Rasopathy Education Day

Precision Medicine in Juvenile Myelomonocytic Leukemia

Elliot Stieglitz, MD
10/11/17
Juvenile Myelomonocytic Leukemia (JMML)

Overlapping myelodysplastic / myeloproliferative disorder

K. White, UCSF Dept. of Hematopathology
JMML is Initiated by Hyperactive Ras

- GM-CSF
- JAK2
- STAT5
- Shc
- Grb2
- SOS
- Gab2
- SHP-2
- Ras-GDP
- Ras-GTP*
- NF1
- c-CBL

Abnormal Proliferation, Survival
Neurofibromatosis Type 1 Related Cancers

1) Germline condition with one NF1 mutation in every cell

2) Patients develop cancer when the 2\textsuperscript{nd} copy is lost
   1) Optic glioma
   2) Glioblastoma
   3) Leukemia
   4) Neuroblastoma
   5) MPNST
   6) GIST
JMML is Initiated by Hyperactive Ras

**Diagram:**
- GM-CSF activates JAK2 and STAT5.
- JAK2 and STAT5 activate Ras-GDP.
- Ras-GTP activates RAF, MEK, and ERK.
- ERK contributes to Abnormal Proliferation and Survival.
- Hyperactive Ras at different points is indicated with percentages: 25%, 35%, and 15%.

**Genes and Disorders:**
- NF1, KRAS, NRAS, CBL, PTPN11.
Outcome was independent of canonical mutation status.
Can We Predict Which Child Will Survive?

PTPN11  

PTPN11
Hypotheses

1) Underlying genetics and epigenetics influence outcome

2) Focusing on relapsed disease will yield new therapeutic opportunities
Exome Sequencing Landscape

Mutations Identified in 100 Patients

Detected At Diagnosis
Detected At Relapse

- NF1
- KRAS
- NRAS
- CBL
- PTPN11
- RRAS
- RRAS2
- SH2B3
- JAK3
- SETBP1
- GATA2
- RUNX1
- ASXL1
- EZH2
- DNMT3A
- ZRSR2
- Mono_7
Validation Cohort

Event Free Survival (Probability)

Time From Diagnosis (Years)

Log Rank p=0.0004

0-1 alterations
2 or more alterations

n=49
n=22
Can We Predict Which Child Will Survive?

PTPN11

PTPN11 + SH2B3
Altered DNA Methylation
JMMML is Initiated by Hyperactive Ras

**Diagram:**
- **GM-CSF**
  - **SH2B3**
  - **JAK2**
  - **STAT5**
- **c-CBL**
- **Grb2**
- **SOS**
- **SHP-2**
- **Shc**
- **Gab2**
- **Ras-GDP**
  - **NF1**
- **Ras-GTP**
  - **RAF**
  - **MEK**
  - **ERK**

**Annotations:***
- **7%**
- **25%**
- **35%**
- **15%**

**Chemical Structures:**
- Trametinib
- 

**Textual Information:**
- **JMML is Initiated by Hyperactive Ras**
- **SH2B3**
- **JAK2**
- **STAT5**
- **c-CBL**
- **Grb2**
- **SOS**
- **SHP-2**
- **Shc**
- **Gab2**
- **Ras-GDP**
- **NF1**
- **Ras-GTP**
- **RAF**
- **MEK**
- **ERK**

**Abnormal Proliferation, Survival**

**Additional Notes:**
- **Orally bioavailable**
- **MEK inhibitor**

**Chemical Structures:**
- Trametinib
Phase II Study of Trametinib in children with relapsed or refractory JMML

*First trial in relapsed JMML in the United States

Day 1:
Begin Trametinib

Day 28:
End of cycle

Cycle:

*Trametinib is administered orally.
Trametinib in Treating Patients With Relapsed or Refractory Juvenile Myelomonocytic Leukemia

Memo

To: Principal Investigators and Clinical Research Associates
From: Catalina Martinez, Protocol Coordinator
Re: Study Activation

Study: ADVL1521, A Phase 2 study of the MEK inhibitor Trametinib (IND#119346, NSC#763093) in Children with Relapsed or Refractory Juvenile Myelomonocytic Leukemia

Date: October 6, 2017
Thoughts for an international trial?

