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Early Stage HER2+ Breast Cancer

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Disclosures

Advisory Committee	Advaxis Inc, Bayer HealthCare Pharmaceuticals, Eisai Inc, MacroGenics Inc, Merck, Novartis, Pfizer Inc, Pierian Biosciences, Syndax Pharmaceuticals Inc
Consulting Agreements	Celgene Corporation, Coherus BioSciences, G1 Therapeutics, Genentech BioOncology, Lilly, Novartis, Pfizer Inc, Puma Biotechnology Inc, Roche Laboratories Inc, Sandoz
Contracted Research	Celgene Corporation, Genentech BioOncology, Novartis, Pfizer Inc

Case presentation: Dr Ma

59-year-old woman

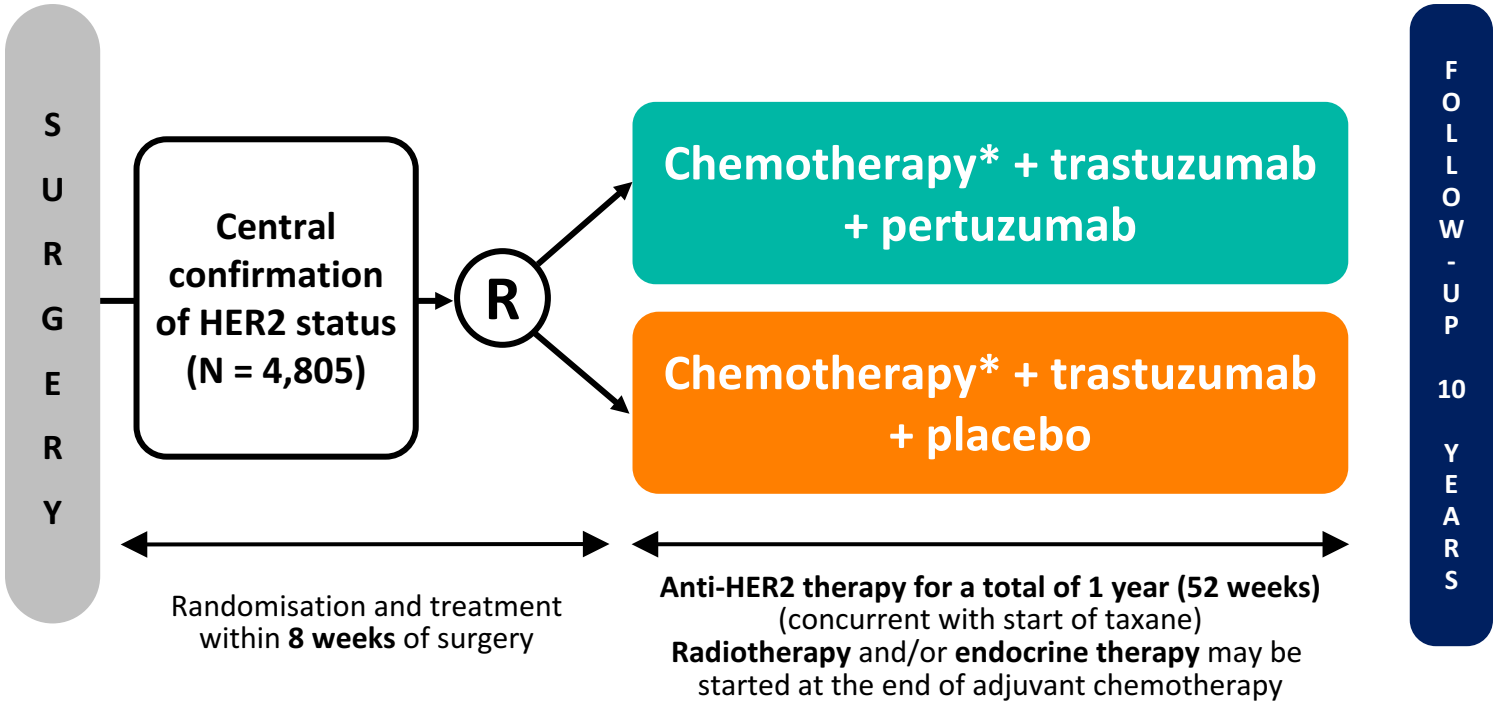
- 2013: Stage IIIB ER/PR-positive, HER2-positive inflammatory BC
  - Neoadjuvant therapy: Dose-dense AC → THP → residual 3-mm tumor → XRT to the chest wall, trastuzumab to 1 year and tamoxifen
- 2016: Cytopenias: Developed MDS → azacitidine → alloSCT
- 2017: Letrozole, currently NED

Case presentation: Dr Agrawal

46-year-old premenopausal woman

- 2016: 2.0-cm, node-positive, ER-positive, HER2-positive BC
- Neoadjuvant TCHP → surgery: Scattered microscopic foci of residual disease spanning 2 cm; no involved lymph nodes
- Adjuvant tamoxifen, radiation and trastuzumab for 1 year
- 2017: Neratinib discussed

APHINITY: A Phase III Trial Design



***A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed**

APHINITY: Statistical Assumptions

	EXPECTED 3-year IDFS rate Placebo vs. Pertuzumab
HR=0.75	**89.2% vs. 91.8% (Δ=2.6%)**

