Memorial Sloan Kettering Cancer Center

Oral CT001

Neratinib in *HER2*- or *HER3*-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study

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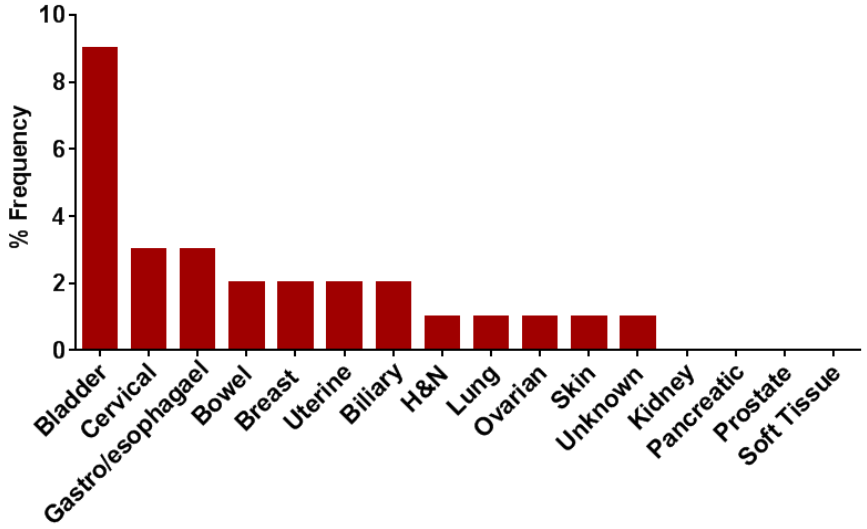
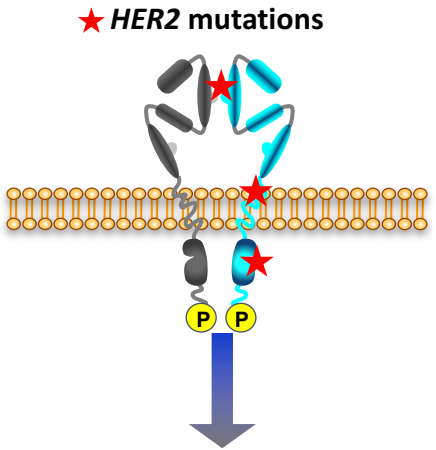
HER2 (ERBB2) mutations

- Subsets of somatic *HER2* mutations are seen at relatively low frequencies across multiple tumor types
- Activating *HER2* mutations result in constitutive kinase signaling, activation of growth promoting/ survival pathways, oncogenic transformation and enhanced tumor growth in preclinical models



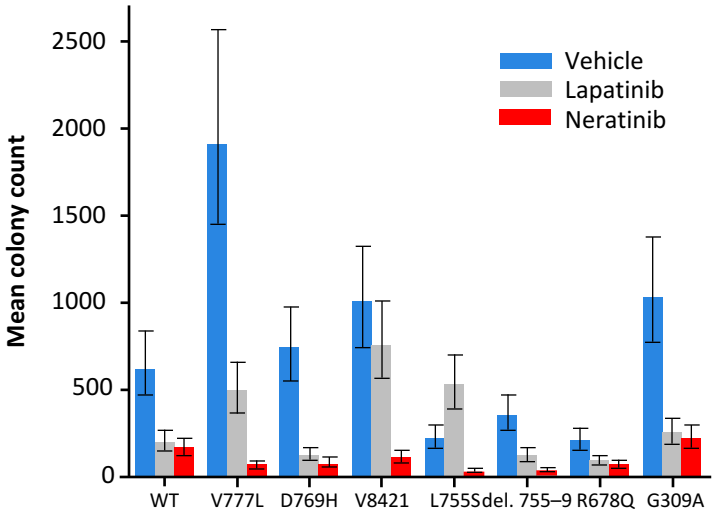


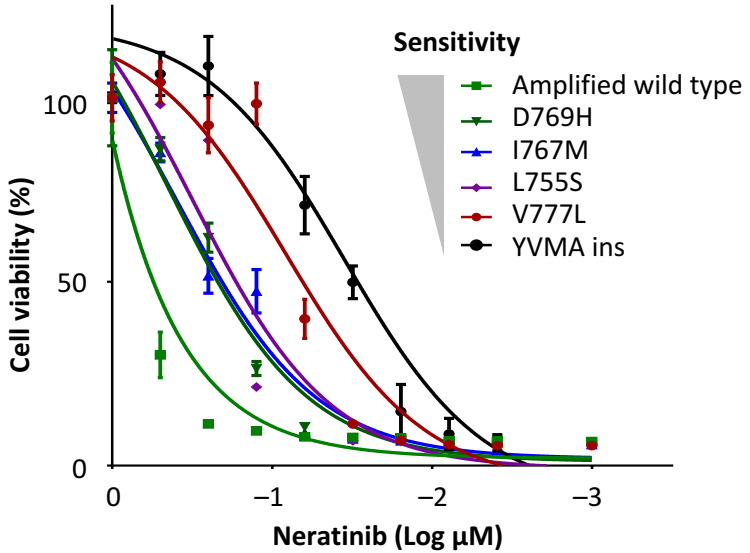
Activation of downstream signal transduction pathways and tumor growth survival

cBioportal.org accessed on 16 March 2017

Neratinib in *HER2*-mutant cancer

- Neratinib is an oral, irreversible pan-HER tyrosine kinase inhibitor
- Neratinib leads to potent inhibition of intracellular signaling, cell proliferation and colony formation of *HER2*-mutant tumor cell lines *in vitro*[1,2]
- *HER2*-mutant alleles have distinct differential sensitivity to neratinib





[1]Bose et al. Cancer Discovery 2013:3;224–237
[2]Carmona et al. Cancer Res 2016:76(14 Suppl);abst 298

