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Neratinib in patients with *HER2*-mutant, metastatic cervical cancer: Findings from the phase 2 SUMMIT basket trial

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Author contributions

AO and CFF contributed equally to this work. DMH, DBS, FMB, and RPB designed the study and supervised the analyses. AO, CFF, LDR, AD'S, IB, FC-B, JG, EAA, VB, ACE, RP, KTMD, ADS, DHM, FMB, DBS, and BJM enrolled patients and provided patient samples. AO, BJM, KK, ASL, LDE, FX, and RPB analyzed clinical and genomic data and performed the integrated safety and efficacy analyses. FX performed biostatistical analyses of the clinical efficacy data. AO, BJM, ASL, and KK wrote the manuscript with input from all authors.

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Declaration of Competing Interest

A. Oaknin: has received advisory board honoraria from Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro, Inmunogen, Genmab, and Deciphera and travel/accommodation support from Roche, AstraZeneca, and PharmaMar.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2020.07.025.

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Abstract

Objective.—Somatic *HER2* mutations occur in ~5% of cervical cancers and are considered oncogenic and associated with poor prognosis. Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, is active in multiple *HER2*-mutant cancers. SUMMIT is a phase II basket trial investigating the efficacy and safety of neratinib in solid tumors.

Methods.—Patients with *HER2*-mutant, persistent, metastatic/recurrent cervical cancer with disease progression after platinum-based treatment for advanced/recurrent disease received oral neratinib 240 mg/day with mandatory loperamide prophylaxis during cycle 1. The primary endpoint was confirmed objective response rate (ORR). Secondary endpoints included: response duration (DOR); clinical benefit rate (CBR); progression-free survival (PFS); overall survival (OS); safety.

Results.—Sixteen eligible patients were enrolled; 10 (62.5%) had endocervical adenocarcinoma. The most common *HER2* mutation was *S310F* (63% of patients). Three of 12 RECIST-measurable patients had confirmed partial responses (ORR 25%; 95%CI 5.5–57.2%); 3 had stable disease ≥16 weeks (CBR 50%; 95%CI 21.1–78.9%). DOR for responders were 5.6, 5.9, and 12.3 months. Median PFS was 7.0 months (95%CI 0.7–18.3 months); median OS was 16.8 months (95%CI 4.1–

NE months). Diarrhea (75%), nausea (44%), and decreased appetite (38%) were the most common adverse events. One patient (6%) reported grade 3 diarrhea. There were no grade 4 events, and no diarrhea-related treatment discontinuations.

Conclusions.—Neratinib monotherapy showed evidence of activity in heavily pretreated patients with *HER2*-mutant cervical cancer, with no new safety signals. Given the few effective options for cervical cancer after platinum-based therapy failure, neratinib warrants further investigation in this molecularly defined patient population.

Trial registration number.—NCT01953926 (ClinicalTrials.gov), 2013–002872–42 (EudraCT).

Keywords

Cervical cancer; *HER2* mutant; Neratinib; Clinical trial; Tyrosine kinase inhibitor

1. Introduction

Cervical cancer is a global health crisis [1] and the fourth most common malignant disease worldwide among women in terms of both incidence and mortality [2], with one woman dying of cervical cancer every 2 min [3]. In the United States, cervical cancer is the second most common cause of cancer death in women aged 20–39 years, leading to 10 premature deaths per week [4]. Although broad screening and the development of human papillomavirus vaccines have reduced the incidence of cervical cancer in some countries, 13% of patients are still diagnosed at an advanced stage [5]. Such patients are at high risk for locally recurrent and/or metastatic disease, which has a poor prognosis with median overall survival of 16.8 months; the 5-year overall survival (OS) rate for all disease stages is 68% [6].

