New Drugs for MPNs (what to look for)

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Agenda

- Monotherapies for MF*
  - Phase 3: Navtemadlin, Imetelstat
  - Early phase: PIM1 kinase inhibitor
- Targeting hepcidin in PV
- Don’t forget about ET: vaccinations against CALR

*Dr Pemmaraju will cover combinations in a later talk

What do MPN patients want?

- Highly effective therapy
- Low toxicity
- Convenient administration
- “Disease course modifying”
- Cure

How do MPN Investigators get there?

- Mechanism based agents
- Preclinical data
- Biomarker evidence of on-target effect
- Disease burden modification

- We understand what the drug targets
- Laboratory evidence of activity in mice and human samples
- Blood and bone marrow samples from treated patients confirm it hits the intended target
- The driver mutation level decreases

Agenda

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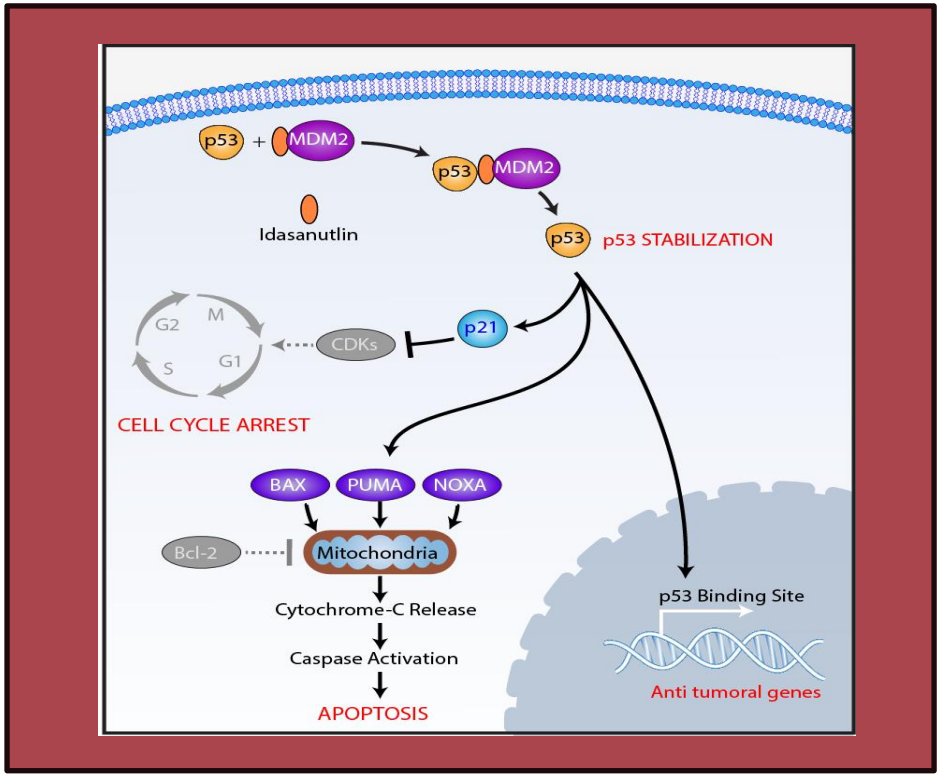
Nutlins Block the MDM2:P53 interaction and activate the P53 pathway



1. Vassilev L. Trends in Mol Med 2007;13:23–31
2. Ding Q, et al. J Med Chem 2013;56:5979–83

Icahn School of Medicine at Mount Sinai

MPD-RC Myeloproliferative Disorders Research Consortium

POSTER 3581

Potential Disease-Modifying Activity of Navtemadlin (KRT-232), a First-in-Class MDM2 Inhibitor, Correlates With Clinical Benefits in Relapsed/Refractory Myelofibrosis (MF)

Pankit Vachhani[1]; Andrzej Lange[2]; Regina Garcia Delgado[3]; Haifa K. Al-Ali[4]; Jesus M. Hernandez-Rivas[5]; Jean-Jacques Kiladjian[6]; Alessandro Vannucchi[7]; Andrew C. Perkins[8]; Venu Valmeekam[9]; Cecile M. Krejsa[9]; Anne Uyei[9]; Jesse McGreivy[9]; Wayne P. Rothbaum[9]; John Mascarenhas[10]; Srdan Verstovsek[11]

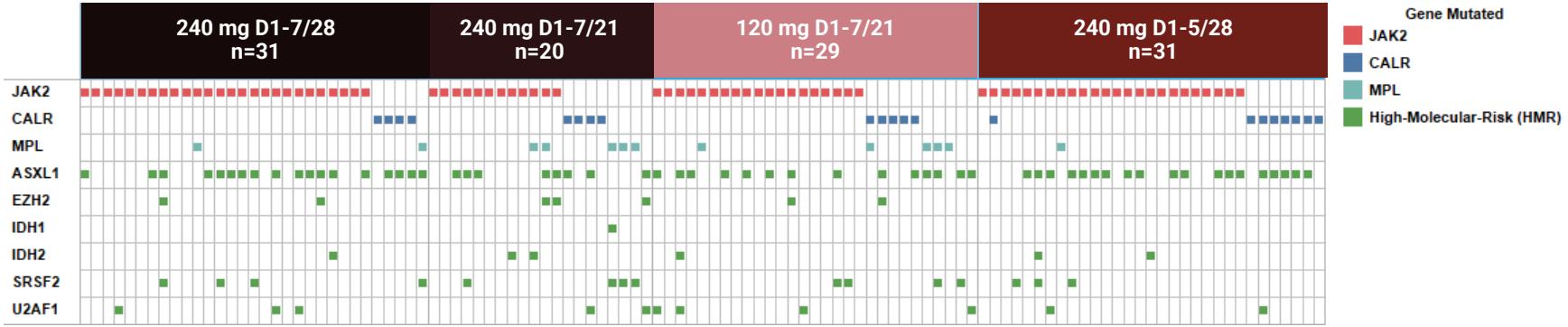
[1]O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL, USA; [2]L. Hirszfeld Institute of Immunology and Experimental Therapy/Lower Silesian Center for Cellular Transplantation with National Bone Marrow Donors Registry, Wroclaw, Poland; [3]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [4]Department of Hematology and Medical Oncology, University Hospital of Halle, Halle, Germany; [5]Complejo Asistencial Universitario de Salamanca Hospital Clínico, Salamanca, Spain; [6]Hopital Saint-Louis, Paris, France; [7]University of Florence, Florence, Italy; [8]Monash University, Melbourne, Australia; [9]Kartos Therapeutics, Inc., Redwood City, CA, USA; [10]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

PRESENTED AT: 63rd ASH ANNUAL MEETING & EXPOSITION

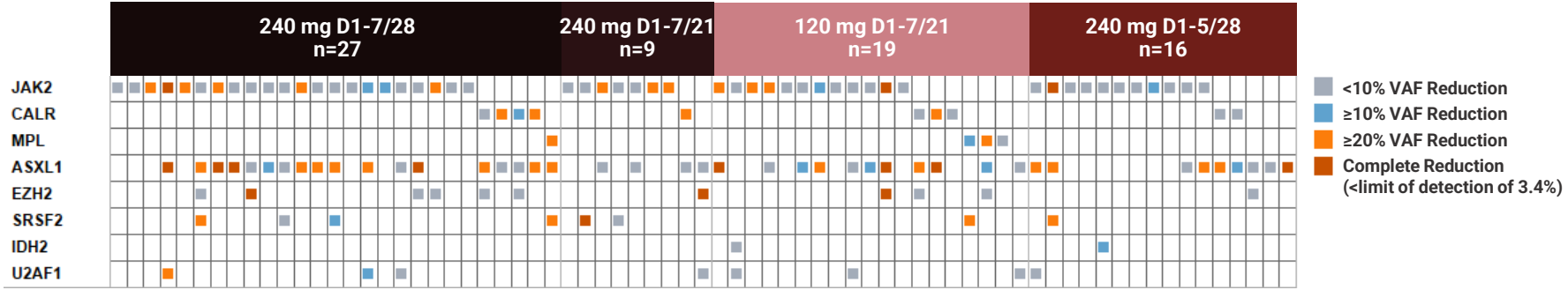
PRESENTED BY: **Pankit Vachhani, MD**
O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL, USA

Driver and HMR Mutations at Baseline and After Navtemadlin Treatment

Distribution of Driver and HMR Mutations at Baseline

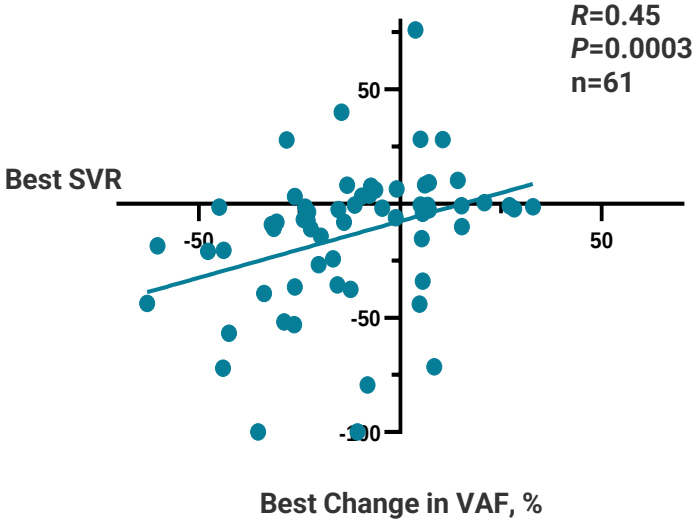


Best Decrease in Mutation Burden on Navtemadlin Treatment

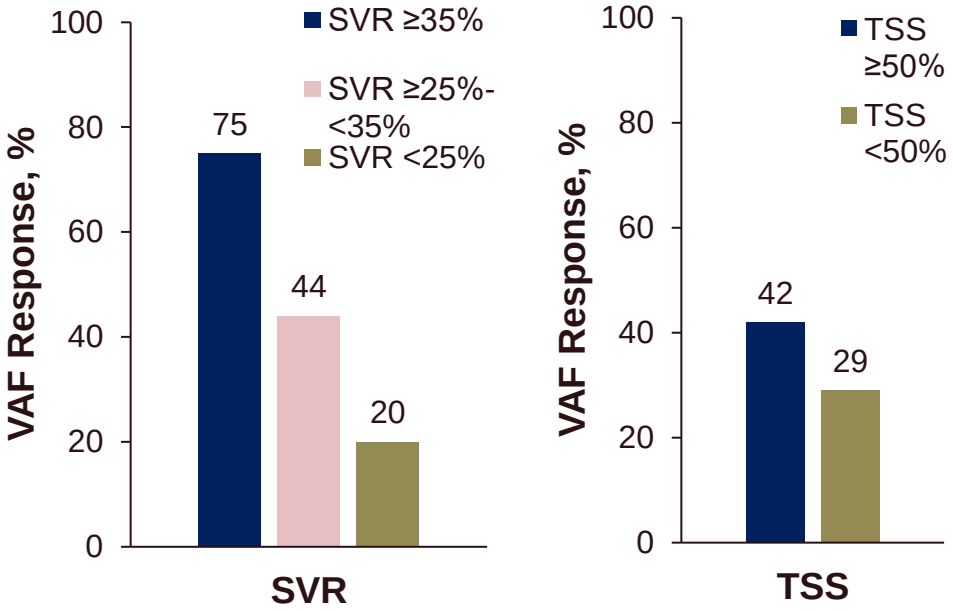


Correlation Between Changes in Driver Mutations and Responses

Correlation Between Driver Gene VAF Reduction and SVR*



Driver Gene VAF Reduction Among Responders†



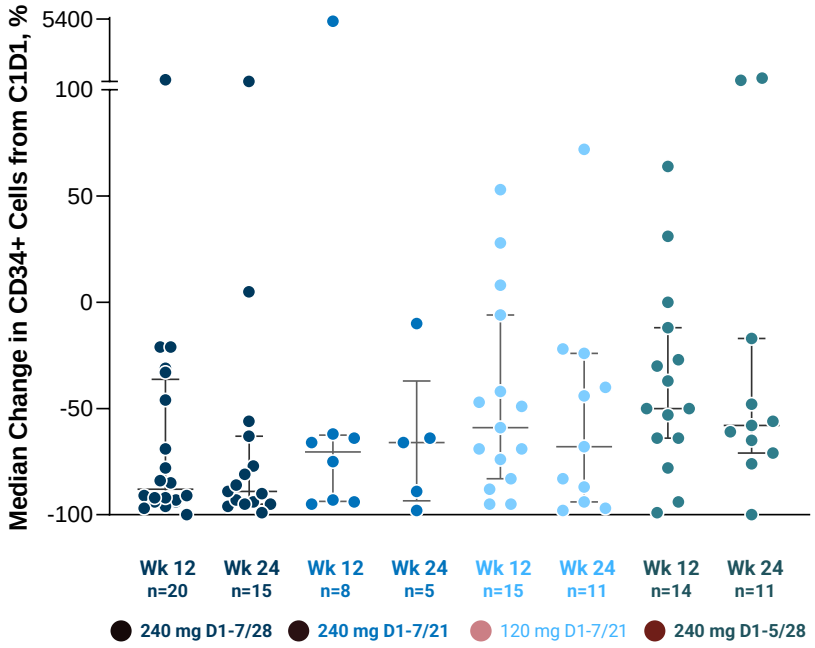
Data cut-off: 19 Apr 2021.