SUMMIT 'basket' study design

***HER2* or *HER3* mutations (documented by local testing)**

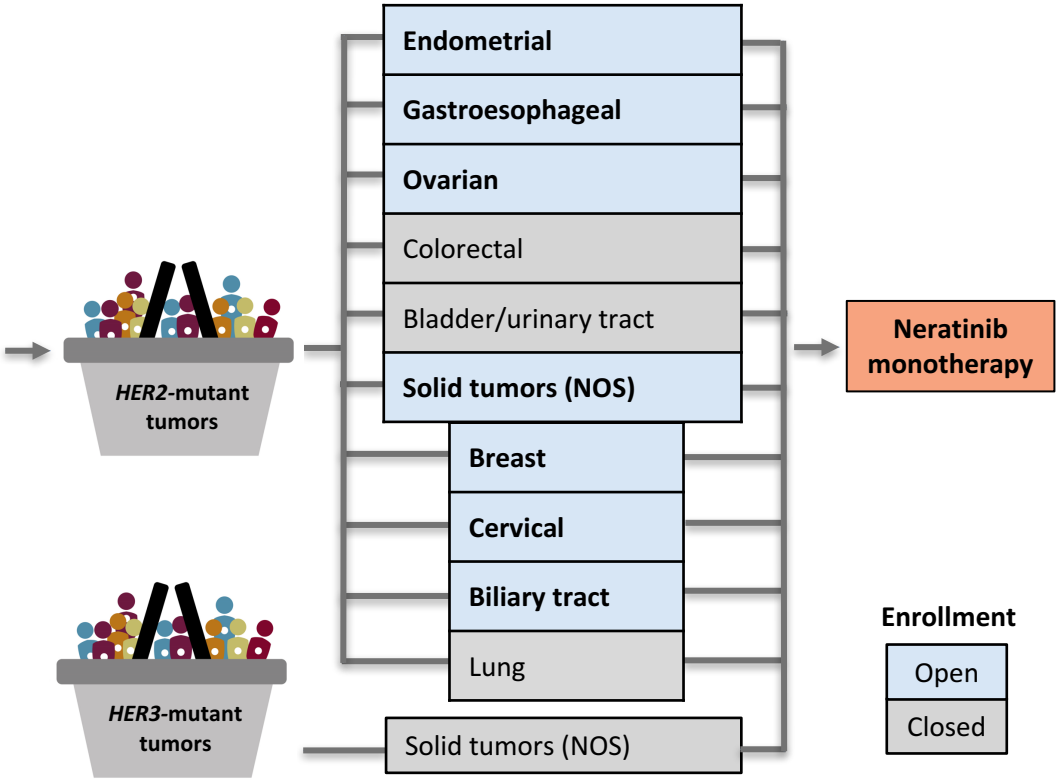
Primary endpoint
- Objective response rate at week 8 (ORR_8)

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

Statistical methods
- ORR_8, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI



- FFPE tumors (archival or fresh pre-treatment biopsies) retrospectively sequenced centrally using NGS (MSK-IMPACT)
- Plasma cfDNA (pre-treatment) retrospectively sequenced centrally using a *HER2* single-gene hybrid capture research assay (MSKCC)

Data cut-off: 10-Mar-2017
NOS = not otherwise specified

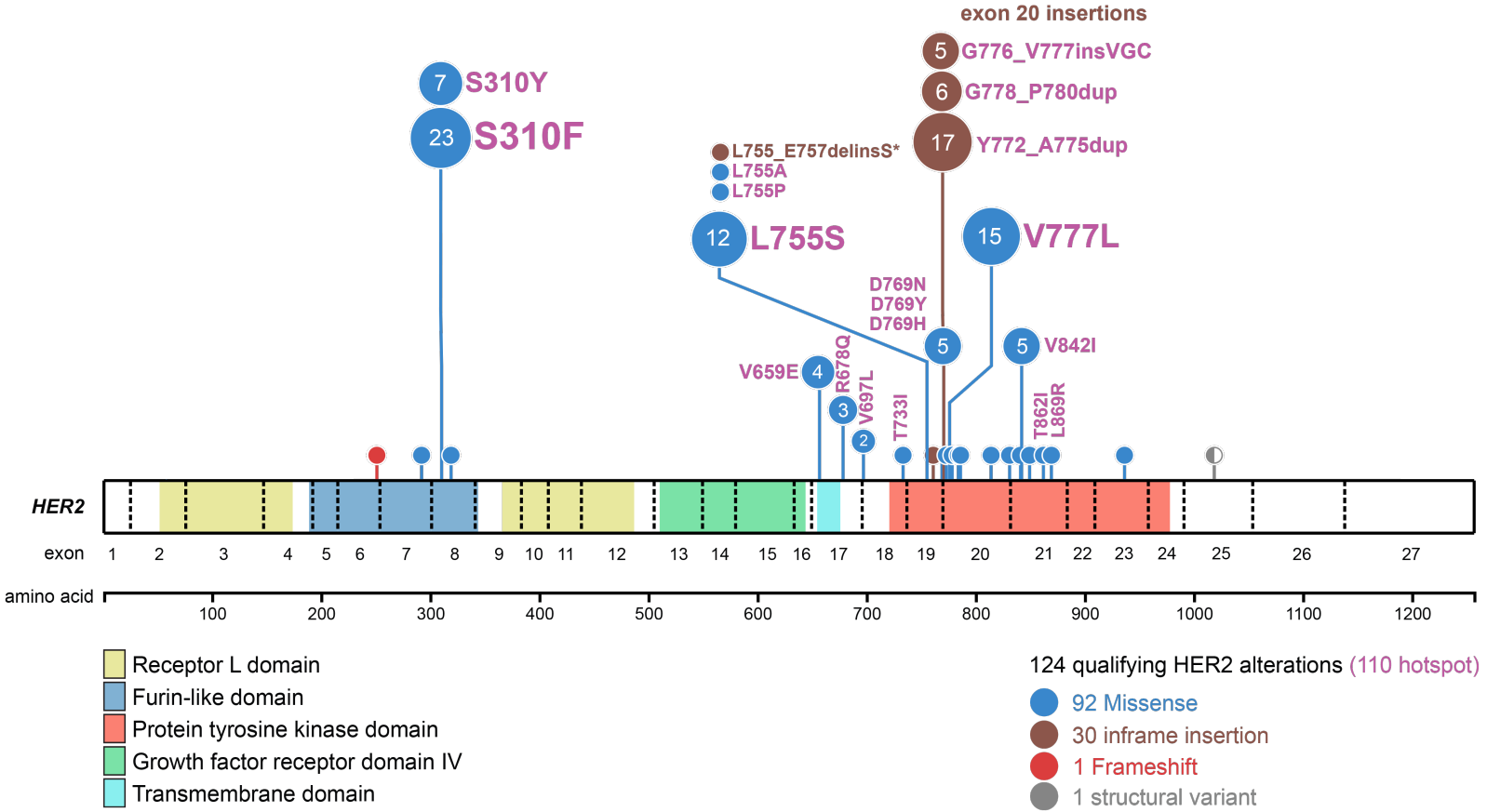
Enrollment by tumor type

	Neratinib monotherapy (n=141)
***HER2*-mutation positive**	
Lung cancer	26 (18.4)
Breast cancer	25 (17.7)
Bladder/urinary tract cancer	16 (11.3)
Solid tumors (NOS)	15 (10.6)
Colorectal cancer	12 (8.5)
Biliary tract cancer	9 (6.4)
Endometrial cancer	7 (5.0)
Cervical cancer	5 (3.5)
Gastroesophageal cancer	5 (3.5)
Ovarian cancer	4 (2.8)
***HER3*-mutation positive**	
Solid tumors (NOS)	17 (12.1)

