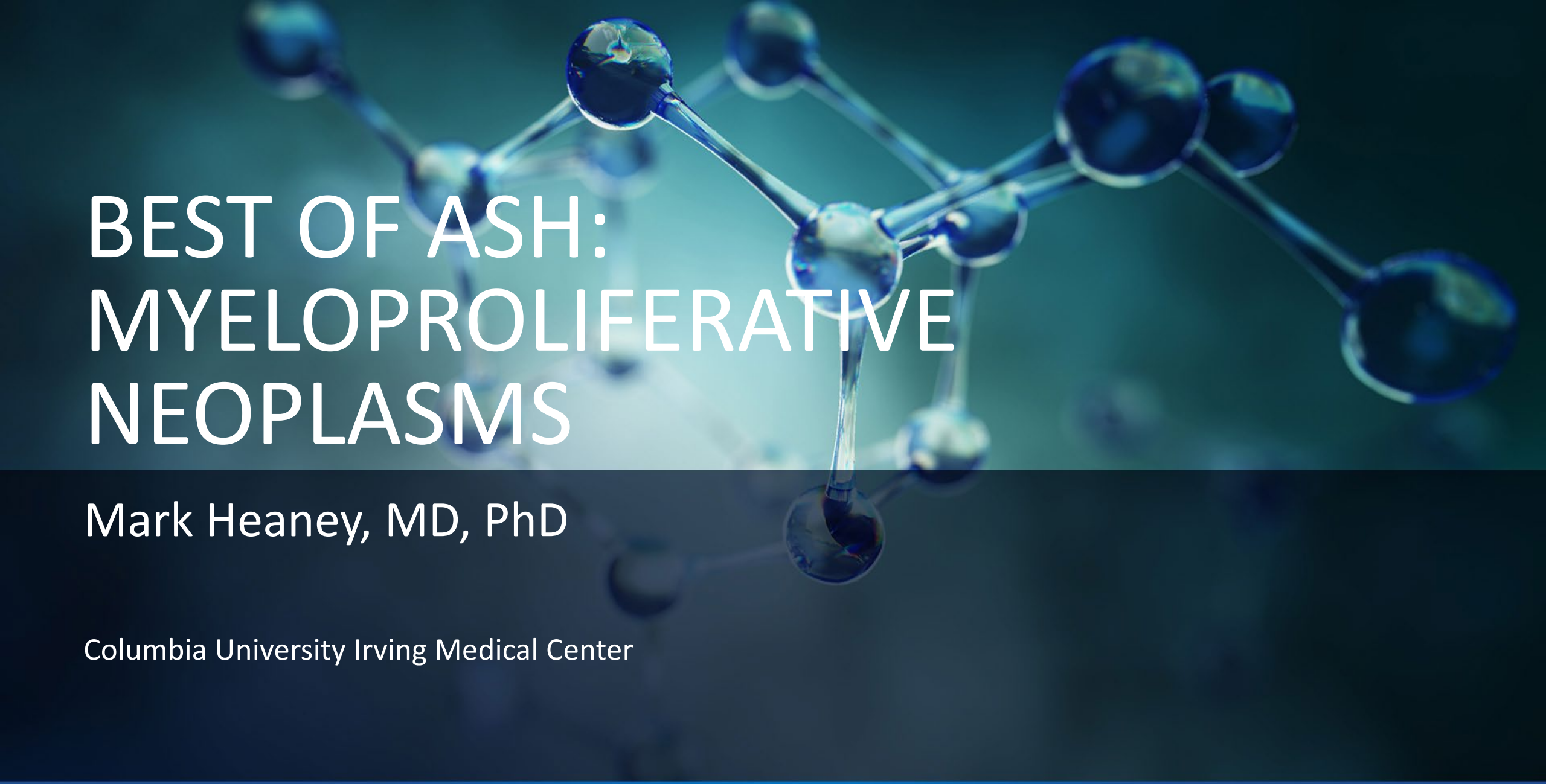

BEST OF ASH: MYELOPROLIFERATIVE NEOPLASMS

Mark Heaney, MD, PhD

Columbia University Irving Medical Center

DISCLOSURES

Consulting and Honoraria

- CTI Pharma
- Novartis
- PharmaEssentia
- Blueprint

Research Funding

- Blueprint
- BMS
- Cogent
- CTI BioPharma
- Incyte
- Kartos
- Sierra Oncology

Risk Stratification in Polycythemia Vera

A JAK2V617F Variant Allele Frequency Greater Than 50% Identifies Patients with Polycythemia Vera at High Risk for Venous Thrombosis

Giuseppe Gaetano Loscocco, MD[1], Paola Guglielmelli, MD, PhD[1], Carmela Mannarelli, PhD[1*], Elena Rossi, MD, PhD[2*], Francesco Mannelli, MD[1*], Francesco Ramundo[2*], Giacomo Coltro, MD[3*], Silvia Betti, MD, PhD[2*], Chiara Maccari[1*], Sara Ceglie, MD[2*], Chiara Paoli, PhD[1*], Tiziano Barbui, MD[4*], Ayalew Tefferi, MD[5], Valerio De Stefano[6*] and Alessandro Vannucchi, MD*

- Background: Current risk stratification based on age >60 y and history of thrombosis
- Evaluated 516 PV patients with strict WHO criteria followed at Univ Florence from 1981-2020
- Independent validation with 289 PV patients from Policlinico Gemelli, Catholic Univ Rome
  - JAK2 VAF was annotated within 3 years of diagnosis
  - Venous and arterial thrombotic events were followed

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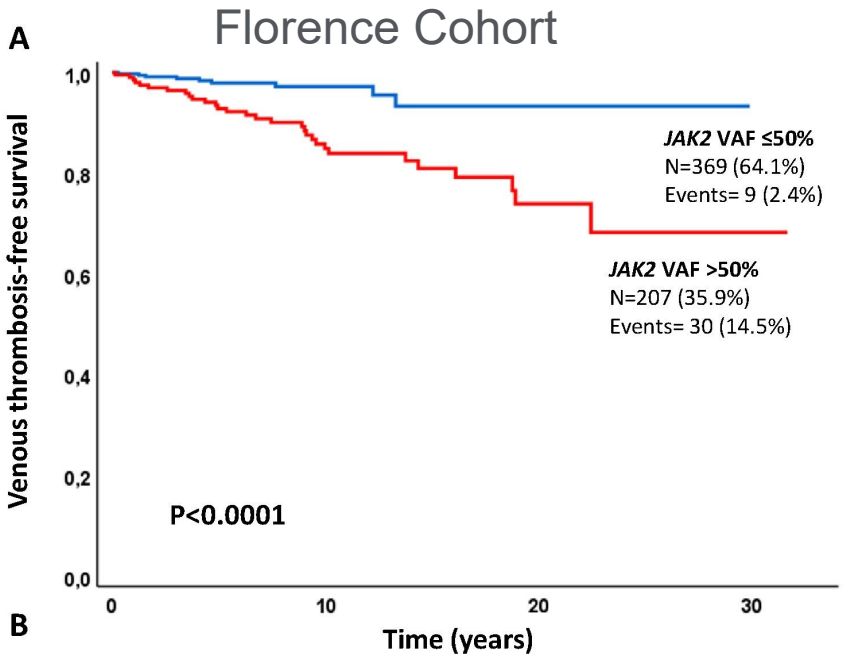
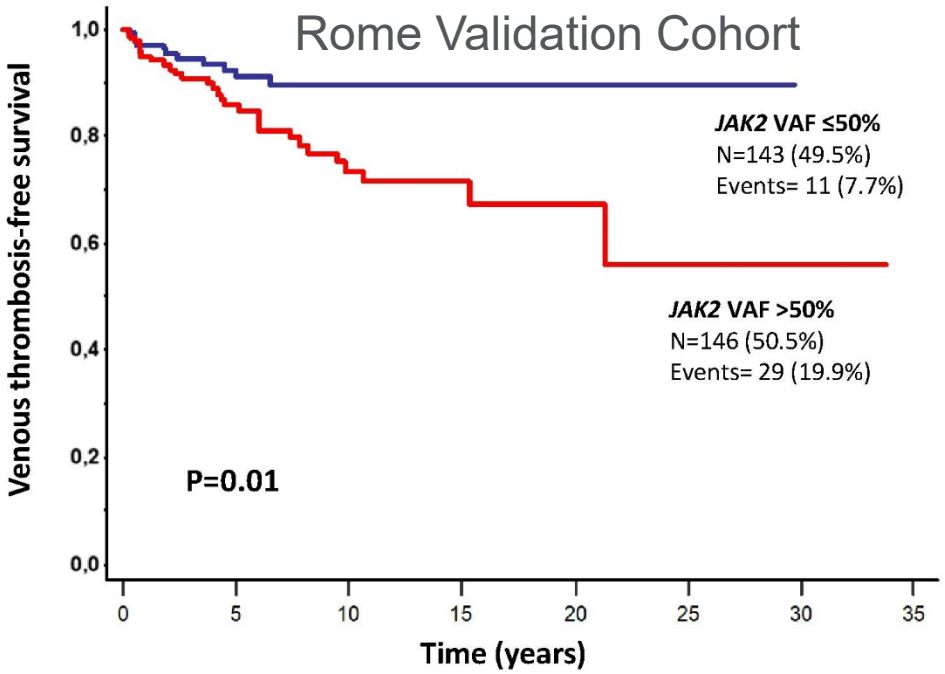
Fig.1





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- JAK2 VAF had no impact on arterial thrombosis risk
- Multivariate analysis confirmed prior thrombosis and JAK2 VAF as independent risk factors

  Age >60 showed only a trend (*P*=0.08)

- The impact of JAK2 VAF on venous thrombosis was particularly significant for conventionally low-risk patients with HR=9.4 in Florence cohort and 3.6 in Rome cohort

Risk Stratification in Polycythemia Vera

A Real-World Evaluation of the Association between Elevated Blood Counts and Thrombotic Events in Polycythemia Vera (Analysis of Data from the REVEAL Study) *Aaron T. Gerds, MD, MS[1], Ruben A. Mesa, MD, FACP[2], John M. Burke, MD[3], Michael R. Grunwald, MD[4], Brady Lee Stein, MD[5], Robyn Scherber, MD, MPH[6], Jingbo Yu, MD, PhD[6], J.E. Hamer-Maansson, MSPH[6*] and Stephen Oh, MD, PhD[7*]*

- Background: Association between HCT and thrombosis has been well established in PV; the contributions of WBC and PLT are less certain
- REVEAL study enrolled 2510 patients, of whom 2271 were eligible, based on at least 3 CBCs, including 1 CBC within 6 months of the thrombotic event

  Analyzed variables also included gender, age, disease duration, TE history at enrollment, and treatment parameters.

