Neratinib + fulvestrant in ERBB2-mutant, HER2 non-amplified, estrogen receptor-positive, metastatic breast cancer: preliminary analysis from the phase II SUMMIT trial

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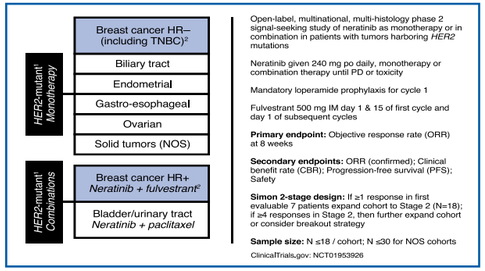
Background

- Neratinib is an oral, irreversible, tyrosine kinase inhibitor of ERBB1 (EGFR), ERBB2 (HER2) and ERBB4 (HER4)[1]
- Somatic *ERBB2* (HER2) mutations occur in approximately: 1.6% of newly diagnosed patients with breast cancer[2]; 2.4% of heavily pre-treated metastatic breast cancer (MBC)[3]; 9% of estrogen receptor (ER)-positive MBC[4]; and 5–15% of invasive lobular cancers,[5,6] and have been identified predominantly in ER-positive breast cancers[2]
- The most common *HER2* mutations in breast cancer include single nucleotide variants and small in-frame insertions that cluster primarily at codons 755–781 of the intracellular tyrosine kinase domain[2]
- Preclinical breast cancer models of *HER2* mutations demonstrate increased cell signaling, oncogenic transformation, and enhanced tumor growth[7]
- Bi-directional signaling between HER2 and ER may limit the effectiveness of endocrine and HER2-directed therapy, if each is given alone, in ER+ MBC with *HER2* amplifications/mutations.[8,9] Preclinical data suggest that dual blockade of ER and HER2 signaling results in enhanced anti-tumor activity in ER+ HER2+ MBC.[9,10]

Figure 1. SUMMIT: study design



The SUMMIT study was amended (17 March 2015) to allow for combination of neratinib + fulvestrant in eligible post-menopausal patients with *HER2*-mutant, ER+ breast cancers

[1]Documented mutations based on local testing. Only data for *HER2*-mutant breast cancer cohorts are presented here

[2]In amendment 1–3, HR+ and HR– patients received neratinib therapy. In amendment 4, HR– patients received neratinib monotherapy

Materials and methods

Patients

- Efficacy evaluable patients defined as those who received ≥1 week of treatment and had ≥1 tumor assessment completed
- Safety evaluable patients defined as those who received ≥1 dose of study treatment

Efficacy endpoints

RECIST v1.1 used for primary endpoint in patients with RECIST measurable disease; PET response was initially used in RECIST non-evaluable patients and the protocol was amended for PET response to be mandatory in all breast cancer patients

- ORR_8: defined as complete response (CR) or partial response (PR) at 8 weeks of study therapy, which corresponds to first scheduled tumor assessment
- ORR: defined as either CR or PR confirmed ≥4 weeks after initial response
- CBR: defined as CR, PR, or stable disease (SD) for ≥24 weeks
- PFS: defined as time from first dose date to first date of recurrence, progression, or death

Molecular profiling

- FFPE tumor subject to central NGS-based profiling using MSK-IMPACT assay[11]
- Molecular profiling of tumor and plasma cell-free DNA

Statistical methods

- ORR_8, ORR, CBR estimated with associated Clopper-Pearson 95% CI
- Median PFS estimated via Kaplan-Meier with associated 95% CI
- Data cutoff: 11 November 2016

Table 1. Baseline demographics in safety evaluable patients

Patient characteristics	Neratinib monotherapy (n=25)	Neratinib + fulvestrant (n=17)
Age		
Median (range), years	57 (37–80)	61 (49–87)
<65 years, n (%)	19 (76.0)	11 (64.7)
≥65 years, n (%)	6 (24.0)	6 (35.3)
Gender[a], n (%)		
Female	24 (96.0)	17 (100.0)
ECOG performance status, n (%)		
0	7 (28.0)	7 (41.2)
1	17 (68.0)	10 (58.8)
2	1 (4.0)	0
Menopausal status, n (%)		
Post-menopausal	23 (92.0)	14 (82.4)
Pre-menopausal	1 (4.0)	3 (17.6)

