ET : Management

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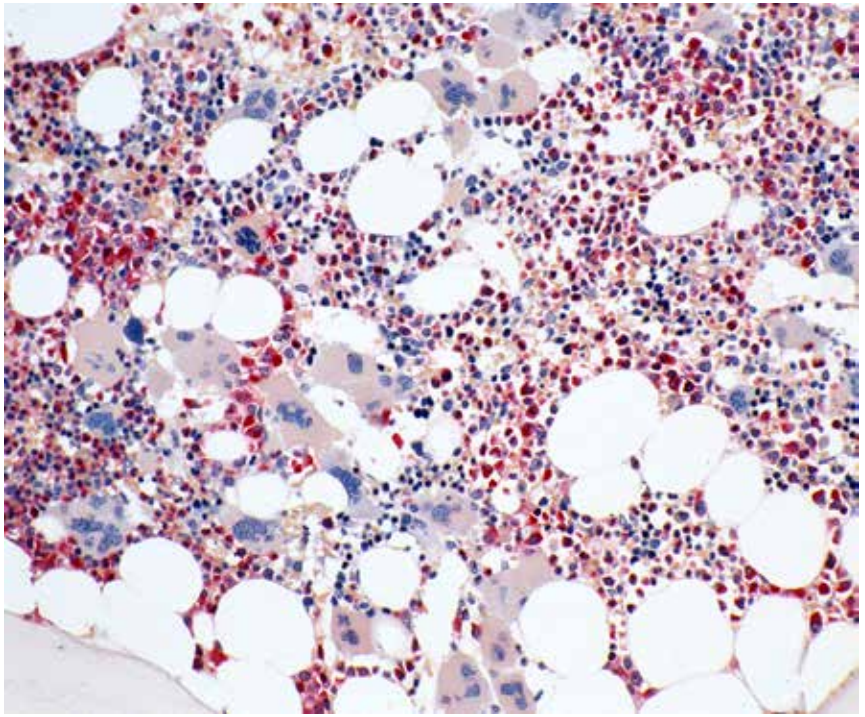
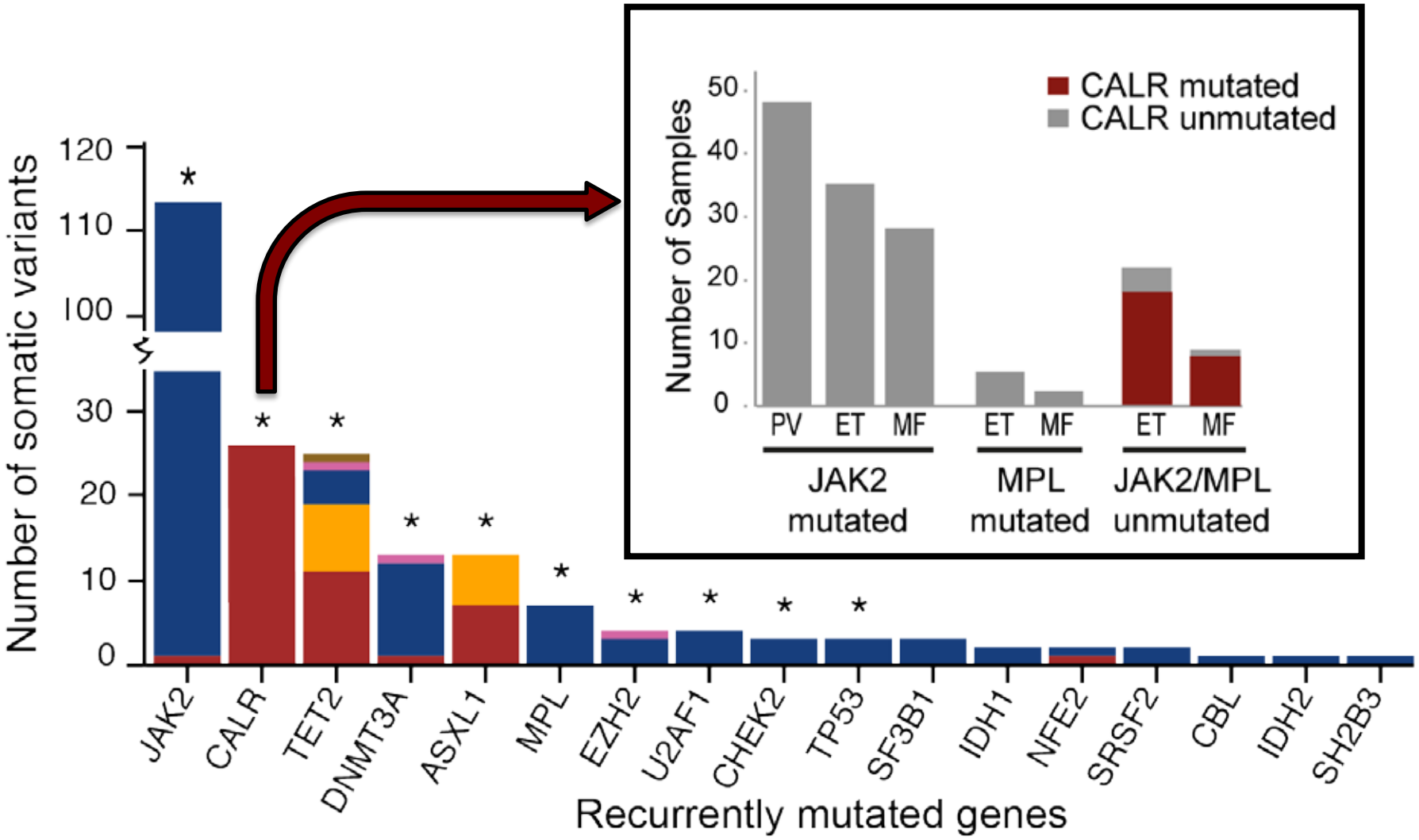
WHO criteria for Essential Thrombocythemia

diagnosis requires meeting all four criteria

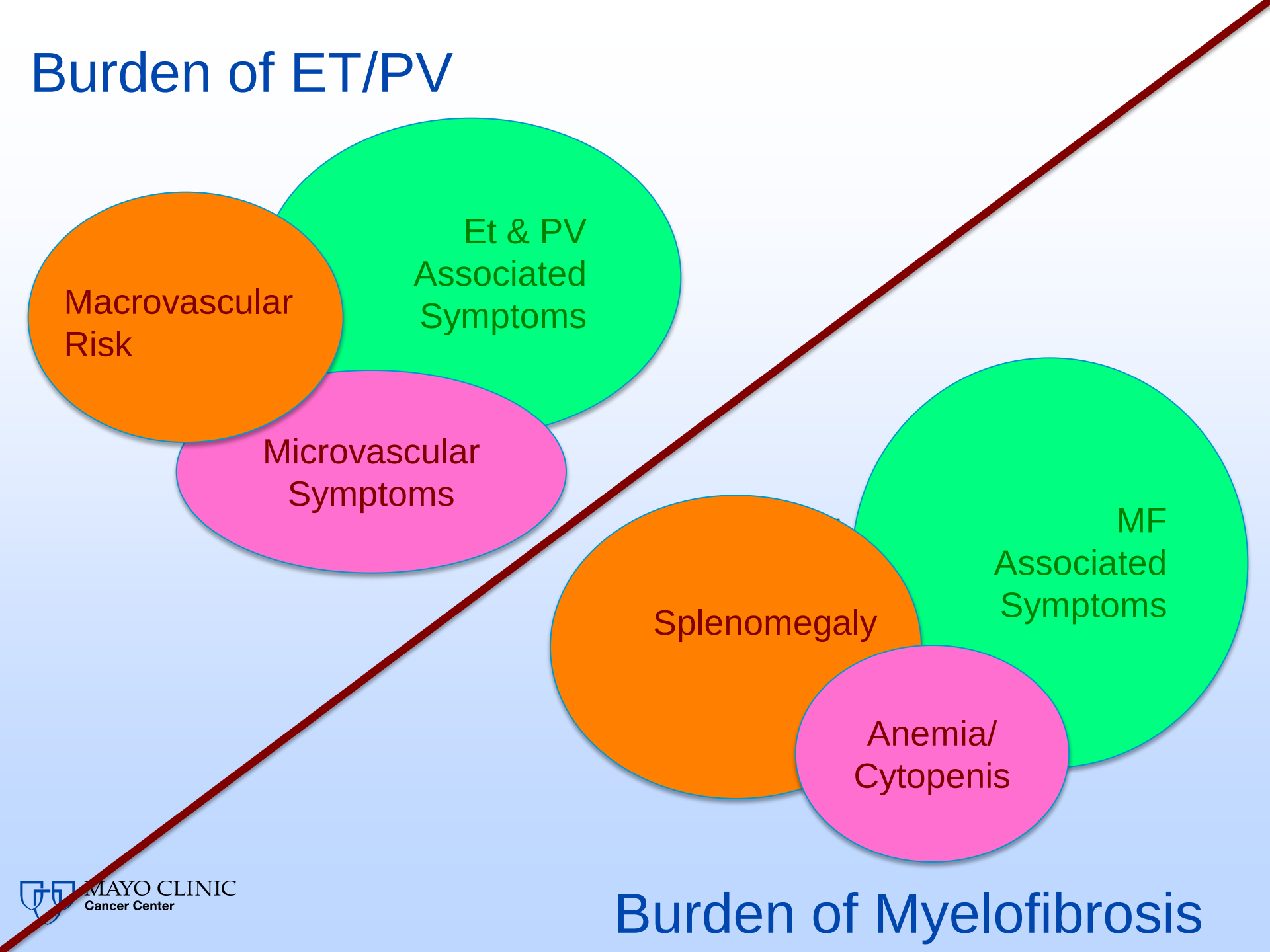
1. Sustained **platelet count** ≥450 x10^9/L
2. **Bone marrow biopsy** specimen showing proliferation mainly of megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis
3. **Not meeting the WHO criteria** for polycythemia vera, primary myelofibrosis, BCR-ABL1 positive chronic myelogenous leukemia or myelodysplastic syndrome or other myeloid neoplasm
4. Demonstration of **JAK2 V6127F** or other clonal marker, or in the absence of JAK2 V617F, no evidence for reactive thrombocytosis