  Median age: 66 y, 54% male

  Median disease duration: 4.1 y, 20.1% had TE history

  56% treated with hydroxyurea

  30 arterial TE (TIA=15), 76 VTE (DVT=37)

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Table 1. Association Between Blood Count Values and TEs

Analysis	HR (95% CI)	*P* Value
Association between elevated HCT and TEs		
Age, y	**1.03 (1.01–1.046)**	**0.0026**
Male sex (M vs F)	**0.54 (0.362–0.799)**	**0.0021**
Disease duration, y	0.98 (0.952–1.017)	0.3438
History of TE (Y vs N)	**2.49 (1.667–3.717)**	**<0.0001**
Treatment (HU vs none)	0.95 (0.626–1.435)	0.8004
Treatment (any other vs none)	0.78 (0.39–1.577)	0.4951
HCT (>45% vs ≤45%)	**1.84 (1.234–2.749)**	**0.0028**

Confirmation of HCT >45 as a risk for thrombosis

Risk Stratification in Polycythemia Vera

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Association between elevated WBC count and TEs (4 WBC levels (<7, ≥7 to <8.5, ≥8.5 to <11, and ≥11×10^9/L)

Age, y	**1.02 (1.006–1.042)**	**0.0076**
Male sex (M vs F)	**0.59 (0.396–0.865)**	**0.0071**
Disease duration, y	0.98 (0.948–1.015)	0.2646
History of TE (Y vs N)	**2.42 (1.618–3.608)**	**<0.0001**
Treatment (HU vs none)	1.00 (0.66–1.509)	0.9932
Treatment (any other vs none)	0.67 (0.336–1.328)	0.2496
WBC (≥7 to <8.5 vs <7×10^9/L)	1.01 (0.504–2.022)	0.9778
WBC (≥8.5 to <11 vs <7×10^9/L)	1.40 (0.76–2.595)	0.2790
WBC (≥11 vs <7×10^9/L)	**2.61 (1.594–4.262)**	**0.0001**

WBC >11 as a risk for thrombosis

Risk Stratification in Polycythemia Vera

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Association between elevated PLT count (>400×10^9/L) and TEs

Age, y	**1.03 (1.01–1.046)**	**0.0022**
Male sex (M vs F)	**0.62 (0.416–0.914)**	**0.0162**
Disease duration, y	0.99 (0.953–1.019)	0.3901
History of TE (Y vs N)	**2.45 (1.64–3.654)**	**<0.0001**
Treatment (HU vs none)	0.87 (0.58–1.319)	0.5223
Treatment (any other vs none)	0.66 (0.334–1.324)	0.2456
PLT (>400 vs ≤400×10^9/L)	**1.60 (1.088–2.359)**	**0.0170**

PLT >40,000 as a risk for thrombosis

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- Conclusions:

  HCT >45, age >60, female gender, and prior TE were risk factors for TE in all models

