Regulatory Perspective on Neoadjuvant Approvals in Breast Cancer

Laleh Amiri-Kordestani, MD
Office of Hematology and Oncology Products, FDA
Laleh.AmiriKordestani@fda.hhs.gov

Disclosures

- Nothing to disclose

Neoadjuvant Therapy for Breast Cancer

- RCTs have found no significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery[1]
- Downstage inoperable tumors
- Potential to increase rate of breast conservation therapy
- Improve surgical outcomes
- pCR: important prognostic factor[2]
  - Individual patients who attain pCR have a more favorable long-term outcome

[1] Mauri JNCI 2005; Rastogi JCO 2008
[2] von Minckwitz JCO 2012; Bardia AACR 2011; Cortazar Lancet 2014

Using Neoadjuvant Therapy Platform to Support Drug Approval

- Smaller sample size
- Shorter time to endpoint assessment (pCR)
- Opportunity to address unmet medical needs more rapidly
- Early access
- Less safety information at the time of approval
- pCR binary endpoint
- Lack of association of pCR with long-term clinical benefit on trial level

Development of Regulatory Framework

- FDA is committed to expedite drug development and approval of highly effective therapies in high-risk patients
- FDA established CTNeoBC working group to learn about endpoints that could support approval in neoadjuvant breast cancer
- FDA pCR Draft Guidance released in May 2012
- June 2012: NEJM Perspective piece on pCR and accelerated approval in EBC
- March 2013 :public pCR workshop

FDA pCR Guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf
Prowell and Pazdur, NEJM, 2012

CTNeoBC Working Group Goals

Is pCR associated to long-term clinical benefit (EFS and OS)?

Which pCR definition is best associated to long-term clinical benefit?

What magnitude of pCR improvement will predict long-term clinical benefit?

Pooled-analysis of Randomized Neoadjuvant Trials

TRIALS	Patients (n)
GBG/AGO: 7	6377
NSABP: 2	3171
EORTC/BIG: 1	1856
ITA: 2	1589
Total # patients	12993

CTNeoBC Pooled-Analysis Findings

1- No pCR association with long term outcomes (EFS and OS)

- Individual patients who attain a pCR have a more favorable long-term outcome.

2- A standard pCR definition that includes the assessment of the nodes (ypT0ypN0 or ypT0/isypN0) should be used in future trials

3- Magnitude of pCR improvement that predicts long-term clinical benefit (EFS and OS improvement) could not be established possibly due to:

- low pCR rates
- heterogeneous population
- lack of targeted therapies (except NOAH trial)
- Or, pCR is not a surrogate for EFS or OS

➢ Larger pCR differences between treatment arms may translate into long-term outcome and may vary according to breast cancer subtype.

Cortazar et al., Lancet, 2014

Regulatory Considerations

- We need a validated endpoint for regular approval
- pCR is not a validated surrogate endpoint
- Uncertainty regarding the ultimate outcome:
  - Long-term efficacy (EFS and OS)
  - Long-term safety
- FDA may grant marketing approval for a new product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit
- AA requires confirmation of benefit

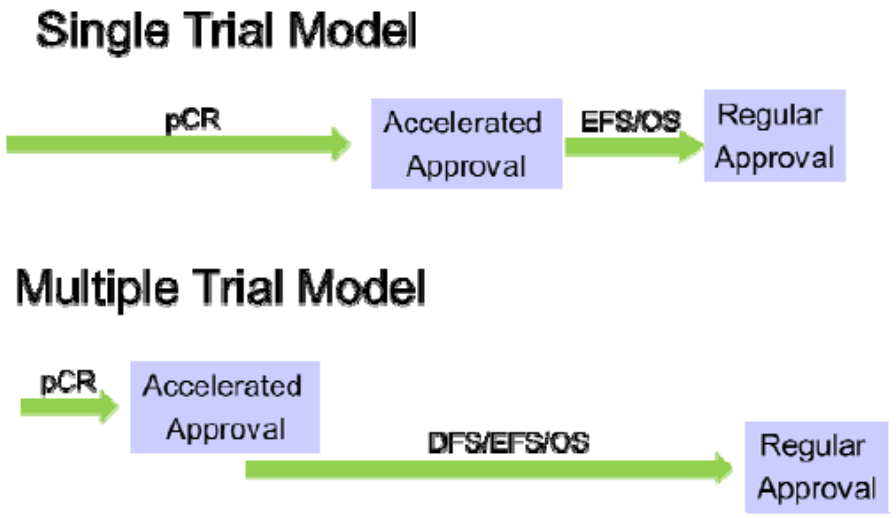
The Neoadjuvant Regulatory Path could be opened through Accelerated Approval

