Disclosures for John Mascarenhas, MD

In compliance with ACCME policy:

- **Consultancy:** Celgene; Incyte; Roche
- **Research Funding:** Celgene; CTI Biopharma; Incyte; Janssen; Merck; Novartis; Promedior; Roche
Objectives

- **ET/PV**
  - Encouraging MPN cells to commit suicide

- **MF**
  - Final stretch for second generation JAK inhibitors
  - Addressing anemia and avoiding RBC transfusions
  - An option to improve/salvage ruxolitinib response
  - An option for post-ruxolitinib failure
  - Reducing/eliminating bone marrow fibrosis
  - “targeted therapy” in the truest sense
Background: MDM2 and PV

- PV CD34+ cells contain higher levels of MDM2 compared to normal CD34+ cells
- Low doses of a Nutlin and Peg-IFNα 2a increase p21 and PUMA protein levels in PV CD34+ cells and promote apoptosis
- Treatment with low doses of a Nutlin and Peg-IFNα 2a reduce the numbers of JAK2V617F-positive cells transplanted in NOD/SCID mice

Baseline MDM2 levels higher in study participants than normal controls

P = 0.01
Evidence of P53 pathway activation: Plasma MIC-1 levels are significantly increased in PV patients following treatment with idasanutlin.
Responses by 2013 ELN-IWG\(^1\) criteria

By 6 cycles of therapy with idasanutlin monotherapy in PART A and combination pegylated interferon-\(\alpha\) in PART B

<table>
<thead>
<tr>
<th></th>
<th>Not evaluable (NE)</th>
<th>No response (NR)</th>
<th>Partial Response (PR)</th>
<th>Complete Response (CR)</th>
<th>Overall Response (PR+CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PART A (n=12)</td>
<td>1(^#)</td>
<td>4</td>
<td>3(^*)</td>
<td>4</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>PART B (n=4)(^\wedge)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>PART A + PART B ORR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 (75%)</td>
</tr>
</tbody>
</table>

- \(^#\) not evaluable due to patient decision to withdraw from study after 4 cycles due to GI toxicity
- \(^*\)Residual splenomegaly likely due to known portal vein thrombosis, likely a CR (n=1)
- \(^\wedge\)4 subjects from PART A that had NR continued on to PART B combination idasanutlin + interferon-\(\alpha\)
- \(^\ast\) not yet completed cycle 7
Driver mutation responses with idasanutlin therapy

Median % reduction -43%
(range -91.9% to +60.3%)

Baseline VAF

52% 82% 69% 89% 87% 2% 24% 23% 45% 36% 6%
Single arm Phase 2 study

Population and endpoint to match Ruxolitinib, explore ELN, molecular criteria for differentiation

Pts. with HU resistant/intolerant PV
- allow for enrichment of ruxolitinib naïve pts
- primary study for Ph3 decision

Idasanutlin
150 mg Daily x 5
N~20

Consider 200 mg for
(NR*, No HCT Control**)

Week 32 (end cycle 8)

Composite Response
(Hct control, spleen)
ELN Response*
HCT Response**
Molecular Response, PROs€
& Histologic Response (BM Bxp)‡

ClinicalTrials.gov Identifier: NCT03287245

*NR per 2009 ELN Criteria
**Patients without measurable splenomegaly at baseline
^spleen imaging at end C5 only if <35% reduction at end C3
€MPN-SAF-TSS, EORTC QLQ-C30, PGIC
‡Bone Marrow biopsy every 6 cycles post week 32 per PI discretion in context of ELN CHR response

C1
150mg QD x 5
PK/MIC-1

End Cycle 3
(week 12)

ELN Response*
Hematocrit Response**
Splenic imaging^
Molecular Response, PROs€

C4 PK/MIC-1 (for 200 mg esc. only)

End cycle 5 (week 20) then every 3 cycles up to 2yrs

Continue Dose to wk 32

12 weeks

Pts. with HU resistant/intolerant PV

ClinicalTrials.gov Identifier: NCT03287245
JAK Inhibitors and Status of Development in Myelofibrosis as lead Indication

