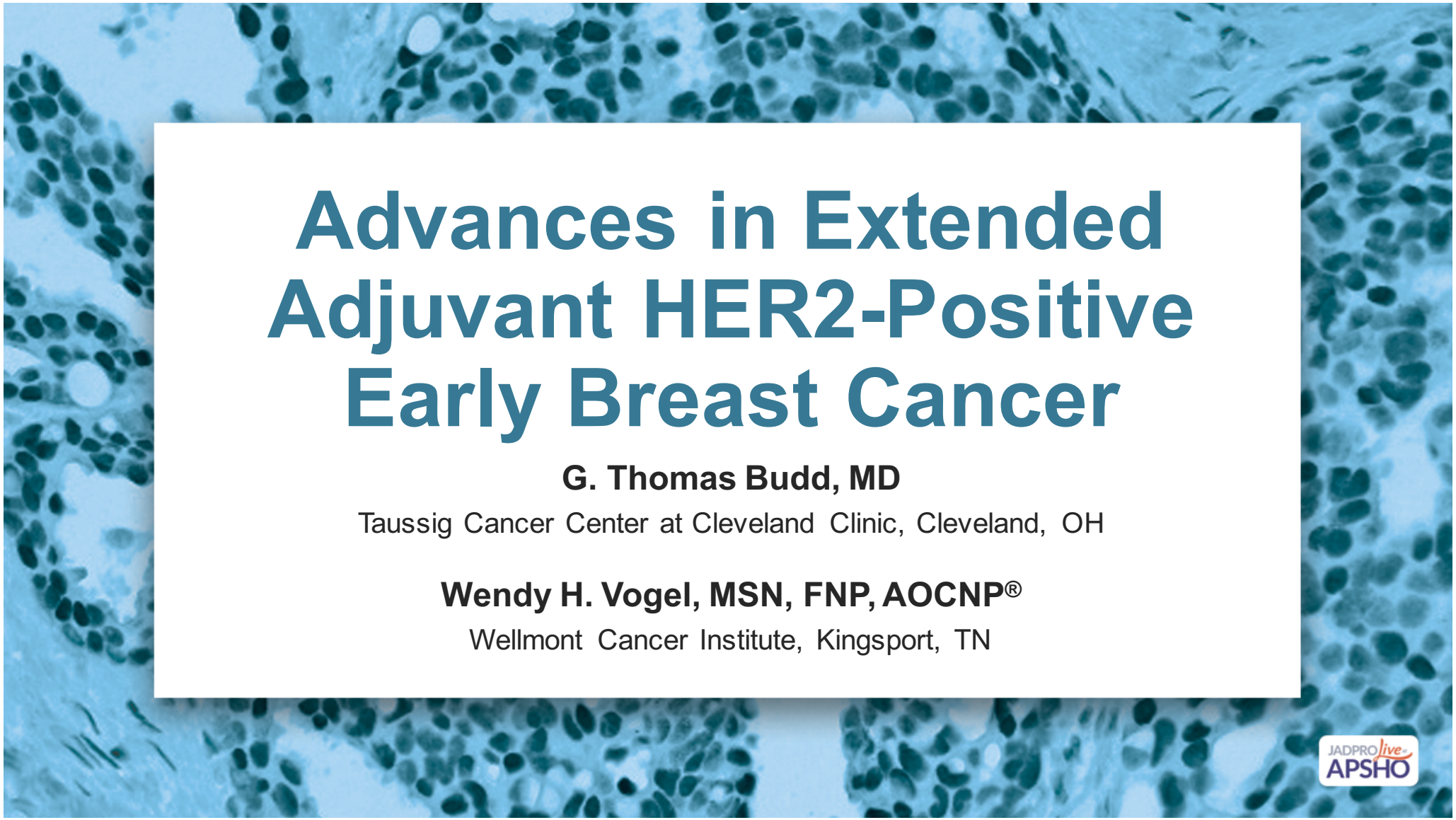

Advances in Extended Adjuvant HER2-Positive Early Breast Cancer

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Disclosures

- G. Thomas Budd: Research funding from CytRx, Eisai, Genentech, Tracon

- Wendy Vogel: Speakers bureau for AMAG, Celgene, Genentech, Ipsen, Janssen, Novartis, Pfizer, Takeda

This activity is supported by an educational grant from Puma Biotechnology, Inc.

Learning Objectives

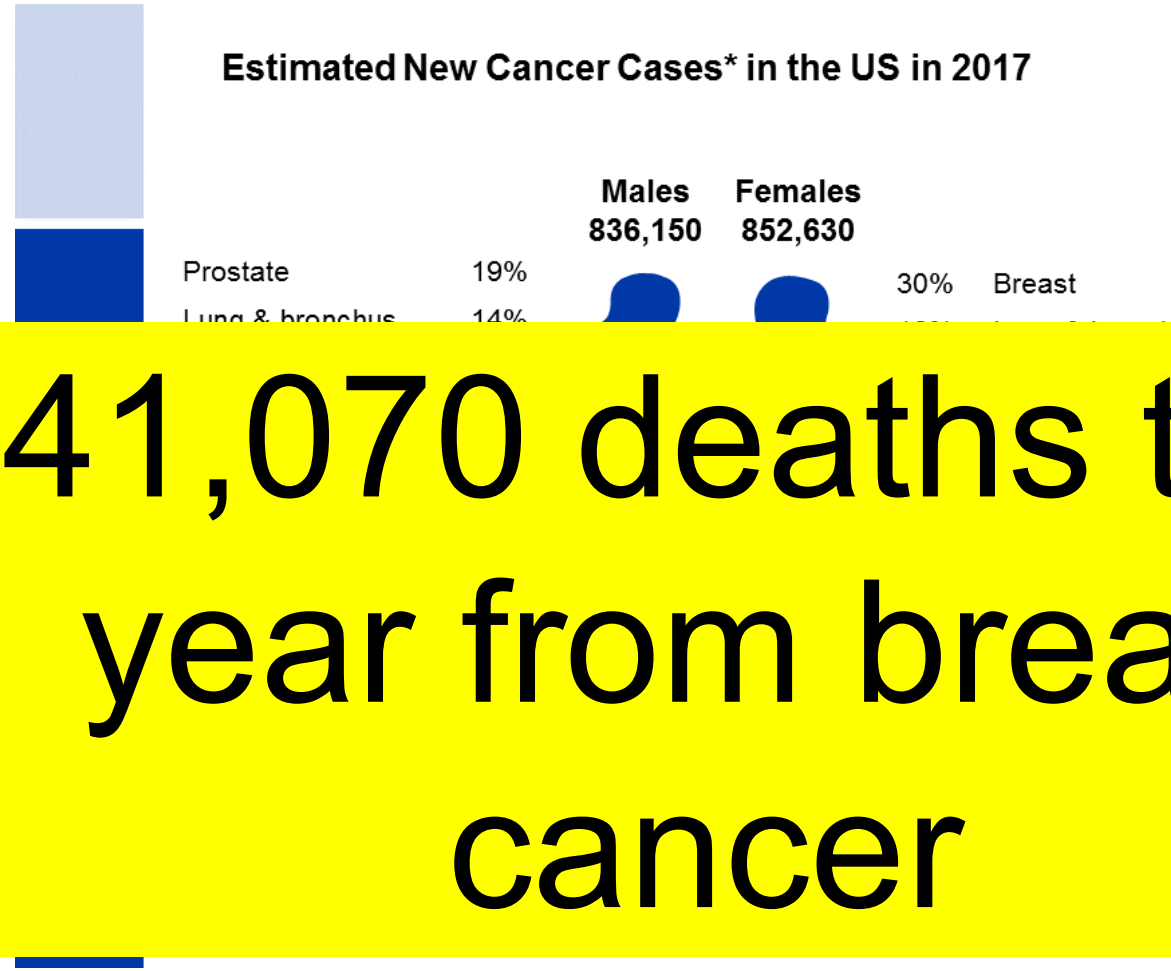
Upon completion of this activity, participants will be able to:

- Describe the mechanisms of action of novel extended adjuvant therapies for early HER2-positive breast cancer
- Utilize evidence-based strategies for prophylaxis of diarrhea and other side effects
- Optimize patient selection for treatment with extended adjuvant therapies
- Implement HER2-status testing in accordance with the latest clinical practice guidelines

Outline

- Breast Cancer Introduction
- HER2+ Breast Cancer Focus
- HER2+ Pathophysiology
- HER2 Testing
- HER2+ Management
- Future Treatment Options
- Symptom Management
- Role of Advanced Practice Providers in Caring for Patients With HER2+ Breast Cancer
- Case Study

Breast Cancer Introduction



41,070 deaths this year from breast cancer

Siegel RL, et al. *CA: Cancer J for Clin*. 2017;67(1):7-30.

Prognosis Based on Staging Alone

- Five year survival
  - Stage 0-1 Almost 100%
  - Stage 2 93%
  - Stage 3 72%
  - Stage 4 22%
- Many other factors affect prognosis

Siegel RL, et al. *CA: Cancer J Clin*. 2017;67(1):7-30.

Breast Cancer Prognostic Factors

- Hormonal status
- HER2/*neu* status
- Grade/histology
- Lymph node status
- Age
- Health
- Treatment
- Response to treatment

Cobain EF, Hayes DF. *Curr Treat Options Oncol*. 2015 May;16(5):23. doi: 10.1007/s11864-015-0340-x.
Sestak I, Cuzick J. *Breast Cancer Res*. 2015 Jan 27;17:10. doi: 10.1186/s13058-015-0516-0.

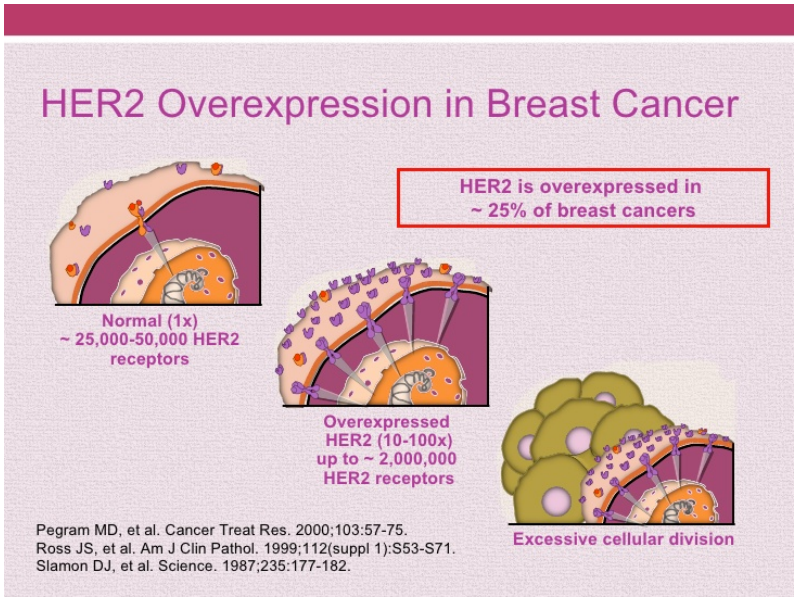
Molecular Subtypes Determine Treatment

Intrinsic Type	Luminal A	Luminal B	HER2 Overexpression	Basal Type
Histological grade	Low to intermediate	Intermediate to high	High	High
Distinguishing markers	ER + PR + HER2 - Low Ki67	ER weaker + PR +/- HER2 +/- Higher Ki67 Mutations TP53	ER - PR - HER2 +	ER - PR - HER2 - CK5/6 + EGFR +
Percentage of breast cancer population	40%	20%	20-30%	~ 15%
Prognosis	Good	Intermediate High risk of relapse	Poor	Poor High frequency of BRCA1 mutations
Targeted therapy	Hormonal	Hormonal therapy HER2 therapy if HER2 positive	HER2 Targeted therapy	No target therapy options

Henry-Tillman RS, Kilmberg VS. *Curr Treat Options Oncol*. 2000 Aug;1(3):199-209.
Hergueta-Redondo M, et al. *Clin Transl Oncol*. 2008 Dec;10(12):777-785.
Robbins SE. *Nat Pract Oncol*. 2007 Sep;4(9):516-525.
Sestak I, Cuzick J. *Breast Cancer Res*. 2015 Jan 27;17:10. doi: 10.1186/s13058-015-0516-0.

HER2-Positive Breast Cancer

HER2 Breast Cancer

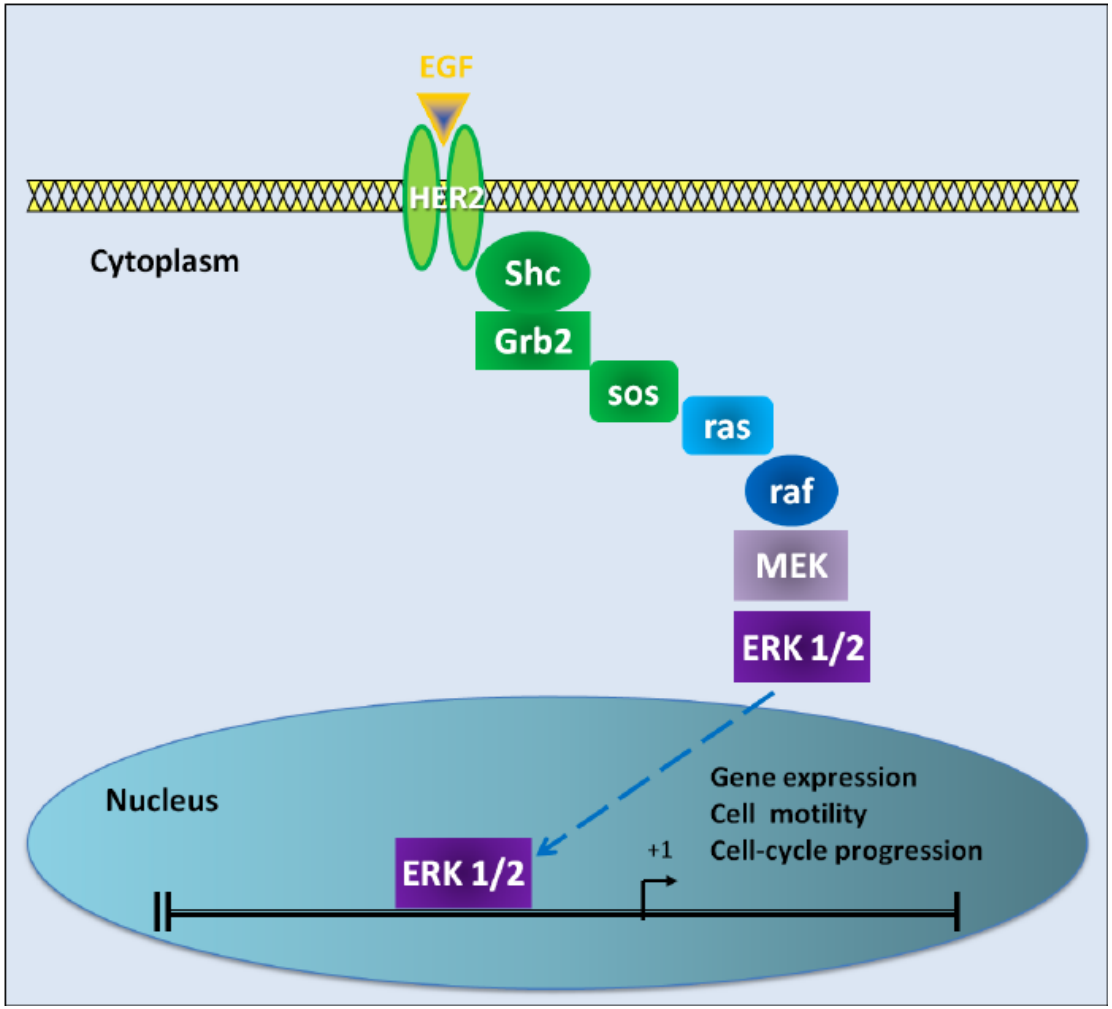


Provided courtesy of Wendy H. Vogel, MSN, FNP, AOCNP.

- HER2 (also called ERBB2)
  - A transmembrane tyrosine kinase receptor
  - Member of the epidermal growth factor receptor family (EGFR)
  - HER2 gene product overexpressed 18-20% of all breast cancers
  - A more aggressive tumor phenotype
  - Poor prognosis with higher rate of recurrence and mortality
    - Independent of other risk factors such as tumor grade, age, stage of patient

Markman & Roth, 2017. Breast Cancer and HER2 Overview of HER2 Breast Cancer. Accessed 10/11/17 at https://emedicine.medscape.com/article/1689966-overview

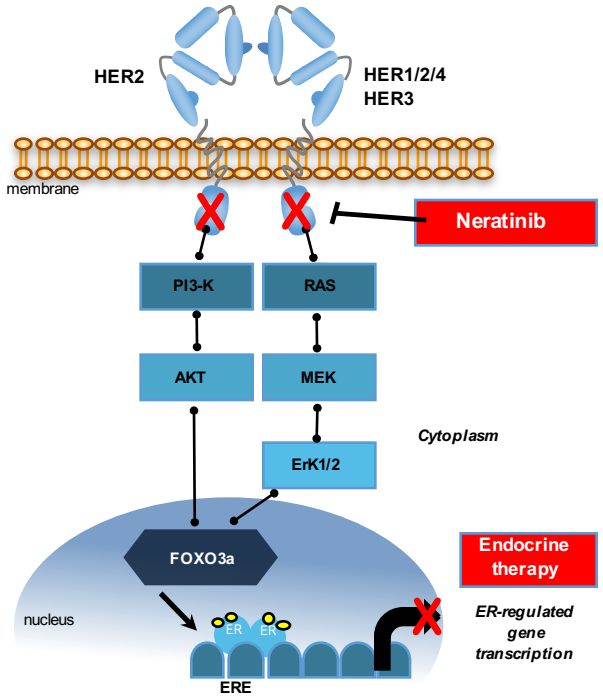
HER2 Pathway



Provided courtesy of Wendy H. Vogel, MSN, FNP, AOCNP.

HER2/Estrogen Receptor (ER) Crosstalk Rationale for Increased Benefit in HR+ Subgroup

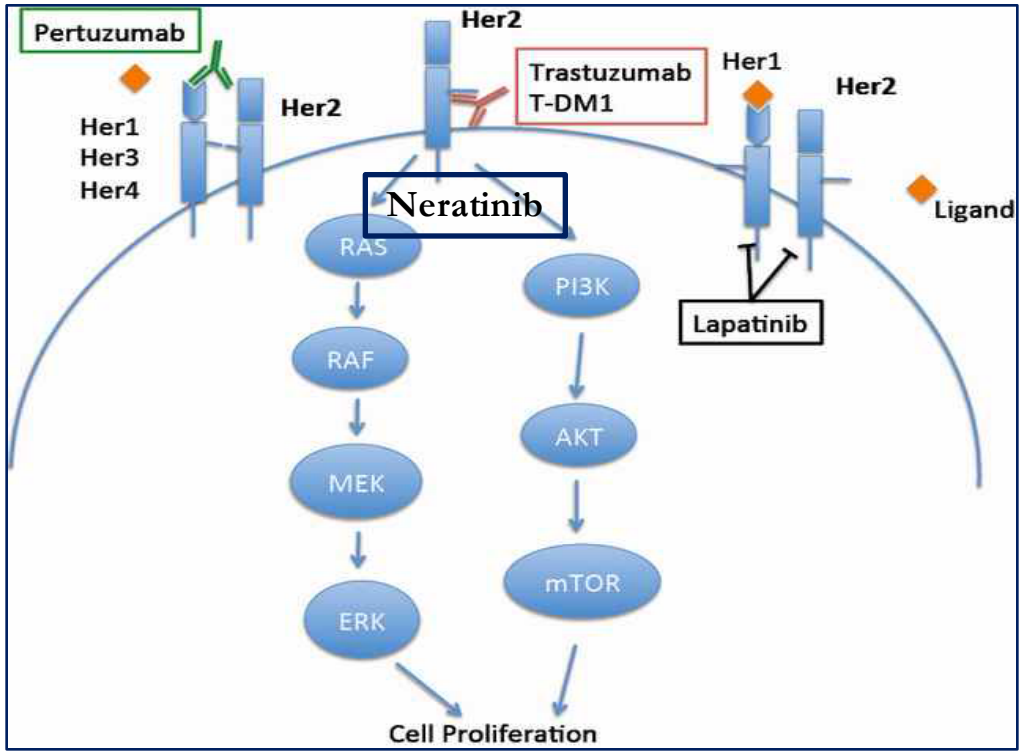
- HER2 downstream activation can lead to endocrine therapy resistance
- Aberrant HER2 signaling decreases ER regulated gene transcription



- HER2 inhibition upregulates ER-regulated gene transcription
- Dual inhibition of HER2 and ER is required for effective blockade of HER2+/HR+ tumors
  - ER+, HER2+ breast tumor cells
  - ER+, *ERBB2*-mutant breast tumor cells

Arpino G, et al. *Endocr Rev*. 2008;29(1):217-233.
Montemurro F, et al. *Ann Oncol*. 2013;24:2715-2724.
Adapted from Paplomata E, et al. *Cancer*. 2015;121(4):517-526.

HER2 Target Leads to Therapeutic Options



Provided courtesy of Wendy H. Vogel, MSN, FNP, AOCNP.
Davis NM, et al. *Oncotarget*. 2014 Jul 15;5(13):4603-4650.


HER2 Testing
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Guidelines for HER2 Testing

- ASCO, 2013: http://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/9751
  - Process of updating: http://www.asco.org/about-asco/press-center/news-releases/asco-and-cap-invite-comment-focused-update-her2-testing
- College of American Pathologists http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/her2-summary.pdf
- NCCN https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf

Wolff AC, et al. *J Clin Oncol*. 2013;31(31):3997-4013.

