Update on HER2-positive Breast Cancer

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Objectives

To discuss advances in:

1. Metastatic breast cancer

2. Adjuvant breast cancer: more vs less

3. HER2 negative!

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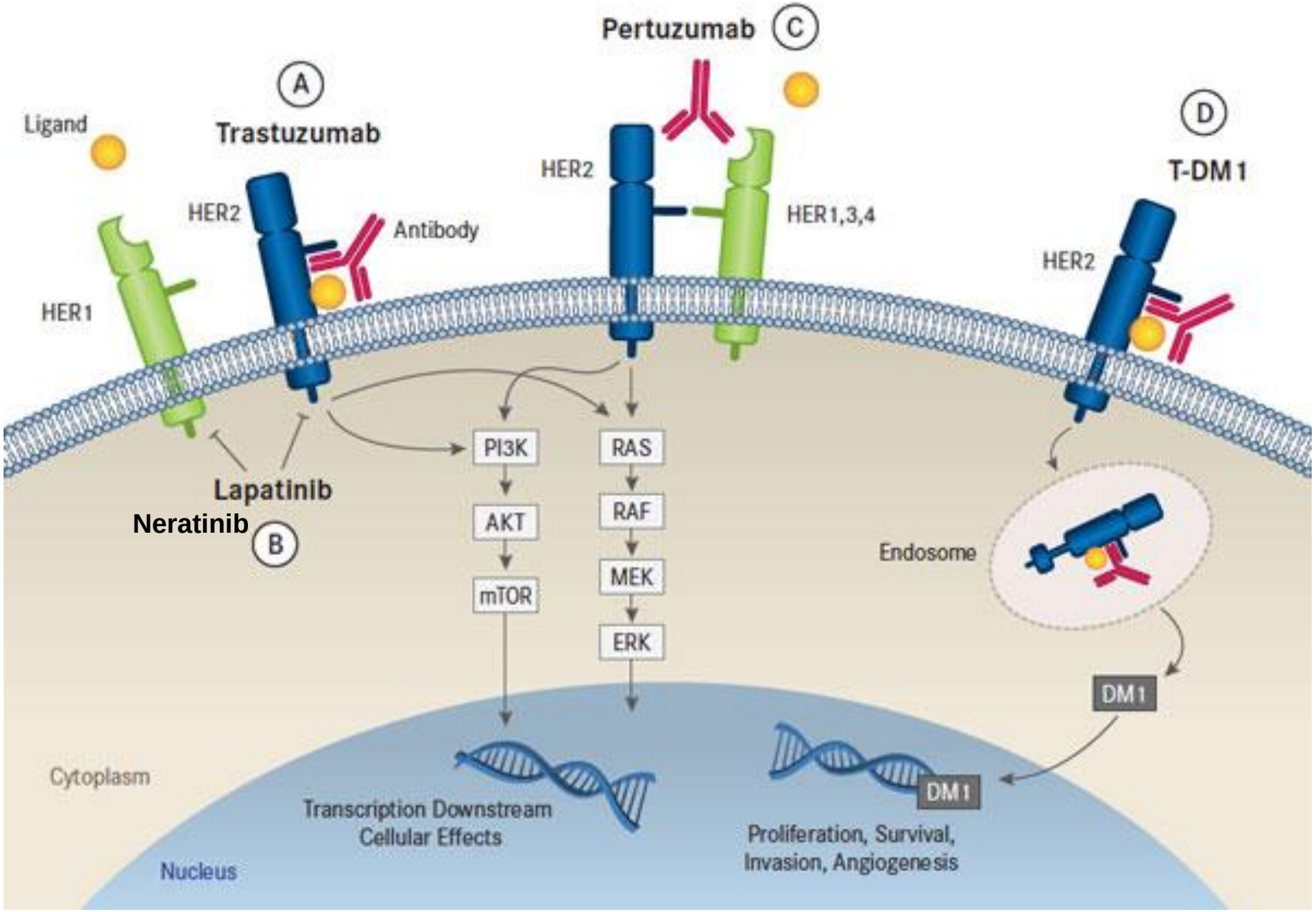

Pertuzumab
C
A
Trastuzumab
Ligand
D
T-DM1
HER2
HER2
HER1,3,4
Antibody
HER2
HER1
PI3K
RAS
AKT
RAF
MEK
mTOR
ERK
Lapatinib
Neratinib
B
Endosome
DM1
Cytoplasm
Transcription Downstream
Cellular Effects
DM1
Proliferation, Survival,
Invasion, Angiogenesis
Nucleus

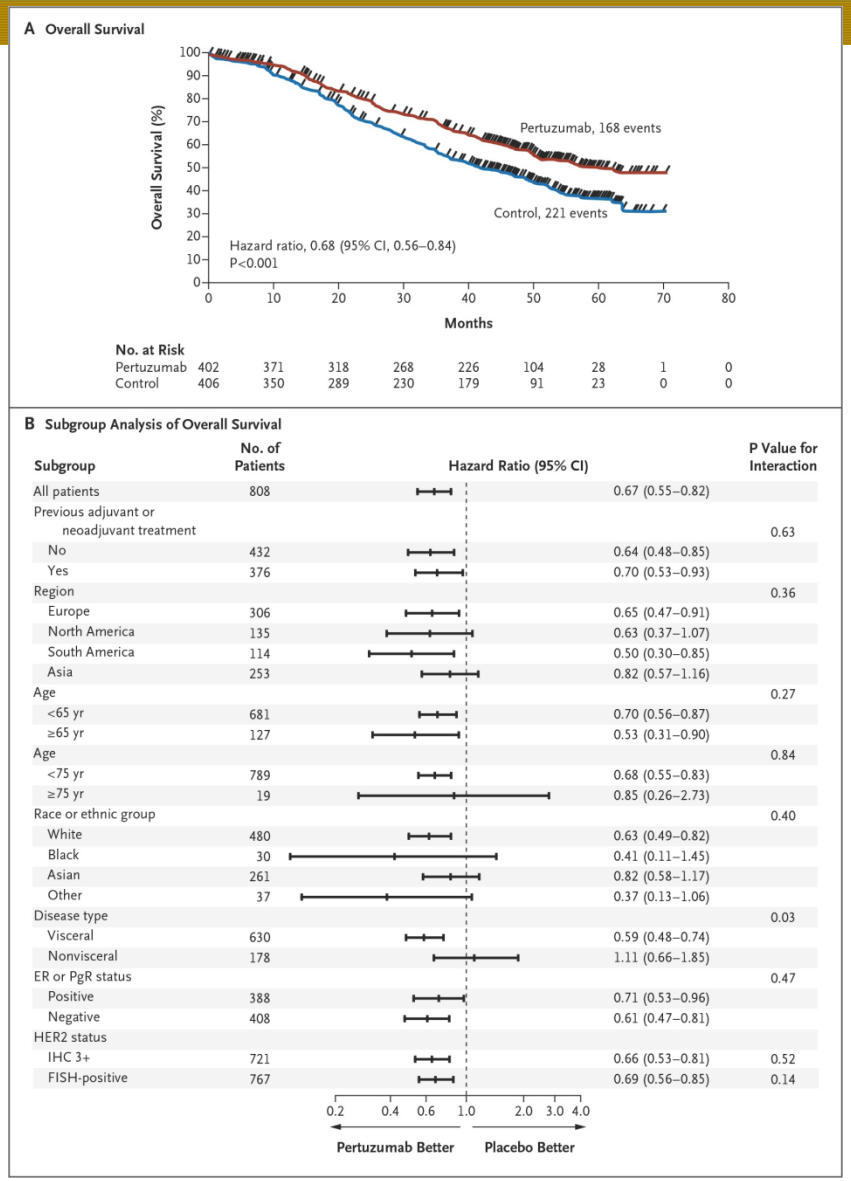
Phase III trials in HER2+ MBC

Trial	Design	Median OS	Population
CLEOPATRA[1]	1st line THP vs TH	56.5 vs 40.8 months	10% prior H
EMILIA[2]	2nd line TDM-1 vs CL	29.9 vs 25.4 months	100% prior H, taxanes
TH3RESA[3]	3rd line TDM-1 vs TPC	22.7 vs 15.8 months	100% prior H, L and taxane
EGF 104900[4]	3rd/4th line HL vs L	14 vs 9.8 months	Prior anthracyclines, taxane, H; Median 3 prior txs

T=docetaxel; H=trastuzumab; P=pertuzumab, C=capectabine; L=lapatinib;
TPC=treatment of physician's choice

1. Swain, et al, NEJM 2015; 2. Dieras, et al, Lancet Onc 2017; 3. Krop, et al, Lancet Onc 2017; 4. Blackwell, et al, JCO 2012

Advances in HER2+ MBC



CLEOPATRA, Swain, et al, NEJM, 2015

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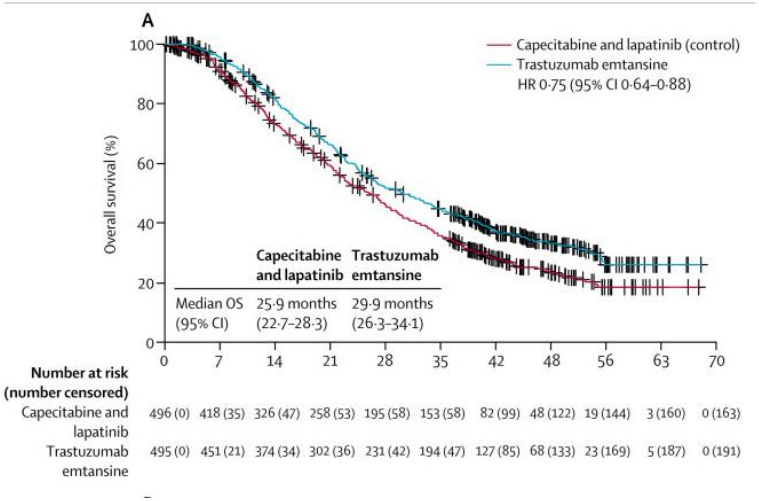
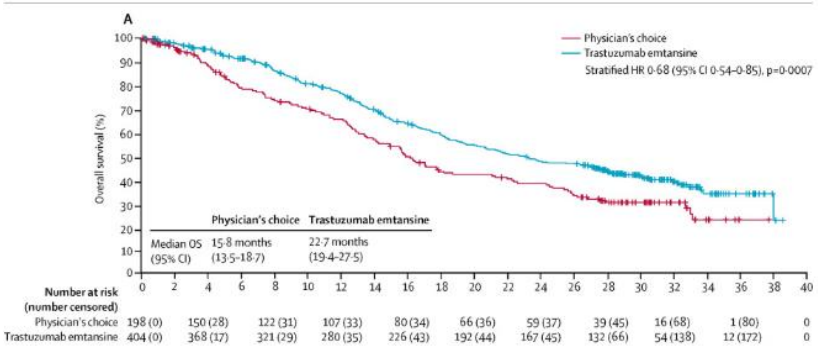
Advances in HER2+ MBC



EMILIA, Dieras, et al, 2017



TH3RESA, Krop, et al, 2017

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Can we go further?

