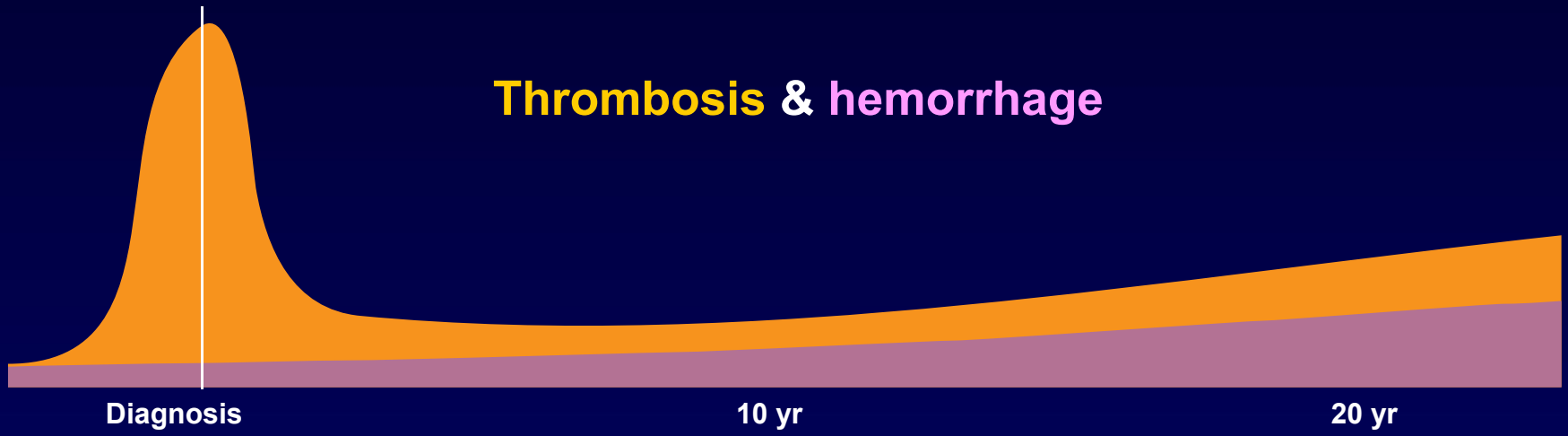
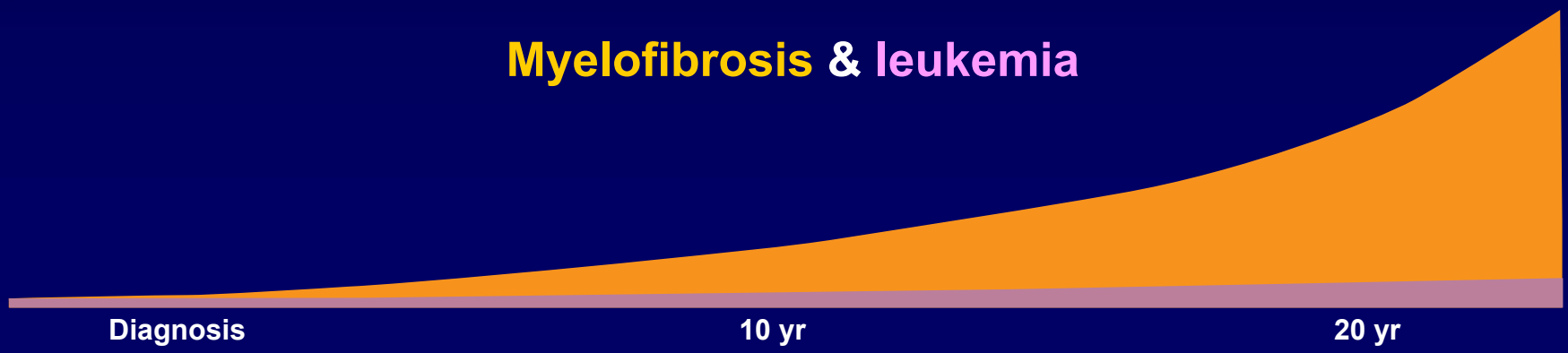
Evolving Therapeutic Strategies in Polycythemia Vera (PV): Novel Agents in Focus

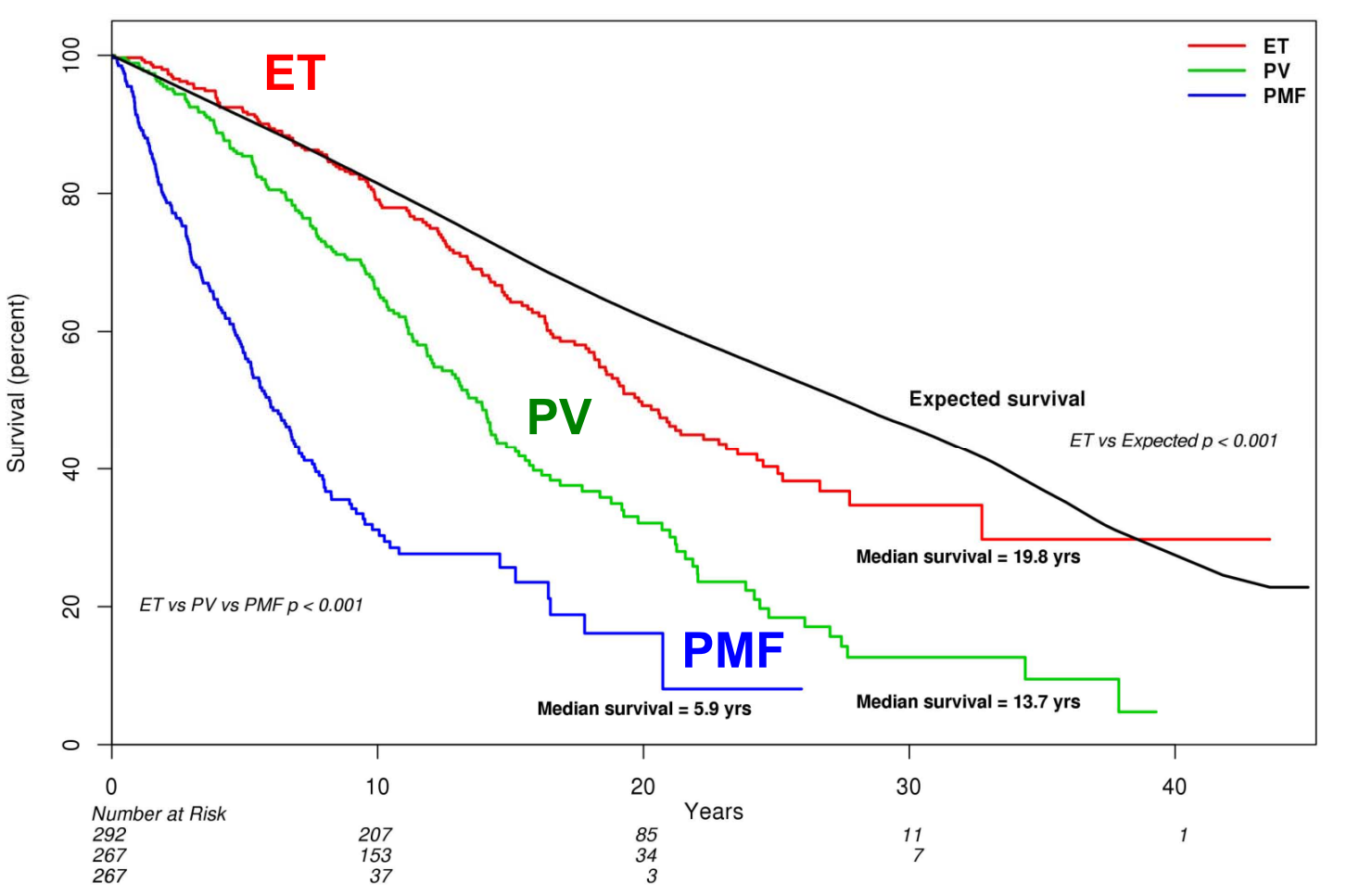
Alessandro Vannucchi, MD
Department of Experimental and Clinical Medicine
University of Florence
Florence, Italy

