Mayo Clinic Treatment Strategy in Essential Thrombocythemia, Polycythemia Vera and Myelofibrosis

2013 Update

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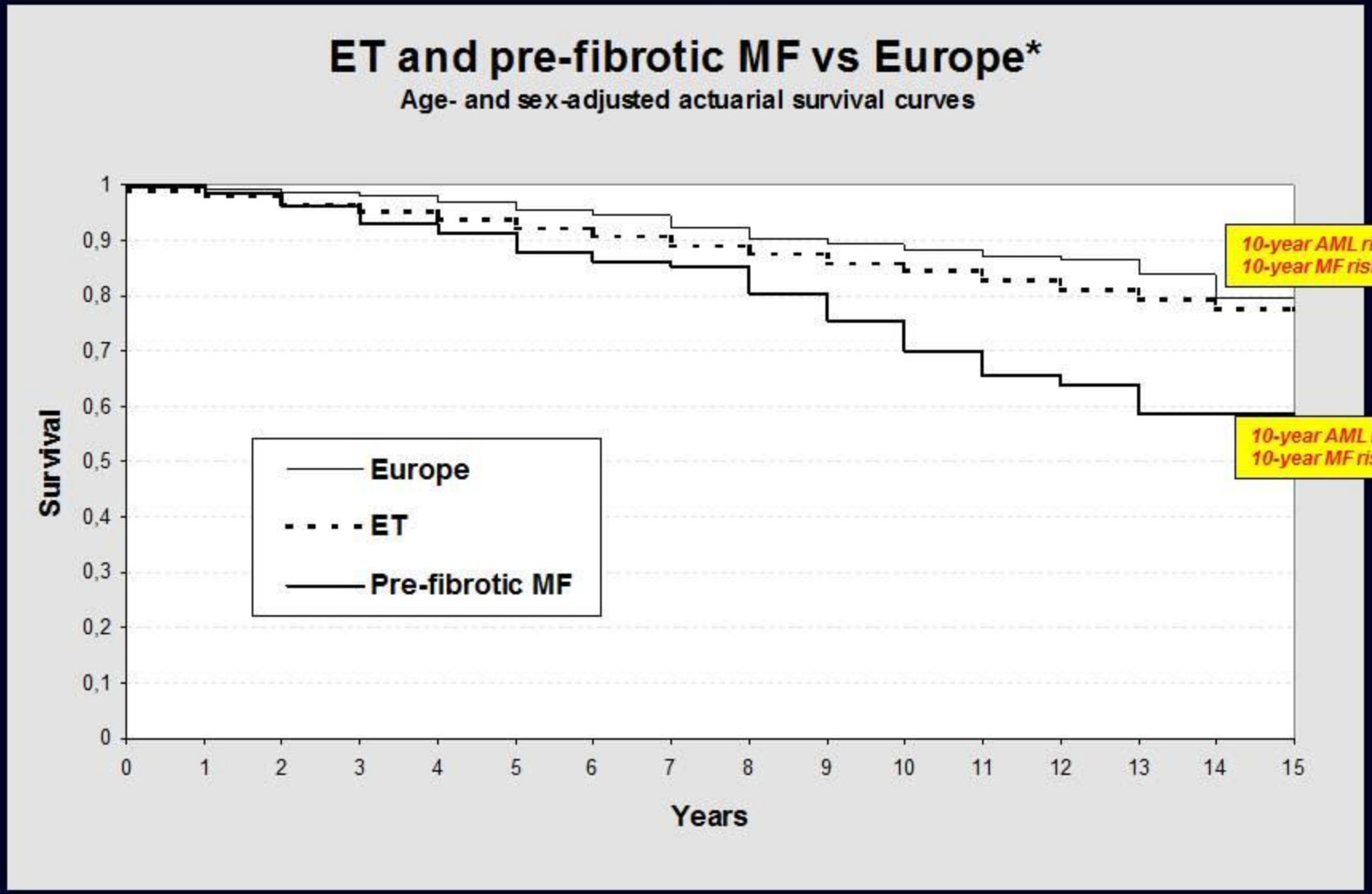
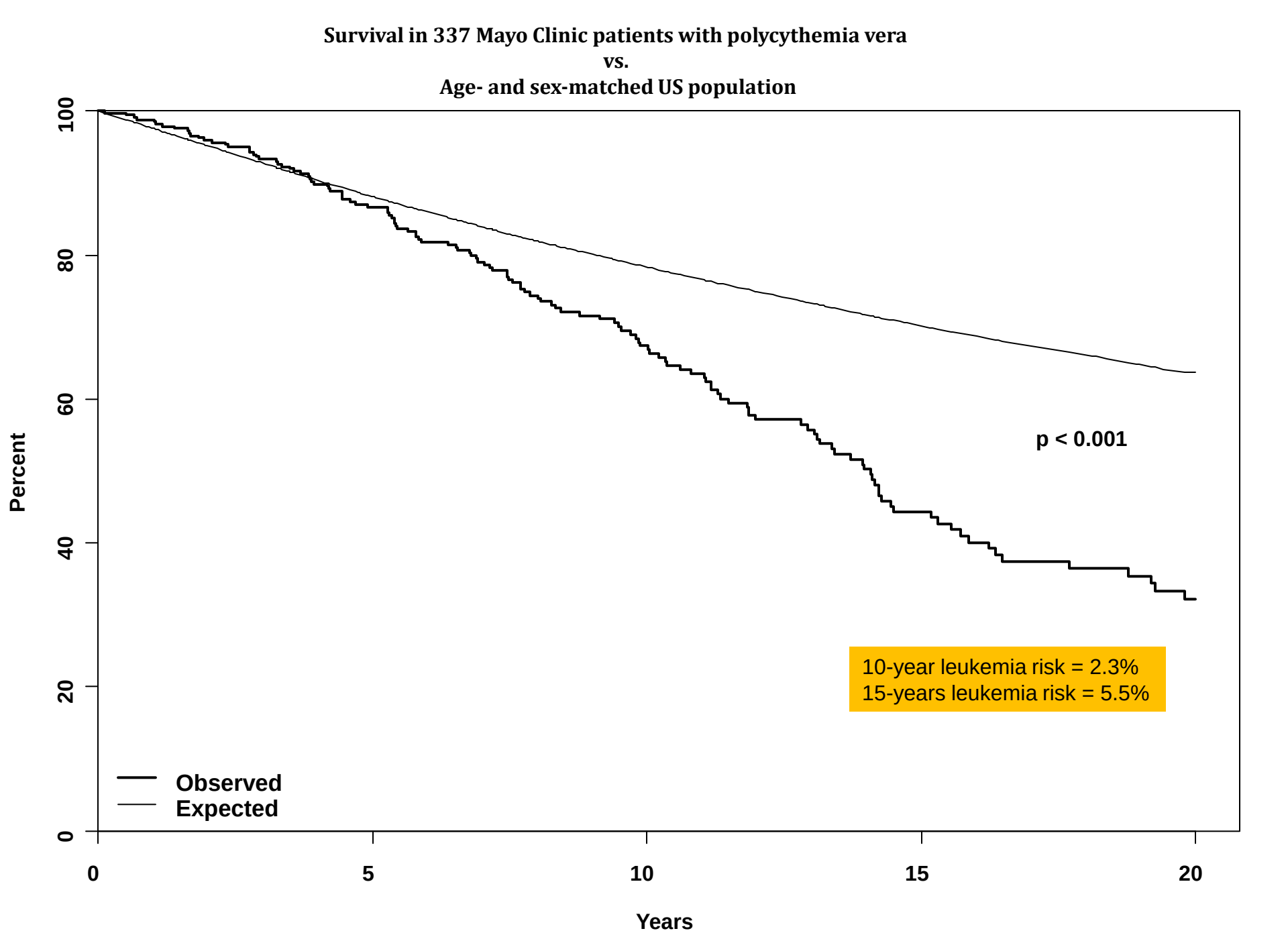
Survival and risk of leukemic transformation in ET are significantly influenced by accurate morphologic diagnosis: An international study of 1,104 patients.

