Managing Essential Thrombocythemia in 2025

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Disclosures:

- None

Essential thrombocythemia (ET):

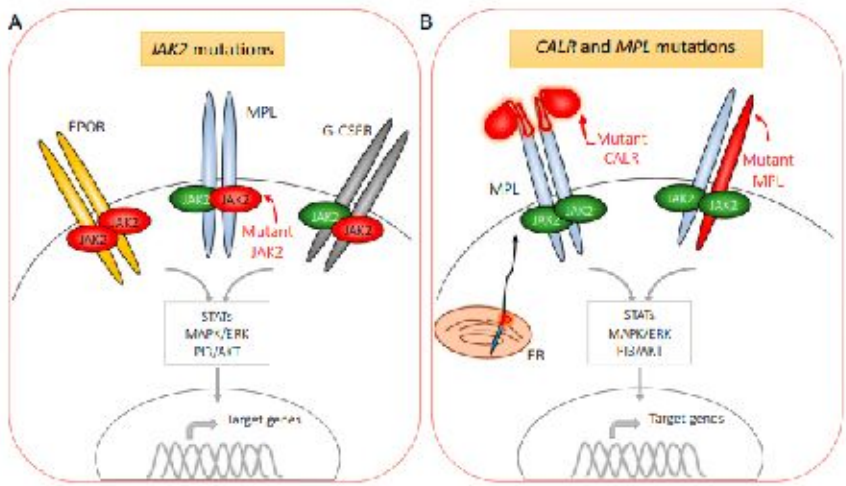
- **What is it?**
- Myeloproliferative neoplasm
- Disease of the hematopoietic stem cell
- Most often harbor 1 of 3 mutually exclusive driver mutations
- Constitutive activation of the JAK-STAT pathway
- Results in hypersensitivity of hematopoietic stem cells to growth factors and cytokines
- Leads to overproduction of mature and functional blood cells
- In the case of ET, sustained elevated platelet counts lead to bleeding and clotting complications

- **How common is it?**
- Annual Incidence of 1.5-2 cases per 100,000 of the population
- Median age at presentation 65yo (up to 15% <40yo)

Essential thrombocythemia (ET):

Driver mutations—

JAK2 V617F	50-60%	-older -higher hemoglobin -higher white blood cell count
MPL	3-4%	-older
CALR Type 1, 52bp deletion Type 2, 5bp insertion	20-25%	-younger -male -higher platelet count (esp type 2) -lower hemoglobin -lower white blood cell count -decreased thrombotic risk
Triple negative	10-15%	-higher platelet count -lowest risk of thrombosis



Nangalia et al. Blood. 2017.

ET: Signs and Symptoms

- Asymptomatic
- Microvascular disturbances
  - Headache
  - Lightheadedness
  - Blurred vision
  - Palpitations
  - Chest pain
  - Erythromelalgia (redness, warmth, and pain in distal extremities)
  - Distal paresthesias
- Splenic discomfort associated with splenomegaly
  - Palpable splenomegaly 13%
- Superficial thrombophlebitis
- Minor mucocutaneous bleeding

ET: Signs and Symptoms

- Overt thrombosis
  - 14% Major arterial thrombosis at or prior to diagnosis
  - 10% Major venous thrombosis at or prior to diagnosis
- Overt bleeding
  - 8% Major hemorrhage at or prior to diagnosis
- Median hb 14
- Median wbc 8.5
  - 16-20% Wbc>11
- Median plt 777
  - 26% Extreme thrombocytosis >1000x$10^{9/L}$

Gangat N et al. Blood Cancer J. 2024.
Loscocco GG et al. Blood Cancer J. 2024.

ET: How do we diagnosis it?

	5th Edition WHO/2022 ICC
Major	Platelet count ≥450x10^9/L
	Bone marrow biopsy— Proliferation mainly of the megakaryocytic lineage, With increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; Very rarely a minor (grade 1) increase in reticulin fibers
	Diagnostic criteria for BCR::ABL1-positive CML, PV, PMF, or other myeloid neoplasms are not met
	Presence of JAK2, CALR, or MPL mutation
Minor	Presence of a clonal marker
	Exclusion of reactive thrombocytosis
	Diagnosis requires either all major criteria OR first 3 major and 1 minor criteria

Khoury J et al. Leukemia. 2022.
Arber D et al. Blood. 2022.

Causes of thrombocytosis:

Reactive	Clonal myeloid disorders
Iron deficiency Blood loss Surgery Acute bacterial infection Chronic inflammation --vasculitis --RA --chronic infection --inflammatory bowel disease Nonmyeloid malignancies --lung ca --colorectal ca Splenectomy/hyposplenism	Myeloproliferative neoplasms --Essential thrombocythemia --Polycythemia vera --Prefibrotic myelofibrosis --Primary myelofibrosis --Chronic myeloid leukemia --MPN, unclassifiable Myelodysplastic syndrome/Myeloproliferative neoplasm overlap --Chronic myelomonocytic leukamia --MDS/MPN with SF3B1 mutation and thrombocytosis --MDS/MPN, not otherwise specified Myelodysplastic syndrome --MDS with low blasts and isolated del(5q)

ET: Diagnosis

- A bone marrow biopsy is necessary to make an accurate diagnosis of ET
- In order to distinguish it from other myeloid neoplasms, in particular, prefibrotic myelofibrosis

2022 ICC Prefibrotic MF:

Major	1. Bone marrow biopsy— --Megakaryocytic proliferation and atypia, --Bone marrow fibrosis grade <2, --Increased age-adjusted bone marrow cellularity, --Granulocytic proliferation and (often) decreased erythropoiesis 2. Diagnostic criteria for BCR::ABL1-positive CML, PV, PMF, or other myeloid neoplasms are not met 3. JAK2, CALR, or MPL mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis
Minor	Anemia not attributed to a comorbid condition Leukocytosis $\geq 11 \times 10^9$/L Palpable splenomegaly LDH above reference range Leukoerythroblastosis
	Diagnosis requires all 3 major and 1 minor

Khoury J et al. Leukemia. 2022.
Arber D et al. Blood. 2022.