Recommendations for HER2 Testing

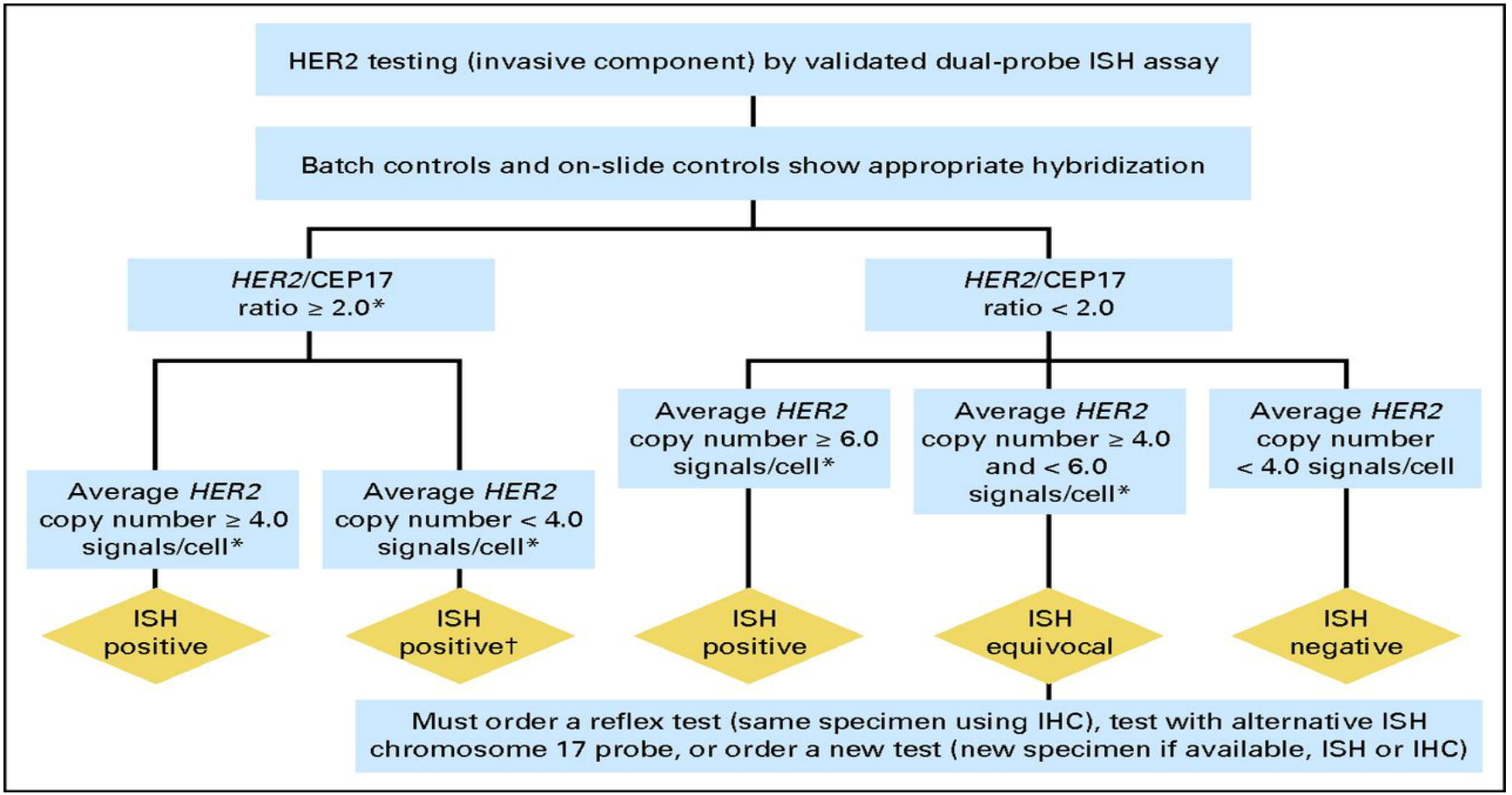
- In all patients with invasive breast cancer
- Positive status is demonstrated by
  - Protein overexpression or
  - Gene amplification
- If results are equivocal, reflex testing should be done with alternative assay; consider repeat testing if results discordant
- Labs should be accredited and should demonstrate high concordance with validated HER2 test on a large and representative set of specimens

Wolff AC, et al. *J Clin Oncol*. 2013;31(31):3997-4013.
NCCN, 2017. NCCN Guidelines Version 2.2017: Invasive Breast Cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf

Immunohistochemistry (IHC) Testing

- 3+: positive for HER2 expression (more than 10% of invasive tumor cells)
- 2+: equivocal for HER2 protein expression (non-uniform or weak membrane staining, but has circumferential distribution in at least 10% of cells)
- 0-1+: negative for HER2 protein expression

Wolff AC, et al. *J Clin Oncol*. 2013;31(31):3997-4013.



Wolff AC, et al. *J Clin Oncol*. 2013;31(31):3997-4013.

Provided courtesy of G. Thomas Budd, MD


HER2-Positive
Management
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Guidelines

- ASCO (2014)
  - http://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/9781
  - http://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/9786
- NCCN www.nccn.org

Treatment of Early-Stage HER2-Positive Disease

Treatment options for a patient with ER-positive, HER2-positive stage II/III breast cancer:

- Neoadjuvant chemotherapy and trastuzumab/pertuzumab
- Surgery/radiation therapy
- Adjuvant therapy with trastuzumab
- Hormone therapy or manipulation

Neoadjuvant Treatment Regimens for HER2-Positive Breast Cancer

- Preferred regimens (NCCN)
  - AC followed by T + trastuzumab +/- pertuzumab
  - TCH
- Other regimens
  - AC followed by docetaxel + trastuzumab +/- pertuzumab
  - Docetaxel + cyclophosphamide + trastuzumab
  - FEC followed by docetaxel + trastuzumab + pertuzumab
  - Paclitaxel + trastuzumab
  - Pertuzumab + trastuzumab + docetaxel followed by FEC
  - Pertuzumab + trastuzumab + paclitaxel followed by FEC

AC: doxorubicin and cyclophosphamide; TCH docetaxel, carboplatin and trastuzumab; FEC fluorouracil, epirubicin, and cyclophosphamide

NCCN Guidelines. Breast Cancer. www.nccn.org/professionals/physician/gls/pdf/breast.pdf
Partridge AH, et al. *J Clin Oncol*. 2014;32(29):3307-3329.
Giordano SH, et al. *J Clin Oncol*. 2014;32(19):2078-2099.

Adjuvant Treatment Regimens for HER2-Positive Breast Cancer

- Hormone receptor-positive
  - Adjuvant endocrine therapy
  - +/- adjuvant chemotherapy + trastuzumab
- Hormone receptor-negative
  - Adjuvant chemotherapy + trastuzumab

NCCN, 2017. NCCN Guidelines. Breast Cancer. www.nccn.org/professionals/physician/gls/pdf/breast.pdf

Extended Adjuvant Therapy

- Rationale
  - ~25% of women treated with adjuvant trastuzumab have breast cancer recurrences (median follow-up of 8-10 years)
  - Studies showed that longer duration of adjuvant trastuzumab did not improve outcome
- New FDA approval for extended adjuvant therapy
  - Neratinib

NCCN, 2017. NCCN Guidelines. Breast Cancer. www.nccn.org/professionals/physician/gls/pdf/breast.pdf

HER2 Agents for Adjuvant Treatment of HER2-Positive Breast Cancer

- Trastuzumab
- Pertuzumab
- Lapatinib
- Neratinib

NCCN Guidelines. Breast Cancer. www.nccn.org/professionals/physician/gls/pdf/breast.pdf
Partridge AH, et al. *J Clin Oncol*. 2014;32(29):3307-3329.
Giordano SH, et al. *J Clin Oncol*. 2014;32(19):2078-2099.


Clinical Trials:
Adjuvant/Neoadjuvant
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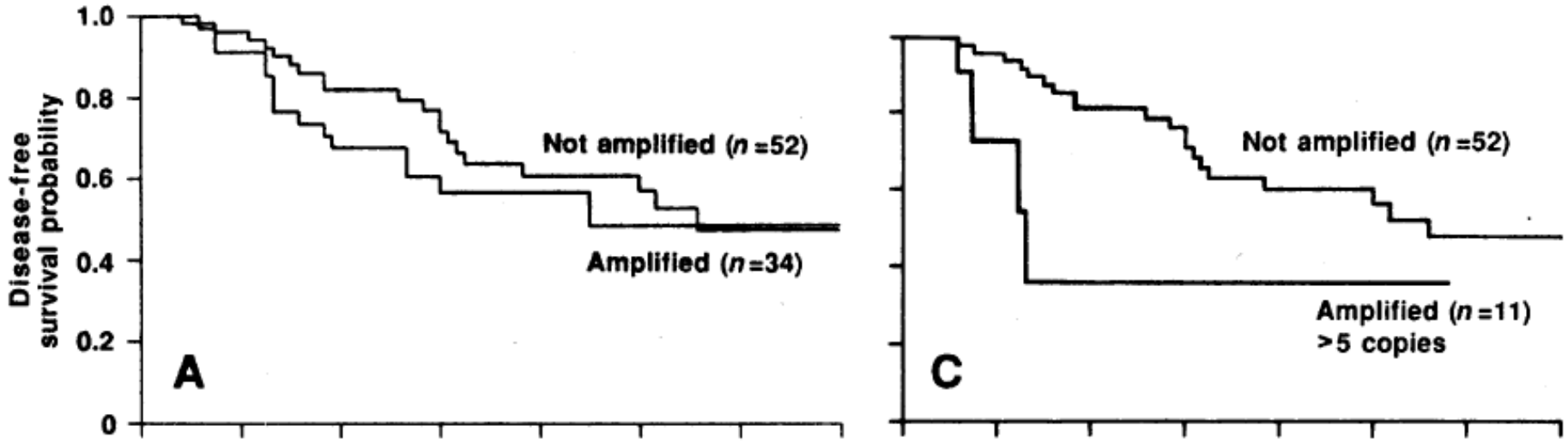
Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN, AXEL ULLRICH, WILLIAM L. MCGUIRE

SCIENCE, VOL. 235 9 JANUARY 1987



Actuarial curve for relapse in (A) node-positive patients with no amplification versus node-positive patients with any amplification (>2 copies) of HER-2/*neu* and (C) node-positive patients with no amplification versus node-positive patients with greater than 5 copies of HER-2/*neu*.

Provided courtesy of G. Thomas Budd, MD.
Slamon DJ, et al. *Science*. 1987;235(4785):177-182.

Univariate and Multivariate Analyses in Node-Positive Patients

Factor	Univariate (*P*)		Multivariate*	
	Survival	Relapse	Survival	Relapse
Number of positive nodes	0.0001	0.0002	0.0003 (0.0938 ± 0.0256)	0.001 (0.0849 ± 0.0266)
HER2/*neu*	0.0011	<0.0001	0.02 (0.0872 ± 0.0388)	0.001 (0.1378 ± 0.0425)
Log (PgR)	0.05	0.05		
Tumor size	0.06	0.06		
Log (ER)	0.15	0.10	0.03 (-0.5158 ± 0.2414)	
Age	0.22	0.61		

*Cox's partially nonparametric regression model was used to evaluate the predictive power of various combinations and interactions of prognostic factors in a multivariate manner. Results are shown as *P* (regression coefficient ± SE).

Oncogene amplification, says Clark, is "the first prognostic factor I've seen that, by itself, is that powerful."

Provided courtesy of G. Thomas Budd, MD.

Slamon DJ, et al. *Science*. 1987;235(4785):177-182.

Trastuzumab plus Adjuvant Chemotherapy for HER2-positive Breast Cancer: Final Planned Joint Analysis of Overall Survival from NSABP B-31 and NCCTG N9831

EH Romond[1,2], VJ Suman[3], J-H Jeong[1,4], GW Sledge, Jr.[5], CE Geyer, Jr.[1,6], S Martino[7], P Rastogi[1,8], J Gralow[9], SM Swain[1,10], E Winer[11], G Colon-Otero[12], C Hudis[13], S Paik[1], N Davidson[8], EP Mamounas[14], JA Zujewski[15], N Wolmark[16], EA Perez[12]

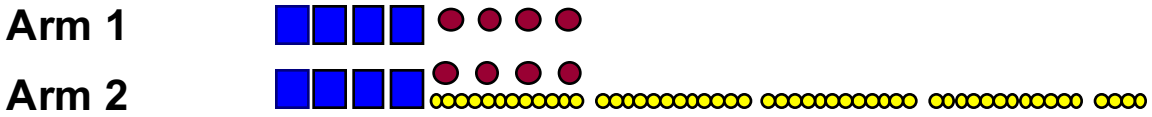
[1]National Surgical Adjuvant Breast and Bowel Project Operations and Biostatistical Centers; [2]University of Kentucky; [3]Mayo Clinic; [4]Department of Biostatistics, University of Pittsburgh Graduate School of Public Health; [5]IU Simon Cancer Center; [6]University of Texas Southwestern Medical Center; [7]The Angeles Clinic and Research Institute; [8]University of Pittsburgh Cancer Institute; [9]University of Washington; [10]Medstar Washington Hospital Center; [11]Dana-Farber Cancer Institute; [12]Mayo Clinic, Jacksonville; [13]Memorial Sloan-Kettering Cancer Center; [14]Aultman Hospital; [15]Division of Cancer Therapy and Diagnosis, Cancer Therapy Evaluation Program, National Cancer Institute, National Institutes of Health, DHHS; [16]Allegheny Cancer Center Allegheny General Hospital

San Antonio Breast Cancer Symposium – December 4-8, 2012

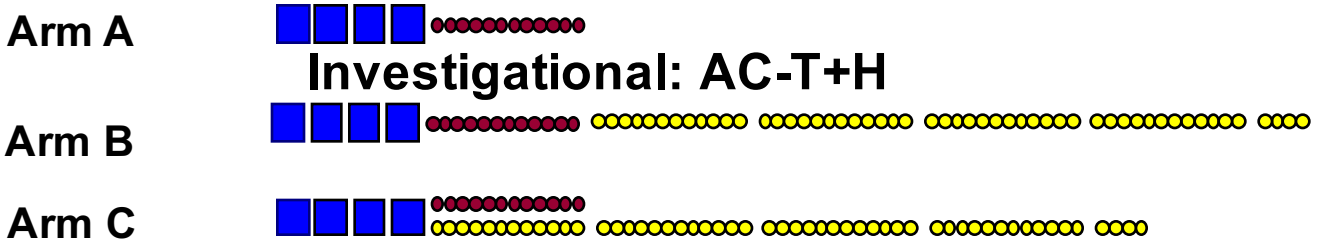
Abstract #S5-5

NSABP B-31

Control: AC-T



NCCTG N9831



= doxorubicin/cyclophosphamide (AC) 60/600 mg/m² q 3 wk x 4

= paclitaxel (T) 175 mg/m² q 3 wk x 4

= paclitaxel (T) 80 mg/m²/wk x 12

= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51

Romond EH, et al. *San Antonio Breast Cancer Symposium*. 2012;Abstract #S5-5.

Provided courtesy of G. Thomas Budd, MD.

Patient and Tumor Characteristics (%)

	AC → Paclitaxel		AC → Paclitaxel + Trastuzumab	
	N=1047 B-31	N=971 N9831	N=1055 B-31	N=973 N9831
Age (yr)				
<50	50	50	51	49
50-59	34	34	33	32
≥60	16	16	16	19
No. Positive Nodes				
0	0	15	0	14
1-3	57	47	58	49
4-9	29	24	29	25
10+	14	13	14	13
Hormone Receptors				
ER and PR neg	44	46	44	46
ER pos or PR pos	56	54	56	54
Tumor Size				
≤2.0 cm	41	40	38	38
2.1-5.0 cm	51	52	51	54
>5.0 cm	8	7	11	8

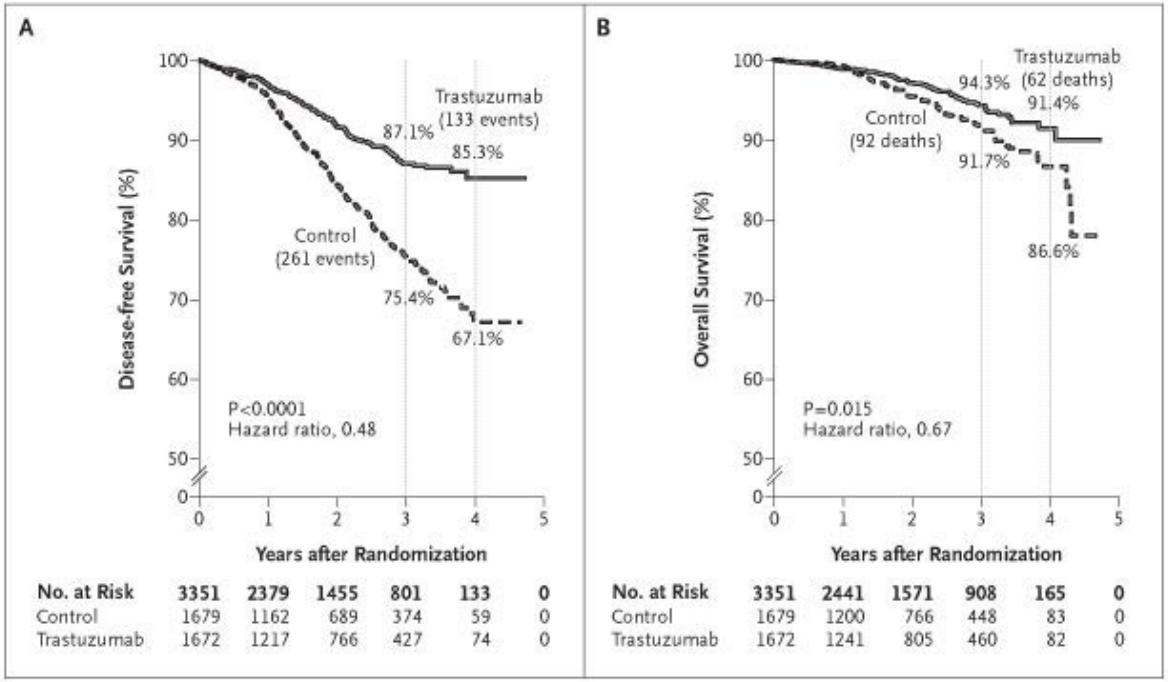
Romond EH, et al. *San Antonio Breast Cancer Symposium*. 2012;Abstract #S5-5.

Joint Statistical Analysis

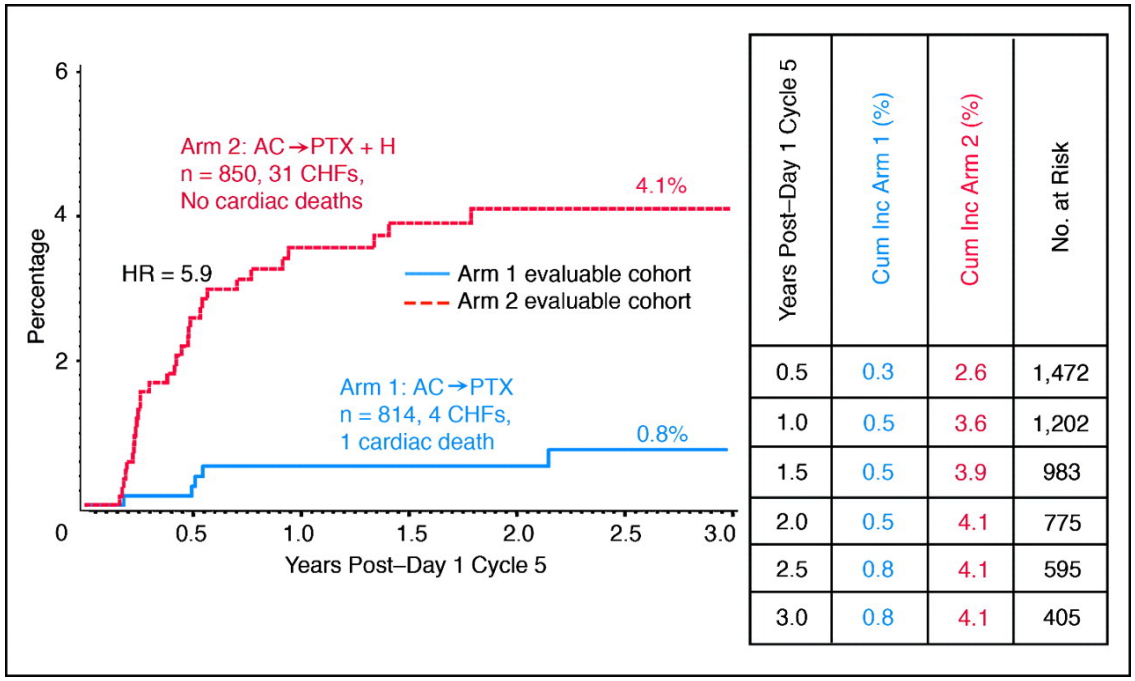
- Median follow-up: 8.4 years
  - Data lock: 15 Sept 2002
- Primary endpoint: DFS
  - Analyzed by intent-to-treat
- Secondary endpoint: OS
  - Analyzed by intent-to-treat
- First interim analysis occurred in 2005 after 355 DFS events
- Definitive survival analysis at 710 OS events

Romond EH, et al. *San Antonio Breast Cancer Symposium*. 2012;Abstract #S5-5.

Kaplan-Meier Estimates of Disease-Free Survival (Panel A) and Overall Survival (Panel B)



Provided courtesy of G. Thomas Budd, MD.
Romond E, et al. *N Engl J Med.* 2005;353(16):1673-1684.