FDA pCR Guidance Highlights

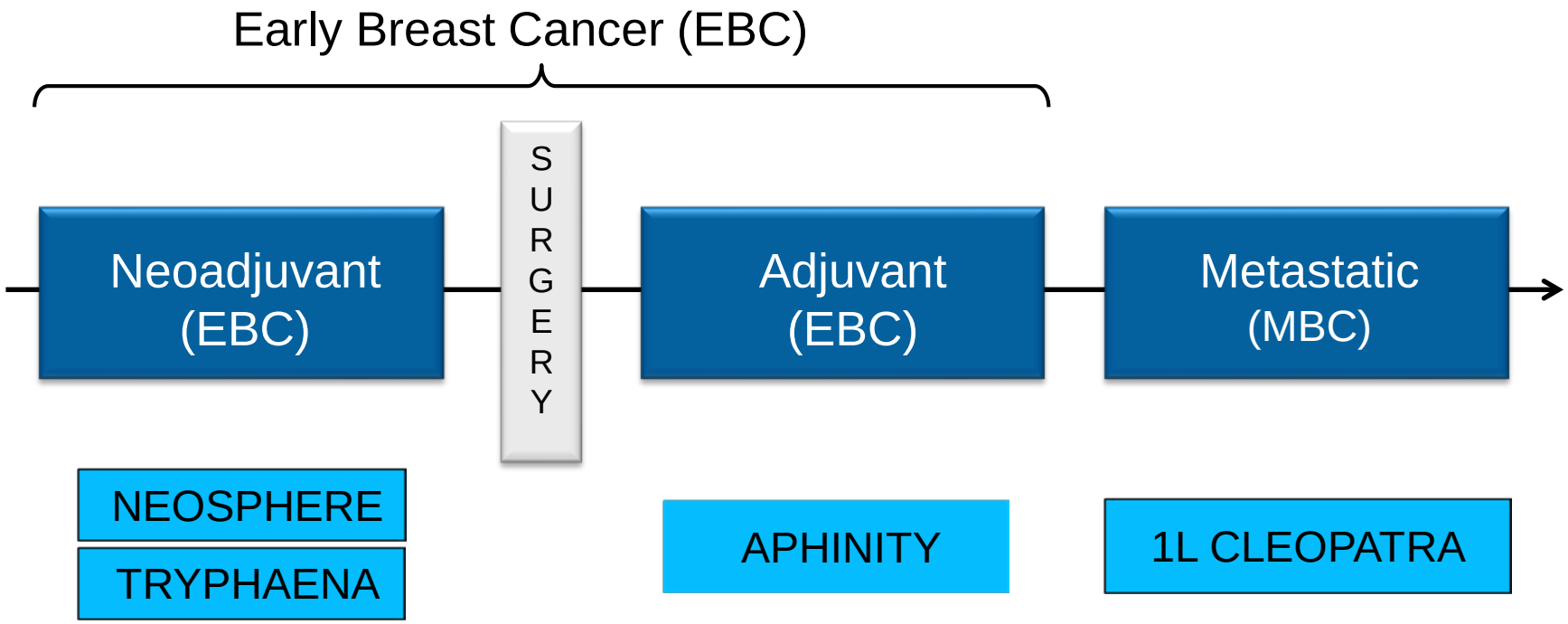
- pCR definition for U.S. marketing approval:
  - Absence of residual invasive cancer – ypT0/Tis ypN0 in AJCC 7 staging system
  - Absence of residual invasive and in situ cancer – ypT0 ypN0 in AJCC 7 staging system
- EFS or OS as long-term clinical benefit endpoints for neoadjuvant trials for regular approval
  - EFS: time from randomization to progression of disease that precludes surgery, local/distant recurrence, death due to any cause
- Outcome assessment: pathologists blinded, standardize nodal assessment, SLNB at time of definitive surgery

