Latest findings from the breast cancer cohort in SUMMIT – a phase 2 'basket' trial of neratinib + trastuzumab + fulvestrant for *HER2*-mutant, hormone receptor-positive, metastatic breast cancer

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Introduction

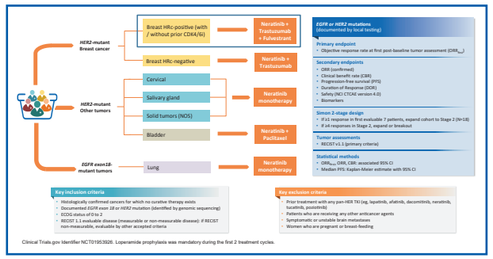
- *HER2* mutations occur in approximately 2% of primary breast cancers and in 7–8% of hormone receptor positive (HR+) metastatic breast cancer (MBC) and have a unique mechanism of oncogenic addiction to HER2 signaling:[1–3]
  - Acquired HER2 mutations may confer resistance to endocrine-based therapies.[3,4]
- Neratinib is an oral, irreversible, pan-HER tyrosine kinase inhibitor that has demonstrated encouraging clinical activity either as a single agent or in combination with fulvestrant in *HER2*-mutated, HER2-non-amplified MBC in the SUMMIT basket trial.[5–7]
- ctDNA analysis of *HER2*-mutated patients from SUMMIT that benefited from neratinib as a single agent or in combination with fulvestrant revealed acquisition of secondary *HER2* mutations and/or *HER2* gene amplification upon progression:[6]
  - Suggests that the combination of neratinib + trastuzumab may improve durability of responses.

Objective

- We investigated whether addition of trastuzumab to neratinib + fulvestrant could further improve clinical benefit in a cohort of patients with *HER2*-mutant, HR+ MBC from SUMMIT.

Methods

Figure 1. Current SUMMIT study design



Clinical Trials.gov Identifier NCT01953926. Loperamide prophylaxis was mandatory during the first 2 treatment cycles.

Results

Table 1. Baseline demographics

Patient characteristics	Safety evaluable patients (n=51)
Median (range), years	58 (25–82)
<65 years, n (%)	36 (70.6)
≥65 years, n (%)	15 (29.4)
Gender, n (%)	
Female	51 (100)
ECOG performance status, n (%)	
0	24 (47.1)
1	26 (51.0)
2	1 (2.0)
Menopausal status, n (%)	
Post-menopausal	45 (88.2)
Pre-menopausal	6 (11.8)
Disease characteristics	
Histological type, n (%)	
Ductal	16 (31.4)
Lobular	33 (64.7)
Mixed ductal and lobular	1 (2.0)
Other	1 (2.0)
HER2 status[a], n (%)	
Negative	49 (96.1)
Equivocal	2 (3.9)
HR (ER/PR) status, n (%)	
HR+ (ER+ and/or PR+)	51 (100)
Location of disease at time of enrollment, n (%)	
Visceral	43 (84.3)
Non-visceral only	8 (15.7)
Median time from first metastasis to enrollment, years (range)	2.90 (0.2–9.1)

Safety evaluable: all enrolled patients who received at least 1 dose of neratinib.
ECOG: Eastern Cooperative Oncology Group.
[a]Negative: IHC=0 or 1+; or FISH (ISH) HER2/CEP 17 ratio <2.0; or FISH (ISH) HER2 gene copy # <4.0. Equivocal: IHC=2+; or FISH (ISH) HER2 gene copy # ≥4.0 and <6.0. Unavailable: data entry pending.

Table 2. Prior therapies in the locally advanced/metastatic setting

Prior therapies	Safety evaluable patients (n=51)
Patients with prior treatment for locally advanced/metastatic disease, n (%)	46 (90.2)[a]
Median number of prior therapies (range)	4 (1–10)
Prior endocrine therapy, n (%)	
Prior aromatase inhibitor	35 (68.6)
Prior fulvestrant	36 (70.6)
Prior tamoxifen	4 (7.8)
Prior chemotherapy, n (%)	35 (68.6)
Prior HER2 antibody-directed therapy, n (%)	2 (3.9)[a]
Prior CDK4/6 inhibitor, n (%)	30 (58.8)
Prior PIK3CA inhibitor, n (%)	4 (7.9)
Prior mTOR inhibitor, n (%)	15 (29.4)

[a]Two patients received prior treatment of trastuzumab + pertuzumab + docetaxel. Five patients did not receive prior treatments for metastatic disease: for one patient, the data was entered after the data snapshot for this poster and this patient had four prior lines of therapy for metastatic disease; for the other four patients no prior therapy for metastatic disease was recorded.

