Abstract #EP829:
Mutations in RAS pathway genes correlate with Type of Failure to Azacitidine: Genomic Analysis at Randomization onto the INSPIRE Trial

Koichi Takahashi, MD¹, Anna Jonasova, MD, PhD², Selina M. Luger, MD, FRCPC³, Aref Al-Kali, MD⁴, David Valcárcel, MD⁵, Erica D. Warlick, MD⁶, Wieslaw W. Jedrzejczak, MD, PhD⁷, María Díez-Campelo, MD, PhD⁸, Patrick S. Zbyszewski, MBA⁹, Christopher Cavanaugh⁹, Richard C. Woodman, MD⁹ & Steven M. Fruchtman, MD⁹, Guillermo Garcia-Manero, MD¹

¹University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX; ²1st Medical Department - Hematology, General Hospital, Prague, Czech Republic; ³Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; ⁴Division of Hematology, Mayo Clinic, Rochester, MN; ⁵Planta Baixa, Hospital Universitari Vall d’Hebron, Barcelona, Spain; ⁶Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN; ⁷MTZ Clinical Research, Medical University of Warsaw, Warsaw, Poland; ⁸Hematology Department, Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, Salamanca, Spain; ⁹Onconova Therapeutics, Inc., Newtown, PA; ¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
Introduction

- More than 45 mutations have been identified in association with HR MDS and the number of mutations increases and changes following HMA failure and leukemic transformation (Haferlach Leukemia 2014, Lindsley NEJM 2017);

- In the majority of patients with MDS (80%) co-mutations are present and the prognostic contribution of each individual mutation remains elusive, especially after adjusting for clinical variables such as IPSS-R score. Only a few mutations are predictive of poor prognosis (e.g. TP53, SF3B1) (Haferlach Leukemia 2014);

- N-RAS and K-RAS mutations as well as regulators of the Ras pathway (e.g. PTPN11, NF1) are frequently observed (15-20%) in HR MDS, however their clinical impact is unclear, especially in de novo MDS (Haferlach Leukemia 2014);

- Rigosertib (RGS) is a non-ATP-competitive small molecule RAS mimetic that has the potential to block RAS-RAF-MEK-ERK and PI3K-AKT-mTOR signaling pathways (Athuluri-Divakar 2016). Rigosertib has the potential to also inhibit wildtype upregulation of RAS;

- We report here the genomic profile of 190 patients with HMA failure HR MDS at the time of study entry prior to receiving rigosertib in the INSPIRE study (NCT025622443) an ongoing phase 3 randomized global study evaluating IV rigosertib vs Physicians Choice (PC) in patients with HR MDS post HMA failure;
INSPIRE (04-30) Study

Eligibility:
- MDS subtypes RAEB-1, RAEB-2, or RAEB-t
- Progression or failure to respond to HMA
- HMA treatment duration ≤ 9 cycles in ≤ 12 months
- < 82 years of age

Stratification at randomization:
- VHR vs. non-VHR IPSS-R
- By geography

Primary Objective: To compare the overall survival (OS) of patients in the rigosertib group vs PC arm in all patients and a sub-group of patients with IPSS-R very high risk;

Exploratory Objective: Correlation of overall survival and clinical responses with mutational status;
Key Inclusion Criteria

- INSPIRE (NCT02562443) is a global randomized Ph3 trial in pts with HR-MDS after HMA failure with an overall target enrollment of 360 pts which has recently been achieved.

- Key inclusion criteria includes:
  
  - age < 82 years,
  
  - RAEB-1, RAEB-2 or RAEB-t and ≥ 1 cytopenia;
  
  - Higher Risk MDS per IPSS-R Intermediate risk (IR), high risk (HR) and very high risk (VHR);
  
  - Duration of prior HMA ≤ 9 cycles within 12 months and last dose of HMA ≤ 6 months before enrollment;
  
  - One of the following:
    - Progression (2006 IWG criteria) at any time after initiation of AZA or DEC treatment or
    - Failure to achieve complete or partial response or HI (according to 2006 IWG) after at least six 4-week cycles of AZA or either four 4-week or four 6-week cycles of DEC or
    - Relapse after initial complete or partial response or HI (according to 2006 IWG criteria) or
    - Intolerance to azacitidine or decitabine;
Methodology