  WBC >11 was a risk factor

  PLT >400,000 was a risk factor

  N.B. PLT >600,000 was NOT a risk factor

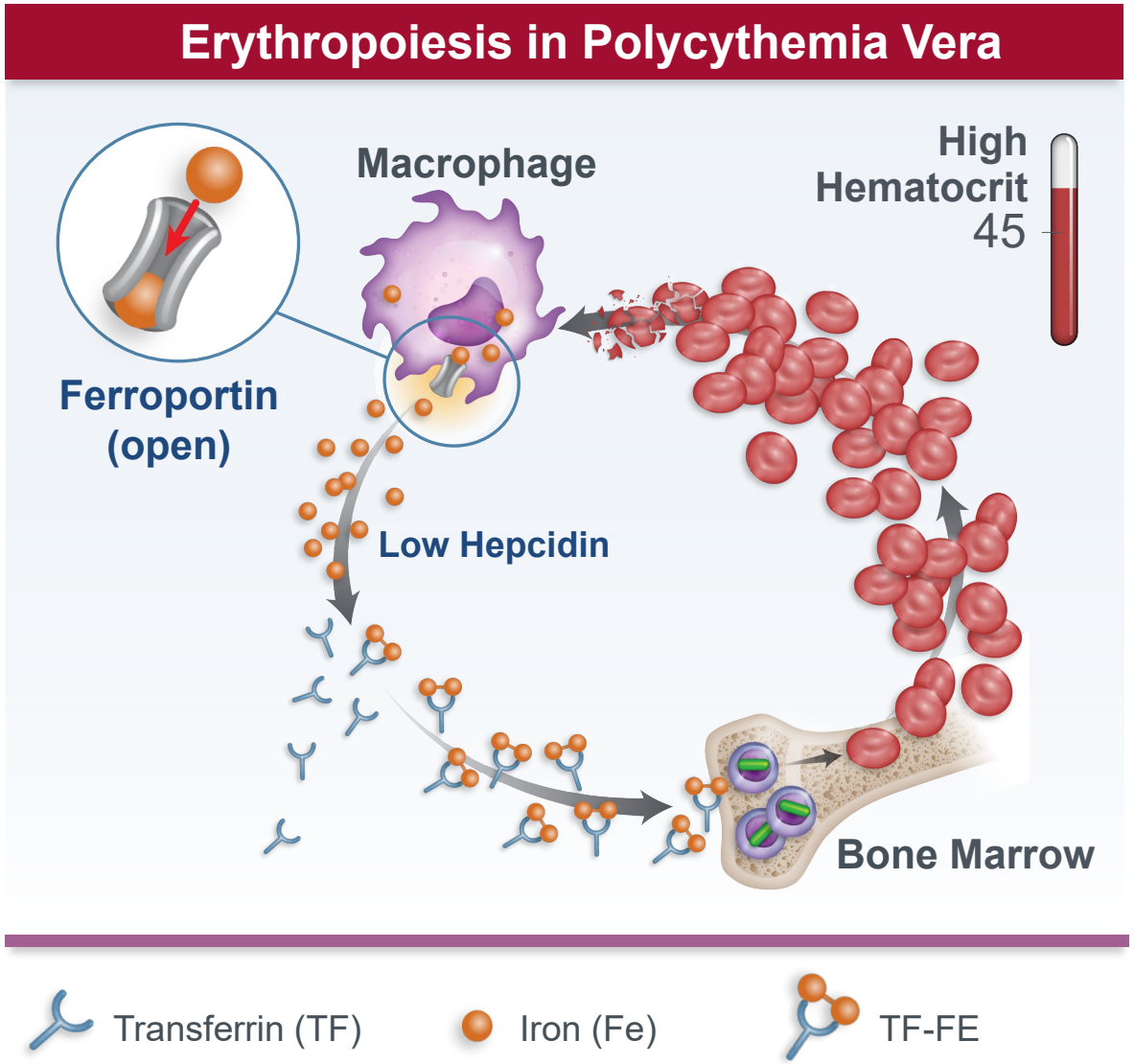
Novel Therapies for Polycythemia Vera

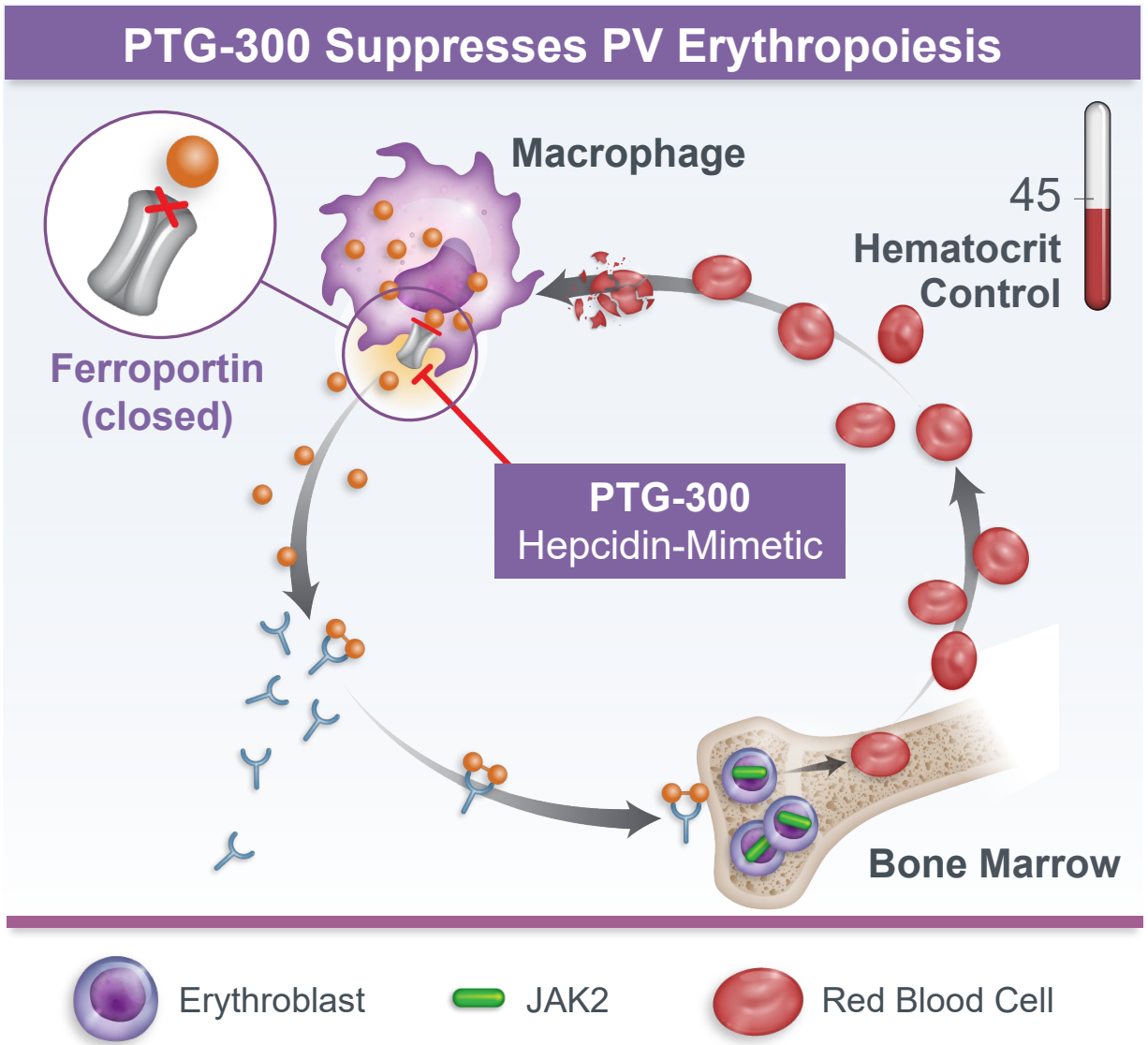
Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients

Ronald Hoffman, MD[1], *Marina Kremyanskaya, MD, PhD*[2], *Yelena Ginzburg, MD*[3], *Andrew T. Kuykendall, MD*[4], *Naveen Pemmaraju, MD*[5], *Abdulraheem Yacoub, MD*[6], *Jay Yang, MD*[7], *Suneel Gupta*[8], *Frank Valone, MD*[9*], *Sarita Khanna, PhD*[8*] *and Srdan Verstovsek, MD, PhD*[10]

- **Background:** PV compared with secondary forms of erythrocytosis is associated with relative suppression of hepcidin, potentially due to greater degrees of expanded erythropoiesis and iron deficiency
- **Rusfertide, a hepcidin mimetic, blocks ferroportin in the macrophage and prevents erythropoiesis**

Rationale for Using Hepcidin-Mimetics (PTG-300) in PV





Courtesy R. Hoffman

Phase 2 Trial of PTG-300 (Rusfertide) in 63 PV Patients

ELIGIBILITY REQUIREMENTS:

Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria

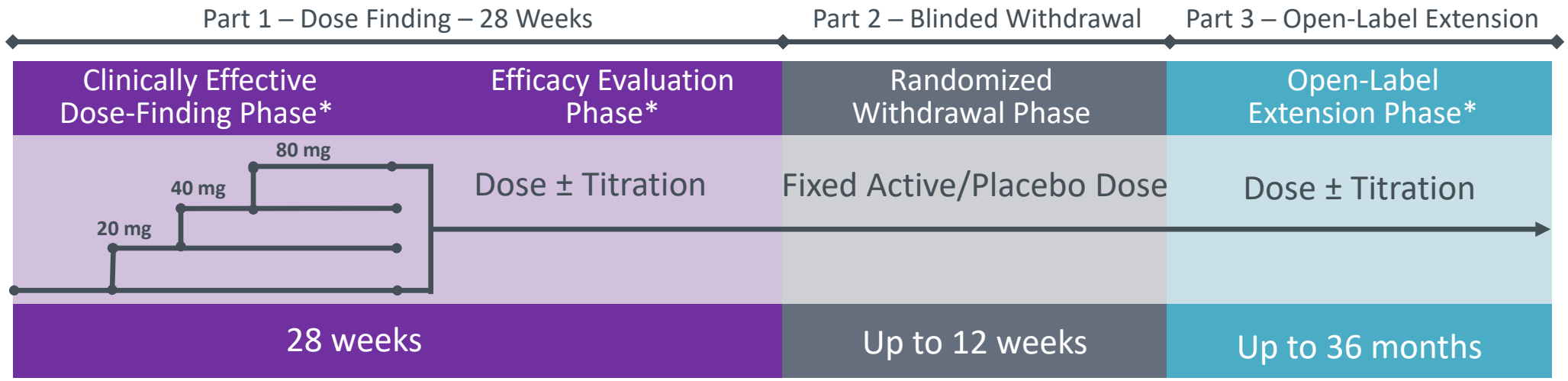
≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy

All patients prior to first PTG-300 dose were phlebotomized to HCT <45% to standardize the starting HCT

PTG-300 doses of 10-120 mg administered subcutaneously weekly added to prior standard therapy

ADD-ON STUDY DESIGN

Clinical GOAL: To maintain hematocrit <45%



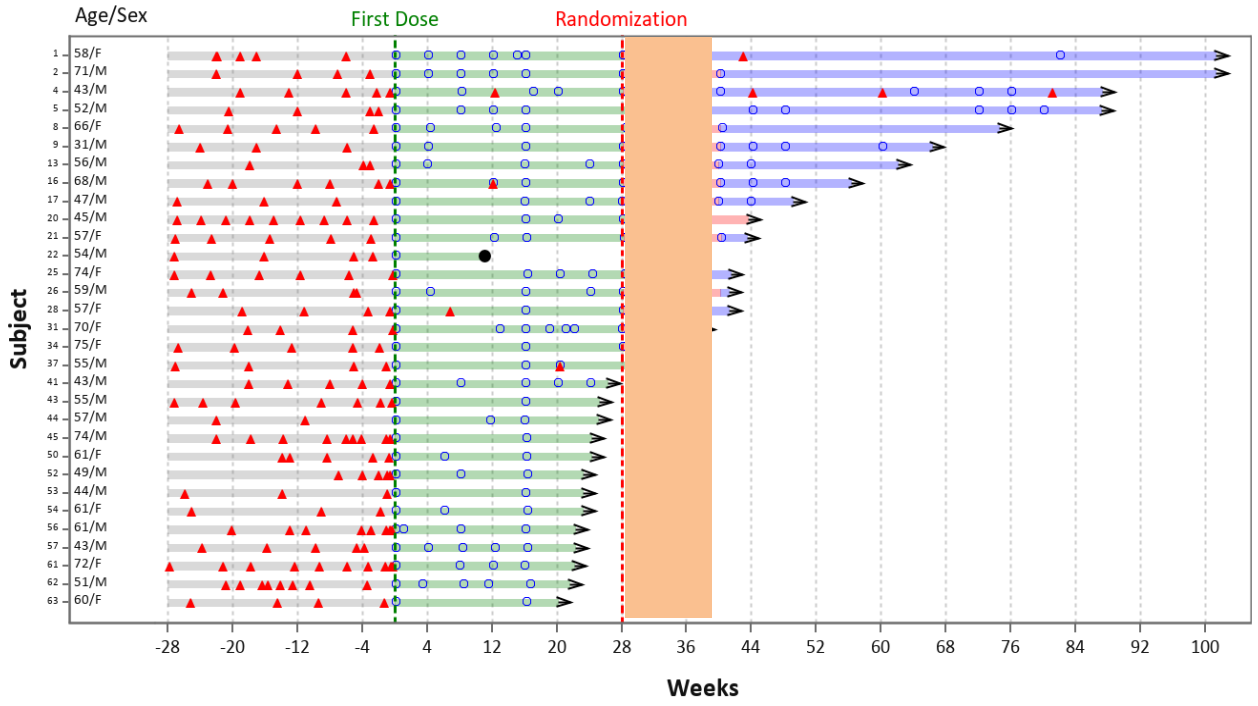
** Titrate every 4 weeks to maintain hematocrit <45%.*

