Neratinib and ado-Trastuzumab-Emtansine (T-DM1) for HER2+ Breast Cancer Brain Metastases (BCBM): Translational Breast Cancer Research Consortium (TBCRC) Trial 022

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Patients and Methods – Cohorts 4A, 4B, 4C

- TBCRC 022 is a prospective, multicenter, phase II study
- Patients must be ≥ 18 years old
- HER2+ BCBM with ≥ 5 measurable brain lesions on baseline imaging
- ≥ 30% of brain lesions must be ≥ 10 mm in maximum diameter
- No recent SRS or WBRT
- ≤ 24 weeks since prior SRS
- ≤ 4 weeks since prior WBRT
- ≤ 4 weeks since prior CNS-directed therapy
- ≤ 30 days since prior chemotherapy
- ≤ 30 days since prior targeted therapy
- ≤ 12 weeks since prior endocrine therapy
- ≤ 12 months since global SACT
- ≥ 4 weeks (or ≥ 2.5 half-lives) from prior T-DM1
- At least 2 weeks (≥ 1 half-life) from prior neratinib
- Adequate organ function

Statistical Design

- Cohorts 4A and 4B were single-stage designs with a planned enrollment of 20 patients each
- Cohort 4C had a two-stage design, with a requirement for at least 1 of the first 9 pts to achieve a response in order to enroll a total of 24 patients
- The primary endpoint = RANO-BM CNS Response
- The secondary endpoints = RANO-BM CNS Complete Response (CNS CR) + PR + SD ≥ 6 mos
- Intracranial activity was observed for the combination of neratinib plus T-DM1 in Cohorts 4A, 4B, and 4C, including those with prior T-DM1 exposure, suggesting a reversal of resistance to T-DM1
- Even with prophylaxis, grade 2-3 diarrhea events still occurred
- Our data provide additional evidence for consideration of neratinib-based combinations in pts with HER2+ BCBM.

Conclusions

- Preclinical data suggest that neratinib may overcome resistance to T-DM1
- Our data provide additional evidence for consideration of neratinib-based combinations in pts with HER2+ BCBM.

Table 3. Adverse Events Across 4A,4B,4C (n=44)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1 (n, %)</th>
<th>Grade 2 (n, %)</th>
<th>Grade 3 (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized muscle weakness</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>1 (2)</td>
<td>2 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (5)</td>
<td>4 (9)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2)</td>
<td>4 (9)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2)</td>
<td>4 (9)</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

Dana-Farber Cancer Institute, Massachusetts General Hospital, Johns Hopkins, U of Michigan, UCSF, Mayo, UPMC, UNC, Georgetown, Baylor