• Bone marrow samples were collected at study baseline and at Months 2, 4 and 6 and every 6 months thereafter as well as at the end of treatment for mutational analysis as an exploratory endpoint;

• In this abstract we report the genomic characterization of baseline samples; future analyses will report longitudinal assessment while on therapy as well as at the time of disease progression;

• Genomic DNA was extracted from diagnostic bone marrow or peripheral blood samples and targeted capture deep sequencing of 295 genes was performed (median sequencing depth 500x) using Agilent’s SureSelect custom panel;

• Modified Mutect and Pindel were used to identify high-confidence somatic mutations;
Table 1: Patient Demographics (N=190)

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67 (35)</td>
</tr>
<tr>
<td>Male</td>
<td>121 (64)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (2)</td>
</tr>
<tr>
<td>White</td>
<td>152 (80)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (4)</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>73</td>
</tr>
<tr>
<td>Range</td>
<td>54 – 82</td>
</tr>
<tr>
<td><strong>ECOG performance Status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40 (21)</td>
</tr>
<tr>
<td>1</td>
<td>87 (46)</td>
</tr>
<tr>
<td>2</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Unknown</td>
<td>44 (23)</td>
</tr>
<tr>
<td><strong>MDS type</strong></td>
<td></td>
</tr>
<tr>
<td>Primary (de novo)</td>
<td>145 (76)</td>
</tr>
<tr>
<td>Secondary</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>33 (17)</td>
</tr>
<tr>
<td><strong>WHO/FAB classification</strong></td>
<td></td>
</tr>
<tr>
<td>RAEB-1</td>
<td>50 (26)</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>78 (41)</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>26 (14)</td>
</tr>
<tr>
<td>Unknown</td>
<td>36 (19)</td>
</tr>
<tr>
<td><strong>Failure type after the last HMA therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>61 (32)</td>
</tr>
<tr>
<td>Failure</td>
<td>59 (31)</td>
</tr>
<tr>
<td>Relapse</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Intolerance</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>33 (17)</td>
</tr>
<tr>
<td><strong>Revised IPSS score</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>19 (10)</td>
</tr>
<tr>
<td>High</td>
<td>44 (23)</td>
</tr>
<tr>
<td>Very High</td>
<td>93 (49)</td>
</tr>
<tr>
<td>Unknown</td>
<td>34 (18)</td>
</tr>
</tbody>
</table>
Figure 1: Genomic Profiling in Patients with HMA Failure at Baseline for INSPIRE Study
Genomic Profiling in Patients with HMA Failure at Baseline Assessment for INSPIRE Study

- Data is presented as blinded aggregate results for both arms of the study;
- Baseline mutations are presented for 190 pts of which 157 pts were randomized and 33 pts were screen failures;
- Median age is 73 years (54-82). IPSS-R scores for the pts randomized were: Intermediate 19 (10%), High 44 (23%) and VHR 93 (49%);
- In total 55 different mutations were identified at baseline prior to pts receiving study treatment with either IV rigosertib or PC and the median number of mutations per pt was 3;
- The most common mutations identified in pts were ASXL1 37%, TP53 26%, RUNX1 26%, TET2 23%, STAG2 21%, DNMT3A 17%, and SRSF2 17%;
Figure 2: Pair-wise Analysis of Mutation Co-Occurrence
Figure 3: Correlation of Mutation and Baseline Clinical Features
Figure 4: Correlation With Mutations and Types of Failure
Conclusions

• The baseline mutational analyses from the INSPIRE study provides important new insights regarding the genomic profile of patients with HMA failure, especially for the subset categorized as VHR;

• The genomic profile is representative of a cohort enriched for the VHR subset;

• RAS pathway mutations were observed more commonly in patients that progressed on HMA therapy vs patients that failed HMA therapy as defined by IWG 2006 criteria;

• Future genomic analyses of the INSPIRE study will expand the data set and will evaluate correlation of clinical responses with changes in mutational status;

• It is anticipated that these analyses will provide important new insights in the selection of mutations, including but not exclusively the RAS pathway, on the development of leukemic progression in patients with HR MDS following HMA failure and treatment rigosertib.
Acknowledgements*

