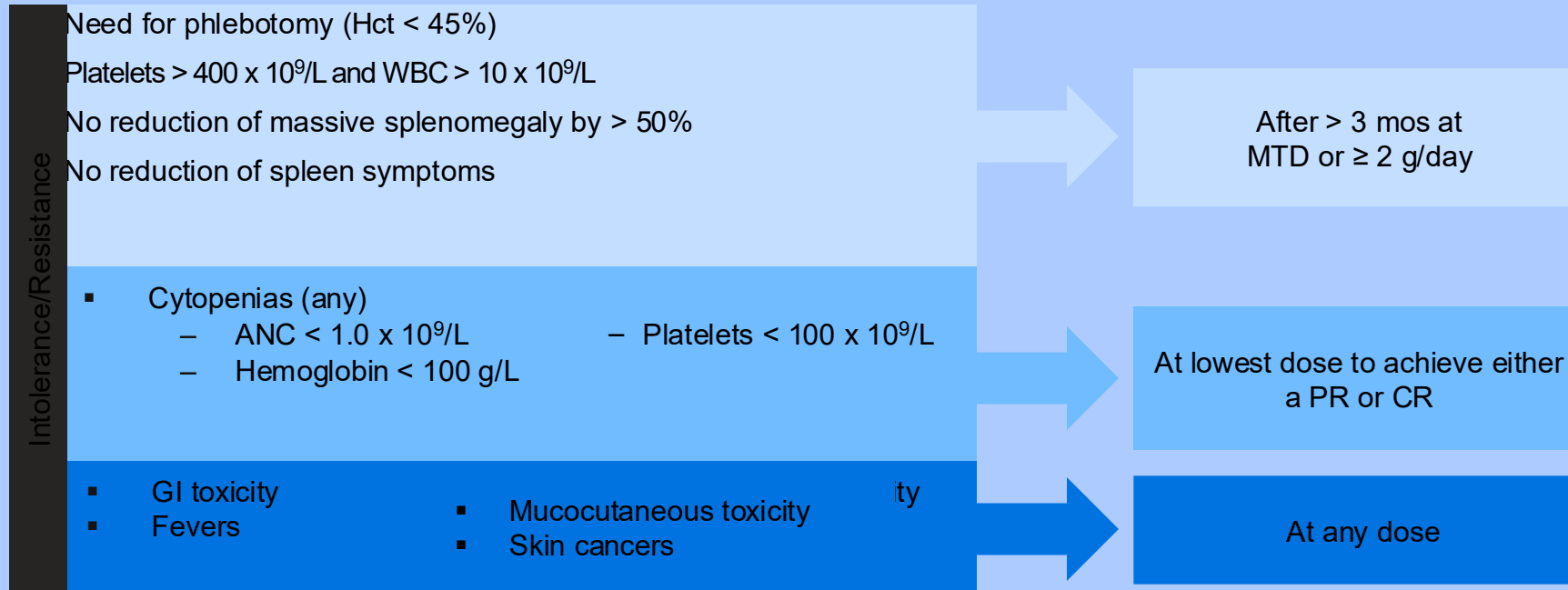
- Ropeg (2%, n=3) vs control 4% (n=5)
- 1 treatment-related death reported in standard therapy group (acute leukaemia)

AEs of Special Interest

	Ropeginterferon alfa-2b (N=127)	Control (N=127)
Endocrine disorders		
Any adverse event	8 (6%)	2 (2%)
Related to treatment	6 (5%)	0
Psychiatric disorders		
Any adverse event	5 (4%)	6 (5%)
Related to treatment	2 (2%)	1 (1%)
Musculoskeletal and connective tissue disorders		
Any adverse event	2 (2%)	0
Related to treatment	2 (2%)	0
Major cardiovascular and major thromboembolic adverse events		
Any major cardiovascular adverse event	13 (10%); 16 events	8 (6%); 25 events
Major thromboembolic adverse event	4 (3%); 6 events	4 (3%); 4 events
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Any neoplasm	9 (7%); 11 events	10 (8%); 12 events
Leukaemic transformation (acute leukaemia)	0; 0 events	2 (2%); 2 events
Skin cancers related to treatment (basal cell carcinoma and melanoma)	0; 0 events	3 (2%); 3 events

Gisslinger H, et al. *Lancet Haematol.* 2020;7:E196-E208.

HU Resistance and Intolerance: ELN Criteria

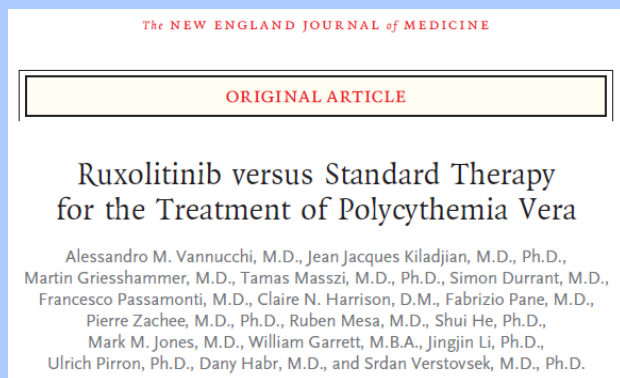


- Resistance and/or intolerance to HU associated with the following in a retrospective analysis of 261 pts
 - Increased risk of disease transformation to AML or MF (HR: 6.8; *P* < .001)
 - Reduced survival (HR: 5.6; *P* < .001)

Barosi G, et al. Br J Haematol. 2010;148:961-963. Sever M, et al. Leuk Lymphoma. 2014;55:2685-90.

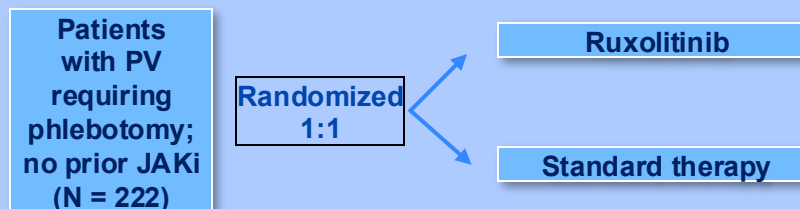
Alvarez-Larrán A, et al. Blood. 2012;119:1363-1369.

Ruxolitinib Phase III Trial (RESPONSE)



Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study

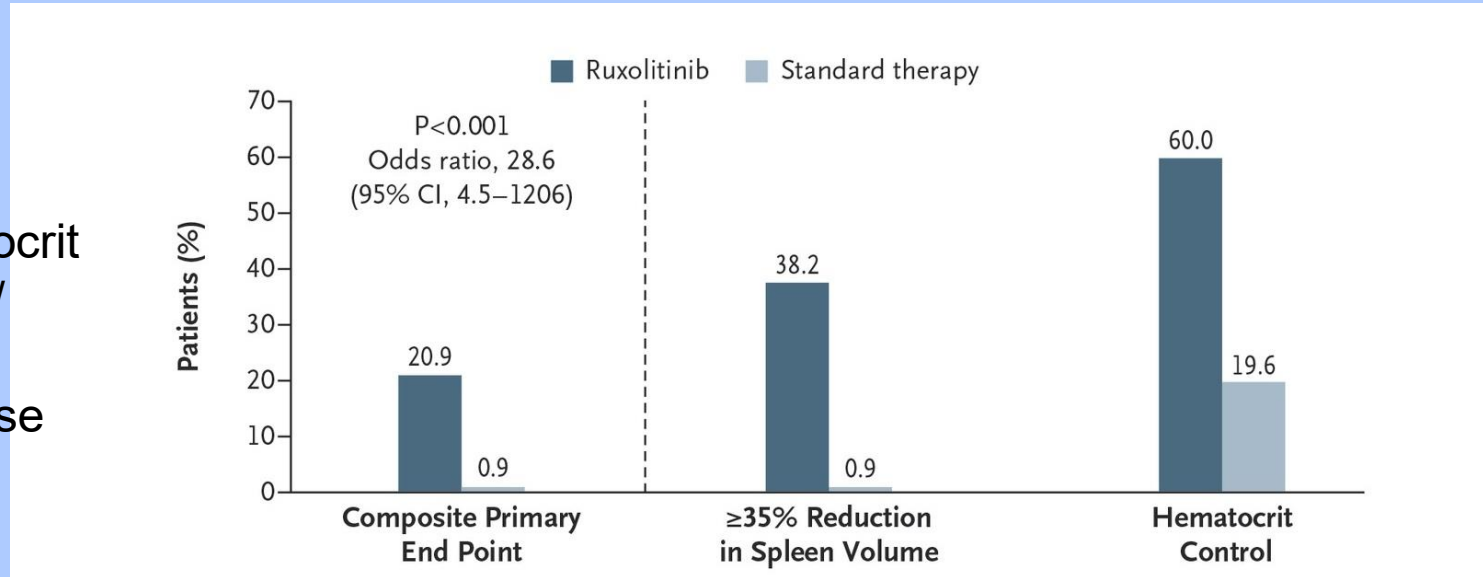
Jean-Jacques Kiladjian, Pierre Zachee, Masayuki Hino, Fabrizio Pane, Tamas Masszi, Claire N Harrison, Ruben Mesa, Carole B Miller, Francesco Passamonti, Simon Durrant, Martin Griesshammer, Keita Kiritto, Carlos Besses, Beatriz Moiraghi, Elisa Rumi, Vittorio Rosti, Igor Wolfgang Blau, Nathalie Francillard, Tuochuan Dong, Monika Wroclawska, Alessandro M Vannucchi, Srdan Verstovsek



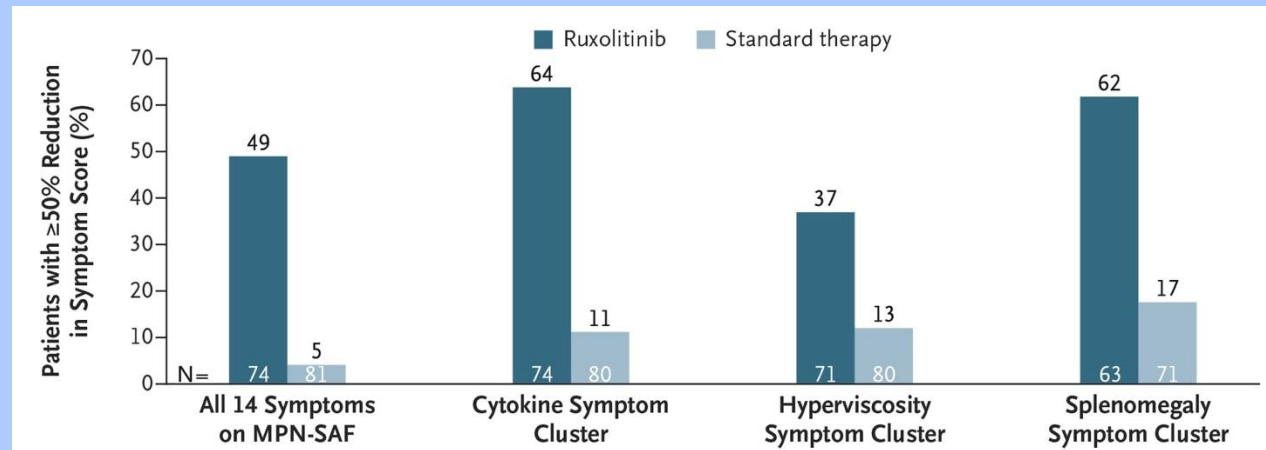
Vannucchi AM, et al. *N Engl J Med*. 2015;372:426.
Kiladjian JJ, et al. *Lancet Haematol*. 2020;7(3):e226.

Ruxolitinib Phase III Trial (RESPONSE)

Hematocrit control/
Spleen response



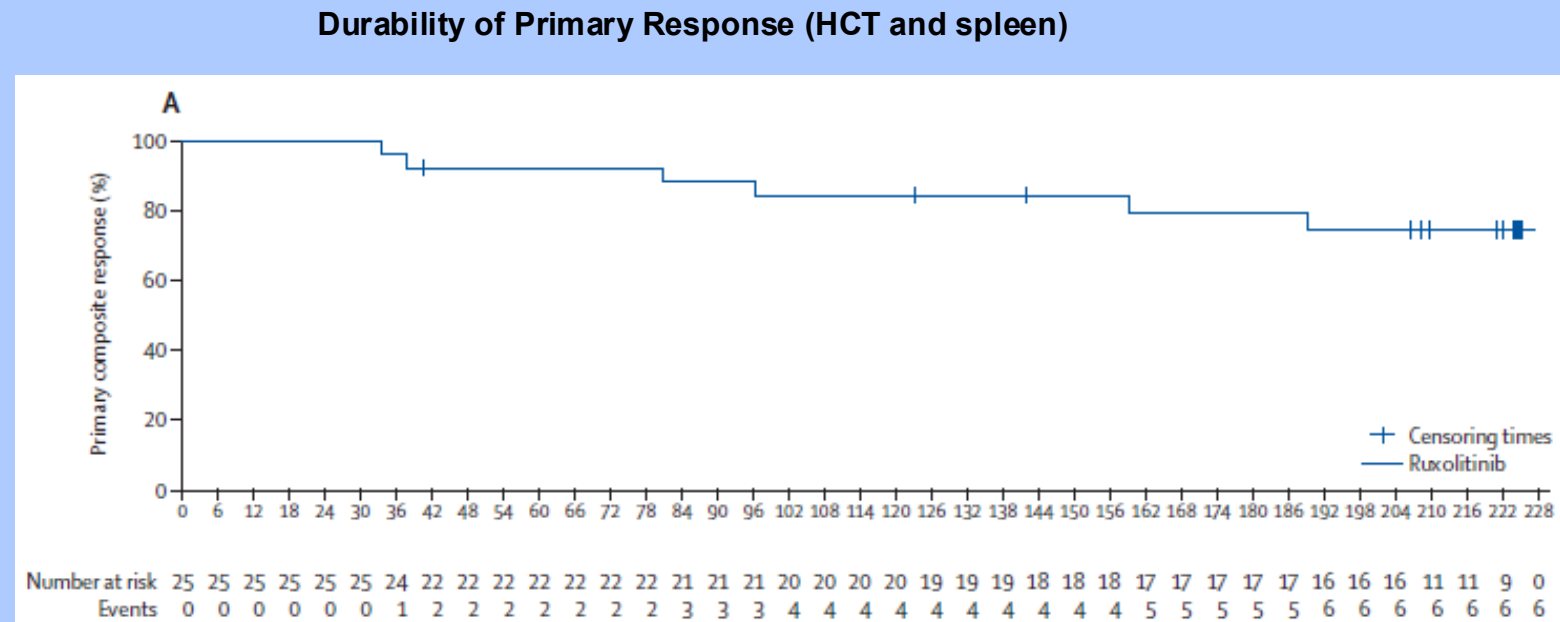
Symptom reduction



72:426.

