

# **Perjeta<sup>®</sup> (pertuzumab) for Neoadjuvant Treatment of HER2+ Early Breast Cancer**

Supplemental BLA 125409/51  
Oncologic Drugs Advisory Committee  
September 12, 2013

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# Introduction and Overview of Perjeta

Sandra Horning, MD  
Senior Vice President  
Global Head, Clinical Hematology/Oncology  
Genentech

# Perjeta for Neoadjuvant Treatment of HER2+ Early Breast Cancer (EBC)

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## **Neoadjuvant treatment (prior to surgery) for EBC:**

- Generally used for patients with larger (>2cm) tumors, inoperable locally advanced or inflammatory disease

## **Genentech seeks accelerated approval of a neoadjuvant treatment indication for Perjeta based on:**

- NEOSPHERE & TRYPHAENA neoadjuvant studies in EBC
- CLEOPATRA study in metastatic breast cancer (MBC)

## **Genentech proposes conversion to full approval based on:**

- APHINITY, ongoing Phase III trial of adjuvant Perjeta in HER2+ EBC

# Significance of Neoadjuvant Breast Cancer Trials to Support Accelerated Approval

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## **Guidance for Industry**

**Pathologic Complete Response in  
Neoadjuvant Treatment of High-Risk  
Early-Stage Breast Cancer: Use as an  
Endpoint to Support Accelerated  
Approval**

*DRAFT GUIDANCE*

May 2012  
Clinical/Medical

# Significance of Neoadjuvant Breast Cancer Trials to Support Accelerated Approval

Potential to expedite drug development and approval of highly effective therapies in high-risk early breast cancer

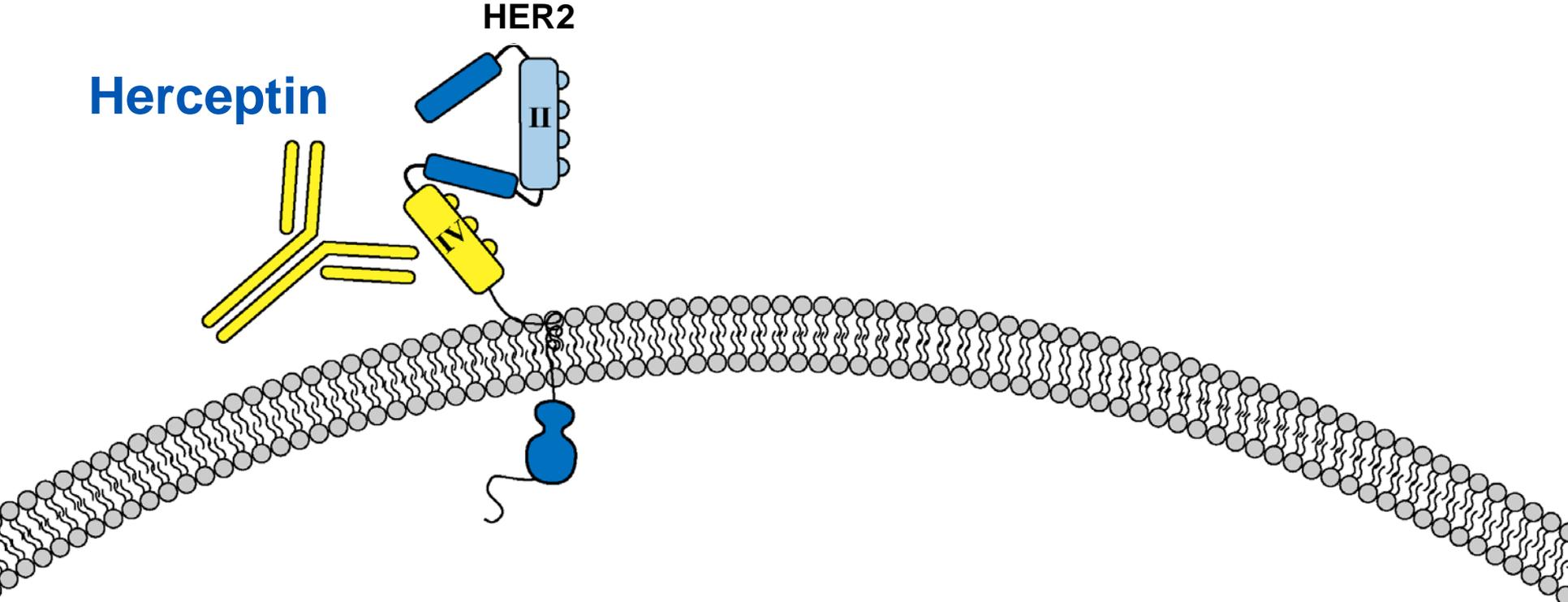
## Guidance for Industry

**Pathologic Complete Response in  
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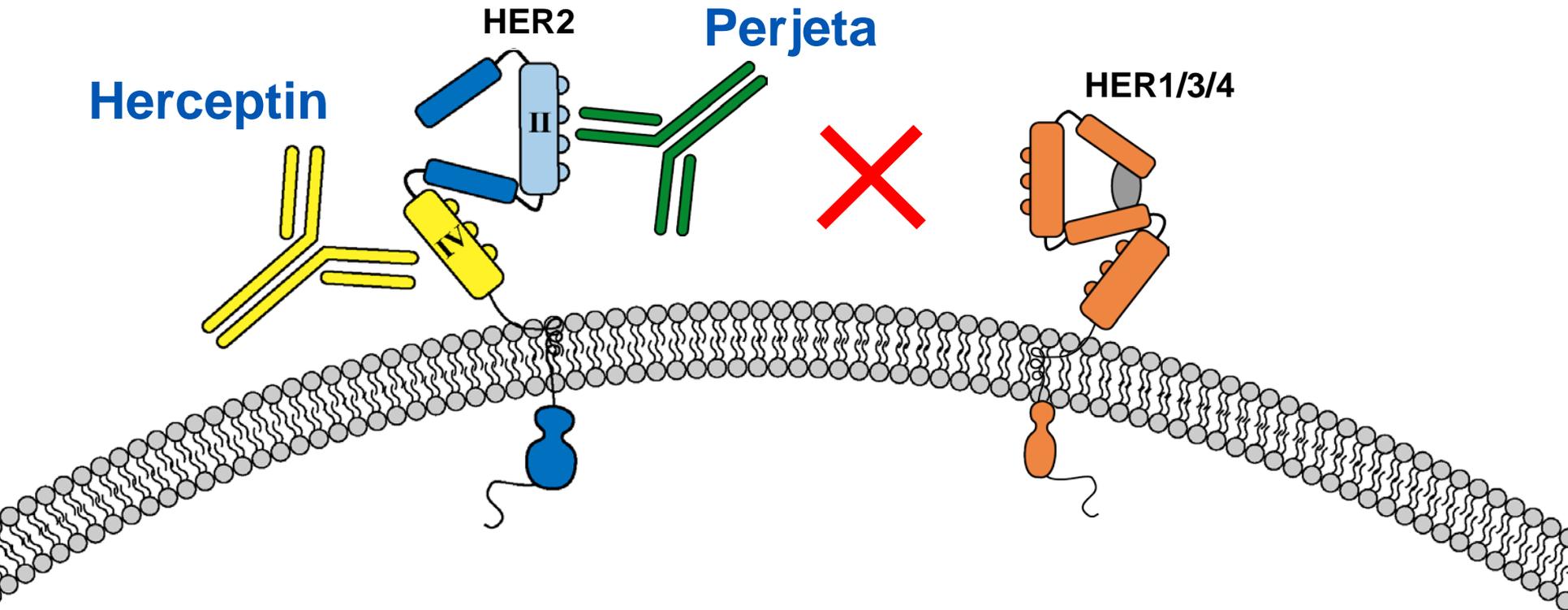
May 2012  
Clinical/Medical

# Longstanding Commitment to HER2 Target



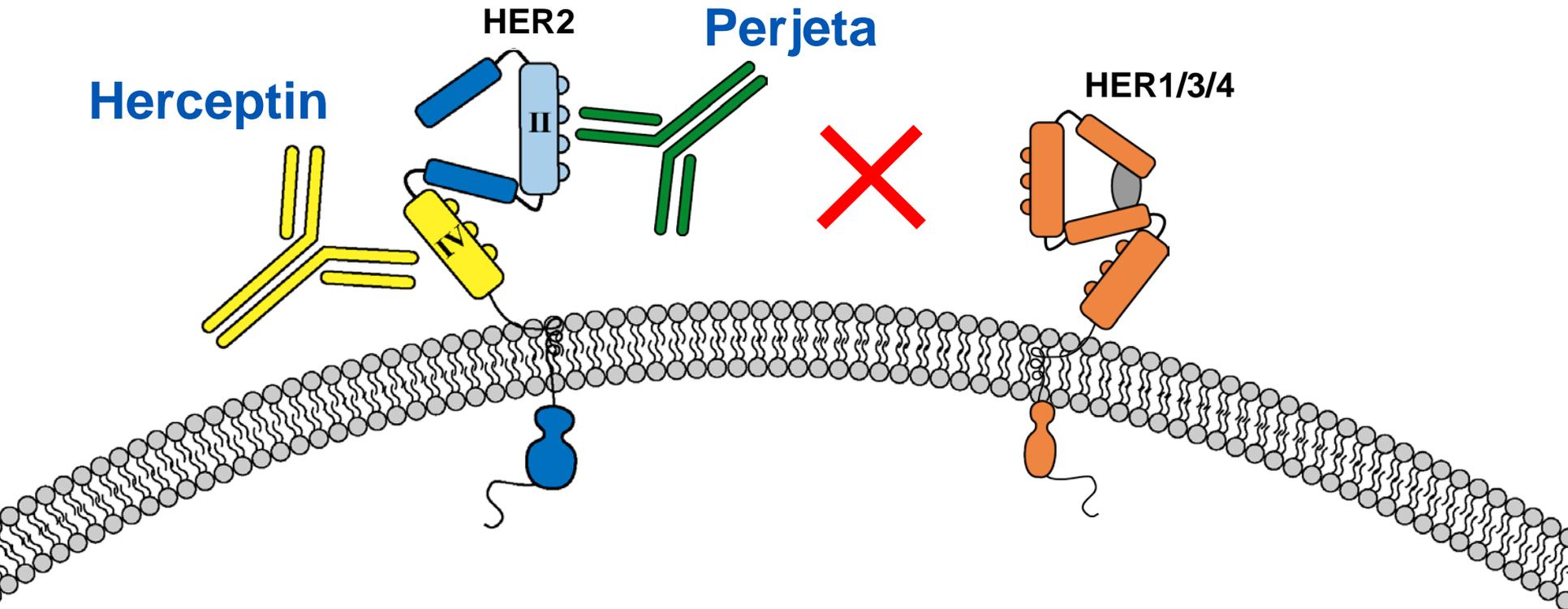
# HER2 as a Therapeutic Target:

*Herceptin + Perjeta*



# HER2 as a Therapeutic Target:

*Herceptin + Perjeta*

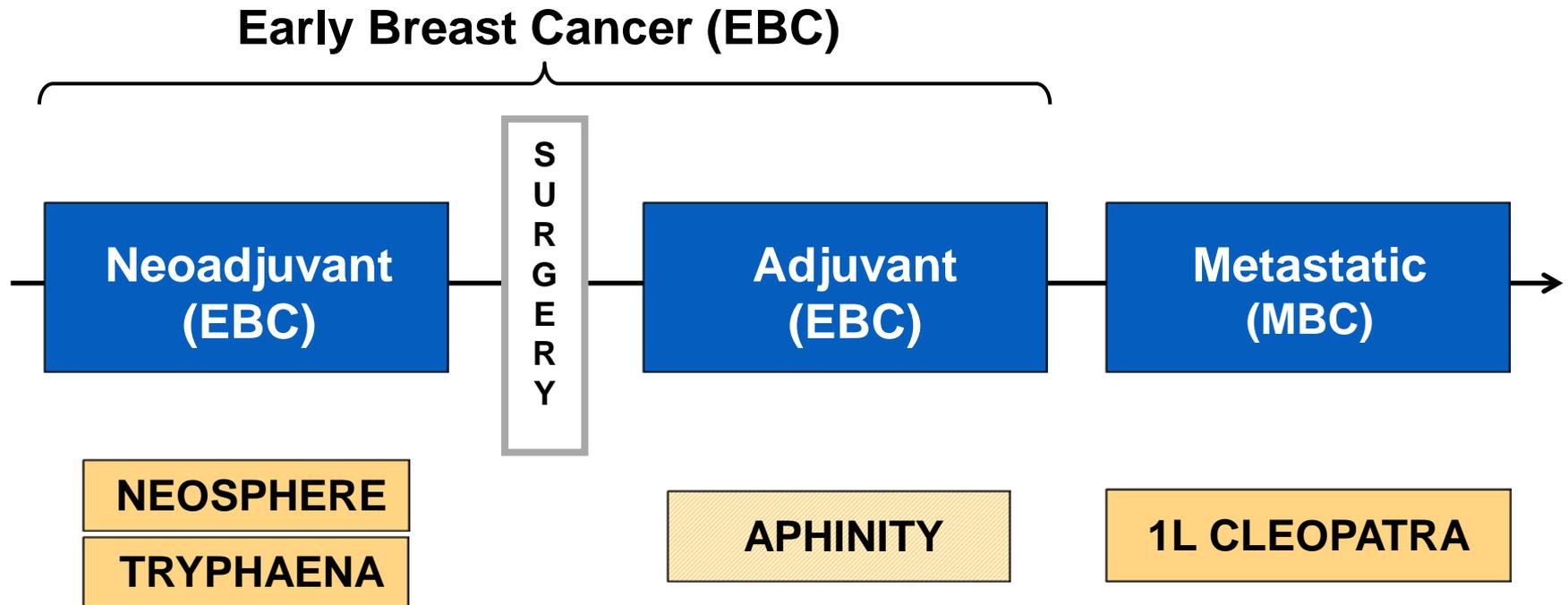


## Herceptin and Perjeta:

- Target **distinct** regions of the HER2 molecule
- Are **complementary** in their mechanisms
- Achieve **dual HER2** blockade

# Perjeta:

*Broad development program in HER2+ breast cancer*



 Data included in this application  Ongoing

# Accelerated Approval of Perjeta in Neoadjuvant Treatment of HER2+ EBC

## Unmet Need

- 6000-8000 US patients die each year from HER2+ breast cancer\*
- Neoadjuvant patients at higher risk for MBC
- HER2+ patient population younger

## Efficacy

- High pathologic CR rates in NEOSPHERE, TRYPHAENA
- Perjeta approved in 1L MBC based on CLEOPATRA

## Safety

- Comprehensive Perjeta clinical development plan
- Large safety database: clinical trials, post-approval
- No new safety signals in neoadjuvant setting

## Conversion

- Phase III APHINITY study with Herceptin, Perjeta and chemotherapy fully enrolled

# Proposed Indication

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**Genentech seeks a positive recommendation for accelerated approval of Perjeta for the proposed indication:**

- Neoadjuvant treatment of high-risk HER2+ early breast cancer
- Combined with trastuzumab and docetaxel
- As part of a complete treatment regimen for early breast cancer

# Agenda and Presenters

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## **Neoadjuvant Treatment of HER2+ Early Breast Cancer**

José Baselga, MD, PhD  
Memorial Sloan-Kettering  
Cancer Center

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## **Overview of Clinical Data in sBLA**

