Innovations in Breast Cancer Drug Development
NEOADJUVANT BREAST CANCER WORKSHOP

Implications of the CTNeoBC Meta-analysis

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Outline

- Summary of CTNeoBC Meta-analysis
- How should we define “high-risk population”?
- What absolute risk of relapse should be considered “high-risk” for regulatory purposes?
- What magnitude of improvement in EFS should be considered clinically meaningful?

Information Needed to Open Regulatory Path for Neoadjuvant Breast Cancer

pCR relationship to long-term clinical benefit (EFS and OS)

Meta-analysis of Randomized Neoadjuvant Trials

Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC)

NSABP
National Surgical Adjuvant Breast and Bowel Project

GBG
GERMAN BREAST GROUP

NATIONAL CANCER INSTITUTE

AGO-B
BREAST STUDY GROUP

UNC
LINEBERGER COMPREHENSIVE CANCER CENTER
N.C. CANCER HOSPITAL

BIG
BREASTINTERNATIONALGROUP

SweBCG SVENSKA BRÖSTCANCERGRUPPEN Swedish Breast Cancer Group

EORTC The future of cancer therapy
European Organisation for Research and Treatment of Cancer

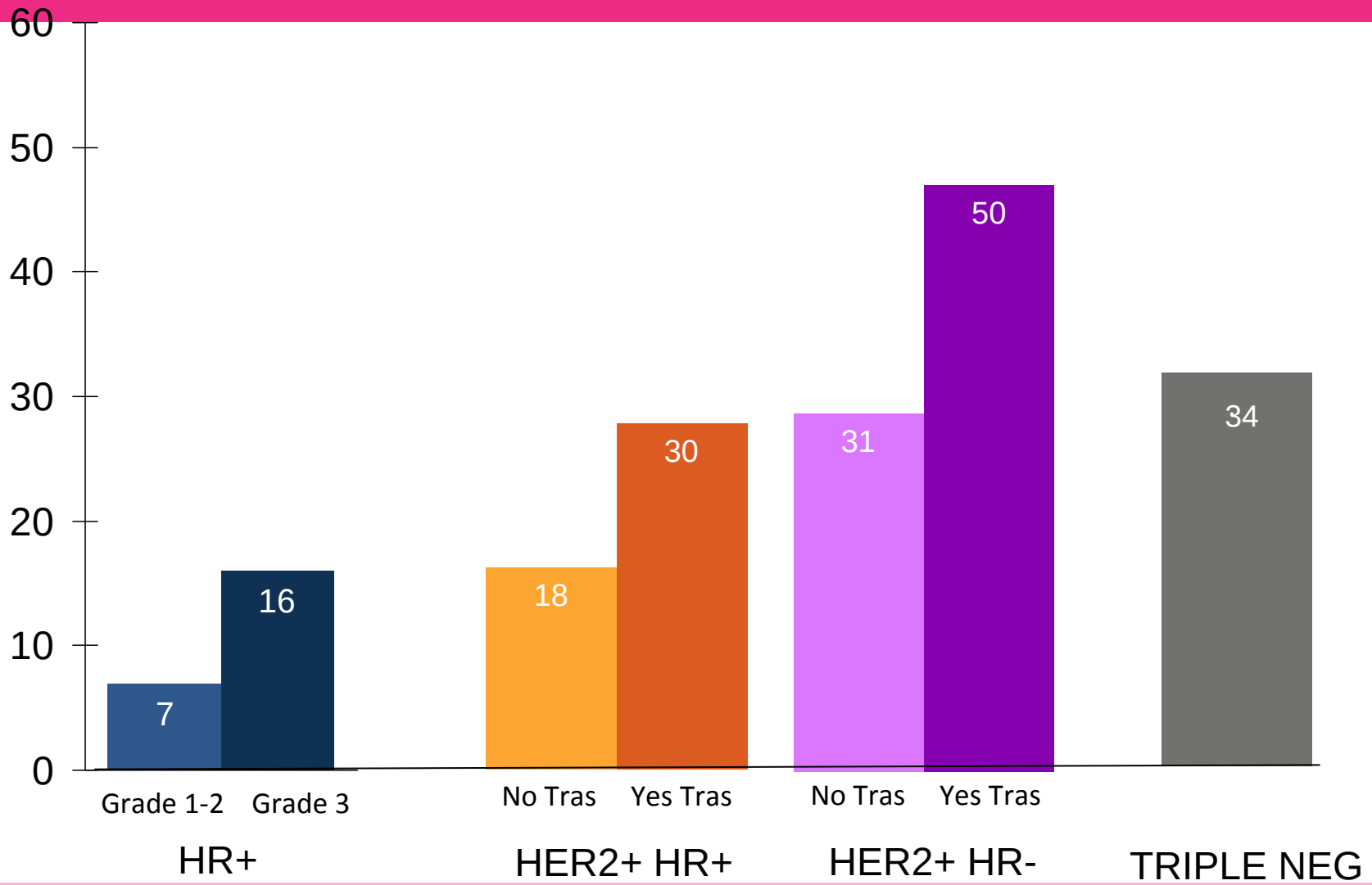
FONDAZIONE MICHELANGELO
avanzamento dello studio e cura dei tumori

