Neratinib + trastuzumab + fulvestrant for HER2-mutant, hormone receptor-positive, metastatic breast cancer: updated results from the phase 2 SUMMIT 'basket' trial

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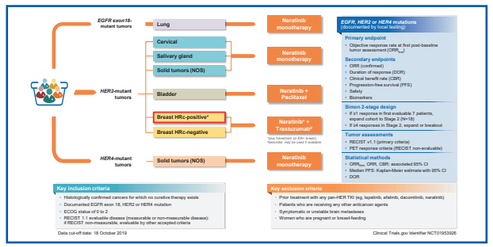
Introduction

- *HER2* mutations occur 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]
- Recent preclinical and clinical studies suggest that acquired or *de novo HER2* mutations in HR+ MBC may confer resistance to prior endocrine therapy but retain sensitivity to neratinib.[2–6]
- 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.[6–8]
- Genomic analyses using paired pre-/post-biopsies suggest that acquired resistance to neratinib may occur by the acquisition of additional *HER2* alterations, including *HER2* amplifications, which may amplify HER2-pathway signaling.[9]
- Here, we investigated whether dual HER2-targeted therapy could improve clinical benefit in a cohort of patients with *HER2*-mutant, HR+ MBC treated with neratinib + trastuzumab + fulvestrant from the SUMMIT 'basket' trial.

Methods

Figure 1. Current SUMMIT study design: Protocol amendment 5



Results

Table 1. Baseline demographics

Patient characteristics	Safety evaluable patients (n=28)	Efficacy evaluable patients (n=17)
Median (range), years	**59 (39–75)**	**59 (39–75)**
<65 years, n (%)	20 (71)	13 (77)
≥65 years, n (%)	8 (29)	4 (24)
Gender, n (%)		
Female	28 (100)	17 (100)
ECOG performance status, n (%)		
0	15 (54)	10 (59)
1	10 (36)	5 (29)
2	1 (4)	1 (6)
Unknown	2 (7)	1 (6)
Menopausal status, n (%)		
Post-menopausal	27 (96)	16 (94)
Pre-menopausal	1 (4)	1 (6)
Disease characteristics		
Histological type, n (%)		
Ductal	10 (36)	6 (35)
Lobular	15 (54)	9 (53)
Other	3 (11)	2 (12)
HER2 status, n (%)		
HER2-negative	27 (96)	16 (94)
HER2-equivocal	1 (4)	1 (6)
HR status, n (%)		
HR+ (ER+ and/or PR+)	28 (100)	17 (100)
Location of disease at time of enrollment, n (%)		
Visceral	24 (86)	16 (94)
Non-visceral only	4 (14)	1 (6)
Median time from first metastasis to enrollment, years (range)	3.1 (0.2–9.1)	2.3 (0.2–9.1)

Safety evaluable: all enrolled patients who received at least 1 dose of neratinib
Efficacy evaluable: patients with RECIST measurable disease at baseline with at least 1 post-baseline tumor assessment
ECOG: Eastern Cooperative Oncology Group

Table 2. Prior therapies in the metastatic setting

Prior therapies	Safety evaluable patients (n=28)	Efficacy evaluable patients (n=17)
Patients with prior treatment for metastatic / locally advanced disease, n (%)	26 (93)	15 (88)
Median number of prior therapies (range)	4 (0–10)	4 (0–10)
Prior endocrine therapy, n (%)	28 (100)	14 (82)
Prior aromatase inhibitor	27 (96)	13 (77)
Prior fulvestrant	17 (61)	8 (47)
Prior tamoxifen	12 (43)	2 (12)
Prior chemotherapy, n (%)	21 (75)	12 (71)
Prior HER2-directed therapy, n (%)	1 (4)[a]	0 (0)
Prior CDK4/6 inhibitor, n (%)	15 (54)	7 (41)
Prior PI3K pathway inhibitor, n (%)	3 (11)	0 (0)
Prior mTOR pathway inhibitor, n (%)	10 (36)	6 (35)

[a]One patient (ER+/PR–/HER2 equivocal) received prior trastuzumab + pertuzumab + docetaxel