MARIANNE Trial: Study Design

- Phase 3 trial
- N = 1095
- HER2-positive LABC* or MBC not treated with chemotherapy
- > 6 mo since use of a vinca alkaloid or taxane

RANDOMIZE

Arm A (either regimen)
- Trastuzumab 8 mg/kg LD then 6 mg/kg + Docetaxel 75 or 100 mg/m² every 3 wk
- Trastuzumab 4 mg/kg LD then 2 mg + paclitaxel 80 mg/m² every wk

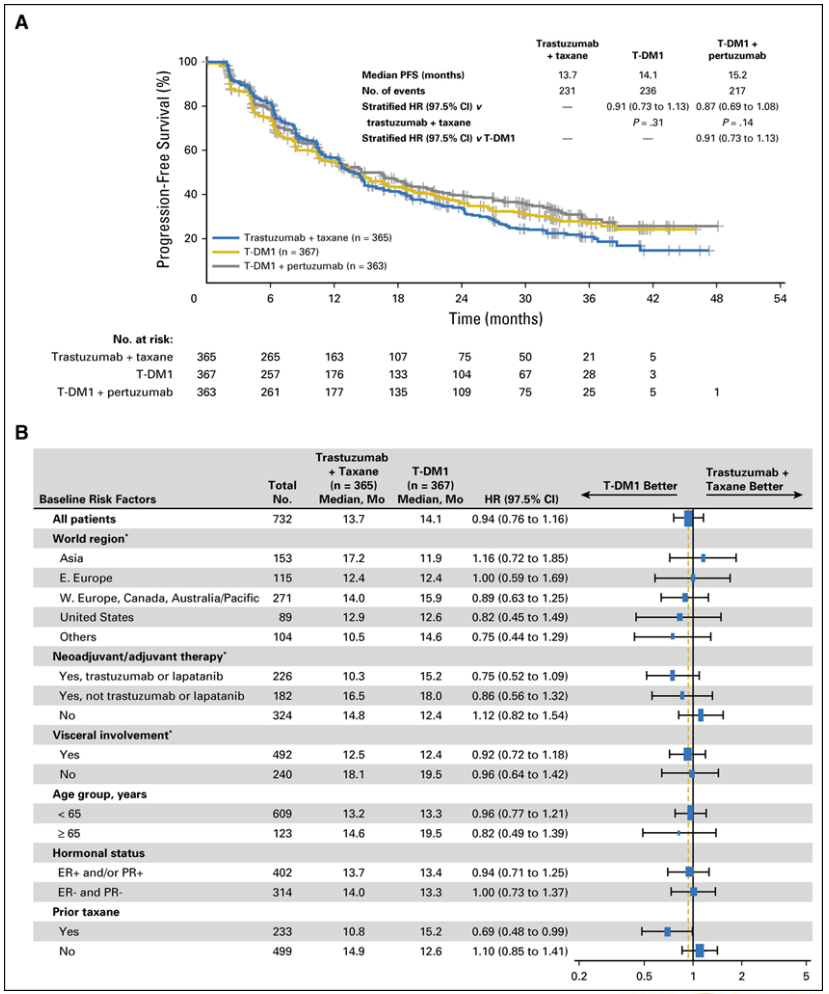
Arm B
T-DM1 3.6 mg/kg + placebo 840 mg LD then 420 mg every 3 wk

Arm C
T-DM1 3.6 mg/kg + pertuzumab 840 mg LD then 420 mg every 3 wk

*Locally progressive or recurrent breast cancer not amenable to resection with curative intent. LD = loading dose.

- Primary end points were PFS assessed by independent review and incidence of AEs
- Secondary end points included OS, PFS by investigator, ORR, and safety

Ellis PA, et al. *J Clin Oncol*. 2015;33(suppl):507.[1]



Perez, et al, JCO 2017

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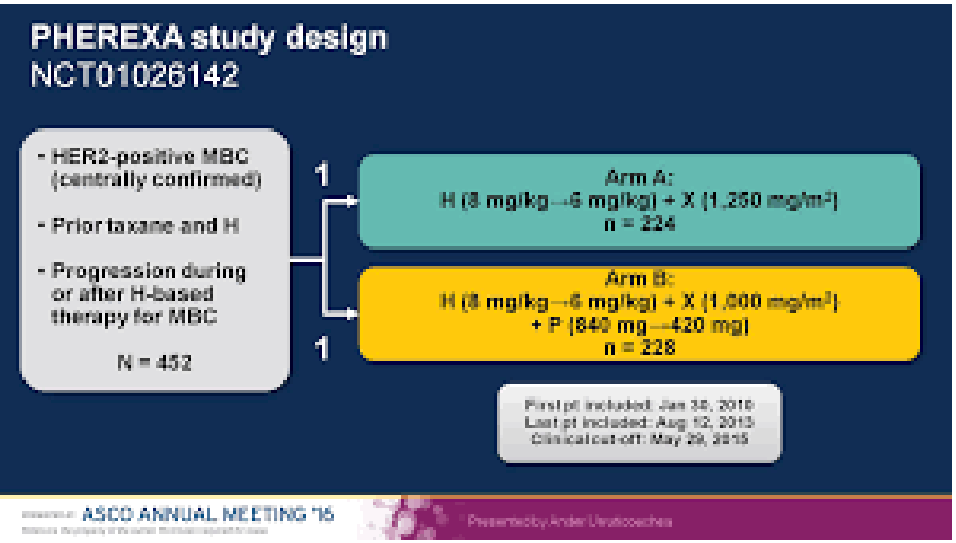
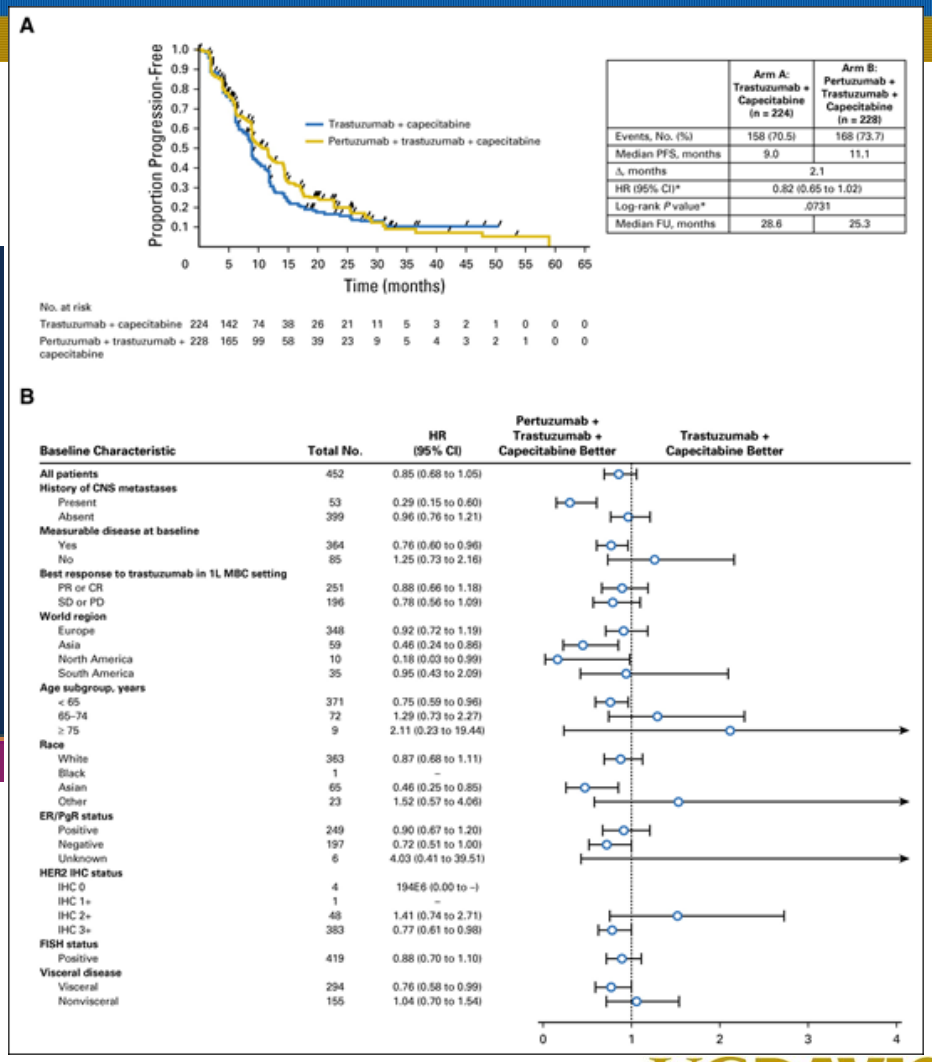
Can we go further?





Urruticoechea, et al, JCO 2017

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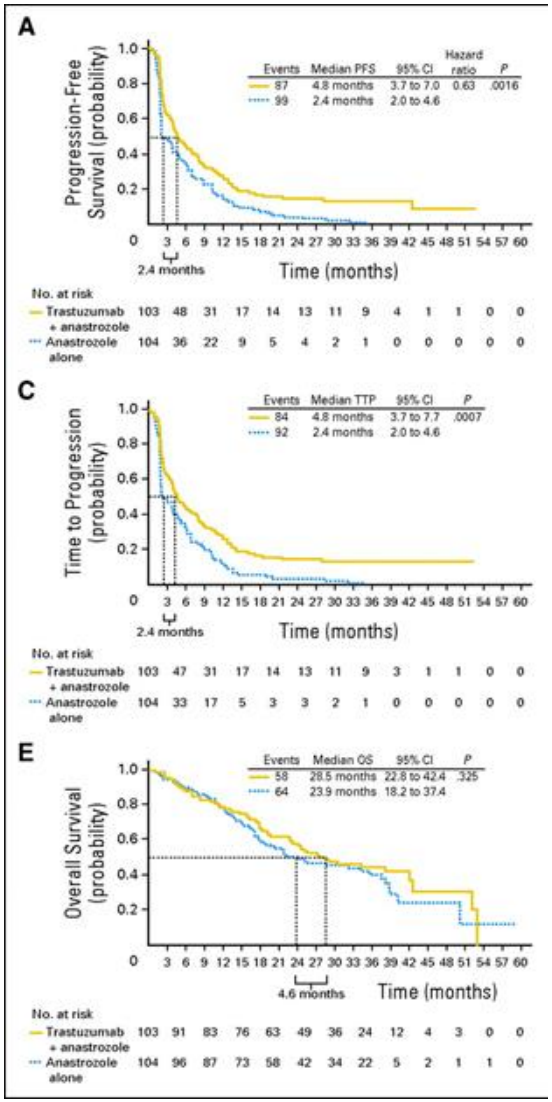
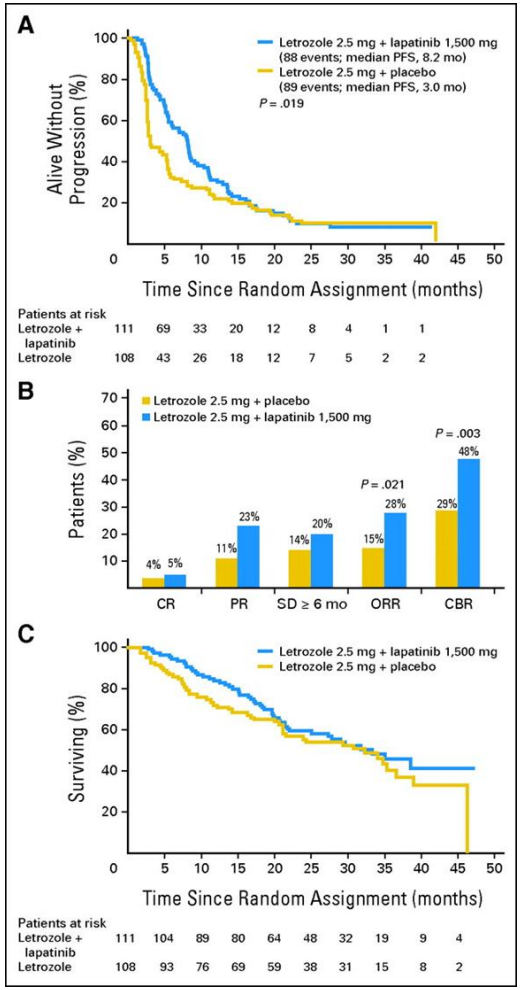
What about endocrine therapy?



