12th Joyce Niblack Memorial Conference on Myeloproliferative Neoplasms

"New Drugs for MPNs"

John Mascarenhas, MD
Associate Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, NY

Icahn School of Medicine at Mount Sinai

MPN-RC Myeloproliferative Neoplasms Research Consortium

Disclosures for John Mascarenhas, MD

In compliance with ACCME policy

- **Consultancy:** Celgene; Incyte; Roche; PharmaEssentia; Constellation, BMS, Geron

- **Research Funding:** CTI Biopharma; Incyte; Janssen; Merck; Novartis; Promedior; Roche; Merus; AROG; Kartos, PharmaEssentia, Forbius

Case Based Agenda

- Lessons learned in PV: great drugs need to be tolerable (or they are not great)
- Phlebotomy freedom in PV: targeting iron distribution is a novel way to control the hematocrit
- Enjoying the benefits of ruxolitinib in MF but still needing RBC transfusions –"the trifecta"
- Starting off on a better foot with ruxolitinib, why wait?
- Recapturing the glory days of JAKi therapy in MF- salvaging response
- Encouraging MPN stem cells die- assisted suicide with meds
- Spleen, symptoms and anemia are important in MF- but I want more life!

Case-1: PV

- 54M with JAK2V617F +, low risk, PV diagnosed 2 yeas ago and receiving therapeutic phlebotomy every 2 months to maintain HCT <45%
- ROS: aquagenic pruritus and progressive fatigue
- Spleen 2cm below LCM
- WBC 18K, hemoglobin 16g/dL, HCT 48%, PLT 622K, no leukoerythroblastosis
- “I chronically feel tired and am anxious about my disease process and potential for progression to MF”
- “Don’t even think about giving me ‘chemotherapy’!”

Safety and Efficacy of Idasanutlin in Patients With Hydroxyurea-Resistant/Intolerant Polycythemia Vera: Results of an International Phase II Study

John Mascarenhas,[1] Brian Higgins,[2] Doreen Anders,[3] Katie Burbury,[4] Tarec Christoffer El-Galaly,[3] Aaron Gerds,[5] Vikas Gupta,[6] Bruno Kovic,[7] Margherita Maffioli,[8] Ruben Mesa,[9] Jeanne Palmer,[10] Francesco Passamonti,[11] Alessandro Rambaldi,[12] David Ross,[13] Alessandro Vannucchi,[14] Abdulraheen Yacoub[15]

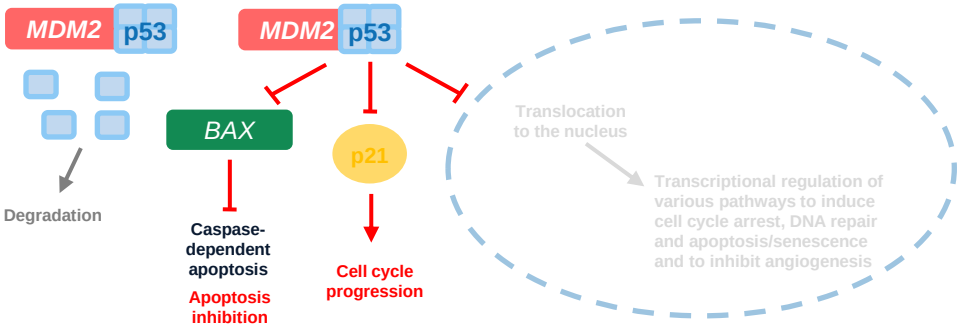
[1] Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2] Genentech, Inc., South San Francisco, CA, USA; [3] F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [4] Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [5] Cleveland Clinic Cancer Center, Cleveland, OH, USA; [6] Princess Margaret Hospital, Toronto, Ontario, Canada; [7] Hoffmann-La Roche Limited, Mississauga, ON, Canada; [8] ASST Sette Laghi, Ospedale di Circolo, Varese, Italy; [9] University of Texas Health Sciences Center in San Antonio, San Antonio, TX, USA; [10] Mayo Clinic, Phoenix, AZ, USA; [11] University of Insubria, Varese, Italy; [12] Department of Oncology and Hematology University of Milan and Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [13] Royal Adelaide Hospital, Adelaide, SA, Australia; [14] Az. Ospedaliero-Universitaria Careggi, Firenze, Italy; [15] University of Kansas Cancer Center, Fairway, KS, USA

Accepted as an Oral Presentation at the 62nd ASH Annual Meeting and Exposition

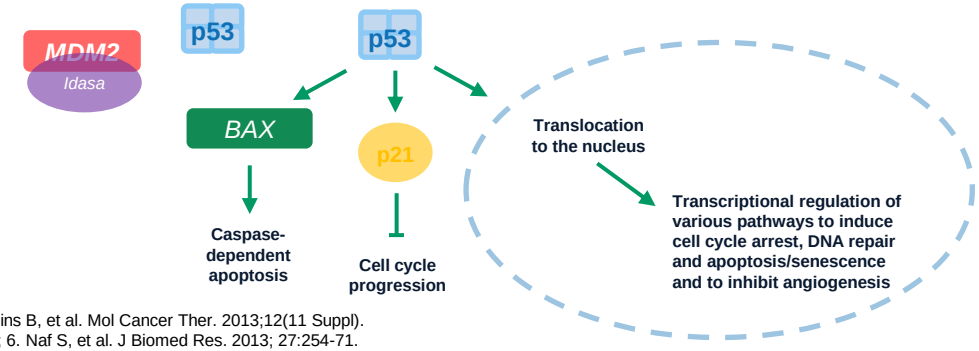
Inhibiting the MDM2-p53 Interaction

- Inhibiting the MDM2-p53 interaction is an appealing treatment strategy for p53 reactivation in cancers in which p53 is wild type or functional
  - E3 ligase MDM2 targets the tumor suppressor p53 for degradation by the proteasome[1]
  - Abnormal MDM2 upregulation due to gene amplification, increased transcription and enhanced translation has been observed in some human cancers,[2] resulting in amplified degradation of p53 and reduction in its activity[1]
- Idasanutlin is a small-molecule MDM2 antagonist that has shown activity in preclinical and clinical studies[3-5]

Overexpression of MDM2 impairs p53 function in cancers[6]



p53 activation via MDM2 inhibition with idasanutlin



Idasa, idasanutlin.

1. Konopleva M, et al. Leukemia. 2020;34:2858-74; 2. Momand J, et al. Nucleic Acids Res. 1998;26:3453–9; 3. Higgins B, et al. Mol Cancer Ther. 2013;12(11 Suppl). [abstract B55]; 4. Yee K, et al. Blood. 2014;124(121). [abstract 116]; 5. Martinelli G, et al. EHA 2016 [abstract S504]; 6. Naf S, et al. J Biomed Res. 2013; 27:254-71.

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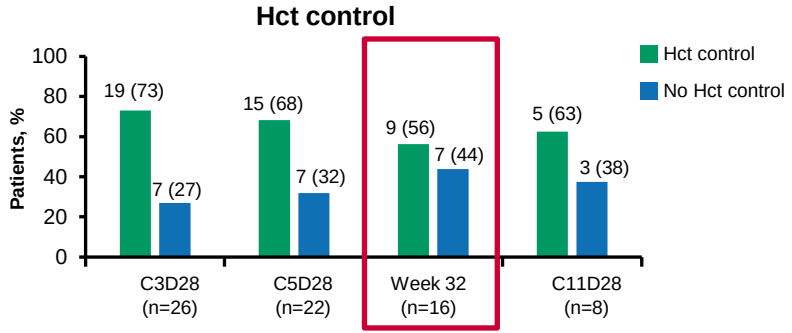
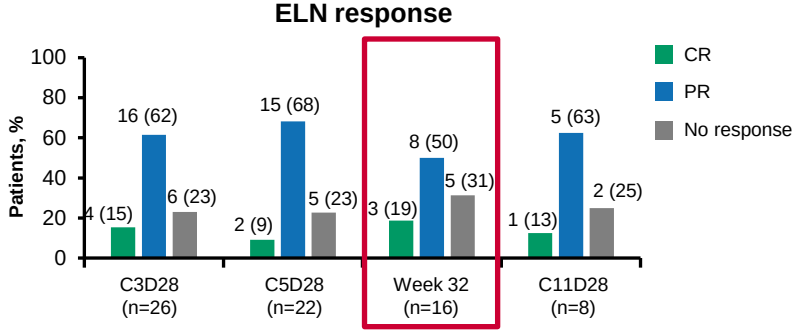
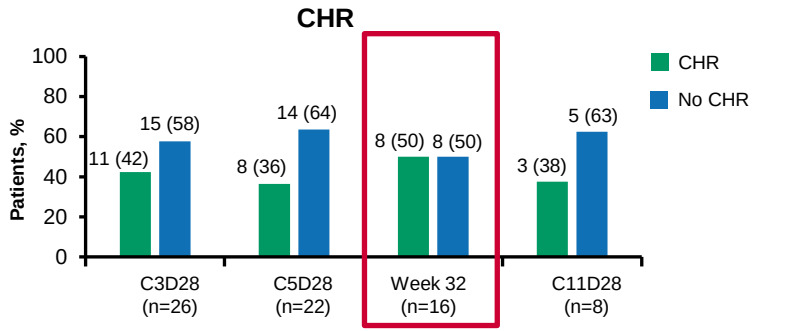
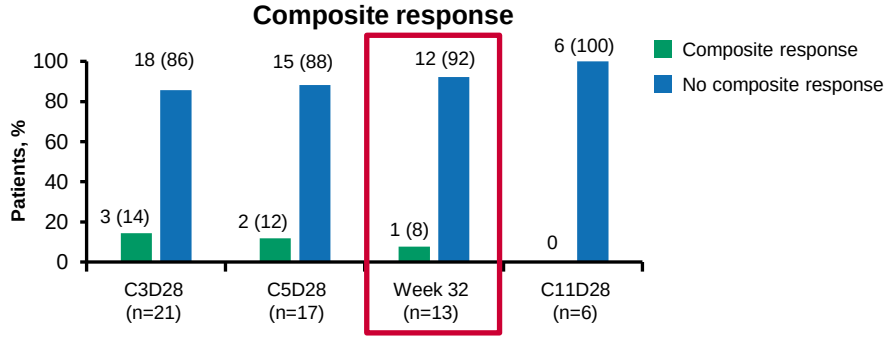
Idasanutlin Showed Clinical Activity in Patients With PV









- 8 of 13 (62%) evaluable patients beyond week 32 had an Hct control duration ≥12 weeks beyond week 32
- 9 of 15 (60%) evaluable patients beyond week 32 had an ELN ORR duration ≥12 weeks beyond week 32
- 6 of 13 (46%) evaluable patients beyond week 32 had a CHR duration ≥12 weeks beyond week 32

WBC, white blood cell. CHR = Hct control, WBC count ≤10 × 10^9/L and platelet count ≤400 × 10^9/L; composite response = Hct control and ≥35% reduction in spleen volume; ELN response = complete or partial response per modified ELN criteria; Hct control = protocol-specified ineligibility for phlebotomy between week 8 and 32 and ≤1 instance of phlebotomy eligibility (Hct of ≥45% that was ≥3% higher than baseline level or an Hct of >48%) between first dose and week 8. Data cutoff: June 3, 2020.

