THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Diagnosing MPNs

MPN Horizons, Netanya Israel Nov 2022

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Novel Agents Beyond RUXO: MPNs 2022 and Beyond

- PV
  - Ropeginterferon
  - PTG-300 (Rusfertide)
- SM
  - Avapritinib, other KIT inhibitors
- 8p11 /FGFR myeloproliferative syndrome
  - Pemigatinib
    - Fight-203 phase 2
    - FDA approved Aug 22, 2022: R/R Myeloid/Lymphoid Neoplasms (MLN) with Fibroblast Growth Factor Receptor 1 (FGFR1) Rearrangement
- MF
  - Novel JAKi beyond RUXO and FEDR:
    - Pacritinib (PAC): FDA approved Feb 28, 2022 int/high-risk MF with plt count <50
    - Momelotinib (MMB)
    - others
  - Novel JAKi + combos →Phase 3
    - BCLxLi + RUXO
    - BRDi/BETi + RUXO
    - PI3Ki + RUXO
  - Completely novel agents beyond JAKi in R/R MF
  - Anemia in MF: New mechanisms/new agents

"Some Speculations on the myeloproliferative syndromes"

William Dameshek
(1900-1966) www.hematology.org (ASH website)

- *"It is possible that these various conditions—'myeloproliferative disorders'—are all…variable manifestations of proliferative activity of the bone marrow cells, perhaps due to a hitherto undiscovered stimulus."*—William Dameshek, 1951, Blood

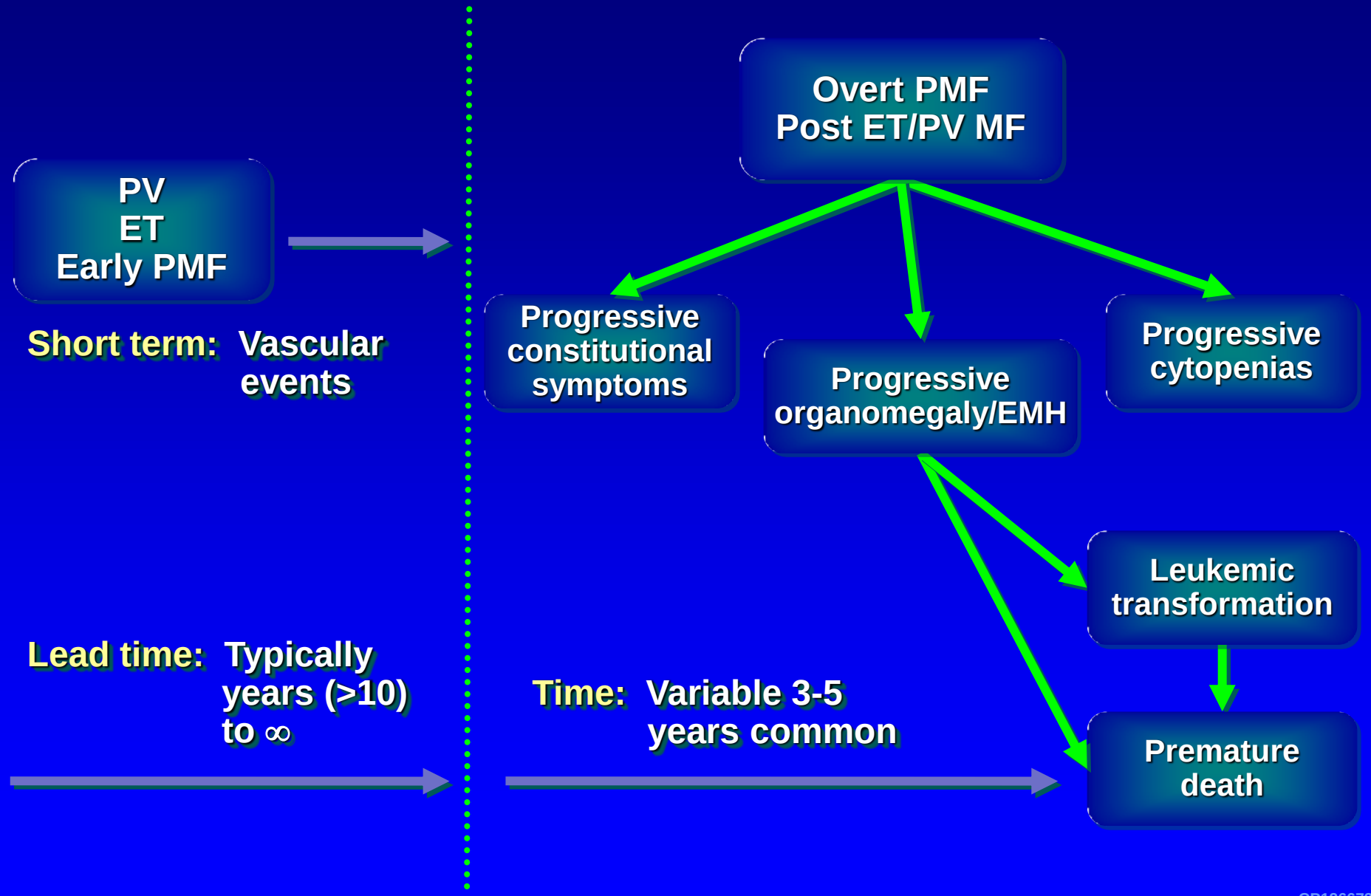
Incidence of Myeloproliferative Diseases