Baseline mutation burden = MPN driver(s) plus each HMR gene (ASXL1, EZH2, IDH1/2, SRSF2, U2AF1). If more than 1 MPN driver gene alteration was present, each gene was counted toward mutation burden. The driver gene with the highest baseline variant allele frequency VAF was used for evaluation of VAF responses.

*All patients with available data are included in the correlations.
†All patients with evaluable data for analysis are included; best SVR responses are shown with all results evaluated centrally.

Changes in Circulating CD34+ Cell Count and Correlation With SVR

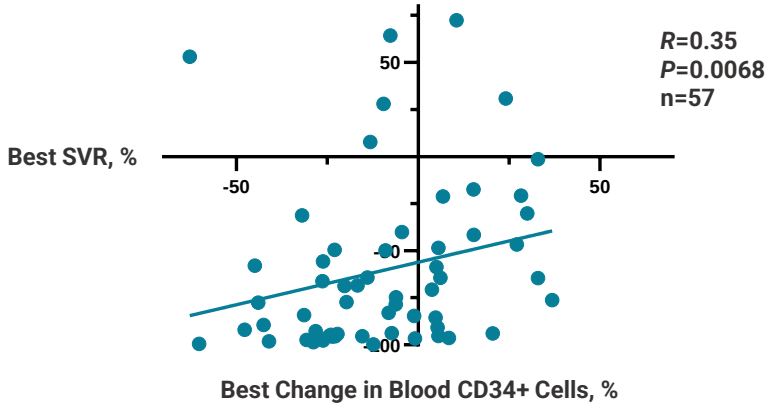
Percent Change in Circulating CD34+ Cell Count



Median Change in CD34+ Cells

Median % Change (IQR)	240 mg D1-7/28	240 mg D1-7/21	120 mg D1-7/21	240 mg D1-5/28
Week 12	-88 (-93, -40) 20 pts	-70 (-94, -63) 8 pts	-59 (-83, -6) 15 pts	-50 (-64, -27) 14 pts
Week 24	-89 (-95, -63) 15 pts	-66 (-89, -64) 5 pts	-68 (-94, -24) 11 pts	-58 (-71, -17) 11 pts

Correlation Between Change in CD34+ Cells and SVR



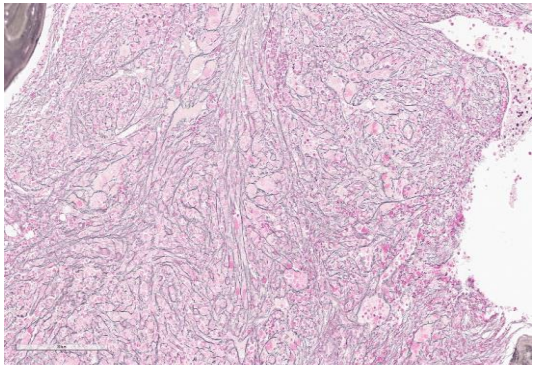
Data cut-off: 19 Apr 2021.

Bone Marrow Fibrosis Improvement and Association With Response

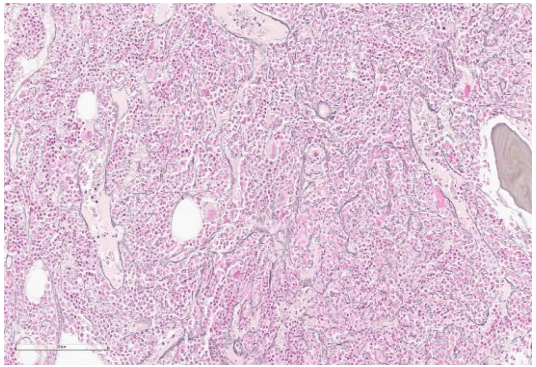
MF Bone Marrow Fibrosis Improvement

Bone Marrow Grade at Week 24	Improved n (%)	Stable n (%)	Worsened n (%)
240 mg D1-7/28 (n=16)	5 (31)	8 (50)	3 (19)*
240 mg D1-7/21 (n=7)	1 (14)	5 (71)	1 (14)
120 mg D1-7/21 (n=10)	3 (30)	6 (60)	1 (10)
240 mg D1-5/28 (n=11)	3 (27)	3 (27)	5 (45)
Total (n=44)	12 (27)	22 (50)	10 (23)

Reticulin Staining



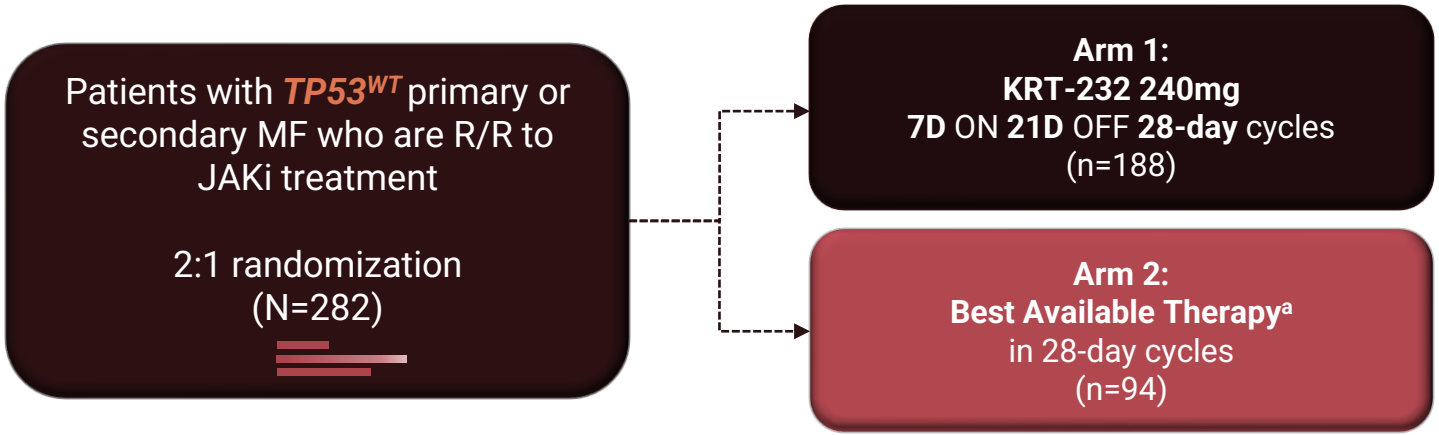
Screening
Grade 2



Week 24
Grade 1

Data cut-off: 19 Apr 2021.
Bone marrow fibrosis scores by central pathology review; European consensus scoring used (Gianelli et al. Haematologica. 2012).
*One patient showed worsened MF fibrosis score 5 months after discontinuation of treatment (D28).

BOREAS Phase 3 Study Design (NCT03662126)



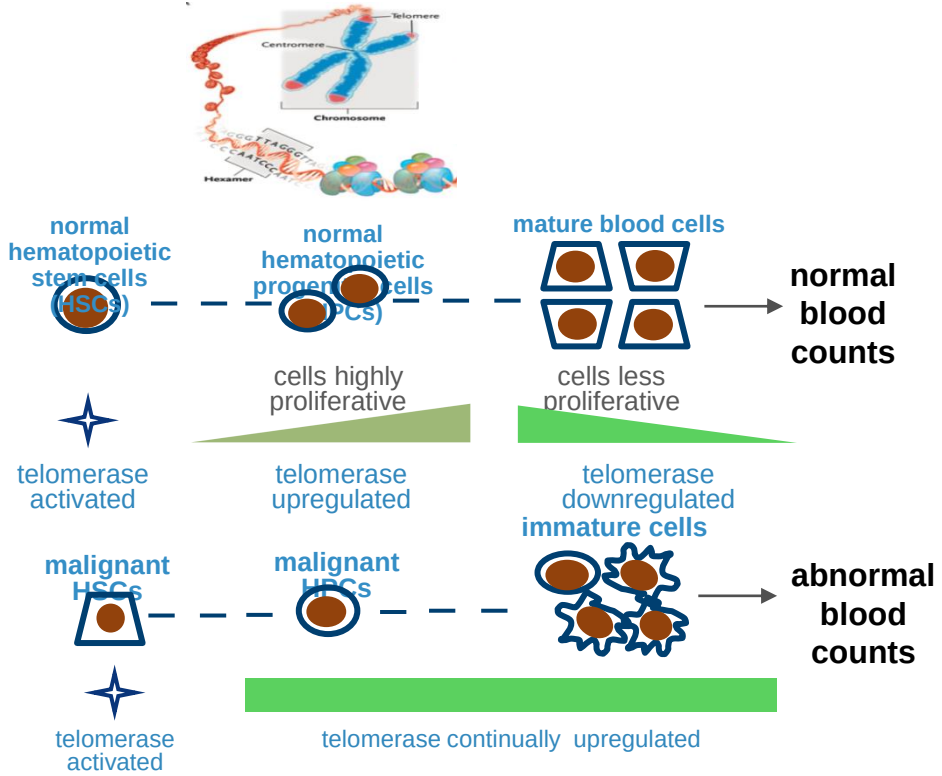
Best available therapy options include hydroxyurea, chemotherapy, or supportive care. JAKi are excluded

Patient Stratification:

- MF type (primary vs secondary)
- Baseline TSS (≤10 vs >10)

JAKi, Janus kinase inhibitor; MF, myelofibrosis; R/R, relapsed/refractory; *TP53*^{WT}, wild-type tumor protein p53 gene.
[a]Treatment selection is at the discretion of the investigator. Patients with documented disease progression at any time or those who complete Week-24 assessments may crossover to the KRT-232 arm.

Telomerase as a novel target

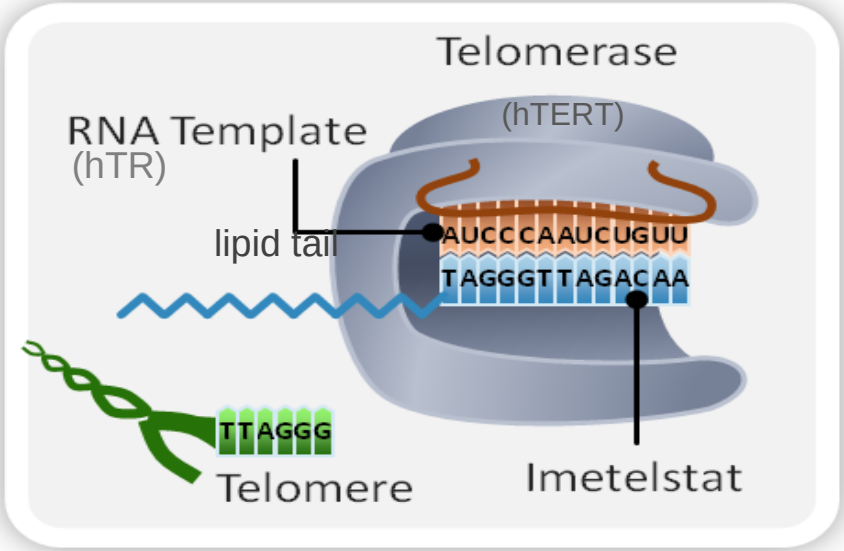


Telomerase enzyme:

- Reverse transcriptase comprised of an RNA component (hTR) and a reverse transcriptase catalytic protein subunit (hTERT)
- Binds to the 3’ strand of DNA and adds TTAGGG nucleotide repeats to offset the loss of telomeric DNA occurring with each replication cycle
- Not active in somatic cells; transiently upregulated in normal hematopoietic progenitor cells to support controlled proliferation
- Highly upregulated in malignant progenitor cells, enabling continued and uncontrolled proliferation

Imetelstat: First in Class Telomerase Inhibitor

imetelstat binds to RNA template preventing maintenance of telomeres



- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability/tissue distribution
- **Long half-life** in bone marrow, spleen, liver (estimated human t½ = 41 hr with doses 7.5 – 11.7 mg/kg);
- **Potent competitive inhibitor of telomerase**: IC50 = 0.5-10 nM (cell-free)
- **Target:** malignant progenitor cell proliferation

Imetelstat, a telomerase inhibitor, induces morphologic and molecular remissions in myelofibrosis and reversal of bone marrow fibrosis

Tefferi A,[1] Begna KH,[1] Laborde RR,[1] Patnaik MM,[1] Lasho TL,[1] Zblewski DL,[1] Finke CM,[1] Schimek L,[1] LaPlant B,[1] Hanson CA,[1] Stuart M,[2] Pardanani A.[1]

[1]Mayo Clinic, Rochester, MN, USA
[2]Geron Corporation, Menlo Park, CA, USA

N Engl J Med. 2015 Sep 3;373(10):908-19.