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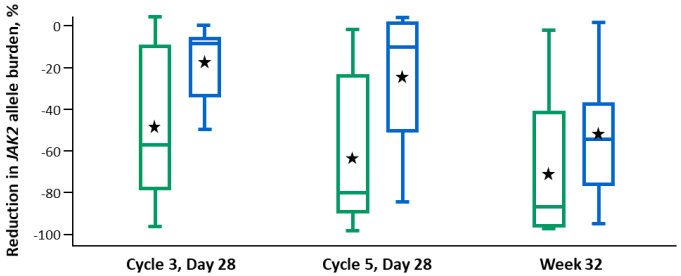
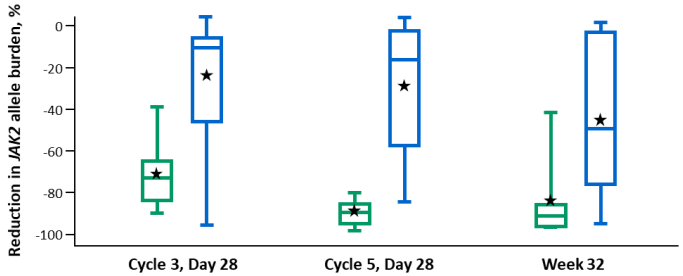
JAK2 Allele Burden in Responders vs Nonresponders

Reduction in *JAK2* allele burden in responders (HTC) vs nonresponders



Responders (HTC)			
n	13	11	7
Median (IQR) change from baseline in *JAK2* allele burden, %	−57.0 (−78.4 to −10.3)	−79.2 (−89.4 to −23.4)	−86.5 (−95.8 to −41.5)
Nonresponders			
n	6	6	6
Median (IQR) change from baseline in *JAK2* allele burden, %	−8.8 (−34.0 to −6.1)	−10.3 (−50.7 to 0.78)	−54.0 (−75.9 to −36.9)
P value	0.04	0.03	0.19

Reduction in *JAK2* allele burden in responders (CHR) vs nonresponders



Responders (CHR)			
n	6	6	6
Median (IQR) change from baseline in *JAK2* allele burden, %	−72.4 (−83.8 to −64.8)	−88.9 (−95.0 to −84.8)	−90.9 (−95.8 to −84.8)
Nonresponders			
n	13	11	7
Median (IQR) change from baseline in *JAK2* allele burden, %	−10.3 (−45.0 to −5.6)	−15.9 (−57.8 to −2.0)	−49.0 (−75.9 to −2.7)
P value	0.006	0.005	0.06

CHR, complete hematologic response; HCT, Hct control; IQR, interquartile range.
Black star represents mean. Data cutoff: June 3, 2020.

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American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

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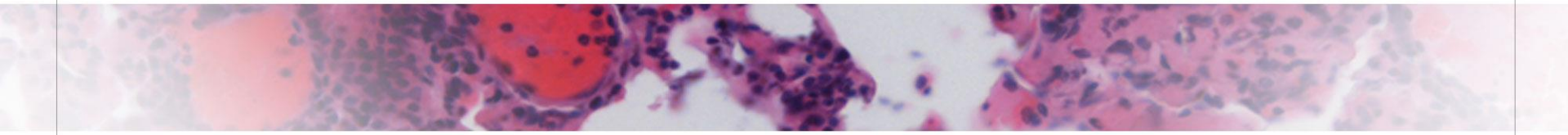

PTG-300 Eliminates the Need for Therapeutic Phlebotomy in Both Low and High-risk Polycythemia Vera Patients

Marina Kremyanskaya[1], Yelena Ginzburg[1], Andrew Kuykendall[2], Abdulraheem Yacoub[3], Jay Yang[4], Suneel Gupta[5], Frank Valone[5], Sarita Khanna[5], Srdan Verstovsek[6], Ronald Hoffman[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, [2]Moffitt Cancer Center, Tampa, FL, [3]Univ of Kansas Health System, Westwood, Kansas, [4]Karmanos Cancer Institute, Detroit, Michigan, [5]Protagonist Therapeutics, Newark, CA, [6]MD Anderson Cancer Center, Houston TX

Potential Mechanism of Action of Hepcidin Mimetic PTG 300 in PV

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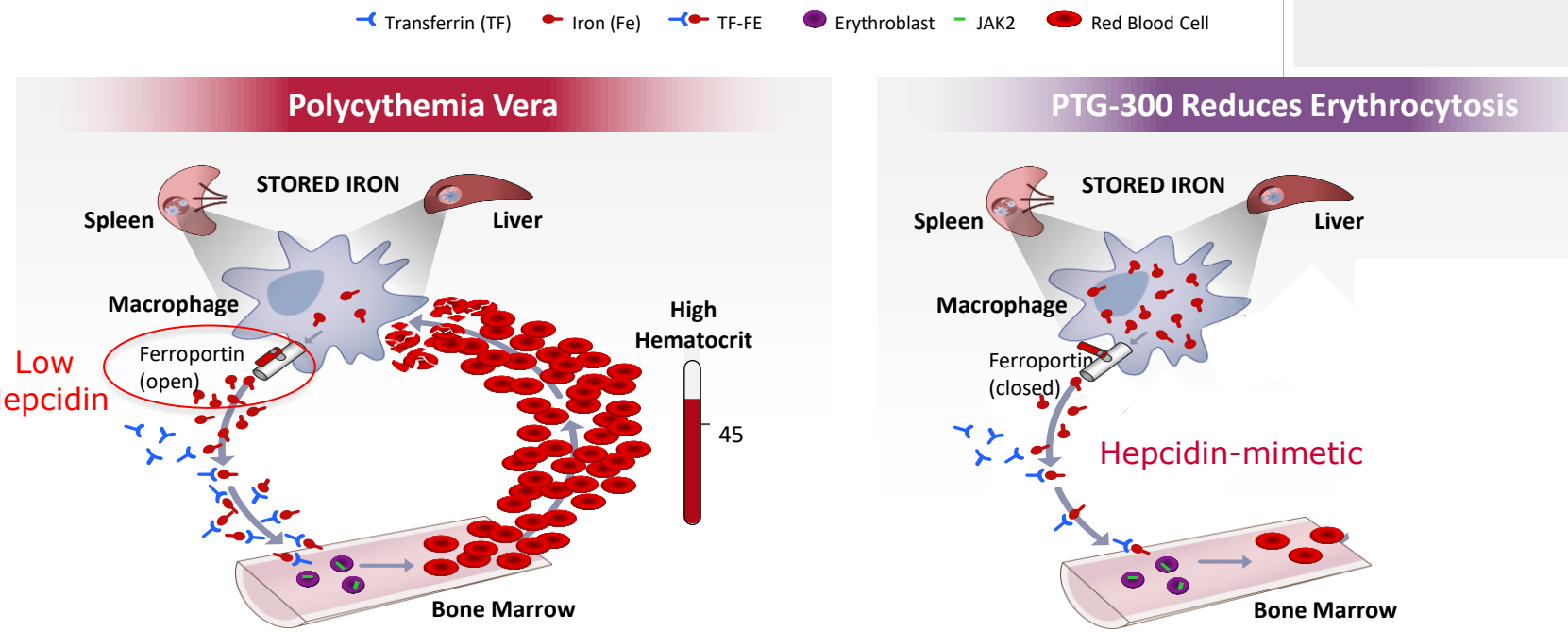

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PTG-300 Results in Decreased HCT and RBC Count in PV patients

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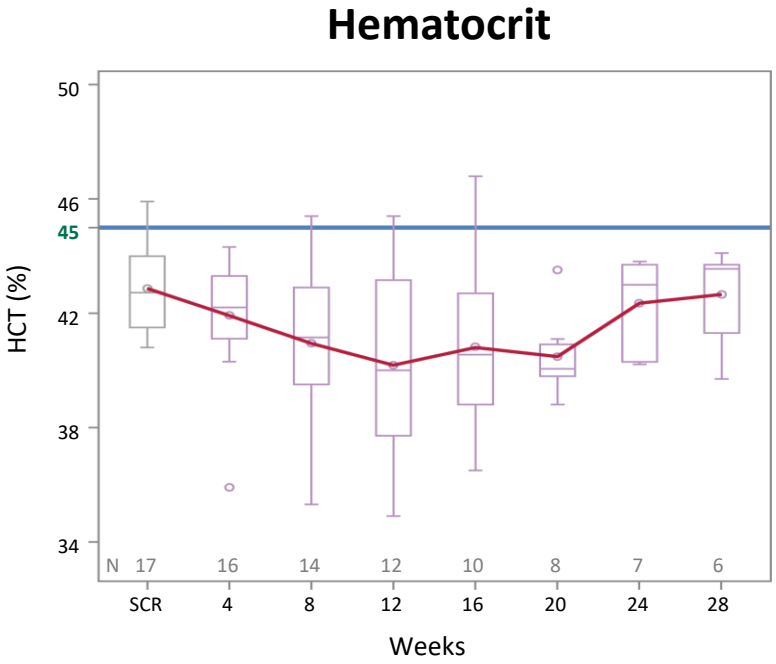

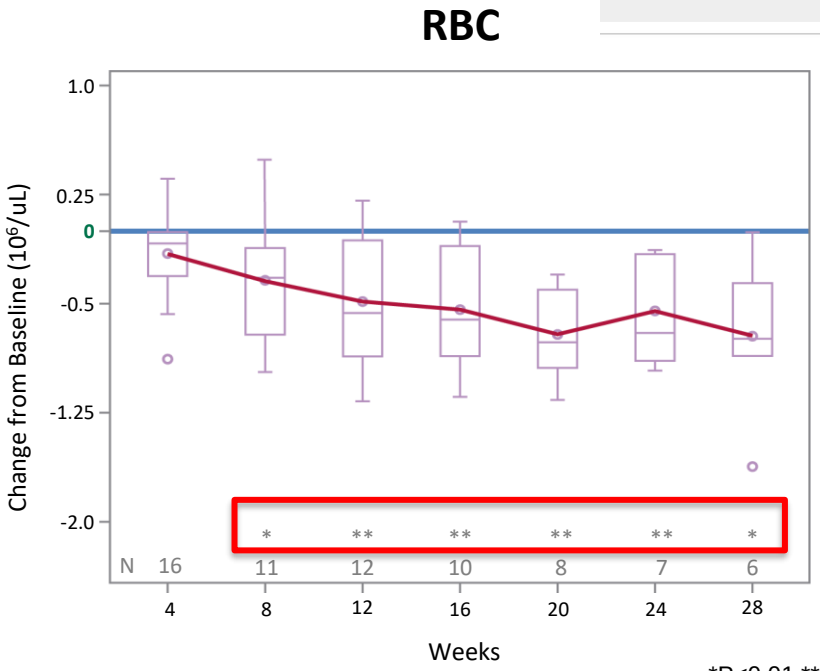

*P<0.01 **P<0.001

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Increase in Ferritin Following PTG-300

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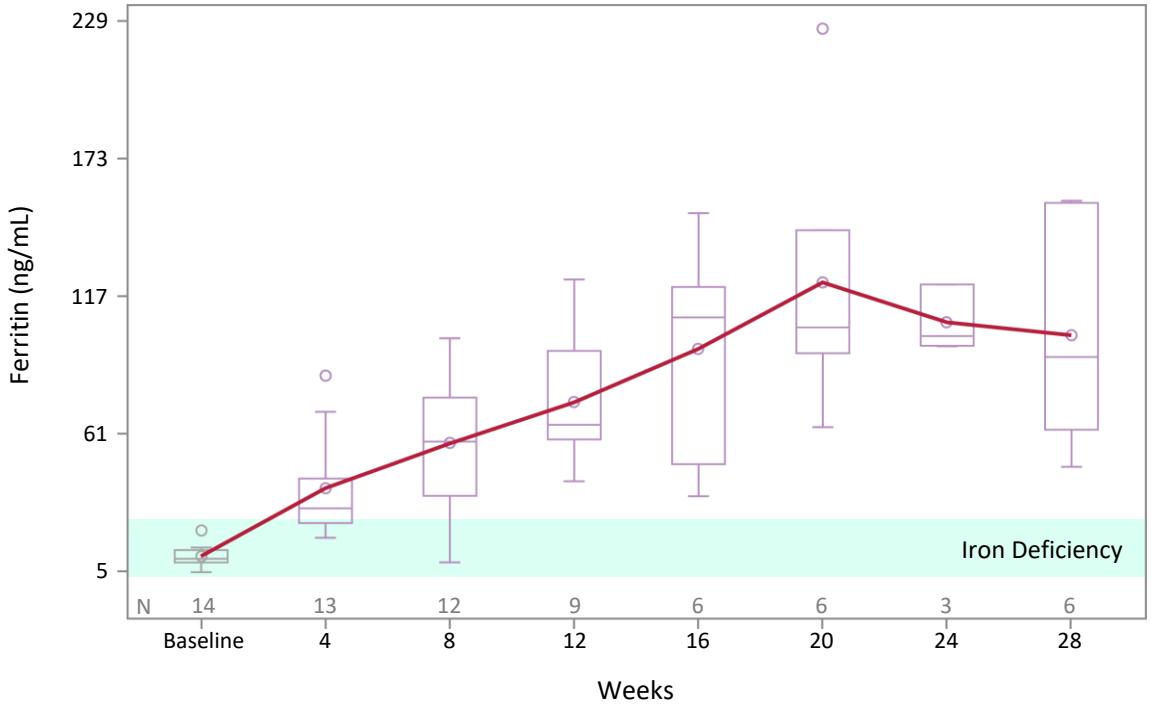