Barbui et al. JCO 2011;29:3179





Tefferi et al. ASH 2011

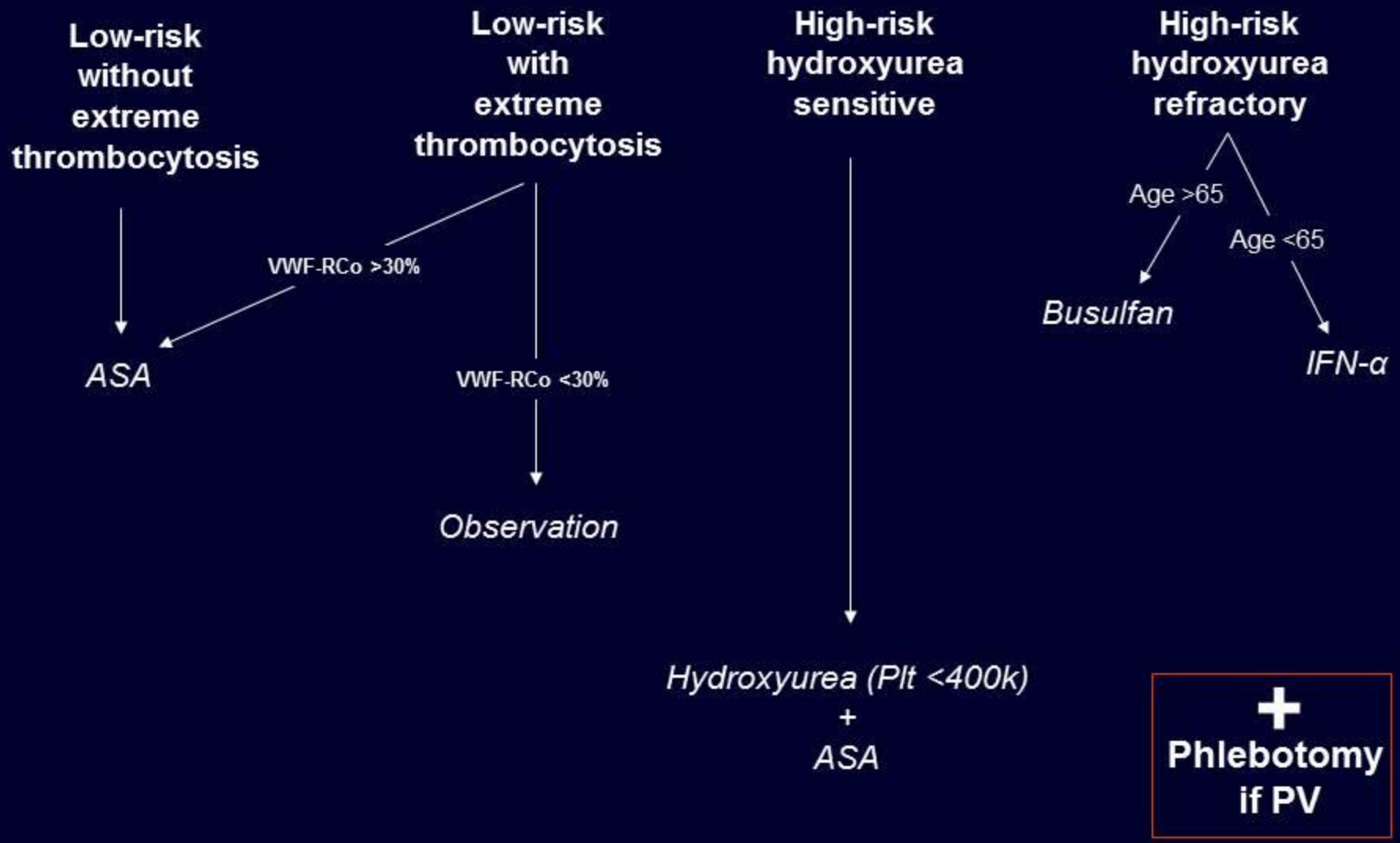
Risk stratification for thrombosis in ET and PV

Low-risk	Age < 60 years *and* No history of thrombosis *and* Platelet count < 1 million	Thrombosis risk is not significantly increased compared to controls*
High-risk	Age ≥ 60 years *or* Previous thrombosis	Thrombosis risk is significantly increased
Low-risk with extreme thrombocytosis	Platelet count ≥ 1 million/μL	**Thrombosis risk might be lower???**

*New data suggests a lower risk of thrombosis associated with extreme thrombocytosis, which however is associated with a bleeding diathesis in the presence of AvWS and aspirin therapy

Barbui et al. JCO *2011;29:3179*

My current treatment algorithm in ET and PV



Additional Questions Regarding Management of Polycythemia Vera and Essential Thrombocythemia

1. What is the role of Pegasys?
2. What is the role of JAK inhibitors?
3. How low should the hematocrit be kept?
4. How can one further optimize treatment?
5. Which patients should consider clinical trials?

PLENARY SCIENTIFIC SESSION:

Tiziano **Barbui**, et al.