CALR mutations in *JAK2* negative ET and MF



Burden of ET/PV



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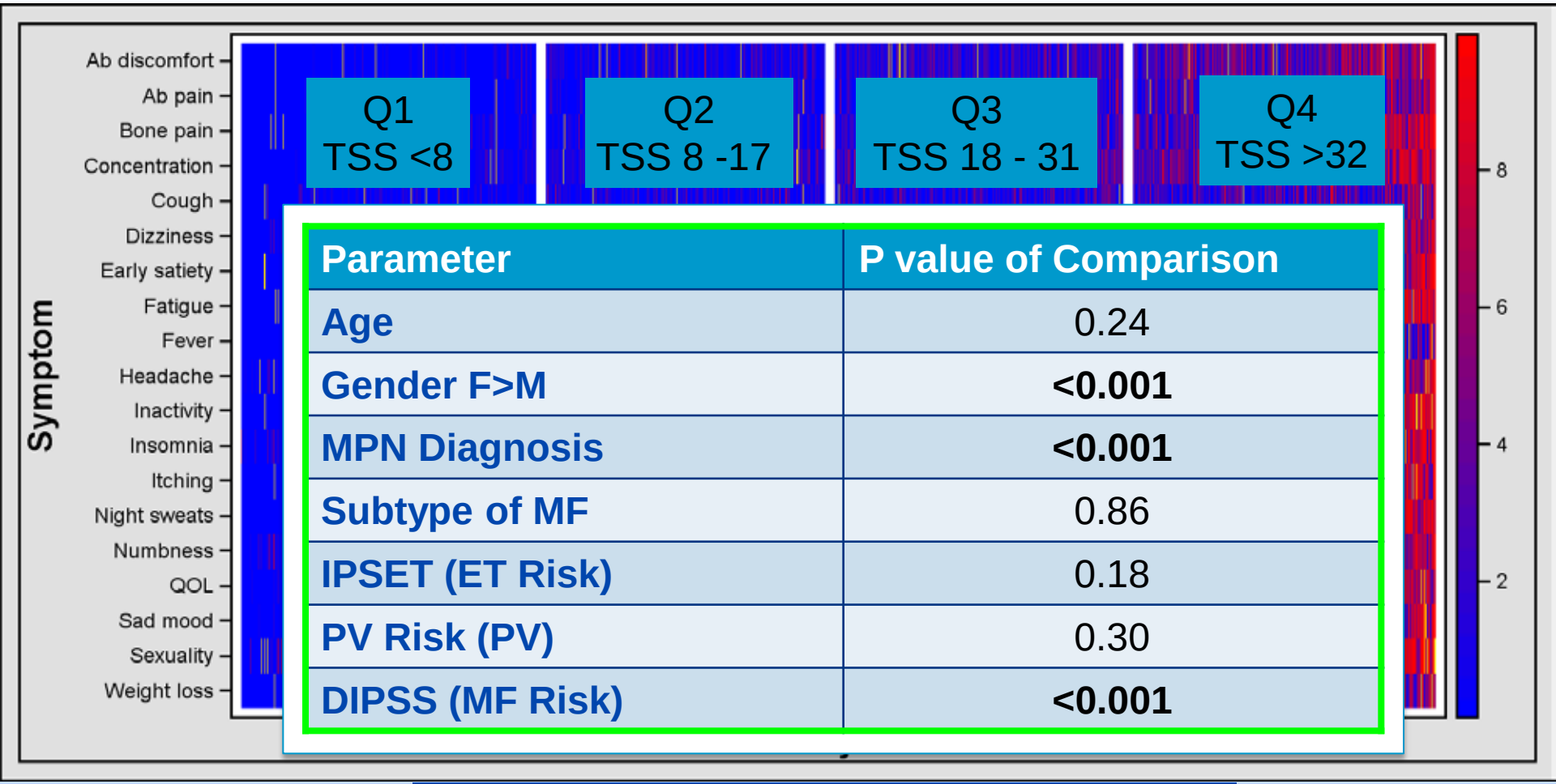
Burden of Myelofibrosis

MPN Symptom Burden by Quartiles

1858 MPN-SAF Respondents



Parameter	P value of Comparison
Age	0.24
Gender F>M	**<0.001**
MPN Diagnosis	**<0.001**
Subtype of MF	0.86
IPSET (ET Risk)	0.18
PV Risk (PV)	0.30
DIPSS (MF Risk)	**<0.001**

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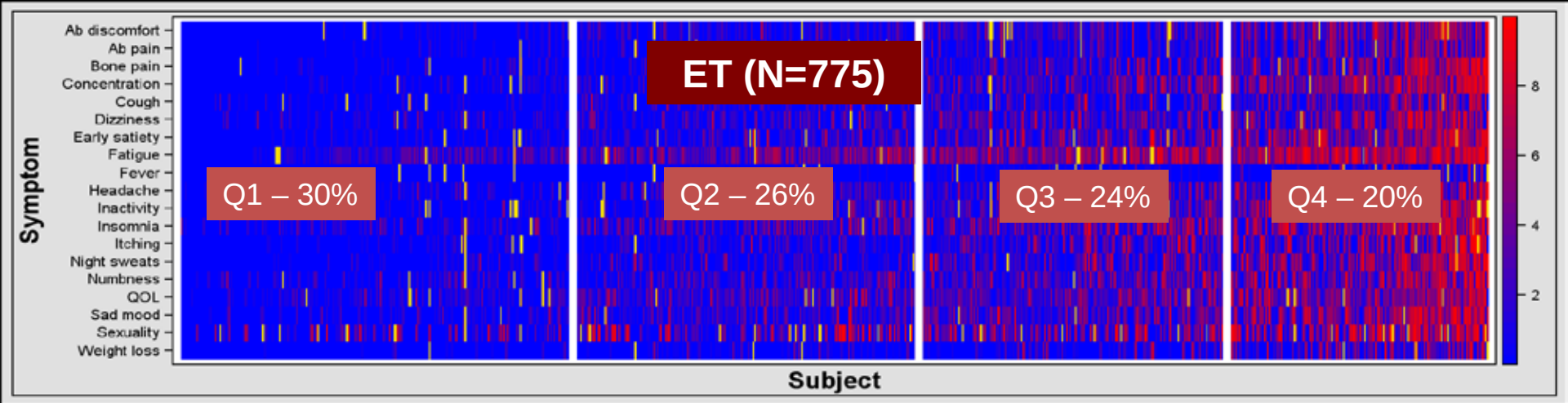
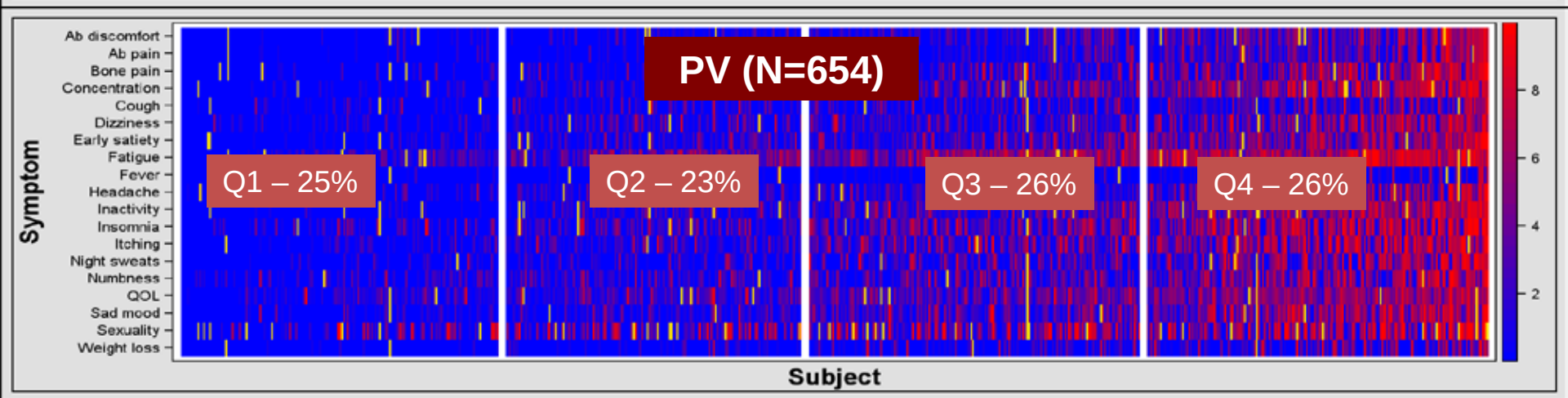
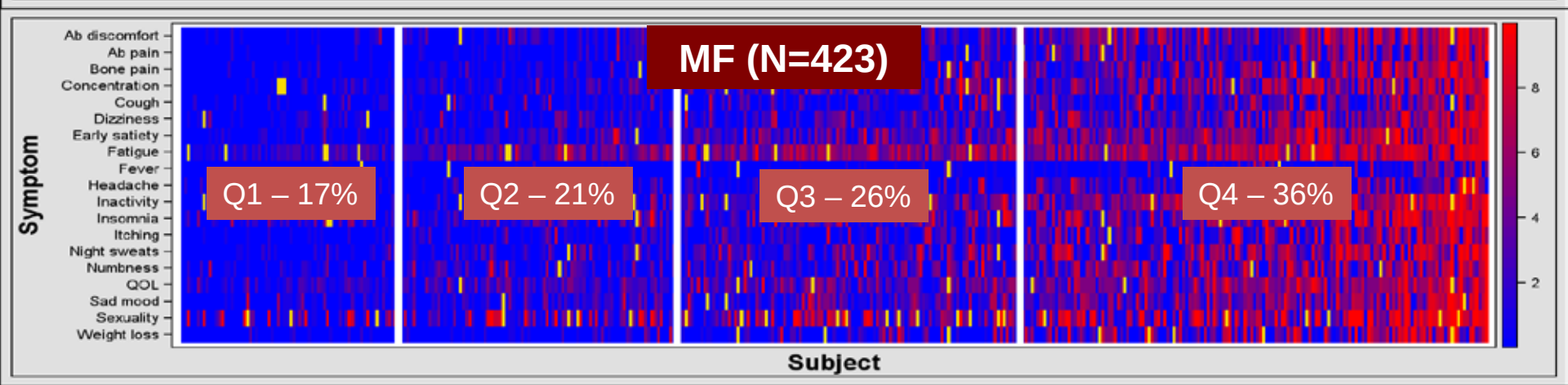
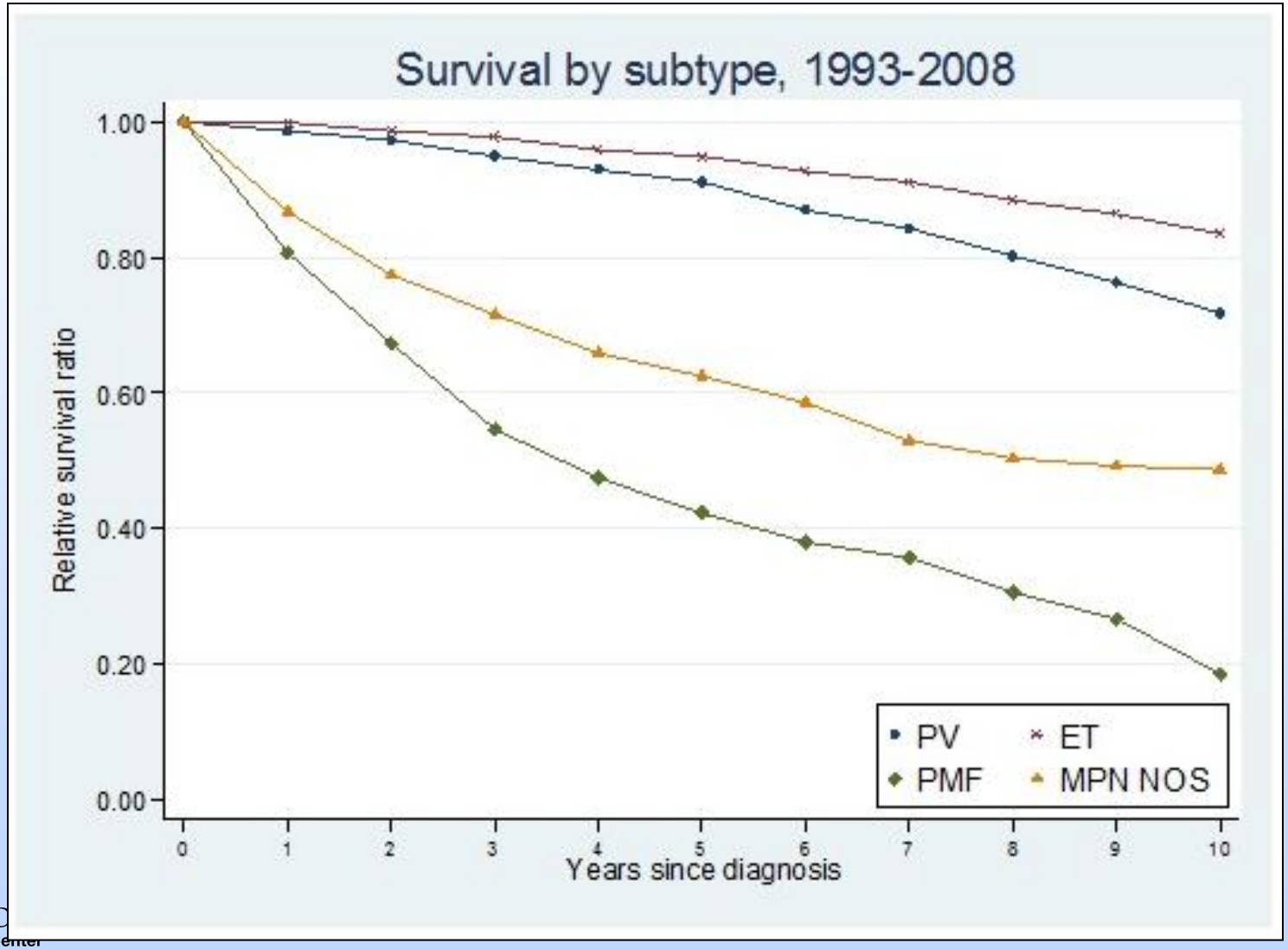
Quartile 1 (Q1): 0-24% Quartile 2 (Q2): 25-49%
Quartile 3 (Q3): 50-74% Quartile 4 (Q4): 75-100%