Annual incidence / 100,000 population

CML	**1.6**
ET	**2.3**
PV	**2.2**
PMF	**1.0**

Natural History of MPNs

courtesy Dr Ruben Mesa, MD, Mayo Clinic



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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

Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

MPNS are Treated by Risk

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Myeloproliferative Neoplasms
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

DIAGNOSIS[i,j]	PROGNOSTIC RISK MODEL	RISK STRATIFICATION
Myelofibrosis	Primary myelofibrosis (PMF)[b] • MIPPS-70 or MIPSS-70+ Version 2.0 (preferred) • DIPSS-Plus (if molecular testing is not available or • DIPSS (if karyotyping is not available) Post-PV or Post-ET MF[c] • MYSEC-PM	Lower-risk (MF-1) • MIPSS-70: ≤3 • MIPSS-70+ Version 2.0: ≤3 • DIPSS-Plus: ≤1 • DIPSS: ≤2 • MYSEC-PM: <14
		Higher-risk (MF-2) • MIPSS-70: ≥4 • MIPSS-70+ Version 2.0: ≥4 • DIPSS-Plus: >1 • DIPSS: >2 • MYSEC-PM: ≥14
Polycythemia vera (PV)[d]	Conventional risk model[k]	Low-risk (PV-1) • Age <60 years and no prior history of thrombosis
		High-risk (PV-2) • Age ≥60 years and/or prior history of thrombosis
Essential thrombocythemia (ET)	IPSET-thrombosis (revised)[l]	Very-low-risk (ET-1) • Age ≤60 years, no *JAK2* mutation, no prior history of thrombosis
		Low-risk (ET-1) • Age ≤60 years, with *JAK2* mutation, no prior history of thrombosis
		Intermediate-risk (ET-2) • Age >60 years, no *JAK2* mutation, no prior history of thrombosis
		High-risk (ET-3) • History of thrombosis at any age or age >60 years with *JAK2* mutation

See Footnotes on MPN-2A

Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

JAK2 V617F Mutation

March 18th, 2005

Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders

Lancet 2005; 365: 1054–61

*These authors contributed equally to this study

E Joanna Baxter*, Linda M Scott*, Peter J Campbell*, Clare East, Nicolas Fourouclas, Sohella Swanton, George S Vassiliou, Anthony J Bench, Elaine M Boyd, Natasha Curtin, Mike A Scott, Wendy N Erber, the Cancer Genome Project†, Anthony R Green

March 24th, 2005

Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis

Ross L. Levine,[1,2,11] Martha Wadleigh,[2,11] Jan Cools,[6] Benjamin L. Ebert,[2,8] Gerlinde Wernig,[1] Brian J.P. Huntly,[1] Titus J. Boggon,[4] Iwona Wlodarska,[6] Jennifer J. Clark,[1] Sandra Moore,[1] Jennifer Adelsperger,[1] Sumin Koo,[1] Jeffrey C. Lee,[8] Stacey Gabriel,[8] Thomas Mercher,[1] Alan D'Andrea,[3] Stefan Fröhling,[1] Konstanze Döhner,[7] Peter Marynen,[6] Peter Vandenberghe,[6] Ruben A. Mesa,[9] Ayalew Tefferi,[9] James D. Griffin,[2] Michael J. Eck,[4] William R. Sellers,[2,8] Matthew Meyerson,[2,8] Todd R. Golub,[5,8,10] Stephanie J. Lee,[2,*] and D. Gary Gilliland[1,2,10,*]

March 27th, 2005

A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythaemia vera

Chloé James[1*], Valérie Ugo[1,2,3*], Jean-Pierre Le Couédic[1*], Judith Staerk[4], François Delhommeau[1,3], Catherine Lacout[1], Loïc Garçon[1], Hana Raslova[1], Roland Berger[5], Annelise Bennaceur-Griscelli[1,6], Jean Luc Villeval[1], Stefan N. Constantinescu[4], Nicole Casadevall[1,3] & William Vainchenker[1,7]

April 28th, 2005

letters to nature

A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythaemia vera

Chloé James[1*], Valérie Ugo[1,2,3*], Jean-Pierre Le Couédic[1*], Judith Staerk[4], François Delhommeau[1,3], Catherine Lacout[1], Loïc Garçon[1], Hana Raslova[1], Roland Berger[5], Annelise Bennaceur-Griscelli[1,6], Jean Luc Villeval[1], Stefan N. Constantinescu[4], Nicole Casadevall[1,3] & William Vainchenker[1,7]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Gain-of-Function Mutation of *JAK2* in Myeloproliferative Disorders

Robert Kralovics, Ph.D., Francesco Passamonti, M.D., Andreas S. Buser, M.D., Soon-Siong Teo, B.S., Ralph Tiedt, Ph.D., Jakob R. Passweg, M.D., Andre Tichelli, M.D., Mario Cazzola, M.D., and Radek C. Skoda, M.D.

