Essential Thrombocythemia

Managing and Thriving in 2023

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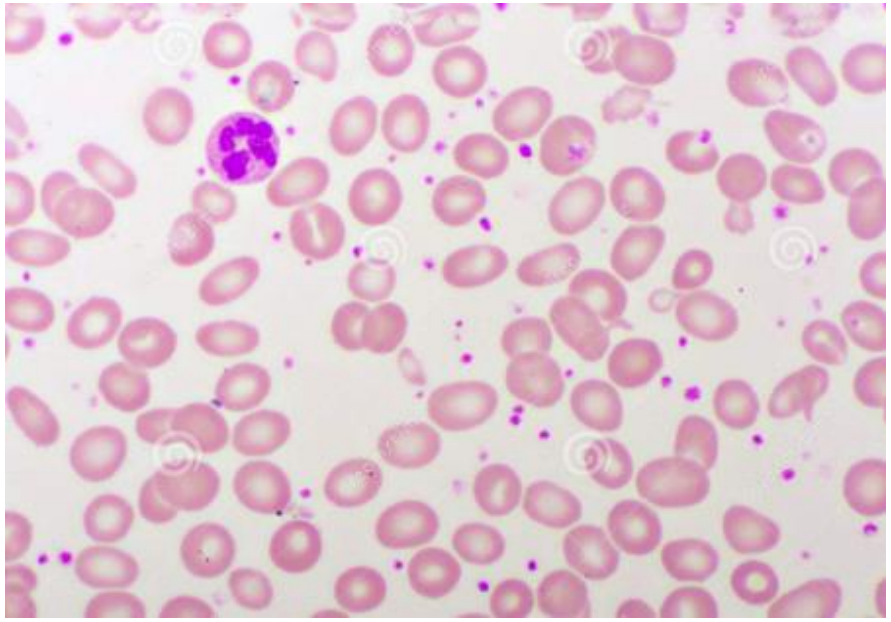
- Advisory/Consulting: Incyte, Curio, Abbvie, Celgene, Sierra Oncology, Nkarta
- Other: ABIM, American Society of Hematology

Topics to Cover Today

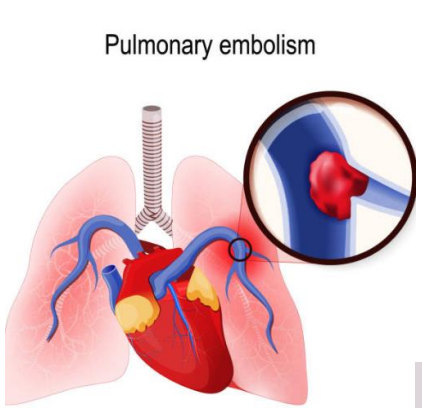
- Presentation and Diagnosis
- Risk Stratification
- Treatment Options
  - Standard of Care
  - Clinical Trials

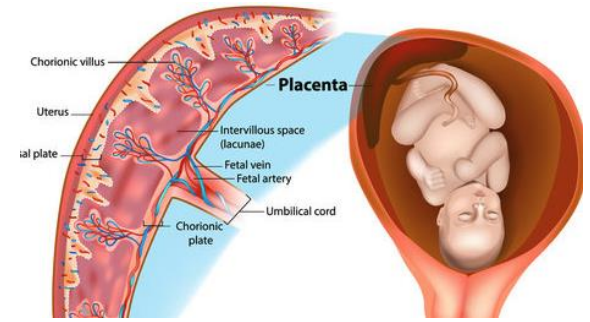
Presentation

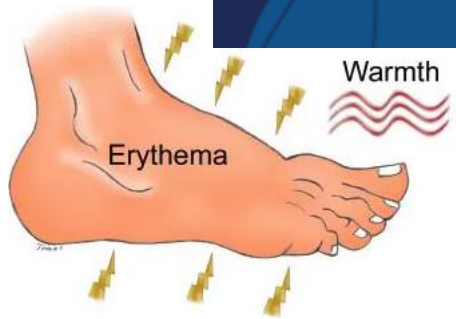
“Incidental Finding”



“Symptomatic Presentation:







History/Physical Exam	Clotting, Obstetric, CVD, Family History	Transfusion History	Organomegaly, Skin
Laboratory Workup	CMP, CBC + Diff, LDH, Uric Acid, Iron Studies, EPO level, Coagulation Testing	Molecular Studies (Blood): BCR/ABL PCR, JAK2V617F with reflex for CALR/MPL	Molecular Studies (Blood) for Myeloid Mutations (prognostic)
Marrow biopsy and aspiration	Morphology, Flow and Cytogenetics, Reticulin	Karyotyping	
Special Circumstances: Eosinophilia, T-cell population on Flow	Tryptase (serum) IHC for CD117, CD25	Cytogenetics for PDGFRa/b; FGFR1; ABL1	

Diagnostic Criteria: Essential Thrombocythemia

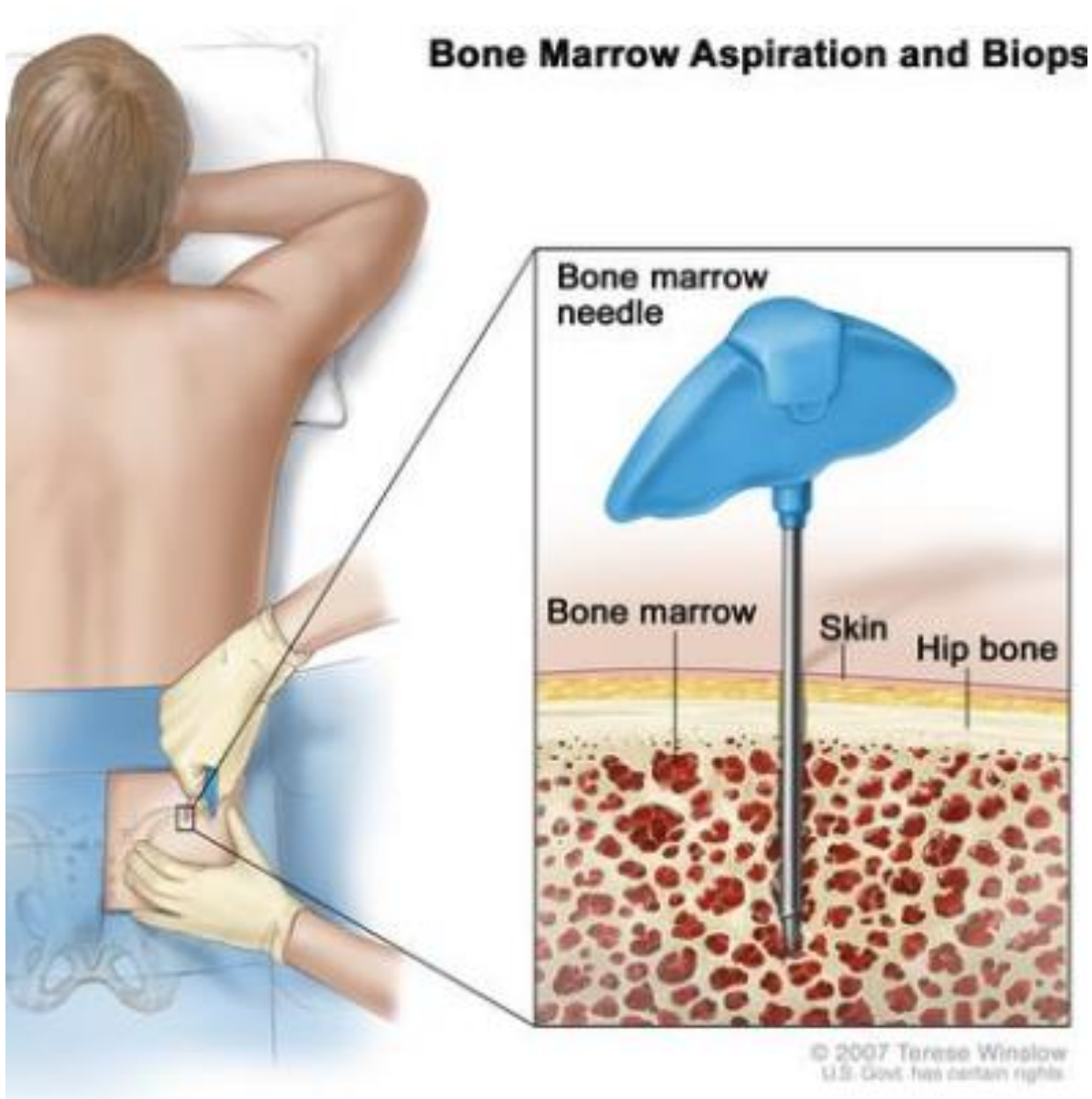
Major criteria

- ❑ Platelet count ≥450 x 10^9/L (≥450,000/microL)
- ❑ Stereotypic BMBX
- ❑ No criteria for *BCR-ABL1*-positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, myelodysplastic syndrome, or other myeloid neoplasm
- ❑ *JAK2*, *CALR*, or *MPL* mutation

Minor criterion

- ❑ Another clonal marker **or** no identifiable cause of thrombocytosis (eg, infection, inflammation, iron deficiency anemia)

Arber et al., Blood 2016; 127:2391-2405;