PTG-300 normalizes iron stores as soon as 4 weeks of treatment

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No Significant Change Observed in WBC and Platelets on PTG-300

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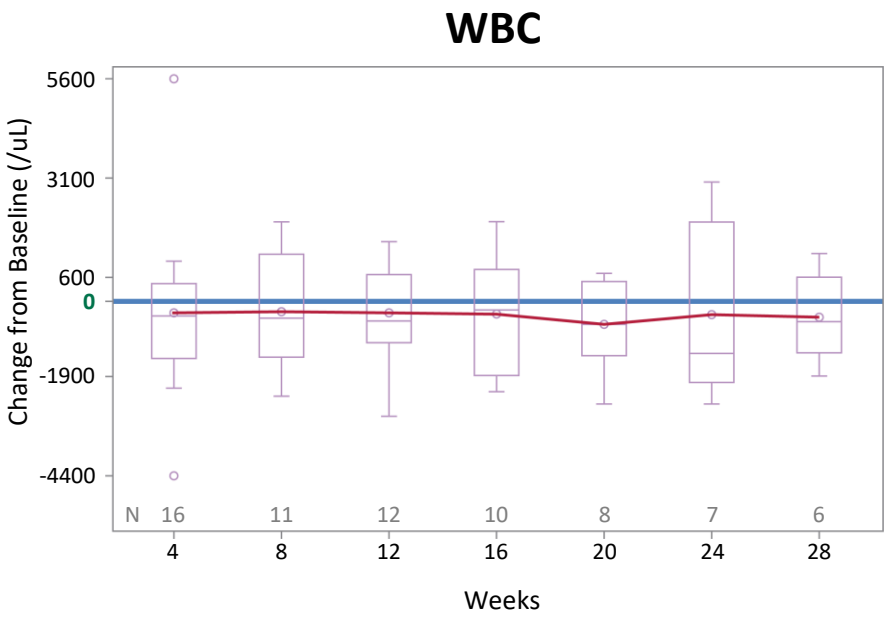

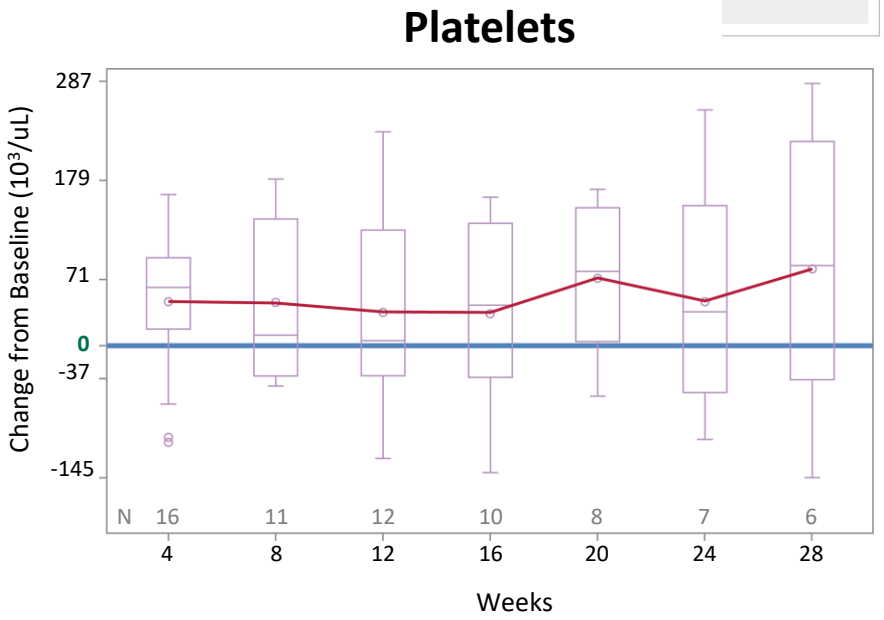

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Case-2: MF

- 73F with CALR+ DIPSS INT-2 PMF for 7 years and taking ruxolitinib 10mg PO BID and needs RBC transfusions every month
- Minimal systemic symptoms, palpable spleen 2cm BLCM
- WBC 4K, hemoglobin 6.1g/dL, PLT 122K, 1% blasts and many nRBC
- “I hate spending the entire day each month in the infusion center getting transfused”

Duration of response to luspatercept in patients requiring red blood cell transfusions with myelofibrosis – updated data from the phase 2 ACE-536-MF-001 study

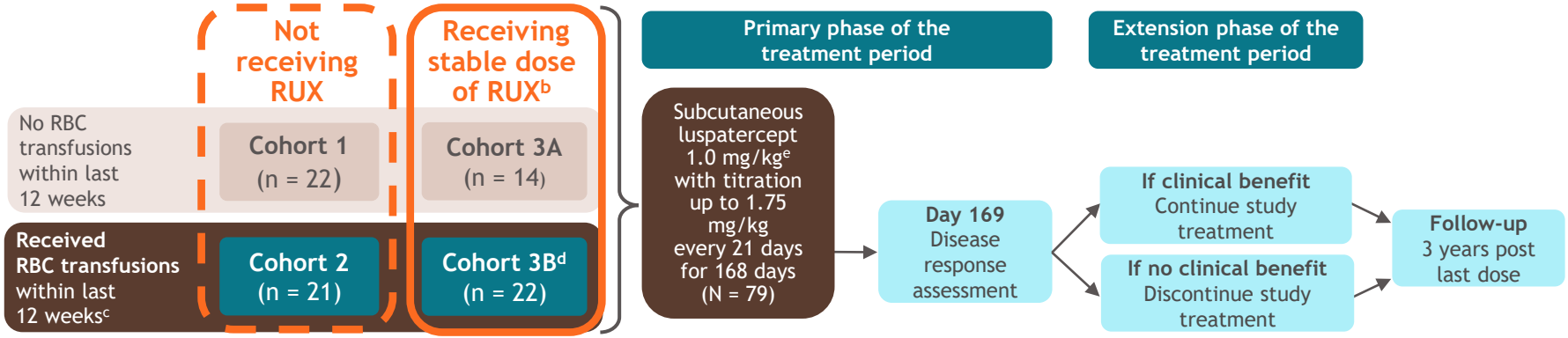
Aaron T. Gerds,[1] Alessandro M. Vannucchi,[2] Francesco Passamonti,[3] Marina Kremyanskaya,[4] Jason Gotlib,[5] Jeanne M. Palmer,[6] Kelly McCaul,[7] Vincent Ribrag,[8] Adam J. Mead,[9] Claire Harrison,[10] Ruben Mesa,[11] Jean-Jacques Kiladjian,[12] Giovanni Barosi,[13] Torsten G. Gerike,[14] Jeevan Shetty,[15] Joseph Pariseau,[14] Gabriel Miranda,[14] Martin Schwickart,[14] Ana Carolina Giuseppi,[14] Jennie Zhang,[14] Jay T. Backstrom,[16] Srdan Verstovsek[17]

[1]Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH; [2]Center for Research and Innovation of Myeloproliferative Neoplasms, AOU Careggi, Florence, Italy; [3]Department of Medicine and Surgery, University of Insubria, Varese, Italy; [4]Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai Hospital, New York, NY; [5]Stanford Cancer Institute, Stanford, CA; [6]Division of Hematology/Oncology, Mayo Clinic, Phoenix, AZ; [7]Avera Cancer Institute, Sioux Falls, SD; [8]Institut Gustave Roussy, Villejuif, France; [9]Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [10]Guy's and St Thomas' NHS Foundation Trust, London, UK; [11]Mays Cancer Center, UT Health San Antonio Cancer Center, San Antonio, TX; [12]Hôpital Saint-Louis et Université Paris Diderot, Paris, France; [13]IRCCS Policlinico San Matteo Foundation, Pavia, Italy; [14]Bristol Myers Squibb, Princeton, NJ; [15]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland; [16]Acceleron Pharma, Cambridge, MA; [17]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

ACE-536-MF-001 study design

- This study reports the results of the ongoing open-label, phase 2 ACE-536-MF-001 trial evaluating luspatercept in subjects with MF and anemia, focusing on response in subjects requiring RBC transfusions (NCT03194542)

Figure 1. ACE-536-MF-001 study design[a]



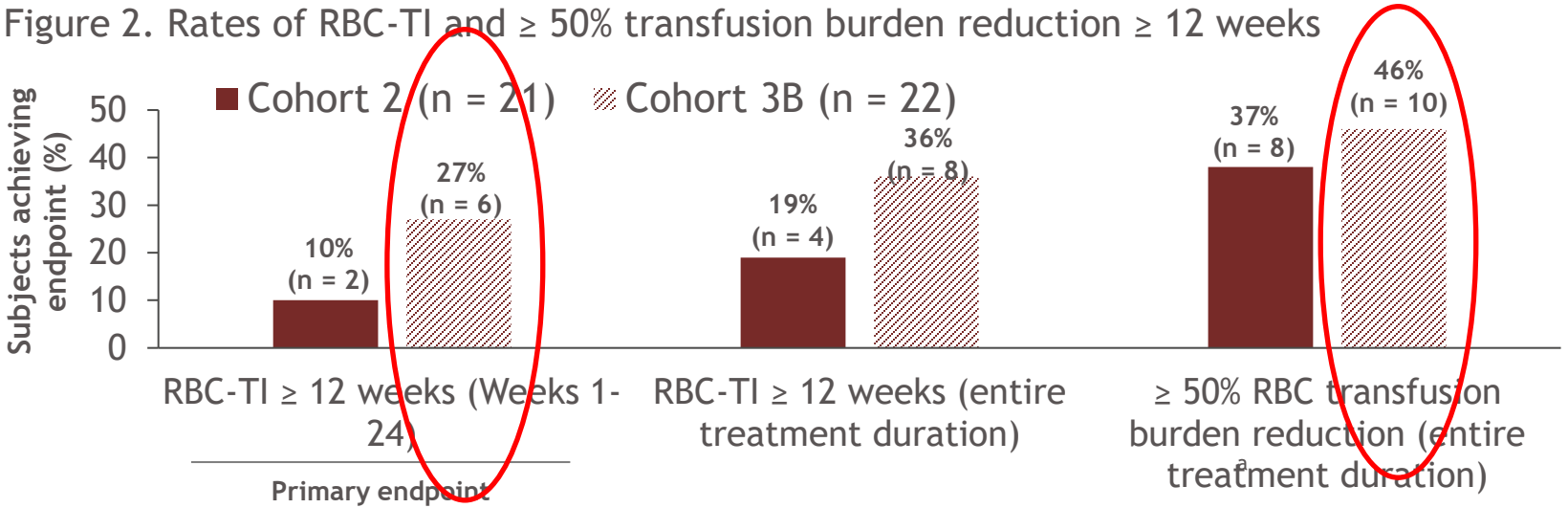
- 79 subjects with MF and anemia had been enrolled by the data cutoff and were included in this updated analysis (March 29, 2020)
- The analyses presented here focus on response in subjects requiring RBC transfusions (Cohorts 2 and 3B); safety is reported for all 79 subjects on study

As of March 29, 2020, 16 (20%) subjects remain on treatment. [a]Enrolled subjects had primary or post-essential thrombocythemia/post-polycythemia vera myelofibrosis; [b]A stable daily dose of RUX for at least 16 weeks at enrollment; for the 3 subjects enrolled in the expansion cohort in Cohort 3B, subjects were receiving a stable RUX dose for 40 weeks; [c]6-12 RBC units/84 days prior to treatment; or 4-12 units/84 days for the 3 subjects enrolled in the expansion cohort in Cohort 3B; [d]Including 3 subjects enrolled in the expansion cohort; [e]The starting dose was 1.33 mg/kg in the expansion cohort subjects. MF, myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.

Gerds et al ASH 2020

Achievement of RBC-TI ≥ 12 weeks, ≥ 50% transfusion burden reduction, and multiple response episodes

Figure 2. Rates of RBC-TI and ≥ 50% transfusion burden reduction ≥ 12 weeks



Achievement of multiple episodes of response

- Of the RBC-TI ≥ 12-week responders in both Cohorts 2 and 3B, 25% experienced 2 separate episodes of RBC-TI ≥ 12 weeks
- Of the subjects who achieved ≥ 50% reduction in RBC transfusion burden over any 12 weeks, 3 subjects in Cohort 2 (38%) and 2 subjects in Cohort 3B (20%) experienced 2 separate ≥ 12-week response episodes
  - 1 subject (13%) in Cohort 2 experienced 3 separate episodes of RBC-TI ≥ 12 weeks

[a]Defined as RBC transfusion burden reduction by ≥ 50% and by ≥ 4 RBC U for ≥ 12 weeks.