ET vs prefibrotic MF: Distinctions

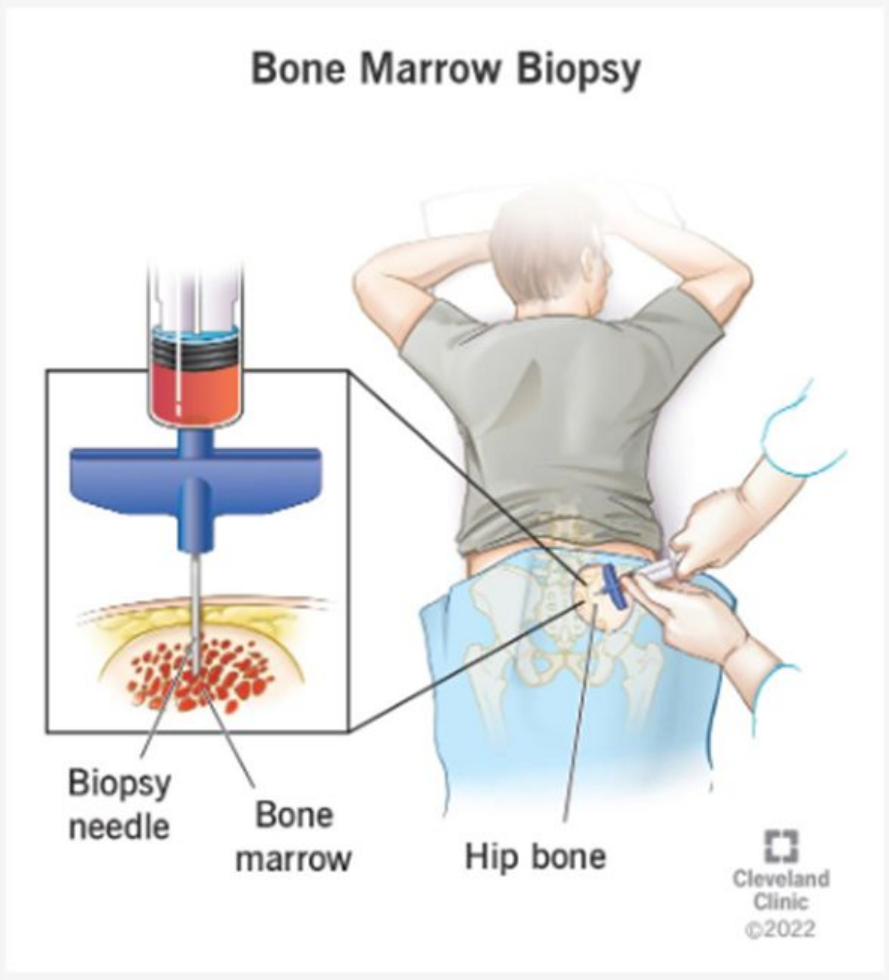
ET	Prefibrotic MF
Normal Hb	Anemia or low MCV or high RDW
Normal LDH	Often elevated LDH
No leukoerythroblastosis on peripheral smear (no nucleated rbc's or immature myeloid cells)	Often do see leukoerythroblastosis
No teardrop cells	Often do see tear drop cells
JAK2 allelic burden usually <20%	Often higher JAK2 allelic burden
At level of marrow: • megs large • mature-appearing • form loose clusters	At level of marrow: • abnormal maturation of megs • hyperchromatic irregularly folded nuclei • form tight clusters

ET vs prefibrotic MF: Why it matters

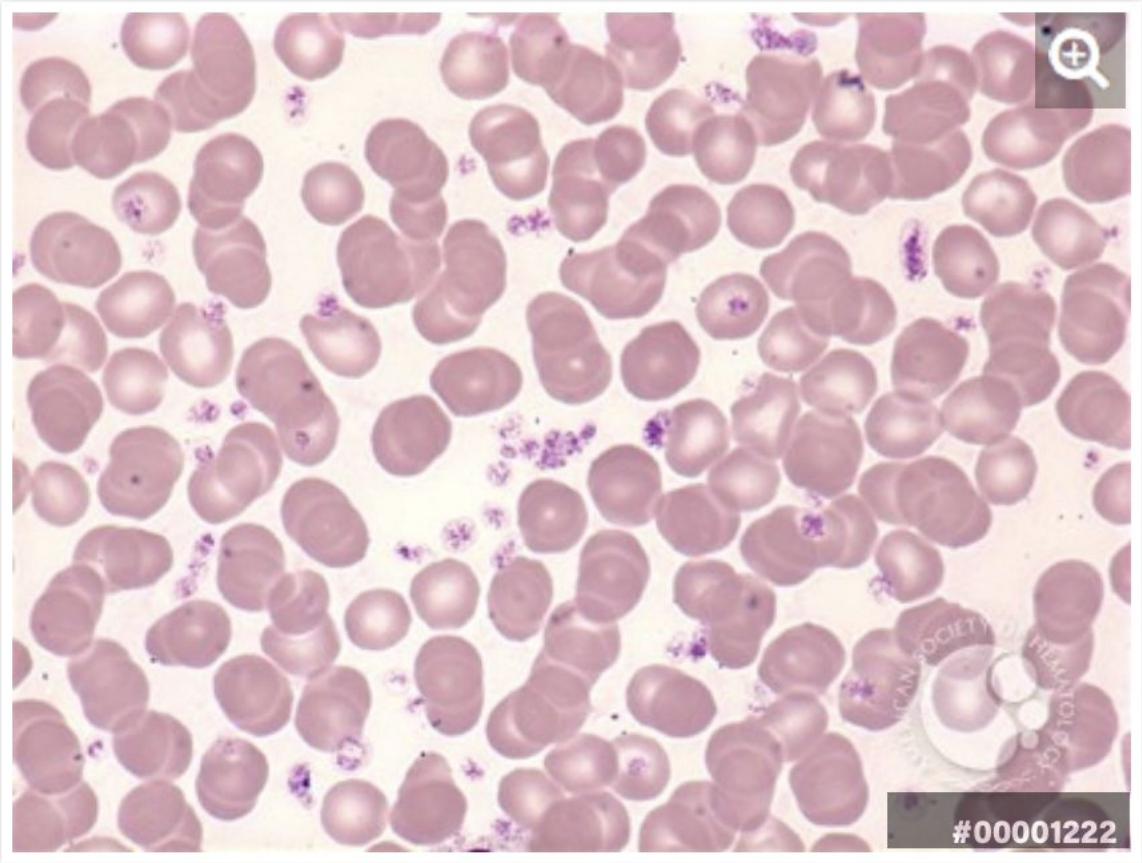
	Leukemic transformation	Fibrotic progression	15yr OS
prePMF	12%	17%	59%
ET	2%	9%	80%

Tefferi et al. Am J Hematol. 2023.

Bone marrow biopsy:

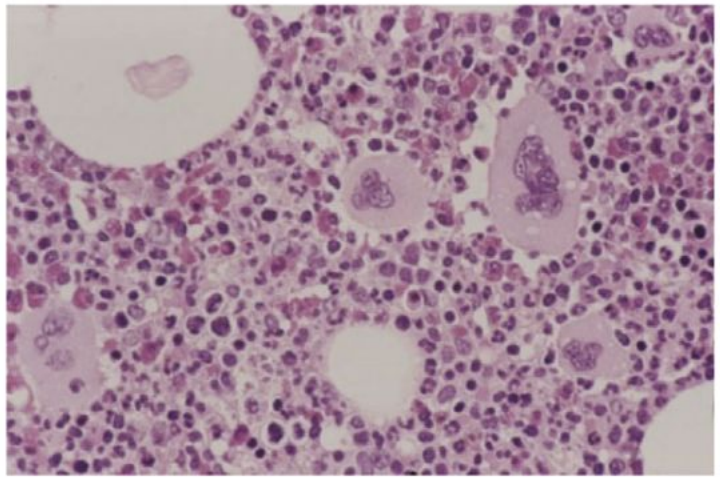


ET: Peripheral blood smear

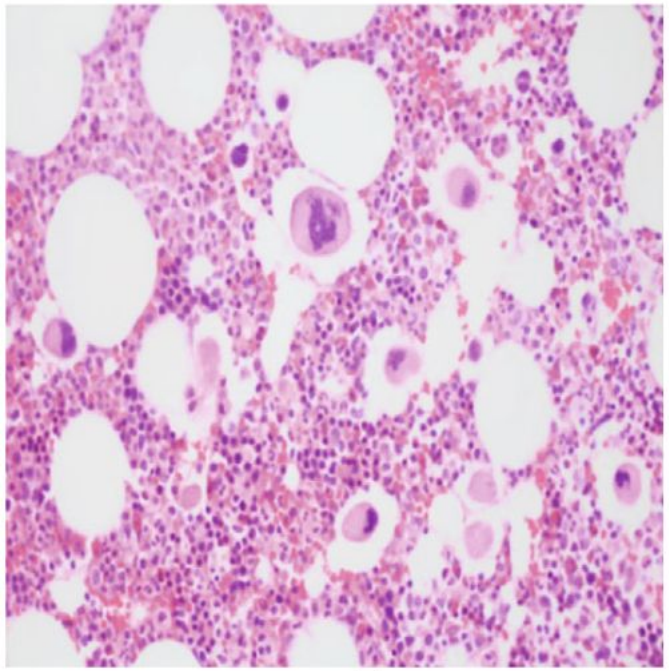


ASH Bank.

