16TH ANNUAL MIAMI CANCER MEETING (MCM)
MARCH 29-31, 2019
MIAMI, FL

ANTI-HER2 THERAPIES IN BREAST CANCER: ADJUVANT AND NEOADJUVANT.

MICHEL VELEZ, MD

DISCLOSURES

- Puma Biotechnology Speakers Bureau, Consultant
- Novartis Consultant Advisory Board
- Agendia Consultant Advisory Board

GOALS OF THERAPY

- **Neoadjuvant:**

  Assess in vivo chemo sensitivity

  Improve rates of BCS

  Decrease rates of Axillary LN dissection

  Prognostic on ER- Her2 positive

  Predict benefit of additional adjuvant therapy

- **Adjuvant:**

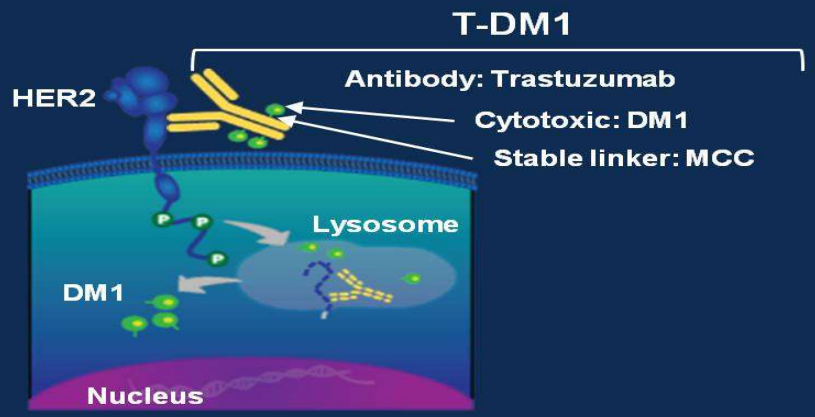
  Decrease disease relapse local vs distant

APPROVED THERAPIES HER2NEU POSITIVE EBC:

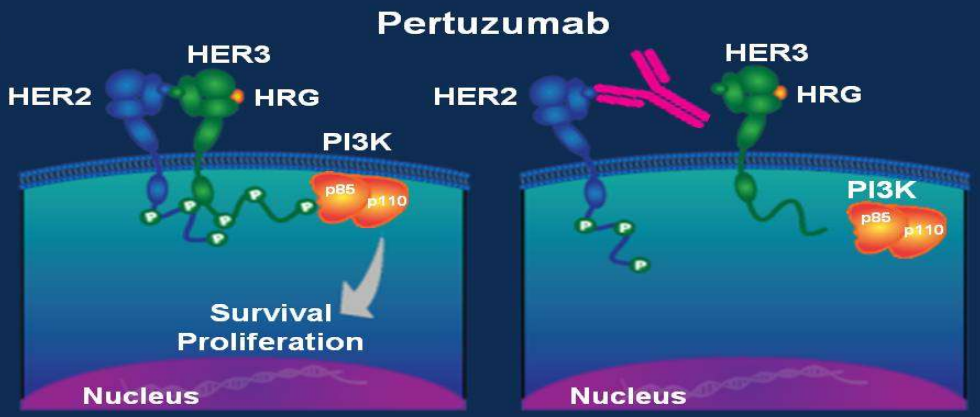
- Chemotherapy (Taxanes, Anthracyclines, Platinum salts)
- Trastuzumab
- Pertuzumab
- Neratinib

- Future expected approval: TDM-1

T-DM1 and Pertuzumab Mechanisms of Action



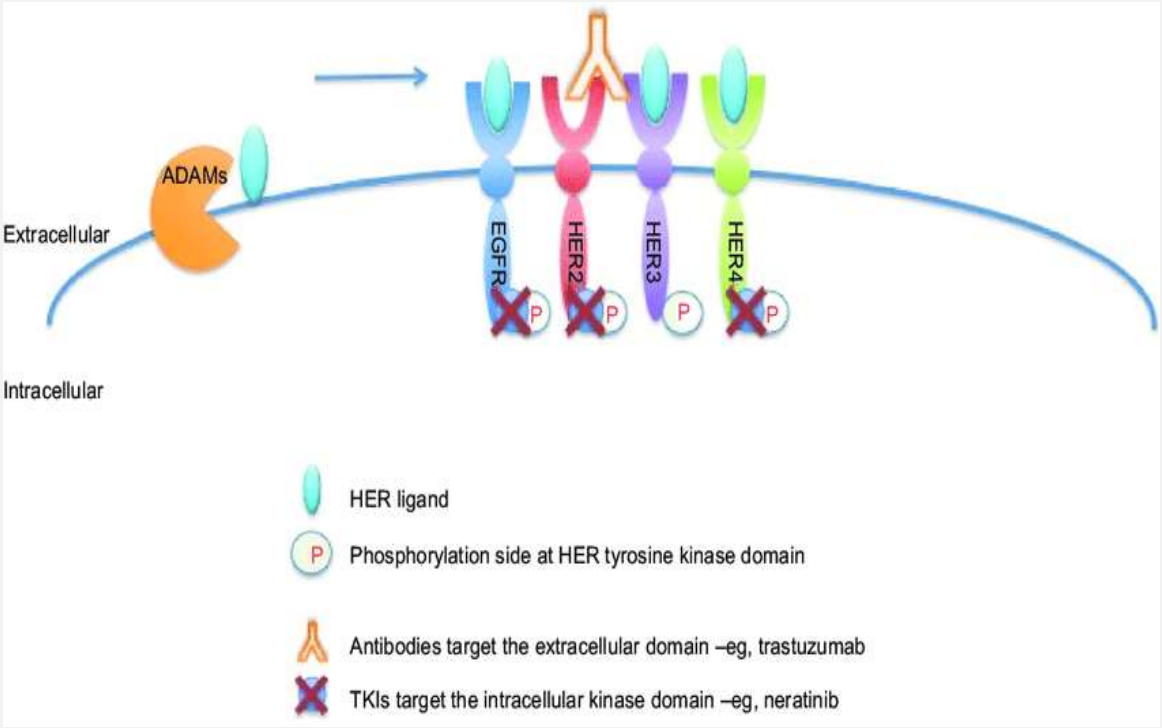
- Antibody–drug conjugate
- Induces cell death by inhibiting microtubule polymerization[1]
- Inhibits HER2 signaling[2]
- Activates antibody-dependent cell-mediated cytotoxicity[2]
- Inhibits HER2 shedding[2]



- HER2/HER3 dimerization inhibitor
- Inhibits ligand-dependent HER2 dimerization and signaling[3]
- Activates antibody-dependent cell-mediated cytotoxicity[4]

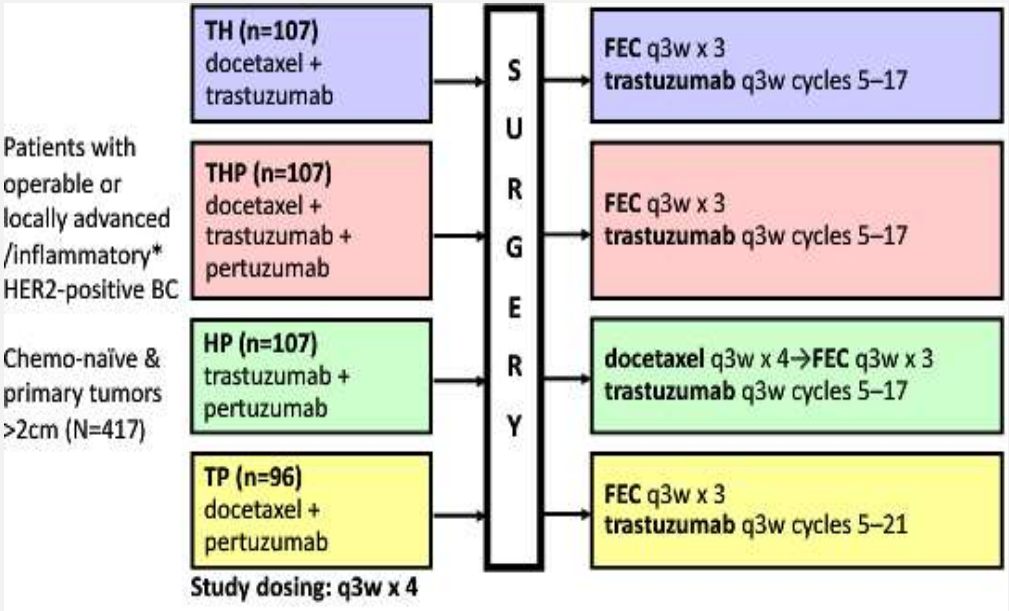
1. Lewis Phillips, *Cancer Res* 2008; 2. Junttila, *Breast Cancer Res Treat* 2010; 3. Baselga, *Nature Rev Cancer* 2009; 4. Scheuer, *Cancer Res* 2009.

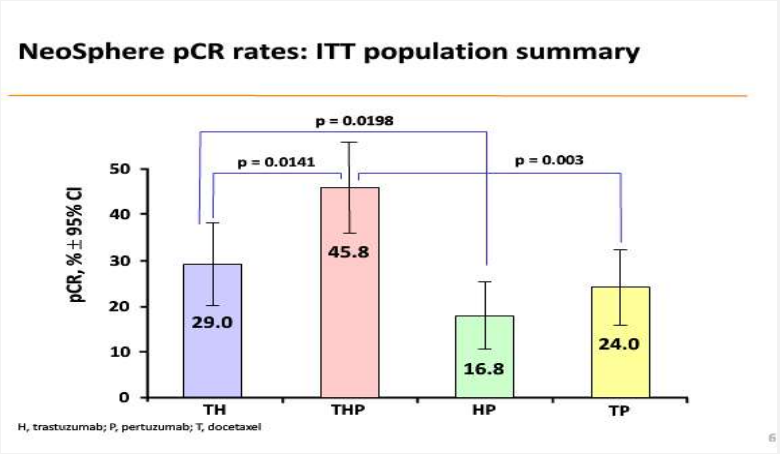
Mechanism of Action of Neratinib

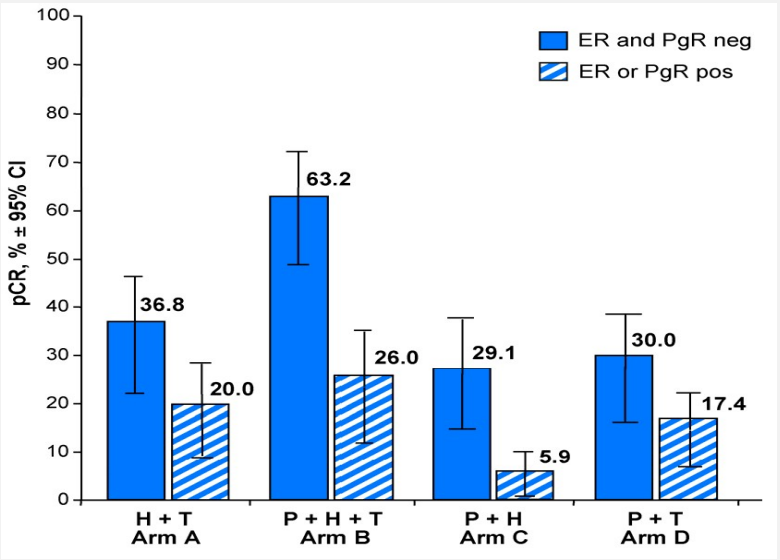


- **Low-molecular-weight, irreversible, pan-HER inhibitor (ErB 1,2,4)**
- **Interferes with ligand-induced dimerization of HER receptors**
- **Disrupts previously formed receptor dimers**
- **Blocks downstream signaling**