A Large-Scale Trial Testing the Intensity of Cytoreductive Therapy to Prevent Cardiovascular Events in Patients with Polycythemia Vera (CYTO-PV trial): Multicenter Italian study

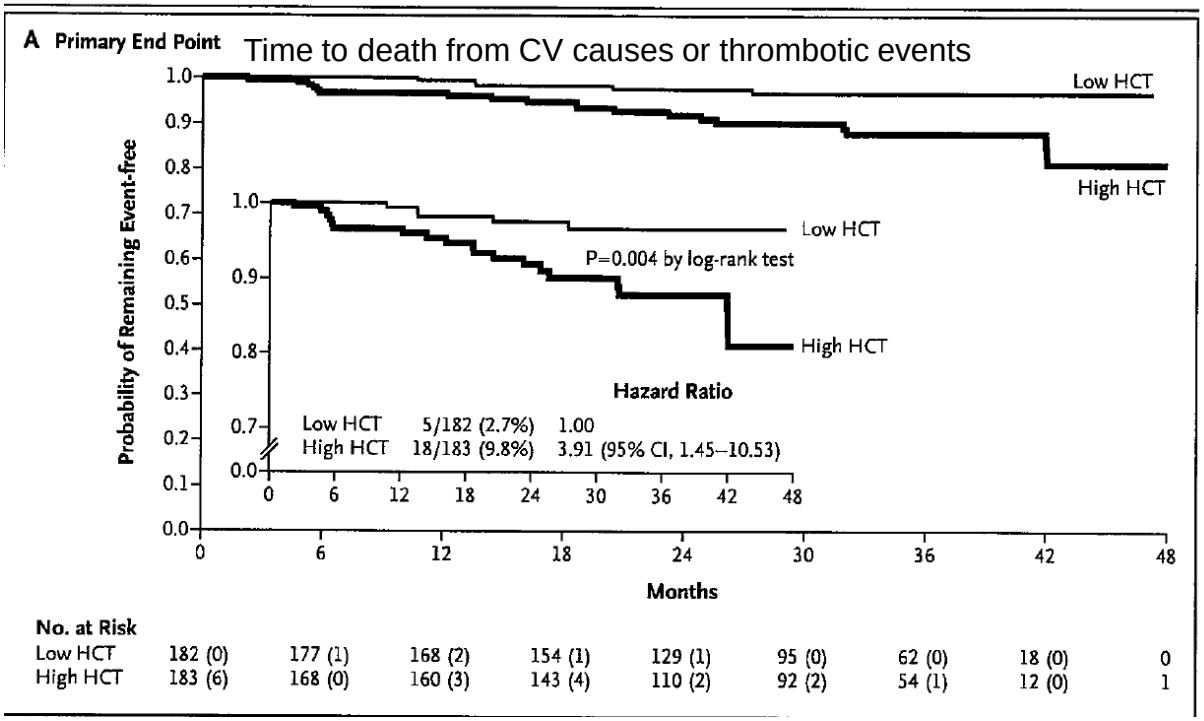
Blood (ASH Annual Meeting Abstracts), Nov 2012; 120: 4.

PV on phlebotomy or HU; *n* = 365

Treated to Hct <45; *n* = 182
Treated to Hct 45 to 50; *n* = 183

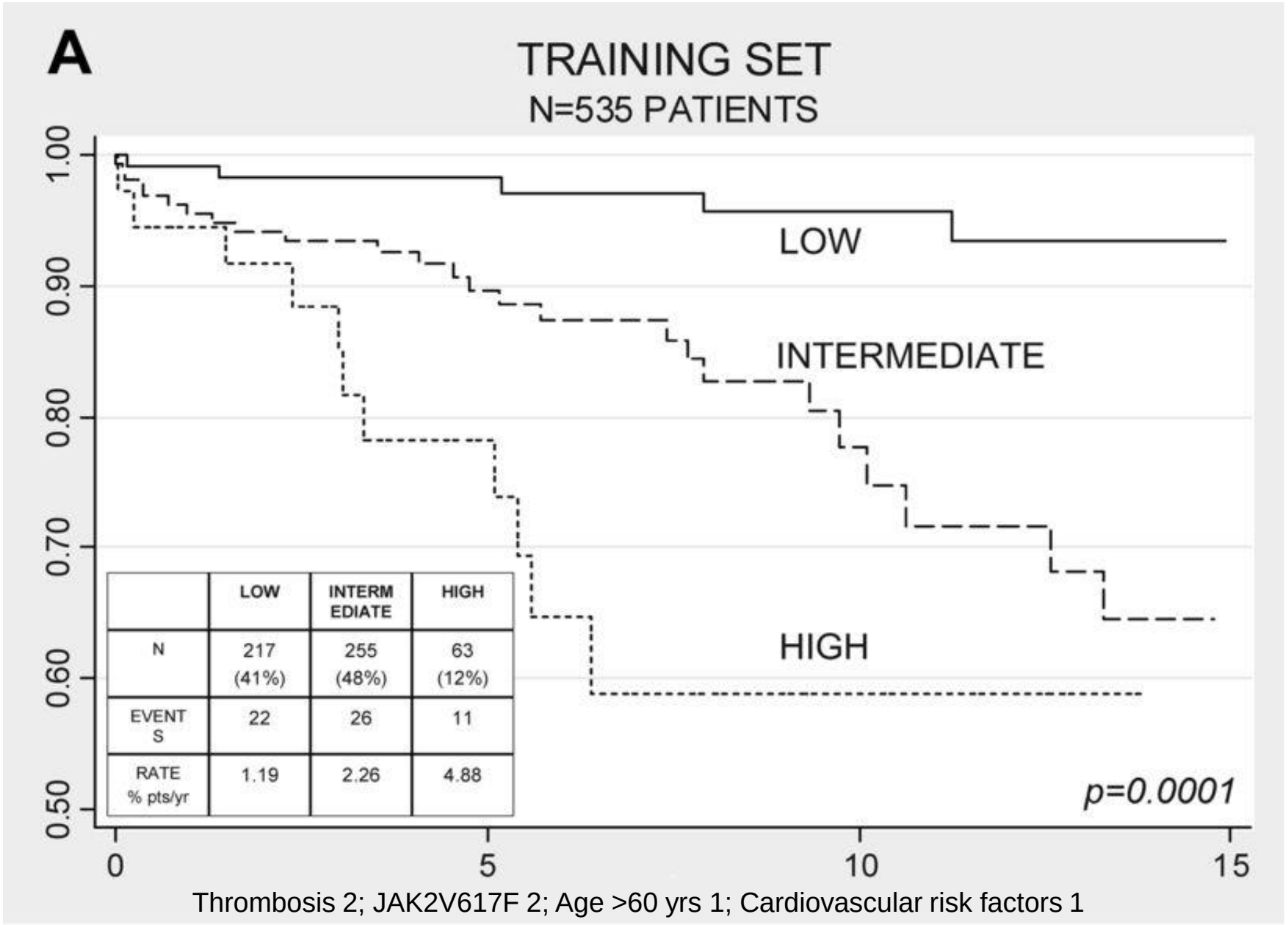
Median f/u; 31 months
Higher frequency and dose of HU use in the high Hct group
Significantly higher WBC in the high Hct group
No difference in platelet count

No difference in total deaths, fibrotic/leukemic transformation, bleeding or secondary cancer



Thrombosis-free survival curves.