Normal megakaryocytes

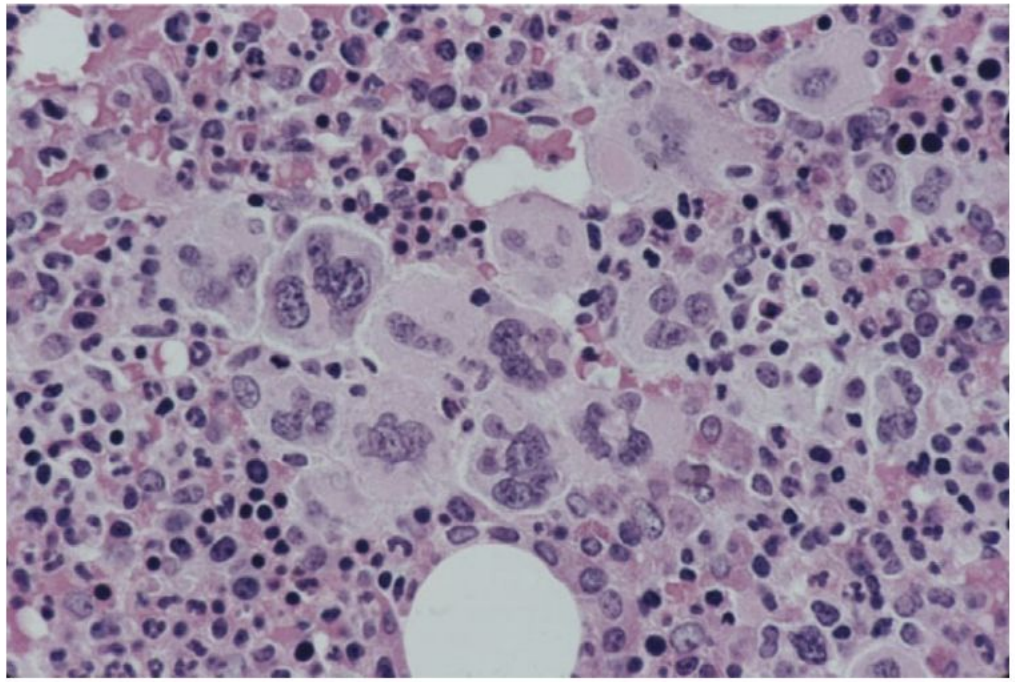


Essential thrombocythemia



Megakaryocytes are:
--large
--mature-appearing
--form loose clusters

Prefibrotic myelofibrosis



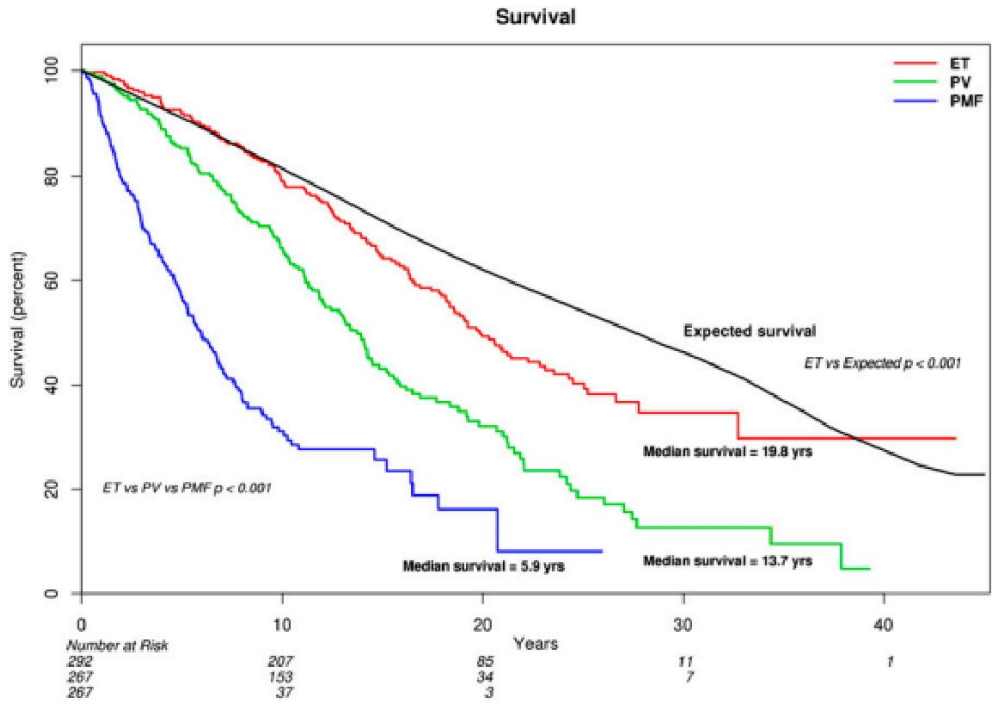
Megakaryocytes are:
--hyperchromatic
--irregularly folded nuclei
--form tight clusters

Tefferi et al. Am J Hematol. 2024.

ET: What are the consequences of having this diagnosis?

ET: Prognosis

- Broadly speaking, overall survival very good
  - Median overall survival 20 years
  - Median overall survival 33 years if <60yo
  - But consistently inferior to that of sex- and age-matched control populations
- <5% risk of transformation to AML
- <10% risk of transformation to MF
- 10-25% risk of thrombosis