Natural History of PV





Survival in PV Is Significantly Reduced Compared to Control Population



PMF, primary myelofibrosis

Tefferi A, et al. *Blood.* 2014 July18. [Epub ahead of print]

Goals of Therapy in Patients With PV

Philadelphia-Negative Classical Myeloproliferative Neoplasms (MPN): Critical Concepts and Management Recommendations

- To avoid first occurrence and/or recurrence of thrombotic and bleeding complications
- To minimize the risk of acute leukemia and post-PV myelofibrosis
- To control systemic symptoms
- To treat complications (thrombosis and hemorrhage)
- To manage risk situations (eg, pregnancy, surgery)

Barbui T, et al. *J Clin Oncol.* 2011;29(6):761-770.

Recommendations for First-Line Therapy

- Manage generic cardiovascular risk factors
- Low-dose aspirin to all

Low risk	Phlebotomies only
High risk*	Hydroxyurea (HU)** / interferon-α ± phlebotomies
Elderly*	Busulfan

* High risk patients are older than 60 yr and/or have a history of thrombotic events
**Use with caution in young patients (<40 years)

Barbui T, et al. *J Clin Oncol.* 2011;29(6):761-770.

ELN Criteria for Resistance / Intolerance to Hydroxyurea

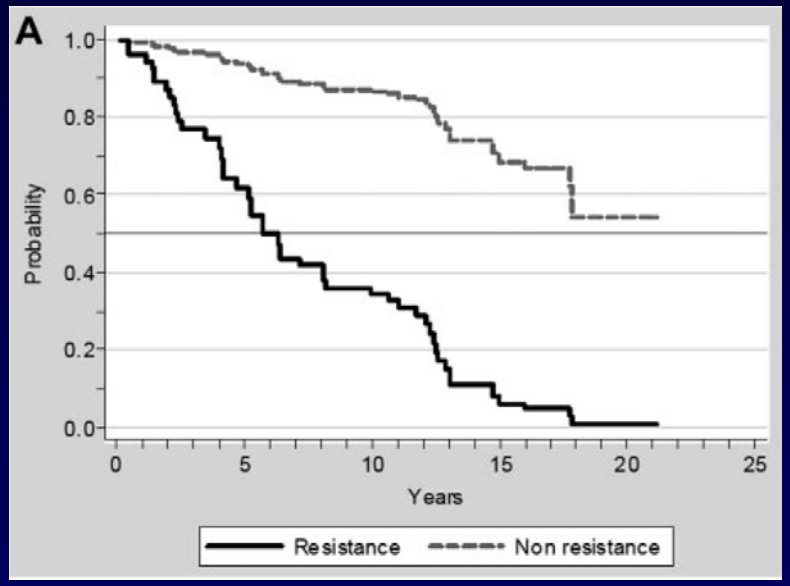
Target -1	Target -2	Target -3	Toxicity	Dose / time
Need of phlebotomy to maintain hematocrit (Hct) <45%				After 3 months of at least 2 g/d HU
	Platelets (PLT) >400x10^9/L *and* WBC >10x10^9/L			After 3 months of at least 2 g/d HU
		Spleen reduction by <50% *or* No complete relief of spleen-related symptoms		After 3 months of at least 2 g/d HU
			ANC <10^9/L *or* PLT <100x10^9/L *or* Hb <100g/L	At the lowest dose required to achieve complete or partial hematologic response (ELN)
			Leg ulcers or other unacceptable HU-related toxicities*	At any dose of HU

*Mucocutaneous, gastrointestinal, pneumonitis, fever

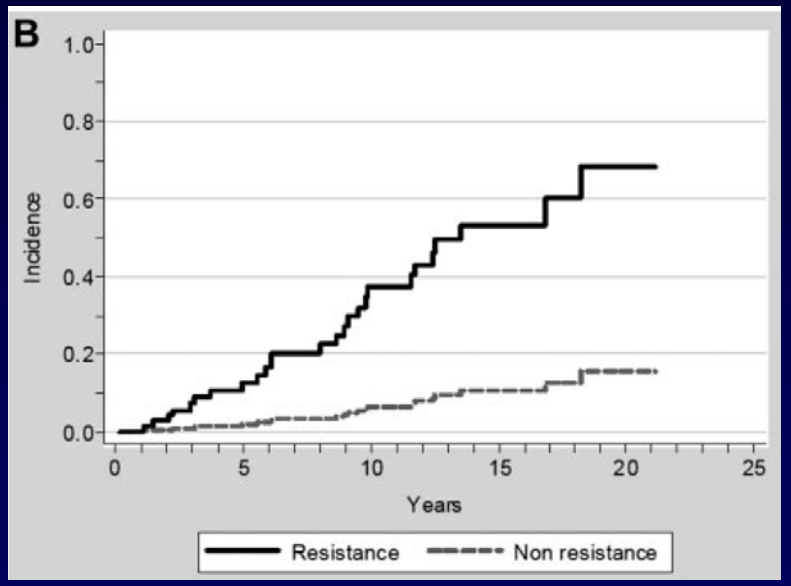
Barosi G, et al. *Br J Haematol.* 2010;148(6):961-963.

Resistance to Hydroxyurea Adversely Affects Survival and Disease Progression in PV

Overall survival



Transformation to PPV-MF and leukemia



- **Resistance and intolerance to hydroxyurea occurred in 11% and 13% of 261 PV patients**
- **Resistance to hydroxyurea implied a 5.6 fold increase in the risk of death and 6.8 fold increase in the risk of transformation**

Alvarez-Larrán A, et al. *Blood.* 2012;119(6):1363-1369.

Second-Line Therapy: Current Drug Options

- Interferon-α, *if HU resistant/intolerant*
- Hydroxyurea, *if IFN-α resistant/intolerant*
- [Pipobroman] busulfan [^{32}P]

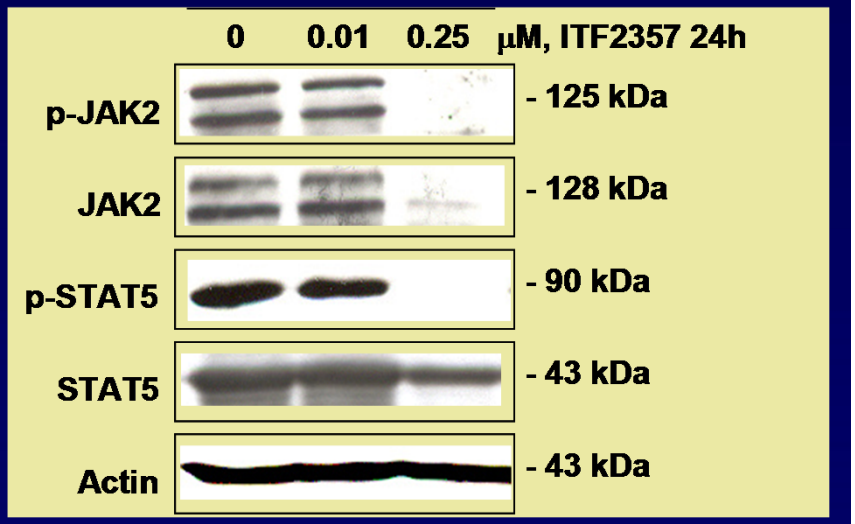
Barbui T, et al. *J Clin Oncol.* 2011;29(6):761-770.