First patient enrolled in Oct 2019 and Last patient enrolled May 2021

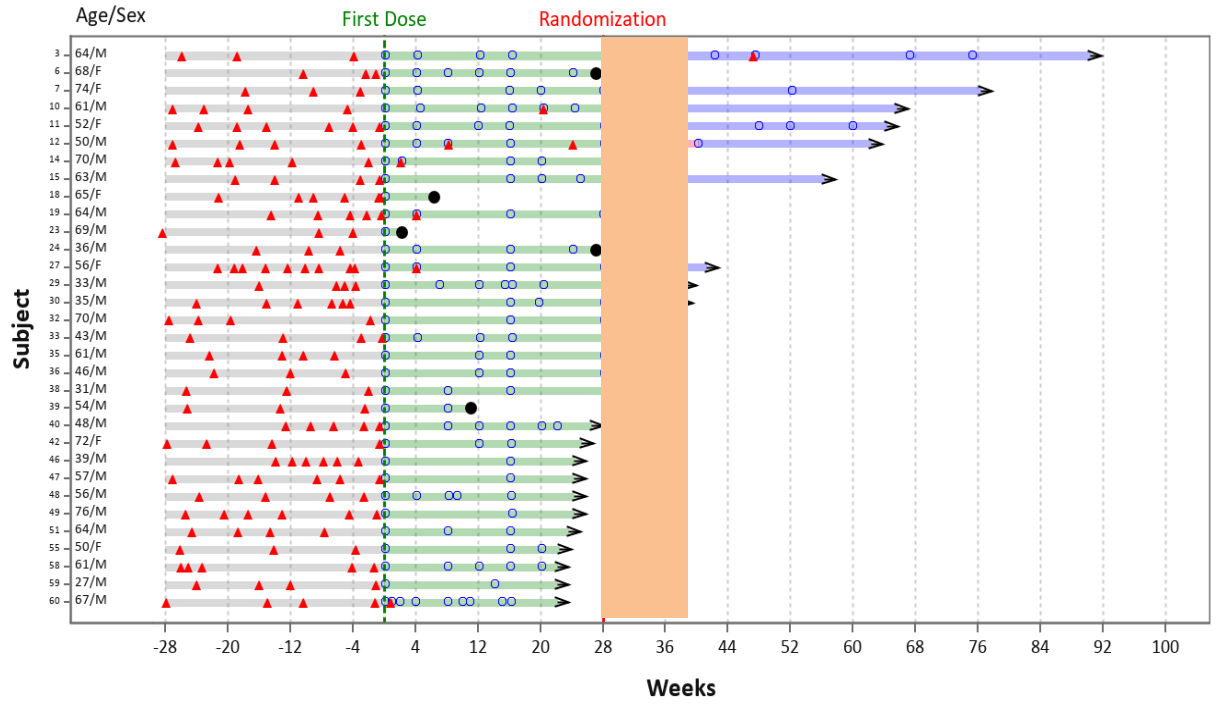
Courtesy R. Hoffman

Effect of Rusfertide on Phlebotomy Frequency

PHLEBOTOMY ONLY (N=31, 49%)



PHLEBOTOMY + CYTOREDUCTIVE (N=32, 51%)

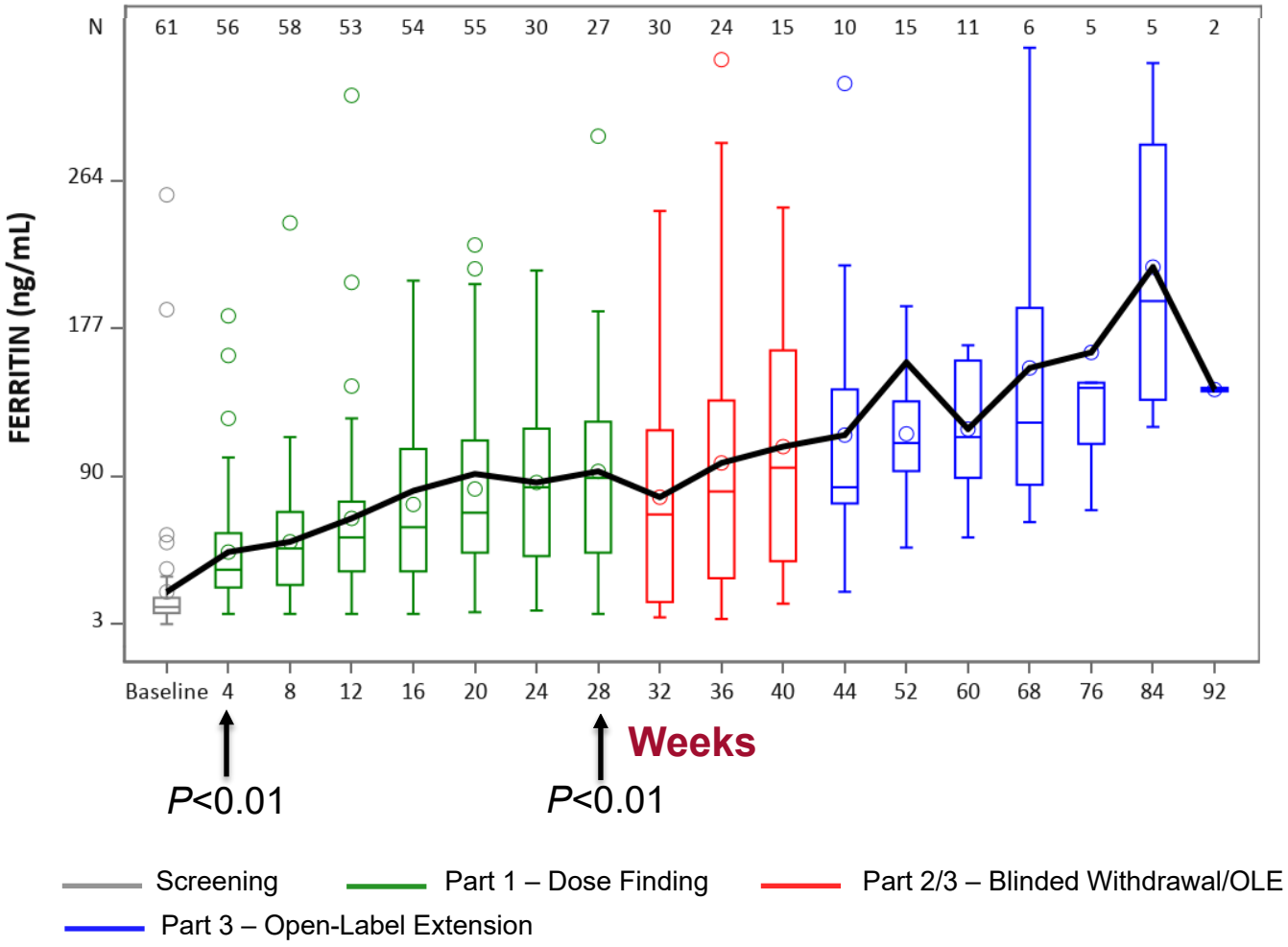


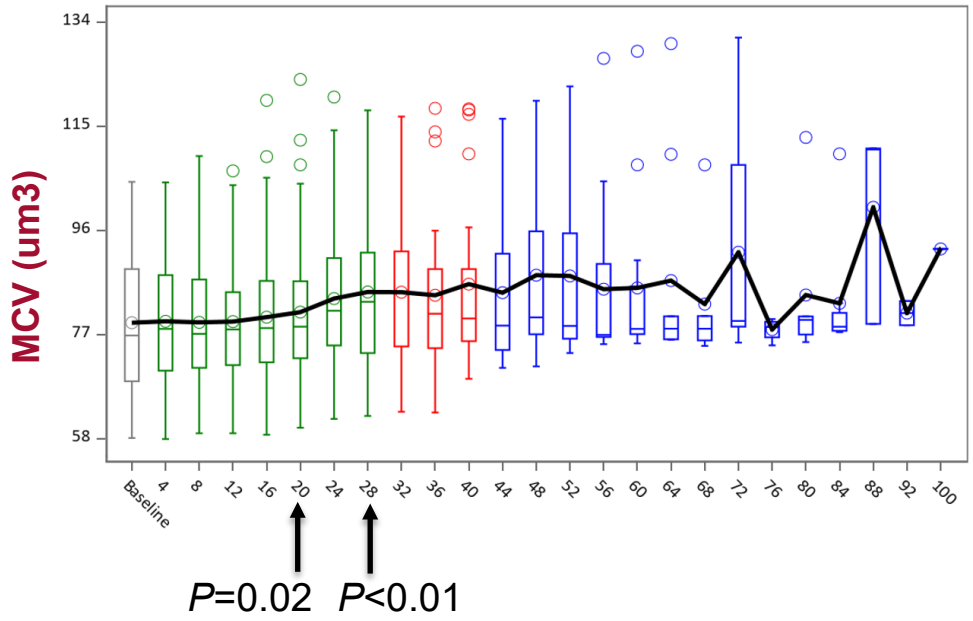
Overall, during the first 28 weeks of treatment, 84% of patients did not require a phlebotomy, 14% required one, and 2% required two phlebotomies.