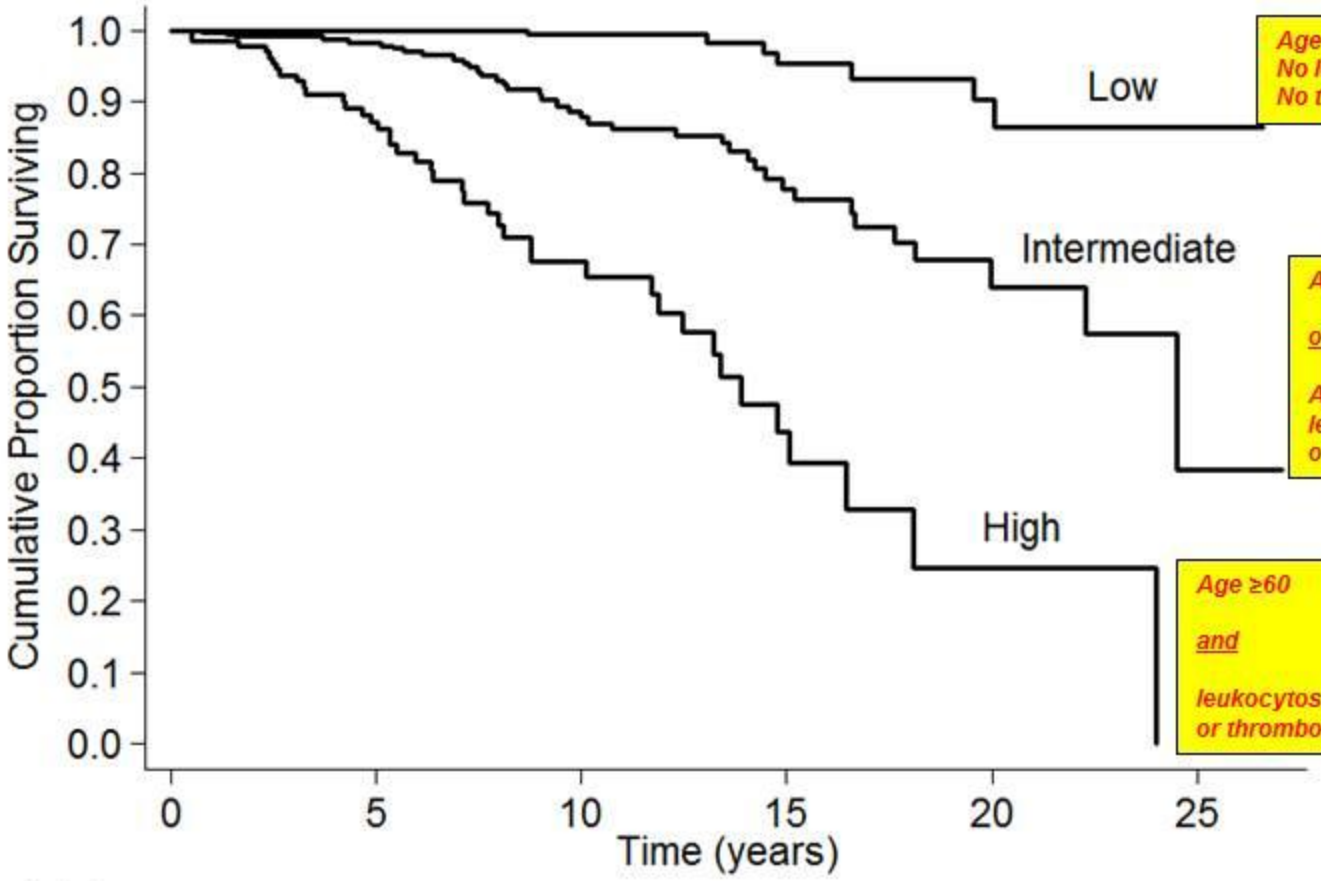
Barbui T et al. Blood 2012;120:5128-5133



Thrombosis 2; JAK2V617F 2; Age >60 yrs 1; Cardiovascular risk factors 1

Low risk implies a score = 0-1; intermediate risk, score = 2; and high risk, score ≥ 3

