Prognosis & MPN Management in 2013

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Understanding MPN Therapy Options

- Prognosis and Goals (Mesa & Camoriano)
- Evolving Rx ET (Vannucchi)
- PV (Silver)
- MF
  - (JAK2 - Verstovsek)
  - (Transplant – Deeg)
  - (New Therapies – Pardanani)

Other Resources for MPN Patients

- Therapy expectations (Mesa)
- MPN Lab Questions (LeClair)
- Is my MPN inherited? (Gotlib)
- Clotting and Bleeding (Noel)
- Living Well! (Selak)

Prognosis & Therapy of MPNs 2013

- Assessment of goals of therapy for MPN patients
- Therapy of ET and PV
- Therapy of MF
- Some Scenarios

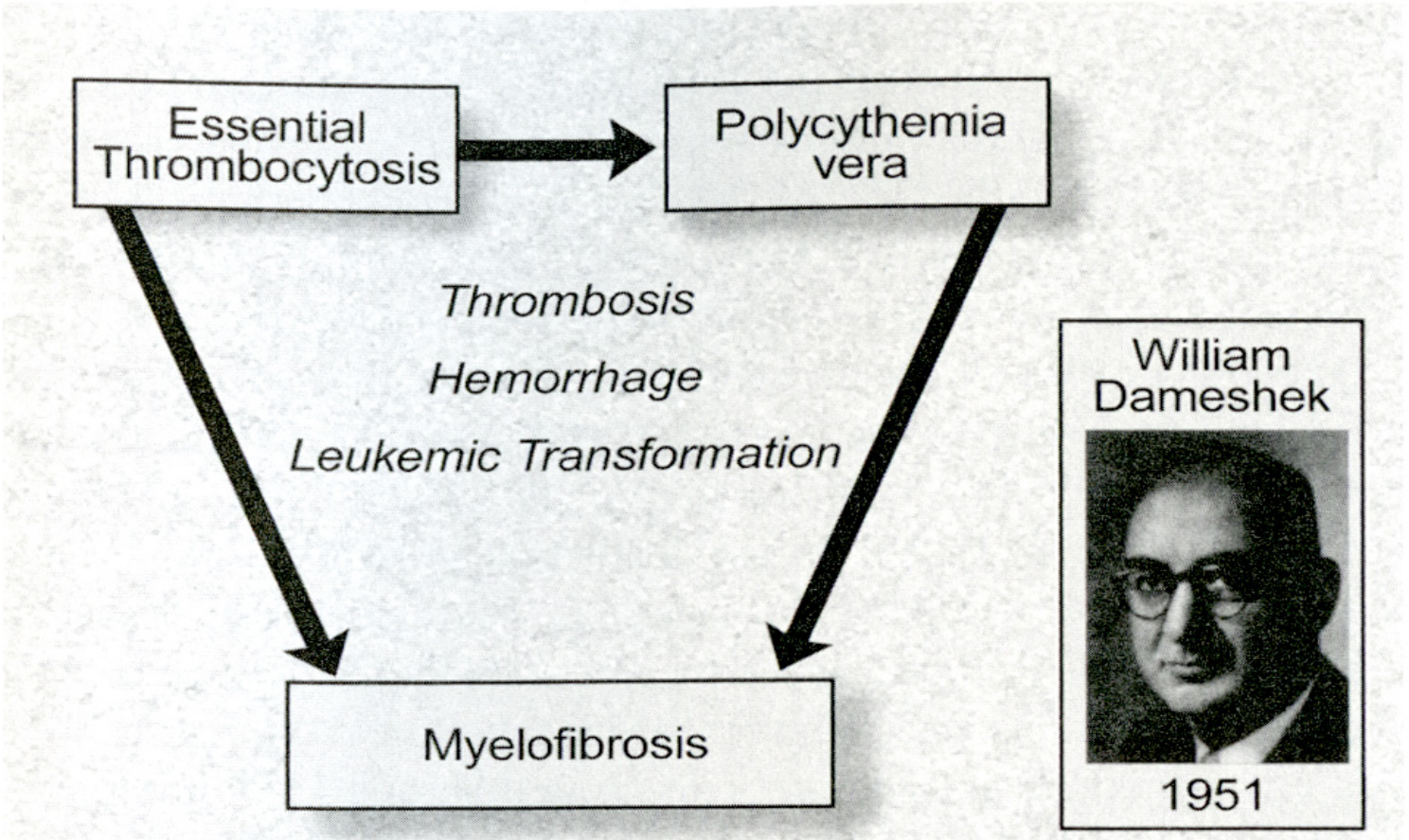


Ilustración 1: trastornos mieloproliferativos negativos para cromosoma Filadelfia, clasificación basada en William Dameshek.

Figure 1. Philadelphia chromosome negative myeloproliferative disorders: classification based on William Dameshek. Illustration by Debra Tyler.

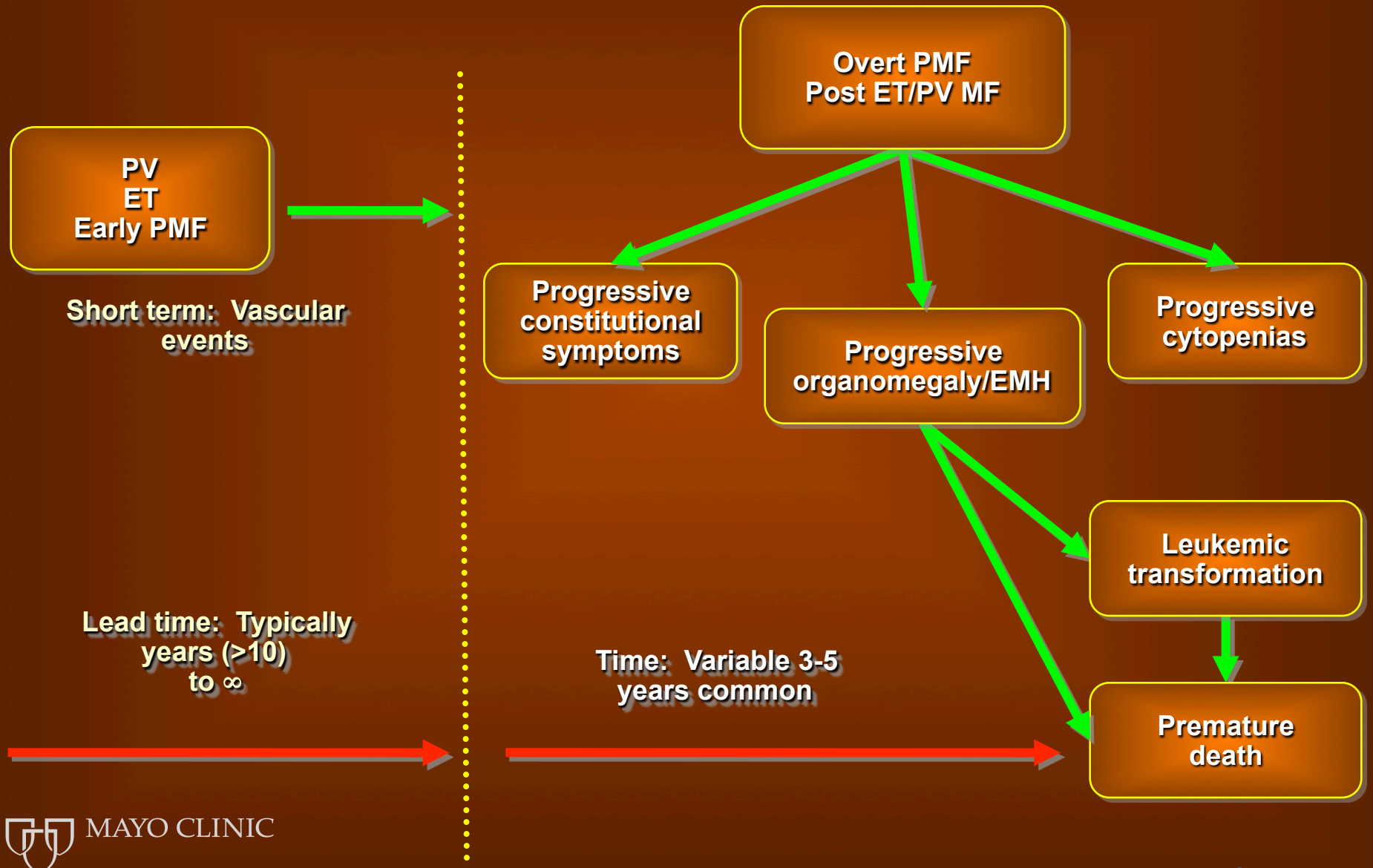
Incidence of Myeloproliferative Diseases

Annual incidence / 100,000 population

CML	1.6
ET	2.3
PV	2.2
PMF	1.0

Mesa; Am J Hematol. 1999;61(1):10
Johannson, J Intern Med 2004:161-5

Natural History of MPNs



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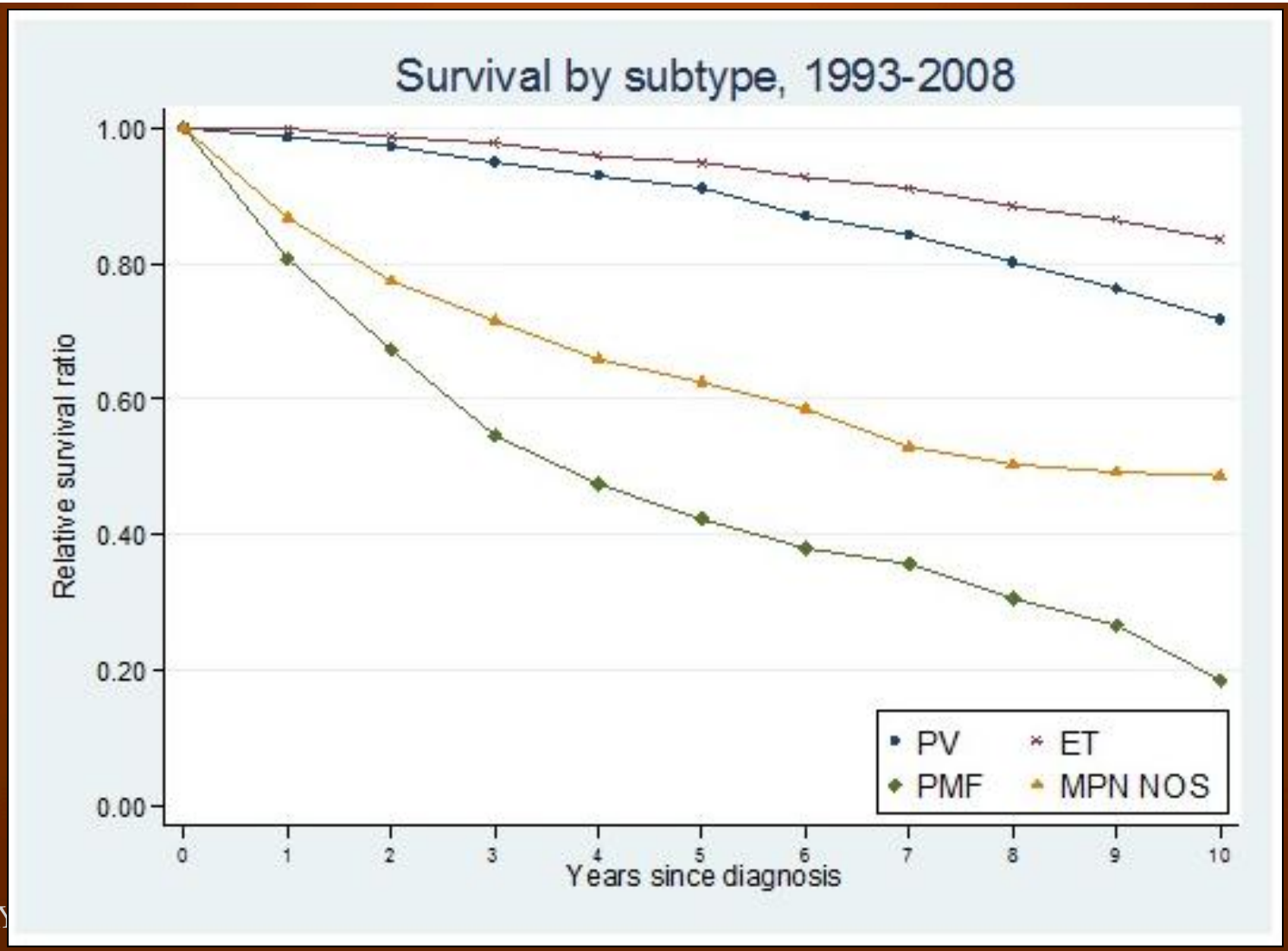
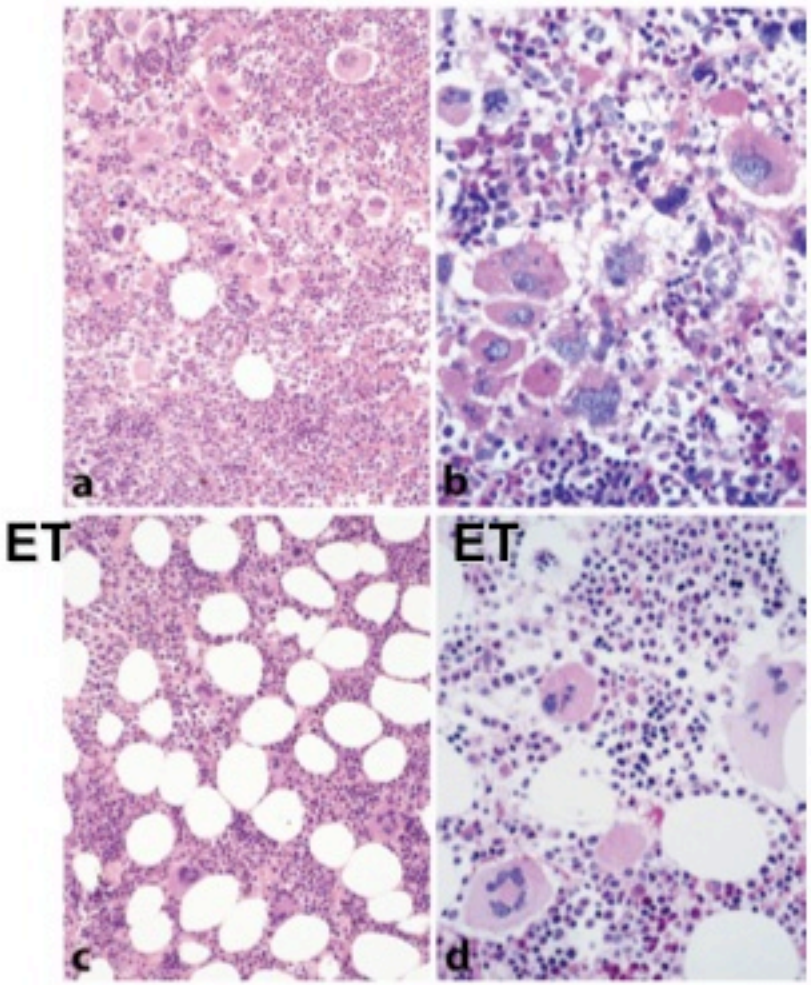
CP1266735-1