**Approved**
- Ruxolitinib

**Failed**
- BMS-911543
- LY2784544
- Lestaurtinib
- AZD1280
- XL019

**Active late phase**
- Pacitritinib
- Fedratinib

**Inactive late phase**
- Momelotinib

**Active mid phase**
- Itacitinib

**Active early phase**
- NS018

**Selective JAK1, combo?**
- Failed phase 3, but is it over?

**Toxicity**
- neuro
- pancreas

**Toxicity derails these, but not over!**

**Combo trials**

**Active in second line**
- Itacitinib

**Failed**
- Toxicity - neuro - pancreas

**Approval Pathway**
PAC203: Dose Ranging Clinical Trial

Eligibility Criteria

- Primary or secondary myelofibrosis, prior RUX and platelet counts ≤100,000/µL
- Who have failed or were intolerant to therapy with RUX
- With platelet count <100,000/µL
- Who are highly symptomatic (DIPSS risk score of intermediate-1 to high risk)
- With splenomegaly (assessed by physical examination).

• PAC203 is dose finding study in patients with PMF, post-PV MF, and post-ET MF:
  – Who have failed or were intolerant to therapy with RUX
  – With platelet count <100,000/µL
  – Who are highly symptomatic (DIPSS risk score of intermediate-1 to high risk)
  – With splenomegaly (assessed by physical examination).

• ClinicalTrials.gov. NCT03165734.
**FED-MF-001**: A Multicenter, Single-arm, Open-label efficacy and safety study of Fedratinib in subjects previously treated with Ruxolitinib and with Intermediate or High-Risk PMF, Post-PV MF, or Post-ET MF

**FEDR-MF-002**: A Phase 3, Randomized, Open-label study of Fedratinib in subjects with Intermediate or High-Risk PMF, Post-PV MF, or Post-ET MF who have been previously exposed to Ruxolitinib

### Key eligibility criteria

- PMF, pET-MF, pPV-MF
- DIPSS: Int/High risk disease
- Spleen ≥450ml or ≥5cm
- Previous exposure with Ruxolitinib
- Platelets ≥50K
- Normal thiamine level

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### Fedratinib 400mg

- **Primary**: Spleen volume response by MRI/CT scan at the End of Cycle 6
- **Secondary**: Safety, Spleen response by palpation, duration of spleen response, symptom response, assess mitigation strategies for WE and GI AEs, QoL

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### Best Available Therapy (BAT)

- **R (2:1)**
- N=192

- Stratification at randomization: platelets, spleen size, R/R vs intolerant
- **Primary Endpoint**: ≥35% reduction in spleen volume at end of cycle 6
<table>
<thead>
<tr>
<th>JAK inhibitor</th>
<th>Combination partner/setting</th>
<th>MPN</th>
<th>Phase</th>
<th>Clinicaltrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>TGR-1202</td>
<td>PV, MF, MDS/MPN</td>
<td>1</td>
<td>NCT02493530</td>
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<tr>
<td>Ruxolitinib</td>
<td>Idelalisib</td>
<td>MF</td>
<td>1</td>
<td>NCT02436135</td>
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<tr>
<td>Ruxolitinib</td>
<td>INC8050465</td>
<td>MF</td>
<td>2</td>
<td>NCT02718300</td>
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<tr>
<td>Ruxolitinib</td>
<td>Danazol</td>
<td>MF</td>
<td>2</td>
<td>NCT01732445</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>Thalidomide</td>
<td>MF</td>
<td>2</td>
<td>NCT03069326</td>
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<tr>
<td>Ruxolitinib</td>
<td>Lenalidomide</td>
<td>MF</td>
<td>2</td>
<td>NCT01375140</td>
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<tr>
<td>Ruxolitinib</td>
<td>Azacytidine</td>
<td>MF, MDS/MPN</td>
<td>2</td>
<td>NCT01787487</td>
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<tr>
<td>Ruxolitinib</td>
<td>Panobinostat</td>
<td>MF</td>
<td>1b/1/2</td>
<td>NCT01433445 NCT01693601</td>
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<tr>
<td>Ruxolitinib</td>
<td>Pracinostat</td>
<td>MF</td>
<td>2</td>
<td>NCT02267278</td>
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<tr>
<td>Ruxolitinib</td>
<td>Decitabine</td>
<td>MPN-AML</td>
<td>1/2</td>
<td>NCT02257138 NCT02076191</td>
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<tr>
<td>Ruxolitinib</td>
<td>PIM447 + LEE011</td>
<td>MF</td>
<td>1</td>
<td>NCT02370706</td>
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<tr>
<td>Ruxolitinib</td>
<td>Vismodegib</td>
<td>MF</td>
<td>1/2</td>
<td>NCT02593760</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>Navitoclax</td>
<td>MF</td>
<td>2</td>
<td>NCT03222609</td>
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<tr>
<td>Ruxolitinib</td>
<td>Pegasys</td>
<td>MF</td>
<td>1/2</td>
<td>NCT02742324</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>HSCT</td>
<td>MF</td>
<td>2</td>
<td>NCT01790295</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>HSCT</td>
<td>MF</td>
<td>Pilot</td>
<td>NCT02917096</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>AutoSCT</td>
<td>MF</td>
<td>Pilot</td>
<td>NCT024699974</td>
</tr>
</tbody>
</table>