NEOSPHERE: WO20697  
TRYPHAENA: BO22280  
CLEOPATRA: WO20698/TOC4129g

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Graham Ross, MD

## **Summary and Conversion Plan**

Dietmar Berger, MD, PhD

# Neoadjuvant Treatment of HER2+ Early Breast Cancer

José Baselga, MD, PhD  
Physician-in-Chief



Memorial Sloan-Kettering  
Cancer Center

# Disclosure for José Baselga, MD, PhD

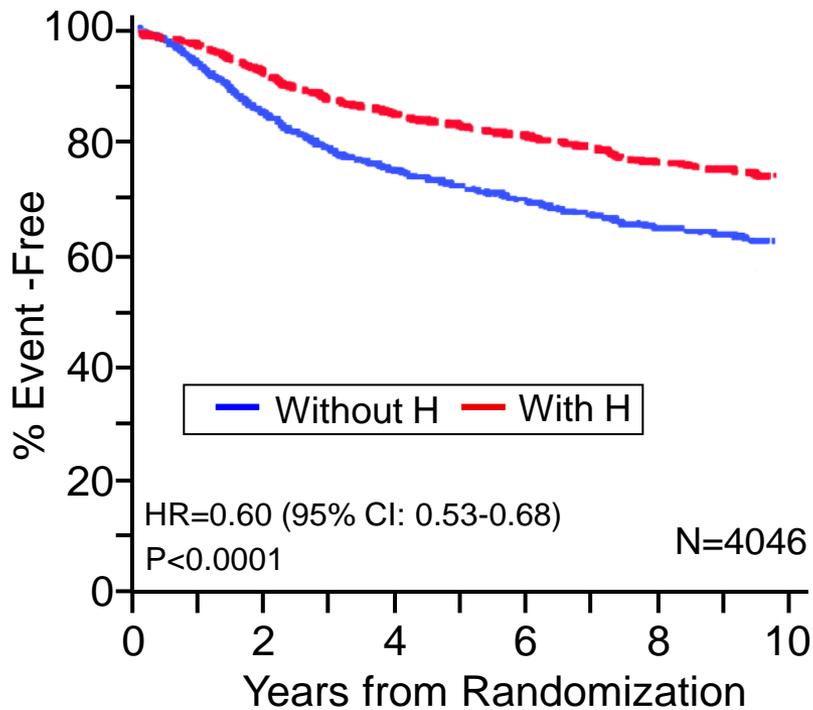
- Investigator for Genentech/Roche sponsored clinical trials including: HERA, NOAH, EMILIA, CLEOPATRA, and APHINITY
- Genentech Clinical Advisory Boards
- Do not own Roche Stock

# Early HER2+ Breast Cancer Need and Challenge

- There is an unmet medical need, patients are still dying from HER2+ breast cancer despite the use of trastuzumab
- New active HER2 targeted agents with complementary mechanisms of action
  - Dual HER2 blockade is superior
- Our challenge as a community is to expedite the approval of effective therapies for patients with high-risk HER2+ EBC
  - EBC is the setting where we can have the biggest impact on patient survival
  - Current path to approval in EBC is slow (large adjuvant trials)

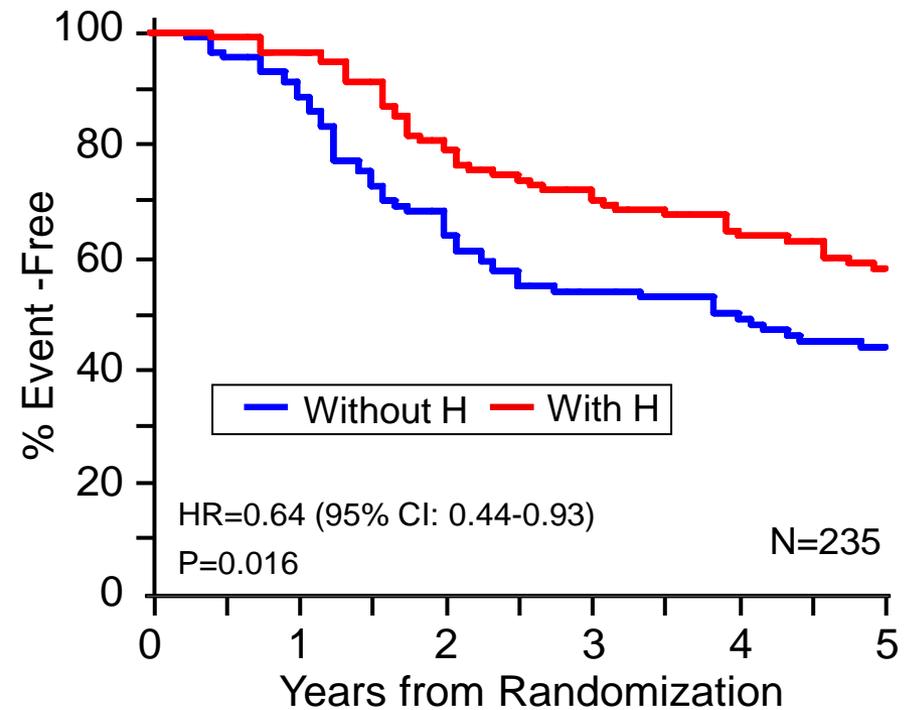
# Unmet Medical Need in Patients with HER2+ EBC Treated with chemotherapy +/- trastuzumab(H)

## Adjuvant US Joint Analysis Disease-Free Survival



EH Romond et al, SABCS 2012.

## Neoadjuvant NOAH Event-Free Survival

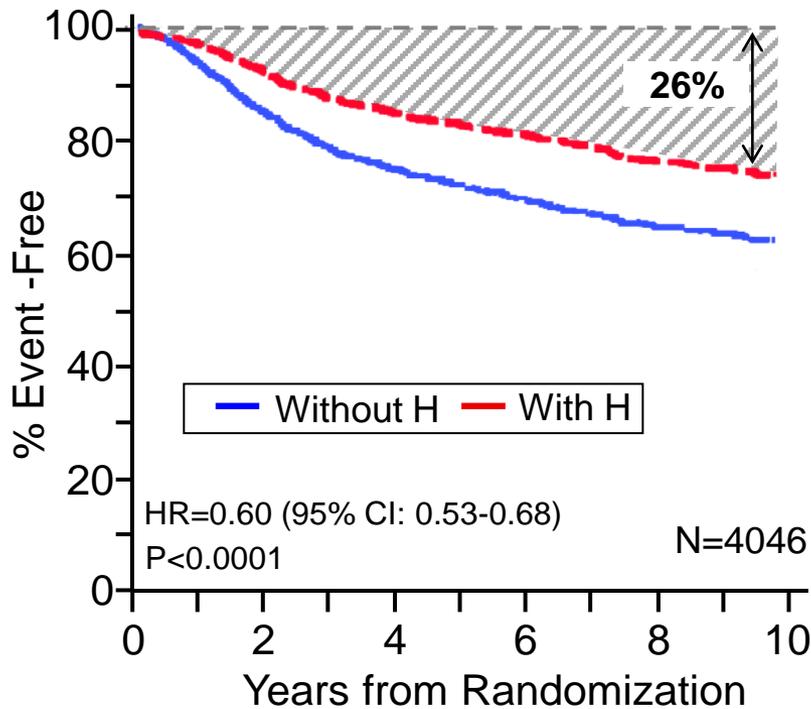


L. Gianni et al, ASCO Annual Meeting 2013.

# Unmet Medical Need in Patients with HER2+ EBC

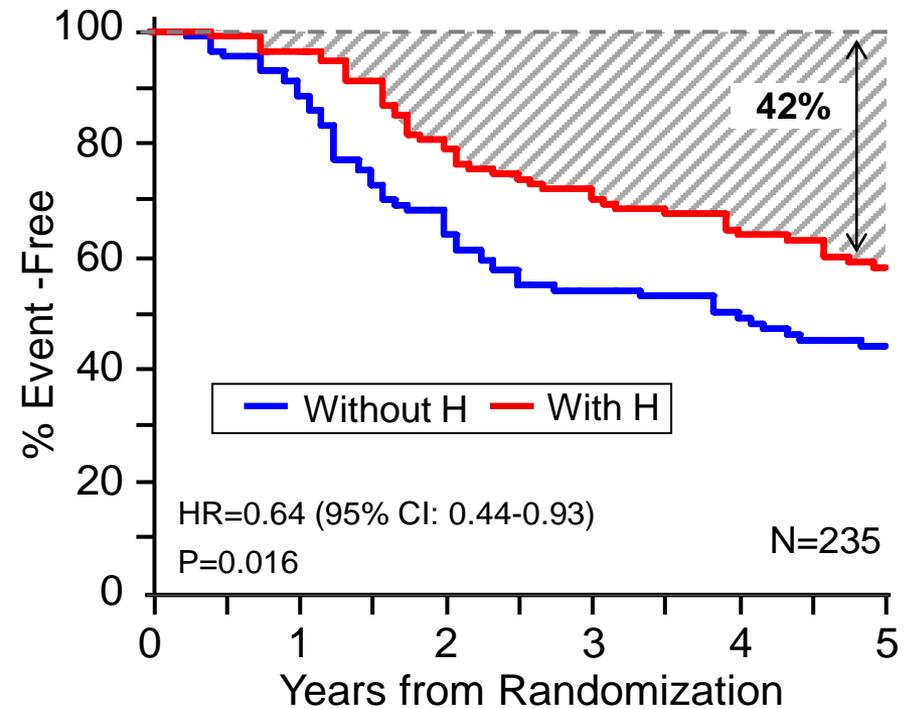
*High recurrence rate despite treatment with trastuzumab*

## Adjuvant US Joint Analysis Disease-Free Survival



EH Romond et al, SABCS 2012.

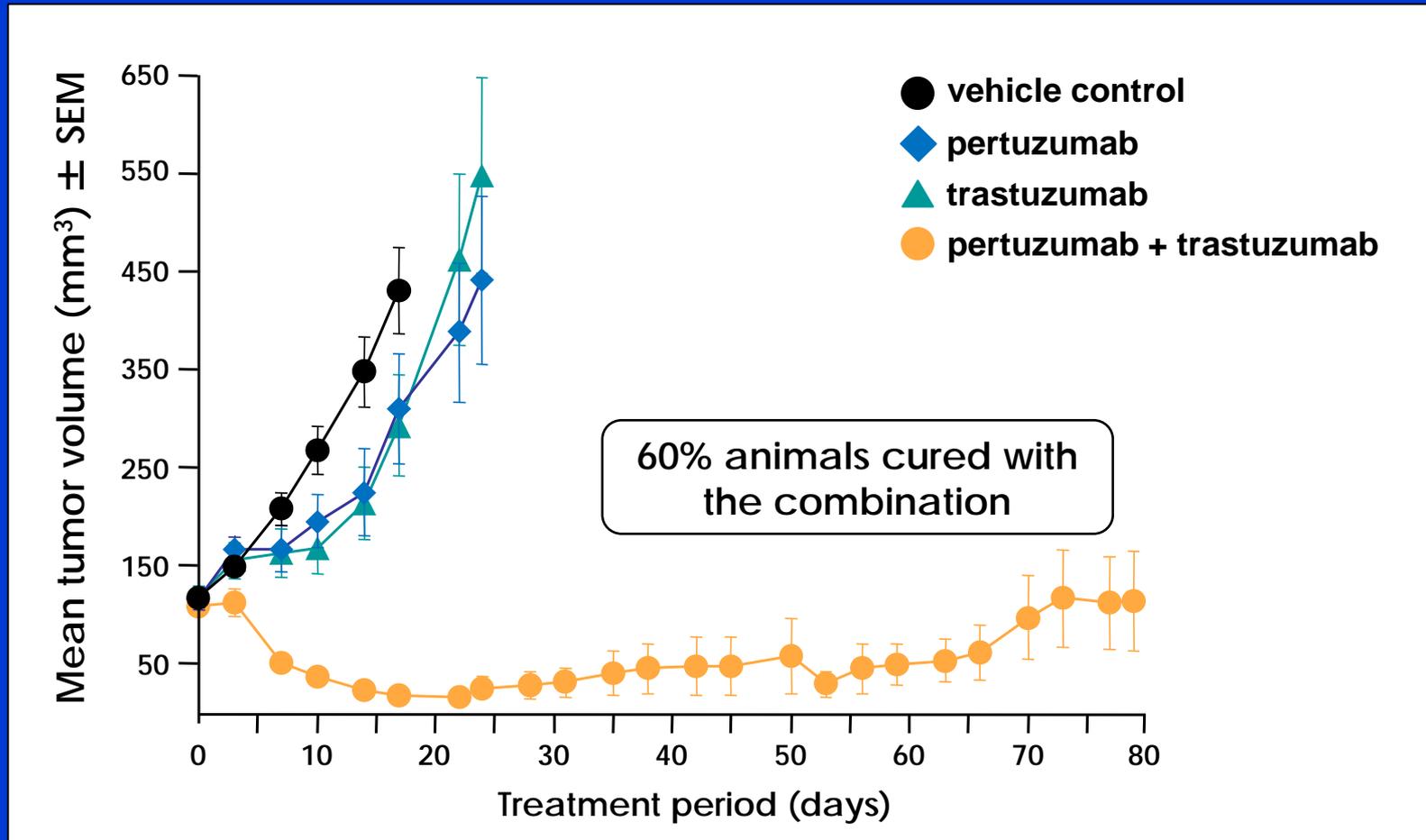
## Neoadjuvant NOAH Event-Free Survival



L. Gianni et al, ASCO Annual Meeting 2013.

# Dual HER2 Blockade: *pertuzumab + trastuzumab*

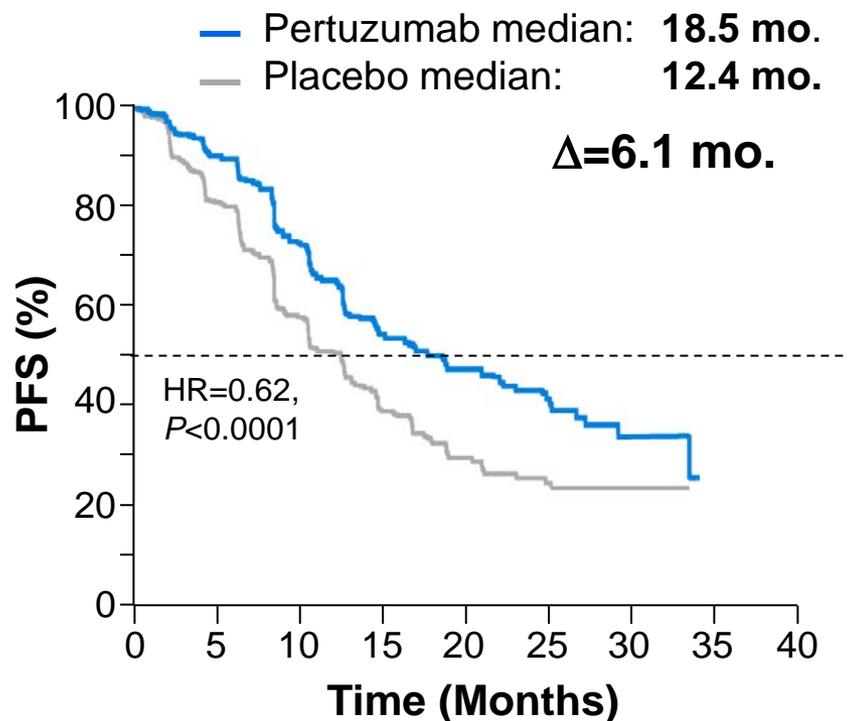
## Synergistic Effect in HER2+ Breast Cancer Model



# CLEOPATRA: PFS and OS

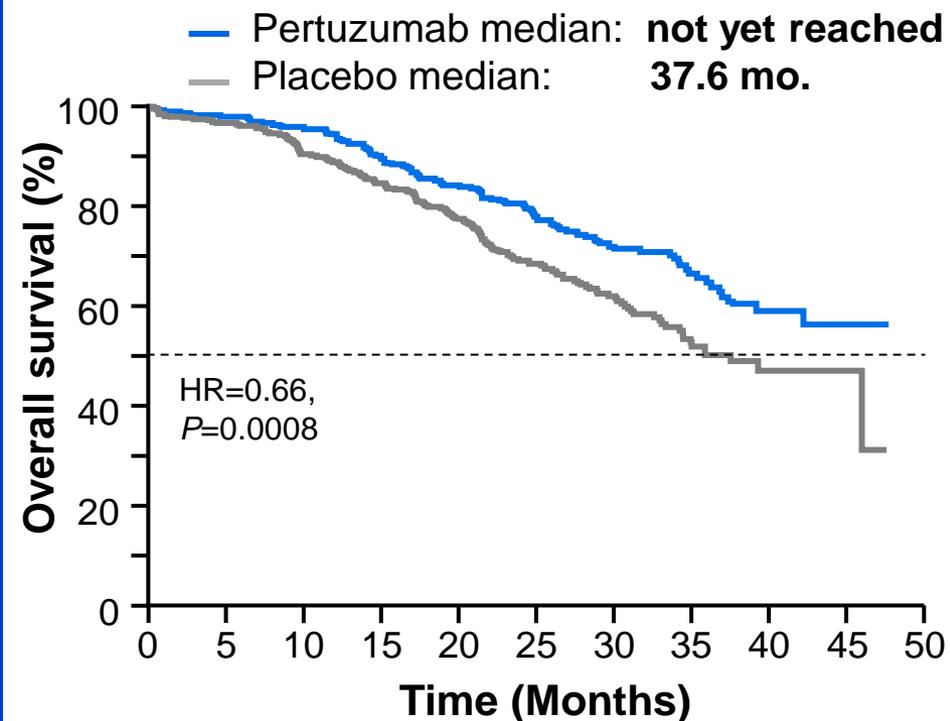
Dual HER2 blockade (pertuzumab+trastuzumab) improves PFS, OS in HER2+ MBC