Bone Marrow Aspiration and Biops
Bone marrow needle
Bone marrow
Skin
Hip bone
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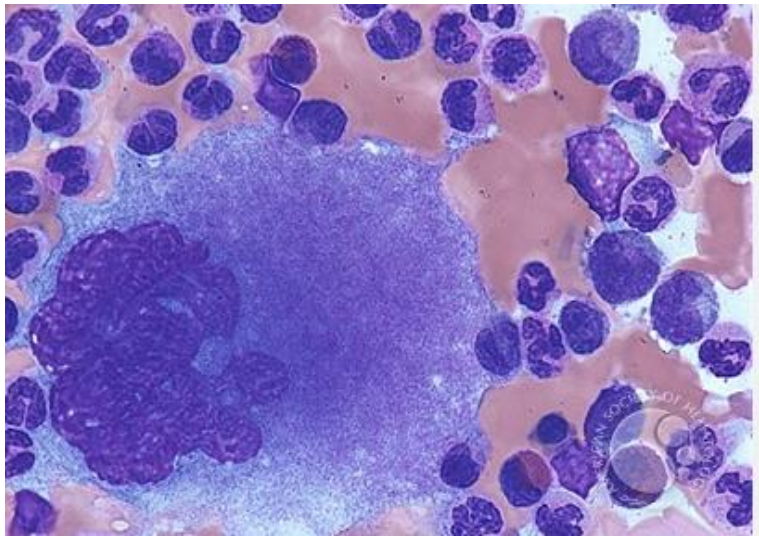

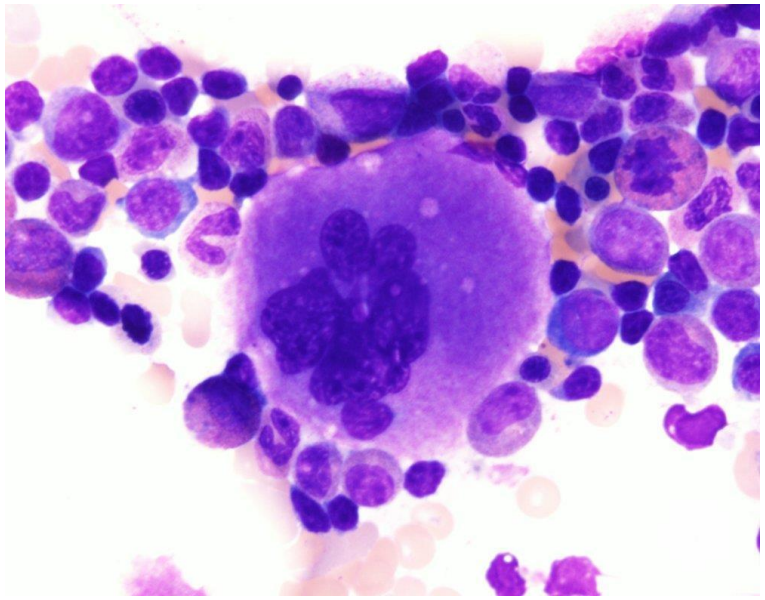

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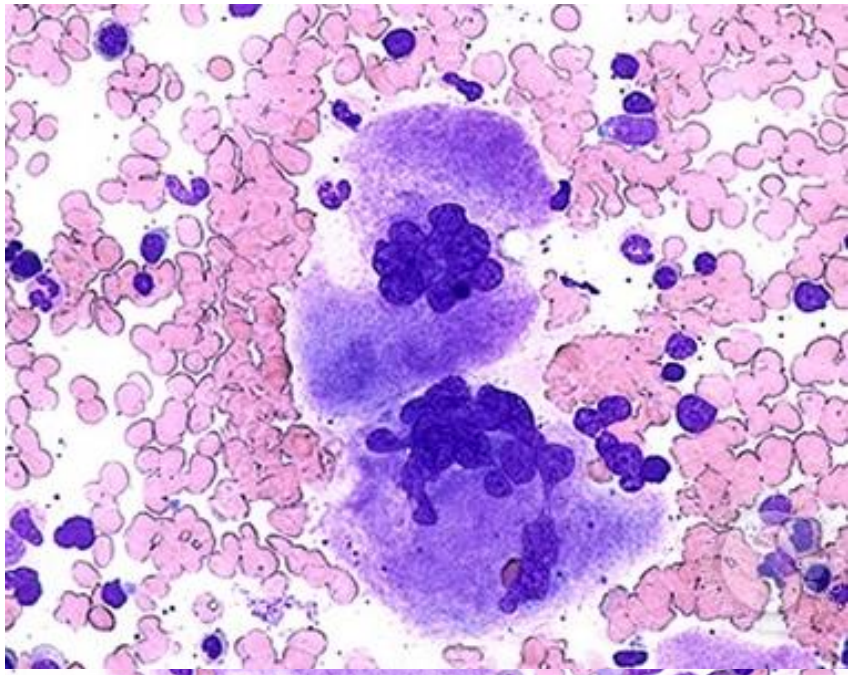
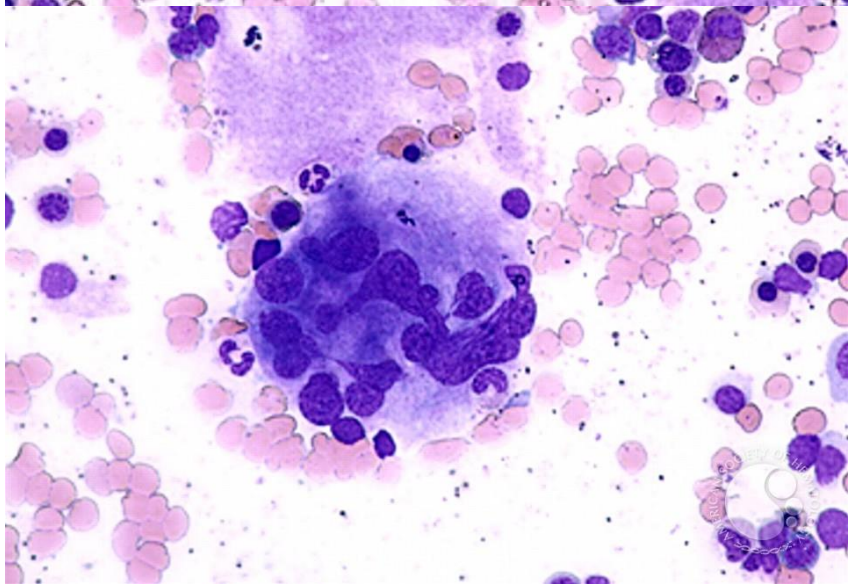
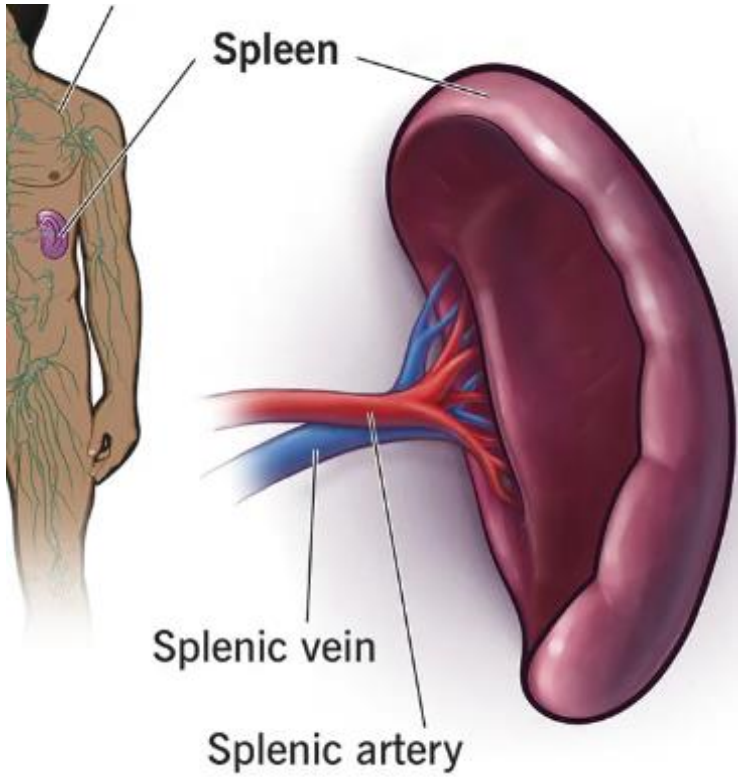
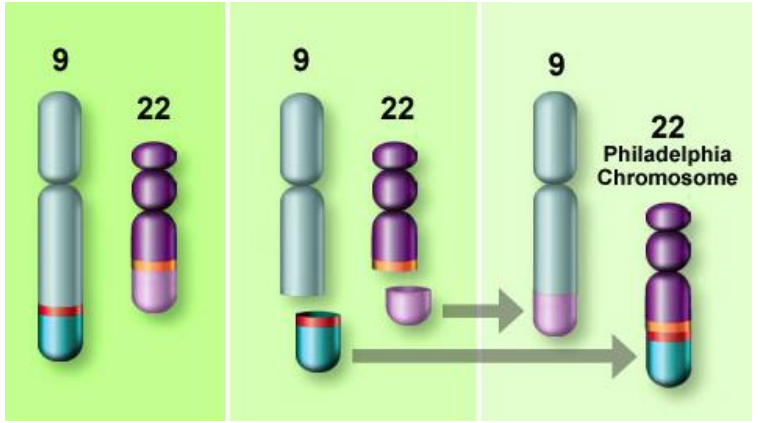





IRON


Spleen
Splenic vein
Splenic artery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Philadelphia
Chromosome

Imposters?