Platinum-based chemotherapy plus bevacizumab is the standard first-line treatment for persistent, recurrent, and metastatic cervical cancer [7,8], but there is an increasing need for more effective therapies for patients who have progressed on or after platinum-based therapy [9]. In the US, the Food and Drug Administration (FDA) approved bevacizumab in 2014 as first-line treatment for persistent, recurrent, or metastatic cervical cancer, and approved pembrolizumab in 2018 for patients with recurrent or metastatic cervical cancer who had progressed on or after platinum-based chemotherapy and whose tumors have a PD-L1 combined positive score (CPS) ≥1. Currently there are no approved targeted treatments for cervical cancer.

HER2 is a member of the HER family of transmembrane receptor tyrosine kinases, which also includes HER1 (EGFR), HER3, and HER4. Increased HER2 expression and the resultant activation of its tyrosine kinase domain are associated with cellular transformation and HER2 is a validated therapeutic target in breast and esophagogastric cancers [10]. Somatic activating *HER2* mutations are a recently identified class of oncogenic drivers that are present in a variety of solid tumor malignancies including bladder, colorectal, lung, breast, and cervical cancers [11–14]. Sequencing studies indicate that *HER2* mutations are present in 3–6% of cervical cancers [15–18] and may be associated with a poor prognosis [16]. Given the clinical utility of HER2-targeted therapies in patients with breast,

esophagogastric, endometrial, and lung cancers, the subset of patients with cervical cancers harboring *HER2* mutations could potentially benefit from HER2-targeted therapies, such as irreversible pan-HER kinase inhibitors [15–17,19].

Neratinib is an oral, irreversible, pan-HER tyrosine kinase inhibitor (TKI) [20] that has demonstrated efficacy in the treatment of patients with early-stage or metastatic HER2-positive breast cancer [21–24]. Neratinib has also demonstrated potent inhibition of cell proliferation in *HER2*-mutant cervical cancer cell lines and potent inhibition of tumor growth in *HER2*-mutant cervical cancer xenograft models [17].

SUMMIT is a phase II basket study investigating the efficacy and safety of neratinib across a broad spectrum of cancer types in patients whose tumors harbor activating *HER2* somatic mutations [25]. We report results from a cohort of heavily pretreated patients with *HER2*-mutant, metastatic cervical cancer receiving neratinib in SUMMIT.

2. Patients and methods

2.1. Study oversight

The SUMMIT study is being conducted in compliance with the principles of good clinical practice and in accordance with the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki. SUMMIT was approved by the independent ethics committee or institutional review board at each study site. All patients provided written informed consent prior to study entry.

2.2. Patient eligibility

Eligible patients were women aged ≥18 years with histologically confirmed metastatic cervical cancer for whom no curative treatment existed and who had a likely pathogenic mutation in *HER2*. Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, with adequate hematopoietic, hepatic, kidney, and cardiac function (defined as a left ventricular ejection fraction ≥50%). Key exclusion criteria included prior therapy with HER2-directed TKIs and prior radiotherapy ≤14 days before treatment initiation. Patients with treated and/or asymptomatic brain metastases were eligible. *HER2* mutations were identified by testing at each participating site; tissue- or plasma-based sequencing assays performed by a Clinical Laboratory Improvement Amendments-certified or regionally equivalent laboratory were accepted.

2.3. Study design and treatment

SUMMIT is an open-label, single-arm, multicohort, multitumor, phase II, basket trial being conducted at 57 centers internationally (NCT01953926; EudraCT 2013–002872–42). Eligible patients received oral neratinib 240 mg once daily with food (recommended to be taken in the morning) on a continuous basis, with mandatory loperamide prophylaxis during cycle 1 (12 mg/day on days 1–14; 8 mg/day on days 15–28) and then as needed thereafter but not exceeding 16 mg/day. Patients were treated until disease progression, unacceptable toxicity, or withdrawal of consent.