## Progression-Free Survival



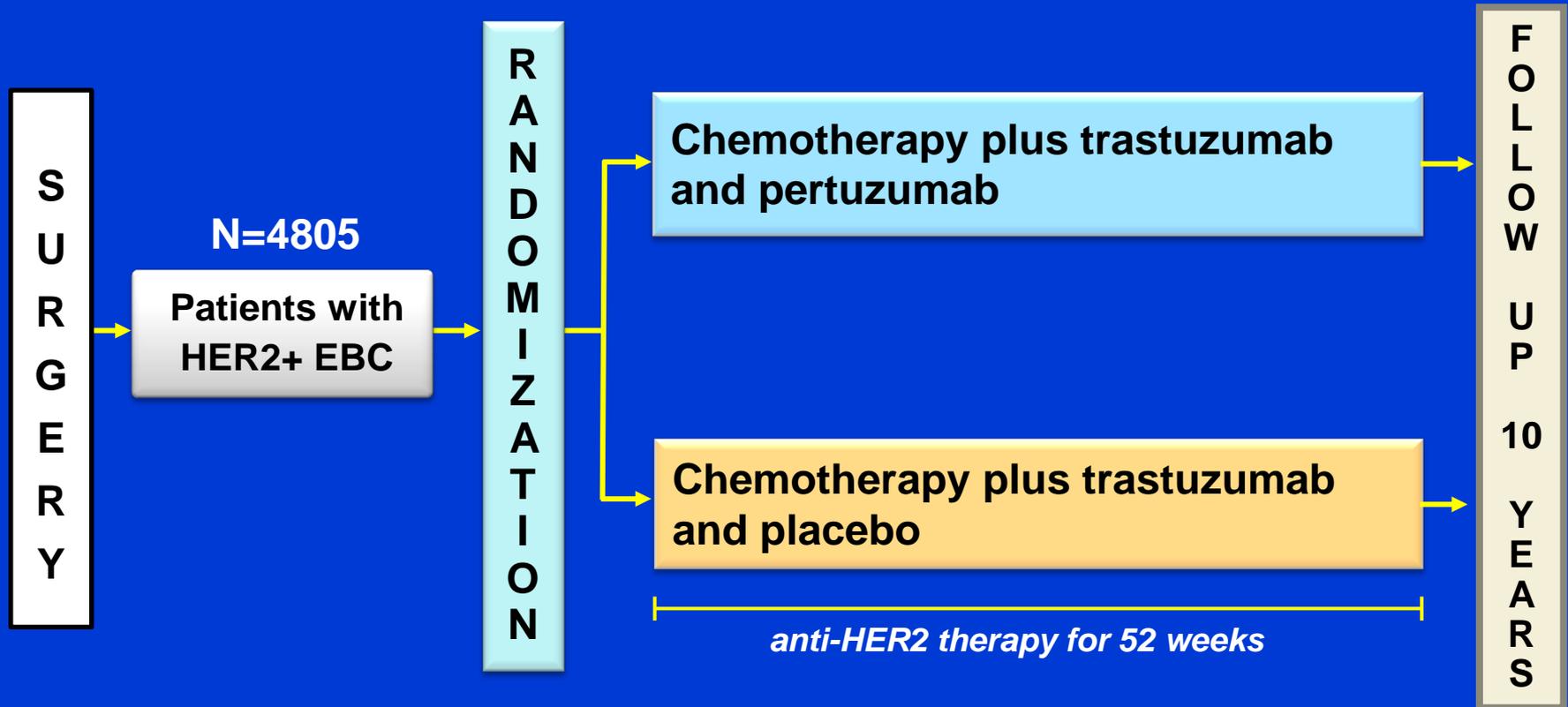
Baselga et al, NEJM 2012.

## Overall Survival: Predefined Interim Analysis



Swain, Baselga, Lancet Oncology 2013.

# APHINITY: Phase III Adjuvant Study HER2+ EBC



1° endpoint: iDFS

Accrued in 21 months: Data expected 2016

# Classical Drug Development Paradigm in HER2+ Breast Cancer

Standard course of drug development

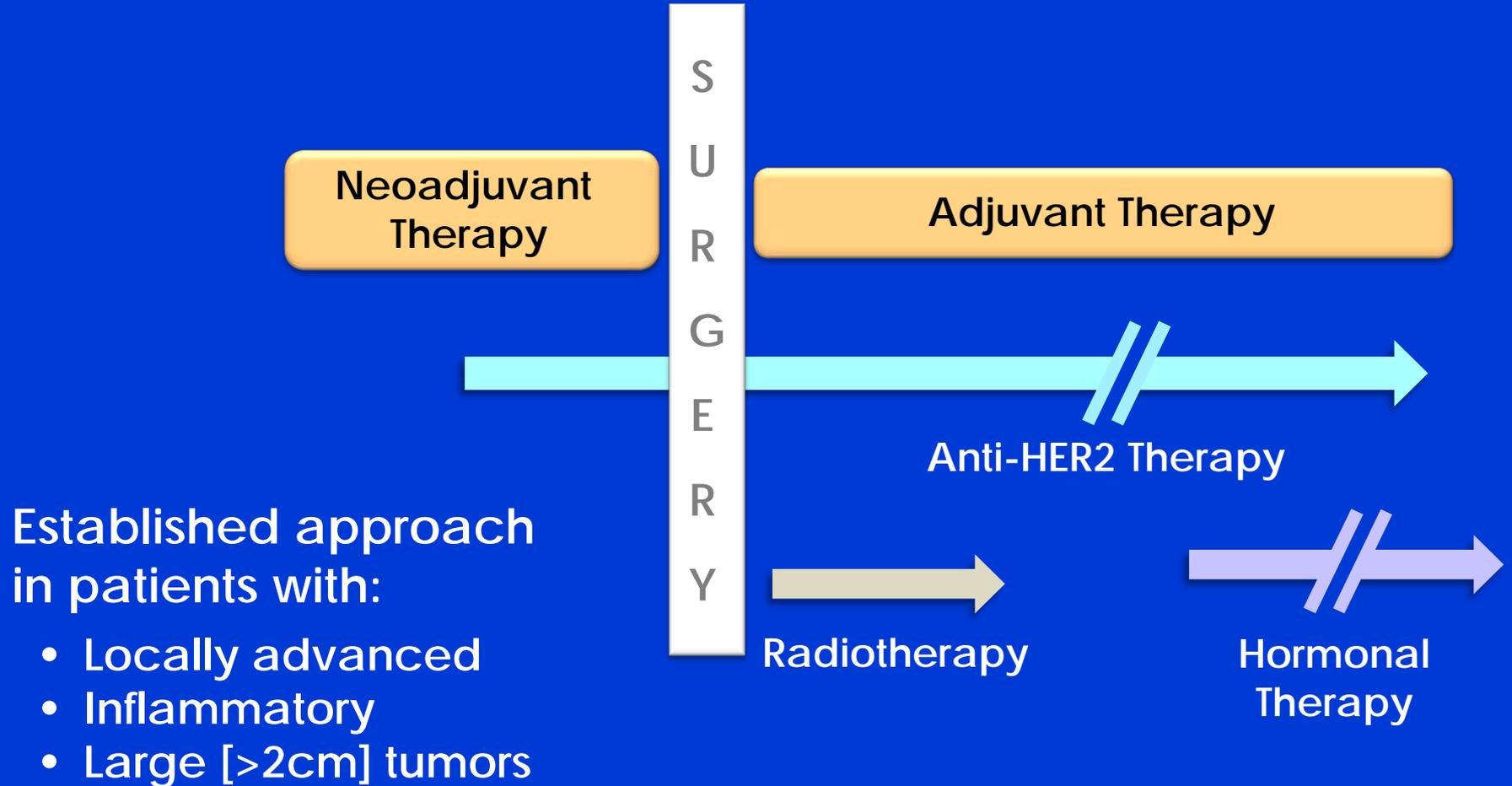
Early Breast Cancer (EBC)



Interval between approvals of agents from the metastatic to the adjuvant setting

Paclitaxel:	5 years
Docetaxel:	8 years
Trastuzumab:	8 years

# A New Drug Development Paradigm in Early HER2+ Breast Cancer

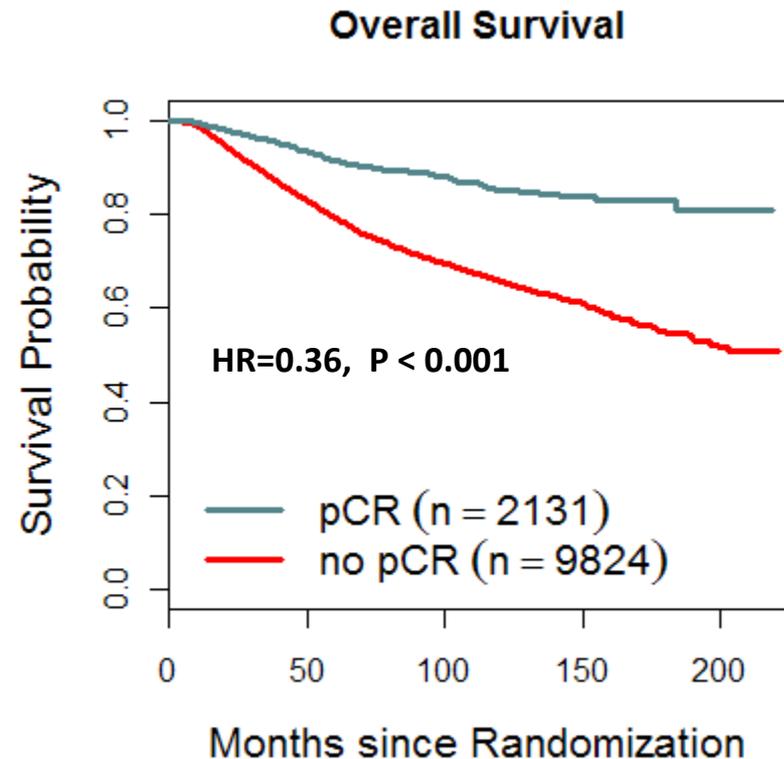
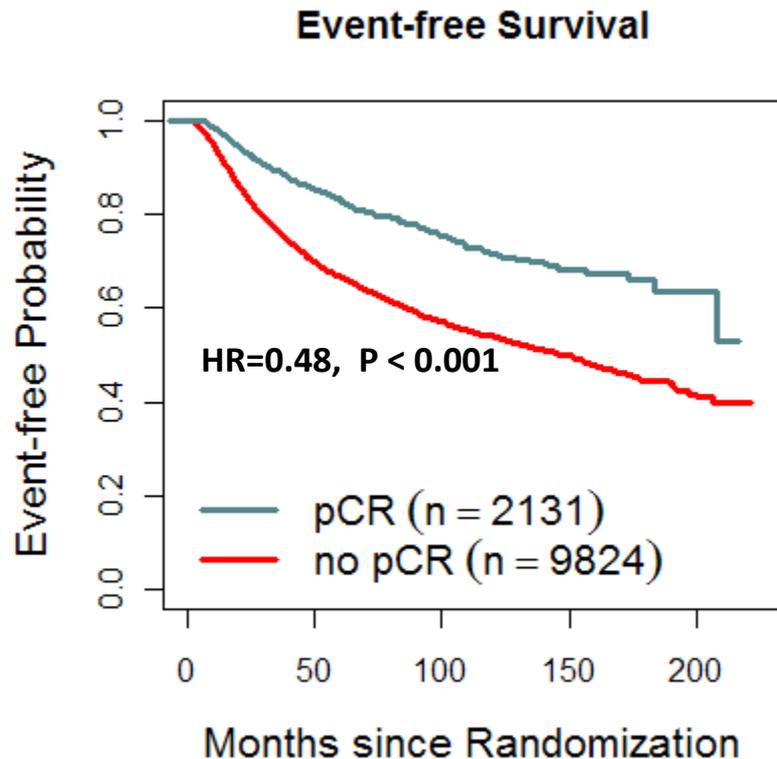


# Neoadjuvant Therapy to Support Drug Approval: Advantages

- Adjuvant studies require large numbers of patients and years to mature
- Neoadjuvant studies:
  - Smaller sample size
  - Shorter time to endpoint assessment (pCR)
- pCR is associated with event-free survival and overall survival
  - Patients who attain pCR have a more favorable long-term outcome
  - Several meta analyses reported: *von Minckwitz (JCO 2012); Bardia (AACR 2011); Cortazar (SABCS 2012)*

# Association of pCR with EFS and OS

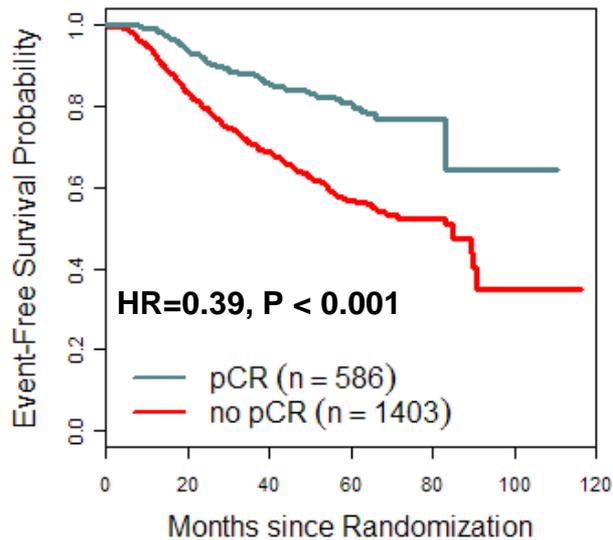
## CTNeoBC Meta-analysis (12,993 patients, 12 trials)



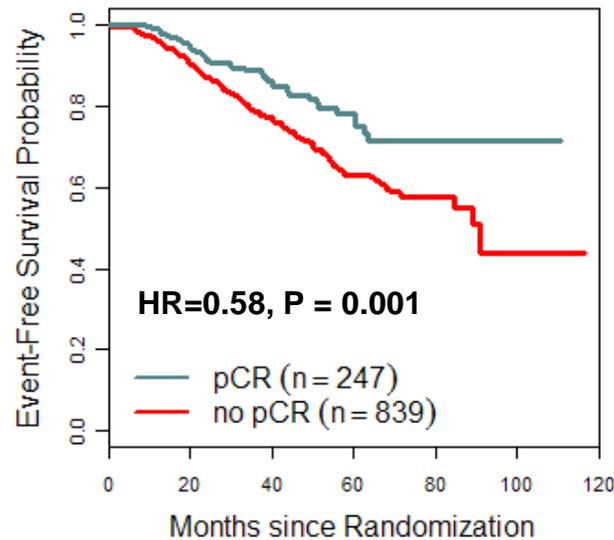
**pCR= total pCR**

# Association of pCR with EFS in HER2+ Subtype CTNeoBC Meta-analysis

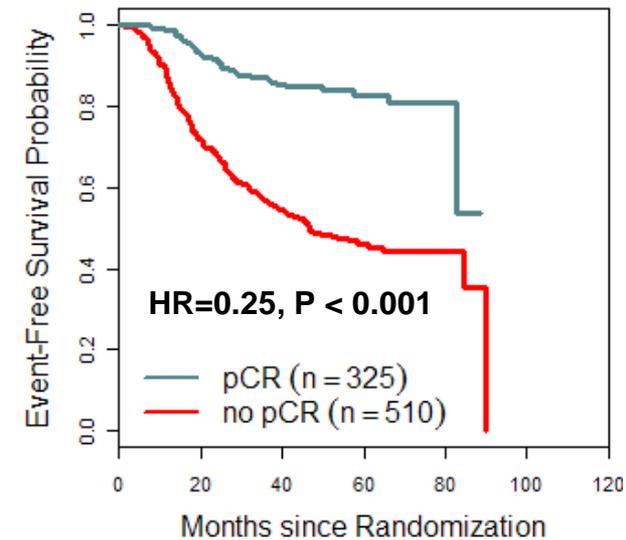
## HER2+



## HER2+ HR+



## HER2+ HR-



**pCR= total pCR**

# Neoadjuvant Therapy to Support Drug Approval: Open Questions

- How much prior safety experience is needed?
  - For a new drug vs. an approved drug
- What is the preferred definition of pCR?