ET (N=775)
Q1 – 30%
Q2 – 26%
Q3 – 24%
Q4 – 20%
Symptom
Ab discomfort
Ab pain
Bone pain
Concentration
Cough
Dizziness
Early satiety
Fatigue
Fever
Headache
Inactivity
Insomnia
Itching
Night sweats
Numbness
QOL
Sad mood
Sexuality
Weight loss
Subject
8
6
4
2


PV (N=654)
Q1 – 25%
Q2 – 23%
Q3 – 26%
Q4 – 26%
Symptom
Ab discomfort
Ab pain
Bone pain
Concentration
Cough
Dizziness
Early satiety
Fatigue
Fever
Headache
Inactivity
Insomnia
Itching
Night sweats
Numbness
QOL
Sad mood
Sexuality
Weight loss
Subject
8
6
4
2


MF (N=423)
Q1 – 17%
Q2 – 21%
Q3 – 26%
Q4 – 36%
Symptom
Ab discomfort
Ab pain
Bone pain
Concentration
Cough
Dizziness
Early satiety
Fatigue
Fever
Headache
Inactivity
Insomnia
Itching
Night sweats
Numbness
QOL
Sad mood
Sexuality
Weight loss
Subject
8
6
4
2

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



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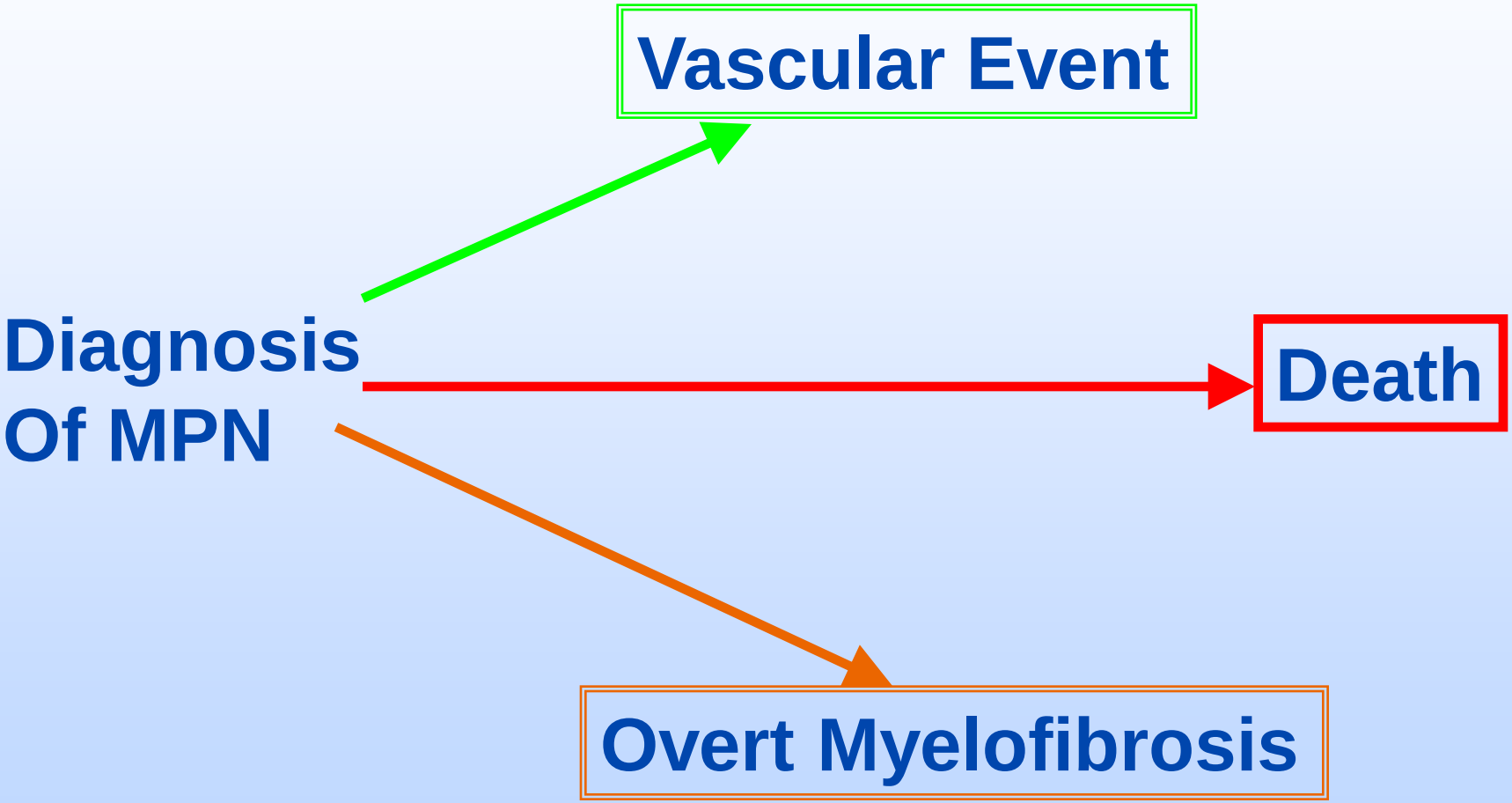
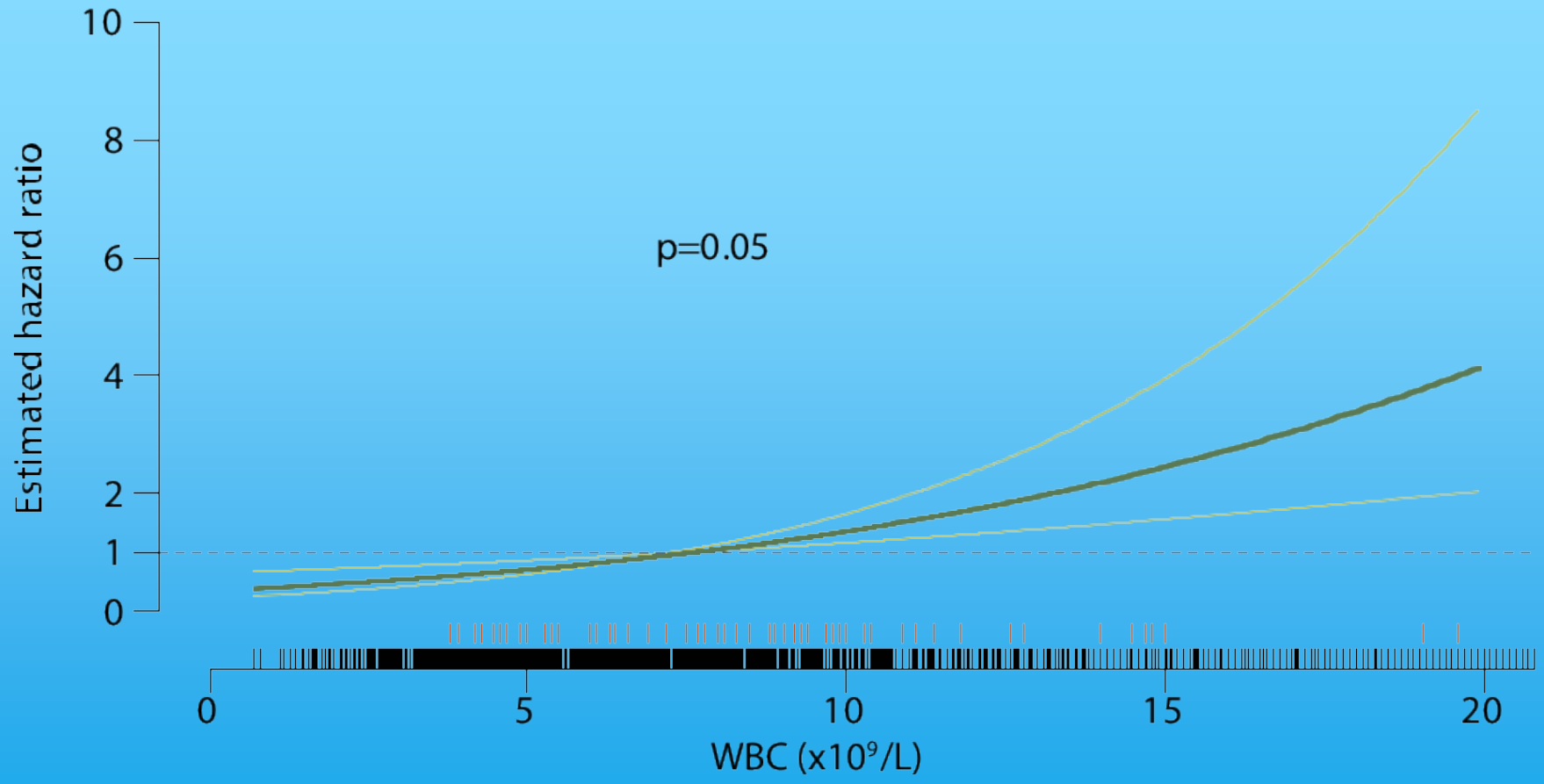
Hultcrantz et al Blood 2010 (a3071)

