A look into the Future: innovative approaches in MPN (why I believe there is hope)

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What do MPN patients want?

• Highly effective therapy
• Low toxicity
• “Disease course modifying”
• Convenient administration
• Cure
What do MPN clinical Investigators want?

• Highly effective therapy
• Low toxicity
• “Disease course modifying”
• Convenient administration
• Cure
• Mechanism based therapy with preclinical rationale and biomarker evidence of on target effect and remission
Emerging Treatments

- JAK2 inhibitor based combination trials in MF
- Telomerase Inhibition in MF (not covering ET)
- Anti-Fibrotic therapy in MF
- JAK2i + DNMTi combination in MPN-AP/BP
- MDM2 antagonist therapy in PV
Ruxolitinib based combination therapy: Setting a higher standard for success?

- Greater spleen reduction
- Greater symptom improvement
- Improvement in disease related cytopenias
- Deeper molecular responses
- Bone marrow morphologic responses
- IWG-MRT/ELN response criteria
## Double and triple combination therapy trials in chronic and advanced phases of myelofibrosis

<table>
<thead>
<tr>
<th>Agent 1 Class</th>
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<th>Agent 2 Class</th>
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<th>Agent 3 Class</th>
<th>Agent 3</th>
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<td>Anti-fibrosing agent</td>
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<td>PIM kinase inhibitor</td>
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Mascarenhas J. Hematology Am Soc Hematol Educ Program. 2015
Efficacy, Safety, and Confirmation of the Recommended Phase 2 Starting Dose of the Combination of Ruxolitinib and Panobinostat in Patients With Myelofibrosis

Claire N. Harrison,1 Jean-Jacques Kiladjian,2 Florian H. Heidel,3 Alessandro M. Vannucchi,4 Francesco Passamonti,5 Amjad Hayat,6 Eibhlin Conneally,7 Bruno Martino,8 Thomas Kindler,9 Daniel B. Lipka,3,10 Suddhasatta Acharyya,11 Prashanth Gopalakrishna,12 Susan Ide,11 Tracy Liu,11 Song Mu,11 Vincent Ribrag13

1Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom; 2Hôpital Saint-Louis et Université Paris Diderot, Paris, France; 3Otto-von-Guericke-University Medical Center, Magdeburg, Germany; 4University of Florence, Florence, Italy; 5Ospedale di Circolo e Fondazione Macchi, Varese, Italy; 6National University of Ireland Galway, Galway, Ireland; 7St James’s Hospital, Dublin, Ireland; 8Divisione di Ematologia, Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria, Italy; 9University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; 10German Cancer Research Center, Heidelberg, Germany; 11Novartis Pharmaceuticals Corporation, East Hanover, NJ; 12Novartis Pharma AG, Basel, Switzerland; 13Institut de Cancérologie Gustave Roussy, Villejuif, France.
**Ba/F3 model:**

**Effects of Ruxolitinib and Panobinostat Treatment on Bioluminescence Imaging on Day 11**

Enhanced efficacy was observed with a combination of RUX and PAN. There was no major change in tolerability, as assessed by body weight, between panobinostat alone or in combination with ruxolitinib.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>RUX 60 mg/kg</th>
<th>PAN 4 mg/kg</th>
<th>PAN 8 mg/kg</th>
<th>PAN 12 mg/kg</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>100%</td>
<td>27% *</td>
<td>20% *</td>
<td>11% *</td>
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<tr>
<td>PAN 4 mg/kg</td>
<td>40% *</td>
<td>22% *</td>
<td>15% *†</td>
<td>3% *† ‡</td>
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<tr>
<td>PAN 8 mg/kg</td>
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<td>PAN 12 mg/kg</td>
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*‡* Enhanced efficacy was observed with a combination of RUX and PAN.  
*†* There was no major change in tolerability, as assessed by body weight, between panobinostat alone or in combination with ruxolitinib.