Phase III RESPONSE: Long-Term Efficacy and Safety (5 Years)

- Duration of **HCT control** at 224 weeks (starting from week 32)
 - **0.73** (95% CI: 0.60-0.83).
- Duration **maintaining $\geq 35\%$ of reduction in the spleen volume** at week 224 (starting from week 32)
 - **0.72** (95% CI: 0.34-0.91)



Second-line Treatment Options for Pts With PV Who Require Cytoreductive Therapy

First line “low risk”: ASA +Phlebotomy (this may change soon)

First line “high risk”: ROPEG-interferon, Hydrea

Second line:

Ruxolitinib

- Indicated for pts with intolerance/inadequate response to HU

PegIFN

- If intolerance/inadequate response to first-line HU

HU

If intolerance/inadequate response to first-line

Emerging:

Rusfertide (hepcidin-mimetic in phase III)

Upfront cytoreductive treatment in low risk

Ruxolitinib [package insert]. 2017. Barbui T, et al. J Clin Oncol. 2011;29:761-770.
Tefferi A, et al. Am J Hematol. 2015;90:162-173.

Essential Thrombocythemia

WHO 2016 Criteria for ET

WHO ET criteria

Major criteria

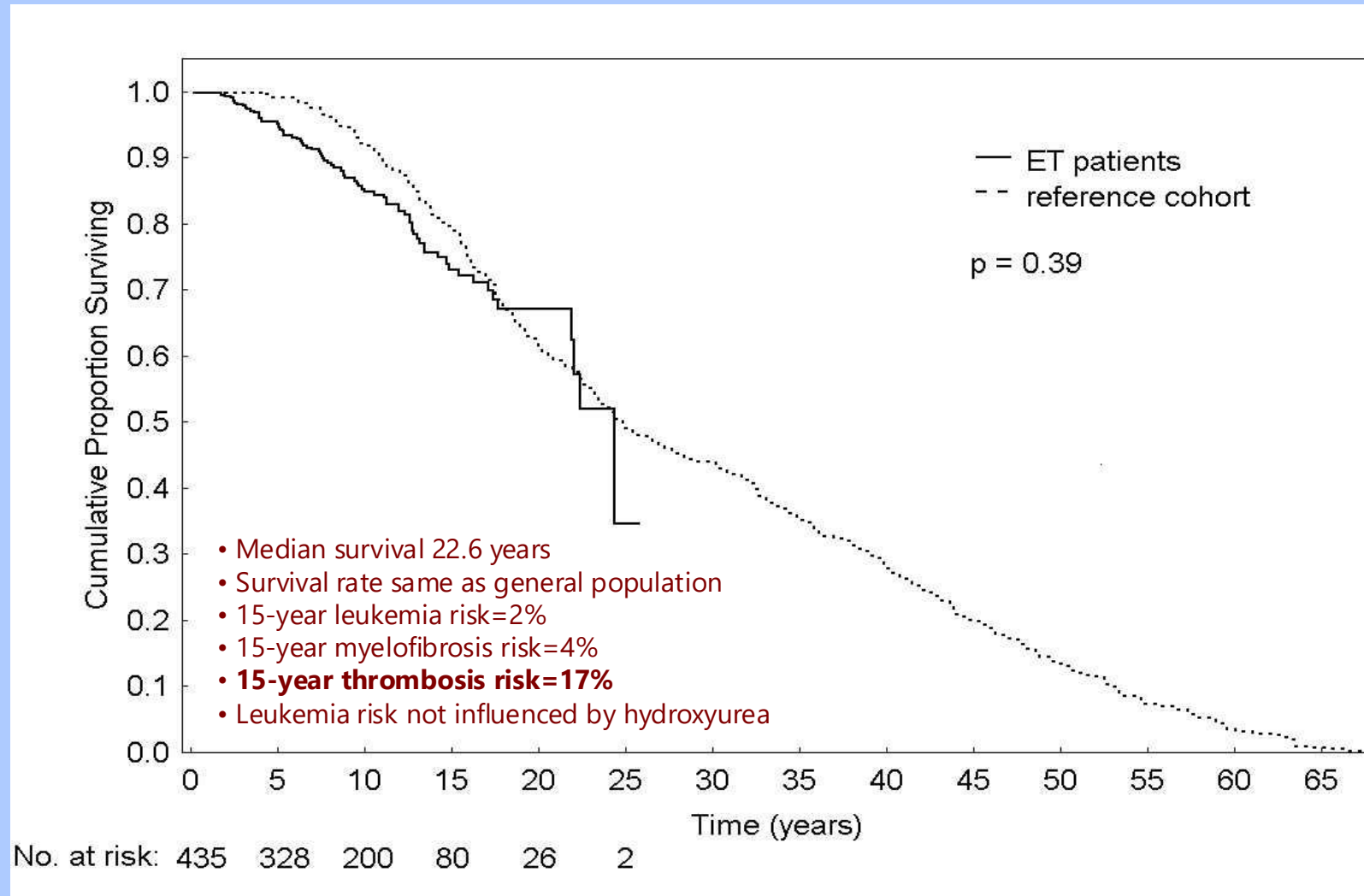
1. Platelet count $\geq 450 \times 10^9/L$
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for *BCR-ABL1*⁺ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of *JAK2*, *CALR*, or *MPL* mutation

Minor criterion

Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

MODERN NATURAL HISTORY OF ET



Essential Thrombocythemia vs Prefibrotic MF: Diagnosis

Parameter	ET	Prefibrotic MF
Blood counts	Sustained thrombocytosis ($\geq 450 \times 10^9/L$)	Sustained thrombocytosis plus ≥ 1 of: anemia, leukocytosis $> 11 \times 10^9/L$, palpable splenomegaly, or \uparrow LDH
Bone marrow	\uparrow enlarged, mature megakaryocytes with hyperlobulated nuclei	Atypical megakaryocyte proliferation with no reticulin fibrosis $>$ grade 1; \uparrow BM cellularity, granulocytic proliferation, and often \downarrow erythropoiesis
Mutations	<i>JAK2, CALR, MPL</i> (~ 90%) or another clonal marker	<i>JAK2, CALR, MPL</i> (~ 90%) or another clonal marker
Overt MF at 15 yrs, %	9.3	16.9
Cumulative AML at 15 yrs, %	2.1	11.7
15-yr survival, %	80	59

Therapy and goals in ET

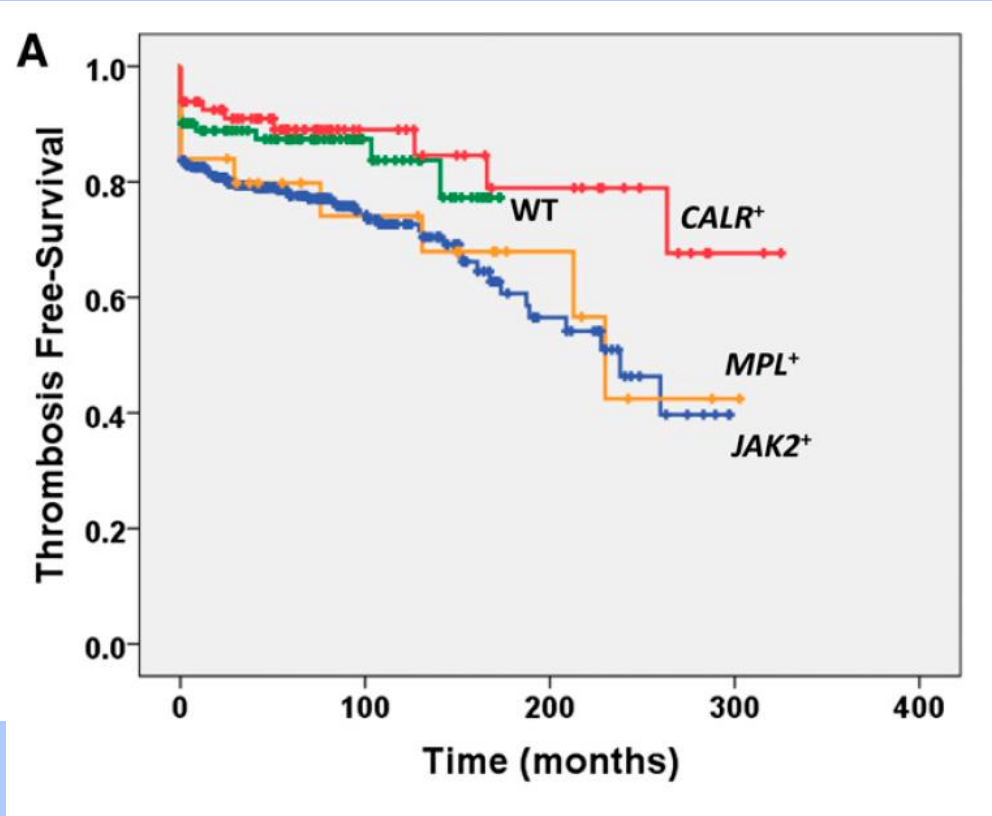
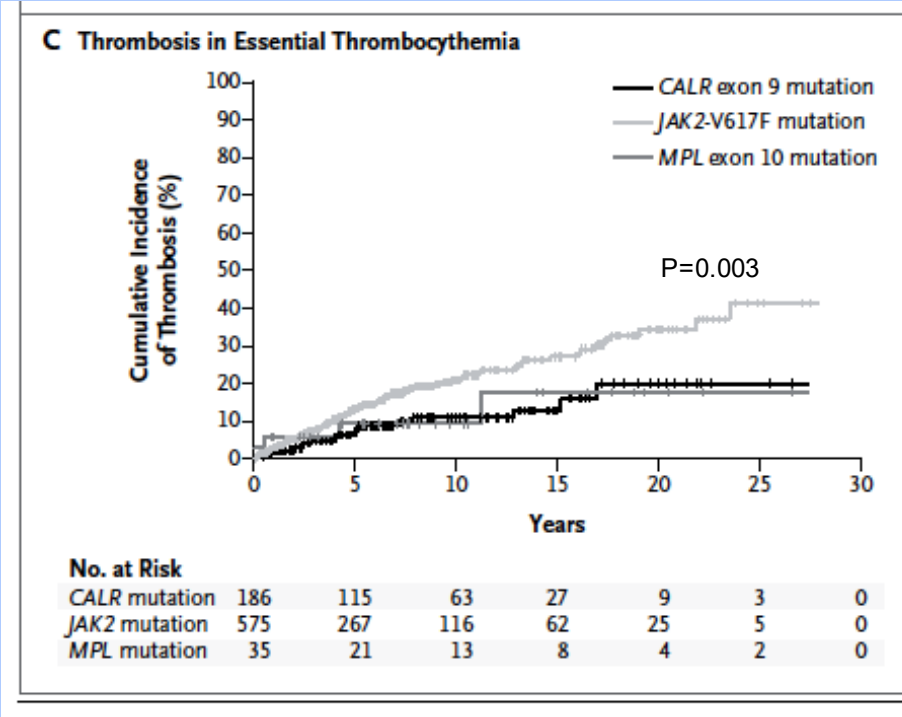
Goals of therapy

- Reduce symptoms burden
- Decrease risk of thrombotic events

Therapeutic modalities

- Cytoreductive therapies: hydroxycarbamide (HU), Interferon, Anagrelide
- Antithrombotic modalities: Aspirin, lifestyle modification