NeoSphere Phase II

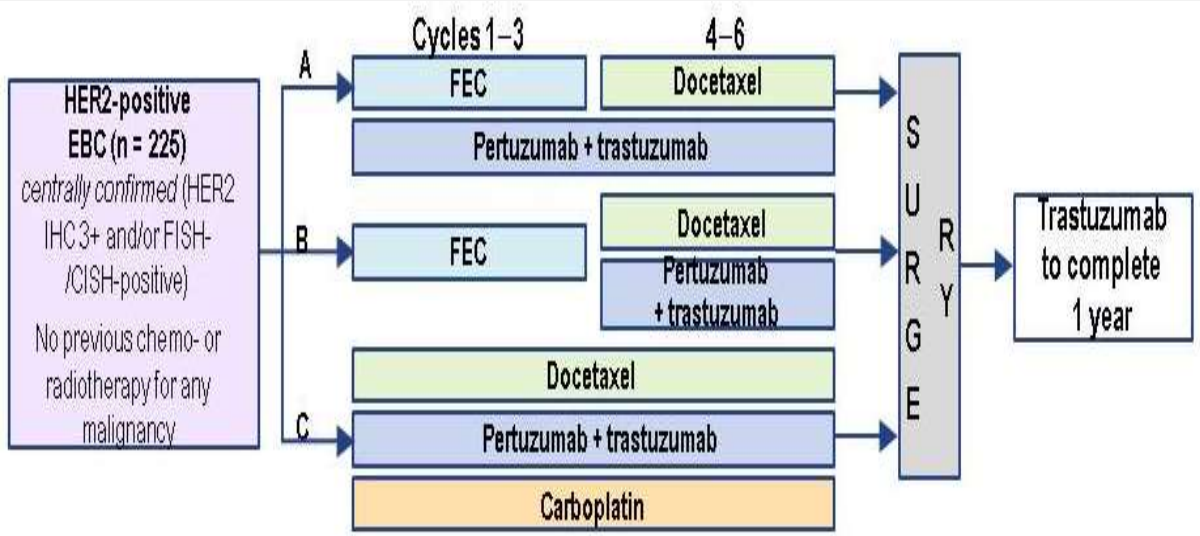


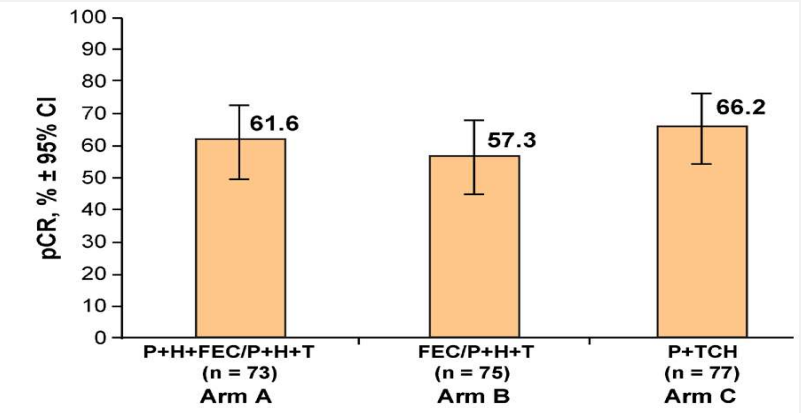


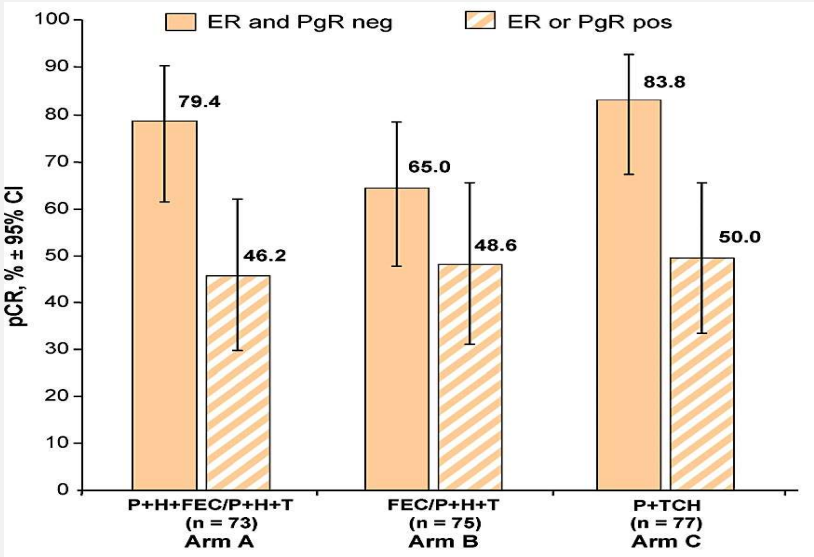


Gianni L et al. Proc SABCS 2010;Abstract S3-2.

TRYPHAENA Phase II





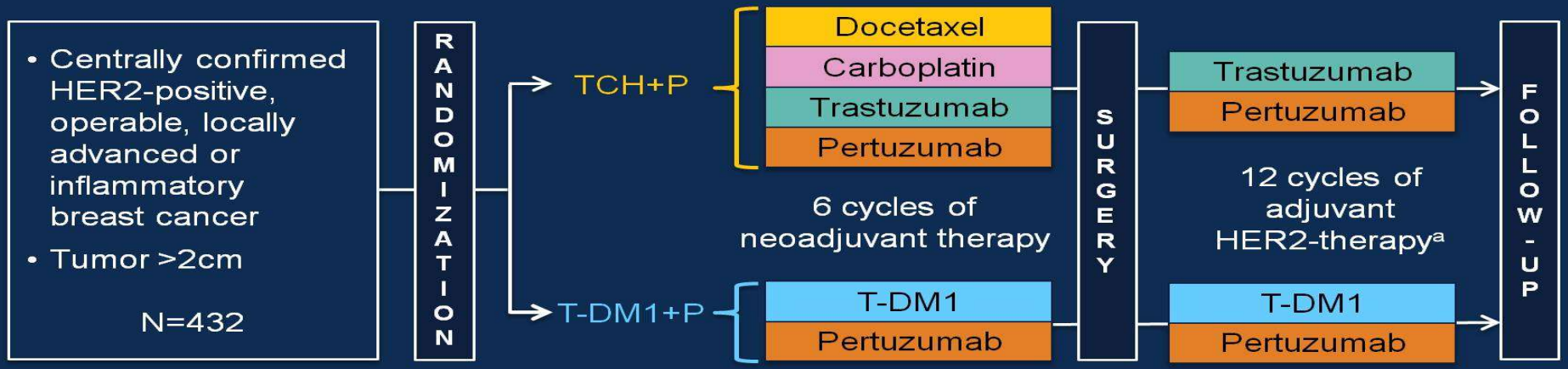


Schneeweiss A, et al. Ann Oncol. 2013 Sep;24(9):2278-84

TRYPHAENA

- 2 pts (2.7% in Arm B) experienced symptomatic LVSD
- 11 patients (Arm A: 4; Arm B: 4; Arm C: 3) had declines in left ventricular ejection fraction of ≥10% points from baseline to <50%.
- Diarrhea was the most common adverse event. Grade 3 (12%) on TCH-P arm.
- No major differences in safety when comparing anthracycline containing vs anthracycline free arms in regards to cardiac safety

KRISTINE Study Design

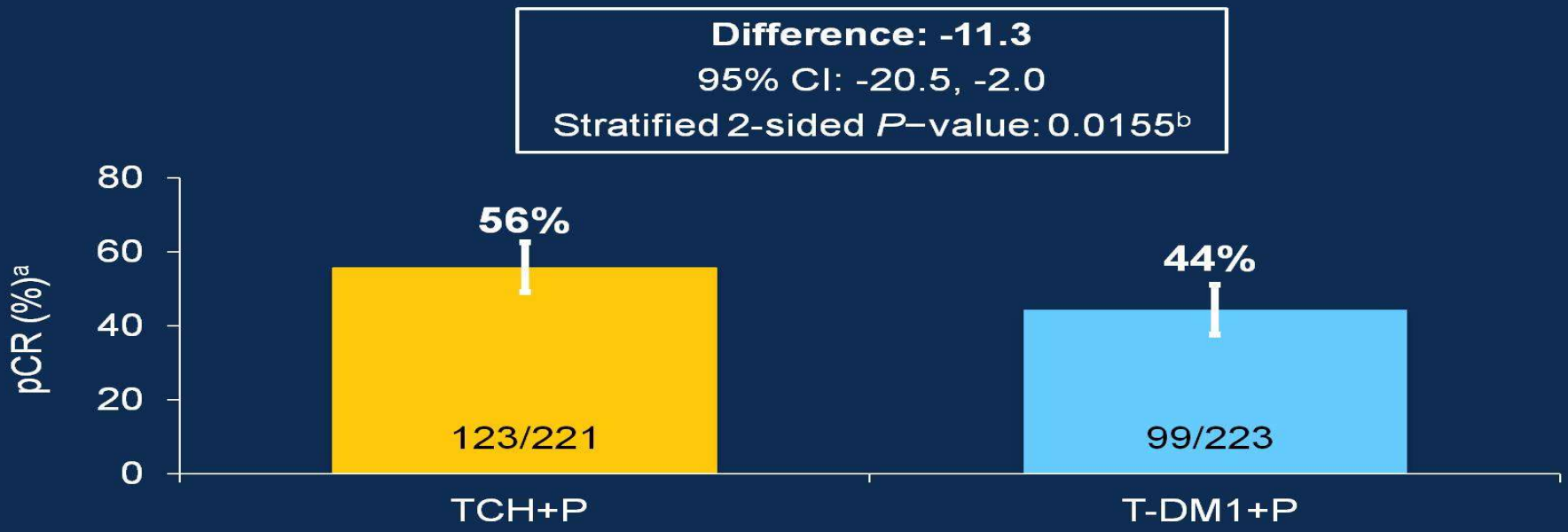


<u>Primary endpoint</u>: pCR by local assessment (ypT0/is, ypN0)

- **Stratification factors:** local HR status, geographic location, and clinical stage at presentation

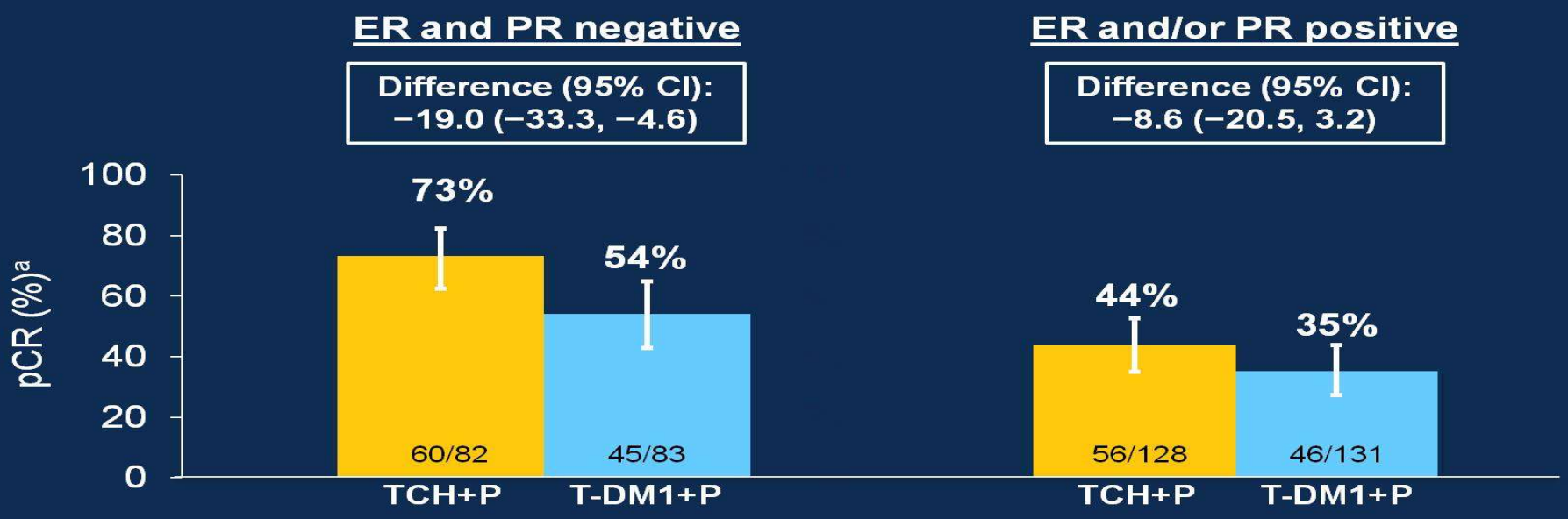
[a]Adjuvant chemotherapy was recommended for patients in the T-DM1+P arm who had residual disease in lymph node(s) or in the breast (>1cm).

Primary Endpoint: pCR (ypT0/is, ypN0)



apCR rate and 95% CI are shown. Patients with missing or unevaluable pCR status were considered nonresponders: TCH+P, 7 (3.2%); T-DM1+P, 18 (8.1%). Treatment discontinuation in the neoadjuvant phase for progressive disease: TCH+P, 0% of patients; T-DM1+P, 7% of patients.
bCochran-Mantel-Haenszel Chi-square.

pCR by Central ER/PR Receptor Status

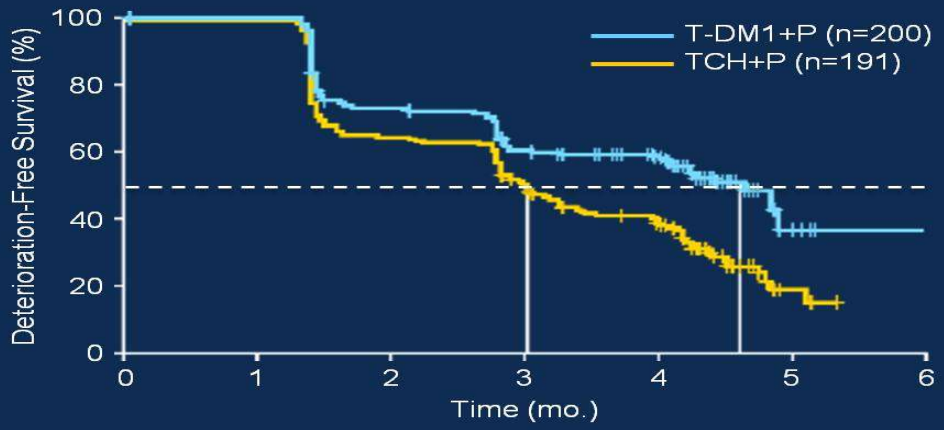


[a]ypT0/is, ypN0; patients with missing or unevaluable pCR status were considered nonresponders. Twenty patients had "unknown" ER/PR status by central analysis.