- Placebo arm IDFS rate was based on BCIRG 006 data[1], assuming a 35% / 65% node-negative / node-positive split
- 379 events and 4,800 patients required for 80% power and alpha of 5%

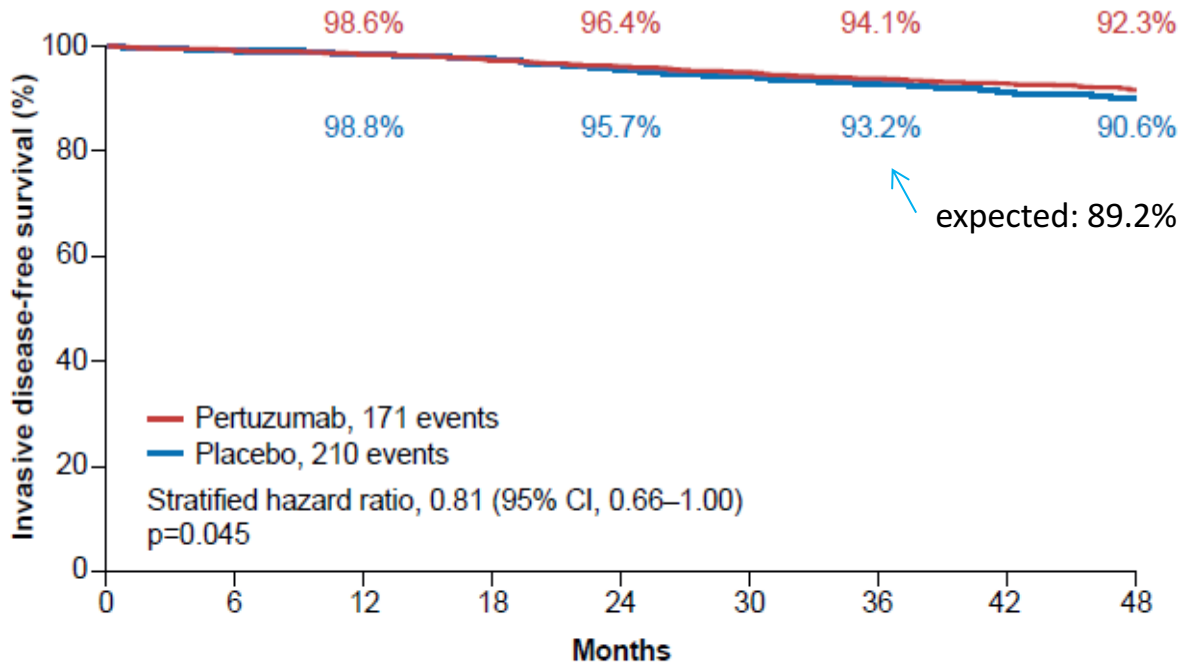
[1] Slamon D, NEJM 2011

APHINITY: Randomization Stratification Factors by Treatment

	Pertuzumab n=2,400	Placebo n=2,404*
Nodal status, n (%)		
0 positive nodes and T ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and T >1 cm*	807 (33.6)	818 (34.0)
1–3 positive nodes	907 (37.8)	900 (37.4)
≥ 4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant chemotherapy regimen (randomised), n (%)		
Anthracycline-containing regimen	1,865 (77.7)	1,877 (78.1)
Non-anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone receptor status (central), n (%)		
Negative (ER- and PgR-negative)	864 (36.0)	858 (35.7)
Positive (ER- and/or PgR-positive)	1,536 (64.0)	1,546 (64.3)
Geographical region, n (%)		
USA	296 (12.3)	294 (12.2)
Canada/Western Europe/Australia – New Zealand/South Africa	1,294 (53.9)	1,289 (53.6)
Eastern Europe	200 (8.3)	200 (8.3)
Asia Pacific	550 (22.9)	557 (23.2)
Latin America	60 (2.5)	64 (2.7)
Protocol Version, n (%)		
Protocol A	1,828 (76.2)	1,827 (76.0)
Protocol Amendment B	572 (23.8)	577 (24.0)

