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ON WOMEN'S CANCER®
HAWAII
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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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HAWAII FIVE-O SGO 50TH ANNUAL MEETING ON WOMEN'S CANCER

SGO Society of Gynecologic Oncology

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Disclosures

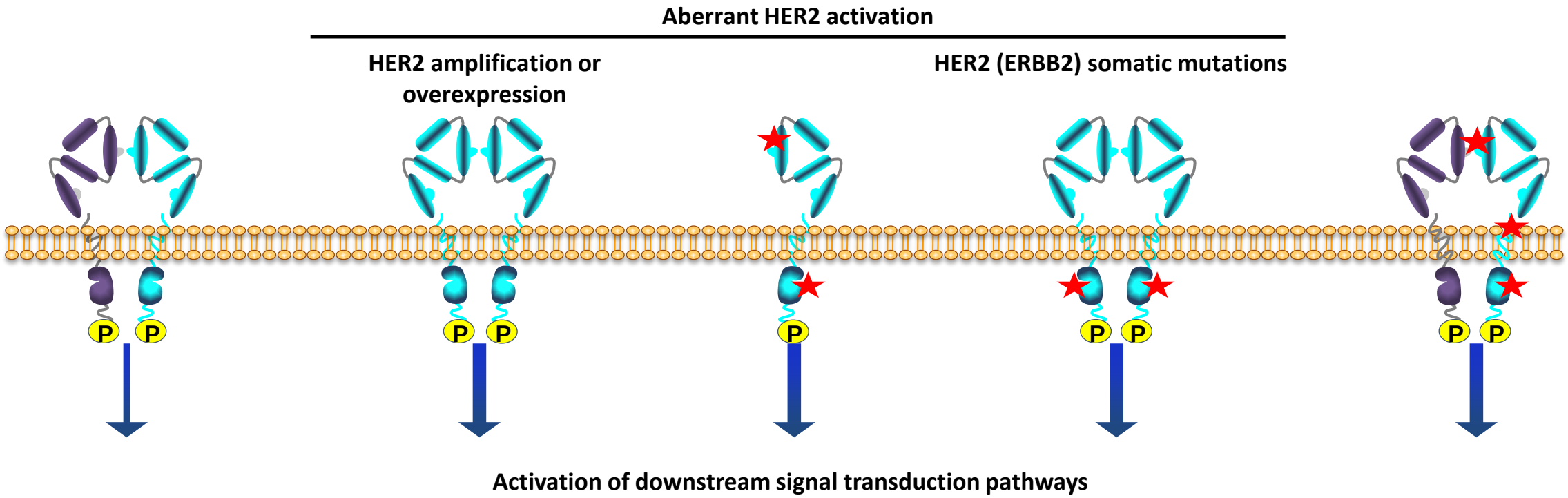
- I have no financial disclosures or conflicts of interest
- I will discuss off-label use and/or investigational use of neratinib

Recurrent cervical cancer

- Relatively treatment-resistant if not resectable
- Few long-term responses
  - GOG-240[1]: PFS 8.2 months (chemo + bev) vs 5.9 months (chemo alone)
  - KEYNOTE-158[2]: PFS 2.1 months (pembrolizumab)
- Need for other options

