Evolving Targets for MPN Therapy

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- **Research Funding:** Incyte, Novartis, Kartos, Blueprint Medicines, Deciphera, Abbvie, Celgene, BMS, Protagonist therapeutics, CTI Biopharma, Promedior

- **Advisory Boards/Honoraria:** Incyte, Novartis, Kartos, Blueprint Medicines, Deciphera, Abbvie, Protagonist therapeutics, PharmaEssentia
Evolution of Drugs for MF-Associated Anemia

2000-2010

Immunomodulatory drugs +/- corticosteroids
(thalidomide, lenalidomide +/- prednisone)

Androgens (Danazol)

2010-2020

Luspatercept ‘erythroid maturation agent (EMA)’

Momelotinib (unanticipated anemia-improving effects by inhibiting activin receptor-like kinase-2 (ALK2))

CPI-0610 (BET inhibitor)

INCB00928 (ALK2 inhibitor)

Red blood cell transfusions; Erythropoiesis Stimulating Agents (ESAs) (Procrit, Aranesp)
ALK2 inhibition reduces liver hepcidin expression, increases sequestered iron mobilization from cellular stores, and stimulates red blood cell production.
CPI-0610: Hemoglobin improvement observed in patients with baseline hemoglobin <10 g/dL

All patients¹
Mean Hgb Over Time

<table>
<thead>
<tr>
<th>Cycles</th>
<th>N</th>
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<tbody>
<tr>
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<td>12</td>
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Patients Without Transfusions¹,²
Mean Hgb Over Time

<table>
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<th>Cycles</th>
<th>N</th>
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<td>11</td>
<td>5</td>
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<tr>
<td>12</td>
<td>5</td>
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</tbody>
</table>

¹ Patients on treatment ≥ 12 wks
² Received no transfusions 12 wks prior to C1D1 and during treatment
Hgb: Hemoglobin
ACE-536-MF-001 study design

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

79 subjects with MF and anemia had been enrolled by the data cutoff and were included in this updated analysis (March 29, 2020)

- The analyses presented here focus on response in subjects requiring RBC transfusions (Cohorts 2 and 3B); safety is reported for all 79 subjects on study

As of March 29, 2020, 16 (20%) subjects remain on treatment. 4 Enrolled subjects had primary or post-essential thrombocythemia/post-polycythemia vera myelofibrosis; 5 A stable daily dose of RUX for at least 16 weeks at enrollment; for the 3 subjects enrolled in the expansion cohort in Cohort 3B, subjects were receiving a stable RUX dose for 40 weeks; 6-12 RBC units/84 days prior to treatment; or 4-12 units/84 days for the 3 subjects enrolled in the expansion cohort in Cohort 3B; 7 Including 3 subjects enrolled in the expansion cohort; 8 The starting dose was 1.33 mg/kg in the expansion cohort subjects. MF, myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.
Luspatercept: Rates of RBC transfusion independence and ≥ 50% transfusion burden reduction ≥ 12 weeks

Achievement of multiple episodes of response

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

*Defined as RBC transfusion burden reduction by ≥ 50% and by ≥ 4 RBC U for ≥ 12 weeks.
Evolution of Drugs for Blast Phase MPN

2000-2010
Intensive AML-type chemotherapy

2010-2020
Hypomethylating Agents [HMA]
(Azacitidine [Aza], Decitabine [Dec])

HMA + Ruxolitinib
Aza/Rux; Dec/Rux

2020 -
Targeted Mutation Approaches
(IDH1, IDH2, FLT3, TP53)

 +/- Transplant
# HMA + Ruxolitinib Combinations in Accelerated and Blast Phase MPN