Kaufman, et al, JCO 2009



Johnston, et al, JCO 2009

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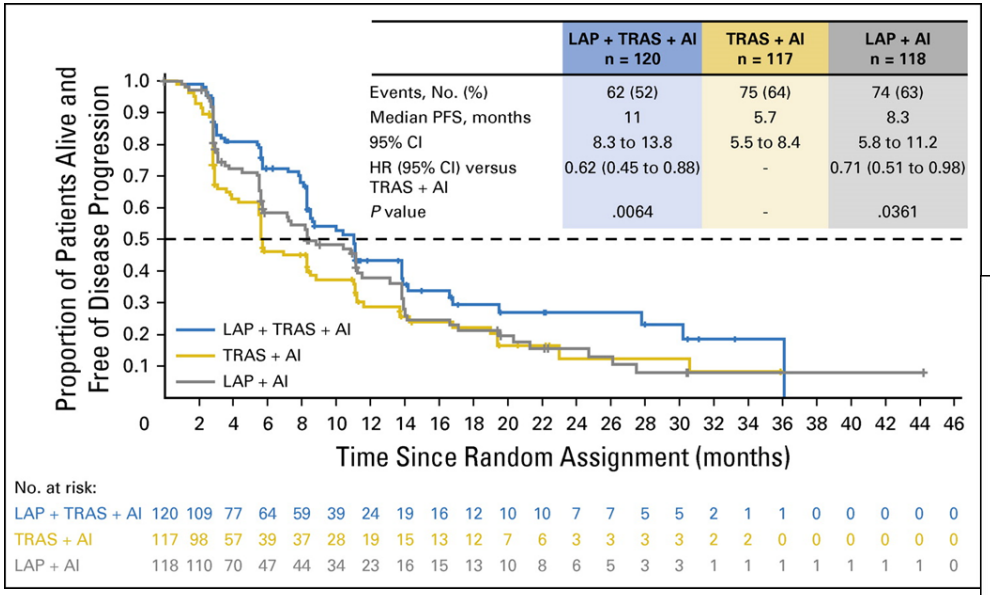
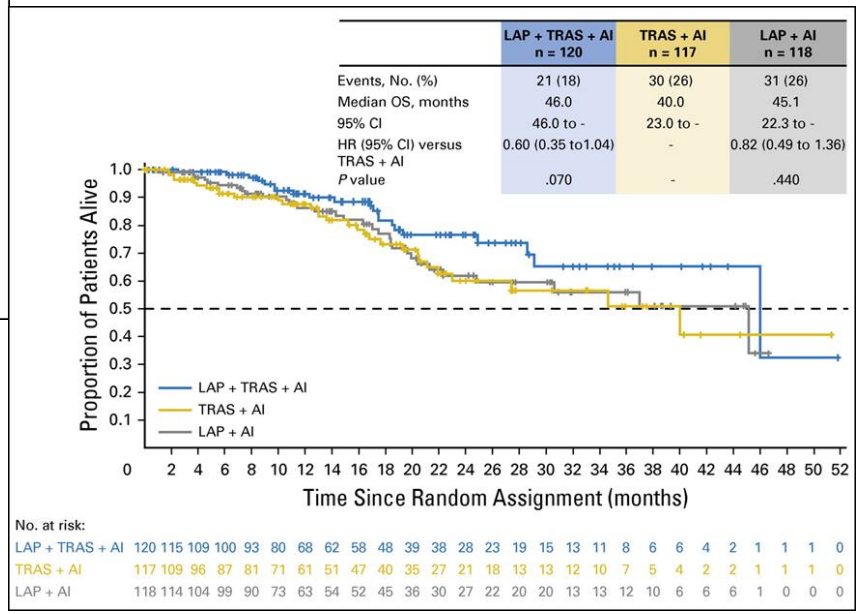
Dual HER2 therapies





13% grade 3/4 diarrhea in L+ Tras arm

Johnston, et al, JCO 2018

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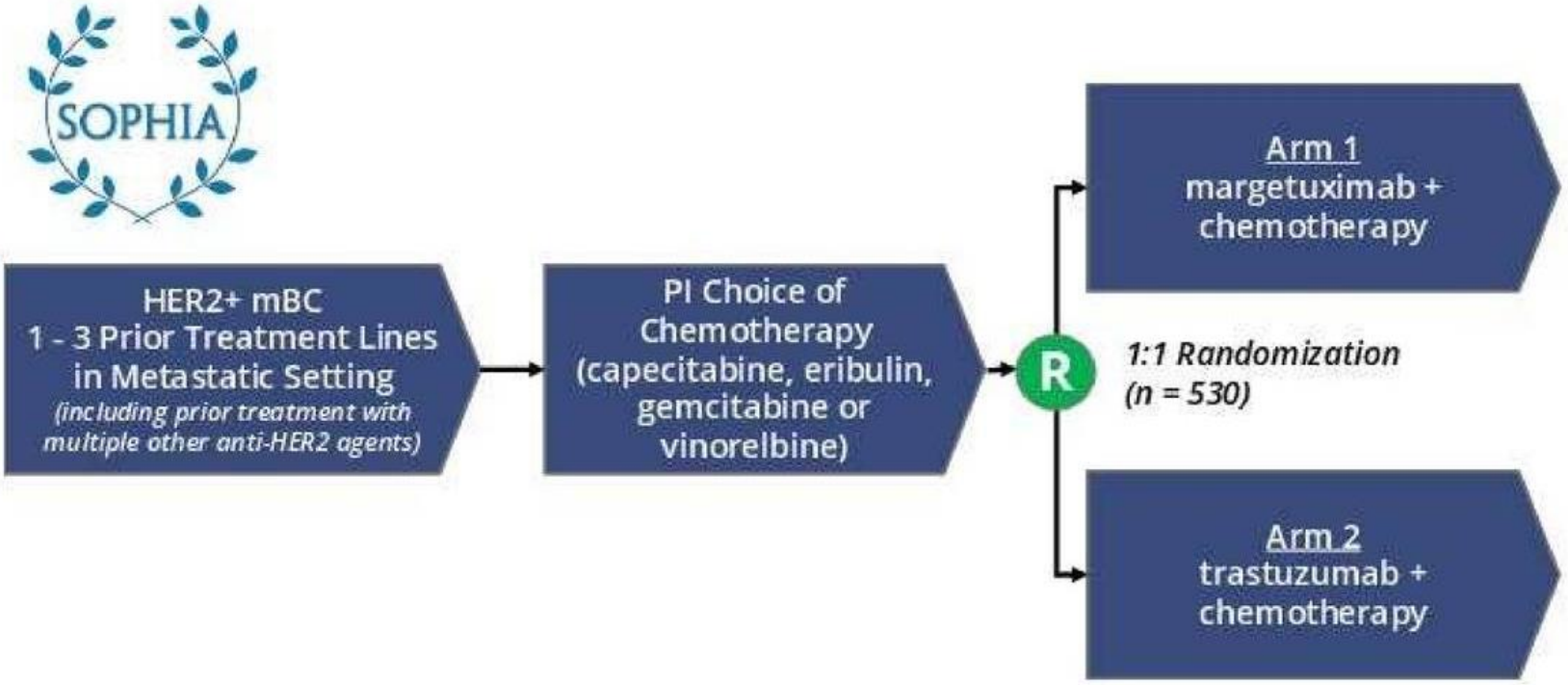
How does this change clinical practice?

- Many effective HER2-directed therapies as continued HER2 blockade necessary
- HER2 therapies effective with chemotherapy, endocrine therapy and on their own
- Unknown efficacy of pertuzumab after trastuzumab exposure

Margetuximab

Phase 3 Study to Establish Superiority to Trastuzumab

Futility analysis anticipated Jan 2018; Enrollment completion expected 4Q18



# of Global sites: ~200

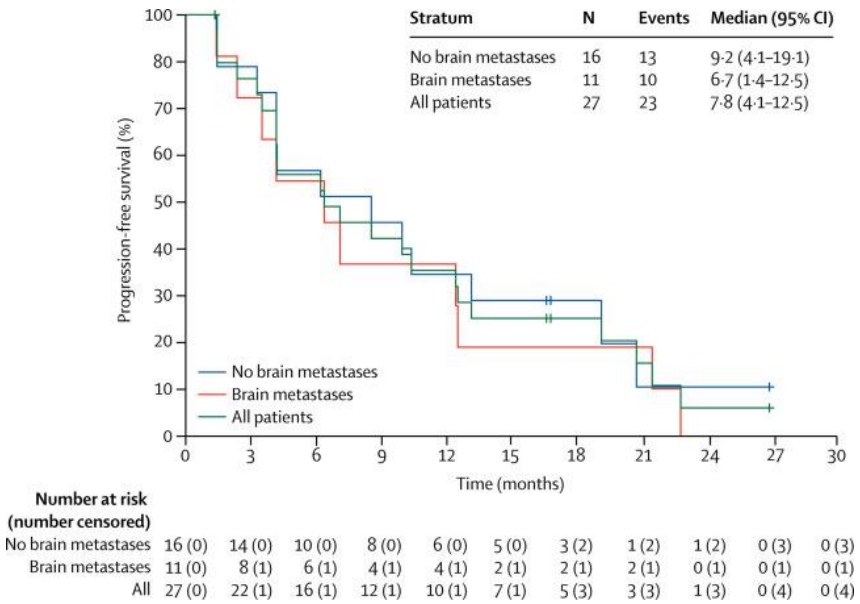
Sequential primary endpoints: Progression-Free Survival & Overall Survival:

PFS (N=257, HR=0.67, α=0.05, power=90%)

OS (N=385, HR=0.75, α=0.05, power=80%)