Prefibrotic/early PMF

Major Criteria – all three required for diagnosis
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 neoplasm
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 – one or more required for diagnosis
• Anemia not related to comorbid condition
• Leukocytosis>=11 X 10^9/L
• Palpable splenomegaly
• Elevated LDH

Arber et al., Blood 2016; 127:2391-2405;

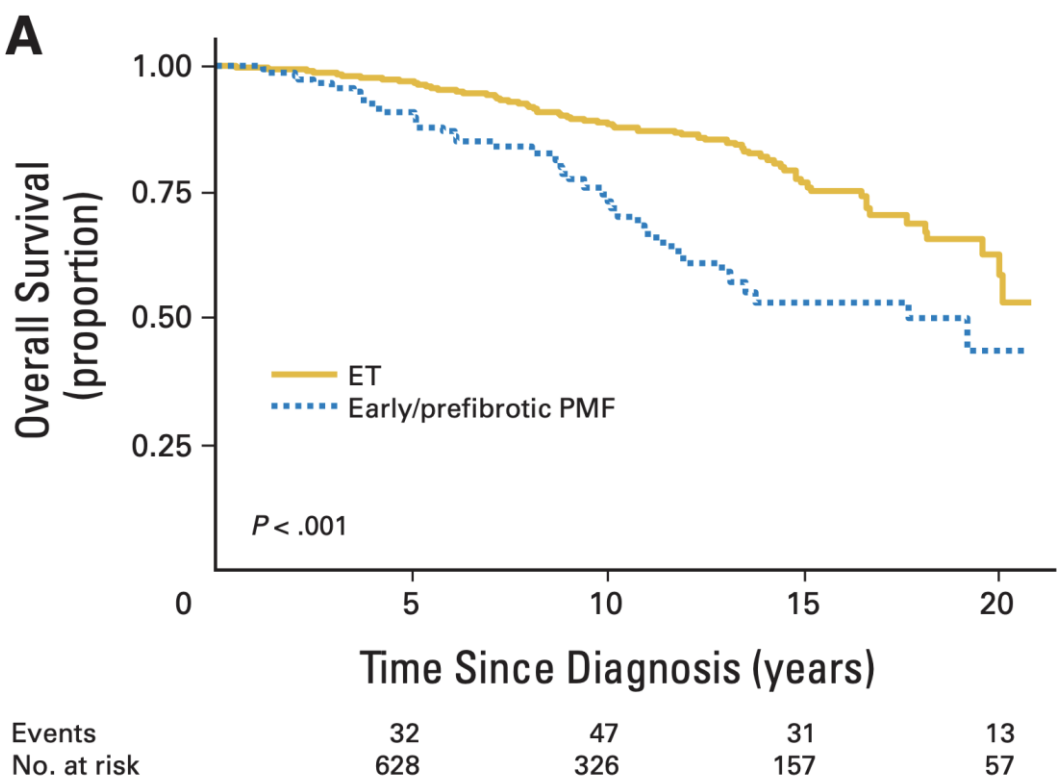
Natural History of Prefibrotic MF

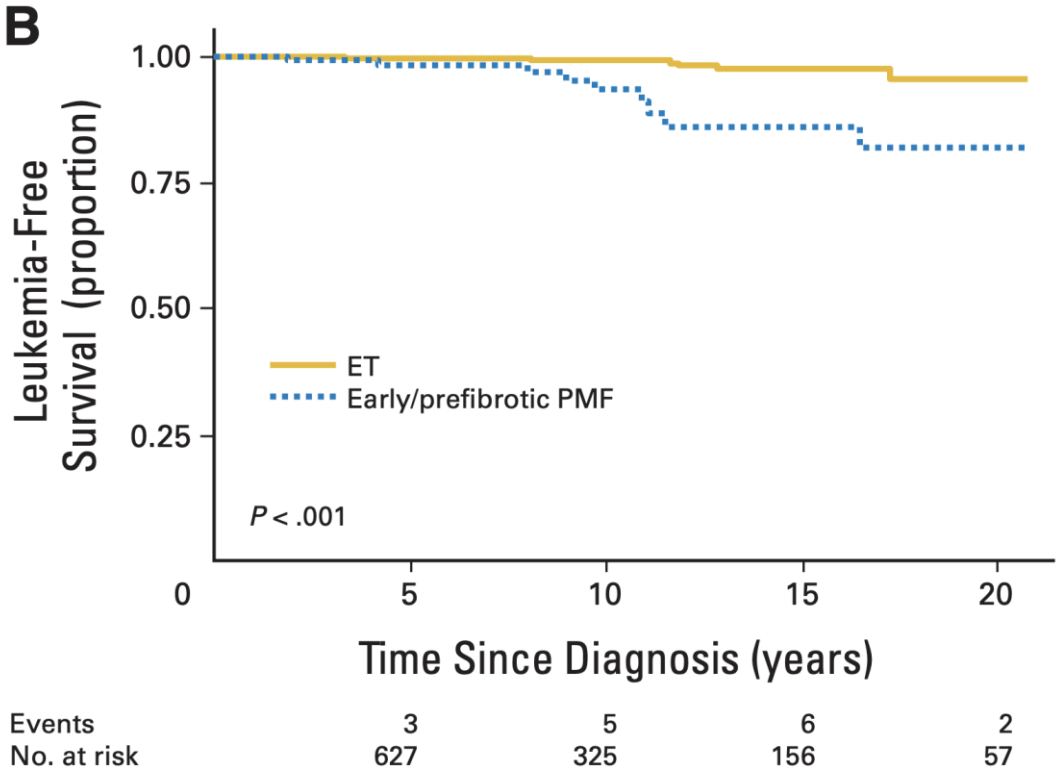
- Evolves over time to more fibrotic phenotype
  - 2003 study of 309 patients with 822 bone marrow samples
  - 67% had progression of fibrosis

- ET vs Prefibrotic MF
- A number of studies have investigated this comparison
  - 2011 International study of >1000 patients diagnosed with ET
  - Central re-review of all bone marrow biopsies
  - 16% reclassified as early/prefibrotic MF
  - In PMF, the 15-year survival was 59% compared to 80% in ET

Thiele et al., 2003 Leukemia and Lymphoma Barbui et al., J Clin Oncol 2011 29:3179-3184.

Prefibrotic MF vs. ET





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Diagnostic Pitfalls

Is the bone marrow sample sufficient?

Have driver mutations been identified?

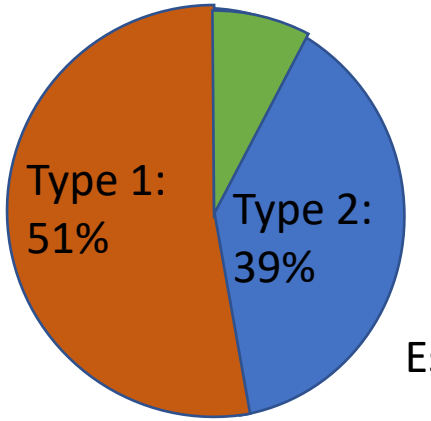
Is the patient triple-negative?

- Recheck for secondary causes of Essential Thrombocythemia
- Next generation sequencing should be performed

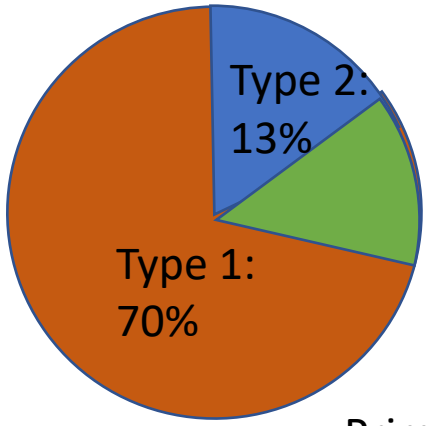
Essential Thrombocythemia

- Driver Mutations
  - *JAK2V617F:* 50-60% of cases
  - *CALR*: 20-25% of cases
    - Occur in *JAK2* negative disease
  - *MPL*: 2-3% of cases
  - "Triple-negative": 10-15%

- *CALR* subtypes
    - 52-bp deletion (type 1)
    - 5-bp insertion (type 2)