Influence of genetic alterations on thrombosis risk

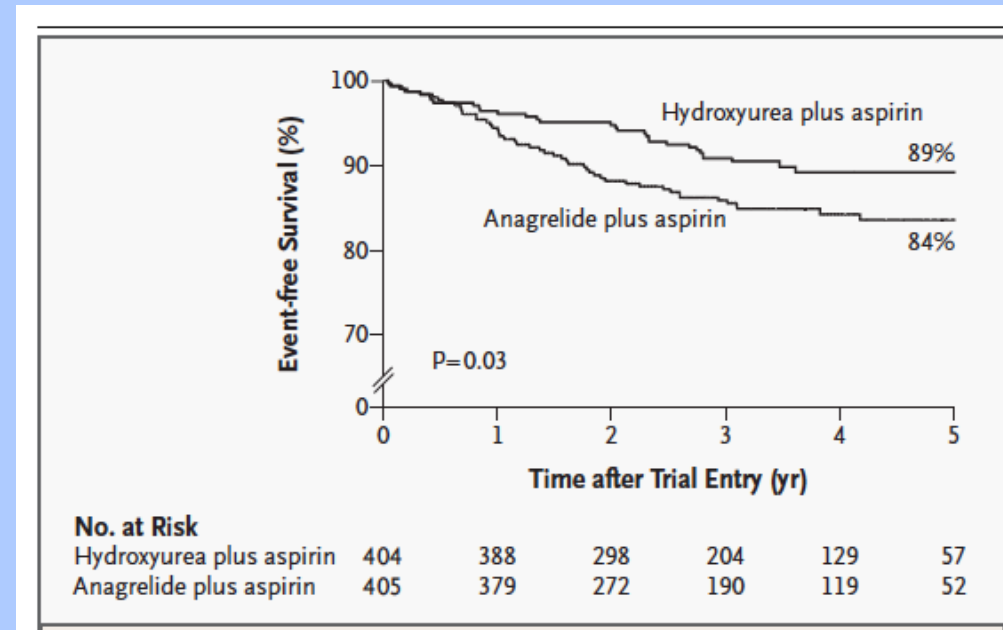
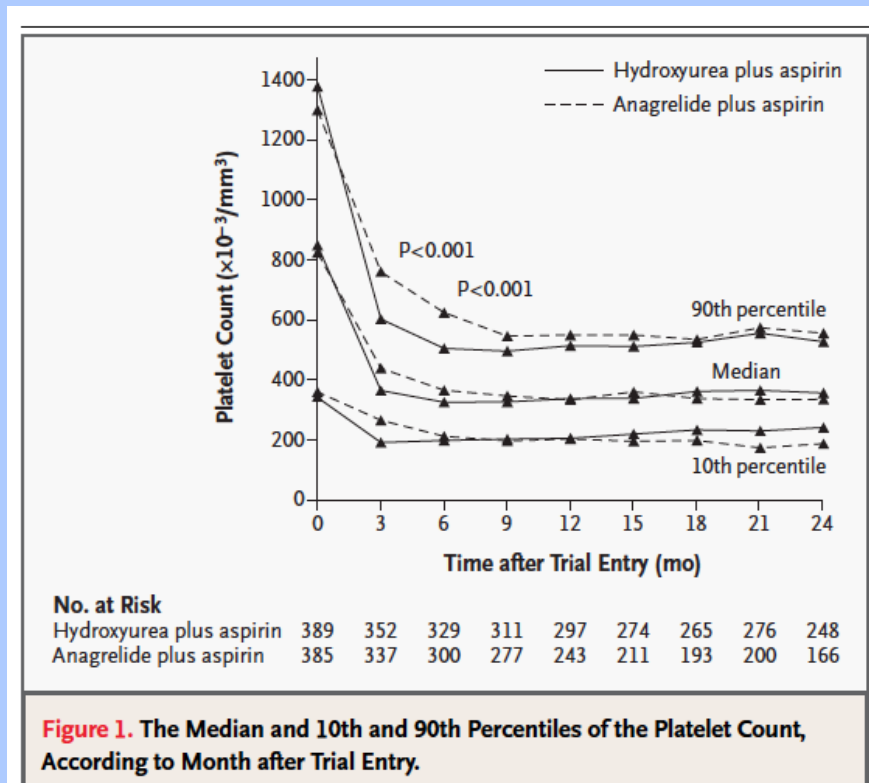


Clinical Decision Making

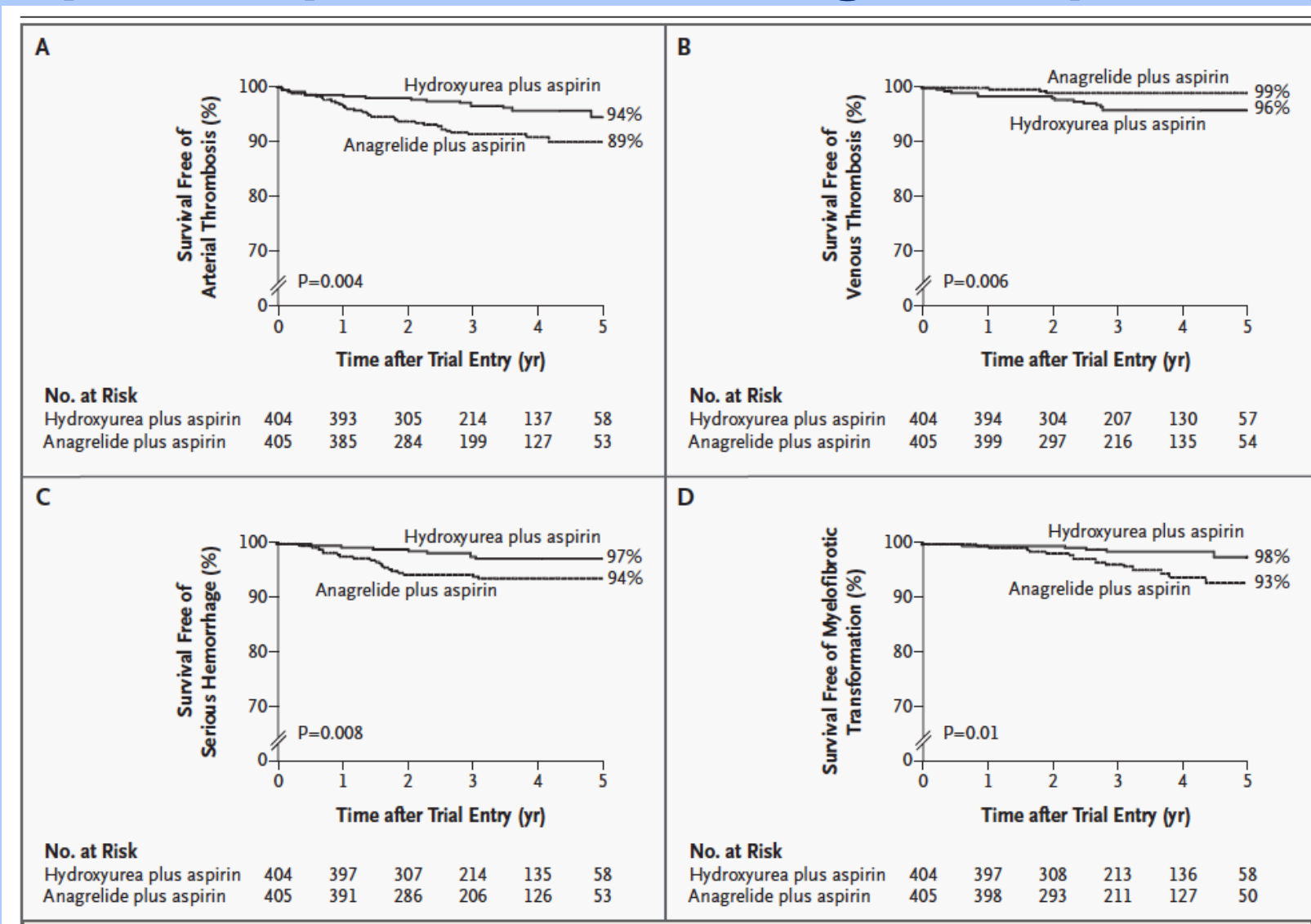
	Revised IPSET-Thrombosis
Very low risk	No prior thrombosis history and Age <61 y and Negativity for the JAK2 V617F mutation
Low risk	No prior thrombosis history and Age <61 y and Positivity for the JAK2 V617F mutation
Intermediate risk	No prior thrombosis history and Age >60 y and Negativity for the JAK2 V617F mutation
High risk	Prior history of thrombosis or Age >60 y and Positivity for the JAK2 V617F mutation

HU plus Aspirin versus Anagrelide plus Aspirin

PT-1: High risk ET patients randomized to low-dose ASA
 Plus either anagrelide or HU.
 Endpoint: thrombotic or hemorrhagic events



HU plus Aspirin versus Anagrelide plus Aspirin



Harrison *NEJM*. 2005

Interferon

Phase II study of PEG-IFN- α -2a

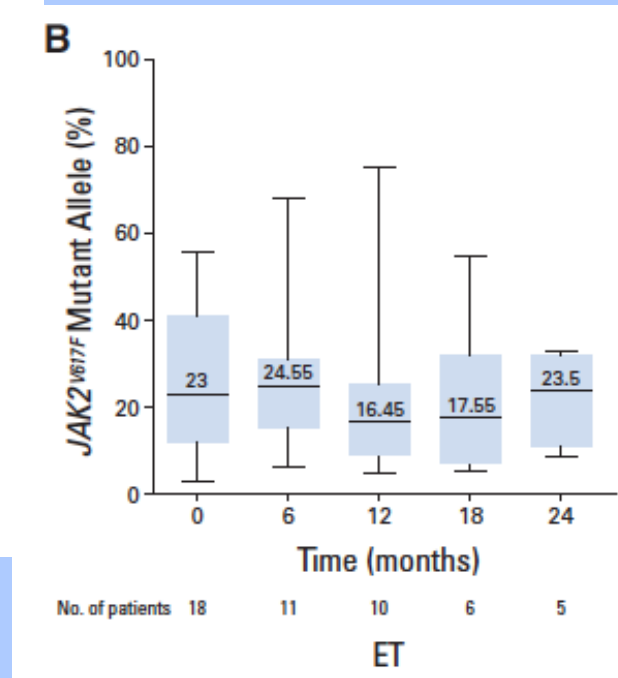
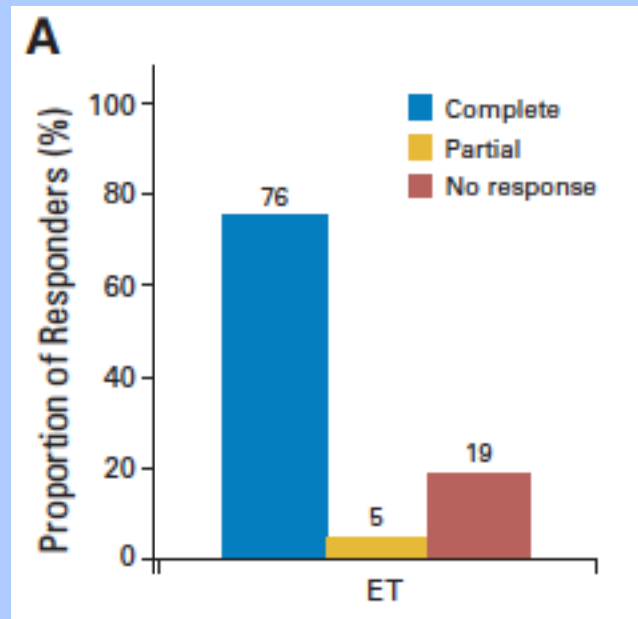
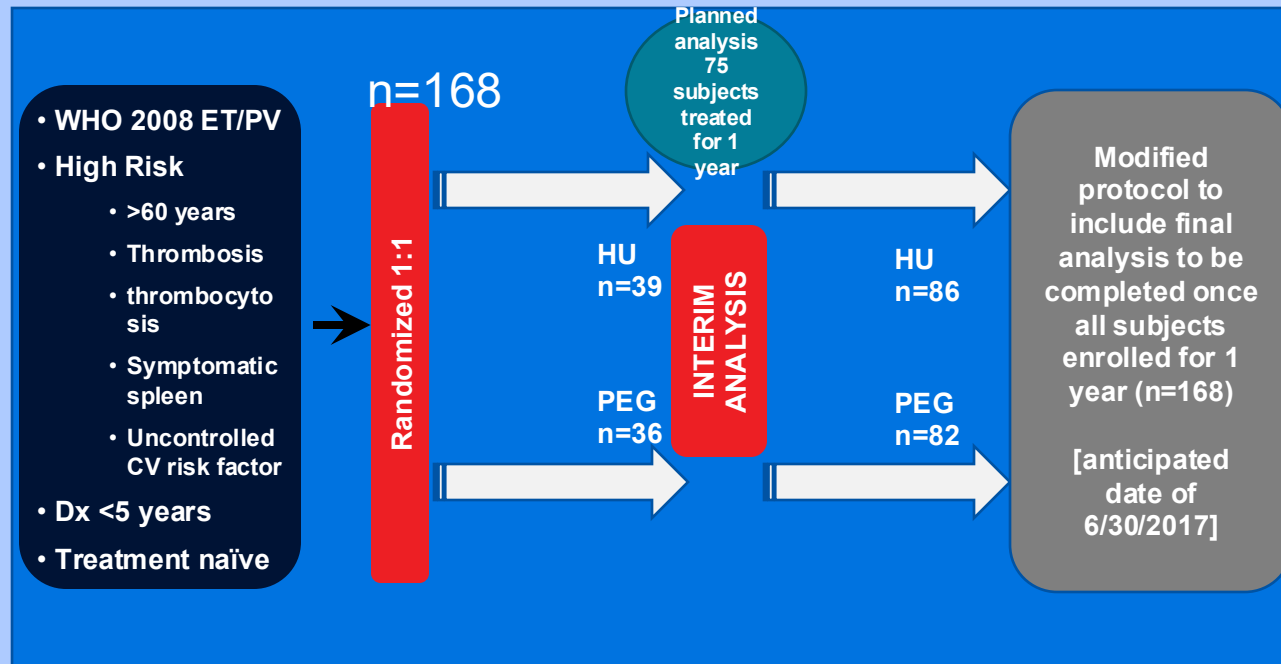


