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Neratinib + fulvestrant + trastuzumab for hormone-receptor positive, *HER2*-mutant metastatic breast cancer, and neratinib + trastuzumab for *HER2*-mutant metastatic triple-negative disease: latest updates from the SUMMIT trial

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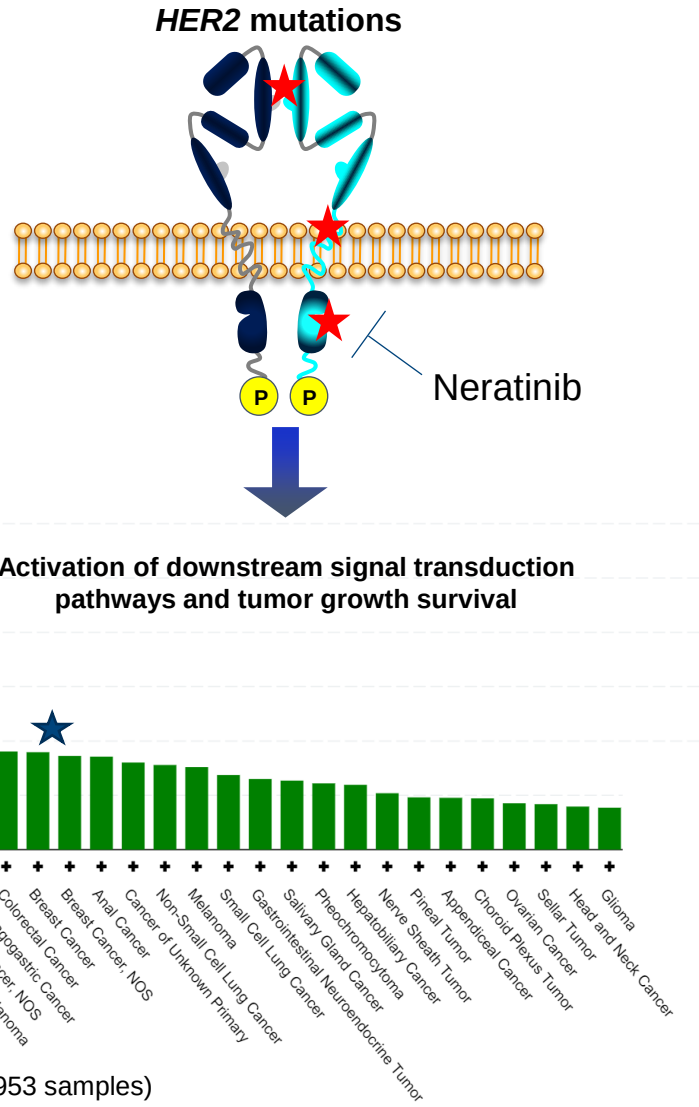
ERBB2 (*HER2*) mutations and neratinib

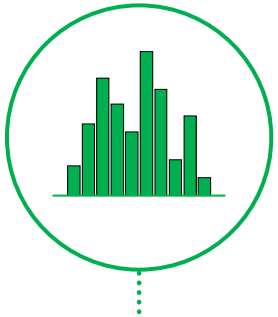
- *HER2* mutations in the absence of gene amplification or protein overexpression are a unique mechanism of oncogenic addiction to HER2 signaling:[1–3]
  - *HER2* mutations are relatively rare, occurring in ~2–12% of solid tumors, depending on histology[4]
- Neratinib is an oral, irreversible, pan-HER tyrosine kinase inhibitor that has been approved for use in HER2-positive (amplified/overexpressed) adjuvant and metastatic breast cancer[5–7]
- Neratinib has demonstrated preclinical and encouraging clinical activity either as a single agent or in combination with fulvestrant in *HER2*-mutated, *HER2*-non-amplified MBC[8–11]
  - Early data also suggested that neratinib + fulvestrant + trastuzumab may be more effective[11,12]



GENIE Cohort v 10.5 (N=120,953 samples)

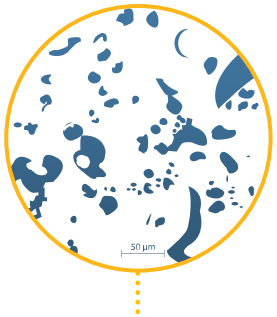
1. Bose et al. Cancer Discovery 2013; 2. Razavi et al. Cancer Cell 2018; 3. Nayar et al. Nat Genet 2019; 4. Cerami et al. Cancer Discovery 2012; 5. Chan et al. Lancet Oncol 2016; 6. Holmes et al. Lancet Oncol 2017
7. Saura et al J Clin Oncol 2020; 8. Hyman et al. Nature 2018; 9. Smyth et al. Cancer Discov 2020; 10. Turner et al. Lancet Oncol 2020; 11. Ma et al. Clin Cancer Res 2017; 12. Jhaveri et al. SABCS 2020

Characteristics of *HER2*-mutant breast cancer[1–8]



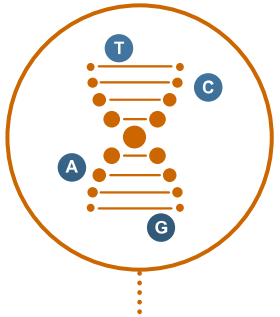
Incidence

- 2% Primary breast cancers
- 2–4% MBC
- 8% ER+ MBC
- Up to 15% in metastatic ILC