Essential Thrombocythemia



Primary Myelofibrosis

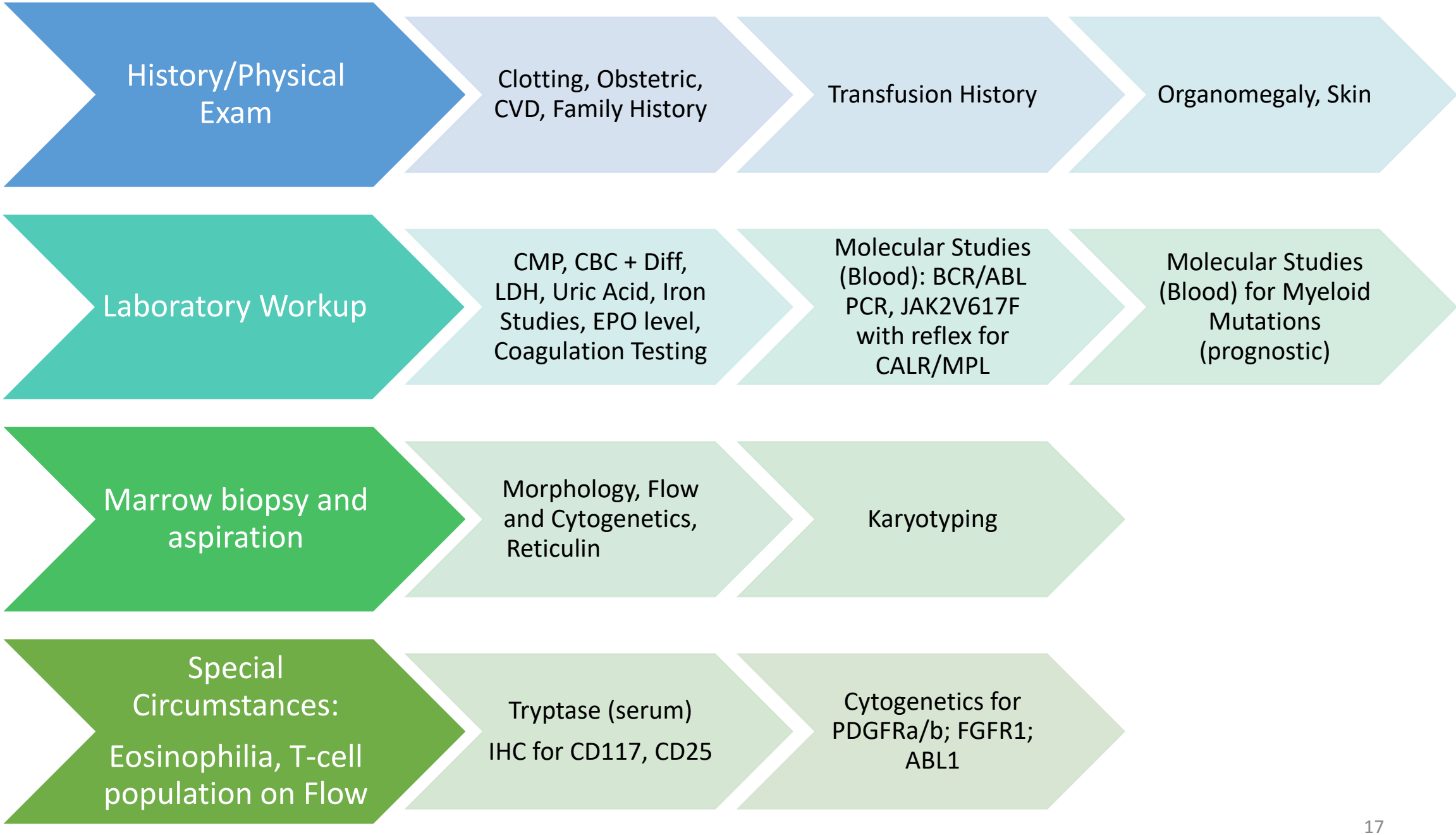
Cabagnols et al, Leukemia (2015) 29, 249-252

Prognostic markers: ET

Clinical	*CALR*	*JAK2V617F*
Platelet count	Higher	Lower
Hemoglobin	Lower	Higher
Leukocyte count	Lower	Higher
Vascular Risk	Lower	Higher
No significant impact on overall survival or myelofibrotic or leukemic transformation		

- Thrombosis Risk in ET
  - Multiple studies published
  - JAK2 mutated vs. Other
  - Risk for thrombosis twice as high (odds ratio range 1.83-1.92)
  - Increased for both arterial and venous thrombosis
  - Studies have not elucidated whether allelic burden matters

Falchi et al Leukemia (2017) 31, 1845-1854; Qin et al In J Hematol 2015; 102:170-180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Clotting, Obstetric, CVD, Family History
Transfusion History
Organomegaly, Skin
Laboratory Workup
CMP, CBC + Diff, LDH, Uric Acid, Iron Studies, EPO level, Coagulation Testing
Molecular Studies (Blood): BCR/ABL PCR, JAK2V617F with reflex for CALR/MPL
Molecular Studies (Blood) for Myeloid Mutations (prognostic)
Marrow biopsy and aspiration
Morphology, Flow and Cytogenetics, Reticulin
Karyotyping
Special Circumstances:
Eosinophilia, T-cell population on Flow
Tryptase (serum)
IHC for CD117, CD25
Cytogenetics for PDGFRa/b; FGFR1; ABL1

Topics to Cover Today

- Presentation and Diagnosis
- Risk Stratification
- Treatment Options
  - Standard of Care
  - Clinical Trials

Risk Stratification

- Risk of Which Consequence?
- Based on Which Patients?
- Patients treated When? With What?
- Helps determine the goals of treatment

Diagnosis: Essential Thrombocythemia

Potential Outcomes

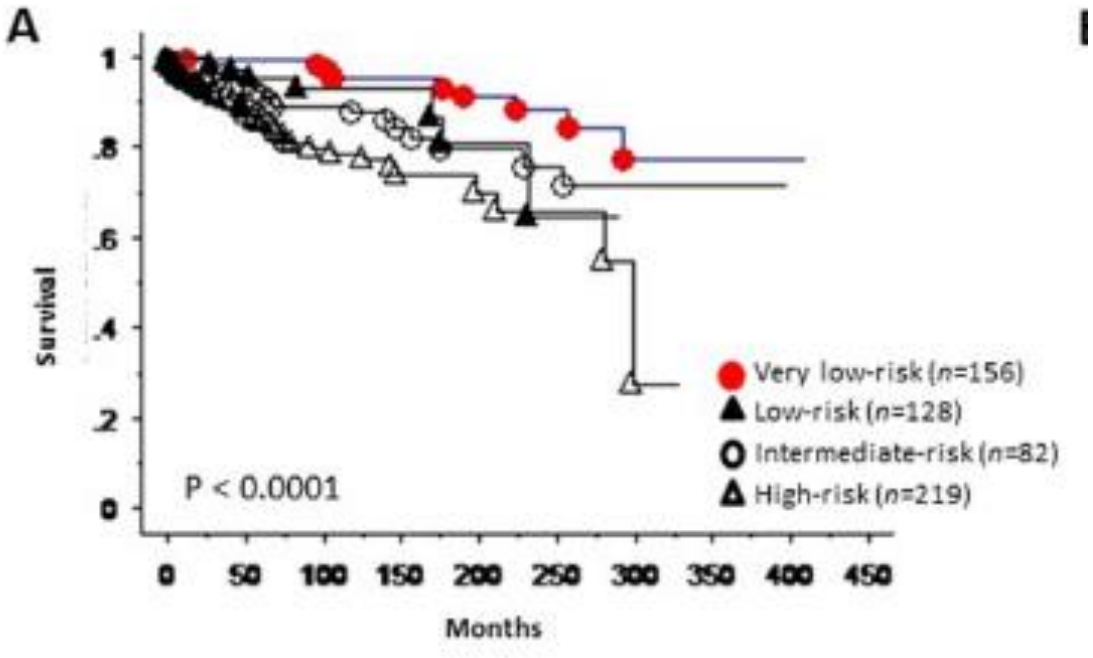
- Debilitating Symptoms
- Bleeding
- Venous or Arterial Blood Clot
- Transformation to Acute Leukemia
- Transformation to Post-ET Myelofibrosis
- None of the Above!

Revised International Prognostic Score for ET

(Haider er al., 2016)

Essential Thrombocythemia	
Age>59 years, CV risk factors Previous thrombosis Mut JAK2 V617F	
No factors	Very Low Risk
Mut JAK2 V617F	Low Risk
Age > 59 yrs	Intermediate Risk
Prior thrombosis or Age >59 yrs and mut JAK2V617F	High risk
Outcome: Thrombosis risk	

Thrombosis-free Survival



Thrombosis Risks

Revised IPSET-T Risk Group	Approximate Risk of thrombosis (%pts/year)
Very Low	0.4-0.6
Low	0.8-1.6
Intermediate	1.4-1.6
High	2.5-4

Clinical Conversations

- Key Lessons
  - This disease is indolent
  - Statistical Calculations Demonstrate: 15-year cumulative risk
    - 10-25% risk for thrombosis (Rumi et al, Blood 2014)
    - 10% for Transformation to Myelofibrosis (Pietra et al, Leukemia 2016)
    - 3% for Transformation to Acute Leukemia (Rumi et al, Blood 2014)
- Control What you Can:
  - Dyslipidemia, Hypertension, Smoking, Obesity
- Screen for other cancers
- Indolent is NOT the same as asymptomatic

Topics to Cover Today

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Therapeutic Considerations

Very Low Risk Disease

- Manage CV risk factors
- 40 to 100 mg/day orally, once twice daily for symptom management

Low Risk/Intermediate Risk Disease

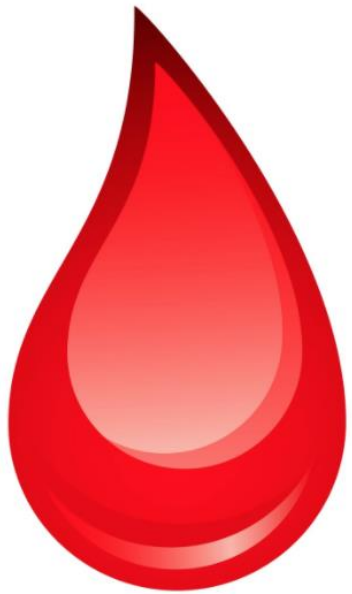
- Manage CV risk factors
- 40 to 100 mg/day orally, once or twice daily

Who should not take aspirin?

People with high bleeding risk

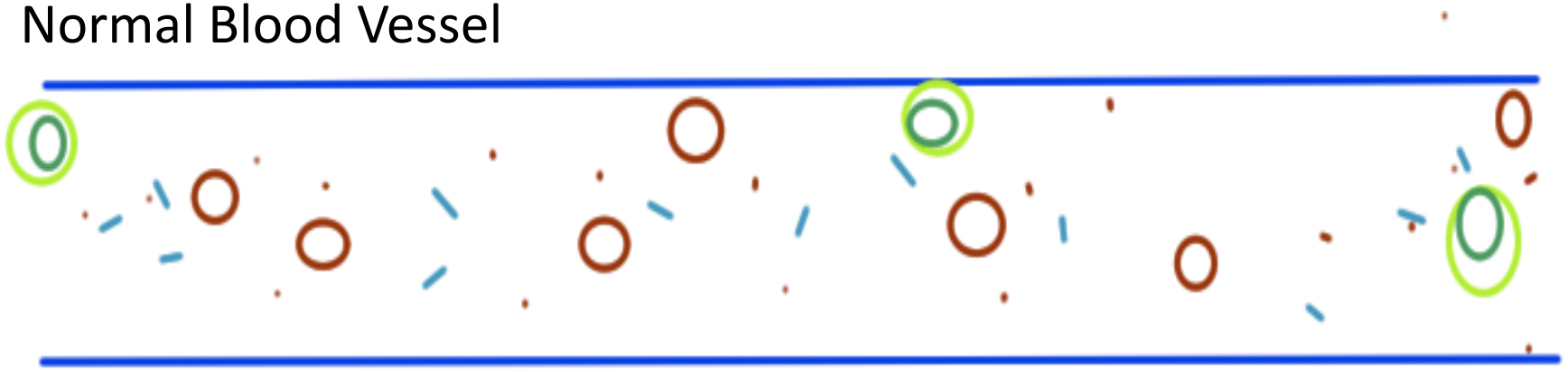
What about bleeding?