Maintenance of HRQoL and Physical Function

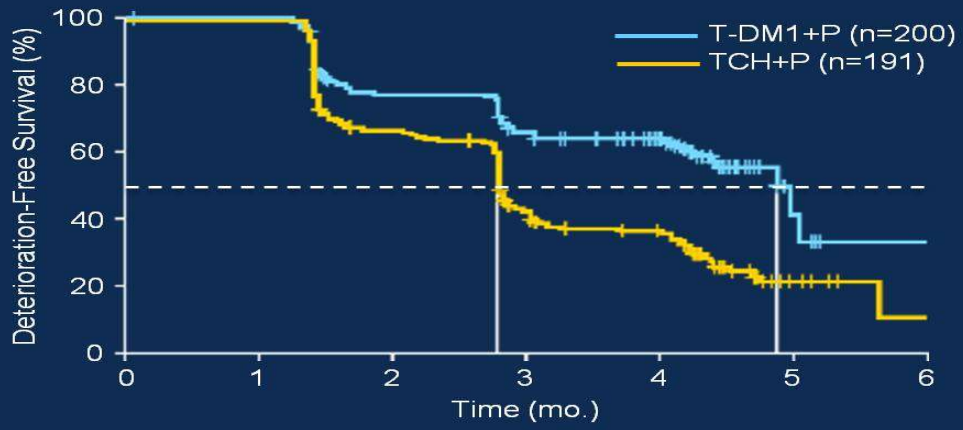
Maintenance of HRQoL[a]

HR (95% CI): 0.60 (0.46–0.78)



Maintenance of physical function[a]

HR (95% CI): 0.47 (0.36–0.62)



[a]Data are based on the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and QLQ-modified breast cancer module (BR23). Maintenance of health-related quality of life (HRQoL) and physical function were assessed as the time to deterioration defined as the time from baseline to first 10-point (or greater) decrease.

Only data from the neoadjuvant treatment phase including pre-surgery visit are used. Patients of the ITT population with a baseline assessment and at least 1 post-treatment assessment are included in this analysis.

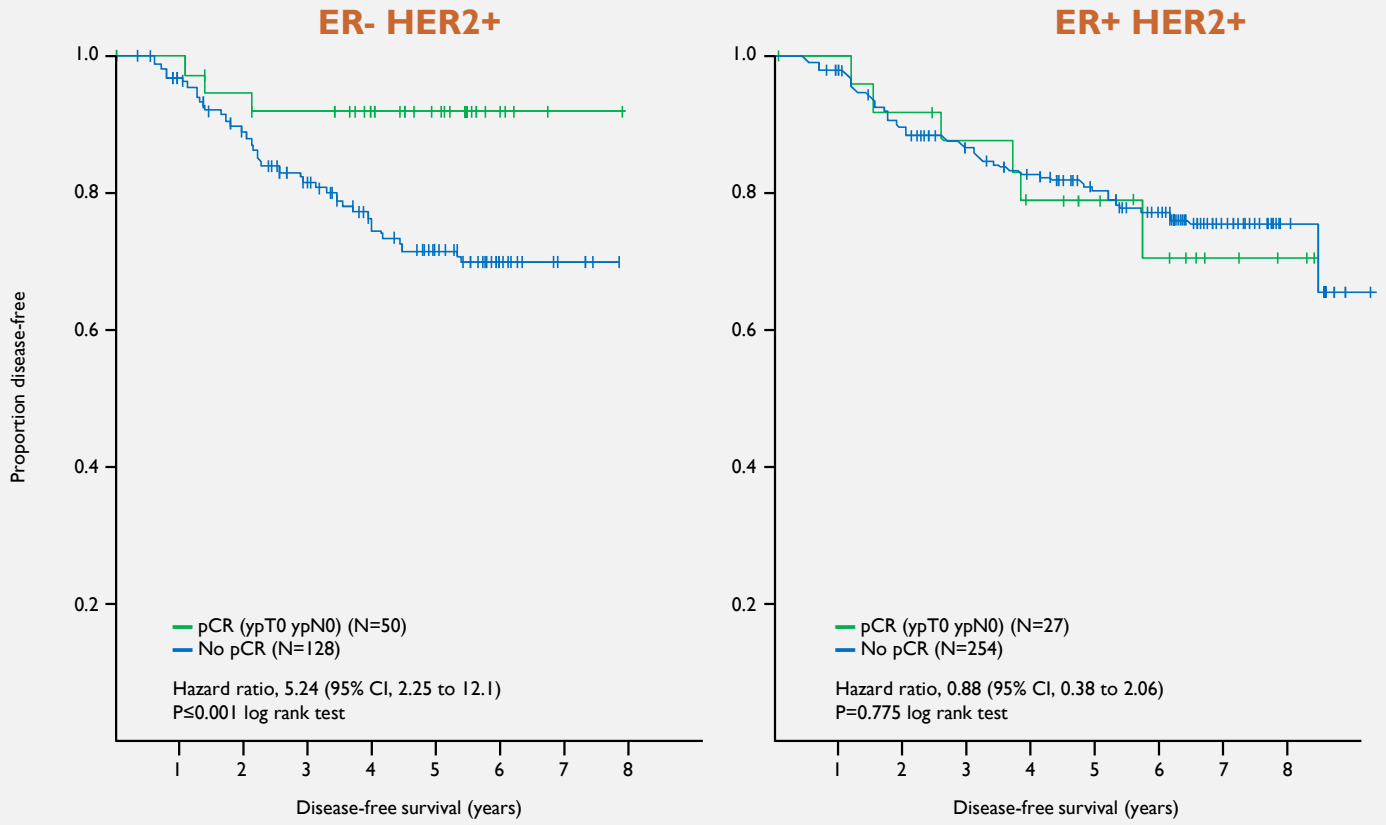
Treatment Exposure and Overview of Adverse Events: Neoadjuvant Phase

	TCH+P (n=219)[a]	T-DM1+P (n=223)[a]
Median number of cycles (min–max)	6 (1–6)	6 (2–6)
Any adverse event, %	98.6	88.3
Serious adverse event, %	28.8	4.9
Grade ≥3 adverse event, %	64.4	13.0
Adverse event leading to treatment discontinuation of any component, %	8.7	3.1
LVEF <50% and ≥10% points decrease from baseline, %	0.5	0.4

- Serious adverse events occurring in ≥1% of patients in the TCH+P arm: febrile neutropenia (12%), neutropenia (3%), diarrhea (4%), vomiting (1.8%), colitis (1%), and neutrophil count decreased (1%).
- No single serious adverse event occurred in ≥1% of patients in the T-DM1+P arm.

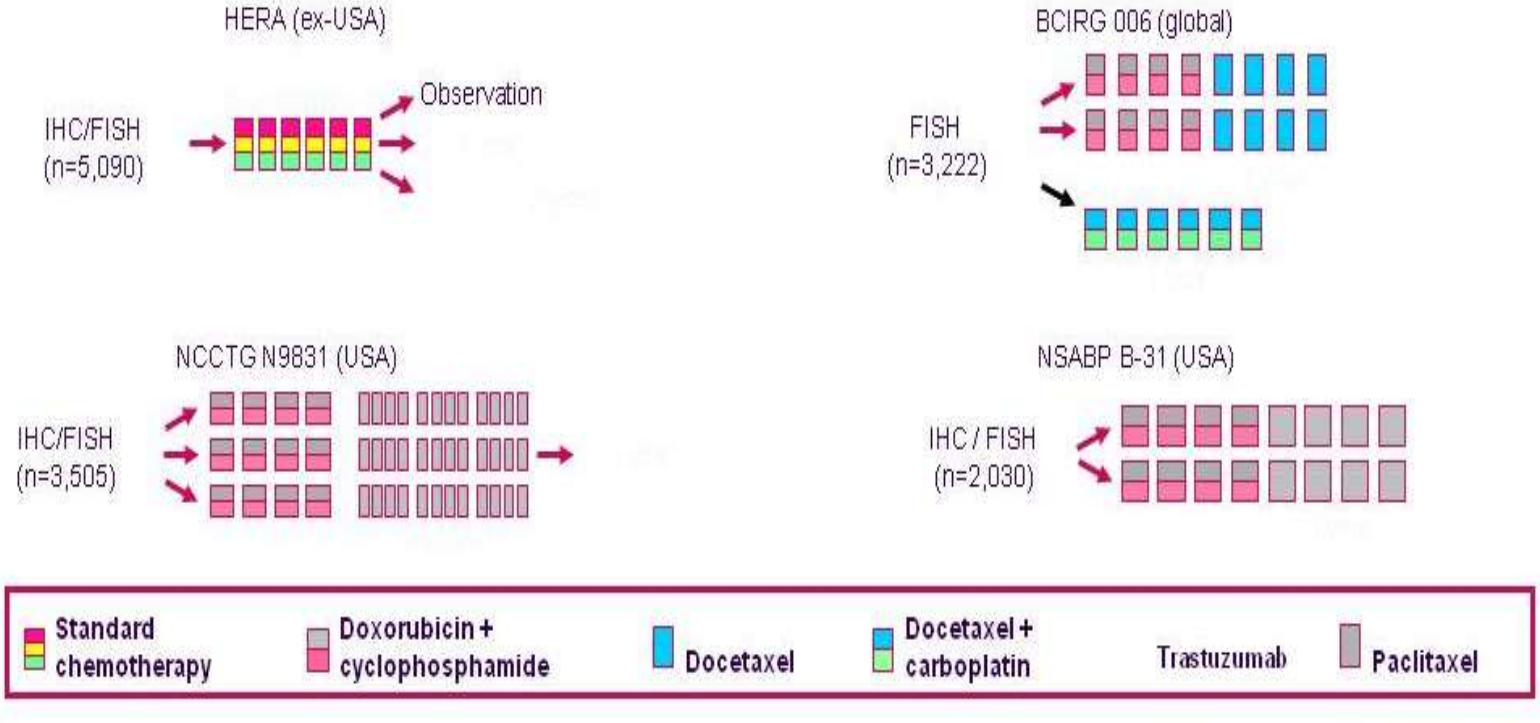
[a]Safety population.
LVEF, left ventricular ejection fraction.