Table 2. Molecular Response Rates to PEG-IFN- α -2a Therapy

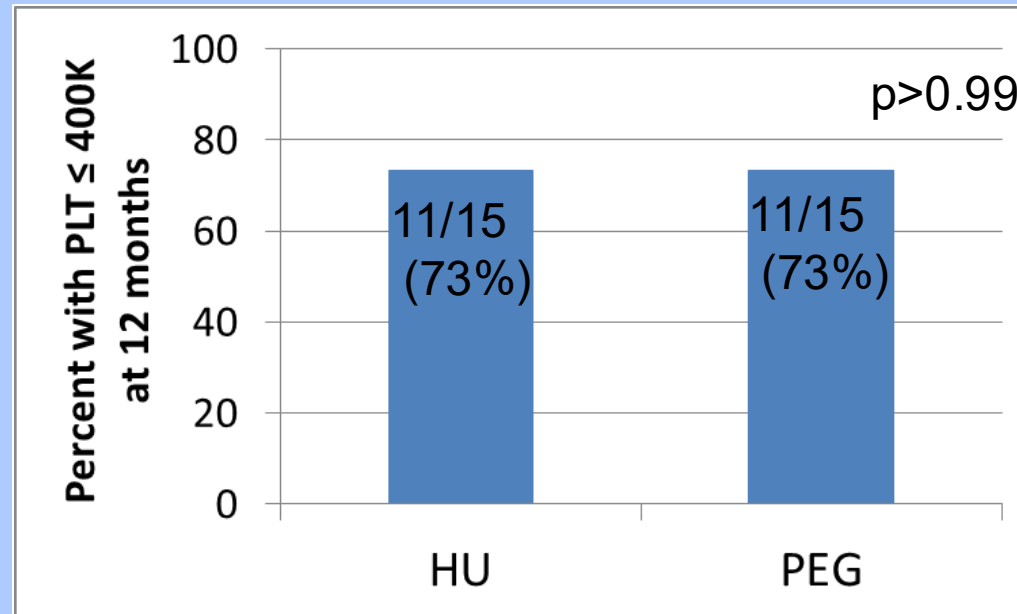
Response	PV (n = 35)		ET (n = 16)	
	No. of Patients	%	No. of Patients	%
CMR (undetectable $JAK2^{V617F}$)	5	14	1	6
PMR ($\geq 50\%$ $JAK2^{V617F}$ decrease)	11	31	2	13
Minor molecular response (20%-49% $JAK2^{V617F}$ decrease)	3	9	3	19
No response (0%-19% $JAK2^{V617F}$ decrease)	16	46	10	62

Abbreviations: PEG-IFN- α -2a, pegylated interferon alfa-2a; PV, polycythemia vera; ET, essential thrombocythemia; CMR, complete molecular response; PMR, partial molecular response.

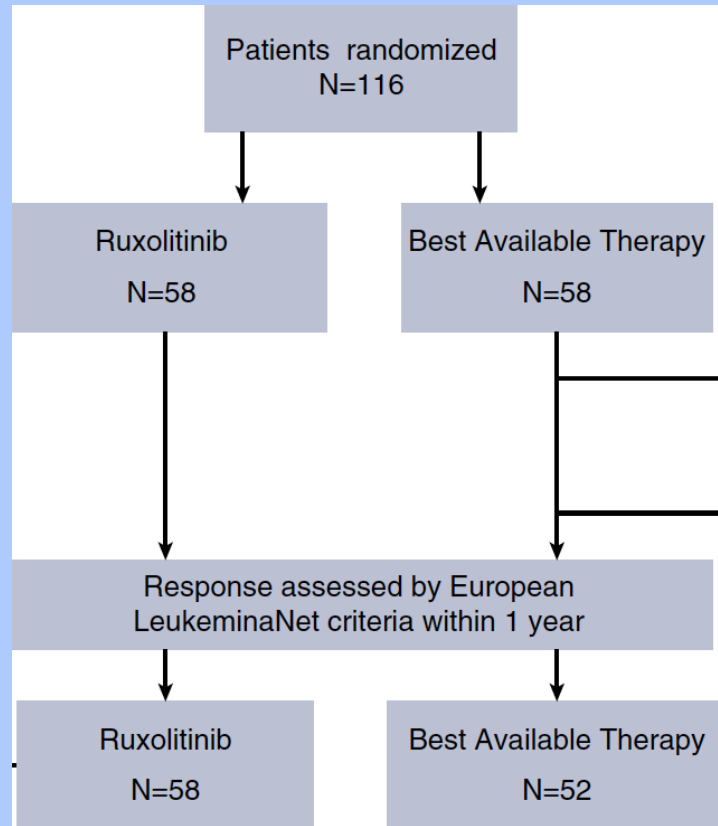
MPD-RC 112 Study Schema



Platelet Control in ET Patients by Treatment Arm (at 12 months or last visit)



Ruxolitinib versus BAT in HU resistant/refractory patients (MAJIC trial – randomized phase II)



- There was no evidence of improvement in complete response within 1 year reported in 27 (46.6%) patients treated with ruxolitinib vs 23 (44.2%) with BAT (P 5 .40)
- At 2 years, rates of thrombosis, hemorrhage, and transformation were not significantly different; however, some disease-related symptoms improved in patients receiving ruxolitinib relative to BAT
- Grade 3 and 4 anemia occurred in 19% and 0% of ruxolitinib vs 0% (both grades) in the BAT arm, and grade 3 and 4 thrombocytopenia in 5.2% and 1.7% of ruxolitinib vs 0% (both grades) of BAT-treated patients
- Rates of discontinuation or treatment switching did not differ between the 2 trial arms

Myelofibrosis

WHO Diagnostic Criteria: MF

Primary Overt MF Diagnosis

Requirement for diagnosis

- All 3 major criteria AND ≥ 1 minor criteria

Major criteria

1. Megakaryocytic proliferation and atypia **with reticulin and/or collagen fibrosis grade 2/3**
2. *JAK2*, *CALR*, or *MPL* mutation, presence of other clonal markers* OR absence of reactive MF
3. Not meeting WHO criteria for other myeloid malignancies

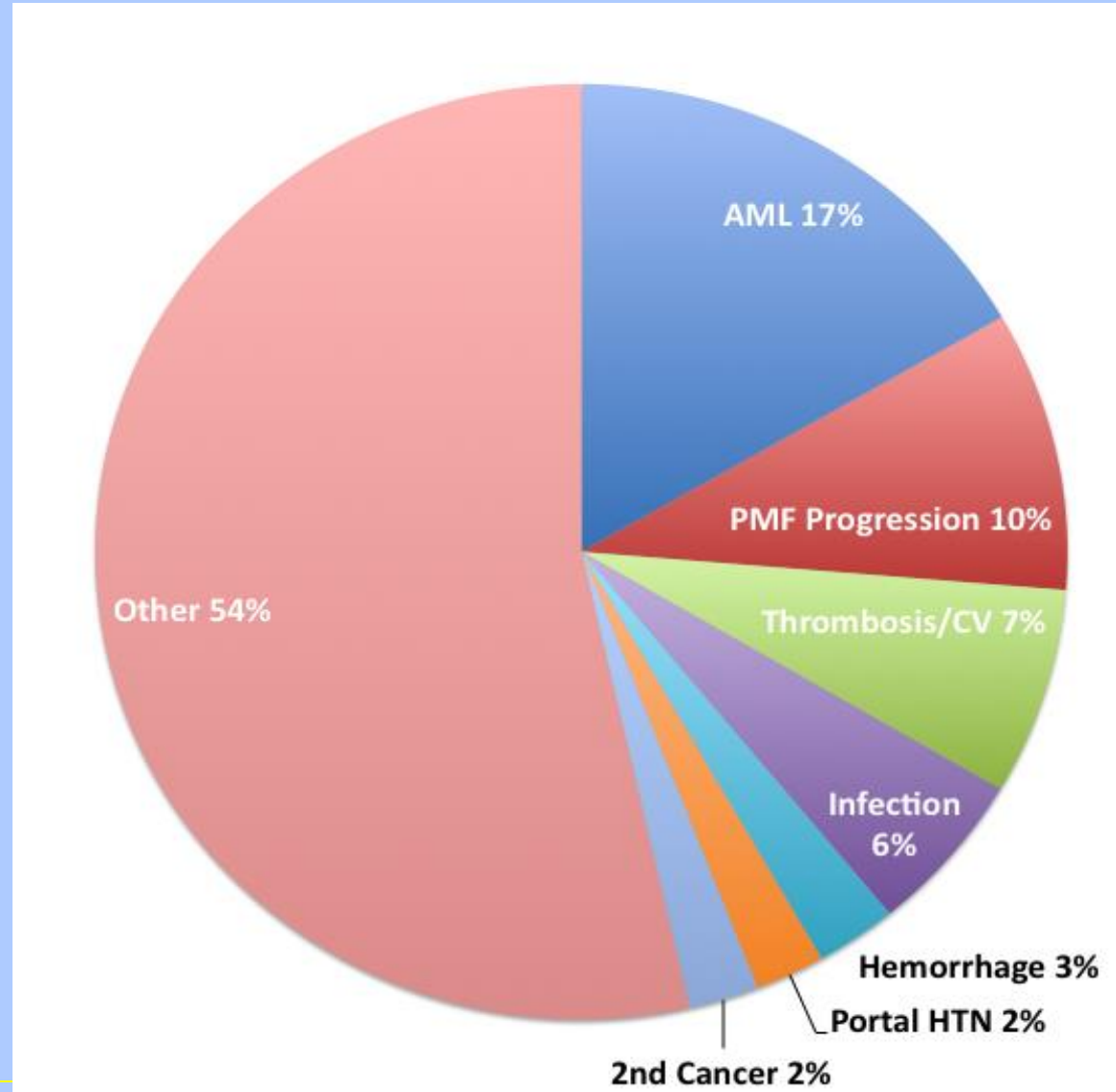
Minor criteria

1. Anemia not attributed to a comorbid condition
2. Leukocytosis $\geq 11 \times 10^9/L$
3. Palpable splenomegaly
4. LDH increased above ULN
5. **Leukoerythroblastosis**

*eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*.

Mortality in PMF

Median Survival 69 Months (517/1001 Expired)



Cervantes *et al. Blood* 2009

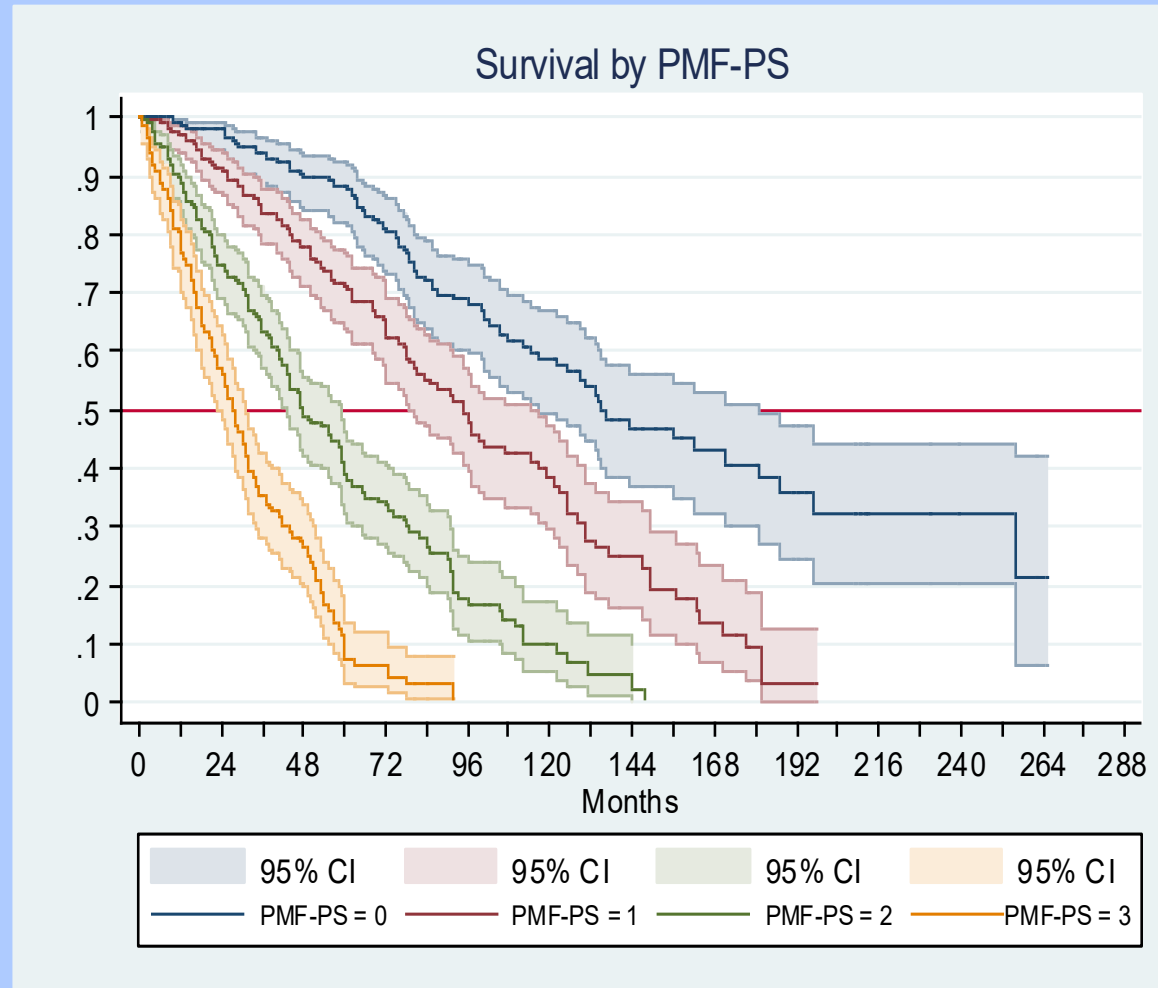
International Prognostic Scoring System (IPSS):

Prognostic factors

- Age > 65 years
- Constitutional symptoms
- Hb < 10 g/dL
- Leukocytes > 25 x 10⁹/L
- Blood blasts ≥ 1%