Primary Endpoint: Overall Response by IWG-MRT

	N = 33 (%)
Overall Response (CR+PR+CI)	12 (36.4%)
Complete Remission (CR)	4 (12.1%)
Partial Remission (PR)	3 (9.1%)
Clinical Improvement (CI) by Anemia	1 (3.0%)
Clinical Improvement (CI) by Spleen	4 (12.1%)
Stable Disease (SD)	21 (63.6%)
Spleen Response (by palpation lasting ≥ 12 weeks)	8/23 (34.8%)
Transfusion dependent becoming transfusion independent	4/13 (30.8%)

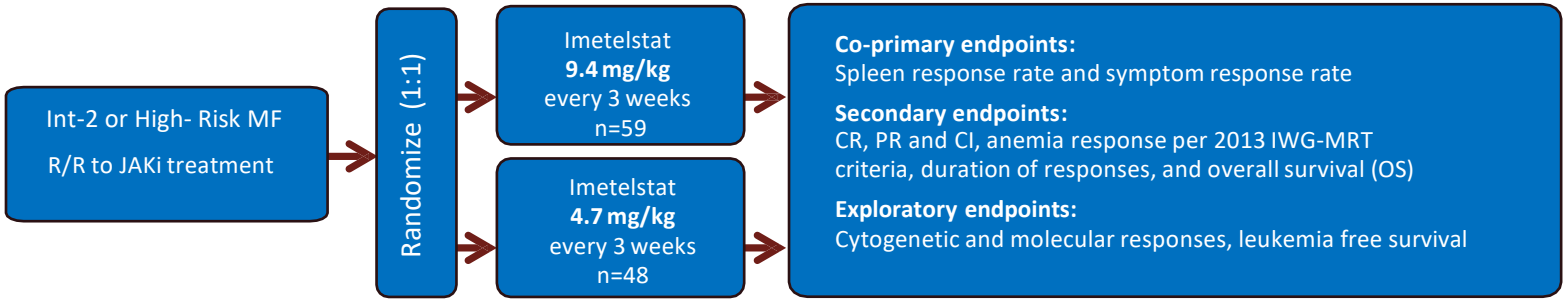
CR/PR/CI: 36.4%

CR/PR: 21.2%

- All 4 CR patients achieved reversal of BM fibrosis and 3 complete molecular response.
- 3 CR/PR patients who were transfusion dependent at baseline became transfusion independent
- 3 CR/PR patients with splenomegaly at baseline achieved splenic response

Tefferi et al. N Engl J Med. 2015 Sep 3;373(10):908-19.

IMbark Phase 2 Trial: Study Design



Patient Population:

- Patients with Intermediate-2 or High-risk MF (Int-2/High-risk) patients who have relapsed after or are refractory to prior treatment with a janus kinase (JAK) inhibitor
- Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
  - Patients must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy and EITHER:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy, OR
    - Worsening splenomegaly at any time after the start of JAKi therapy documented by:
      - Increase in spleen volume from nadir by 25% measured by MRI or CT, or
      - Increase in spleen size by palpation

Mascarenhas et al ASH 2020

Dose Related Clinical Benefits from Treatment with Imetelstat

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)
Symptoms 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 JCO 2021

imetelstat Safety Profile

Manageable and Reversible Cytopenias with Limited Clinical Consequences

n (%)	9.4 mg/kg (n=59) All Grades	Grade ≥ 3
***Hematologic (≥ 10% in either arm)**		
Thrombocytopenia	29 (49)	24 (41)
Anemia	26 (44)	23 (39)
Neutropenia	21 (36)	19 (32)
Leukopenia	8 (14)	8 (14)
Non-hematologic (≥ 20% in either arm)		
Nausea	20 (34)	2 (3)
Vomiting	8 (14)	1 (2)
Diarrhea	18 (31)	0
Fatigue	16 (27)	4 (7)
Cough	9 (15)	0
Dyspnea	14 (24)	3 (5)
Abdominal Pain	14 (24)	3 (5)
Asthenia	14 (24)	6 (10)
Pyrexia	13 (22)	3 (5)
Edema peripheral	11 (19)	0

*Treatment emergent, per reported AEs (not laboratory values). Frequency of reported Grade 3/4 hematologic AEs were consistent with cytopenias reported through lab values.

IMbark

ClincialTrials.gov (NCT02426086)

Thrombocytopenia and neutropenia characterization:

- **Median time to the event:** is 9 weeks (~ 3 cycles)
- **Median duration:** neutropenia 1.1 weeks and thrombocytopenia 1.7 weeks
- **Reversible:** >90% within 4 weeks
- **Manageable with dose hold and modification:** median time to first dose reduction 21 weeks (~7 cycles)
- **Limited clinical consequences:**

n(%)	9.4 mg/kg (n=59)
Grade 3 Febrile Neutropenia	1 (2)
Grade ≥ 3 Hemorrhagic events	3 (5)
Grade ≥ 3 Infections	6 (10)

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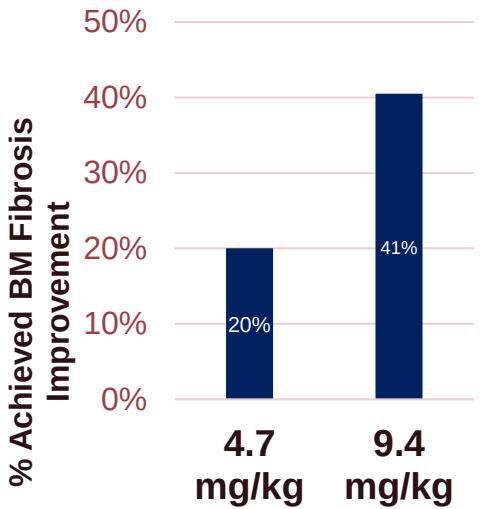
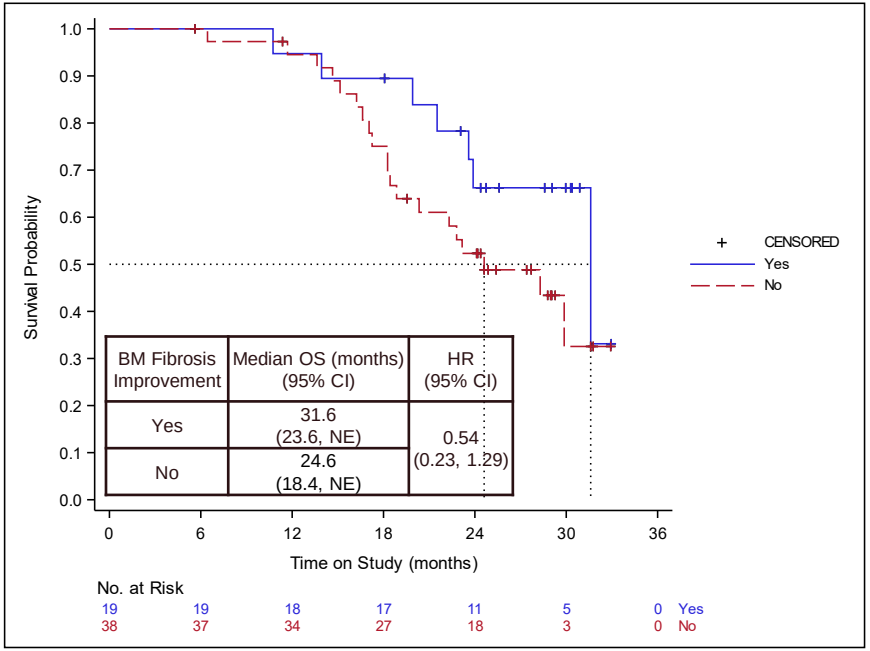
Improved Bone Marrow Fibrosis Correlated to Improved Survival

Significant Dose-Dependent Fibrosis Improvement with imetelstat Treatment



Longer Median OS and Higher Survival Rate in Patients with Improved Fibrosis

IMbark
ClincialTrials.gov (NCT02426086)



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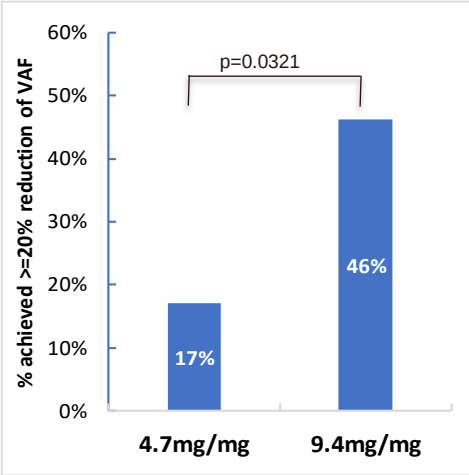
Strong Evidence of Disease Modification Potential

Reduction in Key MF Driver Mutations Correlated to Improved Survival

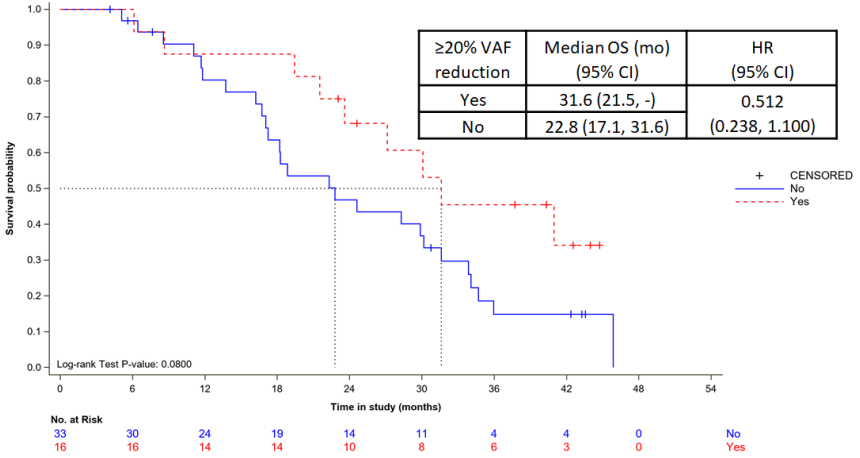
IMbark
ClincialTrials.gov
(NCT02426086)

Significant Dose-Dependent ≥20% VAF Reduction with imetelstat Treatment



VAF = variant allele frequency

Longer Median OS and Higher Survival Rate in Patients Who Achieved ≥ 20% VAF Reduction



≥20% VAF reduction	Median OS (mo) (95% CI)	HR (95% CI)
Yes	31.6 (21.5, -)	0.512 (0.238, 1.100)
No	22.8 (17.1, 31.6)	

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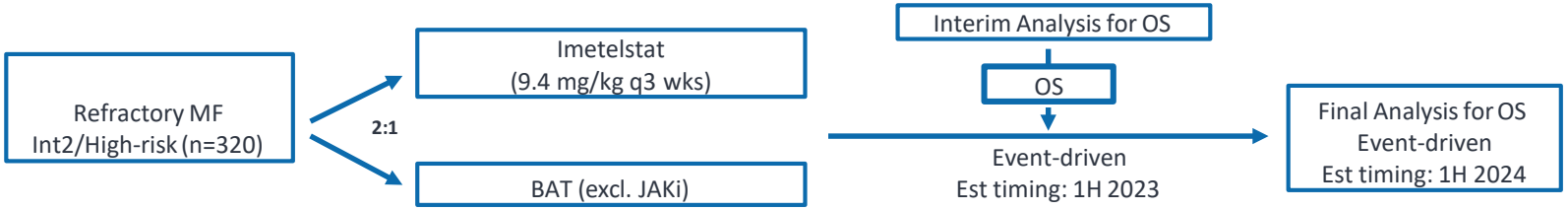
Phase 3 Trial Design in Int-2/HR MF with OS as Primary Endpoint IMpactMF trial



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

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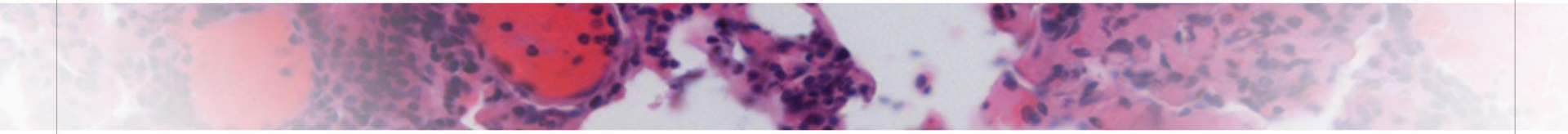
American Society of Hematology
Helping hematologists conquer blood diseases worldwide