What Are the Novel Agents in Focus for PV, and for Whom?

- **HDAC inhibitors** → Their main mechanism of action seems to be destabilizing JAK2
- **JAK inhibitors** → They inhibit signaling from activated JAK2 (either wild type [WT] and V617F mutated)
- **For whom?** → Used in patients with advanced PV resistant/refractory to hydroxyurea

HDAC Inhibitor Givinostat (ITF2357) Has Direct Inhibitory Activity on JAK2 V617F Cells

- GVS is more cytotoxic on JAK2 V617 than JAK2 WT cell lines
- Low doses of GVS inhibit proliferation and erythroid differentiation of primary MPN cells
- GVS does not affect JAK2 mRNA levels but impairs JAK2 half-life
- Low doses of GVS impair JAK/STAT signaling by down-regulating JAK2 and p-JAK2 levels



GVS, givinostat

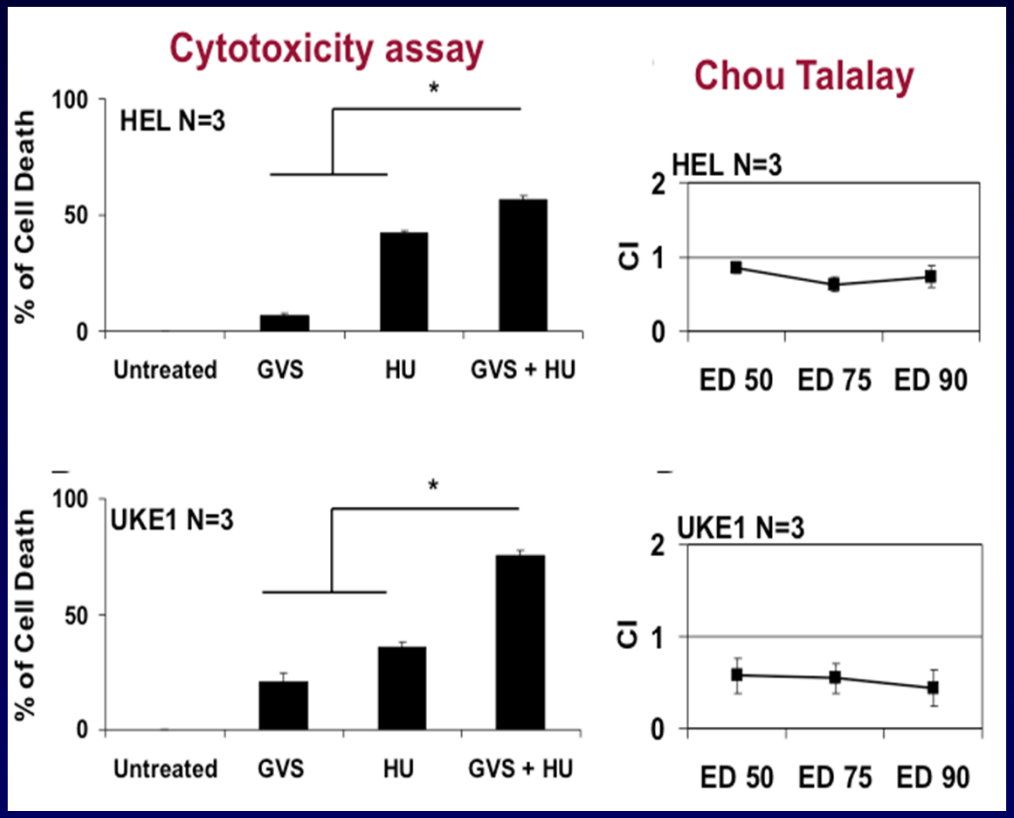
Guerini V, et al. *Leukemia.* 2008;22(4):740-747. Amaru Calzada A, et al. *Exp Hematol.* 2012;40(8):634-645.

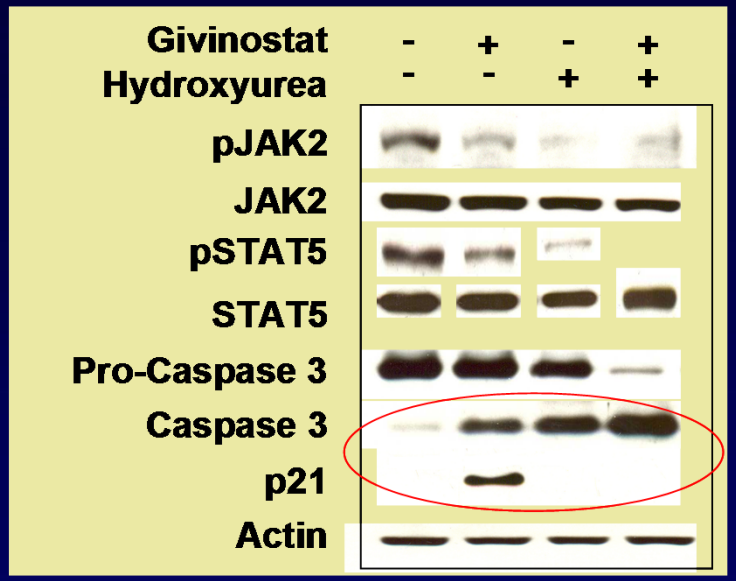
A Pilot Study of Givinostat in Patients With JAK2 V617F Positive MPN

	Clinical response in PV / ET patients		
	Baseline	Week 12	Week 24
HCT >45%	5/13	5/12	4/11
Phlebotomy	7/13	2/12	2/11
Platelets ≥450 x10^9/L	11/13	6/12	6/11
Median (range)	865 (347-1458)	565 (279-1071)	453 (233-1602)
WBC ≥10 x10^9/L	11/13	7/12	7/11
Median (range)	16 (4.9-45)	11 (4-32)	13.3 (3.6-35)
Splenomegaly	8/13	3/12	3/11
Pruritus	11/13	2/12	1/11

Rambaldi A, et al. *Br J Haematol.* 2010;150(4):446-455.