Risk groups

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



Dynamic International Prognostic Scoring System (DIPSS): Survival by risk group

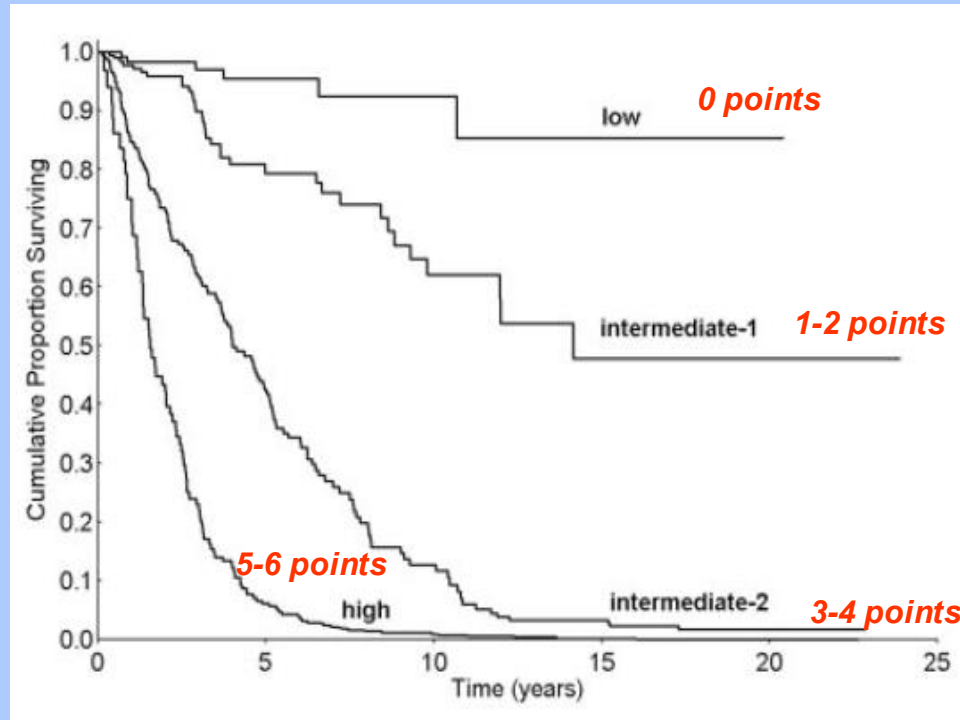


Table 3. DIPSS for survival in primary myelofibrosis

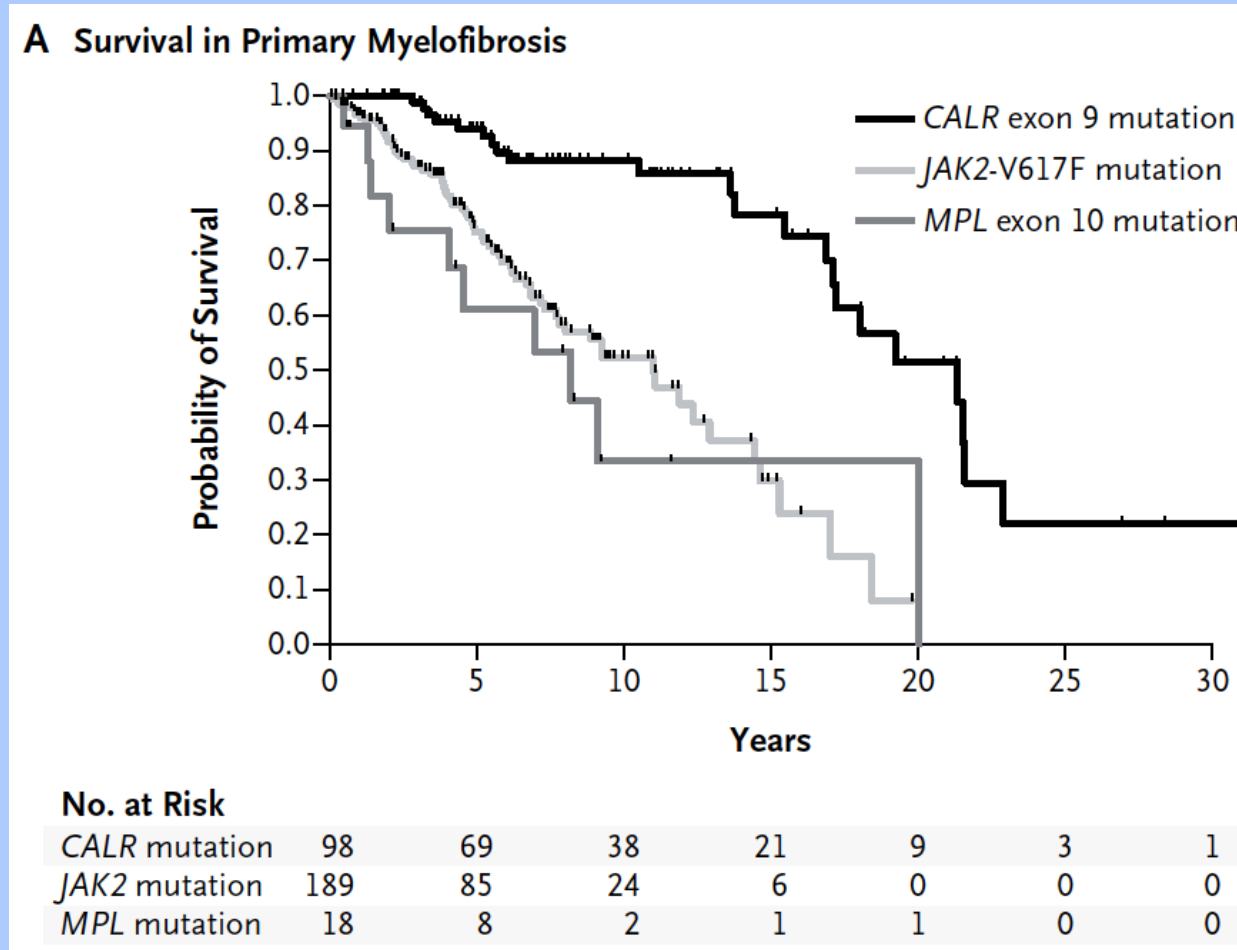
Prognostic variable	Value		
	0	1	2
Age, y	≤ 65	> 65	
White blood cell count, ×10 ⁹ /L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

The risk category is obtained adding up the values of each prognostic variable. Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: 5 or 6.

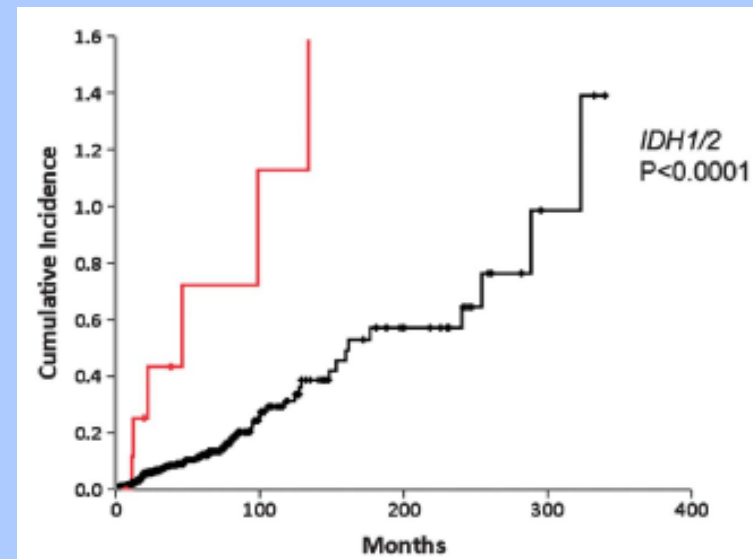
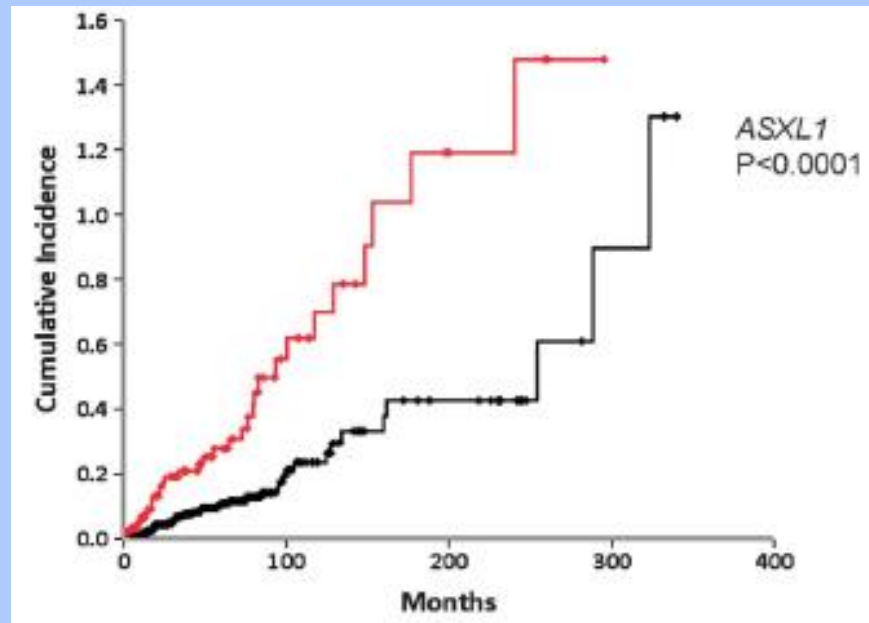
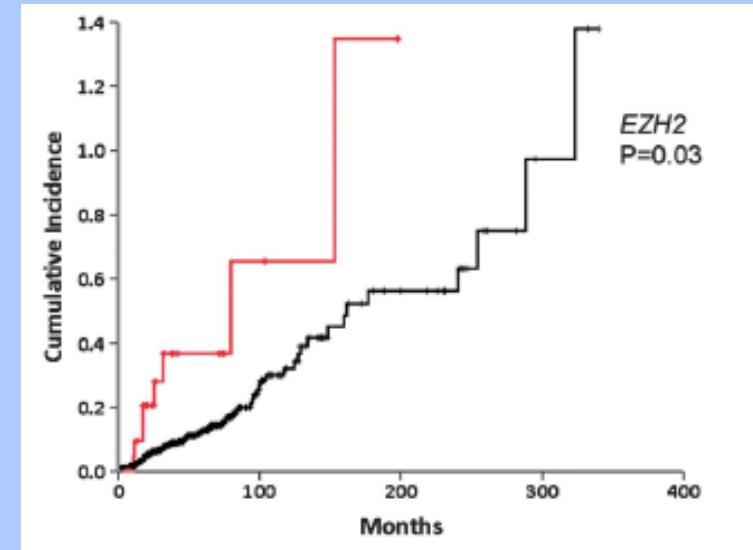
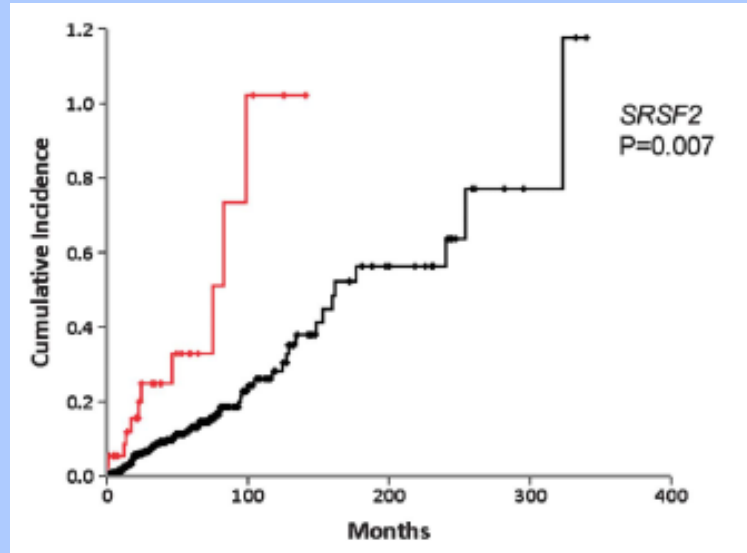
DIPSS indicates Dynamic International Prognostic Scoring System.

- Dynamic International Prognostic Scoring System-PLUS (DIPSS-PLUS): Takes into account transfusion requirements, platelet count, and karyotype (Gangat et al. JCO 2011)

Implications of JAK2, MPL, and CALR mutations



Genetic risk factors for leukemic transformation



MIPSS70-plus Risk Score

Variables Associated with Reduced OS

Variables	HR (95% CI)	P	Weighted value
Hb <100g/L	1.5 (1.1-2.0)	.005	
PB blasts ≥2%	1.6 (1.2-2.3)	.002	1
Constitutional Symptoms	1.9 (1.4-2.5)	<0.001	1
Absence <i>CALR</i> Type1	2.4 (1.7-3.5)	<.001	2
HMR*	1.8 (1.3-2.5)	<.001	1
≥2 HMR mutations	2.4 (1.4-4.0)	<0.001	2
Unfavorable Karyotype**	3.1 (2.3-4.3)	<.001	3

*Any mutation in: *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*

** any abnormal karyotype other than normal karyotype or sole abnormalities of 20q-, 13q-, +9, chr. 1 translocation/duplication, -Y, or sex chromosome abnormality other than -Y.