# Definitions of pCR

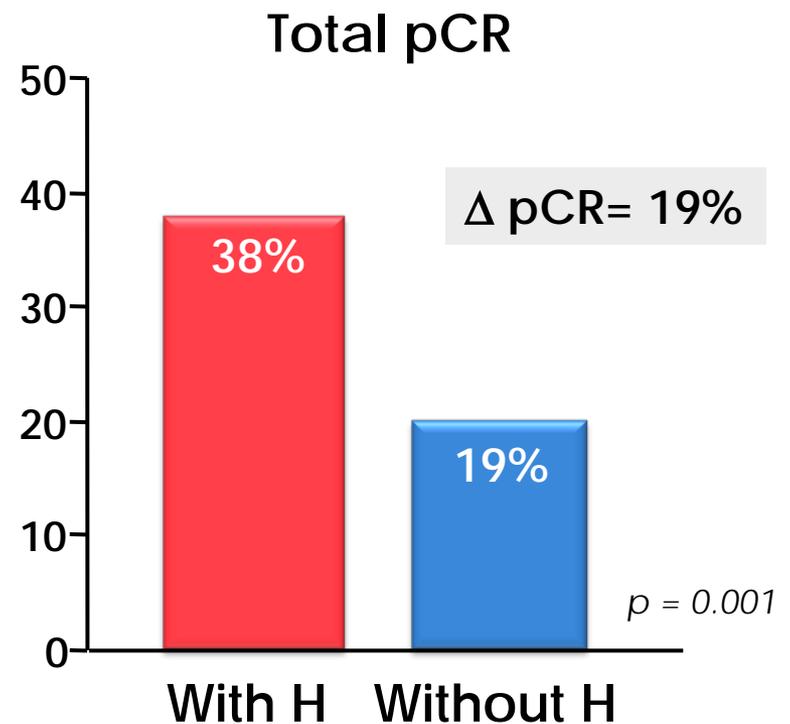
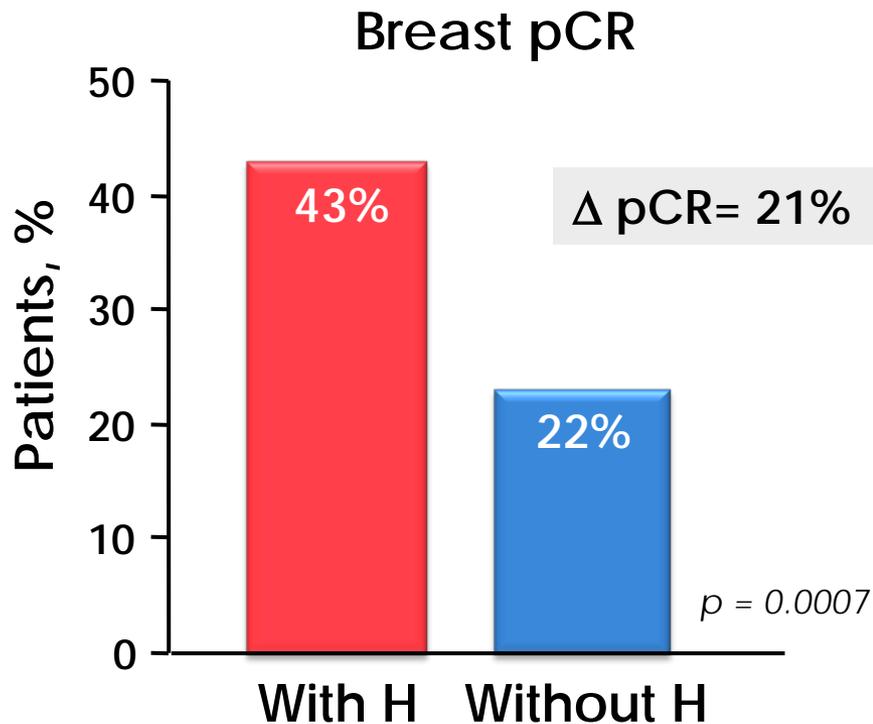
Breast pCR	Total pCR	GBG pCR
ypT0/is	ypT0/is ypN0	ypT0 ypN0
<ul style="list-style-type: none"> <li>• No invasive tumor in the breast</li> </ul>	<ul style="list-style-type: none"> <li>• No invasive tumor in the breast</li> <li>• Node negative at definitive surgery</li> </ul>	<ul style="list-style-type: none"> <li>• No invasive tumor in the breast</li> <li>• Node negative at definitive surgery</li> <li>• No remaining <i>in situ</i> disease</li> </ul>

TNM (tumor, nodes, metastasis) classification; y=status post initial therapy; p=confirmed by pathology after initial treatment; T=tumor; N=nodes; is=in situ; GBG=German Breast Group.

# NOAH:

Randomized study of neoadjuvant chemotherapy  $\pm$  trastuzumab (H)

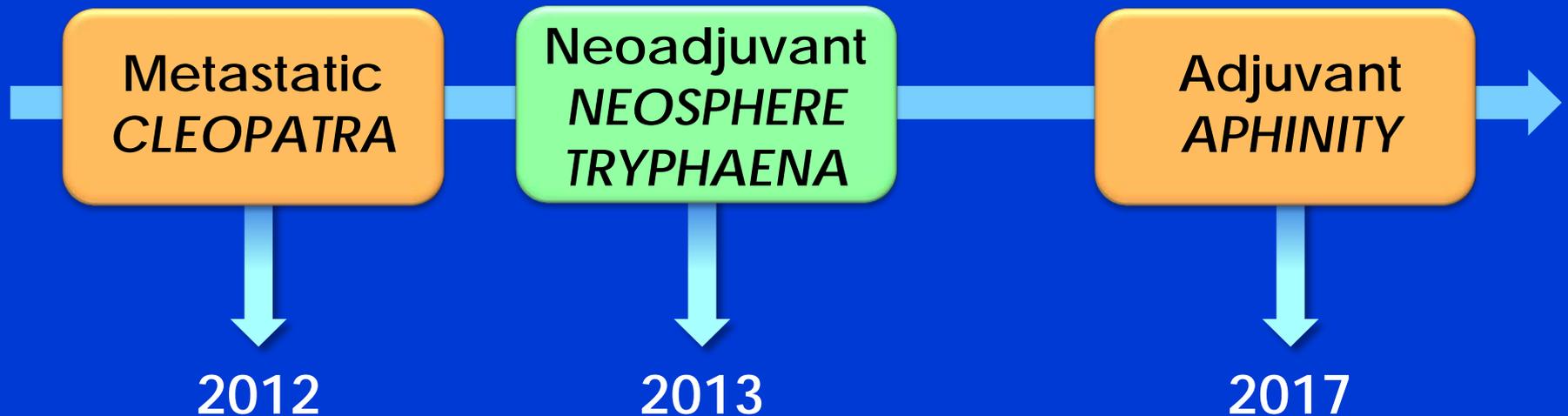
Consistent results using breast pCR or total pCR



# Pertuzumab Timeline



# Pertuzumab: Approval Opportunities



# Conclusions

- Survival in HER2+ EBC has been transformed by trastuzumab
  - Yet, a substantial number of patients are still dying
  - And, within HER2+ EBC, neoadjuvant therapy candidates have worse prognosis
- Dual HER2 blockade is superior
- Neoadjuvant setting offers a new drug development paradigm
  - In HER2+ disease pCR is associated with improved long-term outcomes

# Conclusions

- Pertuzumab
  - Has a well established efficacy and safety profile in MBC
  - Has shown pCR improvement in the neoadjuvant setting
  - The magnitude of pCR benefit is robust
- As a physician who treats a large number of patients with HER2+ EBC, I feel strongly that we should make this therapy available now

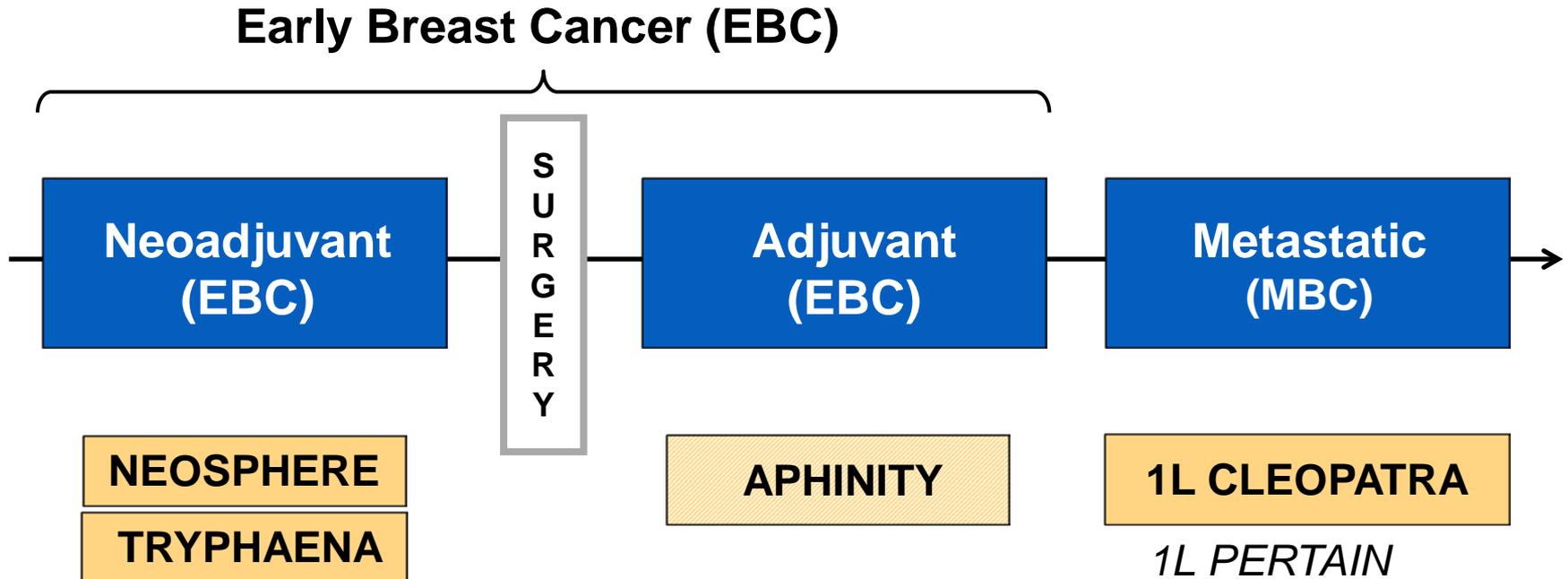
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# Overview of Clinical Data in sBLA