CALR

- Chromosome 19p13.3
  - Exon 9 of CALR (insertions or deletions)
- Calreticulin = protein →Ca++binding function / Endoplasmic reticulum
- Also found in nucleus; possible role transcription regulation
- Klampfel et al NEJM 2013: CALR in 25% pts with JAK2 negative ET, and in 35% in JAK2 negative MF

Klampfl T et al. N Engl J Med 2013;369:2379-2390.

CALR Mutation (NEJM Dec 19, 2013)

- **Klampfl et al NEJM 2013**
- Whole exome seq in 6 pts with MF (JAK2/MPL neg)
- Somatic insertions/or deletions in exon 9 of CALR in all pts
- Reseq in 1107 samples from pts with MPNs= no CALR mutations in PV
- CALR in non-JAK2 mutated ET: 67%; 88% in MF cases
- 36 types of del/insertions found →all caused frameshift to same alternative reading frame→formed a new C-terminal peptide
- Pts with CALR mutation→lower risk thrombosis, increased OS compared to JAK2 mutated

- **Nangalia et al NEJM 2013**
- Whole exome seq from 151 pts with MPNs
- Mutation status of CALR then assessed in 1345 additional heme malignancies, 1517 other cancers and 550 controls
- Somatic CALR mutations: 70-84% of MPNs with nonmutated JAK2
- 148 CALR mutations identified with 19 variants
- Exon 9; +1 base pair frameshift→novel mutant protein with new C-terminal
- CALR-mutated: higher plt count and lower Hb than mutated JAK2

Klampfl T et al. N Engl J Med 2013;369:2379-2390, Nangalia et al NEJM 2013

Essential Thrombocytosis (ET)

ET: WHO 2016

- **Major criteria:**
- **1. Platelet count > 450 x 109 /L**
- **2. Bone marrow 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**

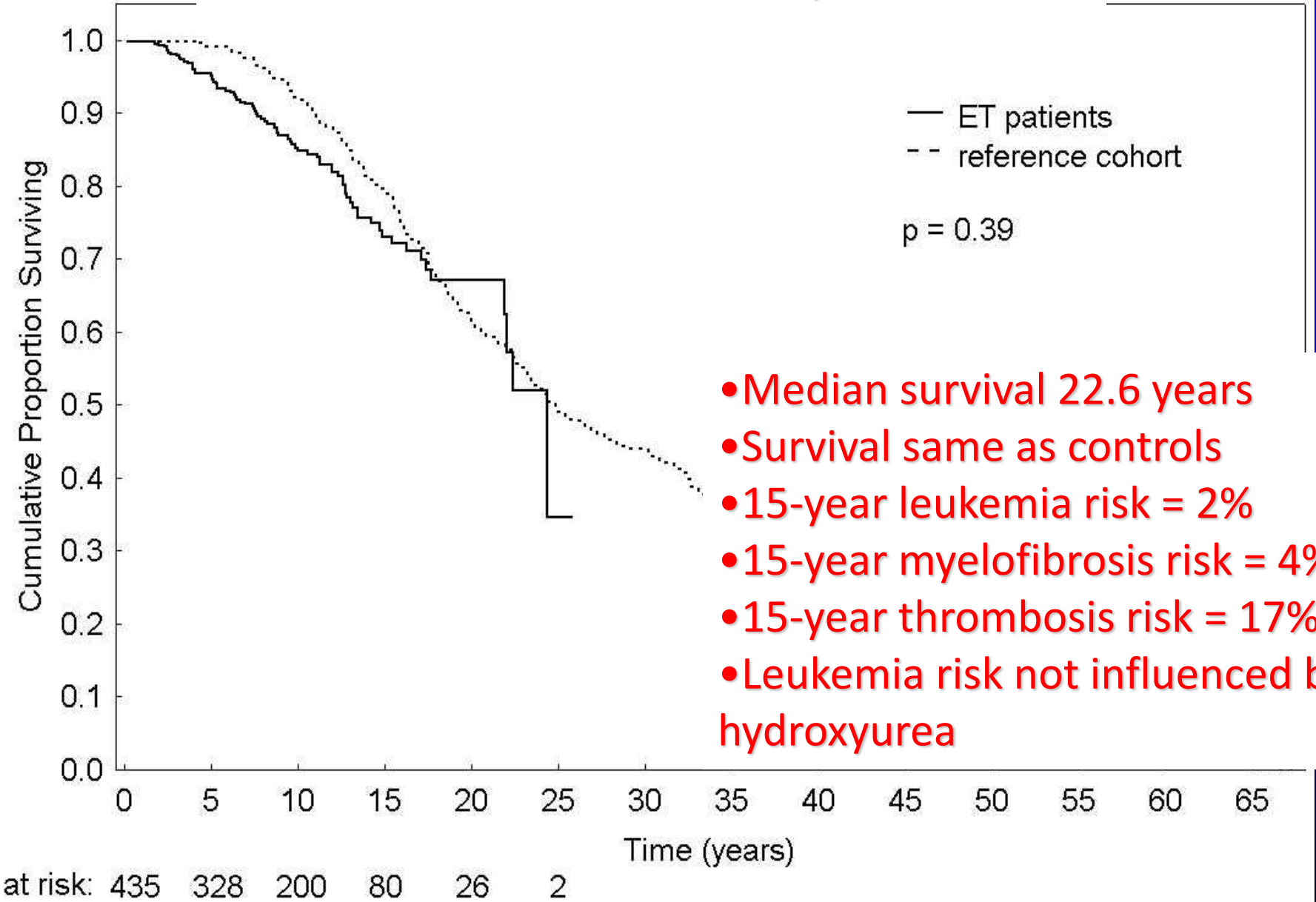
Arber DA et al WHO 2016 Revision Blood. 2016 May 19;1 27(20):2391-405