Cohort 1 (Anemia only): 0 RBC units/84 days up to C1D1 (n = 20)

Cohort 2 (RBC-tx dependent): Avg. 2-4 RBC units/28 days (n = 20)

Cohort 3 (Subjects on rux. as part of SOC therapy): Anemia only and RBC-tx dependent (n = 30)

Day 169 Disease Response Assessment

If clinical benefit: Continue tx for up to 1.5 additional years

If no clinical benefit: Discontinue tx

Posttreatment Follow-up Period

Primary Phase: 168 days

Screening Period: 4 weeks

End of study

ICF Screening

Parallel Enrolling

ClinicalTrials.gov. NCT03194542
BET – Epigenetic "Reader"

Control of Key Oncogenic, Immune, Fibrotic Pathways Leads to Opportunity in Myelofibrosis

- Cancer Genetics
  - MYC, BCL2

- Immune Signaling
  - NF-κB target genes

- Fibrosis
  - TGF-β target genes
Rationale for Combination of BET and JAK Inhibitors in Myelofibrosis
Cooperative reduction of disease associated inflammation
Combination of BET and JAK Inhibitors is Efficacious in MF model
Combination significantly improves spleen weight, fibrosis and tumor burden

Dramatic reduction in bone marrow fibrosis upon combination treatment

Decreased splenomegaly

Decreased mutant cell burden

Kleppa et al. 2018 Cancer Cell

MPLW615L bone marrow transplant model of MF
CPI-0610 Phase 2 Trial in Myelofibrosis

Objectives:
- Evaluate spleen size reduction after 24 weeks of treatment
- Evaluate patient-reported symptom improvement
- Evaluate transfusion independence rate, if applicable

CPI-0610 dosing of 125mg up to 225mg once daily in both arms
CPI-0610 Myelofibrosis Phase 2 Trial Status Update

Data as of May 25, 2018

Significantly reduced spleen size in all four evaluable patients by MRI

Best % Spleen Size Reduction

- Reduced spleen size
- Symptom improvement
- 1 patient with thrombocytosis and 1 patient transfusion dependent at baseline – both resolved
CPI-0160 Improving Hemoglobin Levels and Transfusion Dependence

Data as of May 25, 2018

Example: Transfusion independence and improved hemoglobin levels

- Patient treated with CPI-0610 + ruxolitinib combination therapy
- Patient required regular red blood cell transfusions prior to treatment
- Transfusion independent for more than 24 weeks as of May 25, 2018
- Additionally, hemoglobin increased by 2 g/dL and platelet counts improved despite not receiving red blood cell transfusions

CPI-0610 Improved Hemoglobin Levels in Each Patient Treated

- Patient treated with CPI-0610 monotherapy
- Patient had thrombocytosis, at baseline and was refractory to prior treatment with ruxolitinib, a telomerase inhibitor, pembrolizumab and hydroxyurea
- Patient’s thrombocytosis was accompanied by severe headaches
- Platelet counts normalized after treatment with CPI-0610, and have remained normal for more than 20 weeks as of May 25, 2018
- Patient’s severe headaches were resolved after platelets normalized
Imetelstat Is Effective Treatment for Patients with Intermediate-2 or High-Risk Myelofibrosis Who Have Relapsed on or Are Refractory to Janus Kinase Inhibitor Therapy: Results of a Phase 2 Randomized Study of Two Dose Levels

John Mascarenhas, MD1, Rami S. Komrokji2, Michele Cavo, MD3, Bruno Martino, MD4, Dietger Niederwieser, MD5, Andreas Reiter, MD6, Bart L Scott, MD7, Maria R. Baer, MD8, Ronald Hoffman, MD9, Olatoyosi Odenike, MD10, Jacqueline Bussolari, PhD11, Eugene Zhu, PhD11, Fei Huang, PhD11, Esther Rose, MD11, Laurie Sherman, BSN11, Souria Dougherty, BS, MBA11, Faye M. Feller, MD11 and Jean-Jacques Kiladjian, MD, PhD12