Assessing Risk in MPNs

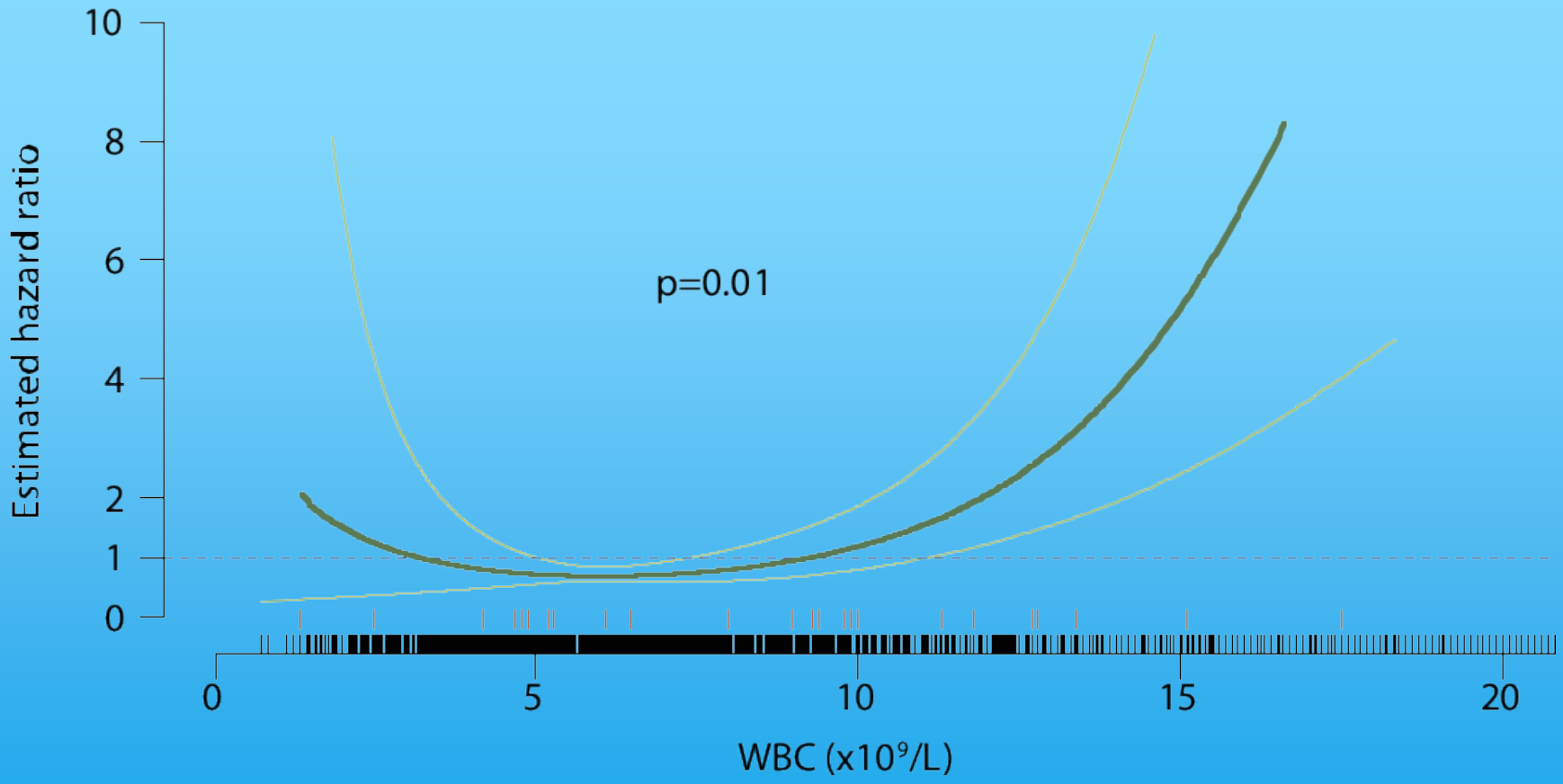


White cell count & thrombosis



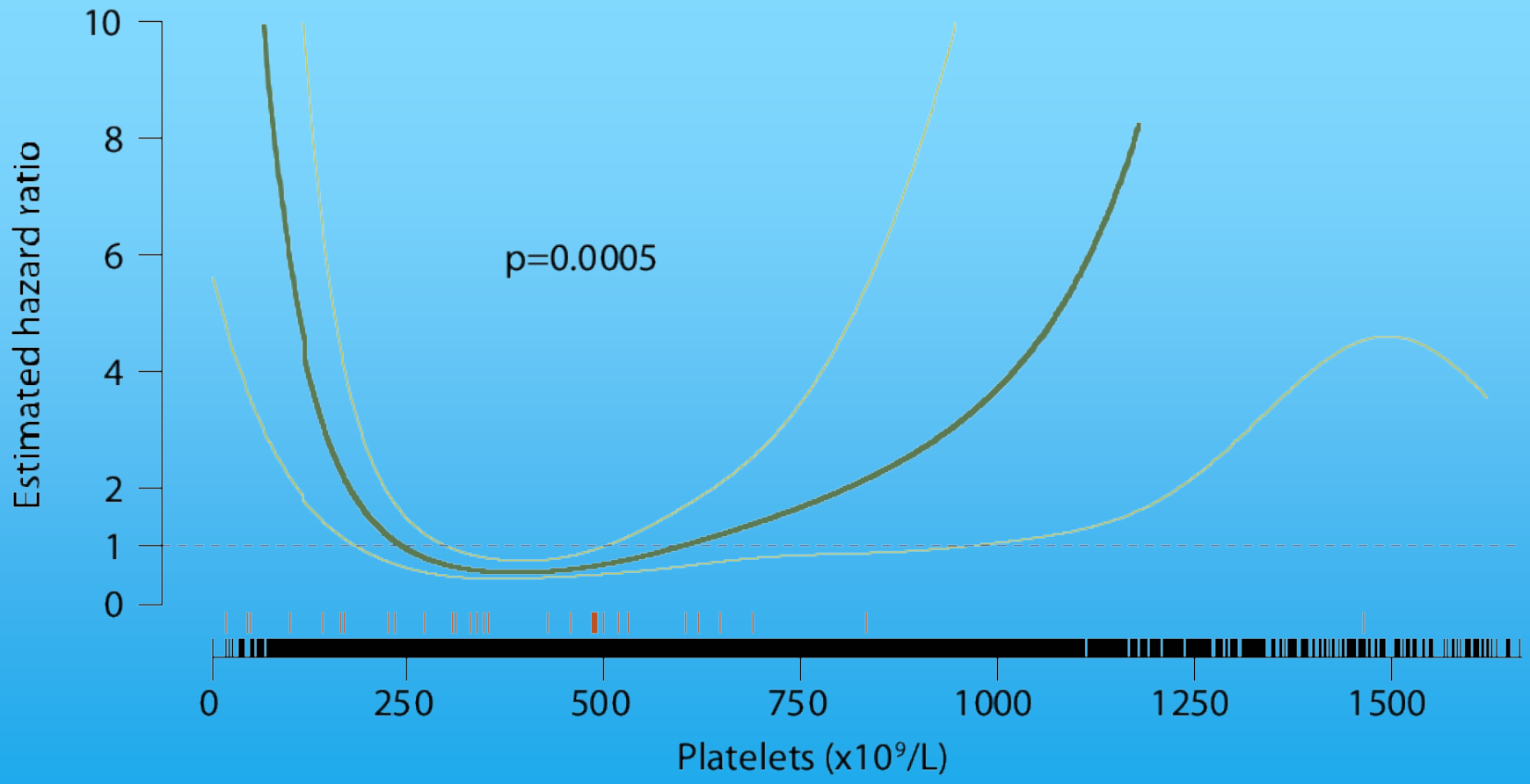
Campbell submitted 2010

WCC & major hemorrhage



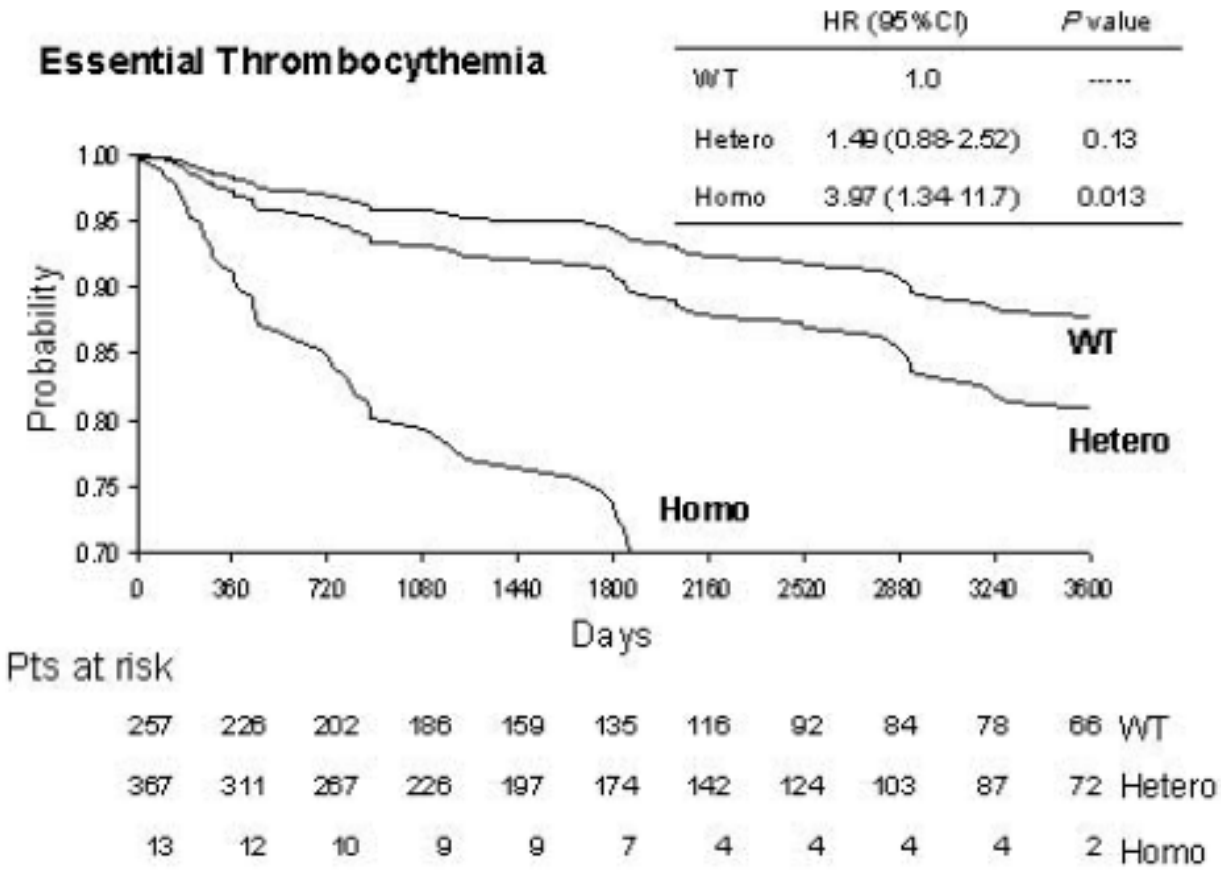
Campbell submitted 2010

Platelets & major hemorrhage



Campbell submitted 2010

Significance of JAK2V617F homozygosity



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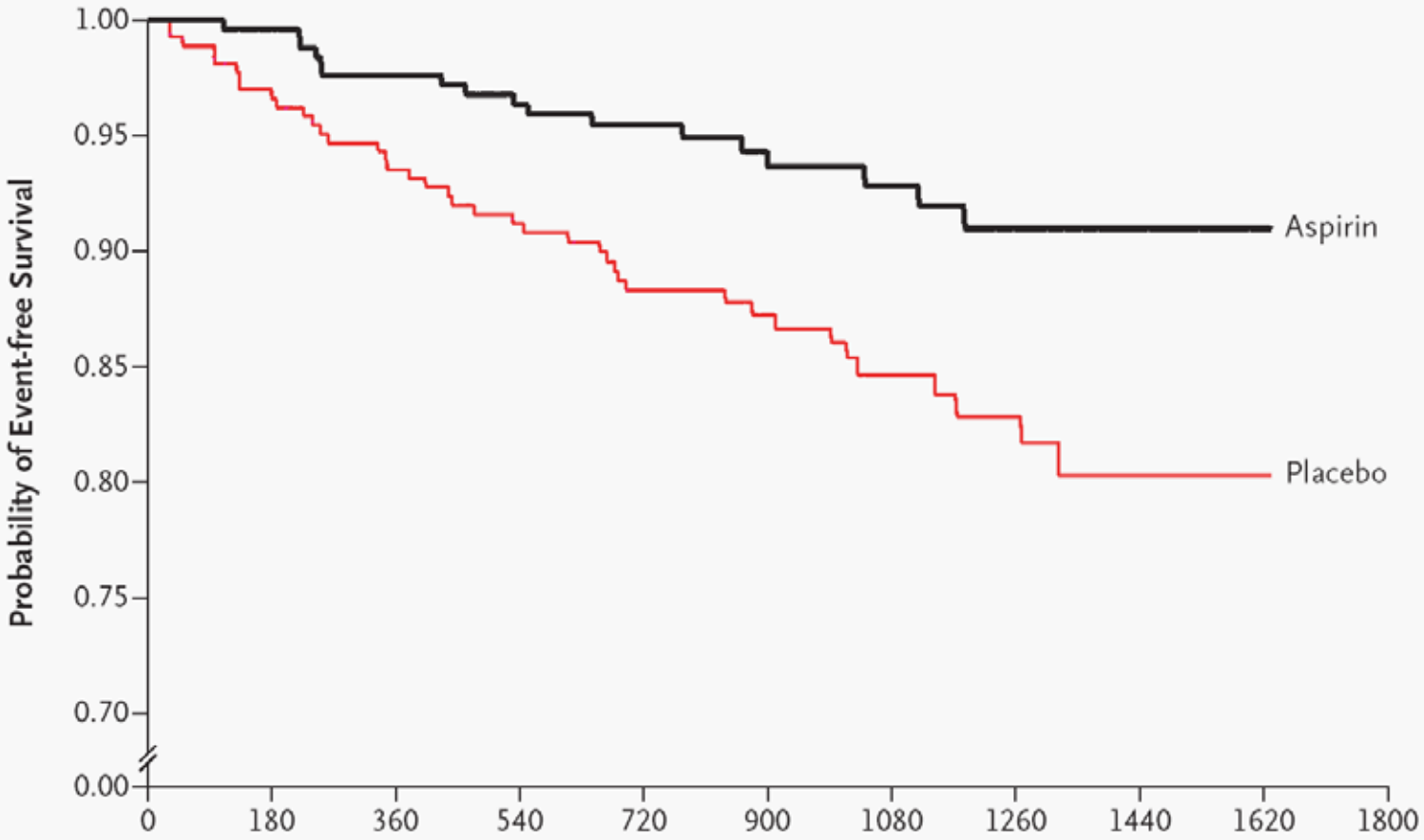
Vannucchi 2007

