New Drugs for MPNs
(what to look for)

John Mascarenhas, MD
Myeloproliferative Disorders Program
Tisch Cancer Institute, Division of Hematology/Oncology
Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, New York
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?

<table>
<thead>
<tr>
<th>Mechanism based agents</th>
<th>We understand what the drug targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical data</td>
<td>Laboratory evidence of activity in mice and human samples</td>
</tr>
<tr>
<td>Biomarker evidence of on-target effect</td>
<td>Blood and bone marrow samples from treated patients confirm it hits the intended target</td>
</tr>
<tr>
<td>Disease burden modification</td>
<td>The driver mutation level decreases</td>
</tr>
</tbody>
</table>
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
Nutlins Block the MDM2:P53 interaction and activate the P53 pathway

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

Pankit Vachhani¹; Andrzej Lange²; Regina Garcia Delgado³; Haifa K. Al-Ali⁴; Jesus M. Hernandez-Rivas⁵; Jean-Jacques Kiladjian⁶; Alessandro Vannucchi⁷; Andrew C. Perkins⁸; Venu Valmeekam⁹; Cecile M. Krejsa⁹; Anne Uyei⁹; Jesse McGreivy⁹; Wayne P. Rothbaum⁹; John Mascarenhas¹⁰; Srdan Verstovsek¹¹

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

Distribution of Driver and HMR Mutations at Baseline

<table>
<thead>
<tr>
<th>Gene</th>
<th>240 mg D1-7/28 n=31</th>
<th>240 mg D1-7/21 n=20</th>
<th>120 mg D1-7/21 n=29</th>
<th>240 mg D1-5/28 n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASXL1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZH2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRSF2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U2AF1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Best Decrease in Mutation Burden on Navtemadlin Treatment

<table>
<thead>
<tr>
<th>Gene</th>
<th>240 mg D1-7/28 n=27</th>
<th>240 mg D1-7/21 n=9</th>
<th>120 mg D1-7/21 n=19</th>
<th>240 mg D1-5/28 n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASXL1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZH2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRSF2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U2AF1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- <10% VAF Reduction
- ≥10% VAF Reduction
- ≥20% VAF Reduction
- Complete Reduction (<limit of detection of 3.4%)
Correlation Between Changes in Driver Mutations and Responses

**Correlation Between Driver Gene VAF Reduction and SVR**

- Best SVR

- Best Change in VAF, %

\[ R = 0.45 \]
\[ P = 0.0003 \]
\[ n = 61 \]

**Driver Gene VAF Reduction Among Responders**

- SVR ≥35%
- SVR ≥25%–<35%
- SVR <25%

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

Data cut-off: 19 Apr 2021.

Median Change in CD34+ Cells from C1D1, %

<table>
<thead>
<tr>
<th>Week 12</th>
<th>240 mg D1-7/28</th>
<th>240 mg D1-7/21</th>
<th>120 mg D1-7/21</th>
<th>240 mg D1-5/28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-88 (-93, -40)</td>
<td>-70 (-94, -63)</td>
<td>-59 (-83, -6)</td>
<td>-50 (-64, -27)</td>
</tr>
<tr>
<td></td>
<td>20 pts</td>
<td>8 pts</td>
<td>15 pts</td>
<td>14 pts</td>
</tr>
<tr>
<td>Week 24</td>
<td>-89 (-95, -63)</td>
<td>-66 (-89, -64)</td>
<td>-68 (-94, -24)</td>
<td>-58 (-71, -17)</td>
</tr>
<tr>
<td></td>
<td>15 pts</td>
<td>5 pts</td>
<td>11 pts</td>
<td>11 pts</td>
</tr>
</tbody>
</table>

Correlation Between Change in CD34+ Cells and SVR

\[ R=0.35 \]
\[ P=0.0068 \]
\[ n=57 \]

Best Change in Blood CD34+ Cells, %

Best SVR, %
Bone Marrow Fibrosis Improvement and Association With Response

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).

