Therapeutic strategies for accelerated and blast phase MPN

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## Disclosures for John Mascarenhas, MD

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tbody>
<tr>
<td>Royalty</td>
<td>N/A</td>
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<tr>
<td>Receipt of intellectual property/Patent holder</td>
<td>N/A</td>
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<tr>
<td>Consulting fee</td>
<td>Incyte</td>
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<td>Speakers bureau</td>
<td>N/A</td>
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<td>Fees for non-CME services</td>
<td>N/A</td>
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<tr>
<td>Contracted research</td>
<td>Incyte, Novartis, Roche, CTI</td>
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<tr>
<td>Ownership interest (stocks, stock options)</td>
<td>N/A</td>
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<td>Other</td>
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N/A = Not Applicable (no conflicts listed)
Presentation includes discussion of off-label or unapproved use of a drug or medical device
Definition
Proposed nomenclature by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)

*de novo* presenting disease

Primary myelofibrosis (PMF)

Myelofibrosis transformation from prior polycythemia vera (PV) or essential thrombocythemia (ET)

Post PV myelofibrosis (post-PV MF)
Post ET myelofibrosis (post-ET MF)

Transformation to acute leukemia

Primary myelofibrosis in blast phase (PMF-BP)
Post PV/ET MF in blast phase
Three phases of MPNs determined by percentage of blasts in peripheral blood or bone marrow

<table>
<thead>
<tr>
<th>MPN</th>
<th>Blasts</th>
<th>Location</th>
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<tbody>
<tr>
<td>CP</td>
<td>ET, PV, MF</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>AP</td>
<td>ET, PV, MF</td>
<td>10-19%</td>
</tr>
<tr>
<td>BP</td>
<td>ET, PV, MF</td>
<td>≥20%</td>
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Outcome and survival
Survival for patients with MPN-AP

(A) AP features at baseline

(B) Survival after the development of AP features in patients who were in CP at baseline

Tam C S et al. JCO 2009;27:5587-5593
Most patients who enter BP first transition through AP

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Tam C S et al. JCO 2009;27:5587-5593
Kaplan-Meier survival curves of 91 patients with MF

Copyrighted material

The effect of treatment strategy on survival
Flowchart outlining the progression of patients through the treatment algorithm at PMH

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Kaplan-Meier survival analysis for MPN-BP in treatment algorithm

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Allogeneic stem cell transplantation for MF-BP: A study from the Myeloproliferative Neoplasm Subcommittee of the CMWP of the European Group for Blood and Marrow Transplantation

OS and PFS after HSCT for MF-BP

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OS after HSCT for MF-BP according to response to induction chemotherapy

Alchalby H et al.
Biol Blood Marrow Transplant
2014; 20:279 - 281
DNMT1 inhibition
Hypermethylation of the P15INK4b and P16INK4a in MF and MPN-BP

Phase II 5-AZA in patients with MF

- Single institution
- 34 patients
- Median age 66 years
- 19 JAK2V617F (median burden 50%)
- Lille risk score
  - 0: 16 patients
  - 1: 11 patients
  - 2: 7 patients
- 76% previously treated (median of 1 prior treatment)

Quintas-Cardama A et al. Leukemia. 2008 May;22(5):965-70
Results

- Median treatment: 5.5 months (2,18)
- Responses: CR (n=0), PR (n=1), CI (n=7)
- Toxicity: Grade 3/4 in 40% patients
- Dose Reductions: 47%
- Discontinuation rate: 97%
  - Loss of response n=10
  - Lack of response n=7
  - Grade 3/4 toxicity n=6
  - Leukemic transformation n=2
  - HSCT n=1
  - Death n=1
  - Intercurrent illness n=5
  - Patient decision n=1
Epigenetic modulation by 5-AZA in treated patients with MF
Groupe Francophone des Myelodysplasies (GFM) experience of AZA treatment in transformed MPN

- 54 patients
  - 26 MPN-BP
  - 28 MPN-MDS
- 52% ORR
  - 24% CR
  - 11% PR
  - 8% marrow CR/Cri
  - 9% HI

Overall survival in patients with MPN-MDS/BP treated with AZA

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11 patients with MPN-BP
Mount Sinai Experience

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<tr>
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<th>DECITABINE (6 pts)</th>
<th>HSCT (5pts)</th>
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<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>
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<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>
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<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>
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*One patient received 4 cycles of DEC and then received HSCT

JAK inhibition
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

IL-6 (100 ng/mL) stimulated levels of pSTAT3 at baseline and 2 hours after administration of 25 mg of ruxolitinib

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Eight patients who benefited from therapy with ruxolitinib had positive JAK2V617F mutation both before and after the therapy.
Characteristics of complete responders

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Combination therapy
Jak2 V617F/Tp53 null mice develop Acute Myeloid Leukemia.