Patterns of Survival and Causes of Death In 9,384 Patients with Myeloproliferative Neoplasms Diagnosed In Sweden Between 1973 and 2008



Hultcrantz et al Blood 2010 (a3071)

Comparative histopathology in early stage PMF and ET



Early Primary Myelofibrosis

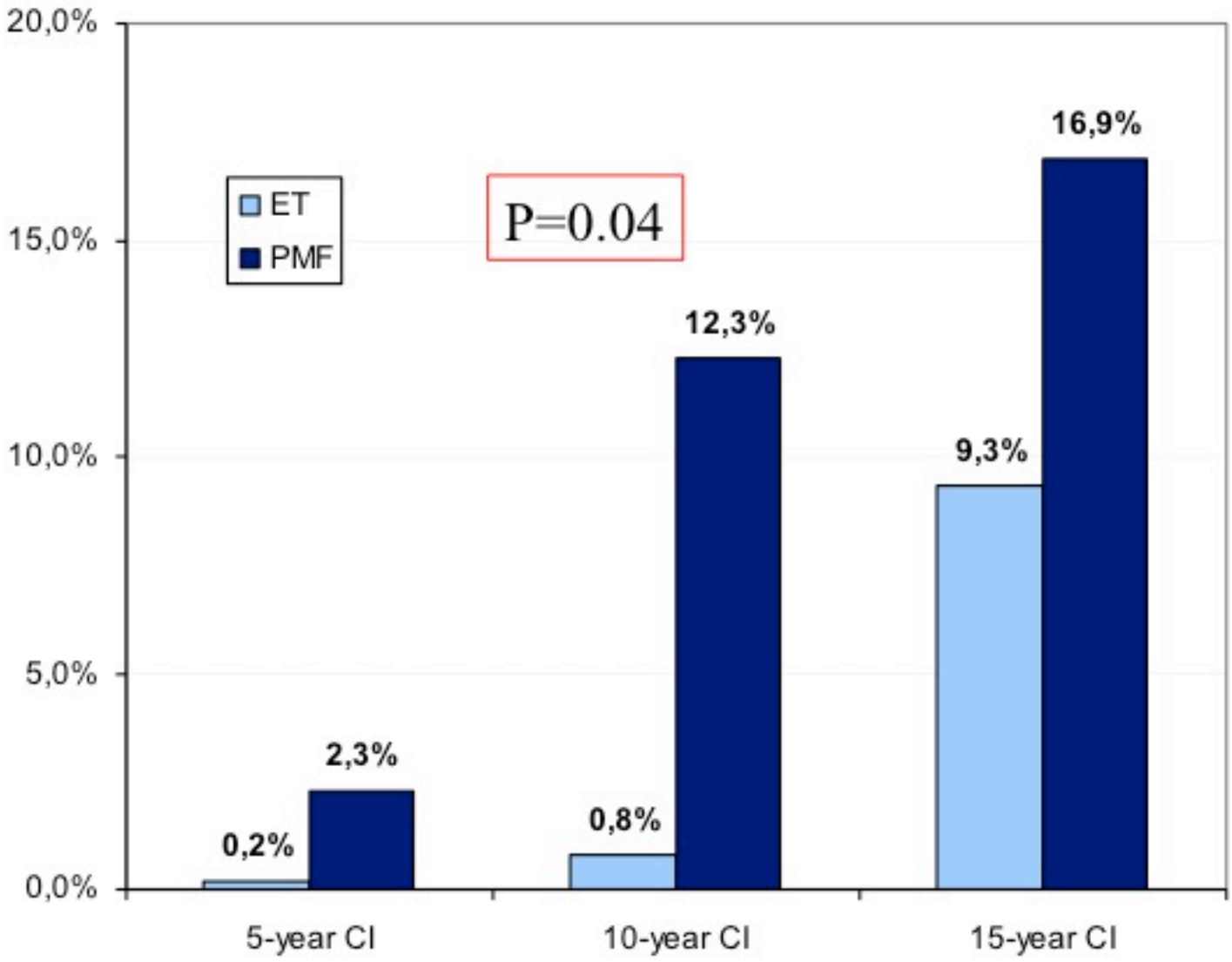
- ✓ hypercellular
- ✓ prominent clustering of abnormal megakaryocytes
- ✓ hypolobulated / hyperchromatic nuclei
- ✓ Granulocytic proliferation