Histology

- Predominantly in hormone receptor-positive (luminal-A) and *HER2*-negative tumors
- Represented in all histology subtypes but enriched in lobular carcinoma



Genomics

- Occur across multiple domains of the protein (KD, ECD, TMD)
- Most common variants:
  – SNVs in KD
  – *Exon 20* insertions
  – S310F/Y in ECD
- Common co-mutations include *TP53*, *PIK3CA, ERBB3* and *CDH1*

Abbreviations: ECD, extracellular domain; ILC, invasive lobular carcinoma; KD, kinase domain; MBC, metastatic breast cancer; SNV, single nucleotide variant; TMD, transmembrane domain

1. Bose et al. Cancer Discovery 2013; 2. Razavi et al. Cancer Cell 2018; 3. Nayar et al. Nat Genet 2019;51; 4. Croessmann et al. Clin Cancer Res 2019
5. Hyman et al. Nature 2018; 6. Smyth et al. Cancer Discov 2020; 7. Ma et al. Clin Cancer Res 2017; 8. Jhaveri et al. SABCS 2020

Initial SUMMIT multi-histology 'basket' study design: Neratinib monotherapy cohorts

Key inclusion criteria

- Documented *HER2* mutation (CLIA/CAP/commercial test)
- 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

- **Bladder**
- **Breast HR+ and HR–**
- **Biliary tract**
- **Cervical**
- **Colorectal**
- **Endometrial**
- **Gastroesophageal**
- **Lung**
- **Ovarian**
- **Salivary**
- **Solid tumors (NOS)**

Neratinib monotherapy (240 mg/day)[a]

Primary endpoint

- Objective response rate at first (8 weeks) post-baseline tumor assessment (ORR_8)

Secondary endpoints

- ORR (confirmed)
- Duration of response (DoR)
- 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

[a]Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

Evolution of breast cancer cohorts in SUMMIT

Rational combinations determined by genomic profiling of pre-treatment and progression biopsies (tissue and ctDNA)

HR+/HER2–

Neratinib monotherapy[1]
ORR*: 17% (4–41)
PFS: 3.6 months (2–4)
N=18

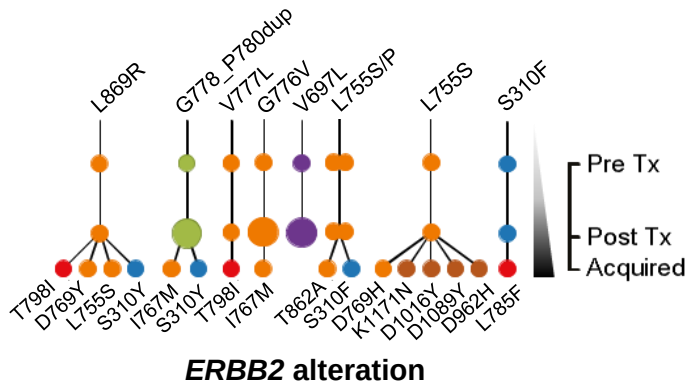
Neratinib + Fulvestrant[2]
ORR: 30% (17–48)
PFS: 5.4 months (3–10)
N=39

14 (37%) received prior CDK4/6i

Neratinib + Fulvestrant + Trastuzumab

100% received prior CDK4/6i

***HER2*-mutant breast cancer**



***ERBB2* alteration**

- Paired (pre-/post-) tumor biopsies and plasma ctDNA revealed acquisition of ≥1 new *HER2* mutation and/or amplification of mutant allele
  - no other broad pattern was observed
- Neratinib + trastuzumab > either agent alone in preclinical models of *HER2*-mutant cancer[3,4]
- Dual targeting of HER2 with addition of trastuzumab to neratinib-containing regimens was implemented

