Neratinib + fulvestrant for HER2-mutant, HR-positive, metastatic breast cancer: Updated results from the phase 2 SUMMIT trial

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Background

- *HER2* mutations define a rare subset of metastatic breast cancer (MBC) with a unique mechanism of oncogenic addiction to HER2 signaling.[1]
- Somatic *HER2* mutations occur in ~2% of MBC,[1] 5% of estrogen receptor (ER)+ MBC,[2] and 5–15% of invasive lobular cancers.[3,4]
- Recent preclinical studies suggest that acquired or *de novo* *HER2* mutations may confer resistance to endocrine therapy.[5,6] In the clinic, *HER2* mutations have been more commonly observed in endocrine-resistant tumors.[2,6,7]
- Neratinib is an oral, irreversible, pan-HER tyrosine kinase inhibitor that has demonstrated single-agent clinical activity in *HER2*-mutant MBC.[7,8]
- In *HER2*-mutant, hormone receptor-positive (HR+) cell lines and PDX models, neratinib + fulvestrant (N+F) appears synergistic vs single-agent neratinib,[6] possibly due to more complete inhibition of bi-directional signaling between *HER2* and ER.[9–12]
- In this poster we present updated results from the N+F treated, *HER2*-mutant, HR+ breast cancer cohort from the SUMMIT trial.

Figure 1. SUMMIT study design (Amendment 4)

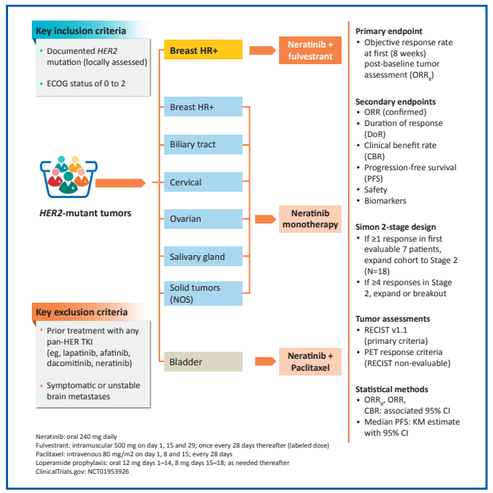


Table 1. Baseline demographics: HR+ breast cohort

Patient characteristics	Neratinib + fulvestrant (n=47)
Median (range), years	60 (43–87)
<65 years, %	29 (62)
≥65 years, %	18 (38)
Gender, n (%)	
Female	47 (100)
ECOG performance status, %	
0	24 (51)
1	22 (47)
2	1 (2)
Menopausal status, n (%)	
Post-menopausal	42 (89)
Pre-menopausal*	5 (11)

ECOG, Eastern Cooperative Oncology Group.
*Received luteinizing hormone-releasing hormone agonist.

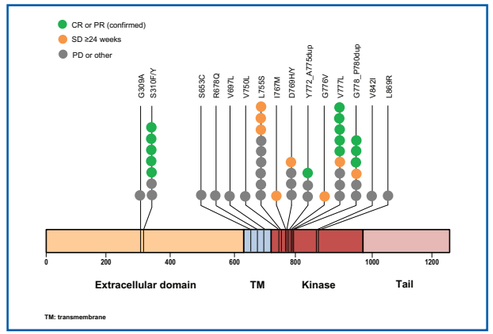
Table 2. Disease characteristics

Disease characteristics	Neratinib + fulvestrant (n=47)
Histological type, n (%)	
Ductal	30 (64)
Lobular	14 (30)
Other / unknown	3 (6)
HER2 status, n (%)	
Non-amplified	43 (92)
Amplified	2 (4)
Equivocal / unavailable	2 (4)
HR status, n (%)	
HR+ (ER+ and/or PR+)	47 (100)
Location of disease at time of enrollment, n (%)	
Visceral	37 (79)
Non-visceral only	10 (21)
Time from first metastasis to enrollment, median (range) in years	2.3 (0.2–19.0)
Patients with measureable disease per RECIST v 1.1 only, n (%)	39 (83)

