Oral presentation #149O

Neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ breast cancer: 5-year analysis of the phase III ExteNET trial

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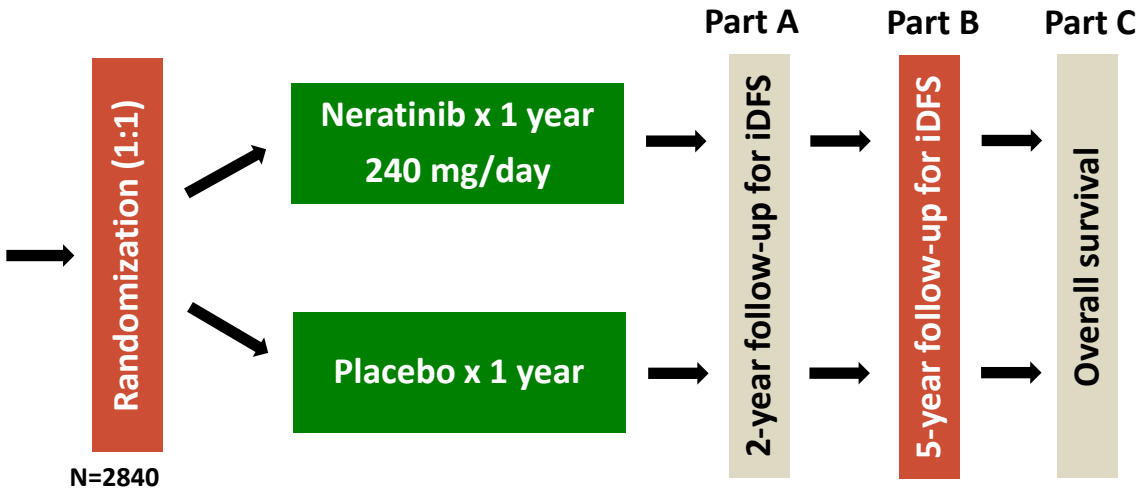
Background

- Adjuvant trastuzumab added to standard chemotherapy significantly improves overall survival in women with early HER2+ breast cancer[1-3]
- Despite the use of trastuzumab-based therapy, 15 to 24% of patients have breast cancer recurrences after a median of 8 to 11 years[1,3]
- New adjuvant therapeutic options are therefore needed in this population

[1]Perez et al. J Clin Oncol 2014
[2]Slamon et al. NEJM 2011
[3]Cameron et al. Lancet 2017

ExteNET: study design

- **HER2+ breast cancer**
  - IHC 3+ or ISH amplified (locally determined)
  - Prior adjuvant trastuzumab + chemotherapy
  - Lymph node +/–, or residual invasive disease after neoadjuvant therapy
- **Stratified by:** nodal status, hormone receptor status, concurrent *vs* sequential trastuzumab



Primary endpoint: invasive disease-free survival (iDFS)

Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety

Other analyses: biomarkers, health outcome assessments (FACT-B, EQ-5D)

Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice

Chan et al. Lancet Oncol 2016
Clinicaltrials.gov identifier: NCT00878709

ExteNET: study analysis

Part A (Primary analysis)

- 2-year analysis for all efficacy endpoints in ITT, except overall survival
- 2-year iDFS rate 93.9% for neratinib *vs* 91.6% for placebo (HR 0.67, *P*=0.0091)[1]
- Performed in July 2014

Part B

- Descriptive 5-year analysis for all efficacy endpoints, except overall survival
- Analysis population: intention-to-treat
- Performed in March 2017

Part C

- Overall survival to be analyzed after 248 deaths; sponsor blinded until that time

[1]Chan et al. Lancet Oncol 2016

ExteNET: results

- Between July 2009 and October 2011, 2840 women were randomly assigned to study treatment (neratinib, n=1420; placebo, n=1420)
  - At the cut-off date, 2117 patients (76.0%) had re-consented to the collection of further data (neratinib, n=1028; placebo, n=1089)

5-year analysis: baseline characteristics

	Intent-to-treat population		Re-consented population	
	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=1028)	Placebo (n=1089)
Median age, years (range)	52 (25–83)	52 (23–82)	52 (25–83)	53 (24–81)
Nodal status, n (%)[a]				
Negative	335 (24)	336 (24)	216 (21)	261 (24)
1–3 positive nodes	664 (47)	664 (47)	506 (49)	510 (47)
4+ positive nodes	421 (30)	420 (30)	306 (30)	318 (29)
Hormone receptor status, n (%)[a]				
Positive	816 (57)	815 (57)	603 (59)	615 (57)
Negative	604 (43)	605 (43)	425 (41)	474 (44)
Prior trastuzumab regimen, n (%)[a]				
Concurrent	884 (62)	886 (62)	621 (60)	671 (62)
Sequential	536 (38)	534 (38)	407 (40)	418 (38)
Median (IQR) time from trastuzumab, months	4.4 (1.6–10.4)	4.6 (1.5–10.8)	4.5 (1.7–10.4)	4.3 (1.5–10.7)