IN HER2+ DISEASE, PCR IS PROGNOSTIC IN ER- BUT NOT ER+



von Mitchwitz SABCS 2011

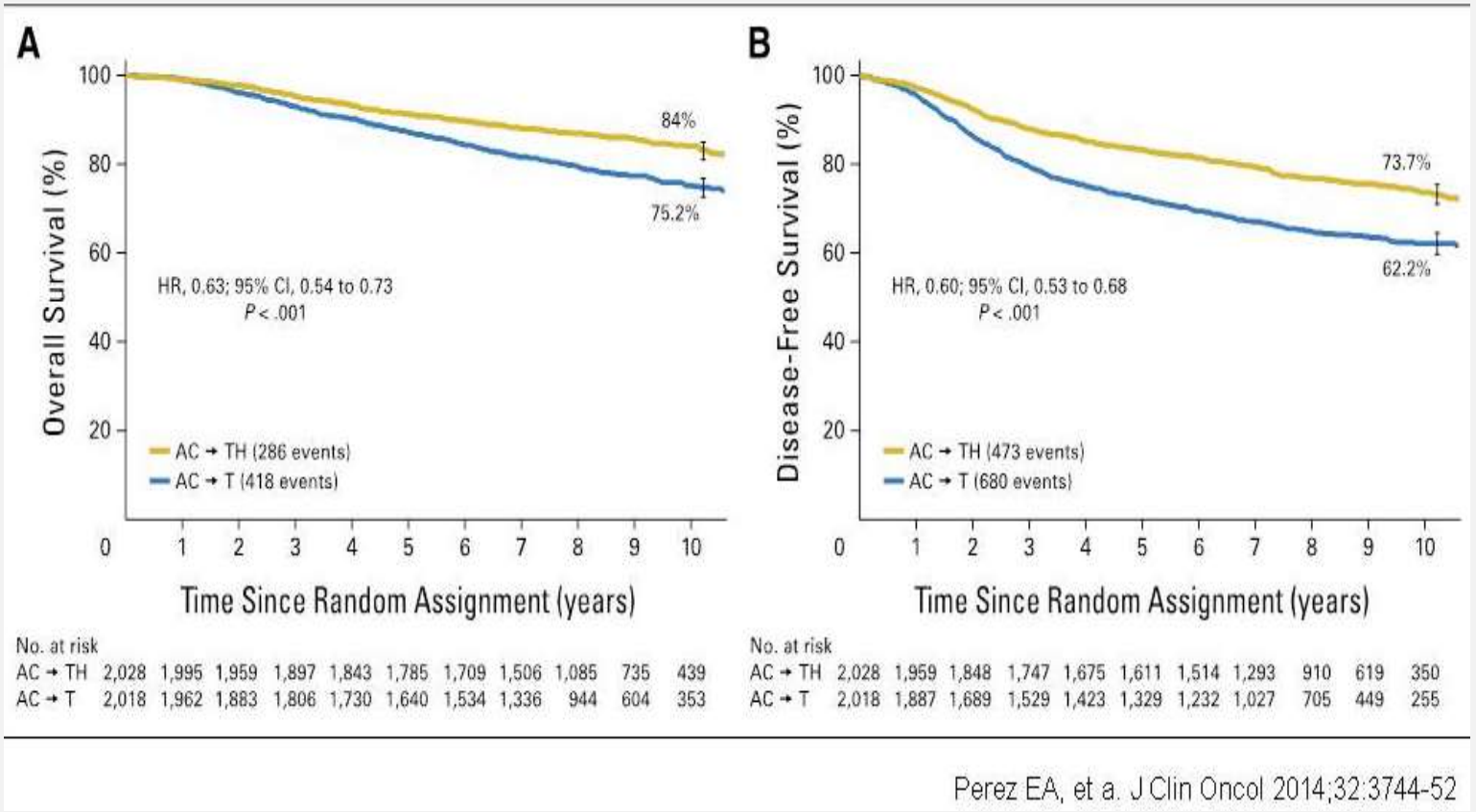
ADJUVANT TRASTUZUMAB TRIALS 2005



FISH = fluorescence *in situ* hybridization

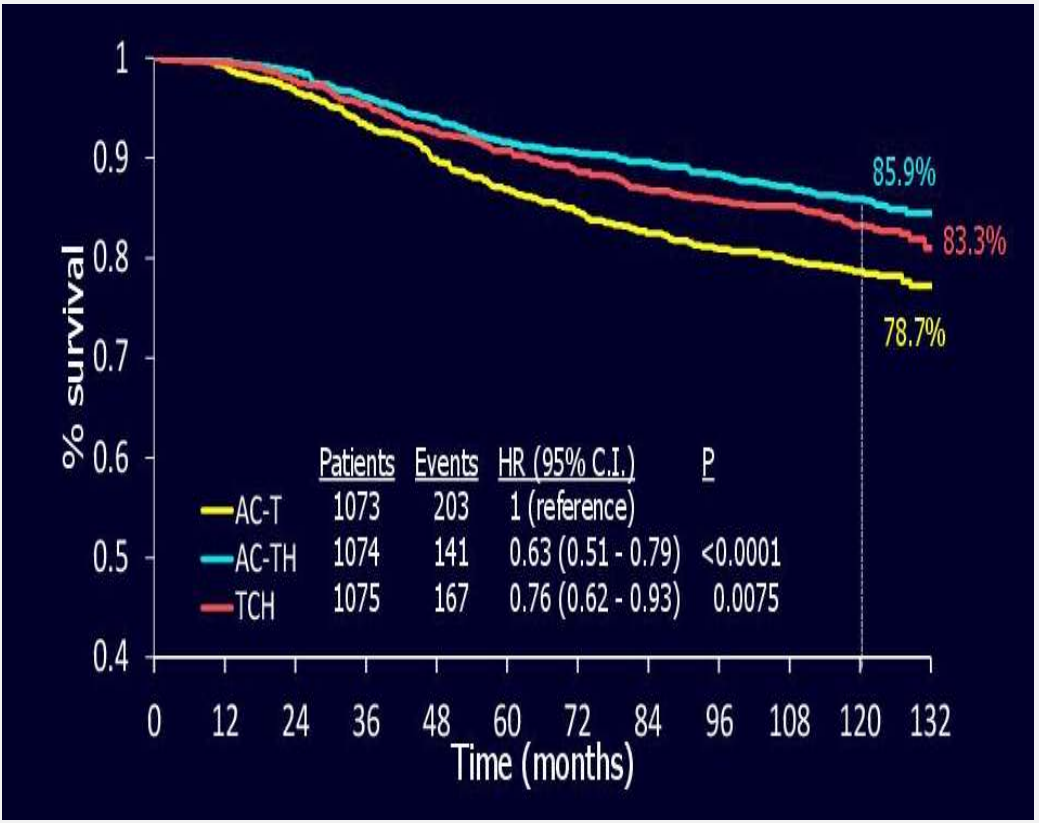
Romond *et al. N Engl J Med* 2005;
Piccart-Gebhart *et al. N Engl J Med* 2005;
Slamon *et al.* SABCS 2006

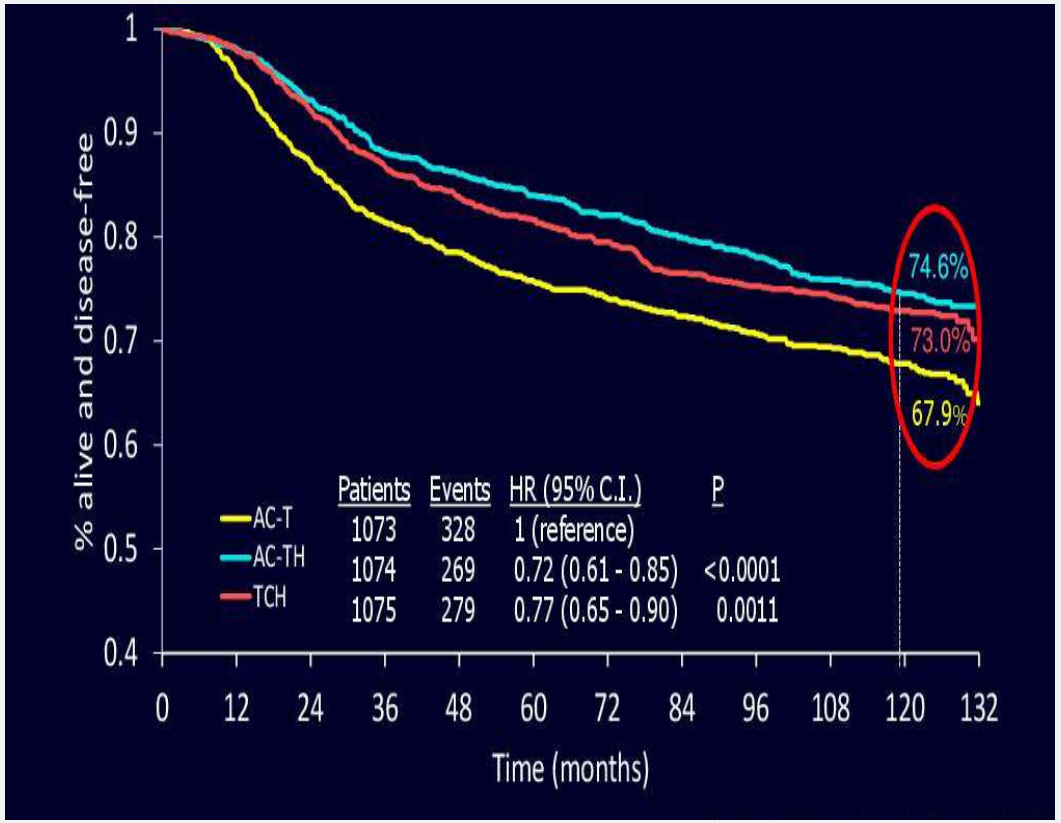
JOINT ANALYSIS NSABP B31 AND NCCTG 9831: 8.4 YEARS MEDIAN F/U



Perez EA, et a. J Clin Oncol 2014;32:3744-52

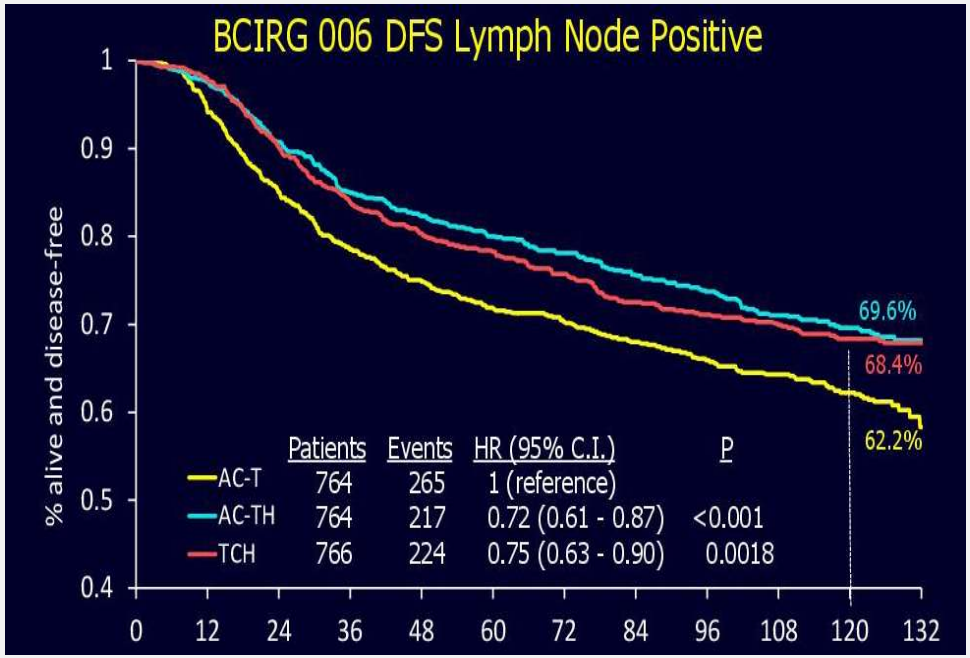
BCIRG-006 DFS/OS ANALYSIS (10.3 YRS)

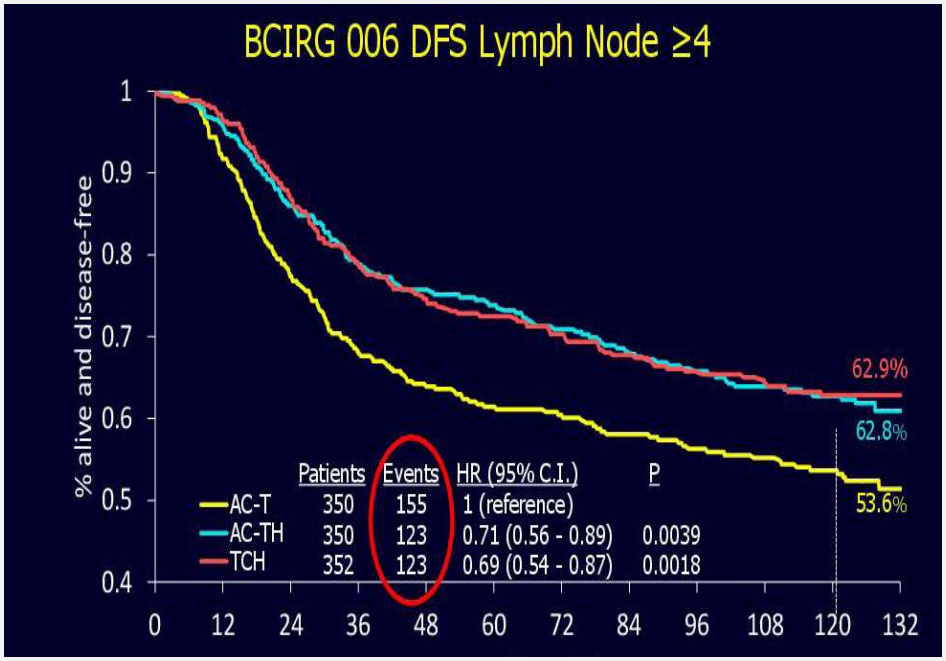




Slamon, et al. SABCS 2015

BCIRG 006 DFS ACCORDING TO LN STATUS



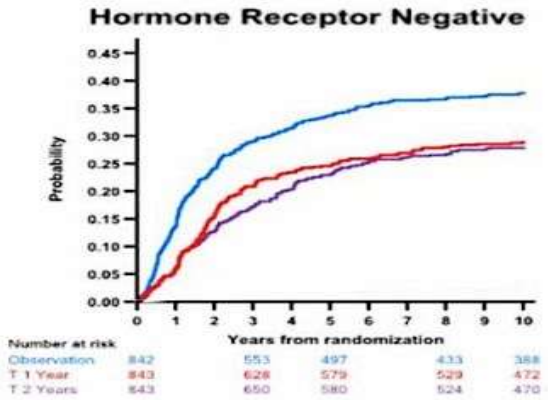


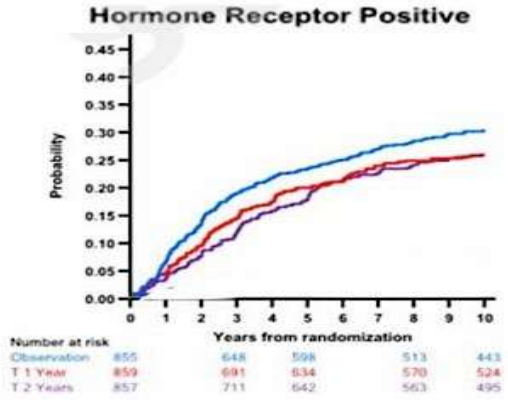
	AC-T N=1,050	AC-TH N=1,068	TCH N=1,056
Cardiac left ventricular function (CHF) Grade 3/4	8	21	4
Acute Leukemia	6	2	1