Case-3: MF

- 70F with CALR+ DIPSS INT-2 PMF for diagnosed 3 months ago with progressive fatigue, nights sweats, bone pains, spleen related complaints and treatment naïve
- ECOG 1, palpable spleen 7cm BLCM and tender
- WBC 9K, hemoglobin 9.1g/dL, PLT 172K, 1% blasts and early myeloid cells
- CALR, TET2, ASXl-1, normal karyotype
- “I realize I need treatment and appreciate the benefits and limitations of a JAK inhibitor, can more be done?”

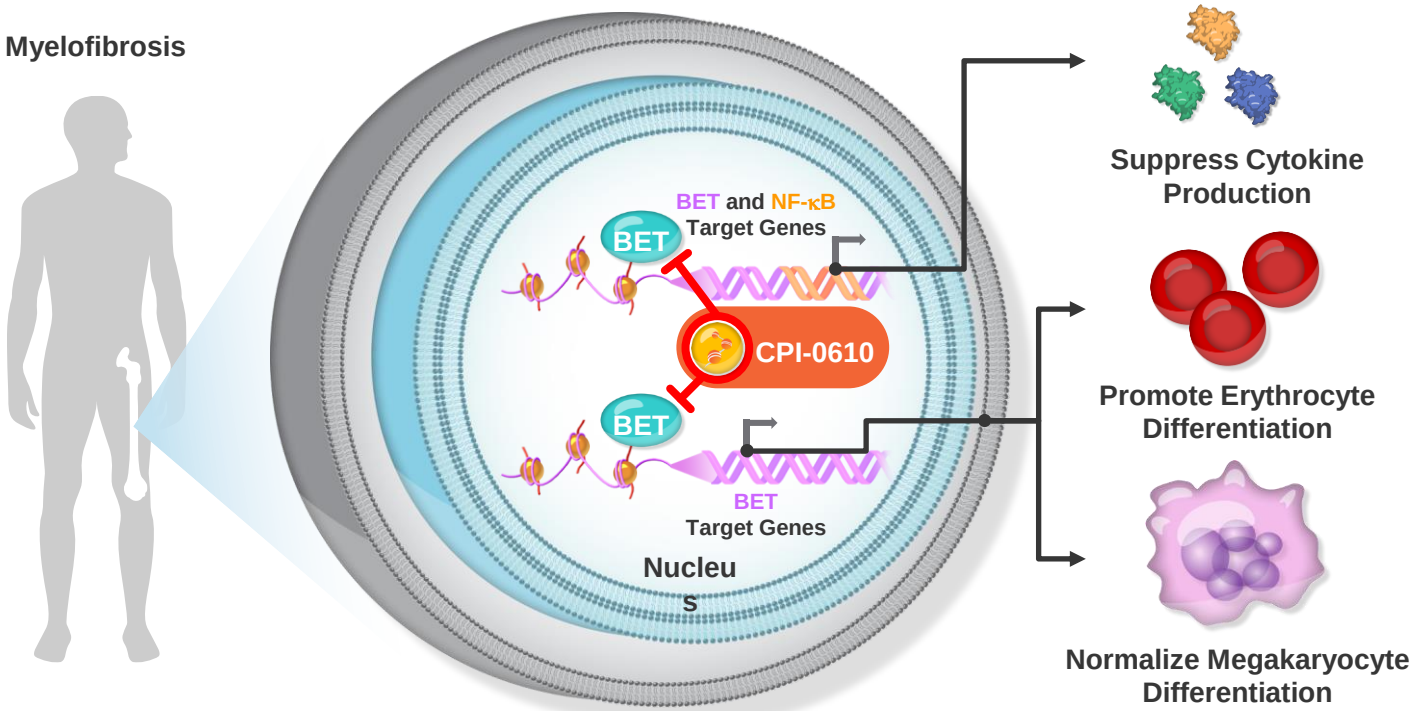
CPI-0610, a Bromodomain and Extraterminal Domain Protein (BET) Inhibitor, in Combination with ruxolitinib, in JAK-Inhibitor-Naïve Myelofibrosis Patients: Update of MANIFEST Phase 2 Study

John Mascarenhas[1], Claire Harrison[2], Andrea Patriarca[3], Timothy Devos[4], Francesca Palandri[5], Raajit K. Rampal[6], Adam J. Mead[7], Marina Kremyanskaya[1], Tim C.P Somervaille[8], Marielle Wondergem[9], Ronald Hoffman[1], Katarina Luptakova[10], Jing Wang[10], Jessica Christo[10], Jennifer A Mertz[10], Gözde Colak[10], James Shao[10], Suresh Bobba[10], Patrick Trojer[10], Adrian Senderowicz[10], Srdan Verstovsek[11], Vikas Gupta[12]

[1]Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; [2]Guys and St Thomas' NHS Foundation Trust, London, United Kingdom; [3]Azienda Ospedaliero Universitaria Maggiore della Carità di Novara SCDU Ematologia, Novara, Italy; [4]University Hospitals Leuven and Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium; [5]Institute of Hematology "L. and A. Seràgnoli", S. Orsola-Malpighi Bologna University Hospital, Bologna, Italy; [6]Memorial Sloan Kettering Cancer Center, New York, NY; [7]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [8]The Christie Hospital, Cancer Research UK Manchester Institute, Manchester, United Kingdom; [9]Academisch Ziekenhuis Vrije Universiteit, Amsterdam, Netherlands; [10]Constellation Pharmaceuticals, Cambridge, MA; [11]The University of Texas, MD Anderson Cancer Center, Houston, TX; [12]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Abstract # 55

CPI-0610 Mechanism of Action in Myelofibrosis



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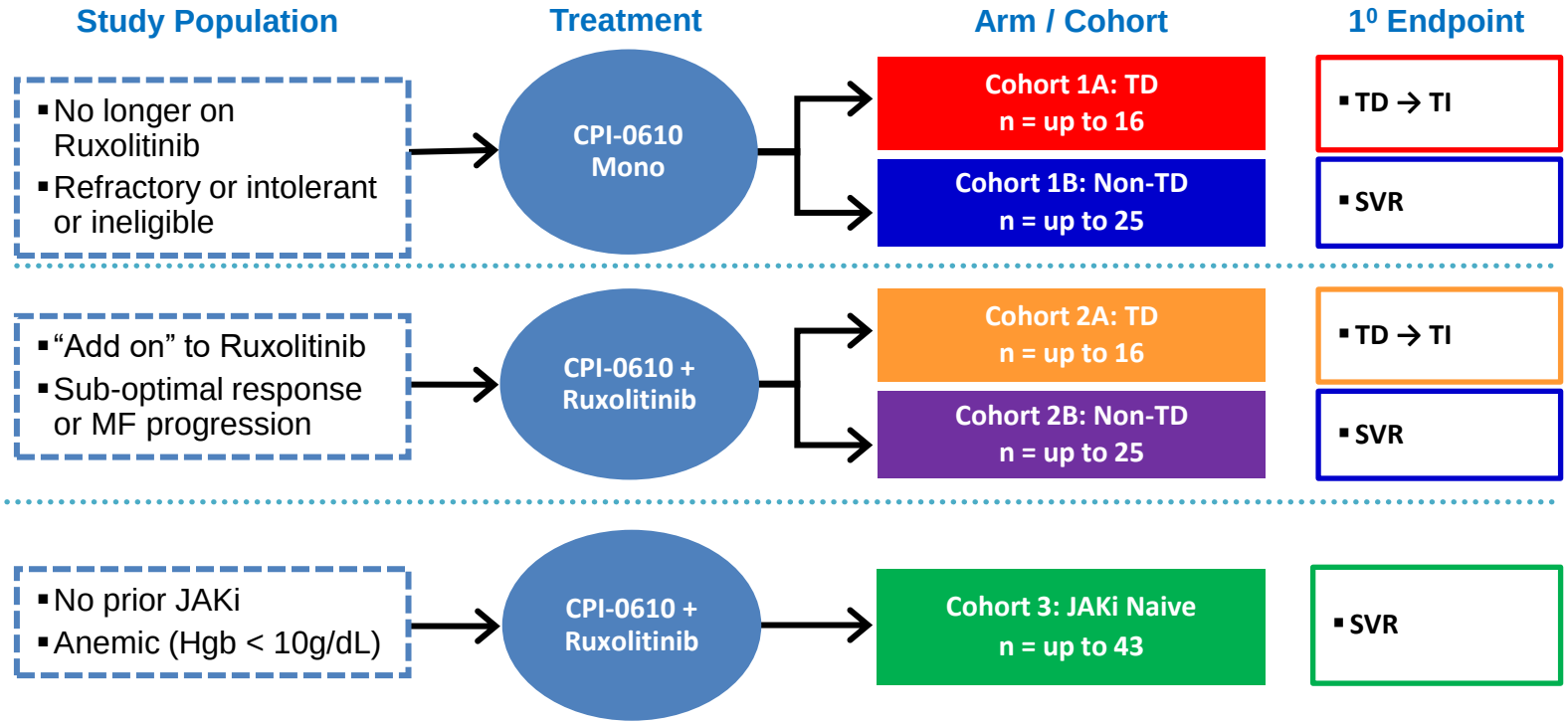
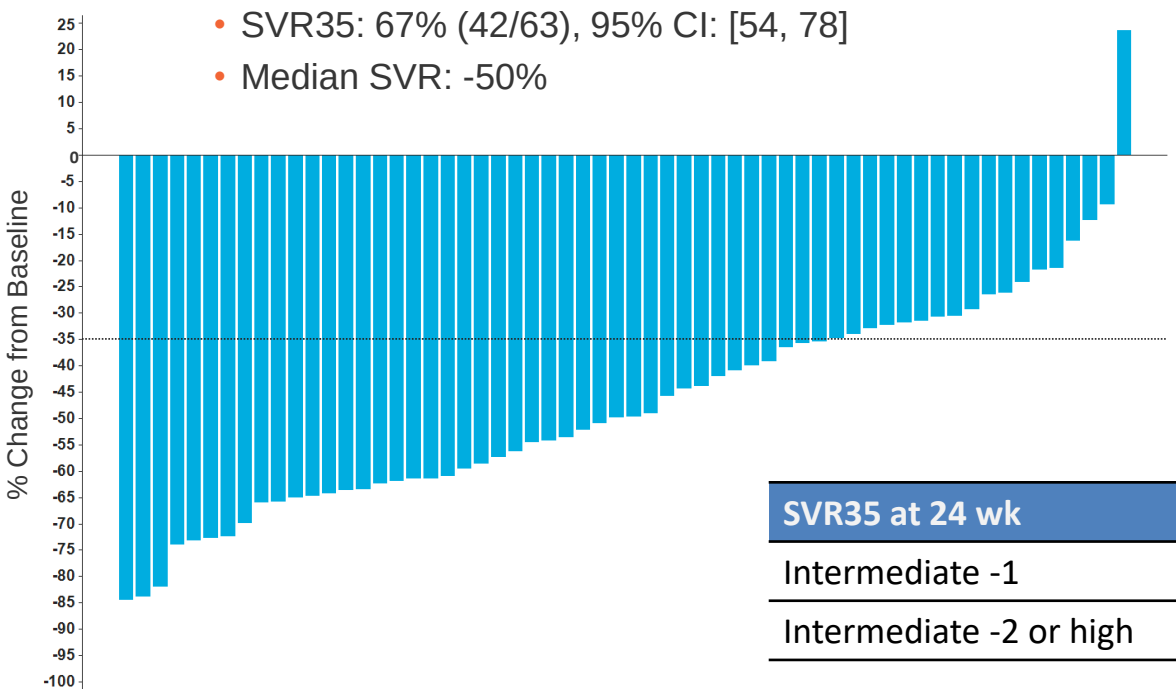
More information in Abstract # 3079

MANIFEST Study Design Overview



- TD = Transfusion Dependent; TI = Transfusion Independent; SVR = Spleen Volume Response
- The starting dose of CPI-0610 is 125 mg, given PO, once daily for 2 weeks on / 1 week off in a 21-day dosing cycle
- Additional endpoints include to evaluate changes in patient reported outcomes (PROs), i.e. total symptom score (TSS) per MFSAF v4 and PGIC; in response categories per the revised 2013 IWG-MRT response criteria; anemia response; and in bone marrow morphology

SVR35 response at week 24



SVR35 at 24 wk	DIPSS	IPSS
Intermediate -1	72 % (13/18)	73% (8/11)
Intermediate -2 or high	64% (29/45)	66% (33/50)

SVR: Spleen volume reduction; SVR35: ≥35% reduction in spleen volume from baseline

DIPSS: Dynamic international prognostic scoring system; IPSS: International prognostic scoring system

Patients are evaluable for SVR35 at wk 24 if they have had wk 24 spleen volume assessment by the data cutoff date or discontinued prior to wk 24 due to any reason. Spleen volume assessments are per local radiologist read.