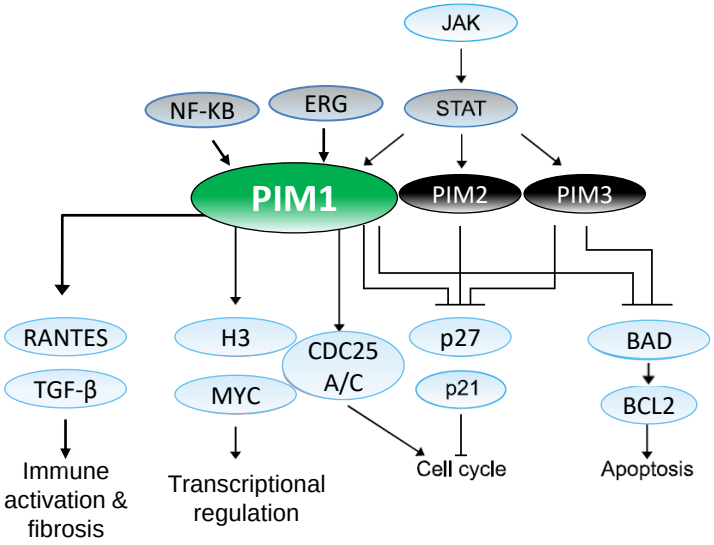
Phase I/II Study of TP-3654, a Selective Oral PIM1 Kinase Inhibitor, in Patients with Myelofibrosis Previously Treated with or Ineligible for JAK Inhibitor Therapy

Firas El Chaer MD[1], James McCloskey MD[2], Lindsay AM Rein, MD[3], Randy A Brown MD[4], Steven D Green MD[5], Jeffrey J Pu MD PhD[6], Shuichi Shirane MD PhD[7], Kazuya Shimoda MD PhD[8], Michiko Ichii MD PhD[9], Junichiro Yuda MD PhD[10], Joseph Scandura MD PhD[11], Sujan Kabir MD[12], Jason M Foulks PhD[13], Jian Mei PharmD[12], Huyuan Yang PhD[12], Mark Wade PhD[12], Carl Stapinski[12], Claudia Lebedinsky MD[12] , and Raajit K Rampal MD PhD[14]

[1]University of Virginia Health System, VA; [2]The John Theurer Cancer Center at Hackensack Meridian Health, NJ; [3]Duke University Medical Center, NC; [4]Shands HealthCare &University of Florida, FL; [5]Roswell Park Comprehensive Cancer Center, NY; [6]University of Arizona Cancer Center, AZ; [7]Juntendo University School of Medicine, Tokyo, Japan; [8]University of Miyazaki, Miyazaki, Japan; [9]Osaka University Graduate School of Medicine, Suita City, Japan; [10]National Cancer Center Hospital East, Kashiwa, Japan; [11]Richard T. Silver, Weill Cornell Medicine, NY; [12]Sumitomo Pharma Oncology, Inc., MA; [13]Sumitomo Pharma Oncology, Inc., UT; [14]Memorial Sloan Kettering Cancer Center, NY

Background: PIM1 Kinase Signaling

- PIM1 is a proto-oncogene regulated in part through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway[3]
- PIM1 kinase also has an essential role in cytokine-induced signal transduction by controlling transcription factors[3]
- Upregulation of PIM1 kinase leads to increased cytokines relevant to immune activation and fibrosis including RANTES and TGF-β[3]



Adapted from Zhang et al 2018.

3. Tursynbay et al. *Biomed Rep*. 2016

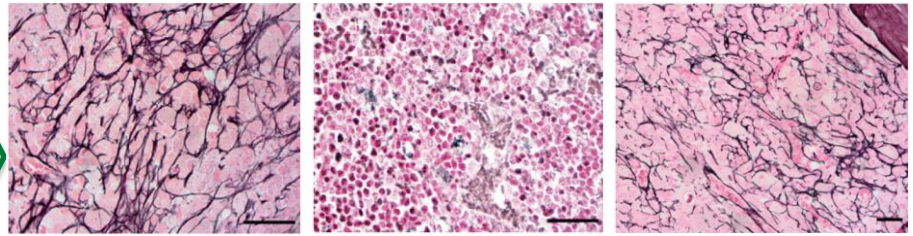
PIM1 Kinase: A Novel Target in MF

- PIM1 expression was shown to be significantly increased in MF patients' bone marrow and PBMC samples[4]

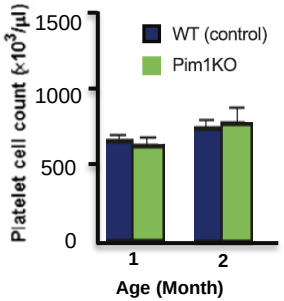
- PIM1 knockout was shown to prevent myelofibrosis progression, but PIM2 knockout has no effect in MF mouse models[4]

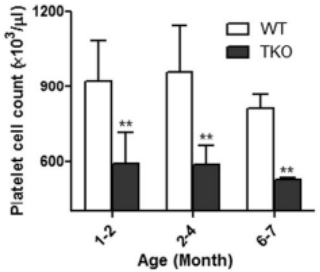
- PIM1 knockout was shown not to cause platelet count decrease, while pan-PIM knockout resulted in thrombocytopenia in mice[5]

MPL^{W515L} Mouse Model Bone Marrow (Reticulin Stain)



PIM WT | PIM1KO | PIM2KO



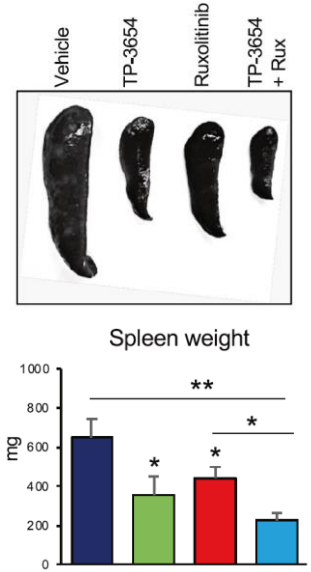


- Novel therapies which **selectively** inhibit PIM1 kinase may provide disease-modifying benefits for MF patients while avoiding cytopenia adverse effects

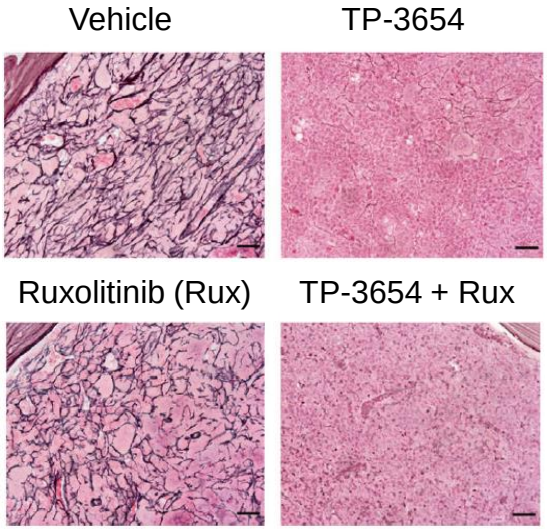
4. Dutta et al. Leukemia 2021 5. An et al. JH&O, 2013

TP-3654: An Oral Selective PIM1 Inhibitor in Murine MPL^{W515L} MF Model

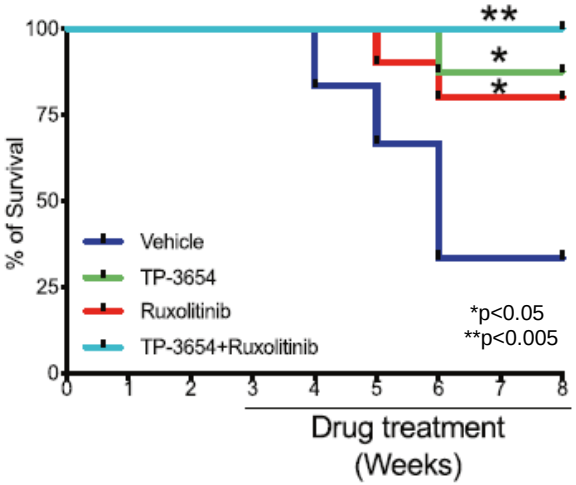
✓ Spleen Size Reduction



✓ Bone Marrow Fibrosis Reduction



✓ Overall Survival Increase



- Similar TP-3654 activity was observed in murine JAK2^{V617F} MF model[4]

4. Dutta et al. Leukemia 2021

TP-3654 Phase I/II Study Design in MF

- **Primary, Post-PV, Post-ET MF**
- **Relapsed, refractory, intolerant, or ineligible for treatment with JAK inhibitors**

Phase 1 Monotherapy Dose Escalation
480 mg QD - 1440 mg BID
Bayesian Dose Escalation

→ **MTD/ RP2D** →

Phase 2 Dose Expansion

Key Eligibility

- DIPSS Intermediate- 1, 2, or high-risk
- **Platelet count ≥ 25 x 10^9/L**
- ECOG ≤ 2
- Splenomegaly (volume of ≥ 450 cm^3)
- At least 2 symptoms by MF-SAF v4.0

Endpoints

- **Primary:**
  - Safety and tolerability
- **Secondary**
  - Spleen volume reduction
  - Total symptoms score reduction (MF-SAF v4.0)
  - Overall survival
  - Bone marrow fibrosis change
  - Pharmacokinetics

TP-3654: Dose Escalation and Safety

Cohort	Number of Patients	DLT
480mg QD	1	None
720mg QD	2	None
360mg BID	1	None
480mg BID	4	None
720mg BID	1 / ongoing	None

- No DLT or related serious AE.
- The most common AEs are Grade 1 diarrhea, nausea, and vomiting, and transient resolving within 1-2 weeks.
- Transient Grade 3 anemia and thrombocytopenia were observed in 1 patient.
- No dose reduction or discontinuation due to AE.

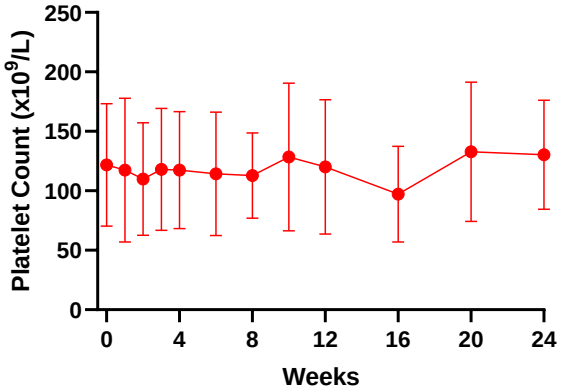
*G3 Bilirubin and G3 Anemia from a patient with baseline G2 bilirubin and transfusion-dependent.

TEAE (≥2 patients) n = 9	Grade 1/2	Grade 3
Non-hematological		
Diarrhea	7 (78%)	0
Nausea	5 (56%)	0
Vomiting	4 (44%)	1 (11%)
Abdominal distension	2 (22%)	0
Abdominal pain	1 (11%)	1 (11%)
UTI	2 (22%)	0
Bilirubin Increased	1 (11%)	1 (11%)*
Muscle spasms	2 (22%)	0
Insomnia	2 (22%)	0
Fatigue	2 (22%)	0
Dyspnea	2 (22%)	0
Hematological		
Platelet count decreased	2 (22%)	1 (11%)
Anemia	1 (11%)	1 (11%)*
Leukocytosis	1 (11%)	1 (11%)

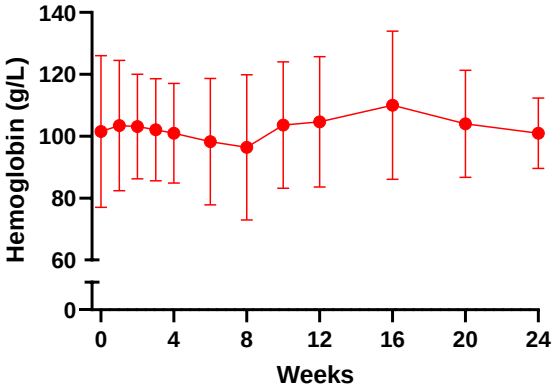
Preliminary data as of 11-OCT-2022

TP-3654: Stable Lab Values in the Dose Escalation with No Worsening of Blood Counts