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

Reticulin Staining

Screening Grade 2

Week 24 Grade 1
BOREAS Phase 3 Study Design (NCT03662126)

Patients with $TP53^{WT}$ primary or secondary MF who are R/R to JAKi treatment

2:1 randomization (N=282)

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

**Patient Stratification:**
- MF type (primary vs secondary)
- Baseline TSS ($\leq$10 vs >10)

**Arm 1:**
KRT-232 240mg
7D ON 21D OFF 28-day cycles
(n=188)

**Arm 2:**
Best Available Therapy$^a$
in 28-day cycles
(n=94)

---

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 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-phosphoramide 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


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

### Primary Endpoint: Overall Response by IWG-MRT

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

- 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.

**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

---

**Randomize (1:1)**
- Imetelstat 9.4 mg/kg every 3 weeks  
  n=59
- Imetelstat 4.7 mg/kg every 3 weeks  
  n=48

**Co-primary endpoints:**
- Spleen response rate and symptom response rate

**Secondary endpoints:**
- CR, PR and CI, anemia response per 2013 IWG-MRT criteria, duration of responses, and overall survival (OS)

**Exploratory endpoints:**
- Cytogenetic and molecular responses, leukemia free survival

Mascarenhas et al ASH 2020
## Dose Related Clinical Benefits from Treatment with Imetelstat

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

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
# imetelstat Safety Profile

## Manageable and Reversible Cytopenias with Limited Clinical Consequences

<table>
<thead>
<tr>
<th></th>
<th>9.4 mg/kg (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td><strong>Hematologic (≥ 10% in either arm)</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Anemia</td>
<td>26 (44)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21 (36)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>8 (14)</td>
</tr>
<tr>
<td><strong>Non-hematologic (≥ 20% in either arm)</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (31)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (24)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>14 (24)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14 (24)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>11 (19)</td>
</tr>
</tbody>
</table>

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

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:**

<table>
<thead>
<tr>
<th>n(%)</th>
<th>9.4 mg/kg (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 Febrile Neutropenia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Grade ≥ 3 Hemorrhagic events</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Grade ≥ 3 Infections</td>
<td>6 (10)</td>
</tr>
</tbody>
</table>
Improved Bone Marrow Fibrosis Correlated to Improved Survival

Significant Dose-Dependent Fibrosis Improvement with imetelstat Treatment

<table>
<thead>
<tr>
<th>% Achieved BM Fibrosis Improvement</th>
<th>4.7 mg/kg</th>
<th>9.4 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>20%</td>
<td>41%</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- **Median OS (months)**
  - Yes: 31.6 (23.6, NE)
  - No: 24.6 (18.4, NE)

- **HR (95% CI)**
  - Yes: 0.54 (0.23, 1.29)

CENSORED

**Survival Probability**

**BM Fibrosis Improvement**

- **Median OS (months)**
  - Yes: 31.6 (23.6, NE)
  - No: 24.6 (18.4, NE)

**HR (95% CI)**

- Yes: 0.54 (0.23, 1.29)

ClinicalTrials.gov (NCT02426086)

Mascarenhas et al JCO 2021
Strong Evidence of Disease Modification Potential
Reduction in Key MF Driver Mutations Correlated to Improved Survival

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

% achieved ≥20% reduction of VAF

VAF = variant allele frequency

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

Mascarenhas et al JCO 2021
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
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, James Mccloskey MD, Lindsay AM Rein, MD, Randy A Brown MD, Steven D Green MD, Jeffrey J Pu MD PhD, Shuichi Shirane MD PhD, Kazuya Shimoda MD PhD, Michiko Ichii MD PhD, Junichiro Yuda MD PhD, Joseph Scandura MD PhD, Sujan Kabir MD, Jason M Foulks PhD, Jian Mei PharmD, Huyuan Yang PhD, Mark Wade PhD, Carl Stapinski, Claudia Lebedinsky MD, and Raajit K Rampal MD PhD