Tucatinib

- Oral, potent HER2-specific TKI
- Phase Ib study of heavily pretreated patients



Murthy, et al, Lancet Oncology 2018

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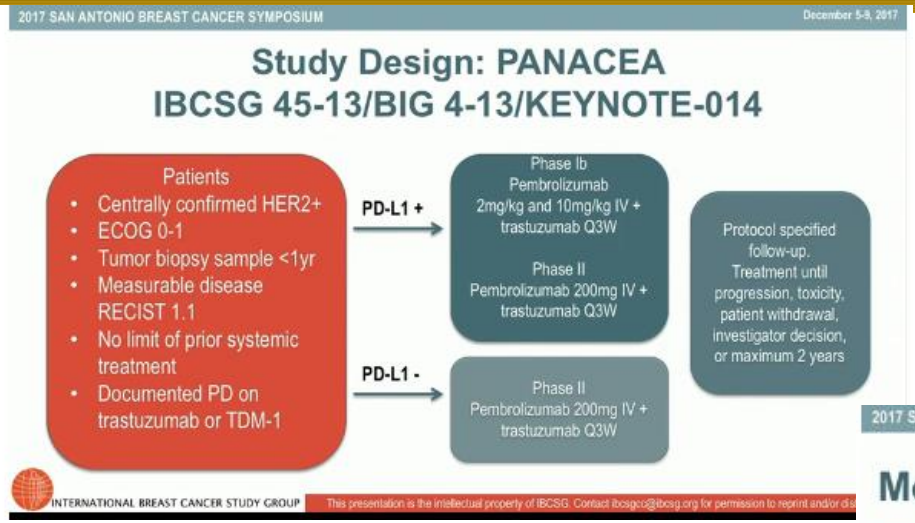
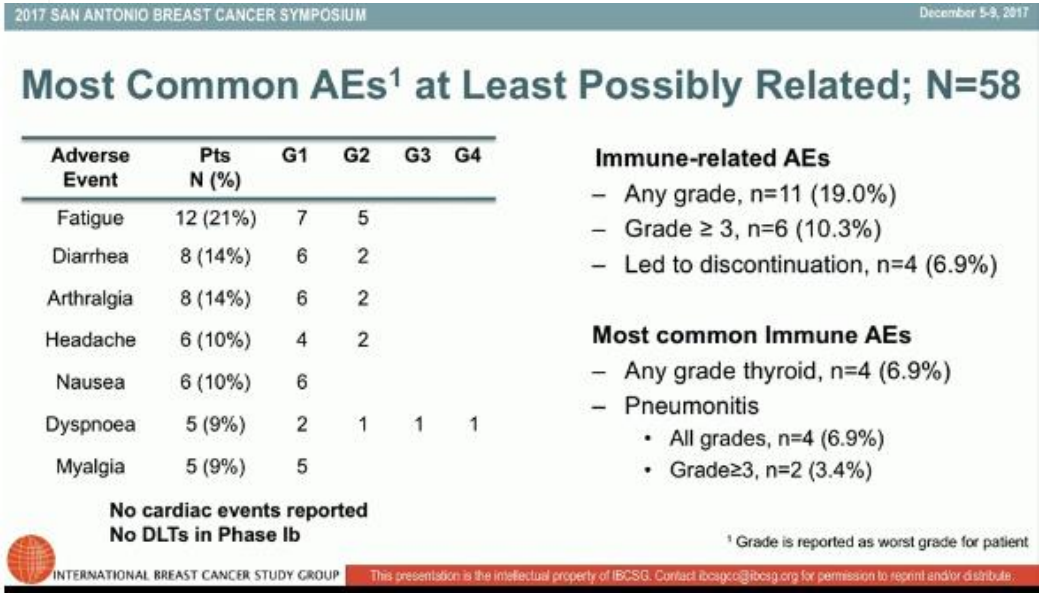
Checkpoint inhibition?





Loi, et al, SABCS 2017

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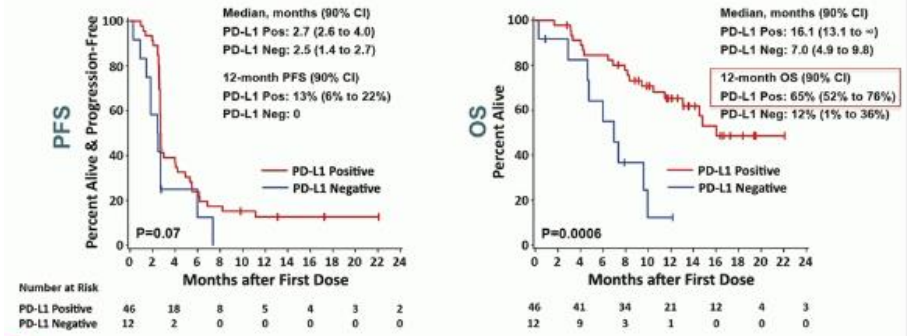
Best Overall Response (RECIST 1.1)

	PD-L1 Positive Phase Ib, n=6	PD-L1 Positive Phase II, n=40	PD-L1 Negative Phase II, n=12
ORR n (%) [90%CI]	**1 (17%) [1-58]**	**6 (15%) [7-29]**	**0 (0%) [0-18]**
DCR[1] n (%) [90%CI]	1 (17%) [1-58]	10 (25%) [14-49]	0 (0%) [0-18]
Best overall response, n (%)			
Complete Response	**1 (17%)**	**1 (2.5%)**	-
Partial Response	-	**5 (12.5%)**	-
Stable Disease	-	**7 (17.5%)**	**2 (16.7%)**
Progressive Disease	**5 (83%)**	**25 (62.5%)**	**9 (75.0%)**
Not Evaluable	-	**2 (5.0%)**	**1 (8.3%)**
Overall PD-L1 + cohort	**ORR 15.2% [7-27]**	**DCR 24% [14-36]**	

[1]DCR: CR, PR, or SD ≥ 6 months

PFS and OS by PD-L1 Status



Loi, et al, SABCS 2017

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Objectives

To discuss advances in:

1. Metastatic breast cancer

2. Adjuvant breast cancer: more vs less

3. HER2 negative!

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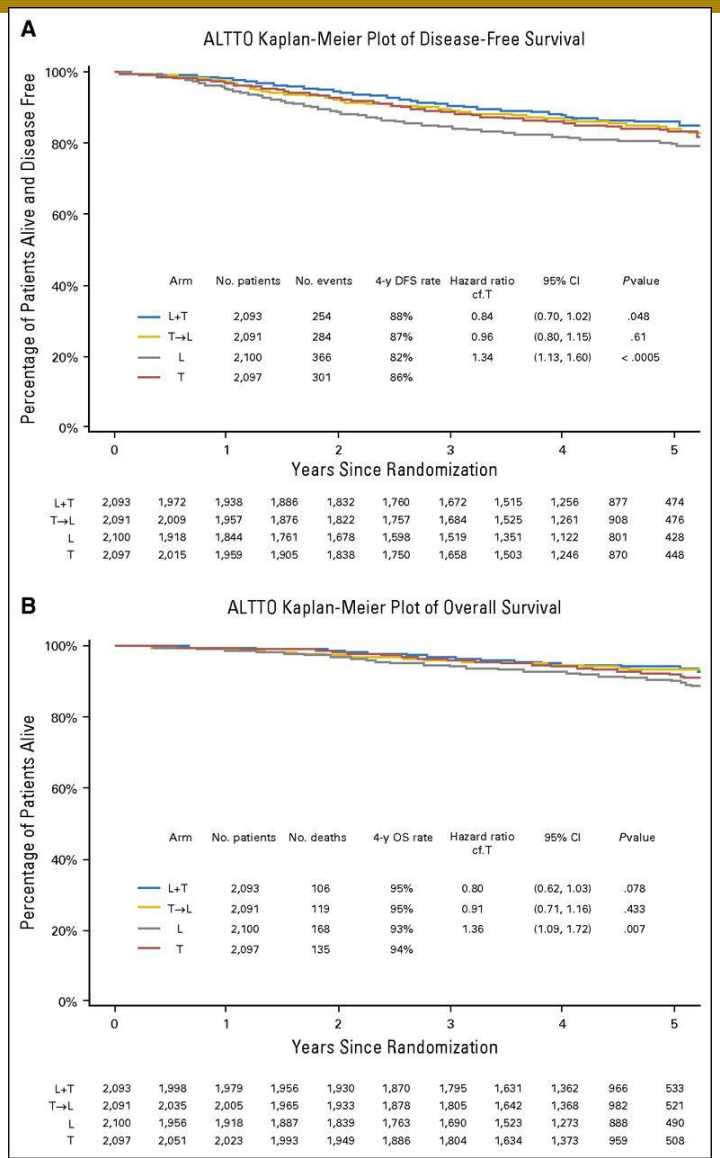
Adjuvant HER2 therapy

Trial	Design	N	DFS
NCCTG 9831 and NSABP B-31[1]	AC→T +/- H	4046	HR 0.48, p<0.0001
HERA[2]	C→ +/- H x 1 year or 2 years	3401	HR 0.54, p<0.0001
BCIRG-006[3]	AC→T AC→TH TCH	3222	 HR 0.64, p<0.001 HR 0.75, p=0.04

1. Romand, et al, NEJM, 2005; 2. Piccart-Gebhart, et al, NEJM 2005;
2. 3. Slamon, et al, NEJM 2011

What about more?



Piccart-Gebhart, et al, JCO 2016

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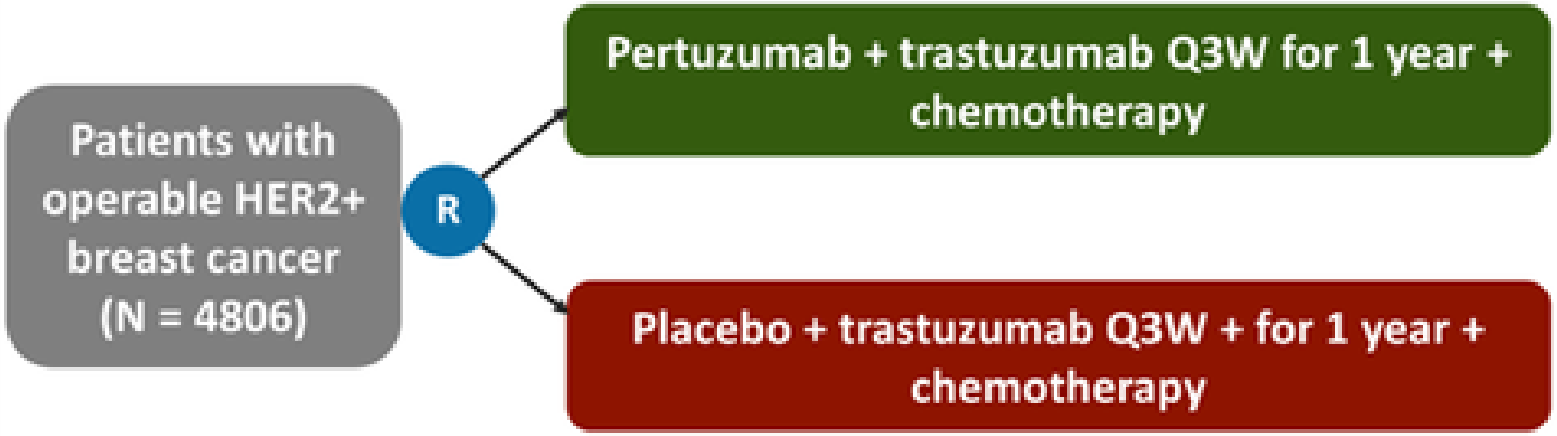
APHINITY: Phase 3 Trial of Adjuvant Pertuzumab and Trastuzumab + Chemotherapy

- Randomized, double-blind, placebo-controlled trial



- Primary endpoints: IDFS duration, percentage of patients with both HF (NYHA Class III or IV), and drop in LVEF of ≥ 10 points from baseline and to below 50%

Clinicaltrials.gov. NCT01358877.