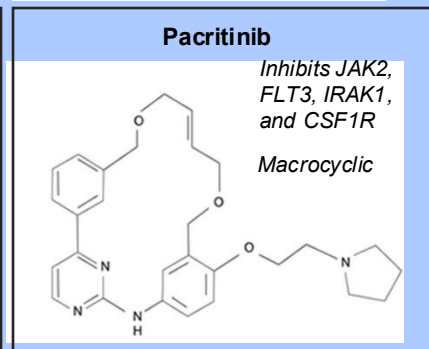
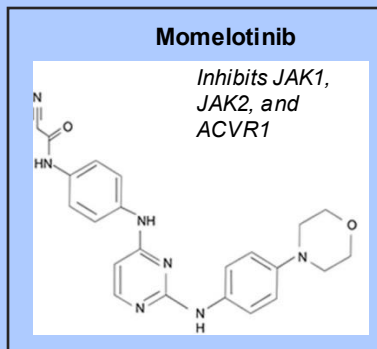
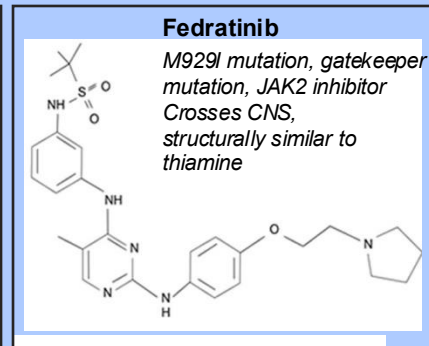
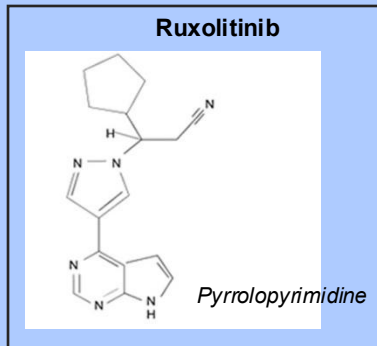
#	Question	Answer
1	Anemia (hemoglobin <100g/L)	<input checked="" type="radio"/> Yes <input type="radio"/> No
2	Leucocytosis >25x10 ⁹ /L	<input type="radio"/> Yes <input checked="" type="radio"/> No
3	Thrombocytopenia (platelet count <100x10 ⁹ /L)	<input type="radio"/> Yes <input checked="" type="radio"/> No
4	Peripheral blood blast count ≥2%	<input checked="" type="radio"/> Yes <input type="radio"/> No
5	Bone marrow fibrosis grade ≥2	<input checked="" type="radio"/> Yes <input type="radio"/> No
6	Constitutional symptoms	<input checked="" type="radio"/> Yes <input type="radio"/> No
7	Absence of CALR type 1/like mutation	<input checked="" type="radio"/> Yes <input type="radio"/> No
8	HMR* category	<input checked="" type="radio"/> Yes <input type="radio"/> No
9	≥2 HMR mutated genes	<input checked="" type="radio"/> Yes <input type="radio"/> No
10	Unfavorable karyotype**	<input checked="" type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not available

Score	Result
MIPSS70	HIGH RISK [5-year OS= 34%]
MIPSS70-plus	VERY HIGH RISK [5-year OS= 46%]

Clinical Needs-Oriented Therapy for MF

Clinical Issue	Treatments	
Anemia	<ul style="list-style-type: none"> ▪ ESAs ▪ Danazol ▪ Corticosteroids 	<ul style="list-style-type: none"> ▪ Thalidomide, lenalidomide (IMiDs)
Symptomatic splenomegaly	<ul style="list-style-type: none"> ▪ Ruxolitinib ▪ Fedratinib ▪ Pacritinib 	<ul style="list-style-type: none"> ▪ Cladribine, IMiDs ▪ Splenectomy ▪ Hydroxyurea
Constitutional symptoms/QoL	<ul style="list-style-type: none"> ▪ Ruxolitinib ▪ Fedratinib ▪ Pacritinib 	
Extramedullary hematopoiesis	<ul style="list-style-type: none"> ▪ Radiation therapy 	
Hyperproliferative (early) disease	<ul style="list-style-type: none"> ▪ Interferon 	
Risk of thrombosis	<ul style="list-style-type: none"> ▪ Low-dose ASA 	
Accelerated/blastic phase	<ul style="list-style-type: none"> ▪ Hypomethylating agents 	
Improved survival	<ul style="list-style-type: none"> ▪ Allogeneic HCT ▪ Ruxolitinib 	

JAK Inhibitors



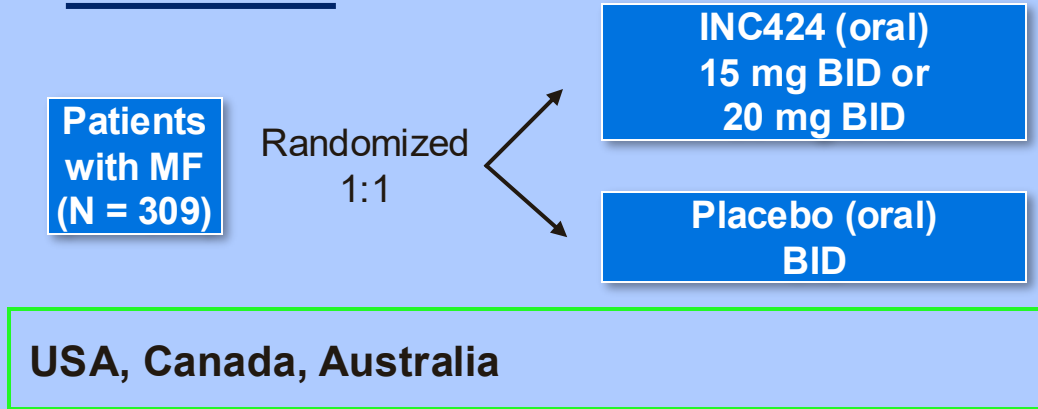
Anilinopyrimidine derivatives

	IC ₅₀ (nanomolar)				AEs
	JAK 1	JAK2	JAK3	TYK2	
Ruxolitinib	2.8	4.5	322	30	Cytopenias (anemia, thrombocytopenia), infection
Fedratinib	105	3	>1000	405	Wernicke encephalopathy
Momelotinib	11	18	155	17	Increased amylase/lipase, thrombocytopenia, PN
Pacritinib	1280	6	18.3	27	GI (diarrhea, nausea)

AE, adverse event; CNS, central nervous system; GI, gastrointestinal; PN, peripheral neuropathy. Duenas-Perez AB, Mead AJ. *Ther Adv Hematol.* 2015;6:186-201.

Ruxolitinib Phase III Registration Trials

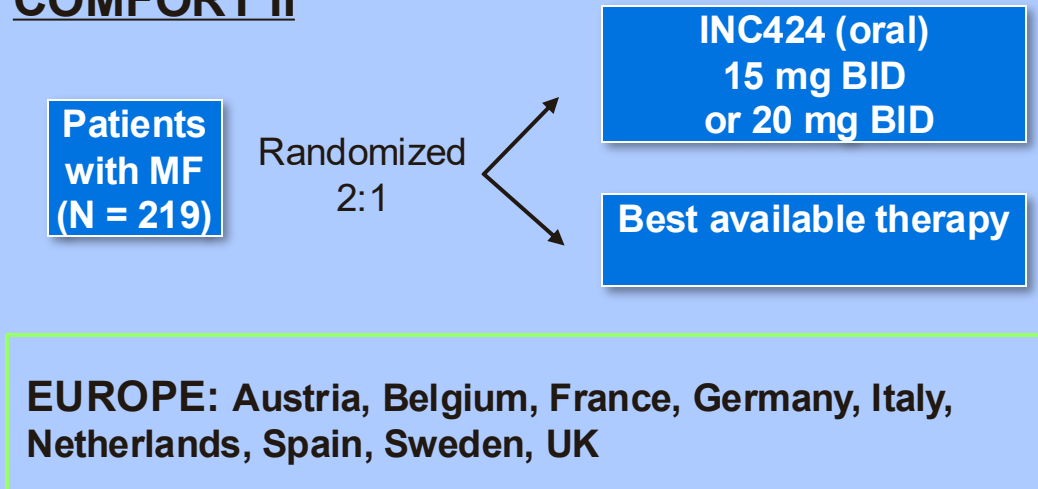
COMFORT I



COMFORT I Primary Endpoint

- Number of subjects achieving $\geq 35\%$ reduction in spleen volume from baseline to week 24*

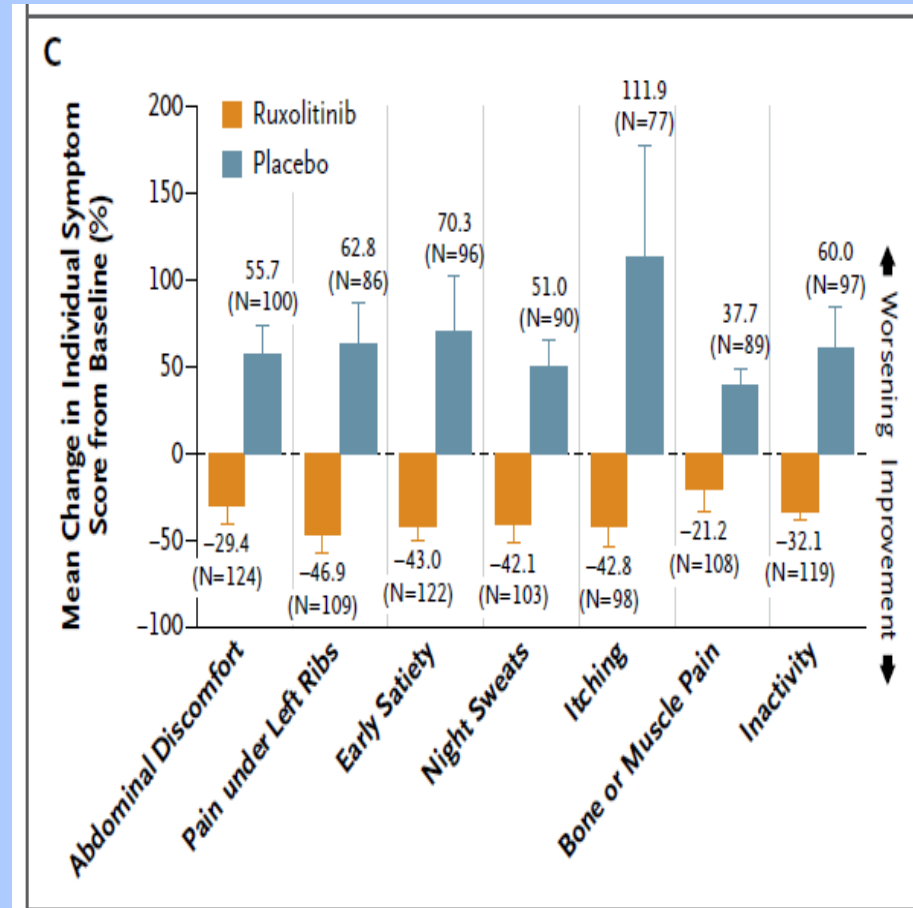
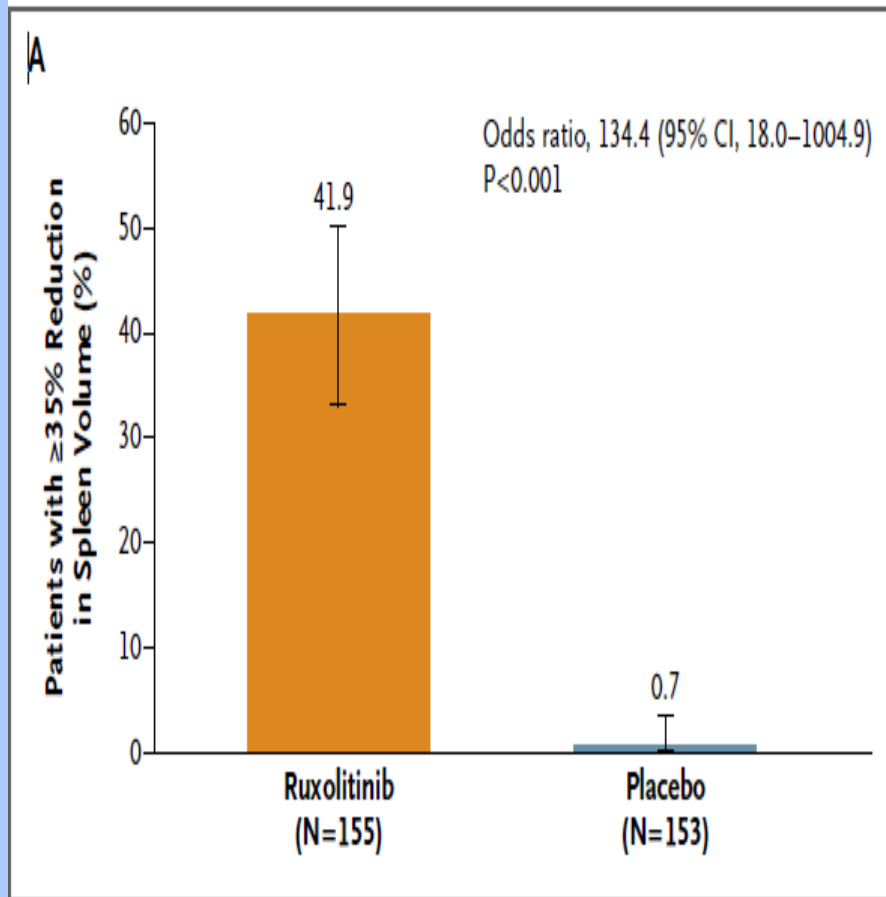
COMFORT II



COMFORT II Primary Endpoint

- Number of subjects achieving $\geq 35\%$ reduction in spleen volume from baseline to week 48*