Monitoring MPNs

Evolving MPN prognostic scales

	IPSET (ET—3 groups) *Survival thrombosis risk*	PV Risk (4 groups) *Survival leukemia rates*	DIPSS (PMF—4 groups) *Survival*
Age, years	≥ 60 (2 pts) vs < 60	≥ 67 (5 pts) 57-66 (2 pts), < 60 (0)	≥ 65 (1 pt) vs < 65
Leukocytes	≥ 11 (1 pt) vs < 11 x 10^9/L	≥ 15 (1 point) vs < 15 x 10^9/L	> 25 (1 pt) vs ≤ 25 x 10^9/L
Hemoglobin			< 10 (2 pts) vs ≥ 10 g/dL
Constitutional symptoms			Present[a] (1pt) vs absent
Blasts			≥ 1% (1pt) vs < 1%
Prior thrombosis	Yes (1 point) vs No	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 Leuk 2014*	*Passamonti Blood 2010*

[a] 10% weight loss over prior 6 months, night sweats, unexplained fever.

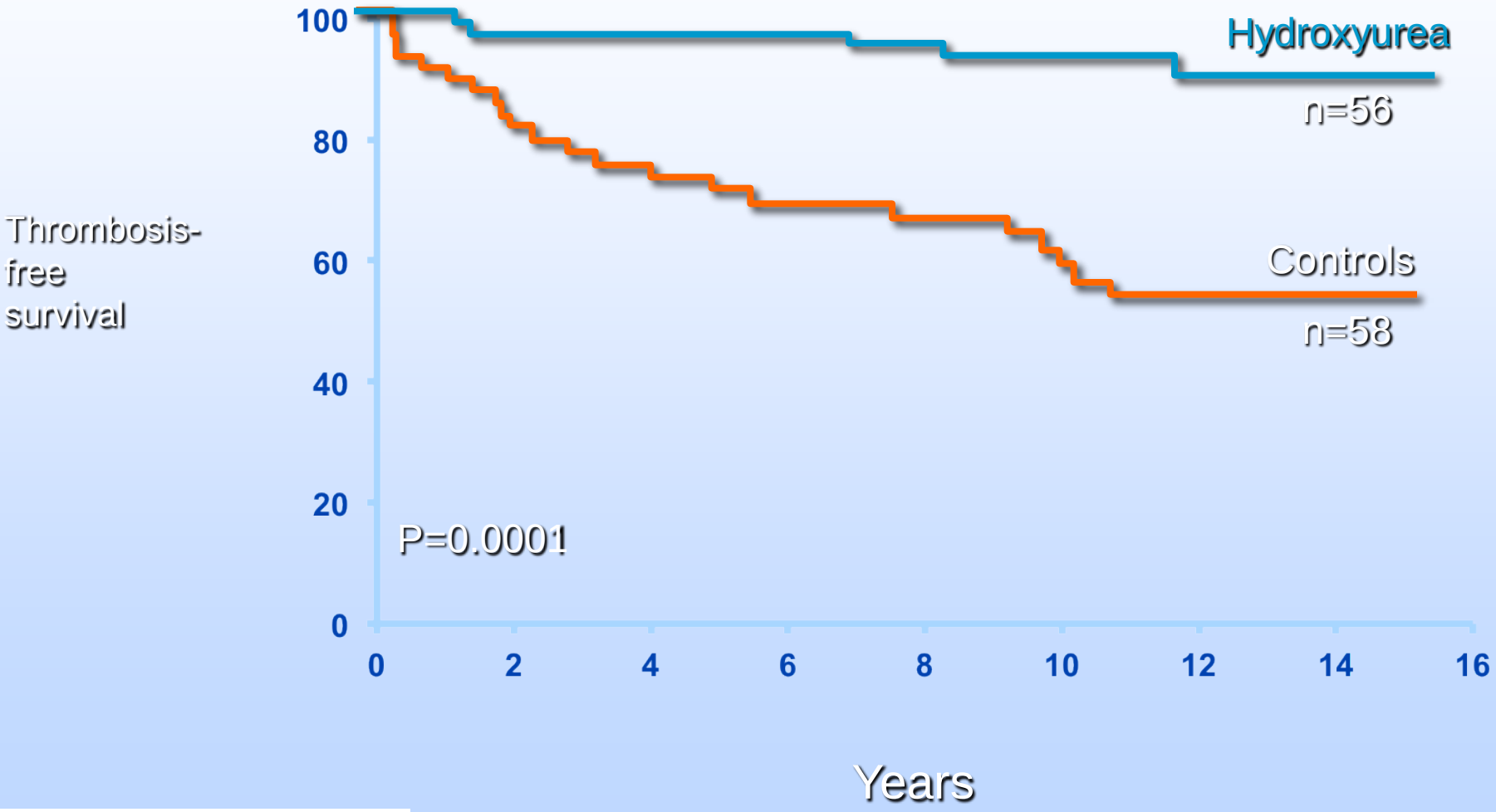


ECLAP analysis:

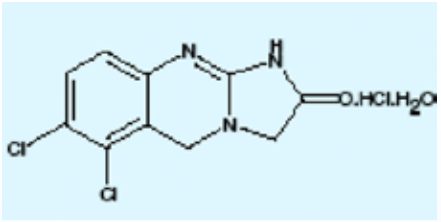
Antiplatelet therapy was significantly associated with a lower risk of fatal and non-fatal cardiovascular events.

Marchioli 2005

HU-Treatment Effect in High-Risk ET



Cortelazzo et al. *NEJM* 1995;332:1132
Finazzi et al. *BJH* 2000;110:577



Published Anagrelide Experience

Study	*N*	*ET*	*PV*	*CML*	*Other*	*Impact*
Silverstein 1988	***20***	***17***	***2***	***1***	***0***	**Initial Trial**
ASG 1992	***577***	***355***	***68***	***114***	***60***	**Response rate 79%**
Petit 1997	***942***	***546***	***113***	***179***	***108***	**Basis for FDA Approval**
Storen 2001	***35***	***35***	***0***	***0***	***0***	**Long Term Safety**
Fruchtman 2005	***3590***	***2425***	***506***	***561***	***458***	**Basis for EMEA License**
Harrison 2005	***805***	***809***	***0***	***0***	***0***	**PT 1 Trial**

PT-1 Trial
Hydrea Vs. Anagrelide (Plus ASA)

- 809 High Risk ET patients randomized
  - Hydrea plus ASA
  - Anagrelide plus ASA

- Composite Endpoints
  - Thrombosis (arterial or venous)
  - Hemorrhage
  - Death

Harrison et. al. NEJM 2005;353:33-45

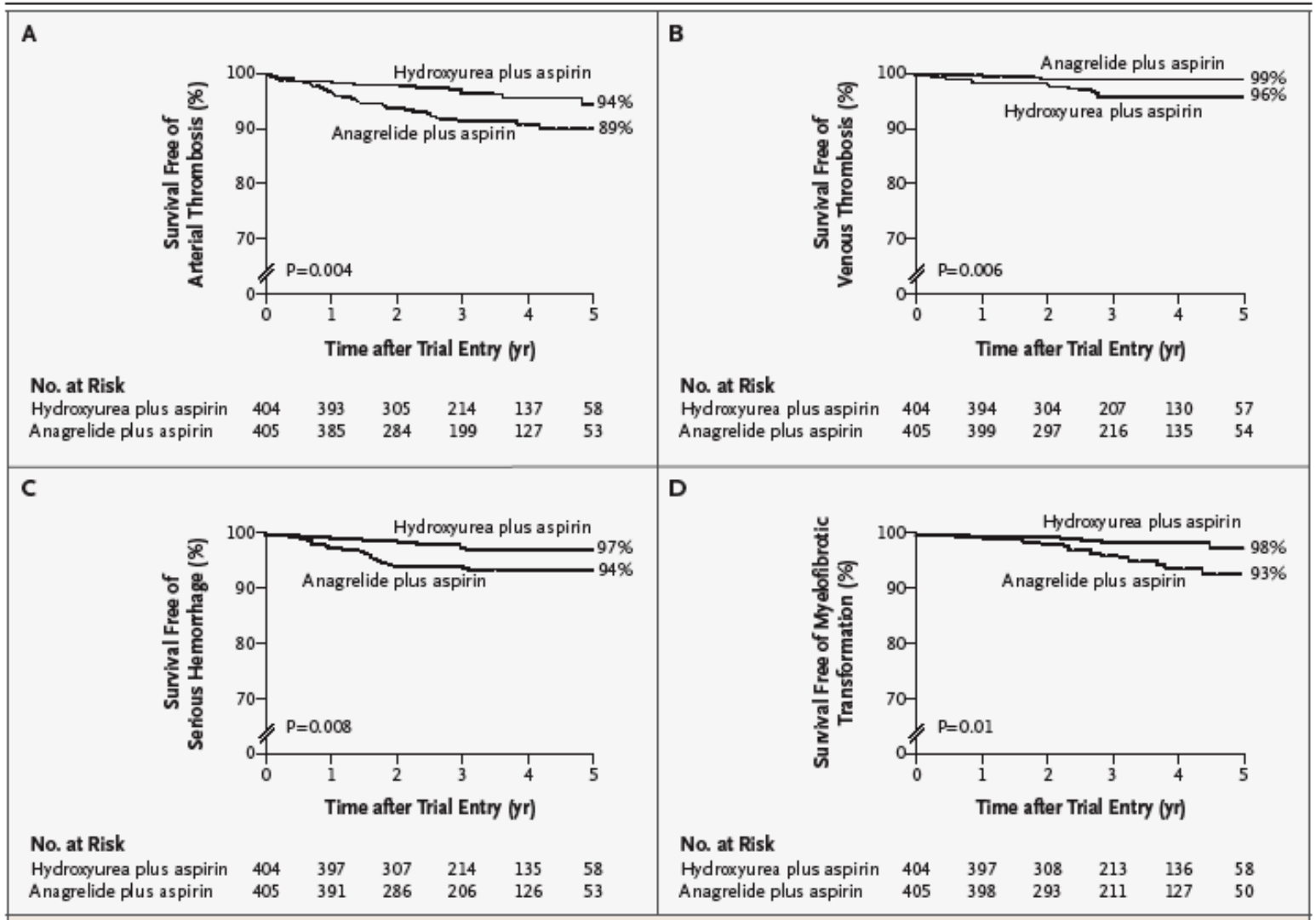


Figure 3. Kaplan–Meier Estimates of Survival Free of the Secondary End Points of Arterial Thrombosis (Panel A), Venous Thrombosis (Panel B), Serious Hemorrhage (Panel C), and Myelofibrotic Transformation (Panel D).