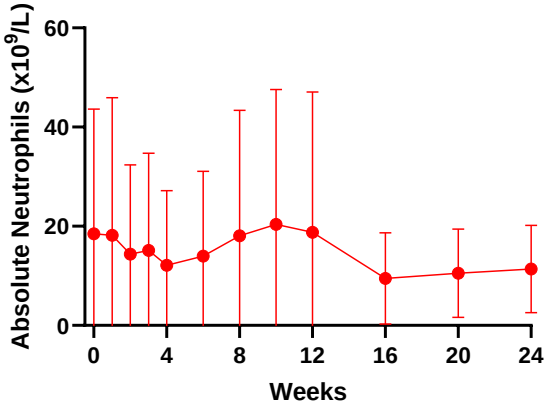
Platelet Count During Treatment*



Hemoglobin During Treatment*



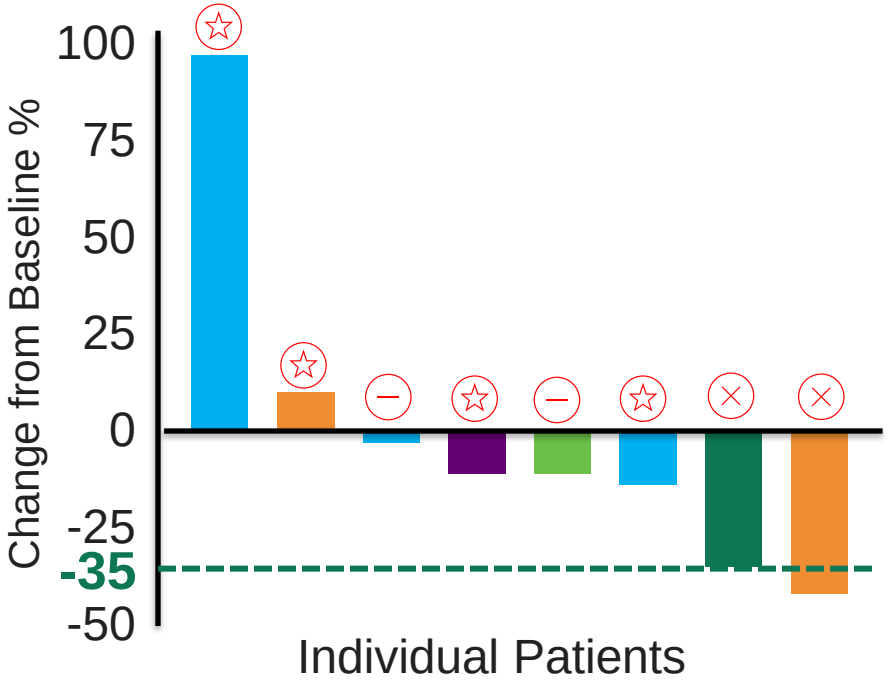
Neutrophil During Treatment*



*N=9; Mean ± SD

Preliminary data as of 11-OCT-2022

TP-3654: Best Spleen Volume Response in Dose Escalation



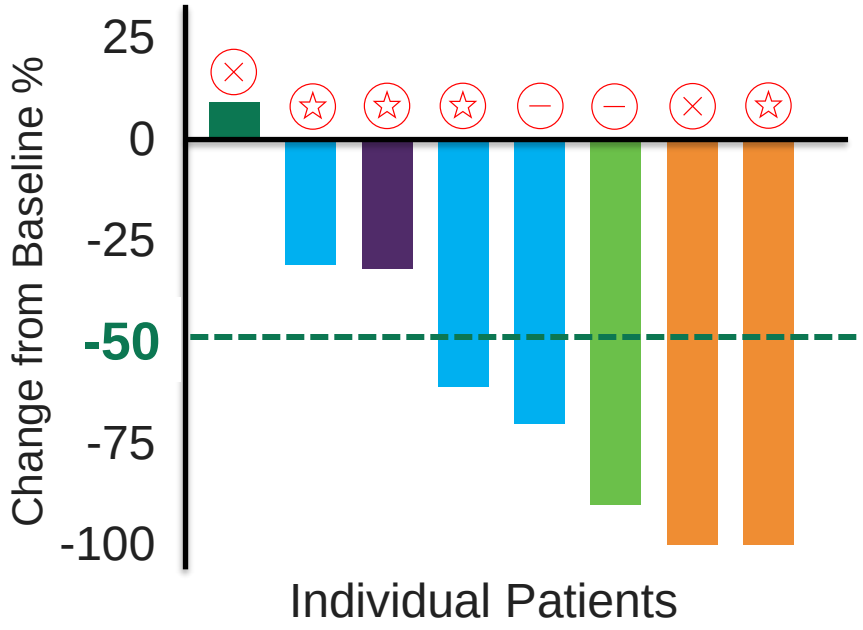
- 8 evaluable patients on treatment ≥ 12 weeks
- Baseline spleen volume median 2535 cm^3 (1189 to 4407)
- 6 of 8 have SVR
  - Median -11%
  - 5 of 8 patients have ≥ 10% SVR
  - 2 of 8 patients have ≥ 35% SVR

Dose 480mg QD | 720mg QD | 360mg BID | 480mg BID | 720mg BID

Response to JAK Inhibitor: ⊗ = Primary Refractory | ☆ = Loss of Response | — = Intolerant

Preliminary data as of 11-OCT-2022

TP-3654: Best Symptoms Response in Dose Escalation



- MF-SAF v4.0 (Max TSS 70): Baseline symptom burden median 21 (4 to 62)
- 8 evaluable patients on treatment ≥ 12 weeks
- 7 of 8 have TSS reduction
  - Median -66%
  - 5 of 8 patients have ≥ 50% TSS reduction

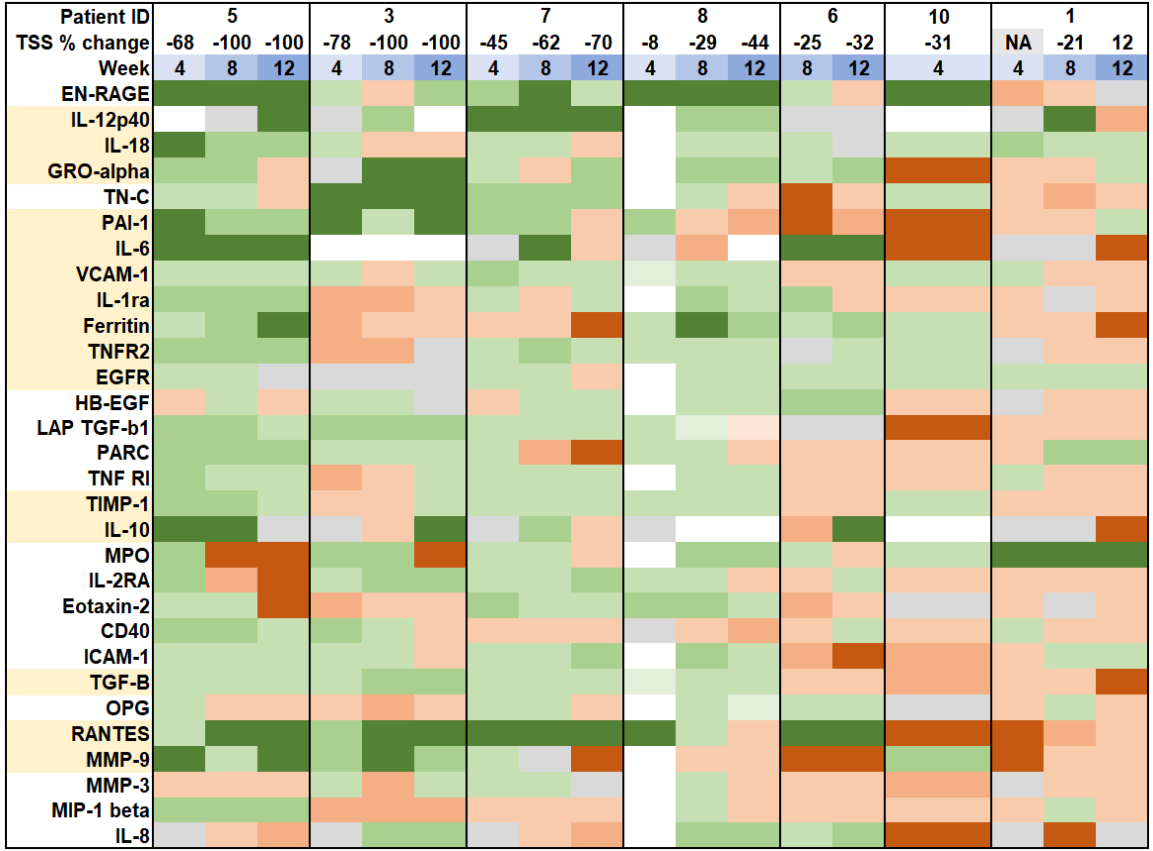
Dose 480mg QD | 720mg QD | 360mg BID | 480mg BID | 720mg BID

Response to JAK Inhibitor: ⊗ = Primary Refractory ☆ = Loss of Response — = Intolerant

Preliminary data as of 11-OCT-2022

TP-3654: PIM1 Inhibition Leads to Early Reduction in Cytokines

- Cytokine reduction observed as early as Week 4 from initial dose cohorts
- Cytokine reduction generally correlate with TSS reduction
- Cytokines associated with MF (IL-6, IL-10, IL-12, IL-18, TGF-b, EGFR, Ferritin, GRO-a, IL-1RA, MMP-9, PAI-1, RANTES, TIMP-1, TNFR-2, VCAM-1) show reduction after treatment



Cytokine change relative to baseline

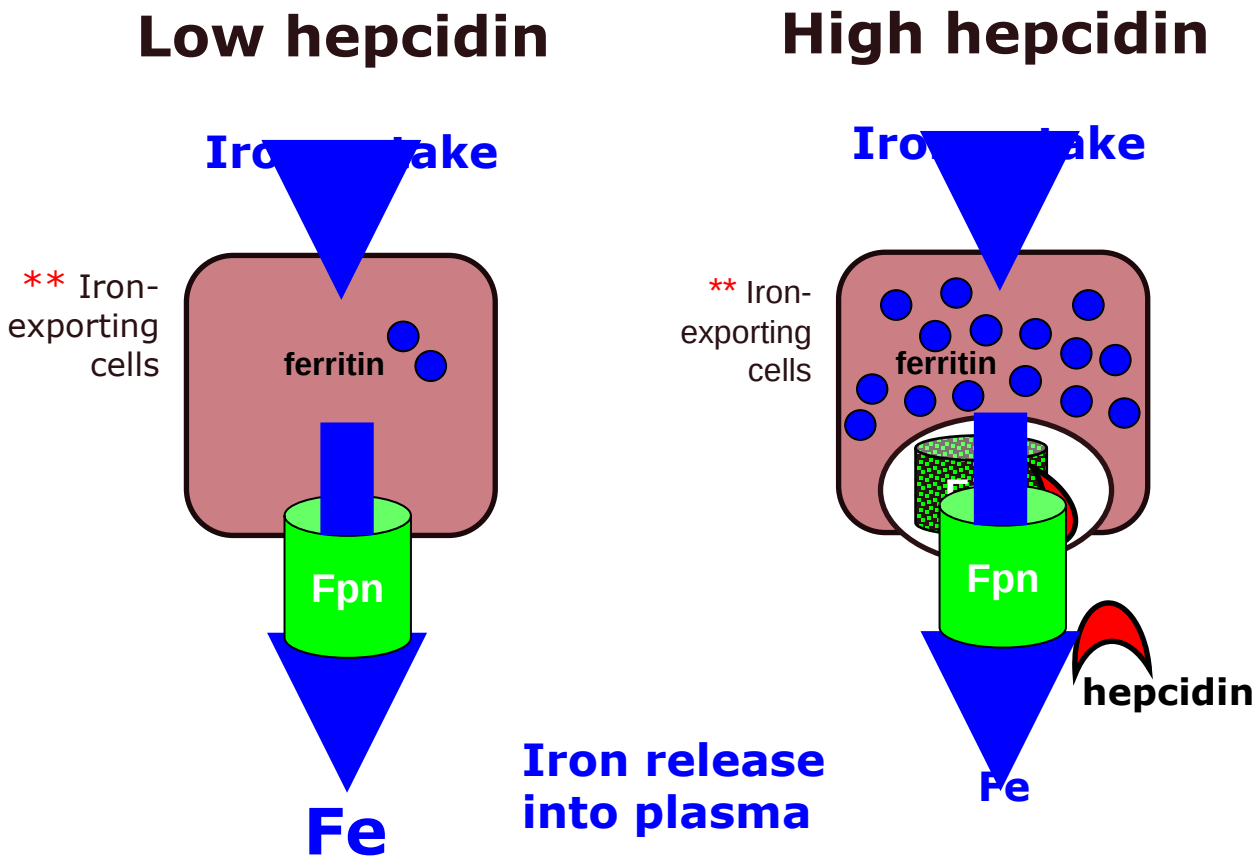
Reduction	> 0 - 25%	>25 - 50%	> 50%
Increase	> 0 - 25%	>25 - 50%	> 50%
No change			