Slamon, et al. SABCS 2015

HERA Trial Final Analysis (10-Year Follow-Up)

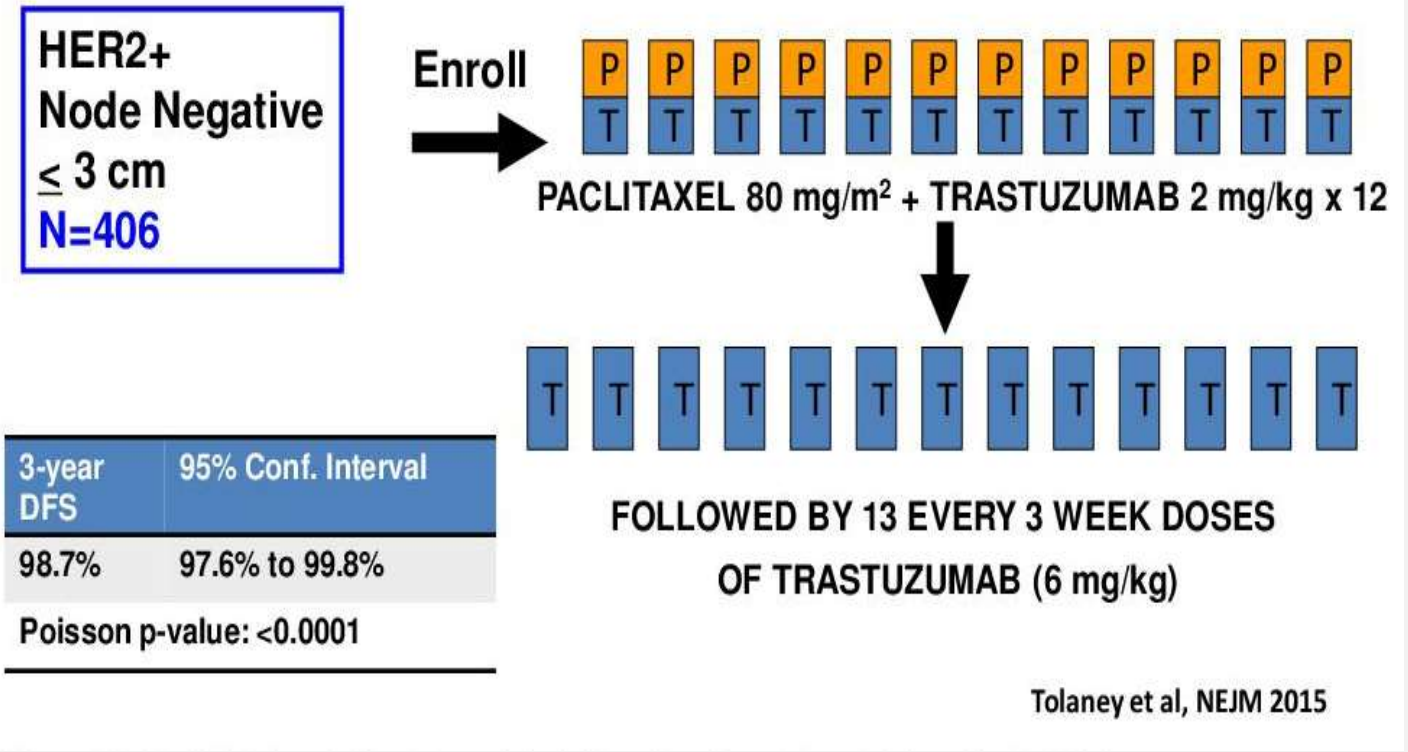
DFS (Breast Cancer Events)





Clinical benefit of trastuzumab is seen in both the HR-positive and HR-negative cohort; however, the timing and rate of DFS events appears different among these cohorts

APT (ADJUVANT PACLITAXEL AND TRASTUZUMAB)TRIAL



3-year DFS	95% Conf. Interval
98.7%	97.6% to 99.8%

Poisson p-value: <0.0001

Tolaney et al, NEJM 2015

Patient Characteristics

		N	%
Age			
<50		132	33
50-70		233	57
≥70		41	10
Size of Primary Tumor			
T1a	≤0.5 cm	77	19
T1b	>0.5-≤1.0	124	31
T1c	>1.0-≤2.0	169	42
T2	>2.0-≤3.0	36	9
Histologic Grade			
I	Well differentiated	44	11
II	Moderately differentiated	131	32
III	Poorly differentiated	228	56
HR Status (ER and/or PR)			
Positive		272	67
Negative		134	33

Disease-Free Survival Events

DFS Event: 7 years	N (%)	Time to event (months)
Any recurrence or death	23 (5.7)	
Local/Regional Recurrence*	5 (1.2)	
Ipsilateral axilla (HER2+)	3	12, 20, 54
Ipsilateral breast (HER2+)	2	37, 65
New Contralateral Primary Breast Cancer	6 (1.5)	
HER2+	1	56
HER2-	3	12, 37, 59
Unknown HER2	2	84, 90
Distant Recurrence	4 (1.0)	27, 46, 59 ,63
Death		
Non-breast cancer related	8 (2.0)	13, 50, 59, 65, 67, 69, 71, 71

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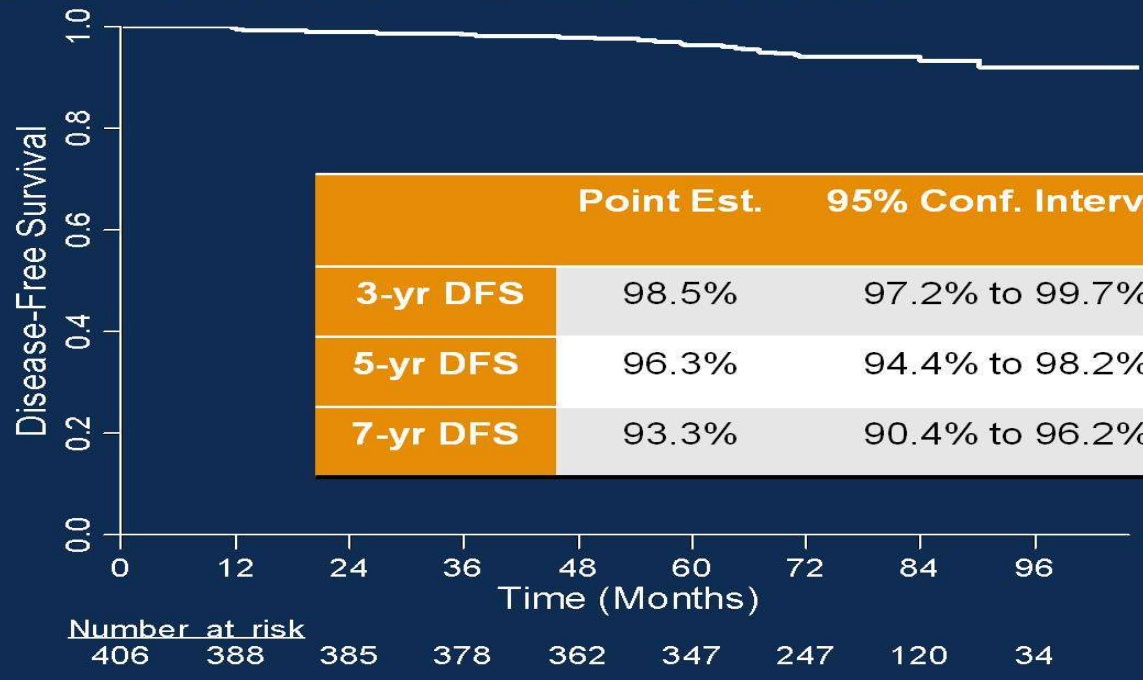
Disease-Free Survival



	Point Est.	95% Conf. Interval	No. of events
3-yr DFS	98.5%	97.2% to 99.7%	6
5-yr DFS	96.3%	94.4% to 98.2%	14
7-yr DFS	93.3%	90.4% to 96.2%	23

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Recurrence Free Interval

RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

	Point Est.	95% Conf. Interval	No. of events
3-yr RFI	99.2%	98.4% to >99.9%	3
5-yr RFI	98.1%	96.8% to 99.5%	7
7-yr RFI	97.5%	95.9% to 99.1%	9

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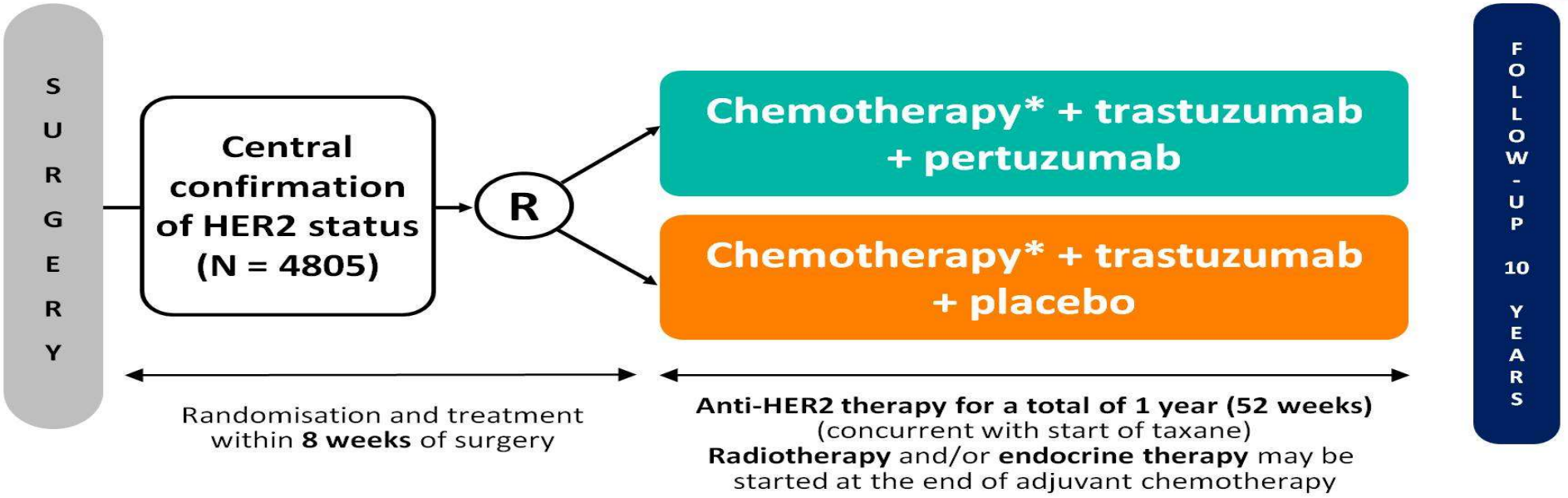
APHINITY: Trial Design



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

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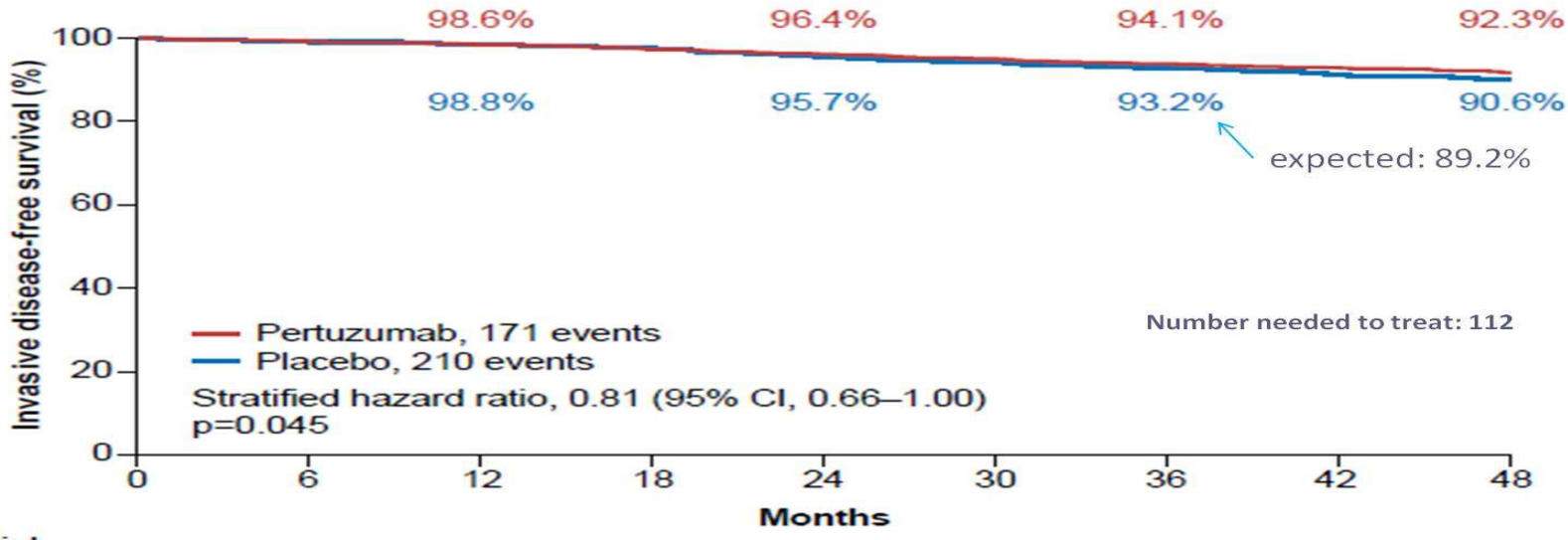
Breast International Group