IPSET model for ET

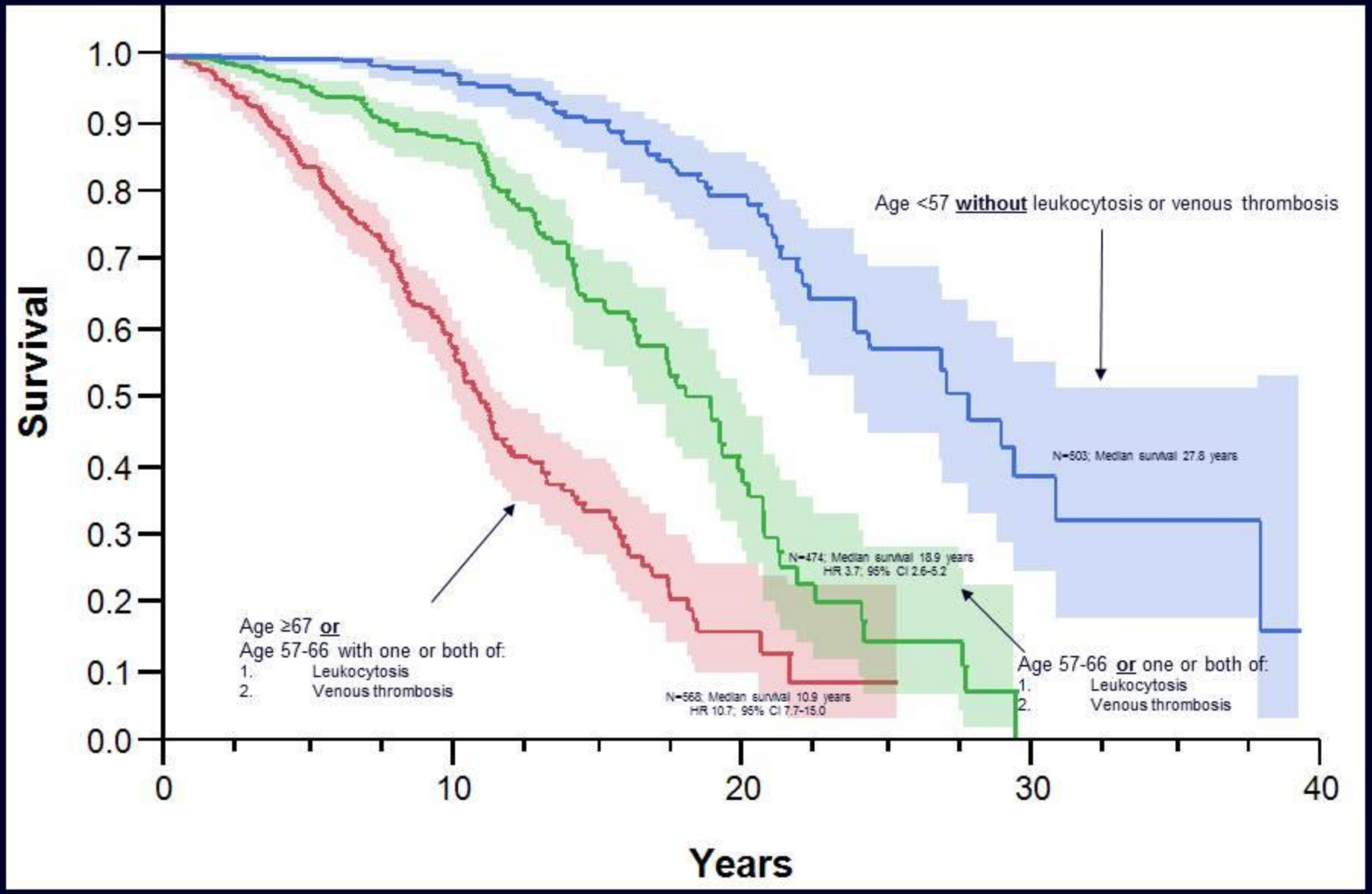


Number at risk						
Low	342	211	123	63	25	3
Intermediate	374	223	109	51	15	2
High	151	84	32	10	2	0

Passamonti et al. Blood 2012

Risk-stratified survival in 1,545 patients with WHO-defined polycythemia vera

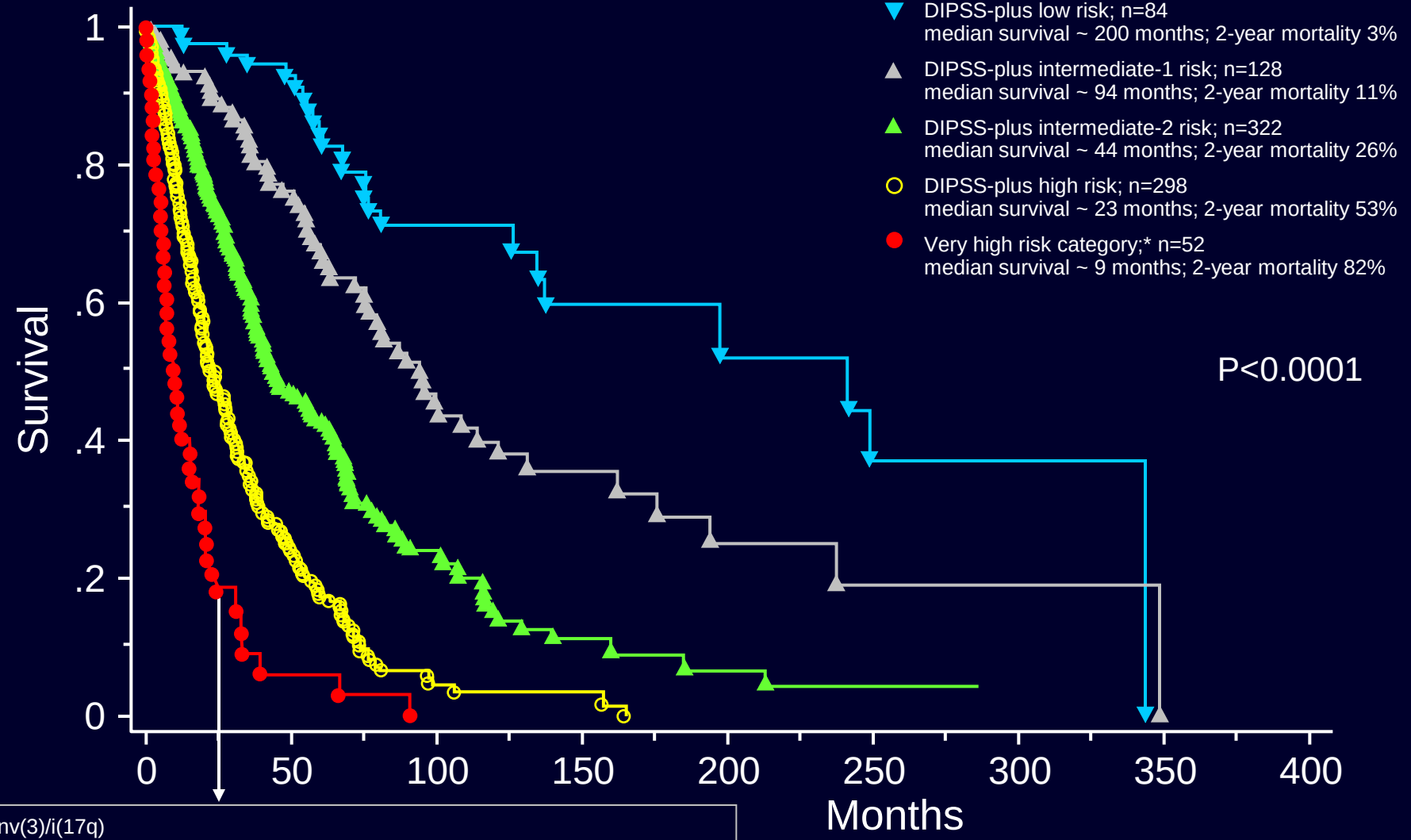
Based on 3 risk factors: age; venous thrombosis; leukocytosis