Demographic and Baseline Disease Characteristics of the Patients.

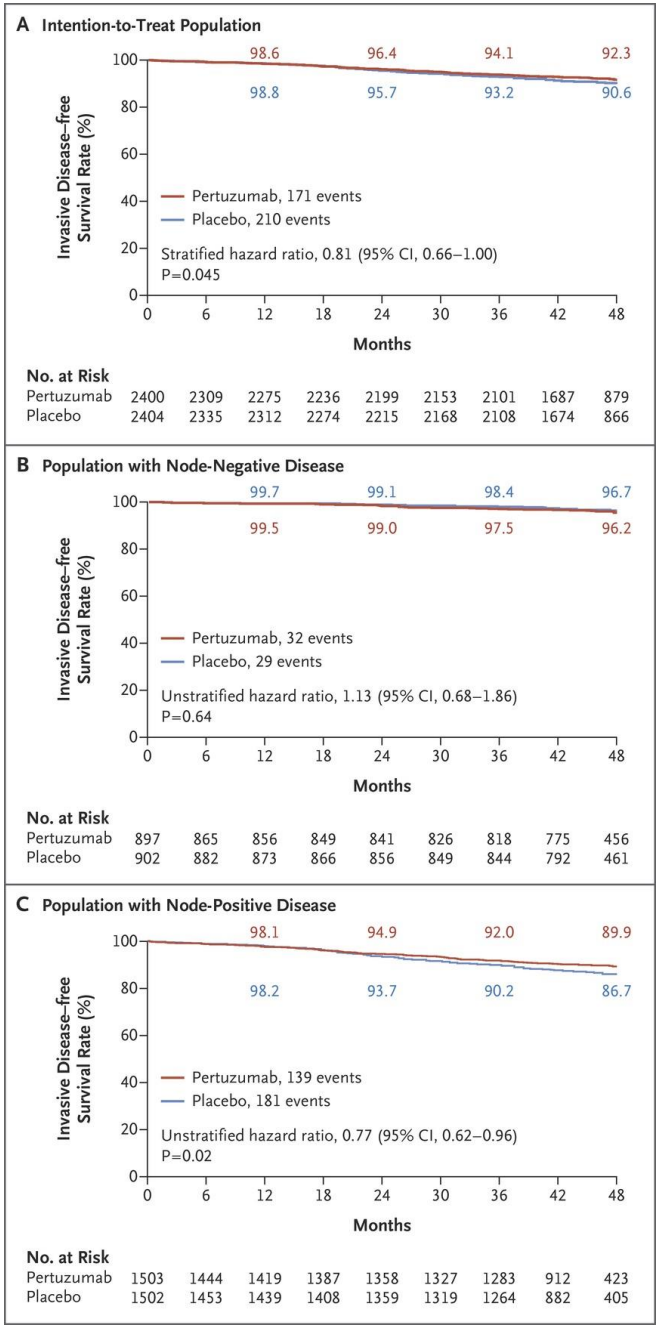
Table 1. Demographic and Baseline Disease Characteristics of the Patients.

Characteristic	Pertuzumab Group (N = 2400)	Placebo Group (N = 2404)
Nodal status — no. of patients (%)		
0 positive nodes and tumor ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and tumor >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 — no. of patients (%)†		
Anthracycline-containing regimen	1865 (77.7)	1877 (78.1)
Non–anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone-receptor status — no. of patients (%)‡		
Negative	864 (36.0)	858 (35.7)
Positive	1536 (64.0)	1546 (64.3)
Protocol version — no. of patients (%)*		
Protocol A	1828 (76.2)	1827 (76.0)
Protocol B	572 (23.8)	577 (24.0)
Age — no. of patients (%)		
<40 yr	326 (13.6)	327 (13.6)
40–64 yr	1759 (73.3)	1784 (74.2)
≥65 yr	315 (13.1)	293 (12.2)
Pathological tumor size — no. of tumors/total no. (%)§		
0 to <2 cm	978/2400 (40.8)	948/2405 (39.4)
2 to <5 cm	1275/2400 (53.1)	1283/2405 (53.3)
≥5 cm	147/2400 (6.1)	174/2405 (7.2)

Minckwitz G et al. N Engl J Med ;377:122-131

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Plot of Invasive-Disease–free Survival



von Minckwitz G et al. N Engl J Med ;377:122-131

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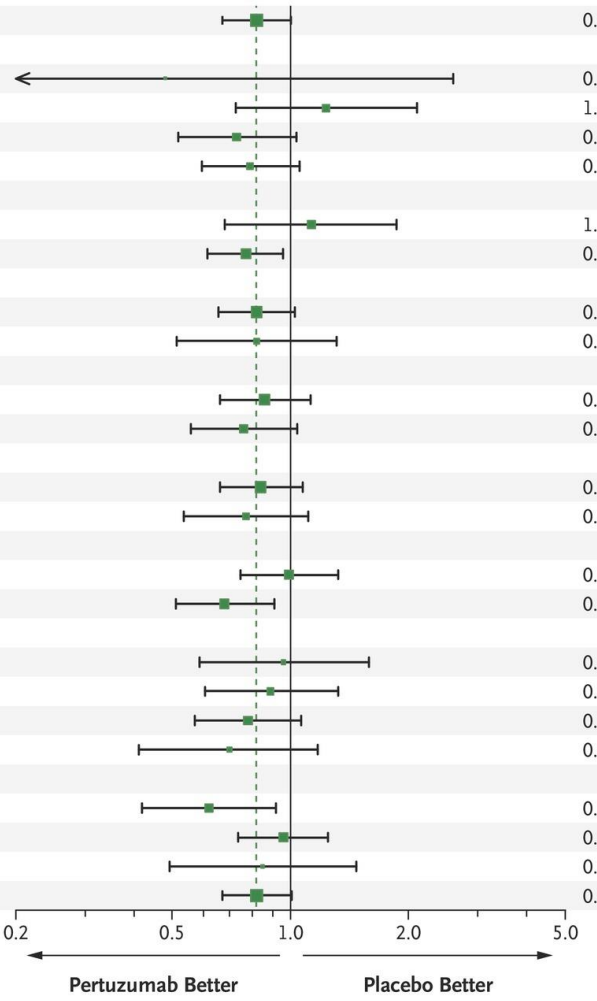
Forest Plot of Invasive-Disease–free Survival

Subgroup	Pertuzumab	Placebo	Unstratified Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate		P Value for Interaction
				Pertuzumab	Placebo	
	no. of patients with an invasive-disease event/total no.			%		
All patients	171/2400	210/2404	0.82 (0.67–1.00)	94.1	93.2	NA
No. of positive nodes						0.37
0 Positive nodes, tumor ≤1 cm	2/90	4/84	0.48 (0.09–2.60)	97.7	97.5	
0 Positive nodes, tumor >1 cm	30/807	25/818	1.23 (0.72–2.10)	97.5	98.5	
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	
Nodal status						0.17
Node-negative	32/897	29/902	1.13 (0.68–1.86)	97.5	98.4	
Node-positive	139/1503	181/1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						1.00
Anthracycline	139/1865	171/1877	0.82 (0.66–1.03)	93.8	93.0	
Nonanthracycline	32/535	39/527	0.82 (0.51–1.31)	94.9	94.0	
Hormone-receptor status						0.54
Positive	100/1536	119/1546	0.86 (0.66–1.13)	94.8	94.4	
Negative	71/864	91/858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						0.69
Protocol A	120/1828	143/1827	0.84 (0.66–1.08)	94.7	94.1	
Protocol B	51/572	67/577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						0.07
Before menopause	93/1152	96/1173	0.99 (0.75–1.32)	93.5	93.7	
After menopause	78/1242	113/1220	0.68 (0.51–0.91)	94.5	92.7	
Age group						0.78
<40 yr	30/326	32/327	0.96 (0.59–1.59)	93.4	93.1	
40–49 yr	48/708	53/702	0.89 (0.60–1.32)	94.5	94.3	
50–64 yr	69/1051	91/1082	0.78 (0.57–1.07)	94.3	93.3	
≥65 yr	24/315	34/293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size						0.20
<2 cm	41/977	64/944	0.62 (0.42–0.92)	97.0	94.6	
2 to <5 cm	108/1273	115/1283	0.96 (0.74–1.24)	92.5	93.0	
≥5 cm	22/147	31/174	0.85 (0.49–1.47)	87.5	87.5	
Female sex	171/2397	209/2396	0.82 (0.67–1.01)	94.1	93.2	NA



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Summary of Adverse Events (Safety Analysis Population).

Table 3. Summary of Adverse Events (Safety Analysis Population).*

Event	Pertuzumab Group (N = 2364)	Placebo Group (N = 2405)
	no. of patients (%)	
Grade ≥3 adverse event	1518 (64.2)	1379 (57.3)
Neutropenia	385 (16.3)	377 (15.7)
Febrile neutropenia	287 (12.1)	266 (11.1)
Neutrophil count decreased	228 (9.6)	230 (9.6)
Diarrhea†	232 (9.8)	90 (3.7)
Anemia	163 (6.9)	113 (4.7)
Fatal adverse event‡	18 (0.8)	20 (0.8)
Primary cardiac event§	17 (0.7)	8 (0.3)
NYHA class III or IV heart failure and substantial decrease in LVEF¶	15 (0.6)	6 (0.2)
Definite or probable cardiac death	2 (0.1)	2 (0.1)
Secondary cardiac event‖	64 (2.7)	67 (2.8)
Identified automatically from LVEF assessments	50 (2.1)	47 (2.0)
Identified by cardiac advisory board	14 (0.6)	20 (0.8)

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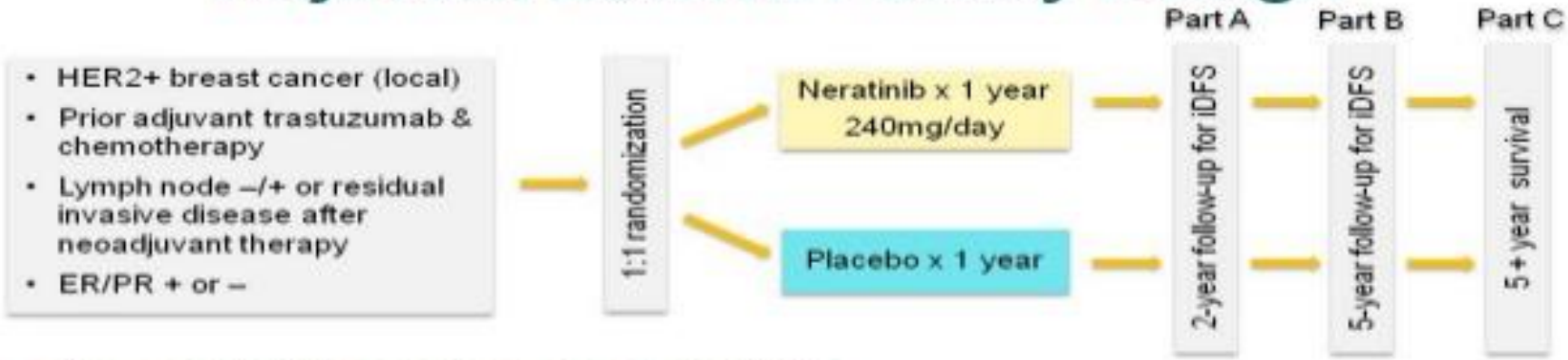
Adjuvant ExteNET Study Design