Essential Thrombocythemia

- ✓ normocellular
- ✓ Dispersed large to giant megakaryocytes

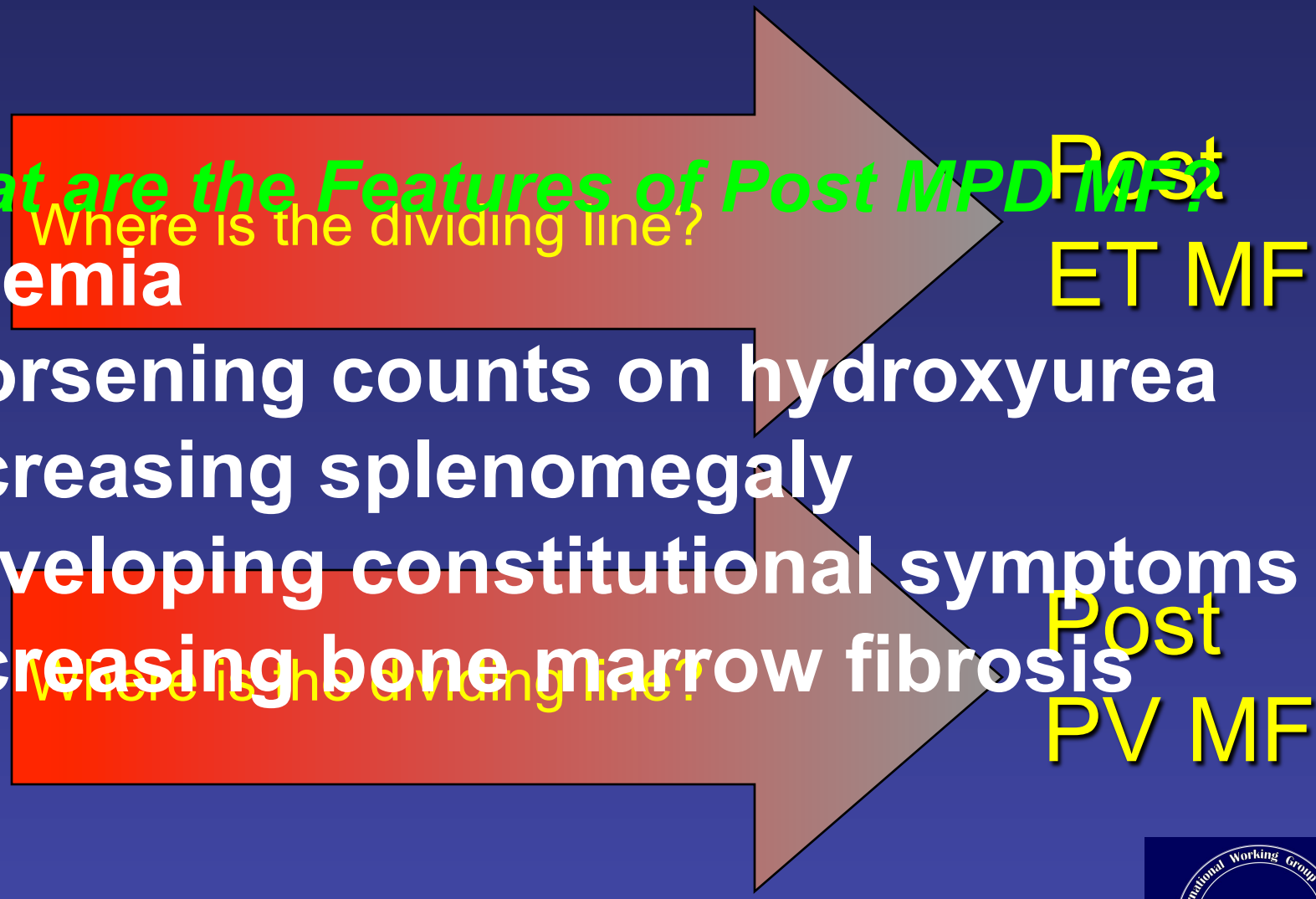
Barbui et. al. Blood 2010

Cumulative Incidence of Myelofibrosis



Barbui et. al. Blood 2010

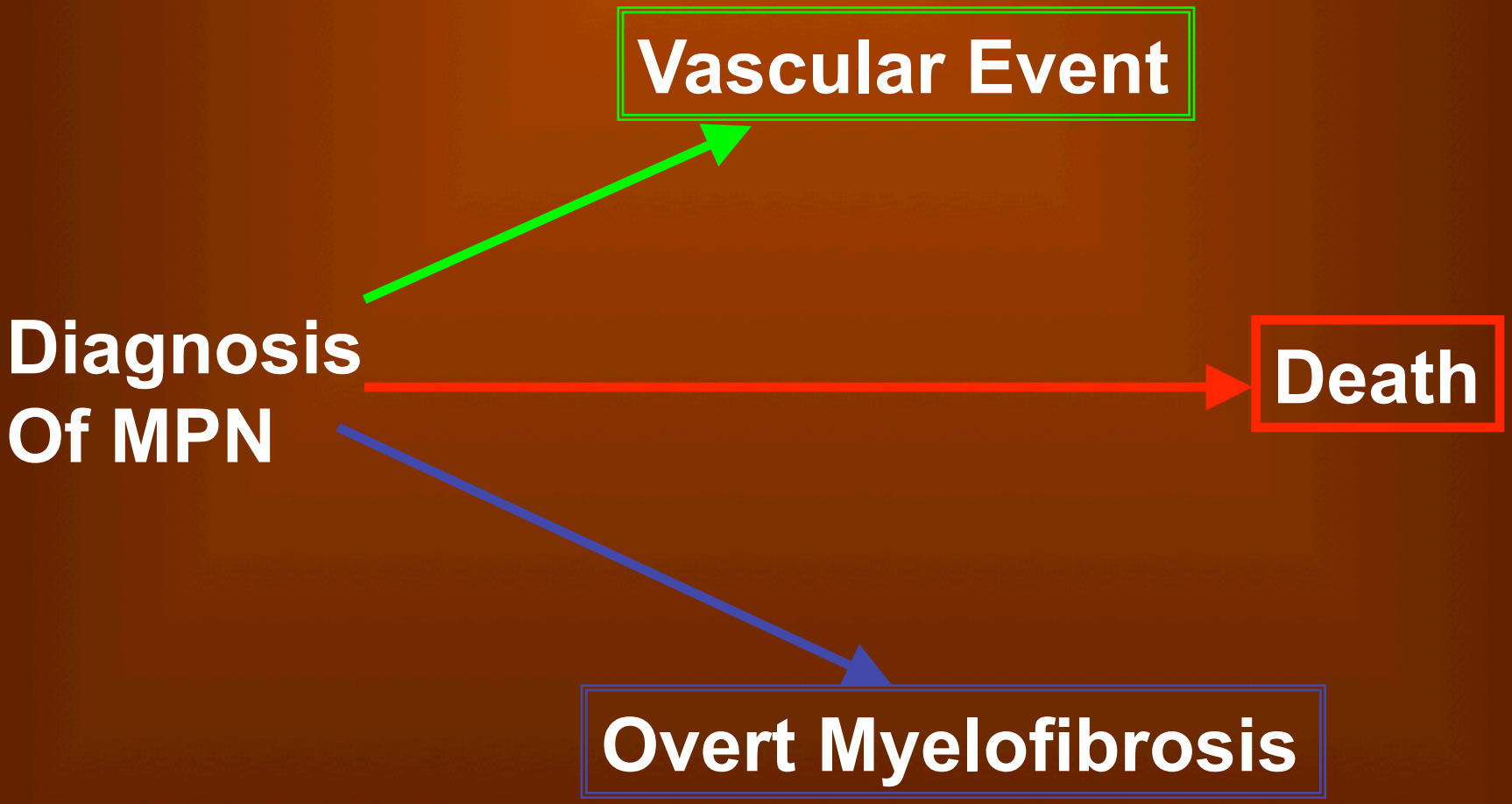
Post ET / PV Myelofibrosis



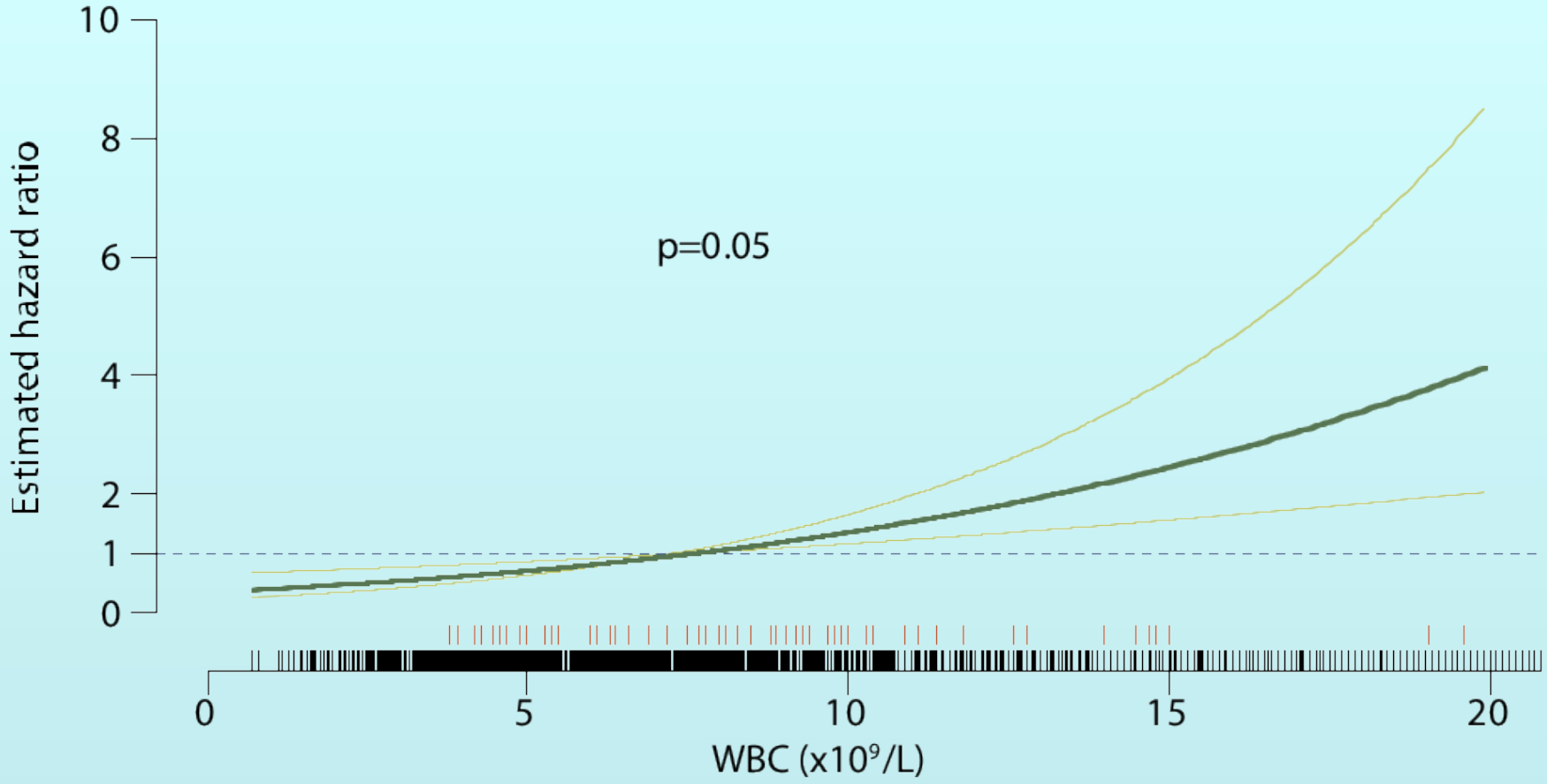
Barosi et. al. *Leukemia* 2007;EPUB August 15, 2007