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

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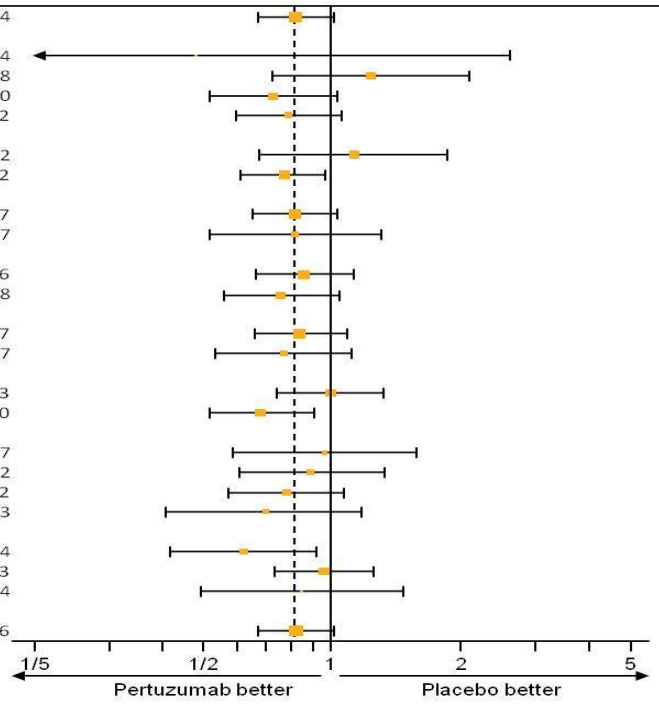
APHINITY: Summary of first Occurrence of an IDFS Event

	Pertuzumab n=2400	Placebo n=2404
Total patients with IDFS event, n (%)	171 (7.1)	210 (8.7)
Category of first IDFS event, n (%)		
Distant recurrence	112 (4.7)	139 (5.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without prior event	28 (1.2)	26 (1.1)
Site of first distant recurrence n (%)		
Lung/liver/pleural effusion	43 (1.8)	61 (2.5)
CNS	46 (1.9)	45 (1.9)
Other	9 (0.4)	9 (0.4)
Bone	21 (0.9)	30 (1.2)

APHINITY: IDFS Forest Plot by Subgroups

Subgroup	No. of Events / No. of Patients: Pertuzumab	No. of Events / No. of Patients: Placebo	Unstratified Hazard Ratio (95%CI)	3-year IDFS Rate, %: Pertuzumab	3-year IDFS Rate, %: Placebo	Interaction test p-value
All patients	171 / 2400	210 / 2404	0.82 (0.67–1.00)	94.1	93.2	NA
Nodal status						
0 positive nodes, tumor ≤1cm	2 / 90	4 / 84	0.48 (0.09–2.60)	97.7	97.5	
0 positive nodes, tumor >1cm	30 / 807	25 / 818	1.23 (0.72–2.10)	97.5	98.5	0.374
1–3 positive nodes	55 / 907	75 / 900	0.73 (0.52–1.04)	94.9	93.8	
≥4 positive nodes	84 / 596	106 / 602	0.79 (0.59–1.05)	87.5	84.7	
0 positive nodes	32 / 897	29 / 902	1.13 (0.68–1.86)	97.5	98.4	0.169
≥1 positive nodes	139 / 1503	181 / 1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						
Anthracycline	139 / 1865	171 / 1877	0.82 (0.66–1.03)	93.8	93.0	0.996
Non-anthracycline	32 / 535	39 / 527	0.82 (0.51–1.31)	94.9	94.0	
Central hormone receptor status						
Positive (ER- and/or PgR-positive)	100 / 1536	119 / 1546	0.86 (0.66–1.13)	94.8	94.4	0.543
Negative (ER- and PgR-negative)	71 / 864	91 / 858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						
Protocol A	120 / 1828	143 / 1827	0.84 (0.66–1.08)	94.7	94.1	0.686
Protocol Amendment B	51 / 572	67 / 577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						
Pre-menopausal	93 / 1152	96 / 1173	0.99 (0.75–1.32)	93.5	93.7	0.069
Post-menopausal	78 / 1242	113 / 1220	0.68 (0.51–0.91)	94.5	92.7	
Age group (years)						
<40	30 / 326	32 / 327	0.96 (0.59–1.59)	93.4	93.1	
40–49	48 / 708	53 / 702	0.89 (0.60–1.32)	94.5	94.3	0.781
50–64	69 / 1051	91 / 1082	0.78 (0.57–1.07)	94.3	93.3	
≥65	24 / 315	34 / 293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size (cm)						
<2	41 / 977	64 / 944	0.62 (0.42–0.92)	97.0	94.6	
2–<5	108 / 1273	115 / 1283	0.96 (0.74–1.24)	92.5	93.0	0.203
≥5	22 / 147	31 / 174	0.85 (0.49–1.47)	87.5	87.5	
Sex						
Female	171 / 2397	209 / 2396	0.82 (0.67–1.01)	94.1	93.2	NA



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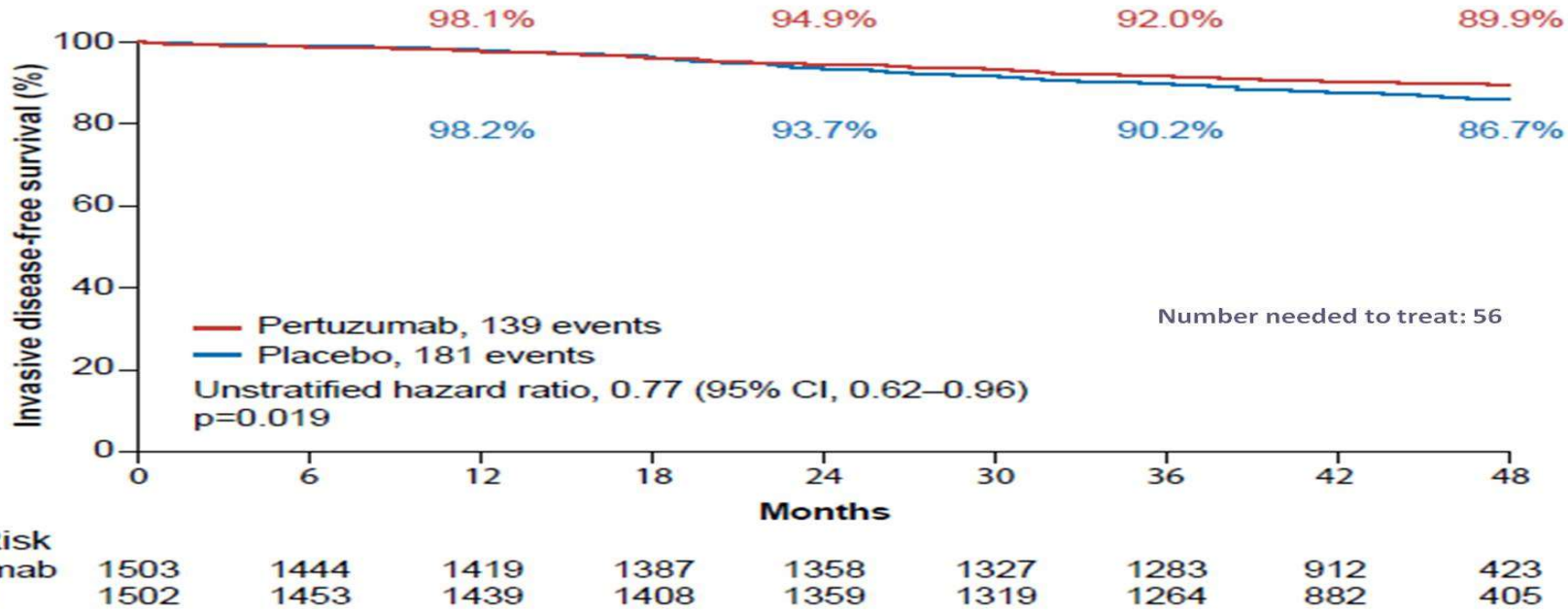
APHINITY: Node-positive Subgroup



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

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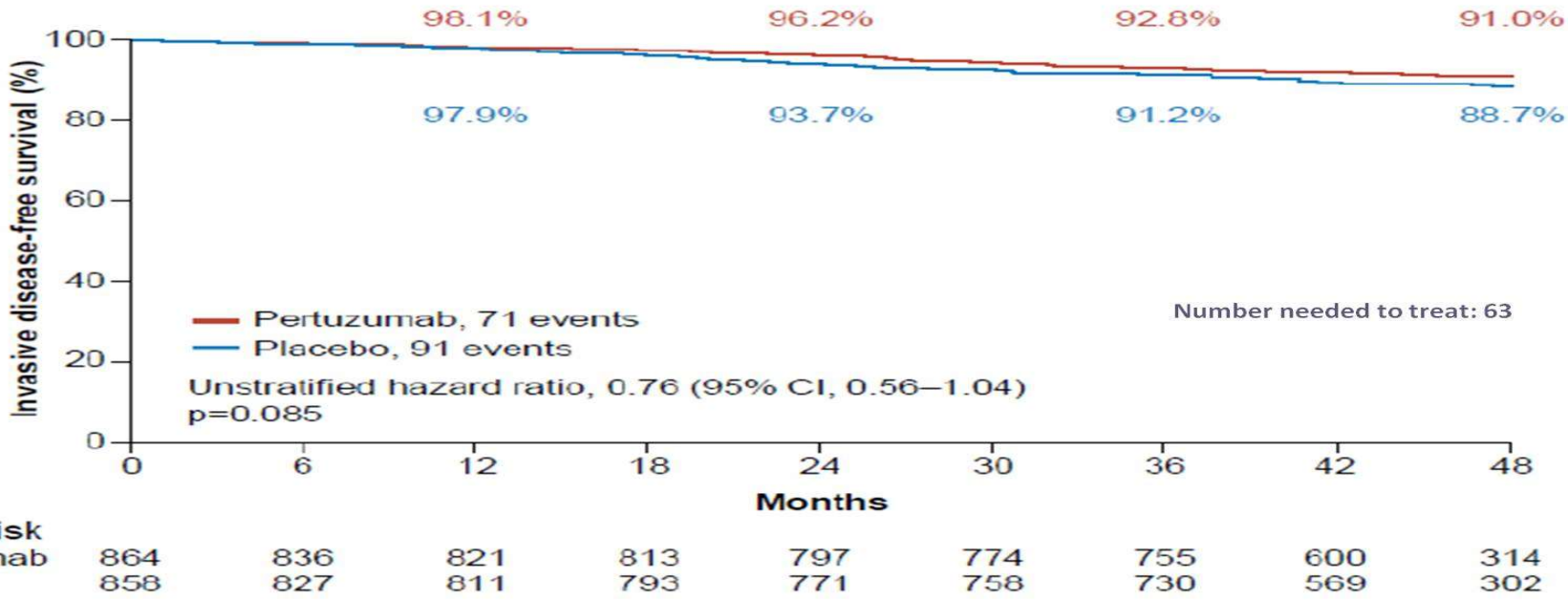
APHINITY: Hormone Receptor-negative Subgroup