TNBC

Neratinib monotherapy[1]
ORR: 20% (2–56)
PFS: 2.0 months (1–5)
N=10

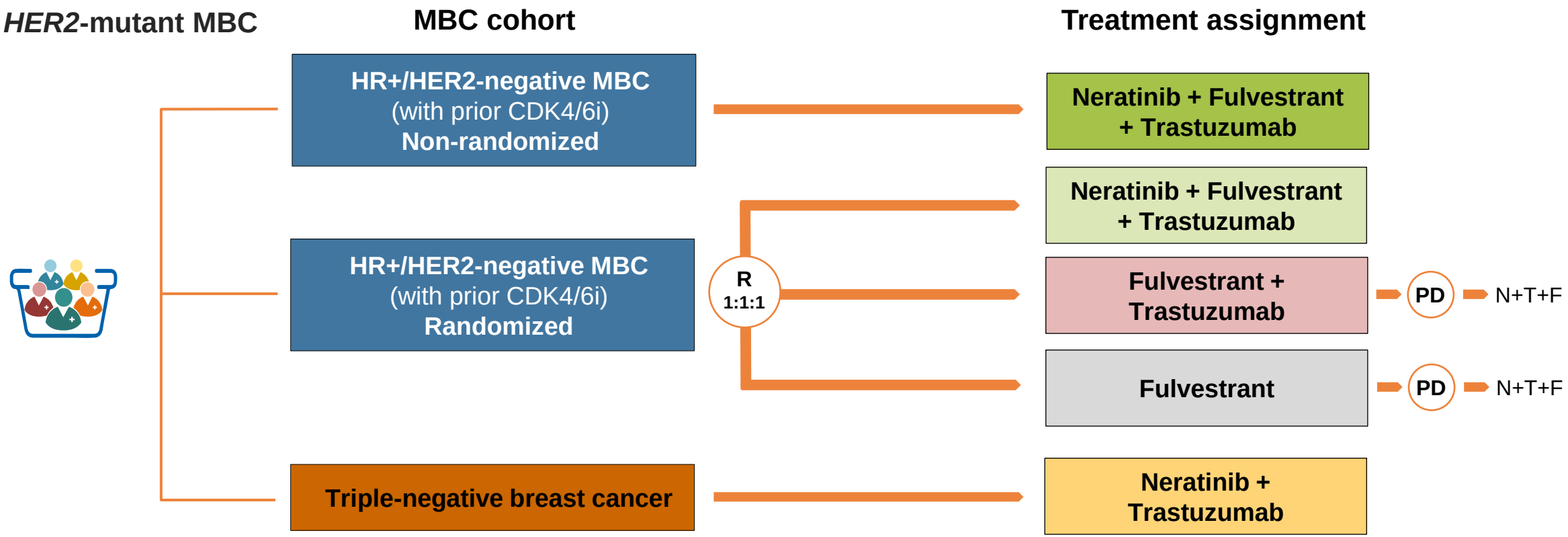
Neratinib + Trastuzumab

[a]ORR defined as confirmed response based on investigator-assessment per Response Evaluation Criteria in Solid Tumors (version 1.1)

1. Hyman et al. Nature 2018; 2. Smyth et al. Cancer Discovery 2020
3. Ivanova et al. Clin Cancer Res 2020; 4. Kavuri et al. Cancer Discovery 2015

Current SUMMIT breast cancer cohorts

- Added inclusion criteria for HR+ cohort to reflect current standard of care: prior CDK4/6 inhibitor therapy



- **Design:** Simon 2-stage
  - If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
  - If ≥4 responses in Stage 2, expand up to 50 patients
- **Primary endpoint:** HR+: confirmed objective response rate (ORR, RECIST v1.1)[a]; TNBC: ORR at first post-baseline tumor assessment (ORR_{first}), RECIST v1.1 or modified PERCIST
- **Key secondary endpoint:** Confirmed ORR[b]

[a]ORR by independent review was a primary endpoint in the randomized HR+ cohorts
[b]ORR by investigator review was a secondary endpoint in the randomized HR+ cohorts

HR+ patients[a]: Key baseline characteristics & prior therapies

Characteristics	Non-randomized (N+F+T, n=26)	Randomized cohort (N+F+T, n=7)	Randomized cohort (F+T, n=7)	Randomized cohort (F, n=7)	All N+F+T (N+F+T, n=33)
ECOG performance status, n (%)					
0	13 (50.0)	3 (42.9)	4 (57.1)	5 (71.4)	16 (48.5)
1	12 (46.2)	4 (57.1)	3 (42.9)	2 (28.6)	16 (48.5)
2	1 (3.8)	0	0	0	1 (3.0)
Histological type, n (%)					
Lobular	17 (65.4)	5 (71.4)	2 (28.6)	1 (14.3)	22 (66.7)
Ductal	7 (26.9)	2 (28.6)	5 (71.4)	5 (71.4)	9 (27.3)
Mixed Ductal and Lobular	1 (3.8)	0	0	0	1 (3.0)
Other	1 (3.8)	0	0	1 (14.3)	1 (3.0)
Median number of prior anti-cancer regimens for locally advanced or metastatic disease (range)	5 (1–11)	6 (2–7)	3 (2–10)	3 (1–7)	5 (1–11)
Prior endocrine therapy, n (%)	26 (100)	7 (100)	7 (100)	7 (100)	33 (100)
Prior aromatase inhibitor	23 (88.5)	5 (71.4)	6 (85.7)	7 (100)	28 (84.8)
Prior fulvestrant	22 (84.6)	5 (71.4)	4 (57.1)	4 (57.1)	27 (81.8)
Prior tamoxifen	13 (50)	4 (57.1)	3 (42.9)	3 (42.9)	17 (51.5)
Prior chemotherapy, n (%)	22 (84.6)	5 (71.4)	4 (57.1)	5 (71.4)	27 (81.8)

[a]All patients had received prior CDK4/6 inhibitor therapy

HR+ non-randomized N+F+T: Efficacy findings

Characteristics	Non-randomized (N+F+T, n=26)
Objective response (confirmed CR/PR)[a], n (%) CR PR	12 (46.2) 0 12 (46.2)
Best overall response (confirmed or unconfirmed PR or CR), n (%)	15 (57.7)
Median DOR[b], months (95% CI)	14.4 (6.4–NE)
Clinical benefit[c], n (%)	15 (57.7)
Median PFS, months (95% CI)	8.2 (4.0–15.1)
Median duration of treatment, months (range)	8.7 (1.0–22.1)

