MEK inhibition with trametinib in patients with non-Langerhans cell histiocytosis irrespective of BRAF mutation status

Filip Janku, Harsh Patel, Vaijayanthi Kandadai Raghavan, Tamara G. Barnes, Razelle Kurzrock
Disclosures

• **Research Funding:** Agios, Asana, Astellas, Astex, Bayer, BioMed Valley Discoveries, Bristol-Myers Squibb, Deciphera, FujiFilm Pharma, Genentech, Novartis, Piqur, Plexxikon, Proximagen, Symphogen

• **Consulting:** Deciphera, Guardant Health, Grail, Ideaya, IFM Therapeutics, Immunomet, Illumina, Jazz Pharma, Novartis, Petra Pharma, PureTech Health, Sotio, Synlogic, Trovagene, Valean

• **Ownership Interests:** Trovagene

• **Other:** Bio-Rad, Biocartis
Brief report

High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses

Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms

Molecular Profiling of Tumor Tissue and Plasma Cell-Free DNA from Patients with Non-Langerhans Cell Histiocytosis

Filip Janku, Eli L. Diamond, Aaron M. Goodman, Vajayanthi Kandadai Raghavan, Tamara G. Barnes, Shumei Kato, Omar Abdel-Wahab, Benjamin H. Durham, Funda Meric-Bernstam, and Razelle Kurzrock

Mol Cancer Ther, 18(6) June 2019
Rationale

- Activation of the MAPK pathway through \textit{BRAF} mutations or other molecular alterations is a hallmark of non-LCH
- Molecular testing of tumor tissue fails to identify targetable molecular alterations in about one third of ECD patients
- Targeting the MAPK kinase pathway with MEK inhibitors can be effective in patients with \textit{BRAF} or other MAPK molecular alterations

\textit{Haroche, Emil Blood} 2012
\textit{Diamond, Durham, Abdel-Wahab Cancer Discov} 2016
\textit{Janku, Diamond, Kurzrock Mol Cancer Ther} 2019
\textit{Diamond Nature} 2019
Methods

- **Eligible patients:** Individuals with non-LCH with unknown or pending molecular testing test (tumor tissue targeted NGS, plasma cfDNA targeted NGS) or any molecular profile

- **Treatment:** Inhibitor of MEK1/2 kinase trametinib administered orally 1-2mg daily

- **Regulatory:** Data collection and analyses were performed in accordance with participating institutions protocol and respective IRBs’ guidelines
Patients (N=16)

- **Type of histiocytosis**
  - ECD: 12
  - RDD: 3
  - ECD/LCH: 1

- **Prior therapies**
  - No prior therapy: 9
  - 1 prior therapy: 1
  - 2 prior therapies: 2
Molecular Profile

- \( \text{BRAF}^{\text{V600E}} \): 3 patients
- MAPK other than \( \text{BRAF}^{\text{V600E}} \): 7 patients*
  - \( \text{CAPZA2-BRAF} \) fusion: 1
  - \( \text{RAF1} \) amplification: 1
  - \( \text{GNAS} \) mutation: 3
  - \( \text{HMGA2} \) rearrangement: 1
  - \( \text{NF1} \) mutation: 1
  - \( \text{KRAS} \) mutation: 1
  - \( \text{MAP2K1} \) mutation: 1

*some patients had more than one molecular alteration
### Results: Response (RECIST 1.1)

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (25)</td>
</tr>
<tr>
<td>CR + PR</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>3 (19)</td>
</tr>
</tbody>
</table>
**Molecular Profile**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed</td>
<td>none</td>
</tr>
<tr>
<td>ASXL1</td>
<td>BRAF, ERBB2</td>
</tr>
<tr>
<td>Failed</td>
<td>none</td>
</tr>
<tr>
<td>Failed</td>
<td>none</td>
</tr>
<tr>
<td>BRAF, ASXL1</td>
<td>BRAF, CCNE</td>
</tr>
<tr>
<td>CBLC</td>
<td>GNAS, CCNE</td>
</tr>
<tr>
<td>CAPZA2-BRAF</td>
<td>RAF1</td>
</tr>
<tr>
<td>Failed</td>
<td>GNAS</td>
</tr>
<tr>
<td>CD36</td>
<td>NF1</td>
</tr>
<tr>
<td>BRAF, ASXL1</td>
<td>BRAF</td>
</tr>
<tr>
<td>not done</td>
<td>APC</td>
</tr>
<tr>
<td>KRAS</td>
<td>GNAS, RB1</td>
</tr>
<tr>
<td>not done</td>
<td>MAP2K1</td>
</tr>
<tr>
<td>HMGA2, ZNF703</td>
<td>none</td>
</tr>
<tr>
<td>none</td>
<td>TP53</td>
</tr>
<tr>
<td>none</td>
<td>STK11</td>
</tr>
</tbody>
</table>

**Time on therapy/without progression**

- CR
- PR
- SD
- non-CR/non-PD
- not evaluated
- off therapy (AE)

**Time on therapy (months)**

- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
40-yo female with ECD/LCH (no molecular alteration) involving brain and bones and no prior therapy treated with trametinib 1mg.

BASELINE

2 MONTHS ON TX

2 YEARS ON TX
60-yo male with ECD (BRAF<sup>V600E</sup>) involving pericardial, perirenal, retroperitoneal areas and bones and no prior therapy treated with trametinib 1mg

**BASELINE**

**4 MONTHS ON TX**
Adverse events: summary

• Most patients started on oral trametinib 1 mg daily, which is lower than FDA approved dose of 2 mg
• Starting on lower dose with possible (de-) escalation is in general well tolerated
• Grade 1 rash was the most frequent AE
• Only 2 patients discontinued therapy because of AE
  – rash and dizziness
  – uveitis
Adverse events: > grade 2

- *Mucositis* (n=2)
- *Rash* (n=2)
- *Dizziness* (n=1)
- *Uveitis* (n=1)
- *Decrease in ejection fraction* (n=1)
CONCLUSIONS

- Oral MEK inhibitor trametinib has encouraging activity in non-LCH patients irrespective of underlying molecular profile.

- Clinical activity has been observed even with 1 mg daily, which is 50% of FDA approved dose for melanoma.

- Our data confirms recently published results with another MEK inhibitor cobimetinib (Diamond Nature 2019).