- Can occur in patients with very high platelet count, i.e. over 1.5 million/uL
- Typically what is called “mucocutaneous”
  - Gums, nosebleeds, hemorrhoids
- Called acquired Von Willebrand’s disease (VWD)
- Treatment
  - Pause aspirin therapy
  - Lower platelet count with cytoreduction

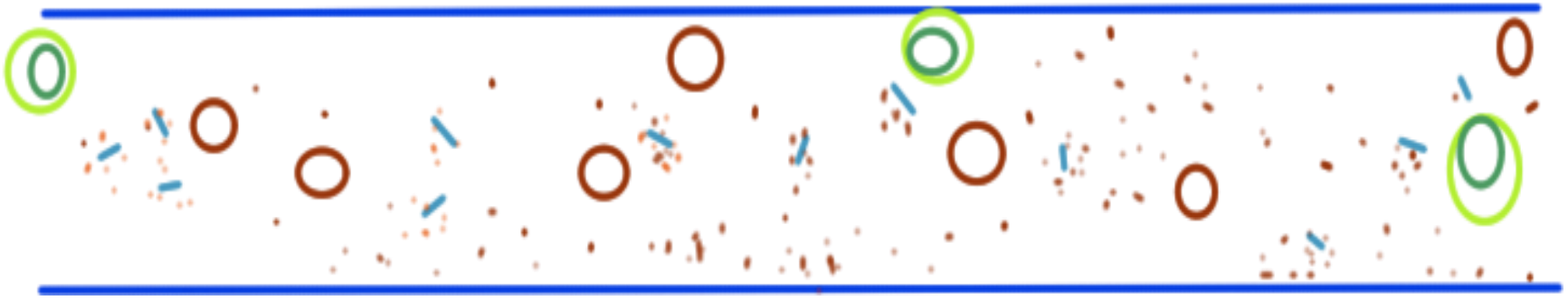


Acquired VWD

Normal Blood Vessel

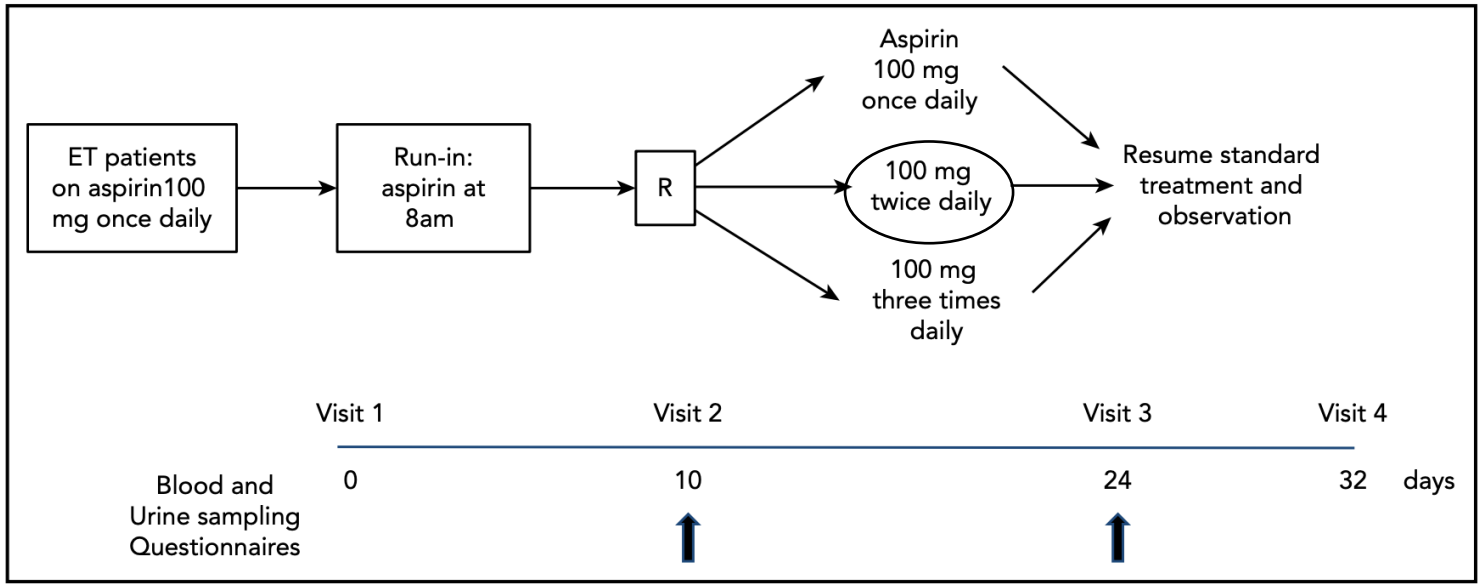


Increase in platelets



Once or Twice Daily Aspirin?

- Rocca et al., Blood 2020
- Recent study – primary outcome was measuring how well the aspirin worked to prevent clotting activities to the platelets
  - *Biomarker of serum thromboxane2*
  - *Did not look at patient events as a primary outcome*



Upfront Therapy

Hydroxyurea

- HU vs Placebo -- Cortelazzo NEJM 1995
- HU vs Anagrilide – Harrison NEJM 2005

Pegylated Interferon

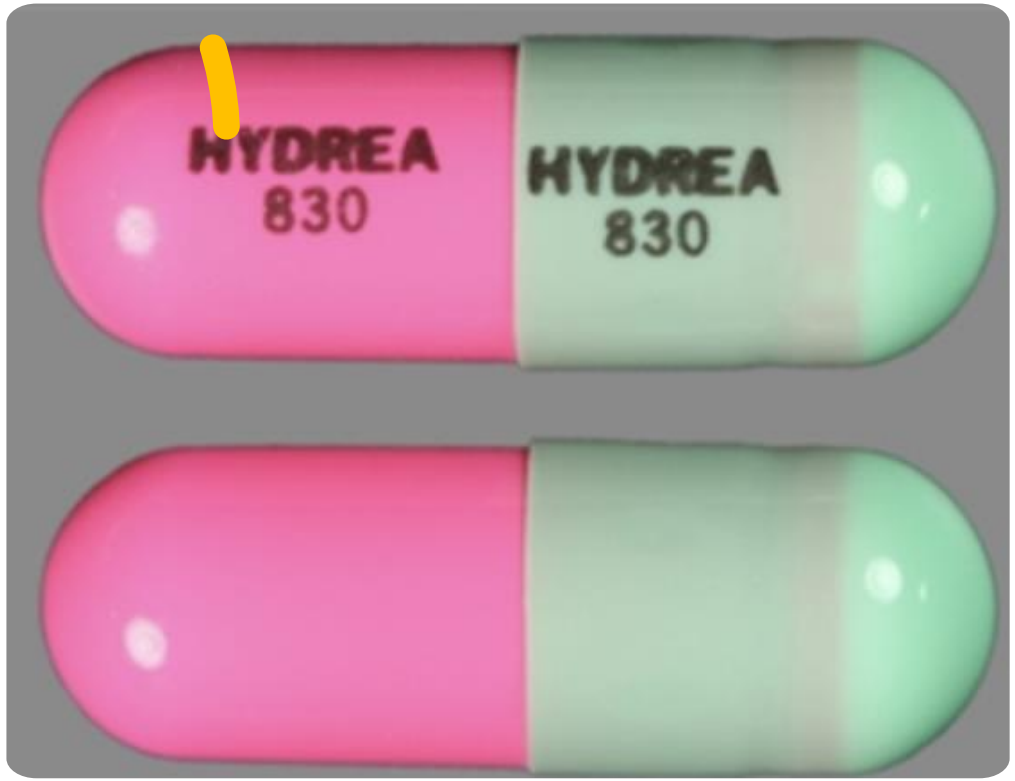
- Single-arm studies
  - Phase II trial – Masarova et al., Lancet Onco. 2017
  - Langer et al., Haematologica 2005
  - Cassinat et al., NEJM 2014
- Phase III Interferon vs HU Mascarhenas et al., Blood Advances 2022

Anagrelide

- HU vs Anagrilide – Gisslinger Blood 2013

Cytoreduction: Hydroxyurea

- Effective
  - Reduces platelet counts rapidly
  - Reduces thrombotic risk
  - Generally well tolerated
- Initial dose
  - 15mg/kg/day
  - Adjust for a platelet dose of <400K/mL
  - Avoid neutropenia and anemia