1. Tewari KS et al. N Engl J Med 2014; 370:734-743
2. Chung HC et al. J Clin Oncol 2018:36; (suppl; abstr 5522)

Abnormal HER2 activation results in tumor growth



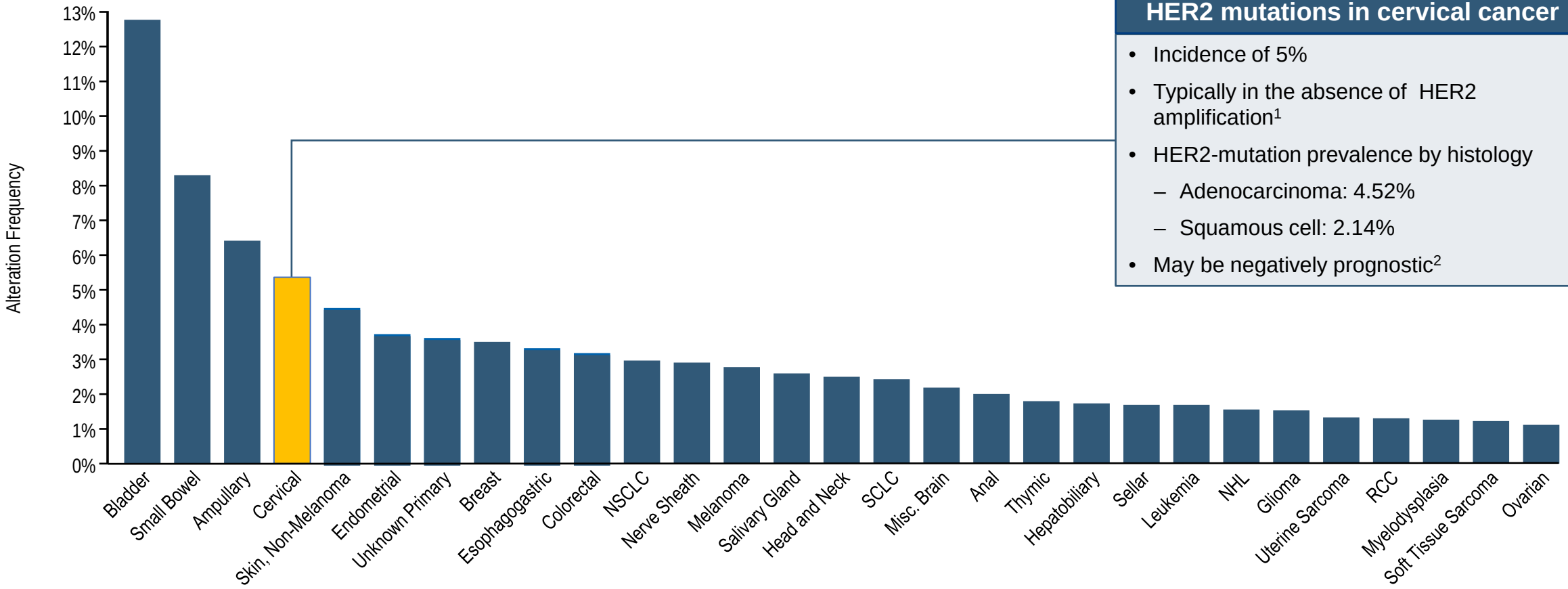
- Constitutive receptor kinase activation and downstream signaling pathways
- Increased transformation, cell proliferation and cell survival
- Increased tumor growth and metastasis

HER2 mutation

P Phosphoprotein

Bose et al. Cancer Discovery 2013;3:224–37

Somatic HER2 mutations and cervical cancer



HER2 mutations in cervical cancer

- Incidence of 5%
- Typically in the absence of HER2 amplification[1]
- HER2-mutation prevalence by histology
  - Adenocarcinoma: 4.52%
  - Squamous cell: 2.14%
- May be negatively prognostic[2]