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Population</th>
<th>HMA</th>
<th>Overall Response Rate</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rampal <em>et al</em>, <em>Blood Advances</em>, 2018</td>
<td>Accelerated and blast phase MPN</td>
<td>Decitabine</td>
<td>53%</td>
<td>7.9 months</td>
</tr>
<tr>
<td>Mascarenhas <em>et al</em>, <em>Blood Advances</em>, 2020</td>
<td>Accelerated and blast phase MPN</td>
<td>Decitabine</td>
<td>44%</td>
<td>9.5 months</td>
</tr>
<tr>
<td>Bose <em>et al</em>, <em>Leukemia</em>, 2020</td>
<td>Blast phase MPN</td>
<td>Decitabine</td>
<td>45%</td>
<td>6.9 months</td>
</tr>
</tbody>
</table>
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Median OS
14.7 vs 9.6 months
# Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Azacitidine plus Venetoclax</th>
<th>Azacitidine plus Placebo</th>
<th>Hazard Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of AML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>120/214 (56.1)</td>
<td>80/110 (72.7)</td>
<td>0.67 (0.51–0.90)</td>
</tr>
<tr>
<td>Secondary</td>
<td>41/72 (56.9)</td>
<td>29/35 (82.9)</td>
<td>0.56 (0.35–0.91)</td>
</tr>
<tr>
<td>Cytogenetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>84/182 (46.2)</td>
<td>62/89 (69.7)</td>
<td>0.57 (0.41–0.79)</td>
</tr>
<tr>
<td>Poor</td>
<td>77/104 (74.0)</td>
<td>47/56 (83.9)</td>
<td>0.78 (0.54–1.12)</td>
</tr>
<tr>
<td>Molecular marker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLT3</td>
<td>19/29 (65.5)</td>
<td>19/22 (86.4)</td>
<td>0.66 (0.35–1.26)</td>
</tr>
<tr>
<td>IDH1</td>
<td>15/23 (65.2)</td>
<td>11/11 (100.0)</td>
<td>0.28 (0.12–0.65)</td>
</tr>
<tr>
<td>IDH2</td>
<td>15/40 (37.5)</td>
<td>14/18 (77.8)</td>
<td>0.34 (0.16–0.71)</td>
</tr>
<tr>
<td>IDH1 or IDH2</td>
<td>29/61 (47.5)</td>
<td>24/28 (85.7)</td>
<td>0.34 (0.20–0.60)</td>
</tr>
<tr>
<td>TP53</td>
<td>34/38 (89.5)</td>
<td>13/14 (92.9)</td>
<td>0.76 (0.40–1.45)</td>
</tr>
<tr>
<td>NPM1</td>
<td>16/27 (59.3)</td>
<td>14/17 (82.4)</td>
<td>0.73 (0.36–1.51)</td>
</tr>
<tr>
<td>AML with myelodysplasia-related changes</td>
<td>56/92 (60.9)</td>
<td>38/49 (77.6)</td>
<td>0.73 (0.48–1.11)</td>
</tr>
<tr>
<td>No</td>
<td>105/194 (54.1)</td>
<td>71/96 (74.0)</td>
<td>0.62 (0.46–0.83)</td>
</tr>
</tbody>
</table>

DiNardo et al, NEJM, 2020
Phase 2 Study of Venetoclax in Combination with Decitabine in Accelerated and Blast-Phase Myeloproliferative Neoplasms

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<thead>
<tr>
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<thead>
<tr>
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<th>Co-Investigator</th>
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</thead>
</table>
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Magrolimab (Formerly 5F9) Is a First-in-Class Macrophage Immune Checkpoint Inhibitor Targeting CD47

CD47 is a “do not eat me” signal that is overexpressed in multiple cancers, including acute myeloid leukemia, leading to macrophage immune evasion.

Magrolimab, an IgG4 anti-CD47 monoclonal antibody, eliminates tumor cells through macrophage phagocytosis.

Magrolimab is being investigated in multiple cancers with >500 patients dosed.
Magrolimab + AZA Induces High Response Rates in AML

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>All AML (N=43)</th>
<th>TP53 mutant AML (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>27 (63%)</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>CR</td>
<td>18 (42%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>CRI</td>
<td>5 (12%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>MLFS</td>
<td>3 (7%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>SD</td>
<td>14 (33%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown.

- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML including similar responses in TP53-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%-20%)

What about CALR?
CALR Therapeutic Targeting

Phase 1 vaccination study in Denmark with a CALR exon 9 peptide vaccine (NCT03566446)

How, Hobbs, Mullally, Blood, 2019
Genome Editing in MPNs?