Study Entry
Genotyping and Methylation analysis
HLA typing

Ras pathway alteration
Low Methylation

MEK inhibitor monotherapy x 2-3 cycles

If disease progression, roll into relapsed clinical trials...

Ras pathway alteration
Intermediate or High Methylation

MEK inhibitor + Azacitidine x 2-3 cycles

Stem cell transplant
Rigosertib in JMML?

One of the best Rigosertinib single agent responses we have seen to date, but overall patient is relatively “resistant to most agents”
NOONAN SYNDROME AND RELATED DISORDERS: Opportunities for Therapy

Bruce D. Gelb, M.D.
Mindich Child Health and Development Institute
Departments of Pediatrics & Genetics and Genomic Sciences
October 2017
“Of particular interest was the recognition of a previously unreported syndrome in 9 patients with valvular pulmonary stenosis. These children were characterized by small stature, hypertelorism, mild mental retardation, and in some instances by ptosis, undescended testes, and skeletal malformations.”

Jacqueline A. Noonan
Midwest Society for Pediatric Research
1962

Published: Am J Dis Child, 1968
Noonan Syndrome
PHENOTYPE

- Major Features
  - Short Stature
  - Facial Dysmorphism
  - Cardiovascular Disease
    - Pulmonic Valve Narrowing
    - Hypertrophic Cardiomyopathy
    - Holes in the heart
    - Aortic Narrowing
Noonan Syndrome
PHENOTYPE

• Skeletal
  – Abnormal breastbone
  – Vertebral
  – Abnormal elbows
• Webbed/Short Neck
• Undescended testes
• Bleeding Tendency
• Intellectual and Developmental Delays (IDD)
Noonan Syndrome

EPIDEMIOLOGY & GENETICS

- Prevalence: 1 in 1,000 - 2,500 Live Births
- Autosomal Dominant
  - High Percentage of Sporadic Cases
- Genetically Heterogeneous
NS Gene Identification

POSITIONAL CANDIDACY

UCSC Genome Browser on Human May 2004 Assembly

Position: chr12:107,510,000-113,553,655
Size: 6,043,656 bp
Image width: 620 pixels

Chromosome Band: 12q24.13

ST marker locations and genetic positions are shown for the region of interest.
Noonan Syndrome

RELATED PHENOTYPES

• Noonan Syndrome with Multiple Lentigines
  (formerly LEOPARD Syndrome)

• Noonan-Like with Loose Anagen Hair

• Cardiofaciocutaneous Syndrome

• Costello Syndrome
RAS PATHWAY DISORDERS

Growth factor

Cell membrane

RTK

SOS1

GRB2

SHC

SHP2

PTPN11/SHP2: NS, LS

HRAS: CS
KRAS: NS, CFCS
NRAS: NS

GDP-RAS

GTP-RAS

RAF1: NS, LS
BRAF: CFCS, NS, LS

RAF

MEK

MEK1: CFCS, NS
MEK2: CFCS

SHOC2: NS/LAH

PP1C

SHOC2: NS/LAH

SPRED1

SPRED1: NFLS

CBL: NS-like phenotype

Ubiquitin

Receptor internalization and degradation

Growth factor

NF1: NF1, NFNS, WS

Neurofibromin

Gelb and Tartaglia, J Clin Invest 2011
Noonan Syndrome

GENOTYPE-PHENOTYPE

- **PTPN11**
  - Increased Pulmonic Valve Narrowing and Atrial Holes
  - JMML (Leukemia)
- **KRAS**
  - Severe with Skin Involvement and IDD
- **SOS1**
  - Normal Stature and Development
  - Skin Involvement
- **RAF1**
  - Hypertrophic Cardiomyopathy
- **SHOC2**
  - Abnormal Hair
RASopathy Drug Therapy

POSSIBILITIES

- Hypertrophic Cardiomyopathy
- Developmental Delay
- Postnatal Valve Narrowing
- Short Stature
- Craniofacial Abnormalities
NS Hypertrophic Cardiomyopathy SURVIVAL