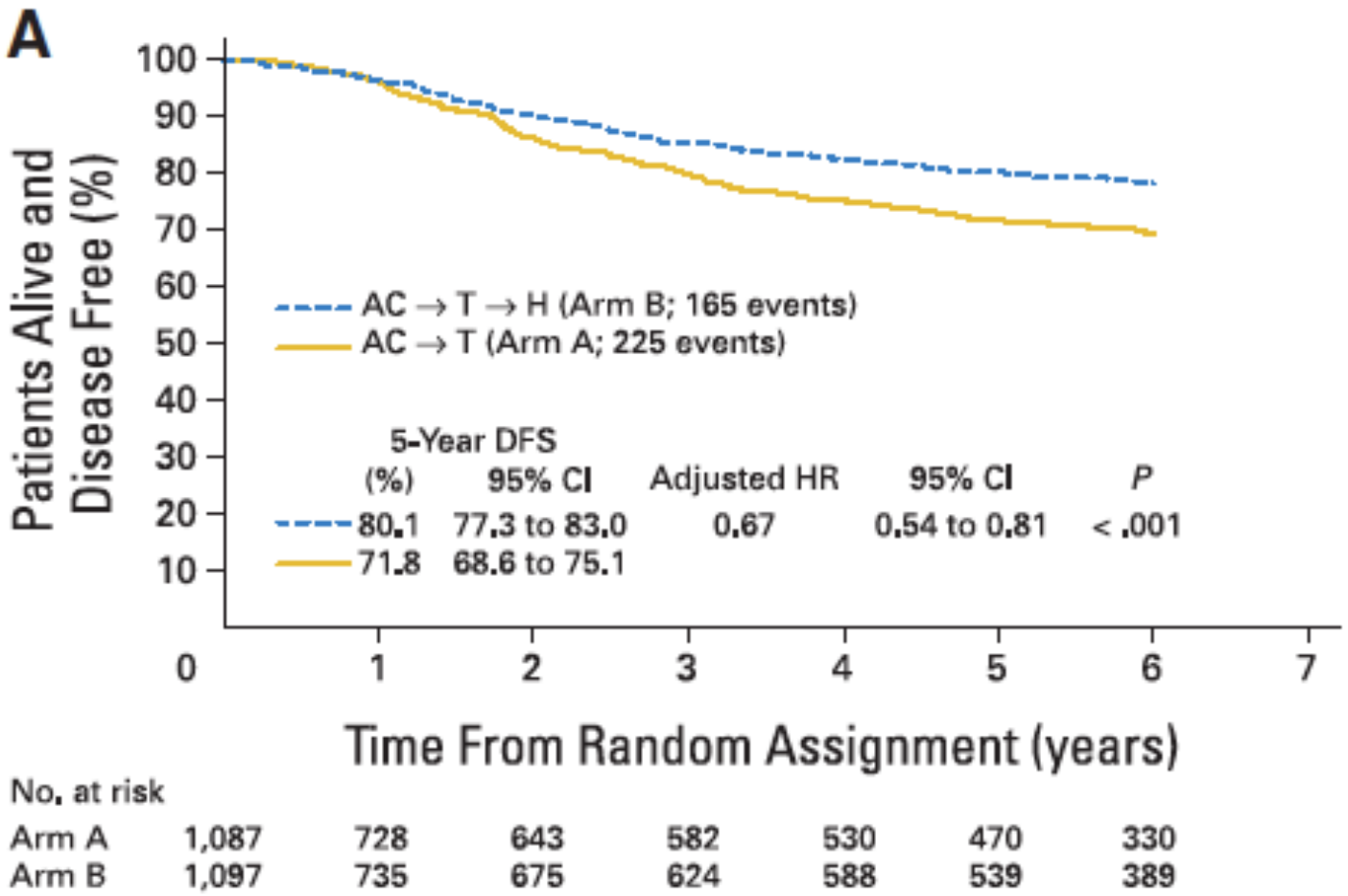


Years Post–Day 1 Cycle 5	Cum Inc Arm 1 (%)	Cum Inc Arm 2 (%)	No. at Risk
0.5	0.3	2.6	1,472
1.0	0.5	3.6	1,202
1.5	0.5	3.9	983
2.0	0.5	4.1	775
2.5	0.8	4.1	595
3.0	0.8	4.1	405

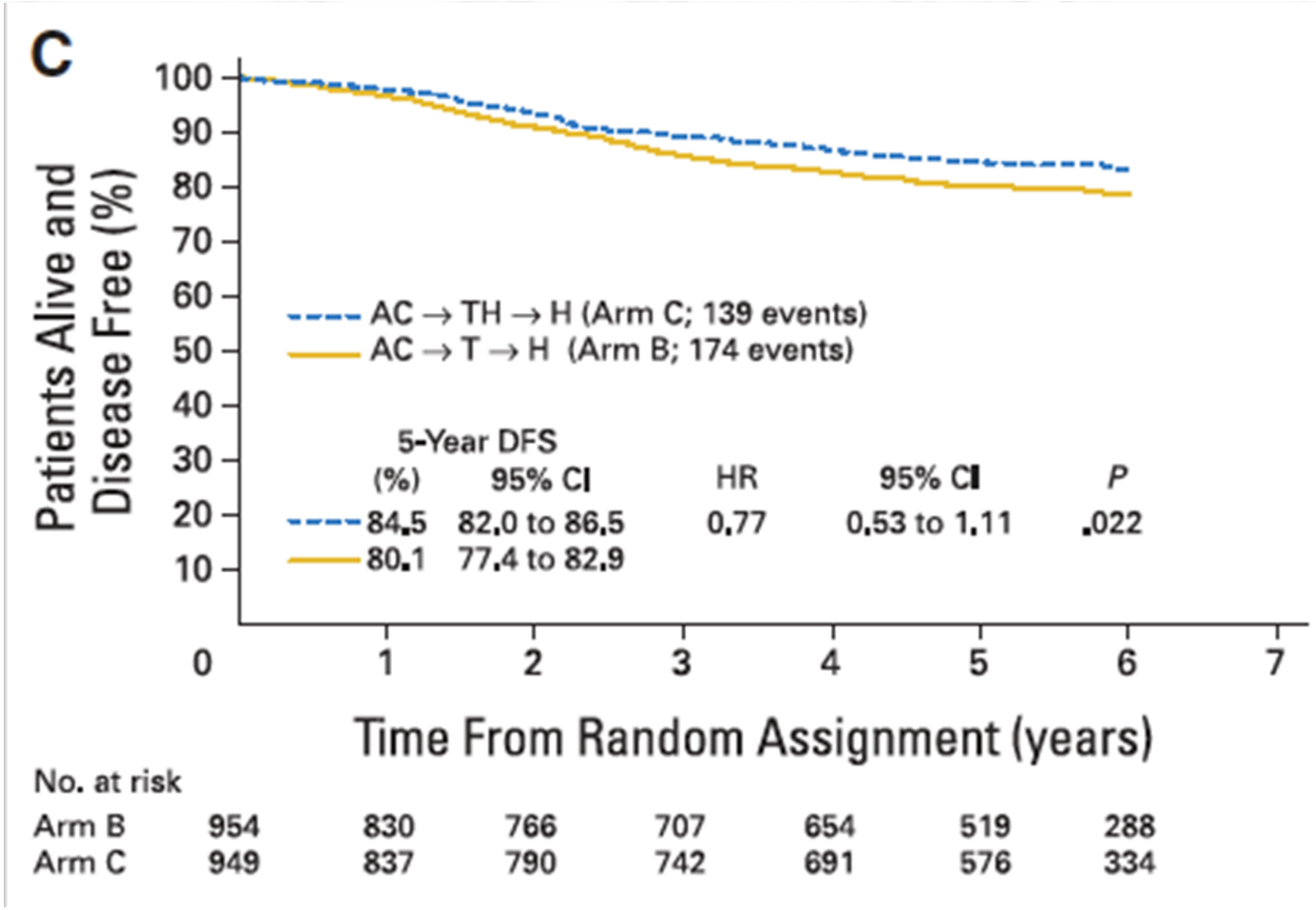
Cumulative incidence (Cum Inc) of cardiac events (congestive heart failure [CHF] or possible cardiac death) in evaluable cohort (arm 1 = doxorubicin and cyclophosphamide [AC] followed by paclitaxel [PTX]; arm 2 = AC followed by PTX plus trastuzumab [H]). Evaluable patients completed AC with a satisfactory post-AC multiple-gated acquisition scan, had no cardiac symptoms, and began treatment with PTX ± H. Time origin is day 1 of cycle 5.

Provided courtesy of G. Thomas Budd, MD.

Tan-Chiu E, et al. *J Clin Oncol.* 2005;23(31):7811-7819.



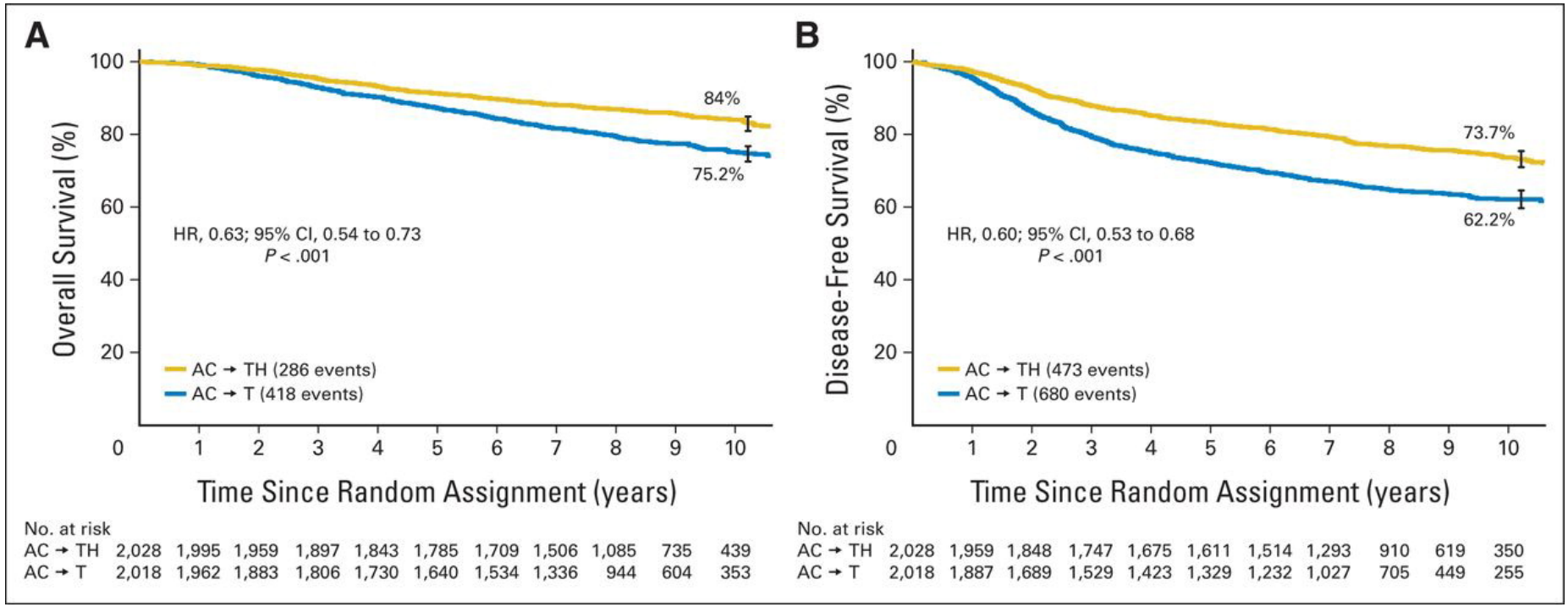
Provided courtesy of G. Thomas Budd, MD.
Perez E, et al. *J Clin Oncol.* 2014;32(33):3744-3752.



Provided courtesy of G. Thomas Budd, MD.
Perez E, et al. *J Clin Oncol.* 2014;32(33):3744-3752.

- Final analysis after 710 survival events
- Median follow-up 8.4 years

Perez E, et al. *J Clin Oncol.* 2014;32(33):3744-3752.



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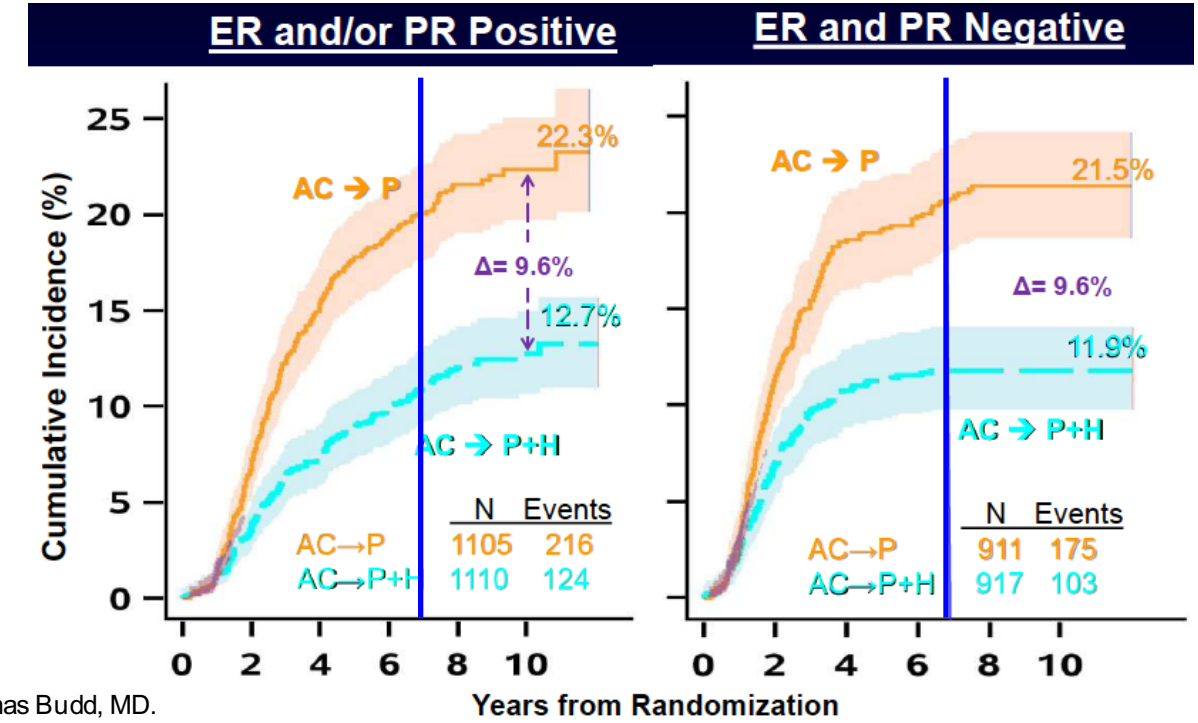
Provided courtesy of G. Thomas Budd, MD.
Perez E, et al. *J Clin Oncol.* 2014;32(33):3744-3752.

Conclusions

- With a median follow-up of 8.4 years, adding trastuzumab to paclitaxel following AC chemotherapy is associated with a significant and substantial improvement in OS with a relative risk reduction of 37% (HR, 0.63)
- For patients with high-risk HER2-positive breast cancer, treatment with this regimen reduces the risk of a DFS event at 10 years by 40% (HR, 0.60)
- A similar relative risk reduction benefit for both DFS and OS was observed in virtually all subsets of patients analyzed

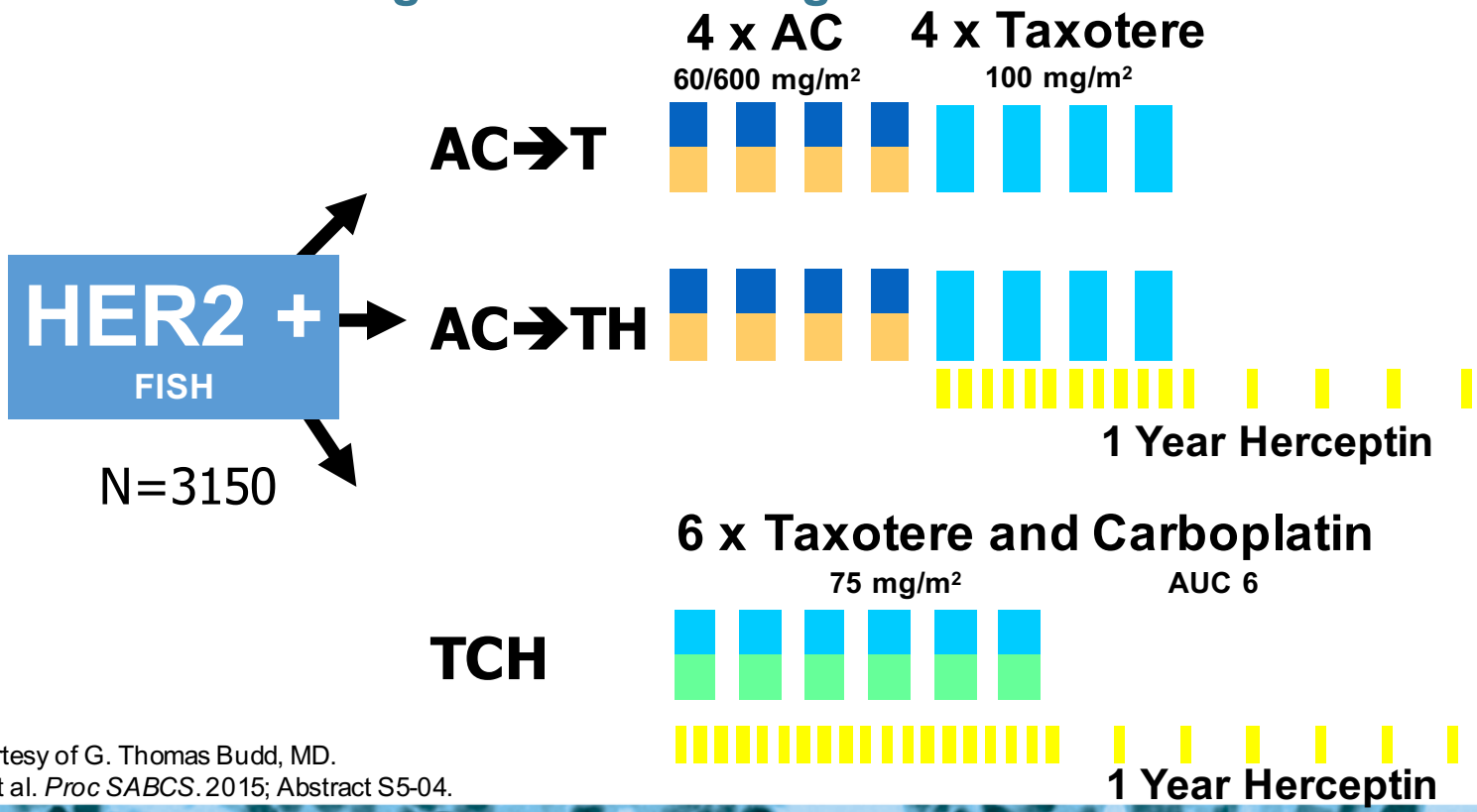
B-31/N9831 Cumulative Incidence of Distant Recurrence as a First Event



Provided courtesy of G. Thomas Budd, MD.
Romond EH, et al. *Proc SABCS*. 2012;Abstract S5-05.

BCIRG 006

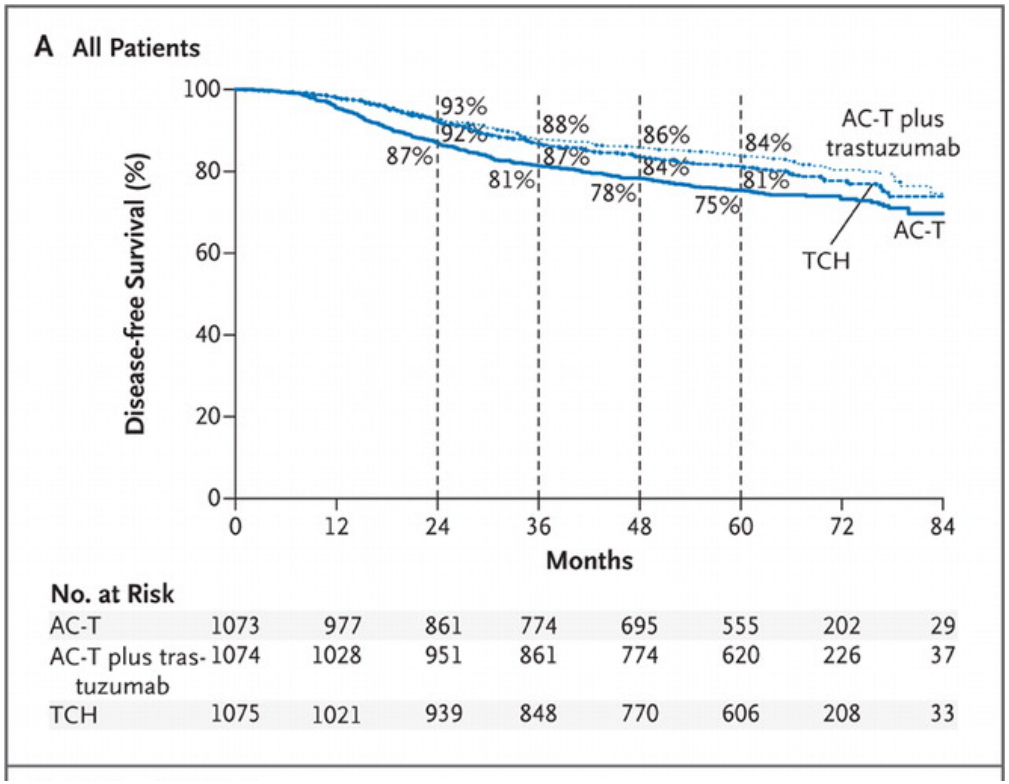
Adjuvant Breast Cancer
Node Positive and High-Risk Node Negative



Provided courtesy of G. Thomas Budd, MD.

Slamon DJ, et al. *Proc SABCS*. 2015; Abstract S5-04.

Disease-Free Survival Among All Patients



Provided courtesy of G. Thomas Budd, MD.
Slamon D, et al. *N Engl J Med.* 2011;365(14):1273-1283.

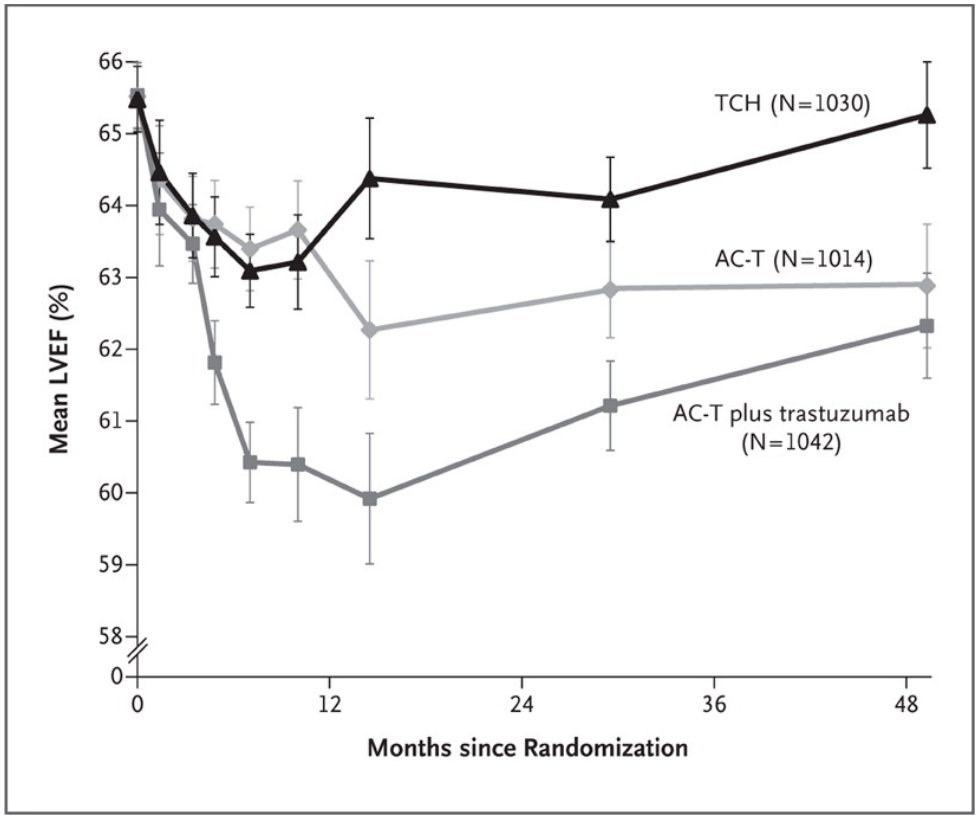
Cardiac Risk Factors and Events*

Variable	AC-T (N=1073)	AC-T plus Trastuzumab (N=1074)	TCH (N=1075)
	Number of patients (percent)		
Risk Factors			
Diabetes	38 (3.5)	36 (3.4)	28 (2.6)
Hypertension	178 (16.6)	178 (16.6)	190 (17.7)
Obesity†	214 (19.9)	242 (22.5)	234 (21.8)
Hypercholesterolemia	54 (5.0)	47 (4.4.)	43 (4.0)
Left-side radiotherapy	378 (35.2)	349 (32.5)	364 (33.9)
Events			
Cardiac-related death	0	0	0
Congestive heart failure‡	7 (0.7)	21 (2.0)	4 (0.4)∫
>10% relative reduction in left ventricular ejection fraction¶	114 (11.2)‖	194 (18.6)	97 (9.4)**

* AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.
† Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more.
‡ This condition was defined as New York Heart Association grade 3 or 4 congestive heart failure.
∫ P<0.001 for the comparison between the group receiving AC-T plus trastuzumab and the TCH group.
¶ Results in this category are for 1018 patients receiving AC-T, 1042 patients receiving AC-T plus trastuzumab, and 1031 patients receiving TCH.
‖ P<0.001 for the comparison between the group receiving AC-T plus trastuzumab and the AC-T group.
** P<0.001 for the comparison between the group receiving AC-T plus trastuzumab and the TCH group.