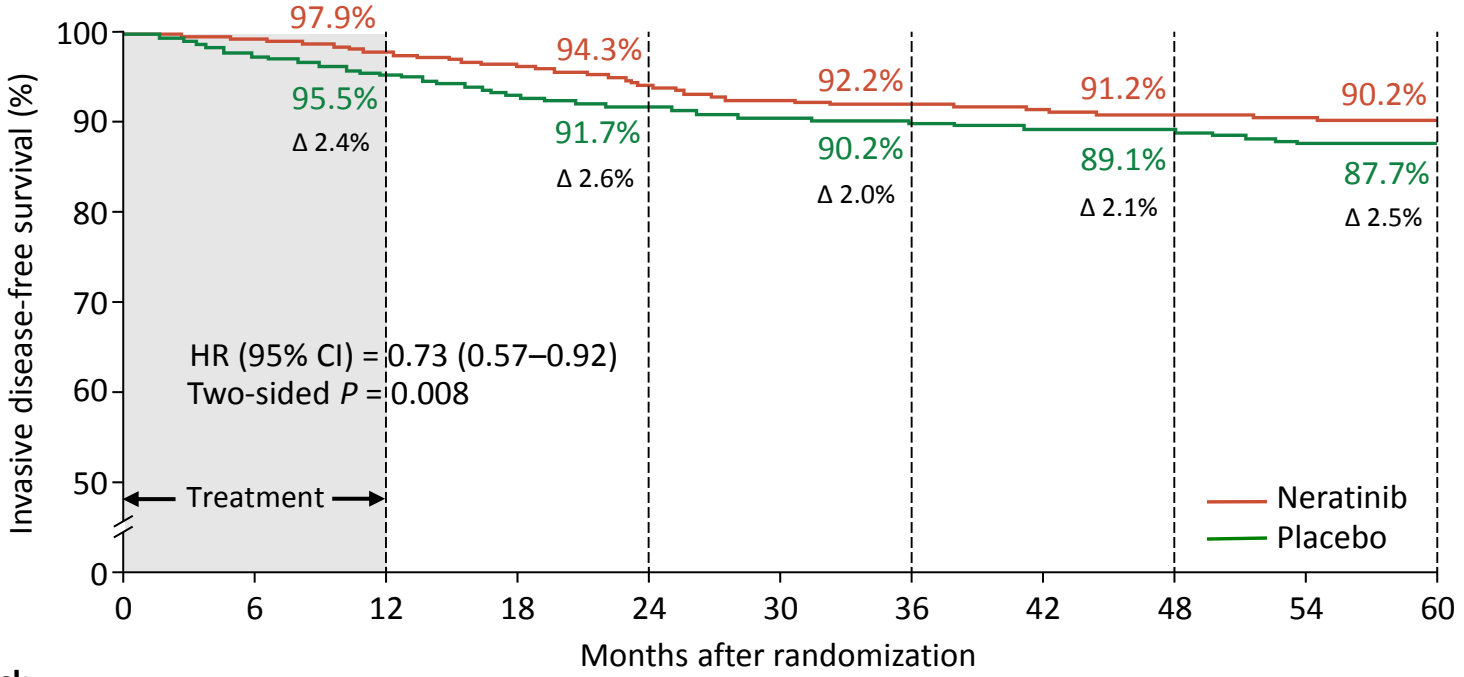
[a]Stratification factor

5-year analysis: iDFS events by site

Event site	Neratinib (n=1420)	Placebo (n=1420)
Any iDFS event, n (%)	116 (8.2)	163 (11.5)
Distant recurrence	91 (6.4)	111 (7.8)
Local/regional invasive recurrence	12 (0.8)	35 (2.5)
Invasive ipsilateral breast cancer recurrence	5 (0.4)	7 (0.5)
Invasive contralateral breast cancer	4 (0.3)	11 (0.8)
Death without prior recurrence	4 (0.3)	5 (0.4)