CTNeoBC Selected Trials

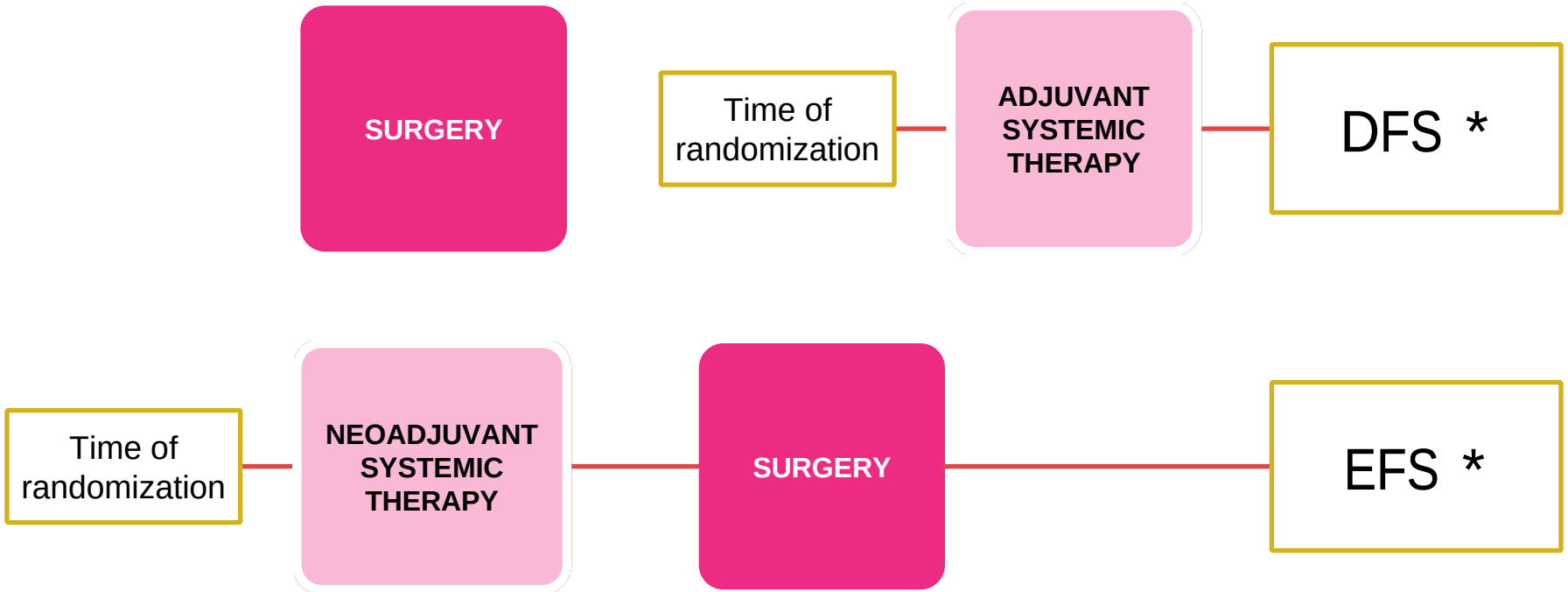
- 12 neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up EFS and OS data collected