- Trial design consideration
  - Randomized, controlled
  - Superiority design
  - Add-on design

Figure 1. Single Trial Model vs. Multiple Trial Model

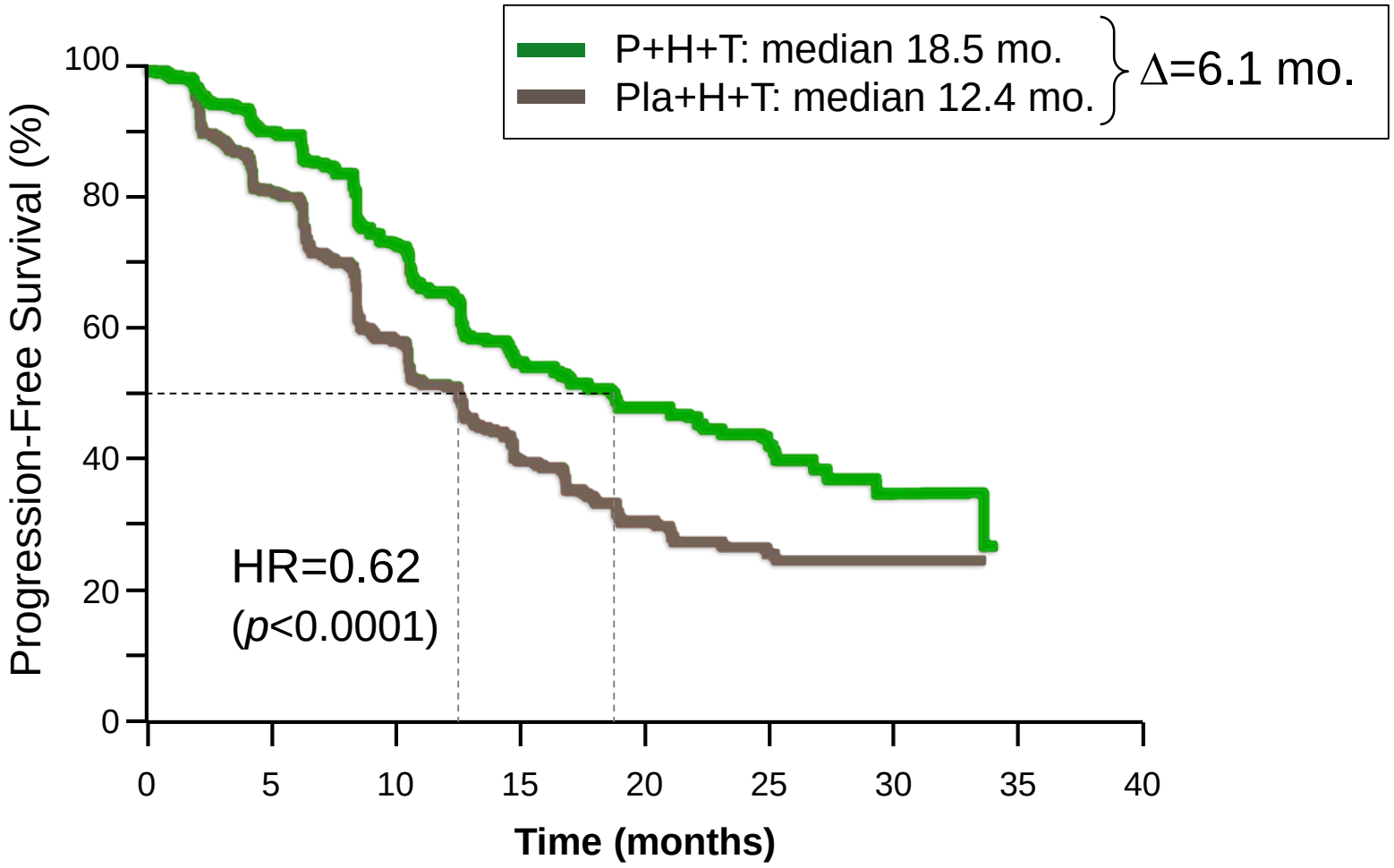


Perjeta First Neoadjuvant Approval



- 2012: Regular approval in metastatic setting (CLEOPATRA)
- 2013: Accelerated Approval in neoadjuvant setting (NeoSphere and TRYPHAENA)
- 2017: Regular Approval in adjuvant setting (APHINITY)