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

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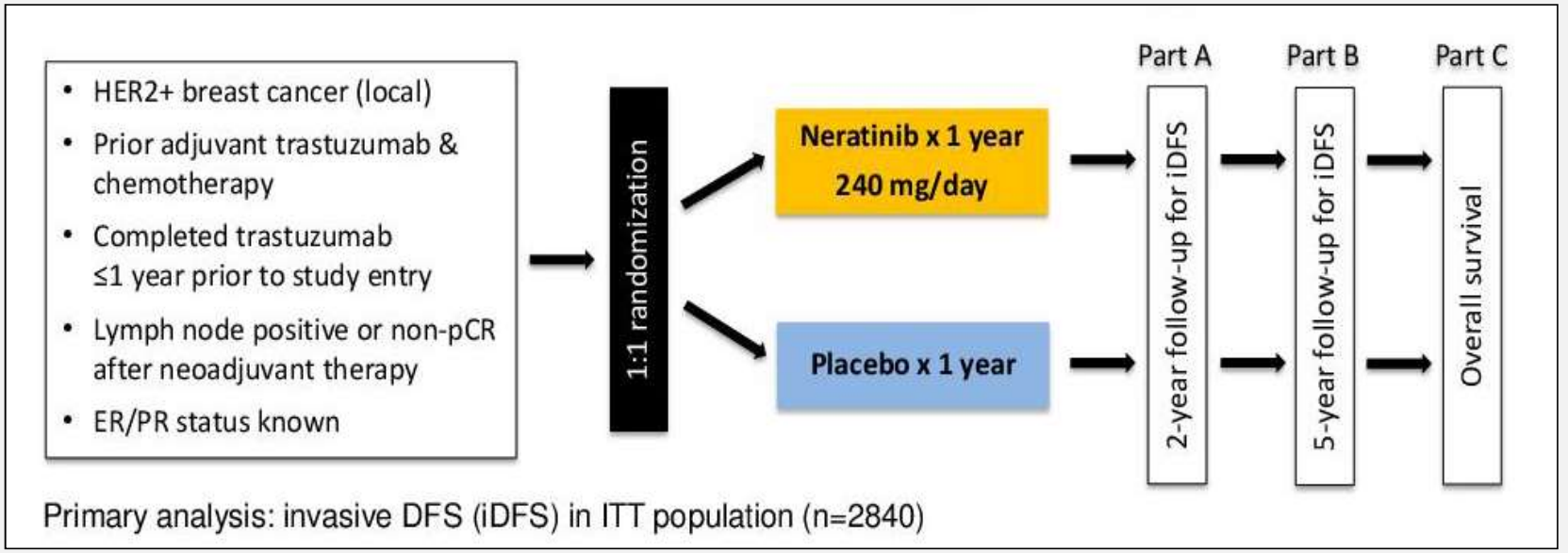
APHINITY: Cardiac Endpoints

N (%)	Pertuzumab n=2364	% Treatment difference (95% CI)	Placebo n=2405
Primary cardiac endpoint	**17 (0.7)**	**0.4 (0.0, 0.8)**	**8 (0.3)**
• Heart failure NYHA III/IV + LVEF drop* • Cardiac death**	15 (0.6) 2 (0.08)		6 (0.2) 2 (0.08)
• Recovered according to LVEF	7		4
Secondary cardiac endpoint Asymptomatic or mildly symptomatic LVEF drop*	**64 (2.7)**	**-0.1 (-1.0, 0.9)**	**67 (2.8)**

*LVEF drop = ejection fraction drop ≥10% from baseline AND to below 50%;
**Identified by the Cardiac Advisory Board for the trial according to a prospective definition