USA
- Dr. Garcia-Manero, Guillermo; University of Texas MD Anderson Cancer Center
- Dr. Silverman, Lewis; Icahn School of Medicine at Mount Sinai
- Dr. Bejar, Rafael; The Regents of the University of California
- Dr. O'Connor, Casey; USC Norris Comprehensive Cancer Center
- Dr. Baer, Maria; University of Maryland Greenebaum Cancer Center
- Dr. Stiff, Patrick; Loyola University Medical Center
- Dr. Scott, Matt; Fred Hutchinson Cancer Research Center
- Dr. Warlick, Erica; University of Minnesota Physicians BMT Clinic
- Dr. Sayar, Hamid; Indiana University Melvin and Bren Simon Cancer Center
- Dr. Luger, Selina; University of Pennsylvania,
- Dr. Arana-Vi, Cecilia; New Mexico Cancer Care Alliance
- Dr. Schaar, Dale; Rutgers Cancer Institute of New Jersey
- Dr. Gamalski, Steven; Henry Ford Health System
- Dr. Fanning, Suzanne; GHS Cancer Institute
- Dr. Moesi, Mehdi; Cancer Specialists of North Florida - Jacksonville
- Dr. Safa, Hana; Tulane University Hematology & Medical Oncology
- Dr. Keng, Michael; University of Virginia Cancer Center
- Dr. Yacoub, Abdelraheem; University of Kansas Cancer Center
- Dr. Al-Kali, Aref; Mayo Clinic
- Dr. Hansen, Vincent; Northern Utah Associates LLC
- Dr. Hansen, Vincent; Northern Utah Associates LLC
- Dr. Patel, Prapti; UT Southwestern Medical Center
- Dr. Mattison, Ryan; University of Wisconsin Clinical Science Center
- Dr. Anz, Bertrand; SCR - Tennessee Oncology - Chattanooga
- Dr. Fenaux, Pierre; Saint-Louis Hospital, Department of Hematology Seniors
- Dr. Wattel, Eric; Centre Hospitalier Lyon Sud
- Dr. Thepot, Sylvain; Centre Hospitalier Universitaire, Angers
- Dr. Quesnel, Bruno; Claude Huriez Hospital, Department of Hematology
- Dr. Legros, Laurence; Archez 1 Hospital, Department of Clinical Hematology
- Dr. Clouseau, Thomas; Canada University Hospital
- Dr. Natarajan-Ame, Shanti; Hôpital Civil
- Dr. Mandac Rogulj, Inga; Clinical Hospital Duran i Godina
- Dr. Jonasova, Anna; General University Hospital in Prague, 1st Internal Clinic
- Dr. Belohlavkova, Petra; University Hospital Hradec Kralove, 4th Internal Clinic of Hematology
- Dr. Hajek, Roman; University Hospital Ostrava, Department of Hematonoconology
- Dr. Machova, Renata; University Hospital Olomouc
- Dr. Giagounidis, Aristoteles; Marien Hospital Duesseldorf GmbH
- Dr. Platzbecker, Uwe; University Hospital Carl Gustav Carus
- Dr. Sockel, Katja; University Hospital Carl Gustav Carus
- Dr. Lunghi, Monia; University Hospital "Maggiore della Carita" of Novara, Department of Oncology, Operating Unit of Hematology
- Dr. Cavo, Michele; Polyclinic S. Orsola-Malpighi, Department of Hematology, Oncology and Laboratory Medicine, Operative Unit of Hematology - Cavo
- Dr. Ferrero, Dario; University Hospital San Giovanni Battista di Turin, Complex Structure of Oncohematology - UO
- Dr. Liberati, Anna Marina; Hospital S. Maria of Terri, Department of Medicine and Medical Specialties, Complex University Structure of Oncohematology
- Dr. Rossi, Giuseppe; Civil Hospital of Brescia, Department of Clinical Oncology, Operative Unit of Hematology
- Dr. Vos, Maria Teresa; Polyclinic Tor Vergata, Department of Medicine, Complex Operative Unit of Hematology
- Dr. Niccola, Pasquale; Hospital S. Eugenio
- Dr. Jedrzejczak, Wieslaw; MTZ Clinical Research Inc.