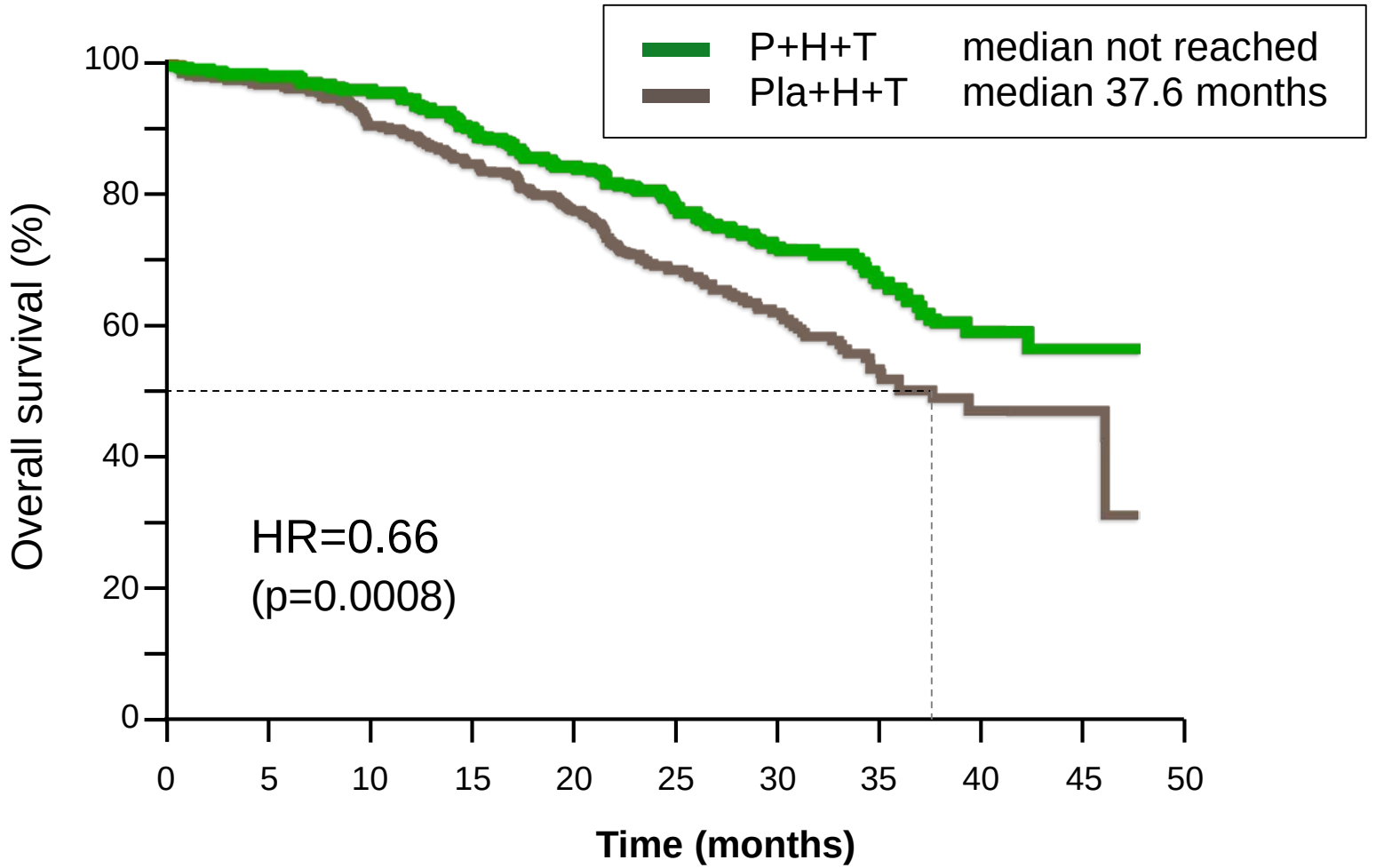
CLEOPATRA : PFS Results



Pla, placebo; P, T, docetaxelpertuzumab; H, trastuzumab;