IWG-MRT

Assessing Risk in MPNs

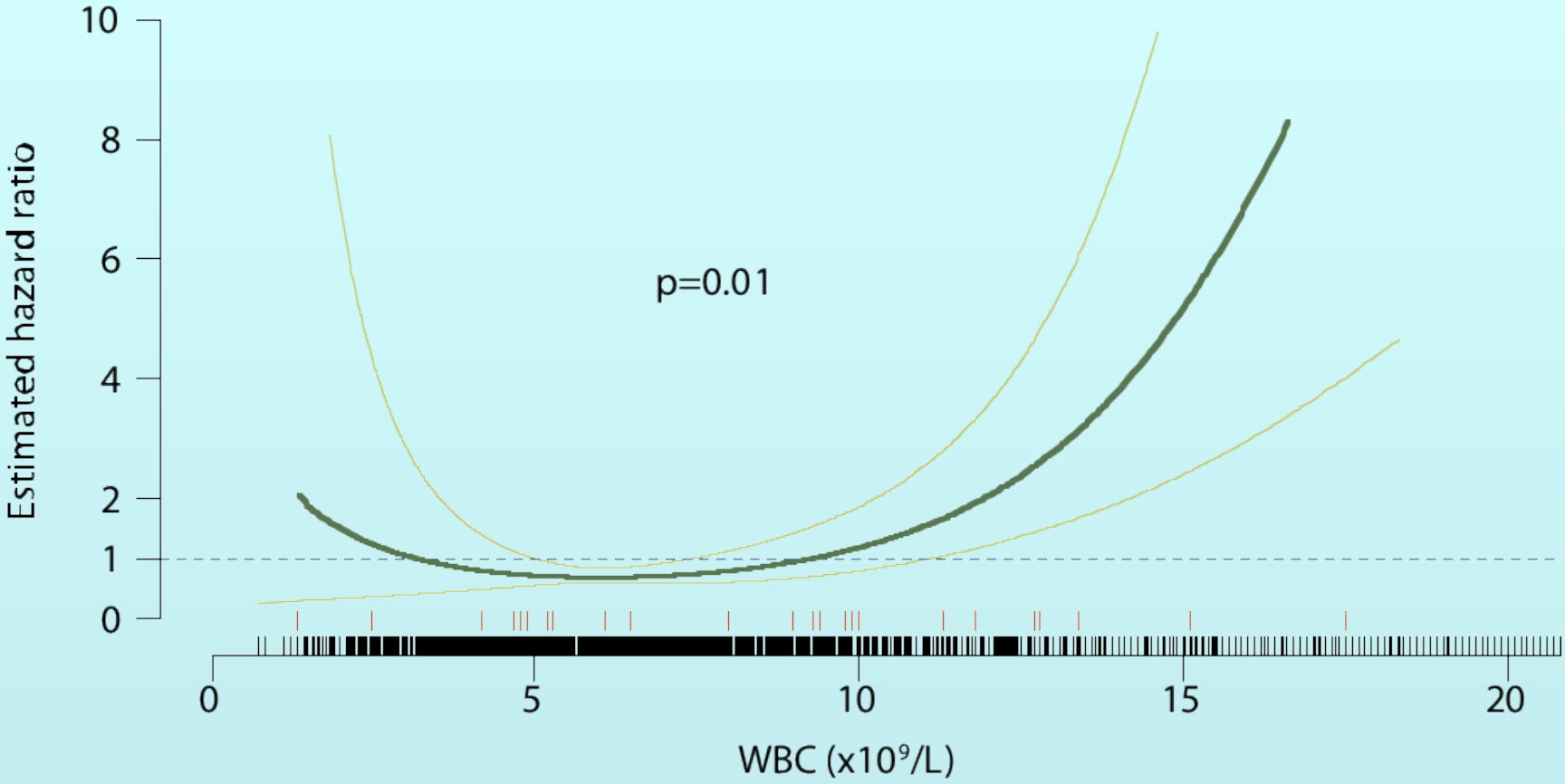


White cell count & thrombosis



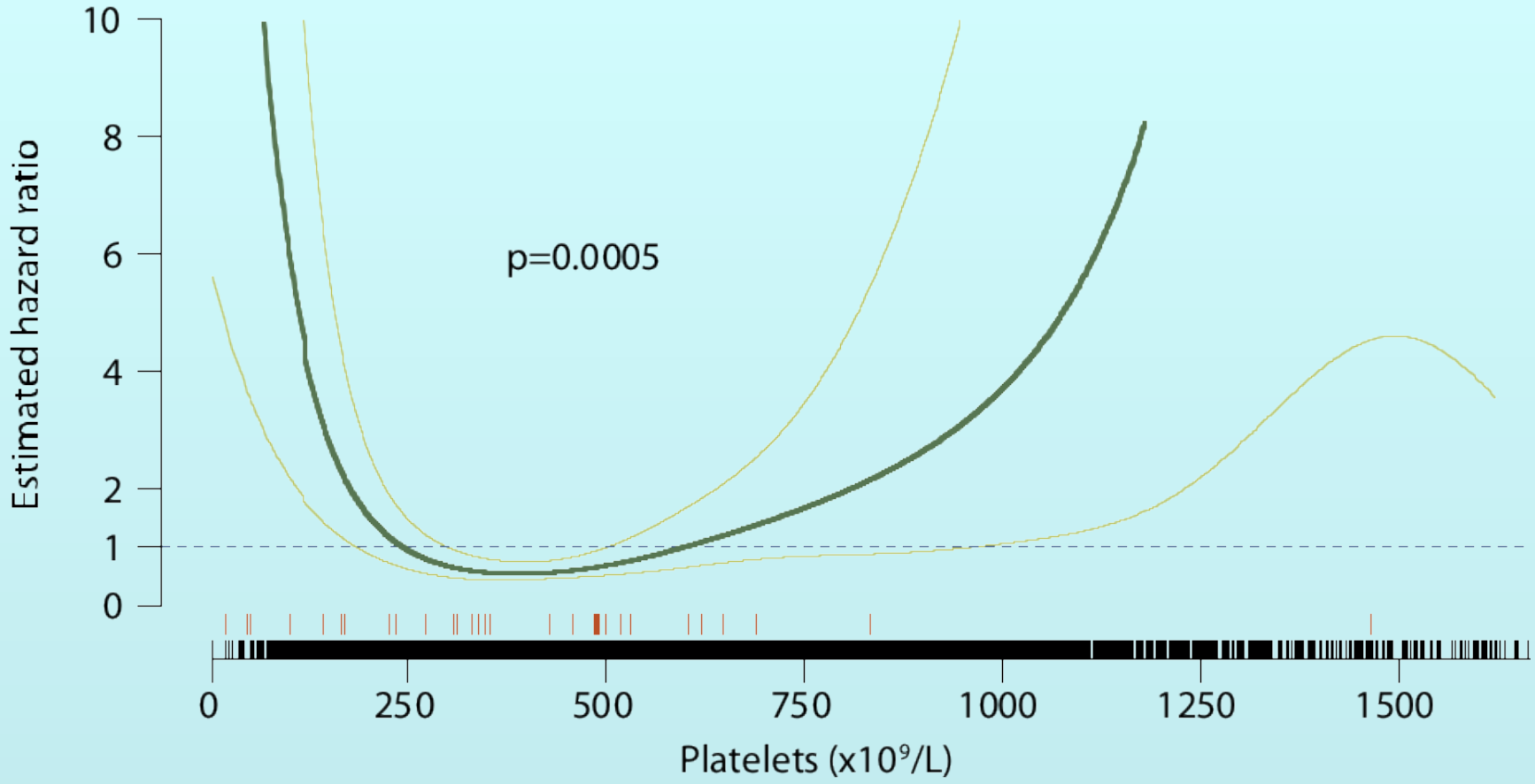
Campbell submitted 2010

WCC & major hemorrhage



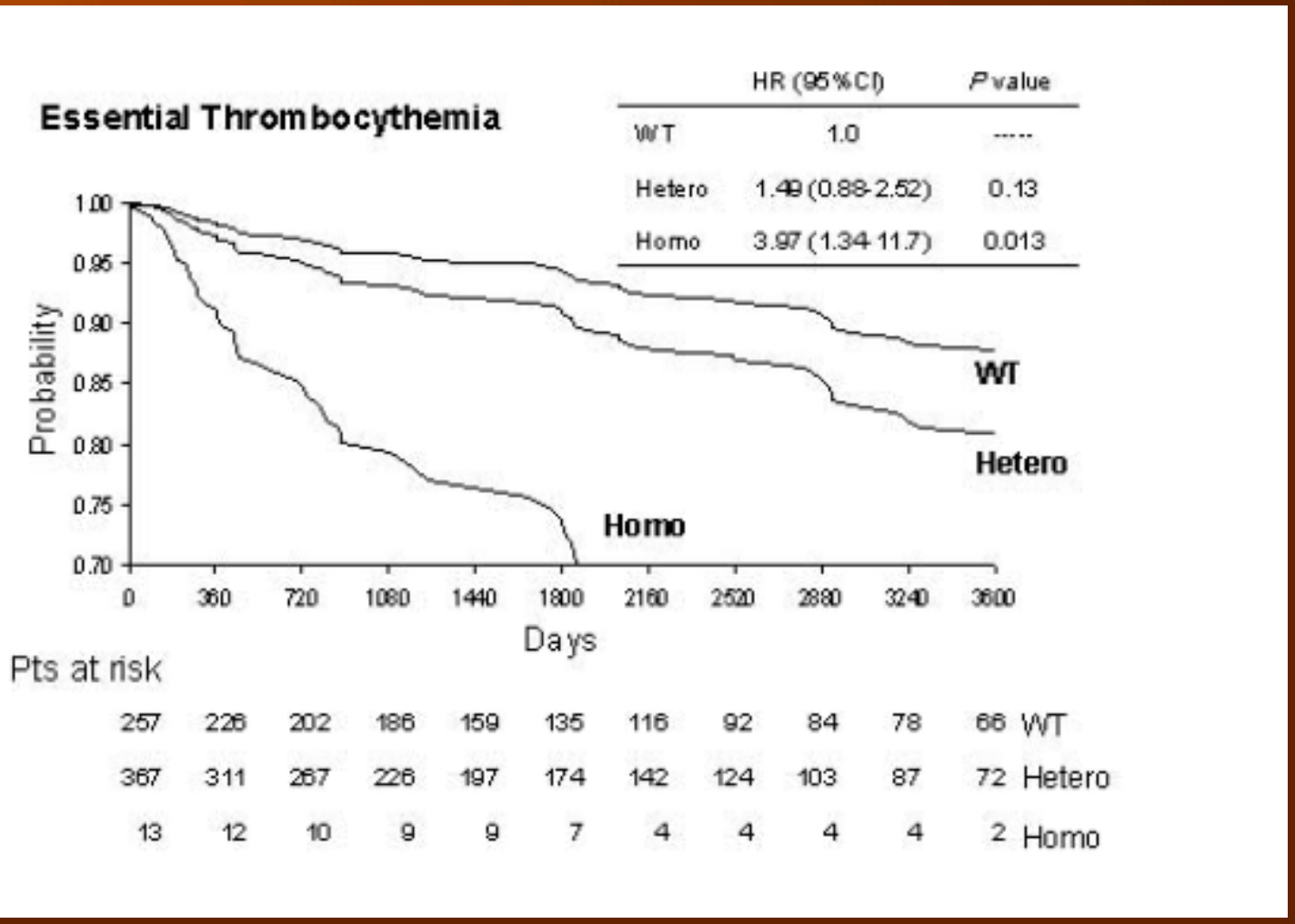
Campbell submitted 2010

Platelets & major hemorrhage



Campbell submitted 2010

Significance of JAK2V617F homozygosity



Vannucchi 2007

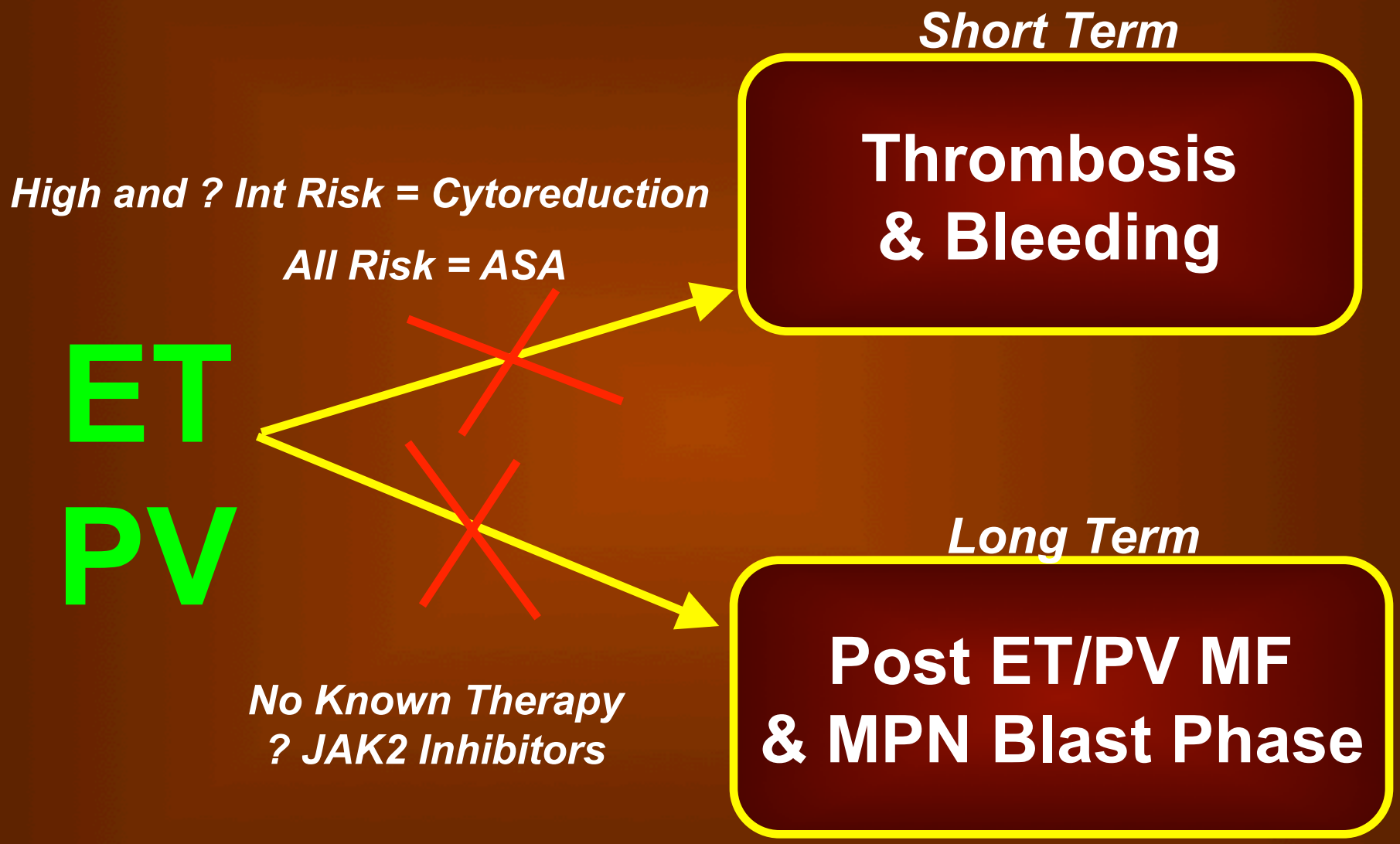
Evolving MPN Prognostic Scales

	IPSET (ET – 3 groups) ***Survival*** ***Thrombosis Risk***	**PV Risk (4 groups)** ***Survival*** ***Leukemia Rates***	**DIPSS (PMF – 4 groups)** ***Survival***
Age	≥ 60 (2pts) vs. < 60	≥70 (3pts) 60-69 (2pts), <60	≥65 (1pt) vs. <65
Leukocytes	≥ 11 (1pt) vs. < 11 x 10^9/L	≥15 (1 point) vs. <15 x 10^9/L	>25 (1pt) vs. ≤25 x 10^9/L
Hemoglobin			<10 (2 pts) vs. ≥10g/dL
Constitutional Symptoms			Present# (1pt) vs. Absent
Blasts			≥1% (1pt) vs. <1%
Prior Thrombosis	Yes (1 point) vs. No		
Risk Group Point Cutoffs	0; 1-2; 3-4 pts.	0; 1-2; 3; 4 pts.	0; 1-2; 3-4; ≥4 pts.
	Passamonti Blood 2012	*Tefferi ASH 2011*	*Passamonti Blood 2010*

= >10% Weight Loss over prior 6 months, Night Sweats, Unexplained Fever

Therapy of MPNs 2013

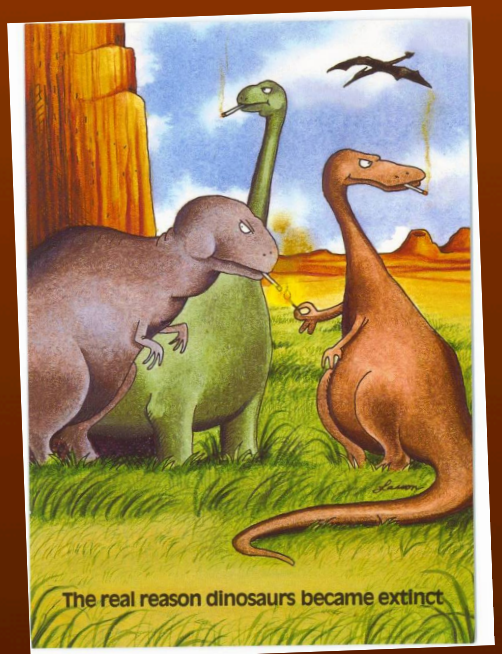
- Assessment of goals of therapy for MPN patients
- Therapy of ET and PV
- Therapy of MF
- Future Directions

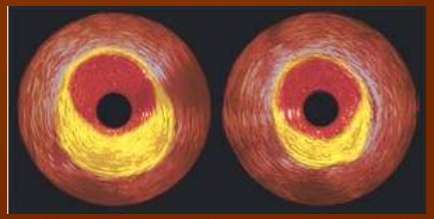

Short Term
Thrombosis & Bleeding
High and ? Int Risk = Cytoreduction
All Risk = ASA
ET
PV
Long Term
Post ET/PV MF & MPN Blast Phase
No Known Therapy
? JAK2 Inhibitors

Management of ET

- All should receive aspirin unless contraindicated (plts>1000 x 10^9/L is a relative contra-indication)

- Aggressively manage all reversible vascular risk factors





NHS National Institute for Health and Clinical Excellence

- Adults with clinical evidence CHD
- Primary prevention >20% 10 year risk CHD
- Secondary prevention Jan 2006