Graham Ross, MD  
Global Clinical Science Lead, Perjeta  
Genentech

# Perjeta HER2+ Breast Cancer Development Program

*Large safety experience*



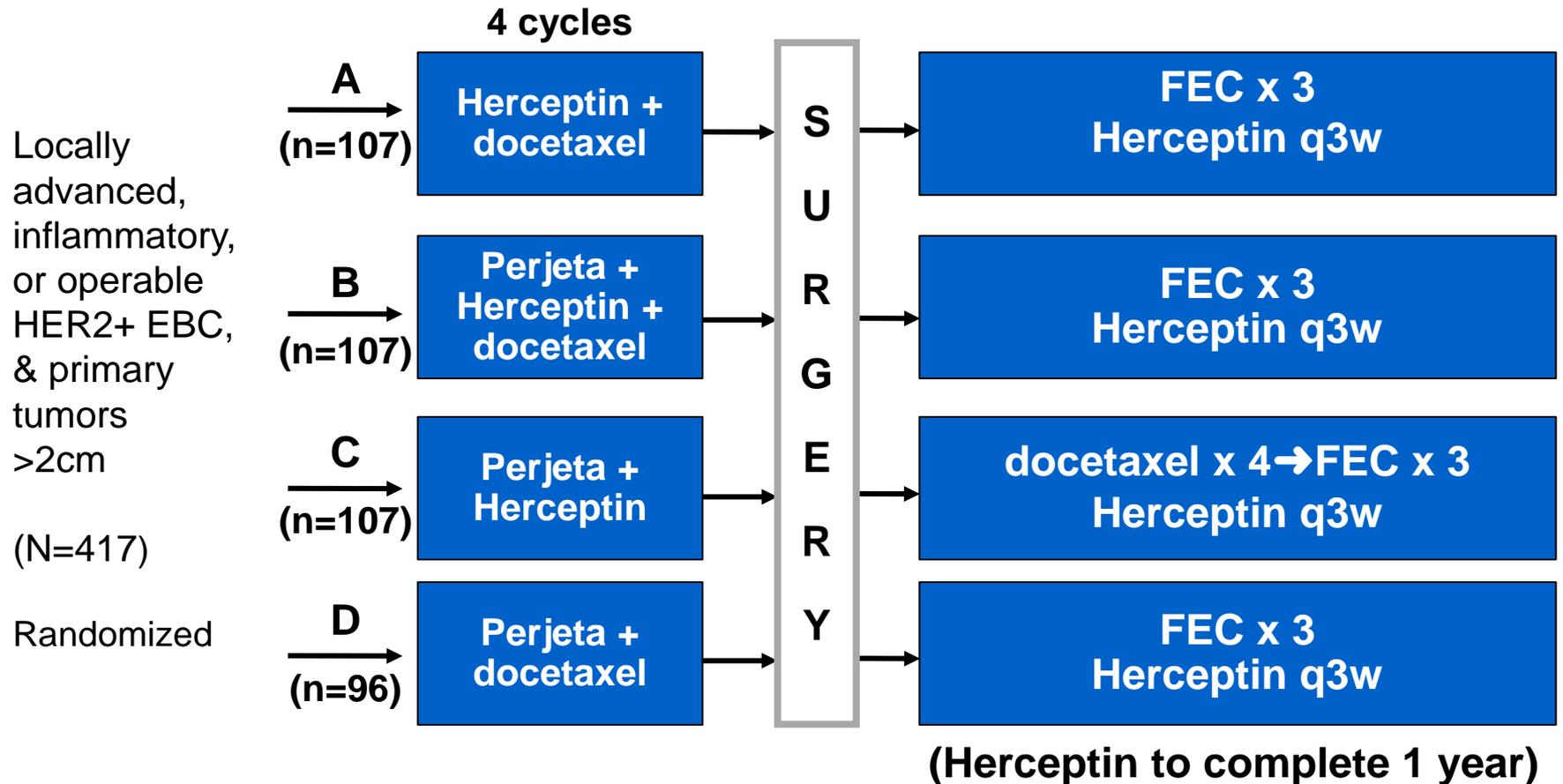
## Perjeta treated patients

- >500 in neoadjuvant studies
- ~4500 in completed or ongoing studies

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# Efficacy Data

# NEOSPHERE: Study Design



Primary endpoint: breast pCR  
Key secondary endpoint: safety

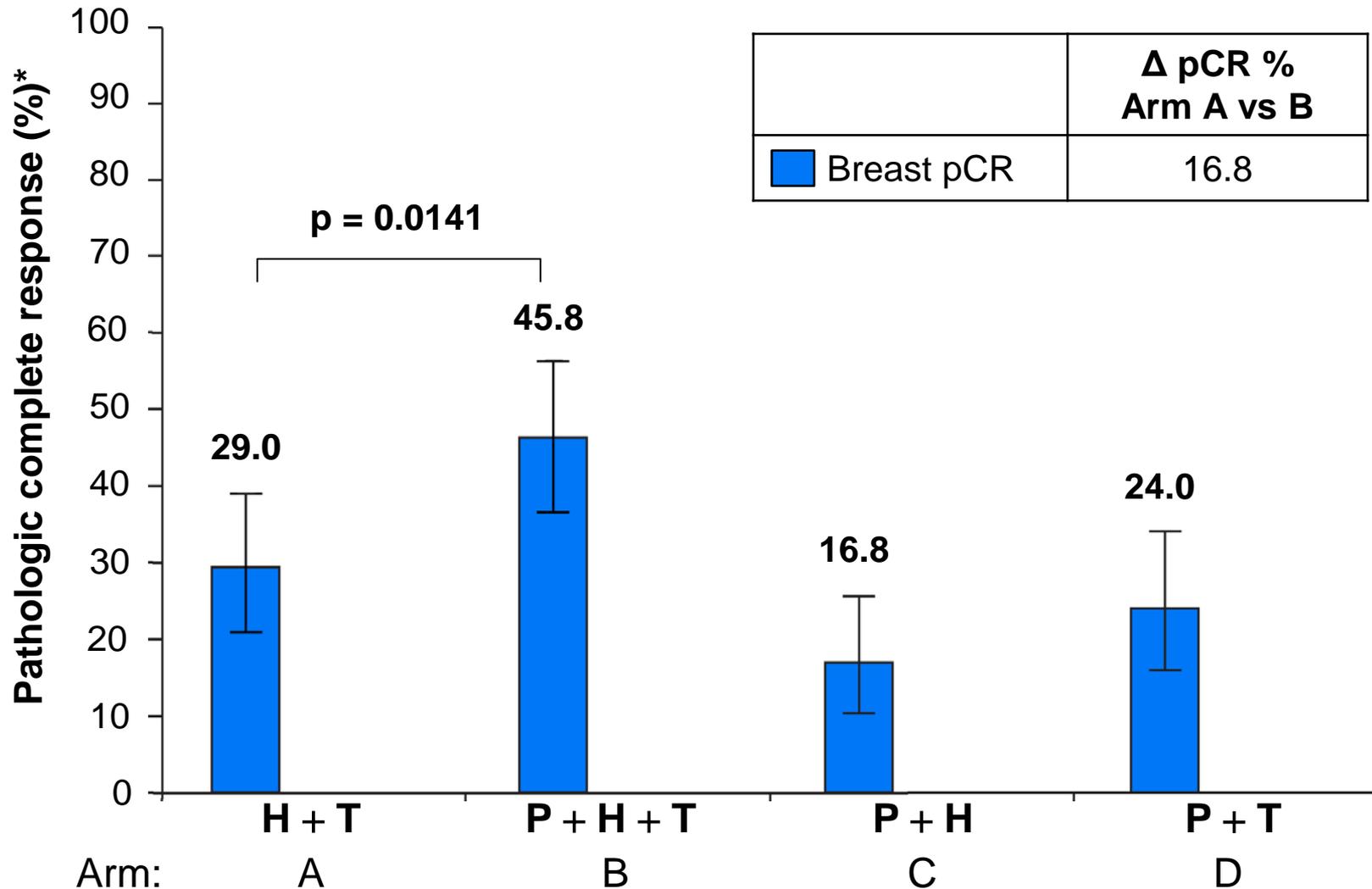
# NEOSPHERE: Baseline Characteristics

*High-risk population, balanced across arms*

	<b>H+T (Arm A) N=107</b>	<b>P+H+T (Arm B) N=107</b>	<b>P+H (Arm C) N=107</b>	<b>P+T (Arm D) N=96</b>
Median age, years	50	50	49	49
Hormone receptor negative, %	53.3	53.3	51.9	52.1
Median tumor size, (cm)	5.0	5.5	5.0	5.0
Node-positive, %	70.1	70.1	70.8	70.8
Locally advanced/inflammatory, %	40.1	39.2	39.2	37.5

# NEOSPHERE

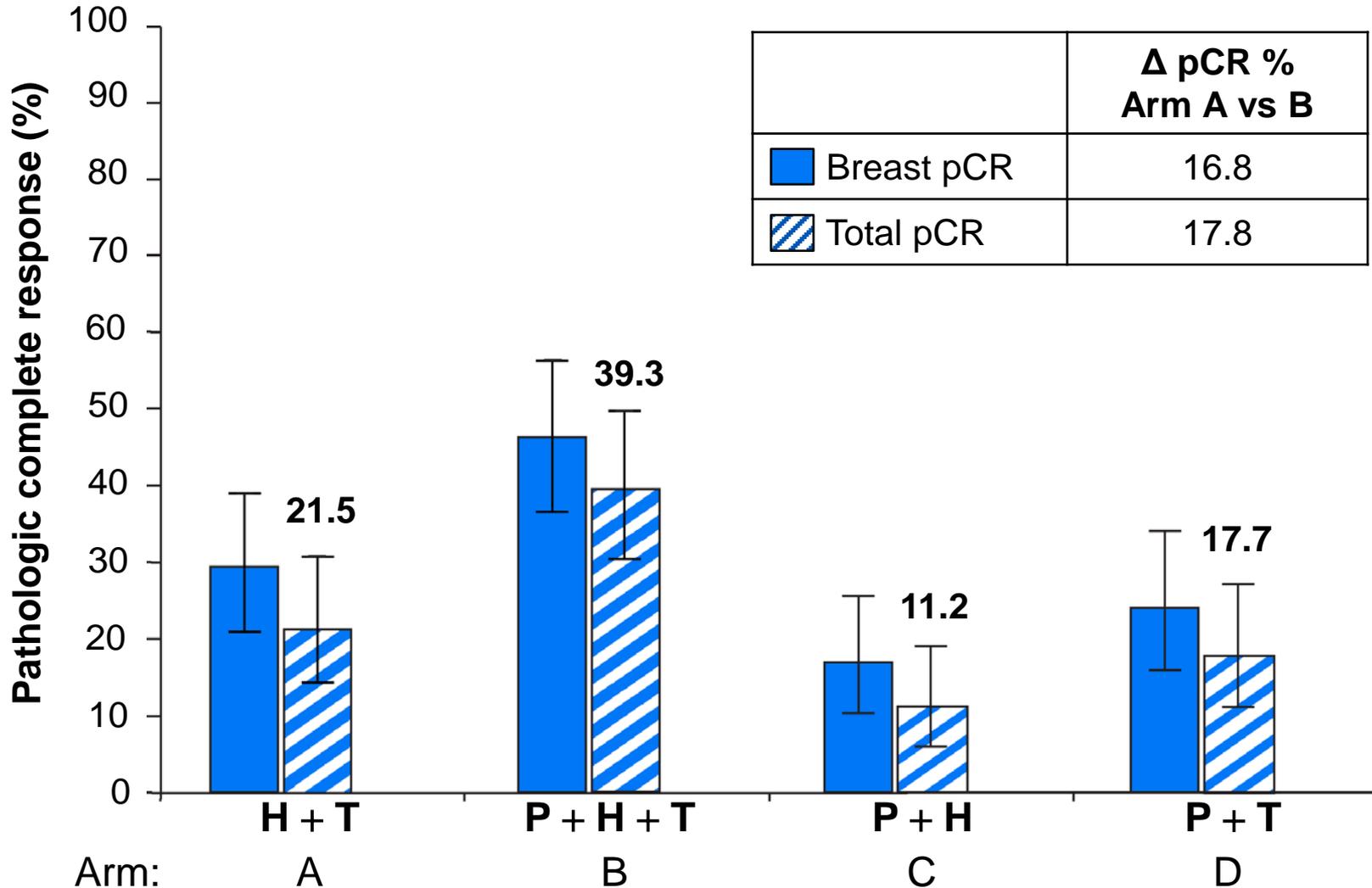
Higher pCR rates with P+H+T



\*  $\pm$ 95% CI.