Baselga et al., NEJM 2012

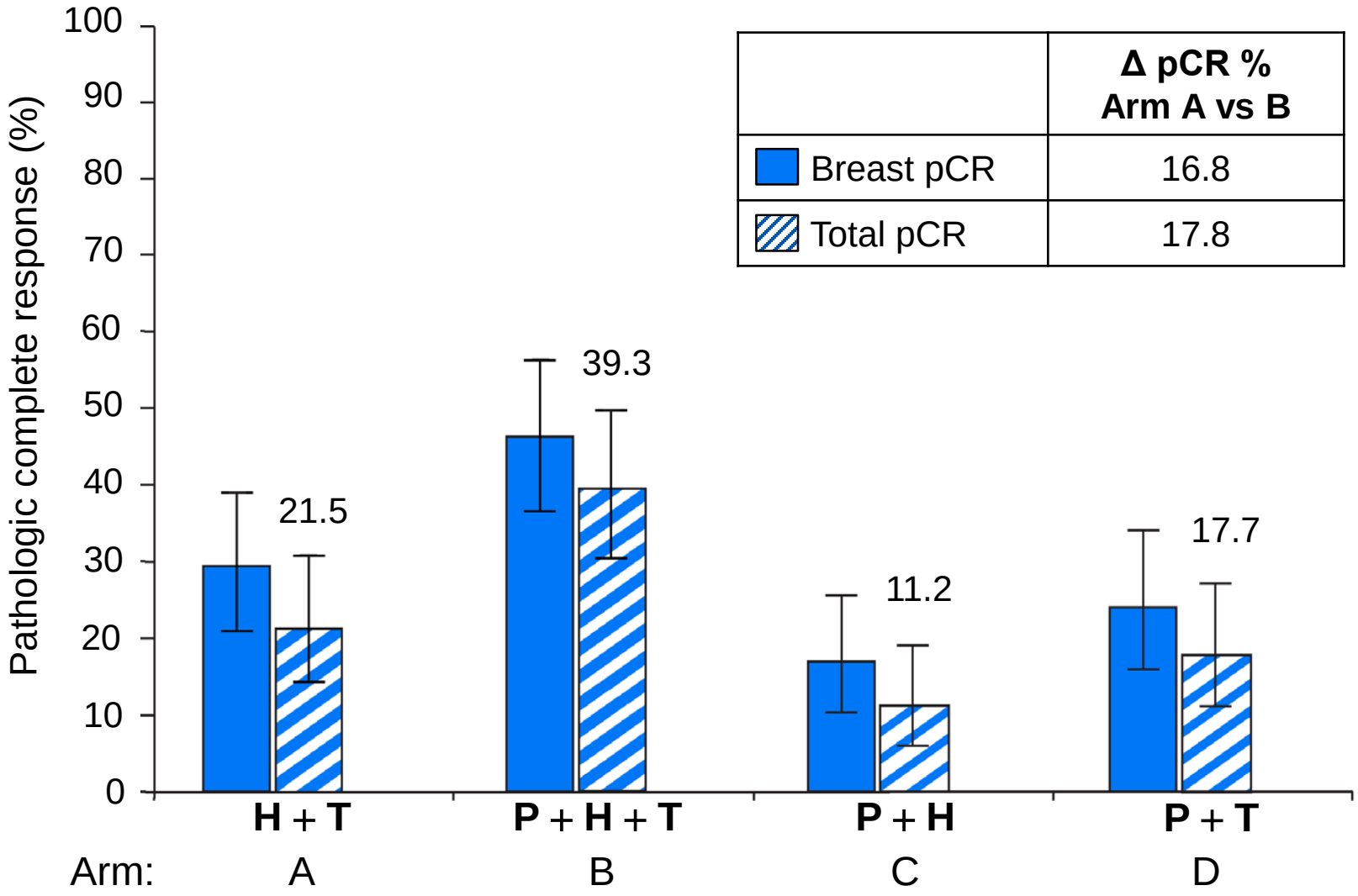
CLEOPATRA: OS Results



Pla, placebo; P, pertuzumab; H, trastuzumab; T, docetaxel

Swain et al., Lancet Oncology, 2013