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

pCR Rates by Tumor Subtypes



EFS Definition

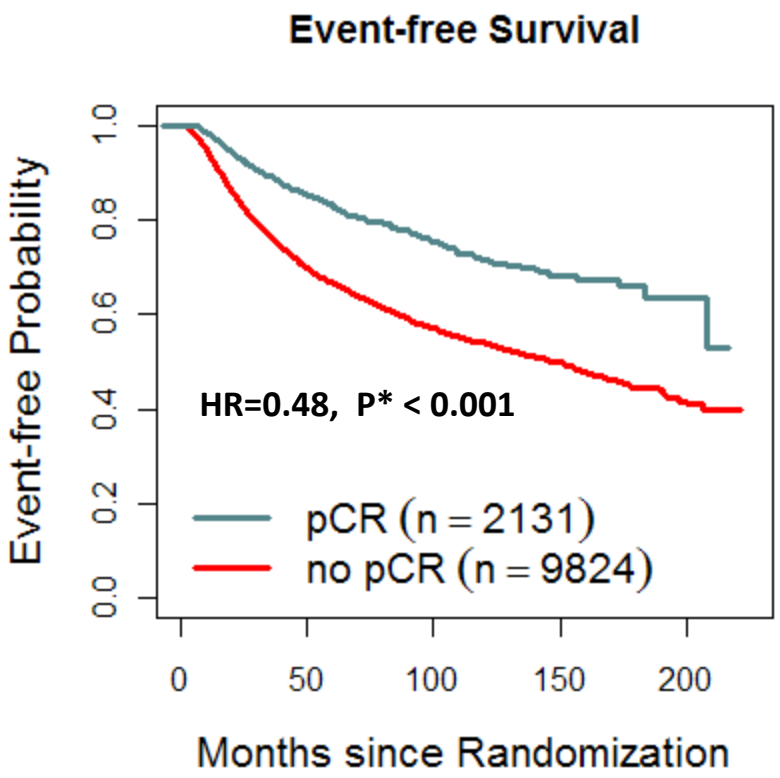


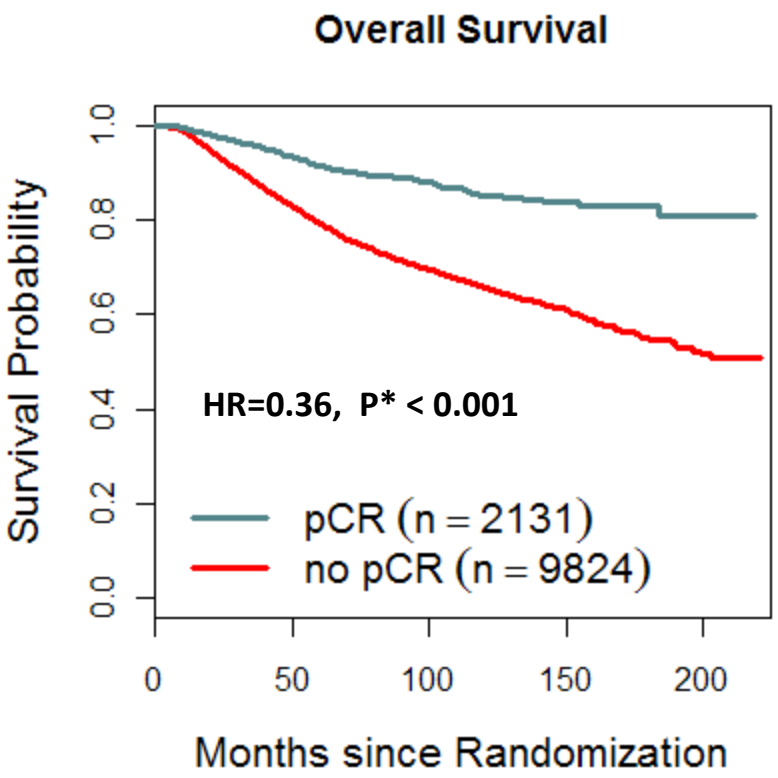
*loco-regional or distant recurrence or deaths from any cause

What did we learn from the CTNeoBC meta-analysis?

1. pCR is associated with long term outcomes (EFS and OS)