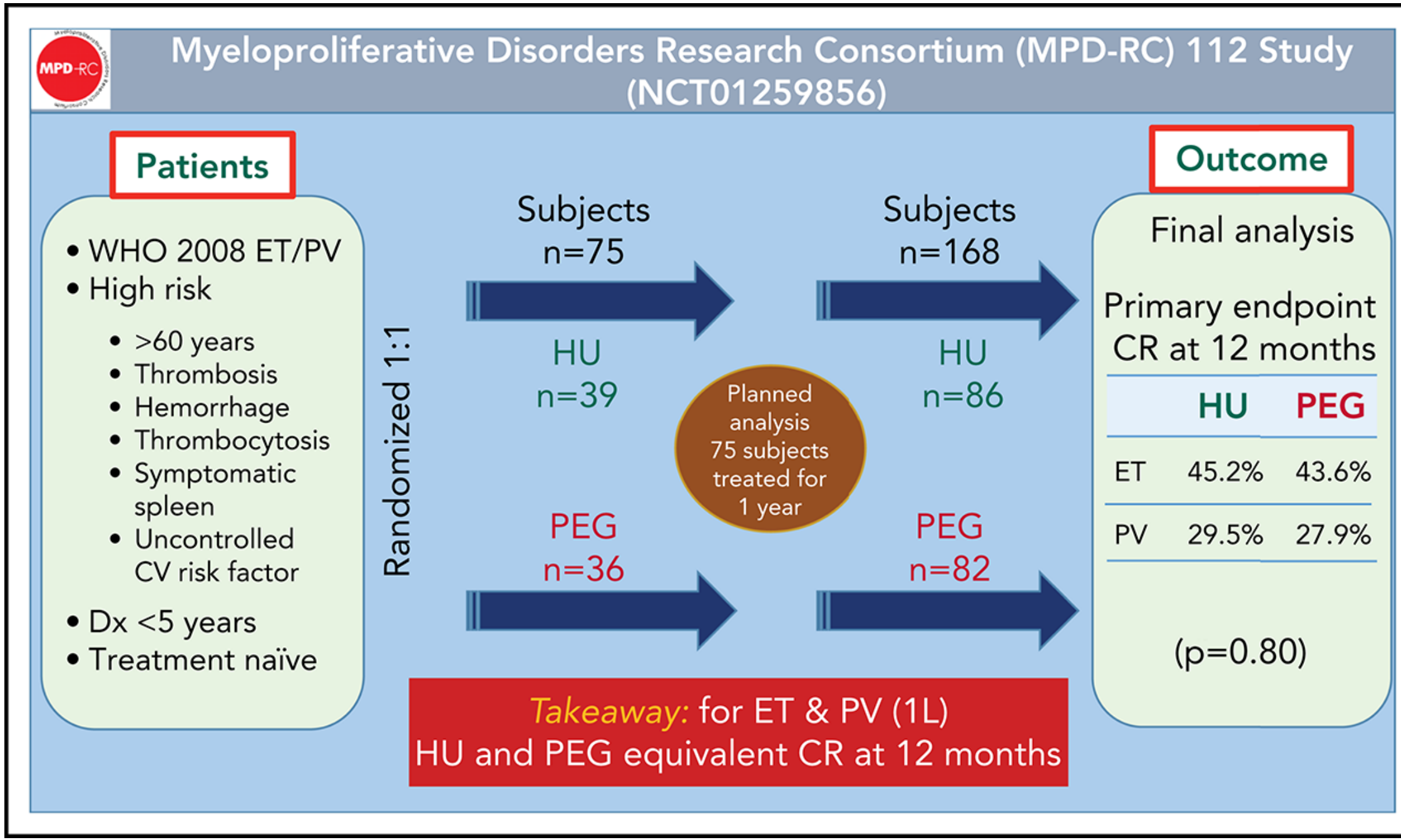


Anagrilide

- Works in a different way than hydrea
- 0.5 mg several times a day depending on dose
- Good control of platelets – some people tolerate this medication well
- Headaches
- Cardiac toxicity can occur (rare)
- Fibrosis of the marrow can occur

Interferon

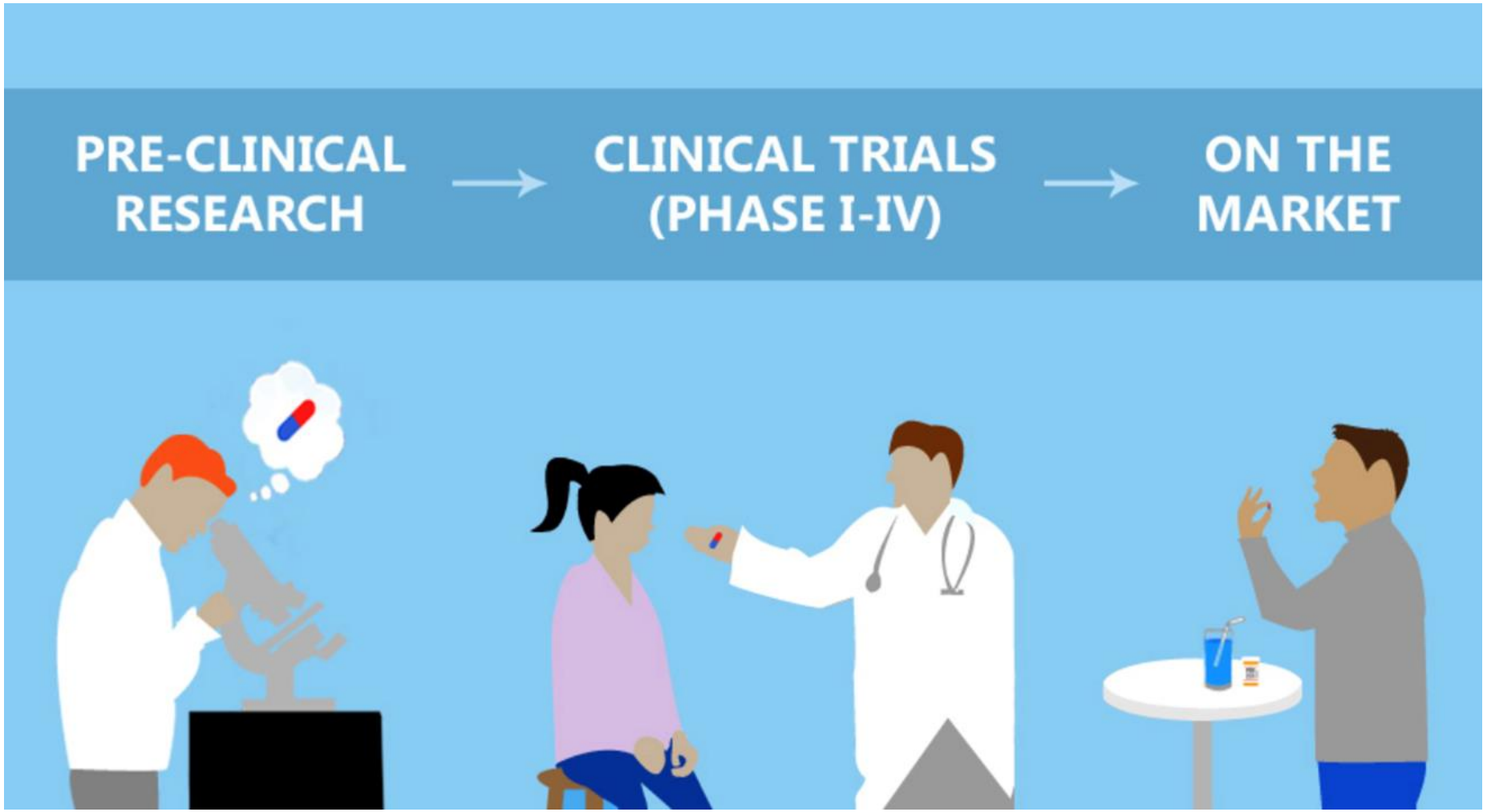
- Once weekly injection (Ropeginterferon is twice monthly)
- Anti-angiogenic, anti-proliferative, pro-apoptotic, immunomodulatory, and differentiating properties


Myeloproliferative Disorders Research Consortium (MPD-RC) 112 Study
(NCT01259856)
Patients
• WHO 2008 ET/PV
• High risk
• >60 years
• Thrombosis
• Hemorrhage
• Thrombocytosis
• Symptomatic spleen
• Uncontrolled CV risk factor
• Dx <5 years
• Treatment naïve
Randomized 1:1
Subjects n=75
HU n=39
PEG n=36
Planned analysis 75 subjects treated for 1 year
Subjects n=168
HU n=86
PEG n=82
Outcome
Final analysis
Primary endpoint CR at 12 months
HU PEG
ET 45.2% 43.6%
PV 29.5% 27.9%
(p=0.80)
Takeaway: for ET & PV (1L) HU and PEG equivalent CR at 12 months

Take Home Lessons

- Hydroxyurea, Anagrilide and Interferon all have a role in the treatment of this disease
- There is randomized data that Interferon and Hydroxyurea control blood counts at the 12-month mark
- Long term risks for skin cancers, immune complications have to be discussed
- This is a good discussion to have with your physician

When to consider a clinical trial?


PRE-CLINICAL RESEARCH
CLINICAL TRIALS (PHASE I-IV)
ON THE MARKET

Phases of Clinical Trials

Phase I

Healthy volunteers or patients to determine safety and tolerability. Drug doses start low and are escalated in additional cohorts of patients until dose-limiting toxicities are observed. A recommended phase II dose is determined.

Phase II

Initial reading of efficacy and to further explore safety in small numbers of patients.

Phase III

Large, pivotal trials to determine safety and efficacy in large numbers of patients in order to obtain drug approval. These are often randomized trials of the drug vs. placebo, best available therapy, or a prior standard of care.

