Encouraging activity of MEK inhibitor trametinib in patients with Erdheim-Chester disease irrespective of *BRAF* mutation status

Filip Janku, Tamara G. Barnes

Investigational Cancer Therapeutics
(Phase I Clinical Trials Program)
MD Anderson Cancer Center
Houston, TX
**Rationale**

- *BRAF* V600E mutation is the most prevalent molecular abnormality present in about 60% of patients Erdheim-Chester disease (ECD)
- ECD patients without *BRAF* V600E mutation often have other molecular aberrations in the MAPK pathway
- We hypothesize that activation of the MAPK pathway is a hallmark feature of ECD irrespective of molecular profile
- MEK inhibitor trametinib is an effective inhibitor of the MAPK pathway signaling
Methods

• Population
  – Patients with unknown or pending molecular testing
  – Patients without targetable molecular alteration

• Molecular testing
  – Tumor tissue targeted next generation sequencing (NGS)
  – Plasma cell-free DNA targeted NGS

• Treatment
  – Trametinib, an oral inhibitor of MEK1/2 kinase at the dose of 1 mg daily (50% of FDA approved dose for melanoma)
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Disease involvement</th>
<th>Prior therapy</th>
<th>Treatment</th>
<th>Molecular testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA20</td>
<td>42/male</td>
<td>Skin, bones</td>
<td>anakinra; everolimus and anakinra</td>
<td>Continues on trametinib 1mg daily for 4+ month with mild symptom improvement. Anakinra was added at month 2</td>
<td>None (targeted plasma cfDNA NGS and plasma BRAF PCR)</td>
</tr>
<tr>
<td>MDA22</td>
<td>42/male</td>
<td>Skin, bones, neurological symptoms</td>
<td>anakinra; everolimus and anakinra</td>
<td>Trametinib 1mg daily for 4 months. His symptoms improved dramatically, but did not resolve, therefore the dose was increased to 1.5mg and he continues on increased dose for 2 months with further improvement</td>
<td>None (targeted plasma cfDNA NGS and plasma BRAF PCR)</td>
</tr>
<tr>
<td>Patient No.</td>
<td>Age/Sex</td>
<td>Disease involvement</td>
<td>Prior therapy</td>
<td>Treatment</td>
<td>Molecular testing</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>---------------------</td>
<td>---------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>MDA23</td>
<td>60/male</td>
<td>Orbits, cardiac, kidneys, bones, sinuses, vertebral arteries</td>
<td>Continues on trametinib 1mg daily for 8+ months with significant symptomatic and radiographic improvement. Dabrafenib was not added because of prolonged QTc</td>
<td>Continues on trametinib 1mg daily for 8+ months with significant symptomatic and radiographic improvement. Dabrafenib was not added because of prolonged QTc</td>
<td>BRAFV600E</td>
</tr>
<tr>
<td>MDA25</td>
<td>48/male</td>
<td>Pituitary, aorta, lungs, bones, kidneys, abdomen</td>
<td>Trametinib 1mg daily for 3 months with mild symptom improvement, the dose increased to 1.5mg and added dabrafenib 75mg BID</td>
<td>Trametinib 1mg daily for 3 months with mild symptom improvement, the dose increased to 1.5mg and added dabrafenib 75mg BID</td>
<td>BRAFV600E</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Trametinib can be an alternative in symptomatic patients without druggable alterations or unknown molecular profile.

- These preliminary results need to be confirmed in larger series.