1University of Virginia Health System, VA; 2The John Theurer Cancer Center at Hackensack Meridian Health, NJ; 3Duke University Medical Center, NC; 4Shands HealthCare &University of Florida, FL; 5Roswell Park Comprehensive Cancer Center, NY; 6University of Arizona Cancer Center, AZ; 7Juntendo University School of Medicine, Tokyo, Japan; 8University of Miyazaki, Miyazaki, Japan; 9Osaka University Graduate School of Medicine, Suita City, Japan; 10National Cancer Center Hospital East, Kashiwa, Japan; 11Richard T. Silver, Weill Cornell Medicine, NY; 12Sumitomo Pharma Oncology, Inc., MA; 13Sumitomo Pharma Oncology, Inc., UT; 14Memorial 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. Used with permission from the Creative Commons License.
PIM1 Kinase: A Novel Target in MF

- PIM1 expression was shown to be significantly increased in MF patients’ bone marrow and PBMC samples⁴
- PIM1 knockout was shown to prevent myelofibrosis progression, but PIM2 knockout has no effect in MF mouse models⁴
- PIM1 knockout was shown not to cause platelet count decrease, while pan-PIM knockout resulted in thrombocytopenia in mice⁵
- Novel therapies which selectively inhibit PIM1 kinase may provide disease-modifying benefits for MF patients while avoiding cytopenia adverse effects

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

- **Spleen Size Reduction**
- **Bone Marrow Fibrosis Reduction**
- **Overall Survival Increase**

- Similar TP-3654 activity was observed in murine JAK2\textsuperscript{V617F} MF model\textsuperscript{4}
TP-3654 Phase I/II Study Design in MF

Key Eligibility
- DIPSS Intermediate- 1, 2, or high-risk
- Platelet count ≥ 25 x 10⁹/L
- ECOG ≤ 2
- Splenomegaly (volume of ≥ 450 cm³)
- 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

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

Bayesian Dose Escalation

MTD/ RP2D

Phase 2 Dose Expansion
## TP-3654: Dose Escalation and Safety

### 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

<table>
<thead>
<tr>
<th>Non-hematological</th>
<th>Grade 1/2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>7 (78%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (56%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (44%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>UTI</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin Increased</td>
<td>1 (11%)</td>
<td>1 (11%)*</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (22%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Hematological

| Platelet count decreased | 2 (22%) | 1 (11%) |
| Anemia                  | 1 (11%) | 1 (11%)*|
| Leukocytosis            | 1 (11%) | 1 (11%) |

---

### Cohort Summary

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number of Patients</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>480mg QD</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>720mg QD</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>360mg BID</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>480mg BID</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>720mg BID</td>
<td>1 / ongoing</td>
<td>None</td>
</tr>
</tbody>
</table>

---

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 cm³ (1189 to 4407)
- 6 of 8 have SVR
  - Median -11%
  - 5 of 8 patients have ≥ 10% SVR
  - 2 of 8 patients have ≥ 35% SVR

Individual Patients

- 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

Individual Patients

Change from Baseline %

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
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

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>TSS % change Week 4</th>
<th>68</th>
<th>100</th>
<th>100</th>
<th>45</th>
<th>62</th>
<th>70</th>
<th>8</th>
<th>29</th>
<th>44</th>
<th>25</th>
<th>32</th>
<th>6</th>
<th>31</th>
<th>10</th>
<th>21</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cytokine change relative to baseline

<table>
<thead>
<tr>
<th>Reduction</th>
<th>&gt; 0 - 25%</th>
<th>&gt; 25 - 50%</th>
<th>&gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>&gt; 0 - 25%</td>
<td>&gt; 25 - 50%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
**Iron-exporting cells**

- **Low hepcidin**
  - Iron uptake
  - Ferritin
  - **Fpn**
  - Fe
  - Iron release into plasma