ET: Overall survival

IPSET

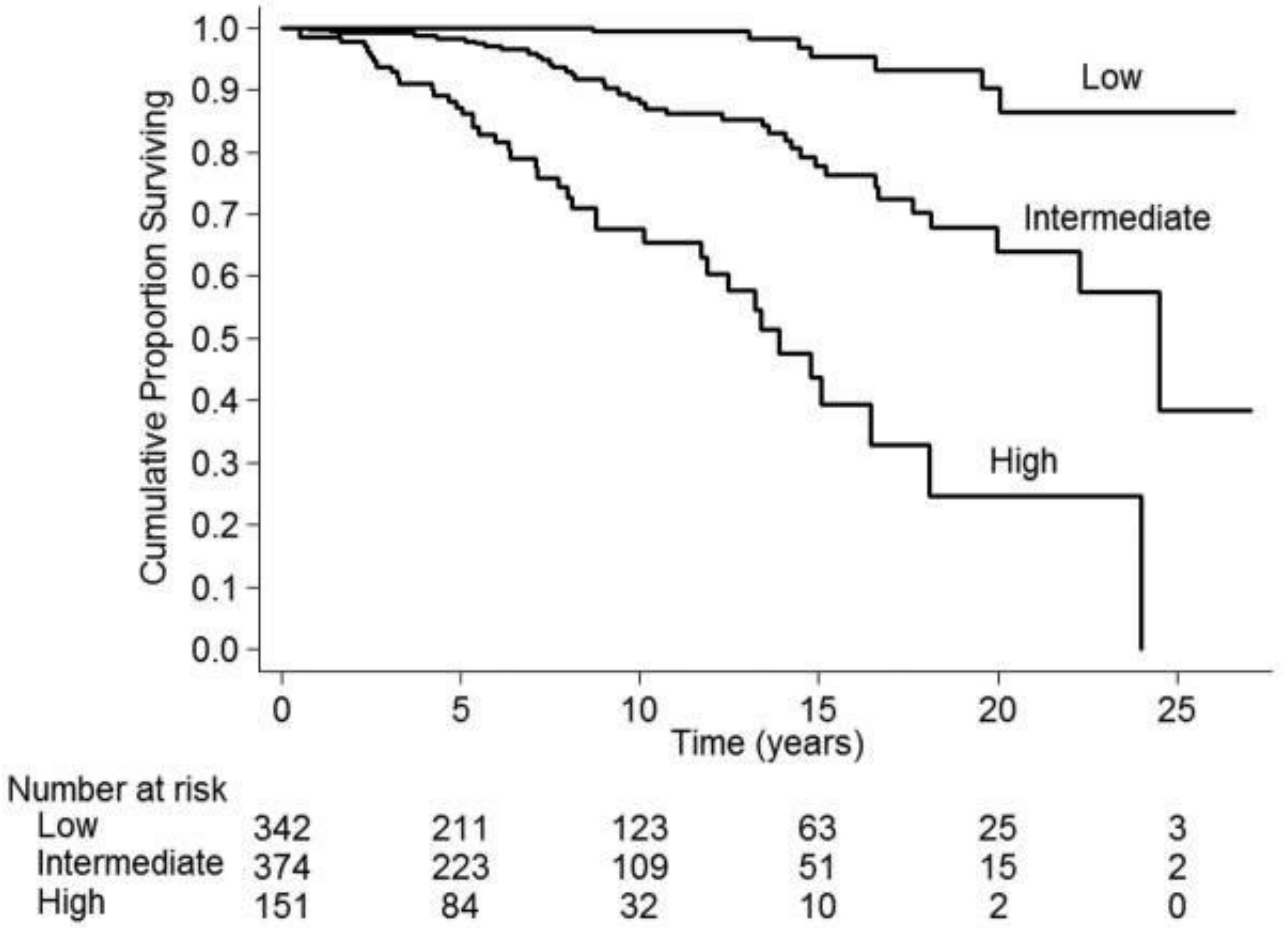
3 risk factors—

- Age≥60 (2pts)
- Wbc>11x10^9/L (1pt)
- Prior thrombosis (1pt)

Low 0 (NR)

Intermediate 1-2 (24.5yrs)

High 3-4 (14.7yrs)



Passamonti et al. Blood. 2012.

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ET: Overall survival

Triple AAA

4 variables—

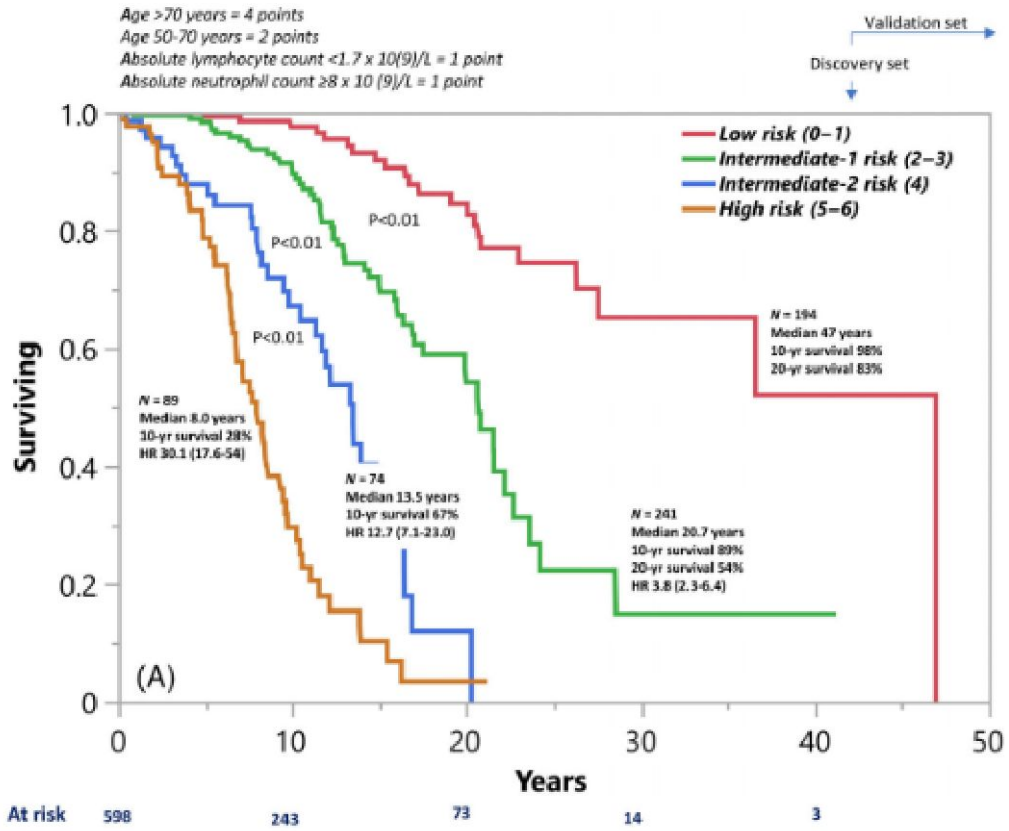
- Age>70 (4pts)
- Age 50-70 (2pts)
- ANC≥8x10^9/L (1pt)
- ALC≤1.7x10^9/L (1pt)

Low 0-1 (47yrs)

Int-1 2-3 (20.7yrs)

Int-2 4 (13.5yrs)

High 5-6 (8yrs)



Tefferi A et al. Am J Hematol. 2023.