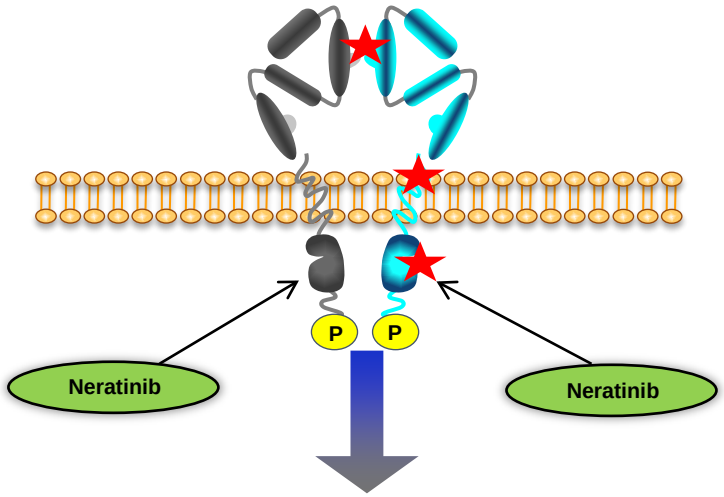
Schram et al, AACR 2017 Abstract LB-103

1. Ojesina et al. Nature 2014;506:371–5
2. Xiang et al. Gyn Oncol 2018;148:311–6

Neratinib is a pan-HER tyrosine kinase inhibitor

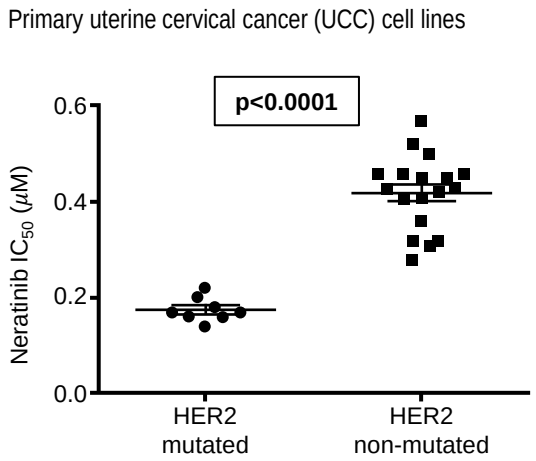
- Oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4)[1]
- Potent inhibition of cell proliferation/tumor growth in HER2-mutant uterine cervical cancer cell lines/xenografts[2]

★ HER2 mutations

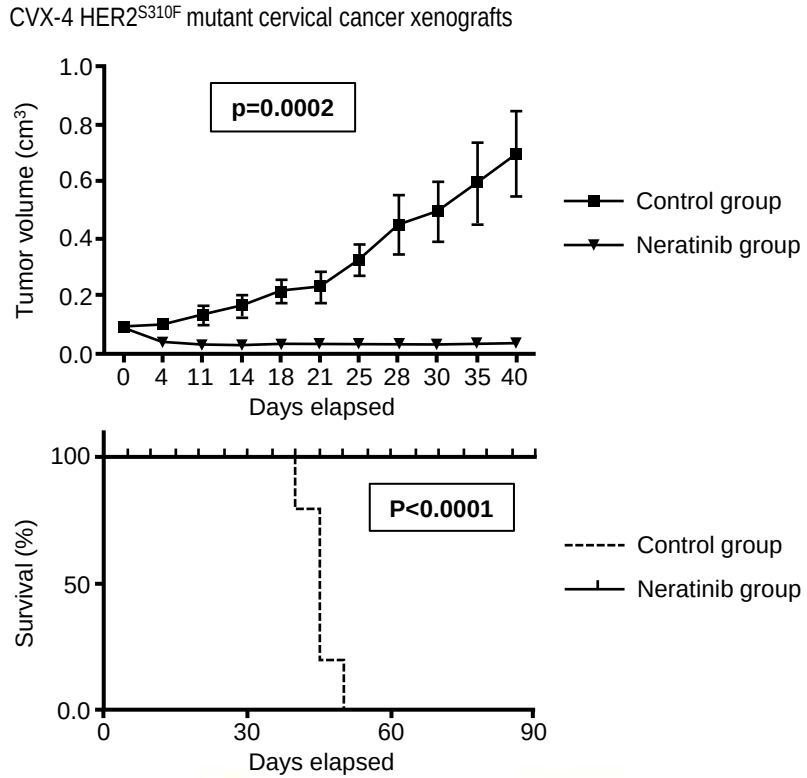


Activation of downstream signal transduction pathways and tumor growth survival[3]

Inhibition of cell proliferation[2]



Tumor growth inhibition[2]



1. Rabindran et al. Cancer Res 2004:64:3958–65
2. Lopez et al. SGO Meeting 2015 (poster 356)
3. Bose et al. Cancer Discovery 2013;3:224–37

SUMMIT basket study design

Key inclusion criteria

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

HER2-mutant tumors

Key exclusion criteria

- Prior treatment with any pan-HER TKI (eg, lapatinib, afatinib, dacomitinib, neratinib)
- Symptomatic or unstable brain metastases

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

→ **Neratinib monotherapy**

- Bladder

→ **Neratinib + Paclitaxel**

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

→ **Neratinib* + Trastuzumab#**

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

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/m^2 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

