Neratinib + fulvestrant + trastuzumab for hormone-receptor positive, HER2-negative, *HER2*-mutant metastatic breast cancer: outcomes and biomarker analysis from the SUMMIT trial

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Introduction

- *HER2* mutations are oncogenic drivers in a subset of metastatic breast cancers (MBC), and may be acquired as a mechanism of resistance to endocrine therapy.[1–4]
- Neratinib (N) is an oral, irreversible, pan-HER tyrosine kinase inhibitor that has demonstrated preclinical and clinical activity against *HER2* mutations.[1–8]
- In the hypothesis-generating SUMMIT basket trial (NCT01953926), HR+, *HER2*-mutant breast cancer treated with N had an ORR of 17%, median PFS of 3.6 months (n=18); patients treated with N + fulvestrant (F) had an ORR of 30% with a median PFS of 5.4 months (n=26).[5,6]
- ctDNA analysis of patients with *HER2* mutations in SUMMIT or MutHER (NCT01670877) who benefited from N as a single agent or in combination with F revealed acquisition of additional *HER2* mutations and/or amplification of the *HER2* mutant allele upon progression.[6] Based on these observations, addition of trastuzumab (T) in five MutHER patients at progression on N+F resulted in three responses and one long-term stable disease.[9]
  - These two independent data sets prompted the hypothesis that addition of T to N+F at the onset of treatment may increase clinical benefit and/or duration of response.
- Addition of T to N+F showed encouraging clinical activity with durable responses in the SUMMIT trial in hormone-receptor positive (HR+), HER2-negative, *HER2*-mutant MBC, including patients who had previously received cyclin-dependent kinase 4/6 inhibitors (CKD4/6i).[8,10]
- A small, randomized Simon's 2-stage comparison (IDMC adjudicated) of N+F+T vs F+T vs F in patients with HR+, *HER2*-mutant MBC who had received prior CDK4/6i demonstrated a dependence upon N for response to the combination of N+F+T.[9]

Objectives

- To evaluate efficacy of N+F+T in patients with HR+, HER2-negative, *HER2*-mutant MBC who were previously treated with CKD4/6i therapy.
- To evaluate response in patients who crossed over to N+F+T after originally receiving F or F+T as part of the small, randomized design.
- To retrospectively centrally assess *HER2* mutation and HER2 expression statuses.
- To explore biomarkers of response to N+F+T, including co-mutations, HER2 receptor levels, and mRNA expression patterns.
- To explore preclinical mechanisms for the increased benefit of addition of T to N in *HER2*-mutant breast cancer models.

Figure 1. SUMMIT study design: HR+, HER2-negative, *HER2*-mutant mBC cohorts

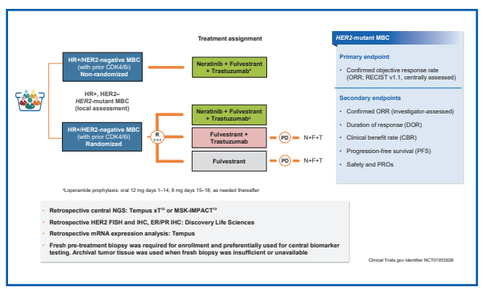


Table 1. Baseline demographics

Characteristics	Non-randomized + Randomized HR+ Prior CDK4/6i (N+F+T, n=51)	Randomized HR+ Prior CDK4/6i (F+T, n=7)	Randomized HR+ Prior CDK4/6i (F, n=7)
Median age, years (range)	57.0 (25–83)	65.0 (37–72)	55.0 (46–80)
Sex, n (%)			
Female	50 (98.0)	7 (100)	7 (100)
Male	1 (2.0)	0	0
Menopausal status, n (%)			
Post-menopausal	43 (84.3)	7 (100)	7 (100)
Pre-menopausal	7 (13.7)	0	0
N/A	1 (2.0)	0	0
ECOG performance status, n (%)			
0	23 (45.1)	4 (57.1)	5 (71.4)
1	27 (52.9)	3 (42.9)	2 (28.6)
2	1 (2.0)	0	0
Histological type, n (%)			
Ductal	20 (39.2)	5 (71.4)	5 (71.4)
Lobular	25 (49.0)	2 (28.6)	1 (14.3)
Mixed ductal and lobular	1 (2.0)	0	0
Other	5 (9.8)	0	1 (14.3)
Location of disease at time of enrollment, n (%)			
Visceral	46 (90.2)	6 (85.7)	7 (100)
Non-visceral only	4 (7.8)	1 (14.3)	0
Missing	1 (2.0)	0	0
Median time from first metastasis to enrollment, years (range)	2.2 (0–15)	1.0 (0–4)	1.6 (0–4)

