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

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Background

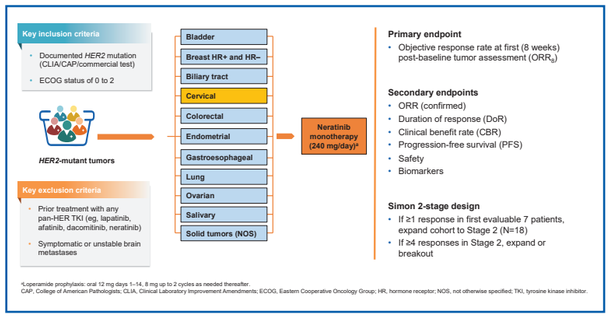
- Standard first-line treatment for recurrent or metastatic cervical cancer is platinum-based chemotherapy + bevacizumab, with pembrolizumab + platinum-based chemotherapy ± bevacizumab recommended for patients with programmed death ligand-1 (PD-L1)-positive tumors:[1]
  - Second-line and subsequent therapies include a range of active agents;[1] however, the highest expected response rate (tisotumab vedotin) has not exceeded 24%,[2,3] and there is a recognized need for new treatment options for patients who have progressed on or after platinum-based therapy.
  - Currently, no targeted therapies have been developed for metastatic cervical cancer.
- Somatic *HER2* mutations are oncogenic drivers in a range of solid tumors:
  - *HER2* mutations are present in ~5% of cervical cancers, and are enriched in adenocarcinoma compared with squamous cell carcinomas.[4-6]
  - Given the clinical utility of HER2-targeted therapies in patients with breast and other cancers, patients with cervical cancers harboring *HER2* mutations may potentially benefit from HER2-directed therapy.
- Neratinib is an irreversible pan-HER tyrosine kinase inhibitor that is approved for HER2-positive (amplified/overexpressed) early and metastatic breast cancer.[7,8]
  - Neratinib displays potent inhibition of cell proliferation and tumor growth in multiple preclinical models, including *HER2*-mutant uterine cervical cancer cell lines and xenografts.[9]
  - Neratinib has demonstrated promising single-agent activity in multiple *HER2*-mutant cancers, including cervical cancer, within the context of the SUMMIT basket trial (Clinicaltrials.gov: NCT01953926).[10,11]
  - We describe final findings from the *HER2*-mutant cervical cancer cohort of the SUMMIT trial.

Methods

Study design

- SUMMIT 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 documented by institutional testing at a CLIA/CAP- (or regionally-equivalent) certified laboratory were eligible for the cervical cancer cohort.

Figure 1. SUMMIT study design: Neratinib monotherapy cohorts



*Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg up to 2 cycles as needed thereafter.
CAP, College of American Pathologists; CLIA, Clinical Laboratory Improvement Amendments; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; NOS, not otherwise specified; TKI, tyrosine kinase inhibitor.

Assessments

- Tumor response was assessed every 8 weeks by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or Positron-Emission Tomography Response Criteria (PERCIST).
- Adverse events were monitored until day 28 after discontinuation of study treatment and classified according to Common Terminology Criteria for Adverse Events version 4.0.

Statistical analyses

- Efficacy and safety outcomes were summarized in the safety analysis set, which included all patients who received at least one dose of neratinib.
- Kaplan–Meier method was used to estimate time-to-event endpoints.
- Clopper–Pearson method was used to calculate 95% confidence intervals for response rates.
- Data cut-off: July 15, 2022.

Results

Patients

- As of July 15, 2022, 22 patients with recurrent or metastatic *HER2*-mutant cervical cancer were enrolled (**Table 1**).
- Median age was 55 (range, 29–74) years, and most patients had adenocarcinomas (82%).
- Prior systemic treatments included platinum-based chemotherapy (100%), bevacizumab (73%), and pembrolizumab (18%).
- Enrolled patients had one (n=18) or two (n=4) *HER2* mutations:
  - Single *HER2* mutations: S310F/Y (n=10); R678Q (n=2); D769H/N (n=2); other (n=4).
  - Double *HER2* mutations included S310F/Y in 3 cases.
- Median duration of neratinib therapy was 3.7 (range, 0.5–67.5) months.