Harrison et. al. NEJM 2005;353:33-45

ANAHYDRET study vs. UK-PT1 study

	ANANAHYDRET* (n=258)	**PT1**** (n=805)
Diagnosis according to (applied criteria)	**WHO criteria** mandatory **BM biopsy** with central review	**PVSG criteria**
Pretreatment	**only newly diagnosed** WHO-ET patients	pretreated PVSG-cohort
Concomitant therapy	preferred **mono**therapy	fixed combination with Asprin

** Gisslinger et al., Blood 2008, ASH Abstract 661*
***Harrison et al., N Engl J Med 2005; 353:33-45*

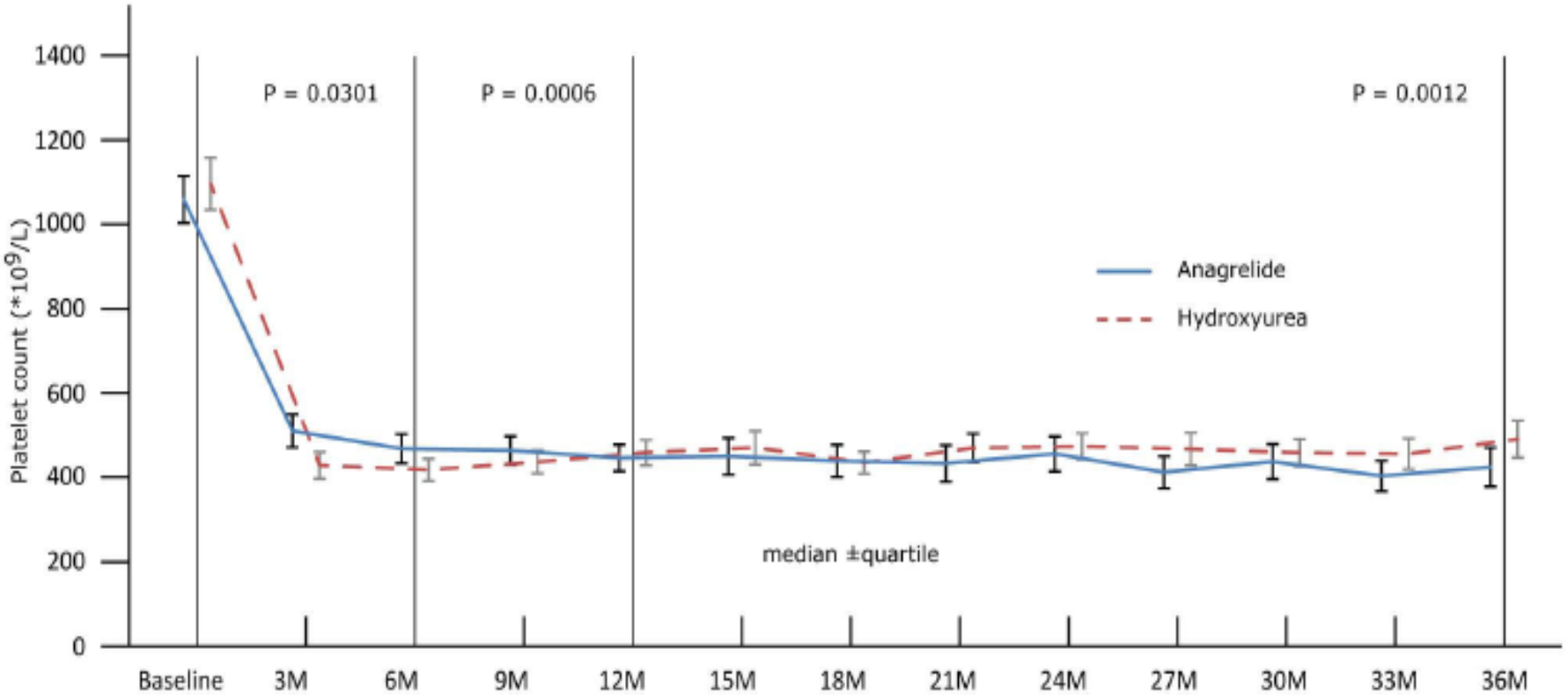
Results of the central bone marrow histopathology and JAK2V617F analysis in 235 study patients

	n	%	JAK2 pos.	JAK2 allele burden Median (%)	JAK2 neg.
ET	194	82.5	79	8.7	73
PMF-0 (fiber grade 0)	16	6.8	10	11.7**	3
PMF-1 (fiber grade 1)	3	1.3	1	-	0
PV (PV-like pattern)	16	6.8	8	10.4	5
UC - unclassifiable	6	2.6	9*		11*

* JAK2V617F analysis was performed in more patients than the bone marrow re-evaluation
** Value denotes pooled PMF-0 and PMF-1

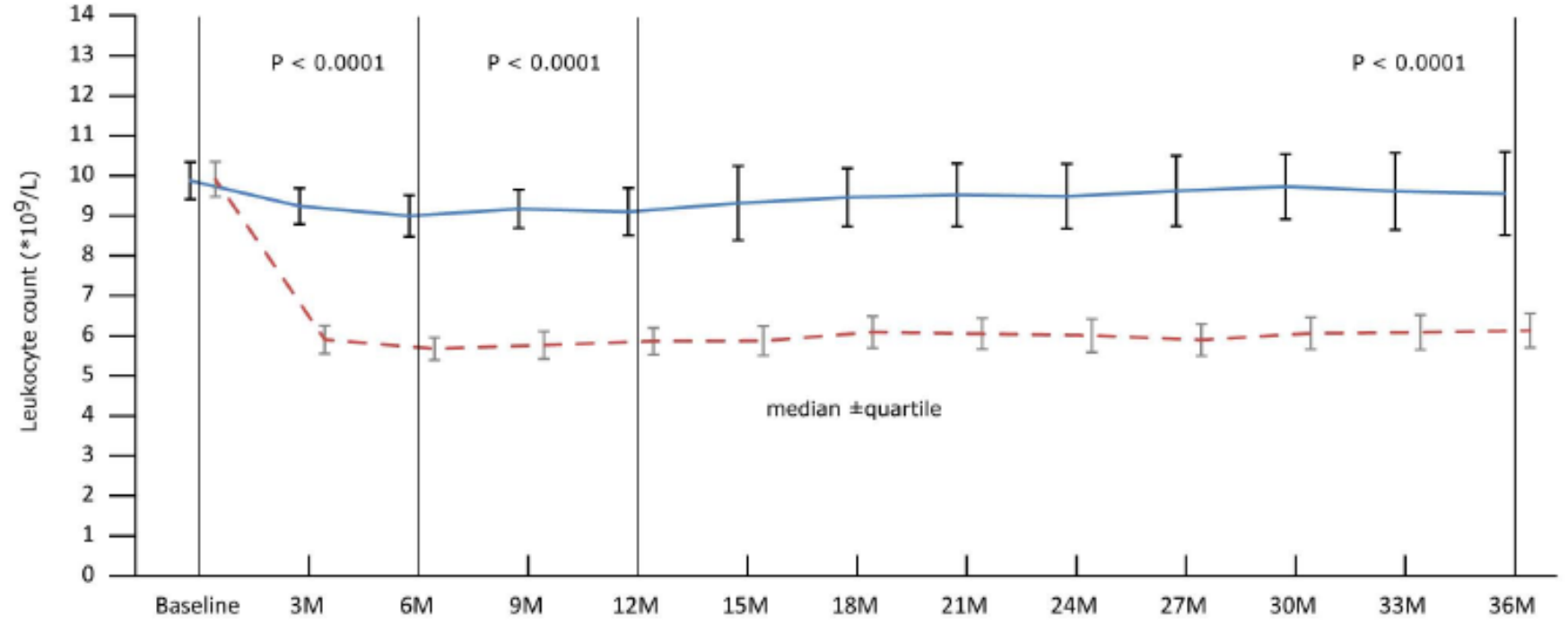
Gisslinger et al, 2013

No difference in platelet lowering effect ANA vs. HU



Gisslinger et al, 2013

Leukocyte counts remained unchanged in ANA treated patients



Patient no.													
Anagrelide	122	122	115	104	105	65	70	66	66	60	57	44	39
Hydroxyurea	131	131	127	121	122	87	84	83	77	74	61	44	46

Gisslinger et al, 2013

Resistance/Intolerance to Hydroxycarbamide in ET

- Platelet count >600x10^9/L after 3 months of at least 2 g/day of HU (2.5 g/day in patients >80 kg)
- Platelets >400x10^9/L and WBC count <2.5x10^9/L or Hb <100 g/L at any dose of HU
- Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HU
- HU-related fever

Barosi *et al.* Leukemia 2007

Hydroxycarbamid
(Hydroxyurea)

Anagrelide
(Xagrid)

P-32

Busulfan

Juggling ET Options

Interferon

Aspirin

ACTIVITIES OF INTERFERONS IN MPN

- Inhibit MK proliferation and TPO-induced MPL signaling
  Wang, Blood, 2000
- Inhibit EEC and endogenous MK colony growth
  Dudley, Br J H, 1990
  Castello, Br J H, 1994
- Predominant activity against clonal BFU-E
- Antagonize PDGF, inhibit the growth of marrow-derived fibroblasts