ECOG, Eastern Cooperative Oncology Group

[a]Included one male patient in the monotherapy cohort

Table 2. Disease characteristics in safety evaluable patients

Disease characteristics	Neratinib monotherapy (n=25)	Neratinib + fulvestrant (n=17)
Histological type, n (%)		
Ductal	18 (72.0)	12 (70.6)
Lobular	7 (28.0)	4 (23.5)
Inflammatory	0	1 (5.9)
HER2 status, n (%)		
Non-amplified	23 (92.0)	15 (88.2)
Amplified	2 (8.0)	2 (11.8)
Hormone receptor status, n (%)		
HR-positive (ER+ and/or PR+)	19 (76.0)	17 (100)
HR-negative (ER– and PR–)	6 (24.0)	0
Location of disease at time of enrollment, n (%)		
Visceral	19 (76.0)	13 (76.4)
Non-visceral only	6 (24.0)	4 (23.5)
Time from first metastasis to enrollment, median (range) in years	2.7 (0.1–15.0)	1.7 (0.4–8.7)
Number of prior lines of therapy in metastatic setting, median (range)	4 (0–8)	4 (1–7)
Number of prior lines of chemotherapy for metastatic disease, median (range)	2 (0–4)	2 (0–5)
Number of prior lines of endocrine therapy, median (range)	2 (0–6)	2 (1–6)
HR+ patients receiving prior endocrine therapy, n (%)	N=19	N=17
Aromatase inhibitor	11 (57.9)	16 (94.1)
Fulvestrant	11 (57.9)	7 (41.2)
Tamoxifen	10 (52.6)	8 (47.1)

Table 3. Subject disposition in safety evaluable patients

Parameter	Neratinib monotherapy (n=25)	Neratinib + fulvestrant (n=17)
Patients continuing on treatment, n (%)	1 (4.0)	9 (52.9)
Treatment discontinuation, n (%)	24 (96.0)	8 (47.1)
Disease progression	22 (88.0)	7 (41.2)
Withdrawal of consent	1 (4.0)	0 (0.0)
Not yet reported	1 (4.0)	1 (5.9)
Patients requiring dose reductions, n (%)		
1 dose reduction[a]	6 (24.0)	2 (11.8)

[a]Neratinib dose reduction to 160 mg/day

Figure 2. Distribution of *HER2* mutations

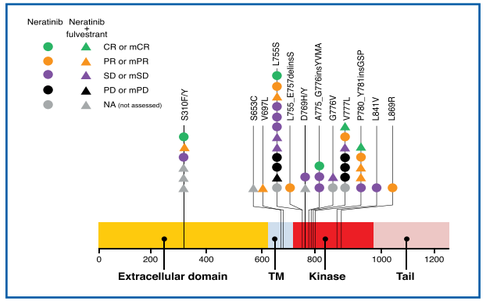
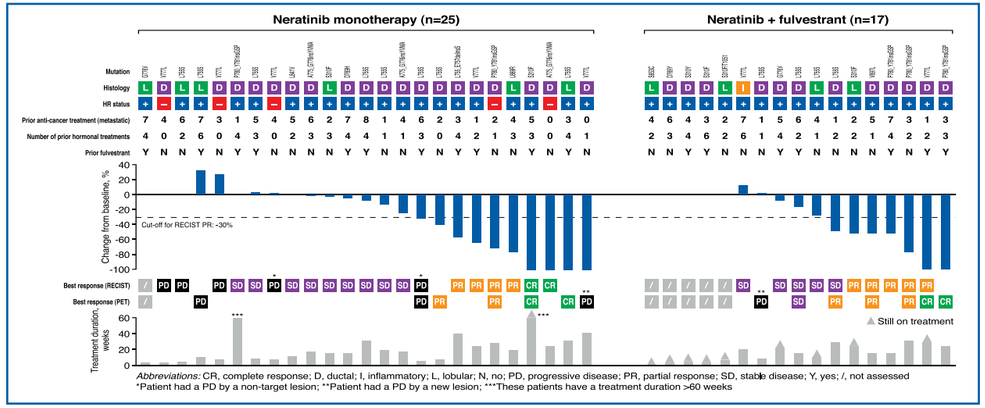


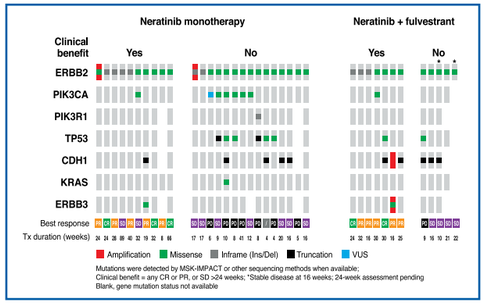
Figure 3. Best change in tumor burden



Abbreviations: CR, complete response; D, ductal; I, inflammatory; L, lobular; N, no; PD, progressive disease; PR, partial response; SD, stable disease; Y, yes; /, not assessed

*Patient had a PD by a non-target lesion; **Patient had a PD by a new lesion; ***These patients have a treatment duration >60 weeks