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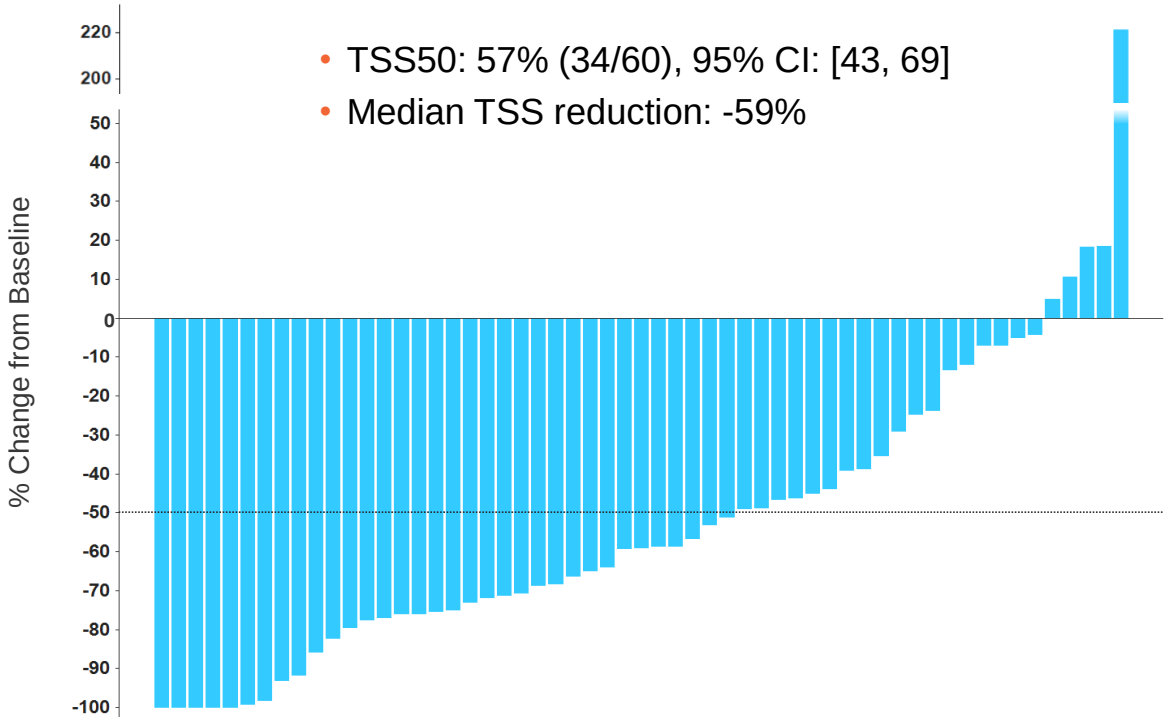
TSS50 response at week 24



TSS: Total Symptom Score; TSS50: ≥50% reduction in total symptom score from baseline

Patients are evaluable for TSS50 at wk 24 if they have had wk 24 TSS assessment by the data cutoff date or discontinued prior to wk 24 due to any reason.

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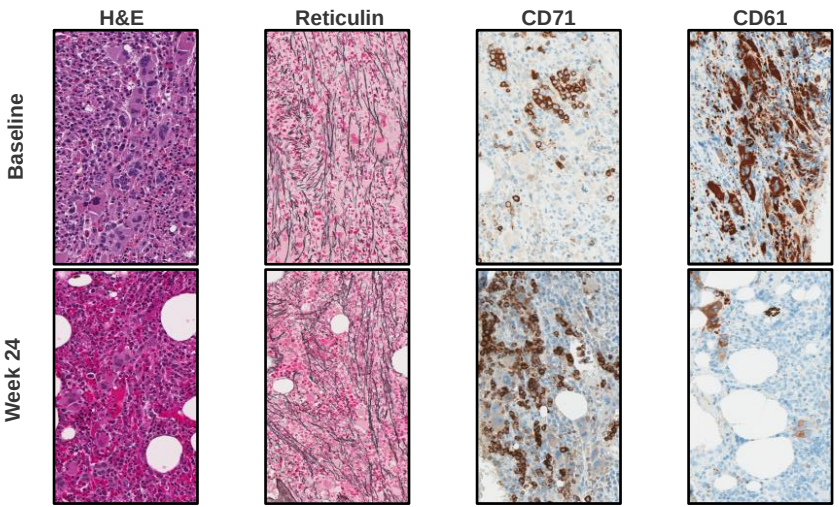
Bone marrow fibrosis grade improvement

- 33% (16/48) of patients had at least one grade improvement in bone marrow fibrosis
- 88% (14/16) of improvements occurred within 6 months of treatment
- 2 patients had worsening in bone marrow fibrosis
- Improvements in erythroid differentiation and normalization of megakaryocyte histotopography observed (Abstract # 3079)

Representative Example of Bone Marrow Biopsy at Baseline and After 24 Wks



Assessments of bone marrow grade or reticulin grade per local pathology read.
H&E: hematoxylin and eosin.

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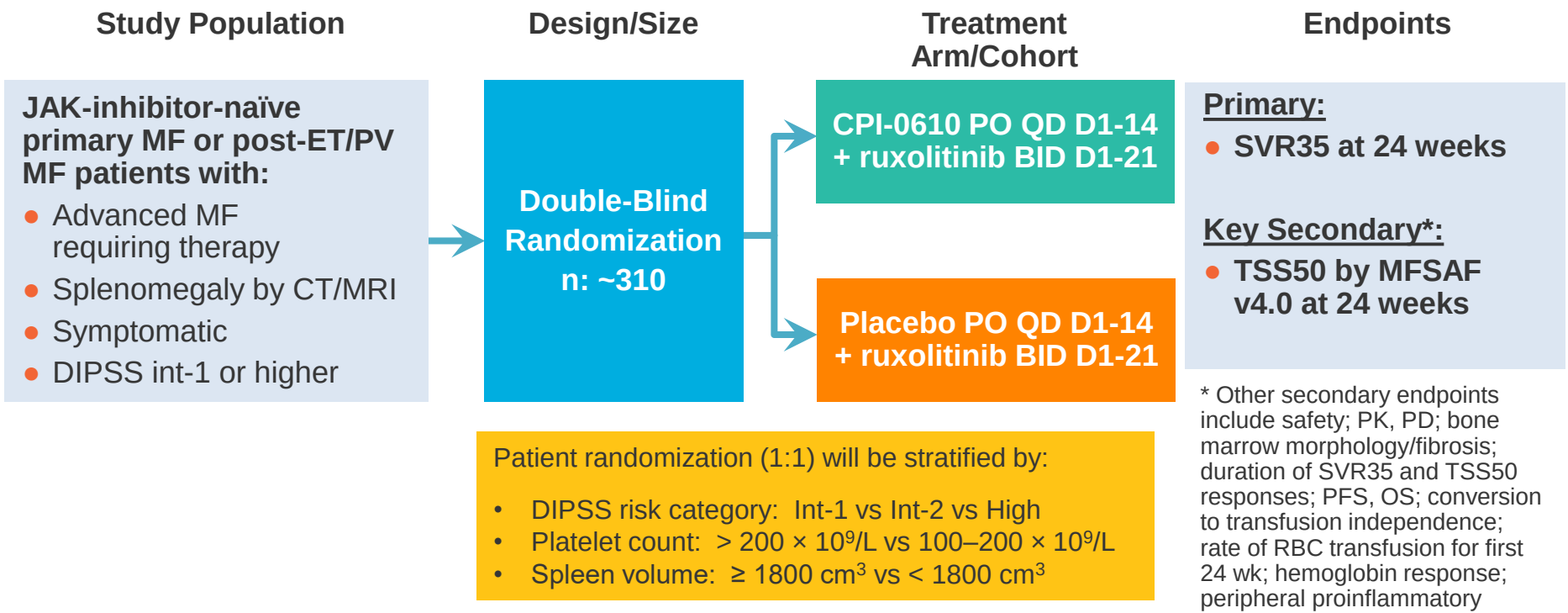
MANIFEST-2 Phase 3 study (Abstract # 3085)



* Other secondary endpoints include safety; PK, PD; bone marrow morphology/fibrosis; duration of SVR35 and TSS50 responses; PFS, OS; conversion to transfusion independence; rate of RBC transfusion for first 24 wk; hemoglobin response; peripheral proinflammatory cytokines

Case-4: MF

- 70F with CALR+ DIPSS INT-2 PMF for diagnosed 3 years ago and initial excellent response ruxolitinib, now with palpable spleen and night sweats, RBC transfusions 1u/4 weeks
- ECOG 1, palpable spleen 10cm
- WBC 4K, hemoglobin 8.1g/dL, PLT 125K, 1% blasts and early myeloid cells
- BM BX confirms PMF and 3% blasts by IHC, MF=3
- “I am no longer feeling well and can not accomplish a normal day of activities and will not accept transplant option”

The Addition of Navitoclax to Ruxolitinib Demonstrates Efficacy Within Different High-Risk Populations in Patients with Relapsed/Refractory Myelofibrosis

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Naveen Pemmaraju, MD[1], Jacqueline S. Garcia, MD[2], Jalaja Potluri, MD[3], Leanne Holes, MBA[3], Jason Harb, PhD[3], Paul Jung, PhD[3], Jessica E. Hutti, PhD[3], Josef T. Prchal, MD[4], Srdan Verstovsek, PhD[1], and Claire Harrison, MD[5]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]AbbVie Inc., North Chicago, IL, USA; [4]University of Utah and Huntsman Cancer Institute, Salt Lake City, UT, USA; [5]Guy's and St Thomas' NHS Foundation Trust, London, UK

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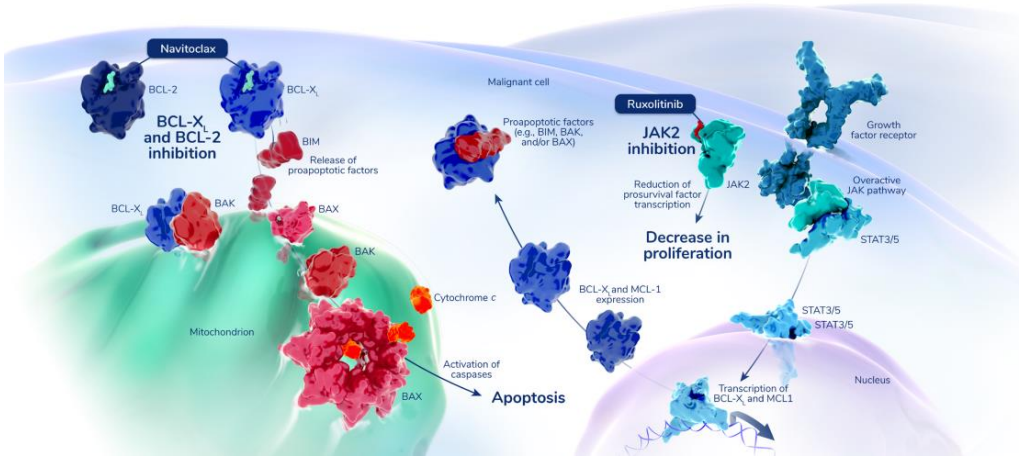
Rationale for Navitoclax for Myelofibrosis