Management of ET

- ALL ET Patients
  - *Low Dose ASA*
  - *Aggressive control of CV risk factors*

- Cytoreduction
  - *High Risk*
  - Medications
    - *Hydroxyurea as Front line*
    - *Anagrelide second line*
    - *Interferon alpha third line*
    - *Busulfan, pipobroman, P-32 for elderly*

Barbui et. al. LeukemiNET Consensus Guidelines JCO 2011 in press

Management of PV

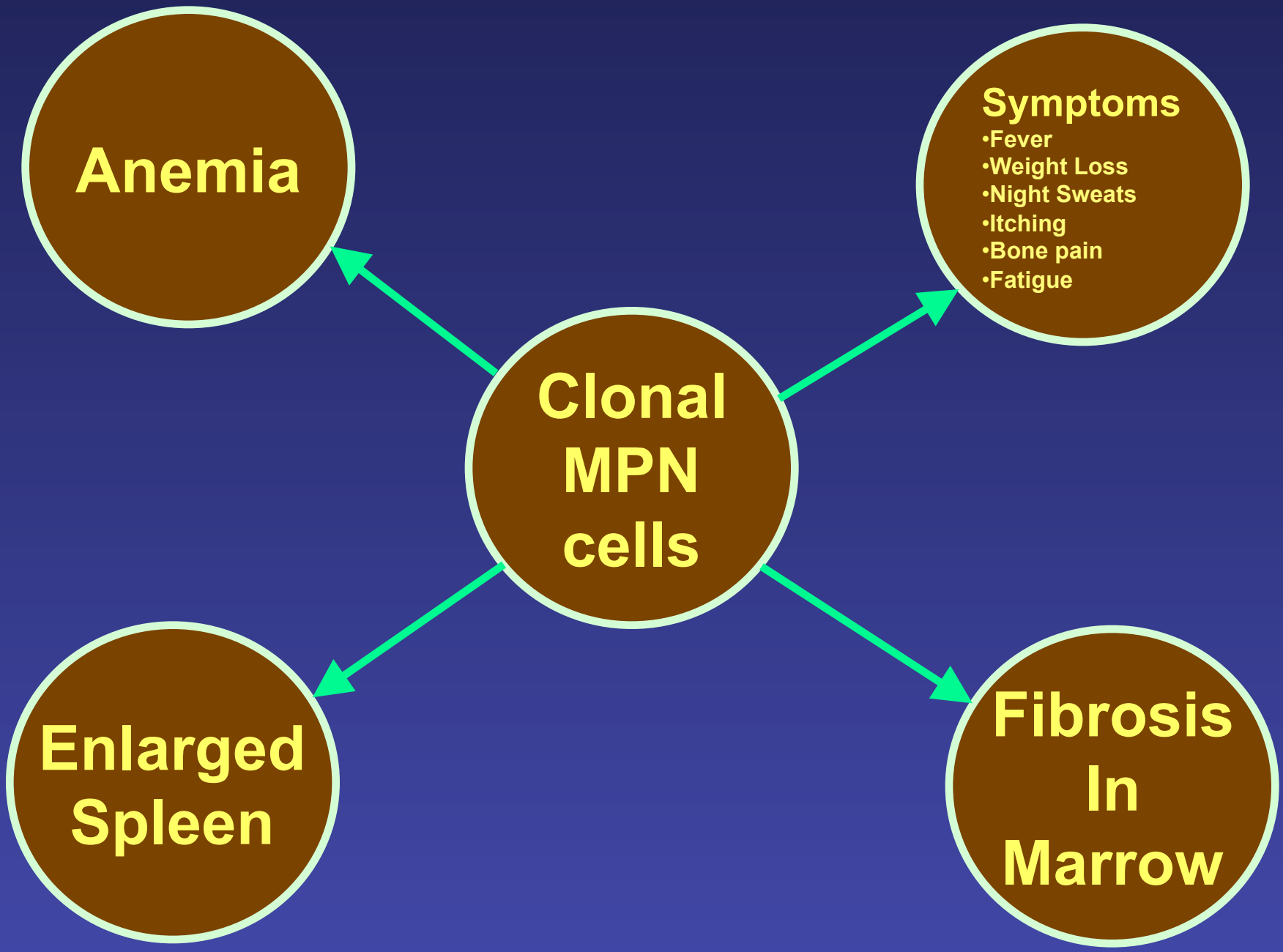
- ALL PV Patients
  - *Maintain HCT <45% Men, 42% Women*
  - *Low Dose ASA*
  - *Aggressive control of CV risk factors*

- Cytoreduction
  - *High Risk or*
  - *Intol to Phlebotomy, Increasing Spleen, Severe Sx*
    Plt >1500 x 10(9)/L, or prog WBC
  - Medications
    - *Hydroxyurea or Interferon alpha as Front line (or second)*
    - *Busulfan, pipobroman, P-32 as second line*

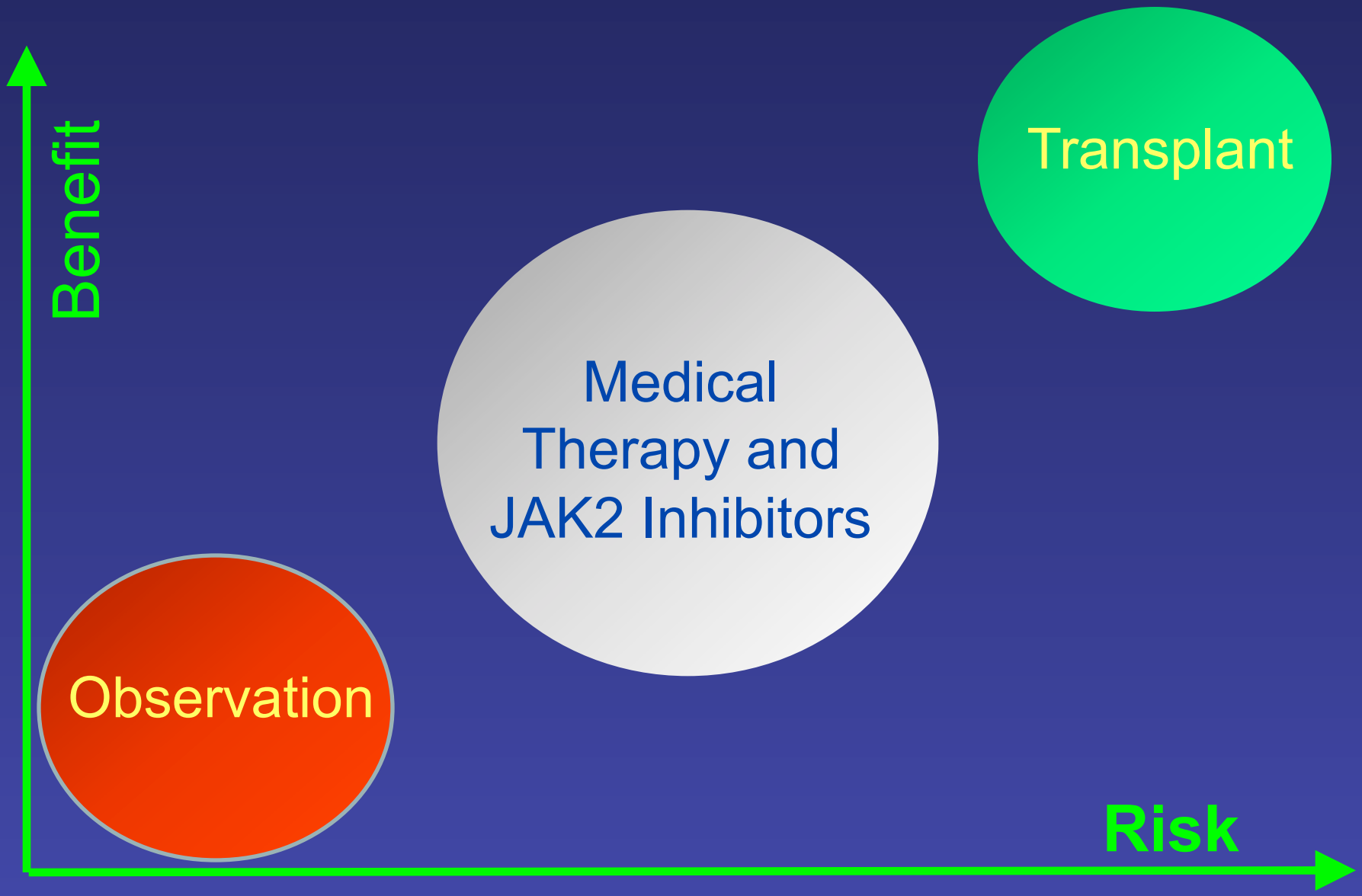
Barbui et. al. LeukemiNET Consensus Guidelines JCO 2011 in press

Therapy of MPNs 2013

- Assessment of goals of therapy for MPN patients
- Therapy of ET and PV
- Therapy of MF
- Scenarios

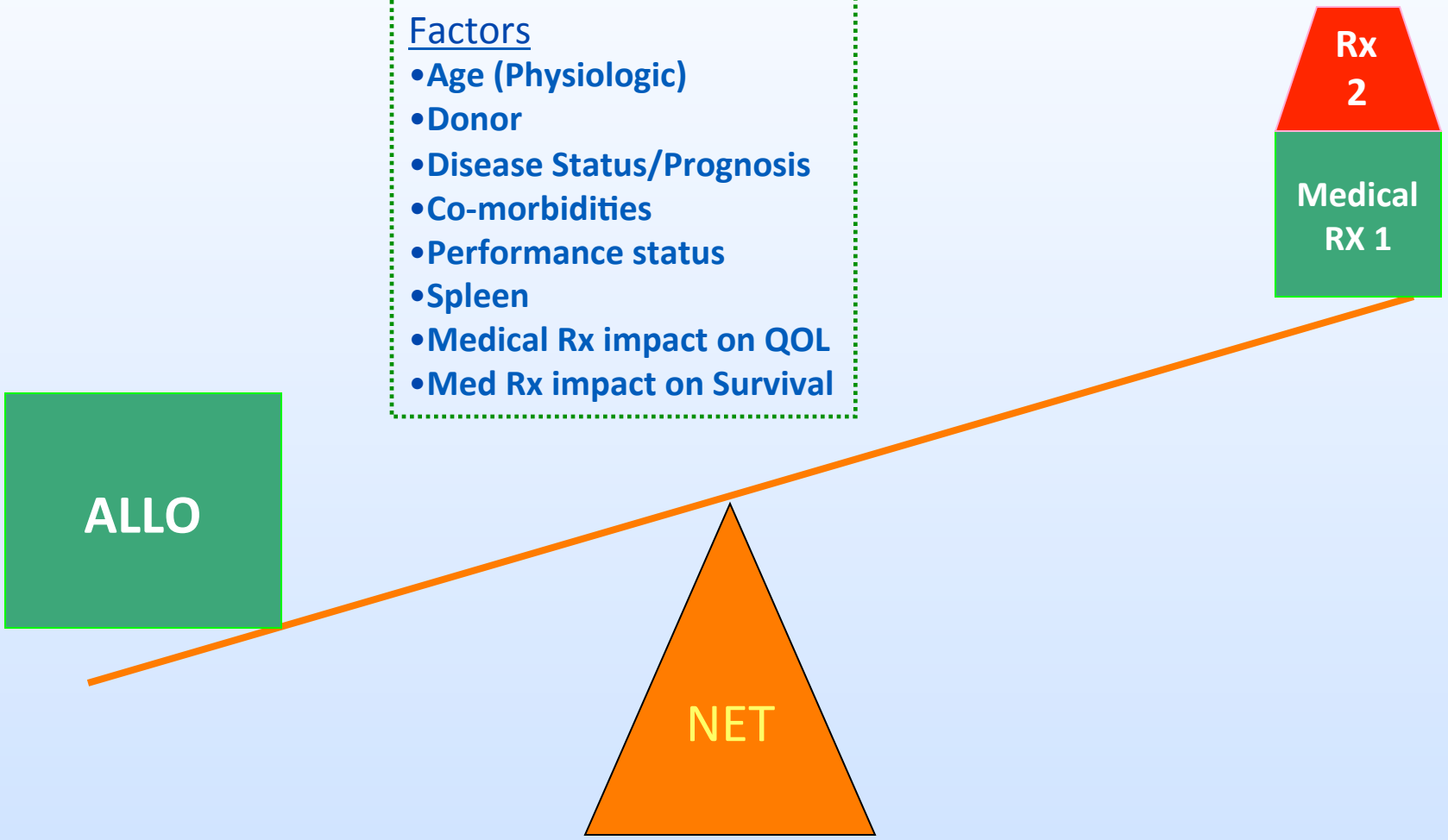

Anemia
Symptoms
•Fever
•Weight Loss
•Night Sweats
•Itching
•Bone pain
•Fatigue
Clonal MPN cells
Enlarged Spleen
Fibrosis In Marrow

