Neratinib in patients with HER2-mutant, metastatic cervical cancer: findings from the phase 2 SUMMIT ‘basket’ trial

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Disclosures

- I have no financial disclosures or conflicts of interest
- I will discuss off-label use and/or investigational use of neratinib
Recurrent cervical cancer

- Relatively treatment-resistant if not resectable
- Few long-term responses
  - GOG-240¹: PFS 8.2 months (chemo + bev) vs 5.9 months (chemo alone)
  - KEYNOTE-158²: PFS 2.1 months (pembrolizumab)
- Need for other options

² Chung HC et al. J Clin Oncol 2018;36; (suppl; abstr 5522)
Abnormal HER2 activation results in tumor growth

- Constitutive receptor kinase activation and downstream signaling pathways
- Increased transformation, cell proliferation and cell survival
- Increased tumor growth and metastasis

Aberrant HER2 activation

<table>
<thead>
<tr>
<th>HER2 amplification or overexpression</th>
<th>HER2 (ERBB2) somatic mutations</th>
</tr>
</thead>
</table>

Activation of downstream signal transduction pathways

![Diagram showing HER2 activation and downstream signaling pathways]

Somatic HER2 mutations and cervical cancer

HER2 mutations in cervical cancer
- Incidence of 5%
- Typically in the absence of HER2 amplification¹
- HER2-mutation prevalence by histology
  - Adenocarcinoma: 4.52%
  - Squamous cell: 2.14%
- May be negatively prognostic²

Neratinib is a pan-HER tyrosine kinase inhibitor

- Oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4)\(^1\)
- Potent inhibition of cell proliferation/tumor growth in HER2-mutant uterine cervical cancer cell lines/xenografts\(^2\)

\* HER2 mutations

Activation of downstream signal transduction pathways and tumor growth/survival\(^3\)

2. Lopez et al. SGO Meeting 2015 (poster 356)
SUMMIT basket study design

Key inclusion criteria
- Documented HER2 mutation (locally assessed)
- ECOG status of 0 to 2

Key exclusion criteria
- Prior treatment with any pan-HER TKI (e.g., lapatinib, afatinib, dacomitinib, neratinib)
- Symptomatic or unstable brain metastases

Primary endpoint
- Objective response rate at first post-baseline tumor assessment (ORRfirst)

Secondary endpoints
- ORR (confirmed)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

Simon 2-stage design
- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments
- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

Statistical methods
- ORRfirst, ORR, CBR: associated 95% CI
- Median PFS: KM estimate with 95% CI

Neratinib: oral 240 mg daily
Fulvestrant: intramuscular 500 mg on day 1, 15 and 29; once every 28 days thereafter (labeled dose)
Paclitaxel: intravenous 80 mg/m² on day 1, 8 and 15; every 28 days
Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

Biliary tract
Cervical
Ovarian
Salivary gland
Solid tumors (NOS)

Neratinib monotherapy

Bladder
Breast HRc-positive*
Breast HRc-negative
Lung
Colorectal
(KRAS/NRAS/BRAF wild-type)

Neratinib + Paclitaxel

Neratinib* + Trastuzumab#

*plus fulvestrant (in ER+ breast)
#biosimilar may be used if available

Tumors (NOS)
- Biliary tract
- Cervical
- Ovarian
- Salivary gland
- Solid tumors (NOS)

HER2-mutant tumors

Neratinib monotherapy

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Clinical Trials.gov Identifier NCT01953926
# Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>HER2-mutant cervical cohort (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>50 (29–64)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>1</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td><strong>Histology, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Squamous</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td><strong>Stage at diagnosis, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>M1</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td><strong>Time from diagnosis to metastasis, median (range) in years</strong></td>
<td>2.2 (0–6.7)</td>
</tr>
<tr>
<td><strong>Time from metastasis to enrollment, median (range) in years</strong></td>
<td>1.8 (0.3–8.4)</td>
</tr>
<tr>
<td><strong>Previous therapeutic interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Median number of prior regimens in patients with recurrent or metastatic disease, n (range)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Prior bevacizumab, n (%)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Prior surgery, n (%)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Prior radiation, n (%)</td>
<td>9 (81.8)</td>
</tr>
</tbody>
</table>
# Efficacy summary