Tefferi et al. ASH 2011

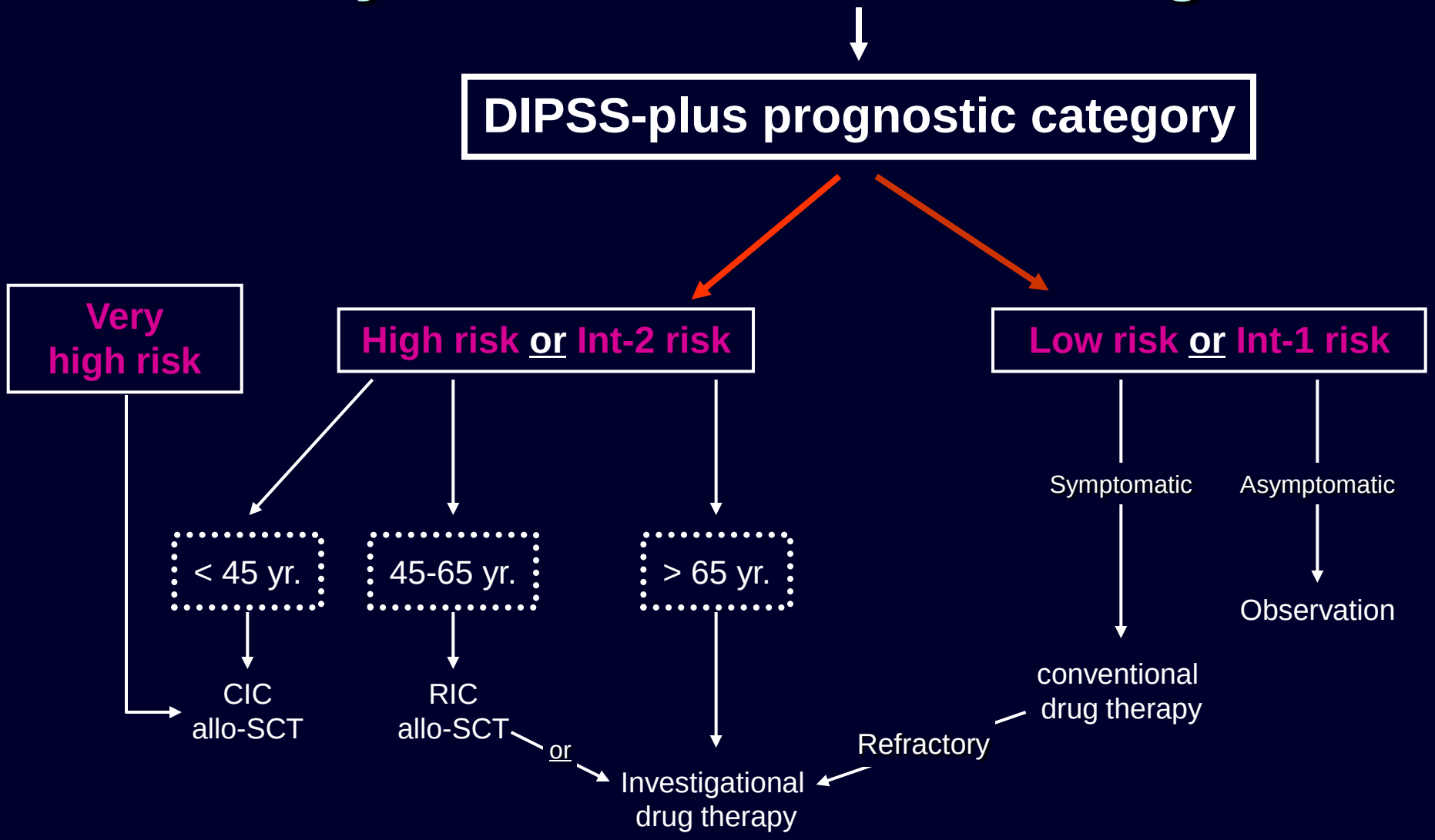
Survival and prognosis in primary myelofibrosis: A Mayo Clinic study of 884 patients

Based on 8 risk factors: Karyotype, Transfusion-dependency, Hgb <10, Plt <100, WBC >25, Circulating blasts 1%, constitutional symptoms, Age >65



Tefferi et al. Blood 2012

Myelofibrosis treatment algorithm



Tefferi. Blood 2011 117:3494

Mutational frequency and distribution for *ASXL1*, *EZH2*, *SRSF2*, *IDH1* and *IDH2* mutations in primary myelofibrosis

ASXL1 tested 279: mutated 85 (30.5%)

SRSF2 tested 358: mutated 52 (14.5%)

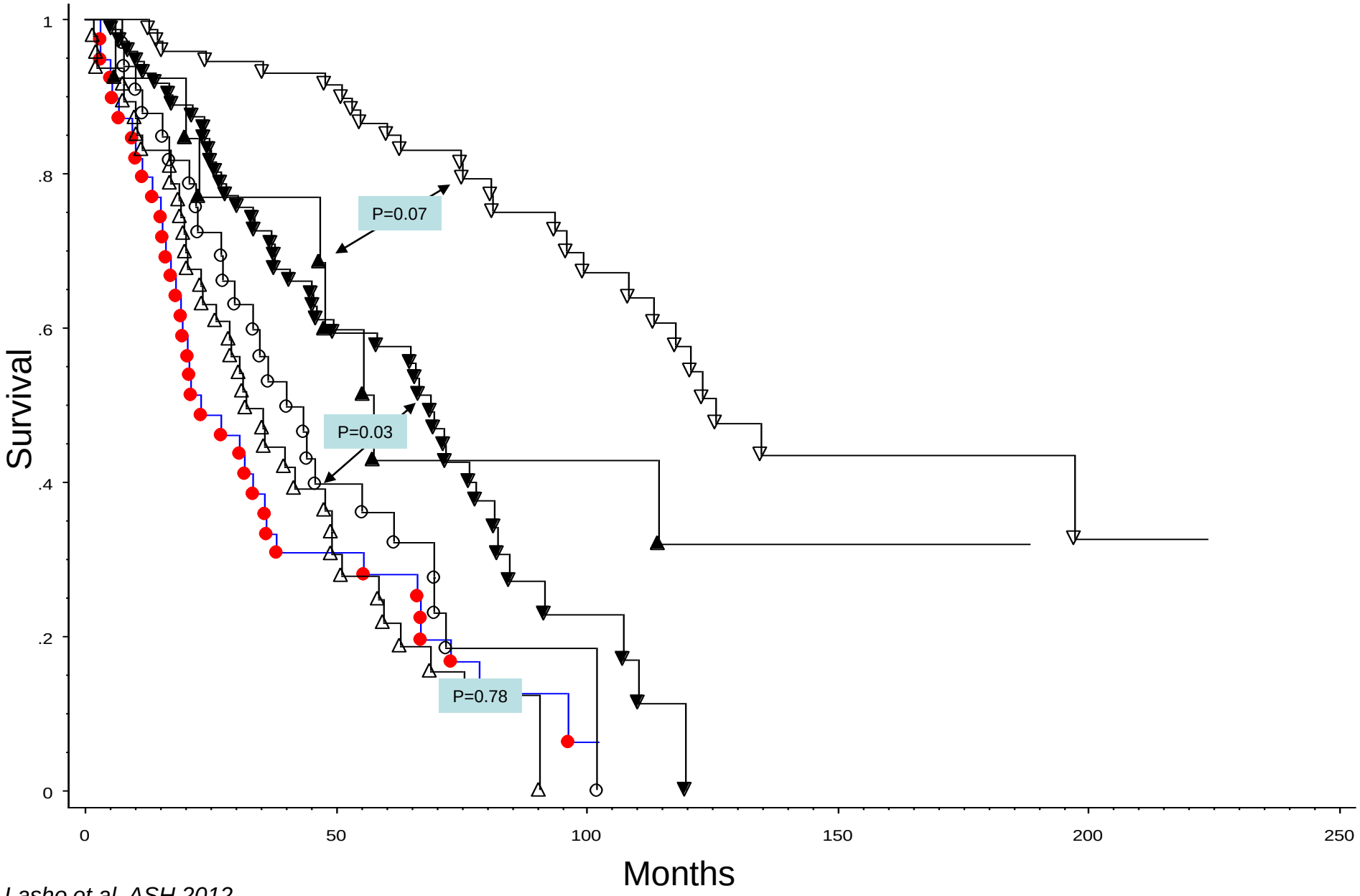
EZH2 tested 270: mutated 15 (5.6%)