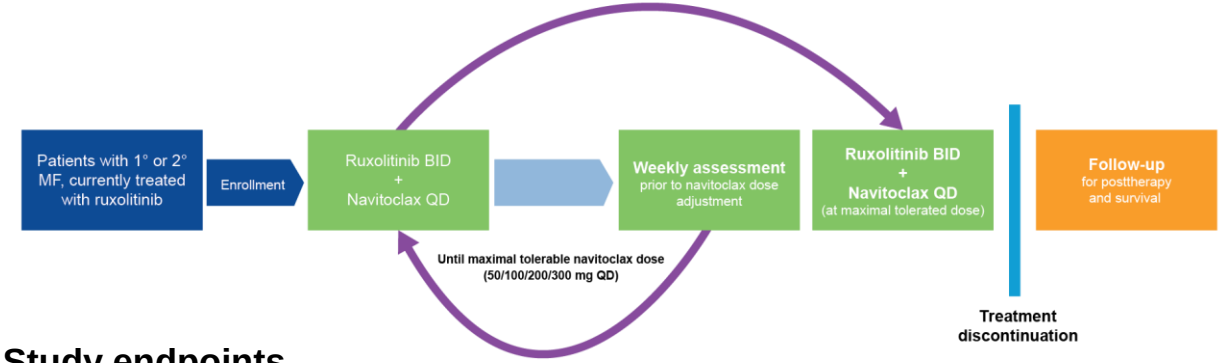
- **Navitoclax is a novel, orally available inhibitor of BCL-X_L and BCL-2, antiapoptotic members of the BCL-2 family[1]**
- **Preclinical studies show that a combination of JAK2 and BCL-2/BCL-X_L inhibition can enhance malignant cell death over JAK2 inhibition alone. In addition, JAK2 + BCL-2/BCL-X_L inhibition could overcome acquired resistance to single-agent JAK inhibitor treatment[2]**
- **A phase 2 study in patients with myelofibrosis (NCT03222609) reported clinical responses after treatment with navitoclax and ruxolitinib in patients who no longer benefited from ruxolitinib[3]**



1. Tse C, et al. *Cancer Res*. 2008;68:3421-3428. 2. Waibel M, et al. Cell Rep. 2013;5:1047-1059. 3. Harrison CN, et al. *HemaSphere*. 2020;4:EP1081.

Study Design and Endpoints

- **Phase 2 single-arm, open-label study that enrolled adult patients with primary or secondary myelofibrosis with splenomegaly who had ruxolitinib failure after ≥12 weeks of continuous treatment**



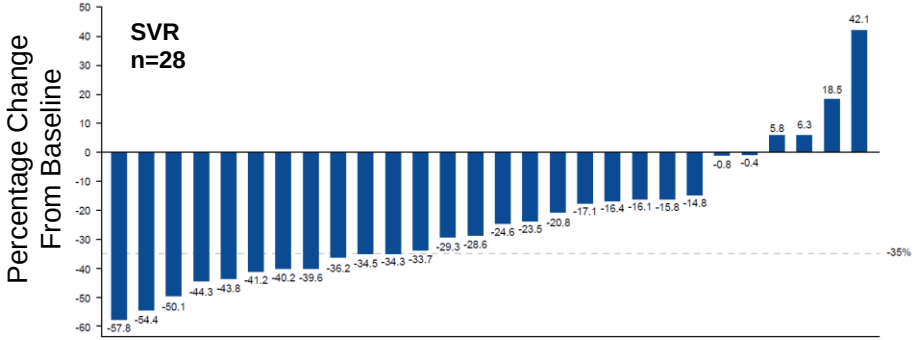
Study endpoints

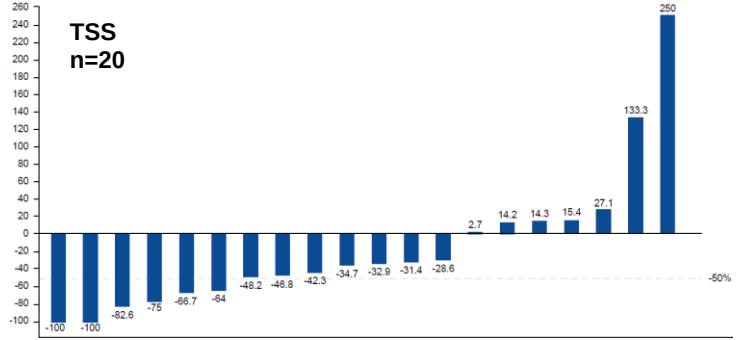
- **Percentage of spleen volume reduction at week 24**
- **Percentage change from baseline to week 24 in total symptom score**
- **Change from baseline in the degree of bone marrow fibrosis**
- **Safety**
- **Exploratory biomarker analyses to assess factors correlating with navitoclax activity**

- **Mutational analyses were performed at baseline and week 24, and included variant allele frequency measurements in peripheral blood samples by next-generation sequencing with the 54-gene Focus::Myeloid™ panel (3% limit of detection)**
- **Cytokine levels were assessed in plasma samples at baseline and weeks 12 and 24 using the Human ExplorerMAP™ version 1.0 panel.**

Overall Efficacy and Safety

- **A total of 9/34 (27%) patients achieved SVR ≥35% at week 24**
- **TSS reduction ≥50% at week 24 was attained in 6/20 (30%) evaluable patients**
- **12/26 (46%) patients had driver gene (*JAK2* or *CALR*) VAF reductions >10% Bone marrow fibrosis improvements of at least one grade at any time were observed in 10/34 (29%) patients**





- **All patients experienced treatment-emergent adverse events (TEAEs)**
  - **The most common TEAEs were thrombocytopenia (88%), diarrhea (68%), and fatigue (62%)**
- **Grade ≥3 TEAEs occurred in 85% of patients**
  - **Most common were thrombocytopenia (53%), anemia (32%), and pneumonia (12%)**
  - **Thrombocytopenia is manageable with dose modifications**

Harrison CN, et al. *HemaSphere*. 2020;4:EP1081.

KRT-232, a First-in-Class, Murine Double Minute 2 Inhibitor, for Myelofibrosis Relapsed or Refractory to Janus-Associated Kinase Inhibitor Treatment

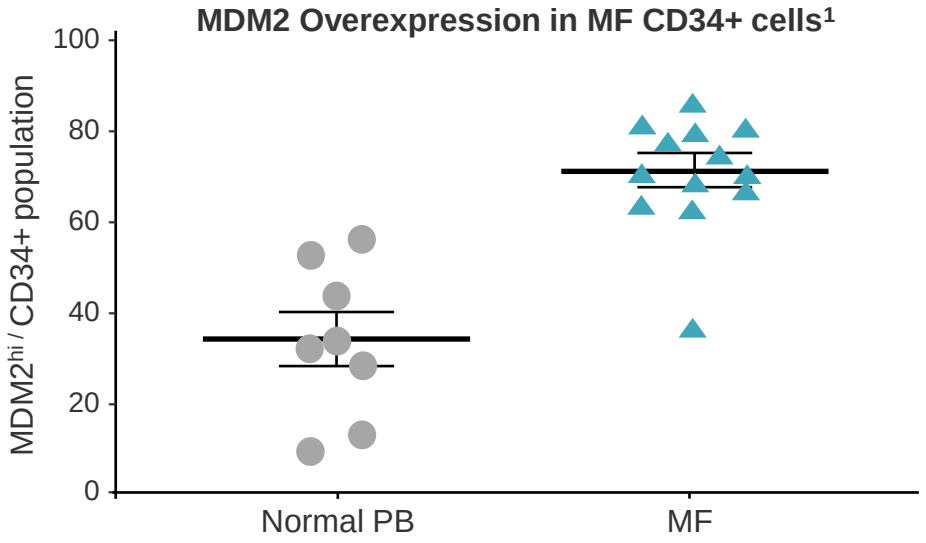
Haifa Kathrin Al-Ali, MD[1]; Regina García Delgado, MD[2]; Andrzej Lange, MD, FRCP[3]; Andrzej Pluta, MD[4]; Donal P. McLornan, MB, BCh (Hons), MRCP, PhD, FRCPath[5]; Pankit Vachhani, MD[6]; Gandhi Laurent Damaj, MD, PhD[7]; Philipp J. Jost, MD[8]; László Rejtő, MD[9]; Marek Hus, MD, PhD[10]; Sebastian Grosicki, MD, PhD[11]; Juan Carlos Hernández-Boluda, MD, PhD[12]; Joanne Ewing, PhD, BMBS, BSc, FRPath[13]; Jesse McGreivy, MD[14]; Wayne P. Rothbaum[14]; Hope Qamoos, CNP[14]; Jean-Jacques Kiladjian, MD, PhD[15]; Srdan Verstovsek, MD, PhD[16]

[1]Department of Hematology and Medical Oncology, University Hospital of Halle, Halle, Germany; [2]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [3]L. Hirszfeld Institute of Immunology and Experimental Therapy/Lower Silesian Center for Cellular Transplantation with National Bone Marrow Donors Registry, Wroclaw, Poland; [4]Szpital Specjalistyczny w Brzozowie Podkarpacki Ośrodek Onkologiczny im. Ks. B. Markiewicza, Brzozów, Poland; [5]Guy's and Saint Thomas' NHS Foundation Trust, London, United Kingdom; [6]University of Alabama at Birmingham, Birmingham, USA; [7]CHU Caen, Caen, France; [8]Technical University of Munich, Munich, Germany; [9]Josa András Teaching Hospital, Nyíregyháza, Hungary; [10]Medical University in Lublin, Lublin, Poland; [11]Silesian Medical University, Katowice, Poland; [12]Hospital Clínico Universitario, Valencia, Spain; [13]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [14]Kartos Therapeutics, Inc., Redwood City, USA; [15]Hopital Saint-Louis, Paris, France; [16]The University of Texas MD Anderson Cancer Center, Houston, USA

PRESENTED BY: **Haifa Kathrin Al-Ali, MD**
Department of Hematology and Medical Oncology, University Hospital of Halle, Halle, Germany

MDM2, Overexpression in Myelofibrosis

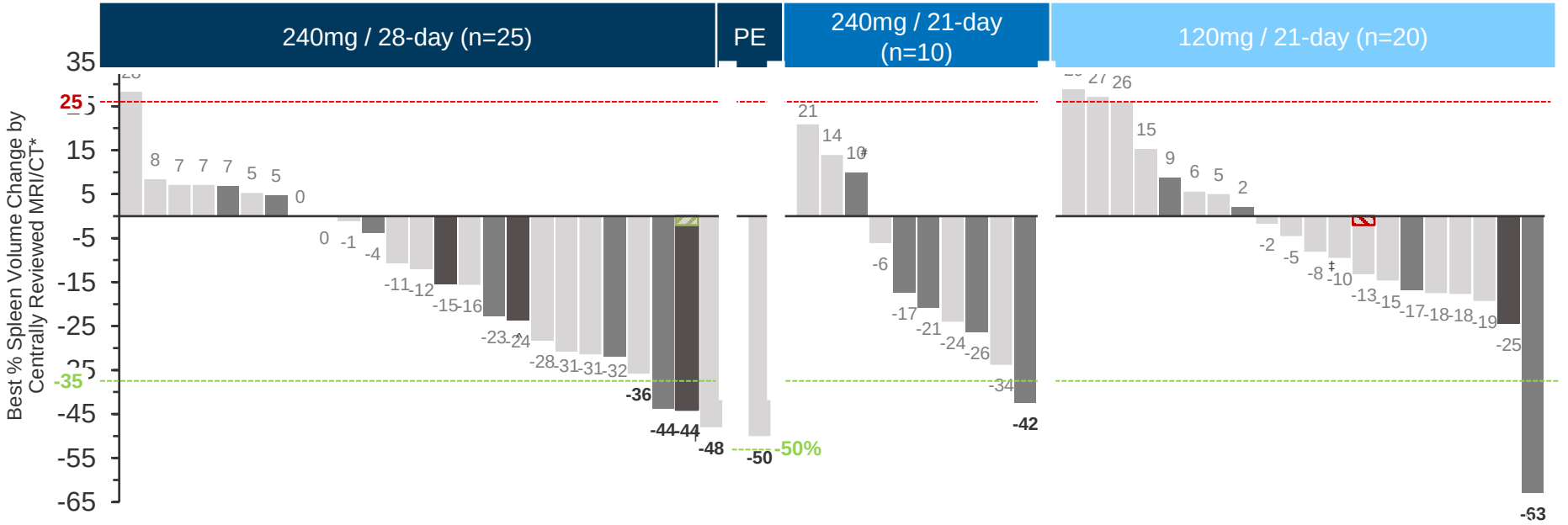
- Somatic gain-of-function mutations such as *JAK V617F* are associated with MDM2 overexpression in circulating CD34+ cells[2]
- Elevated circulating CD34+ cells are a characteristic feature of MF[3]



[1]Figure adapted from Lu M, et al. *Blood.* 2017. [2]Nakatake M, et al. *Oncogene.* 2012. [3]Orvain, et al. *Ann Hematol.* 2016.
Abbreviations: MF, myelofibrosis; PB, peripheral blood.