Table 3. Subject disposition

Parameter	Safety evaluable patients (n=51)
Median duration of treatment, months (range)	6.7 (0.9–31.6)
Patients continuing treatment, n (%)	18 (35.3)
Treatment discontinuation, n (%)	33 (64.7)
Disease progression	30 (58.8)
Death	0
Adverse event	1 (2.0)
Other[a]	2 (4.0)

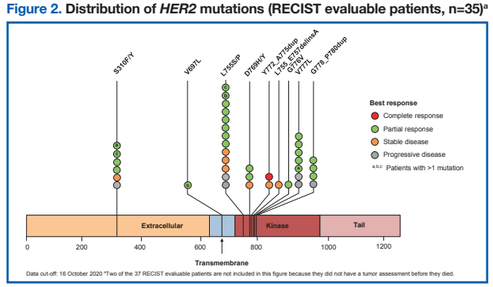
[a]One patient discontinued the treatment due to clinical progression and the other patient due to the treating physician's decision.

Table 4. Efficacy summary (RECIST evaluable patients, n=37)

Parameter	RECIST evaluable patients (n=37)	Subgroups: Prior CDK4/6i (n=23)	Subgroups: Prior fulvestrant (n=25)
Objective response (confirmed)[a] n (%)	17 (45.9)	9 (39.1)	11 (44.0)
CR	1 (2.7)	0	0
PR	16 (43.2)	9 (39.1)	11 (44.0)
Objective response rate, % (95% CI)	**45.9** (29.5–63.1)	**39.1** (19.7–61.5)	**44.0** (24.4–65.1)
Best overall response, n (%)	21 (56.8)	11 (47.8)	13 (52.0)
CR	1 (2.7)	0	0
PR	20 (54.1)	11 (47.8)	13 (52.0)
Best overall response rate, % (95% CI)	**56.8** (39.5–72.9)	**47.8** (26.8–69.4)	**52.0** (31.3–72.2)
Median[b] DOR, months (95% CI)	**10.9** (6.4–NE)	**8.7** (6.4–10.9)	**8.4** (5.8–12.5)
Clinical benefit[c] n (%)	20 (54.1)	12 (52.2)	14 (56.0)
CR or PR	17 (45.9)	9 (39.1)	11 (44.0)
SD ≥24 weeks	3 (8.1)	3 (13.0)	3 (12.0)
Clinical benefit rate, % (95% CI)	**54.1** (36.9–70.5)	**52.2** (30.6–73.2)	**56.0** (34.9–75.6)
Median[b] PFS time to event, months (95% CI)	**8.3** (4.2–14.5)	**8.2** (4.0–15.1)	**8.3** (3.1–12.5)

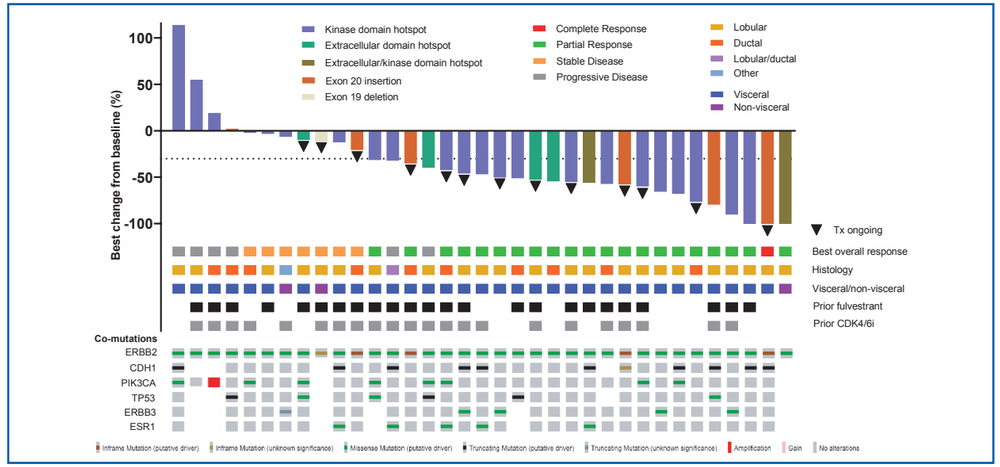
Data cut-off: 16 October 2020. DOR, duration of response; NE, not estimable; PFS, progression-free survival. RECIST evaluable: patients with RECIST measurable disease at baseline with at least 1 post-baseline tumor assessment.
[a]Objective response rate (ORR) is defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis; [c]Clinical benefit rate (CBR) is defined as confirmed CR or PR or stable disease (SD) for ≥24 weeks (within +/– 7-day visit window).