2.4. Assessments

The primary endpoint was the confirmed objective response rate (ORR). Secondary endpoints included duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS), OS, and safety. Tumor response was assessed locally every 8 weeks by computed tomography (CT), magnetic resonance imaging, and/or fluorodeoxyglucose-positron-emission tomography (FDG-PET). Adverse events, classified according to Common Terminology Criteria for Adverse Events (version 4.0), were monitored from the first dose until day 28 after discontinuation of study treatment.

2.5. Statistical analyses

The data cutoff for this report was February 2020. Baseline characteristics, efficacy, and safety were summarized in the safety analysis set, which included all patients who received at least one dose of neratinib. Efficacy analyses of tumor response data were also performed for patients in the Response Evaluation Criteria in Solid Tumors (RECIST) efficacy evaluable set, which included patients with RECIST-measurable disease at baseline who had at least one post-baseline tumor assessment per RECIST or who discontinued treatment prior to the first scheduled post-baseline tumor assessment. One patient in the safety analysis set was only evaluable by FDG-PET, therefore their tumor responses were evaluated by PET Response Criteria (PERCIST). All other patients in the safety analysis set and all patients in the RECIST efficacy evaluable set were evaluated by RECIST (version 1.1). PFS and OS were estimated using the Kaplan–Meier method. The Clopper–Pearson method was used to calculate 95% confidence intervals (CIs) for ORR and CBR. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient demographics and characteristics

Sixteen patients with histologically confirmed metastatic cervical cancer were enrolled and comprised the safety analysis set; 12 of these patients were evaluable for efficacy by RECIST (Fig. S1). All patients had documented evidence of a somatic *HER2* mutation at the time of enrollment, as determined by a local, tumor tissue-based, next-generation sequencing assay. The median age of patients was 55 years (range 29–64 years), the majority (81%) were white, had endocervical adenocarcinoma (62.5%), and an ECOG performance status of 1 (63%) (Table 1). Further details on patient/disease characteristics and previous treatments are provided in Table S1.

All patients had previously been treated with platinum-based chemotherapy; 11 patients (69%) had previously received bevacizumab, and 2 (13%) had received pembrolizumab. The median number of prior systemic chemotherapy regimens was 2 (range 1–3) and 6 patients (38%) had received prior chemoradiation. Nine patients had persistent disease and seven had reoccurred. The most common *HER2* variant was the hotspot S310F/Y mutation, which was identified in 10 of the patients (63%) (Fig. S2). The high prevalence of S310 mutation in this population of patients with cervical cancer with oncogenic *HER2* mutations is consistent with prior reports [15,16,26].

3.2. Efficacy

One patient had a complete response (PERCIST) and 3 had partial responses (RECIST), for a confirmed ORR of 25.0% (95% CI 7.3–52.4%; Table 2) in the safety analysis set. Among the 12 patients with RECIST-measurable disease in the efficacy analysis set, 3 patients with endocervical adenocarcinoma had a confirmed objective partial response (ORR 25%; 95% CI 5.5–57.2%) and 3 additional patients had stable disease lasting ≥16 weeks (CBR 50%; 95% CI 22.1–78.9%; Table 2). Further details on responses to treatment are shown in Table S1.

The 3 patients who achieved a partial response all had reductions in tumor size >50% (−58.3%, −81.4%, and −86.7%; Fig. 1). The durations of response for the 3 responders were 5.6, 5.9, and 12.3 months. The specific *HER2* mutation, duration of treatment, and best response for each of the 16 patients are shown in Fig. 2. Treatment duration ranged from 1 to >168 weeks. At the time of analysis, neratinib treatment was ongoing in 5 patients and 8 patients had died.

All 3 patients who had a partial response had tumors with *HER2* mutations at position S310 (S310F/Y) and one had a second *HER2* V842I co-mutation. Co-mutations in other genes were also identified in these 3 patients, including an oncogenic *PIK3CA* E545K mutation.