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

Funded by Janssen Research & Development and Geron Corporation

Mascarenhas et al. ASH 2018 Oral Presentation
Imetelstat: First in Class Telomerase Inhibitor

- **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
Co-primary endpoints at Week 24
- **Spleen response rate**: proportion of patients achieving ≥ 35% reduction in spleen volume by MRI at 24 weeks
- **Symptom response rate**: proportion of patients achieving ≥ 50% reduction in total symptom score per modified MFSAF v2.0 at 24 weeks

Key secondary endpoints: safety, overall survival (OS), treatment response, and pharmacokinetic and pharmacodynamic relationships

Stratification
- Spleen size ≥ 15 cm (yes/no)
- Platelets 75K – 150K vs ≥ 150K
# Baseline Mutation Summary on Selected Genes

<table>
<thead>
<tr>
<th></th>
<th>Biomarker population, n</th>
<th>4.7 mg/kg</th>
<th>9.4 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>With ≥ 1 mutation</td>
<td>48 (100)</td>
<td>57</td>
<td>103 (98)</td>
<td></td>
</tr>
<tr>
<td>≥ 3 mutations</td>
<td>40 (83)</td>
<td>38 (67)</td>
<td>78 (74)</td>
<td></td>
</tr>
<tr>
<td>Triple Negative</td>
<td>10 (21)</td>
<td>16 (28)</td>
<td>26 (25)</td>
<td></td>
</tr>
<tr>
<td><em>JAK2 V617F</em></td>
<td>32 (67)</td>
<td>32 (56)</td>
<td>64 (61)</td>
<td></td>
</tr>
<tr>
<td><em>CALR</em></td>
<td>2 (4)</td>
<td>7 (12)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td><em>MPL</em></td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>HMR(^a)</td>
<td>36 (75)</td>
<td>35 (61)</td>
<td>71 (68)</td>
<td></td>
</tr>
<tr>
<td><em>ASXL1</em></td>
<td>24 (50)</td>
<td>25 (44)</td>
<td>49 (47)</td>
<td></td>
</tr>
<tr>
<td><em>EZH2</em></td>
<td>10 (21)</td>
<td>18 (32)</td>
<td>28 (27)</td>
<td></td>
</tr>
<tr>
<td><em>SRSF2</em></td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>7 (7)</td>
<td></td>
</tr>
<tr>
<td><em>IDH1</em></td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td><em>IDH2</em></td>
<td>4 (8)</td>
<td>5 (9)</td>
<td>9 (9)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)HMR, high molecular risk; ie, 1 or more mutations in *ASXL1*, *EZH2*, *SRSF2*, *IDH1*, or *IDH2*.
SVR Per IRC at Week 24

- 6 (10%) patients in the 9.4 mg/kg arm had ≥ 35% SVR at Week 24
- 23 (37%) patients in the 9.4 mg/kg arm had ≥ 10% SVR at Week 24

At time of cut-off, 20 patients in the 4.7 mg/kg and 44 patients in the 9.4 mg/kg had Week 24 MRI, however, ITT is used as denominator for percentages.

IRC, Independent Review Committee; SVR, spleen volume reduction.
19 (32%) patients in the 9.4 mg/kg arm had ≥ 50% symptom response at Week 24.

At time of cut-off, 20 patients in the 4.7 mg/kg and 43 patients in the 9.4 mg/kg had Week 24 TSS e-diary entries, however, ITT is used as denominator for percentages.

TSS, total symptom score.
Outcomes After Ruxolitinib Discontinuation

- Retrospective analysis of clonal evolution and outcomes after ruxolitinib discontinuation in an open-label phase 1/2 study (N = 56)
  - Median OS: 14 mo
  - Survival improved if baseline platelets $\geq 260$ vs $< 260 \times 10^9$/L (HR = 2.7; \(P = .006\))
  - Survival improved if follow-up platelets $\geq 100$ vs $< 100 \times 10^9$/L (HR = 4.1; \(P = .001\))
  - 35% of patients acquired a new mutation while on ruxolitinib, most commonly ASXL1

Hashed lines = censored.