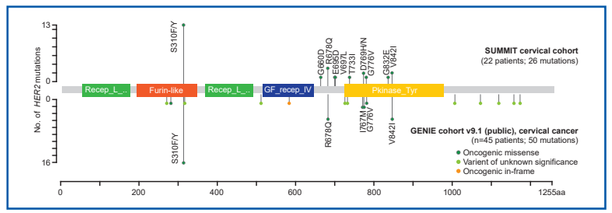
Table 1. Baseline characteristics

	HER2-mutant cervical cancer cohort (N=22)
Median age (range), years	55 (29–74)
Race, n (%)	
White	15 (68.2)
Asian	1 (4.5)
Black or African American	1 (4.5)
Unknown or other	5 (22.7)
ECOG performance status, n (%)	
0	7 (31.8)
1	15 (68.2)
FIGO stage at diagnosis (2018 criteria), n (%)	
Stage I	7 (31.8)
Stage II	5 (22.7)
Stage III	2 (9.1)
Stage IV	6 (27.3)
Missing	2 (9.1)
Histology, n (%)	
Adenocarcinoma	18 (81.8)
Squamous	4 (18.2)
HPV status, n (%)	
Positive	13 (59.1)
Negative	2 (9.1)
Unknown/missing	7 (31.8)
Prior radiotherapy, n (%)	17 (77.3)
Prior surgery, n (%)	14 (63.6)
Prior systemic treatments, n (%)	
Platinum-based chemotherapy	22 (100.0)
Bevacizumab	16 (72.7)
Pembrolizumab	4 (18.2)

FIGO, Federation of Gynecology and Obstetrics; HPV, human papillomavirus.

- The spectrum of *HER2* mutations in the SUMMIT cervical cohort is consistent with that reported in public datasets including Project GENIE (**Figure 2**).
- The majority of *HER2* mutations observed in cervical cancer are at position S310 in the extracellular domain.

Figure 2. Spectrum of *HER2* mutations



Efficacy

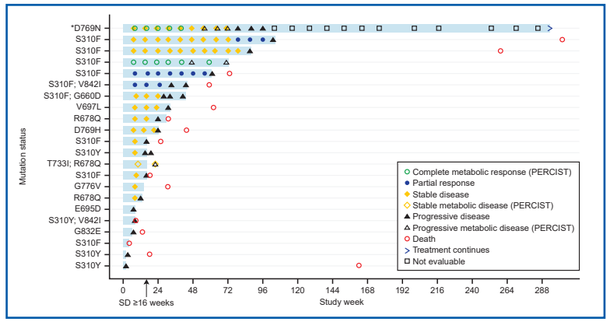
- Key findings with neratinib monotherapy (**Table 2**):
  - Confirmed ORR: 18.2%.
  - CBR: 45.5%.
  - Median DoR: 7.6 months.
  - Median PFS: 5.1 months.
- Five patients had sustained clinical benefit lasting for 12 months or longer (S310F, n=4; D769N, n=1) (**Figure 3**).
- Prior use of bevacizumab did not appear to influence the efficacy of neratinib (**Figure 4**).
- 55.6% (10/18) of patients with cervical adenocarcinoma experienced clinical benefit, while none (0/4) of the patients with squamous cell carcinoma did so (**Table 2**).

Table 2. Efficacy

	Overall	Histology		*HER2* mutation				
Endpoint	*HER2*-mutant cervical cancer cohort (N=22)	Adenocarcinoma (n=18)	Squamous cell carcinoma (n=4)	S310F or S310Y (single mutation) (n=10)	S310F or S310Y (double mutation) (n=3)	D769H or D769N (n=2)	Other kinase domain mutation* (n=2)	Transmembrane domain mutation* (n=5)
Objective response, n (%)	4 (18.2)	4 (22.2)	0	3 (30.0)	1 (33.3)	0	0	0
CR*	1 (4.5)	1 (5.6)	0	1 (10.0)	0	0	0	0
PR	3 (13.6)	3 (16.7)	0	2 (20.0)	1 (33.3)	0	0	0
ORR, % (95% CI)	18.2 (5.2–40.3)	22.2 (6.4–47.6)	0 (0–60.2)	30.0 (6.7–65.2)	33.3 (0.8–90.6)	0 (0–84.2)	0 (0–84.2)	0 (0–52.2)
Median DoR, months (95% CI)	7.6 (5.6–12.3)	7.6 (5.6–12.3)	0	9.3 (5.6–12.3)	5.9 (NE–NE)	0	0	0
Clinical benefit, n (%)	10 (45.5)	10 (55.6)	0	4 (40.0)	2 (66.7)	2 (100.0)	0	2 (40.0)
CR	1 (4.5)	1 (5.6)	0	1 (10.0)	0	0	0	0
PR	3 (13.6)	3 (16.7)	0	2 (20.0)	1 (33.3)	2 (100.0)	0	2 (40.0)
SD (≥16 weeks)	6 (27.3)	6 (33.3)	0	1 (10.0)	1 (33.3)	0	0	0
CBR, % (95% CI)	45.5 (24.4–67.8)	55.6 (30.8–78.5)	0 (0–60.2)	40.0 (12.2–73.8)	66.7 (9.4–99.2)	100 (15.8–100)	0 (0–84.2)	40.0 (5.3–85.3)
Median PFS, months (95% CI)	5.1 (1.7–7.2)	5.5 (3.7–10.9)	1.7 (0.7–3.5)	3.7 (0.5–14.1)	6.5 (1.7–7.7)	11.9 (5.5–18.3)	NE (1.7–NE)	5.1 (1.7–7.2)