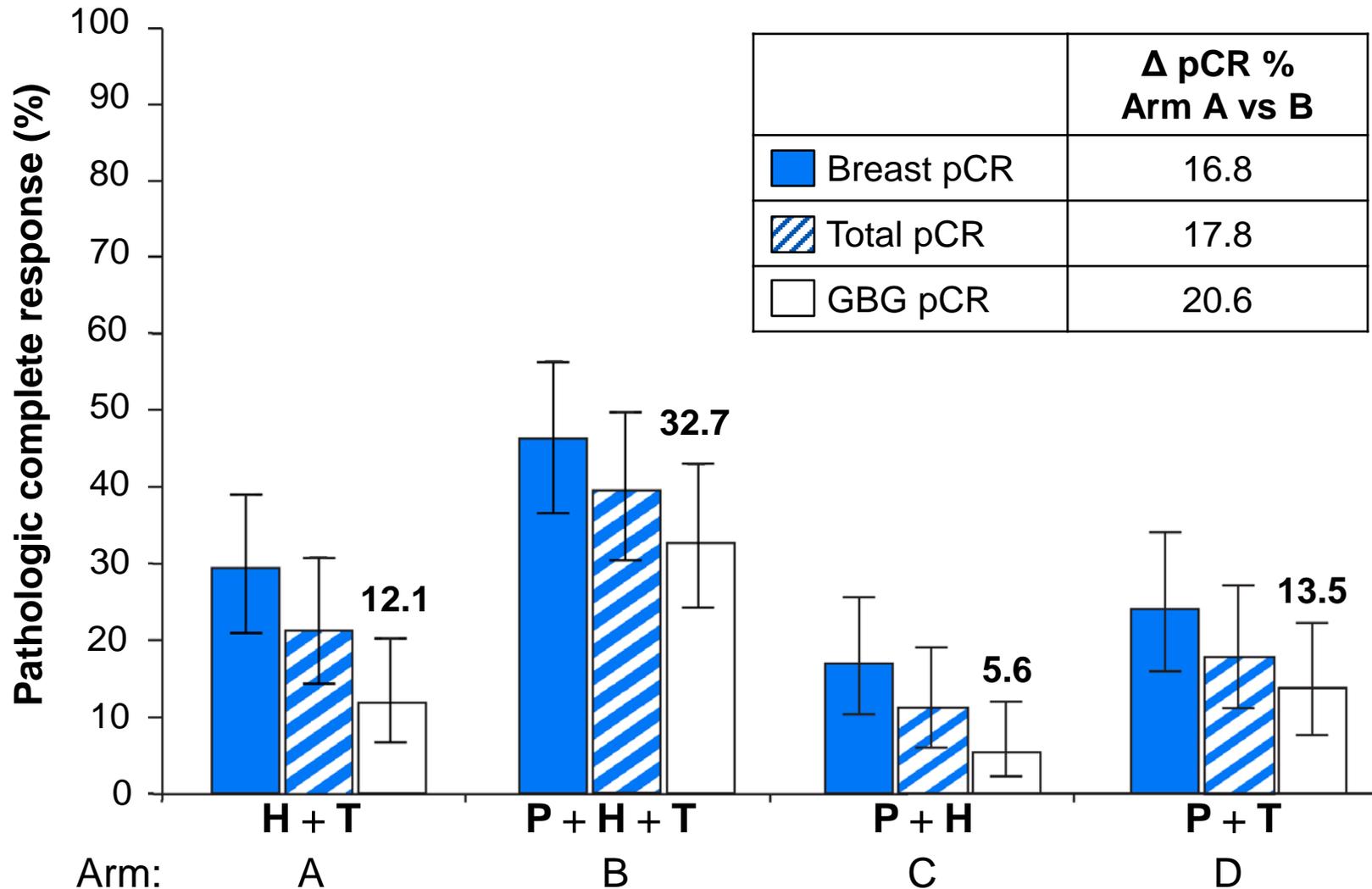
# NEOSPHERE

*Higher pCR rates with P+H+T*



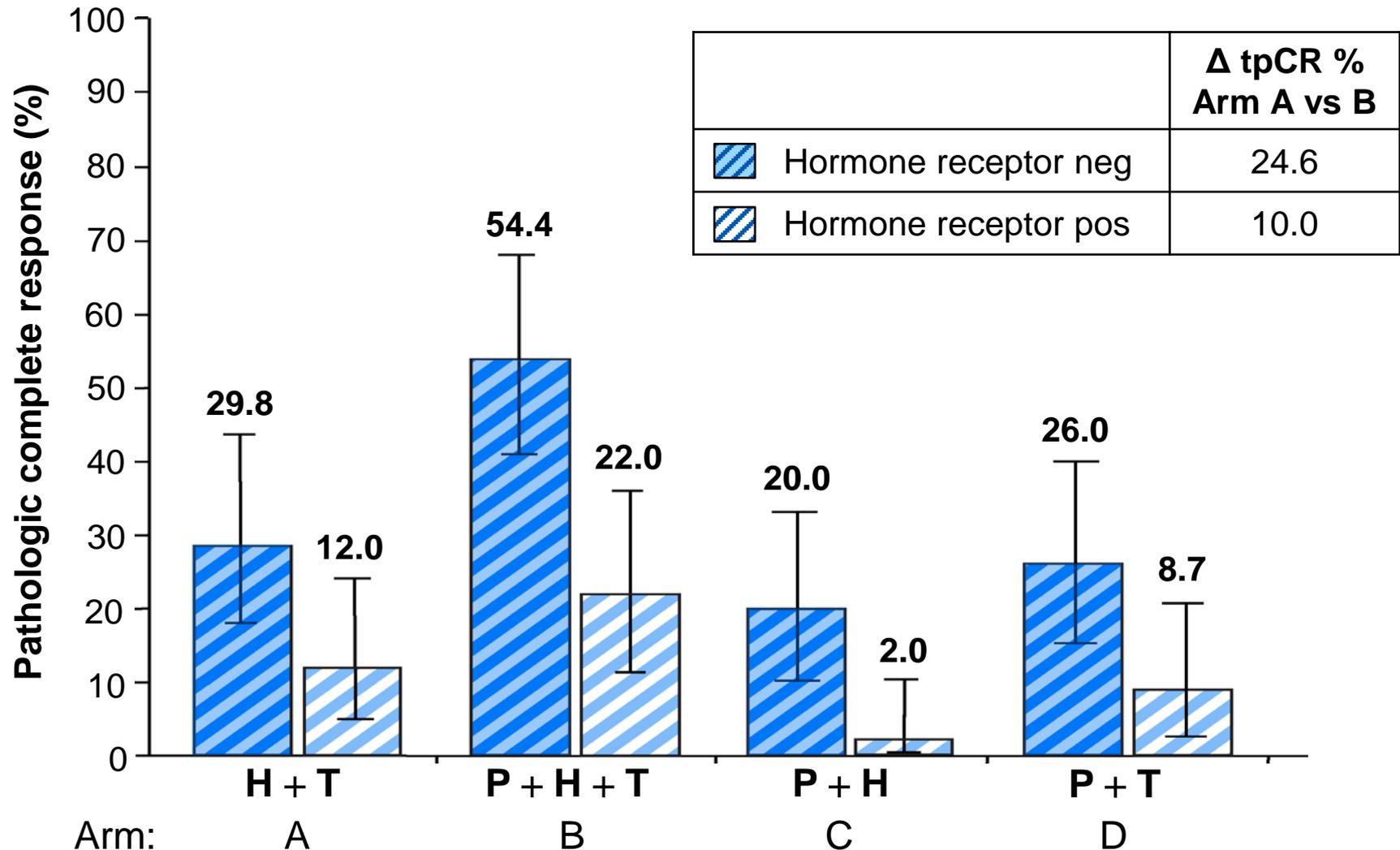
# NEOSPHERE

*Higher pCR rates with P+H+T*



# NEOSPHERE

*Hormone receptor status – tpCR rates higher with P+H+T*

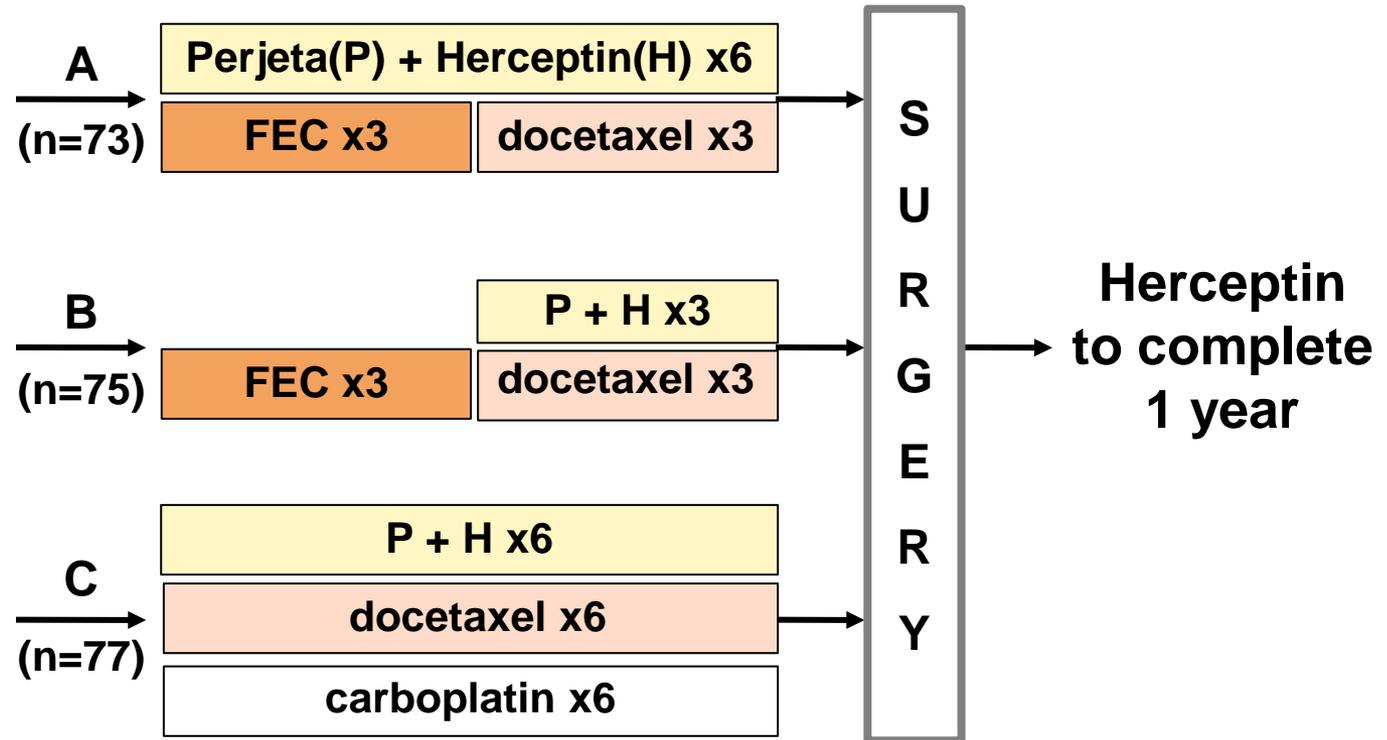


# TRYPHAENA: Study Design

Locally advanced, inflammatory, or operable HER2+ EBC, & primary tumors >2cm

(N=225)

Randomized



Primary endpoint: cardiac safety

Key secondary endpoint: breast pCR

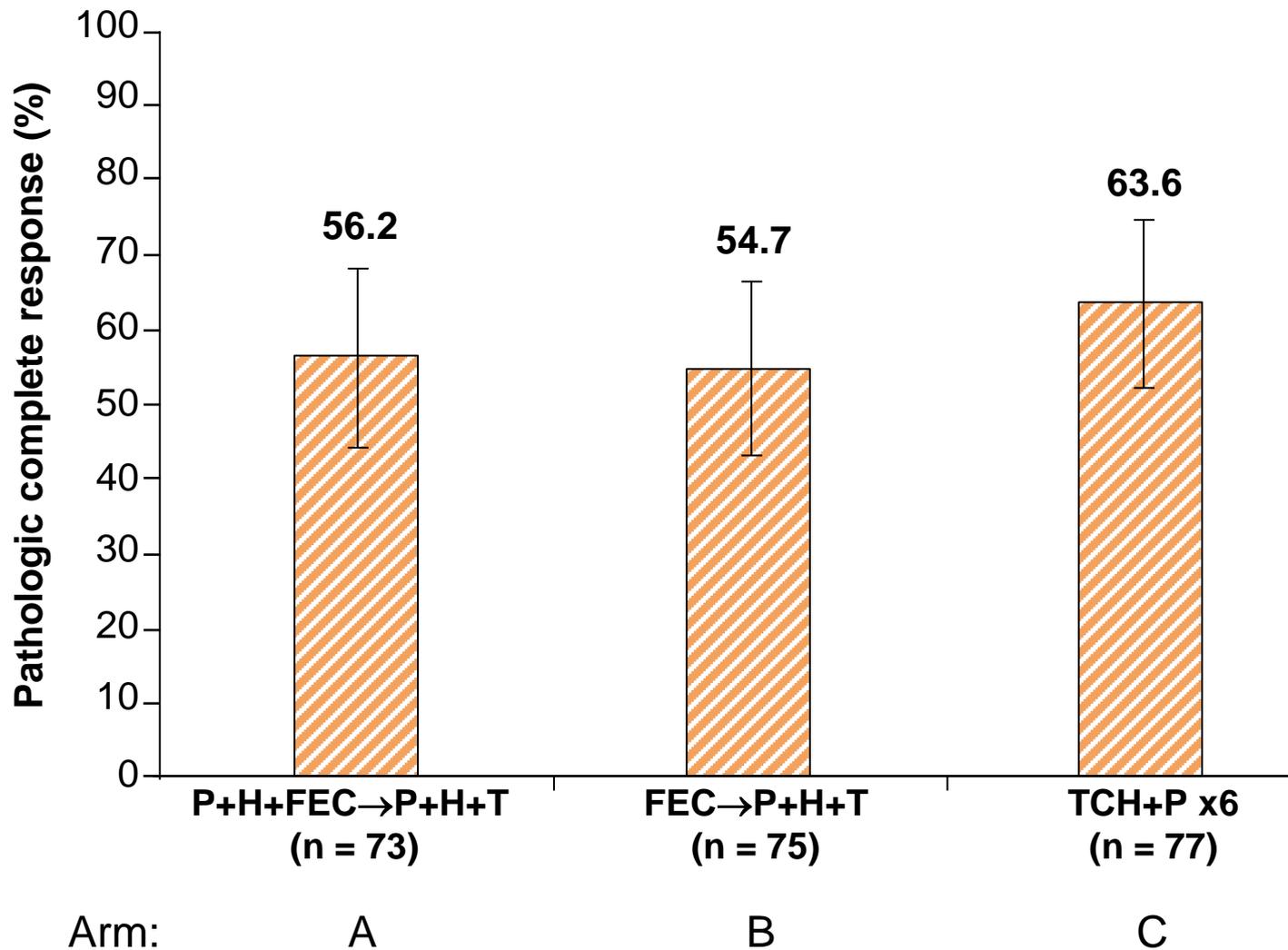
# TRYPHAENA: Baseline Characteristics

*High-risk population, balanced across arms*

	<b>P+H+FEC/ P+H+T (Arm A) N= 73</b>	<b>FEC/P+H+T (Arm B) N= 75</b>	<b>P+TCH (Arm C) N= 77</b>
Median age, years	49	49	50
Hormone receptor negative, %	46.6	53.3	48.1
Median tumor size, (cm)	5.3	4.9	5.0
Node-positive, %	74.0	64.0	68.8
Locally advanced/inflammatory, %	27.3	28.0	36.4

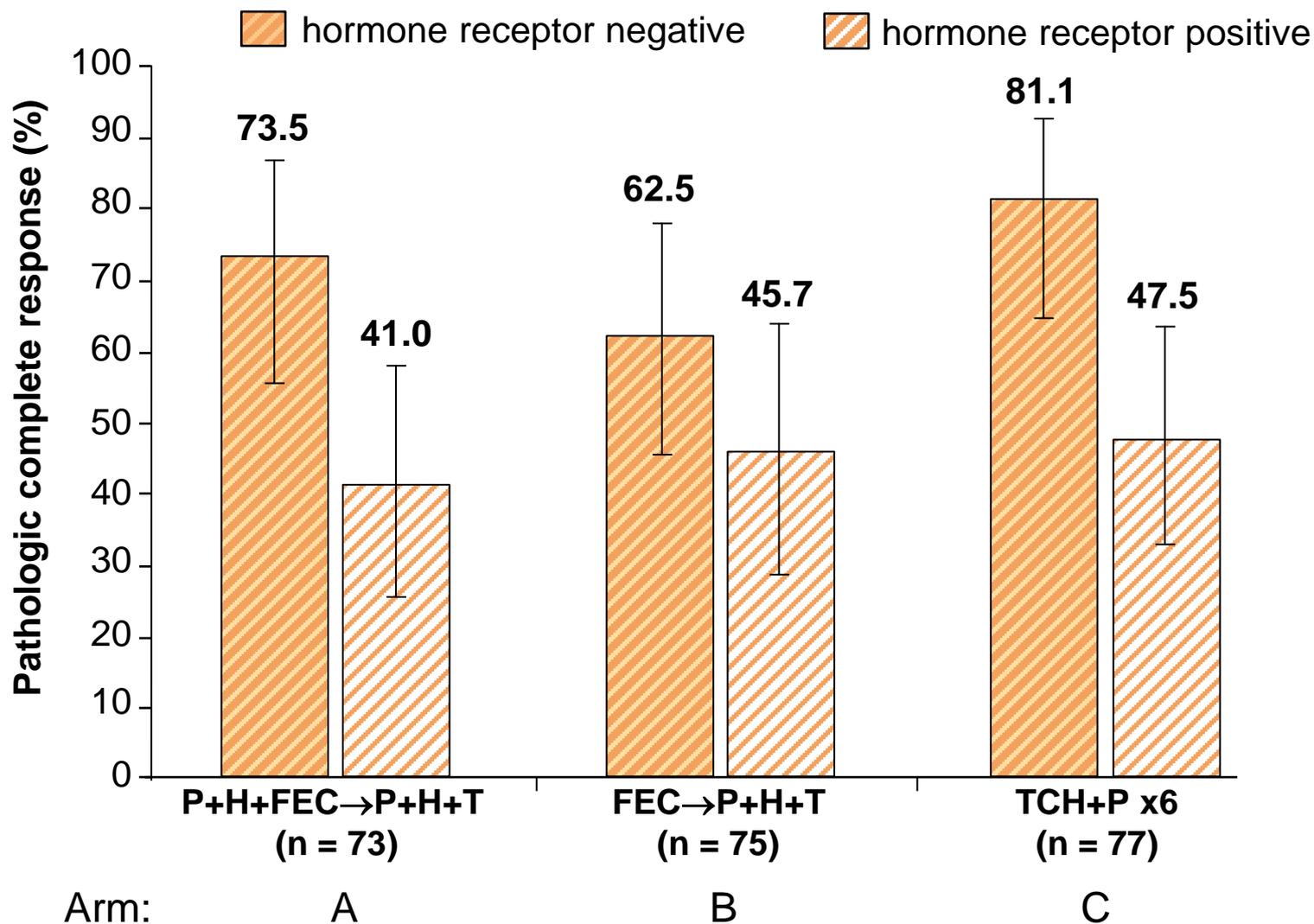
# TRYPHAENA:

Total pCR rates



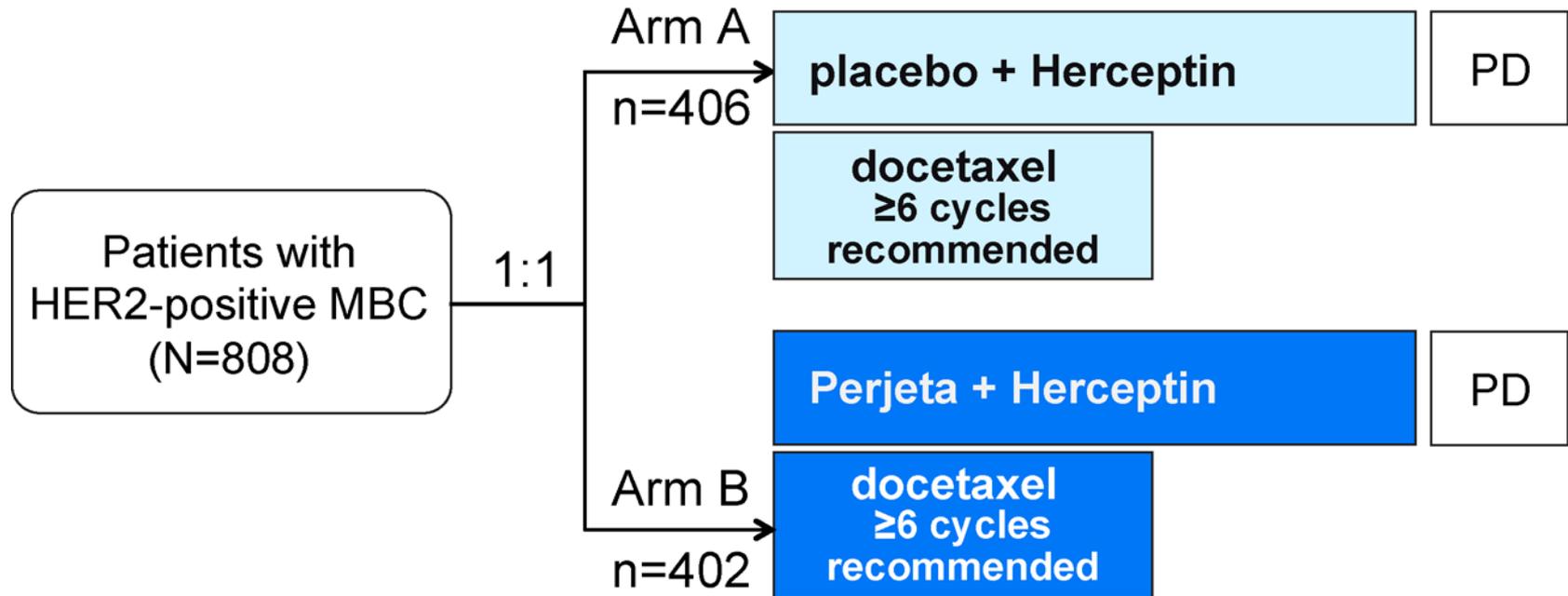
# TRYPHAENA:

Total pCR rates by hormone receptor status



# CLEOPATRA: Study Design

*Phase III study in HER2+ MBC*

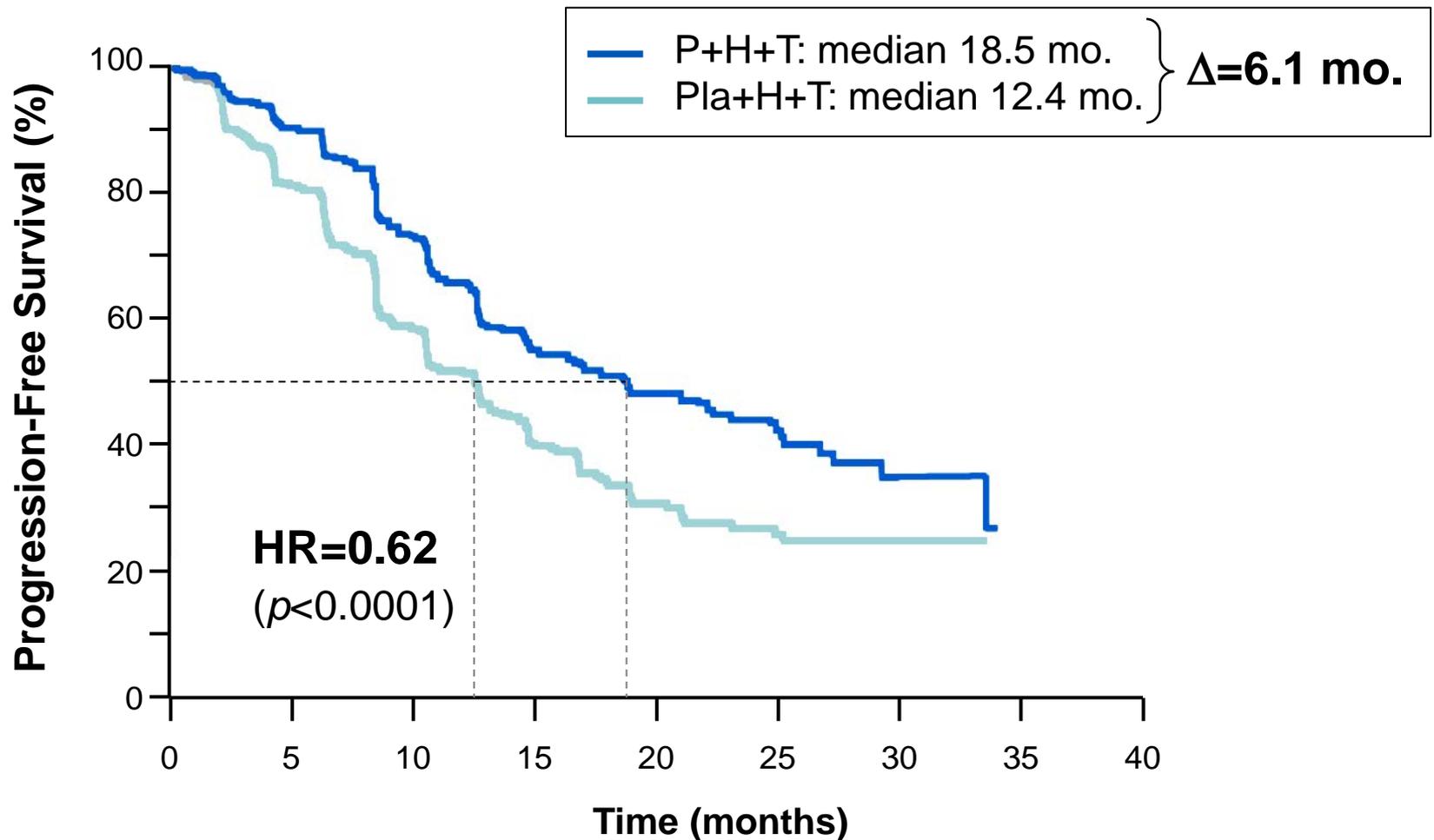


Primary endpoint: PFS (IRF)

Key secondary endpoints: safety, OS

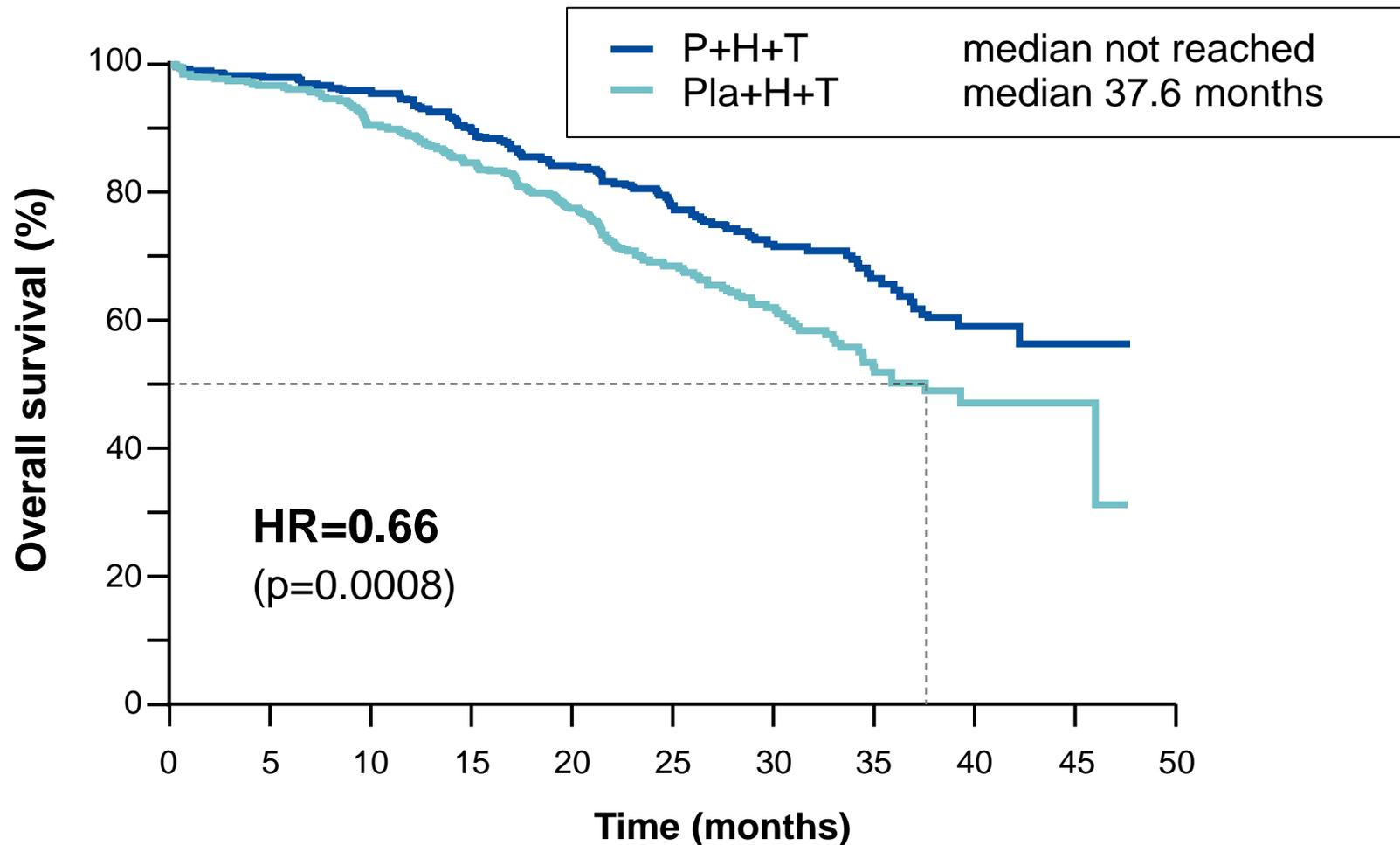
# CLEOPATRA:

*6.1 month improvement in median PFS*



# CLEOPATRA:

*Significant improvement in overall survival\**



Swain et al., Lancet Oncology, 2013.

\* Second interim analysis.

# Efficacy Conclusions

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## **NEOSPHERE:**

- Perjeta added to Herceptin + docetaxel increased total pCR rate from 21.5% to 39.3%, an increase of 17.8%
- Consistent improvements in pCR rates using three pCR definitions
- pCR benefits seen across patient subgroups and hormone receptor status

## **TRYPHAENA:**

- Perjeta added to Herceptin + chemotherapy resulted in total pCR rates of 54.7% – 63.6%

## **CLEOPATRA (MBC):**

- Perjeta added to Herceptin + docetaxel led to significant and clinically meaningful improvements in PFS and OS

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# Safety Data

# NEOSPHERE:

*Key safety data – neoadjuvant period*

	<b>H+T (Arm A) N=107</b>	<b>P+H+T (Arm B) N=107</b>	<b>P+H (Arm C) N=107</b>	<b>P+T (Arm D) N=96</b>
<b>Cycles of Perjeta, median</b>	0	4	4	4
<b>Grade ≥ 3 AEs, %</b>	72.9	62.6	6.5	70.2
<b>Serious AEs, %</b>	16.8	10.3	3.7	17.0
<b>AEs leading to discon. of any study medication, %</b>	0	1.9	2.8	2.1
<b>AEs leading to death, %</b>	0	0.9	0	0

# NEOSPHERE:

*10 most common AEs (all grades) - neoadjuvant period*

	<b>H+T (Arm A) N=107</b>	<b>P+H+T (Arm B) N=107</b>	<b>P+H (Arm C) N=108</b>	<b>P+T (Arm D) N=94</b>
<b>Alopecia, %</b>	65.4	63.6	0.9	67.0
<b>Neutropenia, %</b>	62.6	50.5	0.9	62.8
<b>Diarrhea, %</b>	33.6	45.8	27.8	54.3
<b>Nausea, %</b>	36.4	38.3	13.9	36.2
<b>Fatigue, %</b>	27.1	26.2	12.0	25.5
<b>Mucosal inflammation, %</b>	21.5	26.2	2.8	25.5
<b>Rash, %</b>	21.5	26.2	11.1	28.7
<b>Myalgia, %</b>	22.4	22.4	9.3	21.3
<b>Asthenia, %</b>	17.8	20.6	2.8	16.0
<b>Stomatitis, %</b>	7.5	17.8	4.6	9.6

# NEOSPHERE:

*Grade  $\geq 3$  AEs with incidence  $>5\%$*

	<b>H+T (Arm A) N=107</b>	<b>P+H+T (Arm B) N=107</b>	<b>P+H (Arm C) N=107</b>	<b>P+T (Arm D) N=96</b>
<b>Neutropenia, %</b>	57.0	44.9	0.9	55.3
<b>Febrile neutropenia, %</b>	7.5	8.4	0.0	7.4
<b>Leukopenia, %</b>	12.1	4.7	0.0	7.4
<b>Diarrhea, %</b>	3.7	5.6	0.0	4.3

Grade  $\geq 3$  AEs with incidence of 2–5% in any arm: asthenia, granulocytopenia, menstruation irregular, ALT increased.

# TRYPHAENA:

*Key safety data – neoadjuvant period*

	<b>P+H+FEC/ P+H+T (Arm A) N= 72</b>	<b>FEC/P+H+T (Arm B) N= 75</b>	<b>P+TCH (Arm C) N= 76</b>
<b>Cycles of Perjeta, median</b>	6	3	6
<b>Grade <math>\geq</math> 3 AEs, %</b>	69.4	60.0	73.7
<b>Serious AEs, %</b>	27.8	20.0	35.5
<b>AEs leading to discon. of any study medication, %</b>	5.6	6.7	7.9
<b>AEs leading to death, %</b>	0	0	0

# TRYPHAENA:

*Grade  $\geq 3$  AEs with incidence  $>5\%$*

	<b>P+H+FEC/ P+H+T (Arm A) N= 72</b>	<b>FEC/P+H+T (Arm B) N= 75</b>	<b>P+TCH (Arm C) N= 76</b>
<b>Neutropenia, %</b>	47.2	42.7	46.1
<b>Febrile neutropenia, %</b>	18.1	9.3	17.1
<b>Leukopenia, %</b>	19.4	12.0	11.8
<b>Diarrhea, %</b>	4.2	5.3	11.8
<b>Anemia, %</b>	1.4	2.7	17.1
<b>Thrombocytopenia, %</b>	0.0	0.0	11.8
<b>Vomiting, %</b>	0.0	2.7	5.3

Grade  $\geq 3$  AEs with incidence of 2–5% in any arm: fatigue, ALT increased, drug hypersensitivity, amenorrhea, nausea, dyspnea, LVD, hypokalemia.

# CLEOPATRA:

*Grade  $\geq 3$  AEs with incidence  $>5\%$*

	<b>Pla+H+T (Arm A) N = 396</b>	<b>P+H+T (Arm B) N = 408</b>
<b>Cycles of Perjeta, median</b>	0	24
<b>Neutropenia, %</b>		
<b>Neutropenia, %</b>	46.0	49.0
<b>Febrile neutropenia, %</b>	7.6	13.7
<b>Leukopenia, %</b>	14.9	12.3
<b>Diarrhea, %</b>	5.1	9.1

**Grade  $\geq 3$  AEs with incidence of 2–5% in any arm: asthenia, anemia, fatigue, LVSD, peripheral neuropathy, granulocytopenia, hypertension, dyspnea, pneumonia.**

# Cardiac Monitoring

- Decreases in left ventricular ejection fraction (LVEF) have been reported with drugs that block HER2
  - Cochrane meta-analysis\* of Herceptin adjuvant data; 11.2% LVEF decline, 2.5% symptomatic left ventricular systolic dysfunction (LVSD)
- Cardiac function is monitored frequently in Perjeta studies using the following definitions:

<b>LVEF Decline</b>	≥10% decline to <50% by ECHO (preferred) or MUGA
<b>LVSD Gr ≥ 3</b>	Symptomatic LVSD by NCI CTCAE v3

\*Moja et al, 2012. Cochrane Database Reviews.

# CLEOPATRA

*Cardiac safety\*: placebo-controlled study, independent review*

	CLEOPATRA	
	Pla+H+T (Arm A) N = 396	P+H+T (Arm B) N = 408
<b>Cycles of Perjeta, median</b>	0	24
<b>LVEF Decline, %</b>	7.1	4.9
<b>LVSD Gr <math>\geq</math> 3, %</b>	3.3	1.2
<b>Symptomatic LVSD adjudicated by CRC, %</b>	1.0	1.0
<b>Ongoing LVEF &lt;50%, %</b>	0.3	0.2

\* Overall study period (median time on study ~100 weeks).

CRC= Cardiac Review Committee.

# CLEOPATRA and NEOSPHERE:

*Cardiac safety data\**

	CLEOPATRA		NEOSPHERE			
	Pla+H+T (Arm A) N = 396	P+H+T (Arm B) N = 408	H+T (Arm A) N=107	P+H+T (Arm B) N=107	P+H (Arm C) N=107	P+T (Arm D) N=96
Cycles of Perjeta, median	0	24	0	4	4	4
LVEF Decline, %	7.1	4.9	1.9	8.4	1.9	7.4
LVSD Gr $\geq$ 3, %	3.3	1.2	0	0.9**	0.9	0

\* Overall study period (median time on study: CLEOPATRA ~100 weeks, NEOSPHERE ~200 weeks).

\*\* This patient was asymptomatic.

# CLEOPATRA and NEOSPHERE:

*Cardiac safety data\**

	CLEOPATRA		NEOSPHERE			
	Pla+H+T (Arm A) N = 396	P+H+T (Arm B) N = 408	H+T (Arm A) N=107	P+H+T (Arm B) N=107	P+H (Arm C) N=107	P+T (Arm D) N=96
Cycles of Perjeta, median	0	24	0	4	4	4
LVEF Decline, %	7.1	4.9	1.9	8.4	1.9	7.4
LVSD Gr ≥ 3, %	3.3	1.2	0	0.9**	0.9	0
Ongoing LVEF <50%, %	<b>0.3</b>	<b>0.2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

\* Overall study period (median time on study: CLEOPATRA ~100 weeks, NEOSPHERE ~200 weeks).

\*\* This patient was asymptomatic.

# TRYPHAENA:

## *Cardiac safety data*\*

	<b>P+H+FEC/ P+H+T (Arm A) N= 72</b>	<b>FEC/P+H+T (Arm B) N= 75</b>	<b>P+TCH (Arm C) N= 76</b>
<b>Cycles of Perjeta, median</b>	6	3	6
<b>LVEF Decline**, %</b>	6.9	16.0	10.5
<b>LVSD Gr ≥ 3, %</b>	0	2.7 <sup>^</sup>	1.3

\* Overall study period (median time on study ~115 weeks).

\*\* By local or central reading.

<sup>^</sup> Excludes one patient who went into heart failure before receiving Perjeta.

# TRYPHAENA:

## Cardiac safety data\*

	<b>P+H+FEC/ P+H+T (Arm A) N= 72</b>	<b>FEC/P+H+T (Arm B) N= 75</b>	<b>P+TCH (Arm C) N= 76</b>
<b>Cycles of Perjeta, median</b>	6	3	6
<b>LVEF Decline**, %</b>			
	6.9	16.0	10.5
<b>LVSD Gr ≥ 3, %</b>	0	2.7 <sup>^</sup>	1.3
<b>Ongoing LVEF &lt;50%, %</b>	<b>0</b>	<b>1.3</b>	<b>0</b>

\* Overall study period (median time on study ~115 weeks).

\*\* By local or central reading.

<sup>^</sup> Excludes one patient who went into heart failure before receiving Perjeta.