- Dr. Halla, Janusz; Oncology Center of Warmia and Mazury in Olsztyn, Teaching Department of Hematology
- Dr. Urbanowicz, Alina; Dr. Ludwik Rydygier Provincial Hospital in Suwalki, Department of Clinical Oncology and Hematology
- Dr. Dr. Dr. Wolbrek, Tomasz; Independent Public Clinical Hospital #1 in Wroclaw, Department of Hematology, Blood Tumors and Bone Marrow Transplantation
- Dr. Killick, Sally; Royal Bournemouth Hospital, Department of Hematology
- Dr. Oktatókórház Hematológiai Osztály
- Dr. Polen, Judit; Johann Wolfgang Goethe University Hospital, Center for Internal Medicine, Medical Clinic II
- Dr. Enright, Helen; Adelaide and Meath Hospital Inc. National Children’s Hospital, Department of Hematology
- Dr. Cahil, Mary; Cork University Hospital
- Dr. Arman Sangerman, Montserrat; Institut Català d’Oncologia (ICO L’Hospitalat) - Hospital Duran i Reynals
- Dr. Font Lopez, Patricia; General University Hospital Gregorio Maranon
- Dr. Rosell, Ana-Isabel; Hospital Universitario Virgen de la Victoria Hospital de Dia de Hematologia, 1Planta
- Dr. Diez Campelo, Maria; University Clinical Hospital of Salamanca, Department of Hematology
- Dr. Valcarcel Ferreiras, David; Hospital Universitari Vall de Hebron Servei d’Hematologia i Hemoterapia
- Dr. Xicy Cirici, Blanca; ICO Badalona - Hospital Universitari Germans Trias I Pujol
- Dr. Usuki, Rensuke; NTT Medical Center Tokyo,
- Dr. Suzuki, Kengo; Sanctuary Red Cross Medical Center
- Dr. Maito, Kazuyuki; Tokai Central Hospital
- Dr. Uoshiba, Nobuhiko; Japanese Red Cross Kyoto Daini Hospital
- Dr. Makita, Masanori; National Hospital Organization Okayama Medical Center
- Dr. Nakamura, Shigen; Tokushima University Hospital
- Dr. Hida, Michihito; National Hospital Organization Kumamoto Medical Center
- Dr. Yamauchi, Takahiro; University of Fukui Hospital
- Dr. Ibekwe, Inyin; Kagoshima University Hospital
- Dr. Matsusuma, Itaru; Kindai University Hospital
- Dr. Choi, Ilseung; National Hospital Organization Kyushu Cancer Center,
- Dr. Fujita, Hiroki; Saikeika Yokohamashi Nanko Hospital
- Dr. Vee, Karen; Princess Margaret Cancer Centre
- Canada - Dr. Buckstein, Rona; Sunnybrook Research Institute, Odette Cancer Center
- Croatia - Dr. Assouline, Sarit; Jewish General Hospital
- Czech Republic - Dr. Jonasova, Anna; General University Hospital, Prague 3; Internal Clinic - Clinic of Hematology
- Czech Republic - Dr. Belohlavkova, Petra; University Hospital Hradec Kralove, 4th Internal Clinic of Hematology
- Czech Republic - Dr. Haji, Roman; University Hospital Ostrava, Department of Hematonoconology
- Czech Republic - Dr. Machova, Renata; University Hospital Olomouc
- Sweden - Dr. Grau, Carlos; Hospital Universitario Mont-Godin
- Russia - Dr. Masure, Dominiek; University Hospital Ghent
- Russia - Dr. Delloisla, Dominik; General Hospital Saint-Jan
- Germany - Dr. Brolden, Per Anders; Karolinska University Hospital, Department of Hematology
- Germany - Dr. Korotkov, Polina; Peter the Great Military Medical Academy
- Germany - Dr. Strehler, Elizabeth; Swiss Society for Clinical Research
- Russia - Dr. Barinov, Aleksey; Russkiy Clinical Hospital
- Australia - Dr. Harrup, Rosemary Anne; Royal Hobart Hospital (RHQ), Department of Hematology and Oncology
- Austria - Dr. Pfeifstoecker, Michael; Hannusch Hospital

* Represents sites that contributed patient samples used in this analysis
References