Median PFS was 7.0 months (95% CI 1.0–18.3 months) and median OS was 16.8 months (95% CI 4.1 months–not estimable; Table 2 and Fig. 3). Six- and 12-month estimates for PFS were 52.8% (95% CI 23.4–75.5%) and 35.2% (95% CI 11.2–60.7%), respectively. Corresponding estimates for OS were 77.9% (95% CI 45.9–92.3%) and 60.6% (95% CI 29.2–81.6%), respectively.

3.3. Safety

Diarrhea (75%), nausea (44%), and decreased appetite (38%) were the most common adverse events (Table 3). Twelve of the 16 patients reported having diarrhea (grades 1–3) and were treated with medication, primarily loperamide. One patient (6%) reported grade 3 diarrhea lasting 1 day, but there were no grade 4 diarrhea events and no treatment discontinuations due to diarrhea (Table S2).

4. Discussion

Although early detection and preventive vaccination have reduced the risk of cervical cancer in some countries, locally recurrent and/or metastatic cervical cancer has a dismal prognosis [6]. First-line therapy is platinum chemotherapy with or without bevacizumab; unfortunately, cytotoxic agents tested in the second-line setting have been associated with ORRs of <10% and PFS of only 3 months [27]. Recently, the anti-PD1 antibody pembrolizumab was approved by the FDA for use after failure of prior platinum-based therapy based on a response rate of 12% [28,29]. Retrospective studies have identified oncogenic *HER2* mutations (mainly codon S310 missense substitutions) and gene amplifications in 3–6% [15–17] and 1–12% [30] of cervical cancers, respectively. Other studies have reported that *HER2* alterations are enriched in adenocarcinomas [31,32]. Notably, the incidence of *HER2* mutations may be greater in patients with more advanced cervical cancer as these mutations

may be associated with a worse prognosis or an adaptive mechanism of tumor survival, as seen in breast cancer [33,34].

Preclinical studies indicate that *HER2* mutations can induce cellular transformation, and cancer cells expressing oncogenic *HER2* mutations have been shown to be sensitive to selective HER kinase inhibitors [11–14]. The most prevalent *HER2* mutations in cervical cancer are codon S310 mutations, which are located in the extracellular domain and induce kinase activation through increased receptor dimerization [14–17]. S310 mutations are highly sensitive to neratinib inhibition, which results in potent tumor inhibition in xenograft models [17]. In this study, *HER2*-mutant cervical cancers were predominantly of an adenocarcinoma histotype, which is consistent with other sequencing studies [15,17]. The increased prevalence of *HER2* mutations in adenocarcinoma compared with squamous carcinoma, as seen in cervical cancer, is similar to the patterns observed with other oncogenic driver mutations including *EGFR*, *ALK*, *RET*, and *ROS* in non-small cell lung cancer [35].

With the exception of pembrolizumab, which is approved in PD-L1 CPS-positive patients who have progressed on or after prior platinum-based chemotherapy, there is still an unmet need for effective and well-tolerated therapies for use in the second-line cervical cancer setting and beyond. Targeting *HER2*-mutant cervical cancer with neratinib may represent the first precision medicine strategy for patients with advanced/metastatic cervical cancer. Neratinib was generally well tolerated in the SUMMIT study and no new safety signals were identified. The efficacy of neratinib monotherapy was encouraging and, even though cross-trial comparisons are problematic, the ORR of 25%, CBR of 50%, and median PFS of 7.0 months observed in SUMMIT compare favorably with those reported for platinum-based chemotherapy plus bevacizumab [27,36] and other investigational agents tested in this setting including newer anti-VEGF and anti-PD-L1 therapies, such as apatinib [18,37], nivolumab [38], and pembrolizumab [28,29].

Tumor molecular profiling with the goal of guiding treatment selection is now standard of care in multiple solid tumor types but is not currently performed routinely in patients with metastatic cervical cancer. The promising clinical activity of neratinib in the current study suggests that tumor molecular profiling could provide a much-needed indication of treatment options for patients with platinum-refractory advanced cervical cancer. *HER2* mutations can also be detected in tumor DNA circulating in plasma [39,40], and observational protocols such as HER-Seq (NCT03786107), which use convenient blood-based screening, are currently underway to identify patients who are suitable to participate in neratinib clinical trials.