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ET: Overall survival

MIPSS-ET

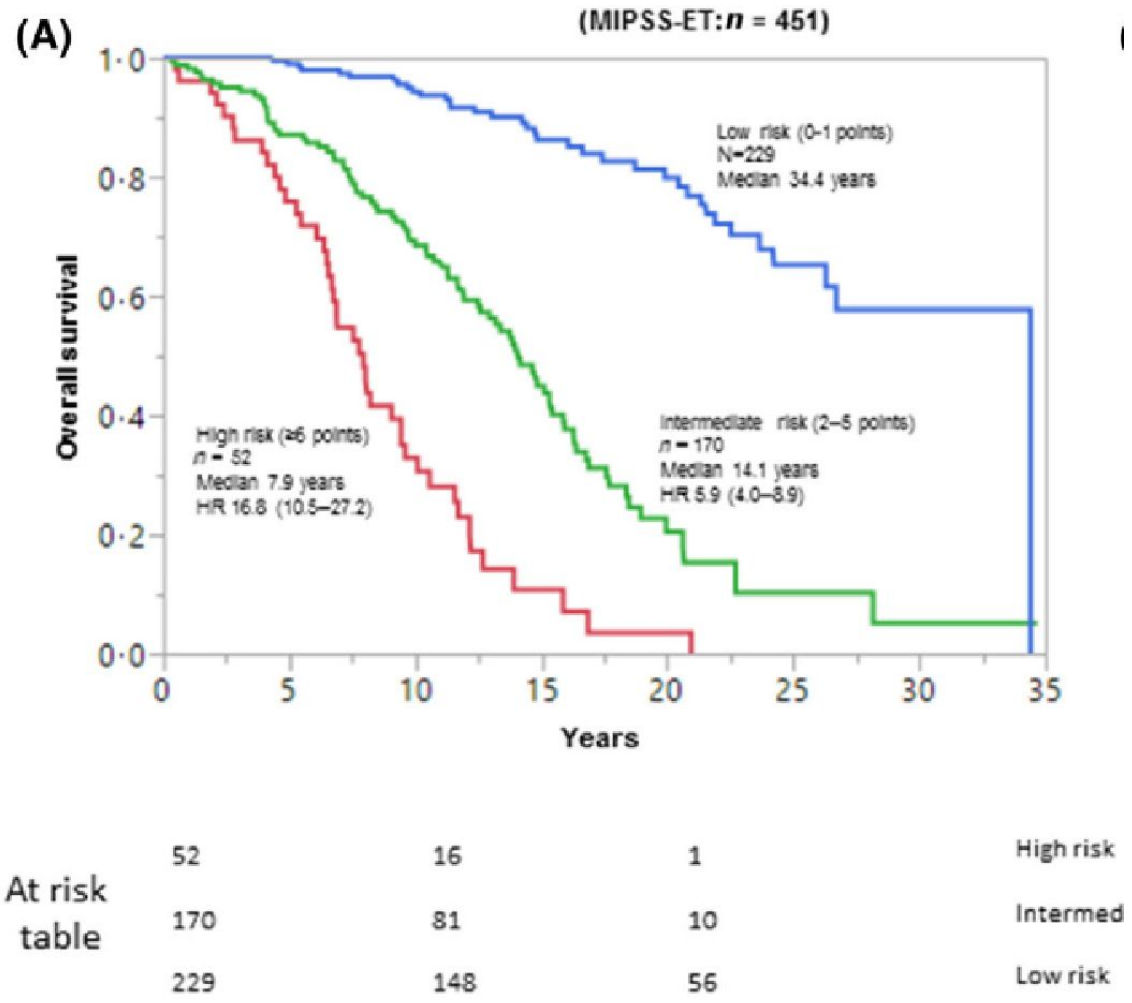
4 variables—

- Age>60 (4pts)
- Male gender (1pt)
- Wbc≥11x10^9/L
- Adverse mutations (2pts)
  - SF3B1
  - SRSF2
  - U2AF1
  - TP53

Low 0-1 (34.4yrs)

Int 2-5 (14.1yrs)

High ≥6 (7.9yrs)



Tefferi A et al. Br J Haematol. 2020.

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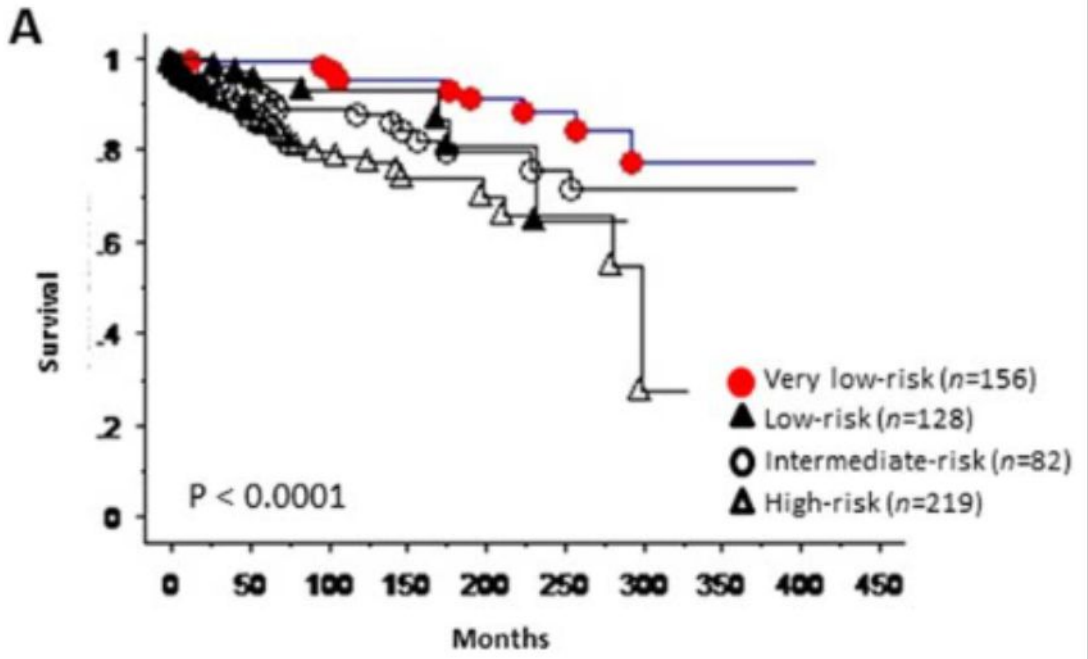
MF free and Leukemia free survival: Negative prognostic factors

- **MF free survival—**
  - Prefibrotic morphology
  - Advanced age
  - Anemia
  - JAK2 V617F VAF>35%
  - CALR type 1 mutn (VAF>60%)
  - MPL mutation
  - Male gender
  - SF3B1, U2AF1 mutations
- **Leukemia free survival—**
  - Prefibrotic morphology
  - Hx of thrombosis
  - Extreme thrombocytosis (>1000x10^9/L)
  - Abnormal karyotype
  - Advanced age
  - TP53, EZH2, SRSF2, IDH1, IDH2, ASXL1, U2AF1 mutations

Barbui T et al. J Clin Oncol. 2011.
Tefferi A et al. Blood Advances. 2016.
Loscocco GG et al. Am J Hematol. 2021.
Guglielmelli P et al. Blood. 2023.
Gangat N et al. Blood Cancer. 2024.

Thrombosis-free survival: Revised IPSET-Thrombosis

Risk Group	Characteristics	Thrombotic risk (% patients/year)
Very low	• Age≤60 • No JAK2 mutation • No hx of thrombosis	0.4-1.1%*
Low	• Age≤60 • +JAK2 mutation • No hx of thrombosis	1.6-2.6%*
Intermediate	• Age>60 • No JAK2 mutation • No hx of thrombosis	1.4-1.6%*
High	• Age>60 • +JAK2 mutation • **OR** • Hx of thrombosis at any age	2.4-4.2%*



- Higher end of range=patients with cardiovascular risk factors (CV RFs=smoking, hypertension, diabetes mellitus)
- No correlation between degree of platelet count elevation and thrombosis

Haider M et al. Am J Hematol. 2016.

ET: Goals of treatment

- No treatment to date that improves overall survival, leukemia-free survival or myelofibrosis-free survival
- We want to control symptoms
- We want to prevent thrombotic or hemorrhagic complications
- As such, treatment algorithm is based on Revised IPSET-Thrombosis

ET: Goal in all patients

- Control cardiovascular risk factors
- Hypertension
- Hyperlipidemia
- Diabetes mellitus
- Smoking
- Diet
- Exercise

ET: Goal in all patients

- Increased risk for secondary malignancies
- Age-appropriate cancer screening
  - Mammograms
  - Colonoscopies

ET: Antiplatelet treatment

- No randomized controlled studies to support use of aspirin in ET
- Recommendations extrapolated from ECLAP study in PV
  - aspirin vs placebo
  - aspirin reduced heart attack, stroke, thromboembolic event like DVT or PE or death from CV cause
  - no increased risk of bleeding
- Good retrospective data has shown that high risk ET patients have increased risk of thrombosis without aspirin
- Can be useful for microvascular symptoms such as erythromelalgia and headaches (once daily or twice a day)

Revised IPSET-Thrombosis Risk Group	Characteristics	Antiplatelet treatment?
Very low	• Age≤60 • No JAK2 mutation • No hx of thrombosis	Only if microvascular symptoms
Low	• Age≤60 • +JAK2 mutation • No hx of thrombosis	Yes
Intermediate	• Age>60 • No JAK2 mutation • No hx of thrombosis	Yes
High	• Age>60 • +JAK2 mutation • **OR** • Hx of thrombosis at any age	Yes

Landolfi R et al. NEJM. 2004.
Alvarez-Larran A et al. Br J Haematol. 2013.