Preliminary data as of 11-OCT-2022

Agenda

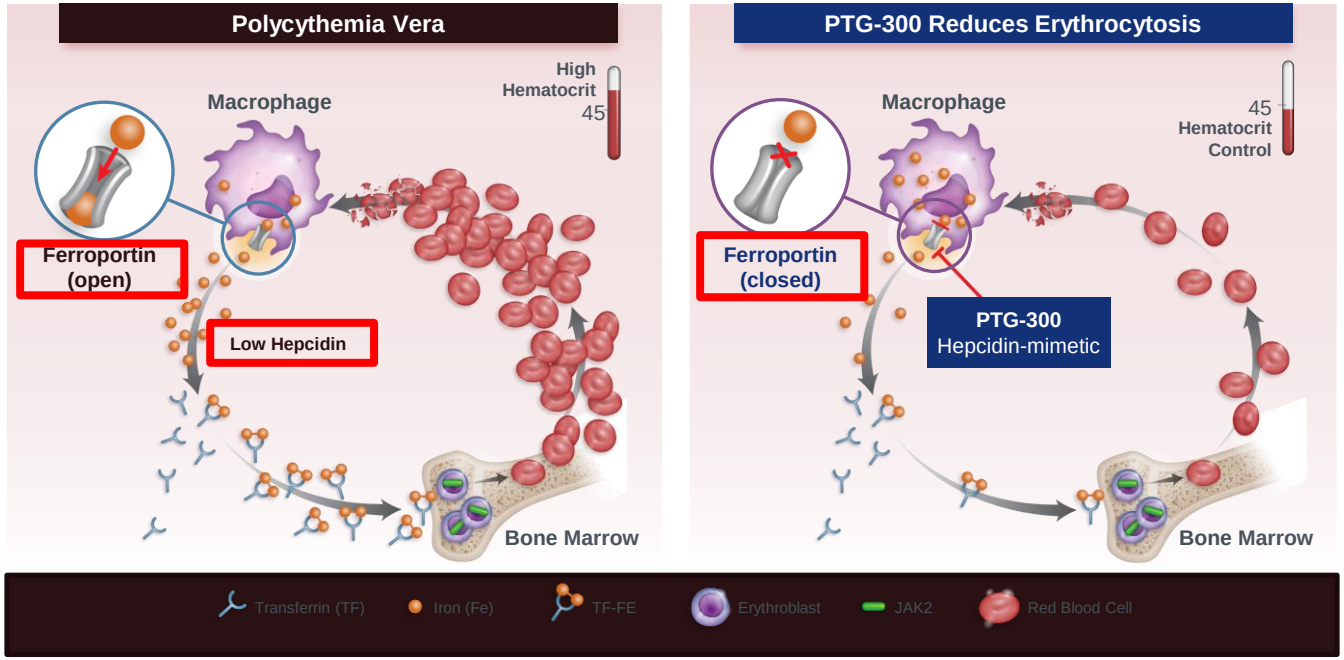
- Monotherapies for MF*
  - Phase 3: Navtemadlin, Imetelstat
  - Early phase: PIM kinase inhibitor
- Targeting hepcidin in PV
- Don’t forget about ET: vaccinations against CALR

*Dr Pemmaraju will cover combinations in a later talk



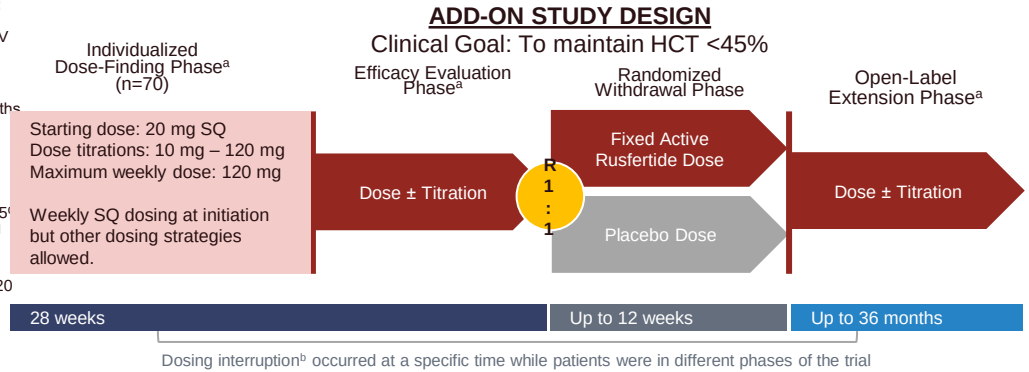
** e.g. duodenal enterocytes, macrophages, hepatocytes

PTG-300 (Hepcidin-mimetic) Mechanism of Action in PV



REVIVE Study Design

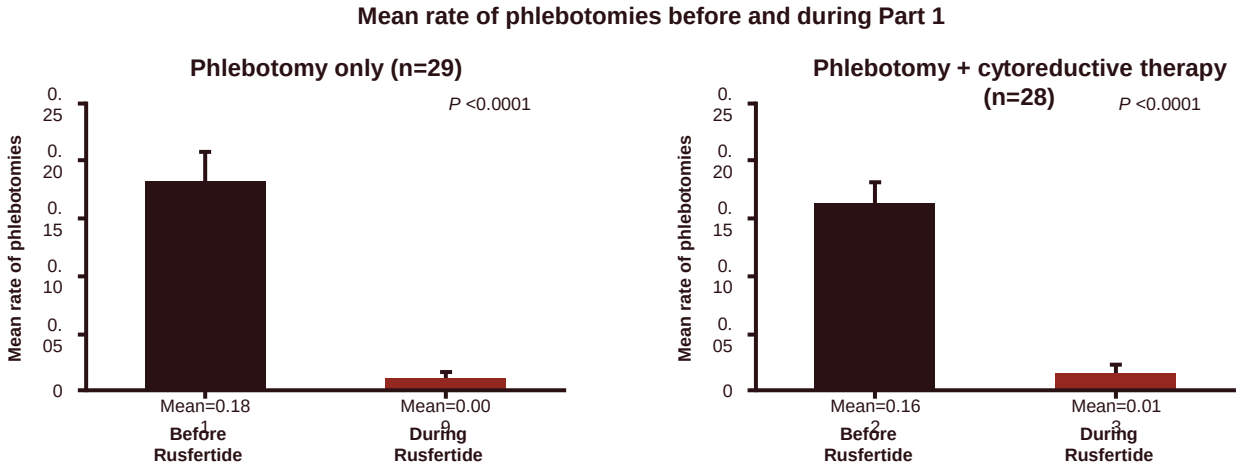
- *First patient enrolled in October 2019, and last patient enrolled March 2022*
- **ELIGIBILITY REQUIREMENTS:**
  - Phlebotomy-dependent PV patients diagnosed per 2016 WHO criteria
  - ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
  - All patients prior to first rusfertide dose were phlebotomized to HCT <45% to standardize the starting HCT
  - Rusfertide doses of 10–120 mg administered subcutaneously added to prior standard therapy



Primary Endpoint: Proportion of patients achieving a response[c] during randomized withdrawal period

Rusfertide Significantly Decreased Phlebotomy Requirements in Patients Treated With Phlebotomy Only or Cytoreductive Therapy Plus Phlebotomy

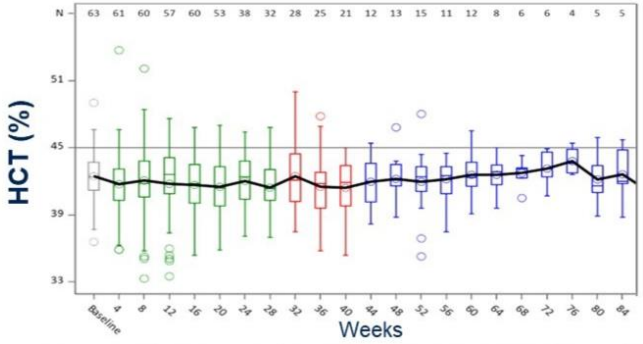
- Mean number of phlebotomies in 28 weeks before treatment with rusfertide: 4.81 (range 2–10)
- Mean number of phlebotomies after starting rusfertide: 0.3 (range 0–2)