Limitations of this analysis were the small sample size due to the scarcity of patients with metastatic cervical cancer, the lack of routine genomic screening in patients with advanced cervical cancer, and the non-randomized, open-label design of the SUMMIT basket trial. Nevertheless, it is important to acknowledge that 16 patients with cervical cancer and *HER2* mutations were enrolled, with a subset demonstrating clinical benefit from neratinib treatment. Enrollment is continuing in this study to better define the response rate following neratinib therapy in various rare cancer types, including cervical cancer.

In conclusion, *HER2* mutations are an important class of oncogenic drivers in cervical cancer, especially in adenocarcinoma. Neratinib was well tolerated and showed promising clinical efficacy in heavily pretreated patients with metastatic cervical cancer. Given the paucity of available treatment options for this population, these results warrant further investigation and confirmation in larger clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Somatic *HER2* mutations are a newly identified class of oncogenic drivers in several solid cancers.
- *HER2* mutations have an estimated incidence of 5% in cervical cancer and may be associated with a poor prognosis.
- A subset of *HER2* mutations are sensitive to inhibition by neratinib, an irreversible pan-HER tyrosine kinase inhibitor.
- Neratinib monotherapy showed promising efficacy in heavily pretreated patients with *HER2*-mutant, cervical cancer.

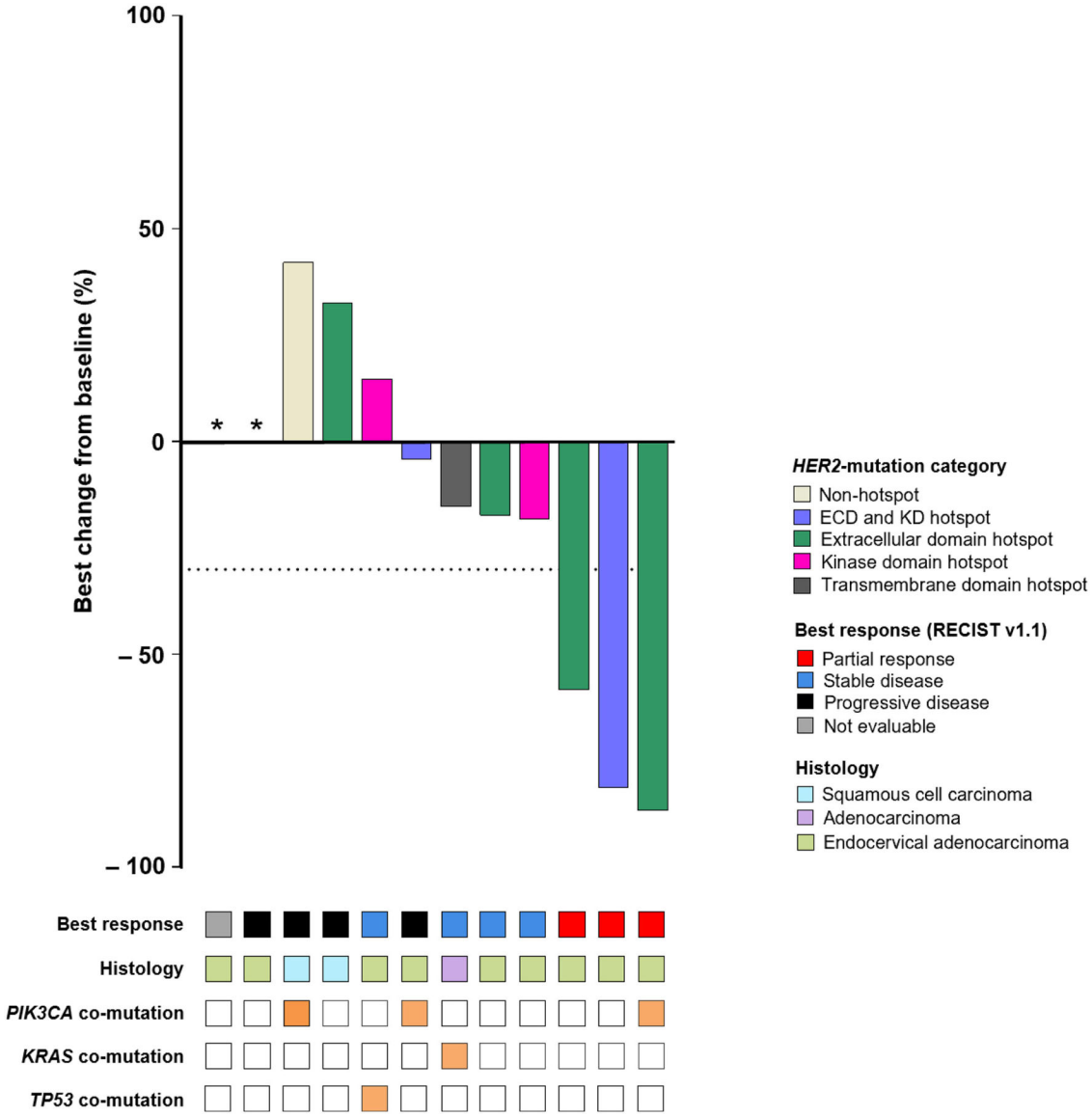

Fig. 1.

Best change in tumor size and characteristics in RECIST efficacy evaluable patients (N = 12). Response based on investigator tumor assessments by RECIST (version 1.1). Only the most common co-mutations, as reported by local testing at time of enrollment, are shown. *Patient developed new lesion (progressive disease) and had no post-baseline target lesion measurement. ECD: extracellular domain; KD: kinase domain; RECIST: Response Evaluation Criteria in Solid Tumors.

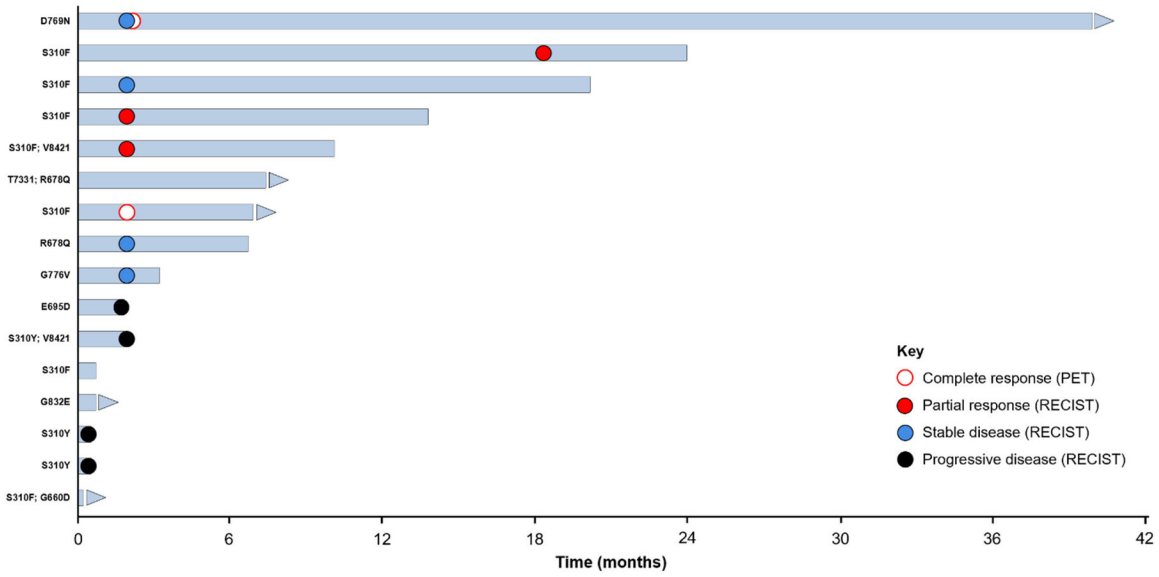

Fig. 2.