Wilkinson et al., Am Heart J 2012
Raf1 L613V Mutant
MOUSE KNOCK IN

Wu et al., J Clin Invest 2011
Raf1 L613V Knock-In Mouse Study

SUMMARY

• Mapk Signaling
  – Increased Erk Activation
  – No Change in p38 or JNK

• Mek Inhibitor (PD0325901)
  – 6-Week Treatment from 4 Weeks of Age
  – Rescued Hypertrophic Cardiomyopathy
• Generated Transgenic NS and NSML Flies

• NS Flies
  – Gain-of-Function Ectopic Wing Veins

• NSML Flies
  – Gain-of-Function Wing Veins & R7 Photoreceptors
Drosophila Learning & Memory

OLFACTORY CONDITIONING

Vosshall, Nature 2007
Drosophila Memory Deficit

SUMMARY

- Specific Long-Term Memory Deficit
- Due to Increased MAPK Activation
- Not Developmental
  - Can Be Induced in Adulthood
- Treatable
  - SHP-2 Inhibitor
  - Altered Training Paradigms
- Does This Apply to Patients with Noonan Syndrome?
LEANING ON CANCER

• Human Cancers
  – 30-40% RAS Pathway Mutations
    • Acquired, Not Inherited
  – Gain in Pathway Signaling
    • Blocking Pathway → Cancer Cell Death

• Drug Companies
  – Developing RAS/MAPK Inhibitors
CAUTIONARY NOTES

• MEK Inhibitor Side Effects
  – Serious Skin Rashes
  – Diarrhea
  – Severe Leukopenia

• Time Course
  – Cancer: Relatively Short
  – RASopathy: ??????
POTENTIAL FOR RIGOSERTIB

• Side Effect Profile
  – Data from MDS Encouraging
  – No Data for Children
    • Could be from JMML Studies?

• Target
  – Severe Hypertrophic Cardiomyopathy
    • Need Pre-Clinical Data
      – Mouse Models Available
Acknowledgments

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Ross Cagan
Susumu Hirabayashi

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Maria Kontaridis
Amy Roberts

**Duke**
Matthew Wolf
Rigosertib
Strategies to the Rasopathies

Steven Fruchtman, M.D.
Chief Medical Officer & Senior Vice President
Research & Development

Rasopathy Conference  NYC
Oct 11 2017
The three RAS genes (HRAS, KRAS and NRAS) comprise the most frequently mutated gene family in cancer (~25%)
RASOPATHIES:
RARE PEDIATRIC DISEASES LINKED BY A COMMON MECHANISM

- A group of genetic syndromes caused by germline and/or somatic mutations in genes that encode components or regulators of the Ras/mitogen-activated protein kinase (MAPK) pathway.

- Typically involve tumors of the bone marrow (JMML- referred to as a Pediatric MDS or MPN)) or the nervous system/soft tissue fascia and may be associated with other end organ abnormalities (cardiac, cranio-facial).
RAS SIGNALS VIA MULTIPLE EFFECTORS

Effector proteins contain common RAS-binding domain (RBD)
RAS/MAPK/ERK PATHWAY AND RASOPATHIES

*More recent factors*
DESCRIPTION OF RIGOSERTIB AS A RAS MIMETIC

A Small Molecule RAS-Mimetic Disrupts RAS Association with Effector Proteins to Block Signaling

Sai Krishna Athuluri-Divakar,¹,² Rodrigo Vasquez-Del Carpio,¹,² Kaushik Dutta,³ Stacey J. Baker,¹,² Stephen C. Cosenza,¹,² Indranil Basu,⁵ Yogesh K. Gupta,¹,² M.V. Ramana Reddy,¹,² Lynn Ueno,⁴ Jonathan R. Hart,⁴ Peter K. Vogt,⁴ David Mulholland,¹,² Chandan Guha,⁵ Aneel K. Aggarwal,¹,² and E. Premkumar Reddy¹,²,*

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³Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, NY 10029, USA
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⁵Department of Radiation Oncology, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461, USA

*Correspondence: ep.reddy@mssm.edu
Rigosertib Mechanism of Action

- **RAS**
  - PI3K
  - Akt
  - Increased by Growth Factor
  - Regulates survival, cell growth, metabolism