ET: Aspirin Caveats

- **Acquired von Willebrand syndrome—**
  - Usually in the setting of extreme thrombocytosis (>1000x10^9/L)
  - Increased degradation of VWF multimers mediated by ADAMTS13
  - Excess bleeding, especially in presence of aspirin
  - Temporarily hold aspirin
  - Correctable with cytoreductive therapy

- **CALR mutation—**
  - Some retrospective data that shows aspirin does not decrease risk of thrombosis but increases risk of bleeding
  - Might consider not giving aspirin in asymptomatic lower risk patients without CV RFs
  - Might consider only using cytoreduction in symptomatic lower risk patients with CV RFs

ET: Cytoreductive treatment

- **An agent to lower the platelet count**

- **First line—**
  - Hydroxyurea (hydrea)
  - Interferon
- **Second line—**
  - Anagrelide
  - Ruxolitinib
  - Interferon

Revised IPSET-Thrombosis Risk Group	Characteristics	Cytoreductive treatment?
Very low	• Age≤60 • No JAK2 mutation • No hx of thrombosis	Only if refractory symptoms
Low	• Age≤60 • +JAK2 mutation • No hx of thrombosis	Only if refractory symptoms
Intermediate	• Age>60 • No JAK2 mutation • No hx of thrombosis	Only if refractory symptoms if no CV RFs Consider if CV RFs
High	• Age>60 • +JAK2 mutation • **OR** • Hx of thrombosis at any age	Yes

- No correlation between degree of platelet count elevation and thrombosis

Cytoreductive treatment: Is there a goal in terms of blood counts?

Table 1. Response criteria for ET

	Criteria
Complete remission	
A	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,† AND
B	Durable* peripheral blood count remission, defined as: platelet count ≤400 $\times 10^9$/L, WBC count <10 $\times$ 10^9/L, absence of leukoerythroblastosis, AND
C	Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND
D	Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis.
Partial remission	
A	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND
B	Durable* peripheral blood count remission, defined as: platelet count ≤400 $\times$ 10^9/L, WBC count <10 $\times$ 10^9/L, absence of leukoerythroblastosis, AND
C	Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND
D	Without bone marrow histological remission, defined as the persistence of megakaryocyte hyperplasia.
No response	Any response that does not satisfy partial remission
Progressive disease	Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome or acute leukemia‡

- European LeukemiaNet (ELN) and International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) response criteria
- Several retrospective studies have evaluated the prognostic impact of ELN response criteria in ET treated with different cytoreductive agents
- Achieving ELN/IWG-MRT response did not seem to change risk of death, thrombosis or bleeding
- Optimal platelet goal is not established
- More or less try to normalize but not at the sacrifice of side effects

*Durable response ≥12 weeks

τLarge symptom improvement ≥10 pt decrease in MPN-SAF TSS (10 question symptom score for patients with MPNs)

Barosi G et al. Blood. 2009.
Hernandez-Boluda JC et al. Br J Heamatol. 2011.
Hernandez-Boluda JC et al. Ann Hematol. 2013.
Barosi G et al. Blood. 2013.

Cytoreductive treatment in ET: Hydrea

- **Oral chemo pill**

- **Data—**
  - *Cartelazzo et al. NEJM. 1995.*
    - ET patients, majority >60, half with hx of thrombosis
    - Randomized: Hydrea vs no cytoreduction
    - Statistically significant decrease in thrombotic events with Hydrea
  - *Harrison et al. NEJM. 2005. PT1 study.*
    - ET patients, high risk for vascular events
    - Randomized: Hydrea+Aspirin vs Anagrelide+Aspirin
    - Fewer arterial thrombosis, venous thrombosis, serious bleeding or death from any of these with Hydrea+Aspirin

- ~20% of ET patients become intolerant or resistant to hydrea
  - Patients with resistance appear to be at increased risk of disease transformation and reduced overall survival

- **Side effects/precautions—**
  - Oral ulcers
  - Skin ulcers
  - Fevers
  - Anemia
  - Increased risk of non-melanoma skin cancers
  - Teratogenic
  - Many studies that do NOT implicate hydrea as being leukemogenic

Cytoreductive treatment in ET: Anagrelide

- **Oral chemo pill**

- **Data—**
  - *Gisslinger et al. Blood. 2013.*

    ANAHYDRET study.
    - High risk ET patients
    - Noninferiority phase 3 trial
    - Randomized: Anagrelide vs Hydrea
    - No significant difference in major/minor arterial or venous thrombosis or major/minor bleeding

- **Side effects/precautions—**
  - Dizziness
  - Palpitations
  - Diarrhea
  - Fluid retention
  - Increased progression to myelofibrosis in PT1 study (versus hydrea arm) and in observational EXELS observational trial
  - Decreases sperm count
  - Teratogenic

Birgegard G et al. Haematologica. 2018.

Cytoreductive treatment in ET: Ruxolitinib

- **Oral JAK inhibitor,** approved in PV and MF
- **Data—**
  - *Harrison et al. Blood. 2017.*
    MAJIC-ET study.
    - High risk ET who were HU-resistant or intolerant
    - Phase 2 Randomized: Ruxolitinib vs BAT
    - No significant difference in CR at 1yr (46.5% Rux vs 44.2% BAT)
    - No significant difference in thrombosis, hemorrhage, disease transformation at 2yrs
    - No significant difference in overall symptom response BUT
    - Max % decrease in symptoms superior with Rux
    - Symptom response more rapid with Rux
  - *Koschmeider et al. Blood. 2022.*
    Ruxo-BEAT study.
    - Treatment-naïve or previously treated high risk ET
    - Phase 2 Randomized: Ruxolitinib vs BAT
    - No significant difference in CR at 6 months BUT
    - Rux better at reducing spleen size, headache and difficulty with concentration
- Mutation agnostic
- **Side effects/precautions—**
  - Anemia
  - Diarrhea
  - Weight gain
  - Increased risk of opportunistic infections and viral reactivation
  - Increased risk of non-melanoma skin cancers
  - Lack of data regarding effect on fertility or safety during pregnancy, usually avoided

Cytoreductive treatment in ET: Interferons

- Interferons are a group of cytokines with immunomodulatory properties
- First immune therapies used in cancers including in hematologic malignancies

- Standard interferon alfa-2b difficult to tolerate
- **Pegylated formulations—**
  - Longer half life
  - Less frequent administration
  - Better tolerability

  - Pegylated interferon alfa-2a (Pegasys)—once weekly sq injection
  - Pegylated interferon alfa-2b (PegIntron)—once weekly sq injection
  - Ropeginterferon alfa-2b (Besremi)—every 2 week sq injection, eventually once monthly maintenance

- **Side effects—**
  - Flu-like symptoms
  - Lowering of white blood cell count
  - Autoimmune disease (hypothyroidism, hepatitis, vasculitis)
  - Depression
  - Liver function test abnormalities

Cytoreductive treatment in ET: Interferons

- Notable response rates have been observed in a number of trials investigating the use of interferon in the treatment of ET for >30 years

Table 1. Listing of clinical studies evaluating the role of interferon in the treatment and management of myeloproliferative neoplasms.

First study (year)	ET patients (n)	Response rate (%)	Discontinuation, n (%)	Type of IFN
Giles (1988)	18	100	0	2a and 2b
Bellucci (1988)	12	NA	4 (33)	2a
Gugliotta (1989)	10	100	NA	2a
Lazzarino (1989)	26	86	9 (35)	2b
Gisslinger (1991)	20	85	10 (50)	2c
Kasparu (1992)	14	86	0	2b
Berte (1996)	12	83	NA	2a/2b
Alvarado (2003)	11	100	2 (18)	PEG-2b
Saba (2005)	20	75	3 (15)	2a
Langer (2005)	36	75	13 (36)	PEG-2b
Samuelsson (2006)	21	70	11 (55)	PEG-2b
Jabbour (2007)	13	70	NA	PEG-2b
Quintás-Cardama (2009 and 2013)	39	81	NA	PEG-2a
Verger (2015)	31	100	39%	PEG-2b
Mascarenhas *et al.* (2016)	31	80	NR	PEG-2a
Gowin (2017)	20	65	NA	PEG-2a

ET: Essential thrombocythemia; IFN: Interferon; MPN: Myeloproliferative neoplasms; NA: Not applicable; NR: Not reported.