Data cut-off: 10 September 2021. Tumor response based on: investigator tumor assessments (RECIST v1.1) for HR+ cohorts
CR, confirmed response; PR, partial response; CI, confidence interval; DOR, duration of response; NE, not estimable; PFS, progression-free survival
[a]Objective response defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis
[c]Clinical benefit is defined as confirmed CR or PR or stable disease (SD) for ≥24 weeks (within +/– 7-day visit window)

HR+ randomized cohorts: Efficacy findings
Neratinib appears to be critical for inhibition of *HER2* mutations

Characteristics	Randomized cohort (N+F+T, n=7)	(F+T, n=7)	(F, n=7)
Objective response (confirmed CR/PR)[a], n (%) CR PR	2 (28.6) 1 (14.3) 1 (14.3)	0 0 0	0 0 0
Best overall response (confirmed or unconfirmed PR or CR), n (%)	3 (42.9)	0	0
Median DOR[b], months (95% CI)	NE	NE	NE
Clinical benefit[c], n (%)	2 (28.6)	0	0
Median PFS, months (95% CI)	6.2 (2.1–NE)	3.9 (1.9–4.1)	4.1 (1.6–4.1)
Median duration of treatment, months (range)	5.0 (0.7–13.2)	3.5 (0.8–4.1)	2.1 (0.7–4.1)

Data cut-off: 10 September 2021. Tumor response based on: investigator tumor assessments (RECIST v1.1) for HR+ cohorts
CR, confirmed response; PR, partial response; CI, confidence interval; DOR, duration of response; NE, not estimable; PFS, progression-free survival
[a]Objective response defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis
[c]Clinical benefit is defined as confirmed CR or PR or stable disease (SD) for ≥24 weeks (within +/– 7-day visit window)

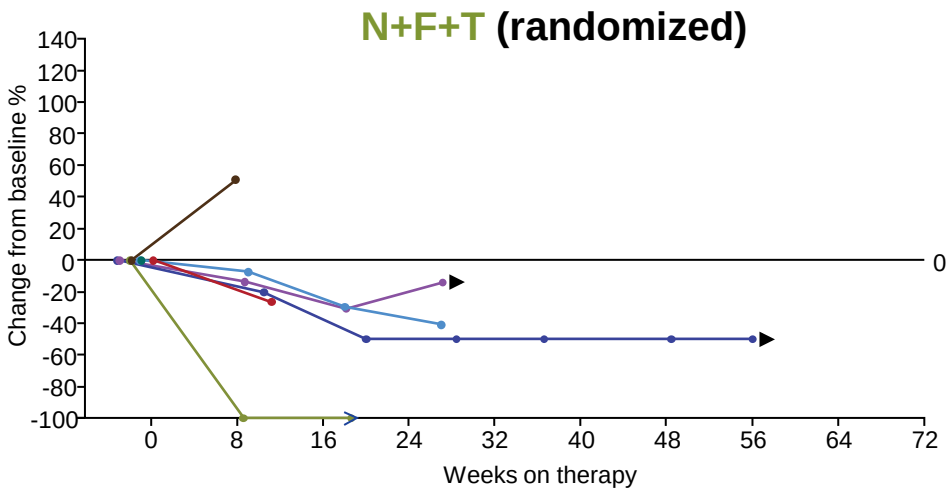
HR+ all N+F+T combined: Efficacy findings
Neratinib appears to be critical for inhibition of *HER2* mutations

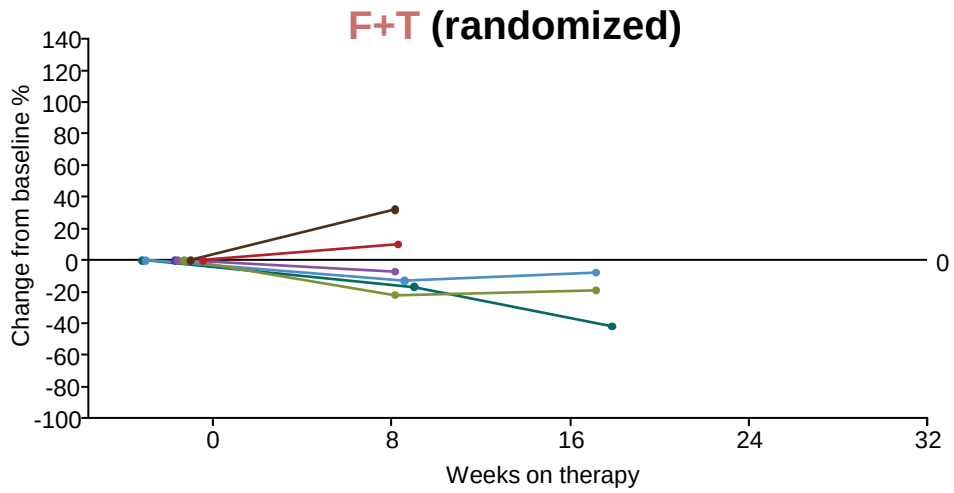
Characteristics	All N+F+T (n=33)	N+F (subset, prior CDK4/6i) (n=14)
Objective response (confirmed CR/PR)[a], n (%) CR PR	14 (42.4) 1 (3.0) 13 (39.4)	4 (28.6) 0 4 (28.6)
Best overall response (confirmed or unconfirmed PR or CR), n (%)	18 (54.5)	4 (28.6)
Median DOR[b], months (95% CI)	14.4 (6.4–NE)	NE
Clinical benefit[c], n (%)	17 (51.5)	5 (35.7)
Median PFS, months (95% CI)	7.0 (4.2–12.7)	2.9 (1.7–11.9)
Median duration of treatment, months (range)	6.5 (0.7–22.1)	3.7 (0.5–48.3)