Issues in MPNs

- Who are the optimal MPN candidates?
- Often multi-mutated besides JAK2, CALR, MPL (esp. myelofibrosis)
- Risk of secondary acute leukemia from conditioning chemotherapy for infusion of edited autologous CD34+ cells
- Off-target editing; unanticipated effects on MPN hematopoietic stem cells

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia


January 2021

Inherited, single-gene diseases
Diseases without increased malignancy potential
Partial correction can lead to dramatic improvement
Aspirational Pursuits...
The risk of developing an MPN is increased by 5–7-fold in first-degree relatives of patients with MPNs

> 20 Statistically significant or suggestive gene loci associated with increased MPN risk:

- JAK2 46/1
- SH2B3
- ZNF521
- GATA2
- MECOM
- RUNX1
- HMGA1
- ATM
- FOXO1
- TET2
- PRKCE
- STXB5
- SMC4
- KPNA4
- SLC12A7
- F2RL1
- MAD1L1
- MKLN1
- FOXG1
- DLK1
- TERT
- CHEK2
- GFI1B
Gene Variants Associated with Increased MPN Risk and Functional Consequences in Hematopoietic Stem Cells

**TERT:** (Telomerase Reverse Transcriptase): protein component of the enzyme telomerase which adds DNA to the ends of chromosomes. Telomerase is reactivated or upregulated in the vast majority of cancers.

*The top two TERT variants for increased telomere length, TERT rs7705526 and rs2853677 were also the lead variants for MPN risk*

**CHEK2:** a protein that acts a tumor suppressor. CHEK2 regulates cell division, and can prevent cells from dividing too rapidly. Usually constrains hematopoietic stem cell expansion.

*The CHEK2 I157T variant reduces the function of CHEK2, promotes hematopoietic stem cell self-renewal, and may therefore increase MPN risk*

**GFI1B:** a master DNA transcription factor that is necessary for maintaining hematopoietic stem cell quiescence.

*The GFI1B rs524137 variant results in decreased expression of GFI1B in hematopoietic stem cells and increases their self-renewal*
Normal Hematopoiesis

TERT, CHEK2, GFI1B Variants

Therapeutic ‘correction’ of germline variants to mitigate future risk of MPN?

Use of genome editing?
Platelet transcriptome (RNA sequencing) in MPNs

Platelet transcriptome represents a critical biomarker of megakaryocytic activity, and provides a snapshot of the underlying hemostatic, thrombotic, and inflammatory derangements associated with MPNs and the potential impact of treatment.
Volcano plots of changes in RNA expression from platelets from ET, PV, & MF patients, and changes on RUX therapy.
Potential Targets for MPNs

*unpublished data

Work by Dr. Anandi Krishnan, Stanford University School of Medicine
Diabodies, small molecules that can dial-up or dial-down the activity of EPO receptor and TPO receptor (MPL)

**EPO Receptor**

- DA5/EpoR complex
- DA10/EpoR complex
- FERM domain
- Pseudokinase domain
- Kinase domain
- JAK2
- STAT pSTAT

**TPO Receptor (MPL)**

- CD41+CD42b+ (Megakaryocytes)
- % Megakaryocytes in CD41+ cells

**Graphs and Images**

1. Bar graph showing Binding/F3 cell number (RU) for mEpoR, mEpoR mJAK2wt, mEpoR mJAK2V617F, untreated, DA10, DA5, DA307, and DA330.
2. Image showing DAPI/CD41 staining for different conditions: Ø, AK111 100 nM, AK113 100 nM, AK119 100 nM, and TPO 100 nM.

**References**

- Moraga et al, Cell, 2015
- Cui et al, PNAS, 2021
Evolving Targets for MPN Therapy

**Evolving Treatment Goals**

- Spleen size
- Symptoms
- Cytopenias
- BM fibrosis
- Mutation burden
- Survival
- Leukemic evolution

Making it Happen with Bench to Bedside Collaboration
Acknowledgements

Stanford
Parveen Abidi
Brizelle Aquilar
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Lenn Fechter
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Cheryl Langford
Cecelia Perkins
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Jim Zehnder

Our Patients & Their Families
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Stanford Cancer Institute
Charles and Ann Johnson Foundation

MPN Education Foundation
Jo Ann Manning
Antje Hjerpe
& Their Team

Our Dedicated MPN Colleagues