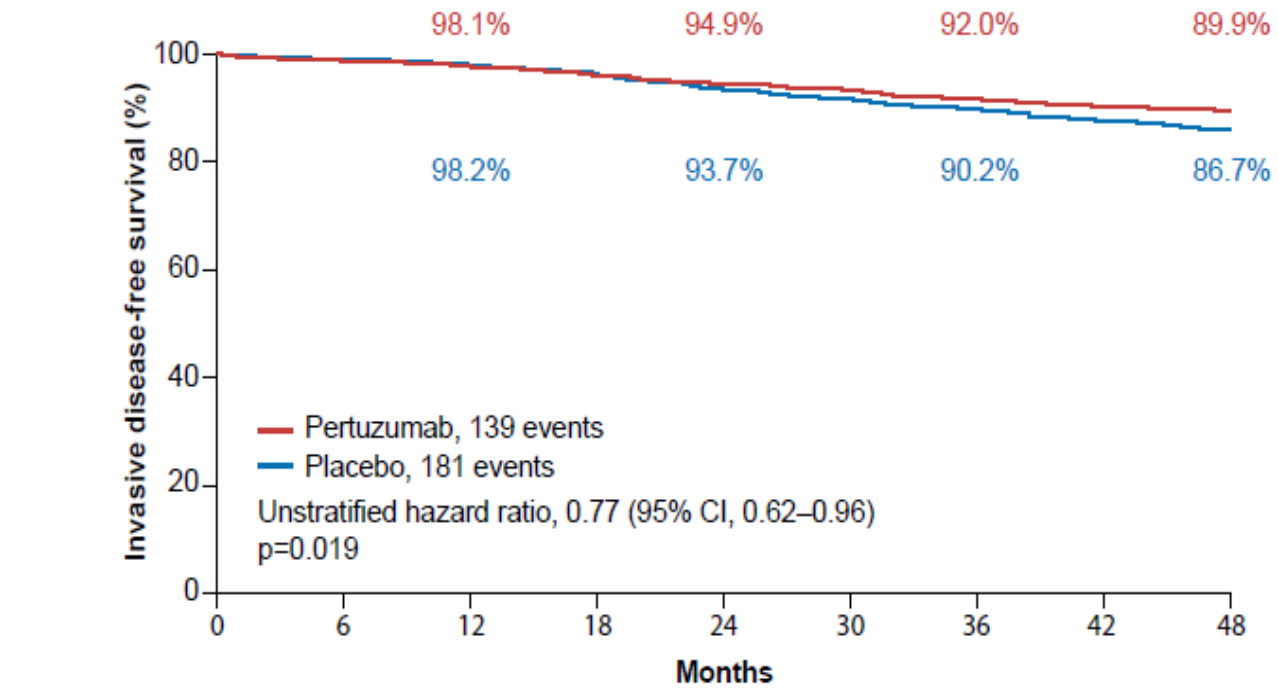
* One patient was excluded from the ITT population due to her falsification of personal information

APHINITY: Intent-to-Treat Primary Endpoint Analysis Invasive Disease-free Survival



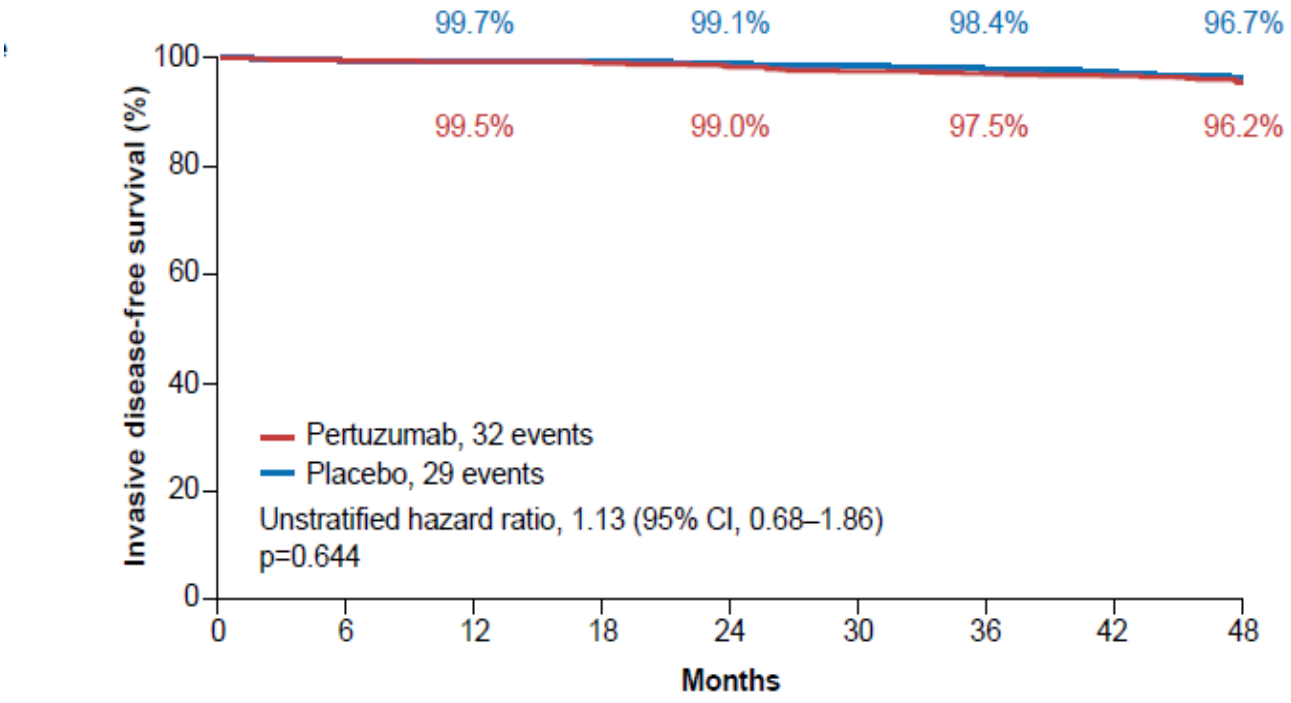
No. at Risk									
Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