Duration of treatment and best response in all patients per RECIST or PERCIST ($N = 16$). Response based on investigator assessment. CT: computed tomography; PET: positron-emission tomography; RECIST: Response Evaluation Criteria in Solid Tumors.

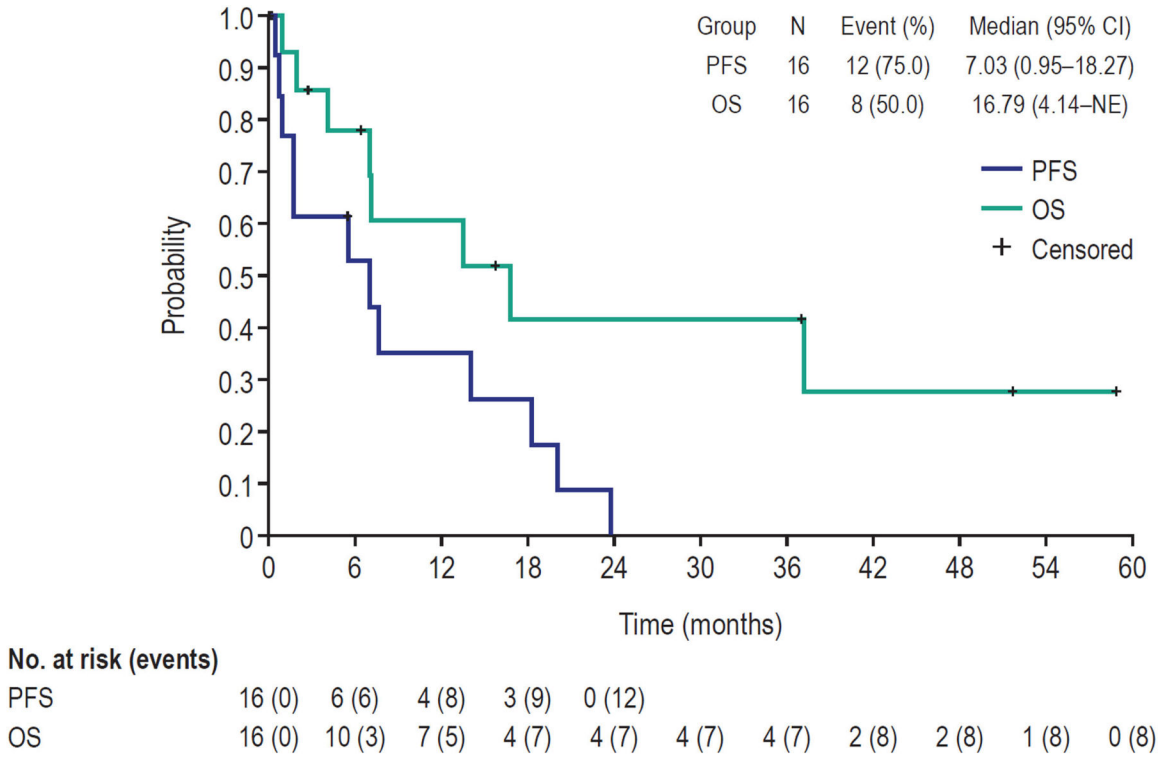

Fig. 3.

Kaplan–Meier estimates of PFS and OS in safety analysis set ($N = 16$). NE: not estimable; OS: overall survival; PFS: progression-free survival.

Table 1

Demographics and patient characteristics – safety analysis set (*N* = 16).