Baseline demographics

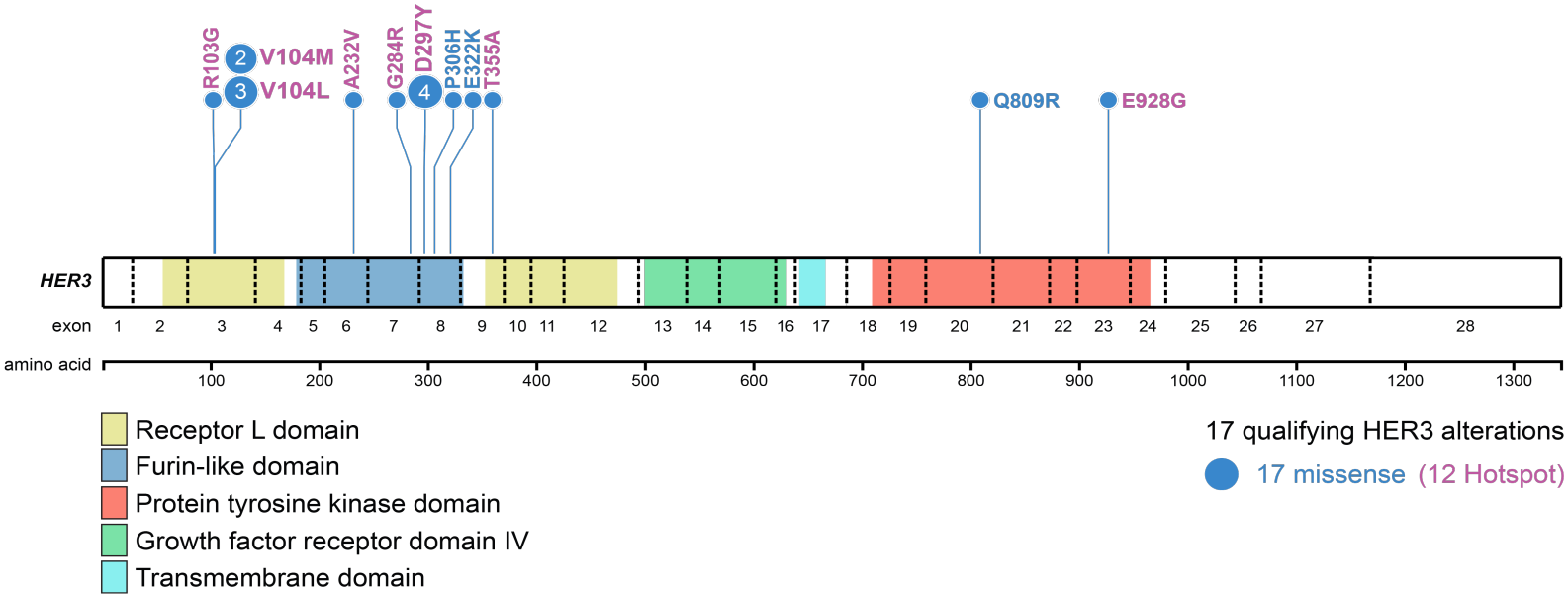
Patient characteristics	*HER2* mutant (n=124)	*HER3* mutant (n=17)	Total (n=141)
Age			
Median (range), years	61 (30–83)	66 (39–82)	61 (30–83)
<65 years, n (%)	81 (64.8)	7 (43.8)	88 (62.4)
≥65 years, n (%)	43 (34.7)	10 (58.8)	53 (37.6)
Gender, n (%)			
Female	79 (63.7)	13 (76.5)	92 (65.2)
Male	45 (36.3)	4 (23.5)	49 (34.8)
ECOG performance status, n (%)			
0	36 (29.0)	2 (11.8)	38 (27.0)
1	83 (66.9)	12 (75.6)	95 (67.4)
2	5 (4.0)	3 (17.6)	8 (5.7)
Prior systemic lines, n (%)			
Any	120 (96.8)	17 (100)	137 (97.0)
None	4 (3.2)	0 (0)	4 (2.8)
1	33 (26.4)	1 (6.3)	34 (24.1)
2	29 (23.4)	12 (70.6)	41 (29.1)
≥3	58 (46.4)	4 (25.0)	62 (44.0)
Median time from metastasis to enrollment, years (range)	1.02 (0.0–15.0)	1.13 (0.3–4.5)	1.03 (0.0–15.0)

Distribution of *HER2* mutations



Distribution of *HER3* mutations

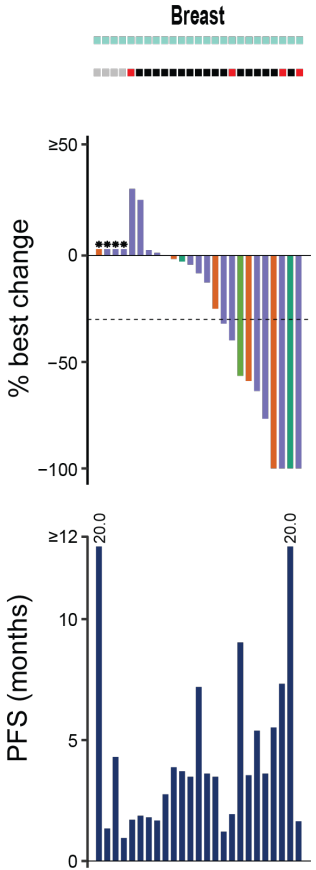
No clinical activity seen in *HER3*-mutant cohort



Patient disposition

Parameter	*HER2* mutant (n=124)	*HER3* mutant (n=17)	Total (n=141)
Patients continuing on treatment, n (%)	10	0	10
Treatment discontinuation, n (%)	114 (91.9)	17 (100.0)	131 (92.9)
Death	2 (1.6)	1 (5.9)	3 (2.1)
Disease progression	88 (71.0)	16 (94.1)	104 (73.8)
Adverse event	5 (4.0)	0 (0.0)	5 (3.5)
Withdrawal of consent	4 (3.2)	0 (0.0)	4 (2.8)
Investigator request	5 (4.0)	0 (0.0)	5 (3.5)
Lost to follow-up	1 (0.8)	0 (0.0)	1 (0.7)
Other	9 (7.2)	0 (0.0)	9 (6.4)
Subjects ended study, n (%)	81 (65.3)	15 (88.2)	96 (68.1)
Death	70 (56.5)	12 (70.6)	82 (58.2)
Withdrawal of consent	5 (4.0)	2 (12.5)	7 (5.0)
Lost to follow-up	5 (4.0)	1 (6.3)	6 (4.3)
Other	1 (0.8)	0 (0.0)	1 (0.7)

