### Disclosures for A Pardanani

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>TargeGen, Cytopia/YM BioSciences, PharmaMar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee</td>
<td>None</td>
</tr>
<tr>
<td>Consultant</td>
<td>None</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>None</td>
</tr>
<tr>
<td>Speakers' Bureau</td>
<td>None</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>None</td>
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Presentation includes discussion of the following off-label use of a drug or medical device. Hydroxyurea, interferon-alpha, imatinib mesylate, 2-CdA, busulfan, anagrelide, thalidomide, lenalidomide, pomalidomide, prednisone, androgens, erythropoiesis stimulating agents, alemtuzumab, INCB18424, TG101348, CYT387, RAD001, PKC412, Panobinostat, Givinostat

### JAK inhibitors in Ph-myeloproliferative neoplasms: survival benefit or palliation?

A. Pardanani, MBBS, PhD
Mayo Clinic
"If you believe that, I've got a bridge to sell you."

brooklyn bridge

Chronic phase

Phenotype-modifying mutations

Disease-transforming mutations

Polyclonal stem cells

Polycythemia Vera

Primary Myelofibrosis

Chronic Myeloid Leukemia

Acute Myeloid Leukemia

JAK2(-)

JAK2(+)
Mutations galore in BCR-ABL1-negative myeloid neoplasms

Figure 1

Clonal hierarchy in a patient with PMF and two distinct LNK mutations, JAK2V617F and IDH2 R140Q

A.

Wild-Type

LNK 955_delA

IDH2 R140Q

LNK 685-691_del GGCCCCG

JAK2 V617F

B.

Wild-Type

LNK685-691_del GGCCCCG

Heterozygous

JAK2 V617F

Wild-Type

IDH2 R140Q

n=1

5%

n=3

15%

C.

LNK685-691_del GGCCCCG

JAK2 V617F

Wild-Type

n=4

20%

Homozygous

JAK2 V617F

Wild-Type

n=7

35%

Homozygous

IDH2 R140Q

n=7

35%

LNK Mutation Studies in Chronic- and Blast-Phase Myeloproliferative Neoplasms and JAK2 Mutation-Negative Erythrocytosis - ASH 2010, abstract M102
‘Targeted’ therapy in MPN
What mutant molecule should we target?

- **JAK2** >95%
- **IDH** <5%
- **ASXL1** <10%
- **EZH2** <5%
- **IKZF1** <1%
- **CBL** <3%
- **TET2** <20%
- **MPL** <10%
- **LNK** <3%

### DIPSS-plus (Dynamic International Prognostic Scoring System + karyotype + platelet count + transfusion status) risk stratification in 793 patients with primary myelofibrosis seen at Mayo Clinic Rochester

- **Low risk** (0 adverse points)
  - n=66; median survival ~ 185 months
- **Intermediate-1 risk** (1 adverse point)
  - n=174; median survival ~ 78 months
- **Intermediate-2 risk** (2 or 3 adverse points)
  - n=360; median survival ~ 35 months
- **High risk** (4 or more adverse points)
  - n=193; median survival ~ 16 months

### Adverse points

1. Hgb < 10 g/dL
2. Circulating blasts ≥1%
3. WBC > 25k
4. Constitutional symptoms
5. Age > 65 years
6. Transfusion need
7. Platelets < 100k
8. Unfavorable karyotype

- Monosomal karyotype
- Complex karyotype
- Trisomy 8
- -7/del(7q)
- Del(5q)
- Inv(3)
- isochromosome 17q17p-13q-11q23 abnormality

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Gangat et al. ASH 2010 abstract #4104
Primary end point for Phase III JAK inhibitor trials in myelofibrosis

- ≥35% decrease in spleen volume by MRI/CT
- OS
- PFS

JAK inhibitor ATP mimetics in clinical trials for myelofibrosis

<table>
<thead>
<tr>
<th>JAK inhibitor/Phase</th>
<th>Anti-JAK2 IC50 (JAK1/JAK3 selectivity)</th>
<th>Non-JAK kinase targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCB018424/1/2</td>
<td>5.7 nM (x1.0/x98)</td>
<td>None of ~28 kinases evaluated</td>
</tr>
<tr>
<td>N=153</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG101348/1/2</td>
<td>3 nM (x35/x332)</td>
<td>FLT3</td>
</tr>
<tr>
<td>N=59</td>
<td></td>
<td>RET</td>
</tr>
<tr>
<td>CYT387/1/2</td>
<td>18 nM (x0.6/x8.6)</td>
<td>JNK1 CDK2</td>
</tr>
<tr>
<td>N=60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEP-701/2</td>
<td>1 nM (x?/x3)</td>
<td>FLT3 TrkA</td>
</tr>
<tr>
<td>SB1518/1/2</td>
<td>22 nM (x58/x24)</td>
<td>FLT3</td>
</tr>
<tr>
<td>AZD1480/1/2</td>
<td>0.26 nM (x5/x15)</td>
<td>TrkA Aurora A FGFR1</td>
</tr>
<tr>
<td>LY2784544/1/2</td>
<td>Scant literature</td>
<td>Scant literature</td>
</tr>
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</table>
Safety and Efficacy of INCB018424, a JAK1 and JAK2 Inhibitor, in Myelofibrosis