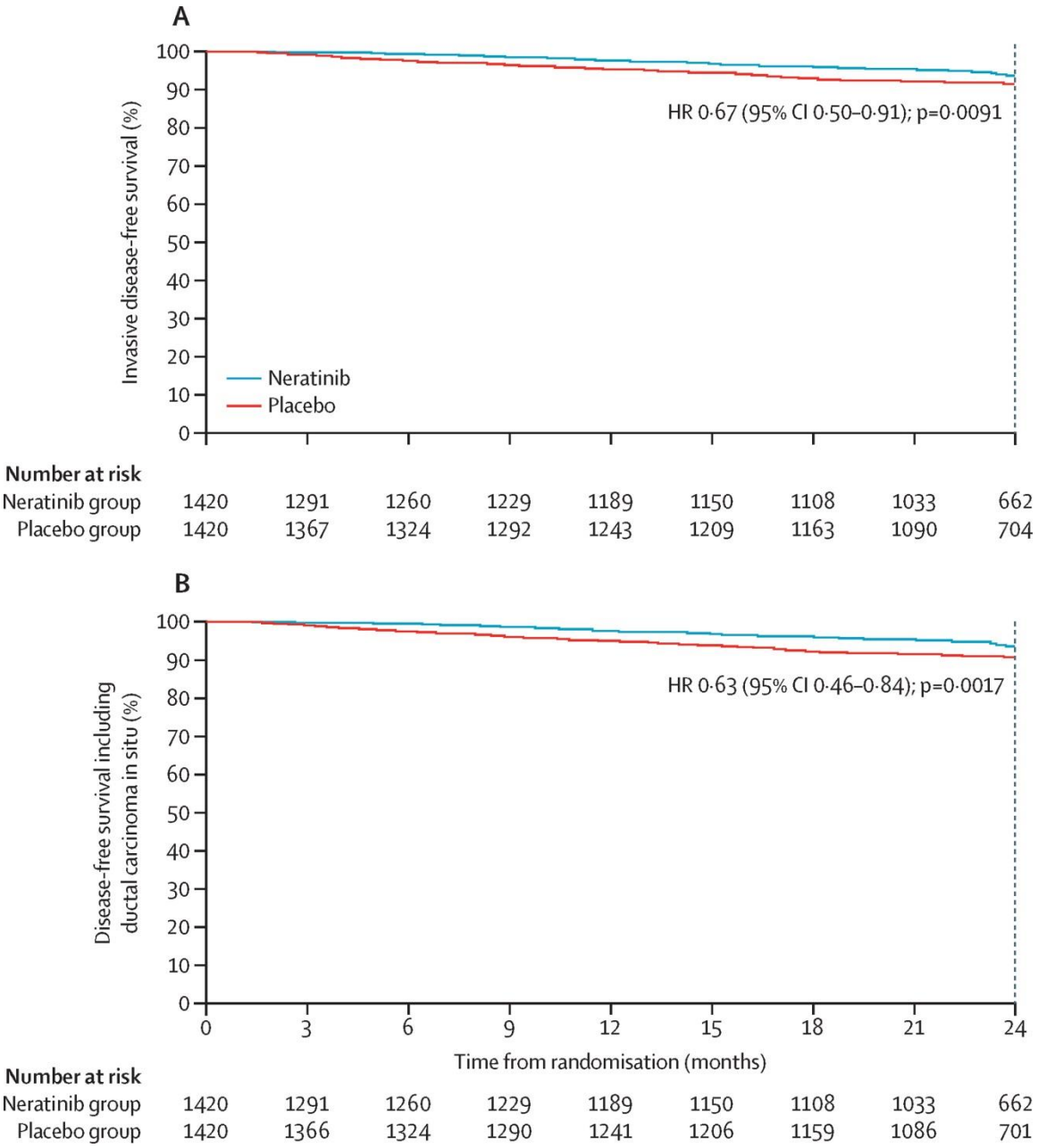


- Primary endpoint: invasive disease-free survival (iDFS)
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- Other analyses: biomarkers, health outcome assessment (FACT-B, EQ-5d)
- Stratified by: nodes 0, 1–3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Chan A , ASCO 2015 ASCO Annual '15 Meeting

Presented By Shanu Modi at 2015 ASCO Annual Meeting

Figure 2



Chan, et al
Lancet Oncology 2016

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

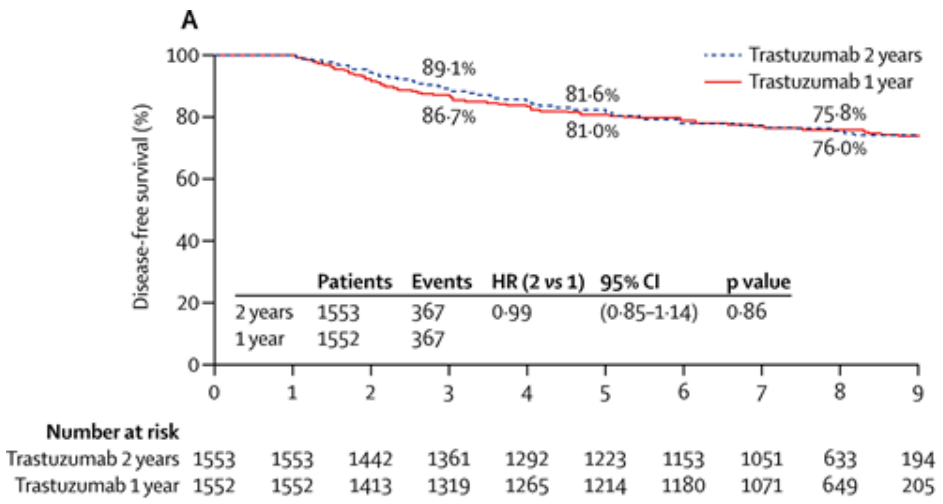
	Neratinib group (n=1408)			Placebo group (n=1408)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	781 (55%)	561 (40%)	1 (<1%)	476 (34%)	23 (2%)	0
Nausea	579 (41%)	26 (2%)	0	301 (21%)	2 (<1%)	0
Fatigue	359 (25%)	23 (2%)	0	276 (20%)	6 (<1%)	0
Vomiting	322 (23%)	47 (3%)	0	107 (8%)	5 (<1%)	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

Chan, et al
Lancet Oncology 2016

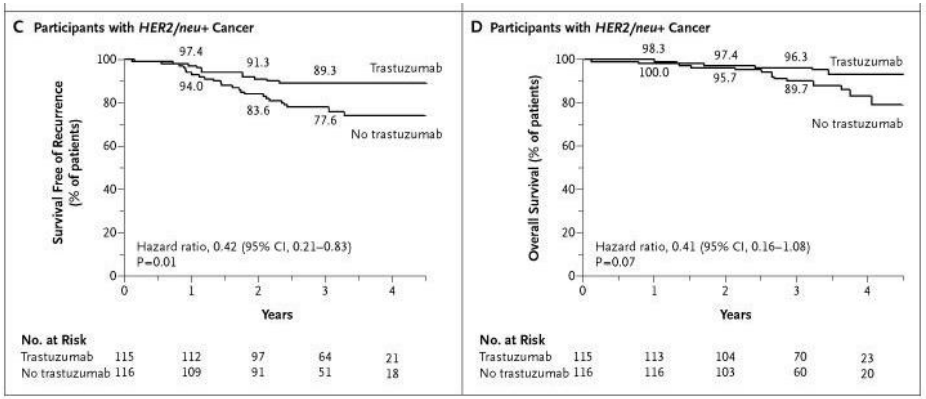
How does this change clinical practice?

- Additional HER2 directed therapies come at cost, both in side effects and dollars.
- Consider a year of adjuvant pertuzumab or a neratinib in high-risk patients:
  - Node positive
  - Residual disease after neoadjuvant therapy

What about less?



Goldhirsch, et al, Lancet 2013



Joensuu, et al, NEJM 2006

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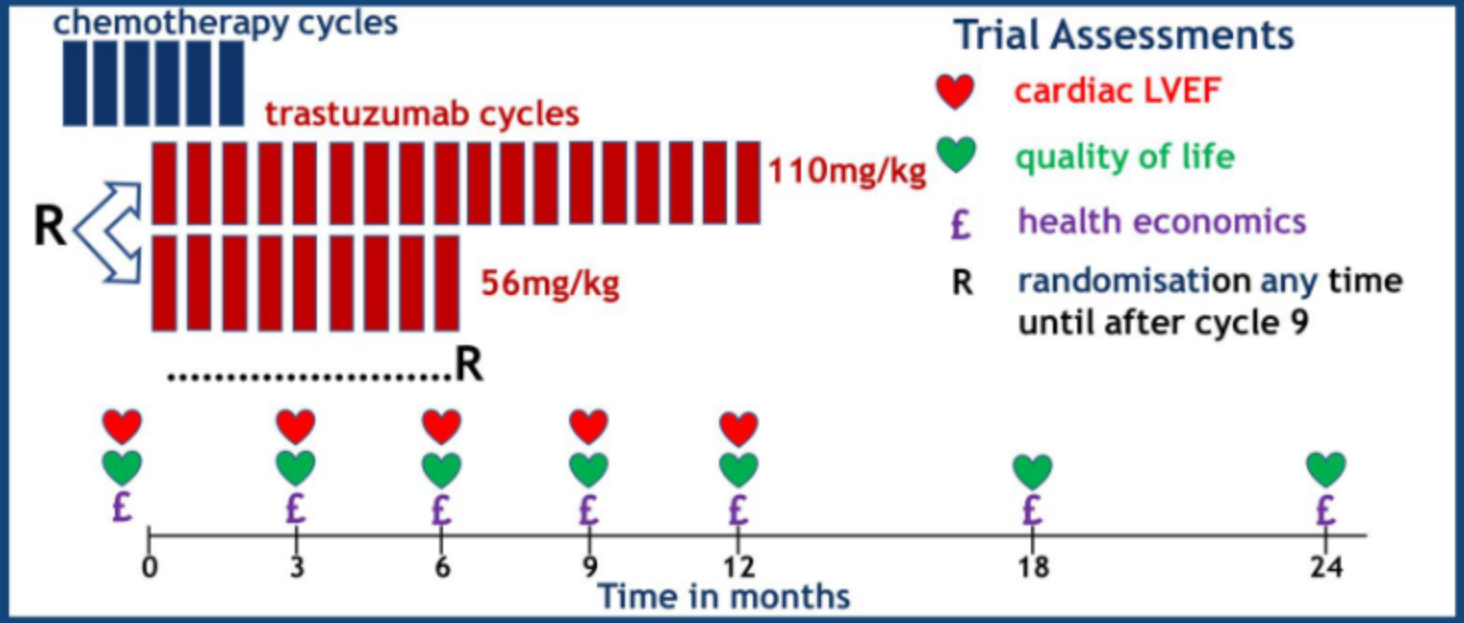
Adjuvant trials of trastuzumab duration

Trial	Non-inferiority DFS HR	Experimental duration vs 12 m	N	Results	Cardiac toxicity?
PHARE[1]	1.15	6 months	3384	HR 1.21	Yes
HORG[2]	1.53	6 months	481	HR 1.57	No difference
Short HER[3]	1.29	9 weeks	1254	1.15 (0.9-1.46)	Yes
SOLD[4]	1.3*	9 weeks	2176	1.39	Yes
PERSEPHONE[5]	1.3	6 months	4000	1.07 (0.93-1.24)	Yes

1. Pivot, et al, Lancet Oncology 2103; 2. Mavroudis, et al, Ann Onc 2015; 3. Conte, et al, ASCO 2017;
4. Joensuu, et al, JAMA Onc 2018; 5. Earl, et al, ASCO 2018.