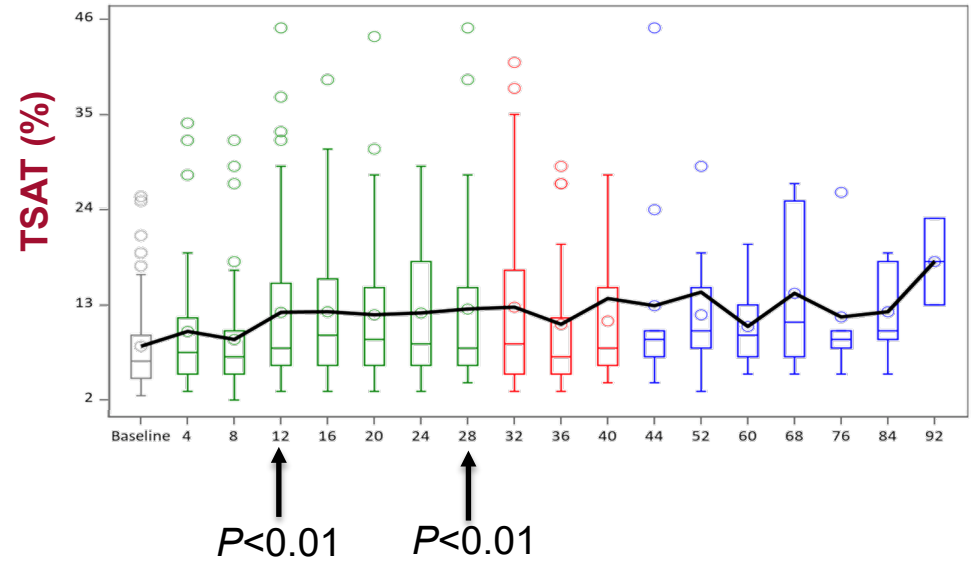
Median Dose 40-60 mg/week

Courtesy R. Hoffman

Rusfertide Normalizes Iron Stores



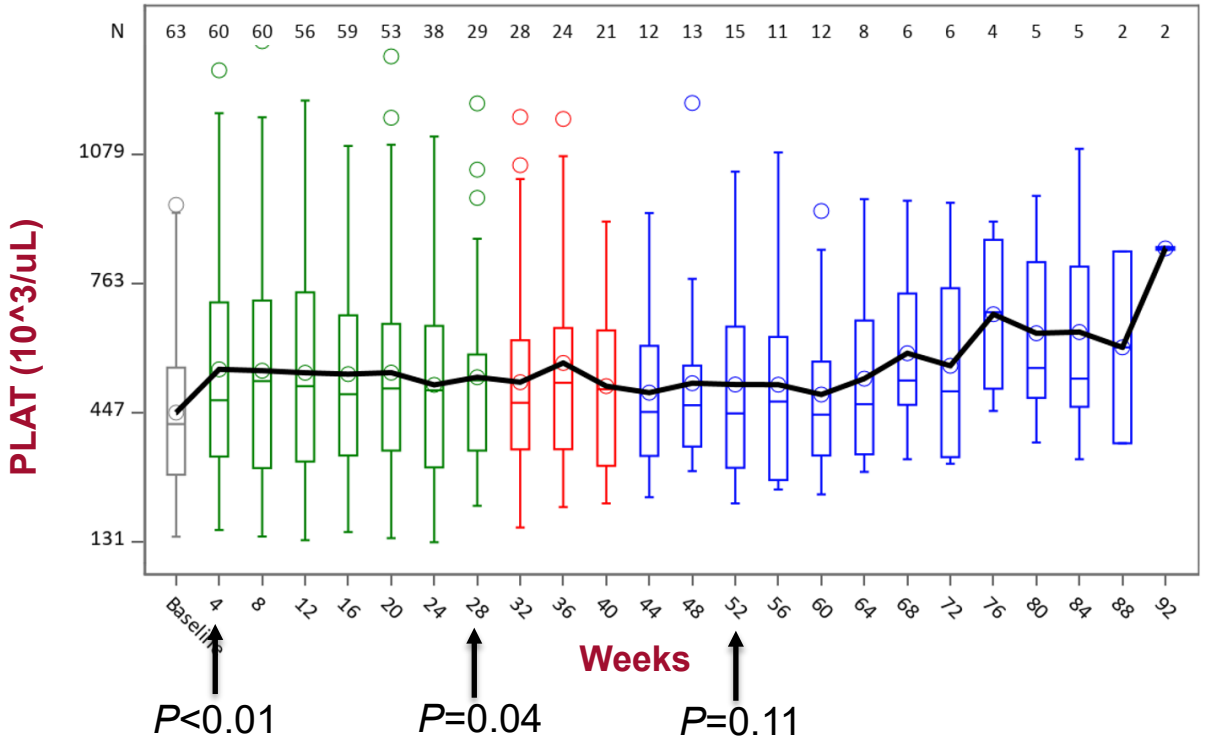




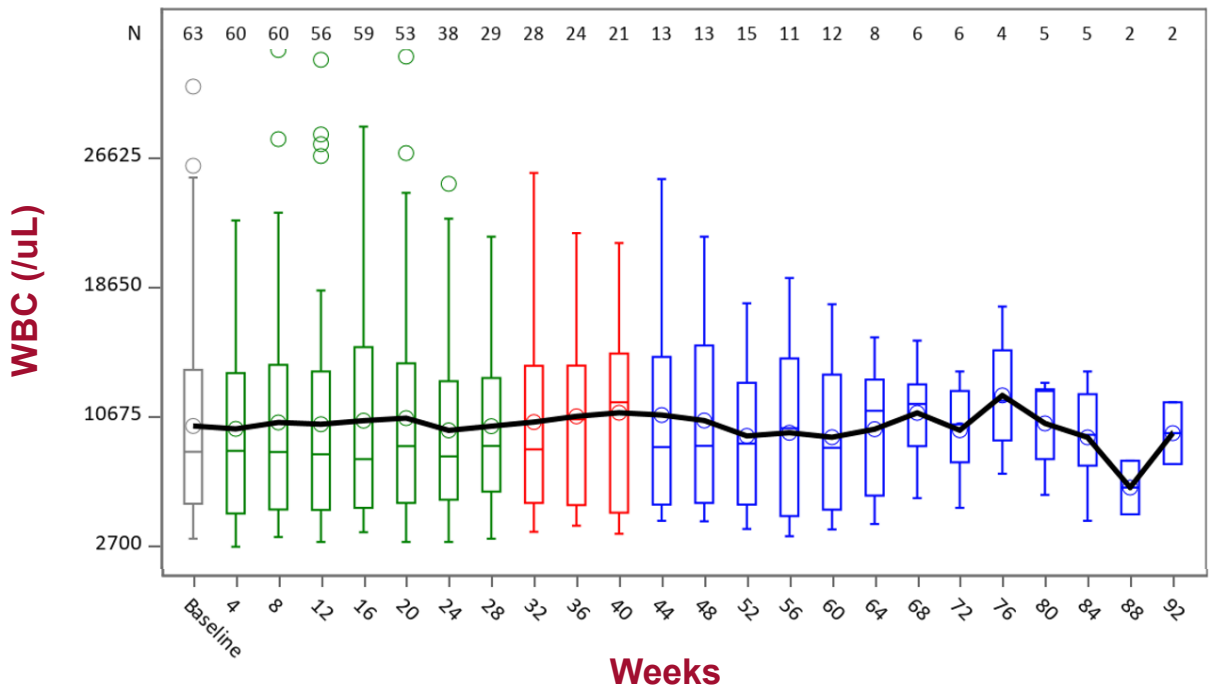
Courtesy R. Hoffman

Effects of Rusfertide on Platelet and WBC Counts

Platelets



WBC



Screening — Part 1 – Dose Finding — Part 2 – Blinded Withdrawal — Part 3 – Open-Label Extension

AVAL = Raw Value
Box whiskers extend up to 1.5 times interquartile range.

All increases in Platelet numbers < 20%

Courtesy R. Hoffman

Adverse Events Experienced on Rusfertide

System Organ Class – Preferred term	AE, n (%)
Total number of subjects	***63***
No. of subjects with treatment-emergent AE	***55 (87)***
Blood and lymphatic disorders	12 (19.0)
Anemia	9 (14.3)
Gastrointestinal disorders	20 (31.7)
Nausea	8 (12.7)
Infections and infestations	11 (17.5)
Metabolism and nutrition disorders	9 (14.3)
Musculoskeletal and connective tissue disorders	27 (42.9)
Nervous system disorders	21 (33.3)
Psychiatric disorders	7 (11.1)
Insomnia	4 (6.3)
Renal and urinary disorders	5 (7.9)
Respiratory	14 (22.2)
Skin and subcutaneous tissue disorders	23 (36.5)
Pruritis	9 (14.3)

- **Most drug-related AEs were Grade 1 or 2**
- No Grade 4 or 5 Events
- **SAEs:** Syncope, peripheral artery aneurism, gastroenteritis, chest pain, AML, squamous cell carcinoma (skin), melanoma, and basal cell carcinoma
- Injection site reaction (ISRs) were most common and associated with 28.1% of injections. All ISRs were transient, and no patient discontinued due to ISR
- One subject stopped treatment due to AE within 2 weeks (asymptomatic thrombocytosis)
- No clinically significant laboratory abnormalities
- No antidrug antibody response was noted in any patient

Courtesy R. Hoffman

Progression of Systemic Mastocytosis

Effective Control of Advanced Systemic Mastocytosis with Avapritinib: Mutational Analysis from the Explorer Clinical Study *Michael W. Deininger, MD, PhD[1], Daniel J. DeAngelo, MD, PhD[2*], Deepti H. Radia, MD[3*], Tracy I. George, MD[4], Guang Yang, PhD[5*], Jayita Sen, PhD[5*], Hui-Min Lin, PhD[5*], Brenton Mar, MD, PhD[5*] and Jason Gotlib, MD, MS[6]*