F, fulvestrant; HR+, hormone receptor positive; N, neratinib; T, trastuzumab

Table 2. Prior therapies in the metastatic setting

Prior therapies	Non-randomized + Randomized HR+ Prior CDK4/6i (N+F+T, n=51)	Randomized HR+ Prior CDK4/6i (F+T, n=7)	Randomized HR+ Prior CDK4/6i (F, n=7)
Patients with prior treatment for locally advanced/metastatic disease, n (%)	**51 (100)**	**7 (100)**	**7 (100)**
Median number of prior anti-cancer regimens (range)	4 (1–10)	2 (1–10)	2 (1–6)
Prior endocrine therapy, n (%)	49 (96.1)	6 (85.7)	7 (100)
Prior aromatase inhibitor	32 (62.7)	5 (71.4)	5 (71.4)
Prior fulvestrant	40 (78.4)	3 (42.9)	4 (57.1)
Prior tamoxifen	7 (13.7)	1 (14.3)	0 (0.0)
Prior chemotherapy, n (%)	32 (62.7)	2 (28.6)	4 (57.1)
Prior HER2 antibody-directed therapy, n (%)	4 (7.8)	1 (14.3)	1 (14.3)
Prior CDK4/6i, n (%)	51 (100)	7 (100)	7 (100)
Prior PIK3CAi, n (%)	6 (11.8)	1 (14.3)	1 (14.3)
Prior mTORi, n (%)	14 (27.5)	0 (0.0)	1 (14.3)

CKD4/6i, cyclin-dependent kinase 4/6 inhibitor; F, fulvestrant; HR+, hormone receptor positive; mTORi, mechanistic target of rapamycin inhibitor; NA, not applicable; N, neratinib; PIK3CAi, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha inhibitor; T, trastuzumab

Table 3. Subject disposition

Parameter	Non-randomized + Randomized HR+ Prior CDK4/6i (N+F+T, n=51)	Randomized HR+ Prior CDK4/6i (F+T, n=7)	Randomized HR+ Prior CDK4/6i (F, n=7)
Median duration of treatment, months (range)	6.2 (0.4–29.0)	3.5 (0.8 4.1)	2.1 (0.7–4.1)
Patients crossed over to N+F+T, n (%)	NA	4 (57.1)	6 (85.7)
Patients continuing treatment, n (%)	16 (31.4)	Before crossover: 0; After crossover: 0	Before crossover: 0; After crossover: 3 (42.9)
Reasons for treatment discontinuation, n (%)		Before crossover / After crossover	Before crossover / After crossover
Disease progression	29* (56.9)	3 (42.9) / 3 (42.9)	1** (14.3) / 3 (42.9)
Death	0	0 / 0	0 / 0
Adverse event	4 (7.8)	0 / 0	0 / 0
Other	2(3.9)	0 / 1 (14.3)	0 / 0

*Includes 2 patients with clinical progression; **Clinical progression
CKD4/6i, cyclin-dependent kinase 4/6 inhibitor; F, fulvestrant; HR+, hormone receptor positive; NA, not applicable; N, neratinib; T, trastuzumab