ET: Pemmaraju's pearls

- Diagnosis of exclusion: from both secondary/non-clonal/reactive causes vs other MPNs
- JAK2V617F+ 50% cases; CALR in 30-40%; MPL515L/K + in 1-4%
- Female 2:1 predominance (contrast to PV)
- Vasomotor sxs: erythromelalgia
- Thrombosis (both arterial+ venous)
- Plt >1.5 M+: Hemorrhage (acquired VWD: resulting from adsorption of VWF to transformed blood cells, particularly plts, 10+%
- Don't forget : can still transform to PV or MF or AML
- Important: when evaluating a pt for ET , remember that isolated thrombocytosis could also be a presenting feature of CML. Don't want to miss: *check for BCR-ABL!*

Modern Natural History of ET
435 pateints followed for a median of 9.5 years

Passamonti et al. Am J Med 2004;117:755



- Median survival 22.6 years
- Survival same as controls
- 15-year leukemia risk = 2%
- 15-year myelofibrosis risk = 4%
- 15-year thrombosis risk = 17%
- Leukemia risk not influenced by hydroxyurea

Conclusions: ET

- JAK2V617 > CALR > MPL
- F>M
- MM: Clots, bleeding (acquired VWD)
- Remember, ET can tx→PV/MF, tx→AML
- Low risk (baby ASA alone) vs high risk (age >60 or prior thrombosis; baby ASA + cytoreductive therapy)

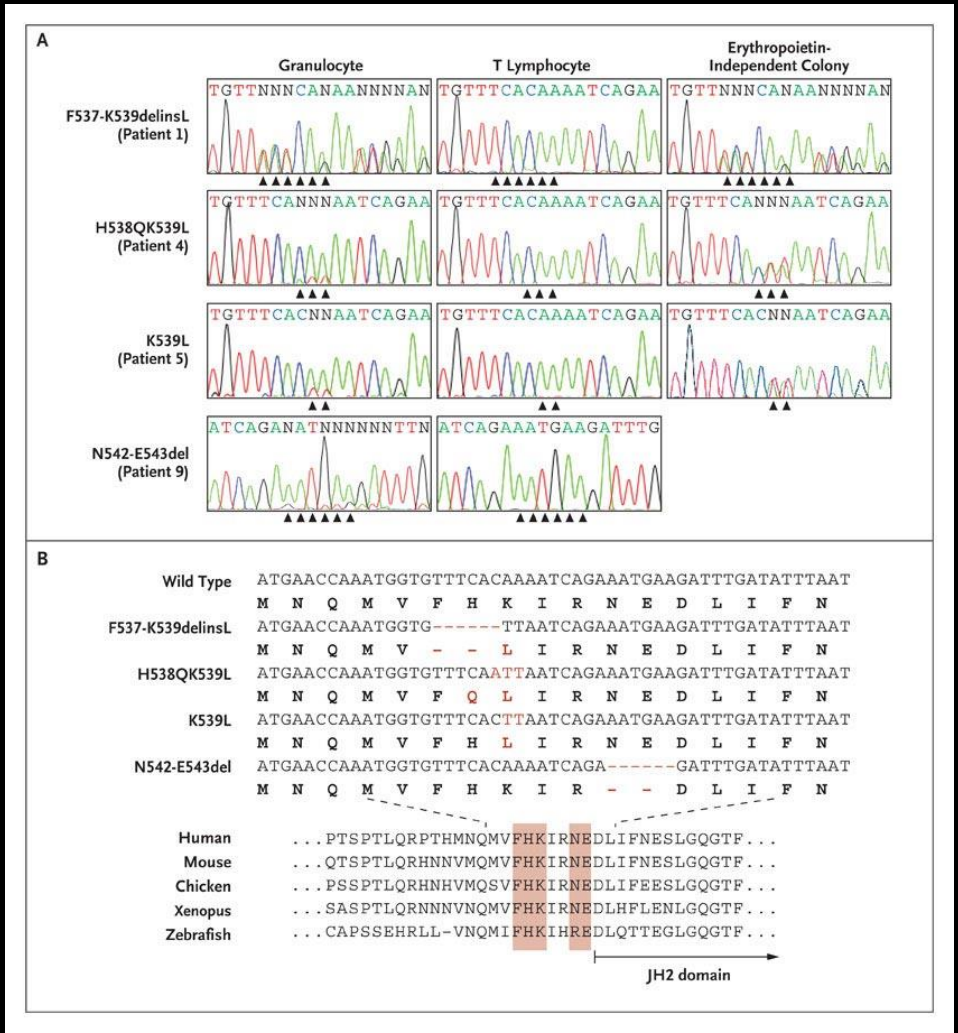
Polycythemia Vera (PV)