**P < 0.05 vs vehicle control**  
**† P < 0.05 vs rux**  
**‡ P < 0.05 vs pan at same dose**

Common Hematologic Adverse Events  
\textit{(in ≥ 5\% of Patients)}

<table>
<thead>
<tr>
<th></th>
<th>Escalation Phase</th>
<th>Expansion Phase</th>
<th>Patients Treated at the RP2D</th>
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<tr>
<td></td>
<td>\textit{n = 38}</td>
<td>\textit{n = 23}</td>
<td>\textit{n = 34}</td>
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<tr>
<td>All grade</td>
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<tr>
<td>Grade 3/4</td>
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<tr>
<td>Anemia</td>
<td>24 (63.2)</td>
<td>18 (78.3)</td>
<td>26 (76.5)</td>
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<td>Thrombocytopenia</td>
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<td>Neutropenia</td>
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<tr>
<td>Leukopenia</td>
<td>1 (2.6)</td>
<td>1 (4.3)</td>
<td>2 (5.9)</td>
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</table>

\textsuperscript{a} Includes AEs in ≥ 5\% of patients regardless of relationship to study treatment at any time during or up to 30 days after last dose.
Change in Spleen Length at Week 48 in the Expansion Phase

Only patients with assessments at baseline and at week 24 (20/23) or at week 48 (19/23) are included.

Patients with a ≥ 50% reduction in spleen length were considered responders.
Change in Spleen Volume at Week 48 in the Expansion Phase\textsuperscript{a}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\end{figure}

\textsuperscript{a} Only patients with assessments at baseline and at week 24 (20/23) or at week 48 (18/23) are included.

\textsuperscript{b} Patients with a \( \geq 35\% \) reduction in spleen volume were considered responders.
JAK2 V617F Allele Burden Over Time on Treatment

- Expansion phase; only patients with ≥ 2 on treatment assessments were included (n =17).
Change From Baseline at Week 24 in Bone Marrow Fibrosis Grade, Spleen Volume, and \textit{JAK2} V617F Allele Burden for Individual Patients\textsuperscript{a}

\textsuperscript{a} For patients with data at baseline and week 24 for any of the following: bone marrow fibrosis grade, spleen volume, or allele burden.

\textsuperscript{b} Each column is for an individual patient. A horizontal line represents no change, and a blank represents missing data.
The PI3Kδ/AKT pathway is constitutively upregulated in MF.

Inhibition of AKT (using a specific AKT inhibitor) reduces signaling in MPN cell lines and MF patient samples.

Khan et al, 2013
Inhibition of AKT decreases spleen and liver size in mice expressing MPL mutations.

Khan et al, 2013
A Study of INCB050465 in Combination With Ruxolitinib in Subjects With Myelofibrosis

Part 2 will be enrolled and conducted provided that a tolerable dose can be established for INCB050465 in combination with ruxolitinib in Part 1 of the study.

Patients with Inadequate Responses to Ruxolitinib

Block randomization with stratification for ECOG 0-1 vs 2

Ruxolitinib + INCB050465 @10 mg QD for 8 weeks followed by 10 mg once weekly
N=30

Ruxolitinib + INCB050465 @20 mg QD for 8 weeks followed by 20 mg once weekly
N=30

Response Assessment

NCT02718300
Novel Non-JAK2 inhibitors in clinical trials for patients with myelofibrosis

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<th>Trial phase</th>
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Emerging Treatments

- JAK2 inhibitor based combination trials in MF
- Telomerase Inhibition in MF (not covering ET)
- Anti-Fibrotic therapy in MF
- JAK2i + DNMTi combination in MPN-AP/BP
- MDM2 antagonist therapy in PV
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

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

Primary Endpoint: Overall Response by IWG-MRT

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

Reversal of Bone Marrow Fibrosis in Patient 4.