Overall Survival (ITT) for Imetelstat at Different Dose Levels

- Median follow-up: 27.4 months
- Median survival:
  - 19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg
  - 29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg

Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAK inhibitor or stem cell transplant and excluding patients who were dose escalated or randomized after closure of the 4.7 mg/kg arm), all generating similar results.
PRM-151 in Myelofibrosis: Efficacy and Safety in an Open-Label Extension Study

December 3, 2018

Dr. Srdan Verstovsek, MD, PhD

S. Verstovsek, MD, PhD,1 R.P. Hasserjian, MD,2 O. Pozdnyakova, MD, PhD,3 I. Veletic, MD,1 R.A. Mesa, MD,4 L. Foltz, MD, FRCPC,5 J. Mascarenhas, MD,6 E.K. Ritchie, MD,7 J. Palmer, MD,8 R.T. Silver, MD,7 M. Kremyanskaya, MD, PhD,6 B. van den Blink, MD, PhD,9 R. Gupta, MD,9 T. Manshour, PhD,1 C.C. Yin, MD, PhD,1 Z. Estrov, MD,1 J. Gotlib, MD10

1The University of Texas MD Anderson Cancer Center, Houston, TX; 2Department of Pathology, Massachusetts General Hospital, Boston, MA; 3Brigham and Women’s Hospital, Boston, MA; 4UT Health San Antonio Cancer Center, San Antonio, TX; 5St. Paul’s Hospital, University of British Columbia, Vancouver, BC, Canada; 6Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; 7Weill Cornell Medicine, New York, NY; 8Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ; 9Promedior, Inc., Lexington, MA; 10Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA.
PRM-151G-101 Stage 1 Study Design

**Main Study**

- PRM-151 10 mg/kg IV weekly
- PRM-151 10 mg/kg IV monthly
- PRM-151 10 mg/kg IV weekly + RUX\(^a\)
- PRM-151 10 mg/kg IV monthly + RUX\(^a\)

**Cycles 1–6 (24 weeks)**

**Open-Label Extension (OLE)**

- PRM-151 10 mg/kg IV monthly
  - n=9
- PRM-151 10 mg/kg IV monthly + RUX\(^a\)
  - n=9

**Up to Cycle 48 (192 weeks)**

**Main Study**

- **Key Eligibility Criteria:**
  - PMF or post-ET/PV MF with grade ≥ 2 BM fibrosis
  - Int-1, Int-2, or high risk disease (IWG-MRT DIPSS)
  - No restrictions for anemia, thrombocytopenia, leukopenia, or spleen size
- **Primary Endpoint:** ORR according to IWG criteria or stable disease with ≥1 grade reduction in BM fibrosis

**OLE**

- Safety and hematology parameters assessed monthly
- MPN-SAF TSS and spleen size assessed every 3 months
- BM biopsies obtained at physician’s discretion

**Primary Endpoints:** safety and efficacy of long-term administration of PRM-151

\(^a\) Patients on RUX were required to be on a stable dose for ≥ 3 months with no decrease in splenomegaly for ≥ 4 weeks.

BM: bone marrow; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; IV, intravenously; IWG-MRT, International Working Group – Myeloproliferative Neoplasms Research and Treatment; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; ORR, overall response rate; PMF, primary myelofibrosis; PV, polycythemia vera; RUX, ruxolitinib.
# Baseline Characteristics of Patients Enrolled in OLE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>66 (51–78)</td>
</tr>
<tr>
<td>Median months since diagnosis (range)</td>
<td>44.7 (6.0–126.3)</td>
</tr>
<tr>
<td>DIPSS stage, n (%): Int-1/Int-2/High</td>
<td>8/9/1 (44/50/6)</td>
</tr>
<tr>
<td>Fibrosis grade&lt;sup&gt;a&lt;/sup&gt;, n (%): MF 3/2/1</td>
<td>9/7/2 (50/39/11)</td>
</tr>
<tr>
<td>Median no. of prior therapies (range)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>Prior or current JAK inhibitor&lt;sup&gt;b&lt;/sup&gt;, n (%)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Mean duration of ongoing RUX (range), years</td>
<td>1.5 (0.6–2.2)</td>
</tr>
<tr>
<td>Median daily RUX dose&lt;sup&gt;c&lt;/sup&gt; (range), mg</td>
<td>30 (10–50)</td>
</tr>
<tr>
<td>Hemoglobin level &lt; 100 g/L, n (%)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Patients receiving RBC transfusions&lt;sup&gt;d&lt;/sup&gt;, n (%)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Platelet count &lt; 50 x 10&lt;sup&gt;9&lt;/sup&gt;/L, n (%)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Platelet count &lt; 100 x 10&lt;sup&gt;9&lt;/sup&gt;/L, n (%)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Patients receiving platelet transfusions&lt;sup&gt;d&lt;/sup&gt;, n (%)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Patients with palpable spleen, n (%)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Mean MPN-SAF TSS (SD)</td>
<td>19.2 (15.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Measured by central pathologists; <sup>b</sup> 5 patients in the PRM-151 monotherapy arm had previously received a JAK inhibitor; <sup>c</sup> One patient in the PRM-151 + RUX arm for the main study discontinued RUX before entering the OLE; all other patients on RUX were on a stable dose throughout the OLE; <sup>d</sup> Within 30 days prior to first PRM-151 dose.

DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; JAK, Janus kinase; MF, myelofibrosis; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; OLE, open-label extension; RBC, red blood cell; RUX, ruxolitinib.
### Reticulin grade

<table>
<thead>
<tr>
<th>Best OLE Result, n (%)</th>
<th>Main Study BL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=2</td>
<td>n=7</td>
</tr>
<tr>
<td>Grade 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (100)</td>
<td>2 (29)</td>
</tr>
</tbody>
</table>

### Collagen grade

<table>
<thead>
<tr>
<th>Best OLE Result, n (%)</th>
<th>Main Study BL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=2</td>
<td>n=2</td>
</tr>
<tr>
<td>Grade 0</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>

- Reticulin grade improvements were observed in 50% (9/18) of patients
- Collagen grade improvements were observed in 44% (8/18) of patients

BL, baseline; OLE, open-label extension.
Bone Marrow Fibrocyte Immunostaining

**Main Study BL**

**Cycle 25**

![Images of immunostained bone marrow](image)

<table>
<thead>
<tr>
<th>Mean Fibrocyte Count in h-BM</th>
<th>BL (n=8)</th>
<th>Cycle 25 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>378.0</td>
<td>81.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibrocytes in h-BM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL (n=8)</td>
</tr>
<tr>
<td>Cycle 25 (n=7)</td>
</tr>
<tr>
<td>11.2</td>
</tr>
<tr>
<td>2.0</td>
</tr>
</tbody>
</table>

**Procollagen I, CD45, CD68**

BL, baseline; h-BM, hematopoietic bone marrow.
Best Percentage Change in Palpable Spleen Size and MPN-SAF TSS from Main Study BL to OLE

Spleen Size

- Best % change, spleen size:
  - Mean: $-37\%$
  - Median: $-26\%$

MPN-SAF TSS

- Best % change, MPN-SAF TSS:
  - Mean: $-54\%$
  - Median: $-64\%$

$^a$ 5/19 OLE patients did not have a palpable spleen at BL.

BL, baseline; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; OLE, open-label extension; pt, patient; RUX, ruxolitinib.
CLINICAL SITES OF THE MPN RESEARCH CONSORTIUM (January 2019)

U.S.

Icahn School of Medicine at Mount Sinai, NY  John Mascarenhas

Memorial Sloan-Kettering Cancer Center, NY  Raajit Rampal

Mays Cancer Center at UT Health San Antonio, TX  Ruben Mesa

Mayo Clinic, AZ  Jeanne Palmer

Wake Forest School of Medicine, NC  Rupali Bhave

University of Kansas Cancer Center, KS  Abdulraheem Yacoub

University of Michigan Rogel Cancer Center, MI  Moshe Talpaz

Cleveland Clinic Taussig Cancer Center, OH  Aaron Gerds

Moffitt Cancer Center, FL  Rami Komrokji

Cedars-Sinai Medical Center, CA  Ronald Paquette

Ex-U.S.