Ruxolitinib Significantly Reduces Spleen Size and Symptom Burden



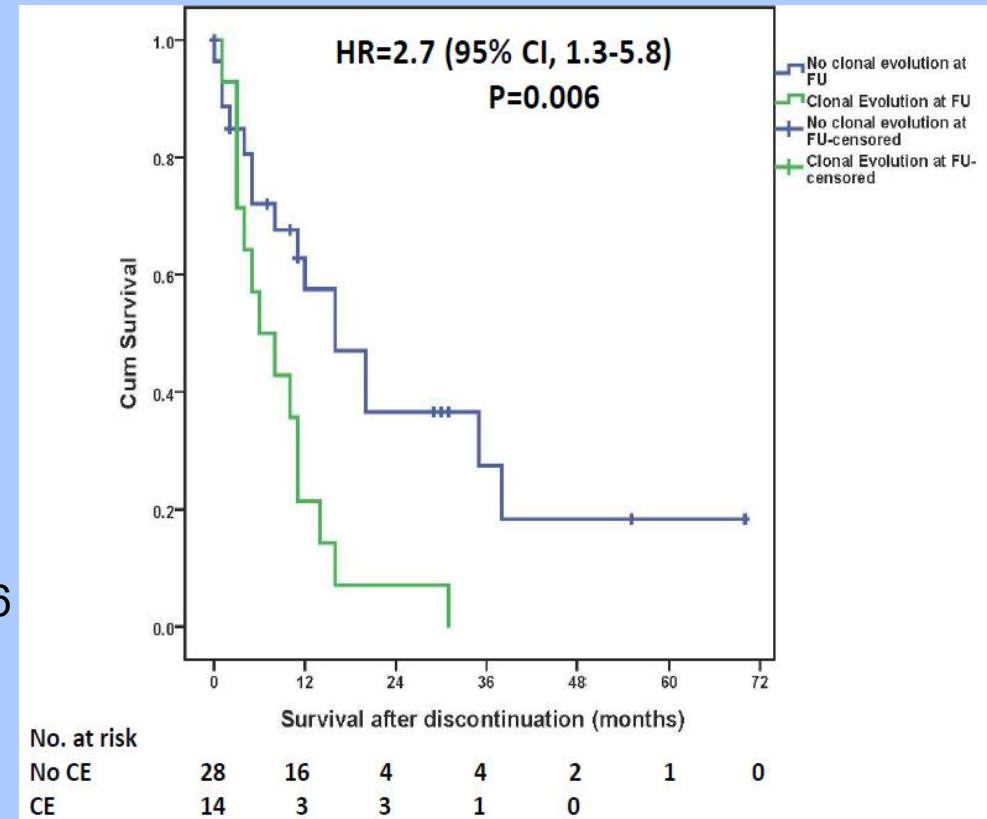
Adverse Events

Table 2. Adverse Events Observed in 10% or More of Patients Who Received Ruxolitinib.

Event	Ruxolitinib (N=155)		Placebo (N=151)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
<i>percent of patients</i>				
Nonhematologic				
Fatigue	25.2	5.2	33.8	6.6
Diarrhea	23.2	1.9	21.2	0
Peripheral edema	18.7	0	22.5	1.3
Ecchymosis	18.7	0	9.3	0
Dyspnea	17.4	1.3	17.2	4.0
Dizziness	14.8	0.6	6.6	0
Nausea	14.8	0	19.2	0.7
Headache	14.8	0	5.3	0
Constipation	12.9	0	11.9	0
Vomiting	12.3	0.6	9.9	0.7
Pain in extremity	12.3	1.3	9.9	0
Insomnia	11.6	0	9.9	0
Arthralgia	11.0	1.9	8.6	0.7
Pyrexia	11.0	0.6	7.3	0.7
Abdominal pain	10.3	2.6	41.1	11.3
Hematologic abnormalities*				
Anemia	96.1	45.2	86.8	19.2
Thrombocytopenia	69.7	12.9	30.5	1.3
Neutropenia	18.7	7.1	4.0	2.0

Outcomes in MF after Ruxolitinib Discontinuation

- Survival after ruxolitinib d/c is poor (median 14 months)
- Shorter survival is associated with low platelets at start and end of therapy
- 35% of patients acquired a new mutation while receiving ruxolitinib; 61% ASXL1
- Patients showing clonal evolution had significantly shorter survival after d/c (6 vs 16 months, $P=0.006$)



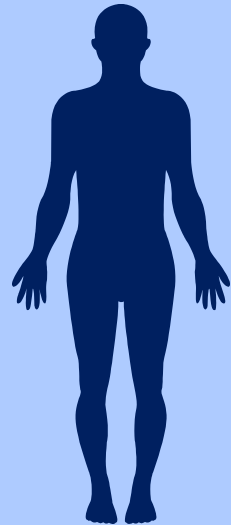
D/c = discontinuation; FU = follow-up.

Newberry et al, 2017; Kuykendall et al, 2018; Gerds et al, 2018.

MPNs: Rajiv Rana, M.D., Ph.D.

Fedratinib in Myelofibrosis

Phase 3 JAKARTA Trial: Fedratinib vs. placebo in patients with Int-2/high-risk MF first line



N = 289

Fedratinib 400 mg

37%

Spleen volume reduction \geq 35%

40%

Symptom burden reduction \geq 50%

14%

Discontinuation due to AEs

Fedratinib 500 mg

40%

Spleen volume reduction \geq 35%

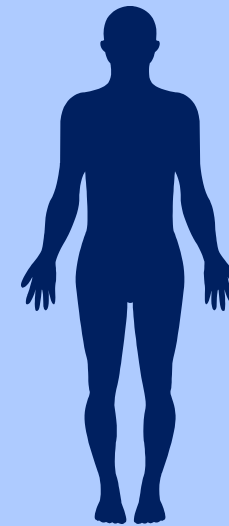
34%

Symptom burden reduction \geq 50%

25%

Discontinuation due to AEs

Phase 2 JAKARTA-2 Trial: Fedratinib in patients with Int-2/high-risk MF resistant or intolerant to ruxolitinib



N = 97
*N = 79

Primary analysis

55%

Spleen volume reduction \geq 35%

11.0%

Discontinuation due to AEs

Reanalysis (2019)*

30%

Spleen volume reduction \geq 35%

27%

Symptom burden reduction \geq 50%

*More stringent criteria for relapse, refractory, and intolerance to ruxolitinib

Fedratinib Adverse Events

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

Black box warning

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

Considerations

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

Fedratinib AEs (JAKARTA)

Encephalopathy

- 1 case of Wernicke encephalopathy (WE)
- 1 case of encephalopathy of unknown origin
- 2 additional cases of WE after data lock

Black box warning:

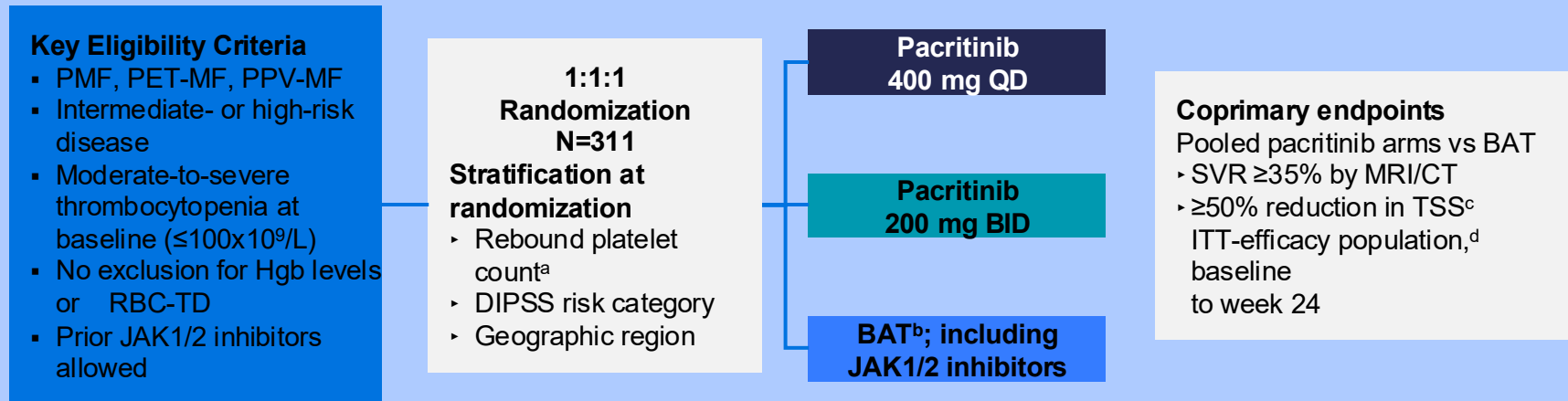
Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with fedratinib. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated. Do not start fedratinib in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue fedratinib and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

Pardanani A, et al. *JAMA Oncol.* 2015;1:643.
JAK2 Inhibitor (JAK2i) prescribing information, rev 8/2019.

Pacritinib: Phase 3 Trial PERSIST-2

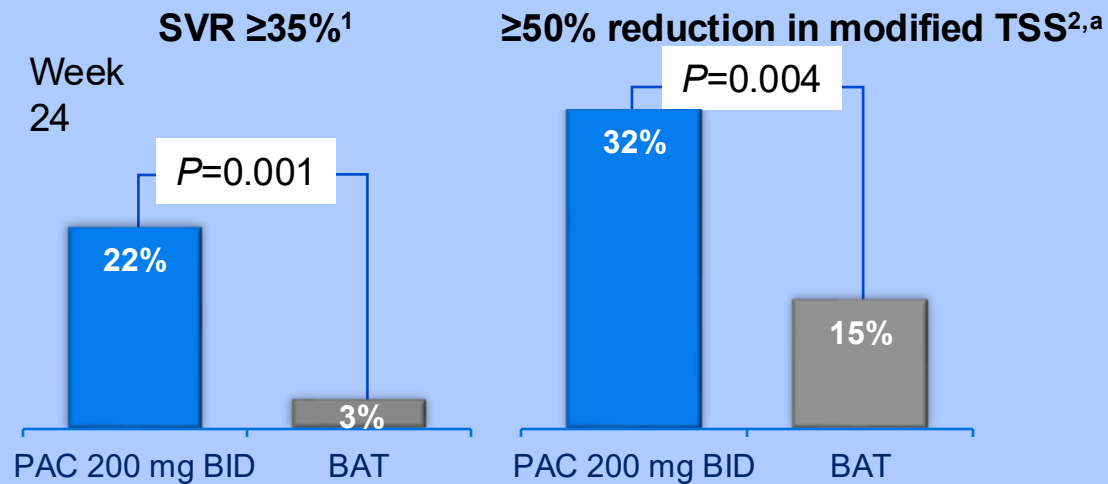
Pacritinib 400 mg QD or 200 mg BID vs BAT (Including JAK1/2 Inhibitors) in MF

- In this phase 3 trial, 200 mg BID was also tested for potentially improved tolerability, given PK modeling data demonstrating increased daily systemic exposure with lower maximum concentration vs 400 mg QD²

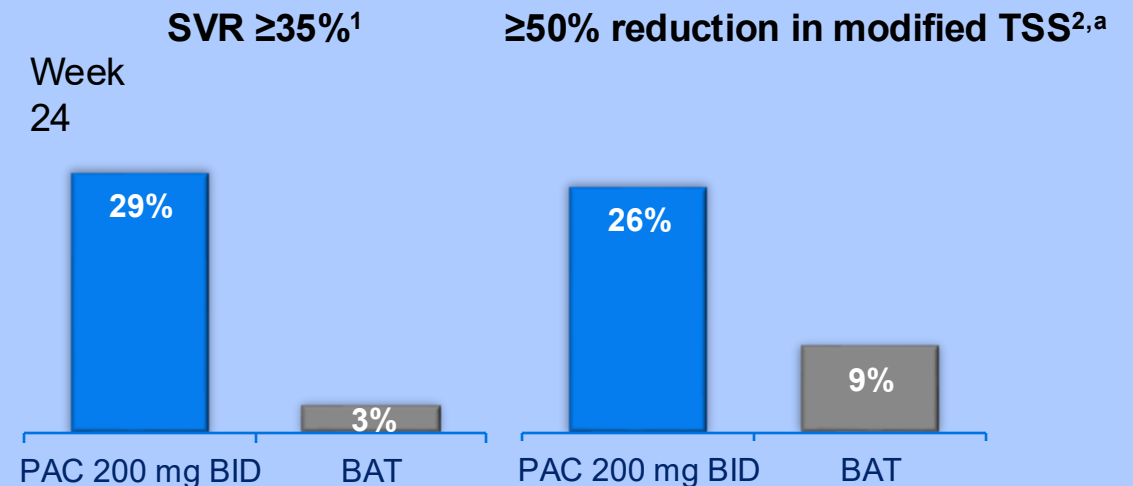


Pacritinib vs. BAT in Thrombocytopenic Patients

ITT Population (plts $100 \times 10^9/L$)



Patients With Platelets $50 \times 10^9/L$



- PERSIST-2 study: prior JAK2 inhibitor allowed (48%), BAT included ruxolitinib (45%)
- Rarely myelosuppressive
- Causes GI side effects

^a Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.

BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.

1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659. 2. Data on File. CTI Biopharma Corp. Pacritinib Clinical Overview.