Givinostat Synergizes With Hydroxyurea

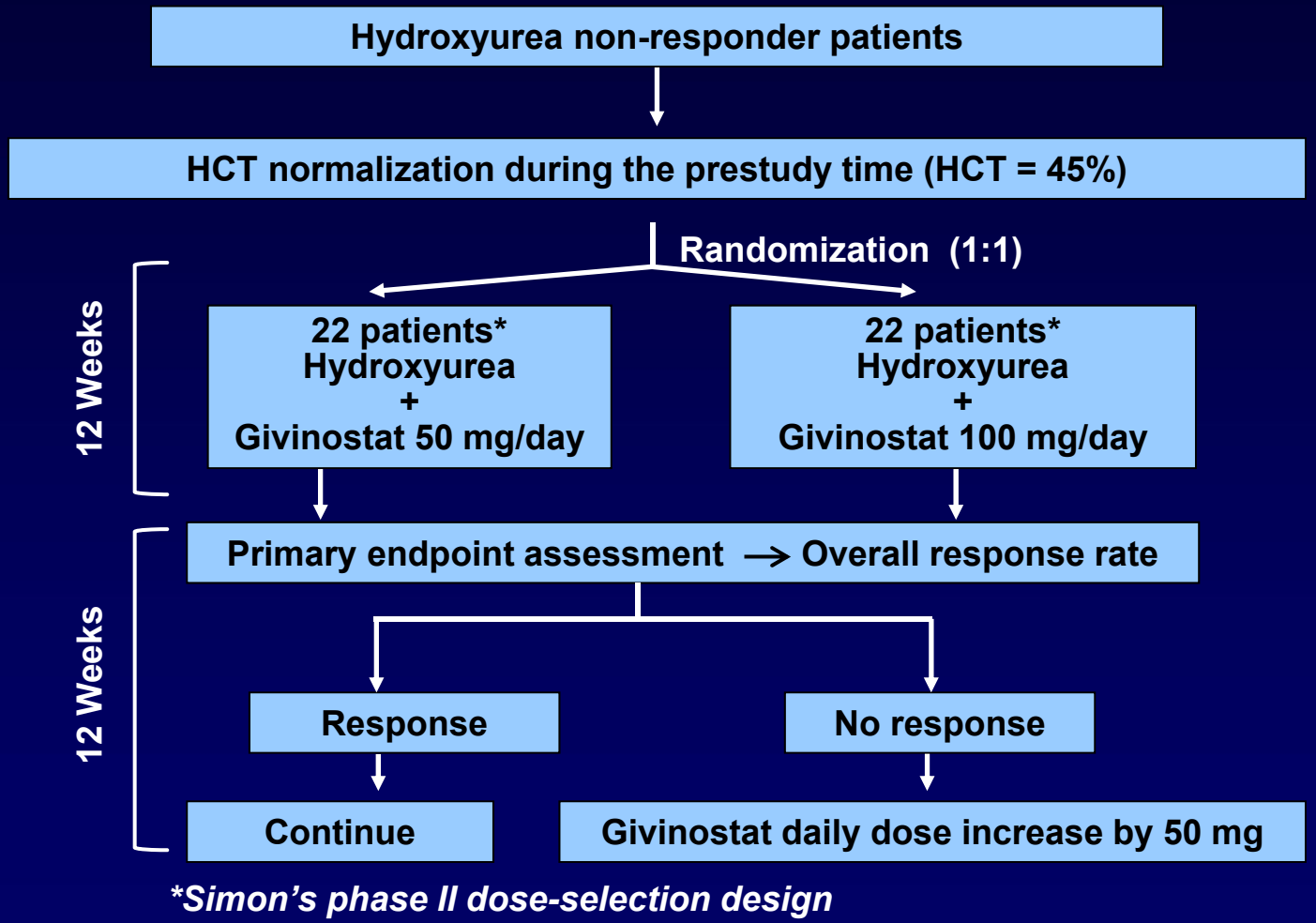




- HU synergizes with GVS in reducing proliferation of JAK2 V617F-mutated cell lines
- Synergism occurs through caspase 3 activation and inhibition of p21CDKN1A induction

Amaru Calzada A, et al. *Exp Hematol.* 2013;41(3):253-260.

A Phase II Study of GVS in Combination With HU in PV Patients Unresponsive to HU Monotherapy



**Simon's phase II dose-selection design*

Finazzi G, et al. *Br J Haematol.* 2013;161(5):688-694.

Slide 13

SKBO7 editorial, please change die into day
Sanneke Koekkoek, BSN, OCN; 14-10-2014

SKBO8 change die into day
Sanneke Koekkoek, BSN, OCN; 14-10-2014

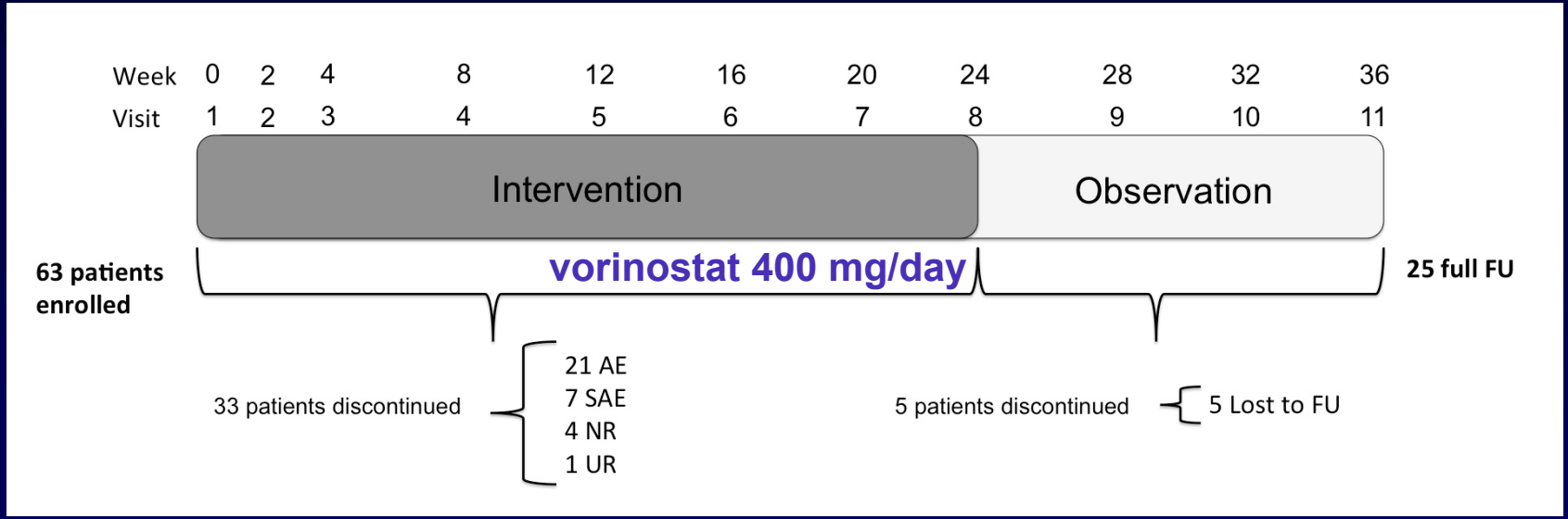
A Phase II Study of GVS in Combination With HU: Response and Safety

	50 mg/day	100 mg/day
Overall response	11 PR = 50%	1 CR + 9 PR = 45%
Hct normalization	28%	42%
WBC normalization	25%	36%
Platelets normalization	36%	20%
Spleen normalization	0%	7%
Pruritus > grade 2 normalization	64%	80%
AE ≥ grade 2	32%	36%
Drop out	9%	14%

PR, partial response; CR, complete response

Finazzi G, et al. *Br J Haematol.* 2013;161(5):688-694.

A Phase II Study of Vorinostat (MK-0683) in Patients With PV and ET



- **Primary objective: Clinicohematological response per the ELN response criteria at the end of the intervention and observation period using vorinostat monotherapy**
- **Second objective: To investigate whether vorinostat influenced the JAK2 mutant allele burden**

Andersen CL, et al. *Br J Haematol.* 2013;162(4):498-508.