Efficacy in *HER2*-mutant patients by tumor type



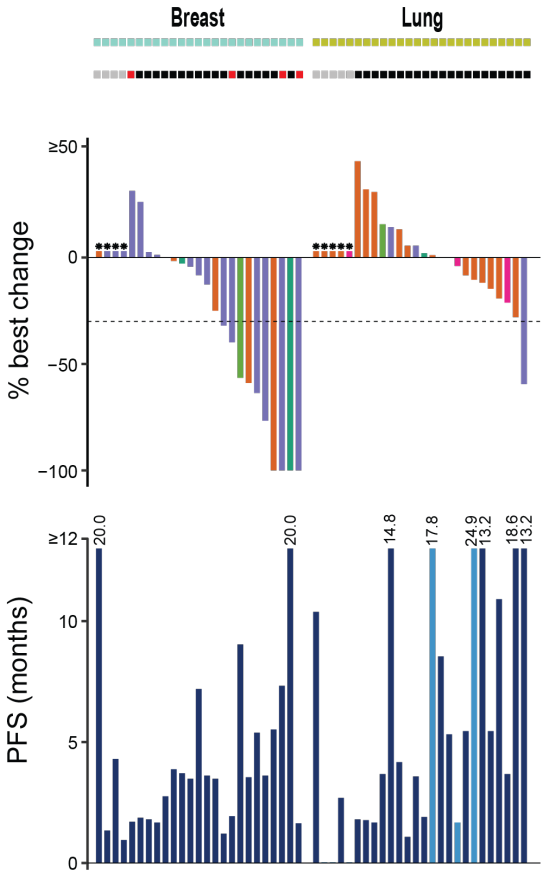
Response criteria
- RECIST 1.1
- PET response criteria
- Not evaluated

*No target lesion measurement

Allele/domain
- S310 hotspot
- Kinase domain hotspot
- Exon20 insertion hotspot
- Other hotspot
- Non-hotspot

Treatment
- Ongoing
- Off

Efficacy in *HER2*-mutant patients by tumor type



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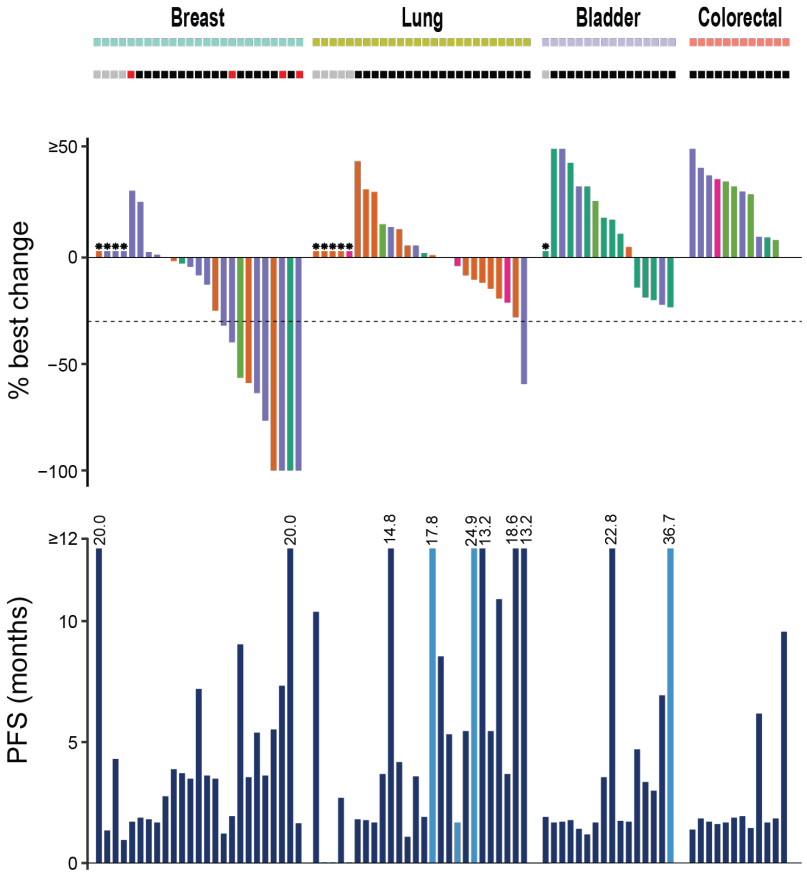

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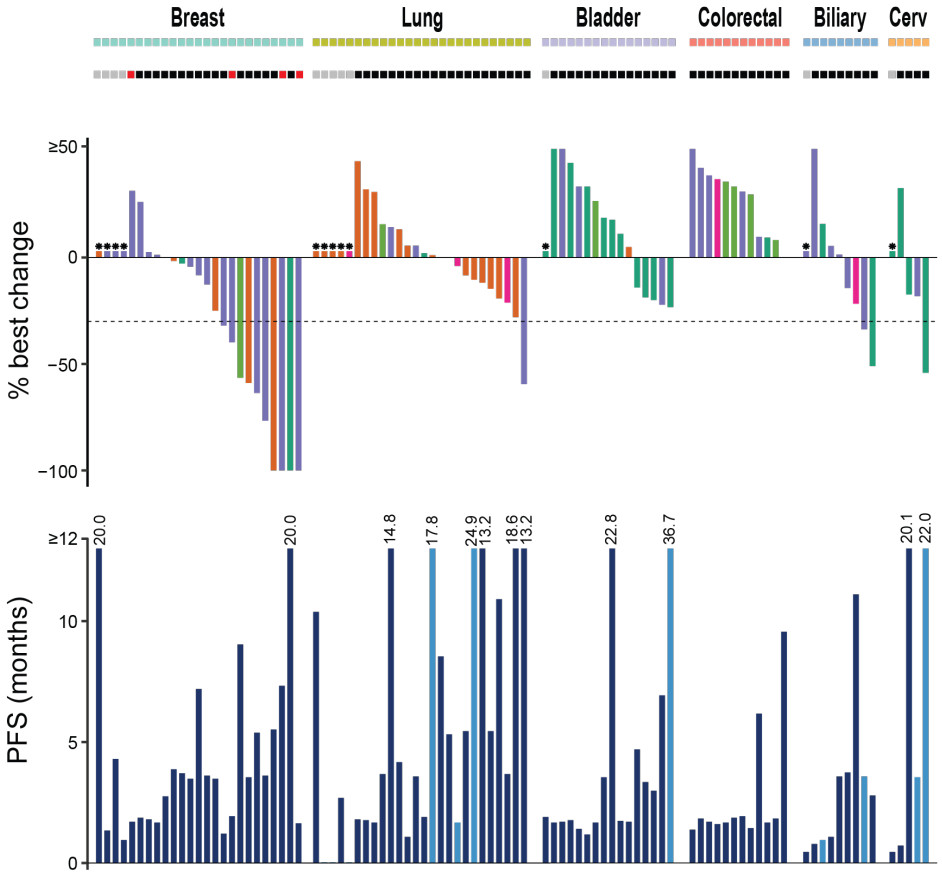