PERSIST-2: Baseline Characteristics and BAT Received

Key Baseline Characteristics in ITT-Efficacy Population ^{1,2}	PAC 200 mg BID (n=74)	BAT (n=72)
Median age, years	67	69
≥65 years, %	62	71
Male, %	65	54
MF diagnosis: PMF, PPV-MF, PET-MF, %	74, 19, 7	60, 22, 18
DIPSS score ^a : Int-1, Int-2, High, %	19, 51, 30	18, 51, 31
Median spleen length, cm ^a	15	13
<i>JAK2</i> ^{V617F} positive, %	80	71
<i>JAK2</i> ^{V617F} allele burden, median	30	25
Platelet count <50x10 ⁹ /L, %	42	44
Hemoglobin <10 g/dL, %	59	57
RBC transfusion dependence ^b : dependent, independent, indeterminate, %	19, 50, 30	19, 51, 29
Prior JAK1/2 inhibitors, %	45	47
Prior ruxolitinib	42	46

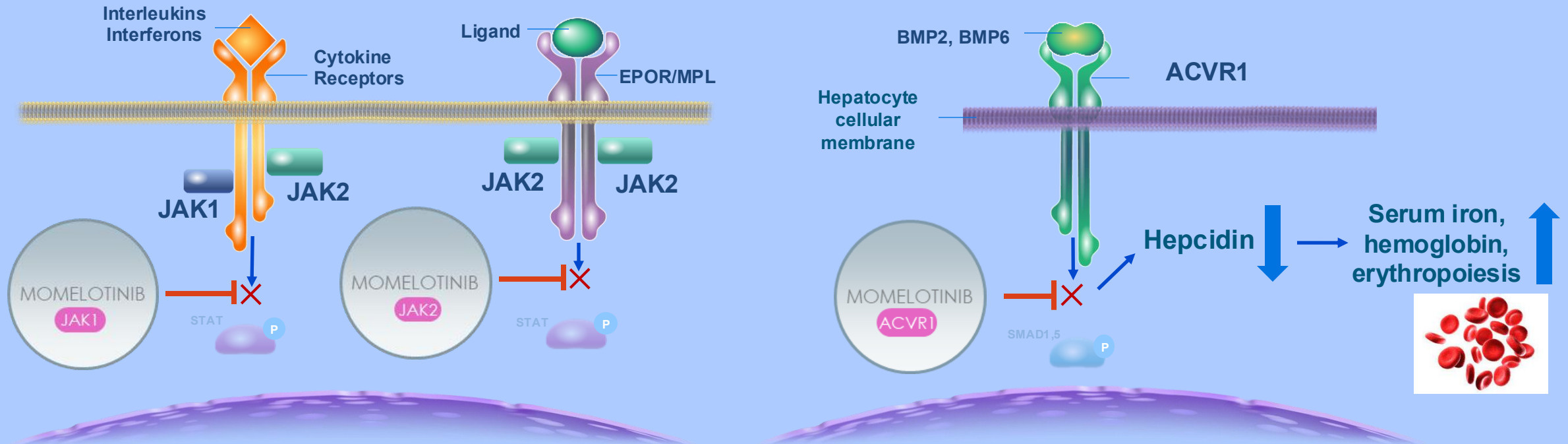
- Of the BAT patients who received ruxolitinib, 93% began treatment at ≤10 mg BID, including 64% at ≤5 mg BID³

BAT Received in >2 Patients, % ¹	BAT (n=98)
Ruxolitinib ^c	45
Hydroxyurea	19
Watch and wait only	19
Prednisone/prednisolone	13
Danazol	5
Thalidomide	3

Note: While allowed on the BAT arm, patients who received pacritinib could not receive corticosteroids or erythropoietic agents.²

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

Momelotinib Inhibits JAK1, JAK2, and ACVR1 to Address MF Symptoms, Spleen, and Anemia



Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis**, **systemic symptoms**, and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**^{1,2}

Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF^{3,4}

ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription
 1. Chifotides HT, et al. *J Hematol Oncol*. 2022; 15(1):7. 2. Verstovsek S, et al. *Future Oncol*. 2021; 17(12):1449-1458. 3. Asshoff M, et al. *Blood*. 2017; 129(13):1823-1830. 4. Oh ST, et al. *Blood Adv*. 2020; 4(18):4282-4291.

More Pacritinib Patients Achieved TI (Gale)

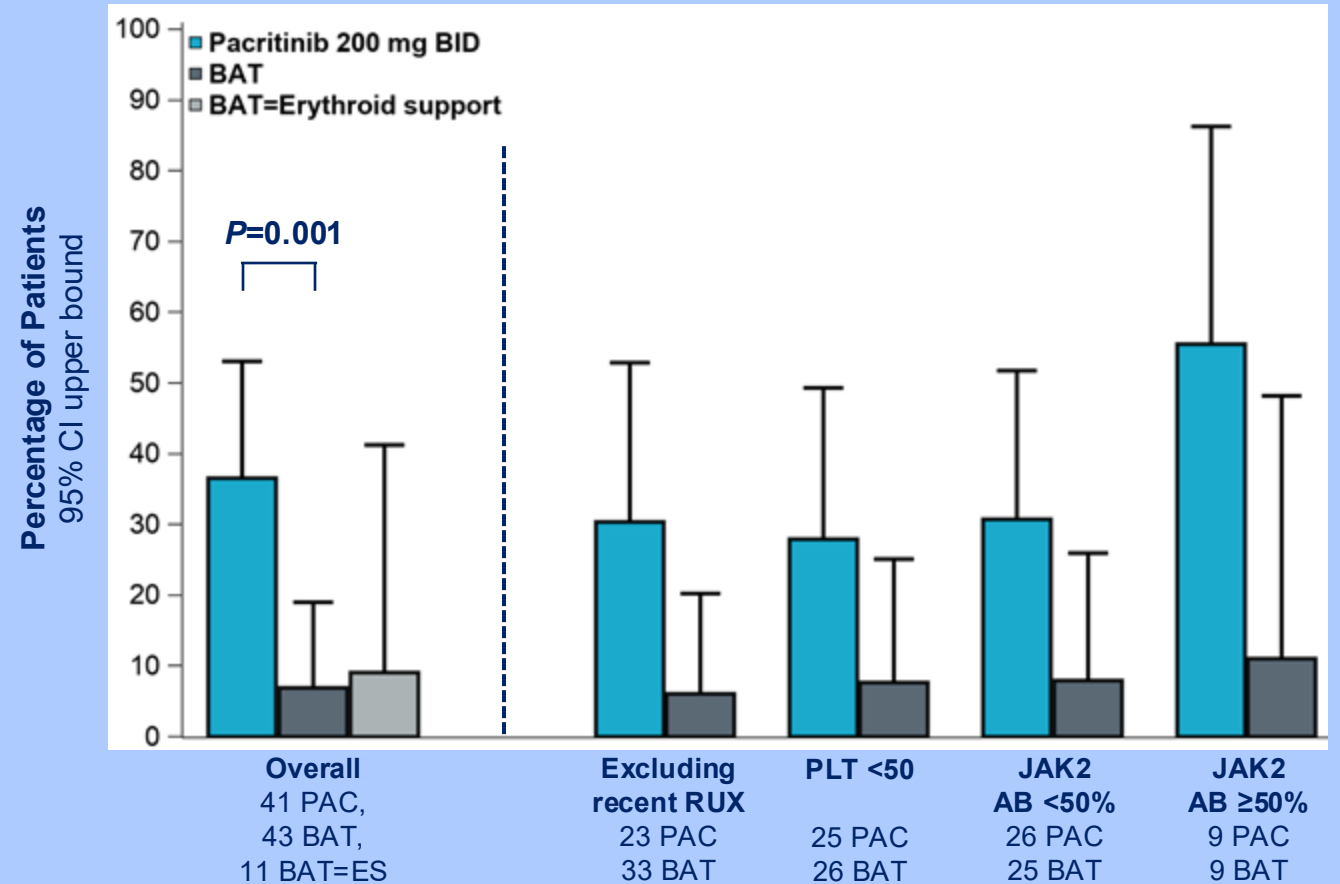
TI Conversion Rate

Pacritinib N=41	BAT N=43	P-value
37%	7%	0.001

TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT

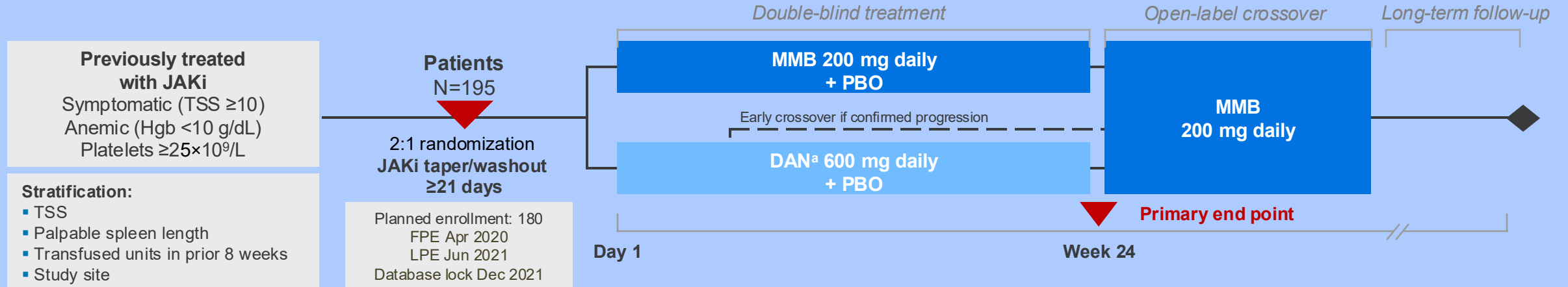
- Erythroid support agents were prohibited on the pacritinib arm

Rate of TI (Gale criteria) through Week 24



AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX=no ruxolitinib in prior 30 days; TI=transfusion independence.

MOMENTUM Is an Ongoing Phase 3 Study of Mometotinib Versus DAN in Symptomatic, Anemic, JAKi-Experienced Patients

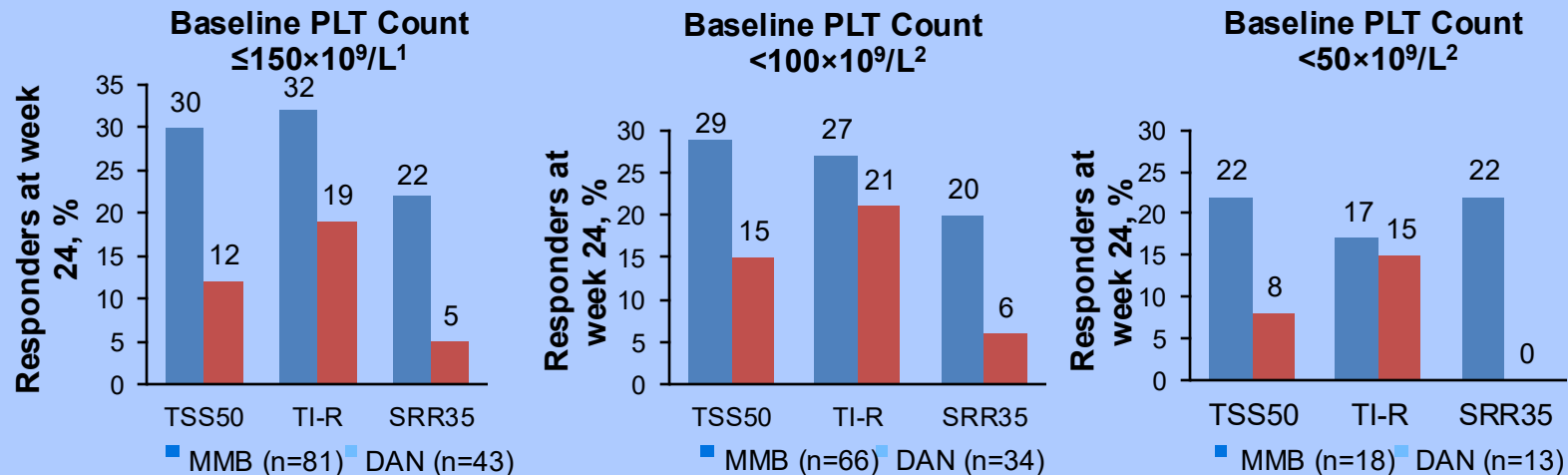


MOMENTUM Results

MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met^{1,2}

	MFSAF TSS ^b response rate (primary end point)	TI response ^c rate	SRR ^d (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	<i>P</i> =.0095 (superior)	1-sided <i>P</i> =.0064 (noninferior)	<i>P</i> =.0006 (superior)

Efficacy in Patients With Thrombocytopenia Was Consistent With the Overall ITT Patient Population



TEAEs in $\geq 10\%$ of Patients During OL MMB Treatment with No New Safety Signals Detected

	MMB→MMB (n=93)		DAN→MMB (n=41)	
	% of patients			
Grade ≥ 3 adverse events	49.5		46.3	
Serious adverse events	31.2		29.3	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Nonhematologic (preferred term)				
Weight decreased	7.5	0	14.6	0
Diarrhea	14.0	1.1	12.2	0
Pyrexia	14.0	0	7.3	0
Hypertension	3.2	0	12.2	2.4
Asthenia	11.8	3.2	0	0
Hematologic (preferred term)				
Thrombocytopenia	14.0	8.6	17.1	14.6
Anemia	10.8	8.6	7.3	2.4
Neutropenia	5.4	5.4	4.9	0
Other				
COVID-19 (pneumonia)	10.8	5.4	0	0
Peripheral sensory neuropathy	2.2	0	2.4	0



Add-on to Ruxolitinib/Post-Ruxolitinib Therapeutic Approaches in Clinical Development

Drug	Mechanism	Phase
Selinexor	XPO1 inhibitor	III
Navtemadlin	MDM2 inhibitor	III
Imetelstat	Telomerase inhibitor	III
TP-3654	PIM Kinase inhibitor	I/II
Abemaciclib	CDK4/6 inhibitor	I
AJX-101	Type II JAK Inhibitor	I
INCB18424	Selective V617F Inhibitor	I
INCA033989	CALRmut antibody	I
JNJ-88549968	CALRmut BiTE	I
DISC-0974	Anti-HJV ab	I/II
Keros	Ligand trap	II
Luspatercept	Ligand trap	III

First Line

Add-on to JAKi or Post-JAKi

Novel JAKi

Mutant CALR Targeting Approaches

Anemia

Questions?