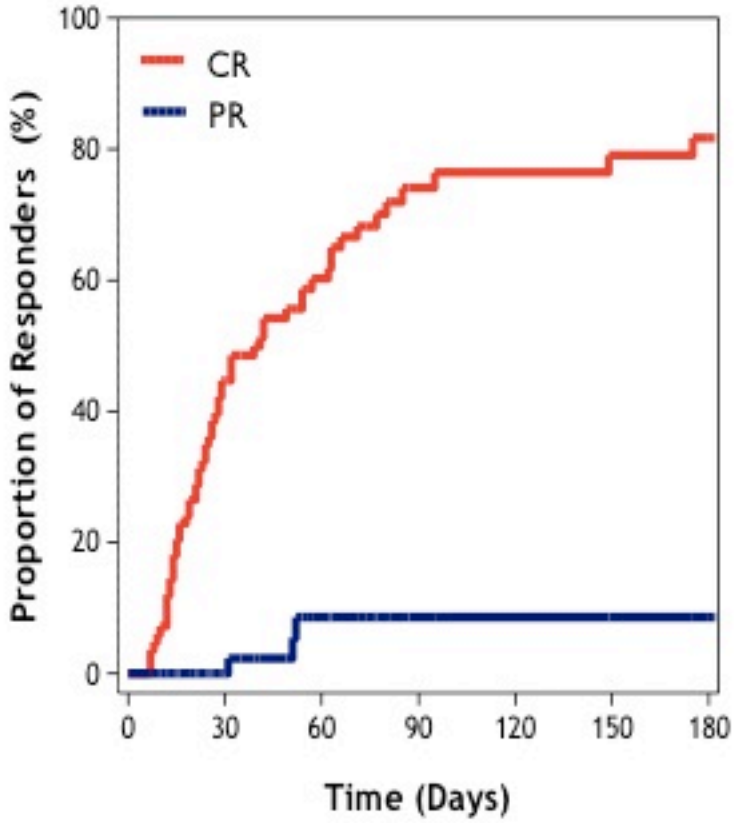
PEG-INFa-2a
PV-ET

Patient Characteristics

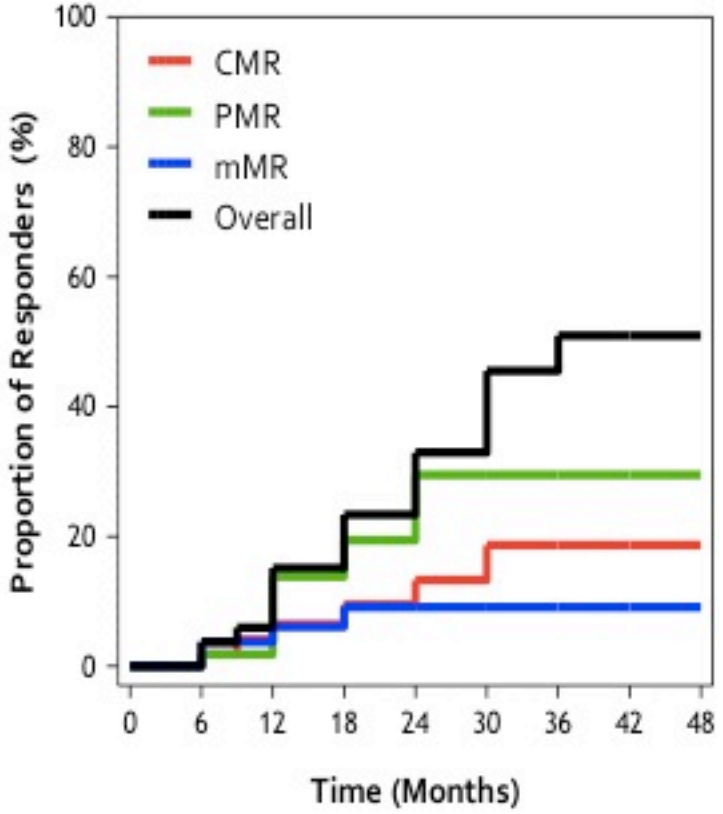
	PV (n=43)	ET (n=40)
Median Age (range)	54 (24-78)	53 (19-75)
Months Dx to Study entry	50 (0-350)	34 (1-277)
No. JAK2^{V617F}+ (%)	40 (93)	19 (48)
Median % JAK2^{V617F} allele	65	23
Abnormal Karyotype (%)	3 (7)	3 (7.5)
No. Prior Therapies (range)	1 (0-4)	2 (0-4)
Phlebotomy (%)	32 (74)	Not Applicable
Hydroxyurea (%)	20 (47)	28 (70)
Anagrelide (%)	9 (21)	22 (55)
IFNα (%)	9 (21)	6 (15)
Untreated (except phlebotomy in PV)	22 (51)	9 (23)

Quintas-Cardama et. al. Blood 2010: a461

Cumulative Incidence of Response



Hematologic Response

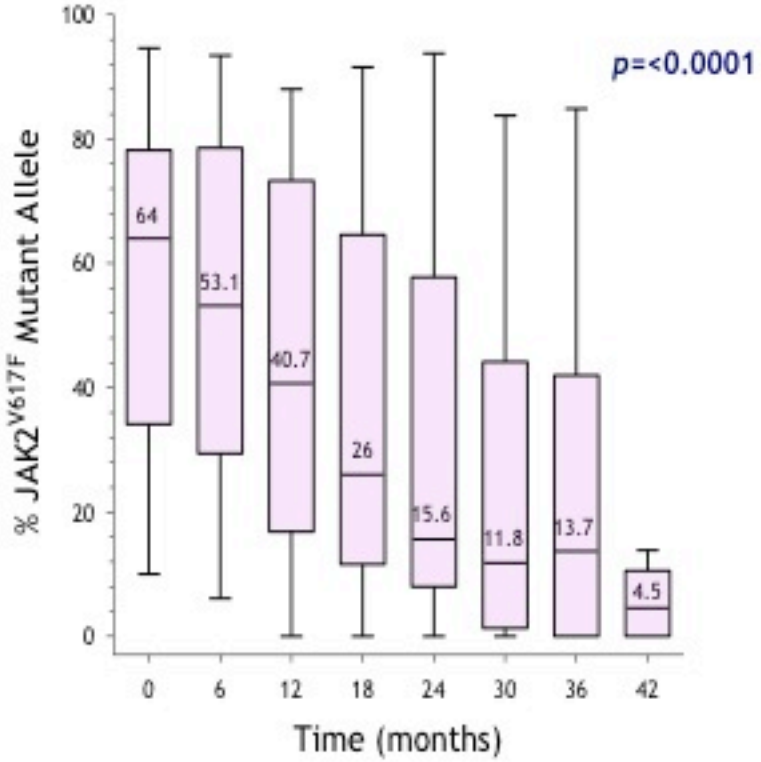


Molecular Response

Quintas-Cardama et. Al. Blood 2010: a461

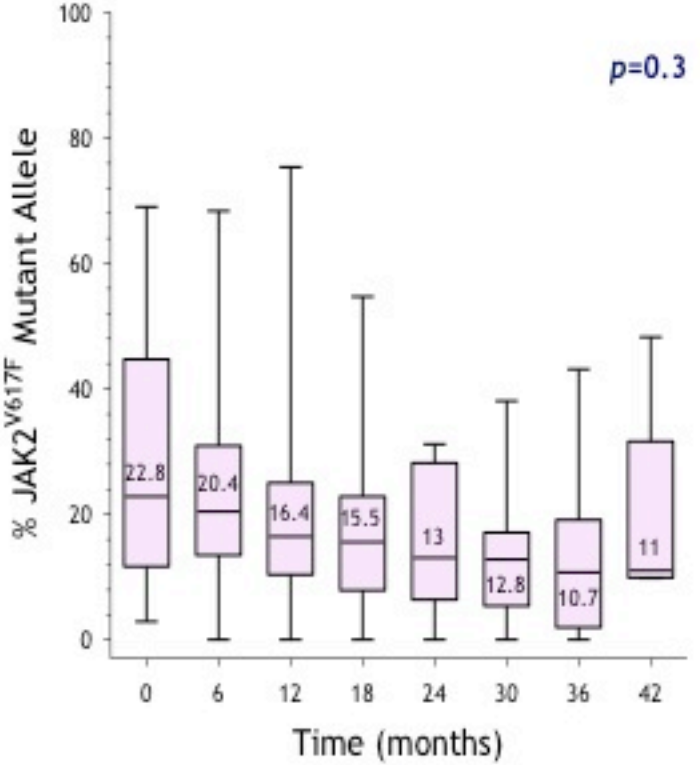
Dynamics of Molecular Response PV and ET Cohorts

No. Patients	42	32	30	28	26	19	18	8
CMR	0	0	1	2	4	4	5	4
PMR	0	3	8	10	10	8	7	4



PV

No. Patients	19	13	14	13	12	10	8	5
CMR	0	1	2	2	2	1	2	0
PMR	0	0	0	0	2	2	2	2



ET

Quintas-Cardama et. Al . Blood 2010: a461

Myeloproliferative Disorders Research Consortium Trial
Polycythemia Vera and Essential Thrombocythemia

MPD-RC 112 (NCT01259856 – clinicaltrials.gov)

Randomized Trial of *Pegylated* Interferon Alfa-2a versus Hydroxyurea Therapy in the Treatment of High Risk Polycythemia Vera (PV) and High Risk Essential Thrombocythemia (ET)

Registered & Randomized
High Risk ET and PV
(< 3 Months Prior Hydroxyurea)

PEG INF Alfa-2a

- Target dose 90 mcg/week
- Weekly Dosing
- ≥2 years of therapy in responders

HYDROXYUREA

- Titrated Dosing to Response
- Daily Dosing
- MPD-RC 111 in HYDROXYUREA Failures

ENDPOINTS

Primary: Complete response by ELN Criteria

Secondary: Partial response rate by ELN criteria, JAK2-V617F Allele Burden, Vascular Events, MPN Symptoms, Tolerability, Progression

Key Eligibility Criteria

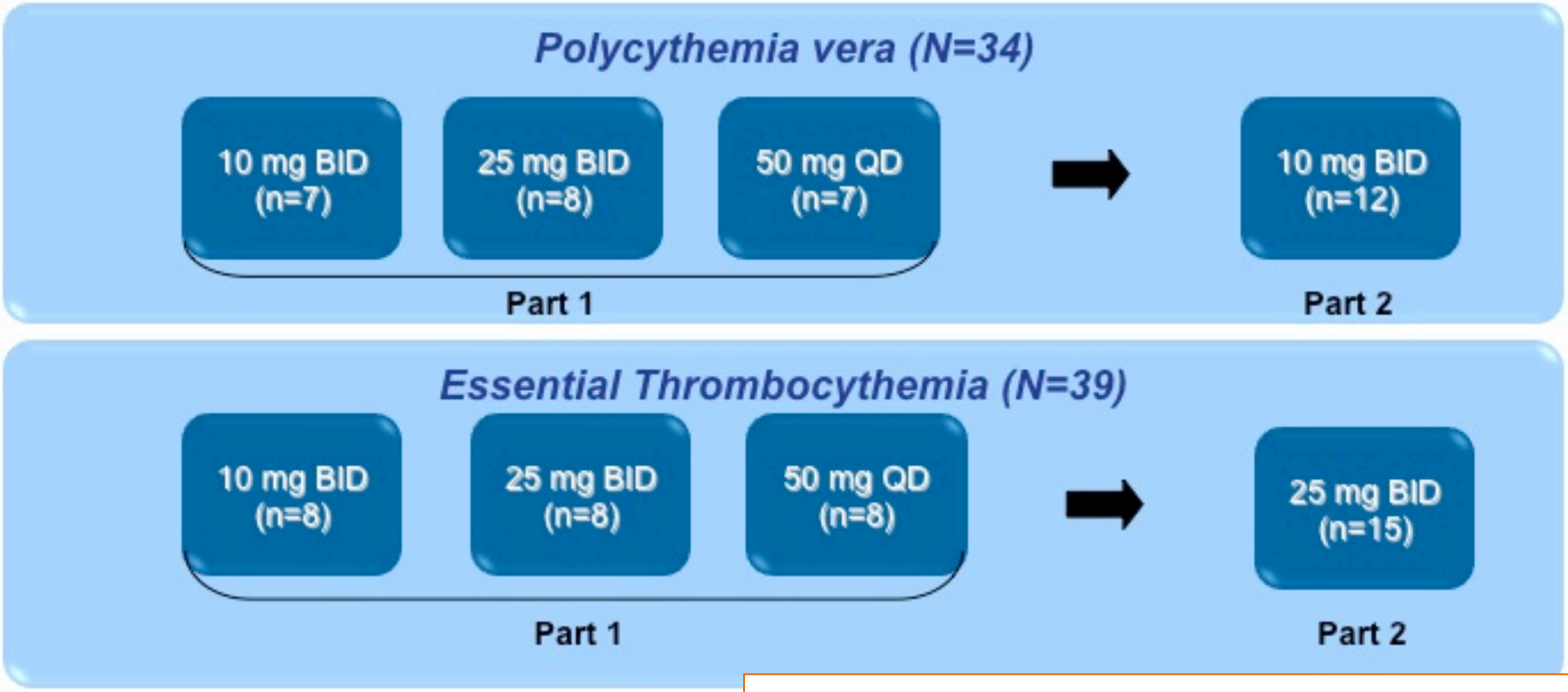
- High risk PV or ET within 3 years from diagnosis
- No prior cytoreductive treatment (interferon or pegasys) other than hydroxyurea for up to 3 months (prior phlebotomy, aspirin, and/or anagrelide allowed)
- Age of 18 or older with relatively normal kidney and liver function
- No other serious medical problems

Questions contact MPD-RC (www.mpd-rc.org)
John Mascarenhas, MD john.mascarenhas@mssm.edu Phone: 1 (212) 241-6756

Phase II Study of INCB 18424 in Patients with Advanced ET and PV

Eligibility Criteria:

- Refractory or intolerant to hydroxyurea (HU) or HU contraindicated
- PV: Hct > 45% OR phlebotomy 2 times in last 6 months, with at least one phlebotomy in last 3 months
- ET: Platelets > 650 x 10^9/L unless on therapy