PV: Pemmaraju's pearls

- Incidence higher in men (2.8 vs 1.3 pt cases/100,000 per year, Olmstead County data)
- Special subgroups: e.g. Young female: 1st presentation: SVT/Budd-Chiari and low/NL counts
  - MPNs = most common etiology for Budd-Chiari syndrome & for non-cirrohotic portal vein thrombosis (Smalberg JH et al Blood 2012)
- Clonal proliferation of progenitor cells in BM→abnormal production of (erythroid) cells and increased red cell mass
- Aquagenic pruritis, erythromelalgia
- Virtually 100% of PV pts: JAK2 mutation (acquired)→V617F; or JAK2 exon 12 mutations (L.Scott et al, NEJM 2007; 356:459-68)
- Important to r/o secondary causes of polycythemia
- M&M: hemorrhage, thrombotic events (including abdominal , cerebral), transformation to MF or AML

Pemmaraju N/Moliterno A: Abdominal Venous Thrombosis presenting in MPN with JAK2V617F mutation, J Med Case Rep 2012; Kiladjian JJ: The Impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchinic vein thrombosis, Blood 2008.; Smallberg JH: MPN in BCS and PVT: meta-analysis, Blood 2012

Somatic Mutations of JAK2 Exon 12 in Patients with Polycythemia Vera or Idiopathic Erythrocytosis



Scott LM et al. N Engl J Med 2007;356:459-468

The NEW ENGLAND JOURNAL of MEDICINE

PV: diagnostic criteria (WHO, 2008)

Major criteria

1. Hb > 18,5 g/dL (M), > 16.5 g/dL (F)
2. *JAK2* (V617F) or other JAK2 mutation

Minor criteria

- Bone marrow biopsy: hypercellularity with trilineage growth
- Low erythropoietin level
- EEC+

Diagnosis: 2 major + 1 minor
First major + 2 minor

PV: WHO 2016

- **Major criteria:**
- **1. Hemoglobin > 16.5 g/dL men**
- **Hemoglobin > 16.0 g/dL women or,**
- **Hematocrit >49% in men Hematocrit >48% in women or,**
- **increased red cell mass (RCM)**

- **2. Bone marrow biopsy showing: hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)**

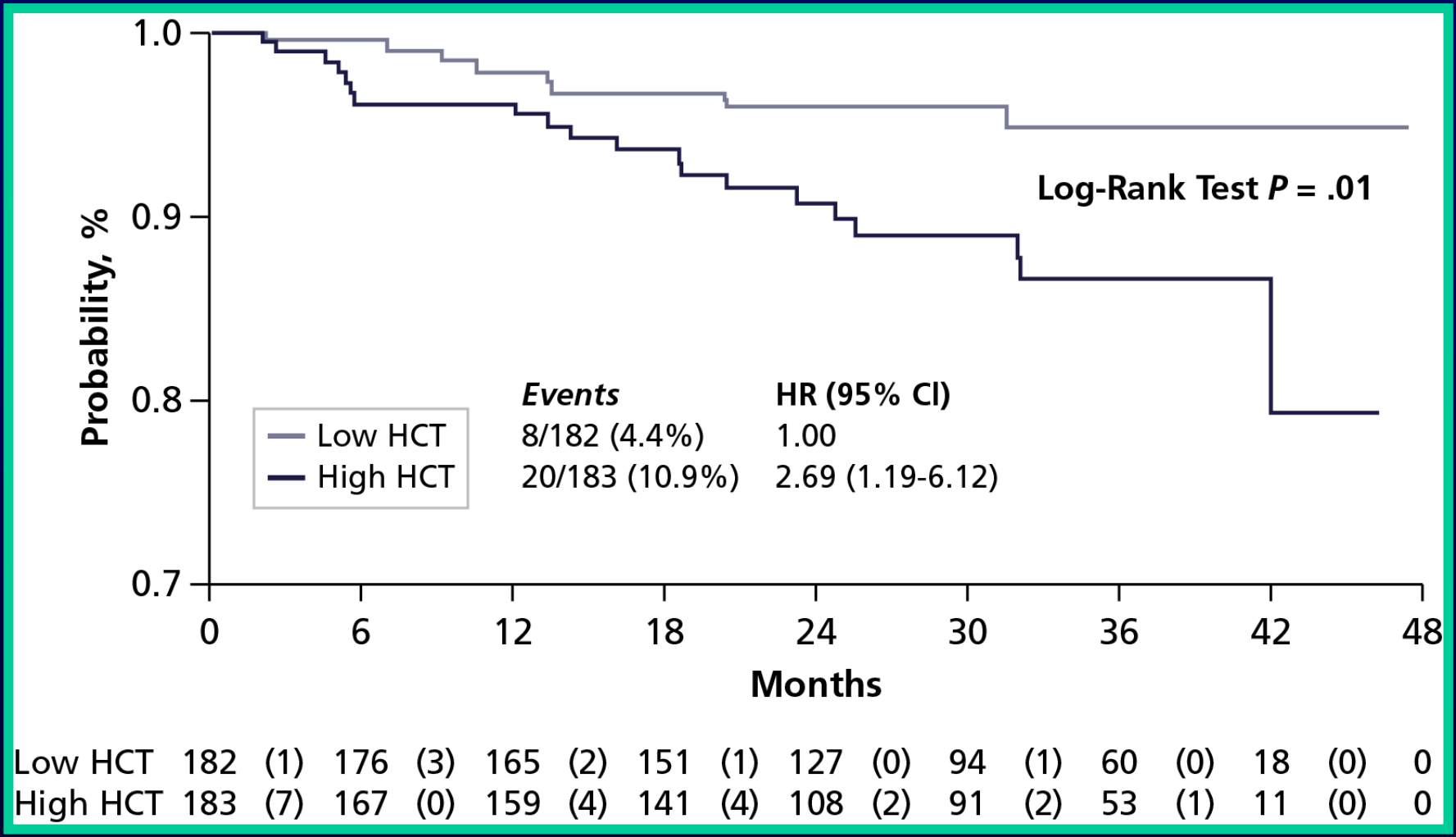
- **3. Presence of JAK2V617F or JAK2 exon 12 mutation**