A Cellularity of >95% at Baseline

B Grade 2 or 3 Fibrosis at Baseline

C Cellularity of 40% after 3 Months of Imetelstat Therapy

D Grade 0 Fibrosis after 3 Months of Imetelstat Therapy
A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects With Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

**Co - Primary Endpoints**
- To evaluate the spleen response rate at Week 24
  - The percentage of participants who achieve ≥ 35% reduction in spleen volume from baseline as measured by MRI
- To evaluate the symptom response rate at Week 24
  - The percentage of subjects who have ≥50% reduction in total symptom score as measured by modified MFSAF v2.0.

**Secondary Endpoints**
- To measure complete remission (CR) or partial remission (PR) per modified 2013 IWG-MRT criteria
- To measure clinical improvement (CI) per modified 2013 IWG-MRT criteria
- PK profile
- Safety profile
- Overall Survival

**Key Eligibility Criteria***
- 18 years of age and older
- Diagnosis of PMF; or PET-MF or PPV-MF
- DIPSS intermediate-2 or high risk MF
- Measurable splenomegaly
- Active symptoms of MF prior to study entry
- Documented progressive disease during or after JAK inhibitor
- ANC ≥ 1,500/ul
- Platelets ≥ 75,000/mm³
- Peripheral blood and bone marrow blast count of <10%

*Not a complete list of inclusion and exclusion criteria
Interim Analysis 9/12/2016

• No new safety signal
• 4.7 mg/kg dosing arm did not meet pre-specified response criteria and is closed
• 9.4 mg/kg did not meet criteria but “encouraging trend” and further enrollment suspended
• Protocol amendment
• Second analysis 2ndQ 2017
Emerging Treatments

• JAK2 inhibitor based combination trials in MF
• Telomerase Inhibition in MF (not covering ET)
  • **Anti-Fibrotic therapy in MF**
• JAK2i + DNMTi combination in MPN-AP/BP
• MDM2 antagonist therapy in PV
PRM-151 in Myelofibrosis: Durable Efficacy and Safety at 72 Weeks

Srdan Verstovsek¹, Olga Pozdnyakova², Robert Hasserjian³, Mohamed Salama⁴, Ruben Mesa⁵, Lynda Foltz⁶, Vikas Gupta⁷, John Mascarenhas⁸, Ellen Ritchie⁹, Ronald Hoffman⁸, Richard Silver⁹, Marina Kremyanskaya⁸, Zeev Estrov¹, Elizabeth Trehu¹⁰, Hagop Kantarjian¹, Jason Gotlib¹¹

¹MD Anderson Cancer Center, Houston, TX, ²Brigham and Women’s Hospital, Boston, MA, ³Massachusetts General Hospital, Boston, MA, ⁴University of Utah, Salt Lake City, UT, ⁵Mayo Clinic, Scottsdale, AZ, ⁶St. Paul’s Hospital, University of British Columbia, BC, CA, ⁷Princess Margaret Hospital, Toronto, ON, CA, ⁸Mt Sinai Medical Center, New York, NY, ⁹Weill Cornell Medical Center, New York, NY, ¹⁰Promedior, Inc., Lexington, MA, ¹¹Stanford Cancer Institute, Stanford, CA
Hypothesis:
Reduction of bone marrow fibrosis will restore hematopoiesis and improve cytopenias

- PTX-2 (فيل) is an endogenous regulator of tissue repair
- PTX-2 binds to damaged tissue (●) and monocytes/macrophages
- PTX-2 prevents and reverses fibrosis in pre-clinical models
- PTX-2 levels are low in MF patients
  - Also low in patients with renal, pulmonary, and liver fibrosis

PTX-2 ( rekombinanta humana pentraxina-2 (PTX-2))
PRM-151G-101 Stage 1 and Extension

27 Patients Enrolled

Monthly PRM-151 10 mg/kg IV
- 1 PD
- 1 lack of benefit
- 24 week treatment period
- Patients with clinical benefit may continue beyond 24 weeks