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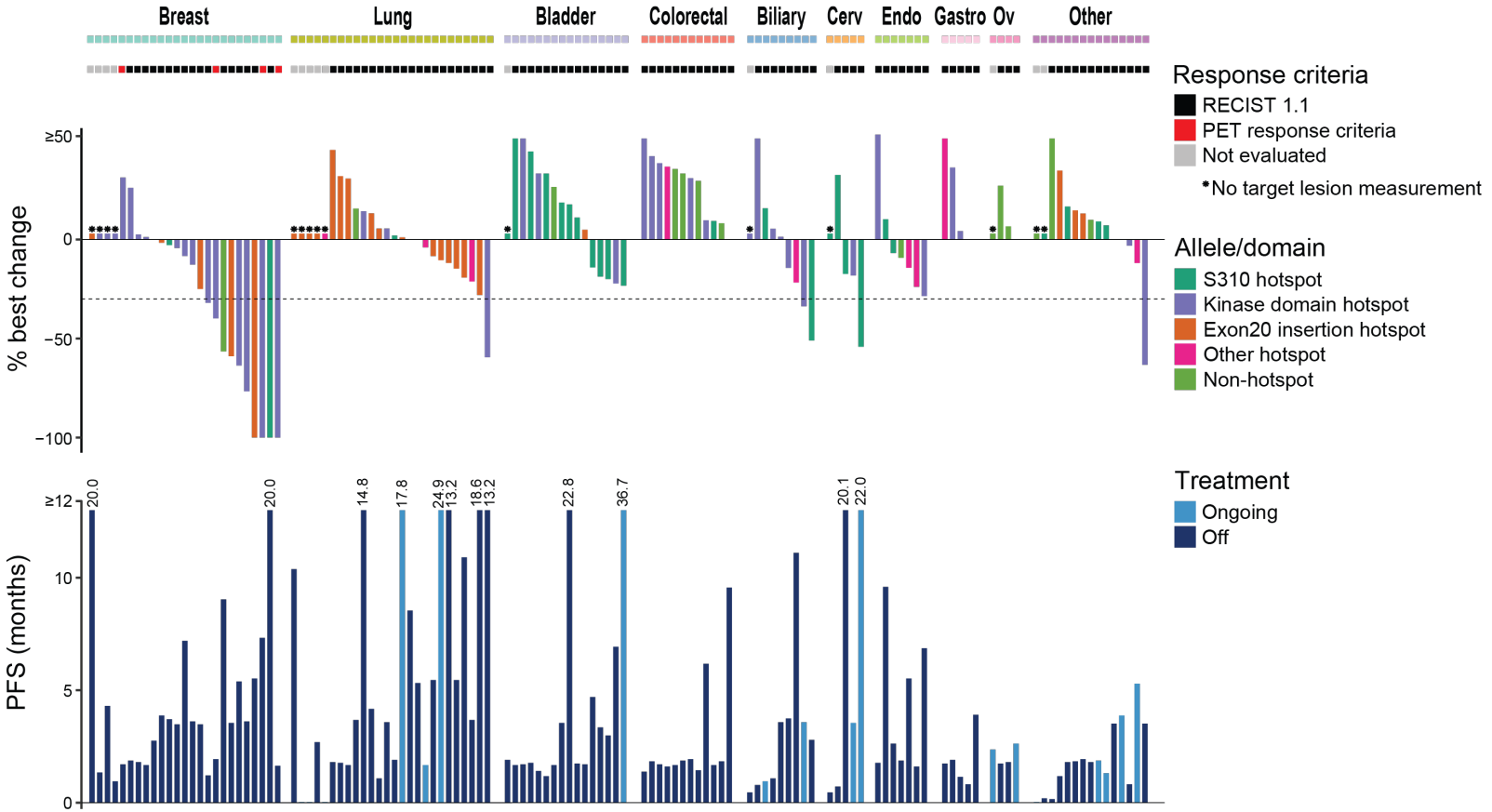
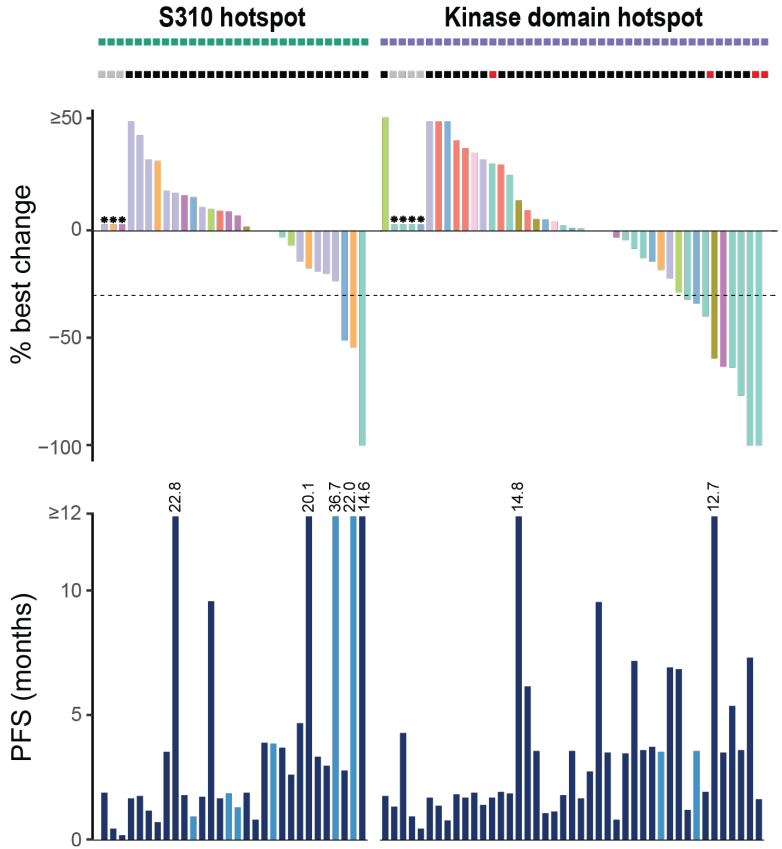