Table 3. Prior therapies

Disease characteristics	Neratinib + fulvestrant (n=47)
Patients with no prior metastatic lines, n (%)	3 (6)
Median number of prior therapies in metastatic setting, n (range)	
Total	3 (1–11)
Chemotherapy	2 (1–6)
Endocrine therapy	2 (1–5)
Prior endocrine therapy at any time, n (%)	47 (100)
Prior aromatase inhibitor	45 (96)
Prior fulvestrant	25 (53)
Prior tamoxifen	24 (51)
Prior HER2-directed therapy, n (%)	
No	40 (85)
Yes	7 (15)
Prior CDK4/6 inhibitor, n (%)	
No	27 (57)
Yes	20 (43)
Prior PI3K/mTOR pathway inhibitor, n (%)	
No	37 (79)
Yes	10 (21)

Figure 2. Distribution of *HER2* mutations



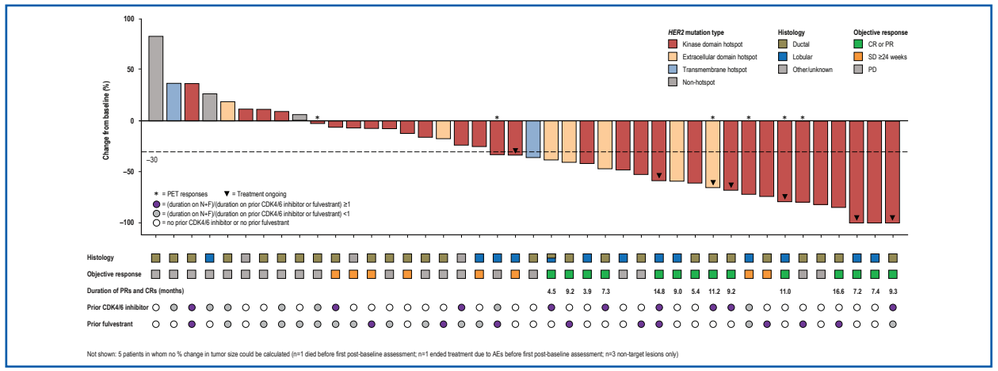
- At the time of data cut-off (19 October 2018), 8 (17%) patients are continuing on study treatment.
- Thirty-nine (83%) patients discontinued study treatment. Reasons for treatment discontinuation are: disease progression (n=34, 72%), death (n=1, 2%), adverse event (n=1, 2%), clinical progression/investigator decision (n=2, 4%), and reason missing (n=1, 2%).

Table 4. Efficacy summary

Efficacy endpoint[a]	Neratinib + fulvestrant: All patients (n=47)	Subgroups: Prior fulvestrant (n=25)	Subgroups: Prior CDK4/6 inhibitor-based therapy (n=20)
Objective response (confirmed)[b] – n	14	4	6
CR	4	0	1
PR	10	4	5
Objective response rate (95% CI)	30 (17–45)	16 (5–36)	30 (12–54)
Median[c] DOR, months (95% CI)	9.2 (5.5–16.6)		
DOR for each responder		9.2; 9.3*; 14.8*; 16.6	4.5; 7.3; 9.2*; 9.3*; 11.2*; 14.8*
Clinical benefit[d] – n	22	9	8
CR or PR	14	4	6
SD	8	5	2
Clinical benefit rate (95% CI)	47 (32–62)	36 (18–58)	40 (19–64)
Median[c] PFS (95% CI) time to event, months	5.4 (3.7–9.2)	3.7 (3.5–6.9)	4.1 (1.9–10.9)
Efficacy endpoint[a]	**Patients with RECIST v1.1 measurable disease: All patients (n=39)**	**Prior fulvestrant (n=21)**	**Prior CDK4/6 inhibitor-based therapy (n=15)**
Objective response (confirmed)[b] – n	12	4	5
CR	2	0	0
PR	10	4	5
Objective response rate (95% CI)	31 (17–48)	19 (5–42)	33 (12–62)
Median[c] DOR, months (95% CI)	9.0 (4.5–16.6)		
DOR for each responder		9.2; 9.3*; 14.8*; 16.6	4.5; 7.3; 9.2*; 9.3*; 14.8*
Clinical benefit[d] – n	18	8	6
CR or PR	12	4	5
SD	6	4	1
Clinical benefit rate (95% CI)	46 (30–63)	38 (18–62)	40 (16–68)
Median[c] PFS (95% CI) time to event, months	5.4 (3.5–10.3)	NA	NA

[a]Response is based on investigator tumor assessments per RECIST v1.1 or modified PERCIST for patients with only PET-evaluable lesions.
[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]Kaplan-Meier analysis.
[d]Clinical benefit rate (CBR) is defined as confirmed CR or PR or stable disease (SD) for at least 24 weeks (within +/- 7 day visit window).
*Patient still on treatment at time of data cut; DOR, duration of response; PFS, progression-free survival; NA, not available.