Table 4. Efficacy summary

Parameter	Non-randomized + Randomized HR+ Prior CDK4/6i (N+F+T, n=51)	Randomized HR+ Prior CDK4/6i (F+T, n=7)	After crossover from F+T to N+F+T (n=4)	Randomized HR+ Prior CDK4/6i (F, n=7)	After crossover from F to N+F+T (n=6)
Objective response (confirmed CR or PR)[a], n (%)	18 (35.3)	0	1 (25.0)	0	2 (33.3)
CR	1 (2.0)	0	0	0	0
PR	17 (33.3)	0	1 (25.0)	0	2 (33.3)
Best overall response (confirmed or unconfirmed PR or CR), n (%)	25 (49.0)	0	1 (25.0)	0	2 (33.3)
Median DOR[b], months (95% CI)	14.3 (6.4–NE)	No response	6.2 (NE–NE)	No response	6.3 (6.2–6.4)
Clinical benefit[c], n (%)	24 (47.1)	0	1 (25.0)	0	5 (83.3)
Median PFS[b], months (95% CI)	8.2 (4.7–12.7)	3.9 (1.9–4.1)	8.25 (NE–NE)	4.1 (1.6–4.1)	NE

Data cut-off: 15 April 2022. Tumor response based on: investigator tumor assessments (RECIST v1.1) CR, confirmed response; PR, partial response; CI, confidence interval; DOR, duration of response; NA, not applicable; 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. For crossover patients, calculated from time of crossover to N+F+T.
[c]Clinical benefit is defined as confirmed CR or PR or stable disease (SD) for ≥24 weeks (within +/– 7-day visit window)

Figure 2. Change in tumor size (target lesion) and characteristics

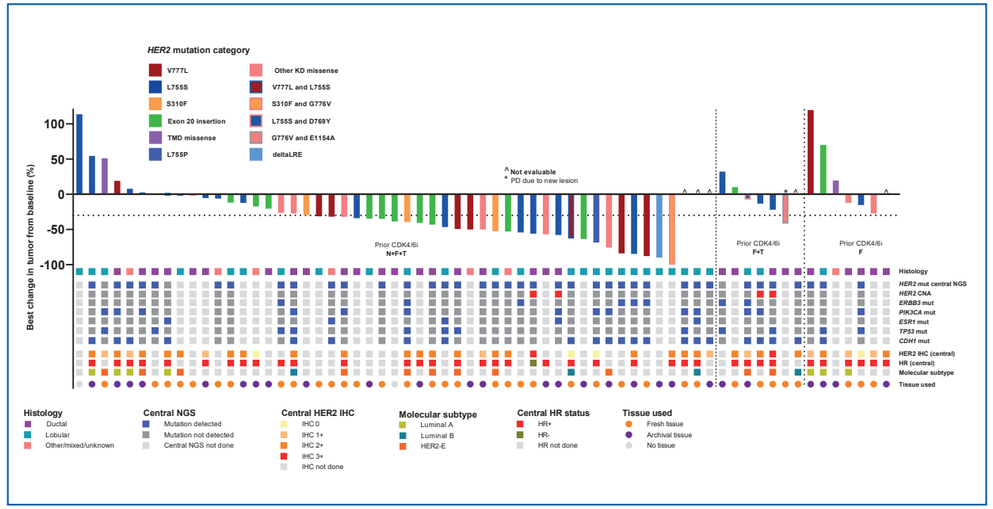


Figure 3. Duration of treatment and best response for patients randomized to F+T or F, before and after crossover to N+F+T