- **Minor criterion: Subnormal serum erythropoietin level**

- **Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion**

Arber DA et al WHO 2016 Revision Blood. 2016 May 19;127(20):2391-405

Risk of Total Cardiovascular Events per HCT



Marchioli R et al. *N Engl J Med*. 2013;368:22-33.

Conclusions: PV

- JAK2V617, JAK2 exon 12
- Differentiate b/t secondary polycythemia
- M & M: Clots (arterial/venous), bleeding, tx-->MF, tx→AML
- Remember: young patient/NL CBC “masked PV”/Budd-Chiari/SVT presentation prior to MPN dx
- WHO 2016: Hb requirement now lower (for both men and women to reflect PV being missed/underdx)
- Triple therapy: baby ASA + phlebotomy goal 45 and below + cytoreductive therapy (Hydrea)
- 2nd line approval: Ruxolitinib (HU intolerance/failure)

Myelofibrosis (MF)

2017 WHO Diagnostic Criteria for prePMF

Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion

Major criteria

- Megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
- Not meeting WHO criteria for BCR-ABL1 + CML, PV, ET, MDS, or other myeloid neoplasms
- Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker, or absence of minor reactive BM reticulin fibrosis

Minor criteria

- Presence of at least one of the following, confirmed in 2 consecutive determinations:
  - Anemia not attributed to a comorbid condition
  - Leukocytosis ≥11 x 10^9/L
  - Palpable splenomegaly
  - LDH increased to above UNL of institutional reference range

NCCN Guidelines. Myeloproliferative Neoplasms. V1.2020

2017 WHO Diagnostic Criteria for Overt PMF

Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

Major criteria

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

Minor criteria

- Presence of at least one of the following, confirmed in 2 consecutive determinations:
  - Anemia not attributed to a comorbid condition
  - Leukocytosis ≥11 x 10^9/L
  - Palpable splenomegaly
  - LDH increased to above UNL of institutional reference range
  - Leukoerythroblastosis

NCCN Guidelines. Myeloproliferative Neoplasms. V1.2020

MF Grading

Grade	Description
MF-0	Scattered linear reticulin with no intersections or crossovers corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersetions, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis
MF-3	Diffuse and dense increase in reticulin with extensive intersections and course bundles of thick fibers consistent with collagen, usually associated with osteosclerosis

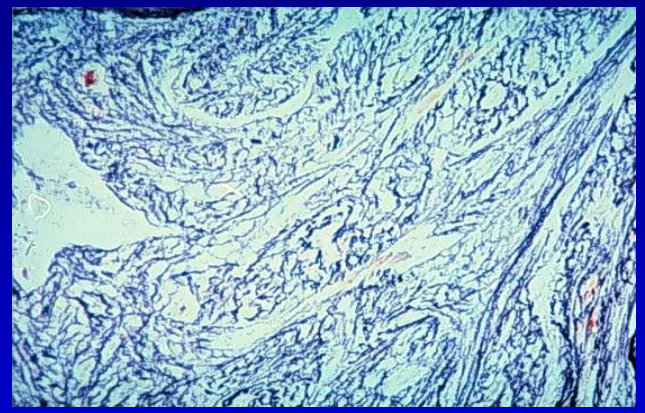
NCCN Guidelines. Myeloproliferative Neoplasms. V1.2020