- **High hepcidin**
  - Iron uptake
  - Ferritin
  - **Fpn**
  - Fe
  - Hepcidin

**e.g. duodenal enterocytes, macrophages, hepatocytes**
PTG-300 (Hepcidin-mimetic) Mechanism of Action in PV

Polycythemia Vera

- Macrophage
- Ferroportin (open)
- Low Hepcidin
- Bone Marrow
- Erythroblast
- JAK2
- Red Blood Cell

PTG-300 Reduces Erythrocytosis

- Macrophage
- Ferroportin (closed)
- Bone Marrow
- PTG-300 Hepcidin-mimetic

Transferrin (TF), Iron (Fe), TF-Fe, Erythroblast
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

**ADD-ON STUDY DESIGN**

Clinical Goal: To maintain HCT <45%

**Dosing interruption** occurred at a specific time while patients were in different phases of the trial.

**Primary Endpoint:** Proportion of patients achieving a response 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)

**Mean rate of phlebotomies before and during Part 1**

**Phlebotomy only (n=29)**

- Before Rusfertide: Mean=0.18
- During Rusfertide: Mean=0.00

**Phlebotomy + cytoreductive therapy (n=28)**

- Before Rusfertide: Mean=0.16
- During Rusfertide: Mean=0.01

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

Data cut off Sept 30, 2021
Improvement in MPN-TSS Scores Following Rusfertide Treatment

Total Symptom Score

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=62</td>
<td>N=56</td>
<td>N=50</td>
<td>N=3</td>
<td>N=24</td>
</tr>
<tr>
<td>Score</td>
<td>16.3</td>
<td>15.2</td>
<td>14.6</td>
<td>13.3</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Worst Level of Fatigue

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20</td>
<td>N=24</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>3.1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Problems with Concentration

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20</td>
<td>N=24</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>1.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Itching-Pruritus

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20</td>
<td>N=24</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>1.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

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

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

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

Tmprss6-ASO as a tool for the treatment of Polycythemia Vera mice
Carla Casu¹, Alison Liu¹, Gianluca De Rosa¹, Audrey Low², Aae Suzuki³, Sayantani Sinha⁴, Yelena Z. Ginzburg⁴, Charles Abrams³, Mariam Aghajanian, Shuling Guo⁵, Stefano Rivella¹,²,³,⁵,⁶,⁷
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 Altamura¹,², Ute Schaefer³, Sibylle Daries³, Kathrin Löffler⁴, Mona Ebermann⁵, Christian Frauenfelder⁵, Katja Müdder¹,², Joana Neves⁶, Martine U. Muckenhuber⁶,²
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
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
CALR is a highly conserved, ubiquitous and **MULTIFUNCTIONAL** protein.

**Extracellular**
- Stimulates proliferation
- Chemoattractant
- ECM interactions

**Cell Surface**
- Cell adhesion
- Migration (integrins, collagen, fibronectin)

**Immunogenic cell clearance**
- Ca\(^{2+}\) homeostasis
- Protein folding – chaperone
- MHC class I loading

**Phagocytosis**

~ 2400 PubMed publications
Exposure of CALR on the cell surface triggers clearance of apoptotic cells and induces immunogenic cancer cell death.
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)™

Simon Two-Stage:
- Primary or Secondary Myelofibrosis (Primary Cohort)
- Accelerated or Blast phase MPN (Exploratory Cohort)

Pembrolizumab 200mg IV every 3 weeks

1st Stage
N=9
≥1/9 respond
<1/9 respond
Stop study

2nd Stage
N=15
<3/24
≥3/24 respond?
No activity
Signal of activity confirmed

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

- 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

Pt that don’t go on maintenance

Pt that go on maintenance
Vaccination: boosting antitumor T cell responses

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
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 breadth 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.
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

John.Mascarenhas@mssm.edu

I'm located here