Association of pCR on EFS and OS

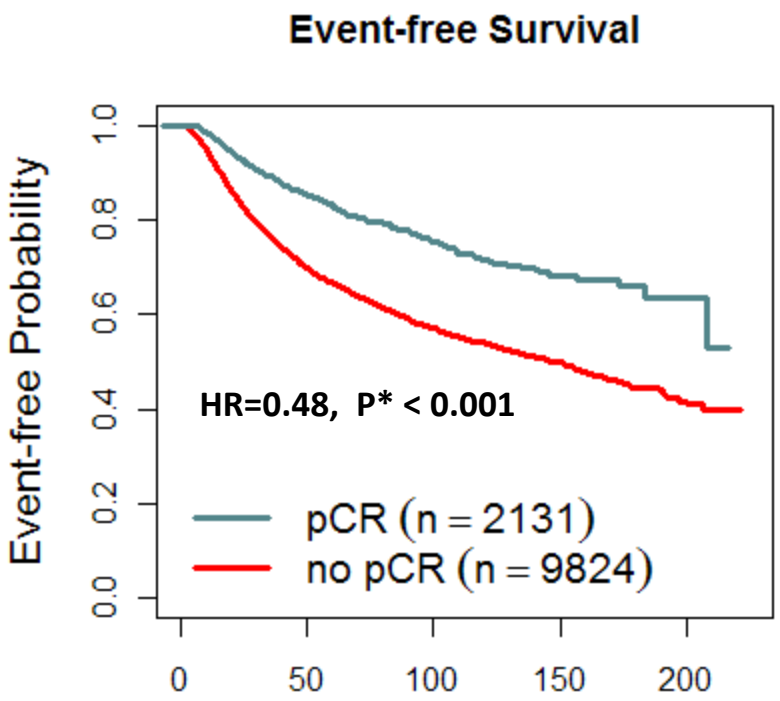


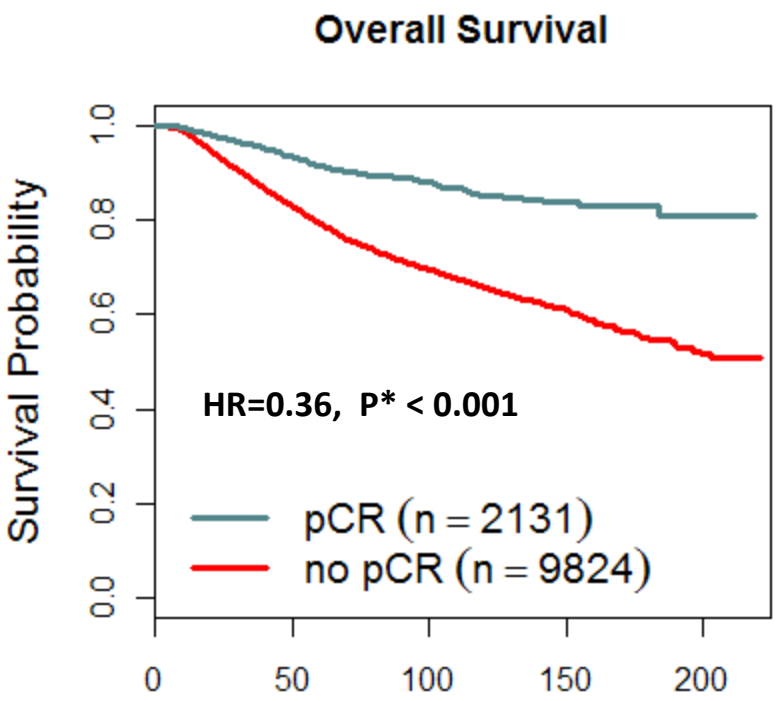


pCR=ypT0/is ypN0

* Nominal p-value

Association of pCR on EFS and OS



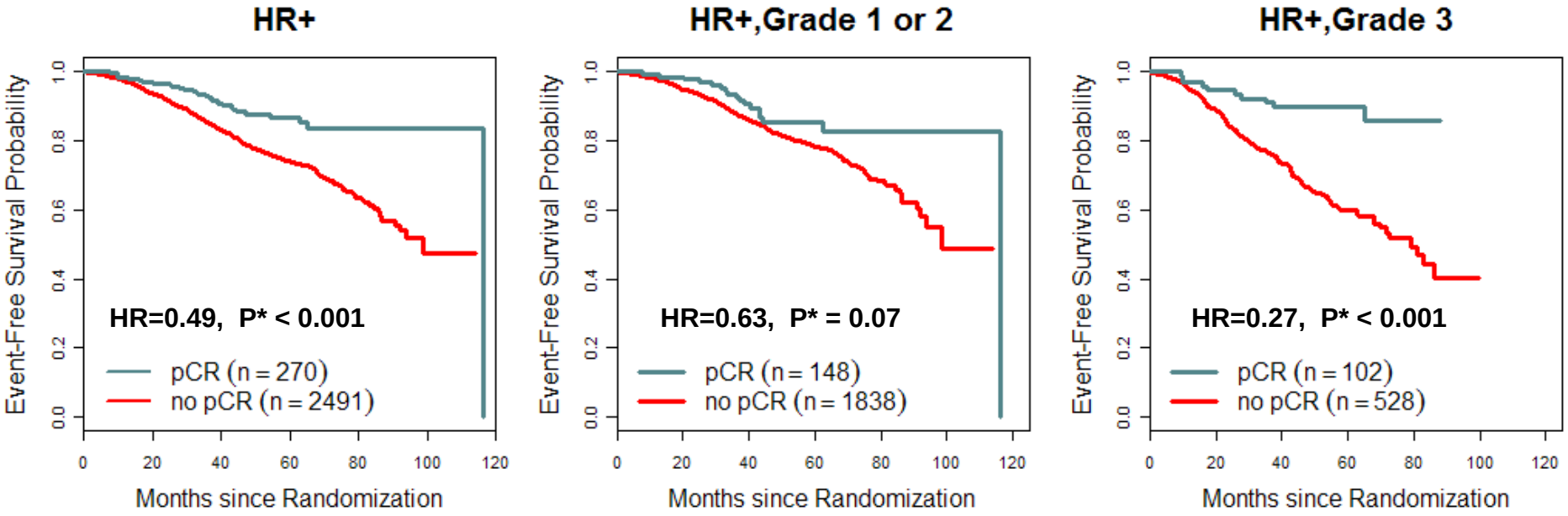


Individual patients who attain a pCR have a more favorable long-term outcome