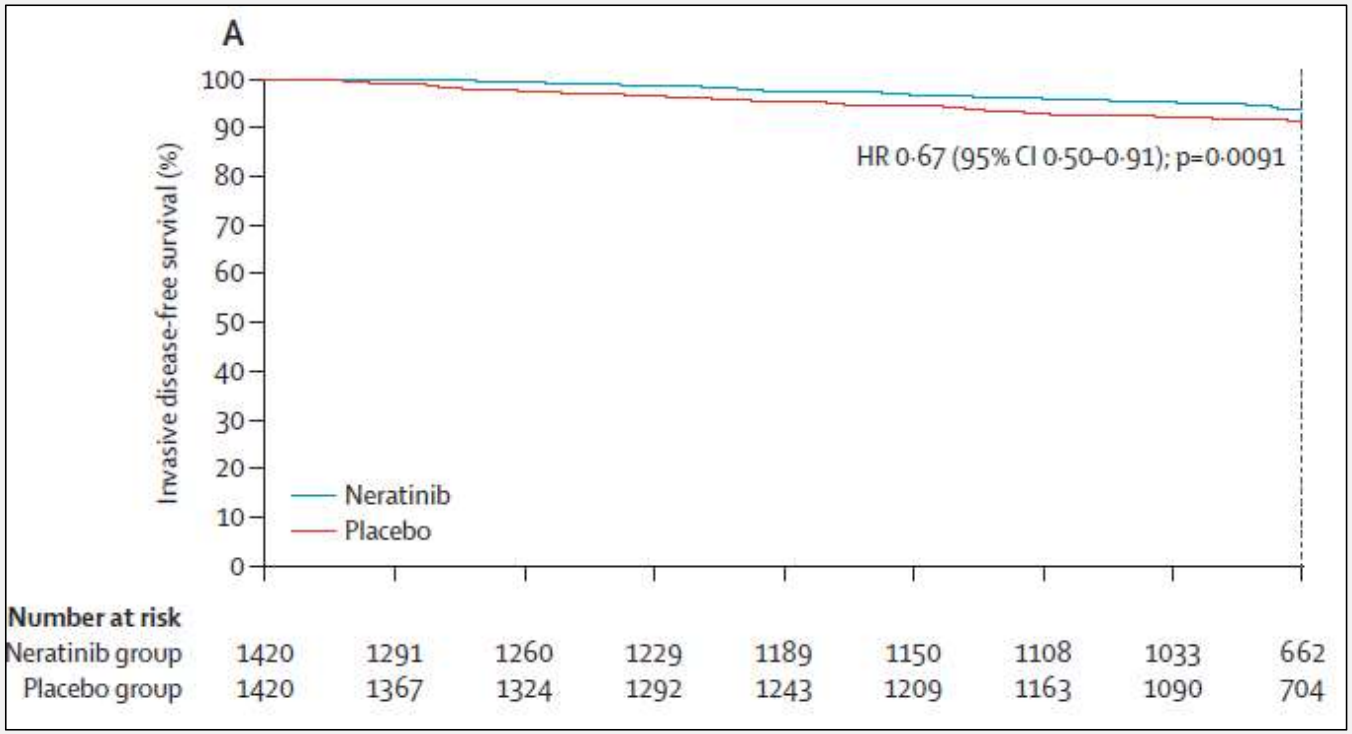
BIG
Breast International Group

EXTENET : FINAL STUDY DESIGN



Chan A, et al. Lancet Oncol 2016

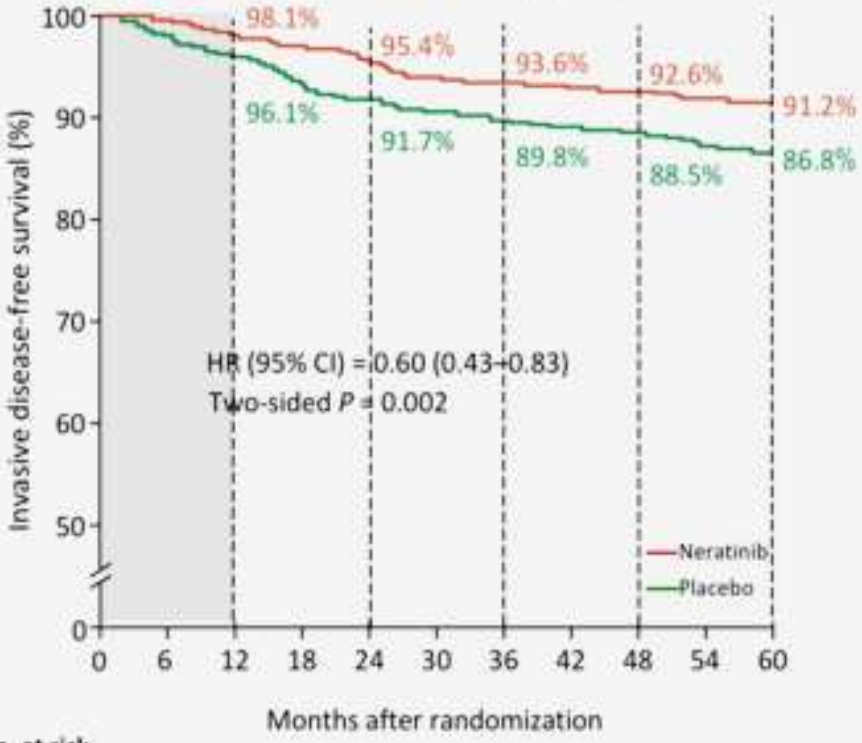
EXTENET:IDFS ITT POPULATION



Chan A, et al. Lancet Oncol 2016

ExteNET: iDFS by hormone receptor status

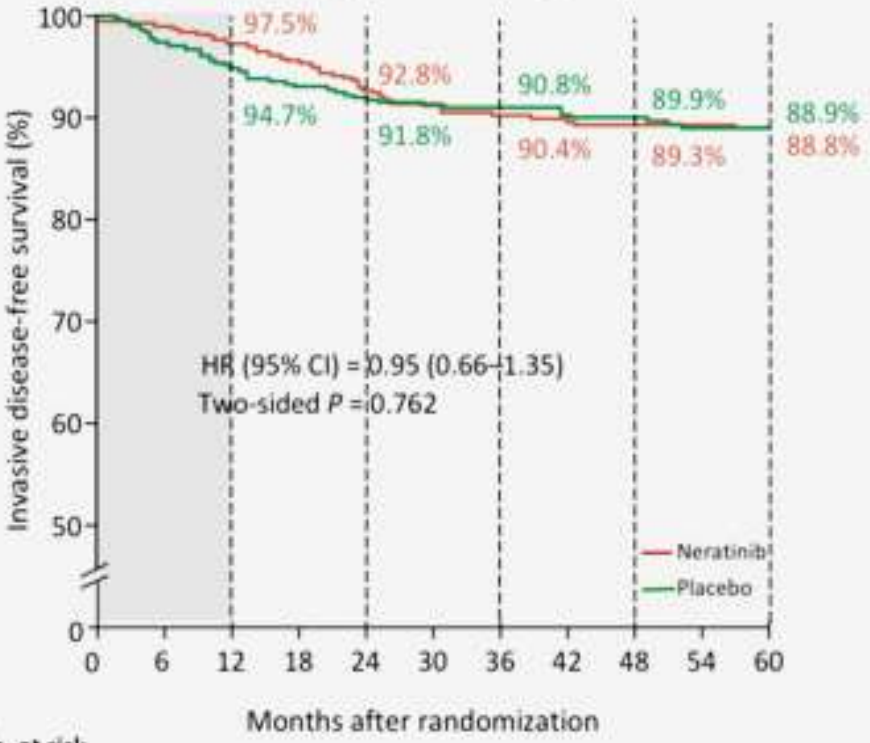
HR-positive subgroup



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

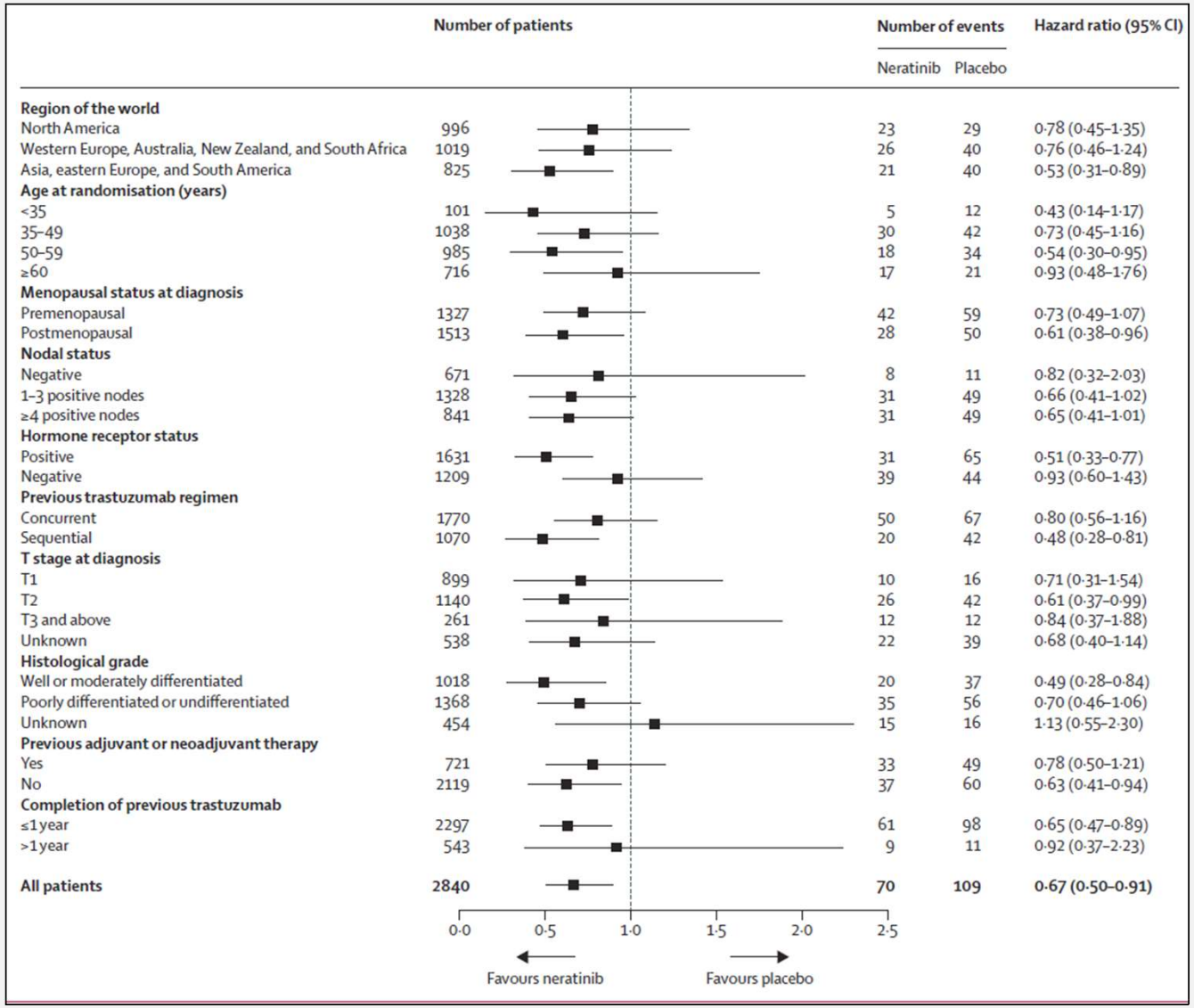
HR-negative subgroup



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



Chan A. et al. Lancet Oncol 2016

EXTENET: ADVERSE EVENTS

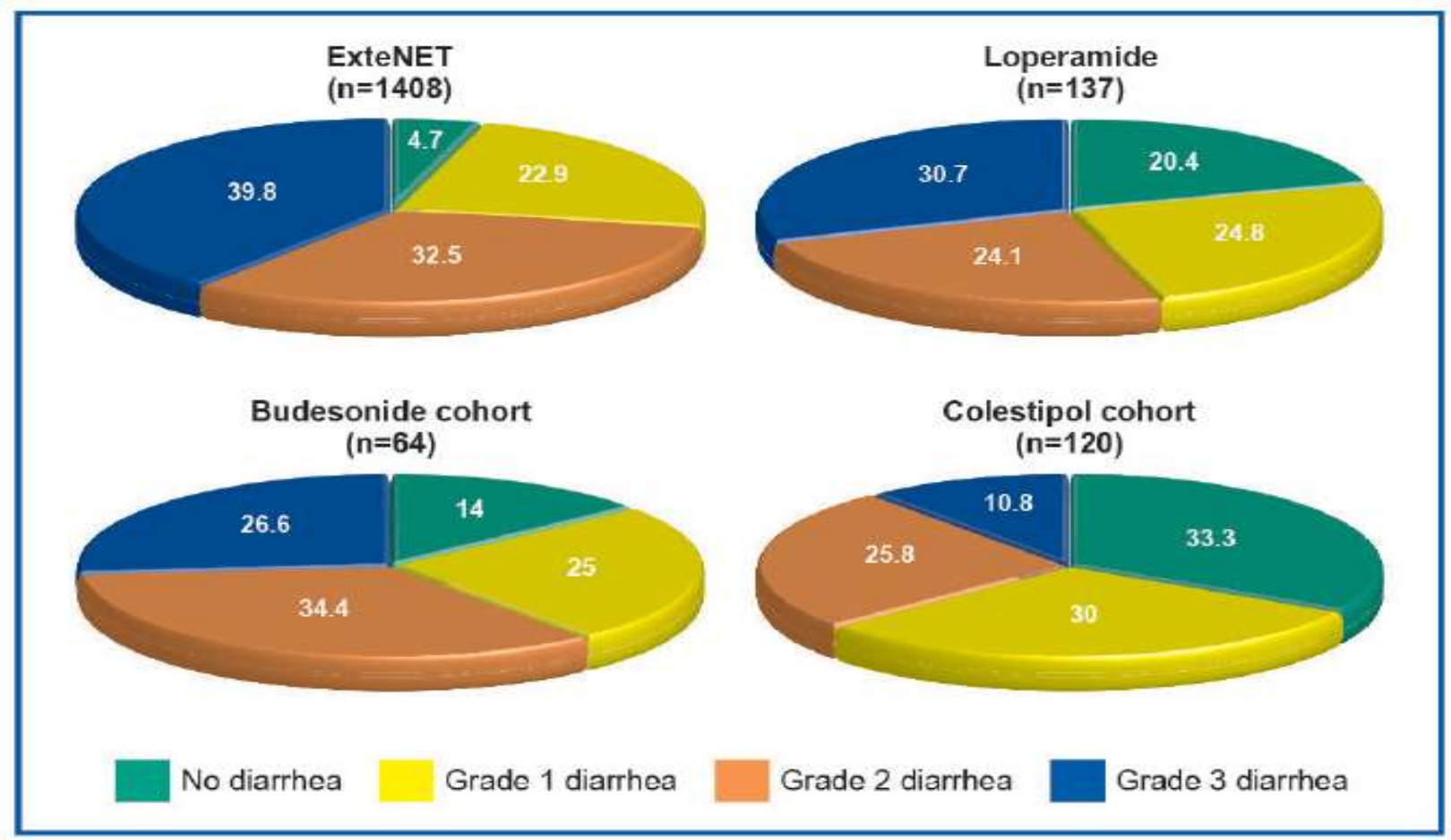
	Neratinib group (n=1408)			Placebo group (n=1408)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	781 (55%)	561 (40%)	1 (<1%)	476 (34%)	23 (2%)	0
Nausea	579 (41%)	26 (2%)	0	301 (21%)	2 (<1%)	0
Fatigue	359 (25%)	23 (2%)	0	276 (20%)	6 (<1%)	0
Vomiting	322 (23%)	47 (3%)	0	107 (8%)	5 (<1%)	0
Abdominal pain	314 (22%)	24 (2%)	0	141 (10%)	3 (<1%)	0
Headache	269 (19%)	8 (1%)	0	269 (19%)	6 (<1%)	0
Upper abdominal pain	201 (14%)	11 (1%)	0	93 (7%)	3 (<1%)	0
Rash	205 (15%)	5 (<1%)	0	100 (7%)	0	0
Decreased appetite	166 (12%)	3 (<1%)	0	40 (3%)	0	0
Muscle spasms	157 (11%)	1 (<1%)	0	44 (3%)	1 (<1%)	0
Dizziness	143 (10%)	3 (<1%)	0	125 (9%)	3 (<1%)	0
Arthralgia	84 (6%)	2 (<1%)	0	158 (11%)	4 (<1%)	0

Data are n (%). Full adverse events are presented in the appendix (p 16).

Table 3: Treatment-emergent adverse events occurring in at least 10% of patients in the safety population

Chan A, et al. Lancet Oncol 2016

CONTROL TRIAL: DIARRHEA PROPHYLAXIS



KATHERINE: STUDY DESIGN

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

N=1486

R
1:1

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

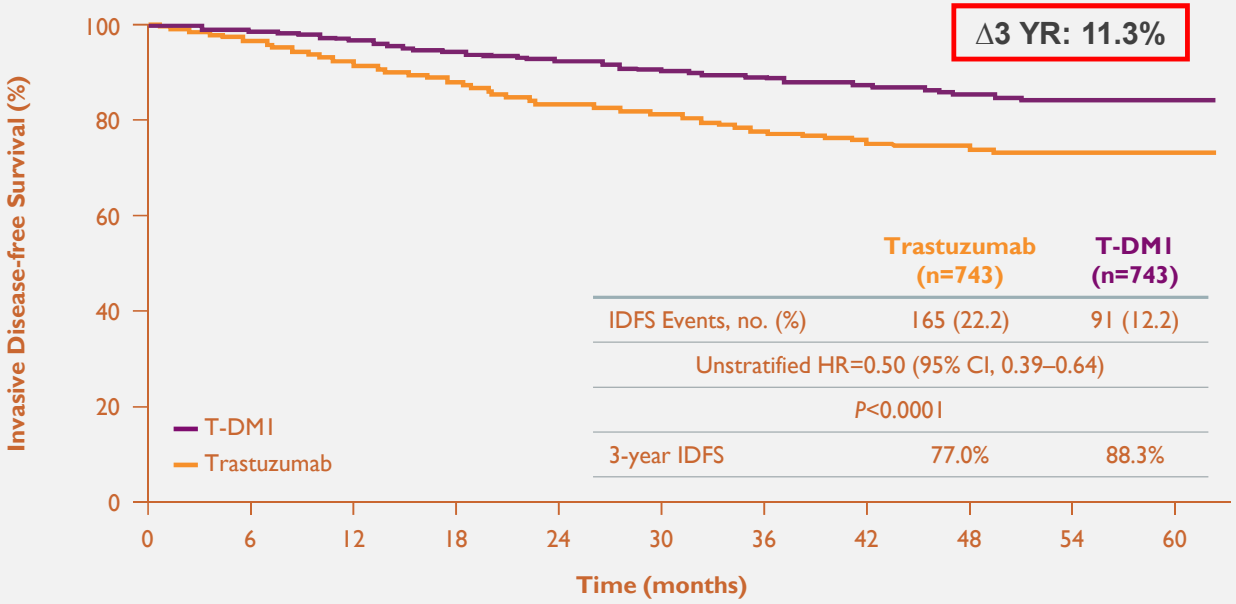
Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz *N Engl J Med.* Feb 14 2019;380(7).

KATHERINE: T-DM1 IMPROVED IDFS VS TRASTUZUMAB



	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)		
P<0.0001		
3-year IDFS	77.0%	88.3%

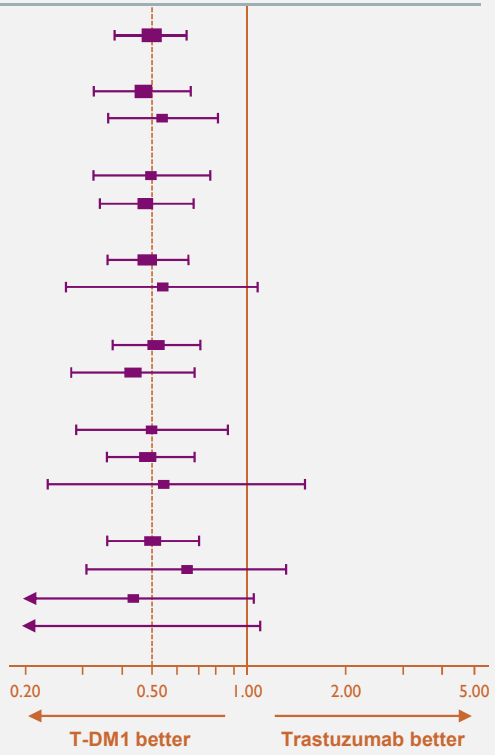
No. at Risk											
T-DM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4

	Trastuzumab (n = 743)	T-DM1 (n = 743)
Median duration of follow up (months)	40.9	41.4

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz *N Engl J Med.* Feb 14 2019;380(7).

KATHERINE: IDFS SUBGROUP ANALYSIS

Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio (95% CI)
All	1486	77.0	88.3	0.50 (0.39-0.64)
Clinical stage at presentation				
Operable	1111	82.8	92.3	0.47 (0.33-0.66)
Inoperable	375	60.2	76.0	0.54 (0.37-0.80)
Hormone receptor status				
Negative (ER negative and PgR negative/unknown)	412	66.6	82.1	0.50 (0.33-0.74)
Positive (ER and/or PgR positive)	1074	80.7	90.7	0.48 (0.35-0.67)
Preoperative HER2-directed therapy				
Trastuzumab alone	1196	75.9	87.7	0.49 (0.37-0.65)
Trastuzumab plus additional HER2-directed agents(s)	290	81.8	90.9	0.54 (0.27-1.06)
Pathological nodal status after preoperative therapy				
Node positive	689	67.7	83.0	0.52 (0.38-0.71)
Node negative/not done	797	84.6	92.8	0.44 (0.28-0.68)
Age group (years)				
<40	296	74.9	86.5	0.50 (0.29-0.86)
40–64	1064	77.1	88.8	0.49 (0.36-0.67)
≥65	126	81.1	87.4	0.55 (0.22-1.34)
Race*				
White	1082	79.1	88.8	0.51 (0.37-0.69)
Asian	129	71.9	82.5	0.65 (0.32-1.32)
American Indian or Alaska Native	86	60.3	81.8	0.44 (0.18-1.03)
Black or African American	40	66.0	94.7	0.13 (0.02-1.10)



* 149 were of multiple races or unknown race.

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz *N Engl J Med.* Feb 14 2019;380(7).

CONCLUSIONS

- Neoadjuvant therapy should be reserved for larger tumors T2>, N1>
- Dual Her2neu blockade a must in the neoadjuvant setting (H+P) + Chemo
- Favor anthracycline free regimen (TCH-P). Likely less cardiac toxicity and no risk of hematological malignancies (Underestimated in small sample)
- Dual Her2neu blockade T+P in the adjuvant setting beneficial for a subgroup of patients (Node positive/ER negative)
- De-escalation in the adjuvant setting to TH x 12 in all patients with T1 tumors is reasonable. May consider in up to 3.0 cm.
- Extended adjuvant Neratinib benefits ER positive. Diarrhea predictable and manageable with Loperamide prophylaxis.
- TDM-1 Benefits all subgroups without PCR after neoadjuvant therapy. Likely to be approved soon