PRESENTED BY: **Haifa Kathrin Al-Ali, MD**
Department of Hematology and Medical Oncology, University Hospital of Halle, Halle, Germany

Best SVR, Central Review MRI/CT (All Doses / Schedules)



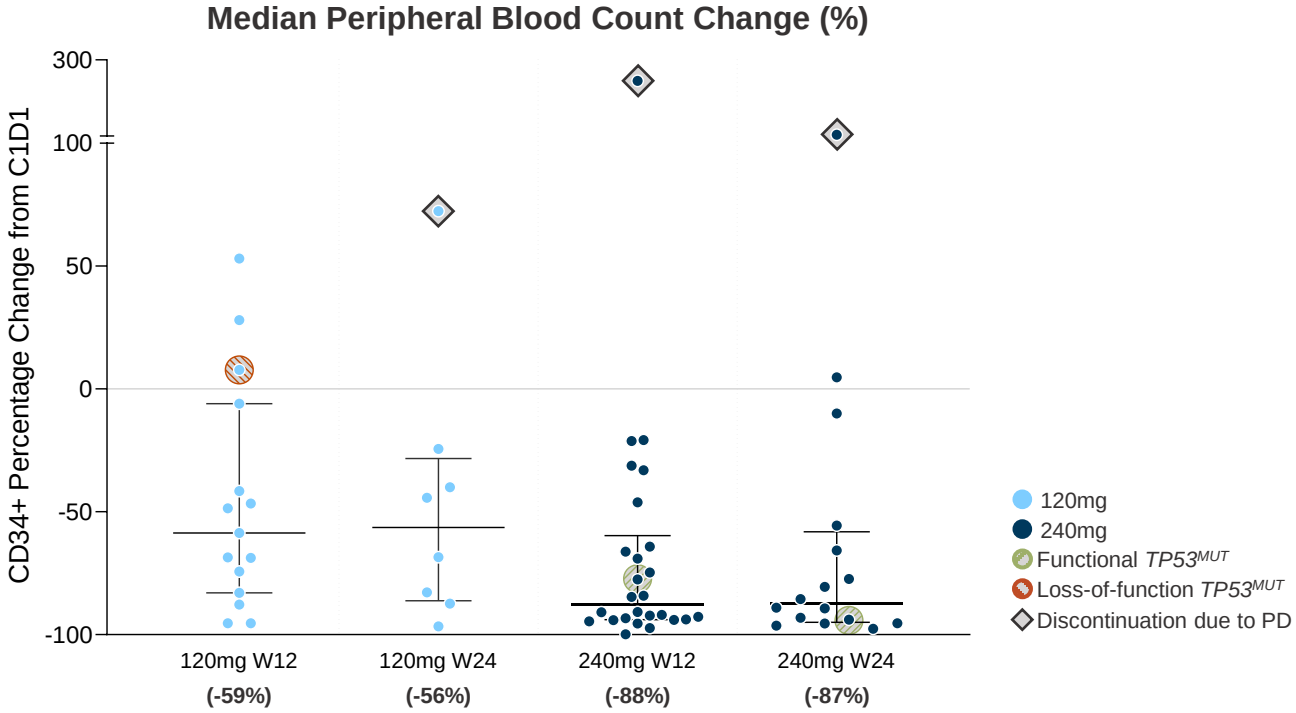
Data cut-off: 01 Mar 2020

*Evaluable: Patients must have baseline and at least one pre-planned post-baseline spleen MRI/CT (Week-12, -24, -36).

^MRI out of window (Wk-37); †MRI out of window (Wk-38), -39% at Week-24; #+6% at Week-20; ‡MRI out of window (Week-13).

Abbreviations: PE, physical examination; SVR, spleen volume reduction.

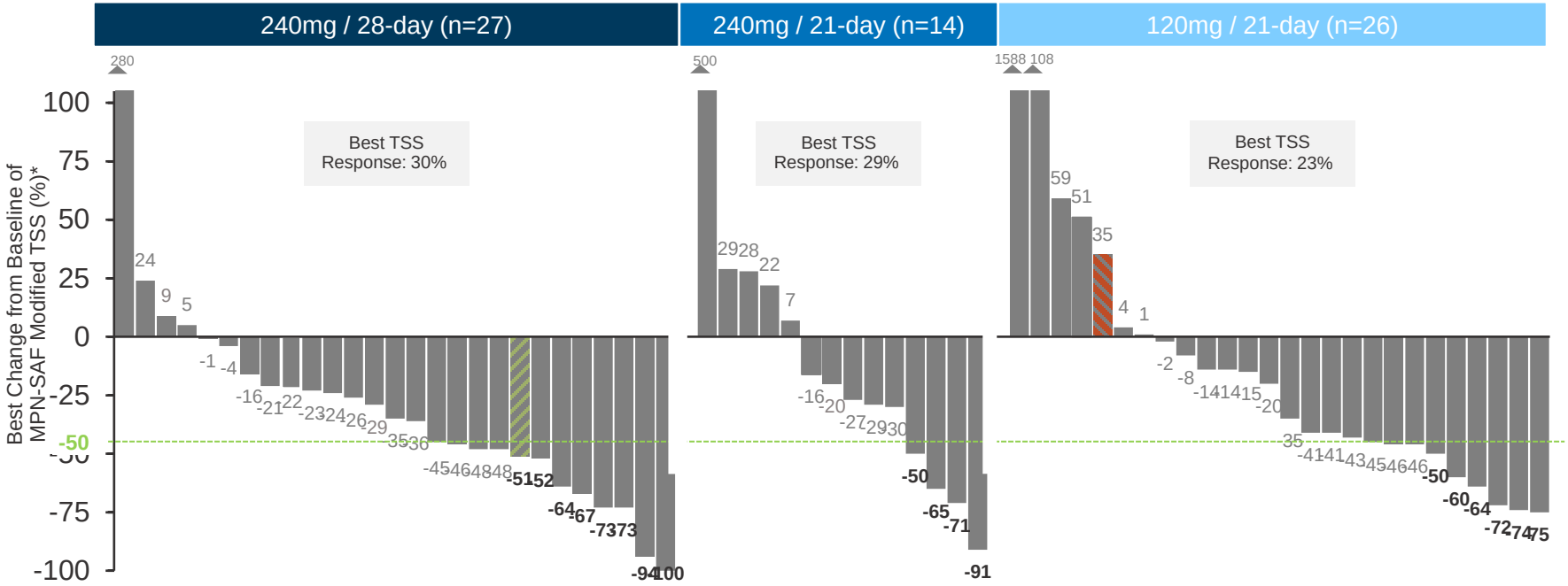
CD34+ Absolute Change, C1D1 to Week 12 / 24



Data cut-off: 01 Mar 2020
Abbreviations: C1D1, cycle 1 day 1; PD, progressive disease; W, week.

PRESENTED BY: **Haifa Kathrin Al-Ali, MD**
Department of Hematology and Medical Oncology, University Hospital of Halle, Halle, Germany

Best Modified Total Symptom Score (TSS), Baseline to 28-day Average (All Doses / Schedules)



Data cut-off: 01 Mar 2020

*Evaluable: Requires patients to have a baseline TSS and > 20-days within a 28-day period reported for post-baseline assessments.

Best Modified TSS: Best change from baseline to trailing 28-day average at end of Week-4, -8, -12, -16, -20, -24, etc.

TSS scores may be confounded by KRT-232 related AEs, particularly in patients with low baseline TSS who experience GI-associated AEs.

Modified MPN-SAF Total Symptom Score (TSS) includes: Early satiety, abdominal discomfort, night sweats, itching, bone pain, and rib pain.

Abbreviations: MPN-SAF, myeloproliferative neoplasm symptoms assessment form V2.0.

Functional *TP53*^{MUT}

Loss-of-function *TP53*^{MUT}

PRESENTED BY: **Haifa Kathrin Al-Ali, MD**
Department of Hematology and Medical Oncology, University Hospital of Halle, Halle, Germany

Treatment-Emergent Adverse Events (TEAEs), ≥10%

	TEAE*, n (%)	240mg / 28-day n=32 All	240mg / 28-day n=32 Gr 3/4	240mg / 21-day n=20 All	240mg / 21-day n=20 Gr 3/4	120mg / 21-day n=30 All	120mg / 21-day n=30 Gr 3/4	ALL N=82 All	ALL N=82 Gr 3/4
	Any TEAE	32 (100)	27 (84)	19 (95)	14 (70)	30 (100)	23 (77)	**81 (99)**	**64 (78)**
Non hematologic (heme)-related	Diarrhea	26 (81)	7 (22)	14 (70)	3 (15)	13 (43)	2 (7)	**53 (65)**	**12 (15)**
	Nausea	12 (38)	3 (9)	9 (45)	0 (0)	16 (53)	3 (10)	**37 (45)**	**6 (7)**
	Vomiting	10 (31)	2 (6)	7 (35)	0 (0)	0 (0)	0 (0)	**17 (21)**	**2 (2)**
	Abdominal pain	7 (22)	3 (9)	4 (20)	0 (0)	5 (17)	1 (3)	**16 (20)**	**4 (5)**
	Asthenia	7 (22)	3 (9)	4 (20)	2 (10)	3 (10)	0 (0)	**14 (17)**	**5 (6)**
	Fatigue	4 (13)	1 (3)	2 (10)	0 (0)	7 (23)	1 (3)	**13 (16)**	**2 (2)**
	Peripheral edema	4 (13)	0 (0)	3 (15)	0 (0)	6 (20)	0 (0)	**13 (16)**	**0 (0)**
	Decreased appetite	6 (19)	0 (0)	2 (10)	1 (5)	4 (13)	0 (0)	**12 (15)**	**1 (1)**
	Cough	5 (16)	0 (0)	1 (5)	0 (0)	4 (13)	0 (0)	**10 (12)**	**0 (0)**
Heme-related	Thrombocytopenia	15 (47)	11 (34)	6 (30)	4 (20)	11 (37)	9 (30)	**32 (39)**	**24 (29)**
	Anemia	16 (50)	13 (41)	5 (25)	4 (20)	9 (30)	7 (23)	**30 (37)**	**24 (29)**
	Neutropenia	4 (13)	4 (13)	6 (30)	5 (25)	2 (7)	2 (7)	**12 (15)**	**11 (13)**
	Leukopenia	3 (9)	1 (3)	3 (15)	3 (15)	3 (10)	3 (10)	**9 (11)**	**7 (9)**

Grade 5 TEAEs (6%): *Related:* Hemorrhagic stroke (240mg / 21-day); endocarditis (240mg / 28-day); *Unrelated:* Pyrexia (120mg / 21-day); respiratory tract infection (240mg / 21-day); respiratory distress (240mg / 28-day).