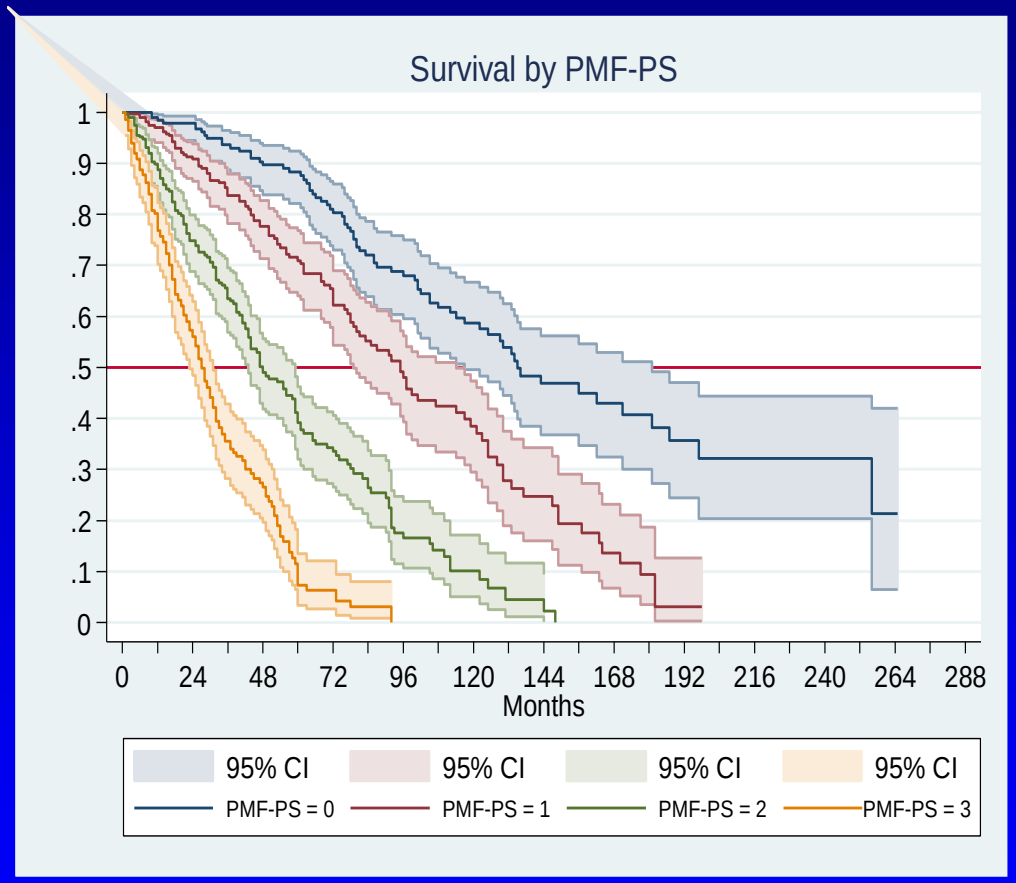
MF: WHO 2016

- **Major criteria:**
- **1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3***
- **2. Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms**
- **3. Presence of JAK2, CALR or MPL mutation or in the absence of these mutations, presence of another clonal marker ** or absence of reactive myelofibrosis ***
- **Minor criteria: Presence of at least 1 of the following, confirmed in two consecutive determinations:**
- **a. Anemia not attributed to a comorbid condition**
- **b. Leukocytosis >11 x 109 /L**
- **c. Palpable splenomegaly**
- **d. LDH increased to above upper normal limit of institutional reference range**
- **e. Leukoerythroblastosis "tear drop" cells**
- **Diagnosis of overt PMF requires meeting all three major criteria, and at least one minor criterion * see Table 8 ** in the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (e.g.ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease**
- ***BM fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies**

Arber DA et al WHO 2016 Revision Blood. 2016 May 19;127(20):2391-405

Heterogeneous clinical outcomes in MF





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

Slide Courtesy: S. Verstovsek

MF: Risk Stratification: Poor prognostic variables

- Age >65 y
- Presence of Constitutional symptoms
- Hgb <10
- WBC >25
- Circulating blasts cells ≥1%

- P-values were all <0.001

- 1054 pts at 7 centers

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

MF: Further scoring systems

- DIPSS (dynamic)—Mayo (Blood 2010;115)
  - Modified IPSS to be able to calculate over time: all 1 pt except Hb (2 points)
  - Age >65
  - WBC >25K
  - Hb <10: 2 points
  - Circulating blasts greater than or equal to 1%
  - Constitutional sxs

- DIPSS Plus—adds 3 new factors, each 1 point (Mayo, 2011 JCO)
  - Unfavorable karyotype
  - Plt count <100K
  - Transfusion need

MF: Treatment based on Risk Stratification-Proposal

- Low risk: supportive care, transfusions, close surveillance, clinical trials
- Intermediate risk: standard treatment, JAK2 inhibitors, clinical trials, consider allo-SCT
- High risk: JAK2 inhibitors, clinical trials, allo-SCT