- **Receptor Tyrosine Kinase**
  - Growth Factor
  - PI3K
  - Akt
  - Cell growth, survival, metabolism

- **PLK1**
  - Aurora A
  - Mitosis
  - Transcription

- **MEK**
  - ERK
  - Mitosis
  - Transcription

- **RAS**
  - PI3K
  - Akt
  - Increased by Growth Factor
  - Regulates survival, cell growth, metabolism

- **Growth Factor**
  - PI3K
  - Akt
  - Cell growth, survival, metabolism
SECONDARY/TERTIARY STRUCTURAL SIMILARITY OF RBDS DESPITE LACK OF EXTENSIVE SEQUENCE HOMOLOGY

Sequence Alignment of RA and RB Domains

Yellow: Hydrophobic Core; Cyan: Conserved Charged Amino Acids; Red: Conserved Hydrophobic AA; Green: Conserved Aromatic AA

RAF/Ral-GDS/PI3K Crystal Structures Superimposed

NMR Structures of 10 RBDs Superimposed

Yellow: Hydrophobic Core; Cyan: Conserved Charged Amino Acids
Red: Conserved Hydrophobic AA; Green: Conserved Aromatic AA
NOVEL MECHANISM OF ACTION OF RIGOSERTIB

History:
- Rigosertib is a first-in-class molecule that targets the multiple signaling pathways driven by RAS.
- Rigosertib achieves this by binding to the RBD of Ras effector proteins including PI3K and Raf, thereby leading to their inactivation.
- This novel mechanism helps to explain the pleiotropic effects of rigosertib, such as inhibition of the PI3K and PLK pathways.

Future directions:
- Exploit the new knowledge to determine the extent of Ras effector proteins targeted by rigosertib and their role in additional tumor types.
- Further characterize the potential for rigosertib in Ras-driven tumors:
  - Tumors with activation of Ras pathways
  - Tumors due to Ras activating mutations
JUVENILE MYELOMONOCYTIC LEUKEMIA OVERVIEW

- Hematopoietic disorder of infancy caused by excessive proliferation of monocytic and granulocytic cells; which infiltrate the spleen/liver, intestines and lungs
- Rare - 2% of pediatric hematologic malignancies (in the US about 50 new cases per year); 1.2 cases per million annually, median age is 2 years
- Present with fever, thrombocytopenia, failure to thrive, and splenomegaly.
- Frequently fatal, allogeneic stem cell transplant only curative approach; which carries an event-free survival (EFS) at 5 years of only 52% due to relapsed disease or transformation to AML
- Historically, myeloid progenitor hypersensitivity to granulocyte macrophage colony-stimulating factor (GM-CSF) is a key diagnostic feature of JMML
GROWTH INHIBITION AND INDUCTION OF APOPTOSIS WITH RIGOSERTIB IN NF1 CELLS

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

SNF-96.2 CELLS

PERCENT OF CONTROL

CONCENTRATION (µM)

FACS Analysis of SNF 96.2 Cells Treated With Rigosertib

PARP Cleavage Assay
TWO RIGOSERTIB FORMULATIONS

- **IV (Phase 3 INSPIRE ongoing)**
  - Continuous infusion using a portable pump
  - >500 patients treated in trials
  - Lead indication 2nd-line HR-MDS

- **Oral (Phase 2 enrolled)**
  - Bioavailability ~35%
  - >200 patients treated
  - Combination with azacitidine for HR-MDS and AML

---

**Plasma Levels of Rigosertib from a Bioavailability Study**

- 24 Hr Inf 800 mg/m2
- Oral-560 mg Fasted
- Oral-560 mg Fed
BONE MARROW ASPIRATE
BEST FOR CELLULAR MORPHOLOGY
DIAGNOSIS OF MDS IS BASED ON MORPHOLOGY
REVISED IPSS-R IN RELATION TO SURVIVAL