Table 3. Subject disposition

Parameter	Safety evaluable patients (n=28)
Median duration of treatment, weeks (range)	19.8 (4.1–88.6)
Patients continuing on treatment, n (%)	15 (54)
Treatment discontinuation, n (%)	13 (46)
Disease progression	11 (39)
Death	0
Adverse event	1 (4)
Other[a]	1 (4)

[a]Treating physician decided to discontinue patient from treatment

Figure 2. Distribution of HER2 mutations

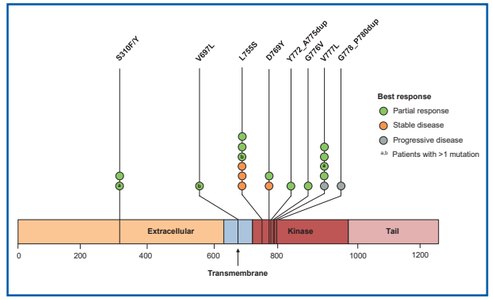


Table 4. Efficacy summary

Parameter	Efficacy evaluable patients (n=17)
Objective response (confirmed),[a] n	9
CR	0
PR	9
Objective response rate, % (95% CI)	**53** (28–77)
Best overall response, n (%)	11 (65)
CR	0
PR	11
Best overall response rate, % (95% CI)	**65** (38–86)
Median[b] DOR, months (95% CI)	**NE** (5.8–NE)
Clinical benefit,[c] n	10
CR or PR	9
SD ≥24 weeks	1
Clinical benefit rate, % (95% CI)	**59** (33–82)
Median[b] PFS time to event, months (95% CI)	**9.8** (4.0–NE)

[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)DOR, duration of response; NE, not estimable; PFS, progression-free survival

Figure 3. Change in tumor size and characteristics

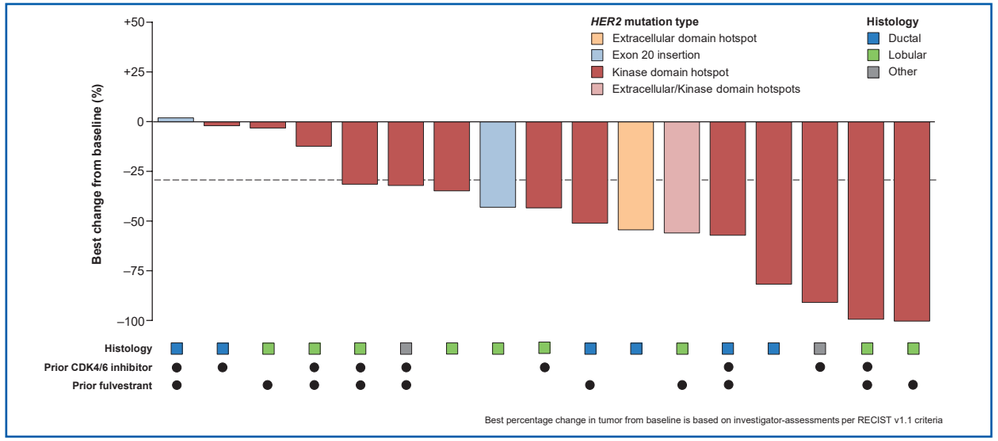


Figure 4. Duration of treatment and best response

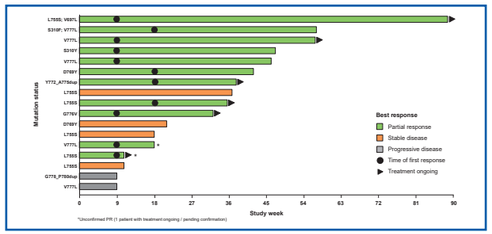


Figure 5. Progression-free survival (PFS)