	***HER2*-mutant cervical cohort (*N* = 16)**
Median age (range), years	55.0 (29–64)
Race, *n (%)*	
White	13 (81.3)
Asian	1 (6.3)
Black	1 (6.3)
Other	1 (6.3)
ECOG performance status, *n* (%)	
0	6 (37.5)
1	10 (62.5)
FIGO stage at diagnosis[a], *n* (%)	
I	7 (43.8)
II	3 (18.8)
IIIB	2 (12.5)
IV	4 (25.0)
Histology, *n* (%)	
Endocervical adenocarcinoma	10 (62.5)
Squamous cell carcinoma	3 (18.8)
Adenocarcinoma	2 (12.5)
Gastric type adenocarcinoma	1 (6.3)
Median time from development of metastatic disease to enrollment (range), years	1.2 (0.1–8.4)
Previous therapeutic interventions[b], *n* (%)	
Cisplatin	5 (31.3)[a]
Carboplatin	10 (62.5)
Paclitaxel	15 (93.8)
Bevacizumab	11 (68.8)
Topotecan	2 (12.5)
Pembrolizumab	2 (12.5)
Prior chemoradiation, *n* (%)	6 (37.5)
Prior surgery, *n* (%)	12 (75.0)

ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics.

[a]Five patients reported receiving cisplatin without concurrent radiation; of these, two had also previously received chemoradiation with cisplatin.

[b]A complete list of previous systemic therapies is available in Supplementary Table S1.

Table 2

Efficacy summary – safety analysis set (*N* = 16) and RECIST efficacy evaluable patients (*N* = 12).

Efficacy endpoint	Safety analysis set[a] (*N* = 16)	RECIST efficacy evaluable patients (*N* = 12)
Objective response (confirmed), *n* (%)	4 (25.0)	3 (25.0)
CR[b]	1 (6.3)	0
PR	3 (18.8)	3 (25.0)
Objective response rate, % (95% CI)	25.0 (7.3–52.4)	25.0 (5.5–57.2)
Duration of response, months	3.7[c], 5.6. 5.9, 12.3	5.6,5.9,12.3
Clinical benefit rate, *%* (95% CI)	43.8 (19.8–70.1)	50.0 (21.1–78.9)
Median PFS, months (95% CI)		7.0 (1.0–18.3)[d]
Median OS, months (95% CI)		16.8(4.1-NE)[d]

CI: confidence interval; CR: complete response; NE: not estimable; OS: overall survival; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors.

[a] Not all patients had RECIST-measurable disease or post-baseline tumor assessments.

[b] Confirmed by PERCIST.

[c] Response ongoing.

[d] PFS and OS calculated in all patients who received at least one dose of neratinib (*N* = 16).

Table 3

Most common treatment-related adverse events in safety analysis set ($N = 16$).

Adverse event, *n* (%)	Any grade	Grade 3/4
Diarrhea	12 (75.0)	1 (6.3)
Nausea	7 (43.8)	0
Decreased appetite	6 (37.5)	0
Abdominal pain	5 (31.3)	1 (6.3)
Constipation	5 (31.3)	0
Dyspnea	4 (25.0)	0
Dry skin	3 (18.8)	0
Epistaxis	3 (18.8)	0
Headache	3 (18.8)	0
Malaise	3 (18.8)	0
Edema peripheral	3 (18.8)	0
Pain	3 (18.8)	0
Vomiting	3 (18.8)	0
Anxiety	2 (12.5)	0
Asthenia	2 (12.5)	1 (6.3)
Back pain	2 (12.5)	1 (6.3)
Cystitis	2 (12.5)	1 (6.3)
Dermatitis acneiform	2 (12.5)	0
Dry mouth	2 (12.5)	0
Dyspepsia	2 (12.5)	0
Fatigue	2 (12.5)	0
Insomnia	2 (12.5)	0
Muscle spasms	2 (12.5)	0
Muscular weakness	2 (12.5)	0
Pain in extremity	2 (12.5)	0
Rash maculo-papular	2 (12.5)	0