Provided courtesy of G. Thomas Budd, MD
Slamon D, et al. *N Engl J Med.* 2011;365(14):1273-1283.

Left Ventricular Ejection Fraction (LVEF) at 48 Months



Provided courtesy of G. Thomas Budd, MD.
Slamon D, et al. *N Engl J Med*. 2011;365(14):1273-1283.

The NEW ENGLAND JOURNAL of MEDICINE

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Trastuzumab Cardiac Toxicity

- Less common if anthracyclines avoided
- Reversible in most cases
- May treat through it in high-risk disease

Trastuzumab US FDA Prescribing Information.

Adjuvant Therapy

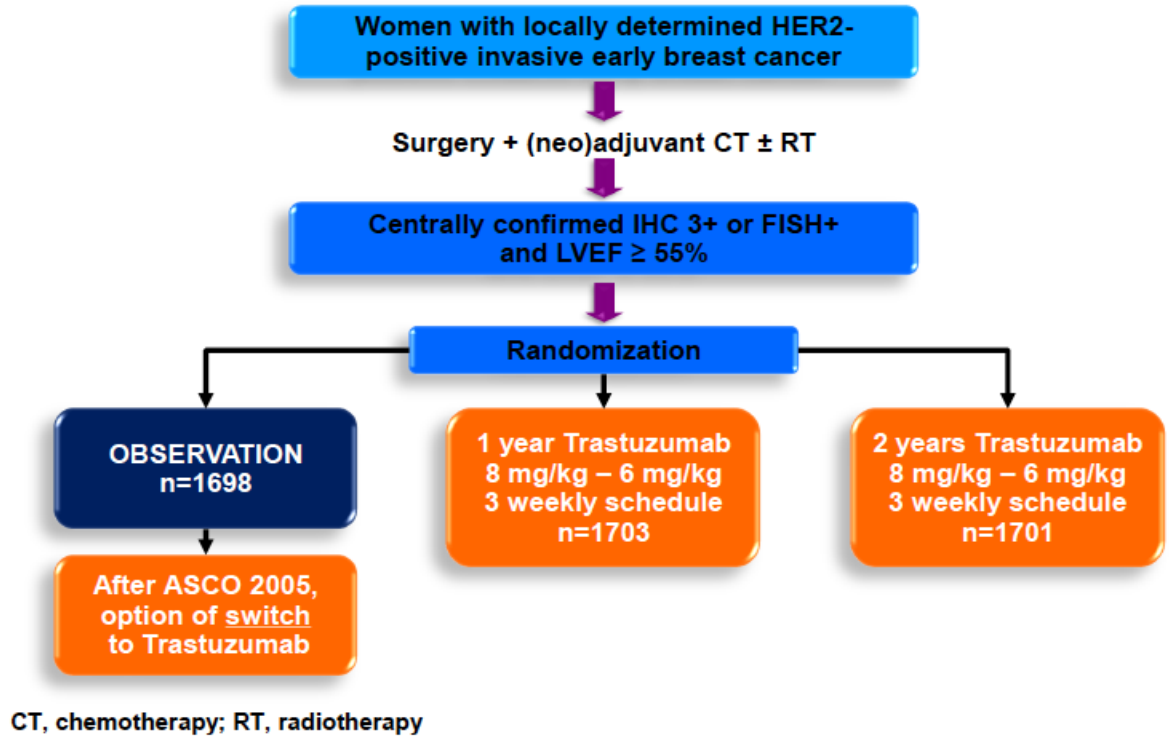
How long should we give adjuvant trastuzumab?

- HERA
- PHARE

HERA TRIAL: 2 years vs. 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow-up

HERA TRIAL DESIGN

ACCRUAL 2001 – 2005 (N=5102)

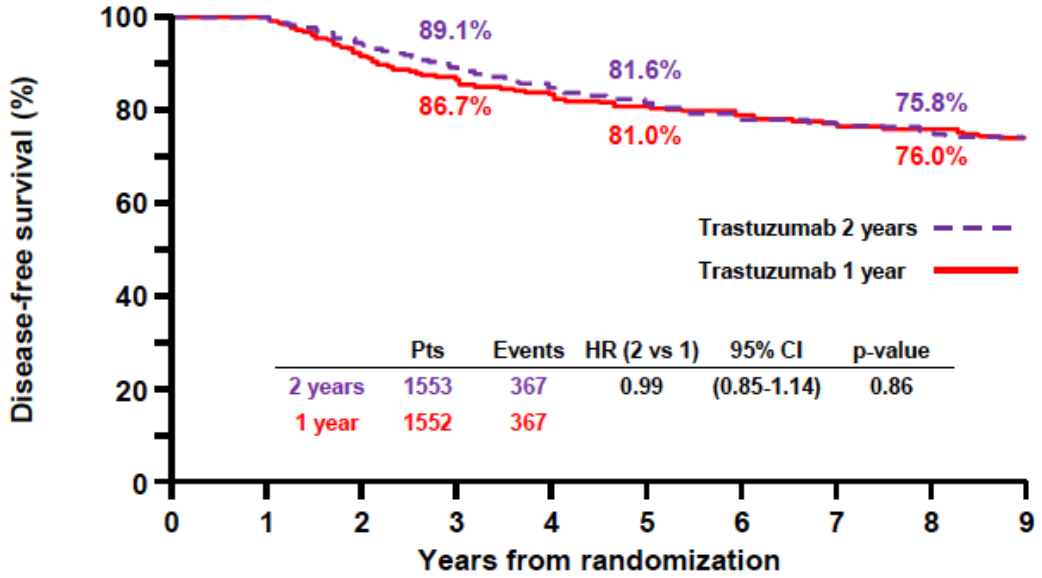


CT, chemotherapy; RT, radiotherapy

Provided courtesy of G. Thomas Budd, MD.

Goldhirsch A, et al. *Lancet*. 2013;382(9897):1021-1028.
Smith I, et al. *Lancet*. 2007;369(9555):29-36.

DFS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU

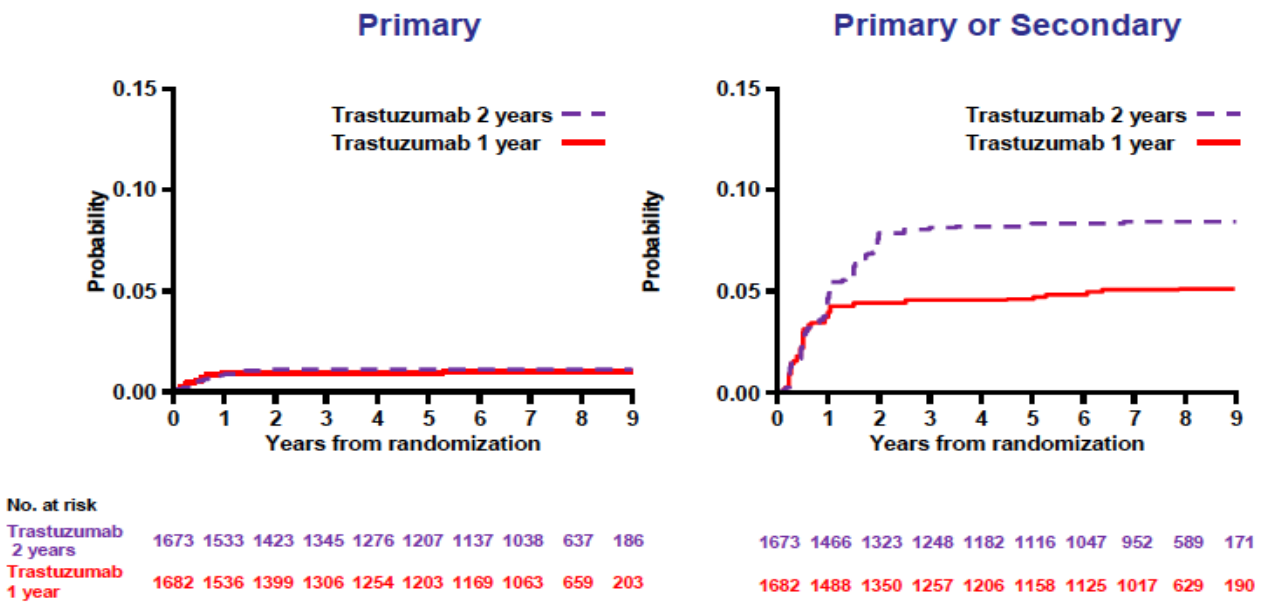


No. at risk										
Trastuzumab 2 years	1553	1553	1442	1361	1292	1223	1153	1051	633	194
Trastuzumab 1 year	1552	1552	1413	1319	1265	1214	1180	1071	649	205

Provided courtesy of G. Thomas Budd, MD.

Goldhirsch A, et al. *Lancet*. 2013;382(9897):1021-1028.
Smith I, et al. *Lancet*. 2007;369(9555):29-36.

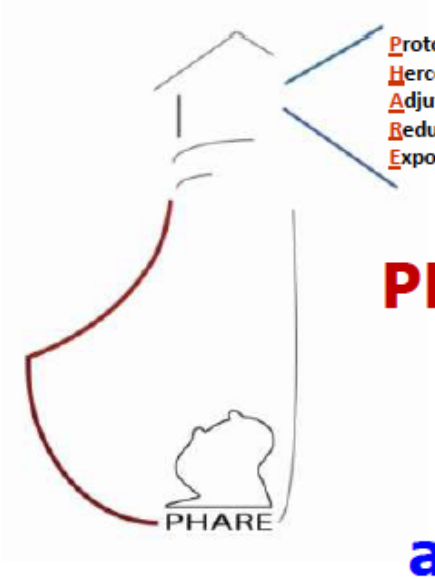
CUMULATIVE INCIDENCE OF CARDIAC ENDPOINTS*



* **Competing risk analysis with disease-free survival events considered as competing risks**
The majority of cardiac events are reversible (Procter et al. JCO 2010)

Provided courtesy of G. Thomas Budd, MD.

Goldhirsch A, et al. *Lancet*. 2013;382(9897):1021-1028.
Smith I, et al. *Lancet*. 2007;369(9555):29-36.



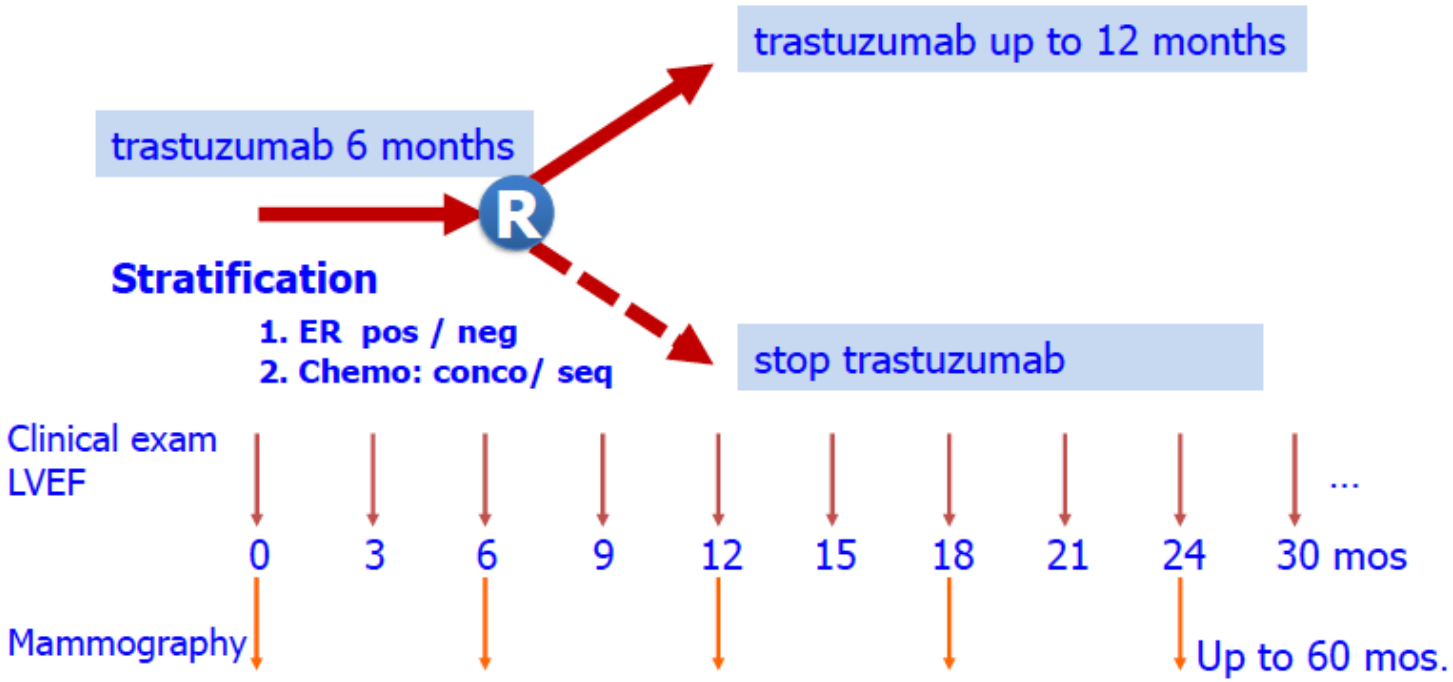
INSTITUT NATIONAL DU CANCER

PHARE* Trial results of subset analysis comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer

Xavier Pivot, Gilles Romieu, Marc Debled, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David Khayat, Iris Pauporté, Andrew Kramar.

*lighthouse in French

Study Design



Provided courtesy of G. Thomas Budd, MD.

Pivot X, et al. *Cancer Res.* 2012;72(24): S5-3.
Pivot X, et al. *Lancet Oncol.* 2013;14(8):741-748.

R: Randomization after informed consent

Statistical Methods

- **Non-inferiority randomized trial**
  - 2% variation in terms of absolute difference of recurrence
  - 95% CI HR margins should not cross 1.15
  - 1,040 DFS events required for 80% power at 5% level

    or

    4 years of accrual and at least 2 years of follow-up
  - HR were estimated from the stratified Cox model

- **Accrual target: 3,400 patients**

Pivot X, et al. *Cancer Res.* 2012;72(24): S5-3.
Pivot X, et al. *Lancet Oncol.* 2013;14(8):741-748.

From: **How to Use a Noninferiority Trial: Users' Guides to the Medical Literature**

JAMA. 2012;308(24):2605-2611.

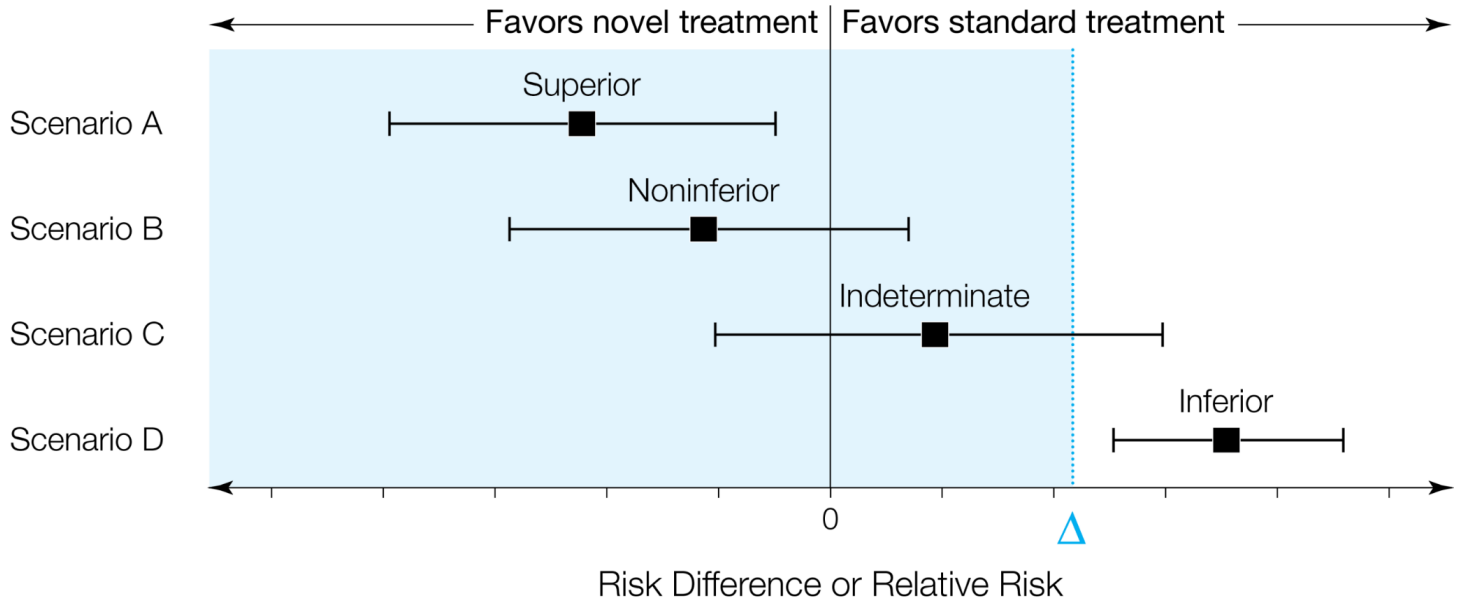
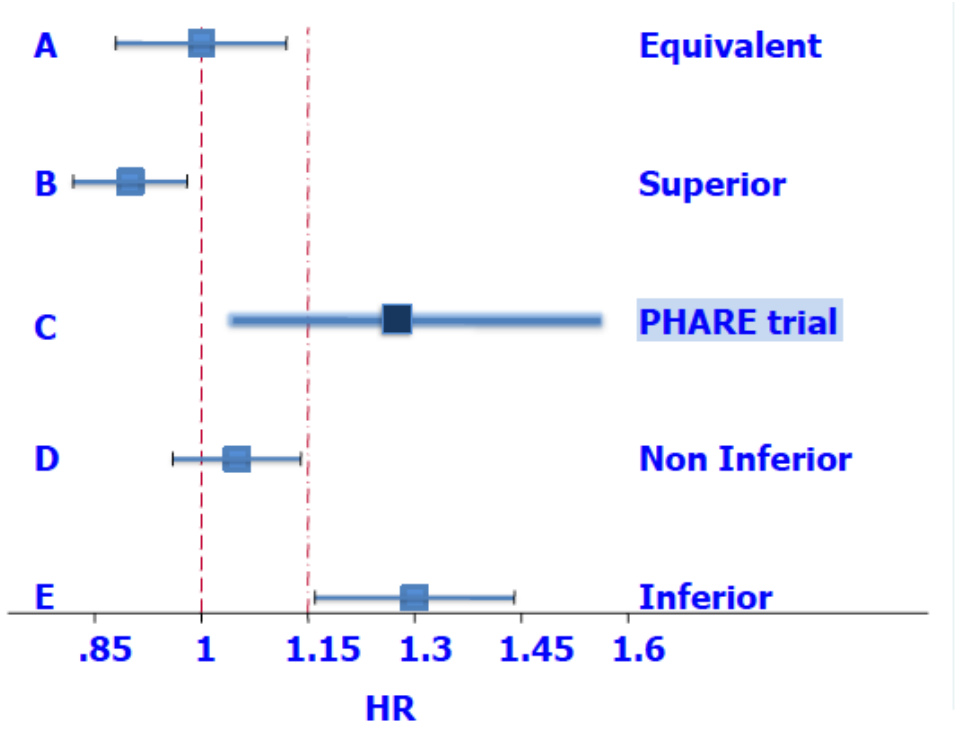


Figure Legend:

The blue dashed line labeled Δ represents the noninferiority threshold or the maximum allowable excess of outcome events arising from the novel treatment compared with the standard treatment. The tinted area represents the noninferiority zone.

Primary Endpoint Scenarios



Provided courtesy of G. Thomas Budd, MD.
Pivot, X et al. *ESMO* 2012, LBA5_PR

PHARE and Balanced Conclusions

- PHARE did not demonstrate non-inferiority at 6 months vs. 12 months of trastuzumab
- Other trials address this issue
  - PERSEPHONE
  - SHORTHER (also indeterminate)
  - SOLD

Pivot X, et al. *Cancer Res*. 2012;72(24): S5-3.
Pivot X, et al. *Lancet Oncol*. 2013;14(8):741-748.

Adjuvant Trastuzumab

- 12 months of adjuvant trastuzumab begun concurrently with taxane chemotherapy remains the standard of care for HER2+ early breast cancer
- Patients who stop trastuzumab early due to toxicity can be reassured that they have received some benefit

Adjuvant Trastuzumab Limbo

How low do we go?

- How small a tumor warrants treatment?