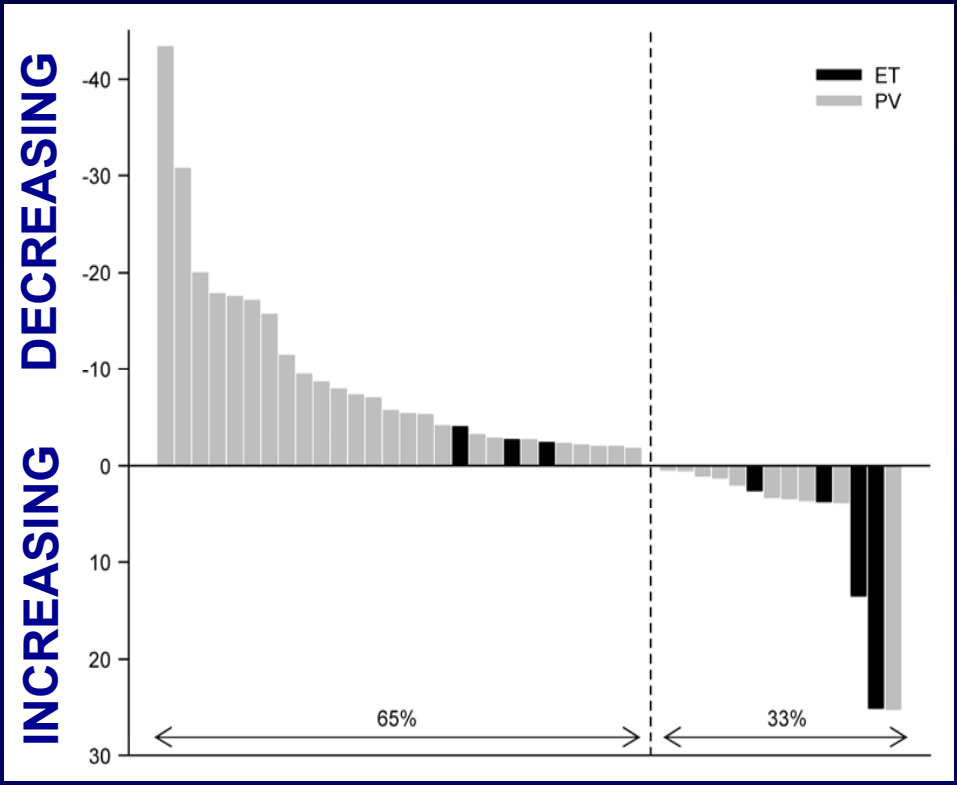
A Phase II Study of Vorinostat (MK-0683) in Patients With PV and ET: Clinical Responses

- **End of intervention**
  - **Intention-to-treat (ITT) analysis: 35% responses (3 in CR, 19 in PR) according to ELN**
- **End of observation**
  - **ITT analysis: 9.5% responses (2 in CR, 4 in PR)** (only patients treated with vorinostat in the intervention period)

Andersen CL, et al. *Br J Haematol.* 2013;162(4):498-508.

A Phase II Study of Vorinostat (MK-0683): Effects on JAK2V617F Burden

CHANGES IN *JAK2* V617F ALLELE BURDEN



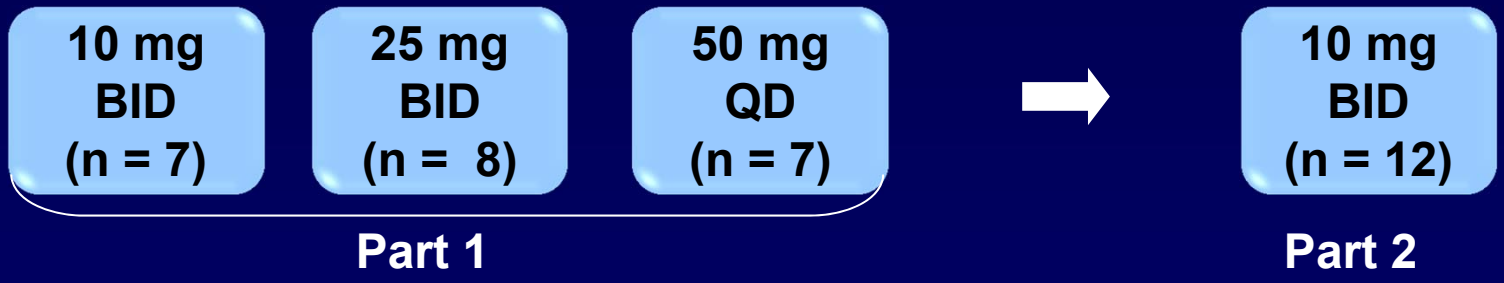
- Sixty-five percent experienced a decrease in *JAK2* V617F allele burden (P = .006). However, the median decrease was only 5.6%
- At end of observation period, no difference from baseline values
- No *JAK2* positive patients experienced a major molecular response defined as undetectable *JAK2*V617F by qPCR

Andersen CL, et al. *Br J Haematol.* 2013;162(4):498-508.

Phase II Study of Ruxolitinib in Patients With Advanced PV

Eligibility criteria:

- Refractory or intolerant to HU or HU contraindicated
- Hct >45% or phlebotomy 2 times in last 6 months, with at least one phlebotomy in last 3 months



- Patients received ruxolitinib for a median of 152 weeks (range, 31-177 weeks)

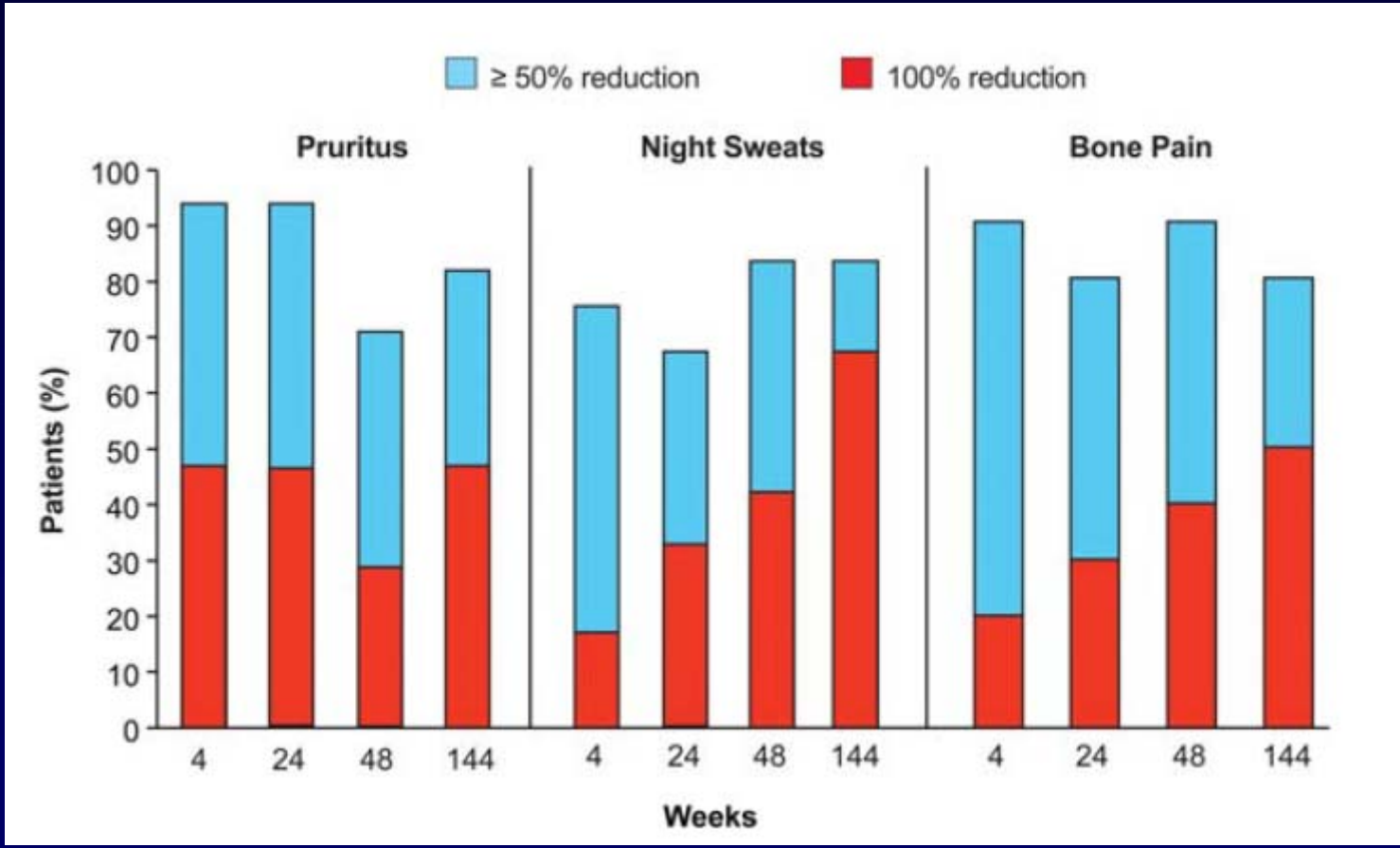
Verstovsek S, et al. *Cancer.* 2014;120(4):513-520.