Greenberg et al. *Blood* 2012;120:2454-65
CAUSE OF DEATH IN MDS

Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial

Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, Gianluca Gaidano, Bart L Scott, Peter Greenberg, Uwe Platzbecker, David P Steensma, Suman Kambhampati, Karl-Anton Kreuzer, Lucy A Godley, Ehab Atallah, Robert Collins Jr, Hagop Kantarjian, Elias Jabbour, Francois E Wilhelm, Nozar Azarnia, Lewis R Silverman, for the ONTIME study investigators*

Summary

Background Hypomethylating drugs are the standard treatment for patients with high-risk myelodysplastic syndromes. Survival is poor after failure of these drugs; there is no approved second-line therapy. We compared the overall survival of patients receiving rigosertib and best supportive care with that of patients receiving best supportive care only in patients with myelodysplastic syndromes with excess blasts after failure of azacitidine or decitabine treatment.
PATIENT POPULATION FOR PHASE 3 INSPIRE TRIAL

Data from ONTIME Paper* Recently Published in Lancet Oncology

**ITT for ONTIME Trial**
- 299 Patients

**Subpopulation for INSPIRE Trial (ONTIME subset)**
- 116 Patients

- ITT OS analysis of ONTIME – HR= 0.87; NS survival benefit
- ITT OS of proposed INSPIRE population – HR = 0.48; P = 0.0008

## ONTIME TRIAL: ITT SUBGROUPS CORRELATED WITH BETTER SURVIVAL BENEFIT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Rigosertib</th>
<th></th>
<th></th>
<th>HR (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (mos)</td>
<td>N</td>
<td>Median (mos)</td>
<td></td>
</tr>
<tr>
<td><strong>Monosomy 7</strong></td>
<td>16</td>
<td>5.6</td>
<td>13</td>
<td>2.8</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.09-0.66)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Trisomy 8</strong></td>
<td>22</td>
<td>9.5</td>
<td>8</td>
<td>4.5</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.12-0.95)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Very high risk per IPSS-R</strong></td>
<td>93</td>
<td>7.6</td>
<td>41</td>
<td>3.2</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.37-0.84)</td>
<td>0.005</td>
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</table>
### SAFETY OF SINGLE-AGENT IV RIGOSERTIB IN MDS

Treatment-related Adverse Events Reported in ≥5% of Patients with MDS Treated with IV Rigosertib as Monotherapy (N=355)

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>All Grades</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related AE</td>
<td>238 (67)</td>
<td>55 (15)</td>
<td>70 (20)</td>
<td>71 (20)</td>
<td>37 (10)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>64 (18)</td>
<td>51 (14)</td>
<td>10 (3)</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>63 (18)</td>
<td>18 (5)</td>
<td>38 (11)</td>
<td>6 (2)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>51 (14)</td>
<td>37 (10)</td>
<td>10 (3)</td>
<td>4 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>40 (11)</td>
<td>32 (9)</td>
<td>7 (2)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>25 (7)</td>
<td>1 (&lt;1)</td>
<td>4 (1)</td>
<td>18 (5)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (7)</td>
<td>17 (5)</td>
<td>5 (1)</td>
<td>2 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysuria</td>
<td>20 (6)</td>
<td>14 (4)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19 (5)</td>
<td>14 (4)</td>
<td>4 (1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
INSPIRE: RIGOSERTIB PHASE 3 TRIAL

Post-HMA HR-MDS (N=225)

Key Eligibility Criteria:
- Failed HMA < 9 months DoT
- < 82 years of age
- Last HMA within 6 months

Randomization 2:1

IV rigosertib + BSC
N = 150

Follow-up

Physician's Choice + BSC
N = 75

Overall Survival
- Interim analysis (88 events)
- Intent-to-treat analysis (176 events)

• Statistical analysis: two analysis planned
  1. Power 0.80; Target HR < 0.625; (reduce mortality by > 37.5%)
  2. \(\alpha\) for ITT = 0.04; \(\alpha\) for IPSS-R VHR = 0.01
  3. Trial can succeed in two ways: ITT population or IPSS-R Very High Risk

• Genomic sequencing of patient samples

Oral Rigosertib + Azacitidine for HR-MDS
EPIGENETIC AND GROWTH FACTOR PATHWAY MUTATIONS SYNERGIZE INDUCING LEUKEMIC TRANSFORMATION