**INCB018424**

- Phase 1/2 study
- N=153
- Median f/u=14.7 months

- DLT=Gr 3/4 thrombocytopenia
- MTD=25 mg BID or 100 mg QD

### Study discontinuation rate=25%


### Longer-Term Follow up with TG101348 Therapy In Myelofibrosis Confirms Sustained Improvement In Splenomegaly, Disease-Related Symptoms, and JAK2V617F Allele Burden

JAK-2
TG101348

- Phase 1 study
- N=59
- Median f/u=380 days

- DLT=Gr 3/4 elevated amylase/lipase
- MTD=680 mg QD

TG101348: safety and tolerability

study discontinuation rate = 44%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All subjects N=59</th>
<th>MTD cohort N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Nausea</td>
<td>66%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>54%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>ALT increased</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>AST increased</td>
<td>25%</td>
<td>2%</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Alkaline-phosphatase increased</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin exfoliation</td>
<td>14%</td>
<td>0%</td>
</tr>
</tbody>
</table>

MTD cohort: 70% required dose reduction

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All subjects N=59</th>
<th>MTD cohort N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Anemia (N=37)</td>
<td>8%</td>
<td>35%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17%</td>
<td>24%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63%</td>
<td>10%</td>
</tr>
</tbody>
</table>

ASH 2010, Abstract #460

**JAK-1/JAK-2**

**CYT387**
- Phase 1/2 study
- N=60
- Median f/u 4.9 months
- DLT Gr 3 elevated lipase/headache
- MTD 300 mg QD
**CYT387: safety and tolerability**

study discontinuation rate = 5%

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased transaminases</td>
<td>20%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased lipase</td>
<td>7%</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased amylase</td>
<td>5%</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Alb</td>
<td>7%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QTc</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Lightheadedness</td>
<td>43%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Systolic BP Decrease &gt;20 mm Hg</td>
<td>10%</td>
<td>10%</td>
<td>63%</td>
</tr>
</tbody>
</table>

- All patients (n=60)
- Starting dose 150 mg/day
- Starting dose 300 mg/day

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Grades 1/2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>7%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42%</td>
<td>18%</td>
<td>8%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2%</td>
<td></td>
<td>5%</td>
</tr>
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</table>

Platelet inclusion criteria: INCB018424: 100k; TG101348: 50k; CYT387: 50k

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**The two pathogenetic faces of myelofibrosis**

- **Secondary inflammatory state (cytokine-mediated)**
  - Bone marrow stromal reaction
  - Abnormal cytokine milieu
  - Ineffective hematopoiesis (anemia)
  - Extramedullary hematopoiesis (splenomegaly)
  - Hypercatabolic symptoms, pruritus and cachexia

- **JAK-STAT-driven clonal myeloproliferation**
  - AML Survival
  - Leukocytosis
  - Thrombocytosis
**JAK2V617F allele burden**

**Baseline**  
60% (23-100%)  

**Cycle 6**  
31% (4-100%)  

**Cycle 12**  
32% (7-100%)  

$p < 0.01$

**Interleukin-6**  

**Interleukin-8**  

**Interleukin-2**  

**TNF-α**  

**TG101348**

**JAK1 inhibition**  

**JAK1/2 inhibition**  

**JAK2 inhibition**  

**JAK2V617F inhibition**

Can targeting cytokines favorably impact survival in MF?

Plasma cytokines in primary myelofibrosis are abnormally increased and correlate with phenotype and prognosis. IL-8, IL-2R, IL-12, IL-15 and CXCL10 were independently associated with poor survival.

90 treatment-naive patients with PMF
- Plasma IL-8 and IL-2R in the normal range (n=60) Median survival ~80 months
- One or both cytokines elevated (n=30) Median survival ~17 months

Only intermediate-1 risk patients considered; N = 27
- Plasma IL-8 and IL-2R in the normal range (n=21) Median survival "not reached"
- One or both cytokines elevated (n=6) Median survival ~17 months

J Clin Oncol. 2011 Apr 1;29(10):1356-63
The fallacy of retrospective comparisons

Mature survival data for 288 young patients (age ≤65 years) with primary myelofibrosis stratified by year of diagnosis

P=0.003

What can we expect from JAK inhibitor therapy in PV or ET?

Survival and risk of leukemic transformation in ET are significantly influenced by accurate morphologic diagnosis: An international study of 1,104 patients.

Barbui et al. Blood 2010; 2010 ASH abstract #457

Fibrotic progression was significantly less in the presence of JAK2V617F
What is the prognosis for JAK inhibitors in Ph- myeloproliferative neoplasms?

• **Myelofibrosis**
  – Well tolerated, significant palliation
  – Disease modifying?
  – Combination with other agents

• **Polycythemia vera / Essential thrombocythemia**
  – Limited niche (e.g. refractory pruritus)
  – Unproven benefit wrt clinically relevant end points