Primary endpoint

- Objective response rate at first post-baseline tumor assessment (ORR_{first})

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

- ORR_{first}, ORR, CBR: associated 95% CI
- Median PFS: KM estimate with 95% CI

Patient characteristics

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

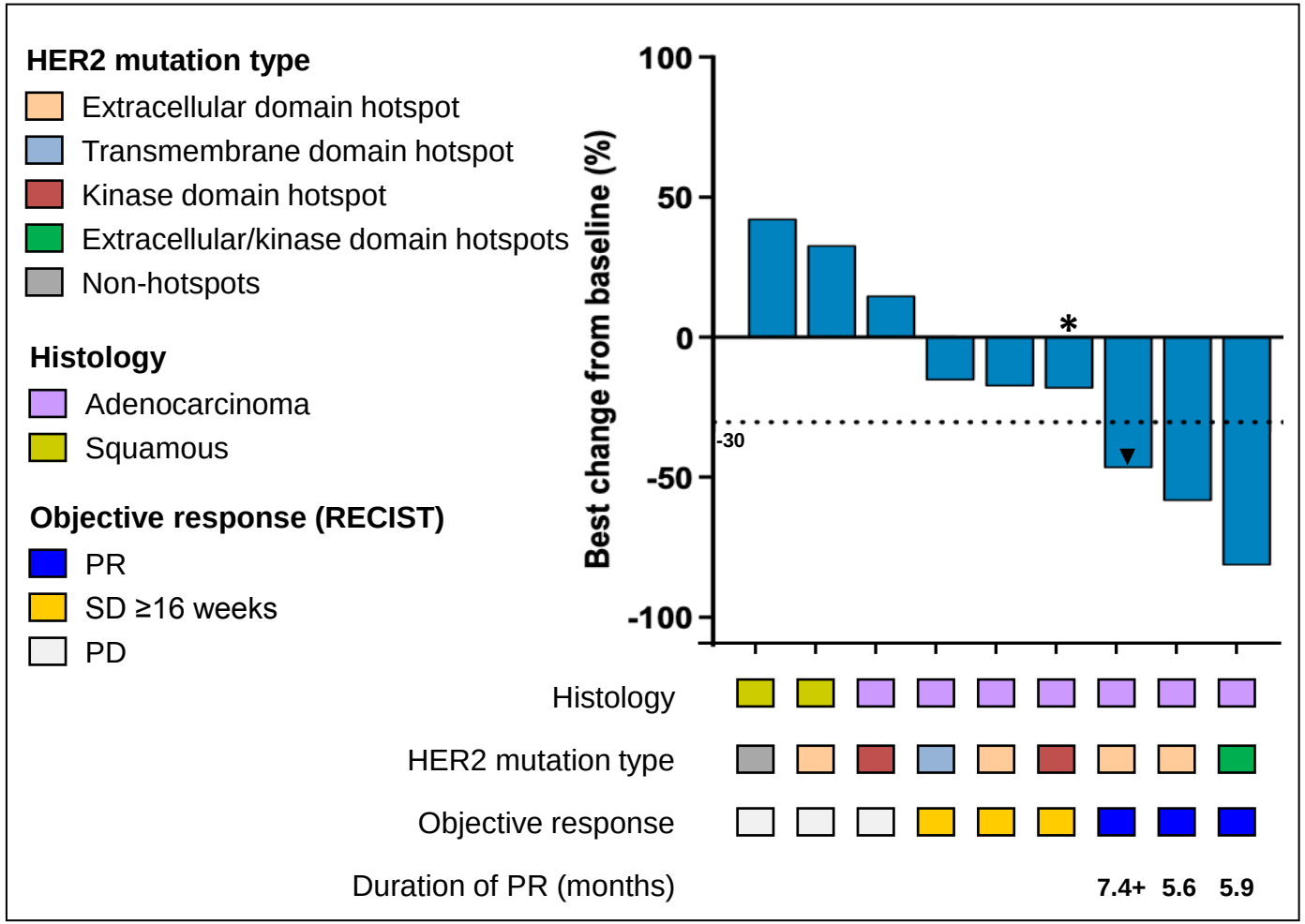
Efficacy summary

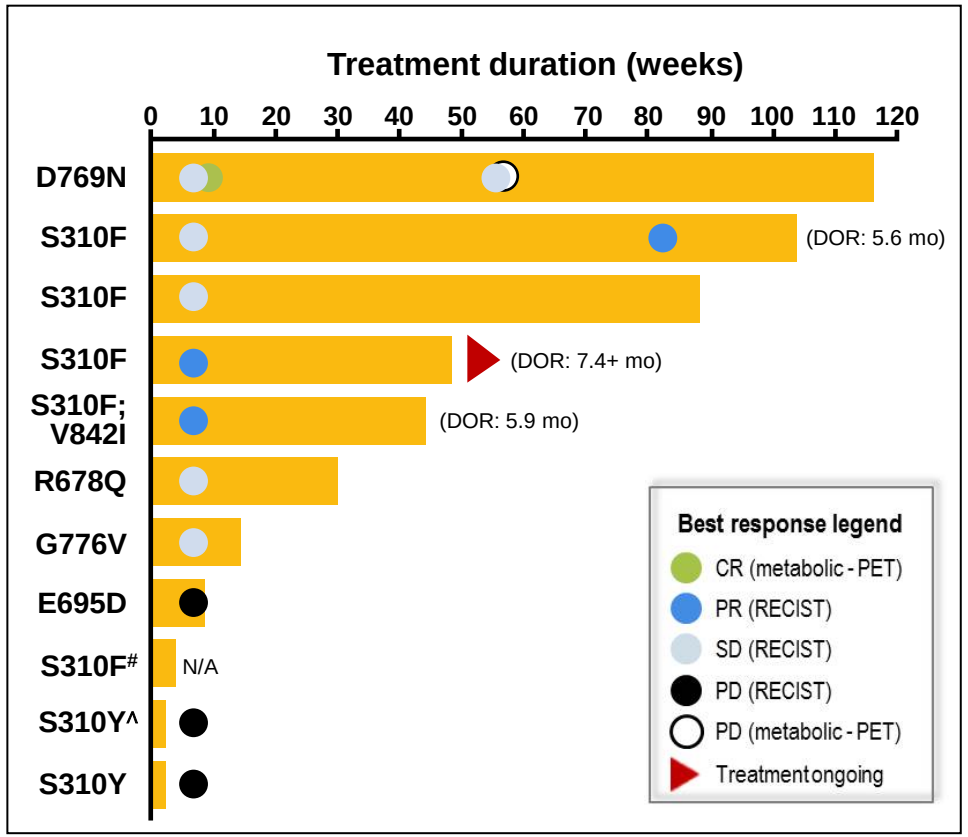
Efficacy endpoint[a]	HER2-mutant cervical cohort (n=11)
Objective response (confirmed)[b] – n CR PR Objective response rate, % (95% CI)	3 0 3 **27.3 (6.0–61.0)**
DOR for each responder, months	**5.6, 5.9, 7.4***
Clinical benefit[c] – n CR PR SD ≥16 weeks Clinical benefit rate, % (95% CI)	6 0 3 3 **54.5 (23.4–83.3)**
Median[d] PFS (95% CI), mo	**7.0 (0.7–20.1)**

[a]Response is based on investigator tumor assessments per RECIST v1.1
[b]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
[c]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)
[d]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