Adapted from Papaemmanuil et al., 2013 Blood

Preclinical/clinical evidence suggest combination of epigenetic therapy plus growth factor signaling inhibitor could be effective in curbing MDS pathogenesis
RIGOSERTIB + AZACITIDINE

- Despite activity in MDS, single-agent DNMT inhibitors are limited by low CR and PR rates (7-20%) with median duration of 15 months

- Combinations should not add burdensome toxicities

- DNMT inhibition may be complemented by combination with novel mechanisms to improve response rates and duration
PRE-CLINICAL BACKGROUND

- Combination of rigosertib with AZA produced an increase of 1.7- to 2.9-fold in cytotoxicity (p<0.05) in HL-60 cells*

- Interaction resulted in a synergistic effect with combination indexes between 0.3 and 0.75

- Sequence of administration influenced degree of cytotoxicity; rigosertib priming offered optimal results

- These pre-clinical results provided rationale for combining agents in a Phase 1/2 study in MDS and AML patients with optimal sequence

RIGOSERTIB + AZACITIDINE

UPDATED PHASE 2 DATA ASH 2016*

- ORR of 85% in 20 HMA naïve patients
- ORR of 62% in 13 patients who progressed/failed prior HMA
- Median DoR for CR is 8.0 months; median time to best response is 3.3 cycles

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Eval (n=33)</th>
<th>HMA Naïve (n=20)</th>
<th>HMA Failure** (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission (CR %)</td>
<td>8 (24%)</td>
<td>7 (35%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Overall Response Rate (ORR %)</td>
<td>25 (76%)</td>
<td>17 (85%)</td>
<td>8 (62%)</td>
</tr>
</tbody>
</table>

* Data shown as of data cut off Oct 1, 2016; response based on IWG 2006 criteria

**10 patients received previous therapy with azacitidine, 2 with decitabine and 1 with both HMAs; prior HMA cycles ranged from 4-20

CBC TRENDS FOR PATIENT ON RIGO + AZA

- 12 cycles of AZA – stable disease
- RBC and platelet transfusions
- Blasts 7%
- Monosomy 7
- Runx-1
- AZA + RIG in 09-08 for 20+ months
- Complete remission
- RBC transfusion independent
- <5% blasts
- PB CR criteria
# Rigosertib in Rasopathies - Status

<table>
<thead>
<tr>
<th>Target</th>
<th>Collaboration</th>
<th>Goal</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-clinical</td>
<td>Dr. E. P. Reddy&lt;br&gt;Mount Sinai School of Medicine, New York&lt;br&gt;Dr. Elliot Stieglitz&lt;br&gt;UCSF, San Francisco</td>
<td>Proof of concept</td>
<td>• NF1 studies conducted&lt;br&gt;• Models of JMML &amp; rigosertib testing</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>National Institutes of Health</td>
<td>Pediatric tumor rasopathies</td>
<td>CRADA and protocol being developed</td>
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<tr>
<td>Advocacy</td>
<td>Leukemia &amp; Lymphoma Society&lt;br&gt;RasopathyNet Foundation</td>
<td>Collaboration and support for studies</td>
<td>Discussion</td>
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<tr>
<td></td>
<td>Academic collaborator, USA (UCSF)</td>
<td>Explore JMML</td>
<td>Protocol discussions</td>
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<tr>
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<td>Academic collaborator, EU (Dr Charlotte Niemeyer, Freiburg, Germany)</td>
<td>Explore JMML</td>
<td>Early discussions</td>
</tr>
</tbody>
</table>

**Target**
- Non-clinical studies
- Clinical trials
- Advocacy

**Collaboration**
- Dr. E. P. Reddy
- Mount Sinai School of Medicine, New York
- Dr. Elliot Stieglitz
- UCSF, San Francisco
- National Institutes of Health
- Academic collaborator, USA (UCSF)
- Academic collaborator, EU (Dr Charlotte Niemeyer, Freiburg, Germany)
- Leukemia & Lymphoma Society
- RasopathyNet Foundation
THANK YOU

- Please hold questions for a panel following all 3 presentations.