Princess Margaret Cancer Center, Toronto CA  Vikas Gupta
Phase I study of AVID200 in patients with myelofibrosis (Myeloproliferative Neoplasms Research Consortium [MPN-RC] 118)

Study Chairs
Mascarenhas and Mesa
Trial Rationale

• Transforming growth factor-beta (TGF-β) is a pleiotropic cytokine implicated in the promotion of angiogenesis, tumor growth, collagen fibrosis, metastatic spread and down-regulation of anti-tumor immunity.
• TGF-β1 has also been shown to be the fibrogenic cytokine involved in the pathogenesis of BMF (Shehata 2004).
• Increased levels of TGF-β1 were detected in serum, plasma and BM and positively correlated with both grade of BMF and extent of leukemic cell infiltration in the marrow.
• TGF-β plays a key role in the negative regulation of granulocytes, erythroid, megakaryocyte, and macrophage progenitor cell proliferation (Hino 1988, Hooper 1991, Fortunel 2000).
• TGF-β is expressed in early CD34+ hematopoietic stem cells (HSC) and exerts a negative regulatory function on cell cycle progression in an autocrine fashion (Le Bousse-Keridiles 1999).
• Paradoxically, TGF-β has normal expression levels in CD34+ HSC and increased expression in megakaryocytes in patients with MF
AVID200

- Targets TGFβ1&3 and not 2 (murine and human)
- Minimizes cardiotoxicity since not pan-TGFβ inhibitor
- Ligand trap linked to IgG Fc region
- Reduced immunogenicity
- The ligand sequestration approach using decoy ectodomain-based traps has been previously validated with approvals of etanercept (targeting tumor necrosis factor [TNF]) and aflibercept (targeting vascular endothelial growth factor [VEGF]) both of which are traps that utilized a similar design.

Avidity-enhanced decoy trap with very high and selective potency

100 fold more potent than 1D11 benchmark neutralizing antibody against TGFβ
Study Summary

• This is a first in human, open-label, multicenter, Phase I/ Ib trial of AVID200.

• Patients must have intermediate-2 or higher primary myelofibrosis (PMF), post-essential thrombocythemia or polycythemia-vera related MF (Post ET/PV MF).

• This study will enroll up to 24 patients.

• AVID200 follows the Modified toxicity probability interval (mTPI) dose escalation design
  o Dose levels— 180 mg/m², 550 mg/m2, or 1100 mg/m²

• AVID200 is delivered by IV infusion on day 1 of each 3 week cycle
**MPN-RC 118 Schema**

- PMF, post-PV, post-ET MF
- Int-1 or higher MF by DIPSS
- Bone marrow fibrosis grade 2+

**Cycle 1**
- 21 days evaluable for MTD
- Screening period
- Days -30 to 0
- AVID200 dosing*
- Day 1
- Days 2 to 21

**Cycles 2-6**
- AVID200 dosing
- Response > CI or SD with reduction in BMF
- Day 1
- Days 2 to 21
- Response < CI and no reduction in BMF

**Cycles 7+**
- Continue AVID200 dosing
- Days 2 to 21
- Discontinue AVID200
- Day 1
- Days 2 to 21

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*Eligible patients with signed consent who have completed all requisite screening tests and procedures are to start Cycle 1 Day 1 within 30 days of signing consent.

*All adverse events captured during the first 21 days of treatment with AVID200 used to assess safety and tolerability and will be used in determining dose escalation as described in section 4.2.*

*Patients who do not develop a DLT within Cycle 1 will continue to Cycle 2.*

*Cycles will be a minimum of 21 days.*

*Following cycle 6, response will be assessed by IWG/ELN consensus criteria and patients will continue AVID200 if response was deemed a CI, PR or CR or SD with at least 1 grade reduction in bone marrow fibrosis.*

*AVID200 dose cohorts of 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg administered intravenously over an hour on day 1 of a 21 day cycle.*
**IDH2 mutations in MPNs**

- GAIN OF FUNCTION
- 15q26.1
- Cluster in normal or trisomy 8 karyotype
- Associated with increase risk of LT (Tefferi Leukemia. 2012 Mar;26(3):475-80)
- *IDH2* mutations in 21% of MPN-BP (Pardanani Leukemia volume 24, pages 1146–1151 (2010))
- *IDH1/2* and *JAK2V617F* are poor prognostic combo
- 50% of IDH2 mutants co-express JAk2V617F
Leukemia Free Survival for PMF patients (301) stratified by mutation status

JAK2/IDH2 mutant murine model mimics a pre-leukemic MPN phenotype
Treatment of Idh2R140Q Jak2V617F combined mutant mice with combined JAK2 and IDH2 inhibitor:

(A) 2HG quantification in plasma,

(B) spleen weights,

(C) hematocrit levels

(D) WBC count, (E-F) representative images of stained sections of spleen tissue. (F) CD34+ straining.
Enasidenib (Idhifa) selective IDH2 inhibitor
A Phase II Open-label Study of Combined Ruxolitinib and Enasidenib in Patients with Accelerated/Blast-phase Myeloproliferative Neoplasm or Chronic-phase Myelofibrosis with an IDH2 Mutation (Myeloproliferative Neoplasms Research Consortium [MPN-RC] 119)