Baseline Characteristics of the Patients

Characteristic	Patients (N=406) no. (%)
Age group	
<50 yr	132 (32.5)
50-59 yr	137 (33.7)
60-69 yr	96 (23.6)
≥70 yr	41 (10.1)
Sex	
Female	405 (99.8)
Male	1 (0.2)
Race†	
White	351 (86.5)
Black	28 (6.9)
Asian	11 (2.7)
Other	16 (3.9)

Characteristic	Patients (N=406) no. (%)
Primary tumor	
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Nodal status	
N0	400 (98.5)
N1mic	6 (1.5)
Histologic grade	
I: well-differentiated	44 (10.8)
II: moderately differentiated	131 (32.3)
III: poorly differentiated	228 (56.2)
Unknown	3 (0.7)

Characteristic	Patients (N=406) no. (%)
HER2-positive status	406 (100)
Estrogen-receptor status	
Positive	260 (64.0)
Negative	141 (34.7)
Borderline	5 (1.2)
Progesterone-receptor status	
Positive	201 (49.9)
Negative	196 (48.3)
Borderline	8 (2.0)
Unknown	1 (0.2)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)

*Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor type 2, N0 no regional lymph-node involvement, and N1mic lymph-node involvement with tumor larger than 0.2 mm in diameter but smaller than 2 mm.
†Race was self-reported.

Provided courtesy of G. Thomas Budd, MD.
Tolaney SM et al. *N Engl J Med*. 2015;372(2):134-141.

Paclitxel 80 mg/m2/wk x q12 + Trastuzumab x 1 year

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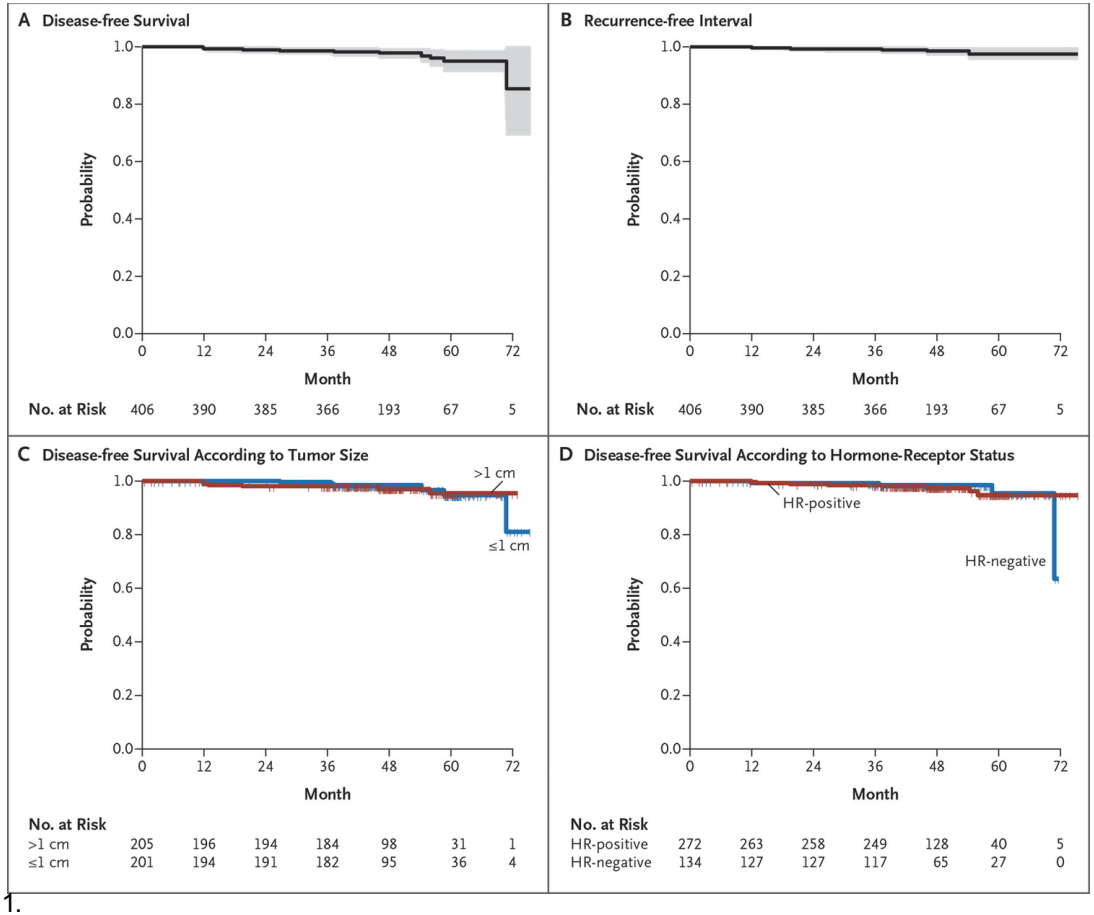
Provided courtesy of G. Thomas Budd, MD.
Tolaney SM et al. *N Engl J Med*. 2015;372(2):134-141.

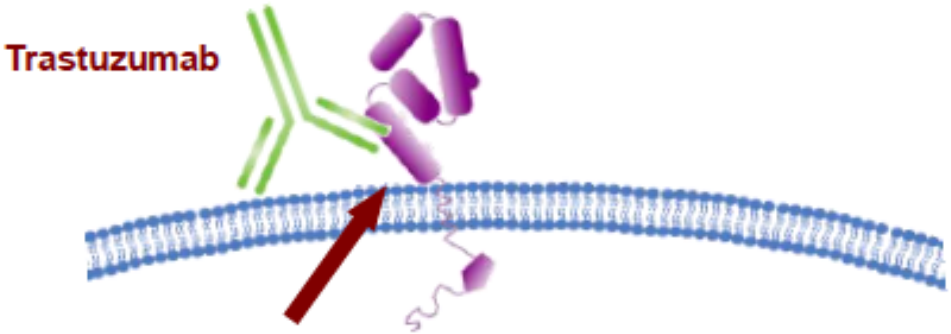
Probabilities of Disease-Free Survival and Recurrence-Free Interval



The NEW ENGLAND JOURNAL of MEDICINE

Provided courtesy of G. Thomas Budd, MD.
Tolaney SM et al. *N Engl J Med*. 2015;372(2):134-141.

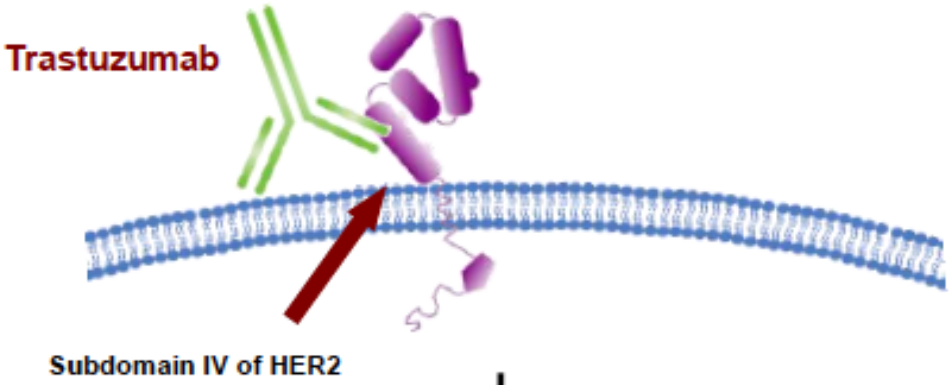
Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity



- Trastuzumab suppresses HER2 activity
- Flags cells for destruction by the immune system

Provided courtesy of G. Thomas Budd, MD.

Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity



- Trastuzumab suppresses HER2 activity
- Flags cells for destruction by the immune system

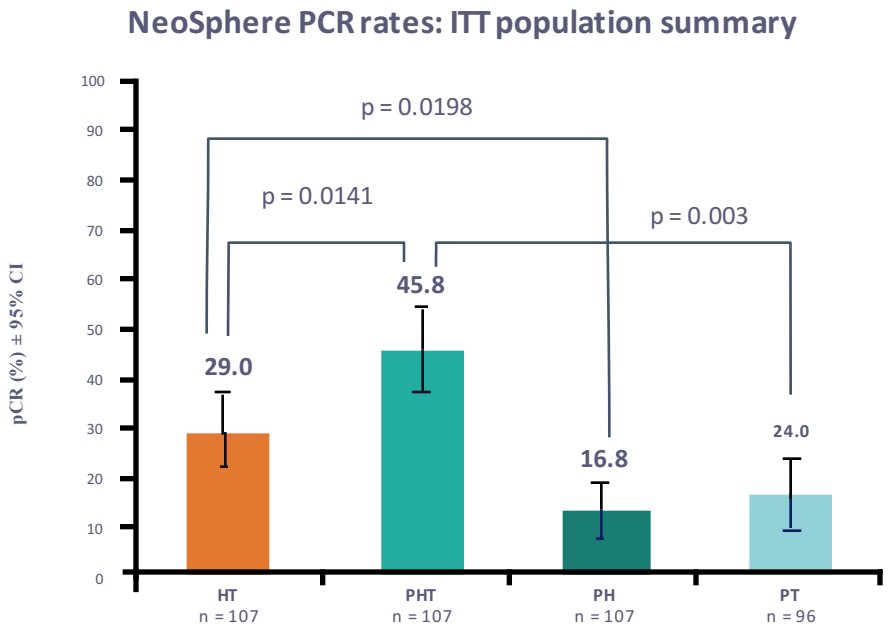
- Pertuzumab inhibits HER2 heterodimerization
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system

Provided courtesy of G. Thomas Budd, MD.

APHINITY: Rationale

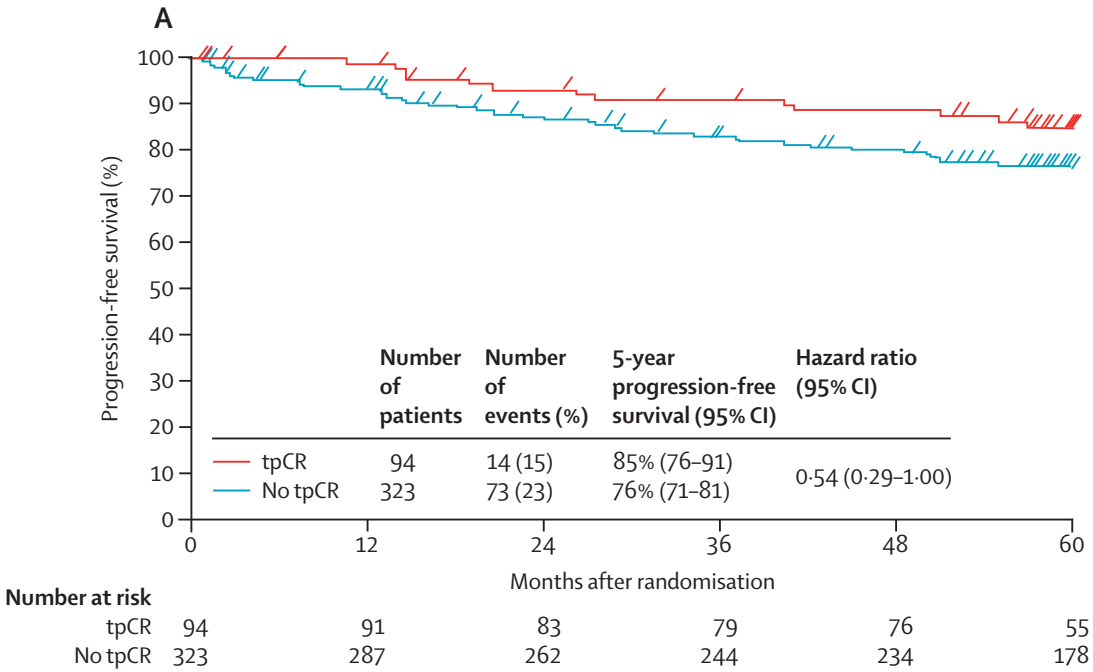
- Pertuzumab has complementary mechanisms of action with trastuzumab.[1-3]
  - Trastuzumab binds close to the transmembrane domain, inhibiting HER2 dimerization
  - Pertuzumab binds to the dimerization domain, inhibiting HER2 hetero-dimerization with other HER family receptors [4-7]
- In patients with HER2-positive metastatic breast cancer, pertuzumab added to trastuzumab and docetaxel significantly improved both PFS and OS.[8,9]
- In the neoadjuvant setting, the addition of pertuzumab to trastuzumab plus docetaxel significantly improved pathological complete response rate.[10,11]
- Recurrences of HER2-positive early breast cancer still occur for a significant proportion of patients in the long-term.[12]

Provided courtesy of G. Thomas Budd, MD.



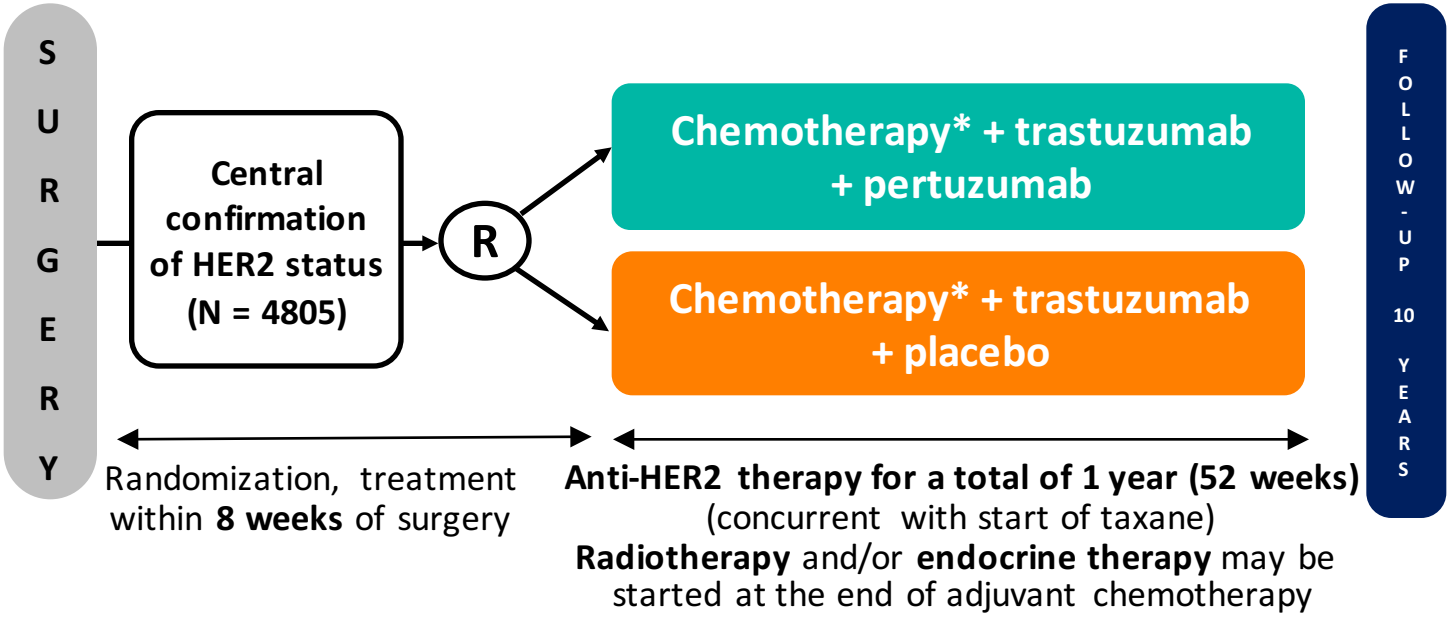
[1]Baselga J, *Nat Rev Cancer* 2009; [2]Scheuer W, *Cancer Res* 2009; [3]Hubbard SR *Cancer Cell* 2005; [4]Molina MA et al. *Cancer Res* 2001; [5]Junttila TT et al. *Cancer Cell* 2009; [6]Franklin MC et al. *Cancer Cell* 2004; [7]Agus DB et al. *Cancer Cell* 2002 [8]Baselga J, *NEJM* 2012; [9]Swain SM, *NEJM* 2015; [10]Swain SM, *Oncologist* 2013; [11]Gianni L, *Lancet Oncol* 2012; [12]Cameron D, *Lancet* 2017

NeoSPHERE Progression-Free Survival



Provided courtesy of G. Thomas Budd, MD.
Gianni L, et al. *Lancet Oncol.* 2016;17(6):791-800.

APHINITY: Trial Design



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

von Minckwitz G, et al. *J Clin Oncol*. 2017;35(suppl; abstr LBA500).
von Minckwitz G, et al. *N Engl J Med*. 2017;377(2):122-131.

Provided courtesy of G. Thomas Budd, MD.

APHINITY: Key Eligibility Criteria

Inclusion Criteria

- HER2-positive status confirmed by a central review (IHC 3+ or FISH-/CISH-positive)*
- Node-positive, any tumor size except T0
- Node-negative
  - Tumor size >1 cm

    OR
  - For tumors >0.5 and ≤1 cm, at least 1 of:
    - Histological/nuclear grade 3

      OR
    - ER- and PR-negative

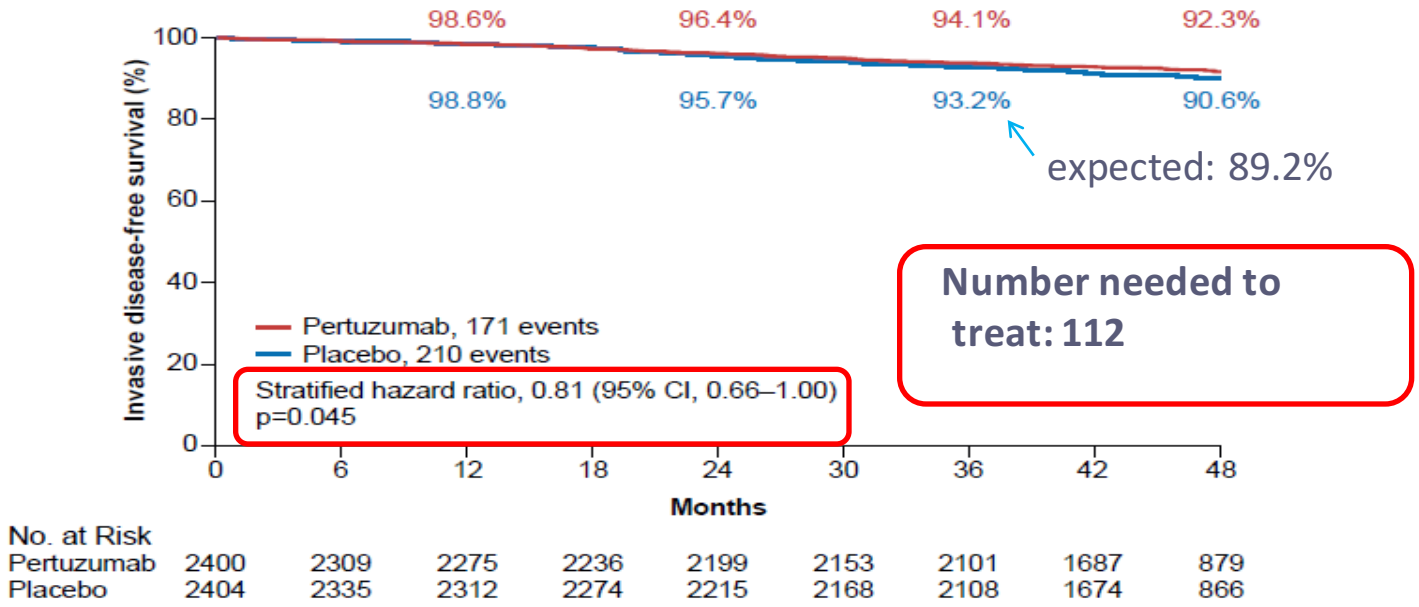
      OR
    - Age <35
- Baseline LVEF ≥55%

Exclusion Criteria

- Prior invasive breast cancer
- Non-operable breast cancer
- Metastatic disease (stage IV)
- Previous non-breast malignancies (except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin)
- Previous or current anti-cancer therapy or previous radiotherapy for any malignancy
- Cardiac dysfunction or serious medical conditions

von Minckwitz G, et al. *J Clin Oncol*. 2017;35(suppl; abstr LBA500).
von Minckwitz G, et al. *N Engl J Med*. 2017;377(2):122-131.

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



Provided courtesy of G. Thomas Budd, MD.

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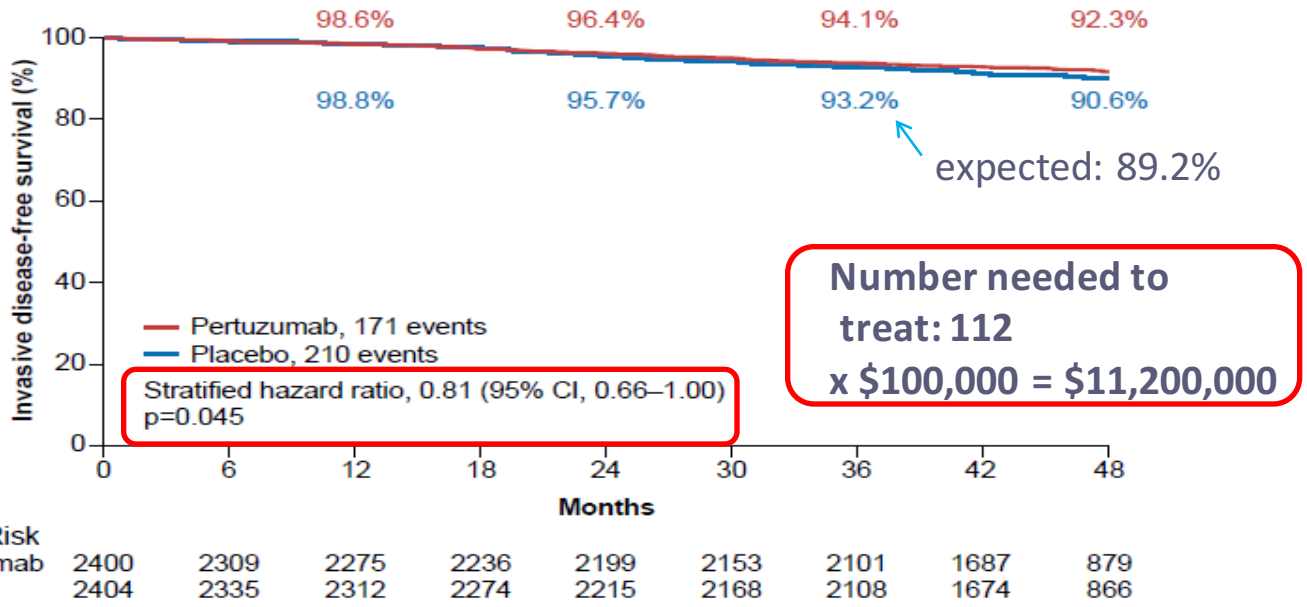


Provided courtesy of G. Thomas Budd, MD.

von Minckwitz G, et al. *J Clin Oncol*. 2017;35(suppl; abstr LBA500).