- **Background: Advanced systemic mastocytosis most commonly manifests as a myeloid malignancy (especially MDS and MPN overlap) occurring in the setting of c-kit–mutated mastocytosis in the bone marrow**
- **Avapritinib is a kit inhibitor that is highly effective in reducing the c-kit–mutated mast cell clone**
- **Patients may progress despite control of the mastocytosis**
- **Mutation-Adjusted Risk Score** (Jawhar M, et al. *J Clin Oncol.* 2019;37:2846–2856) **was used to evaluate patients on the Explorer trial**

Progression of Systemic Mastocytosis

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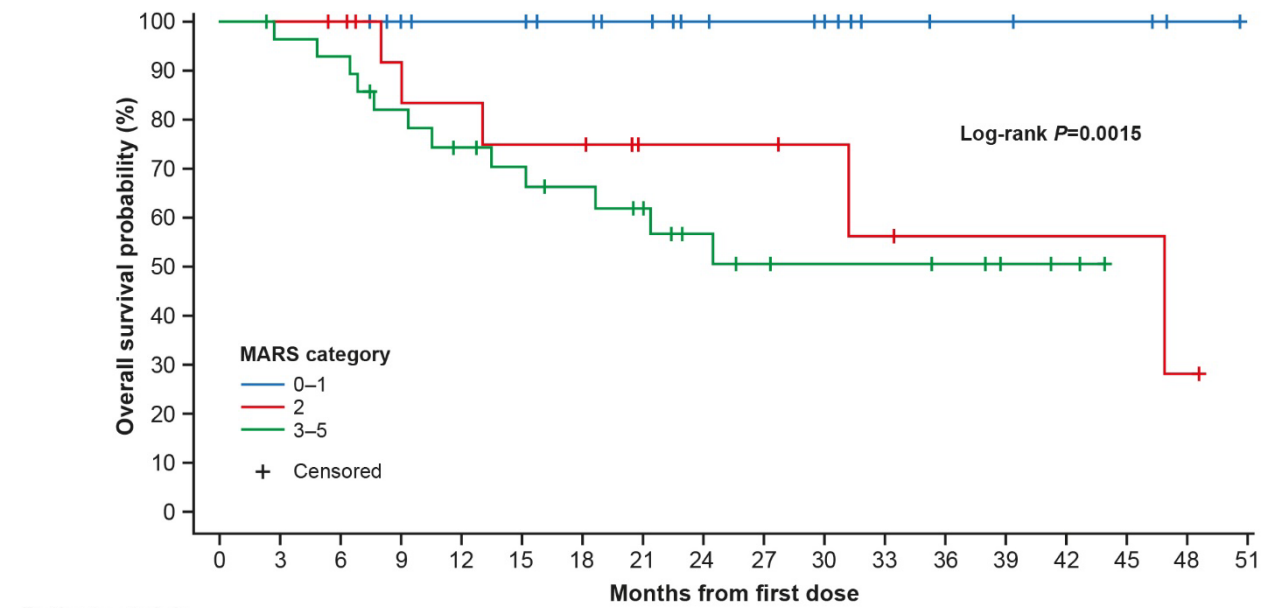
Figure. Overall survival by MARS category in the EXPLORER study



Novel Treatments for Essential Thrombocythemia

A Phase 2 Study of the LSD1 Inhibitor Img-7289 (bomedemstat) for the Treatment of Essential Thrombocythemia (ET)

Francesca Palandri, MD, PhD[1], Nicola Vianelli, MD[2,3*], David M. Ross, MBBS, PhD, FRACP, FRCPA[4*], Tara Cochrane, MBBS, FRCPA, FRACP[5], Steven W. Lane, MD, PhD[6], Stephen R. Larsen, MBBS PhD FRACP FRCPA[7], Aaron T. Gerds, MD, MS[8], Anna B. Halpern, MD[9], Jake Shortt, FRACP, FRCPA, PhD[10], James M. Rossetti, DO[11], Kristen M. Pettit[12], Amber Jones, MA[13*], Jennifer Peppe, BS[14*], Georges Natsoulis, Ph.D.[15*], Willis Navarro, MD[16], Wan-Jen Hong, MD[16], William S. Stevenson, MBBS, PhD[17], Claire N. Harrison, DM[18], Moshe Talpaz, MD[12] and Hugh Young Rienhoff Jr., MD[19]*

Background: Bomedemstat is an oral inhibitor of LSD-1, which is critical for the maturation of progenitors to megakaryocytes.

Ongoing clinical trials in myelofibrosis

Phase 2 study of patients with ET requiring cytoreduction: first 30 patients

77% failed HU, 10% anagrelide, 7% IFN, 3% busulfan, 3% ruxolitinib

50% JAK2V617F, 44% CALR mutant; all wt MPL

Median time on study: 16 weeks

- **Objectives: PLT <400,000, no thrombosis or disease progression**

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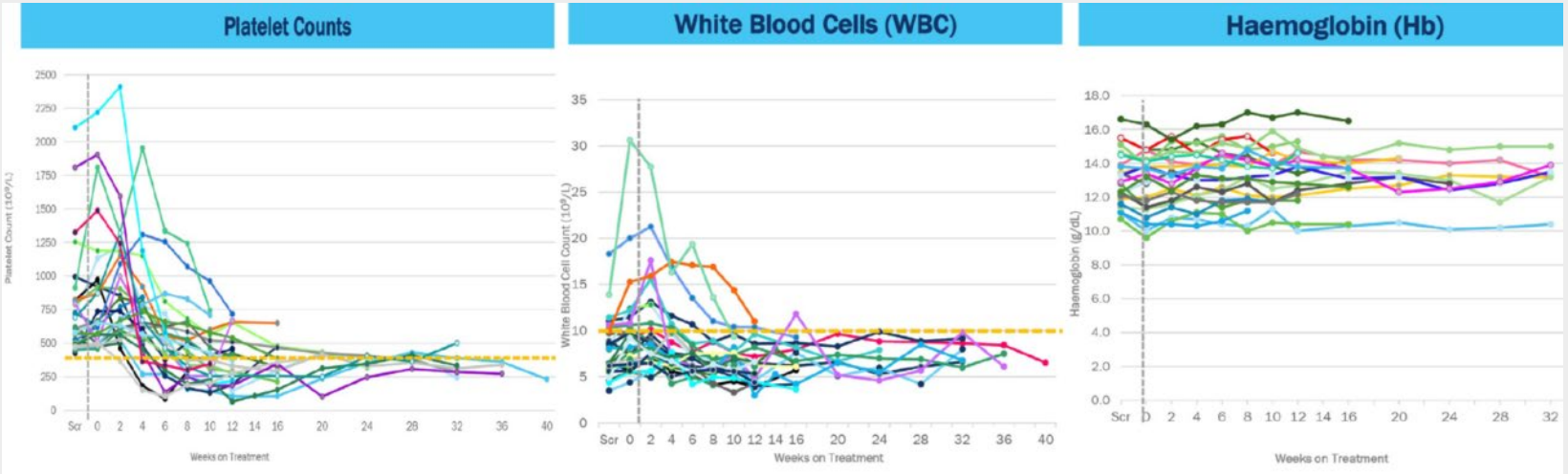


AE	%
Dysgeusia	40
Fatigue	17
Thrombocytopenia	17
Constipation	17
Diarrhea	17

Of patients treated at least 6 weeks, 81% achieved PLT <400 and no thrombosis or progression

New Treatments for Chronic Myeloid Leukemia

Efficacy and Safety Results from Ascembl, a Multicenter, Open-Label, Phase 3 Study of Asciminib, a First-in-Class STAMP Inhibitor, Vs Bosutinib in Patients with Chronic Myeloid Leukemia in Chronic Phase after ≥2 Prior Tyrosine Kinase Inhibitors: Update after 48 Weeks

Michael J. Mauro, MD[1], Yosuke Minami, MD, PhD[2], Delphine Rea, MD, PhD[3], Andreas Hochhaus, MD[4], Elza Lomaia, MD, PhD[5], Sergey Voloshin, MD, PhD[6*], Anna G. Turkina, Prof., MD[7], Dong-Wook Kim, M.D., Ph.D.[8], Jane F. Apperley, FRCP, FRCPath, MB[9], Jorge E. Cortes, MD[10], Andre N.R. Abdo, MD[11*], Laura Fogliatto[12], Dennis Dong Hwan Kim, MD, PhD[13*], Philipp D le Coutre, MD[14], Susanne Saussele, MD [15], Mario Annunziata, MD[16*], Timothy P. Hughes, MD, MBBS, FRACP, FRCPA[17], Naeem A. Chaudhri, MD[18], Lynette C.Y. Chee, MBBS, PhD, FRACP, FRCPA[19], Valentín Garcia Gutierrez, MD, PhD[20], Koji Sasaki, MD[21], Shruti Kapoor[22*], Alex Allepuz, MD, MPH[23*], Sarah Quenet[24*], Véronique Bédoucha[24*] and Carla Boquimpani, MD[25*]*