NEOSPHERE: pCR Results



	Δ pCR % Arm A vs B
Breast pCR	16.8
Total pCR	17.8

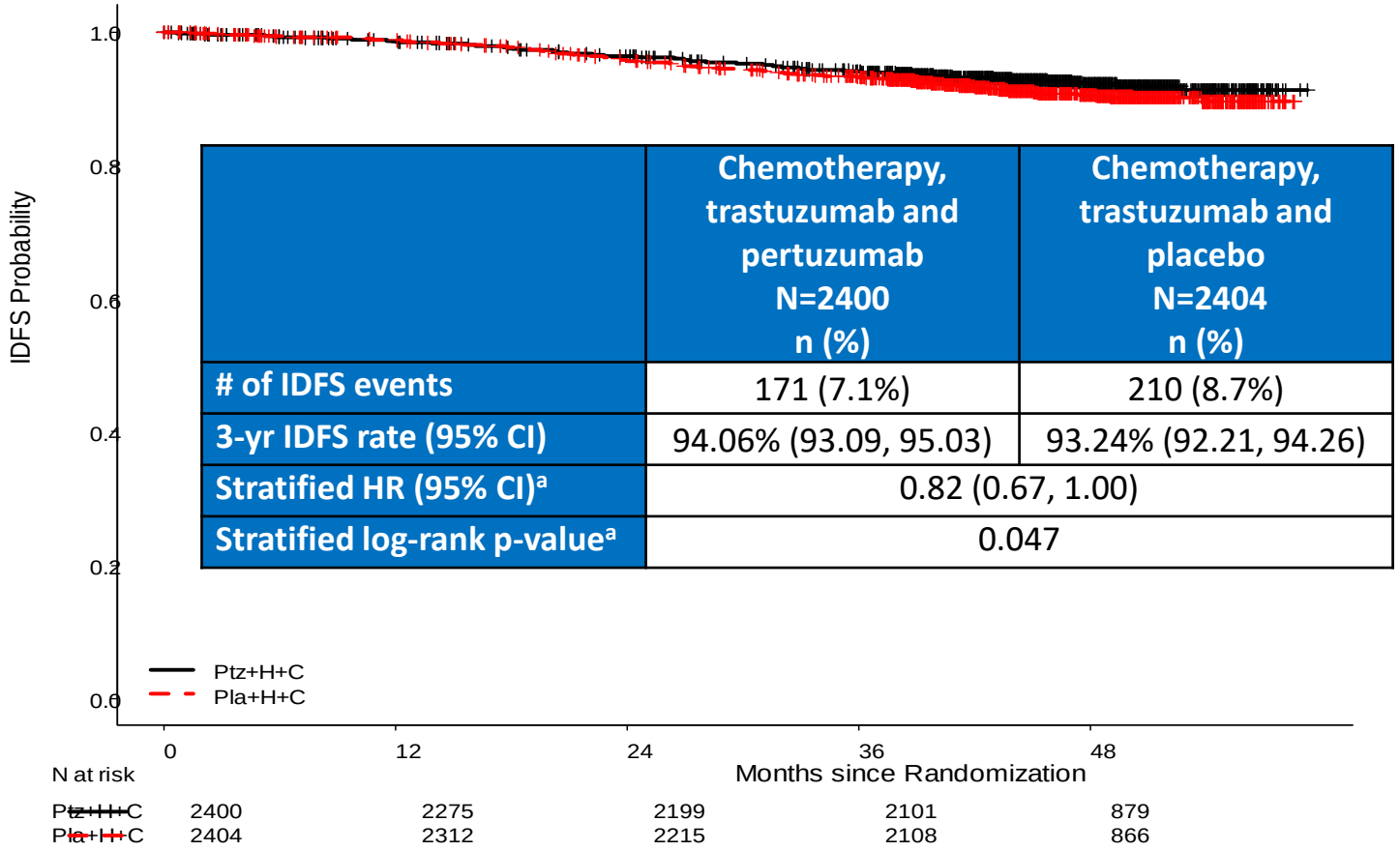
P, pertuzumab; H, trastuzumab; T, docetaxel.