Cut-off date: July 15, 2022. *Complete metabolic response (PERCIST evaluated; no RECIST-evaluable lesion); †G776V, G823E. ‡R678Q, V697L, E695D.
CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

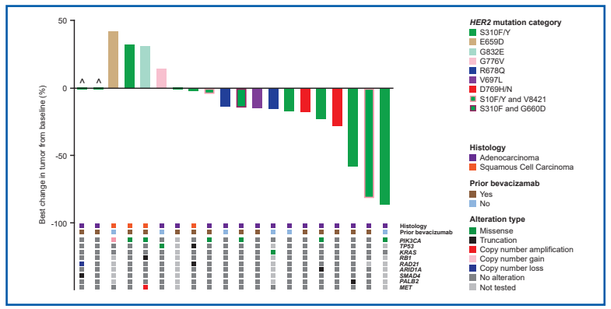
Figure 3. Individual response by duration of treatment



Cut-off date: July 15, 2022. *Note: Extreme responder had surgical resection at week 96 and so was not evaluable.

- The majority of SUMMIT cervical cancer patients had tumors that harbored S310F/Y mutation (45.5%, 10/22 with a single S310F/Y mutation plus 13.6%, 3/22 with S310F/Y as one of two *HER2* mutations).
- Confirmed objective response was observed in 30% (3/10) patients whose tumors harbored a single S310F/Y mutation, and 33.3% (1/3) of those with S310 plus one additional *HER2* mutation (**Table 2**).
- Long-term stable disease was observed across multiple *HER2* mutation types (**Table 2**).

Figure 4. Individual best change in target lesion from baseline (RECIST-evaluable)



Cut-off date: July 15, 2022. RECIST-evaluable patients at baseline (n=20); 2 other patients not shown were PERCIST evaluable only. Co-mutation data based on local/enrollment assays.

Safety

- Safety profile of neratinib in patients with *HER2*-mutant cervical cancer was consistent with other reports of neratinib monotherapy (Table 3).
- Diarrhea was common but manageable with antidiarrheal prophylaxis.
- No diarrhea events led to treatment discontinuation or dose reductions.

Table 3. Safety

Adverse event, n (%)	All adverse events (N=22)		Treatment-related adverse events (N=22)	
	All grades	Grade ≥3*	All grades	Grade ≥3
Patients with at least 1 adverse event	22 (100)	10 (45.5)	19 (84.6)	5 (22.7)
Diarrhea	20 (90.9)	5 (22.7)†	18 (81.8)	5 (22.7)
Constipation	12 (54.5)	0 (0)	2 (9.1)	0 (0)
Nausea	12 (54.5)	0 (0)	9 (40.9)	0 (0)
Decreased appetite	9 (40.9)	0 (0)	4 (18.2)	0 (0)
Vomiting	9 (40.9)	0 (0)	5 (22.7)	0 (0)
Abdominal pain	8 (36.4)	2 (9.1)	4 (18.2)	1 (4.5)
Dyspepsia	5 (22.7)	0 (0)	2 (9.1)	0 (0)
Dysphea	5 (22.7)	1 (4.5)	0 (0)	0 (0)
Headache	5 (22.7)	0 (0)	1 (4.5)	0 (0)
Asthenia	4 (18.2)	1 (4.5)	1 (4.5)	0 (0)
Fatigue	4 (18.2)	0 (0)	1 (4.5)	0 (0)
Pain	4 (18.2)	0 (0)	0 (0)	0 (0)
Malaise	4 (18.2)	0 (0)	1 (4.5)	0 (0)
Dysgeusia	4 (18.2)	0 (0)	4 (18.2)	0 (0)
Dry skin	4 (18.2)	0 (0)	2 (9.1)	0 (0)

Cut-off date: July 15, 2022. Table shows events reported in ≥4 patients.
*There were no grade 4 adverse events and two grade 5 (fatal) adverse events: dyspnea (n=1) and embolism (n=1). Neither grade 5 event was reported as related to neratinib treatment.
†None of the diarrhea events resulted in dose reductions or discontinuation of neratinib in the cervical cancer cohort.

Conclusions

- Neratinib led to durable responses and disease control in patients with metastatic or recurrent *HER2*-mutant cervical cancer.
- The predominance of S310F/Y in the SUMMIT cervical cancer cohort was consistent with the genomic spectrum of *HER2* mutations reported in public datasets for *HER2*-mutant cervical cancer, including Project GENIE:
  - All patients with a confirmed response had tumors harboring an S310F/Y mutation.
- Patients with *HER2*-mutant cervical adenocarcinoma may respond 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 adenocarcinoma.
- Neratinib safety profile was consistent with previous reports in metastatic HER2-positive or *HER2*-mutant tumors.
- Diarrhea was not a treatment-limiting toxicity with antidiarrheal prophylaxis.
- These encouraging results support further investigation of neratinib in patients with persistent, metastatic or recurrent *HER2*-mutant cervical cancer following platinum failure.

Acknowledgements

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