Therapy Choices



Allotransplant Decision

Factors
- Age (Physiologic)
- Donor
- Disease Status/Prognosis
- Co-morbidities
- Performance status
- Spleen
- Medical Rx impact on QOL
- Med Rx impact on Survival



Medications for MF prior to JAK2 Inhibitors

Medicines for MF Anemia

- *Androgens*
- *EPO*
- *Thalidomide*

Medicines for MF Spleen

- *Hydroxyurea*
- *Busulfan*
- *2-CDA*

- *Splenectomy*
- *Splenic Radiation*

Medicines for Anemia & Spleen

- *Lenalidomide*

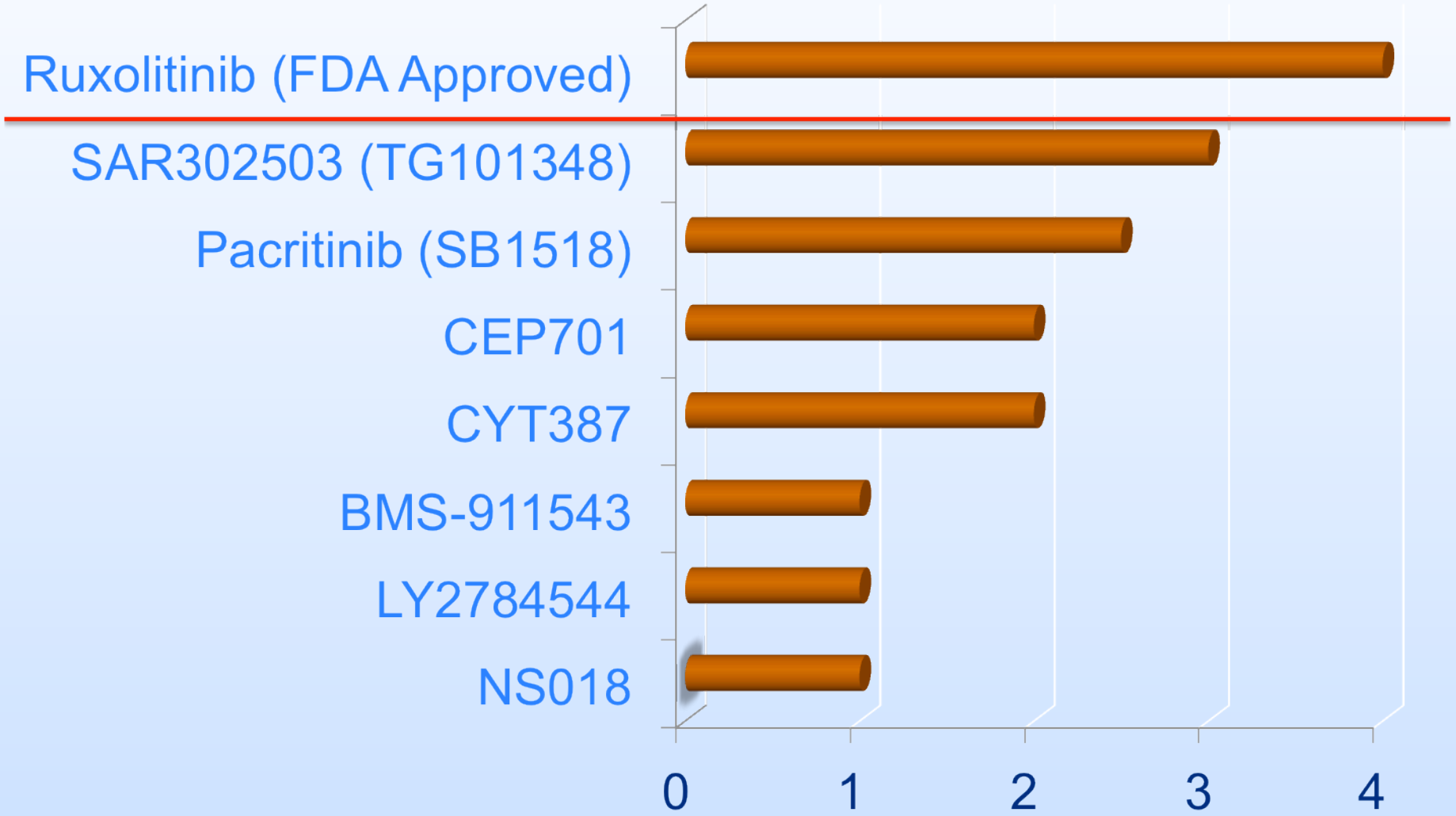
Medicines for MF Symptoms

- *None*

Available IMIDs in MF

	HB	PLT	SPLN	REF
THALIDOMIDE	29%	38%	41%	Barosi 2002
THALIDOMIDE-PREDNISONE	62% 23%	75% 23%	19% 14%	Mesa 2002 Thapilaya 2010
LENALIDOMIDE	22%	50%	33%	Tefferi 2006
LENALIDOMIDE -PREDNISONE	19%	N/A	10%	Mesa 2010
LENALIDOMIDE -PREDNISONE	30%	N/A	42%	Quintas-Cardama 2009

JAK2 Inhibitors in Clinical Use/ Development



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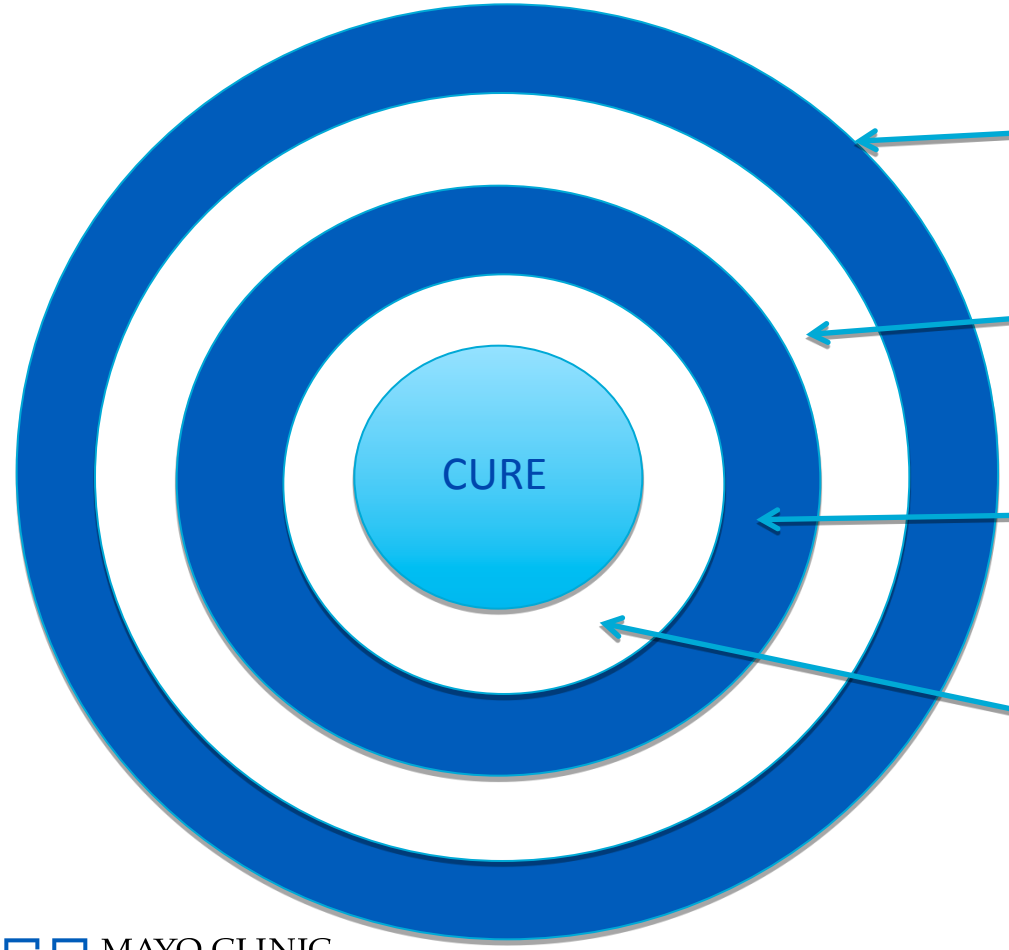
Cancer Center

Individualizing MPN Pharmacotherapy



Patient Goals & Input

Improving Symptom Burden /HR QOL

"Balancing" Spleen/ Cytoses/ Cytopenias

Extending Life

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Case 1 – ET (with minimal CV risk factors)

- Presented 2008, age 67, with a 14 yr history of platelets above normal. Platelets > 1.6 million. JAK-2 +. WBC NI

- No symptoms whatsoever

- Her parents both died in their late 80's of "natural causes". For the prior 35 yrs She ran 5 miles a day, 5-6 days a week, was a vegetarian and never smoked.

- She has been followed ever since with one aspirin per day.

- Latest labs showed WBC of 1.675 million and potassium 6.1

This ET Case Illustrates……

- The power of lifestyle and vascular risks
- The fact that not everyone needs therapy
- Platelets, when really high can falsely elevate the potassium level.
- Aspirin alone is often adequate therapy
- This is NOT the approach for a patient who has a history of thrombotic or bleeding condition.

Case 2 - PV

- P.vera: March of 2008 at the age of 38 when presented with LUQ pain from 16 cm spleen.
- BM biopsy was 60% cellular with atypical megakaryocytes. JAK2 testing was positive and hematocrit was 51.2.
- With hydroxyurea, aspirin, and phlebotomy, he did well for a couple of years but later developed fatigue & lower extremity discomfort in the feet especially.

Case-2 PV (continued)

- In August of 2010, he presented to the Mayo Clinic with complaints of fatigue and painful feet. Hydrea stopped and he got better 6 mo.
- By 9-2011 he had pruritus and spleen pain even though the spleen was normal in size. Hgb 12.3, MCV 71, plts 311.
- Pegylated interferon started.
- By 11/2012 all of his symptoms had improved and his JAK-2 burden decreased with megakaryocytes normalizing in BM.

This PV case illustrates….

- That sometimes therapy is indicated just to see if therapy could help with vague symptoms.
- Therapy may be indicated even if WBC and platelets are not elevated.
- Patients can go back and forth on hydrea and anagrelide (sometimes lower doses of BOTH) at different times depending on suspected toxicities.
- Pegylated interferon may help PV symptoms even when counts are not affected.

Case 3 – Evolving Post PV MF

- In 1994 at prostatectomy for prostate cancer his platelets were 500,000 and Hct 52.
- BM Bx showed MPD in 1998. Started Hydrea.
- Hydrea associated with leg lesions and had to be switched over to anagrelide in 2003.
- Anagrelide associated with chest symptoms in 2007 prompting a switch back to hydroxyurea.
- 3/2009 leg ulcers due to Hydrea-> anagrelide