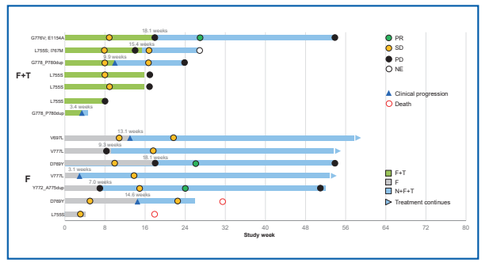


Table 5. Efficacy by histology and *HER2* mutation in N+F+T patients

	Histology			*HER2* mutation							
Parameter	Lobular (n=25)	Ductal (n=20)	Other/mixed /unknown (n=6)	L755S (n=16)	Exon 20 insertion (n=11)	Other KD[a] missense (n=9)	V777L (n=7)	S310F (n=3)	TMD[a] missense (n=2)	Dual *HER2* mutations[a] (n=2)	Exon 19 deletion (n=1)
Objective response (confirmed CR or PR)[b], n (%)	10 (40.0)	7 (35.0)	1 (16.7)	4 (25.0)	4 (36.4)	3 (33.3)	4 (57.1)	1 (33.3)	0	2 (100)	0
CR	1 (4.0)	0	0	0	0	0	0	0	0	1 (50.0)	0
PR	9 (36.0)	7 (35.0)	1 (16.7)	4 (25.0)	4 (36.4)	3 (33.3)	4 (57.1)	1 (33.3)	0	1 (50.0)	0
Best overall response (confirmed or unconfirmed PR or CR), n (%)	13 (52.0)	11 (55.0)	1 (16.7)	5 (31.3)	6 (54.5)	5 (55.6)	5 (71.4)	1 (33.3)	0	2 (100)	1 (100)
Median DOR[c], months (95% CI)	14.4 (5.0–NE)	14.3 (4.1–NE)	NE	14.3 (11.1–NE)	NE	6.4 (5.0–18.6)	NE	8.2 (NE–NE)	NE	NE	NE
Clinical benefit[d], n (%)	12 (48.0)	11 (55.0)	1 (16.7)	7 (43.8)	5 (45.5)	4 (44.4)	4 (57.1)	1 (33.3)	0	2 (100)	1 (100)
Median PFS[c], months (95% CI)	8.3 (4.2–18.6)	6.2 (3.9–18.6)	4.0 (1.9–NE)	15.1 (2.6–NE)	10.2 (1.9–NE)	7.0 (2.0–20.5)	6.1 (1.9–NE)	3.4 (1.9–10.2)	1.8 (NE–NE)	NE	12.7 (NE–NE)

Table 6. Most common treatment-emergent adverse events*

	Non-randomized + Randomized HR+ Prior CDK4/6i (N+F+T, n=51)		Randomized HR+ Prior CDK4/6i (F+T, n=7)		Randomized HR+ Prior CDK4/6i (F, n=7)	
Adverse event, n (%)	**Any grade**	**Grade 3****	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Diarrhea***	46 (90.2)	26 (51.0)	2 (28.6)	0	0	0
Nausea	37 (72.5)	2 (3.9)	1 (14.3)	0	2 (28.6)	0
Vomiting	27 (52.9)	4 (7.8)	0	0	0	0
Fatigue	22 (43.1)	3 (5.9)	0	0	1 (14.3)	0
Constipation	21 (41.2)	0	2 (28.6)	0	0	0
Decreased appetite	20 (39.2)	4 (7.8)	0	0	0	0
Abdominal pain	13 (25.5)	1 (2.0)	1 (14.3)	0	0	0
Headache	12 (23.5)	0	1 (14.3)	0	1 (14.3)	0
Asthenia	9 (17.6)	0	0	0	1 (14.3)	0
Muscle spasms	9 (17.6)	0	0	0	0	0
Urinary tract infection	9 (17.6)	0	0	0	0	0

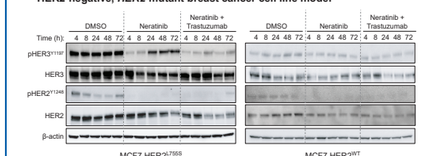
*Table includes any treatment-emergent adverse events occurring in >15% of patients in the N+F+T arm
**Two grade 4 AEs were reported (coma, n=1; muscle weakness, n=1)
***Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