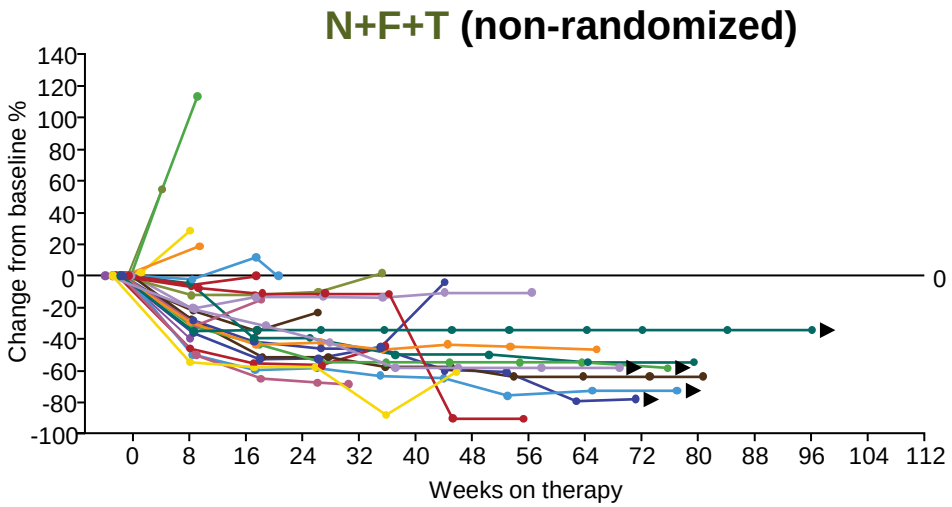
Data cut-off: 10 September 2021. Tumor response based on: investigator tumor assessments (RECIST v1.1) for HR+ cohorts
CR, confirmed response; PR, partial response; CI, confidence interval; DOR, duration of response; NE, not estimable; PFS, progression-free survival
[a]Objective response defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis
[c]Clinical benefit is defined as confirmed CR or PR or stable disease (SD) for ≥24 weeks (within +/– 7-day visit window)

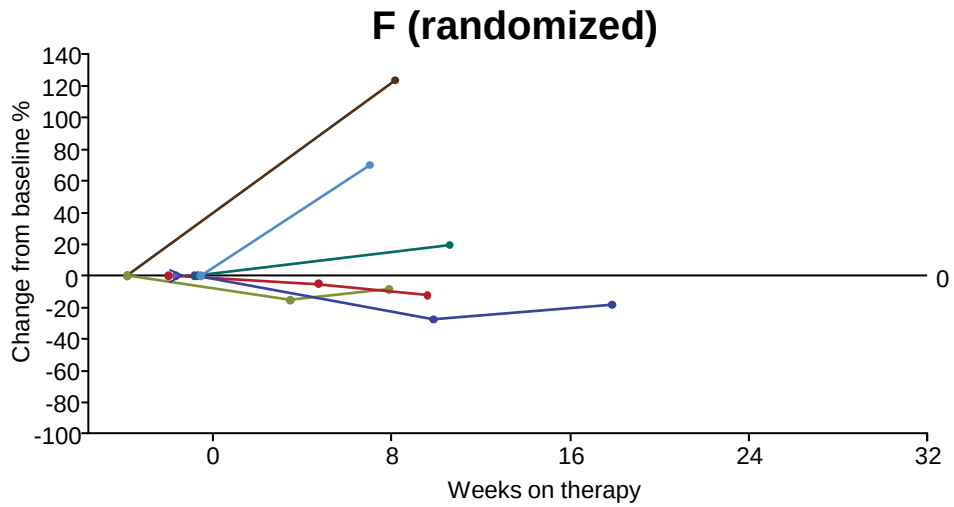
HR+ patients: Response and duration of treatment

- Patients receiving N+F+T had greater decreases in tumor size and longer treatment duration than patients not treated with neratinib









Each colored line in the spider plots represents an individual patient. An arrow indicates that the patient remains on treatment

HR+ all N+F+T combined: Safety

Most common treatment-emergent adverse events[a], n (%)	All N+F+T (n=33)	
	Any grade	Grade 3/4
Diarrhea	30 (90.9)	15 (45.5)*
Nausea	27 (81.8)	0
Vomiting	16 (48.5)	3 (9.1)
Fatigue	16 (48.5)	3 (9.1)
Constipation	13 (39.4)	0
Decreased appetite	13 (39.4)	3 (9.1)
Asthenia	7 (21.2)	0
Headache	7 (21.2)	0
Abdominal pain	8 (24.2)	0
Muscle spasms	7 (21.2)	0
Urinary tract infection	7 (21.2)	0
Reasons for treatment discontinuation, n (%)		
Disease progression	20 (60.6)	
Clinical progression	2 (6.1)	
Adverse event (1 diarrhea, 1 asthenia and nausea)	2 (6.1)	
Investigator decision	1 (3.0)	
Diarrhea characteristics		
Median time to first diarrhea event, days (range)	4 (1–68)	
Median duration of each episode of grade 3 diarrhea, days (range)	2 (1–23)	
Median cumulative duration grade 3 diarrhea, days (range)	4 (1–23)	
Prescribed dose reductions due to diarrhea, n (%)	7 (21.2)	
Total discontinuation due to diarrhea, n (%)	1 (3.0)	