Case 3 – Evolving Post PV MF

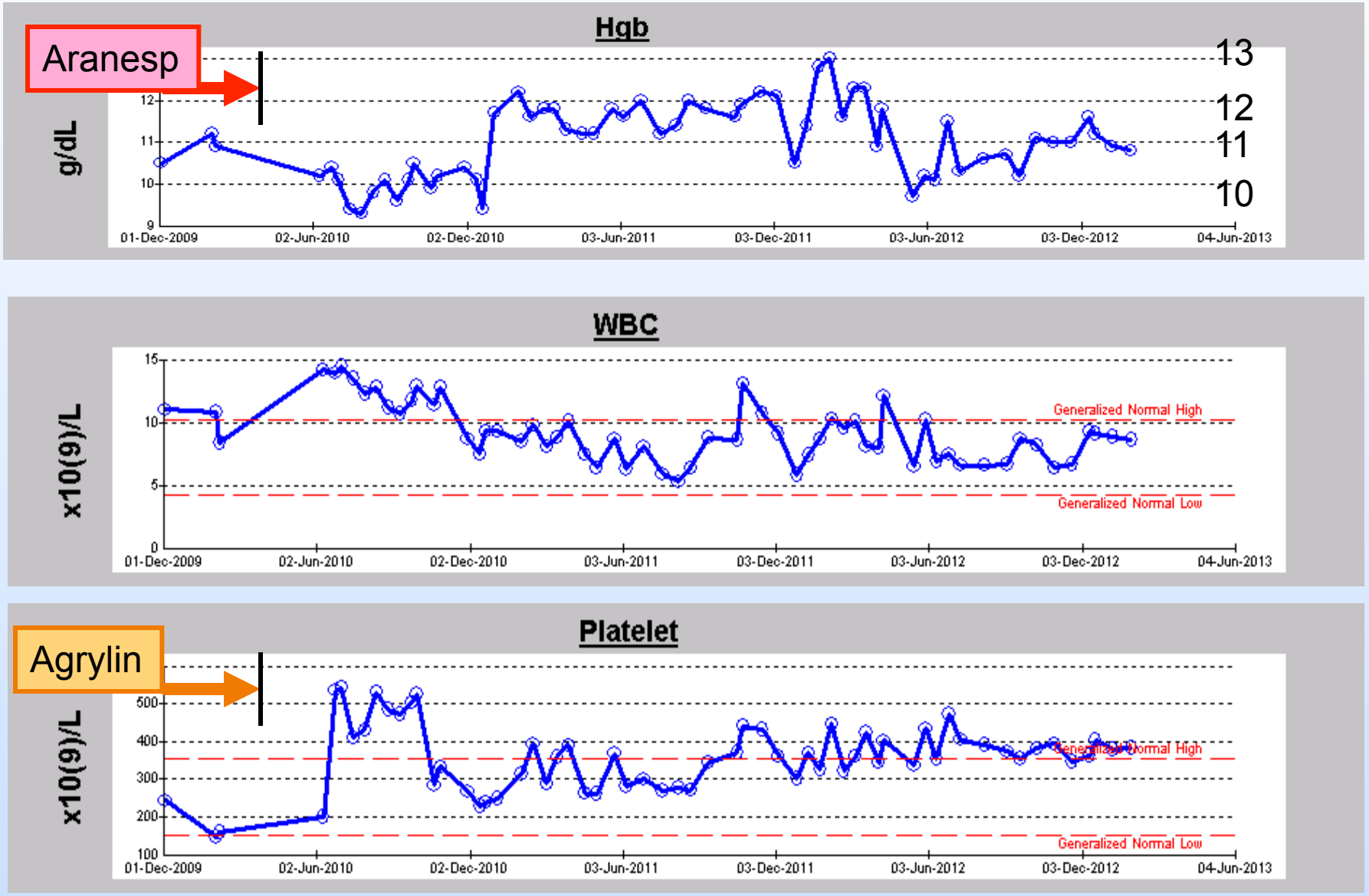
- On and off of Aranesp for anemia from 2005 to 2010 with variable benefit.
- 6/2009 immature white cells in the peripheral blood including blasts.
- BM Bx 8/21/09 ->myelofibrosis (G3+ reticulin)
- 1st @ Mayo Clinic in June of 2010 with new splenomegaly while on Aranesp & Agrylin.
- Stopped Agrylin and Aranesp both. Spleen got better but he had anemia by August 2010

Case 3 – Evolving Post PV MF DIPPS

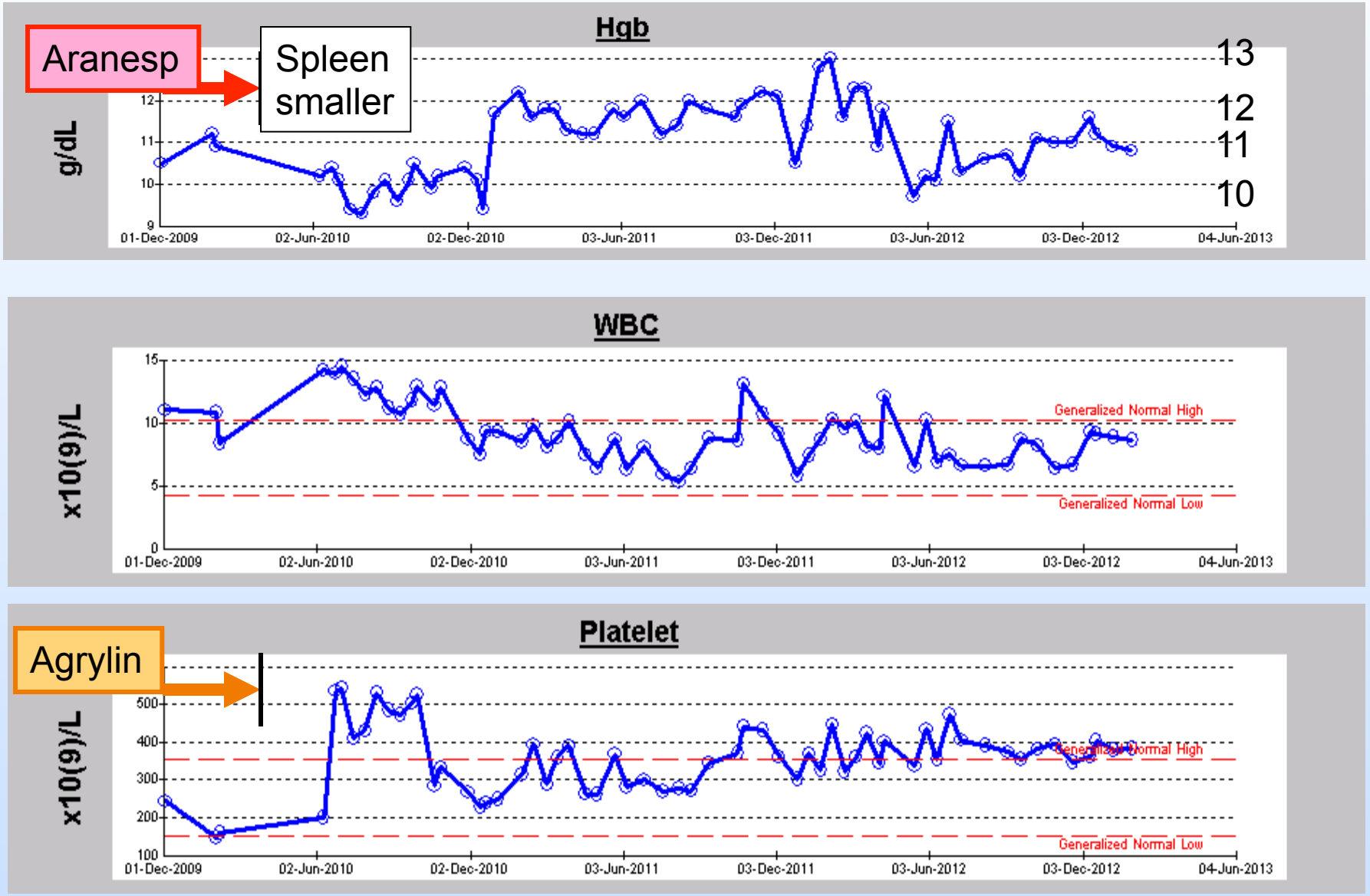
- ***Presence of constitutional symptoms (ie, weight loss >10 percent, night sweats, or fever) NO***
- ***Age >65 years YES 69 yo***
- ***Hemoglobin <10 g/dL: ? (Maybe)***
- ***Leukocyte count >25,000/microL= ? (NO)***
- ***Circulating blast cells ≥1 percent (YES)***

- None (low risk) = 135 months
- 1 (intermediate risk-1) = 95 months
- **2 (intermediate risk-2) = 48 months**
- ≥3 (high risk) = 27 months