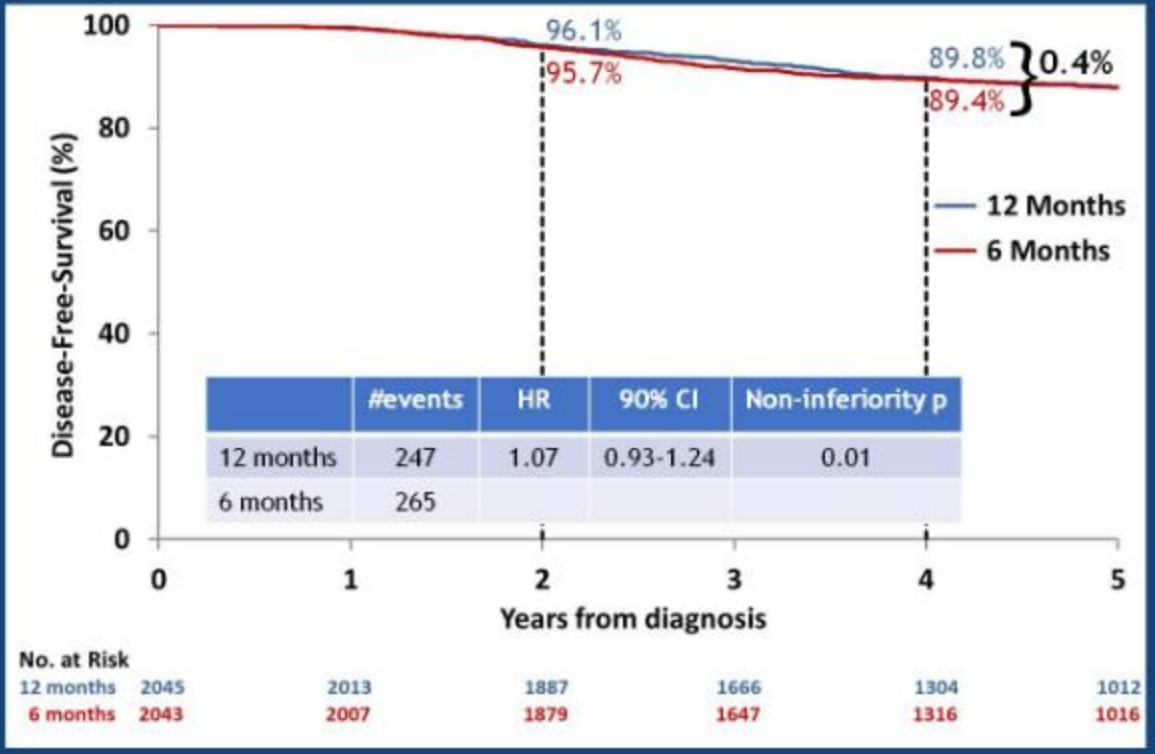
Persephone Study Design



1º : DFS [Diagnosis to 1st relapse (local or distant) or death]

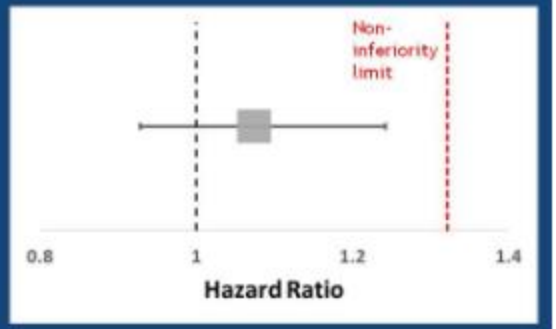
2º :OS ; Cost effectiveness ; Cardiac function

Disease-free survival



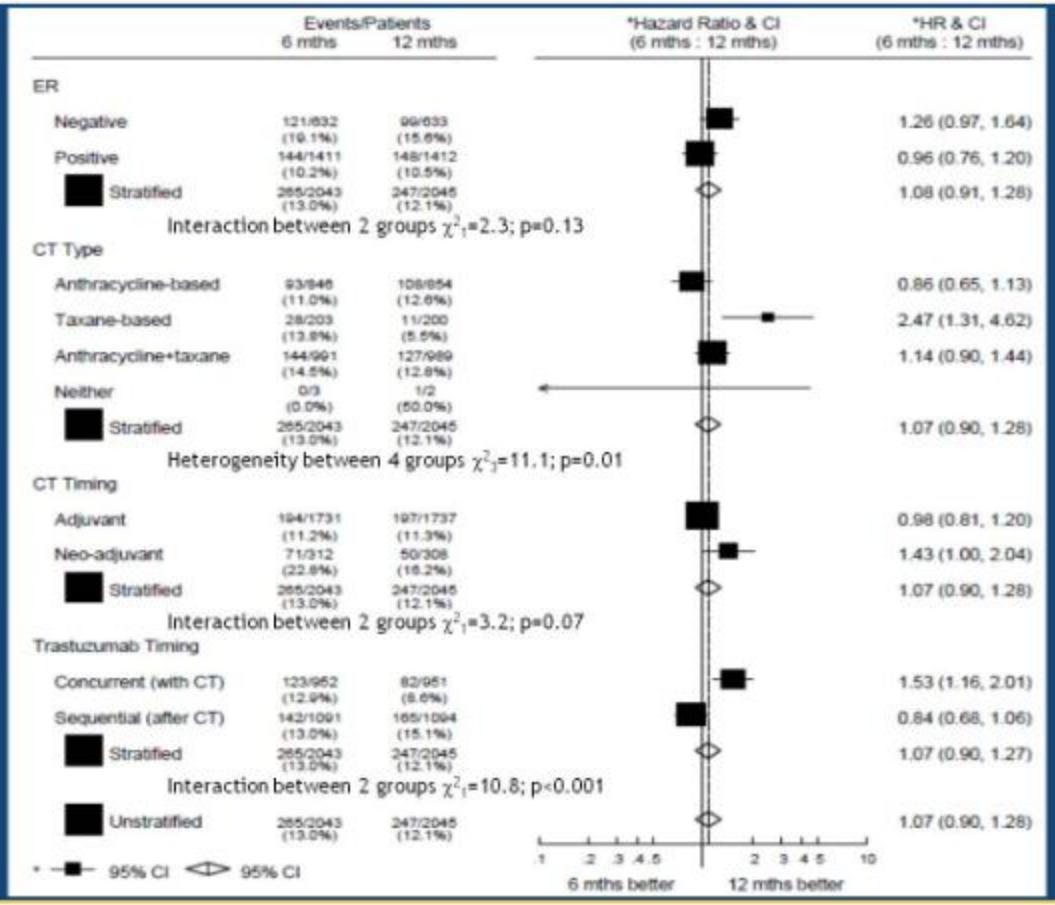
	#events	HR	90% CI	Non-inferiority p
12 months	247	1.07	0.93-1.24	0.01
6 months	265			

No. at Risk						
12 months	2045	2013	1887	1666	1304	1012
6 months	2043	2007	1879	1647	1316	1016

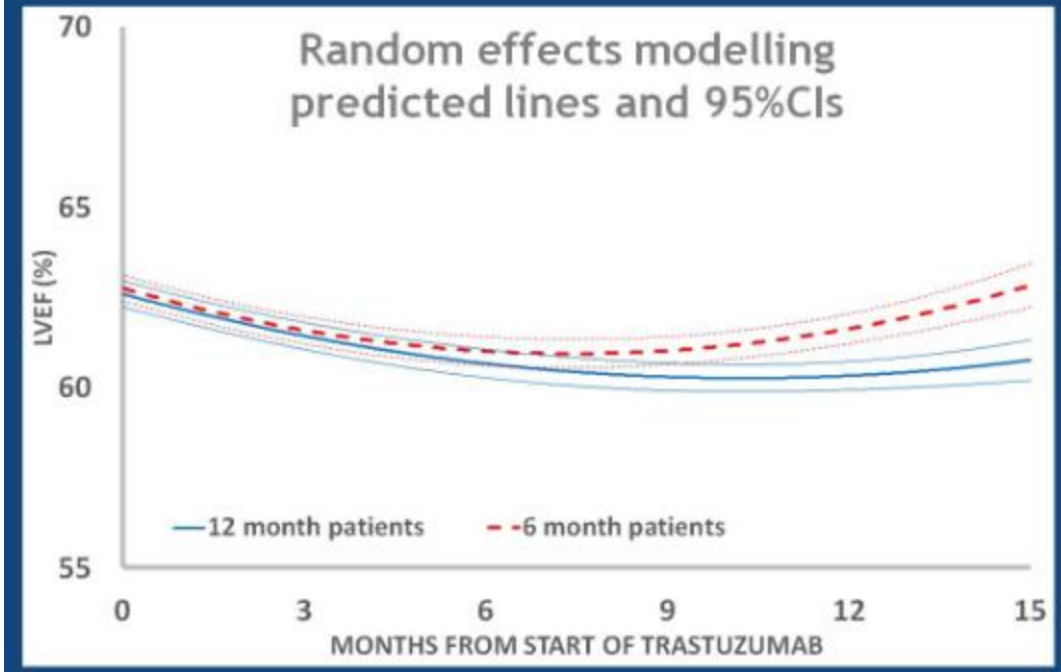


DFS:

