TP53 Abnormalities Correlate with Immune Infiltration and Associate with Response to Flotetuzumab Immunotherapy in Acute Myeloid Leukemia

• Research funding, NanoString Technologies, Seattle, WA
• Research funding, MacroGenics, Rockville, MD
• Research funding, Kura Oncology, San Diego, CA
Somatic TP53 mutations and deletions of 17p, to which TP53 is mapped, occur in 8-10% of de novo AML and are associated with chemotherapy resistance, high risk of relapse and dismal prognosis even after hematopoietic stem cell transplantation.

A recent analysis of The Cancer Genome Atlas (TCGA) transcriptomic data from 10,000 non-hematologic tumors has indicated that TP53 mutations correlate with higher proportions of PD-L1-expressing CD8+ T cells, and with increased expression of T-cell effector genes and interferon (IFN)-γ-related genes.

We have recently identified bone marrow (BM) IFN-γ-related transcriptional profiles that stratify patients with AML into an immune-infiltrated and an immune-depleted subtype, and that enrich in patients with chemotherapy-refractory disease (Vadakekolathu J, et al. Sci. Transl. Med. 2020; 12: eaaz0463).
• Do TP53 abnormalities correlate with the composition and functional orientation of the immunological tumor microenvironment (TME) in AML?

• Are patients with TP53-mutated, relapsed/refractory AML responsive to treatment with flotetuzumab, an investigational CD123 × CD3 bispecific DART® molecule?
Patients and Methods

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=45)</th>
<th>Patients with <em>TP53</em> mutations and/or 17p abnormalities (n=15^)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median and range)</td>
<td>61 (27-81)</td>
<td>61 (27-81)</td>
</tr>
<tr>
<td>Males/Females, n/n</td>
<td>24/21</td>
<td>8/7</td>
</tr>
<tr>
<td>AML risk stratification (2017 ELN; n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>3 (6.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8 (17.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Adverse</td>
<td>34 (75.6%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Secondary AML (n)</td>
<td>15 (33.3%)</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>Number of prior lines of therapy (median and range)</td>
<td>2 (1-9)</td>
<td>2 (1-4)</td>
</tr>
</tbody>
</table>

- ^BM samples from 13/15 patients were available for immune gene expression profiling. All 15 patients with *TP53* mutations/17p abnormalities were treated on the study and included in clinical analyses.
- Microenvironmental RNAs were profiled using the PanCancer IO 360™ gene expression panel on the nCounter® platform.
- Disease status was assessed by modified International Working Group (IWG) criteria. Specifically, overall response rate (ORR), collectively complete response, was defined as <5% bone marrow (BM) blasts (CR, CRh, CRi or morphologic leukemia-free state [MLFS]). Partial response (PR) was defined as >50% decrease or decrease to 5-25% BM blasts.
N=118 cases with available information on prognostic molecular lesions, including TP53 mutations (n=14)
TP53 Mutations Associate with High Immune Infiltration in Primary AML Samples – SAL Cohort

A: 
- 84% TP53 missense
- 12% TP53 no missense
- 4% N.A.

B: 
- TP53 status
- Mutated
- WT/NA/ND

C: 
- TP53 status
- Low
- High
- Intermediate

D: 
- In collaboration with Martin Bornhäuser, Technische Universität Dresden, Germany

**TP53 Mutations Associate with Immune Infiltration and with Response to Flotetuzumab**

A

Immune infiltration int.-to-high in 10/13 (77%) patients with mutated TP53

B

Overall response rate in evaluable patients with TP53 mutations and/or 17p abnormalities was 60% (9/15), with 47% (7/15) achieving complete response (<5% BM blasts on study)

In responders with TP53 mutations, median OS was 10.3 months (range 3.3-21.3)
TP53 Mutations Associate with Immune Infiltration and with Response to Flotetuzumab

A.

B.

C.

D.

E.

Mike Rettig, WashU

Top-ranking genes associated with response

AUROC (CD8B) = 0.879
• *TP53* mutations in AML are associated with higher T cell infiltration, expression of immune checkpoints and IFN-γ-driven transcriptional programs

• The above gene expression profiles, which have previously been shown to enrich in patients with chemotherapy resistance, correlate with disease control in response to flotetuzumab (51.2% reduction of BM blasts; 60% [9/15] overall response rate; 47% [7/15] complete response rate)

• These results encourage further study of flotetuzumab immunotherapy in patients with *TP53*-mutated AML
## Acknowledgements

### Co-authors and Collaborators

<table>
<thead>
<tr>
<th>University/Institution</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nottingham Trent University</strong></td>
<td>Stephen Reeder, Payton Tau, Jayakumar Vadakekolathu, Tasleema Patel, Sarah K. Tasian, Philadelphia, PA</td>
</tr>
<tr>
<td><strong>Johns Hopkins University</strong></td>
<td>Heidi Altmann, Martin Bornhäuser, Jörn Meinel, Marc Schmitz, SAL Studienallianz Leukämie, Dresden, Germany</td>
</tr>
<tr>
<td><strong>NANOSTRING</strong></td>
<td>Ivana Gojo, Leo Luznik, Sidney Kimmel Comprehensive Cancer Centre, Baltimore, MD</td>
</tr>
<tr>
<td><strong>MACROGENICS</strong></td>
<td>Joseph M. Beechem, Alessandra Cesano, Michael Bailey, James Gowen-MacDonald, Thomas Smith, Sarah E. Church, Tressa Hood, Sarah E. Warren, Seattle, WA</td>
</tr>
<tr>
<td><strong>The Princess Margaret Hospital Foundation</strong></td>
<td>Mark D. Minden, Toronto, Canada</td>
</tr>
<tr>
<td><strong>The Children's Hospital of Philadelphia</strong></td>
<td>Stephen Reeder, Payton Tau, Jayakumar Vadakekolathu, Tasleema Patel, Sarah K. Tasian, Philadelphia, PA</td>
</tr>
</tbody>
</table>

### Funding Sources

- **National Priorities Research Programme, 2016-2020**
- **Mainstream QR funding, 2017-2019**
- **John and Lucille van Geest Foundation**
- **NTU**
- **Qatar National Research Fund**
- **Higher Education Funding Council for England**

Please email your questions to sergio.rutella@ntu.ac.uk