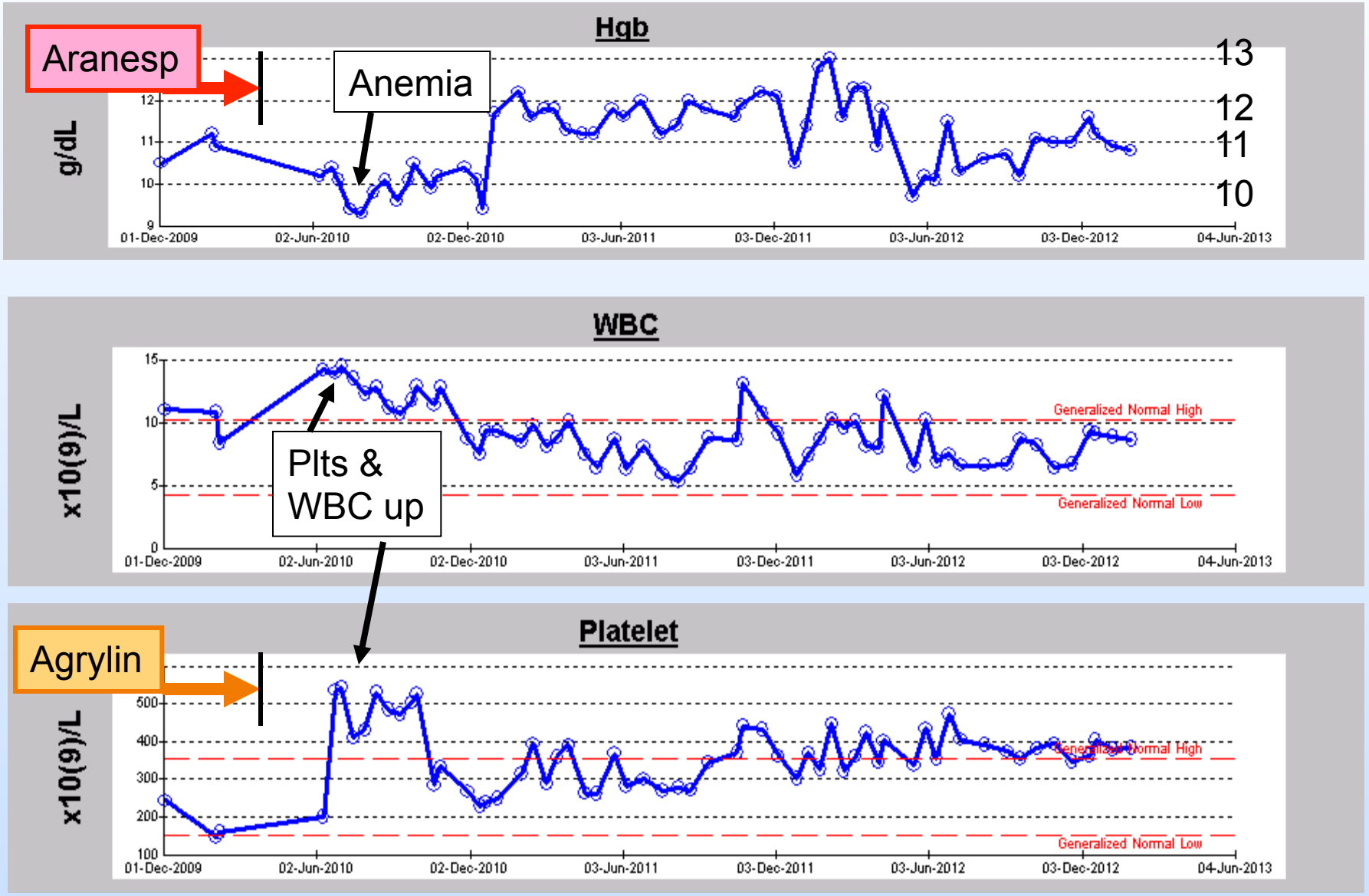
Clinical Course and Adjustments



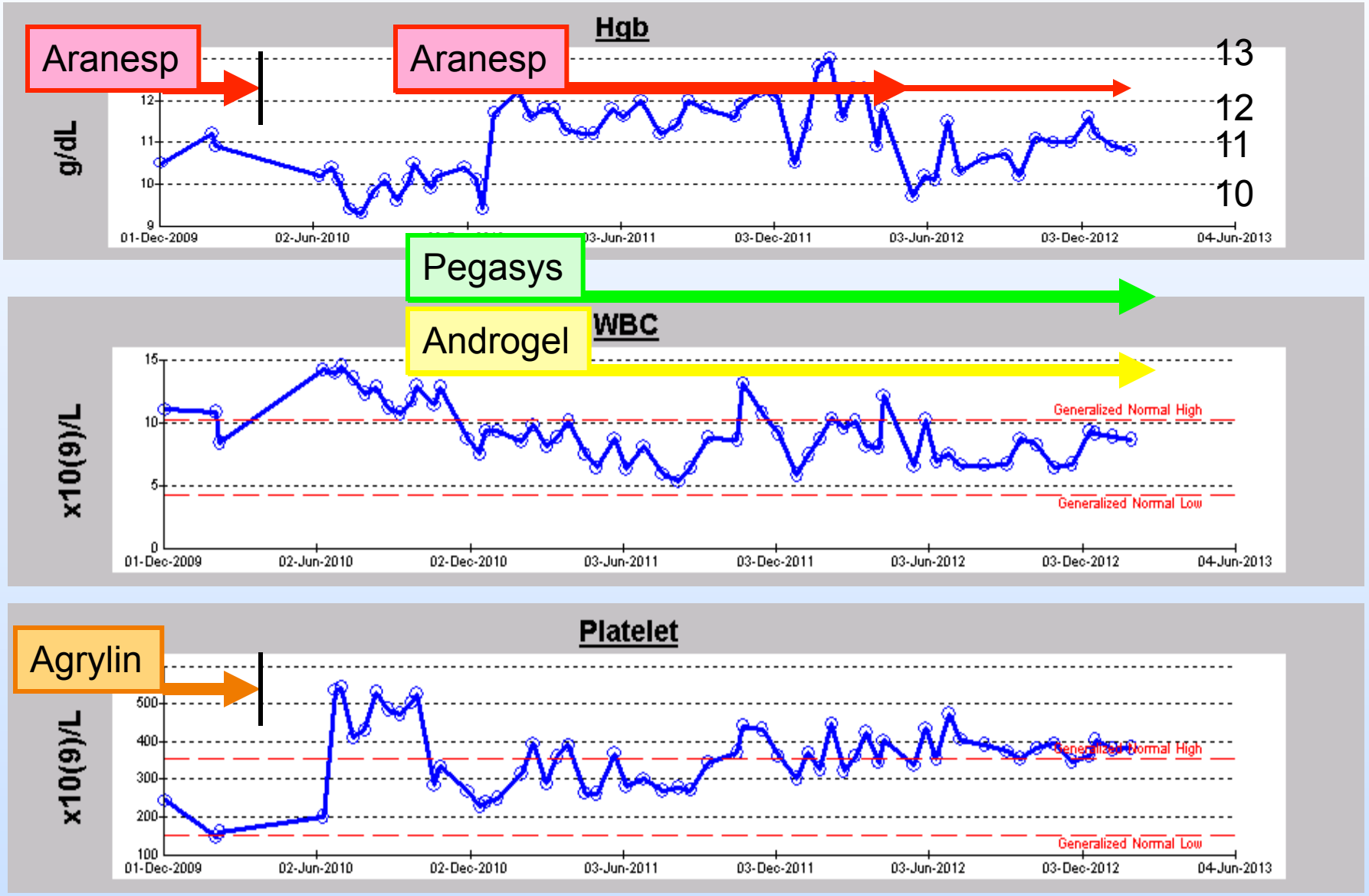
Clinical Course and Adjustments



Clinical Course and Adjustments



Clinical Course and Adjustments

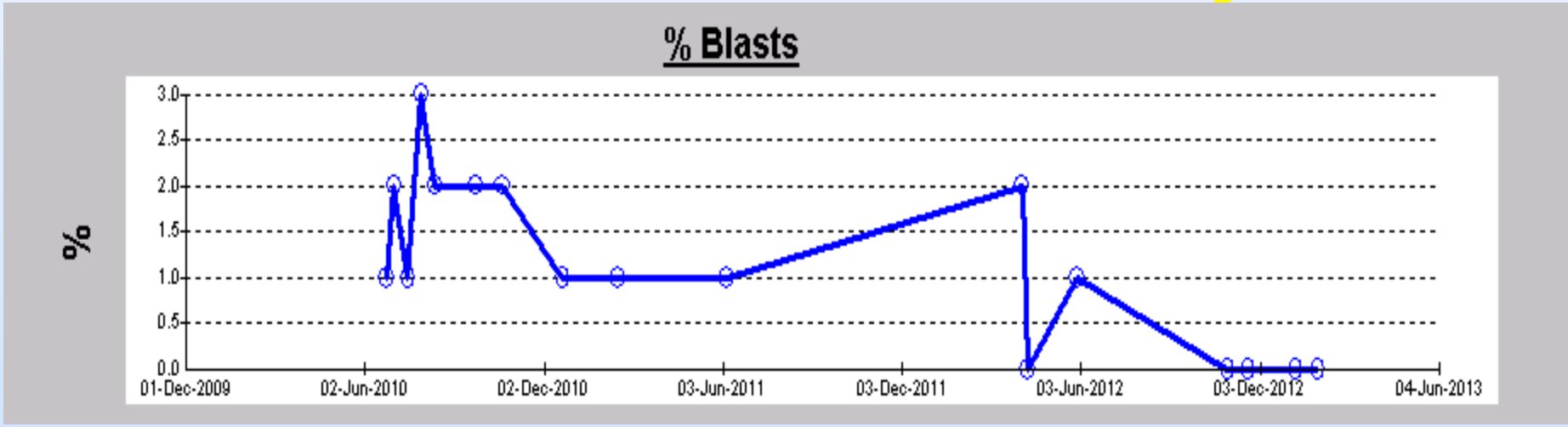


Case 3 – Evolving Post PV MF Dynamic DIPPS

- ***Age >65 years: 1 point YES***
- ***Leukocyte count >25,000/microL: 1 point NO***
- ***Hemoglobin <10 g/dL: 2 points YES***
- ***Circulating blast cells ≥1 percent: 1 point YES***
- ***Presence of constitutional symptoms: 1 point NO***

- *No factors "0" (low risk)= 135 months*
- *1 to 2 (intermediate-1) = 95 months*
- ***3 to 4 (intermediate-2) = 48 months***
- *5 to 6 points (high risk) = 27 months*

Clinical Course and Adjustments



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Case 3 of MF illustrates….

- Aranesp can improve Hgb but may increase spleen size unless countered by other drugs like hydrea or interferon
- Offering androgens may help improve Hgb.
- Hydrea can cause ankle ulcers and anagrelide may be associated with higher MF conversion.
- Dynamic DIPPS may worsen or improve over time and be affected by therapy.
- Multiple therapies may be the future of MF therapy and is sometimes helpful now.

Case 4 - PMF

- Presented age 42 with P. Vera in1986.
- In 2008 (age 64) she no longer needed phlebotomy and started having splenomegaly. MF was seen in bone marrow in 2010. JAK-2+
- A trial of hydrea in 2009 was attempted for splenomegaly but she had flu-like symptoms and did not remain on it.
- Splenomegaly has dominated her clinical complaints for the last 2-3 years.
- Rx = 3 cycles of radiation (27 total) each with transient benefit for less than 1 yr.

Case 4 - PMF

- Last XRT 7/2011. Presented to Mayo 12-2011.
- Spleen tip was palpable at the LCM in the MCL at 10.5 cm. It was 8 cm to the left of midline.
- Also mild night sweats since age 20 or so and pruritus after hot showers that bother her.
- Quite fit rock climbing and hiking.
- Dynamic DIPPS of Intermediate-1

Case 4 - PMF

- ***Age >65 years: 1 point YES***
- ***Leukocyte count >25,000/microL: 1 point No***
- ***Hemoglobin <10 g/dL: 2 points No***
- ***Circulating blast cells ≥1 percent: 1 point No***
- ***Presence of constitutional symptoms: 1 point Yes***

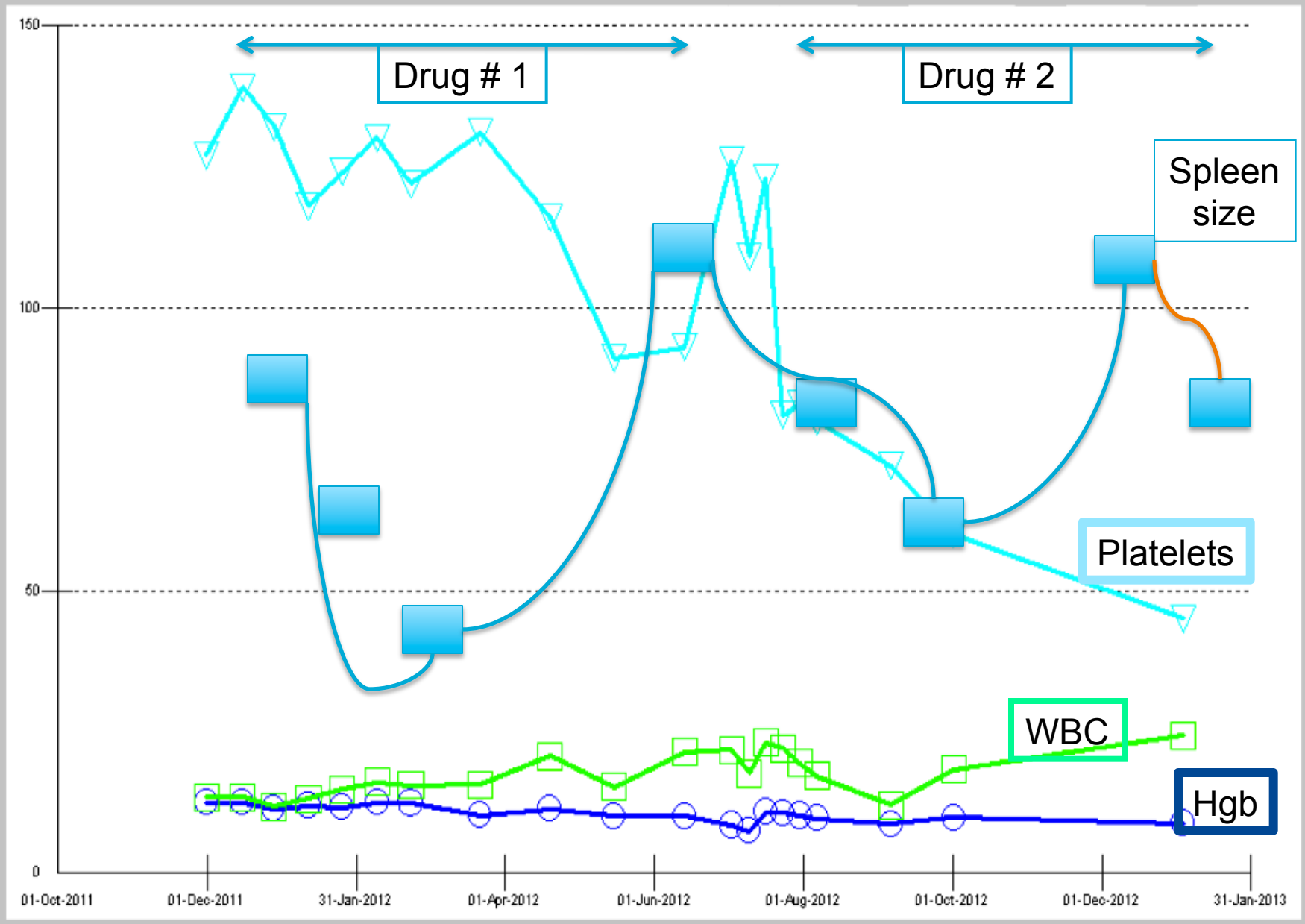
- *No factors "0" (low risk)= 135 months*
- ***1 to 2 (intermediate-1) = 95 months***
- *3 to 4 (intermediate-2) = 48 months*
- *5 to 6 points (high risk) = 27 months*

Was deemed too good to Be considered for BMT

Case 3 - PMF

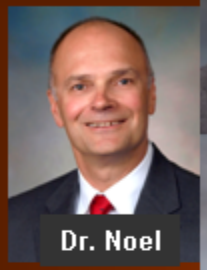
- Placed on "A “Phase 2 Study of IPI-926 in Patients with Myelofibrosis“ (Hedgehog inhibitor).
- By day 15 January 2012 spleen 10.5->7cm and by 6 weeks it was 5 cm. By June of 2012 however, her spleen was 13 cm and she went off study.
- July 2013 started on NS-Pharma 018 trial and in 1 month spleen decreased from 13 to 9 cm. By Oct. 2012 spleen was 7 cm but plts dropped so drug held. In 3 weeks spleen was back to 13 cm. Drug was resumed at a lower dose.

Hgb, WBC, & Platelet



MF Patient #2 Illustrates…….

- How drug studies can be used with the target goal in mind (spleen reduction vs anemia etc)
- Duration of response may vary (and sometimes be short)
- Unanticipated side effects may limit the effectiveness of the drugs being studied.
- Benefits in one direction can be countered by side effects in another direction.
- Newer drugs do seem to have some activity against the symptoms of MF.



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GENERATIONS OF MPN FOCUS

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- Mayo Clinic
  - Amylou Dueck, PhD
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  - Tim Beebe, PhD
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  - Bjorn Andreasson, MD
  - Jan Samuelsson, MD
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- Denmark
  - Hans Hasselbalch, MD
- Germany
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CMPD EDUCATION FOUNDATION

MPD FOUNDATION Searching for a cure for Myeloproliferative Disorders