<table>
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<th>Efficacy endpoint&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HER2-mutant cervical cohort (n=11)</th>
</tr>
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<tbody>
<tr>
<td><strong>Objective response (confirmed)&lt;sup&gt;b&lt;/sup&gt; – n</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate, % (95% CI)</td>
<td>27.3 (6.0–61.0)</td>
</tr>
<tr>
<td><strong>DOR for each responder, months</strong></td>
<td>5.6, 5.9, 7.4&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Clinical benefit&lt;sup&gt;c&lt;/sup&gt; – n</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>6</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
</tr>
<tr>
<td>SD ≥16 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Clinical benefit rate, % (95% CI)</td>
<td>54.5 (23.4–83.3)</td>
</tr>
<tr>
<td><strong>Median&lt;sup&gt;d&lt;/sup&gt; PFS (95% CI), mo</strong></td>
<td>7.0 (0.7–20.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Response is based on investigator tumor assessments per RECIST v1.1

<sup>b</sup>Objective response rate (ORR) is defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met

<sup>c</sup>Clinical benefit rate (CBR) is defined as confirmed CR or PR or stable disease (SD) for at least 16 weeks (within +/- 7-day visit window)

<sup>d</sup>Kaplan-Meier analysis

*Patient still on treatment at time of data cut; DOR, duration of response; PFS, progression-free survival
Best change in tumor and treatment duration

**HER2 mutation type**
- Extracellular domain hotspot
- Transmembrane domain hotspot
- Kinase domain hotspot
- Extracellular/kinase domain hotspots
- Non-hotspots

**Histology**
- Adenocarcinoma
- Squamous

**Objective response (RECIST)**
- PR
- SD ≥16 weeks
- PD

**Duration of PR (months)**
- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100
- 110
- 120

**Best change from baseline (%)**

**Treatment duration (weeks)**

- **D769N**
- **S310F**
- **S310F**
- **S310F**
- **S310F**
- **V842I**
- **R678Q**
- **G776V**
- **E695D**
- **G776V**
- **S310F**
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**Best response legend**
- CR (metabolic-PET)
- PR (RECIST)
- SD (RECIST)
- PD (RECIST)
- PD (metabolic-PET)
- Treatment ongoing

**2 patients did not have a measurable post-baseline tumor assessment**
- # Patient died prior to first post-baseline baseline scan
- ^ Tumor lesions were not measurable on post-baseline scan; evaluated as PD due to development of new lesion

**Treatment ongoing**

* Confirmed complete metabolic response (per PET response criteria)
Progression-free survival (n=11)

Median PFS (95% CI)
7.0 (0.7–20.1) months
## Incidence of treatment-emergent adverse events (≥3 patients)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>HER2-mutant cervical cancer cohort (n=11)</th>
<th>All SUMMIT monotherapy patients (n=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Subjects with at least 1 adverse event, n (%)</td>
<td>11 (100.0)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (81.8)*</td>
<td>1 (9.1)#</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (54.5)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (45.5)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (36.4)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (36.4)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (27.3)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (27.3)</td>
<td>0</td>
</tr>
<tr>
<td>Malaise</td>
<td>3 (27.3)</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>3 (27.3)</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (27.3)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (27.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*None of the diarrhea events resulted in dose reduction, dose discontinuation or hospitalization within the cervical cancer cohort

#Single episode of grade 3 diarrhea in the cervical cohort; time to grade 3 event was 4 days and duration of grade 3 event was 1 day
Summary

• HER2 mutations represent a clinically actionable, oncogenic driver in metastatic cervical cancers
  – 5% incidence in cervical cancers
  – Can be detected by readily available NGS assays
  – Observed more frequently in adenocarcinomas
  – Predominantly extracellular domain (S310) mutations

• Neratinib led to durable responses and disease control in metastatic patients with HER2-mutant cervical cancer
  – ORR 27.3%; CBR 54.5%; median PFS 7.0 months

• Neratinib safety profile is consistent with previous reports in metastatic HER2-amplified and HER2-mutant tumors
  – Diarrhea was not a treatment-limiting toxicity with anti-diarrheal prophylaxis

• Enrollment continues in the cervical cancer cohort
  – Future directions include a liquid biopsy pilot screening program (HER-Seq) to identify patients with HER2 mutations
Acknowledgements

The authors would like to thank:

• All of the patients and their families

• SUMMIT study investigators and clinical trial staff