Table 7. Efficacy by exploratory biomarker: N+F+T patients

Central NGS mutation	No. of patients	ORR n (%)	CBR n (%)	Median PFS months (95% CI)
HER2				
Yes	30	14 (46.7)	15 (50.0)	7.0 (2.6–18.6)
No	2	0	0	3.0 (1.9–4.1)
Insufficient tissue	19	4 (21.1)	9 (47.4)	8.2 (4.7–18.6)
HER2* and *ERBB3	6	4 (66.7)	4 (66.7)	NE
HER2* and *ESR1	4	2 (50.0)	2 (50.0)	8.7 (1.9–18.6)
HER2* and *CDH1	16	7 (43.8)	7 (43.8)	7.0 (1.9–20.5)
HER2* and *TP53	7	2 (28.6)	2 (28.6)	2.0 (1.0–15.1)
HER2* and *PIK3CA	11	3 (27.3)	4 (36.4)	2.5 (1.0–18.6)
***HER2* and none of above**	7	4 (57.1)	4 (57.1)	10.2 (3.9–NE)
IHC category				
0/1+	9	2 (22.2)	3 (33.3)	7.0 (1.8–NE)
2+	18	6 (33.3)	8 (44.4)	6.2 (2.4–NE)
3+	1	0	0	3.9 (NE)
Insufficient tissue	23	10 (43.5)	13 (56.5)	8.3 (4.2–18.6)
Molecular subtype				
Luminal A	4	0	0	3.1 (1.0–NE)
Luminal B	4	2 (50.0)	2 (50.0)	NE
HER2-enriched	9	4 (44.4)	5 (55.6)	10.2 (1.8–20.5)
Insufficient tissue	34	12 (35.3)	17 (50.0)	8.2 (6.0–15.1)

Figure 4. Addition of T to N in *HER2*-mutant cell line model

- **Addition of T to N prolongs suppression of HER3 phosphorylation in HR+, HER2-negative, *HER2*-mutant breast cancer cell line model**



Addition of T to N prevents rebound of phospho-HER3 during prolonged treatment. MCF7 HER2^{L755S} or targeted wild-type (WT) knock-out in breast cancer cells were treated with vehicle (DMSO) or 100 nM neratinib ± 20 µg/ml trastuzumab in estrogen-deprived media for the indicated time periods. Lysates were probed with the indicated antibodies. β-actin was used as a loading control.

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:
  - Confirmed ORR 35.3%, median DOR 14.3 months, CBR 41.7%, median PFS 8.2 months.
- Preclinically, the addition of T to N prolonged suppression of HER3 phosphorylation in HR+, *HER2*-mutant breast cancer models, consistent with the reported increase in PFS for patients treated upfront with N+F+T compared with N or N+F.
- N appears to be a critical component of the combination therapy, as demonstrated by lack of response in the small cohort of patients treated with F or F+T, and by response in a subset of those upon crossover to N+F+T.
- Responses to N+F+T were observed in patients with both ductal and lobular histology; as opposed to apparent association of lobular histology with response to N+F reported in the MutHER trial.[10]
- Responses to N+F+T were observed across patients whose tumors harbored *HER2* extracellular domain missense mutations (*S310F/Y*), exon 20 insertions, and several kinase domain missense mutations, even *L755S*, which had been reported to be associated with lower response to N+F.[10]
- Co-occurrence of *HER2* and *HER3* mutations did not preclude response to N+F+T, in contrast with the lack of clinical benefit reported for patients whose tumors harbored dual *HER2/HER3* mutations who were treated with N or N+F.[6,10,11]
- Negative HER2 status (local FISH/IHC) was a criterion for enrolment; central retrospective testing revealed that 64.2% (n=18/28) of samples tested from patients treated with N+F+T were IHC 2+.
- All retrospective biomarker analyses were limited by the lack of adequate tissue for central NGS assessment of fresh, pretreatment biopsies.

Future directions

- Centrally assess *HER2* FISH copy number and FISH ratio in patient tumors with adequate tissue remaining.
- Broaden understanding of HER2 receptor expression patterns in *HER2*-mutant MBC by mining large datasets, such as Project GENIE[14], and comparing with the SUMMIT population:
  - Are the majority of all *HER2*-mutant MBC patients also 'HER2-low' and, if so, what are the implications?
- Evaluate baseline ctDNA and mechanisms of acquired resistance to N+F+T by performing NGS on serial liquid biopsies.
- Further explore preclinically the mechanistic rationale for addition of T to N.

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