Verstovsek S et al. Future Oncology. 2022.

Interferon: Frontline in ET

- **MPN-RC 112 trial—**
  - Phase 3
  - Treatment-naïve high risk ET and PV
  - Randomized: Hydrea vs Pegylated interferon alfa-2a (Pegasys)

ET cohort	HU	PEG-IFN
	n=42	n=39
12m CR	45%	44%
24m CR	25%	38%
36m CR	17%	40%
Entire cohort		
CI thrombosis	2%	2%
≥gr 3 AEs	37%	46%

Mascarenhas J et al. Blood. 2022.

Interferon: Frontline in ET

- **DALIAH trial—**
  - Phase 3
  - Treatment-naïve (mostly) ET, PV, prefibrotic MF, overt MF
  - Randomized: Hydrea vs Pegylated interferon (Pegasys, PegIntron)

	HU	PEG-IFN
24m CHR	26%	21%
Discontinuation rate 2/2 adverse events	13%	34%

  - Those with CHR had greater reduction in JAK2 VAF

Knudsen et al. Blood Advances. 2022.

Interferon: Second line in ET

- **MPN-RC 111 trial—**
  - Phase 2
  - High risk ET and PV refractory to/intolerant of hydrea (n=65 with ET)
  - All received Pegylated interferon-2a (Pegasys)

	12 months
CR	43.1%
PR	26.2%
Platelet≤400	69.2%
Major vascular event	2%

- CR rates higher in CALR mutated patients (56.5% vs 28%, p=0.01)
- Those with CR had reduction in JAK2 VAF
- Histopathologic remission seen in n=5 ET patients
- More patients than not had an improvement in MPN-related symptoms
- 13.9% patients discontinued treatment due to adverse events

Yacoub A et al. Blood. 2019.

Interferon:

- **Single institution retrospective study—**
  - MPN patients 2000-2020
  - on IFN for ≥3 months
  - 381 patients (169 had ET)
- 77.2% achieved CHR
- At median follow up of 72.4 months,
  - 131 still on IFN
  - 250 had discontinued IFN (toxicity, prolonged CHR, failure, other)
- At time of discontinuation,
  - No significant difference in MPN subtype, clinical or molecular characteristics
  - 66.9% were in CHR
  - Median VAF 12%
- 61 patients lost CHR and had IFN re-introduced
  - 83.6% achieved CHR a 2nd time
- VAF≥10% at time of IFN discontinuation associated with higher incidence of relapse
- Overall survival was not significantly different between patients who discontinued vs continued IFN
- A treatment-free remission may be achievable with Interferon treatment

De Oliveria et al. Blood (supplement). 2020

Ropeginterferon alfa-2b (Besremi):

- Stable IFN alfa analog
- Structural characteristics that give it
  - beneficial PK and PD properties
  - allows for less frequent dosing
  - favorable safety and tolerability profile
- FDA approved for treatment of PV
  - PROUD-PV
  - CONTINUATION-PV
  - PEGINVERA

- **EXCEED ET—**
  - Single arm
  - Multicenter, North America
  - Cytoreductive agent naïve or HU exposed ET
- **ROP-ET—**
  - Single arm
  - Multicenter, Ex-US
  - Intolerant, resistant and/or not eligible for available cytoreductive agents
- **SURPASS-ET—**
  - Phase 3 Randomized study
  - High risk ET resistant to or intolerant of HU
  - Ropeginterferon alfa-2b vs Anagrelide

	Clinical response at 9m and 12m	Change in JAK2 VAF from baseline to 12m
Ropeginterferon alfa-2b	42.9%	-8.4%
Anagrelide	6%	-2.4%

https://us.pharmaessentia.com/interferon-therapy-mpn/clinical-trials/

Agent under investigation: Bomedemstat

- LSD1 = lysine-specific demethylase-1
- Enzyme critical for self-renewal potential of malignant cells and hematopoietic differentiation

- Bomedemstat = oral LSD1 inhibitor

- Loss of LSD1 activity is associated with loss of self-renewal in malignant hematopoietic stem cells

- In mouse models of MPN, Bomedemstat—
    - Decreases counts
    - Decreases splenomegaly
    - Decreases inflammatory cytokines
    - Decreases mutant cell burden
    - Increases overall survival

Bomedemstat:

- **Phase 2 trial—**
- ET patients resistant to or intolerant of at least 1 standard treatment

- For patients treated ≥24 weeks:
  - 95% achieved plt<400 without new thromboembolic event in median of 10 weeks
  - 83% of patients treated ≥24 weeks maintained their plt response ≥12 weeks

- In patients with baseline symptom score>20, at week 24:
  - 79% had improvement
  - 64% had ≥10point improvement

- At week 24:
  - 85% had decrease in mutant allele frequency

- Side effects—
  - Dysgeusia
  - Fatigue
  - Thrombocytopenia
  - Arthralgia
  - Diarrhea

Gill H et al. Blood (supplement). 2022.
Goethert JR et al. Blood (supplement). 2023.

Bomedemstat: Active trials

- **Treatment-naïve ET—**
- Phase 3 randomized
- Bomedemstat vs Hydrea
- Multinational, multicenter

- **Hydrea resistant or intolerant ET—**
- Phase 3 randomized
- Bomedemstat vs BAT
- Multinational, multicenter

Targeting mutant CALR:

- Mutant CALR translates with a novel C terminus that leads to aberrant binding to the extracellular domain of the thrombopoietin receptor, MPL
- Results in constant activation of the JAK/STAT pathway
- Because this neoantigen is only expressed on neoplastic cells, targeting it may allow for eradication of the mutant clone without compromising normal hematopoiesis

How et al. Blood. 2019.

Targeting mutant CALR: INCA033989

- Human monoclonal antibody
- Selectively targets mutant CALR
- Disrupts oncogenic signaling

- **Preclinical studies—**
  - INCA0339989 binds to human CD34+ cells expressing mutant CALR and inhibits their proliferation
  - In an MPN mouse model,
    - Treatment with INCA033989 prevents development of mutant CALR-driven elevation in platelet count
    - Lowered % of CALR-mutated precursor cells

- **Phase I, multicenter, ex-US—**
  - INCA033989 monotherapy or in combination with ruxolitinib in mutated CALR ET (and MF)
  - 2nd line +

- **Phase I, multicenter, US—**
  - INCA033989 monotherapy in mutated CALR ET (and MF)
  - 2nd line +

Reis et al. Blood. 2024.