Intention-to-treat population. Cut-off date: March 1, 2017

5-year analysis: iDFS



No. at risk

Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

Intention-to-treat population. Cut-off date: March 1, 2017

5-year analysis: by endpoint

Endpoint	Estimated event-free rate,[a] %		Hazard ratio[b] (95% CI)	*P* value[b] (2-sided)
	Neratinib (n=1420)	Placebo (n=1420)		
Invasive disease-free survival	90.2	87.7	0.73 (0.57–0.92)	0.008
Disease-free survival with DCIS	89.7	86.8	0.71 (0.56–0.89)	0.004
Distant disease-free survival	91.6	89.9	0.78 (0.60–1.01)	0.065
Time to distant recurrence	91.8	90.3	0.79 (0.60–1.03)	0.078
CNS recurrences	1.30	1.82	–	0.333[c]

Intention-to-treat population. Cut-off date: March 1, 2017

CI, confidence interval; CNS, central nervous system; DCIS, ductal carcinoma in situ

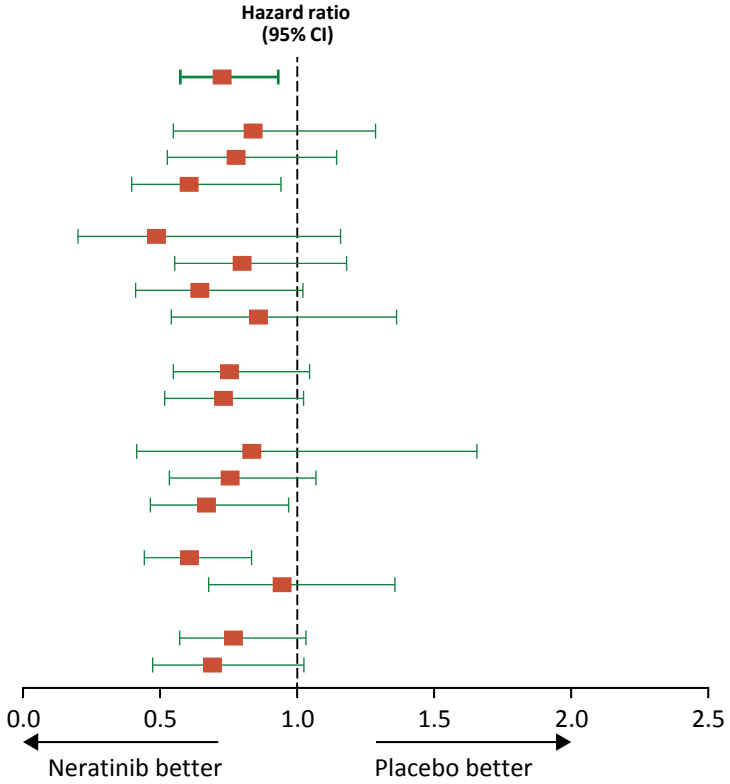
[a]Event-free rates for all endpoints, except CNS recurrences which is reported as cumulative incidence

[b]Stratified by randomization factors

[c]Gray's method

5-year subgroup analysis: iDFS

Subgroup	No. of patients	No. of events Neratinib vs. Placebo	HR (95% CI)
All patients	**2840**	**116 vs. 163**	**0.73 (0.57–0.92)**
Region of the World			
North America	996	40 vs. 46	0.84 (0.55–1.28)
W. Europe, AUS & S. Africa	1019	43 vs. 63	0.78 (0.52–1.14)
Asia, E. Europe & S. America	825	33 vs. 54	0.61 (0.39–0.93)
Age at randomization			
<35 years	101	7 vs. 15	0.49 (0.19–1.15)
35–49 years	1038	47 vs. 59	0.80 (0.54–1.17)
50–59 years	985	31 vs. 48	0.65 (0.41–1.01)
≥60 years	716	31 vs. 41	0.85 (0.53–1.36)
Menopausal status			
Premenopausal	1327	60 vs. 81	0.74 (0.53–1.04)
Postmenopausal	1513	56 vs. 82	0.72 (0.51–1.01)
Nodal status			
Negative	671	14 vs. 19	0.83 (0.41–1.65)
1–3 positive nodes	1328	55 vs. 74	0.75 (0.53–1.06)
≥4 positive nodes	841	47 vs. 70	0.67 (0.46–0.96)
Hormone receptor status			
Hormone positive*	1631	59 vs. 100	0.60 (0.43–0.83)
Hormone negative	1209	57 vs. 63	0.95 (0.66–1.35)
Prior trastuzumab			
Concurrent	1770	73 vs. 101	0.76 (0.56–1.03)
Sequential	1070	43 vs. 62	0.69 (0.47–1.02)