IDH2 tested 374: mutated 10 (2.7%)

IDH1 tested 374: mutated 7 (1.9%)

Lasho et al. ASH 2012

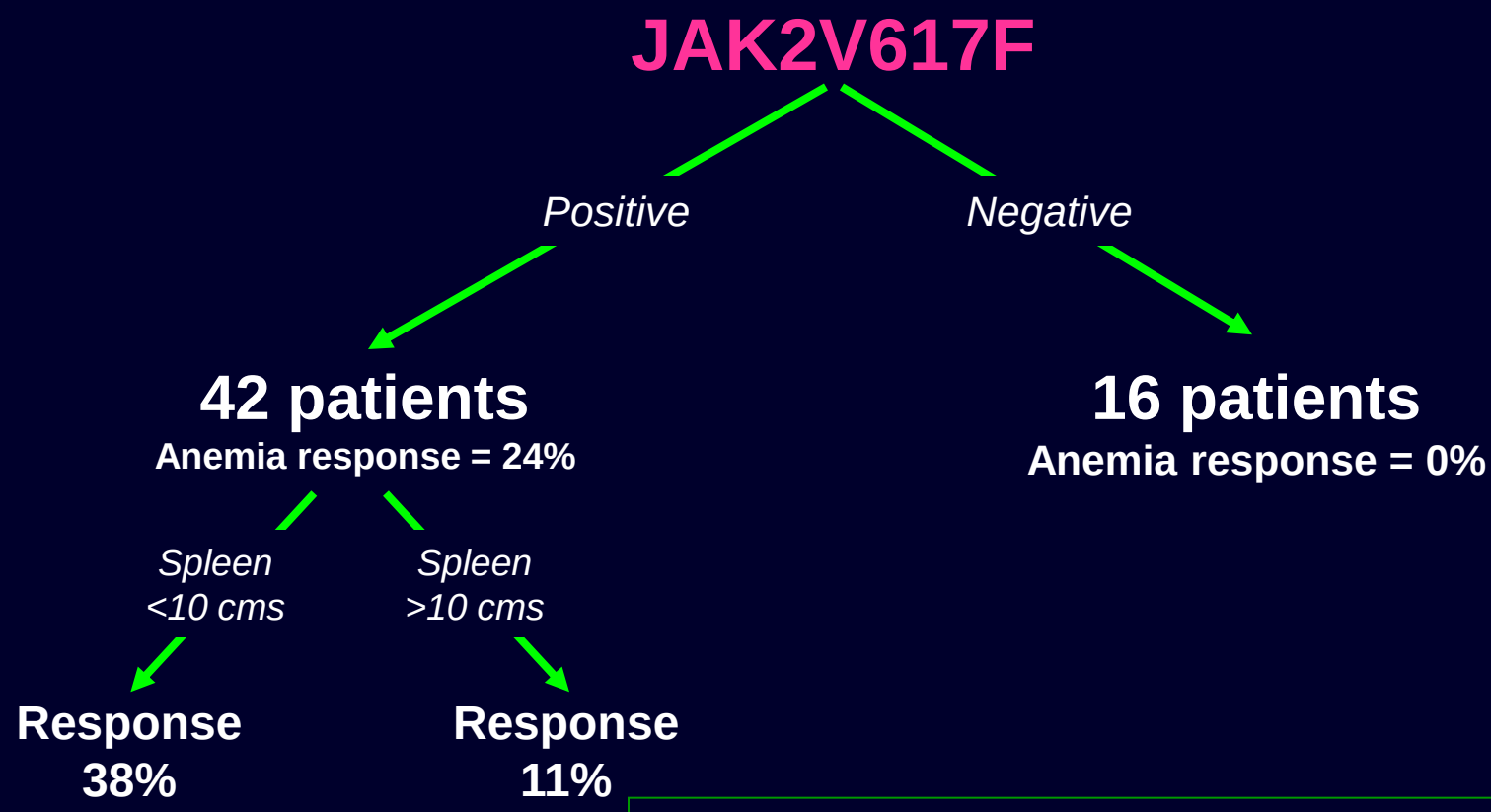
Three-tiered DIPSS-plus stratified survival data in 279 patients with primary myelofibrosis sub-stratified according to *ASXL1* mutation status



Lasho et al. ASH 2012

Pomalidomide 0.5 mg/day

Mayo Clinic study of 58 patients with myelofibrosis and anemia



Additional observations:

1. Well tolerated with little or no myelosuppression, neuropathy or thrombosis
2. Early basophilia predicted anemia response
3. 58% platelet response in patients with < 100k platelets
4. No spleen responses
5. Increasing dose to 2 mg/day did not increase anemia response