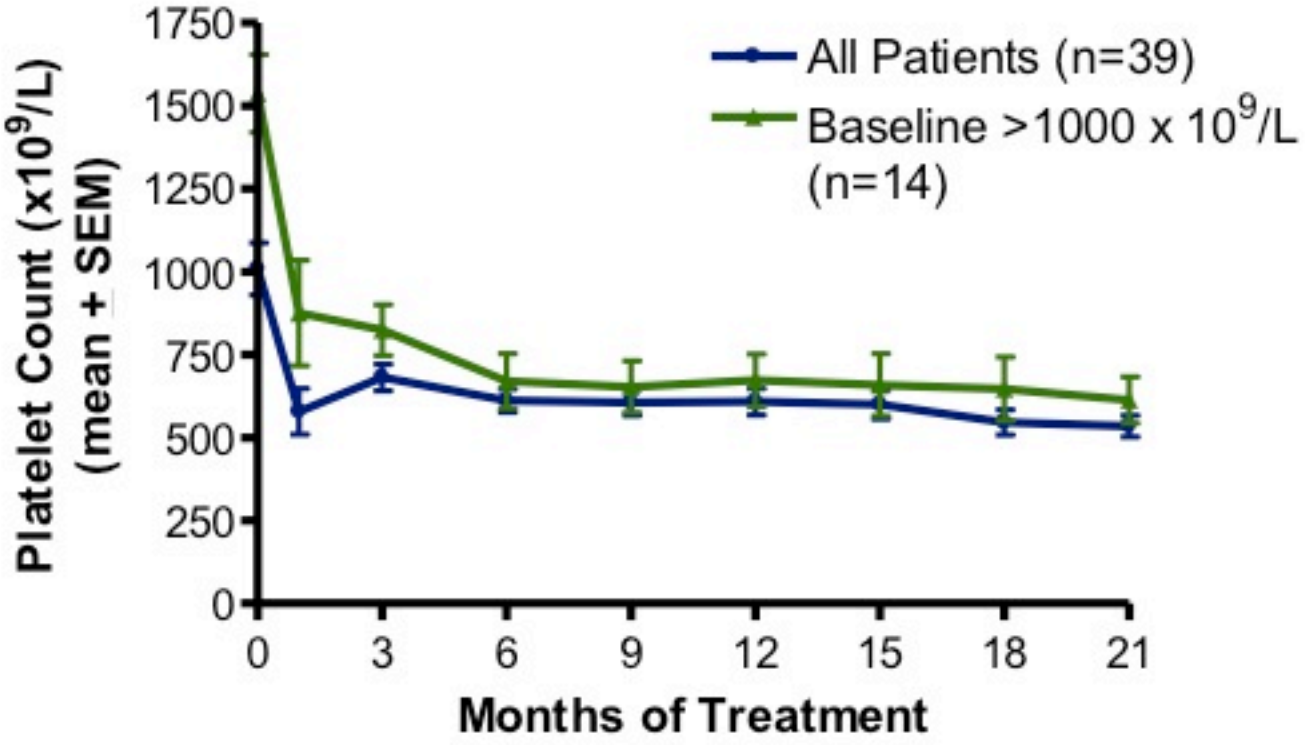
Verstovsek et. al. ASH 2010; Abstract 313

Patient Characteristics

Characteristic (median)	ET (n = 39)	PV (n = 34)
Age, years	51	58
Female	64%	50%
Months from Diagnosis	88	115
Refractory to HU	87%	74%
No. Prior Therapies	1 (1-3)	1 (1-3)
Hct %	41.0	46.7
Platelets $x10^9/L$	849 (mean 1009)	76%
WBC $x10^9/L$	8.2	527
Splenomegaly Size, cm (range)	10% 5 (3-7)	13.2
$JAK2^{V617F}$ positive	65%	74%
$JAK2^{V617F}$ allele burden	16%	9 (1-21) 100%

Verstovsek et. al. ASH 2010; Abstract 313

Platelet Count Reduction in ET



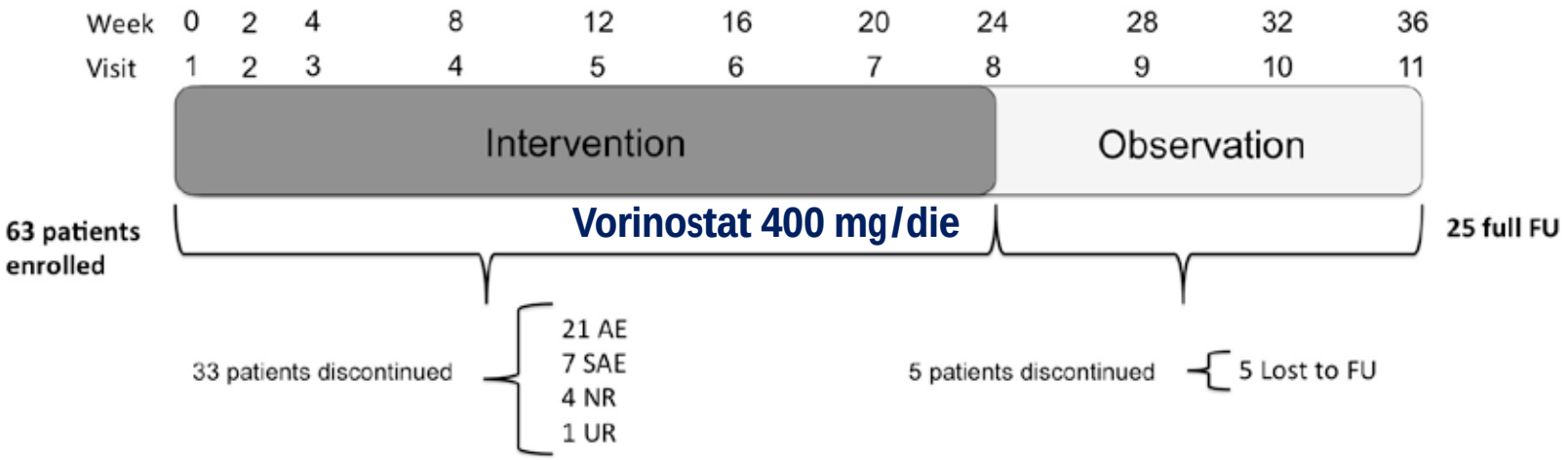
- 49% achieved normal platelet counts and 79% achieved <600,000 or a ≥50% reduction as of last follow-up visit
- 13 of 14 subjects with baseline platelet counts >1,000,000 have achieved a greater than 50% reduction

Verstovsek et. al. ASH 2010; Abstract 313

Oral Session

A Phase II Study of Vorinostat (MK-0683) in Patients with Polycythemia Vera and Essential Thrombocythemia

Christen Lykkegaard Andersen, On Behalf of The COSMYD Group and The Nordic MPN Group (A803)



- ***Vorinostat*** inhibits enzymes (histone deacethylases) that regulate the transcription of genes in proteins
- Approved for some cutaneous lymphomas

RESULTS

- RESPONSES : 35% at the end of intervention phase, 9% at the end of observation phase
- No effect on the amount of JAK2V617F mutation
- High discontinuation rate with 52% during intervention phase due to side effects

----- à **at least at the dose employed, Vorinostat had minimal clinical activity and frequent side effects**

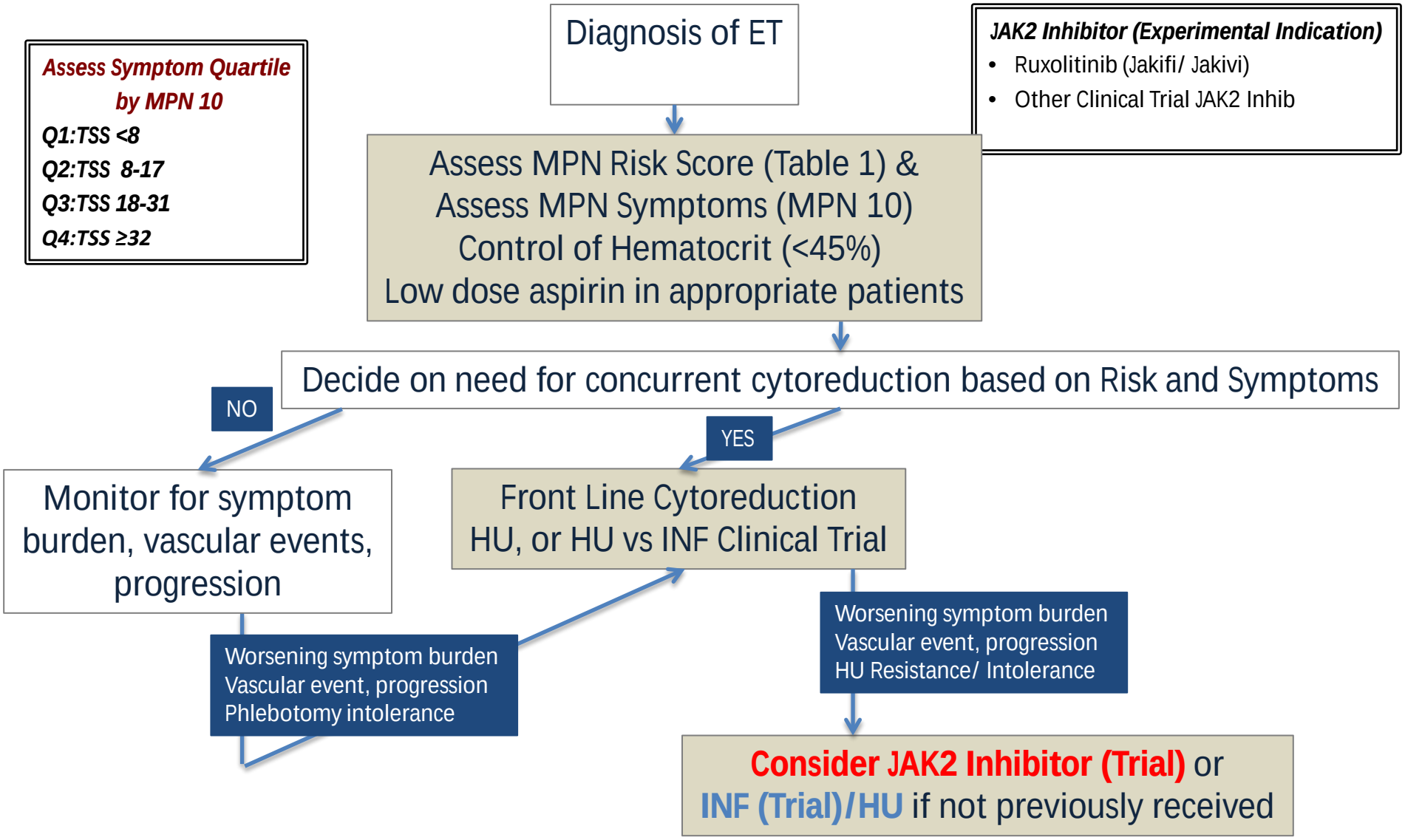
Oral Session

Imetelstat Rapidly Induces and Maintains Substantial Hematologic and Molecular Responses in Patients with Essential Thrombocythemia Who Are Refractory or Intolerant to Prior Therapy: Preliminary Phase II Results.

GM. Baerlocher, E Oppliger Leibundgut, C Ayran, M Blaney, B Burington, D Morfeld, O Odenike, O Ottman, A Reddy, A Roeth, G Spitzer, M J. Stuart, S Verstovsek, D S. Snyder

- Abnormally high levels of **telomerase**, an enzyme that acts on DNA, are expressed by neoplastic progenitor cells
- There is evidence that Imetelstat can reduce the growth of abnormal megakaryocyte progenitors in ET more selectively compared with control subjects
- **IMETELSTAT** is the first specific telomerase inhibitor in clinical development

Proposed Algorithm of Therapy of ET in 2015



ET in 2015

- ET is also a heterogeneous MPN
- Amongst those with JAK2 mutations an overlapping phenotype with PV exists
- Management begins with anti-platelet therapy
- HU, anagrelide, and even interferon all have a role
- JAK inhibition for control of thrombocyosis, as single agent, not yet established