(Phase 4): These are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies

MAJIC-ET: Ruxolitinib in ET

- 110 patients
- All had ET and their disease had failed hydrea
- All needed treatment
- Half got Ruxolitinib, half were treated with “best available therapy”
- Monitored for “CR” and ”PR”

	RUX	BAT
CR	46.5%	44%
CR+PR	93%	96%

- Both arms achieved some symptom response
- Rux patients had deeper symptom relief and it lasted longer

Ruxolitinib in ET: MAJIC trial

- *In conclusion, the MAJIC-ET trial suggests that ruxolitinib does not have improved treatment efficacy compared with BAT for most clinically relevant events.*
- *Symptom responses were superior with ruxolitinib therapy*
- *… there was no difference in this study for control of blood counts or other relevant endpoints, such as transformation, thrombosis, or hemorrhage.*

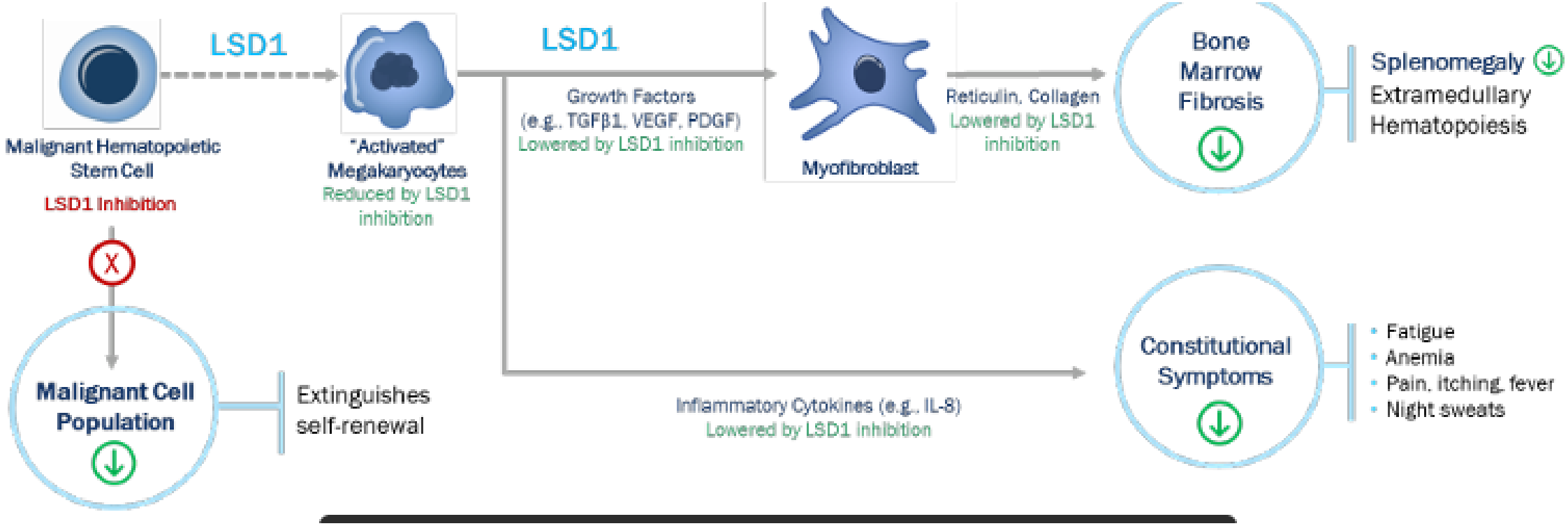
Ropeginterferon Alfa-2b

- Studied already in Polycythemia Vera
- Now there are ongoing trials for treatment of ET
- How is it different from pegylated interferon
  - Longer lasting
  - Shares antiviral, antiproliferative, anticancer, and immune-modulating effects with Pegylated interferon

- Why might Interferon work?
  - PEG-IFN-alpha-2a studied at MD Anderson
  - Overall hematologic response rate = 81% in ET
  - Molecular response rate 38% in ET
  - Decent tolerability

IMG-7289 (Bomedemstat)

- Lysine-Specific demthylase 1(LSD1) demythylates chromatin-associated proteins
- Loss of LSD1 activity is associated with loss of self-renewal in malignant HSCs
- Inhibiting LDS1 can reduce hallmark symptoms of MPNs



Gill et al., EHA 2021

Data in Essential Thrombocythemia

Phase 2 Study of IMG-7289 in Patients with Essential Thrombocythaemia *(NCT04254978, International Study)*

Primary Endpoints:

- Safety and tolerability
- Platelet count reduction (≤400 x 10^9/L) in the absence of thromboembolic events

Exploratory Endpoints:

- Durability of platelet and WBC count reduction
- Changes in cytokine profiles
- Symptom reduction (MPN-SAF TSS)
- Changes in mutant allele frequencies (MAF)

Key Eligibility Criteria:

- Dx of ET
- High-risk classification
- Failed at least one standard therapy
- Platelets >450 x 10^9/L
- Peripheral blasts <1%
- Fibrosis Score <2 per protocol criteria

  (Arber et al., 2016)
- Haemoglobin >10 g/dL

Latest Report: Palandri et al., June 2022

Number Enrolled	44
Median age (years)	68 (42-92)
Med TSS (baseline)	15 (0-74)
Adverse Events	
Dysgeusia	52%
Fatigue	34%
Constipation	32%

- Median time on treatment = 29 weeks
- If treated > 12 weeks, 91% (31/34) achieved target platelet count
- If treated >24 weeks, 83% achieved a durable response.
- Responses noted in TSS and in allele frequencies
- 84% remain on study at censoring date

Navitoclax

- Oral, bioavailable BCL-2 inhibitor
- High affinity for BCL-2 anti-apoptotic proteins
- Clinical trials have demonstrated diminished platelet counts as a regular effect
- Published data on benefit in patients with PMF no longer benefiting from JAK-inhibition

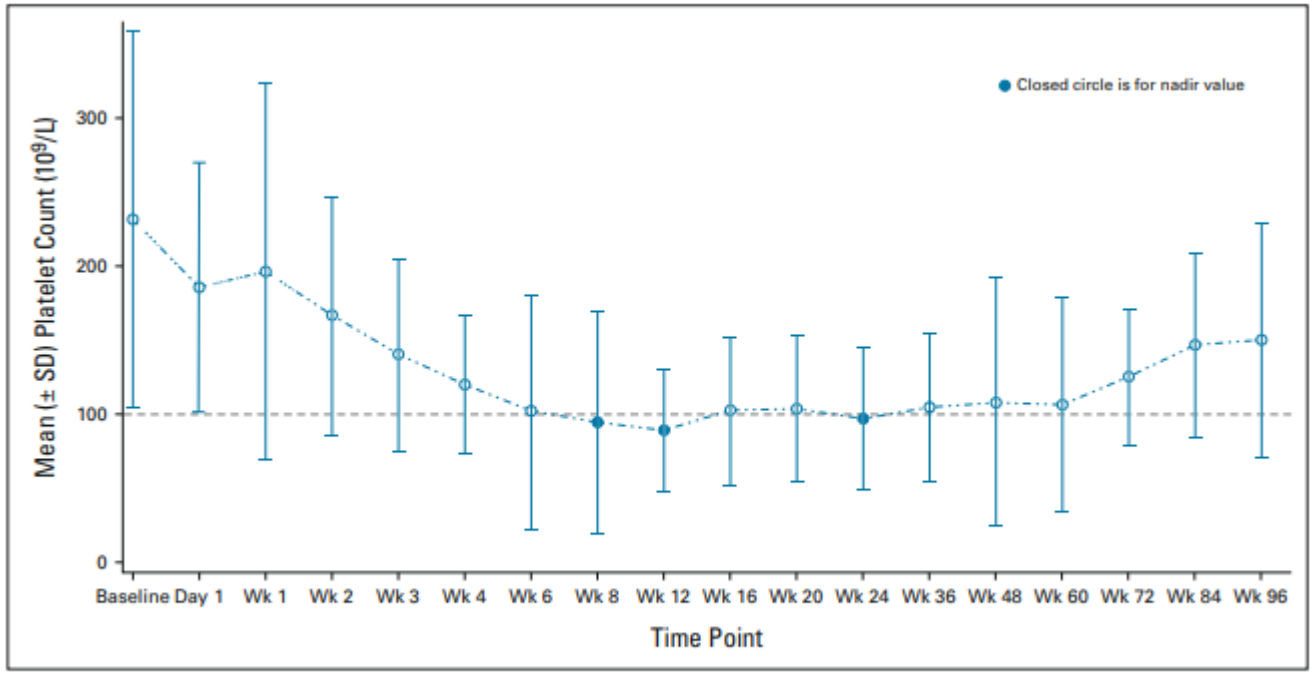


FIG 3. Mean platelet count over time. Platelet nadir was defined as $< 100 \times 10^9$ cells/L as indicated by the dashed line. SD, standard deviation; Wk, week.

A note on blood thinners….