Efficacy in *HER2*-mutant patients by allele



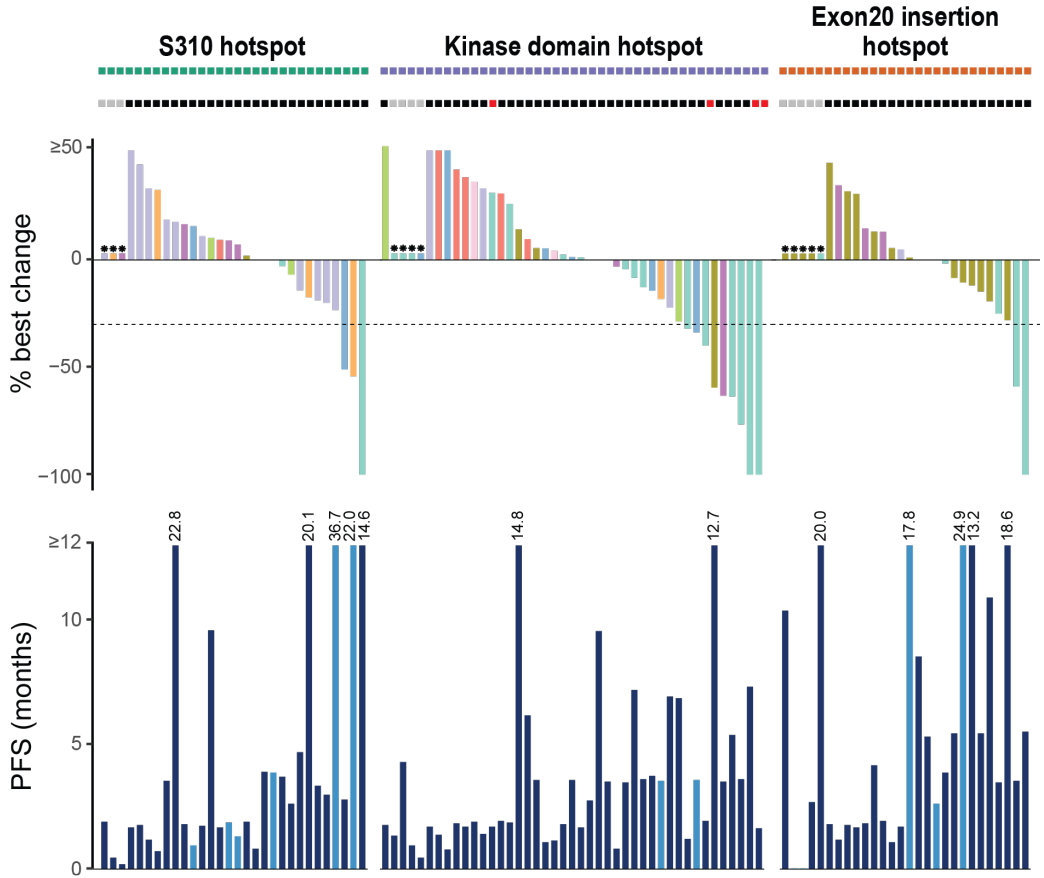
Response criteria
- RECIST 1.1
- PET response criteria
- Not evaluated

*No target lesion measurement

Tumor type
- Breast
- Lung
- Bladder
- Colorectal
- Biliary
- Cervical
- Endometrial
- Gastroesophageal
- Ovarian
- Other

Treatment
- Ongoing
- Off

Efficacy in *HER2*-mutant patients by allele



Response criteria
- RECIST 1.1
- PET response criteria
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*No target lesion measurement

Tumor type
- Breast
- Lung
- Bladder
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- Other