Data cut-off: 01 Mar 2020

*All events reported regardless of causality

PRESENTED BY: **Haifa Kathrin Al-Ali, MD**
Department of Hematology and Medical Oncology, University Hospital of Halle, Halle, Germany

Case-5: MF

- 70F with PPV-MF with progressive spleen and systemic symptoms on ruxolitinib 15 mg PO BID
- ECOG 2, palpable spleen 15cm, liver 5cm
- WBC 23K, hemoglobin 9.5g/dL, PLT 700K, 2% blasts and early myeloid cells
- BM BX confirms MF and 5% blasts by IHC, MF=3
- “I feel miserable and my goal is to live long enough to see my grandchild born and I would consider transplant as well”

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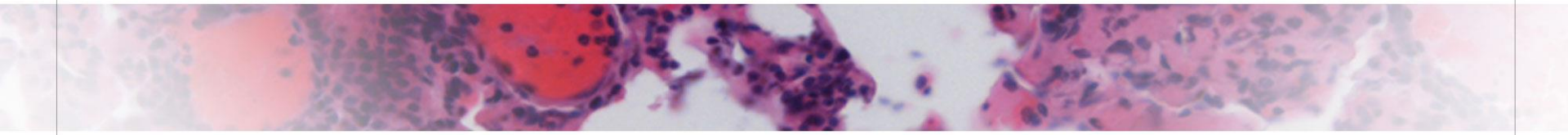
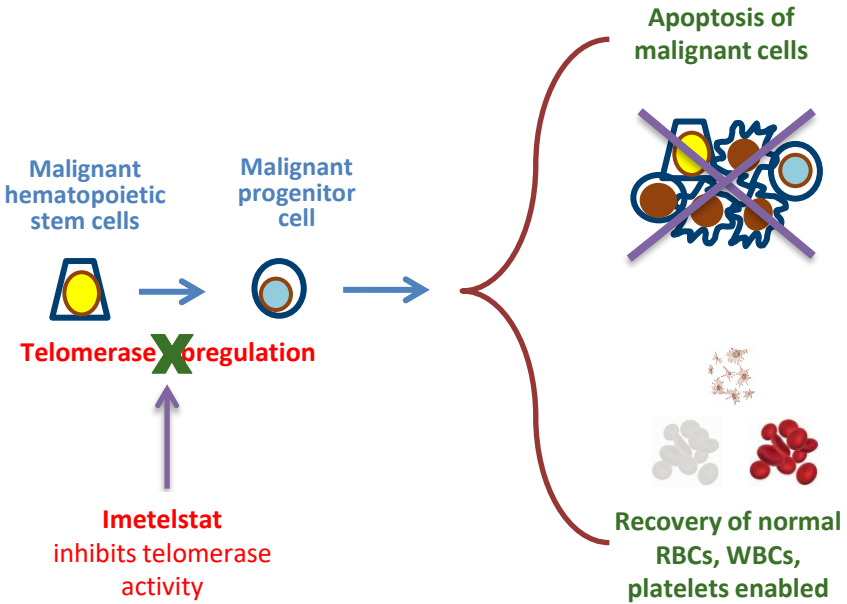


Potential Disease-Modifying Activity of Imetelstat Demonstrated By Reduction in Cytogenetically Abnormal Clones and Mutation Burden Leads to Clinical Benefits in Relapsed/Refractory Myelofibrosis Patients

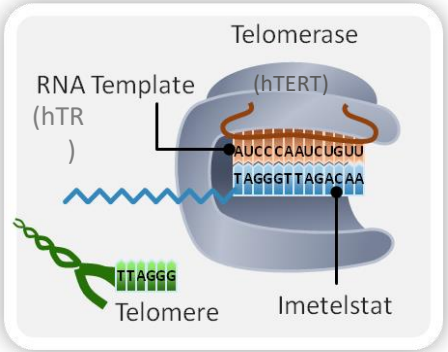
John Mascarenhas, MD[1], Rami S. Komrokji MD[2], Michele Cavo, MD[3], Bruno Martino, MD[4], Dietger Niederwieser, MD[5], Andreas Reiter, MD[6], Bart L Scott, MD[7], Maria R. Baer, MD[8], Ronald Hoffman, MD[9], Olatoyosi Odenike, MD[10], Laurie Sherman, BSN[11], Souria Dougherty, BS, MBA[11], Faye M. Feller, MD[11], Tymara Berry, MD[11], Libo Sun, PhD[11], Ying Wan, MD, PhD[11], Aleksandra Rizo, MD[11], Fei Huang, PhD[11], Jean-Jacques Kiladjian, MD, PhD[12]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; MPN-RC (US), [2]H Lee Moffitt Cancer Center (US), [3]"Seràgnoli" Institute of Hematology, University of Bologna (IT), [4]Grande Ospedale Metropolitano-G.O.M. Bianchi-Melacrino-Morelli (IT), [5]University Hospital Leipzig (DE), [6]University Hospital Mannheim (DE), [7]Fred Hutchinson Cancer Research Center (US), [8]University of Maryland Greenebaum Comprehensive Cancer Center (US), [9]Tisch Cancer Institute, Mount Sinai School of Medicine (US), [10]University of Chicago (US), [11]Geron Corporation (US), [12]Hôpital Saint-Louis, Université Paris (FR)

Imetelstat: First-in-Class Telomerase Inhibitor with Disease-Modifying Potential



Imetelstat binds to RNA template, preventing maintenance of telomeres



Mechanism of Action

- **Potent competitive inhibitor of telomerase activity**
- **Structure:** Proprietary 13-mer thio-phosphoramidate (NPS) oligonucleotide, with covalently-bound lipid tail to increase cell permeability
- **Disease-modifying potential: selective killing** of malignant stem and progenitor cells enabling normal blood cell production

IMbark Phase 2 Trial: Dose-dependent Clinical Benefits Observed with Imetelstat Treatment

IMbark (MYF2001; NCT02426086) was a randomized, single-blind phase 2 study to evaluate the activity of 2 dose levels of imetelstat (9.4 mg/kg or 4.7 mg/kg, IV every 3 weeks) in intermediate-2/high-risk myelofibrosis (MF) relapsed/refractory (R/R) to prior Janus kinase inhibitor (JAKi) treatment.

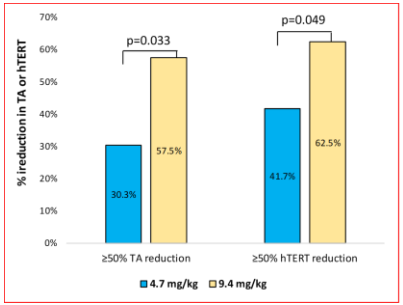
Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
Symptom Response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7%)	15 (25.4%)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3%)	3/12 (25.0%)
Reduction in bone marrow fibrosis , n/N (%)	4/20 (20.0%)	16/37(43.2%)
≥ 25% Reduction in VAF of JAK2, CALR or MPL , n/N (%)	1/18 (5.6%)	8/19 (42.1%)

CALR = calreticulin gene, CI = confidence interval, JAK = Janus kinase, IWG-MRT = International Working Group – Myeloproliferative Neoplasms Research and Treatment, MPL = thrombopoietin receptor gene, OS = overall survival, PFS = progression free survival, SVR = spleen volume reduction, TSS = total symptom score,
VAF = variant allele frequency

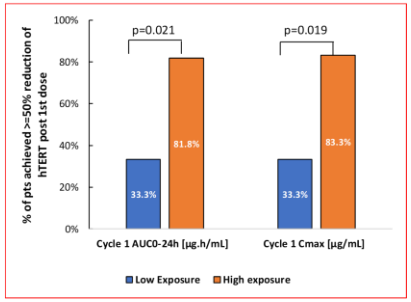
Mascarenhas, et al. *Blood* 2018;132:68.5.
Mascarenhas, et al. EHA 2020 EP1107.

TELOMERASE ACTIVITY, TELOMERE LENGTH AND hTERT EXPRESSION CORRELATE WITH CLINICAL OUTCOMES IN HIGHER-RISK MF R/R TO JAK INHIBITOR TREATED WITH IMETELSTAT

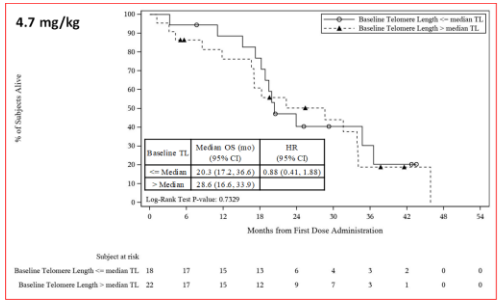
Dose-dependent PD Effect

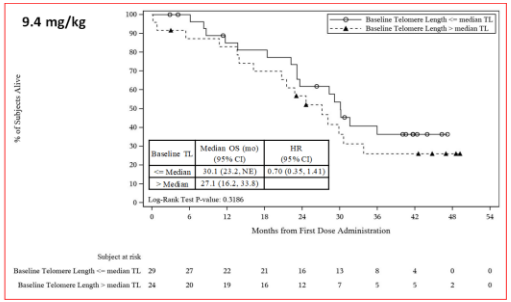


Exposure-dependent PD effect

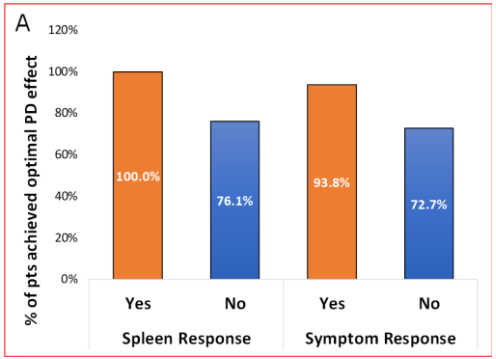


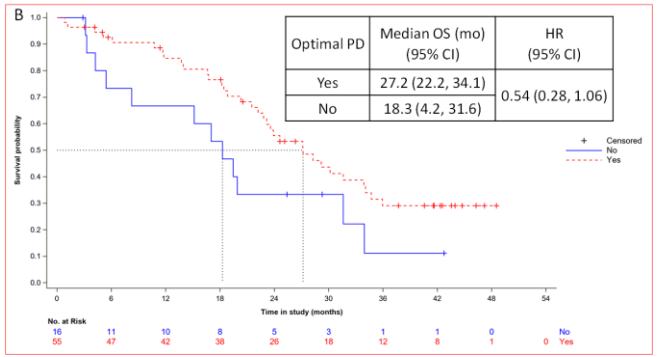
shorter baseline TL associated with better OS compared longer TL when treated with 9.4 mg/kg imetelstat





Optimal PD effect correlated with clinical responses and longer OS



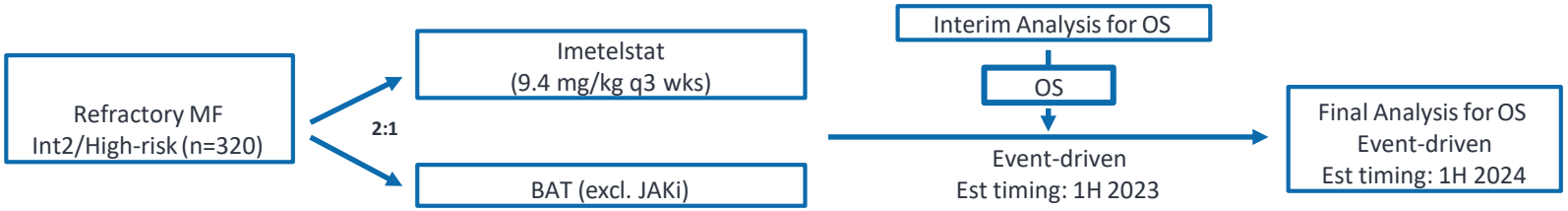


Mascarenhas et al ASH 2020

Phase 3 Trial Design in Int-2/HR MF with OS as Primary Endpoint

Plan to open for enrollment 1Q 2021

Principal Investigators: **John Mascarenhas, M.D., Icahn School of Medicine, Mt. Sinai**
Srdan Verstovsek, M.D., MD Anderson Cancer Center



Population: Int-2/High-risk MF refractory to a JAKi

- Inadequate spleen or symptom response after treatment with JAKi for ≥ 6 months, including an optimal dose of JAKi for at least 2 months
- Inadequate spleen or symptom response after treatment with maximal doses of JAKi for ≥ 3 months

Primary endpoint: Overall Survival (OS; HR=0.6)

- Secondary endpoints include: symptom response, spleen response, progression free survival, complete response, partial response, clinical improvement, duration of responses, safety, pharmacokinetics, patient reported outcomes

Imetelstat treatment arm: 9.4 mg/kg every 3 weeks

Comparator arm: Best Available Therapy (BAT), excluding JAKi

Conclusions

- Laboratory studies inform clinical investigation
- What we learn in trials of novel agents for advanced patients frequently moves earlier in the disease course to impact overall outcomes
- We have not forgotten about ET, and what we learn in PV and MF may help in ET
- JAK inhibitors were (are) a huge step forward but only the beginning
- Cutting edge trials today are mechanism based and have rationale
- Overall survival in MF is now a regulatory endpoint!
- Laboratory scientists, clinical investigators, pharmaceutical sponsors, NCI, EMA, FDA, patient advocacy groups and patients must work in concert to cure these diseases

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Andrew Kuykendall
Rami Komrokji
Rupali Bhave
Amylou Dueck
Heidi Kosiorek
Rona Weinberg
Mohamed Salama

Contact me @
John.mascarenhas@mssm.edu

MPN – RC Myeloproliferative Neoplasms Research Consortium