Updates in the Management of Brain Metastases

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Disclosures

• None

Brain metastases are a frequent site of metastatic dissemination

• 50% of patients with metastatic HER2+ breast cancer
• 25-50% of patients with metastatic TNBC
• 10-15% of patients with ER+ MBC
  • 30% of patients with PIK3CA mutant ER+ MBC
• 50% of patients with gBRCA1/2 associated MBC

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Survival has improved after BCBM Dx, especially in HER2+ pts

The Evidence Base for Local Therapy is Best for Initial BCBM Tx, but Much Less Robust for Subsequent Tx

- Multiple prospective, randomized trials comparing upfront WBRT vs SRS for patients with 1-4 mets
  - Demonstrated equivalent OS and better neurocognitive/QOL outcomes for upfront SRS (though worse intracranial control for SRS)
  - Typically included only ~30-50% breast cancer patients
- Much less robust data for outcomes in HER2+ BCBM pts for repetitive rounds of SRS
  - Ideally: pre-specified and standard response criteria, defined imaging interval, reporting of intracranial PFS (not just treated lesion response/progression), info on systemic therapy, extracranial outcomes, overall survival, neurocognitive outcomes — and no randomized data vs systemic approaches

Current Landscape of HER2-Targeted Tx for HER2+ BCBM

- Lapatinib
- Neratinib
- Tucatinib
- Trastuzumab
- TDM1
### TBCR 022: Neratinib + Capecitabine Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subgroup A: Lapatinib-naive N=0</th>
<th>Subgroup B: Lapatinib pre-treated N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.5 (29.6-66.4)</td>
<td>59.5 (41.8-68.9)</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>15 (30)</td>
<td>5 (42)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prior MSI</td>
<td>24 (47)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Prior brain</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>36 (70)</td>
<td>15 (125)</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>81 (96)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Lapatinib value</td>
<td>5.4 (5.0-5.6)</td>
<td>6.0 (5.1-6.5)</td>
</tr>
<tr>
<td>Lapatinib pre-treated</td>
<td>11.8 (11.0-12.6)</td>
<td>11.8 (11.0-12.6)</td>
</tr>
</tbody>
</table>

### Summary and Conclusions (2)

- There is still room to improve
  - CNS GMR >50% in the most successful studies – and virtually all patients eventually progress
  - Prevention of CNS metastasis remains an unsolved challenge

- Many potential opportunities
  - Optimized HER2-n+ with CNS penetration
  - Further gains possible with HER2 TKI
  - Trial designs to test CNS prevention approaches
  - Preclinical models to guide drug development
  - Novel combinations and targets

- Continued progress depends on our collective commitment as a community to:
  - Include patients with brain metastases in clinical trials – including those with new/progressive brain mets
  - Design trials that rigorously evaluate CNS endpoints
  - Measure outcomes important to patients


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Thank you