Treatment
- Ongoing
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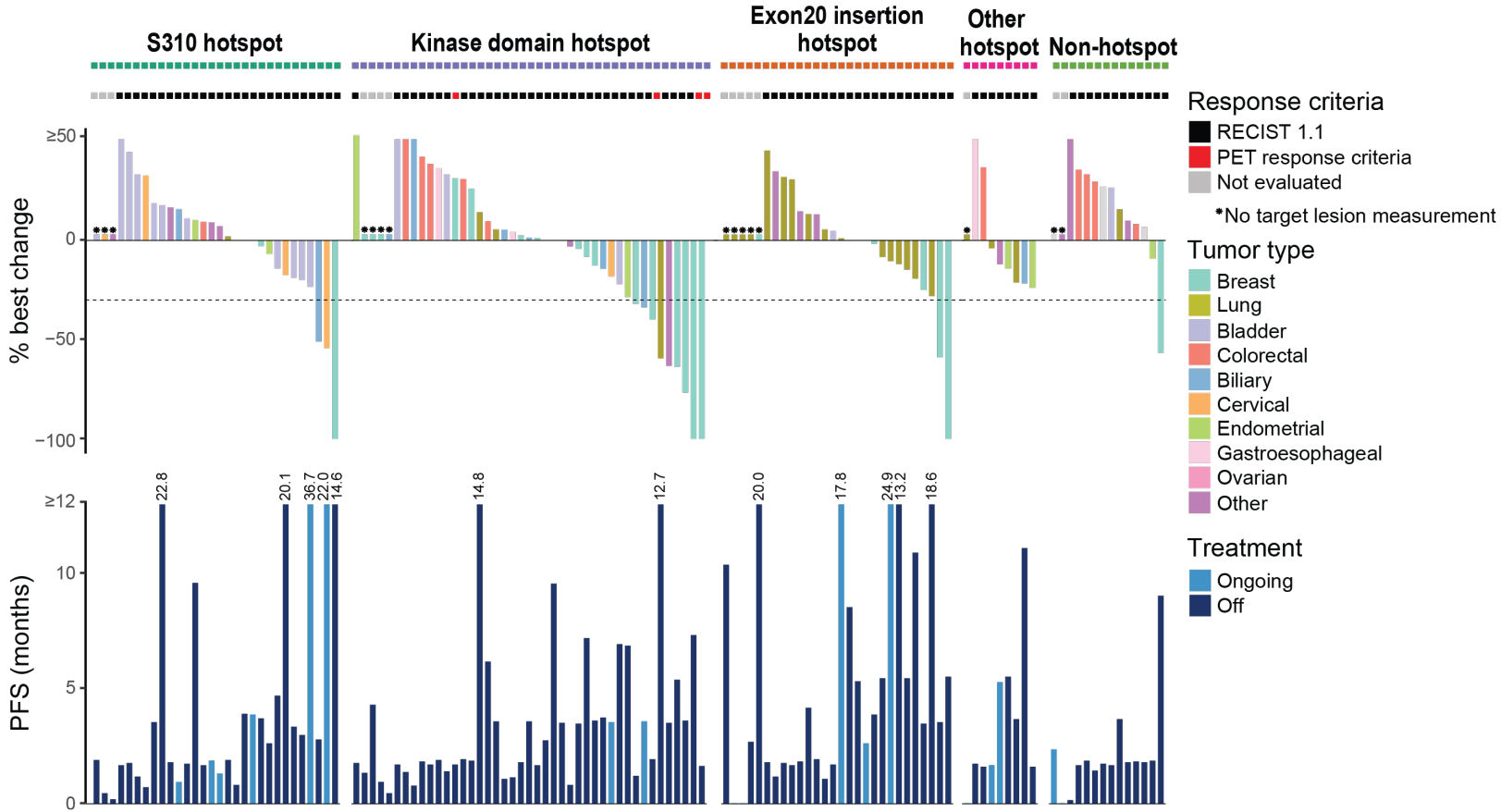
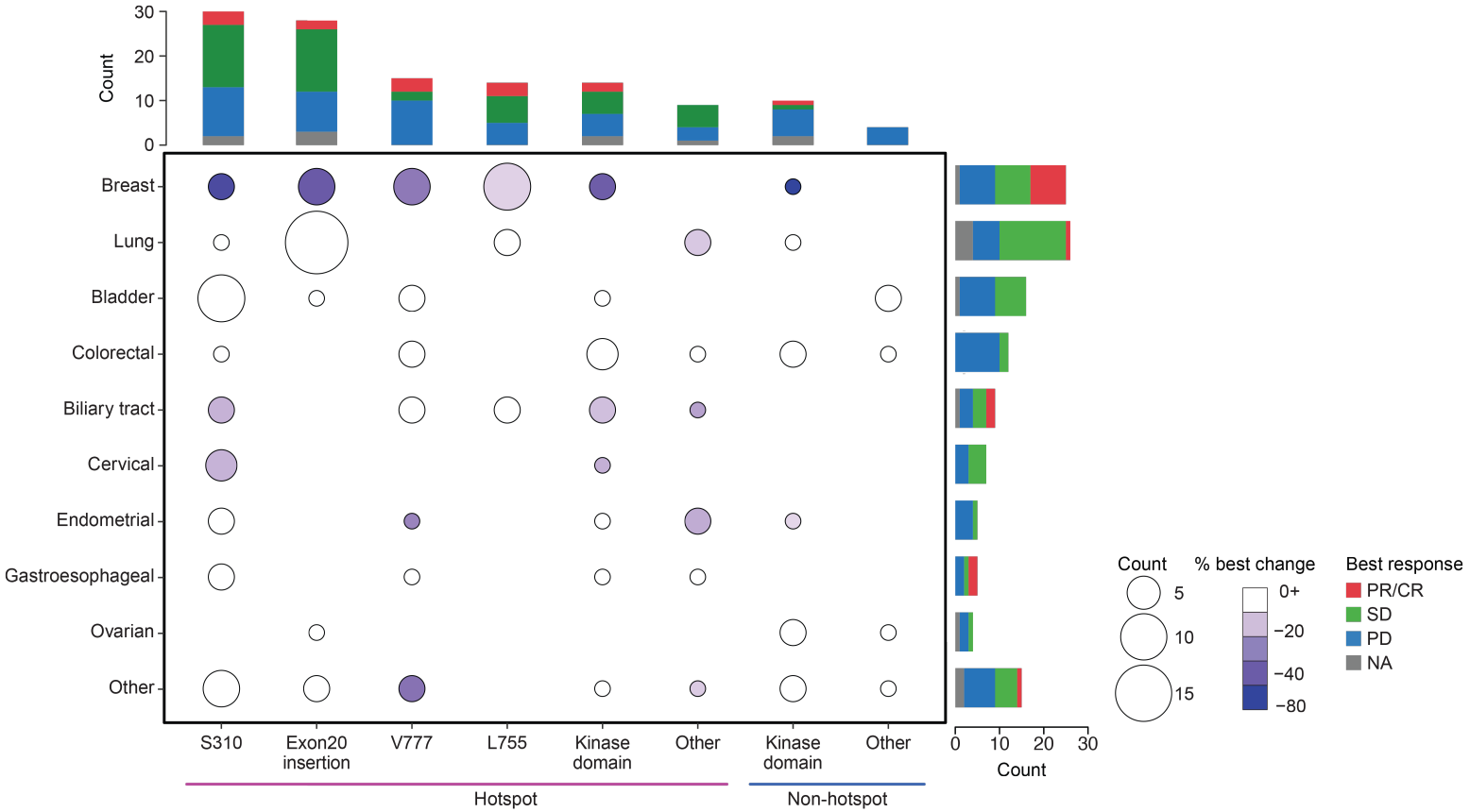
Efficacy in *HER2*-mutant patients by allele



Integrated efficacy by tumor type and *HER2* mutation



Efficacy summary

	HER2^{mut}						*HER3*^{mut}
	Breast (n=25)	**Bladder (n=16)**	**Lung (n=26)**	**Colorectal (n=12)**	**Biliary tract (n=9)**	**Cervical (n=5)**	**NOS (n=17)**
ORR at week 8, n (%) [95% CI]	8 (32.0) [14.9–53.5]	0 (0.0) [0.0–20.6]	1 (3.8) [0.1–19.6]	0 (0.0) [0.0–26.5]	2 (22.2) [2.8–60.0]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–20.6]
ORR, n (%) [95% CI]	6 (24.0) [9.4–45.1]	0 (0.0) [0.0–20.6]	1 (3.8) [0.1–19.6]	0 (0.0) [0.0–26.5]	0 (0.0) [0.0–33.6]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–20.6]
Clinical benefit rate, n (%) [95% CI]	10 (40.0) [21.1–61.3]	3 (18.8) [4.0–45.6]	11 (42.3) [23.4–63.1]	1 (8.3) [0.2–38.5]	3 (33.3) [7.5–70.1]	3 (60.0) [14.7–94.7]	2 (11.8) [1.6–38.3]
Median PFS, months (95% CI)	3.5 (1.9–4.3)	1.8 (1.7–3.5)	5.5 (2.7–10.9)	1.8 (1.4–1.9)	2.8 (0.5–3.7)	20.1 (0.5–NA)	1.7 (1.4–2.0)

Incidence of treatment-emergent adverse events (≥10%)