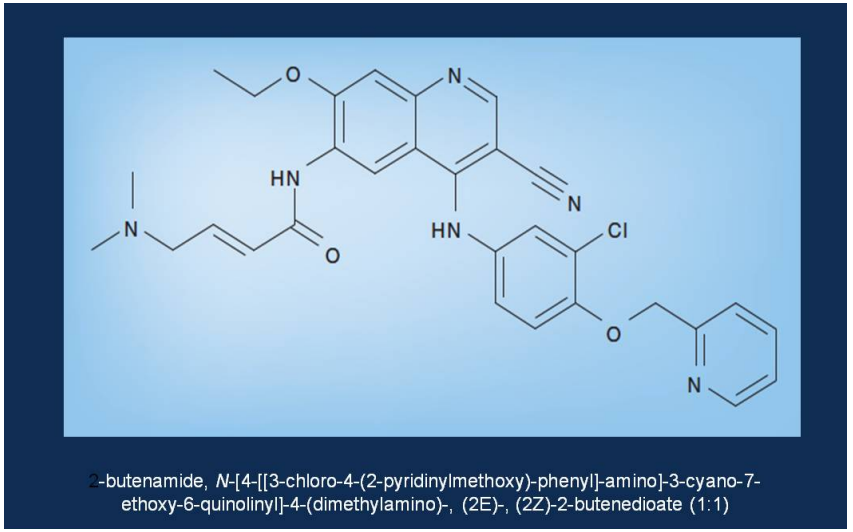
von Minckwitz G, et al. *N Engl J Med*. 2017;377(2):122-131.

What is the Role of Pertuzumab in Adjuvant Rx?

- Not justified in ER-positive, node-negative disease
- Would consider in ER-negative, node-positive disease
- Unclear about patients in between
- What about patients receiving pre-operative pertuzumab/trastuzumab?
- What is the role of pre-operative Rx in HER2-positive disease?

Neratinib

- Neratinib is an oral TKI targeting HER2, HER4, and HER 1 (EGFR)
- Neratinib binds irreversibly at ATP binding site
- 240 mg daily was the dose selected for phase II trials
  - Diarrhea is the main toxicity



2-butenamide, *N*-[4-[[3-chloro-4-(2-pyridinylmethoxy)-phenyl]-amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-, (2E)-, (2Z)-2-butenedioate (1:1)

Presented By Miguel Martin at 2016 ASCO Annual Meeting

Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

*Miguel Martin, Frankie A Holmes, Bent Ejlertsen, Suzette Delaloge, Beverly Moy, Hiroji Iwata, Gunter von Minckwitz, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Zorica Tomašević, Neelima Denduluri, Robert Šeparović, Erhan Gokmen, Anna Bashford, Manuel Ruiz Borrego, Sung-Bae Kim, Erik Hugger Jakobsen, Audrone Ciceniene, Kenichi Inoue, Friedrich Overkamp, Joan B Heijns, Anne C Armstrong, John S Link, Anil Abraham Joy, Richard Bryce, Alvin Wong, Susan Moran, Bin Yao, Feng Xu, Alan Auerbach, Marc Buyse, Arlene Chan, for the ExteNET Study Group**

Martin, M, et al. *Lancet Oncol.* Published online November 17, 2017. [http://dx.doi.org/10.1016/S1470-2045(17)30717-9]

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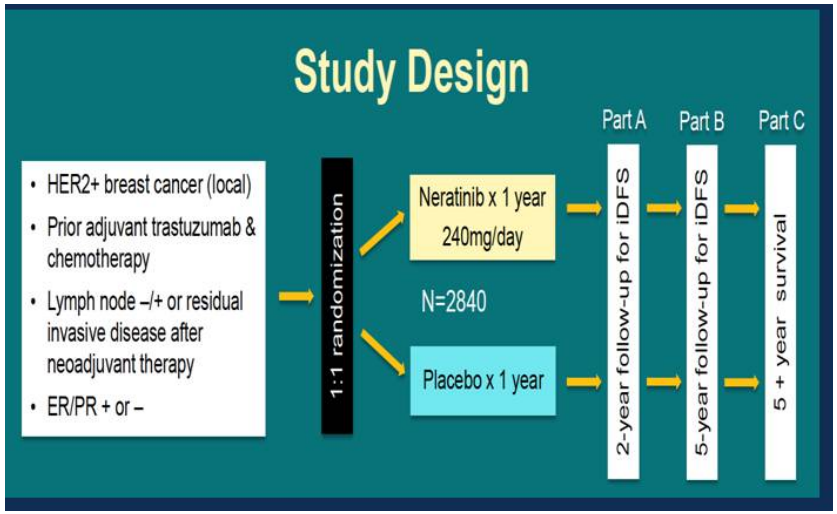


Martin M, et al. *Lancet Oncol.* Published online November 17, 2017. [http://dx.doi.org/10.1016/S1470-2045(17)30717-9]
Image provided courtesy of G. Thomas Budd, MD.

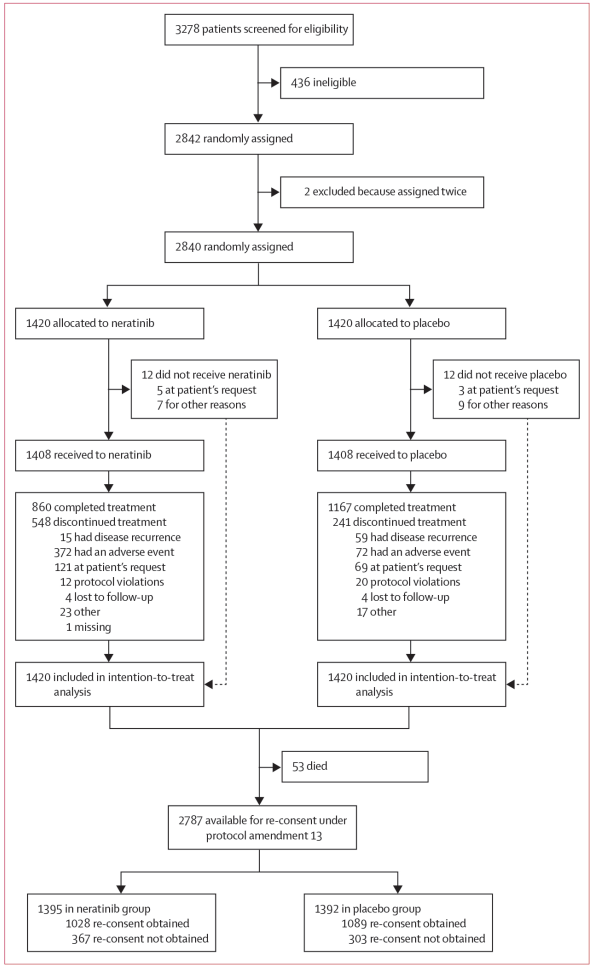


Figure 1: **ExteNET trial profile**

Provided courtesy of G. Thomas Budd, MD.

Martin M, et al. *Lancet Oncol.* Published online November 17, 2017. [http://dx.doi.org/10.1016/S1470-2045(17)30717-9]

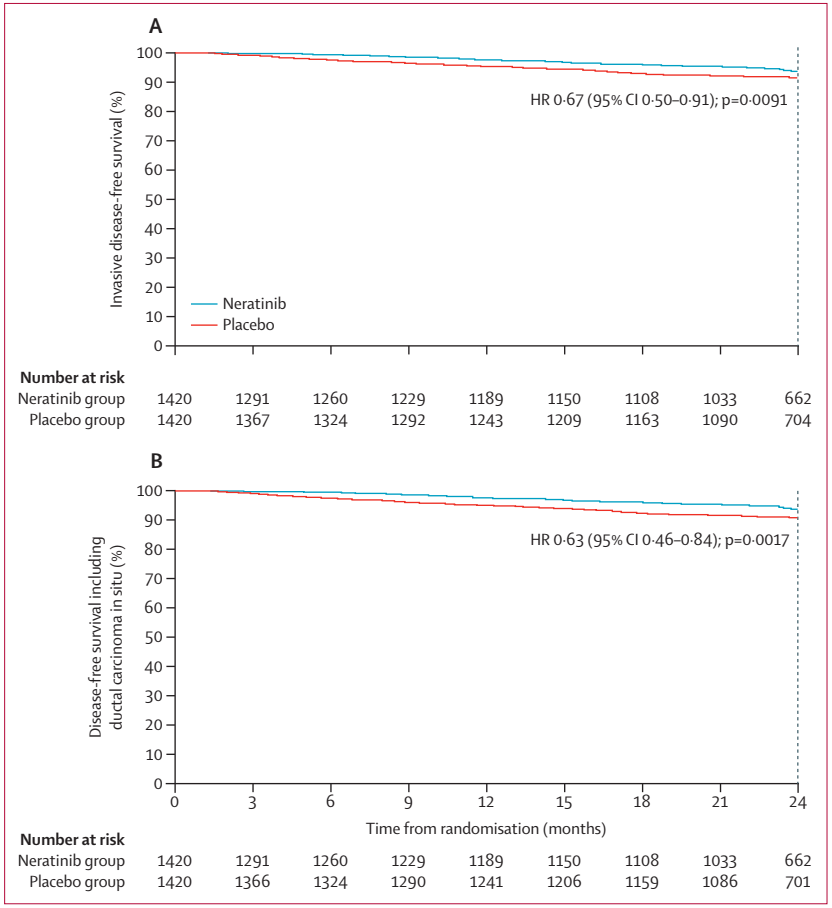


***Figure 2*: Kaplan–Meier curves for invasive disease-free survival (A) and disease-free survival including ductal carcinoma in situ (B) in the intention-to-treat population**

Provided courtesy of G. Thomas Budd, MD.

Chan A, et al. *Lancet Oncol.* 2016;17(3):367-377.

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

Martin M, et al. *Lancet Oncol.* Published online November 17, 2017. [http://dx.doi.org/10.1016/S1470-2045(17)30717-9]

EXTENET Trial

	Events (n)/patients (N)		Hazard ratio (95% CI)	Test of interaction p value (two-sided)
	Neratinib group	Placebo group		
Region of the world				
North America	40/519	46/477	0·84 (0·55–1·28)	0·590
Western Europe, Australia, and South Africa	43/487	63/532	0·78 (0·52–1·14)	
Asia, eastern Europe, and South America	33/414	54/411	0·61 (0·39–0·93)	
Age at randomisation (years)				
<35	7/46	15/55	0·49 (0·19–1·15)	0·544
35–49	47/523	59/515	0·80 (0·54–1·17)	
50–59	31/497	48/488	0·65 (0·41–1·01)	
≥60	31/354	41/362	0·85 (0·53–1·36)	
Menopausal status at diagnosis				
Premenopausal	60/663	81/664	0·74 (0·53–1·04)	0·891
Postmenopausal	56/757	82/756	0·72 (0·51–1·01)	
Nodal status*				
Negative	14/335	19/336	0·83 (0·41–1·65)	0·844
1–3 positive nodes	55/664	74/664	0·75 (0·53–1·06)	
≥4 positive nodes	47/421	70/420	0·67 (0·46–0·96)	
Hormone receptor status*				
Positive	59/816	100/815	0·60 (0·43–0·83)	0·063
Negative	57/604	63/605	0·95 (0·66–1·35)	
Previous trastuzumab regimen*				
Concurrent	73/884	101/886	0·76 (0·56–1·03)	0·666
Sequential	43/536	62/534	0·69 (0·47–1·02)	
Race				
Asian	14/188	26/197	0·55 (0·28–1·04)	0·573
White	99/1165	130/1135	0·77 (0·59–1·00)	
Black or other	3/67	7/88	0·61 (0·13–2·21)	
T stage at diagnosis				
T1	20/440	25/459	0·88 (0·48–1·57)	0·715
T2	45/585	69/555	0·63 (0·43–0·92)	
T3 and above	15/144	18/117	0·69 (0·34–1·37)	
Unknown	36/251	51/289	0·83 (0·54–1·27)	
Histology grade				
Well or moderately differentiated	41/537	48/481	0·78 (0·51–1·18)	0·850
Poorly differentiated or undifferentiated	56/670	86/698	0·69 (0·49–0·97)	
Unknown	19/213	29/241	0·81 (0·45–1·44)	
Surgery type				
Lumpectomy only	26/468	46/511	0·63 (0·39–1·02)	0·414
Mastectomy	90/951	117/908	0·76 (0·58–1·00)	
Prior radiotherapy				
Yes	96/1130	137/1150	0·73 (0·56–0·94)	0·893
No	20/290	26/270	0·78 (0·43–1·39)	
Prior neoadjuvant therapy				
Yes	48/342	69/379	0·78 (0·54–1·13)	0·690
No	68/1078	94/1041	0·73 (0·53–0·99)	
Completion of prior trastuzumab				
≤1 year	99/1152	145/1145	0·70 (0·54–0·90)	0·406
>1 year	17/268	18/275	1·00 (0·51–1·94)	
All patients			**0·73 (0·57–0·92)**	

Figure 3: **Subgroup analysis of invasive disease-free survival in the intention-to-treat population**
The vertical dashed line indicates a hazard ratio of 1·00—the null hypothesis value. Error bars represent 95% CIs. *Stratification factor.

Martin M, et al. *Lancet Oncol.* Published online November 17, 2017. [http://dx.doi.org/10.1016/S1470-2045(17)30717-9]

ExteNET Toxicity

	Neratinib Group (n=1408)			Placebo group (n=1408)		
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Diarrhea	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

Martin M, et al. *Lancet Oncol.* Published online November 17, 2017. [http://dx.doi.org/10.1016/S1470-2045(17)30717-9]

Clinical Trials in Early-Stage HER2-Positive Breast Cancer

B31/N9831	AC-Pac ± T
HERA	Chemo → No T vs. 1 yr vs. 2 yr
BCIRG 006	AC → D ± T vs. DCH
NOAH	A Pac → Pac → CMF ± T
GeparQuattro	Pre-operative chemo/T
FinHer	D vs Vin ± T (9 weeks) → FEC
PHARE	Chemo-T (up to 12 months) vs. stop T
(neo)ALTTO	Chemo with T ± lapatinib
TEACH	Lapatinib vs. placebo
NeoSphere	Pre-operative chemo/T ± P
TRYPHAENA	Pre-operative chemo/T/P
APHINITY	(TP vs. T) with AT or TC
KATHERINE	T vs. T-DM1
KRISTINE	Pre-operative TCH + P vs. T-DM1 + P
MA.17R	Adjuvant letrozole vs. placebo

AC = doxorubicin + cyclophosphamide;
A Pac = doxorubicin and paclitaxel;
AT = anthracycline and taxane-based chemotherapy;
CMF = cyclophosphamide, methotrexate, and fluorouracil;
D = docetaxel;
DCH = docetaxel, carboplatin, and trastuzumab;
FEC = fluorouracil, epirubicin, and cyclophosphamide;
P = pertuzumab;
Pac = paclitaxel;
T = trastuzumab;
TC = docetaxel and carboplatin;
TCH = docetaxel, carboplatin, trastuzumab;
T-DM1 = trastuzumab emtansine;
TP = trastuzumab and pertuzumab;
Vin = vincristine

www.clinicaltrials.gov

HER2-Positive Therapy: Trastuzumab and Pertuzumab

- NeoSphere 5-year data show neoadjuvant pertuzumab is beneficial when combined with trastuzumab and docetaxel in women with early-stage HER2-positive breast cancer
- According to the ASCO clinical practice guideline, trastuzumab/pertuzumab/taxane is recommended for first-line neoadjuvant treatment

Gianni L, et al. *Lancet Oncol*. 2016;17(6):791-800.
Giordano SH, et al. *J Clin Oncol*. 2014;32:2078-2099.

Breast Cancer Recurrence

- EBCTCG study: after 5 years of endocrine therapy, recurrence steadily continued from year 5 to 14 and at least to year 20
- Adding trastuzumab to paclitaxel after doxorubicin and cyclophosphamide in early HER2-positive breast cancer yielded a sustained reduction in cancer recurrence

Pan H, et al. 2016 ASCO Annual Meeting (Abstract 505).
Perez EA, et al. *J Clin Oncol*. 2014;32:3744-3752.


Future Treatment Options
JADPRO Live
APSHO

Clinical Trials

- KATHERINE
  - Trastuzumab emtansine versus trastuzumab as adjuvant therapy in patients with residual tumor in breast or LNs after neoadjuvant therapy
  - Randomized to trastuzumab emtansine 3.6 mg/kg or trastuzumab 6 mg/kg IV q 3 wks for 14 cycles
- KAITLIN
  - Trastuzumab emtansine plus pertuzumab following anthracyclines vs. trastuzumab plus pertuzumab and a taxane following anthracyclines as adjuvant therapy
  - Post surgery and anthracycline-based chemotherapy, participants will receive either trastuzumab emtansine 3.6 mg/kg and pertuzumab 420 mg IV q 3 wks or trastuzumab 6 mg/kg and pertuzumab 420 mg IV q3w in combination with a taxane

https://clinicaltrials.gov/ct2/show/NCT01772472
https://clinicaltrials.gov/ct2/show/NCT01966471

Selective Symptom Management for HER2 Therapeutic Agents

Cardiotoxicity

- Usually an asymptomatic decrease in left ventricular ejection fraction (rare – clinical heart failure) (Type II cardiac dysfunction)
  - Loss of contractility
  - Less likely to be associated with myocyte death or clinical heart failure
- Does not appear to be related to cumulative dose
- Generally reversible with treatment discontinuation
- Can rechallenge after recovery

Keefe DL. *Cancer.* 2002;95(7):1592-1600.
Perez EA, Rodeheffer R. *J Clin Oncol*. 2004;22(2):322-329.
Fiúza, M. *Adv Ther.* 2009;26(Suppl 1):S9-17.
Slamon DJ, et al. *N Engl J Med.* 2001;344(11):783-792.

Cardiotoxicity

- Risk factors
  - Previous chemotherapy (particularly anthracyclines)
  - Concurrent treatment with anthracyclines
  - Pre-existing heart disease
  - Age >50 years
  - Obesity
- NOT a risk factor
  - Concurrent treatment with radiation

Suter TM, et al. *J Clin Oncol.* 2007;25(25):3859-3865.
Bowles EJ, et al. *J Natl Cancer Inst.* 2012;104(17):1293-1305.
Guenancia C, et al. *J Clin Oncol.* 2016;34:31573165.
Halyard MY, et al. *J Clin Oncol.* 2009;27:2638-2644.

Monitoring of Cardiotoxicity

- Baseline and serial assessment of LVEF
  - Normal baseline: proceed with therapy
  - LVEF 40-50% with risk factors – evaluate risk/benefit, proceed with increased vigilance
- Monitor for heart failure
  - Increased heart rate
  - Increased in weight (≥2 kg in 1 week)
  - Edema
  - S3 gallop
  - New dyspnea on exertion
  - Elevated jugular venous pressure
  - Sinus tachycardia
  - Tachypnea
  - Crackles
- Optimal surveillance not well defined:
  - Generally 3, 6, 9, 12 months
  - Anytime symptoms of heart failure appear

Ezaz G, et al. *J Am Heart Assoc.* 2014;3:e000472.
Ewer MS, et al. *J Clin Oncol* 2005;23:7820-7826.
Ewer SM, Ewer MS. *Drug Saf.* 2008;31(6):459-467.

Management of HER2 Cardiotoxicity

- Trastuzumab
  - LVEF decrease of 16% or more from baseline OR 10-15% from baseline to below the lower limit of normal (LLN), HOLD for 4 weeks, then reassess
    - If LVEF has not recovered, discontinue trastuzumab
  - If symptomatic heart failure during treatment, trastuzumab should be discontinued
- Lapatinib
  - For LVEF decrease to <50%, LVEF decreased to institution LLN, if development of clinical heart failure - HOLD
  - Dose reduction recommended if LVEF recovers to normal after a minimum of 2 weeks and patient is asymptomatic

Trastuzumab and Lapatinib US FDA Prescribing information

Management of HER2 Cardiotoxicity

- Ado-trastuzumab emtansine
  - If LVEF falls to <40% OR is 40-45 % with ≥10% absolute decrease below the pretreatment value – HOLD
- Pertuzumab
  - Assess LVEF every 3 mo in metastatic setting and every 6 weeks in neoadjuvant setting
  - If LVEF is <45% OR 45-49% with ≥10% absolute decrease below baseline – HOLD both pertuzumab and trastuzumab
  - Repeat LVEF assessment in 3 weeks
  - Discontinue pertuzumab and trastuzumab if the LVEF has not improved or declines further, unless the benefits for the individual patient outweigh the risks

Ado-Trastuzumab and Pertuzumab US FDA prescribing information

Management of HER2 Cardiotoxicity

- Standard medical management
  - Beta blockers
  - Angiotensin converting enzyme (ACE) inhibitors

Ado-Trastuzumab and Pertuzumab US FDA prescribing information

Diarrhea With HER2 Therapy

Most common side effect with HER2 therapy

- Increased incidence with lapatinib, pertuzumab, and neratinib: EGFR/HER2 dual inhibitors
  - Neratinib - Grade 3 diarrhea
- Up to 95% of patients
- Incidence varies between agents
- Disrupts heterodimerization between HER2 and EGFR (HER1), HER3, and HER4
- Risk may increase with concomitant chemotherapy

DeMichele A and Lattimer JG. *JAPRO*. 2016;7(Supp 2).
Swain SM, et al. *Ann Oncol*. 2017;28(4):761-768.
Dranitsaris G, Lacouture ME. *Breast Cancer Res Treat*. 2014;147(3):631-638.