[a]Table includes any treatment-emergent adverse events occurring in >20% of patients

*No grade 4 diarrhea was reported

TNBC cohort: baseline characteristics and efficacy

Baseline characteristics	TNBC (N+T, n=18)
ECOG performance status, n (%)	
0	9 (50.0)
1	9 (50.0)
Histological type, n (%)	
Lobular	3 (16.7)
Ductal	7 (38.9)
Mixed Ductal and Lobular	0
Other	8 (44.4)
Median number of prior anti-cancer regimens (range)	3.5 (1–7)

Efficacy	TNBC (N+T, n=18)
Objective response (confirmed CR/PR)[a], n (%)	6 (33.3)
CR	1 (5.6)
PR	5 (27.8)
Best overall response (confirmed or unconfirmed PR or CR), n (%)	7 (38.9)
Median DOR[b], months (95% CI)	NE
Clinical benefit[c], n (%)	7 (38.9)
Median PFS, months (95% CI)	6.2 (2.1–8.2)
Median duration of treatment, months (range)	4.4 (0.3–15.4)

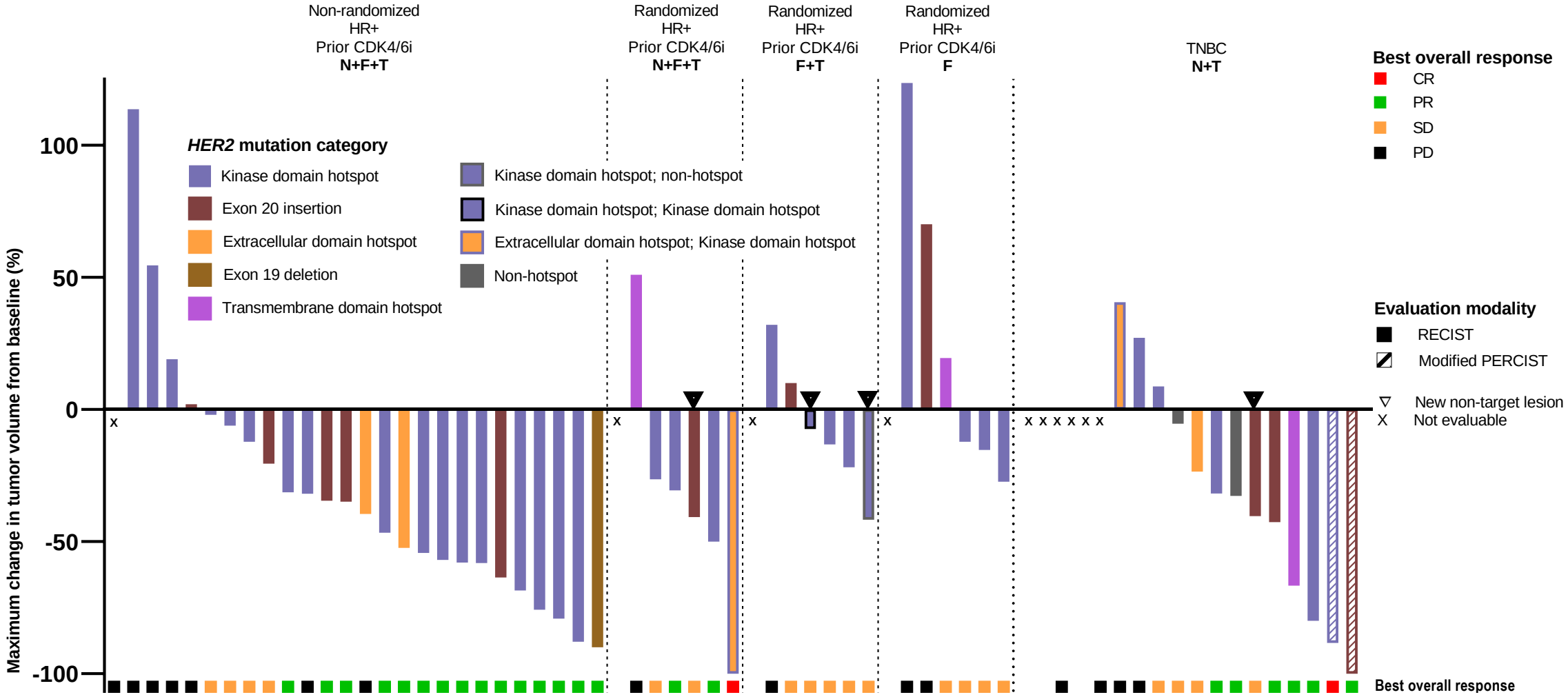
Data cut-off: 10 September 2021. Tumor response based on: investigator tumor assessments (RECIST v1.1 or modified PERCIST for TNBC cohort; TNBC cohort analysis ongoing
CR, confirmed response; PR, partial response; CI, confidence interval; DOR, duration of response; NE, not estimable; PFS, progression-free survival
[a]Objective response defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis
[c]Clinical benefit is defined as confirmed CR or PR or stable disease (SD) for ≥24 weeks (within +/– 7-day visit window)