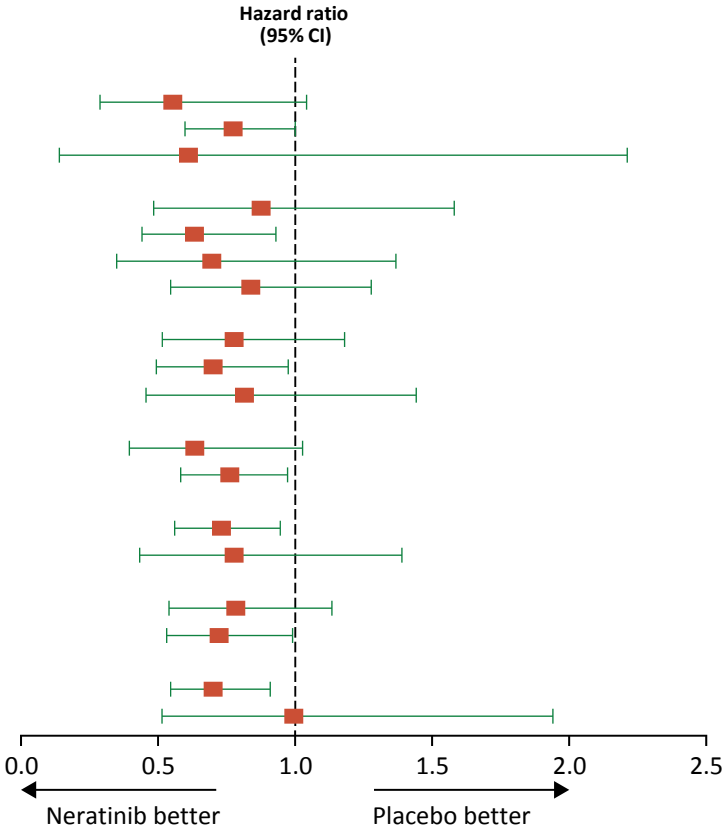


Intention-to-treat population

*Most (>93%) of patients with HR-positive tumors received concurrent endocrine therapy

5-year subgroup analysis: iDFS (cont'd)

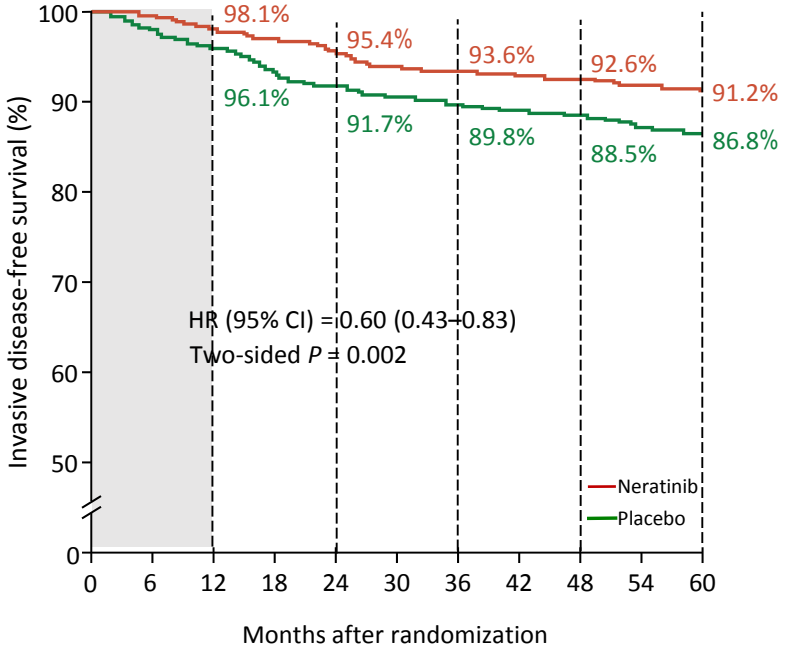
Subgroup	No. of patients	No. of events Neratinib vs. Placebo	HR (95% CI)
Race			
Asian	385	14 vs. 26	0.55 (0.28–1.04)
White	2300	99 vs. 130	0.77 (0.59–1.00)
Black or other	155	3 vs. 7	0.61 (0.13–2.21)
T-stage at diagnosis			
T1	899	20 vs. 25	0.88 (0.48–1.57)
T2	1140	45 vs. 69	0.63 (0.43–0.92)
T3 and above	261	15 vs. 18	0.69 (0.34–1.37)
Unknown	540	36 vs. 51	0.83 (0.54–1.27)
Histology grade			
Well/Moderately differentiated	1018	41 vs. 48	0.78 (0.51–1.18)
Poor/Undifferentiated	1368	56 vs. 86	0.69 (0.49–0.97)
Unknown	454	19 vs. 29	0.81 (0.45–1.44)
Surgery type			
Lumpectomy only	979	26 vs. 46	0.63 (0.39–1.02)
Mastectomy	1859	90 vs. 117	0.76 (0.58–1.00)
Prior radiotherapy			
Yes	2280	96 vs. 137	0.73 (0.56–0.94)
No	560	20 vs. 26	0.78 (0.43–1.39)
Prior neo-adjuvant therapy			
Yes	721	48 vs. 69	0.78 (0.54–1.13)
No	2119	68 vs. 94	0.73 (0.53–0.99)
Completion of prior trastuzumab			
≤1 year	2297	99 vs. 145	0.70 (0.54–0.90)
>1 year	543	17 vs. 18	1.00 (0.51–1.94)