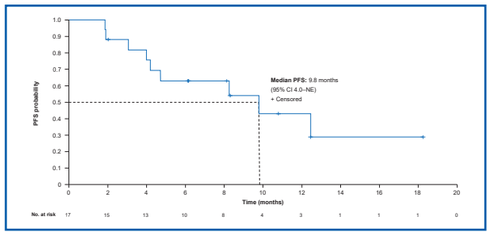
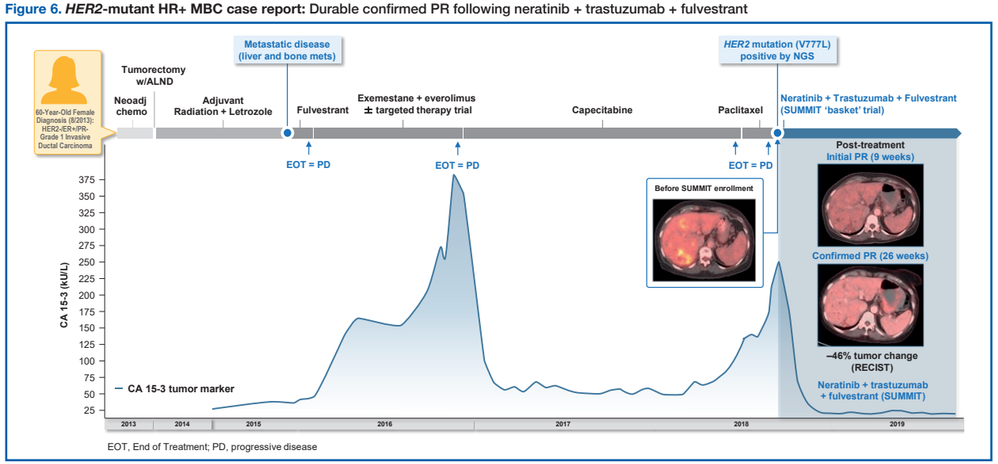


Figure 6. *HER2*-mutant HR+ MBC case report: Durable confirmed PR following neratinib + trastuzumab + fulvestrant



EOT, End of Treatment; PD, progressive disease

Table 5. Incidence of treatment-emergent adverse events

Adverse event, n (%)	Safety evaluable patients (n=28)	
	All grade	Grade 3 or 4
Subjects with at least 1 adverse event, n (%)	26 (93)	16 (57)
Diarrhea	24 (86)	10 (36)[a]
Nausea	15 (54)	0
Vomiting	13 (46)	1 (4)
Constipation	10 (36)	0
Fatigue	8 (29)	1 (4)
Decreased appetite	8 (29)	1 (4)
Stomatitis	5 (18)	0
Muscle spasms	5 (18)	0
Myalgia	5 (18)	0
Urinary tract infection	5 (18)	1 (4)

[a]There was no Grade 4 diarrhea

Table 6. Characteristics of diarrhea

	Safety evaluable patients (n=28)
Incidence of diarrhea, n (%)[a]	
Any grade	24 (86)
Grade 1	8 (29)
Grade 2	6 (21)
Grade 3	10 (36)
Action taken with neratinib, n (%)	
Leading to temporary hold	10 (36)
Leading to dose reduction	5 (18)
Leading to permanent discontinuation	0
Leading to hospitalization	1 (4)
Cumulative duration of grade 3 diarrhea per patient, median (range) in days	5.5 (1–34)

[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 and trastuzumab demonstrates encouraging clinical activity in previously treated *HER2*-mutant, HR+, HER2 non-amplified MBC patients:
  - ORR 53%; median DoR not estimable (5/9 responses still ongoing); median PFS 9.8 months.
- Rate of grade 3 diarrhea, the most common AE, was higher than that observed with single-agent neratinib in SUMMIT, although this was manageable by loperamide prophylaxis:
  - The median cumulative duration of grade 3 diarrhea was 5.5 days.
  - No patients discontinued study treatment due to diarrhea.
- In conclusion, the combination of neratinib + fulvestrant + trastuzumab resulted in an encouraging response rate and was a well-tolerated regimen in predominantly heavily pretreated *HER2*-mutant HR+ breast cancers.
- The SUMMIT trial is ongoing and continues to enroll patients.

References

1. Bose et al. Cancer Discovery 2013;3:224–37.
2. Razavi et al. Cancer Cell 2018;34:427–38.
3. Nayar et al. Nat Genet 2019;51:207–16.
4. Croessmann et al. Clin Cancer Res 2019;25:277–89.
5. Medford et al. NPJ Precis Oncol 2019;3:18.
6. Cocco et al. Sci Signal 2018;11; pii: eaat9773.
7. Hyman et al. Nature 2018;554:189–94.
8. Smyth et al. SABCS 2018 (abstract PD3-06).
9. Ma et al. Clin Cancer Res 2017;23:5687–95.
10. Won et al. AACR 2019 (abstract 929).

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