TNBC cohort: safety

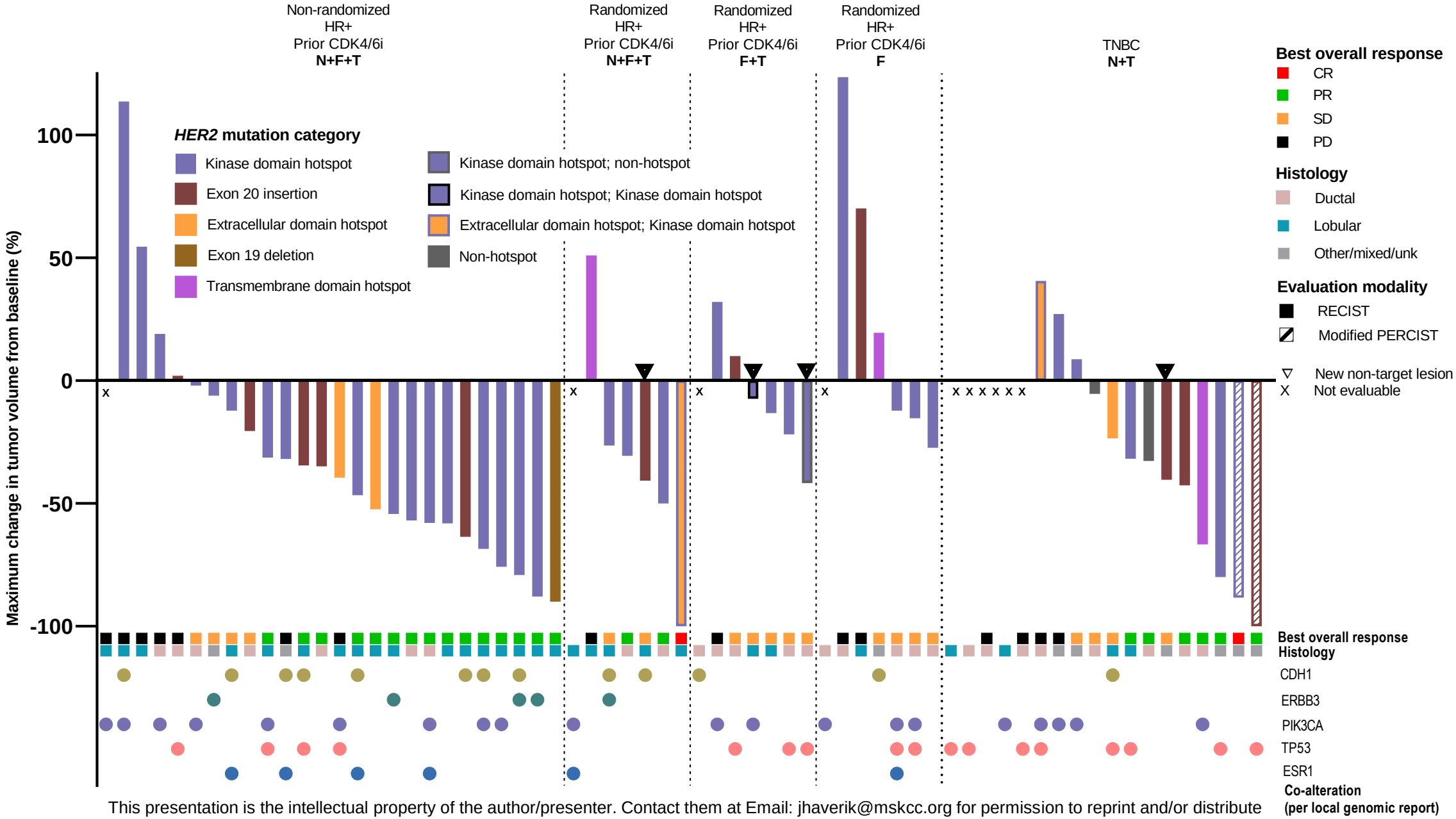
Most common TEAEs, n (%)	TNBC (N+T, n=18)	
	Any grade	Grade 3/4
Diarrhea	16 (88.9)	3 (16.7)*
Nausea	9 (50.0)	1 (5.6)
Vomiting	9 (50.0)	1 (5.6)
Constipation	7 (38.9)	0
Fatigue	5 (27.8)	3 (16.7)
Decreased appetite	4 (22.2)	0
Abdominal pain	2 (11.1)	1 (5.6)
Muscle spasms	2 (11.1)	0
Asthenia	1 (5.6)	1 (5.6)
Headache	1 (5.6)	0
Urinary tract infection	1 (5.6)	0
Reasons for treatment discontinuation, n (%)		
Disease progression	13 (72.2)	
Death	0	
Adverse event	0	
Investigator decision	1 (5.6)	