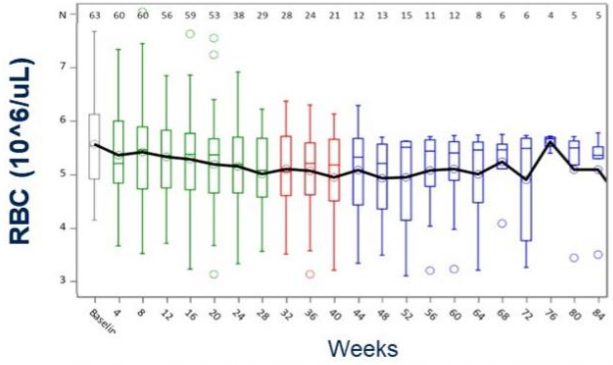
N. Pemmaraju et al SOHO 2022

Effect of Rusfertide on HCT, RBC, WBC, Platelet Counts

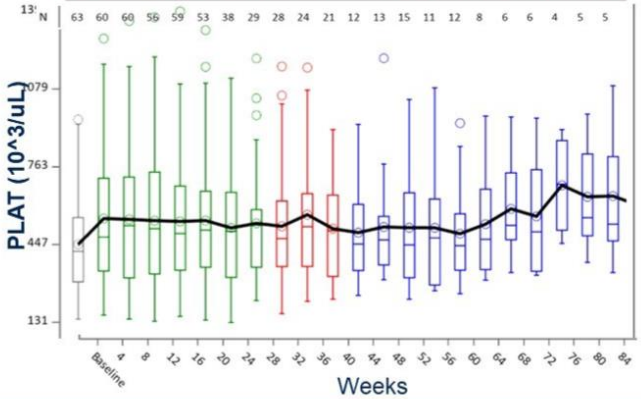
RUSFERTIDE CONTROLS HCT



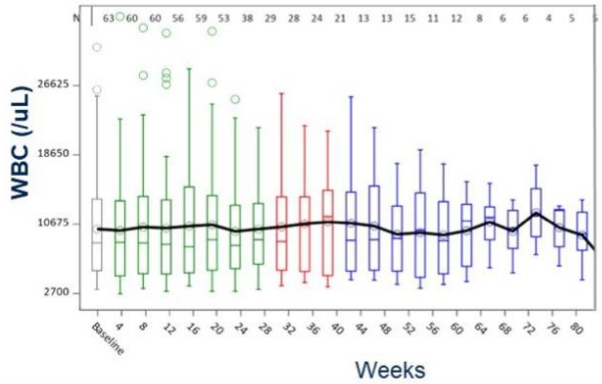
RUSFERTIDE REDUCES RBC COUNT



NO CLINICALLY SIGNIFICANT CHANGES IN PLATELETS



NO CLINICALLY SIGNIFICANT CHANGES IN WBC



Screening

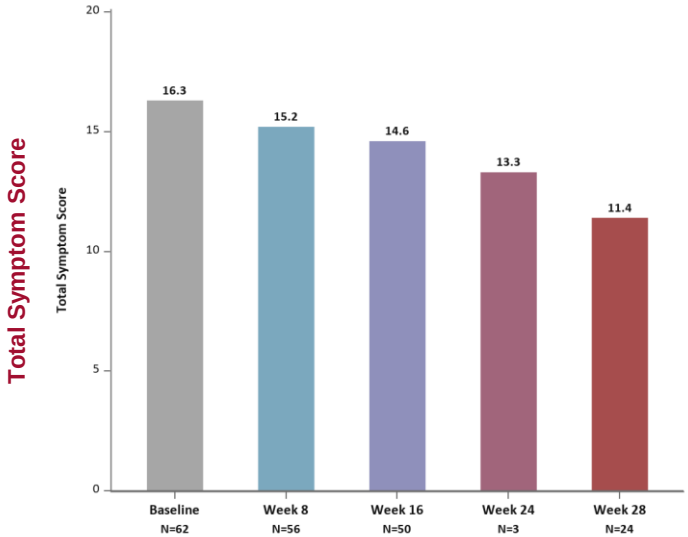
Part 1 – Dose Finding

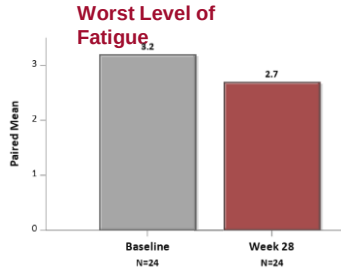
Part 2/3 – Blinded Withdrawal/OLE

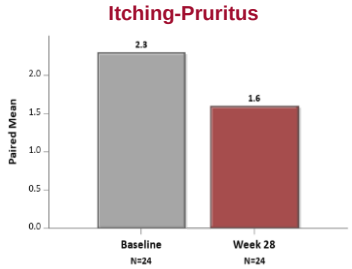
Part 3 – Open Label Extension

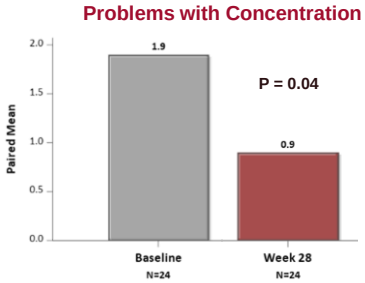
Data cut off Sept 30, 2021

Improvement in MPN-TSS Scores Following Rusfertide Treatment









Hoffman R et al *ASH meeting abstract* 2021

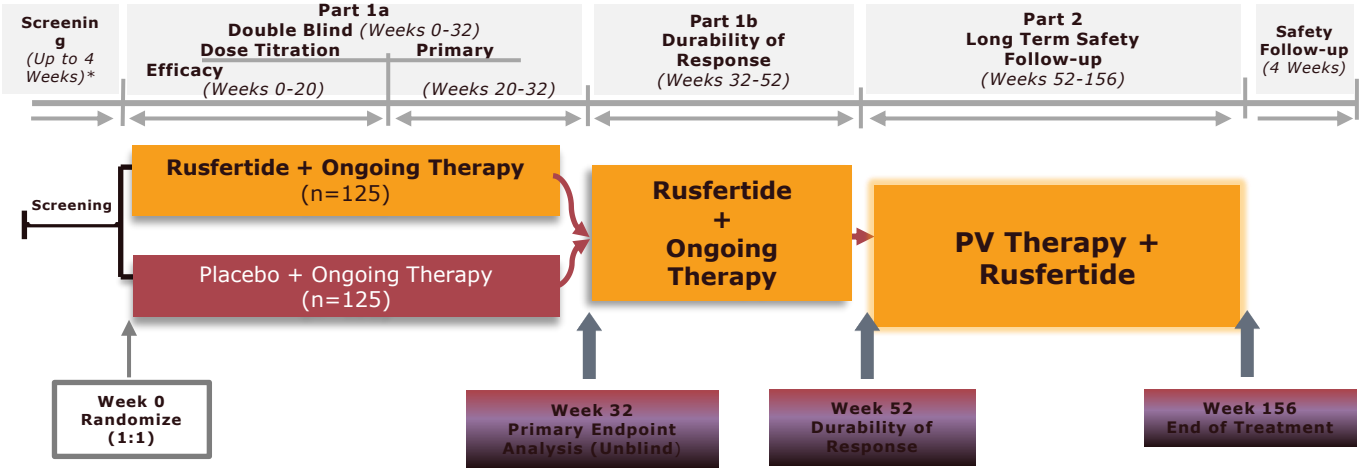
Safety: Rusfertide (PTG-300)

- ***Most treatment-emergent adverse events (TEAEs) were grade 1- 2***
  - *Injection site reaction (ISRs) were the most common AE and occurred in 85.6% of patients. All ISRs were transient, and no patient discontinued due to an ISR*
- ***No grade 3 events related to rusfertide***
- ***No grade 4 or 5 TEAEs***
- ***2 withdrawals due to TEAEs***
  - *1 popliteal aneurysm, 1 pulmonary embolism identified on study*
- ***Secondary malignancies***
  - *5 patients (5.5%) had secondary malignancies (6 skin cancers, 1 AML) in all rusfertide-treated patients in phase 2 trials (N=90)*
  - *All skin cancers were in situ or stage 1*
  - *All newly developed cancers were in patients with previous rux and/or HU. The patient with AML had also experienced radioactive iodine exposure*

Any-grade TEAE in ≥10% (preferred term)	n (%)
Total number of patients	**70**
Injection site reaction	77 (85.6)
Fatigue	20 (28.6)
Headache	17 (24.3)
Pruritus	17 (24.3)
Arthralgia	16 (22.9)
Dizziness	15 (21.4)
Nausea	15 (21.4)
Anemia	12 (17.1)
COVID-19	9 (12.9)
Dyspnea	9 (12.9)
Hyperhidrosis	9 (12.9)
Diarrhea	8 (11.4)
Insomnia	8 (11.4)
Myalgia	8 (11.4)
Pain in extremity	7 (10.0)
Paresthesia	7 (10.0)

VERIFY Trial: Randomized, Double-blind, Placebo-Controlled Phase 3 Study Design in PV patients

N~250 subjects



* Phlebotomy history for up to 52 weeks

Currently enrolling patients

Additional Hepcidin-mimetic Agents Currently in Trials for PV Patients

A Phase 2a, Randomized, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ISIS 702843 Administered to Patients with Phlebotomy Dependent Polycythemia Vera (PD-PV)

Liver-targeted ASO against TMPRSS6, sapablursen (NCT05143957), SQ monthly

Tmprss6-ASO as a tool for the treatment of Polycythemia Vera mice

Carla Casu[1]*, Alison Liu[1], Gianluca De Rosa[1], Audrey Low[2], Aae Suzuki[3], Sayantani Sinha[1], Yelena Z. Ginzburg[4], Charles Abrams[3], Mariam Aghajan[2], Shuling Guo[2], Stefano Rivella[1,3,5,6,7]

PLOS ONE | https://doi.org/10.1371/journal.pone.0251995 December 10, 2021

SLN124, a GalNAc-siRNA Conjugate Targeting TMPRSS6, Efficiently Prevents Iron Overload in Hereditary Haemochromatosis Type 1

Sandro Altamura[1,2], Ute Schaeper[3], Sibylle Dames[3], Kathrin Löffler[3], Mona Eisermann[3], Christian Frauendorf[3], Katja Müdder[1,2], Joana Neves[1], Martina U. Muckenthaler[1,2]

HemaSphere (2019) 3:6 www.hemaspherejournal.com

Liver-targeted double-stranded siRNA against TMPRSS6, SQ every 6 weeks

SLN124-004

Phase 1/2 study with an open-label dose escalation phase followed by a randomized, double-blind phase of SLN124 in patients with Polycythemia Vera.

Agenda

- Monotherapies for MF*
  - Phase 3: Navtemadlin, Imetelstat
  - Early phase: Selinexor, PIM kinase inhibitor
- Targeting hepcidin in PV
- Don’t forget about ET: vaccinations against CALR

*Dr Pemmaraju will cover combinations in a later talk

Mount Sinai

Peptide Based Vaccine in Patients with Myeloproliferative Neoplasm Harboring CALR Mutations

Marina Kremyanskaya MD PhD

Ronald Hoffman MD
Michal Bar Nathan MD
John Mascarenhas MD

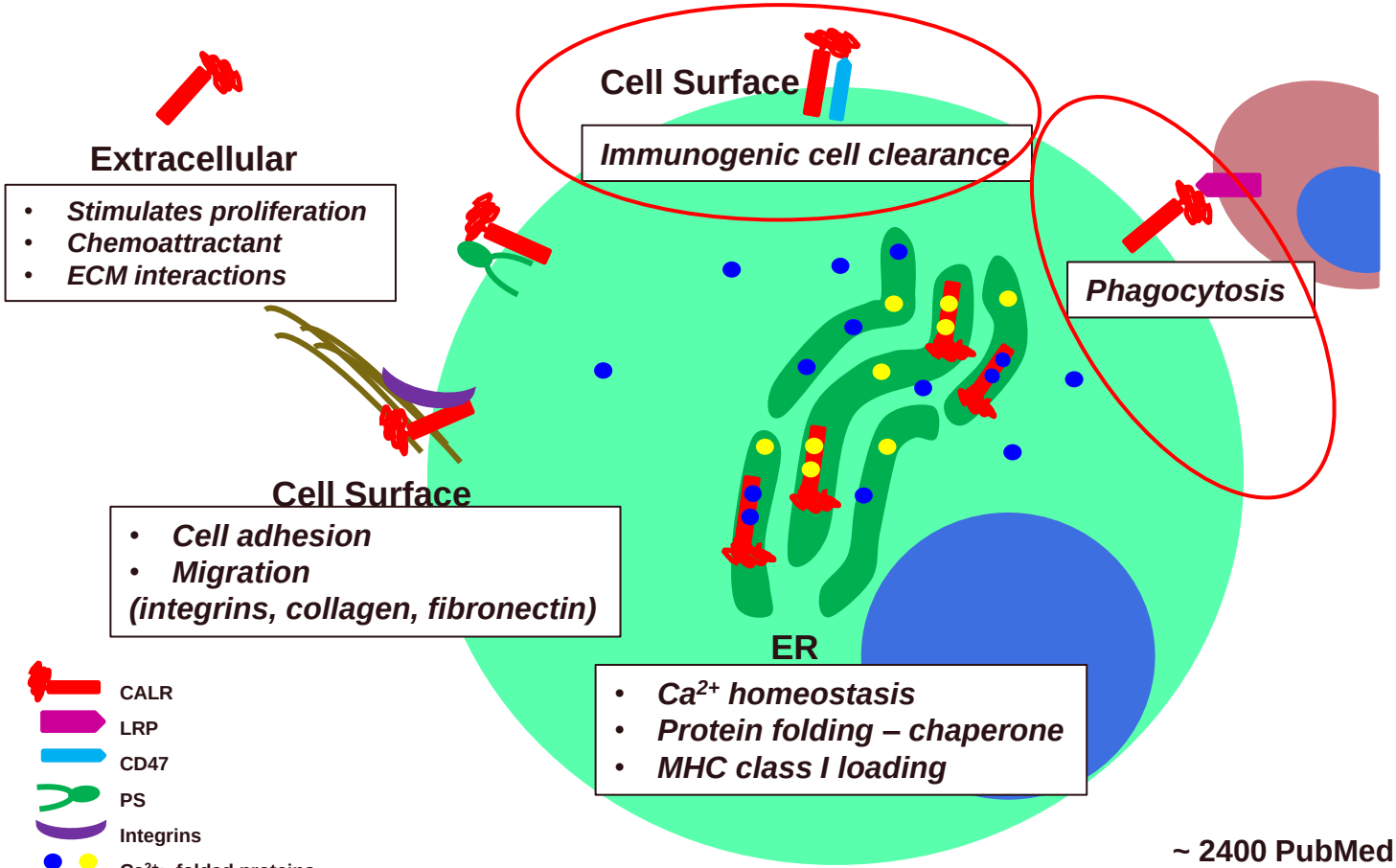
Nina Bhardwaj MD PhD
Cansu Cimen Bozkus PhD
Camelia Iancu-Rubin PhD

MPN RESEARCH FOUNDATION
CHANGE YOUR PROGNOSIS

PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

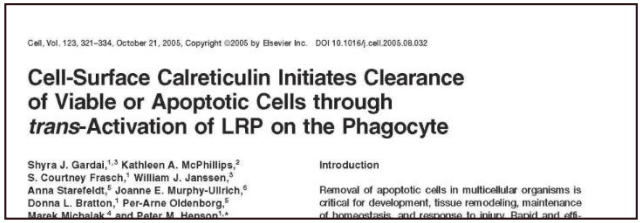
LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

CALR is a highly conserved, ubiquitous and MULTIFUNCTIONAL protein



~ 2400 PubMed publications

Exposure of CALR on the cell surface triggers clearance of apoptotic cells and induces immunogenic cancer cell death



Cell, Vol. 123, 321–334, October 21, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2005.08.032

Cell-Surface Calreticulin Initiates Clearance of Viable or Apoptotic Cells through *trans*-Activation of LRP on the Phagocyte

Shyra J. Gardai,[1,3] Kathleen A. McPhillips,[2] S. Courtney Frasch,[1] William J. Janssen,[3] Anna Starefeldt,[2] Joanne E. Murphy-Ullrich,[2] Donna L. Bratton,[1] Per-Arne Oldenborg,[4] Marek Michalak,[4] and Peter M. Henson[1,*]

Introduction

Removal of apoptotic cells in multicellular organisms is critical for development, tissue remodeling, maintenance of homeostasis, and response to injury. Rapid and effi-

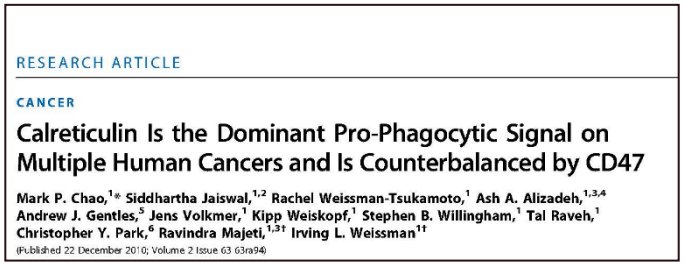
nature.com/naturemedicine

Calreticulin exposure dictates the immunogenicity of cancer cell death

Michel Obeid[1–3], Antoine Tesniere[1–3], François Ghiringhelli[2–4], Gian Maria Fimia[5], Lionel Apetoh[2–4], Jean-Luc Perfettini[1–3], Maria Castedo[1–3], Grégoire Mignot[2–4], Theoharis Panaretakis[1–3], Noelia Casares[1–3], Didier Métivier[1–3], Nathanael Larochette[1–3], Peter van Endert[6,7], Fabiola Ciccosanti[5], Mauro Piacentini[5,8], Laurence Zitvogel[2–4,9] & Guido Kroemer[1–3,9]

[1]INSERM U848, [2]Institut Gustave Roussy, [3]Faculté Paris Sud-Université Paris 11, and [4]INSERM U805, 39 Rue Camille-Desmoulins, F-94805 Villejuif, France. [5]National Institute for Infectious Diseases Lazzaro Spallanzani, Via Portuense 292, I-00149 Rome, Italy. [6]INSERM U580, Hopital Necker, and [7]Université Paris Descartes, 161 Rue de Sevres, Paris F-75015, France. [8]Department of Biology, University of Rome Tor Vergata, Via della Ricerca Scientifica, I-00173 Rome, Italy. [9]These authors contributed equally to this work.