APHINITY: Node-positive Subgroup



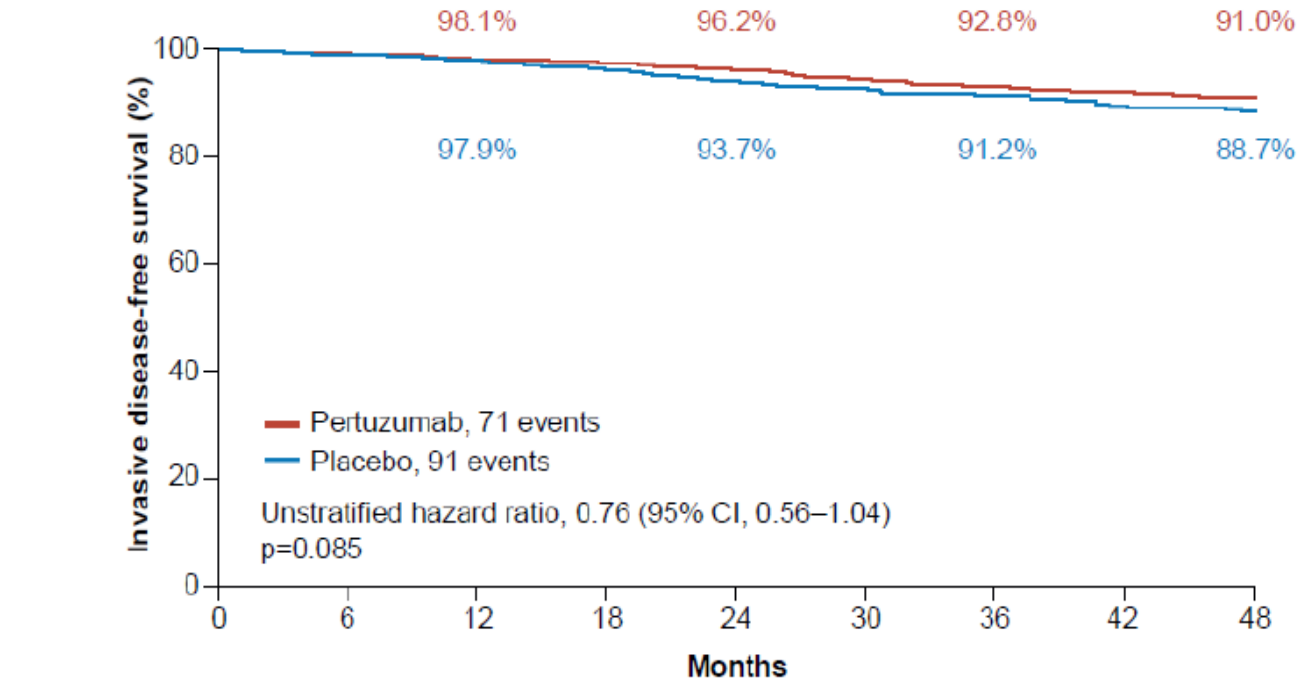
No. at Risk									
Pertuzumab	1503	1444	1419	1387	1358	1327	1283	912	423
Placebo	1502	1453	1439	1408	1359	1319	1264	882	405

APHINITY: Node-negative Subgroup



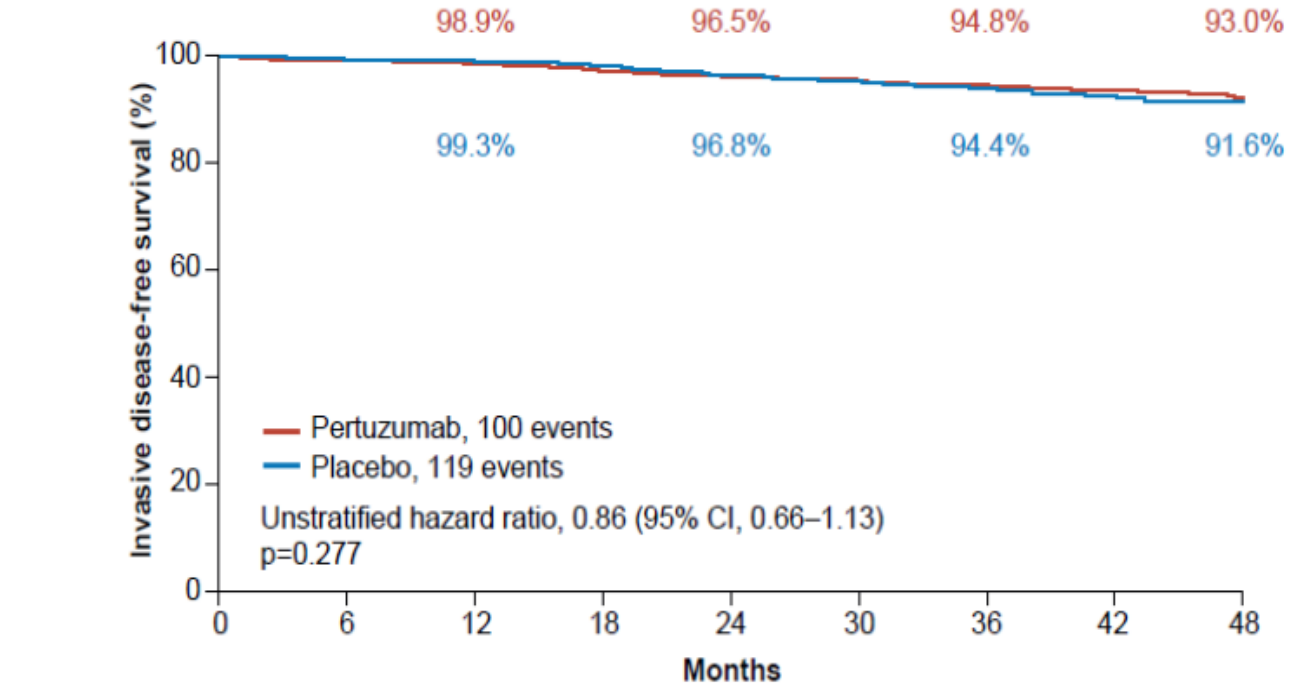
No. at Risk									
Pertuzumab	897	865	856	849	841	826	818	775	456
Placebo	902	882	873	866	856	849	844	792	461