Adverse event, n (%)	Neratinib monotherapy (N=141)	
	Any grade	Grade ≥3
Diarrhea	104 (73.8)	31 (22.0)
Nausea	61 (43.3)	3 (2.1)
Vomiting	58 (41.1)	3 (2.1)
Constipation	49 (34.8)	2 (1.4)
Fatigue	45 (31.9)	5 (3.5)
Decreased appetite	40 (28.4)	1 (0.7)
Abdominal pain	33 (23.4)	7 (5.0)
Anemia	22 (15.6)	10 (7.1)
Dyspnea	18 (12.8)	5 (3.5)
Dehydration	17 (12.1)	8 (5.7)
Aspartate aminotransferase increased	15 (10.6)	5 (3.5)
Asthenia	15 (10.6)	1 (0.7)
Weight decreased	15 (10.6)	0

Characteristics of diarrhea

Adverse event, n (%)	Neratinib monotherapy (N=141)
Incidence of diarrhea, n (%)[a]	
Any grade	104 (73.8)
Grade 3	31 (22.0)
Action taken with neratinib, n (%)	
Permanent discontinuation	4 (2.8)
Dose reduction	2 (1.4)
Temporary hold	21 (14.9)
Serious diarrhea (hospitalized or important medical event)	15 (10.6)
Median (range) number of grade 3 episodes of diarrhea per patient	1 (1–12)
Median (range) time to first grade 3 diarrhea, days	10 (4–87)
Median (range) duration of grade 3 diarrhea per episode, days	2 (1–18)

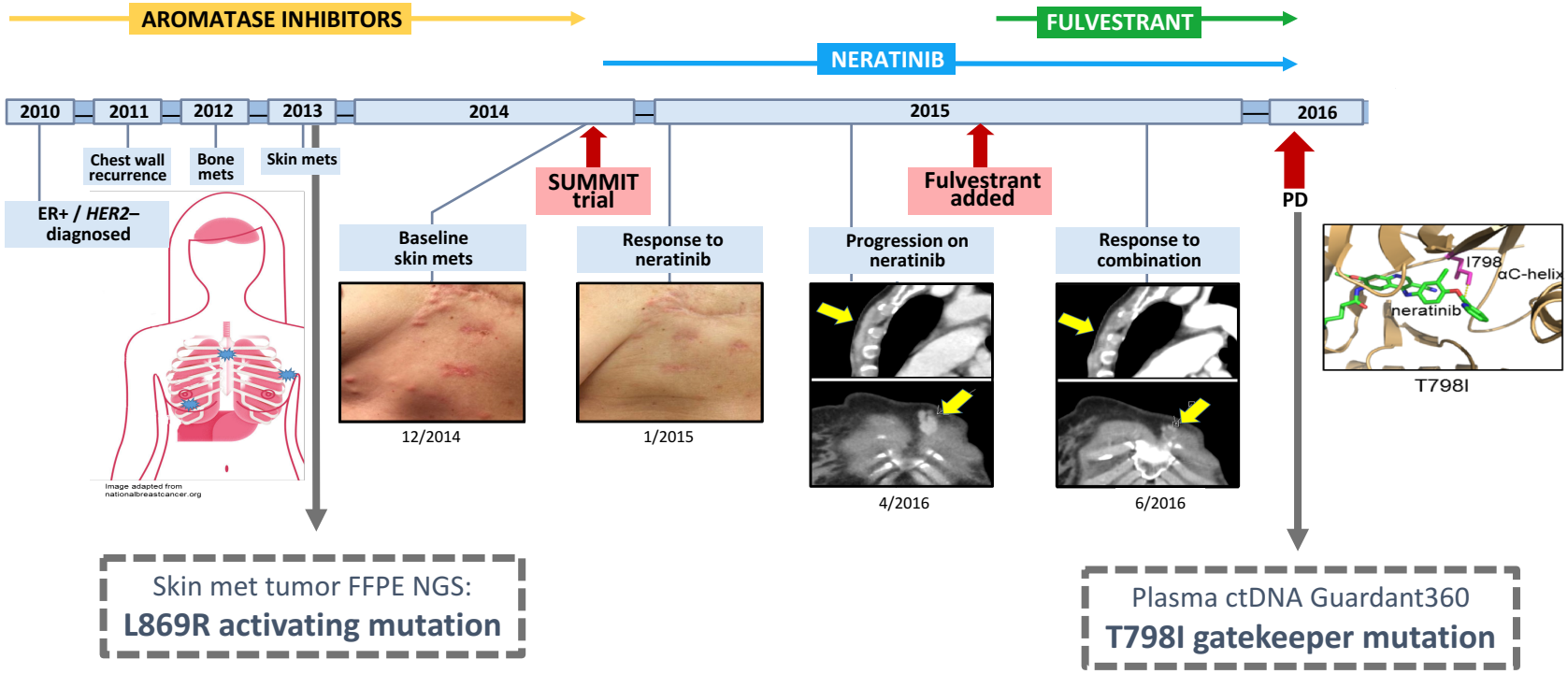
[a]No grade 4/5 diarrhea reported

Agreement between local and central assessment of *HER2* mutations

		Enrollment assay (n=124)	
		Local test (n=96)	**Archival FFPE tumor (MSK-IMPACT[1]) (n=28)**
Central testing (retrospective)	**Archival FFPE tumor (MSK-IMPACT[1])**	98% (48/49)	N/A
	Screening cfDNA (RUO assay[2])	100% (60/60)	100% (20/20)

[1]Cheng et al. J Mol Diagn 2015;17:251–64
[2]*HER2* single-gene hybrid capture research-use-only assay (MSKCC)

Plasma ctDNA at time of neratinib clinical progression reveals acquired *HER2* (T798I) gatekeeper mutation that induces resistance



Hanker et al. Advanced Online Publication; doi: 10.1158/2159-8290; Cancer Discovery 2017

Conclusions

- Neratinib activity was influenced by both tumor lineage and mutation type:
  - **Breast cancer:** single-agent activity observed. Combination with fulvestrant in ER+ disease underway
  - **Biliary cancer and cervical cancer:** preliminary single-agent activity; enrollment ongoing
  - **Lung cancer:** response rate low but promising prolonged disease stabilization in heavily-pretreated patients
  - **Colorectal cancer and bladder cancer, and *HER3* cohort:** insufficient single-agent activity
  - **Mutation class:** missense mutations appear more sensitive compared with exon 20 insertions, although comparison partially confounded by tumor-lineage associations
- Single-agent neratinib shows activity in some cohorts; combinations may be needed to improve activity and durability (similar to HER2-targeted therapy in *HER2*-amplified tumors)
- Neratinib safety profile consistent with previous reports in metastatic *HER2*-amplified tumors
  - Diarrhea was not a treatment-limiting toxicity with anti-diarrheal prophylaxis

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