Pre-defined subgroup analysis



Cardiotoxicity



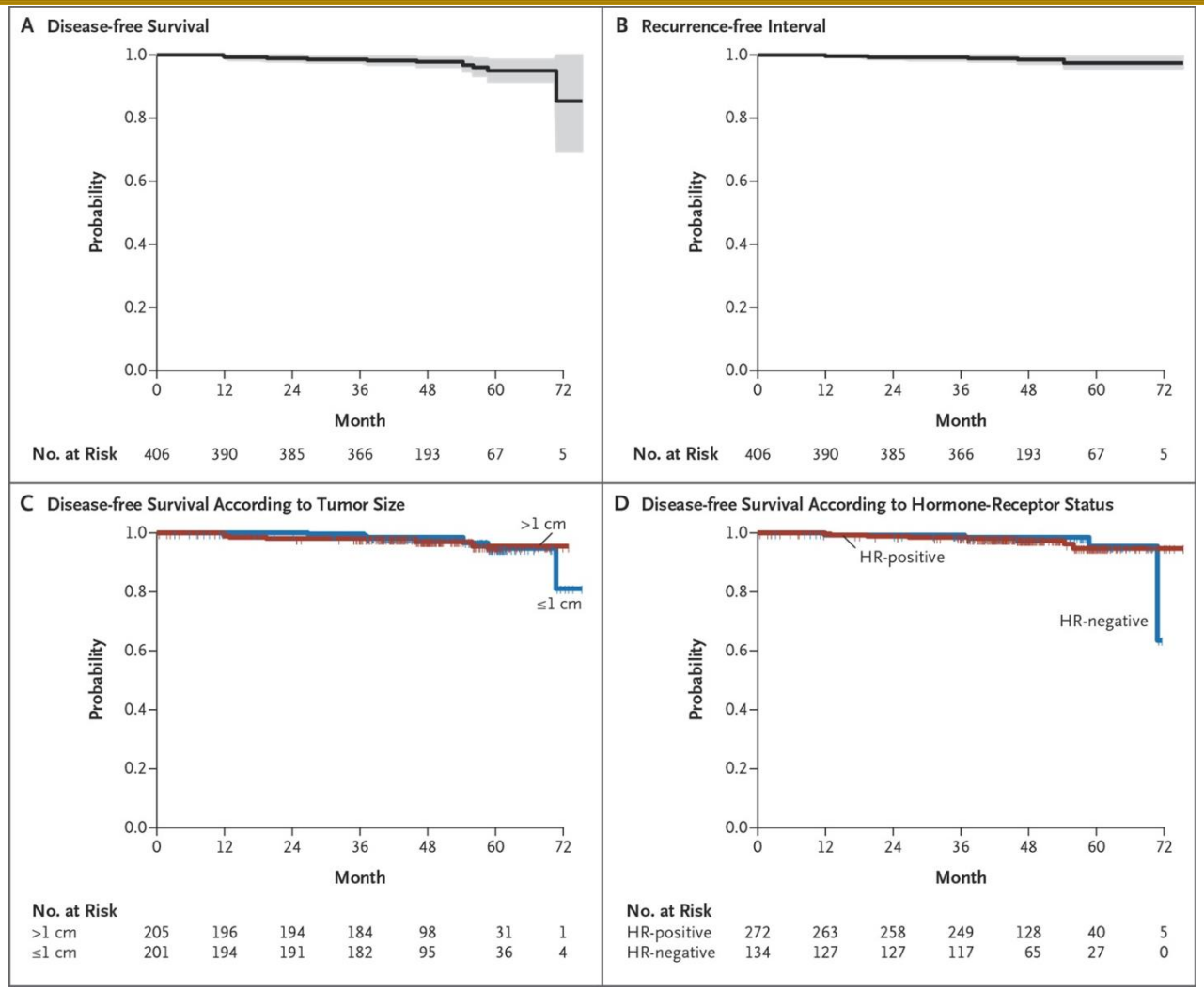
Stopped trastuzumab because of cardiotoxicity
- in **8%** of 12-month patients
- in **4%** of 6-month patients

(p<0.0001)

- Cardiac function recovers post-trastuzumab (p<0.0001)
- 6-month patients had a more rapid recovery (p=0.02)

Ref: Earl et al. British Journal of Cancer (2016) 115, 1462–1470

De-escalating chemotherapy



Tolaney, et al, NEJM 2015

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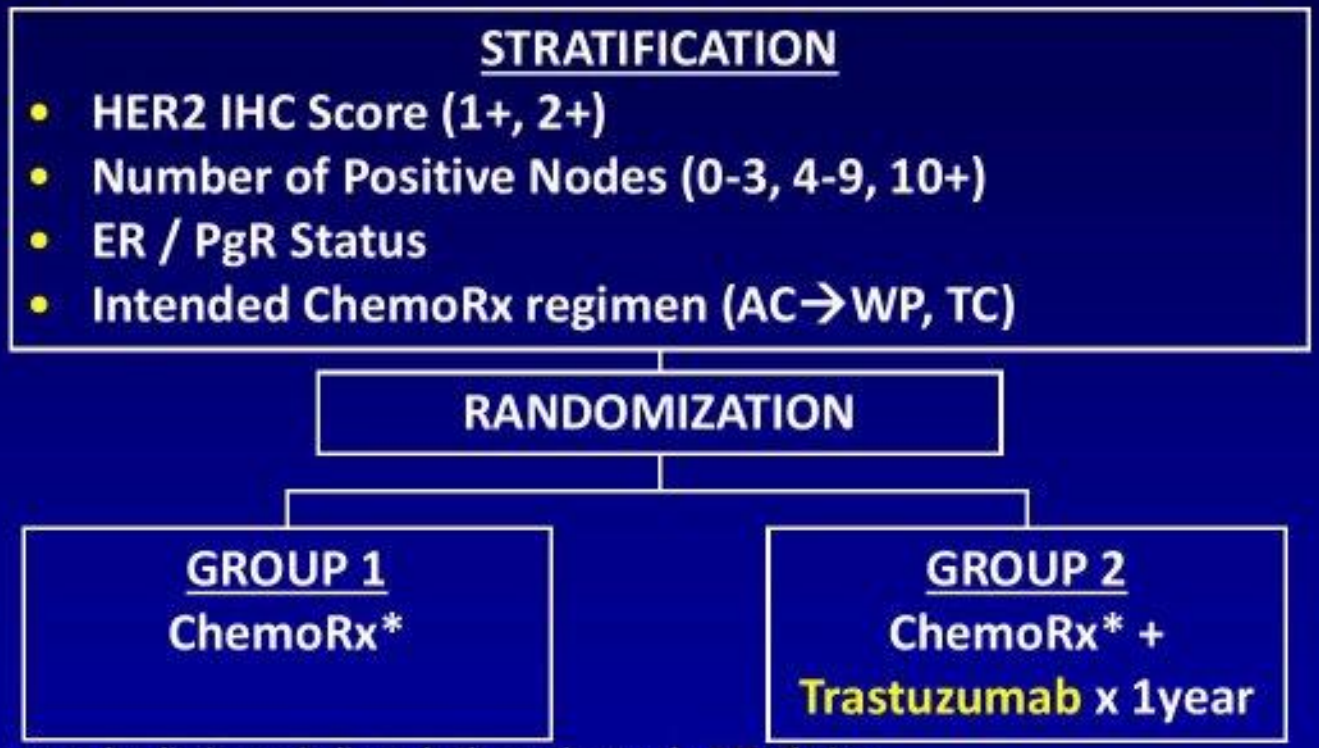
How does this change clinical practice?

- Duration of adjuvant trastuzumab remains 1 year
- Can be reassured if patient cannot complete a year
- Focus is on de-escalating chemotherapy rather than HER2 directed therapy

B-47: Adjuvant Trastuzumab in HER2 Low Breast Cancer

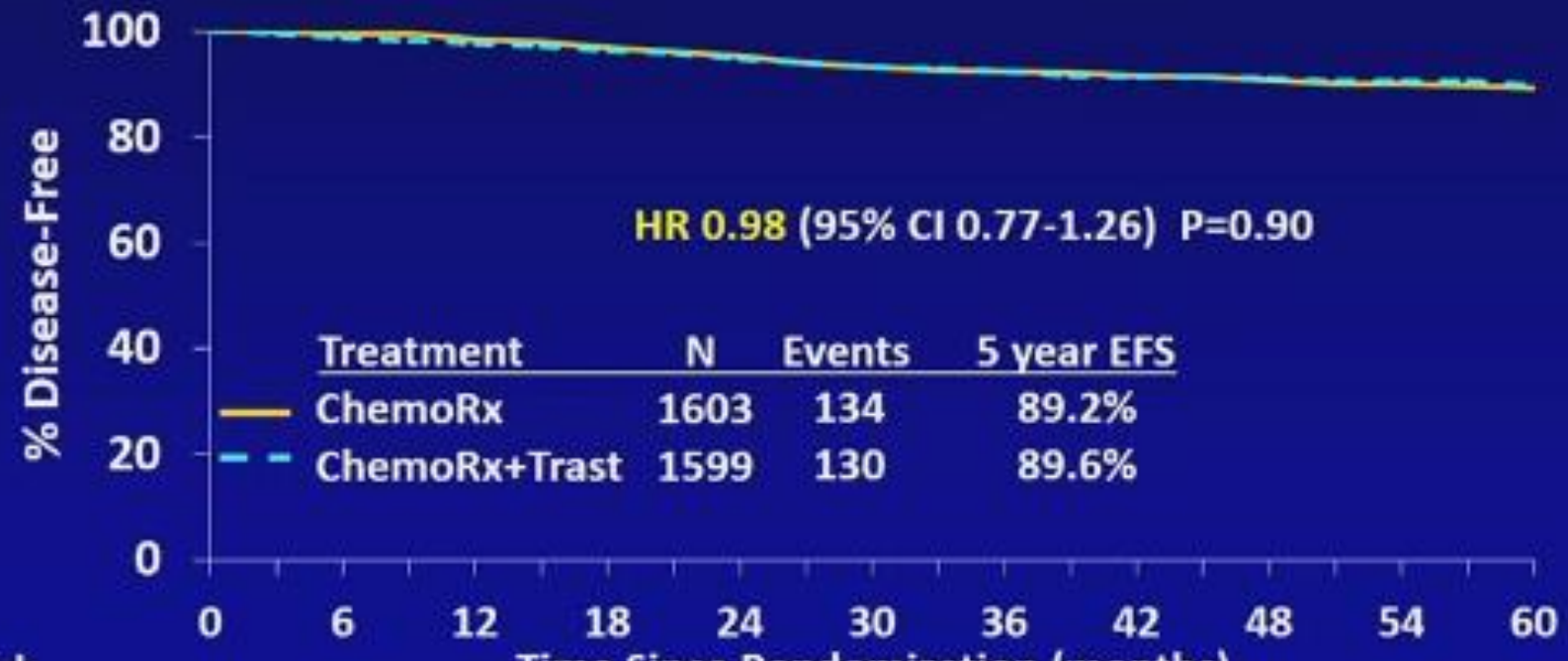


Hormonal therapy and radiation as indicated. Chemotherapy by MD Choice:

*AC→WP: Doxorubicin 60mg/m2 and Cyclophosphamide 600mg/m2 q2 or 3 wks x 4 followed by qwk paclitaxel x 12
or TC: Docetaxel 75mg/m2 + Cyclophosphamide 600mg/m2 q3wk x 6

San Antonio Breast Cancer Symposium, December 5-9, 2017

B-47: Invasive Disease-Free Survival



No. at Risk						
ChemoRx	1603	1558	1423	1003	595	140
ChemoRx+Trast	1599	1528	1403	1009	591	117

How does this change clinical practice?

- No role for trastuzumab in HER2 low early stage breast cancer

Thank you.
Questions?

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