Study Chairs
Rampal and Bar-Natan
Study Schema

MPN-RC 119 Schema

- MPN-AP / MPN-BP OR
- Chronic phase MF with 4-9% circulating blasts
- IDH2 mutation

Cycle 1
28 days
Safety run-in

- Screening period
- Days -30 to 0
- Ruxolitinib + Enasidenib*
  - Day 1
  - Days 2 to 28

Cycles 2-6

- Ruxolitinib + Enasidenib 100 mg
  - Day 1
  - Days 2 to 28

Response ≥ CI
Response < CI

Cycles 7+

- Continue treatment
- Discontinue treatment
  - Day 1
  - Days 2 to 28

Eligible patients with signed consent who have completed all requisite screening tests and procedures are to start Cycle 1 Day 1 within 30 days of signing consent.

All adverse events captured during the first 28 days of treatment with Ruxolitinib and Enasidenib will be used to assess safety and tolerability in the first 6 patients on study.

Cycles will be a minimum of 28 days.

Following cycle 6, response will be assessed by IWG/ELN consensus criteria and patients will continue treatment if response was deemed a PR/CRI or CR for MPN-AP and MPN-BP patients. For chronic phase MF, response will also include clinical improvement.

*Ruxolitinib dosing based on platelet counts; Enasidenib 100 mg for MPN-AP or MPN-BP and 50 mg for chronic phase MF for cycle 1
**For chronic phase MF, response also includes clinical improvement
Summary

• Novel therapy for ET and PV
  – Idasanutlin shows early clinical activity and ongoing phase 2 results pending
• Addressing anemia
  – Keep an eye on luspatercept
• Improving upon JAK inhibition for myelofibrosis
  – Many different combination trials ongoing with different goals
  – BET inhibitor (CPI-0610) is a rational combination partner with early signal of activity
• Improving outcomes after ruxolitinib failure
  – Imetelstat may offer opportunity for survival benefit
• Targeting bone marrow fibrosis
  – PRM-151 is safe and can be combined with ruxolitinib
  – AVID200 is aiming at TGF-β and now the trial is activating across North America
• Mutational-targeted therapy
  – Combination ruxolitinib + IDH2 inhibitor (enasidenib) in IDH2 mutated MF patients
BACK UP ADDITIONAL SLIDES
Treatment Exposure

• 107 patients were enrolled at 55 institutions

• Clinical cutoffs for analyses:
  o April 26, 2018 – Primary analysis of efficacy and safety, with a median follow-up of 22.6 (0.2-27.4) months
  o October 22, 2018 – Overall survival, with a median follow-up of 27.4 (0.2-33.0) months

• Median treatment duration: 26.9 (0.1-118.1) weeks
  o Median duration on treatment was 33.3 weeks on the 9.4 mg/kg arm and 23.9 weeks on the 4.7 mg/kg arm
  o The 4.7 mg/kg arm had been closed early, influencing duration of treatment
OS in Triple Negative Disease

In 9.4 mg/kg arm, lower death rate seen in Triple Negative (TN) group compared to Non-TN group.

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>4.7 mg/kg</th>
<th>Death Rate</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN</td>
<td>10</td>
<td>60%</td>
<td>23.1 (17.0, NE)</td>
</tr>
<tr>
<td>Non-TN</td>
<td>38</td>
<td>55%</td>
<td>19.4 (17.1, NE)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>9.4 mg/kg</th>
<th>Death Rate</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN</td>
<td>16</td>
<td>25%</td>
<td>NE (NE, NE)</td>
</tr>
<tr>
<td>Non-TN</td>
<td>41</td>
<td>51%</td>
<td>24.6 (20.7, NE)</td>
</tr>
</tbody>
</table>

4.7 mg/kg

- TN: 60% Death Rate
- Non-TN: 55% Death Rate
- Median Survival: 23.1 (17.0, NE) months

9.4 mg/kg

- TN: 25% Death Rate
- Non-TN: 51% Death Rate
- Median Survival: NE (NE, NE) months

Percentage survival over time for 4.7 mg/kg and 9.4 mg/kg treatments in TN and Non-TN patients.