Phase II Study of Ruxolitinib in Patients With Advanced PV: Main Results

- Hematocrit <45% without phlebotomy was achieved in 97% of patients by week 24
- Among patients with palpable splenomegaly at baseline, 44% and 63%, respectively, achieved nonpalpable spleen at weeks 24 and 144
- Thrombocytopenia and anemia were the most common adverse events.Thrombocytopenia of grade 3 or anemia of grade 3 occurred in 3 patients each (9%) (1 patient had both) and were managed with dose modification

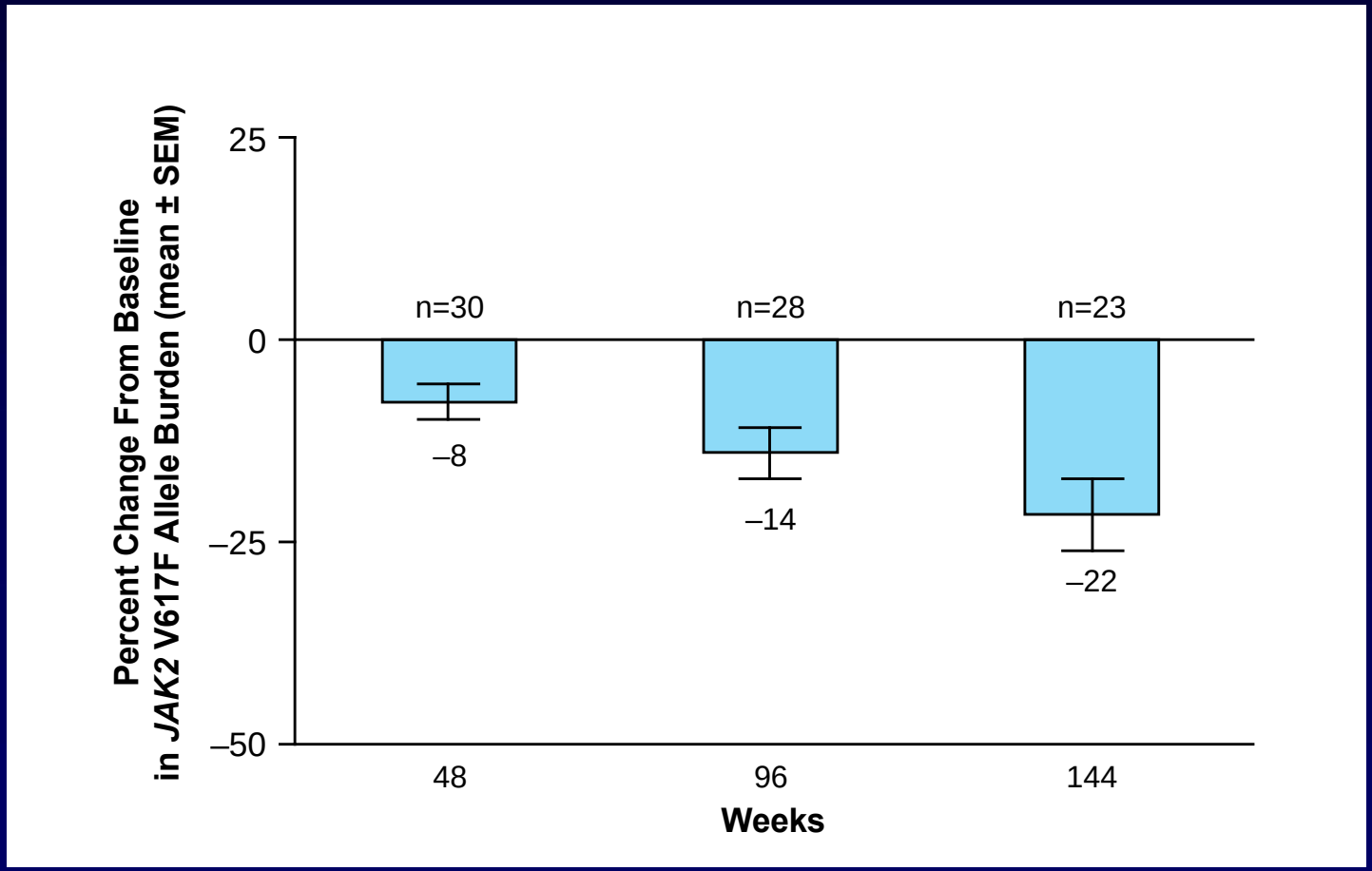
Verstovsek S, et al. *Cancer.* 2014;120(4):513-520.

Reduction in PV-Associated Symptoms With Ruxolitinib Therapy



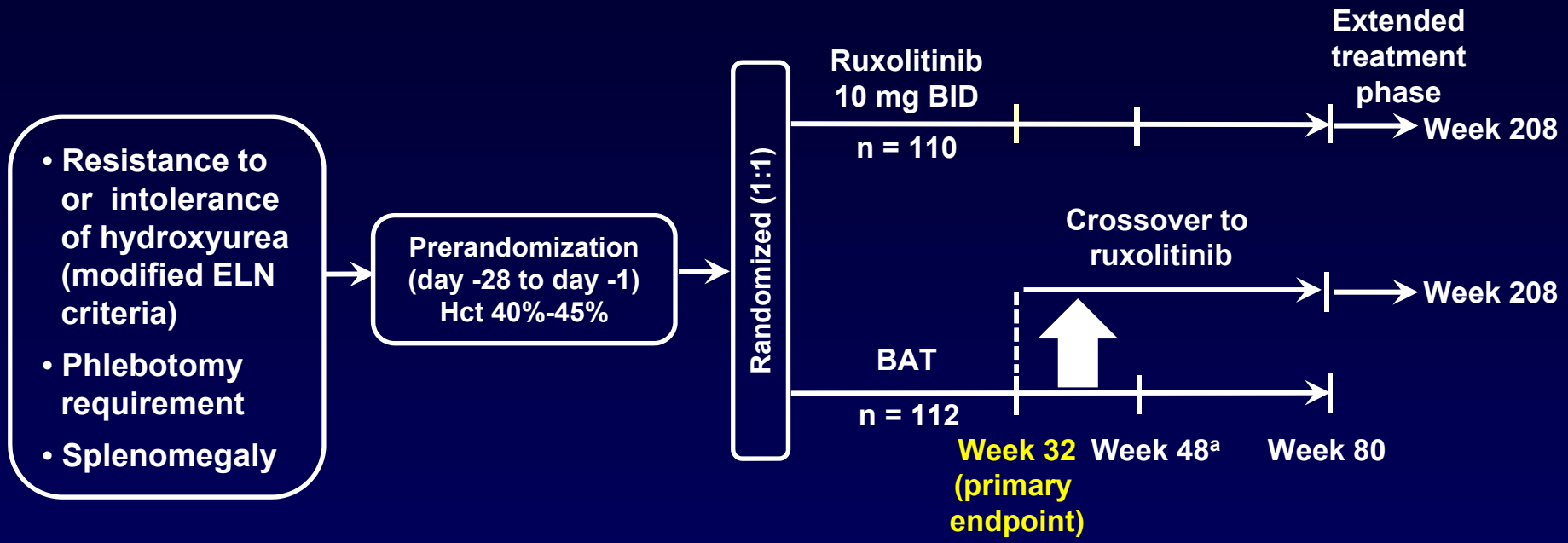
Verstovsek S, et al. *Cancer.* 2014;120(4):513-520.