Perjeta Accelerated Approval Benefit/Risk Assessment

- Improvement in pCR rate may be reasonably likely to result in long-term improvements in EFS or OS.
- High-risk early-breast cancer population
- Confirmatory Study underway
- Based on totality of the data
  - Evidence of OS in metastatic setting
  - Knowledge of biological pathway
  - Experience with drugs in same class or same target

➢Oct 1, 2013: accelerated approval in neoadjuvant setting

APHINITY: IDFS Results

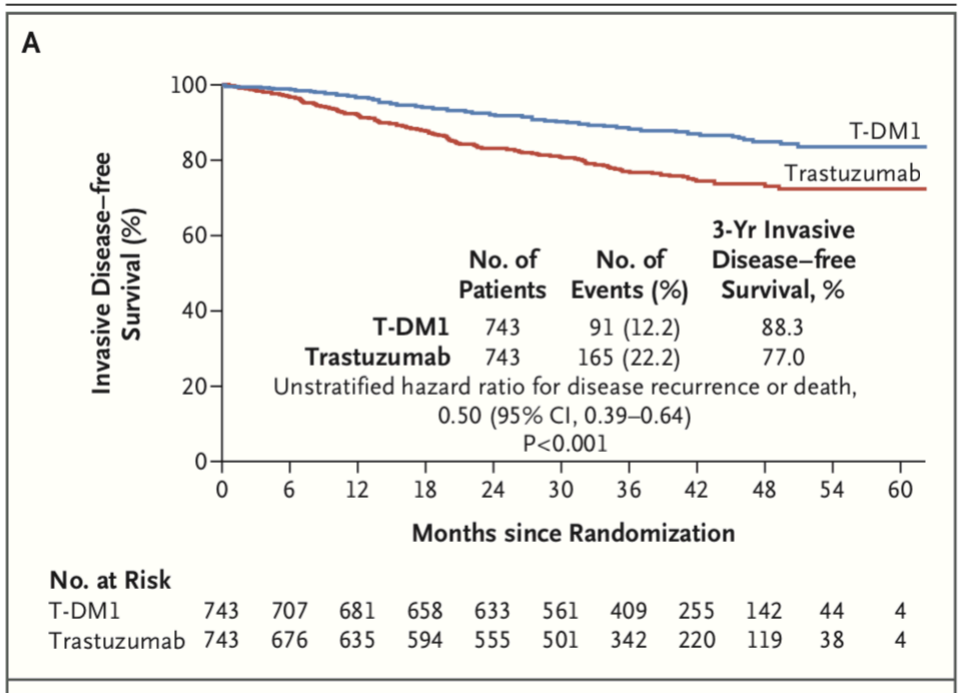


	Chemotherapy, trastuzumab and pertuzumab N=2400 n (%)	Chemotherapy, trastuzumab and placebo N=2404 n (%)
# of IDFS events	171 (7.1%)	210 (8.7%)
3-yr IDFS rate (95% CI)	94.06% (93.09, 95.03)	93.24% (92.21, 94.26)
Stratified HR (95% CI)[a]	0.82 (0.67, 1.00)	
Stratified log-rank p-value[a]	0.047	