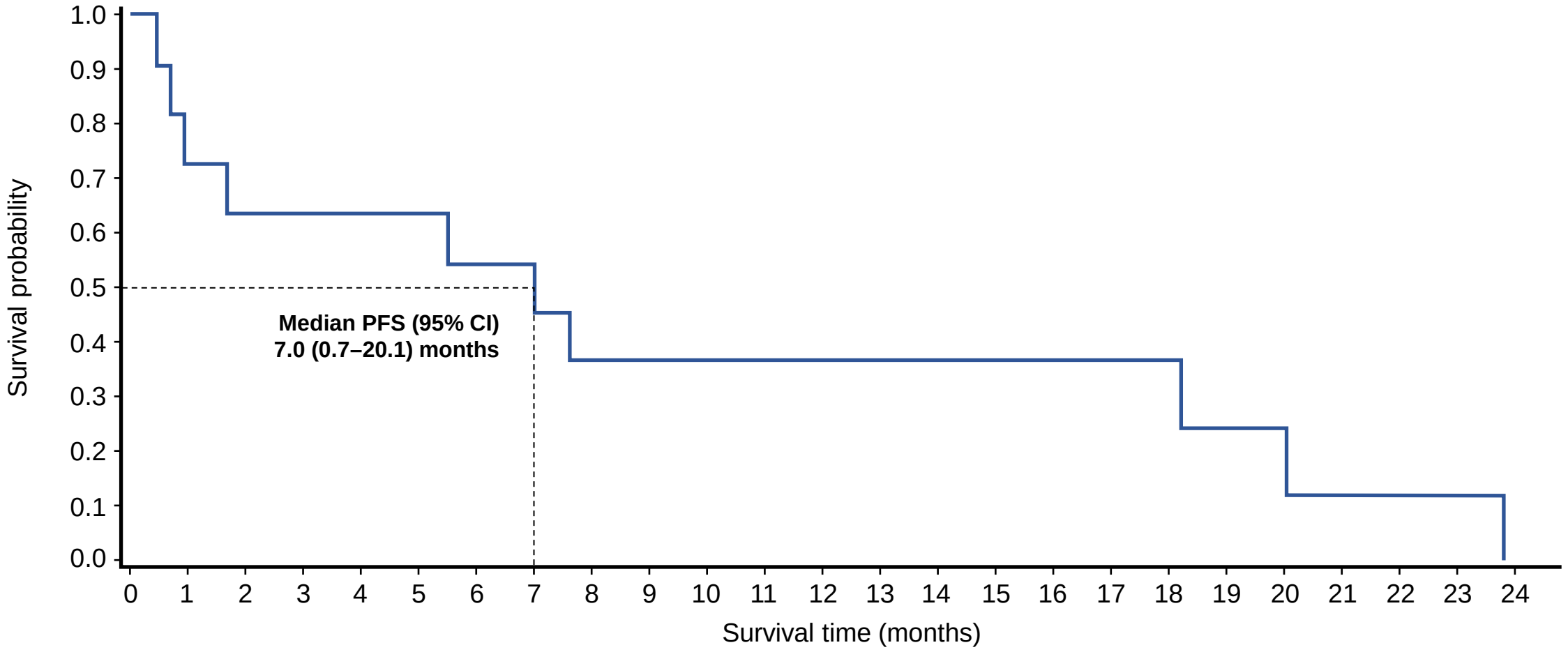


2 patients did not have a measurable post-baseline tumor assessment
Patient died prior to first post-baseline baseline scan
^ Tumor lesions were not measurable on post-baseline scan; evaluated as PD due to development of new lesion

▼ *Treatment ongoing*

✻ *Confirmed complete metabolic response (per PET response criteria)*

Progression-free survival (n=11)



Incidence of treatment-emergent adverse events (≥3 patients)

Adverse event, n (%)	HER2-mutant cervical cancer cohort (n=11)		All SUMMIT monotherapy patients (n=233)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Subjects with at least 1 adverse event, n (%)	11 (100.0)	5 (45.5)	225 (96.6)	122 (52.4%)
Diarrhea	9 (81.8)*	1 (9.1)[#]	153 (65.7)	44 (18.9%)
Nausea	6 (54.5)	0	91 (39.1)	3 (1.3%)
Decreased appetite	5 (45.5)	0	54 (23.2)	1 (0.4%)
Abdominal pain	4 (36.4)	0	47 (20.2)	10 (4.3%)
Dyspnea	4 (36.4)	0	22 (9.4)	5 (2.1%)
Epistaxis	3 (27.3)	0	6 (2.6)	0
Headache	3 (27.3)	0	21 (9.0)	0
Malaise	3 (27.3)	0	7 (3.0)	0
Edema peripheral	3 (27.3)	0	20 (8.6)	0
Pain	3 (27.3)	0	8 (3.4)	3 (1.3%)
Vomiting	3 (27.3)	0	77 (33.0)	6 (2.6%)

*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

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