Diarrhea can lead to…

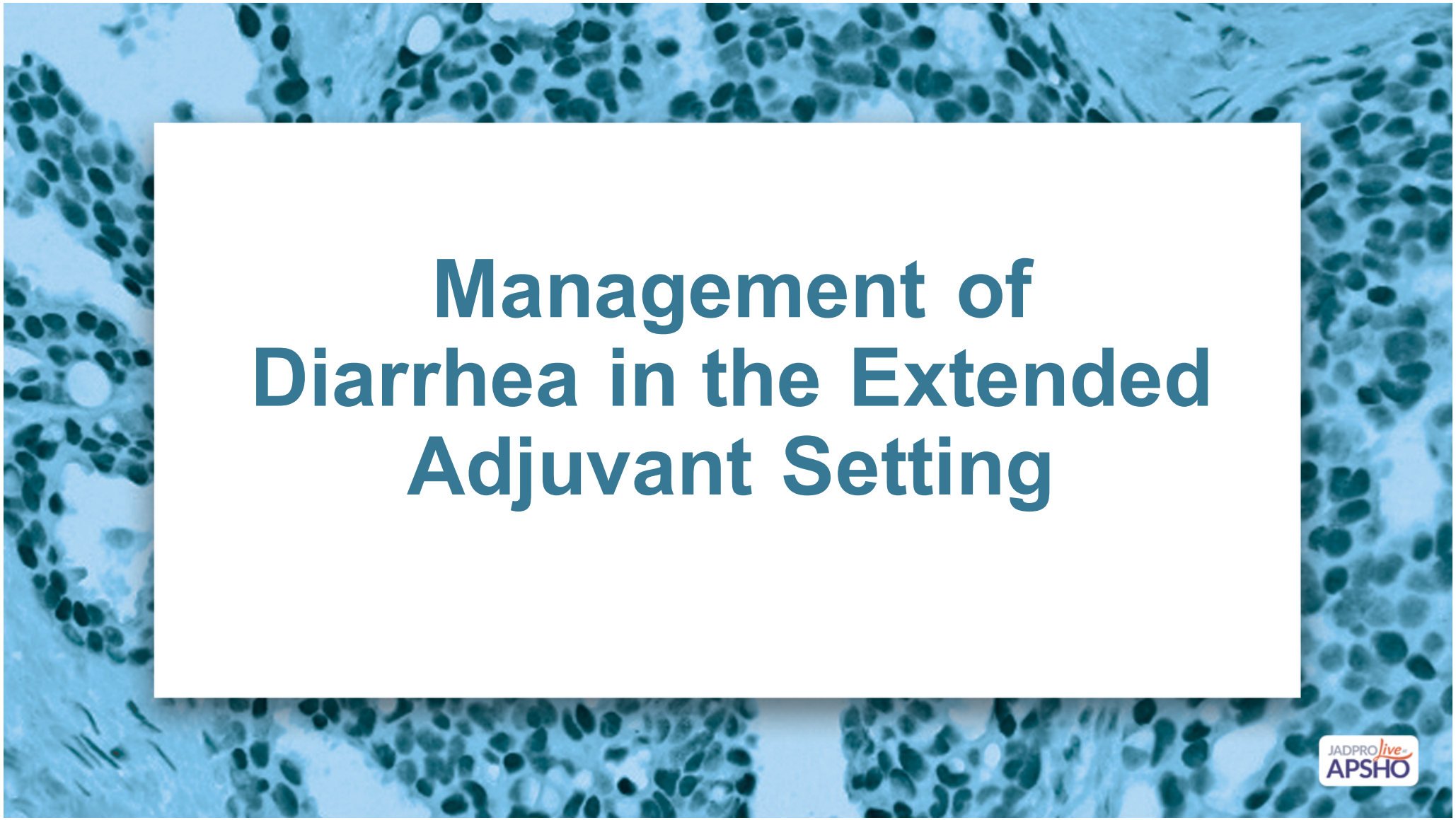
- Dose reductions
- Dose delays
- Reduced quality of life
- Increased costs
- Reduced treatment adherence
- Potentially life-threatening

Dranitsaris G, Lacouture ME. *Breast Cancer Res Treat*. 2014;147(3):631-638.

Predictive Factors for Grade 2+ Diarrhea

- Age (3% increase in risk per year)
- Grade 1 diarrhea in prior cycle (two-fold increased risk)
- Therapy started in spring (two-fold increased risk)

Dranitsaris G, Lacouture ME. *Breast Cancer Res Treat*. 2014;147(3):631-638.



Management of Diarrhea in the Extended Adjuvant Setting

Phase II Trial of Neratinib With Loperamide Prophylaxis in HER2-Positive Early Breast Cancer After Adjuvant Trastuzumab

CONTROL Trial

Incidence and severity of diarrhea with neratinib plus intensive loperamide prophylaxis in patients with HER2-positive early-stage breast cancer: interim analysis from the multicenter, open label, phase II CONTROL trial

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#P2-11-03

Background

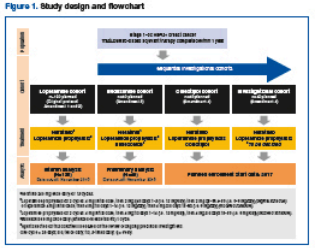
- Neratinib (Puma Biotechnology Inc.) is an irreversible pan-HER tyrosine kinase inhibitor.[1]
  - Results from the randomized, Phase III ExteNET study demonstrated that a 1-year course of neratinib after trastuzumab-based adjuvant therapy reduced the risk of disease recurrence or death by 33% relative to placebo after 2 years' follow-up in women with HER2-positive early-stage breast cancer.[2]
  - Patient follow-up is ongoing; the final 5-year efficacy analysis is anticipated in 2017.
- Diarrhea is the main toxicity of neratinib and is common in the absence of proactive management.[2]
  - In the ExteNET trial, where antidiarrheal prophylaxis was not protocol mandated:
    - Median duration of grade ≥3 diarrhea was 5 days
    - Neratinib dose reductions and dose holds due to diarrhea occurred in 26.4% and 33.9% of patients, respectively.[2]
  - As most diarrhea events occur early in the course of neratinib treatment, a structured (intensive) prophylactic regimen of loperamide given for 1–2 cycles has been introduced in all clinical trials of neratinib to better manage this toxicity.[3]
  - Recent preclinical studies suggest that multiple mechanisms may be involved in the pathogenesis of neratinib-induced diarrhea, including elements of secretory and inflammatory diarrhea.[4] In particular, in a rat model, inflammation was observed in the terminal ileum.[3]
- CONTROL is an international, open-label, phase II study designed to investigate the efficacy of 1–2 cycles of loperamide prophylaxis in the prevention of neratinib-associated diarrhea in patients with HER2-positive early-stage breast cancer.
  - The study has been expanded to include additional patient cohorts treated with agents targeting possible underlying mechanisms (e.g. anti-inflammatories, bile acid sequestrants) to determine if they can further reduce neratinib-associated diarrhea.
  - We report an interim analysis from the CONTROL study, and preliminary findings from the first investigational cohort testing budesonide, a locally acting corticosteroid used for inflammatory gastrointestinal conditions.

Methods

Study design

- CONTROL (PUMA-NER-5201) is an international, open-label, phase II study (Clinicaltrials.gov identifier NCT02400476).

Figure 1. Study design and flowchart



Patient population

- Adults ≥18 years of age.
- Histologically confirmed stage 1–3c breast cancer.
- Documented HER2 overexpression or amplification determined locally.

Study treatments

- Details of treatment schedules are presented in Figure 1.
- Eligible patients were to receive:
  - Oral neratinib 240 mg/day for 1 year.
  - Oral loperamide prophylaxis for 2 cycles according to one of two schedules:
    1. Original schedule (first protocol).
    2. Modified schedule to simplify dosing and improve efficacy (protocol amendments 1–3).
  - Oral budesonide for 1 cycle (protocol amendment 3).
- Loperamide (≤16 mg/day) was given as needed after day 56.
- Treatment-emergent diarrhea was managed with dietetic measures and additional pharmacological treatments depending on grade (i.e. diphenoxylate plus atropine, octreotide, IV fluids, antibiotics).

Assessments

- Clinic visits were scheduled on day 1 of cycles 1, 2, 3, 4, 7 and 10, and treatment end.
- Patients were followed for 28 days after the last dose of neratinib.
- Adverse events were graded according to NCI-CTCAE (version 4.0).

Endpoints

- *Primary endpoint:* incidence of grade ≥3 diarrhea during treatment with neratinib.
- *Secondary endpoints:* frequency distribution of maximum-grade diarrhea; incidence and severity of diarrhea by loperamide exposure; serious adverse events; adverse events of interest.
- *Exploratory endpoints:* patient-reported outcomes; biomarkers for disease recurrence.

Statistical methods

- All analyses were descriptive and were performed in the safety population, defined as all patients who received ≥1 dose of neratinib.
- A protocol-defined interim analysis was performed when approximately 120 patients from the loperamide cohort had completed 2 cycles of neratinib plus loperamide prophylaxis. A preliminary analysis of the budesonide cohort was also performed.
- The ExteNET trial (neratinib arm), which included an analogous patient population but no protocol-mandated antidiarrheal prophylaxis,[2] was used as a historical control.

Results

Table 1. Baseline characteristics

Variable	CONTROL: Loperamide cohort (N=135)	CONTROL: Budesonide cohort (N=40)	ExteNET: Neratinib arm (N=1420)
Female, %	100	100	100
Median age (range), years	53 (30–86)	50 (29–78)	52 (25–85)
Tumor stage at diagnosis,[a] %			
I	29.9	22.5	9.8
IIA, B	54.8	42.5	42.0
IIIA, B, C	14.8	17.5	31.2
Hormone receptor status,[b] %			
Positive (ER and/or PR positive)	74.1	62.5	57.5
Negative (ER and PR negative)	25.2	25.0	42.5
Prior (neo)adjuvant therapy,[c] %			
Trastuzumab	100	97.5	100
Taxanes	95.6	90.0	90.1
Anthracycline	25.9	25.0	77.3
Pertuzumab	40.0	55.0	–
Median (range) duration of prior trastuzumab, months	11.5 (2.4–24.9)	11.0 (1.2–15.0)	11.5 (0.7–56.9)
Median (range) time since last trastuzumab dose, months	4.1 (0.1–19.8)	4.3 (0.7–11.7)	4.4 (0.2–30.9)

ER, estrogen receptor; PR, progesterone receptor.
[a]Unknown: loperamide cohort, n=2; budesonide cohort, n=7; ExteNET (neratinib arm), n=241.

- A total of 135 patients were included in the interim analysis of the loperamide cohort (original loperamide schedule, n=28; modified loperamide schedule, n=107).
- Forty patients were included in the preliminary analysis of the actively enrolling budesonide cohort (Figure 1).
- Baseline characteristics are presented in Table 1.

Treatment-emergent diarrhea

- Incidence of grade ≥3 diarrhea, the primary study endpoint, was 28.1% (95% CI 20.8–36.5%) with loperamide prophylaxis (loperamide cohort) and 15.0% (95% CI 5.7–29.8%) with loperamide prophylaxis plus budesonide (budesonide cohort) vs 39.9% without protocol-mandated loperamide prophylaxis in the ExteNET trial.
- A summary of treatment-emergent diarrhea is presented in Table 2.

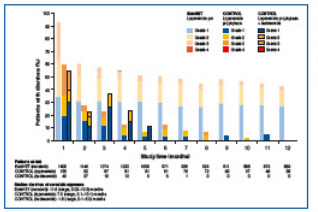
Table 2. Characteristics of treatment-emergent diarrhea

	CONTROL: Loperamide cohort: Original schedule (n=28)	CONTROL: Loperamide cohort: Modified schedule (n=107)	CONTROL: Loperamide cohort: Total (N=135)	CONTROL: Budesonide cohort: Loperamide + budesonide (N=40)	ExteNET:[a] Neratinib arm: Loperamide prn (N=1420)
Diarrhea, %					
Any grade	82.1	73.8	75.6	65.0	95.4
Grade 1	35.7	21.5	24.4	32.5	22.9
Grade 2	21.4	23.4	23.0	17.5	32.5
Grade 3[b]	25.0	29.0	28.1	15.0	39.8
Grade 4	0	0	0	0	0.1
Median cumulative duration, days					
Grade ≥2	5.0	4.0	4.0	3.0	10.0
Grade ≥3[b]	2.0	3.0	3.0	2.5	6.0
Median diarrhea episodes/patient					
Any grade	2	2	2	2	8
Grade ≥2	2	1	2	1	3
Grade ≥3[b]	1	1	1	1	2
Action taken, %					
Dose hold	7.1	12.1	11.1	7.5	33.9
Dose reduction	10.7	7.5	8.1	5.0	26.4
Discontinuation	28.6	15.9	18.5	5.0	16.8
Hospitalization	0	1.9	1.5	0	1.4
Duration of neratinib treatment, months					
Median	9.7	7.4	7.5	1.8	11.6
Range	0.1–13.1	0.1–12.8	0.1–13.1	0.1–6.3	0.03–13.3

[a]Non-compliance with loperamide prophylaxis in patients with grade 3 diarrhea was 71% with the original loperamide schedule, 35% with the modified loperamide schedule, and 0% with loperamide prophylaxis plus budesonide.
[b]No grade 4 events in the CONTROL study; one grade 4 event in the ExteNET study.

- There were also marked reductions in the median cumulative duration of diarrhea and in the median number of diarrhea episodes per patient with loperamide prophylaxis given with or without budesonide vs ExteNET (Table 2).
- The proportion of patients requiring concomitant dose holds and dose reductions was also

Figure 2. Treatment-emergent diarrhea by month: CONTROL vs ExteNET[a]



Potential factors contributing to diarrhea

- Grade 3 diarrhea rates seen in the loperamide cohort have increased over what was previously reported in December 2015 (grade 3 diarrhea, 16%, n=50 (data cut-off: September 2015)).
- Adherence to loperamide prophylaxis was assessed based on total daily dose of loperamide recorded over the first 2 cycles of neratinib treatment. Non-compliance rates with loperamide prophylaxis in patients with grade 3 diarrhea were 71% (original loperamide schedule), 35% (modified loperamide schedule), and 0% (loperamide prophylaxis plus budesonide).
- During the course of the CONTROL study, there has been an increase in the proportion of patients previously treated with pertuzumab in the neoadjuvant and adjuvant settings:
  - In the loperamide cohort, 18% of patients had previously received pertuzumab (September 2015 data cut-off) increasing to 40% (November 2016 data cut-off).
  - In the budesonide cohort, for which enrollment started most recently, 55% of patients had previously received pertuzumab.
- Table 3 shows an exploratory analysis of the incidence of grade 3 diarrhea by previous pertuzumab exposure.
  - In the loperamide cohort, grade 3 diarrhea in pertuzumab-naïve patients (23.5%) was numerically lower than in patients previously treated with pertuzumab (35.2%).
  - This may suggest that previous treatment with pertuzumab results in a higher incidence of grade 3 diarrhea with neratinib that is not able to be prevented/reduced with loperamide prophylaxis alone.
  - Early results suggest that adding budesonide to loperamide prophylaxis may reduce grade 3 diarrhea both in patients previously treated (13.6%) and not previously treated with pertuzumab (16.7%).

Table 3. Incidence of grade 3 diarrhea by pertuzumab treatment status

	Prior pertuzumab treatment: Loperamide cohort: Yes (n=54)	Prior pertuzumab treatment: Loperamide cohort: No (n=81)	Prior pertuzumab treatment: Budesonide cohort: Yes (n=22)	Prior pertuzumab treatment: Budesonide cohort: No (n=18)
Grade 3 diarrhea, %	35.2	23.5	13.6	16.7

Other adverse events

- Aside from diarrhea, the overall tolerability profile of neratinib with loperamide prophylaxis given with or without budesonide was similar to that reported in the ExteNET trial, with the exception of an increase in grade 1/2 constipation (Table 4).
- The incidence of other gastrointestinal events (i.e. nausea, vomiting, and abdominal

Table 4. Other common treatment-emergent adverse events (≥10% in either CONTROL cohort)

	CONTROL: Loperamide cohort: Loperamide (N=135): All grade	CONTROL: Loperamide cohort: Loperamide (N=135): Grade 3/4	CONTROL: Budesonide cohort: Loperamide + budesonide (N=40): All grade	CONTROL: Budesonide cohort: Loperamide + budesonide (N=40): Grade 3/4	ExteNET:[a] Neratinib arm: Loperamide prn (N=1420): All grade	ExteNET:[a] Neratinib arm: Loperamide prn (N=1420): Grade 3/4
Adverse event, %						
Constipation	64.1	0	47.5	0	8.2	0
Nausea	55.6	0.7	40.0	0	43.0	1.8
Fatigue	52.6	3.7	30.0	7.5	27.1	1.6
Vomiting	34.4	1.5	20.0	5.0	35.2	3.3
Abdominal pain	24.4	1.5	20.0	0	24.1	1.7
Decreased appetite	18.5	0	17.5	0	12.1	0.2
Headache	18.5	0	7.5	0	19.7	0.6
Abdominal distension	14.8	0	5.0	0	5.2	0.3
Dizziness	14.1	0	5.0	0	10.4	0.2
Dry mouth	11.9	0	5.0	0	3.3	0.1
Dehydration	5.9	1.5	10.0	2.5	3.6	0.9
Dyspepsia	5.7	0	10.0	0	9.9	0.4
Rash	3.7	0	10.0	0	15.0	0.4

Conclusions

- A structured loperamide prophylactic regimen for 2 cycles reduces the incidence, severity and duration of neratinib-associated diarrhea compared with events observed in the ExteNET trial.
- Preliminary data suggest that adding budesonide to loperamide prophylaxis may further diminish the duration and number of episodes of diarrhea, as well as decreasing the number of neratinib dose holds, dose reductions and discontinuations.
- ExteNET showed a profile for diarrhea that was chronic and characterized by higher-grade diarrhea (grades 2 and 3) that was highest in month 1 and still present in a larger proportion of patients in months 2-12. In the CONTROL study cohorts, diarrhea was characterized by a lower percentage of high-grade diarrhea in month 1 and a much lower incidence in months 2-12.
- There appears to be some adaptation to the effects of neratinib, as higher-grade diarrhea occurs early and does not typically recur.
- By controlling early diarrheal events, loperamide prophylaxis may help to improve long-term adherence and help to ensure that the efficacy benefits of neratinib are realized.
- Enrollment into the budesonide cohort is ongoing, with testing of additional investigational agents planned.
- The final analysis of the CONTROL study will be performed when all patients have completed 12 months of neratinib therapy.

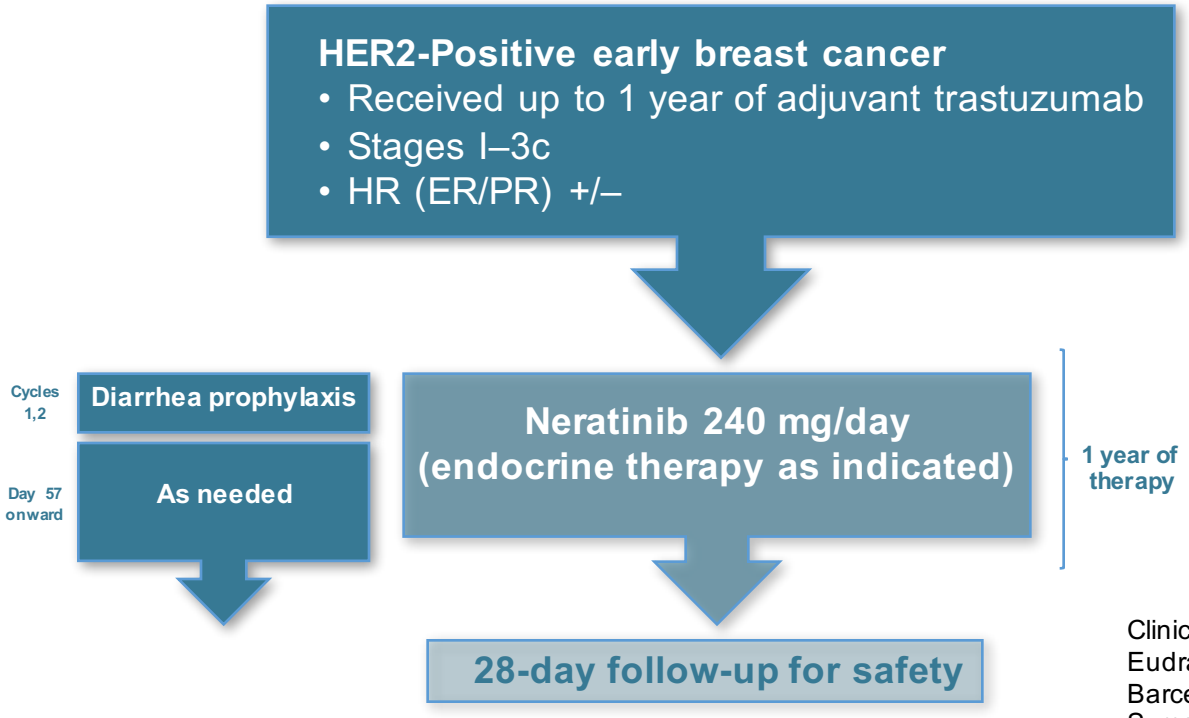
References

1. Rabindran SK. *Cancer Lett* 2005;227:9–23.
2. Chan A, et al. *Lancet Oncol* 2016;17:367–77.
3. Ustaris F, et al. *Am J Hematol/Oncol* 2015;11:13–22.
4. Puma Biotechnology Inc., data on file.

Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.

CONTROL: Study Design

Phase II study to characterize the incidence and severity of diarrhea in patients with HER2+ early breast cancer treated with neratinib and loperamide prophylaxis



Final analysis: when all patients have completed 13 cycles of therapy or have discontinued the study

Interim analysis: when all patients have completed 2 cycles of neratinib + loperamide prophylaxis

Study objectives

- Primary endpoint: incidence and severity of diarrhea
- Secondary endpoints: association between loperamide exposure and incidence and severity of diarrhea; serious adverse event; other adverse events of special interest
- Exploratory endpoint: patient-reported health outcomes (EQ-5D-5L and FACT-B)

ClinicalTrials.gov identifier: NCT02400476
EudraCT number: 2012-004492-38.
Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.

