Neratinib in HER2-mutant, recurrent/metastatic cervical cancer: updated findings from the phase 2 SUMMIT basket trial

Claire F. Friedman, Anilka D’Souza, Anna Trinkel, Elena Corrao, Viktoriya Gambardella, Jonathan Goldman, Shervin Lali, Mitchell E. Melisko, Ana Dukol, Ben Spanggaard, Art Van Vonderen, Alison E. Foxler, Bo Jiang, Lisa D. Gil, David B. Seil

Background
Neratinib is a tyrosine kinase inhibitor (TKI) of HER2, with erlotinib (E7080) and lapatinib (Tykerb) recommended for patients with progesterone receptor-negative (PR-), human epidermal growth factor receptor 2-negative (HER2-), and human epidermal growth factor receptor 2-positive (HER2+)
- Second-line and subsequent therapies include a range of active agents, however, the highest reported response rates (Complete Response or Clinical Benefit Rate) are observed in HER2+ patients.
- Currently, no targeted therapies have been developed for metastatic cervical cancer.
- Sensitivity to HER2 mutations is oncogenic drivers in a range of solid tumors.
- HER2 mutations are present in ~1% of cervical cancers, and are enriched in adenocarcinomas compared with squamous cell carcinoma.
- Given the diverse activity of HER2-targeted therapies in patients with breast and other cancers, patients with cervical cancers harboring HER2 mutations may potentially benefit from TKI-directed therapy.
- Neratinib is a strongly pan-HER tyrosine kinase inhibitor that is approved for HER2-positive (amplified/rearranged) early and metastatic breast cancer.}

Methods
Study design
SHAPE IT is an international, open-label, multi-cohort, multi-tumor, phase 2 basket trial (Figure 1).

Patients with persistent, recurrent or metastatic cervical cancer and a HER2 mutation were eligible for this trial (Table 1).

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Cervical cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 (range, 26–74)</td>
<td>55 (range, 26–74)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female: 61 (93.0); Male: 4 (6.0)</td>
<td>Female: 61 (93.0)</td>
</tr>
<tr>
<td>Race</td>
<td>Black or African American: 35 (52.2); White: 34 (50.0); Other: 1 (1.5)</td>
<td>Black or African American: 35 (52.2); White: 34 (50.0); Other: 1 (1.5)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0: 18 (26.9); 1: 32 (48.5); 2: 17 (25.6)</td>
<td>0: 18 (26.9); 1: 32 (48.5); 2: 17 (25.6)</td>
</tr>
<tr>
<td>FIGO stage at diagnosis</td>
<td>1: 1 (1.5); 2: 1 (1.5); 3: 14 (21.9); 4: 37 (56.3)</td>
<td>1: 1 (1.5); 3: 14 (21.9); 4: 37 (56.3)</td>
</tr>
<tr>
<td>Prior systemic treatments</td>
<td>Platinum-based chemotherapy: 69 (100.0); bevacizumab: 52 (76.5); paclitaxel: 6 (8.9); platinum-free chemotherapy: 3 (4.4); bevacizumab: 4 (5.9); others: 3 (4.4)</td>
<td>Platinum-based chemotherapy: 69 (100.0); bevacizumab: 52 (76.5); paclitaxel: 6 (8.9); platinum-free chemotherapy: 3 (4.4); bevacizumab: 4 (5.9); others: 3 (4.4)</td>
</tr>
<tr>
<td>Prior treatment duration</td>
<td>&lt;12 months: 37 (54.4); 12–24 months: 16 (23.5); &gt;24 months: 16 (23.5)</td>
<td>&lt;12 months: 37 (54.4); 12–24 months: 16 (23.5); &gt;24 months: 16 (23.5)</td>
</tr>
<tr>
<td>HER2 mutation type</td>
<td>S310F/Y: 10 (14.5); R678Q: 2 (2.9); D769H/N: 2 (2.9); other: 4 (5.9)</td>
<td>S310F/Y: 10 (14.5); R678Q: 2 (2.9); D769H/N: 2 (2.9); other: 4 (5.9)</td>
</tr>
</tbody>
</table>

Results
 Patients
As of July 15, 2022, 73 patients with recurrent or metastatic HER2+ cervical cancer were enrolled (Table 2).

- Median age was 55 years (range, 26–74 years), and most patients had adenocarcinomas (89%).
- Prior systemic treatments included platinum-based chemotherapy (100%), bevacizumab (74%), and platinum plus bevacizumab (34%).
- Overall duration of treatment for HER2+ cancers was 5.1 months (range, 0.5–14.1 months).

Table 2. Efficacy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Cervical cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>18.2%, 95% CI 0.6–47.6</td>
<td>22 (100.0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>45.5%, 95% CI 5.3–85.3</td>
<td>22 (100.0)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>15.1%, 95% CI 0.5–14.1</td>
<td>22 (100.0)</td>
</tr>
</tbody>
</table>

Conclusions
Neratinib led to durable responses and disease control in patients with metastatic or recurrent HER2+ cervical cancer.

The predominance of S310F/Y in the SUMMIT cervical cohort was consistent with the genomic spectrum of HER2 mutations reported in public databases for HER2+ cervical cancer, including Project幫協力。PATIENTS

All patients with a confirmed response had tumors harboring an HER2+ mutation.

Patients with HER2+ cervical adenocarcinomas may require better than those with squamous cell carcinoma, although this is limited by small numbers and may reflect the fact that HER2+ mutations are enriched in adenocarcinomas.

Neratinib safety profile was consistent with previous reports in metastatic HER2+ positive or HER2+ tumors.

Diabetes was not a treatment-limiting toxicity with antiHER2 therapies.

Those encouraging results support further investigation of neratinib in patients with persistent or recurrent HER2+ cervical cancer following platinum failure.

Acknowledgements

Puma Biotechnology Inc, Los Angeles, CA, USA.

References

1. NCBI Clinical Trials Guidelines for Development of Genomic Medicine.
3. European Society for Medical Oncology. Guidelines for the management of patients with metastatic breast cancer.

COI disclosures: Claire Friedman

No financial disclosures.

Affiliation:
- E7080 Scientific Advisor Board: BMS: consultant.
- MyPathway Scientific Advisor Board: Genentech: MyPathway Scientific Advisor Board.
- Expansion of neratinib activity in a range of solid tumors.

Figure 1. SUMMIT study design: Neratinib-multitumor cohorts

Figure 2. Spectrum of HER2 mutations

The spectrum of HER2 mutations in the SUMMIT cervical cohort is consistent with that reported in public databases for HER2+ cervical cancer: (S310F/Y) 14.5%; D769H/N 2.9%; R678Q 2.9%; other 5.9%.

Figure 3. Individual best response by duration of treatment

Figure 4. Individual best change in target lesion from baseline (BEST-evaluation)

Dr. David B. Seil, MD
The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Richard J. Schilsky, MD
USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Acknowledgements

Copyright 2022 Puma Biotechnology

Presented at the ESMO Congress, 9–13 September 2022, in Paris, France.

This presentation is the intellectual property of the authors/presenter. Contact them at: Friedman@mskcc.org for permission to reprint and/or distribute.