APHINITY: Hormone Receptor-negative Subgroup



No. at Risk									
Pertuzumab	864	836	821	813	797	774	755	600	314
Placebo	858	827	811	793	771	758	730	569	302

APHINITY: Hormone Receptor-positive Subgroup



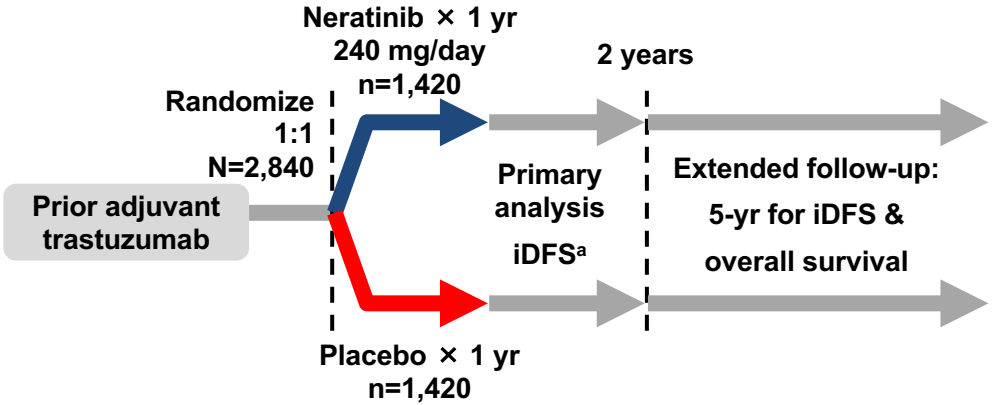
No. at Risk									
Pertuzumab	1536	1473	1454	1423	1402	1379	1346	1087	565
Placebo	1546	1508	1501	1481	1444	1410	1378	1105	564

APHINITY: Secondary Efficacy Endpoints

3-year	Pertuzumab n=2,400	Placebo n=2,404	Hazard ratio (95% CI)	p value
IDFS (primary endpoint), %	94.1	93.2	**0.81 (0.66, 1.00)**	**0.045**
Secondary efficacy endpoints, %				
IDFS incl. second primary non-BC events (STEEP definition)	93.5	92.5	**0.82 (0.68, 0.99)**	**0.043**
Disease-free interval	93.4	92.3	**0.81 (0.67, 0.98)**	**0.033**
Recurrence-free interval	95.2	94.3	**0.79 (0.63, 0.99)**	**0.043**
Distant recurrence-free interval	95.7	95.1	**0.82 (0.64, 1.04)**	**0.101**
Overall survival (first interim analysis)*	97.7	97.7	**0.89 (0.66, 1.21)**	**0.467**