CONTROL: Loperamide Schedule

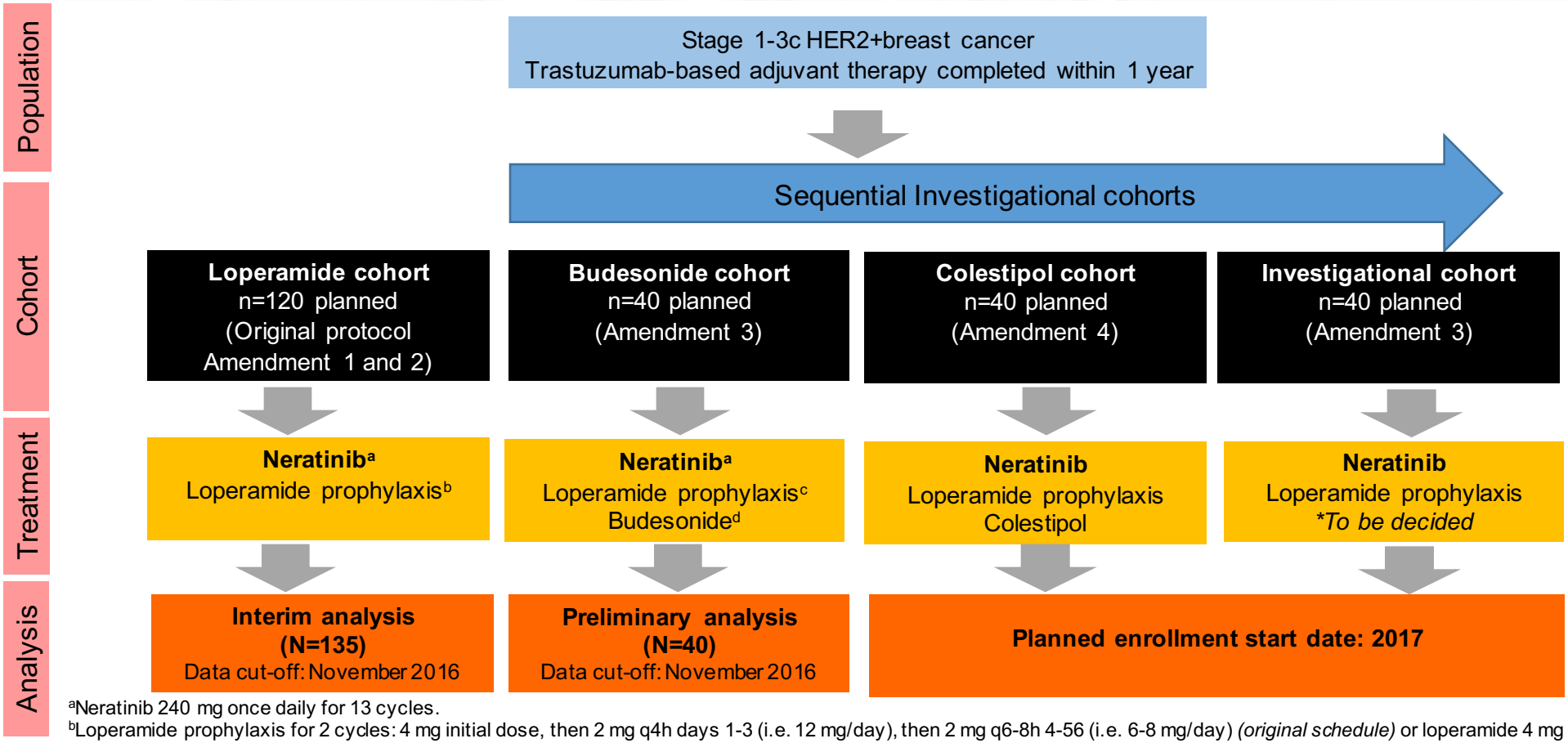
- Original protocol dosing
  - Loperamide 16 mg (4 mg +2 mg q 4 hr) on day1
  - Loperamide 12 mg/day (2 mg q 4 hr) days 2-3
  - Loperamide 6-8 mg/day (2 mg (q 6 or q 8 hr) days 4-56
  - Then prn from day 57 onward
- Amendment dosing:
  - Loperamide 16 mg (4 mg +4 mg TID) on day1
  - Loperamide 12 mg/day (4 mg TID) days 2-14
  - Loperamide 8 mg/day (4 mg BID) days 15-56
  - Then prn from day 57 onwardn

- Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.

Two Cohorts Later Added…

- Combination of loperamide and budesonide
  - Budesonide: locally acting corticosteroid believed to target the inflammation associated with neratinib-induced diarrhea in a preclinical model
  - Budesonide 9 mg once daily (extended-release tablets) for first cycle
- Combination of loperamide plus colestipol
  - Colestipol: sequestrant believed to target the bile acid malabsorption also seen in preclinical models of neratinib-induced diarrhea
  - For first cycle

Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.



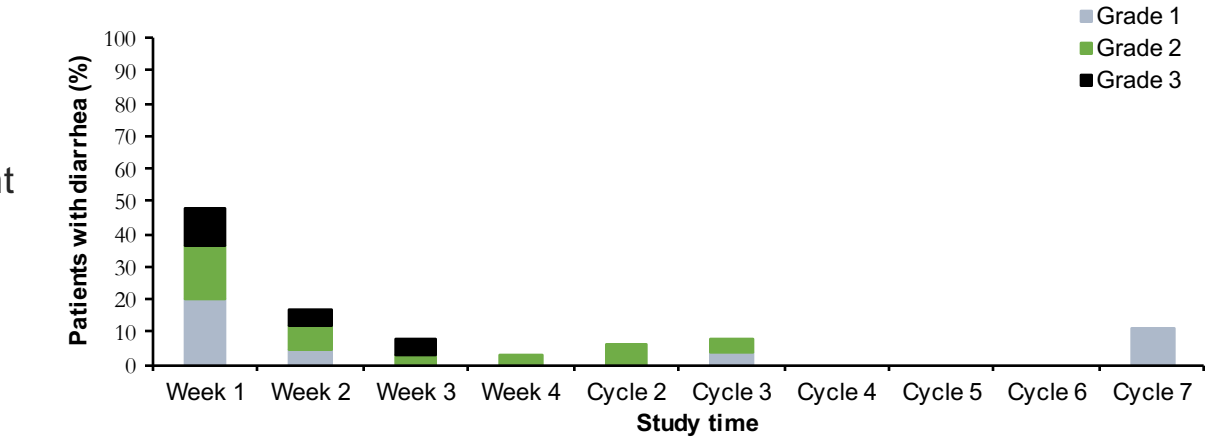
[a]Neratinib 240 mg once daily for 13 cycles.
[b]Loperamide prophylaxis for 2 cycles: 4 mg initial dose, then 2 mg q4h days 1-3 (i.e. 12 mg/day), then 2 mg q6-8h 4-56 (i.e. 6-8 mg/day) *(original schedule)* or loperamide 4 mg initial dose, then 4 mg tid days 1-14 (i.e. 12/mg/day), then 4 mg bid days 15-56 (i.e. 8 mg/day) *(modified schedule)*.
[c]Loperamide prophylaxis for 2 cycles: 4 mg initial dose, then 4 mg tid days 1-14 (i.e. 12 md/day), then 4 mg bid days 15-56 (i.e. 8 mg/day) *(modified schedule)*.
[d]Budesonide 9 mg once daily (extended-release tablets) 1 cycle.
[e]Agent selected for this cohort will be based on the review of ongoing preclinical investigations.
One cycle = 28 days; bid, twice daily; tid, 3-times daily; q = every.

Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.

CONTROL: Neratinib Treatment-Emergent Diarrhea

Most events occur during the first treatment cycle

- Loperamide prophylaxis given for 2 cycles
- 75% of all diarrheal events occur within the first 4 weeks of treatment
- Over half of all grade 3 events occur within the first week
- No grade 3 events after the first cycle
- No grade 4 diarrhea observed



Cycle 1	Week 1	Week 2	Week 3	Week 4						
Pts at risk	50	42	37	36	31	26	18	15	14	9

Data for total CONTROL safety population (N = 50).

·Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.

Characteristics of Treatment-Emergent Diarrhea

	CONTROL				ExteNET
	Loperamide cohort			Budesonide cohort	Neratinib arm
	Original schedule (n=28)	Modified schedule (n=107)	Loperamide total (N=135)	Loperamide + budesonide (N=40)	Loperamide prn (N=1408)
Diarrhea, %					
Any grade	82.1	73.8	75.6	65.0	95.4
Grade 1	35.7	21.5	24.4	32.5	22.9
Grade 2	21.4	23.4	23.0	17.5	32.5
Grade 3	25.0	29.0	28.1	15.0	39.8
Grade 4	0	0	0	0	0.1
Median cumulative duration, days					
Grade ≥2	5.0	4.0	4.0	3.0	10.0
Grade ≥3	2.0	3.0	3.0	2.5	5.0

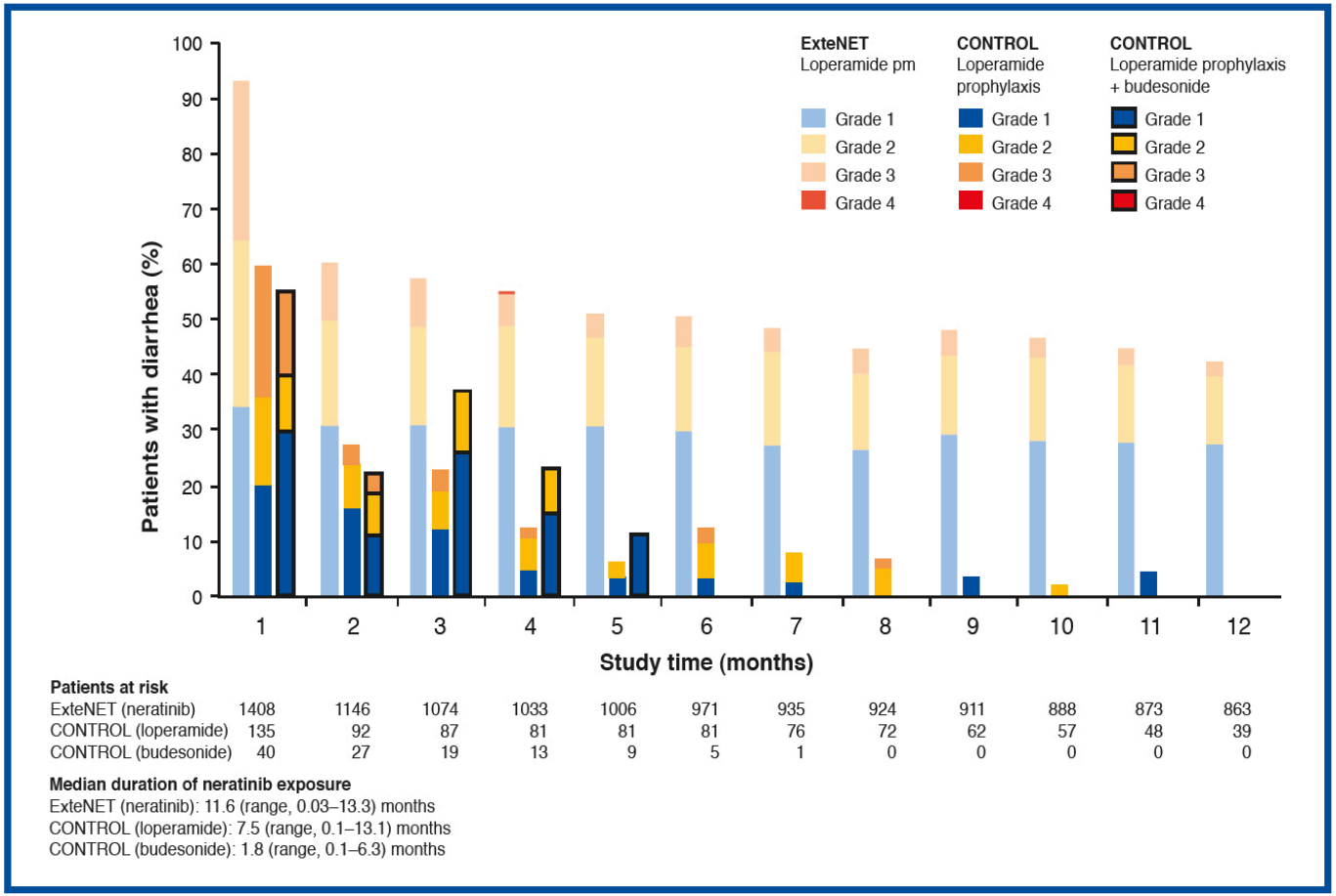
Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.
See also: Ibrahim E, et al. Presented at the 2017 AACR Annual Meeting, April 1-5, Washington, DC. Abstract CT128 [Cancer Research.2017;77(13 Suppl].

Characteristics of Treatment-Emergent Diarrhea

	CONTROL				ExteNET
	Loperamide cohort			Budesonide cohort	Neratinib arm
	Original schedule (n=28)	Modified schedule (n=107)	Loperamide total (N=135)	Loperamide + budesonide (N=40)	Loperamide prn (N=1408)
Median diarrhea episodes/patient					
Any grade	2	2	2	2	8
Grade ≥2	2	1	2	1	3
Grade ≥3	1	1	1	1	2
Action taken, %					
Dose hold	7.1	12.1	11.1	7.5	33.9
Dose reduction	10.7	7.5	8.1	5.0	26.4
Discontinuation	28.6	15.9	18.5	5.0	16.8
Hospitalization	0	1.9	1.5	0	1.4
Duration of neratinib treatment, months					
Median	9.7	7.4	7.5	1.8	11.6
Range	0.1-13.1	0.1-12.8	0.1-13.1	0.1-6.3	0.03-13.3

Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.
See also: Ibrahim E, et al. Presented at the 2017 AACR Annual Meeting, April 1-5, Washington, DC. Abstract CT128 [Cancer Research.2017;77(13 Suppl].

Figure 2. Treatment-emergent diarrhea by month: CONTROL vs ExteNET[2]



Barcenas C, et al. Presented at the 2016 San Antonio Breast Cancer Symposium, December 6-10, San Antonio, TX. Abstract P2-11-03.

Conclusions

- A structured loperamide prophylactic regimen for 2 cycles reduces the incidence, severity and duration of neratinib-associated diarrhea compared with events observed in the ExteNET trial.
- Preliminary data suggest that adding budesonide to loperamide prophylaxis may further diminish the duration and number of episodes of diarrhea, as well as decrease the number of neratinib dose holds, dose reductions and discontinuations.
- ExteNET demonstrated diarrhea which was often characterized by high-grade diarrhea (grades 2/3), highest in month 1 and persistent in a larger proportion of patients in months 2-12. In the CONTROL study cohorts, diarrhea was characterized by a lower percentage of high-grade diarrhea in month 1 and a much lower incidence in months 2-12.

Conclusions

- Adaptation to the effects of neratinib are observed, as higher-grade diarrhea occurs early and does not typically recur.
- By controlling early diarrheal events, loperamide prophylaxis may help to improve long-term adherence and ensure that the efficacy benefits of neratinib are realized.
- Budesonide cohort enrollment is ongoing, with testing of additional investigational agents planned.
- The final analysis of the CONTROL study will be performed when all patients have completed 12 months of neratinib therapy.

Role of the Advanced Practitioner in Caring for Patients Undergoing HER2-Positive Breast Cancer Therapy

AP Role in Managing Patients on HER2 Therapy

- Patient selection for treatment
  - Knowledge of treatment options
- Essential baseline assessments
  - Extent of disease
  - Cardiovascular history and subjective assessments (LVEF)
  - Gastrointestinal history and subjective assessments as needed
- Patient education
  - Disease process
  - Treatment
  - Self-management of potential toxicities – PROACTIVE not reactive
  - Report adverse toxicities: when and to whom
- Staff education

NCCN Guidelines. Breast Cancer. www.nccn.org/professionals/physician/gls/pdf/breast.pdf
Frankel C, Palmieri FM. *Clin J Oncol Nurs*. 2010;14(2):223-233.

Monitoring Tolerance to Treatment

- Grading of toxicities
- Oversee triage calls
  - Diarrhea from HER2 therapy differs from chemotherapy-induced diarrhea
- High index of suspicion for problems – face-to-face assessments
  - Physical exam should include examination of the abdomen and rectal area
  - Weight assessment
  - VS
  - Nutritional assessment – refer to dietician
  - Assess for electrolyte abnormalities
- Assess adherence
  - To cancer therapy
  - To toxicity management

NCCN Guidelines. Breast Cancer. www.nccn.org/professionals/physician/gls/pdf/breast.pdf
Frankel C, Palmieri FM. *Clin J Oncol Nurs*. 2010;14(2):223-233.

Oral Treatment Challenges

- ADHERENCE
  - Studies have shown that adherence to oral agents, as well as monitoring patients for side effects, dosing titration, and psychosocial issues, impacts clinical outcomes
- Unique toxicities
  - Patients may not connect toxicity with treatment
- Challenging dosing schedules
- Drug-drug interactions
- Drug-food interactions

Kirk M and Hudis C. *Clin Breast Cancer*. 2008 Apr;8(2):155-161.
Weingart SN, et al. *J Natl Cancer Network*. 2008;6(suppl 3):S1-S16.

Recognized Barriers to Adherence to Oral Agents

- Complex treatment regimens
- Inadequate supervision
- Poor communication with healthcare providers
- Patient dissatisfaction with care
- Inadequate social support

Partridge AH, et al. *J Natl Cancer Inst.* 2002;94:652-661.
Weingart SN, et al. *J Natl Cancer Network.* 2008;6(suppl 3):S1-S16.


Case Study
JADPRO Live
APSHO

Case Study: Initial Report

- LM
  - 59-year-old postmenopausal woman
  - Palpates a mass in the right middle quadrant of her breast

Case Study: Patient History

Medical History

Obesity and irritable bowel disease

Medication History

Hormone replacement therapy duration of 10 years, now discontinued

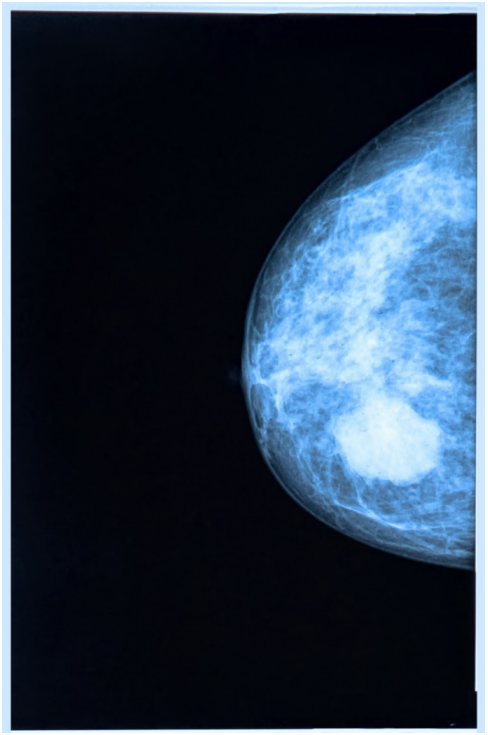
Surgical History

C-section at age 28

Family History

Father died of lung cancer

Case Study: Diagnostic Workup



- Diagnostic mammography and ultrasound reveal a 3.0 x 2.5 cm hypoechoic mass
- Three metastatic lymph nodes are noted as well
- PET/CT is negative for distant metastasis

Case Study: Diagnostic Workup

- Core biopsy
  - Invasive ductal carcinoma, grade III (Nottingham), vascular invasion not present
  - Excisional biopsy of the single right axillary node is consistent with metastatic carcinoma
  - ER positive (50%), PR positive (25%)
  - HER2/*neu* overexpression (3+ by immunohistochemistry)
  - Ki67 proliferative index of 20%
- Clinical stage IIIA (T2N2M0)

Case Study: Neoadjuvant Therapy and Surgery

- The tumor board recommends: Neoadjuvant therapy with trastuzumab/pertuzumab/taxane
- LM completes neoadjuvant therapy followed by bilateral skin-sparing mastectomies and sentinel node biopsy
- Post surgery, LM's pathologic stage is ypT1a, pN0

Case Study: Adjuvant Therapy

- Following recovery, LM continues to receive trastuzumab for 1 year
- Extended adjuvant therapy is recommended and neratinib is prescribed
- She also begins anastrozole (1 mg daily) at the time she resumes maintenance therapy

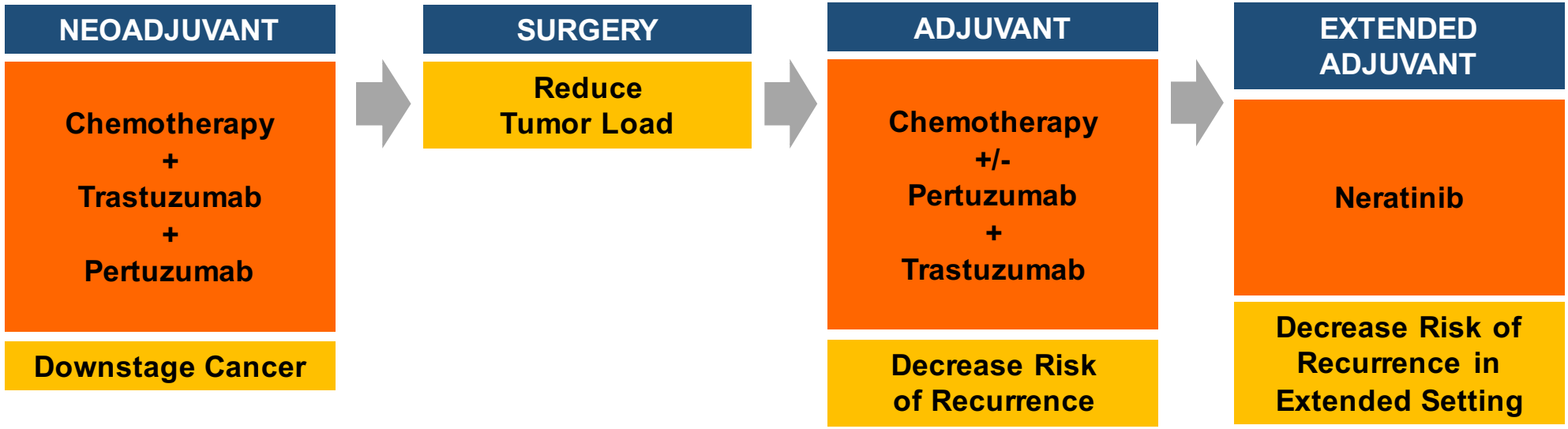

Case Discussion
Questions?
JADPRO Live
APSHO

Concluding Comments

Summary

- HER2 is overexpressed in 18-20% of all breast cancers
  - It is a more aggressive tumor phenotype and associated with poorer prognosis with higher rate of recurrence
- HER2 testing should be preformed on every breast cancer patient
  - IHC
  - FISH
- HER2 pathway presents opportunities to target drug therapy, including:
  - Trastuzumab
  - Pertuzumab
  - Lapatinib
  - Neratinib
- These agents may be given in the neoadjuvant, adjuvant, or extended adjuvant setting

One Example of Sequencing of Treatments in HER2-Positive/HR-Negative Breast Cancer



Advances in Extended Adjuvant HER2-Positive Early Breast Cancer

THANK YOU FOR PARTICPATING!