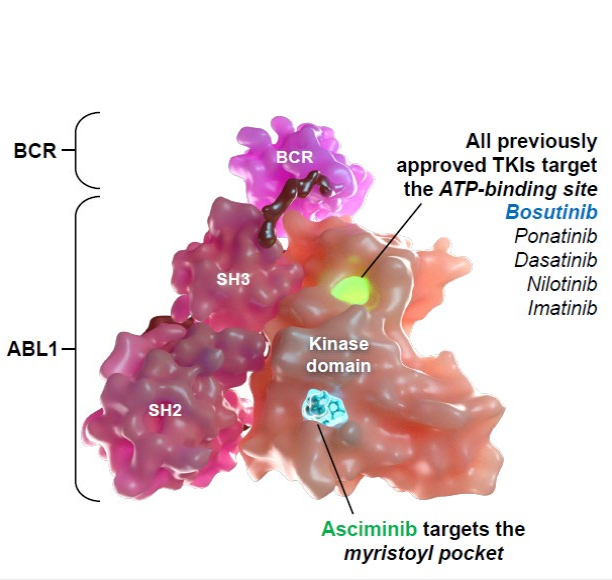
Background: Asciminib binds to ABL myristoyl pocket

Ascembl is a phase 3 trial of asciminib randomized 2:1 vs bosutinib

-failure or intolerance to at least 2 TKIs

-Asciminib 40 mg bid 157 pts

-Bosutinib 500 mg bid 76 pts (bosutinib failures could cross over)



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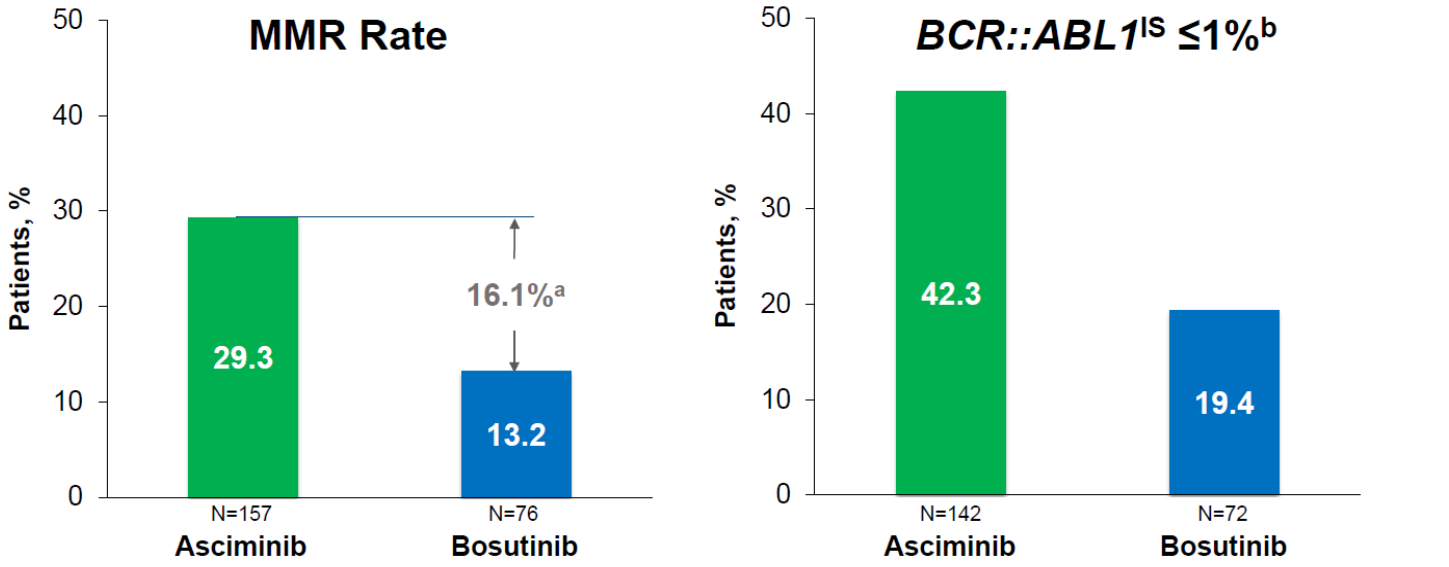
Response Rates at Week 48



- Response rates continued to be higher with asciminib than bosutinib with longer follow-up

[a] The treatment difference after adjusting for MCyR status at baseline was 16.1% (95% CI, 5.7%-26.6%).
[b] *BCR::ABL1*^{IS} ≤1% at week 48 was based on 142 of 157 patients (90.4%) receiving asciminib and 72 of 76 (94.7%) receiving bosutinib who did not have this level of response at baseline.

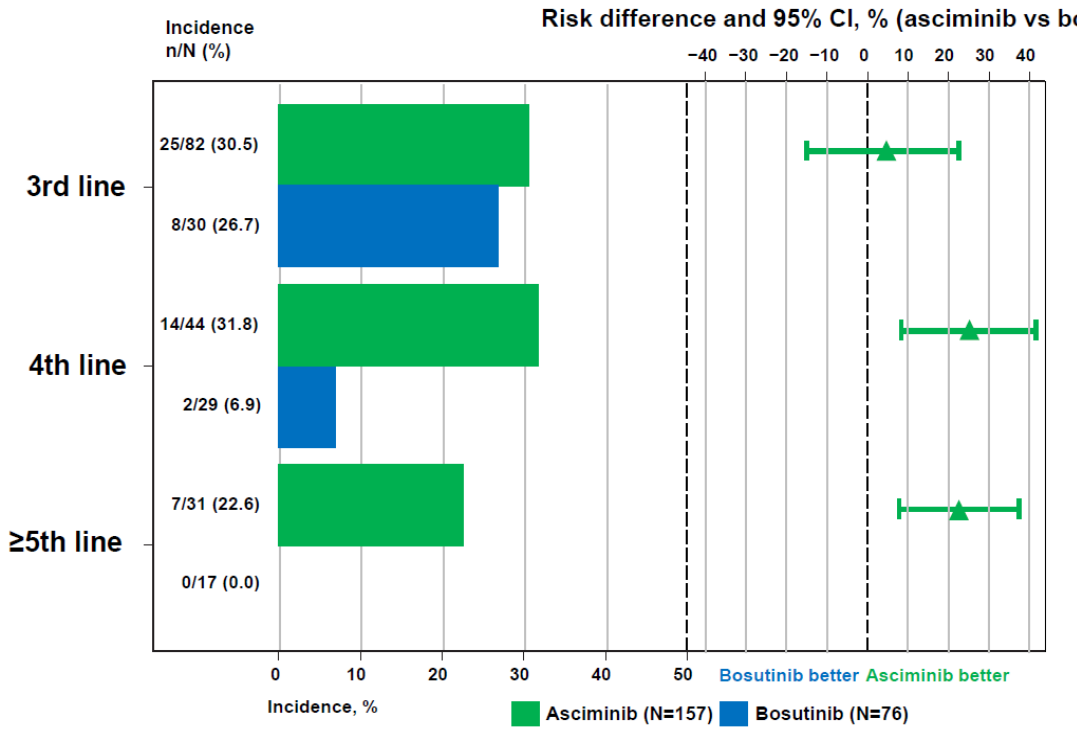
5

Oral presentation at: 63rd ASH Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA, and virtual.

New Treatments for Chronic Myeloid Leukemia

Efficacy and Safety Results from Ascembl, a Multicenter, Open-Label, Phase 3 Study of Asciminib, a First-in-Class STAMP Inhibitor, Vs Bosutinib in Patients with Chronic Myeloid Leukemia in Chronic Phase after ≥2 Prior Tyrosine Kinase Inhibitors: Update after 48 Weeks

MMR Rate at Week 48 by Line of Therapy



- A consistent treatment effect in favor of asciminib was seen across all lines of therapy

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Oral presentation at: 63rd ASH Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA, and virtual.

New Treatments for Chronic Myeloid Leukemia

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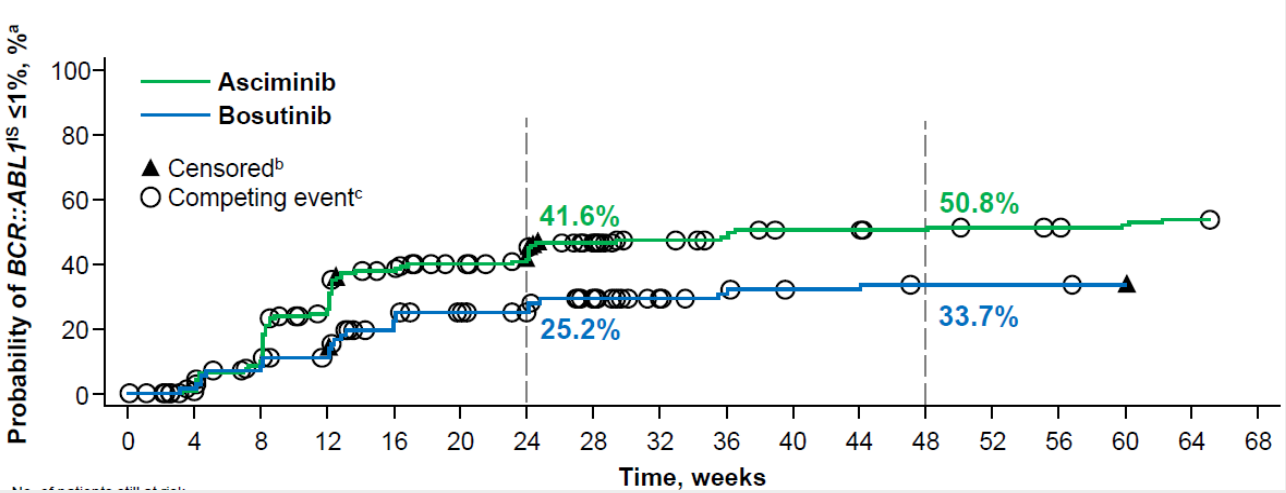