Decline in *JAK2* V617F Allele Burden Over Time Under Ruxolitinib Treatment



Verstovsek S, et al. *Cancer.* 2014;120(4):513-520.

RESPONSE Study Design



- Ruxolitinib-randomized patients were individually titrated for efficacy and safety (to a maximum of 25 mg BID)
- Investigator-selected best available therapy (BAT) as monotherapy (hydroxyurea, IFN/peg-IFN, anagrelide, pipobroman, IMIDs, or observation); BAT could be changed in case of lack of response or BAT-related toxicity requiring drug discontinuation

[a]The primary analysis occurred after all patients completed week 48.

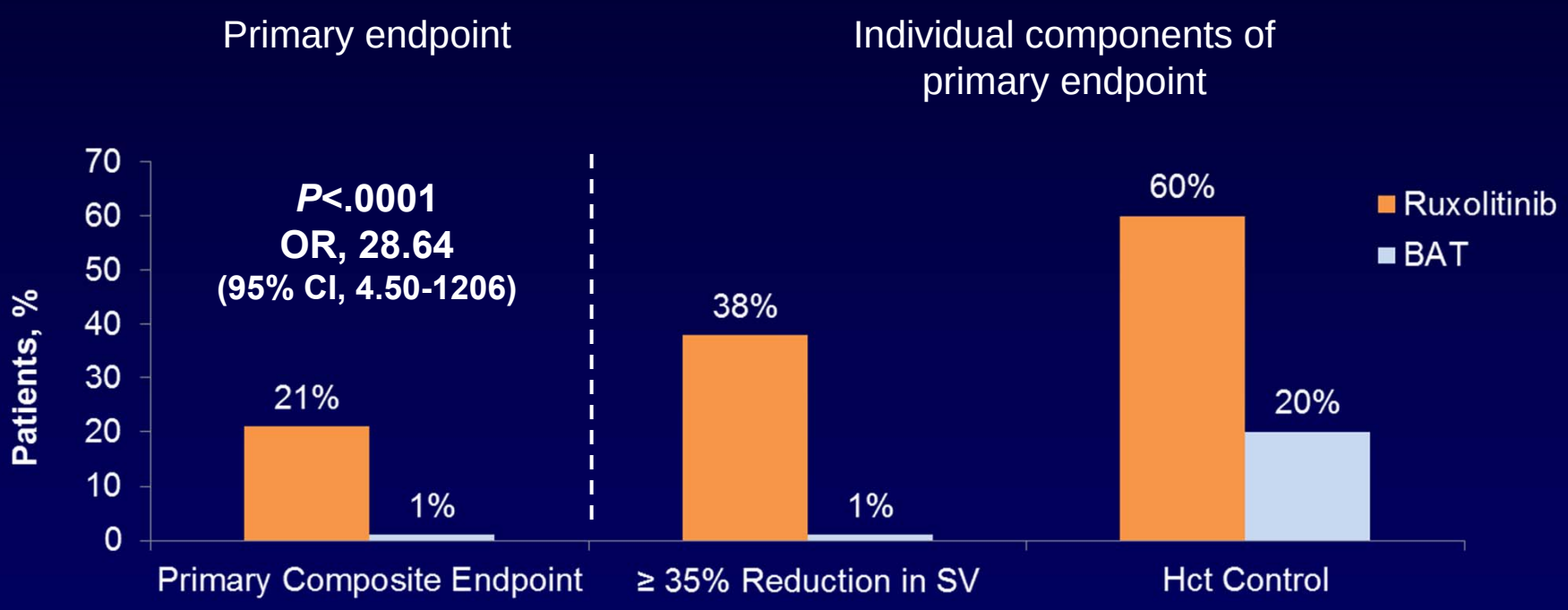
Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Efficacy Measures and Endpoints

- **Primary endpoint (composite):** Percentage of patients who achieved both Hct control and spleen response at week 32
  - Hct control
    - Absence of phlebotomy eligibility from week 8 to 32, with only 1 post-randomization phlebotomy allowed prior to week 8
      - Phlebotomy eligibility defined as Hct >45% and ≥3% higher than baseline or >48%
  - Spleen response
    - ≥35% reduction from baseline in spleen volume as assessed by MRI
- **Key secondary endpoints**
  - % of patients who maintained primary response at week 48
  - % of patients who achieved complete hematologic remission (CHR) at week 32
    - CHR = Hct control, PLT count ≤400 x 10^9/L, and WBC count ≤10 × 10^9/L
- **Other endpoints**
  - Durability of CHR at week 48
  - Symptom improvement by MPN-SAF diary
  - Safety

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Primary Response at Week 32



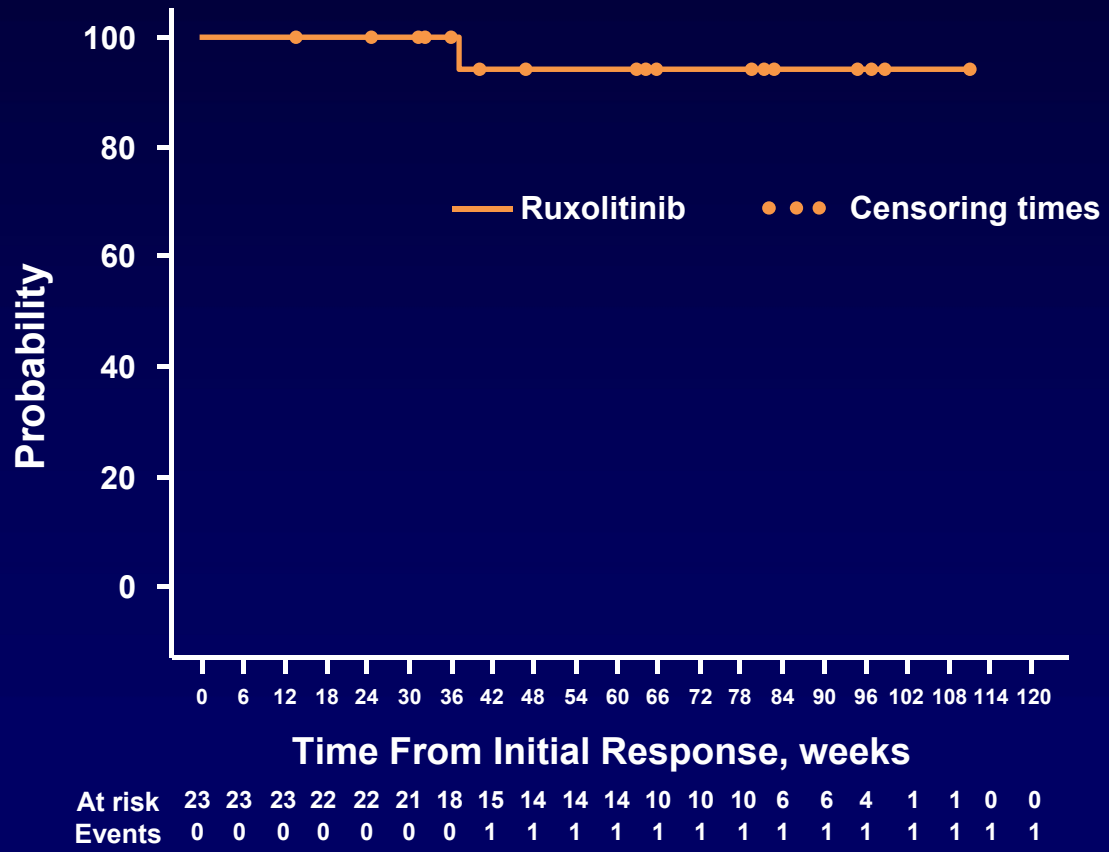
- **77% of patients randomized to ruxolitinib met at least 1 component of the primary endpoint**