Dec 20, 2017: Regular approval in neoadjuvant and adjuvant setting

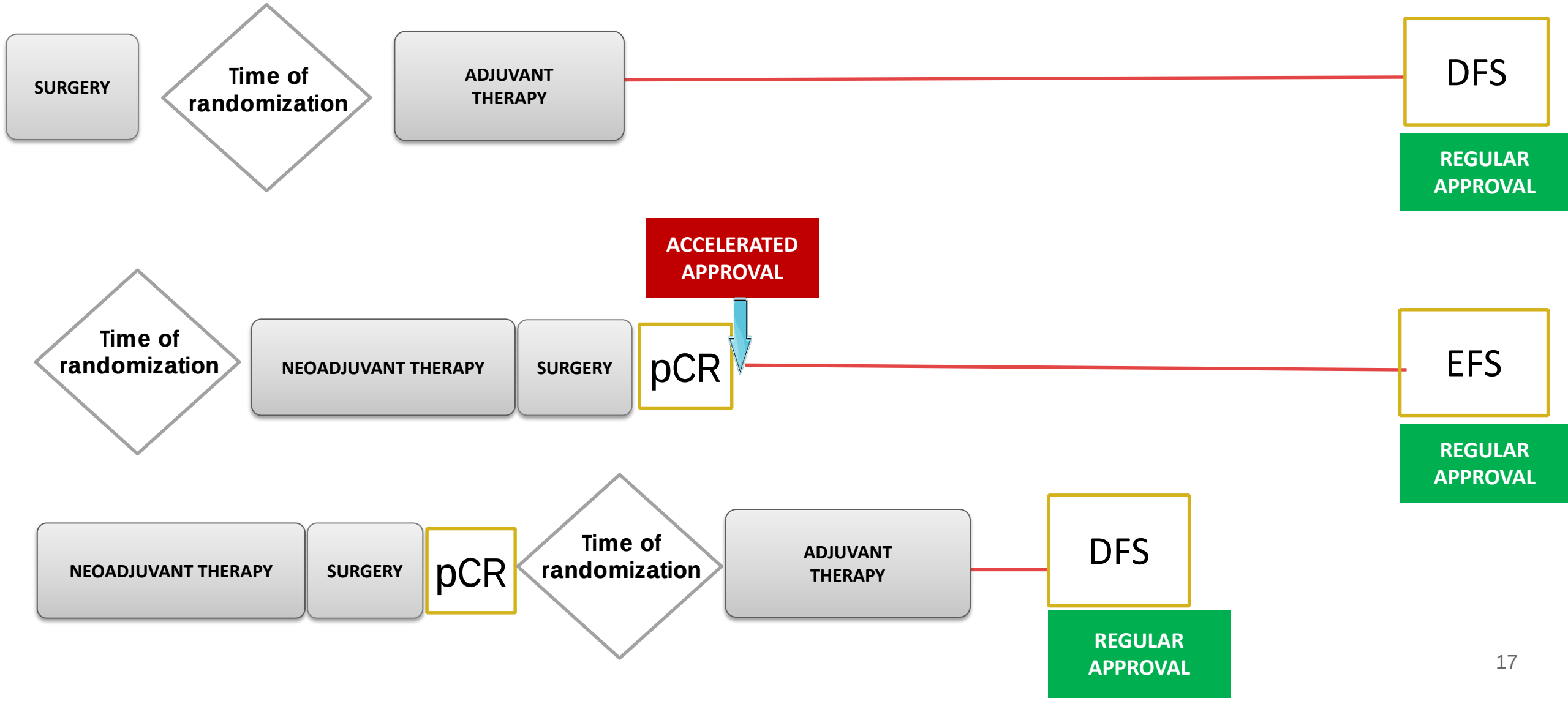
Lack of pCR As a Biomarker for Enrichment

- pCR: Prognostic factor
- Residual disease
- High-risk patient selection for adjuvant studies
- Example: Kadcyla regular approval based on Katherine Trial



Von Minckwitz G et al, NEJM 2019
Prowell et al NEJM 2019

Summary: Trial Designs & Endpoints



Regulatory Lessons Learned

- Standardize definition of pCR and Central review
- Challenges of confirmation of benefit in a single trial model due to post surgery therapies
- Confirmatory trial in a high-risk population

Acknowledgements

- Patients
- CTneoBC collaborators (Patricia Cortazar and Lijun Zhang)
- Tatiana Prowell
- Julia Beaver
- Marc Theoret
- Richard Pazdur