Received 27 July; accepted 20 November; published online 24 December 2006; doi:10.1038/nm1523



RESEARCH ARTICLE

CANCER

Calreticulin Is the Dominant Pro-Phagocytic Signal on Multiple Human Cancers and Is Counterbalanced by CD47

Mark P. Chao,[1]* Siddhartha Jaiswal,[1,2] Rachel Weissman-Tsukamoto,[1] Ash A. Alizadeh,[1,3,4] Andrew J. Gentles,[5] Jens Volkmer,[1] Kipp Weiskopf,[1] Stephen B. Willingham,[1] Tal Raveh,[1] Christopher Y. Park,[6] Ravindra Majeti,[1,3†] Irving L. Weissman[1†]

(Published 22 December 2010; Volume 2 Issue 63 63ra94)

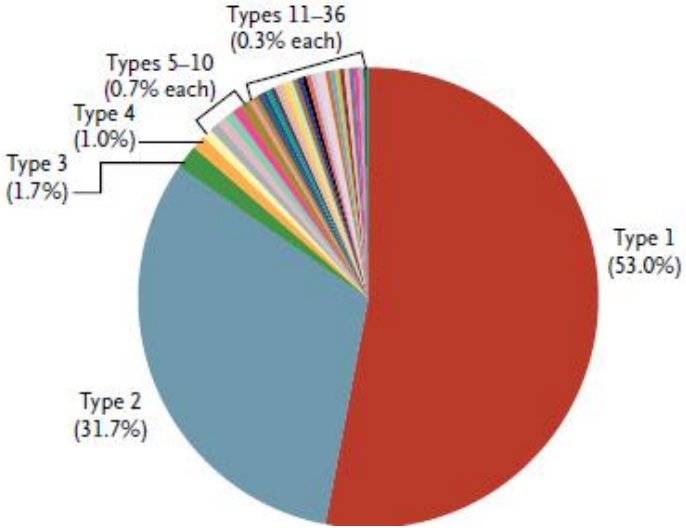
Citation: Cell Death and Disease (2010) 1, e104; doi:10.1038/cddis.2010.82

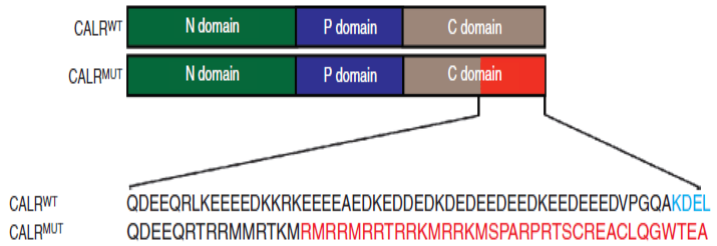
www.nature.com/cddis

Calreticulin exposure on malignant blasts predicts a cellular anticancer immune response in patients with acute myeloid leukemia

M Wemeau[1,2,3,4], O Kepp[2,4,5], A Tesnière[2,4,5], T Panaretakis[2,4,5,6], C Flament[1,2,3], S De Botton[2,7], L Zitvogel[1,2,3,4], G Kroemer*[,2,5,8,9,10,11] and N Chaput*[,1,2,3,12]

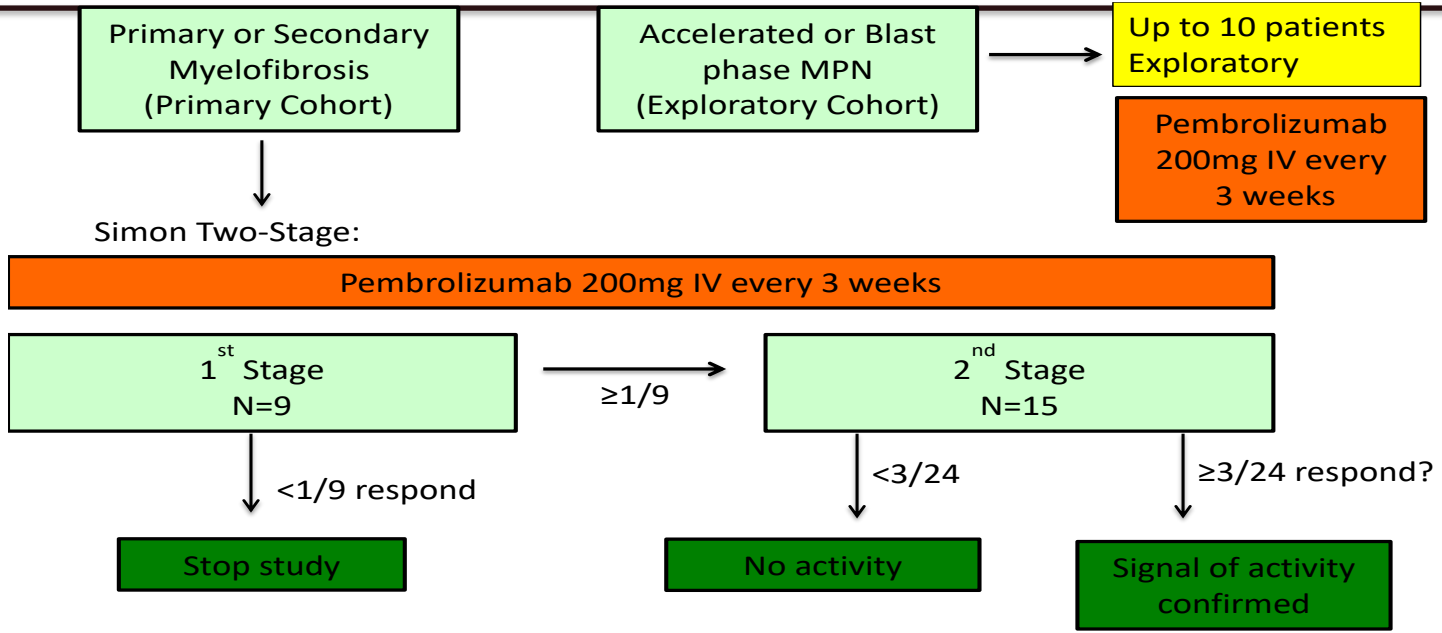
Mutations in CALR generates a novel C-terminal peptide.





CALR mutations in MPN are heterogeneous but regardless of the mutation type they result in an unique epitope shared among all patients with mutated CALR-identical 36-AA sequence in the C-terminus of the protein

PD-1 inhibition in advanced MPN (NCT03065400)
Study drug: Pembrolizumab (Keytruda)™



	Baseline (at screening)	Start of Cycle 3	End of Cycle 6	End of Cycle 12
Blood	✓	✓	✓	✓
Bone marrow	✓	x	✓	✓

Hobbs et al Blood Advances 2021

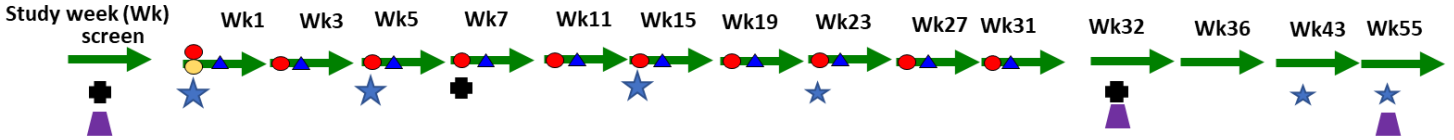
Vaccination: boosting antitumor T cell responses

- Mutant-CALR Vaccine
- KLH
- Poly-ICLC Vaccine
- Correlative study blood draw (no more than 90mL)
- Correlative study blood draw (200mL)
- Bone marrow biopsy

-Ten doses of Mutant-CalR peptides with poly-ICLC and KLH as helper peptide
-administered Q2 weeks for the first 4 doses and then Q4 weeks for 6 doses

Mount Sinai

Pt that don't go on maintenance



Pt that go on maintenance

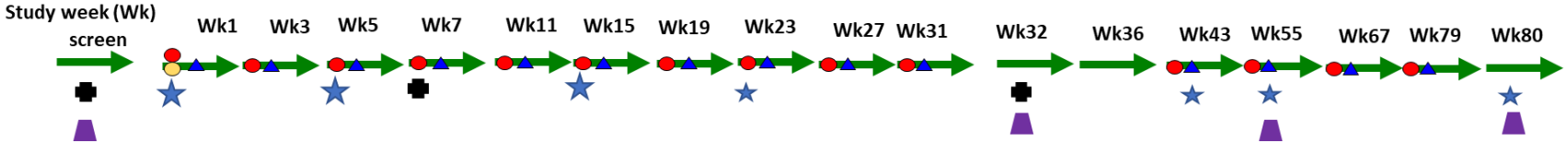
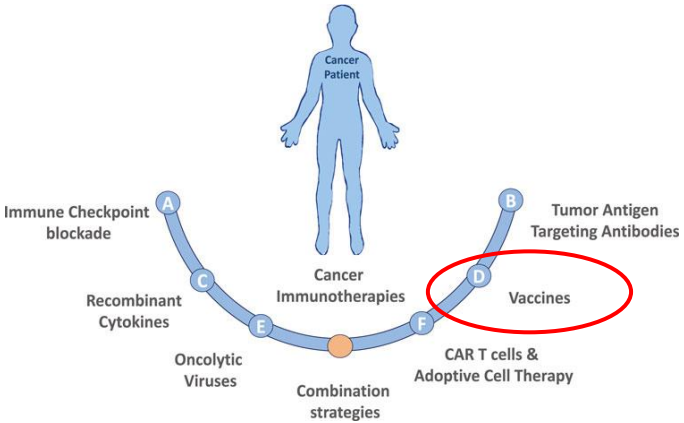


Figure by Dr. Mansi Saxe

Vaccination: boosting antitumor T cell responses



frontiers in Oncology

ORIGINAL RESEARCH
published: 26 February 2021
doi: 10.3389/fonc.2021.63742

Therapeutic Cancer Vaccination With a Peptide Derived From the Calreticulin Exon 9 Mutations Induces Strong Cellular Immune Responses in Patients With *CALR*-Mutant Chronic Myeloproliferative Neoplasms

OPEN ACCESS

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Specialty section:
This article was submitted to Hematologic Malignancies, a section of the journal Frontiers in Oncology

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200 ug 36aa C-terminal, s.c., with montanide.

15 doses total: 1st 6 doses every 2 weeks, remaining 9 doses every 4 weeks.

No clinical responses were observed

Inventions and discoveries (in comparison to Denmark vaccination trial)

- Vaccine formulation: overlapping peptides (instead of a single 36 aa peptide)
  - The use of overlapping peptides is expected to increase the efficiency of antigen presentation, yielding a greater amount of immunogenic epitopes, thereby improving the anti-tumor T cell immunity the vaccine will elicit.
- Target sequence: 44 aa (instead of 36 aa)
  - Targeting the 44 aa of mutated protein, instead of 36 aa, is likely to increase the breath of T cell responses elicited after immunization by providing additional neoepitopes.
- Poly-ICLC and KLH (instead of montanide)
  - Poly-ICLC and KLH are reported to have immune-enhancing properties.

Summary

- Exciting monotherapy and combination therapy approaches are ongoing in MPNs
- Trials are built on laboratory data that supports a rational mechanism
- Trials sample blood and bone marrow from treated patients to prove the drug is on-target and killing MPN cells
- Approaches to limit MPN stem cells from expanding and encouraging them to commit suicide are promising in MF
- Choking the bone marrow supply of iron with a hepcidin mimetic can remove the need for phlebotomy in PV
- Turning on p53 to kill PV stem cells needs to be perfected so it can be tolerated better
- Redirecting the immune system to naturally get rid of CALR mutated cells in ET and early PMF
- Clinical trials today bring wide access to better drugs tomorrow

THANK YOU

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