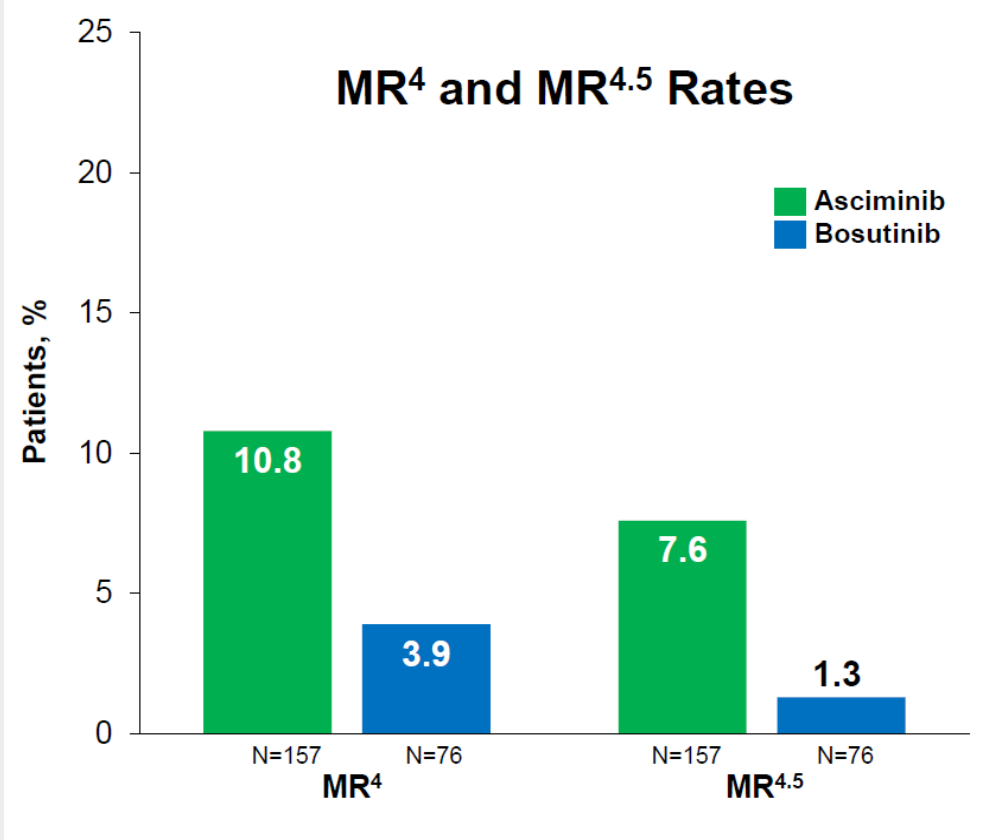

Cytogenetic responses seem to be cumulative over time and deep responses were seen more frequently with asciminib than bosutinib

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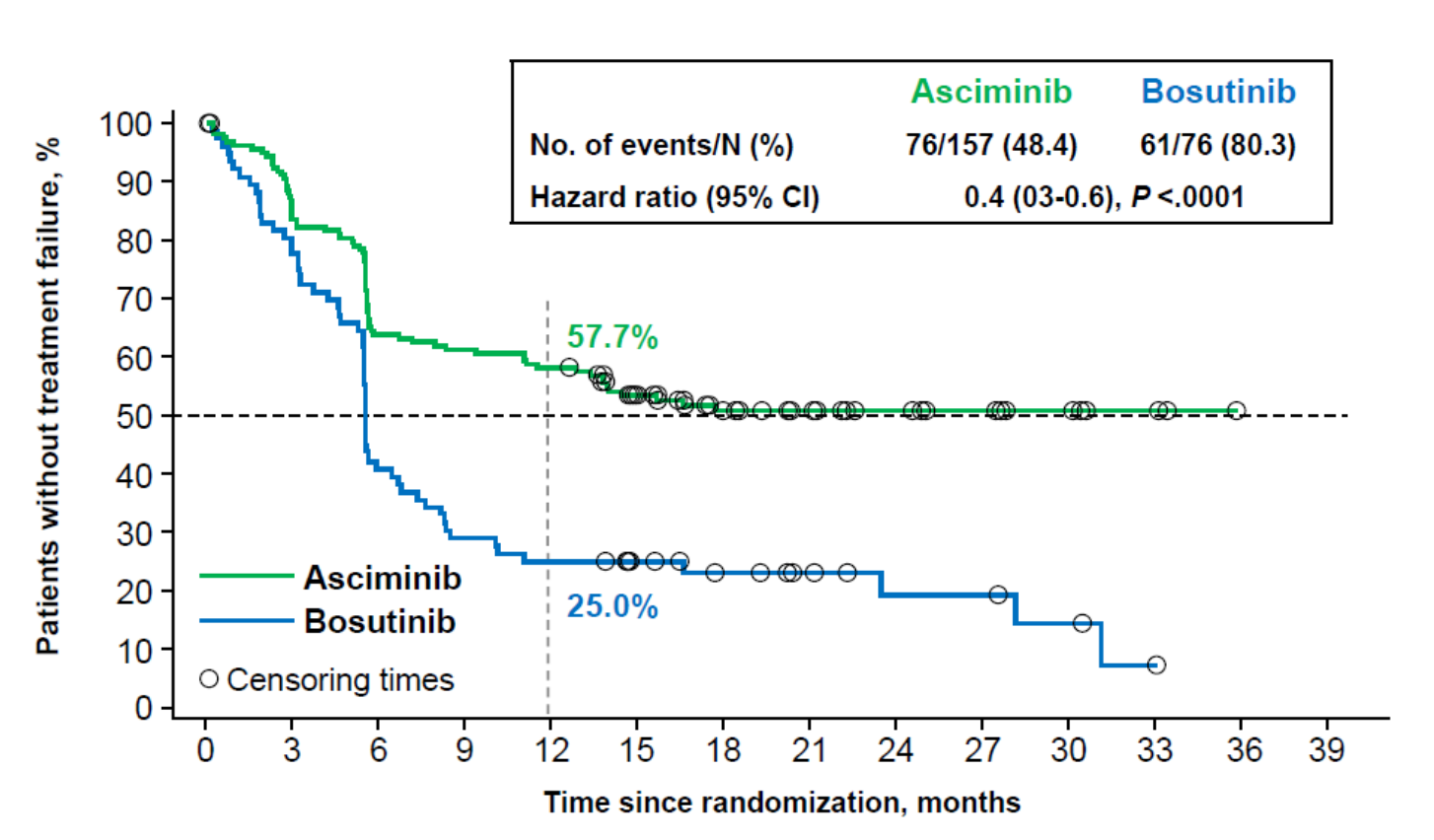

Fewer subjects had treatment failure with asciminib (48.4%) than bosutinib (80.3%)

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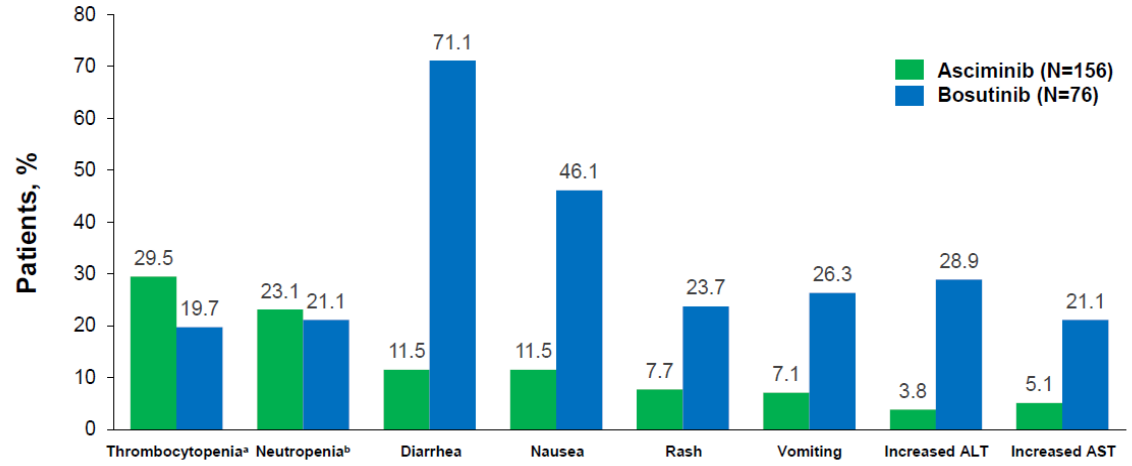
Most Frequent All-Grade AEs (in ≥20% of Patients in Any Arm)



- Despite the longer duration of exposure, the safety and tolerability profile of asciminib continued to be better than that of bosutinib after longer follow-up

[a] Includes thrombocytopenia and platelet count decreased.
[b] Includes neutropenia and neutrophil count decreased.

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Advanced Systemic Mastocytosis-Future Directions

Conclusions

- Midostaurin and avapritinib are FDA-approved TKIs active in advanced SM
- Avapritinib has activity in patients previously treated with midostaurin
  - Less GI toxicity
  - Potential for clearance of KIT D816V-mutated cells
- New highly selective agents are entering clinical trials
- TKIs may not address AHN disease component
  - Potential need for other treatment modalities:
    - Hypomethylating agents
    - ~~?~~Cladribine/interferon
    - AlloSCT