Begna et al. Leukemia. 2011;25:301

	JAK2 IC50 (nM)	JAK1 IC50 (nM)	JAK3 IC50 (nM)	TYK2 IC50 (nM)	Other targets	Current stage	Symp Resp	Spleen Resp	Anem Resp	Side effects
Ruxolitinib	2.8	3.3	428	19	None reported	FDA approved	>50%	29% (MRI)	14%	Anemia Thrombocytopenia "ruxolitinib withdrawal syndrome"*
SAR302503	3	105	1040	405	FLT3, RET	Phase-3	>50%	39%	0%	Nausea/Diarrhea Anemia Thrombocytopenia Transaminasemia Hyper-lipase/amylasemia
Lestaurtinib	<1	–	3	–	FLT3, TRKA VEGFR2, RET	Phase-2	NR	>18%	25%†	Nausea/Diarrhea Anemia Thrombocytopenia
CYT387	18	11	155	17	PKD3, PKCμ CDK2, ROCK2 JNK1, TBK1	Phase-2	>50%	45%	50%	Thrombocytopenia Headaches 1st dose effect** Peripheral neuropathy Transaminasemia Hyper-lipase/amylasemia
SB1518	23	1280	520	50	FLT3	Phase-2	>50%	32% (MRI)	††	Nausea/Diarrhea
LY2784544	–	–	–	–	–	Phase-1/2	NR	>22%	NR	Nausea/Diarrhea Anemia Electrolyte abnormalities/TLS? Increases in serum creatinine
XL019	2	134	195	344	–	Halted	>50%	33%	NR	Peripheral neuropathy
AZD1480	<0.5	1.3	3.9	–	Aurora-A, TRKA FGFR1, FLT4	Phase-1/2				
BMS911543	1.1	356	73	66	None reported	Phase-1/2				
NS-018	<1	33	39	22	SRC, FYN ABL, FLT3	Phase-1/2				

Transfusion Independence Response

Response by Dose (Core Study)	150 mg QD (n=52)	300 mg QD (n=60)	150 mg BID (n=42)	Total[1] (n=166)
Transfusion dependent at baseline (evaluable)	24	28	14	68
Transfusion independence rate (12 wks)	63%	75%	57%[2]	68%
Minimum 2 g/dL increase in hemoglobin level (8 wks)	11%	8%	14%	13%
IWG-MRT anemia response rate	48%	55%	36%	48%

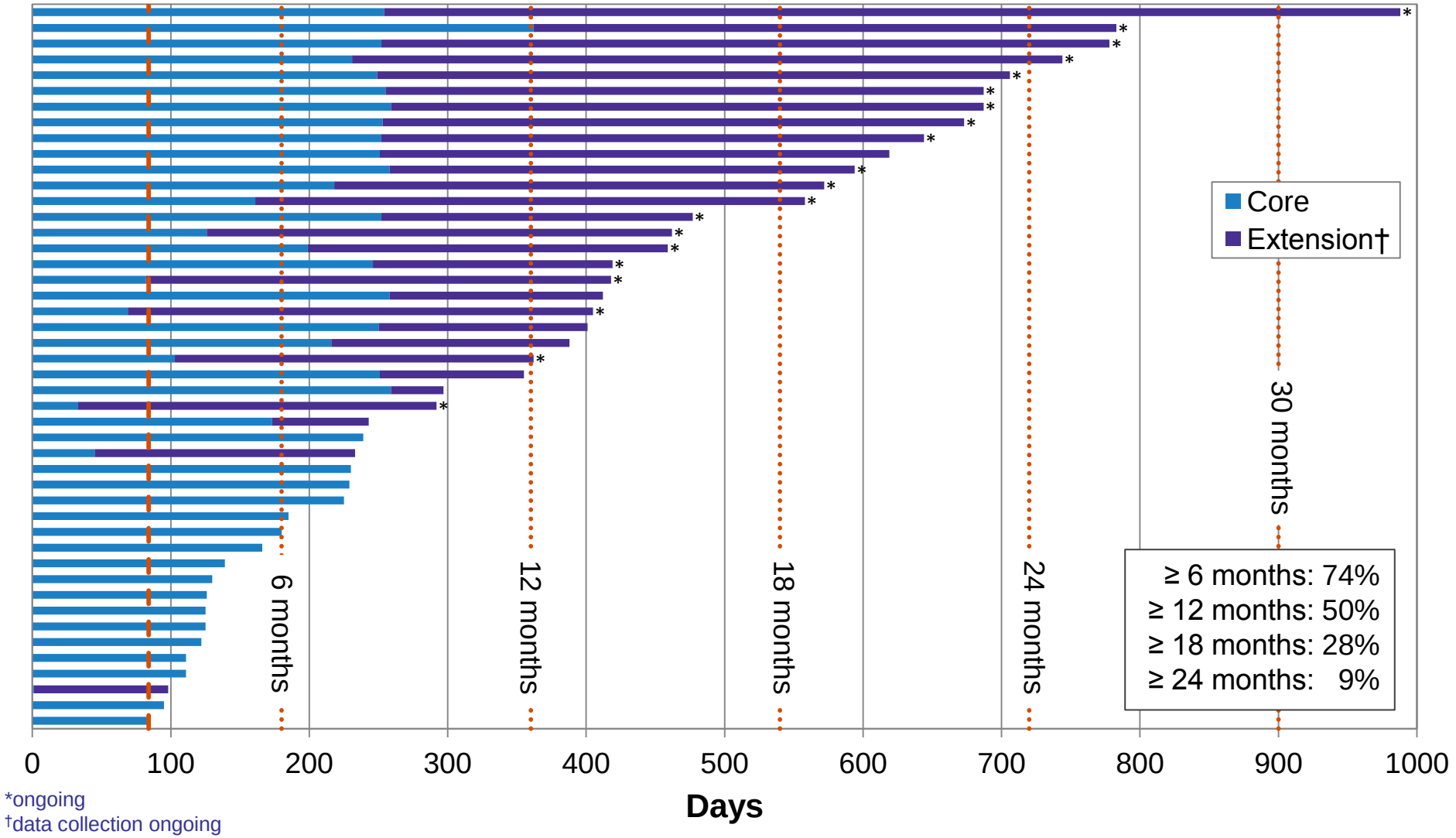
- Of the transfusion dependent patients who did not achieve a full transfusion independence response, 23% achieved at least a 50% reduction in transfusion requirement in any 3-month period

Onset and Durability of Response (Core and Extension Study)	Median	Min-Max
Time to confirmed response (12 weeks) (Core; days)[3]	85	85-353
Duration of transfusion-free period (12 weeks) (Core and Extension; days)[3]	Not yet reached	85-988*

- 3 additional subjects achieved 12 week transfusion independence response during the Extension Study

[1] Includes 100mg QD (n=3), 200mg QD (n=3), and 400mg QD (n=6) doses
[2] Not statistically significant vs. 300mg QD
[3] Data based on responders
* Ongoing as of November 2012

Maximum Duration of Transfusion-Free Period (responders with onset in Core Study; n=46)



*ongoing
†data collection ongoing