Intention-to-treat population

iDFS by hormone receptor status

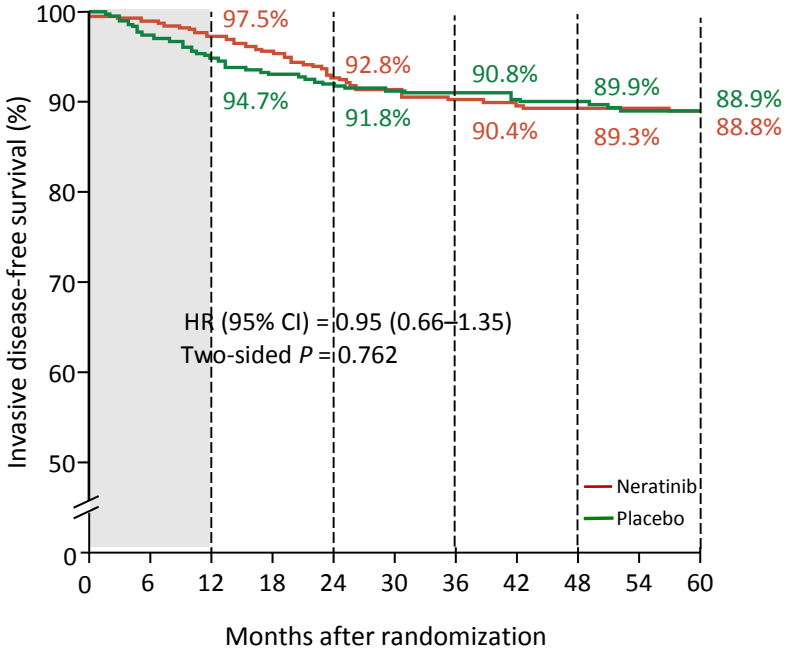
HR-positive subgroup



No. at risk

Neratinib	816	757	731	705	642	571	565	558	554	544	523
Placebo	815	779	750	719	647	581	567	556	551	542	525

HR-negative subgroup



No. at risk

Neratinib	604	559	541	520	464	407	400	391	384	376	362
Placebo	605	575	548	529	495	448	444	435	427	416	402

Intention-to-treat population. Cut-off date: March 1, 2017

ExteNET: long-term safety and HRQoL

- Serious adverse events reported after treatment discontinuation showed no evidence of:
  - Long-term toxicity, specifically increased symptomatic cardiac toxicity or second primary malignancies, with neratinib versus placebo
  - Late-term consequences from neratinib-associated diarrhea
- ExteNET HRQoL data will be presented as a separate poster[1]
  - Transient HRQoL impairment with neratinib during the first month of treatment was observed, possibly due to treatment-related diarrhea, followed by a steady recovery towards baseline

[1]Delaloge et al. ESMO 2017

ExteNET: conclusions

- The 5-year analysis of the ExteNET trial confirms sustained benefit with extended adjuvant neratinib:
  - 2.5% absolute benefit in intent-to-treat population (HR=0.73; *P*=0.008)
  - 4.4% absolute benefit in HR-positive cohort (HR=0.60; *P*=0.002)
- No evidence of long-term toxicity (i.e. no increased symptomatic cardiac toxicity or second primary malignancies) with neratinib versus placebo or late-term consequences from neratinib-associated diarrhea
- Overall survival data expected to mature in 2019

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