Figure 2. Distribution of *HER2* mutations (RECIST evaluable patients, n=35)[a]



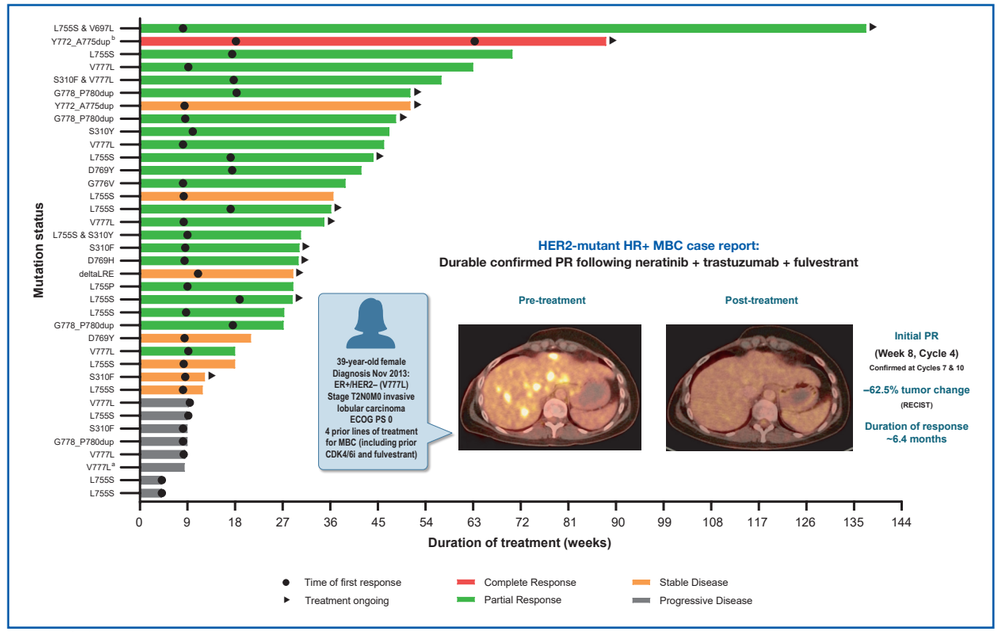
Data cut-off: 16 October 2020 [a]Two of the 37 RECIST evaluable patients are not included in this figure because they did not have a tumor assessment before they died.

Figure 3. Change in tumor size and characteristics (n=35)[a]



Data cut-off: 16 October 2020.
[a]Two of the 37 RECIST evaluable patients are not included in this figure because they did not have a tumor assessment before they died.

Figure 4. Duration of treatment and best response (RECIST evaluable patients, n=37)



Data cut-off: 16 October 2020.
[a]This patient died in hospice due to clinical progression and did not have a tumor assessment before she died.
[b]This patient had a first partial response at week 18 and a first complete response at week 63.

Table 5. Most common treatment-emergent adverse events

Adverse event, n (%)	Safety evaluable patients (n=51): All grade	Safety evaluable patients (n=51): Grade 3 or 4
Subjects with at least 1 adverse event, n (%)	49 (96.1)	33 (64.7)
Diarrhea	45 (88.2)	20 (39.2)[a]
Nausea	34 (66.7)	0
Constipation	21 (41.2)	0
Fatigue	18 (35.3)	3 (5.9)
Vomiting	22 (43.1)	2 (3.9)
Decreased appetite	20 (39.2)	3 (5.9)
Abdominal pain	12 (23.5)	0
Headache	8 (15.7)	0

[a]No Grade 4 diarrhea was reported.

Table 6. Characteristics of diarrhea

	Safety evaluable patients (n=51)
Incidence of diarrhea, n (%)[a]	
Any grade	45 (88.2)
Grade 1	13 (25.5)
Grade 2	12 (23.5)
Grade 3	20 (39.2)
Action taken with neratinib, n (%)	
Leading to temporary hold	21 (41.2)
Leading to dose reduction	11 (21.6)
Leading to permanent discontinuation	0
Leading to hospitalization	1 (2.0)
Median cumulative duration of grade 3 diarrhea per patient (Q1, Q3), days	6 (1–16.5)

Conclusions

- *HER2* mutations are oncogenic in a subset of MBC and are clinically actionable with HER2-directed therapies.
- The combination of neratinib + fulvestrant + trastuzumab demonstrated encouraging clinical activity in heavily pre-treated *HER2*-mutant, HR+, HER2-non-amplified MBC, including patients who had previously received either fulvestrant and/or CDK4/6 inhibitor-based therapies:
  - ORR 45.9%; median DoR 10.9 months; median PFS 8.3 months.
- The spectrum of *HER2* mutations is consistent with previously evaluated SUMMIT cohorts and with literature-reported prevalence.
- While the rate of grade 3 diarrhea was higher than that observed with single-agent neratinib in SUMMIT, this was manageable through loperamide prophylaxis. No patient discontinued treatment due to diarrhea.
- SUMMIT has recently been amended to evaluate neratinib + fulvestrant + trastuzumab, trastuzumab + fulvestrant and fulvestrant alone (1:1:1 randomization) and continues to enroll patients:
  - Patients who receive single-agent fulvestrant or fulvestrant + trastuzumab are eligible to crossover to triplet therapy upon progression.

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