Targeting mutant CALR:

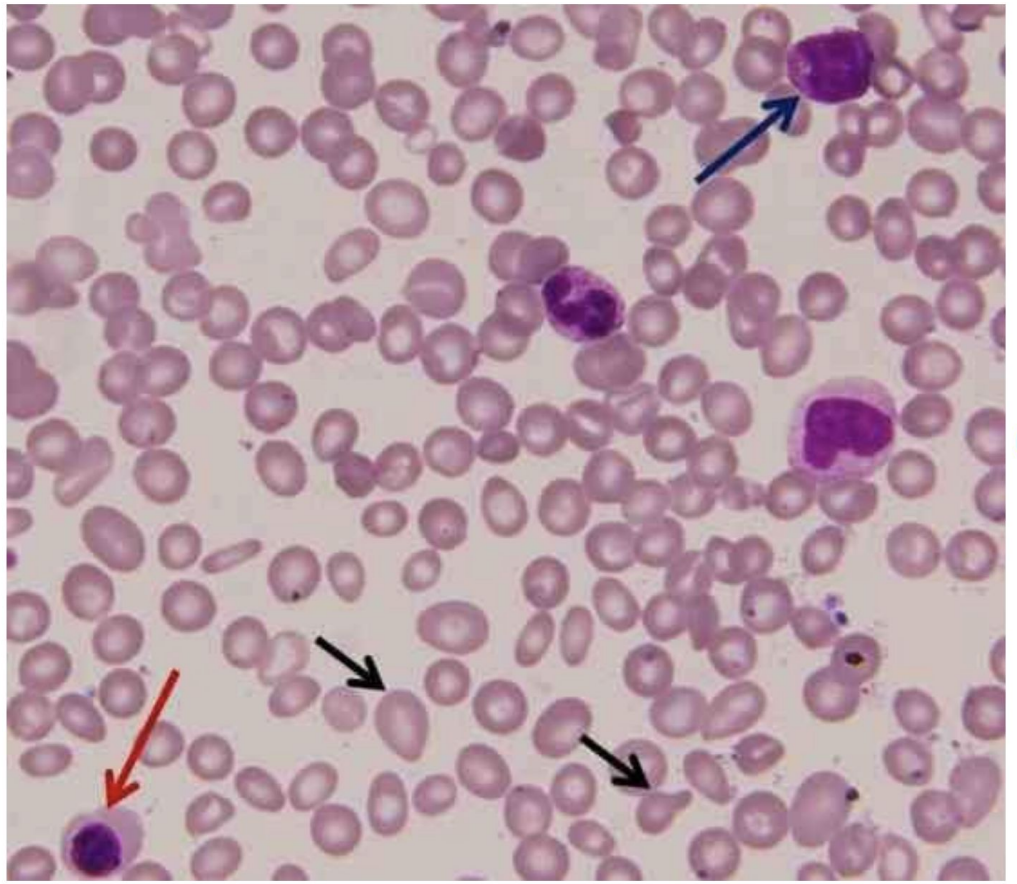
- **NCT05025488—**
  - Mutant CALR-peptide based vaccine in patients with mutated CALR MPNs
  - High risk ET, HU failure or intolerant

- **NCT06150157—**
  - First-in-human study
  - Safety, PK, and PD of JNJ-88549968, a T-cell redirecting bispecific antibody for mutated CALR MPNs

Post-ET myelofibrosis:

- <10% risk of transformation to MF

Post ET MF
Required: 1. Prior documentation of WHO defined ET 2. Bone marrow fibrosis grade 2 or 3
Additional criteria (2 required): 1. Anemia and >2g/dl decrease in hb 2. Leukoerythroblastic blood smear 3. Increase in palpable splenomegaly 4. Development of constitutional symptoms 5. Elevated LDH



Leukoerythroblastic blood picture. Peripheral smear shows presence of nucleated red cells (red arrow), metamyelocyte (blue arrow) and tear drop cells (black arrow).

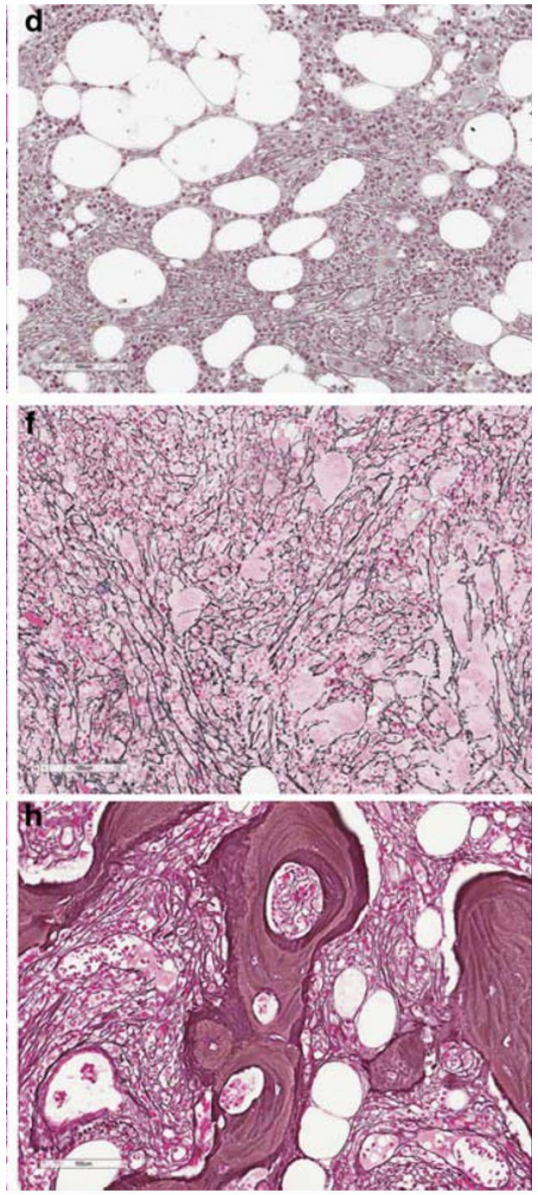
Constitutional symptoms:

- >10% unintentional weight loss in 6 months
- Night sweats
- Unexplained fever

ASH Bank.

Post-ET Myelofibrosis:

- Bone marrow biopsy—



Grade 1

Grade 2

Grade 3

ASH Bank.

ET: Young patients

- ET is the most common type of MPN to be diagnosed in Adolescent Young Adult (AYA) patient population (15-39yo)
- More triple negative cases (lower risk of thrombosis)
- More venous thrombosis in atypical locations (splanchnic vein, cerebral vein)
- Estrogen-containing contraception generally not recommended
    - Has been associated with increased venous thrombosis
    - vs estrogen being used for hormone replacement therapy in menopause usually lower doses and thus likely okay

Gangat et al. Cancer. 2006.

ET: Pregnancy

- Increased risk of 1st trimester miscarriages, preterm delivery, and small-for-gestational age infants
- Therapeutic impact of aspirin, low molecular weight heparin (LMWH), and Interferon (IFN) on fetal and maternal outcomes in pregnant women with ET must be interpreted with caution
- No controlled studies to allow for an informed strategy
- There is some data indicating low dose aspirin reduces risk of 1st trimester fetal loss
- If cytoreductive agent is needed, IFN is considered safe
- If history of pregnancy loss, can consider IFN and low molecular weight heparin (LMWH)
- If hx of vascular event, IFN and consider LMWH

ET: Other issues

- Need for cytoreductive therapy if thrombotic event is splanchnic vein thrombosis is not clear
- Direct oral anticoagulants (DOAC=Eliquis or Xarelto) likely safe
- Benefit of continuing aspirin if on a DOAC (ie for atrial fibrillation) likely outweighed by risk of bleeding

Conclusions:

- Essential thrombocythemia is a neoplasm that overall has a good prognosis
- Does need to be followed and managed carefully to minimize complications (clotting, bleeding) and to look out for progression/transformation
- We have some strategies to reduce risk of bleeding and clotting (aspirin, hydrea) but could use more
- We have some agents that seem to change the biology of the disease (interferon)
- But it has yet to be shown in ET whether this translates into something clinically meaningful
    - less thrombotic events
    - less bleeding events
    - less risk of progressing to MF or AML
    - longer overall survival
- Active investigation ongoing to see if interferons and other agents can accomplish this

- Thank you