Weekly PRM-151 10 mg/kg IV
- 1 PD
- 2 deaths

Monthly PRM-151 10 mg/kg IV + ruxolitinib
- 1 death
- 1 splenectomy

Weekly PRM-151 10 mg/kg IV + ruxolitinib
- 1 death

20 Patients completed 24 weeks
- 5
- 2 stopped < 72 weeks
- 5 switched to monthly

13 patients completed 72 weeks
- 9
- 1 stopped rux
- 3 stopped < 72 weeks
- 5 switched to monthly
- 2 stopped < 72 weeks

- PRM-151 + RUX: stable RUX dose ≥3 months with no decrease in splenomegaly for ≥ 4 weeks
- No eligibility restrictions for anemia, thrombocytopenia, leukopenia, or spleen size
## All Possibly Related Adverse Events Events Through 72 Weeks (n=13)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Total</th>
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<td>COUGH NONPRODUCTIVE</td>
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<td>HYPERURICEMIA</td>
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<td>TOOTH INFECTION</td>
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<td></td>
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<tr>
<td>SKIN INFECTION</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HSV INFECTION</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HOT FLASHES</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>SWEATING</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

6 SAEs in 4 patients - none related: wound infection, multiple fractures, bladder rupture, bowel obstruction, focal pneumonia, and unspecified infection
Bone Marrow Fibrosis Improvement as Measured by WHO Criteria

- Response assessment by central hematopathologists blinded to patient, treatment and time point. WHO MF Response = % of patients with ≥1 grade reduction in MF score at any time point
- Reduction in BM fibrosis was associated with normalization of bone marrow architecture: Normal erythroid clustering, Normal or decreased myeloid:erythroid ratio, Fewer paratrabecular megakaryocytes
Hemoglobin and RBC Transfusions

Patients with baseline Hgb < 100 g/L who completed ≥ 72 weeks (n=5)

Median Hgb (g/L) and % receiving RBC transfusions
Platelets and Platelet Transfusions

Patients with Baseline Platelets $< 100 \times 10^9$/L who completed $\geq 72$ weeks (n=9)

- Median PLT ($\times 10^9$/L)
- % pts receiving plt transfusions

<table>
<thead>
<tr>
<th>% of patients with PLT transfusion</th>
<th>Platelets $\times 10^9$/L and</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30</td>
</tr>
<tr>
<td>Week 12</td>
<td>20</td>
</tr>
<tr>
<td>Week 24</td>
<td>30</td>
</tr>
<tr>
<td>Week 36</td>
<td>50</td>
</tr>
<tr>
<td>Week 48</td>
<td>40</td>
</tr>
<tr>
<td>Week 60</td>
<td>30</td>
</tr>
<tr>
<td>Week 72</td>
<td>40</td>
</tr>
</tbody>
</table>

4/9
Symptom Improvements

MPN-SAF TSS Best % Change from Baseline (n=13)

TSS % Change from Baseline

PRM-151 alone

PRM-151 + RUX
Spleen Reductions

Patients with palpable spleen at baseline (n = 10)

Best spleen % Change From Baseline

<table>
<thead>
<tr>
<th></th>
<th>PRM-151 alone</th>
<th>PRM-151 + RUX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Spleen</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Spleen Reduction</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>PRM-151 alone</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>PRM-151 + RUX</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>PRM-151 + RUX</td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>

*1 patient had no improvement
Next Steps

• Stage 2 of this adaptive study has now completed enrollment:
  • Single agent PRM-151 Q4W x 36 weeks: blinded randomization to 1 of 3 doses
  • Patients may continue beyond 36 weeks in open label extension
  • Eligibility
    – DIPSS Intermediate -1, Intermediate-2, or High Risk
    – WHO Grade 2 or 3 myelofibrosis
  • Patients not candidates for ruxolitinib based on:
    – **EITHER** Hgb < 100 g/L, requiring ≥ 2 units RBC in prior 12 weeks, and intolerance of or inadequate response to ruxolitinib
    – **AND/OR** Platelet count < 50 x 10⁹/L
Targeting TGF-β