Direct Oral Anticoagulants (DOACs) in MPNs

- Convenient
- Current randomized trial (AIRPORT MPN NCT NCT04243122) will randomize patients to apixaban vs aspirin
- But what about secondary prophylaxis?
  - Recent systemic review *(Baysal et al., Expert Rev Hematology, Feb 2023)*
  - 11 Studies, 944 patients – Not high quality data
  - Initiation of DOACS
    - Secondary prophylaxis for thrombosis (arterial or venous)
    - Atrial fibrillation (AF)
    - Recurrent throbotic event rate 8.9%
  - ISTH Analysis *(Barbui et al., Res Prac Thromb Haemost 2022)*

TABLE 1 Incidence rate of recurrent thrombosis and bleeding in MPN patients with DVT at common sites or with splanchnic vein thrombosis treated with VKAs or DOACs

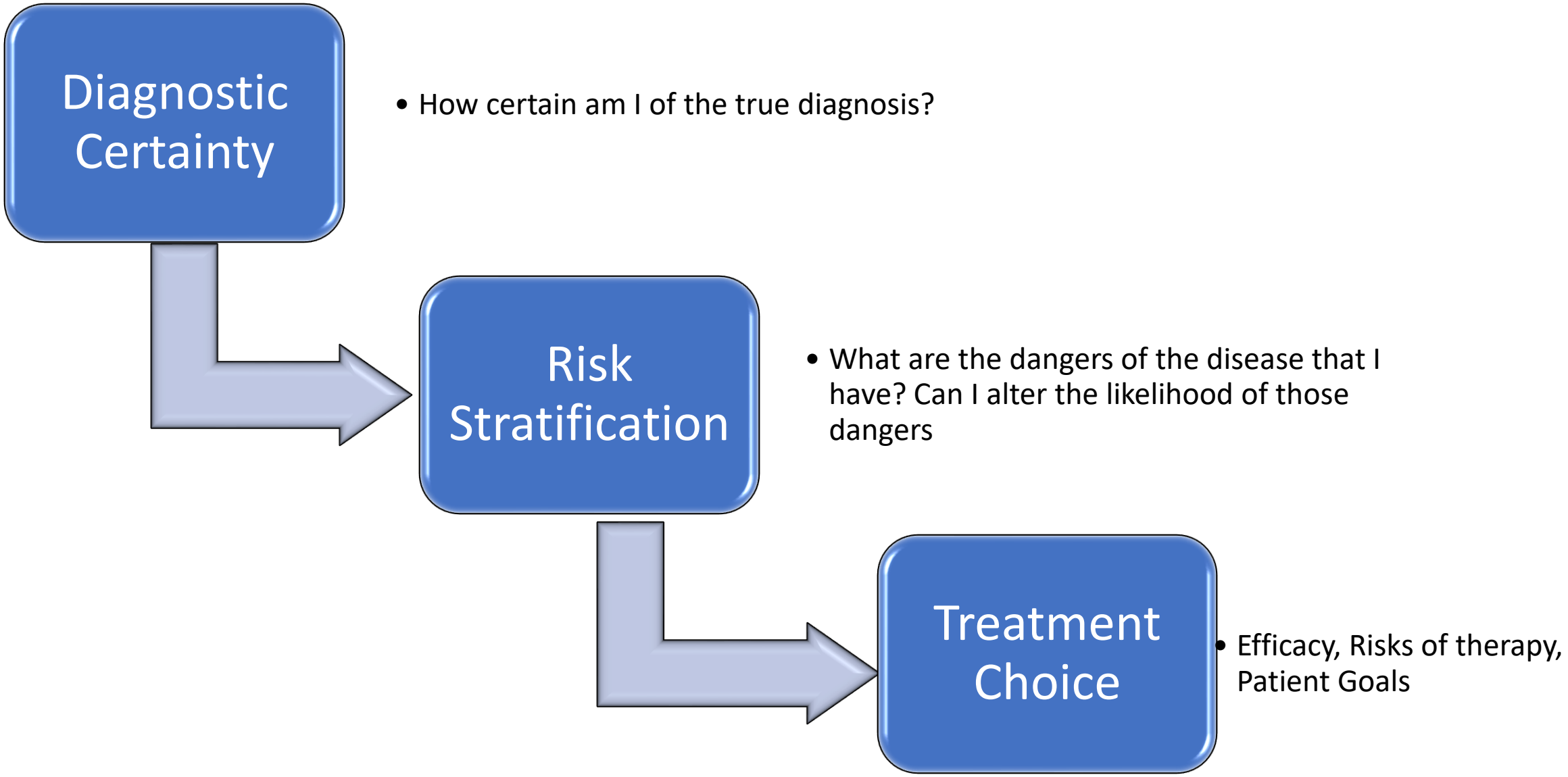
Treatment	Patients (*N*)	IR of recurrent thrombosis /100 person-years (95% CI)	IR of bleedings /100 person-years (95% CI)
VKAs60	DVT of legs ± PE (206)	5.3 (3.2–8.4)	2.4 (1.1–4.5)
DOACs67	DVT of legs ± PE (158)	4.5 (2.9–6.8)	2.7 (1.4–5.2)
VKAs62	SVT (139)	3.9 (2.4–5.8)	2.0 (1.1–3.5)
DOACs67	SVT (51)	3.2 (1.2–8.6)	0.8 (0.1–5.5)

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; IR, incidence rate; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; VKA, vitamin K antagonist.

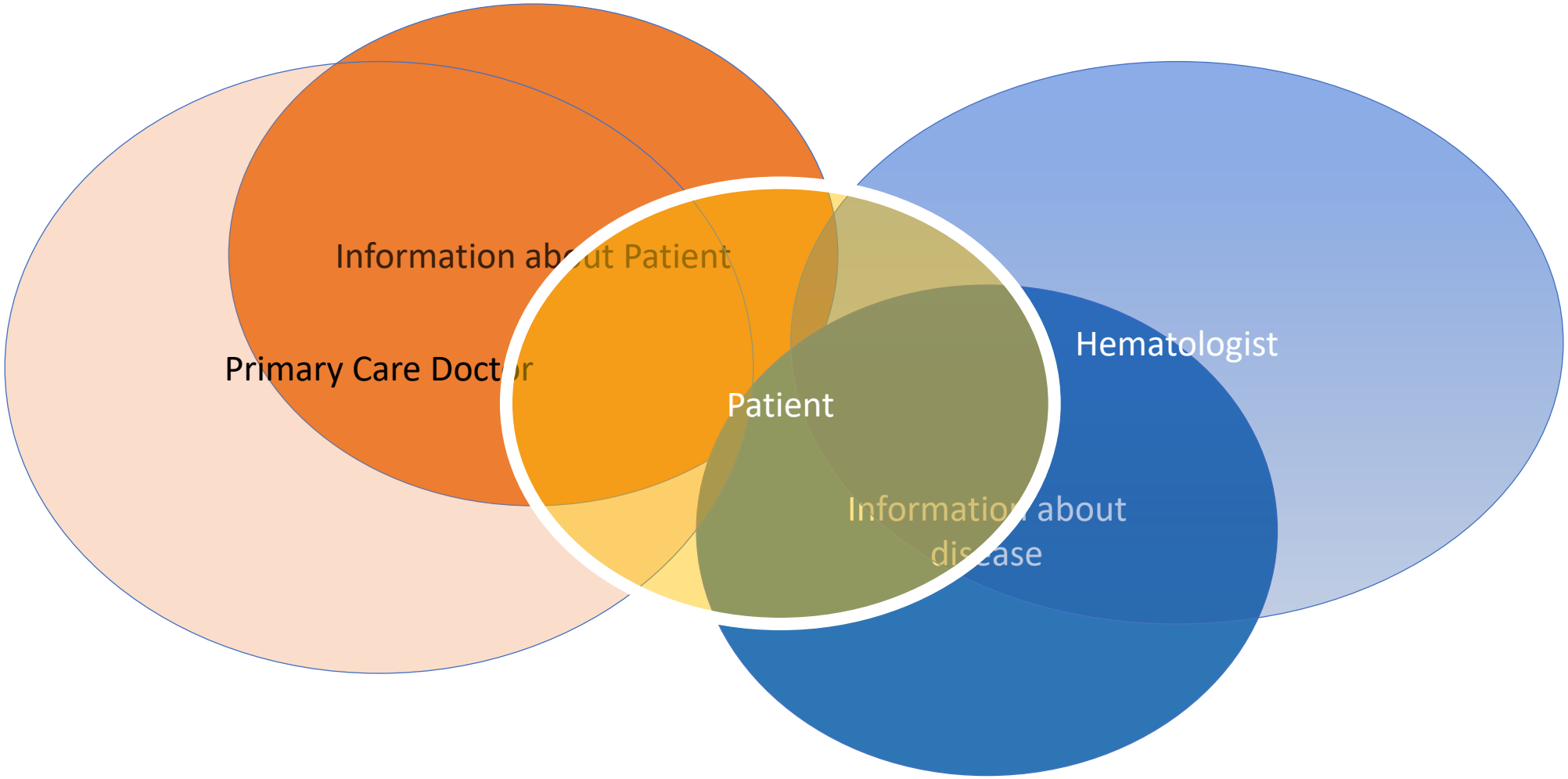
Topics to Cover Today

- Presentation and Diagnosis
- Risk Stratification
- Treatment Options
  - Standard of Care
  - Clinical Trials
- Conclusions

Remember the basics



Communication



Provider Collaboration

- Communication between providers critical
- Lots of ways you can facilitate
  - Keep your own records to bring back and forth
    - i.e. information about labs, clinical trials
  - Ask about sharing EMR
  - Encourage communication
  - Work with ancillary staff
  - Engage in your care
- Any other suggestions?

Control what you can

"You're fifty-seven years old. I'd like to get that down a bit."

Other cancers?

- Slightly increased risk for solid tumors
  - Italian Study
    - Roughly 4 times as likely to acquire lymphoma-type diseases
  - Danish Study
    - Incidence of solid tumors slightly higher in patients with ET, PV and CML
  - Swedish Study
    - Increased incidence of thyroid and parathyroid cancers and skin cancers
  - MD Anderson Study
    - Statistically significant increase in solid tumors

Preventative Health

- Everybody
  - No tobacco
  - Good sun protection; Regular skin evaluations
  - Healthy diet; Weight control
  - Limit alcohol
- Age-specific (start date depends on family history)
  - Mammogram, colonoscopies, PAP smears, prostate exams
  - Low-dose CT scans if smoker

Thank You to YOU

For all you've done to advance this field and improve the future for one another and for those who get these diseases in the future

Happy to take any questions