SV, spleen volume

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Duration of Primary Response

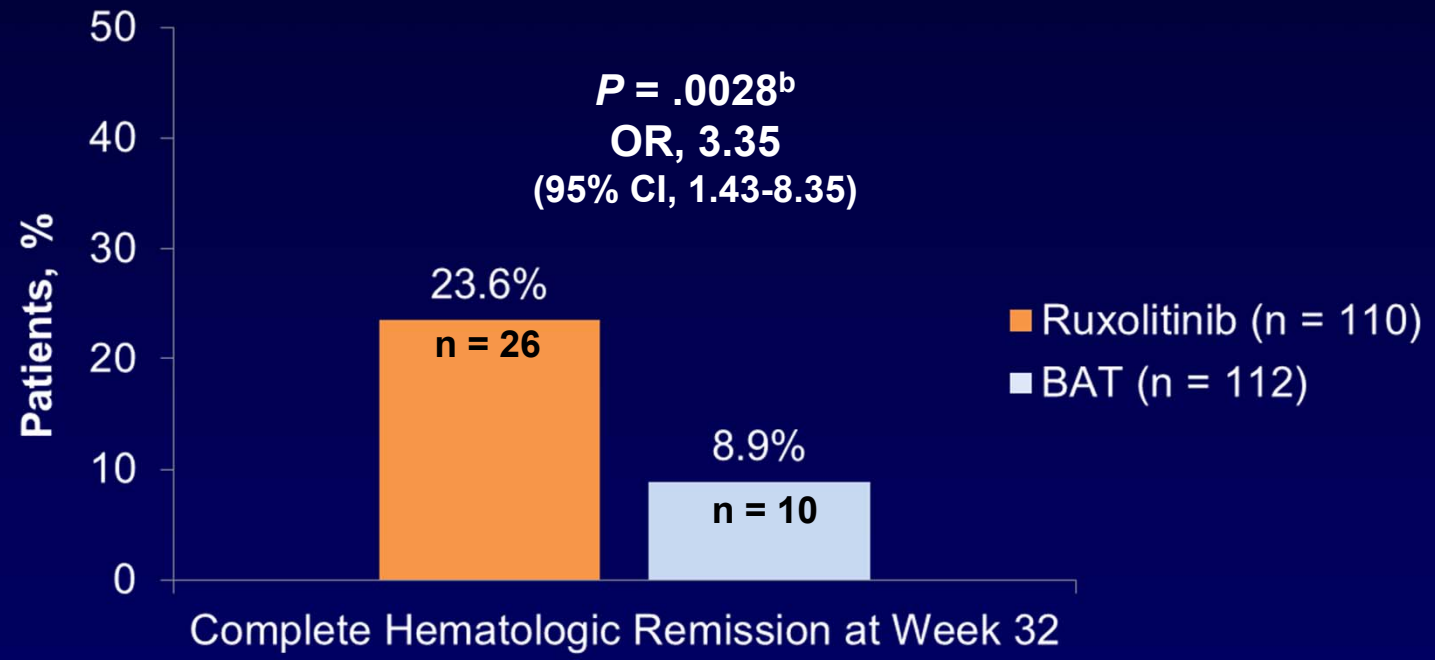
- Only 1 patient lost primary response 37.1 weeks after start of that response



- The probability of maintaining primary response for 1 year was 94%

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Complete Hematologic Remission at Week 32



- **88.5% of patients who achieved CHR had a durable response at week 48**

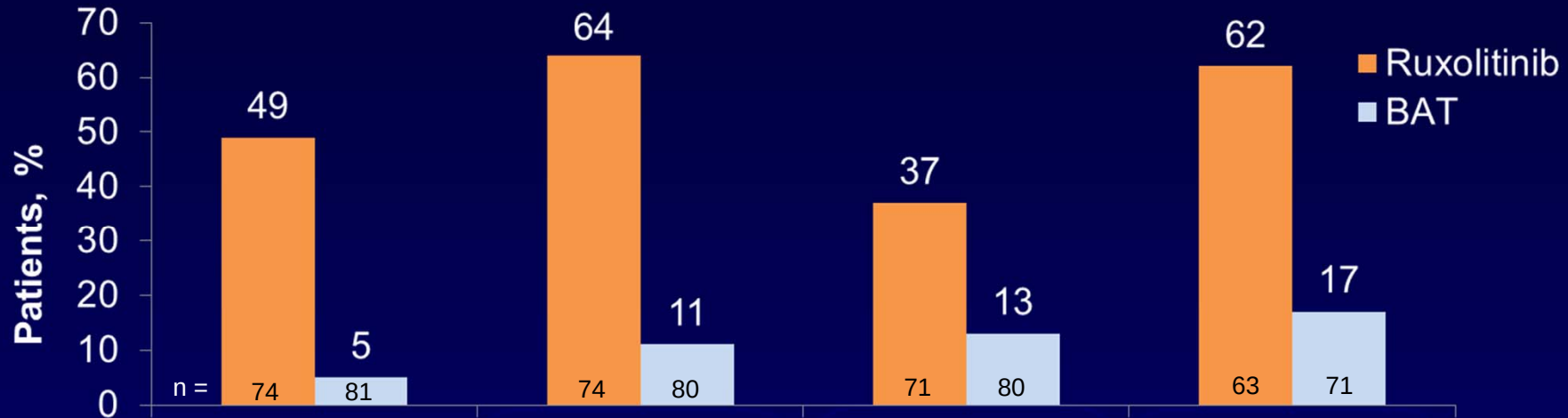
CHR is defined as Hct control, PLT count ≤400 × 10^9/L, and WBC count ≤10 × 10^9/L.

[b]*P* value, odds ratio and 95% CI were calculated using stratified exact Cochran-Mantel-Haenszel test by adjusting for the WBC/PLT status (abnormal vs normal) at baseline. WBC/PLT status was defined as abnormal if WBC count was >15 × 10^9/L, and/or PLT count >600 × 10^9/L.

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Improvement in Symptoms (Week 32)

Percentage of patients with a ≥50% improvement in MPN-SAF symptom score at week 32[a]



Tiredness
Itching
Muscle ache
Night sweats
Sweating while awake

Headache
Dizziness
Skin redness
Vision problems
Ringing in ears
Concentration problems
Numbness/tingling in hands/feet

Fullness/early satiety
Abdominal discomfort

[a]In patients with scores at both baseline and week 32
MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

RESPONSE: Additional Findings

- The rate of thromboembolic events was lower in the ruxolitinib group (1 thrombosis compared with 6 thromboses in the BAT arm)
- Ruxolitinib was generally well tolerated
  - 85% of patients in the ruxolitinib arm were still on treatment at a median follow-up of 81 weeks
  - Most adverse events were grade 1/2, and few patients developed grade 3/4 cytopenias
- The safety profile of ruxolitinib in this study is generally consistent with that observed in the phase III COMFORT studies[1,2] of ruxolitinib for the treatment of MF

1. Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807. 2. Harrison CH, et al. *N Engl J Med*. 2012;366(9):787-798.

Concluding Key Points

- Limited choice of conventional treatments, but effective and well tolerated in most patients
- Role of IFN to be clearly assessed as studies in PV are underway
- In need of alternative treatments for selected categories of patients, including those resistant / refractory / intolerant to best available therapy
- JAK inhibitor(s) are promising therapies for selected patient categories