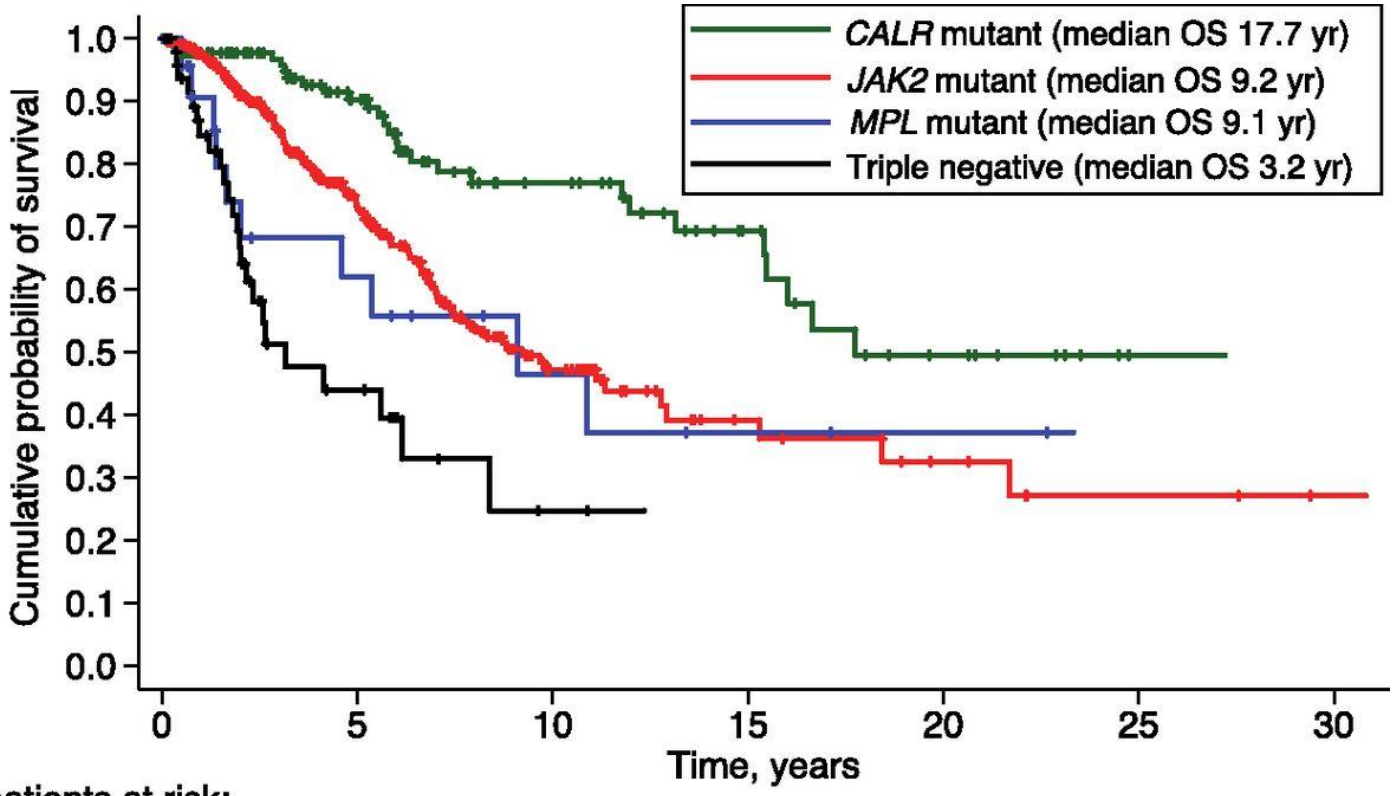
Triple Negative MF (JAK2-/CALR-/MPL-)

- **N=617**
  - **N=399 (65%)=JAK2 (V617F)**
  - **N=140 (23%)= CALR (exon 9 indel)**
  - **N=25 (4%) = MPL (W515)**
  - **N=53 (9%) = none of these 3; aka "Triple Negative"**

- **CALR alone: 1)lower risk of developing anemia, thrombocytopenia & leukocytosis; and lower risk of thrombosis than JAK2**

Rumi et al Blood Aug 2014.

Kaplan-Meier analysis of survival of PMF patients stratified according to their driver mutation.



No. of patients at risk:

CALR mutant	140	72	37	19	9	1
JAK2 mutant	396	135	39	13	7	3
MPL mutant	25	10	5	3	2	0
Triple negative	53	11	2	0	0	0

Elisa Rumi et al. Blood 2014;124:1062-1069

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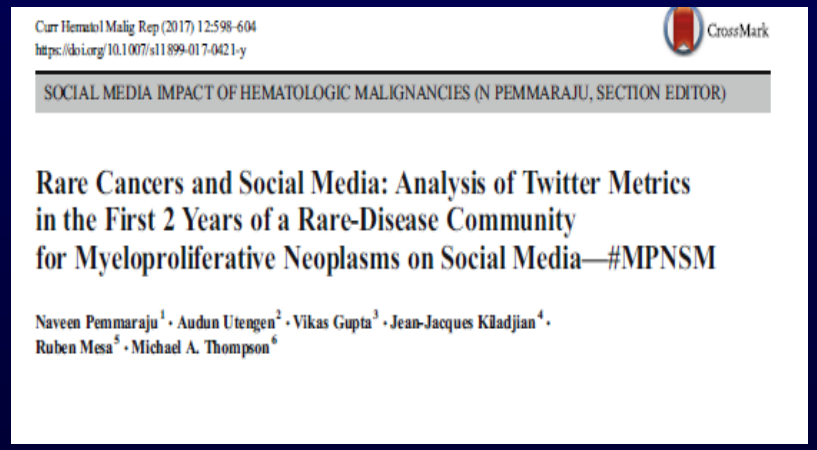
Thank you: MPN and BPDCN and Rare Diseases communities

- Please email me npemmaraju@mdanderson.org or call me 713-792-4956 if you have any questions

- #MPNSM: Twitter @doctorpemm



Curr Hematol Malig Rep (2017) 12:598-604
https://doi.org/10.1007/s11899-017-0421-y

SOCIAL MEDIA IMPACT OF HEMATOLOGIC MALIGNANCIES (N PEMMARAJU, SECTION EDITOR)

Rare Cancers and Social Media: Analysis of Twitter Metrics in the First 2 Years of a Rare-Disease Community for Myeloproliferative Neoplasms on Social Media—#MPNSM

Naveen Pemmaraju[1] · Audun Utengen[2] · Vikas Gupta[3] · Jean-Jacques Kiladjian[4] · Ruben Mesa[5] · Michael A. Thompson[6]

- Hagop Kantarjian
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