*** 1st interim analysis at 26% of the target events for the final overall survival analysis**

ExteNET Phase III Study Design

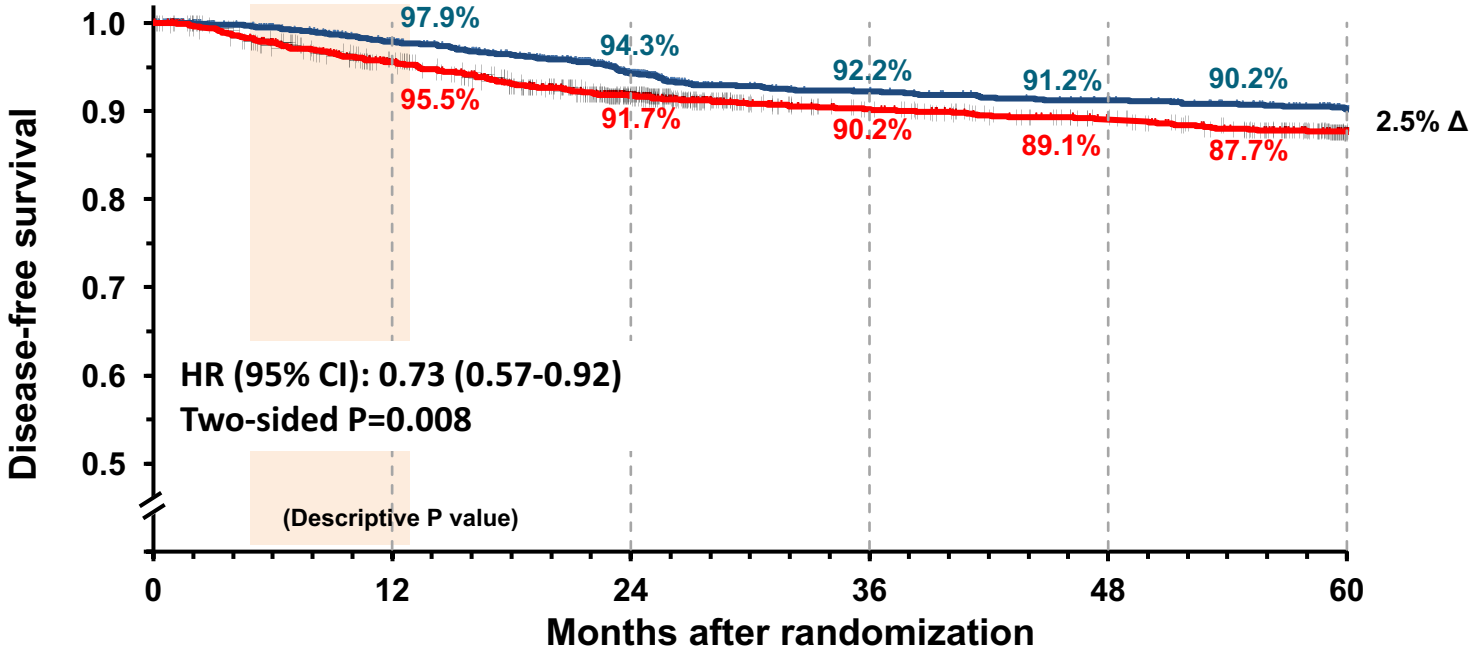


- Primary endpoint: invasive disease-free survival (iDFS)[a]
- Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,
- Stratification: nodes 0, 1-3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab
- Study blinded: Until primary analysis; OS remains blinded

[a] All iDFS events up to the cutoff date of 2 years + 28 days for each patient were included in the primary analysis.

FDA Oncologic Drugs Advisory Committee. May 24, 2017. Accessed June 13, 2017.

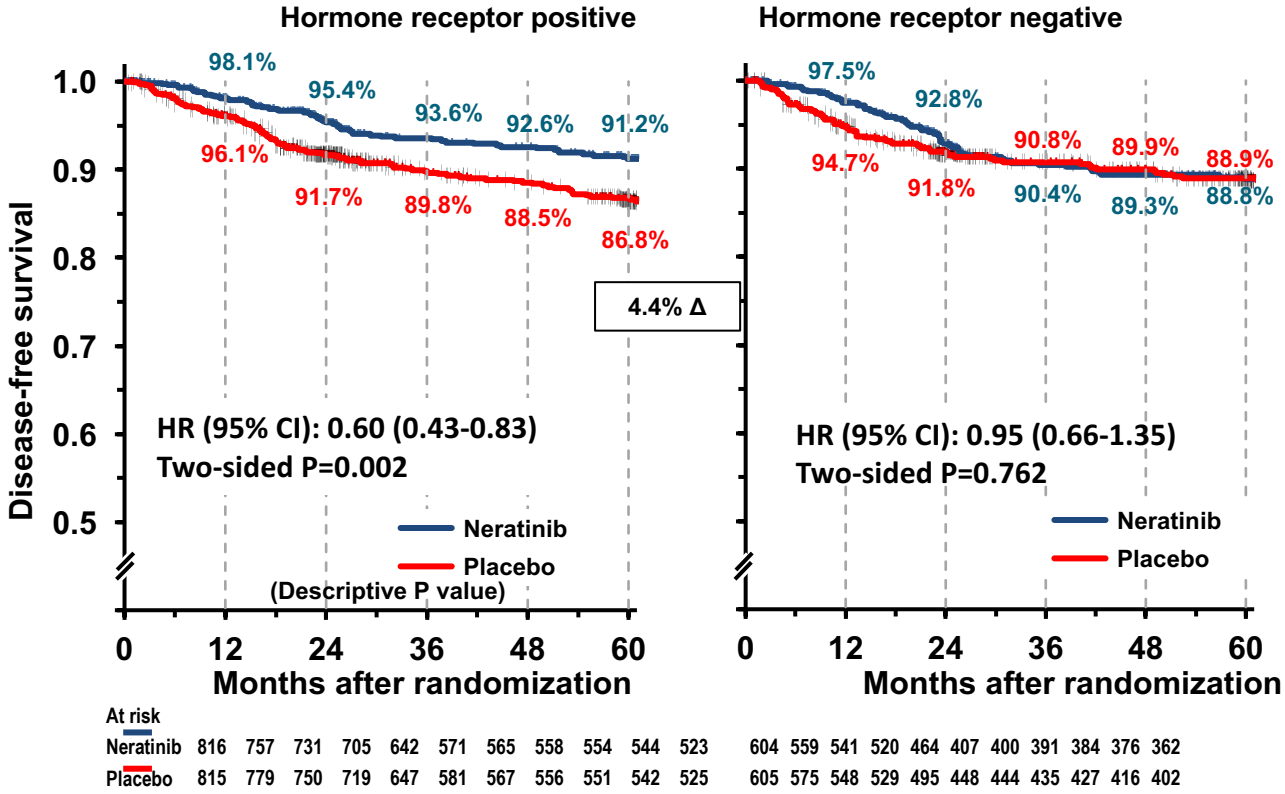
5-year Analysis Shows Durable iDFS Benefit
ITT Population



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

FDA Oncologic Drugs Advisory Committee. May 24, 2017. Accessed June 13, 2017.

iDFS by Hormone Receptor Status
5-Year Analysis



FDA Oncologic Drugs Advisory Committee. May 24, 2017. Accessed June 13, 2017.