Anti-transforming growth factor beta (TGF-β) therapy in patients with myelofibrosis (NCT01291784)

John Mascarenhas¹, Timmy Li¹, Lonette Sandy¹, Carrie Newsom¹, Bruce Petersen², James Godbold³, and Ronald Hoffman¹

¹Tisch Cancer Institute, Mount School of Medicine, New York, New York, USA
²Department of Pathology, Mount School of Medicine, New York, New York, USA
³Department of Preventative Medicine, Mount School of Medicine, New York, New York, USA
Model for MPN Disease Progression

Acquisition of driver mutations

- ET
- PV
- prePMF

Pro-inflammatory milieu of MPN supportive microenvironment

Acquisition of additional mutations and alterations in chromatin structure

Overt MF

MPN-BP
In solid tumors, disease progression is favored by a TGF-β circuit that promotes proliferation of cancer stem cells

- Cancer stem cells activate a TGF-β-dependent process(s) that leads to formation of activated fibroblasts (CAF).
- CAF provide the “niche” that support proliferation of cancer stem cells.

Orimo & Weinberg, Cell Cycle. 5:1597, 2006
Therapeutic Hypothesis

Treatment with a TGF-β inhibitor may treat PMF by providing proliferative advantage to healthy HSC in the marrow and preventing formation of myelofibrosis-HSC supporting niches in the spleen.
Myeloproliferative Disorders-Research Consortium (MPD-RC)
MPD-RC Protocol # 118
Phase II study of Galunisertib in patients with myelofibrosis

Mandatory Companion Protocol MPD-RC 107

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Emerging Treatments

- JAK2 inhibitor based combination trials in MF
- Telomerase Inhibition in MF (not covering ET)
- Anti-Fibrotic therapy in MF
  - JAK2i + DNMTi combination in MPN-AP/BP
- MDM2 antagonist therapy in PV
Kaplan-Meier survival curves of 91 patients with MF

## 11 patients with MPN-BP
Mount Sinai Experience

<table>
<thead>
<tr>
<th></th>
<th>DECITABINE (6 pts)</th>
<th>HSCT (5 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>PMF, Post ET/PV MF, MDS/MPN</td>
<td>0,3,1,2</td>
<td>1,3,0,1</td>
</tr>
<tr>
<td>JAK2V617F</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>Unfavorable karyotype</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>Median # Cycles of DEC (range)</td>
<td>5.5 (2,14)</td>
<td>4*</td>
</tr>
<tr>
<td>Median Overall Survival from MF in months (range)</td>
<td>33 (12, 152+)</td>
<td>25 (12,165+)</td>
</tr>
<tr>
<td>Survival from BP (median, range)</td>
<td>Not yet reached at 9 months (5,45+)</td>
<td>Not yet reached at 20 months (9,23)</td>
</tr>
</tbody>
</table>

*One patient received 4 cycles of DEC and then received HSCT

Phase II ruxolitinib in patients with refractory leukemia (NCT00674479)

- Single center Phase II
- 38 patients
- Median age 69 years
- Median (range) cycles: 2 (1,22)
- 18 MPN-BP patients
- 12 (31%) JAK2V617F-positive
- Well tolerated, grade 3/4 in 4 patients
- 3 CR/CRi

Jak2V617F/Tp53 null mice develop Acute Myeloid Leukemia

Tp53 wildtype mice (control)

Tp53 null mice

Spectrum of anti-leukemic agents demonstrate efficacy in murine post-MPN AML

Myeloproliferative Disorders-Research Consortium (MPD-RC)
MPD-RC 109
Combination Therapy of Ruxolitinib and Decitabine in patients with Myeloproliferative Neoplasms in Accelerated and Blast Phase Disease
NCT02076191