# Safety Conclusions

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- The safety profile of Perjeta is well established, based on Phase III CLEOPATRA trial (MBC) and other studies
  - ~4500 patients have received Perjeta in clinical trials
- Neoadjuvant setting:
  - Most common adverse events of neoadjuvant P+H+T: neutropenia, diarrhea, nausea, fatigue, mucosal inflammation, rash
  - Perjeta does not appear to add symptomatic cardiac toxicity when given with Herceptin-based neoadjuvant or metastatic regimens
  - Neoadjuvant therapy with Perjeta did not result in new or unexpected safety signals
- The Perjeta safety profile remains as described in the current Perjeta Prescribing Information

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# Summary and Conversion Plan

Dietmar Berger, MD, PhD  
Vice President  
Global Head, HER2 Program  
Genentech

# Rationale for Use of Perjeta in Neoadjuvant Treatment of HER2+ EBC

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- Long-term survivorship can be achieved in early stages of HER2+ breast cancer
- Strong rationale for bringing an effective treatment sooner to patients with HER2+ EBC
  - Perjeta is approved for first line treatment of metastatic HER2+ breast cancer (CLEOPATRA study)
- pCR is reasonably likely to predict positive long-term outcomes in HER2+ breast cancer
- NEOSPHERE and TRYPHAENA studies provide evidence for patient benefit of Perjeta in neoadjuvant treatment of HER2+ EBC

# Accelerated Approval of Perjeta in Neoadjuvant Treatment of HER2+ EBC

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**Unmet Need**

**Efficacy**

**Safety**

**Conversion**

# Accelerated Approval of Perjeta in Neoadjuvant Treatment of HER2+ EBC

## Unmet Need

Efficacy

Safety

Conversion

- 6000 – 8000 US patients die from HER2+ breast cancer each year\*
- Relapse rates in HER2+ EBC 17 – 40% after 5 years
- Younger patient population

# Accelerated Approval of Perjeta in Neoadjuvant Treatment of HER2+ EBC

Unmet Need

Efficacy

Safety

Conversion

- NEOSPHERE: increase of total pCR rate from 21.5% to 39.3%, an improvement of 17.8%
- TRYPHAENA: tpCR rates of 55% – 64%, with anthracycline and TCH-based regimens
- Proven efficacy in MBC
- HER2 well-known, validated target
- pCR reasonably likely to predict long-term outcomes

# Accelerated Approval of Perjeta in Neoadjuvant Treatment of HER2+ EBC

Unmet Need

Efficacy

**Safety**

Conversion

- Well established safety profile in 1L MBC, CLEOPATRA
- Neoadjuvant Perjeta was well tolerated with H+chemotherapy:
  - Most common adverse events: neutropenia, diarrhea, nausea, fatigue, mucosal inflammation, rash
  - Perjeta does not appear to add symptomatic cardiac toxicity when given with Herceptin-based regimens
- No new or unexpected safety signals

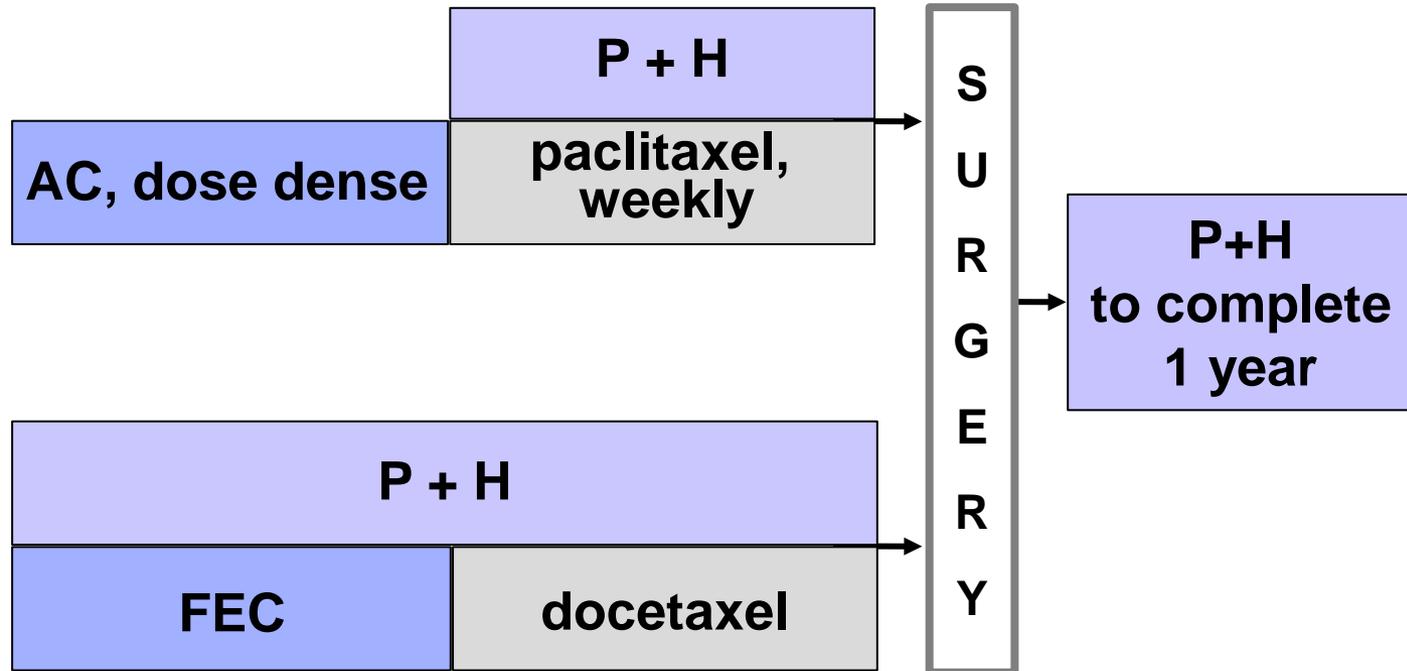
# Neoadjuvant Anthracycline Study Design

*Proposed post-marketing study*

Locally advanced,  
inflammatory,  
or operable  
HER2+ EBC,  
and primary  
tumors >2cm

(N~240)

Parallel cohorts



Primary endpoint: cardiac safety

Key secondary endpoint: total pCR

AC= doxorubicin + cyclophosphamide.

P+H= Perjeta + Herceptin.

# Accelerated Approval of Perjeta in Neoadjuvant Treatment of HER2+ EBC

Unmet Need

Efficacy

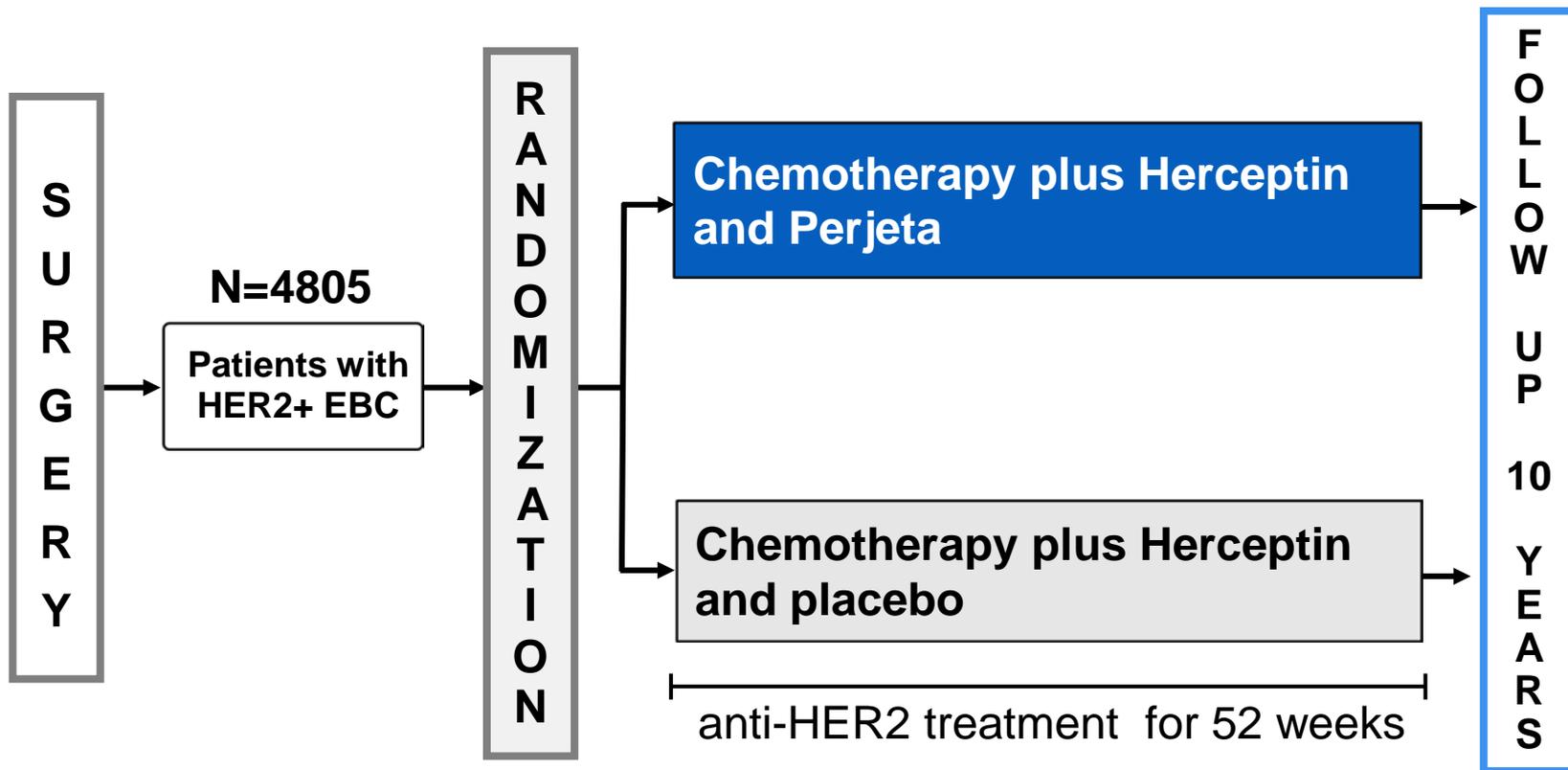
Safety

**Conversion**

- APHINITY study fully recruited with a total of 4805 patients
- Will provide data on efficacy, safety, and long-term outcomes
- Data expected in 2016

# APHINITY: Phase III Adjuvant Study

*Confirmatory trial*



Primary endpoint: iDFS

- Large Global trial: US highest enrolling country
- Anthracycline or non-anthracycline based chemo allowed
- IDMC and Independent Cardiac Review Committee

# Perjeta Benefit/Risk Assessment

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Perjeta should receive accelerated approval for neoadjuvant treatment for HER2+ EBC in line with the FDA draft guidance on pCR based on:

- Unmet medical need
- Proven, positive benefit/risk in the first line MBC setting
- Favorable benefit/risk profile in the neoadjuvant setting
- Conversion plan in place

# Proposed Indication

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**Genentech seeks a positive recommendation for accelerated approval of Perjeta for the proposed indication:**

- Neoadjuvant treatment of high-risk HER2+ early breast cancer
- Combined with trastuzumab and docetaxel
- As part of a complete treatment regimen for early breast cancer

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# Back Up Slides

# Table 4. Baseline Characteristics in NEOSPHERE and TRYPHAENA

	NEOSPHERE				TRYPHAENA		
	H+T (Arm A) N=107	P+H+T (Arm B) N=107	P+H (Arm C) N=107	P+T (Arm D) N=96	P+H+FEC/ P+H+T (Arm A) N=73	FEC/ P+H+T (Arm B) N=75	P+TCH (Arm C) N=77
Median age, years	50.0	50.0	49.0	49.0	49.0	49.0	50.0
ER and PgR-negative, %	53.3	53.3	51.9	52.1	46.6	53.3	48.1
Poorly differentiated or anaplastic, %*	44.9	49.3	55.7	54.0	44.6	41.9	44.3
Median tumor size (cm)	5.0	5.5	5.0	5.0	5.3	4.9	5.0
Node-positive, %	70.1	70.1	70.8	70.8	74.0	64.0	68.8
Operable disease (T2-3, N0-1), %	59.8	60.7	60.7	62.5	72.6	72.0	63.6
Locally Advanced (T2-3, N2 or N3; T4a-c, any N), %	33.6	29.9	32.7	32.3	20.5	22.7	31.2
Inflammatory (T4d, any N), %	6.5	9.3	6.5	5.2	6.8	5.3	5.2

ER=estrogen receptor; FEC=5-fluorouracil, epirubicin, cyclophosphamide; H=Herceptin; P=Perjeta; PgR=progesterone receptor; T=docetaxel; TCH=docetaxel/carboplatin/Herceptin.

\*% of patients with known histological grade.

# Table 7. NEOSPHERE: Disease Progression and Disease Recurrence

	<b>H+T (Arm A) N=107</b>	<b>P+H+T (Arm B) N=107</b>	<b>P+H (Arm C) N=107</b>	<b>P+T (Arm D) N=96</b>
<b>Clinical cutoff 9 March 2012</b>				
Median duration of follow-up (weeks)	149.0	150.0	146.5	143.0
Disease recurrence/ progression, %	11.2	10.3	17.8	16.7
Death, %	1.9	0.9*	0.9	5.2
<b>Clinical cutoff 28 February 2013</b>				
Median duration of follow-up (weeks)	192.0	202.0	188.0	187.5
Death, %	2.8	1.9	1.9	7.3

H=Herceptin; P=Perjeta; T=docetaxel.

\*One death due to fulminant hepatitis occurred during neoadjuvant period and was attributed by the investigator and the Study Steering Committee to docetaxel.

# Table 11. Summary of Exposure in NEOSPHERE, TRYPHAENA, and CLEOPATRA (Overall Treatment Period)

Parameter	NEOSPHERE				TRYPHAENA			CLEOPATRA	
	H+T (Arm A) N=107	P+H+T (Arm B) N=107	P+H (Arm C) N=108	P+T (Arm D) N=94	P+H+FEC/ P+H+T (Arm A) N=72	FEC/ P+H+T (Arm B) N=75	P+TCH (Arm C) N=76	Pla+H+T (Arm A) N=396	P+H+T (Arm B) N=408
Median # of cycles of P per pt	0	4	4	4	6	3	6	0	24
Median cumulative P dose per pt (mg)	0	2100	2100	2100	2940	1680	2940	0	10500
Median cumulative H dose per pt (mg)	6968	6534	6774	6185	6629	6520	6727	6158	9514
Median cumulative T dose per pt (mg)	600	600	598	580	425	426	725	1008	941
Median cumulative F dose per pt (mg)	3078	2970	3015	2952	2468	2460	-	-	-
Median cumulative E dose per pt (mg)	465	450	451	436	492	490	-	-	-
Median cumulative C dose per pt (mg)	3078	2975	3015	2952	2945	2940	-	-	-

FEC=5-fluorouracil, epirubicin, cyclophosphamide; H=Herceptin; P=Perjeta; Pla= placebo; pt=patient; T=docetaxel; TCH=docetaxel, carboplatin, Herceptin.

# Tumor Burden in Patients by Breast Cancer Staging: NEOSPHERE and TRYPHAENA

Breast Cancer Stage/Type	NEOSPHERE N=417	TRYPHAENA N=225
Inflammatory	29 (7.0%)	13 (5.8%)^
Locally advanced	134 (32.1%)^	56 (24.9%)^
Operable	254 (60.9%)	156 (69.3%)

^ Includes one patient with TNM classification not provided.

# Decisions Made at Baseline Tended Not to Change

	NEOSPHERE				TRYPHAENA		
	H+T (Arm A)	P+H+T (Arm B)	P+H (Arm C)	P+T (Arm D)	P+H+FE C/ P+H+T (Arm A)	FEC/ P+H+T (Arm B)	P+TCH (Arm C)
<b>Total number of patients</b>	107	107	107	96	73	75	77
<b>Number with T2-T3 tumors and planned mastectomy</b>	62	56	61	60	46	36	37
<b>T2-3, planned mastectomy, underwent BCS</b>	14 (22.6%)	13 (23.2%)	11 (18.0%)	19 (31.7%)	10 (21.7 %)	6 (16.7 %)	10 (27.0 %)

- Clinical responses: >66% across the studies and treatment arms
- ≤ 32% of patients with T2-T3 tumors (i.e. candidates for BCS) subsequently underwent BCS
- Suggesting BCS was mainly determined by baseline factors

# CLEOPATRA Results by HR Status