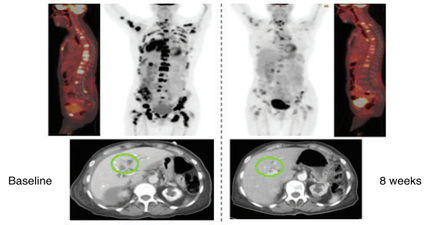
Figure 4. Somatic mutations detected from FFPE biopsy



Mutations were detected by MSK-IMPACT or other sequencing methods where available.
Clinical benefit = any CR or PR, or SD >24 weeks; *Stable disease at 16 weeks; 24-week assessment pending
Blank, gene mutation status not available

Figure 5. Sample case

***HER2*-mutant (P780_Y781insGSP) ER+/HER2– ductal carcinoma**
Neratinib + fulvestrant treatment



45% partial response by RECIST v1.1 at 8 weeks

Table 4. Efficacy summary in efficacy evaluable patients

	Neratinib monotherapy (n=24)	Neratinib + fulvestrant (n=12)
Best response,[a] n	8	7
CR	3	2
PR	5	5
Best response rate (95% CI)	33.3 (15.6–55.3)	58.3 (27.7–84.8)
Objective response at week 8, n	8	5
CR at week 8	2	2
PR at week 8	6	3
Objective response rate at week 8 (95% CI)	33.3 (15.6–55.3)	41.7 (15.2–72.3)
Overall objective response (Confirmed CR or PR), n	6	3
CR	3	1
PR	3	2
Objective response rate (95% CI)	25.0 (9.8–46.7)	25.0 (5.5–57.2)
Clinical benefit, n	10	7
Clinical benefit rate (95% CI)	41.7 (22.1–63.4)	58.3 (27.7–84.8)
Median PFS[b] (95% CI), months	3.5 (1.9–4.3)	3.7 (2.1–6.7)

[a]Defined as a CR or PR with or without a confirmation at any time during treatment

[b]PFS may not be mature in the combination treatment cohort as 9 of 17 patients continue to receive study treatment with ongoing assessment

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

	Neratinib monotherapy (n=25)		Neratinib + fulvestrant (n=17)	
	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3
Any adverse event, n (%)	24 (96.0)	13 (52.0)	14 (82.4)	2 (11.8)
Diarrhea	15 (60.0)	6 (24.0)	9 (52.9)	2 (11.8)
Fatigue	11 (44.0)	0	2 (11.8)	0
Vomiting	11 (44.0)	0	2 (11.8)	0
Nausea	10 (40.0)	0	4 (23.5)	0
Constipation	7 (28.0)	0	0	0
Headache	5 (20.0)	0	1 (5.9)	0
Abdominal pain	4 (16.0)	1 (4.0)	1 (5.9)	0
Arthralgia	4 (16.0)	0	1 (5.9)	0
Asparate aminotransferase increased	4 (16.0)	3 (12.0)	0	0
Decreased appetite	4 (16.0)	0	4 (23.5)	0
Pruritus	4 (16.0)	0	1 (5.9)	0
Pyrexia	4 (16.0)	0	1 (5.9)	0
Rash	4 (16.0)	0	2 (11.8)	0

Table 6. Characteristics of diarrhea

	Neratinib monotherapy (n=25)	Neratinib + fulvestrant (n=17)
Incidence of diarrhea, n (%)[a]		
Any grade	21 (84.0)	11 (64.7)
Grade 1	7 (28.0)	4 (23.5)
Grade 2	8 (32.0)	5 (29.4)
Grade 3	6 (24.0)	2 (11.8)
Action taken with neratinib, n (%)		
Leading to temporary hold	5 (20.0)	2 (11.8)
Leading to dose reduction	0	1 (5.9)
Leading to permanent discontinuation	0	0
Diarrhea leading to hospitalization	3 (12.0)	1 (5.9)
Time to first grade 3 diarrhea, median (range) in days	8 (4–64)	14 (9–19)
Duration of grade 3 diarrhea per episode, median (range) in days	1 (1–9)	1 (1–9)

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

Conclusions

- Neratinib demonstrates single-agent clinical activity in heavily pre-treated *HER2*-mutant breast cancer patients
- Additional enrollment and longer follow-up is needed to determine the duration of the clinical benefit of the combination of neratinib + fulvestrant
  - Preliminary clinical activity observed in fulvestrant pre-treated and fulvestrant-naïve patients
- Diarrhea was not a treatment-limiting toxicity with anti-diarrheal prophylaxis and management
- No additive safety concerns were noted with patients treated with neratinib + fulvestrant

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