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### Study Schema

#### Cycle 1
- 35 day evaluable phase 1 portion of study
  - **Screening period**
    - **Days** -30 to 0
  - **Induction phase**
    - Single agent ruxolitinib
      - **Days** 1-7
    - Combination ruxolitinib and decitabine
      - **Days** 8 to 13
    - Single agent ruxolitinib
      - **Days** 14-35
  - **Cycles 2+ Extension**
    - Combination ruxolitinib and decitabine
      - Days 1 to 5
    - Single agent ruxolitinib
      - Days 6+

#### Dose level
<table>
<thead>
<tr>
<th>Dose level</th>
<th>Ruxolitinib dose</th>
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</thead>
<tbody>
<tr>
<td>-1</td>
<td>5mg PO BID</td>
</tr>
<tr>
<td>1</td>
<td>10mg PO BID</td>
</tr>
<tr>
<td>2</td>
<td>15mg PO BID</td>
</tr>
<tr>
<td>3</td>
<td>25mg PO BID</td>
</tr>
<tr>
<td>4</td>
<td>50mg PO BID</td>
</tr>
<tr>
<td></td>
<td>10mg BID</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>CR</td>
<td>-</td>
</tr>
<tr>
<td>CRi</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>NR</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>CR/CRi</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Overall response rate (CR/CRi/PR)</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>
Survival OS: 10.4 months (95% CI 3.3 mo - not reached).

<table>
<thead>
<tr>
<th></th>
<th>10mg</th>
<th>15mg</th>
<th>25mg</th>
<th>50mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median cycles received (range)</td>
<td>10.5 (1-22)</td>
<td>4.0 (1-6)</td>
<td>2.0 (1-16)</td>
<td>2.5 (1-7)</td>
<td>3.0 (1-22)</td>
</tr>
</tbody>
</table>
Emerging Treatments

- JAK2 inhibitor based combination trials in MF
- Telomerase Inhibition in MF (not covering ET)
- Anti-Fibrotic therapy in MF
- JAK2i + DNMTi combination in MPN-AP/BP
- MDM2 antagonist therapy in PV
P53/MDM2 in MPNs

- P53 regulates cell cycle, apoptosis, DNA repair, and senescence
- Wild type p53 seen in chronic phase MPN
- Inactivating p53 mutations frequency in MPN-BP
- Down regulation of p53 by MDM2 overexpression
  - Promotes proteosomal degradation
  - Inhibits p53 transcription
  - Inhibits transactivation
  - Facilitates export from nucleus

JAK2V617F, MDM2, La autoantigen, P53


Lu and Hoffman Oncotarget (2012) 3 (10) 1052-1053.
PV CD34+ cells contain higher levels of MDM2

Treatment with low doses of RG7112 and Peg-IFNα 2a reduced the numbers of JAK2V617F-positive cells in NOD/SCID mice.

RG7388 (Idasanutlin)

- Roche compound 2\textsuperscript{nd} generation nutlin family member
- Oral selective small molecule inhibitor of MDM2
- Improved pharmacological properties over RG7112
Open Label Phase I Study of Single Agent Oral RG7388 in Patients with Polycythemia Vera and Essential Thrombocythemia
(With pilot feasibility study in combination with pegylated interferon alfa 2a for patients who do not respond to the single agent at each dose level)

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Future Direction- 5 year view summary

• Combination studies
• Molecularly personalized approaches
  – IDH inhibitor
• Immunomodulation
  – PD-1 pathway
  – Dendritic vaccine
• Gene editing CRISPR?
• CAR-T?
• Optimizing Hematopoietic stem cell transplantation
Conclusions

• The portfolio of trials available indicate continued and sincere interest in developing better therapies for MPN
• Combination therapy is the mainstay of treatment for most malignancies and the future of MPN therapy
• Genetic and epigenetic insights gained today inform the therapies of tomorrow
• Clinical trial participation drives us closer to cure
• It will happen
Thank You

Mount Sinai MPD Program