Phase III ExteNET: Estimated 5-year iDFS

	n	Neratinib	Placebo	HR	*p*-value
ITT	2840	90.2%	87.7%	0.73	0.008
HER2-positive	1796	90.4%	88.2%	0.74	0.047
HR-positive	1631	91.2%	86.8%	0.60	0.002
HR-negative	1209	88.8%	88.9%	0.95	0.762
Completed trastuzumab ≤1 y of randomization	2297	89.7%	86.5%	0.70	0.006

Jimenez M et al. *Proc ESMO* 2017;Abstract 149O.

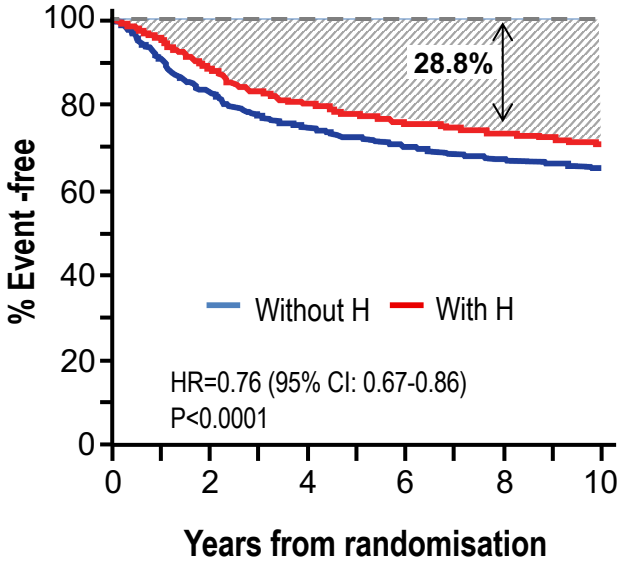
Antidiarrheal Prophylaxis Reduces Cumulative Duration of Diarrhea
ExteNET (Study 3004) and CONTROL (Study 6201)

	Median cumulative duration per patient, days		
		CONTROL prophylactic regimen	
	ExteNET Loperamide prn n=1408	Loperamide n=137	Budesonide + loperamide n=64
Any grade	**59**	12	6
Grade ≥2	10	4	3
Grade 3	5	3	3
Median neratinib exposure, months	12	9	3

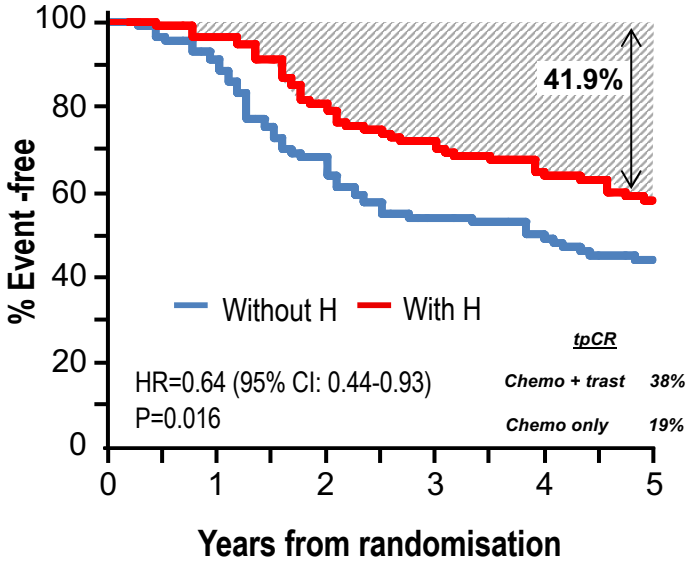
FDA Oncologic Drugs Advisory Committee. May 24, 2017. Accessed June 13, 2017.