Tp53 wildtype mice (control)

Tp53 null mice

Rampal R et al. PNAS, in press
Spectrum of anti-leukemic agents demonstrate efficacy in murine post-MPN AML

INCB18424

Decitabine

Decitabine/
Ruxolitinib

Rampal R et al. PNAS, in press
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

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Key eligibility criteria

- Accelerated phase MPN as defined by 10%-19% blasts in the peripheral blood or bone marrow and evidence of dysplastic marrow features with a concomitant diagnosis of ET, PV or PMF or a diagnosis of AML as defined by 20% blasts in the blood or bone marrow following a previous diagnosis of ET, PV or PMF.

- >18 years of age

- ECOG Performance status of 0-2.

- Total bilirubin < 1.5 times the upper limit of normal (ULN) unless due to Gilbert’s disease or hemolysis

- AST and ALT ≤ 2.5 times ULN

- Serum creatinine ≤ 1.5 x ULN
Phase I study schema

**Cycle 1**
35 day evaluable phase I portion of study

- **Screening period**
  - **Induction phase**
    - Single agent ruxolitinib*
  - Combination ruxolitinib and decitabine
  - Single agent ruxolitinib

- **Days -30 to 0**
  - **Days 1 to 7**
    - **Days 8 to 12**
    - **Days 13 to 35**

Patients that are determined eligible after signing IC and have completed all requisite tests and procedures are to start Cycle 1 Day 1 within 30 days.

All adverse events captured during the first 35 days will be used to assess safety and tolerability and will be used in determining dose escalation.

Patients who do not develop a DLT within Cycle 1 and have at least SD as defined in this protocol will continue to Cycle 2.

Cycles will be repeated every 4 weeks* and Interval Milestone Response Assessment (IMRA) should be performed as per study schedule.
Phase I exploratory objectives

• Examine the mutational status of a panel of genes that are commonly mutated in patients with de novo or secondary AML.

• Investigate the pattern of CD34+ cell engraftment and clonal evolution in a murine xenotransplantation system as a predictor of treatment response.

• Explore somatic mutations that may be more expressed in leukemic blasts using whole exome sequencing.

• Explore novel transcripts, alternative splicing, gene fusion events, SNVs, and indels as identified by RNAseq.

• Explore the effect of ruxolitinib and decitabine combination therapy on cytokine expression at specified time points.

• Compare the JAK2 allele burden prior to and during treatment with ruxolitinib in both the granulocyte and mononuclear cells.
A novel target
The Role of Eph/Ephrin System in Cancer

- Eph Receptors constitute the largest family of Receptor Tyrosine Kinases (RTKs)\(^1\)
- Eph Receptors bind to membrane-tethered Ephrin ligands\(^2\)
- Eph/Ephrin signaling is bi-directional\(^2\)
- Eph/Ephrin system plays a key role in embryonic development, neurological functions & cell communication:
  - **Morphogenesis:** coordination of cell segregation, cell positioning, tissue boundary formation and segmentation, vascular and skeletal morphogenesis, tissue patterning\(^3,4\)
  - **Neurological functions:** Triggers cell movement, cell migration, axon guidance and topographic mapping\(^3\)
  - **Homing of hematopoietic cells:** influences hematopoietic stem cell adhesion and trafficking patterns\(^5\)

**Role of Ephs in Cancer:** As oncogenes, re-expressed and over-expressed Eph Receptors can function in tumor (stem) cell positioning, differentiation, adhesion, neoangiogenesis and invasive tumor growth as well as tumor (stem) cell survival\(^4,6\)

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KB004 has 4 Postulated Mechanisms of Action

1. ADCC Mediated Killing of Tumor Cells¹

2. Direct Apoptosis of Tumor Cells¹,²

3. Disruption of Tumor Vasculature through Cell Rounding²

4. Anti-fibrotic Mechanism³,⁴

Emergent clinical data shows an anti-fibrotic effect of KB004 in AML and MF, by a potentially novel, unknown mechanism of action (MOA).

KB004-01 Phase 1/2 Study Schema

DOSE ESCALATION PHASE
(DEP, Ph 1, n=50)

RP2D

250 mg

190 mg

140 mg

100 mg

70 mg

40 mg

20 mg

330 mg

COHORT EXPANSION PHASE
(CEP, Ph 2, n=80, n=20 per cohort)

AML 250 mg

MDS 250 mg

MF 250 mg

AML 20 mg

Once-weekly infusion until disease progression

Swords R et al. ASH 2014:a3756
A Simplified H Score (SHS) was calculated by multiplying the percentage of nucleated cells positive for EphA3 expression by the staining intensity on a scale of 0 to 3.

ND=no data

*IWG responder
MPN-BP treatment strategy conclusions

• Improved understanding of genetic and epigenetic events leading to leukemic transformation will continue to guide future clinical trial design
• DNMT1 inhibition is an active therapeutic approach for MPN-BP
• Combination trials of DEC + Rux are ongoing
• Novel approaches such as targeting Epha3 should be explored
• HSCT can offer potential for cure for some patients (likely while in AML-CR after induction therapy or DEC)
• MPN-BP remains an unmet clinical need and patients should be enrolled in clinical trials whenever possible