* No grade 4 diarrhea was reported

Change in tumor size (target lesion) and characteristics

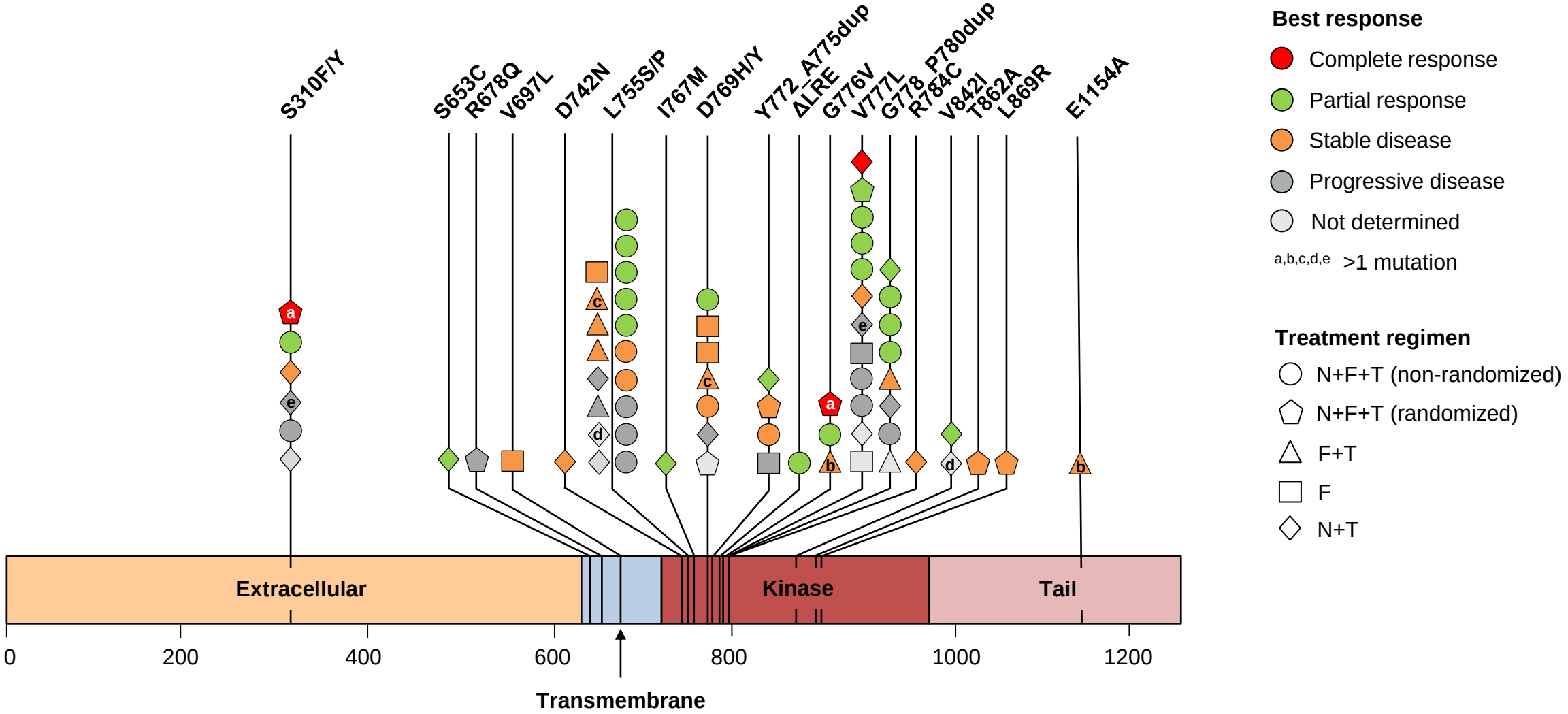


Change in tumor size (target lesion) and characteristics



Distribution of *HER2* mutations and best response

- *HER2* mutations were distributed throughout the kinase, transmembrane, and extracellular domains
- Responses were reported in patients with *HER2* mutations in any of these domains, in all neratinib-containing cohorts



Conclusions

- The combination of N+F+T demonstrated encouraging clinical activity in patients with heavily pretreated HR+, HER2-negative, *HER2*-mutant MBC who had previously received CDK4/6i:
  - Objective response rate 42.4% (1 CR and 13 PRs); median PFS 7.0 months
- Following guidance from the Independent Data Monitoring Committee, the F+T and F arms of SUMMIT were closed
- The N+T combination showed promising clinical activity in heavily pretreated *HER2*-mutant TNBC:
  - Objective response rate 33.3% (1 CR and 5 PRs); median PFS 6.2 months
- Grade 3 diarrhea was higher than anticipated with the triplet combination of N+F+T and compliance with loperamide prophylaxis is imperative

Next steps

- Following closure of the F+T and F arms of the randomized cohort, additional patients with HR+, HER2-negative, *HER2*-mutant MBC and prior CDK4/6i have been enrolled, totaling n=50 who have received N+F+T:
  - Safety and efficacy outcomes of these patients will be evaluated
- Continue to enroll patients with TNBC for treatment with N+T
- Assess whether patients with HR+ MBC who crossed over after progression on F or F+T arms derive clinical benefit from N+F+T
- Incorporate neratinib dose escalation as defined in the CONTROL study per a recent update to the US Package Insert
- Prospective central testing and companion diagnostic development may be incorporated for submission to regulatory authorities

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