Figure 3. Waterfall plot – best % change in tumor size



Not shown: 5 patients in whom no % change in tumor size could be calculated (n=1 died before first post-baseline assessment; n=1 ended treatment due to AEs before first post-baseline assessment; n=3 non-target lesions only)

Figure 4. Progression-free survival

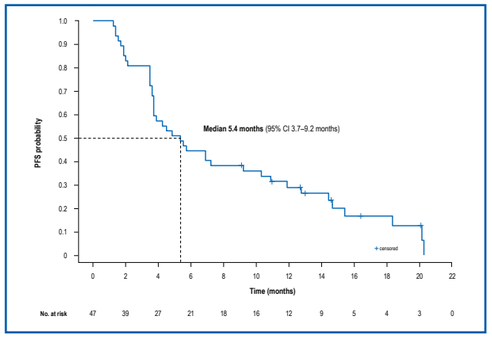


Table 5. Incidence of treatment-emergent adverse events (≥15%)

Adverse event, n (%)	Neratinib + fulvestrant (n=47): Grade 1 or 2	Grade 3 or 4[b]
Subjects with at least 1 adverse event, n (%)	23 (49)	22 (47)
Diarrhea	29 (62)	11 (23)
Nausea	21 (45)	0
Constipation	15 (32)	0
Decreased appetite	13 (28)	0
Fatigue	12 (26)	0
Dry skin	9 (19)	0
Vomiting	9 (19)	1 (2)
Abdominal pain	8 (17)	0
Back pain[a]	8 (17)	0

[a]Grade (G) was not reported for one back pain event.
[b]1 G4 event (unrelated atrial fibrillation); other G3 events: AST increased, anaemia, dyspnoea, pain, pleural effusion, aspiration, asthenia, cancer pain, cataract, cellulitis, chest pain, clostridium difficile colitis, dizziness, failure to thrive, fall, hypoalbuminaemia, hypokalaemia, hypotension, hypoxia, infected cyst, lymphangitis, staphylococcal infection, syncope.

Table 6. Characteristics of diarrhea

	Neratinib + fulvestrant (n=47)
Incidence of diarrhea, n (%)[a]	
Any grade	40 (85)
Grade 1	11 (23)
Grade 2	18 (38)
Grade 3	11 (23)
Action taken with neratinib, n (%)	
Leading to temporary hold	5 (11)
Leading to dose reduction	6 (13)
Leading to permanent discontinuation	0
Leading to hospitalization	1 (2)
Time to first grade 3 diarrhea, median (range) in days	14 (1–132)
Duration of grade 3 diarrhea per episode, median (range) in days	1.5 (1–11)

[a]No grade 4 or 5 diarrhea events were reported.

Conclusions

- *HER2* mutations represent a clinically actionable, oncogenic driver in MBC.
- Neratinib combined with fulvestrant demonstrates encouraging clinical activity in *HER2*-mutant, HR+ MBC patients:
  - ORR 30%; median DOR 9.2 months; median PFS 5.4 months.
- Responses were observed in fulvestrant- and CDK4/6 inhibitor-pretreated patients:
  - Patients with prior CDK4/6-inhibitor exposure had a longer median duration on study treatment (5.6 months) than on their prior CDK4/6-inhibitor therapy (3.5 months).
- No new safety signals were identified with patients treated with neratinib + fulvestrant:
  - The rate of diarrhea, the most common AE, was similar to that observed with single-agent neratinib, was not dose-limiting, and was manageable by loperamide prophylaxis.
- The SUMMIT study has been amended to evaluate combining neratinib with trastuzumab ± fulvestrant in *HER2*-mutated breast cancer patients.

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