Unmet medical need remains in HER2+ eBC

Adjuvant[1]
HERA
Disease-free survival

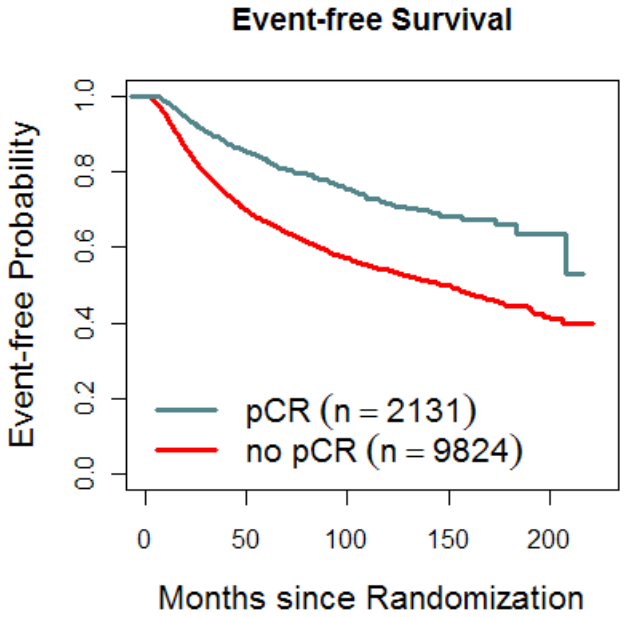


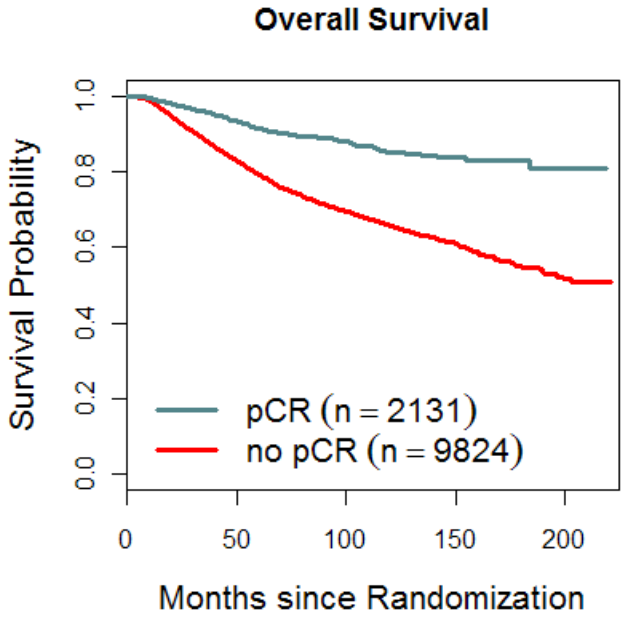
Neoadjuvant[2]
NOAH
Event-free survival



1. Goldhirsch, *et al. Lancet* 2013 (suppl.); 2. Gianni, *et al. Lancet Oncol* 2014

CTNeoBC Pooled Analysis: Total pCR is associated with improved EFS/OS





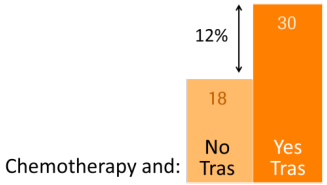
pCR=ypT0/is ypN0

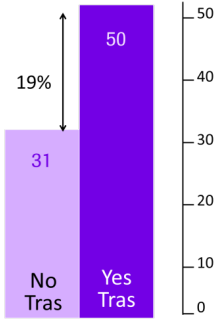
Cortazar, *et al*. *Lancet* 2014

Patients with HER2+ eBC, who achieve a pCR, demonstrate a long-term benefit irrespective of HR status

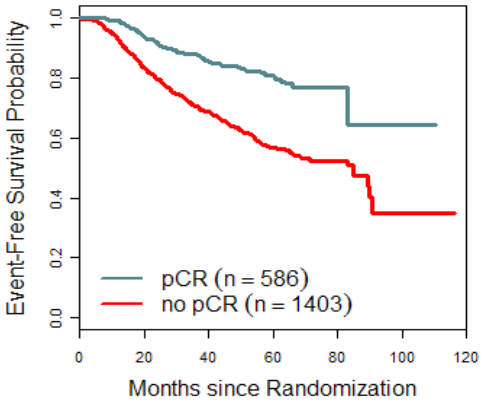
*Nominal p-value

pCR=ypT0/is ypN0



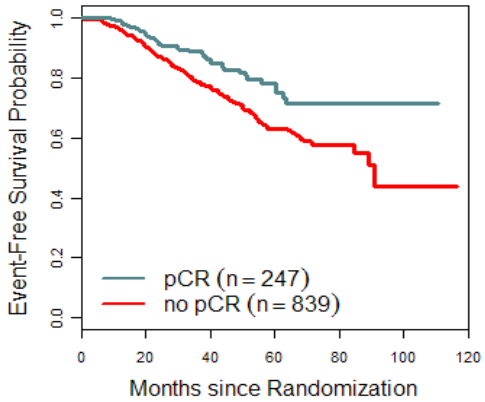


HER2+



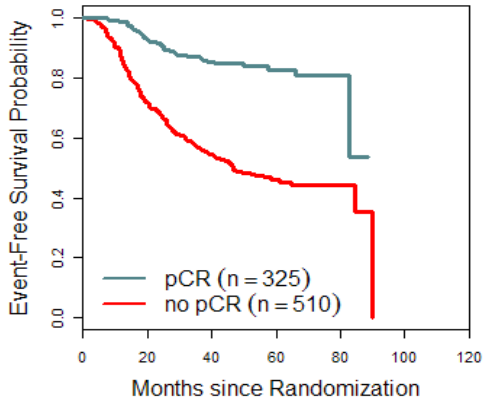
HR=0.39, P* < 0.001

HER2+ HR+



HR=0.58, P* = 0.001

HER2+ HR-



HR=0.25, P* < 0.001

Disease-Free Survival in Neoadjuvant, Adjuvant and Postadjuvant Studies of HER2-Positive Breast Cancer by Hormone Receptor (HR) Status

	DFS (hazard ratio)	
	HR-negative	HR-positive
NEOSPHERE[1]	0.60*	0.86*
TEACH[2]	0.68	0.98
N9831/B-31[3]	0.62	0.61
APHINITY[4]	0.76	0.86
ExteNET[5]	0.95	0.60

* Progression-free survival

1 Gianni L et al. *Lancet Oncol* 2016;17(6):791-800 (Appendix).
2 Goss PE et al. *Lancet Oncol* 2013;14(1):88-96.
3 Perez EA et al. *J Clin Oncol* 2014;32(33):3744-52.
4 von Minckwitz G et al. *N Engl J Med* 2017;377(2);122-31.
5 Jimenez MM et al. *Proc ESMO* 2017;Abstract 149O.