Association of pCR with EFS by breast cancer subtype:

2. Larger Association in patients with aggressive breast cancer tumor subtypes
   Smaller Association in patients with less agressive tumors

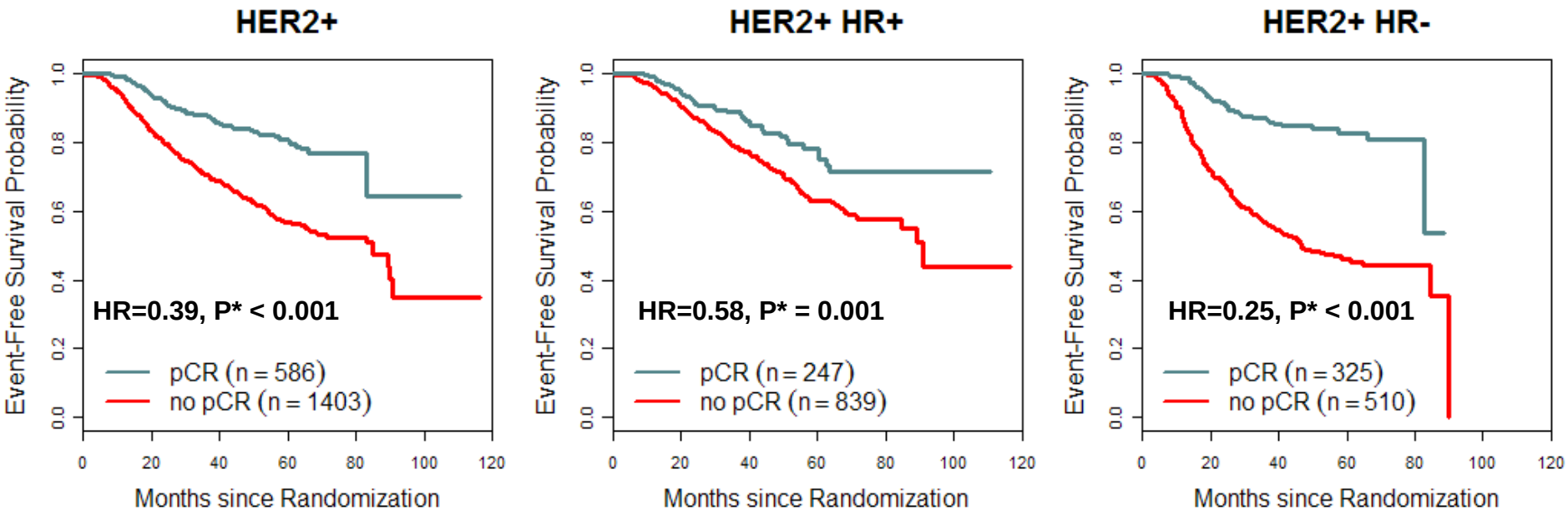
Association of pCR with EFS in HR+ HER2-Subtype



pCR=ypT0/is ypN0

* Nominal p-value

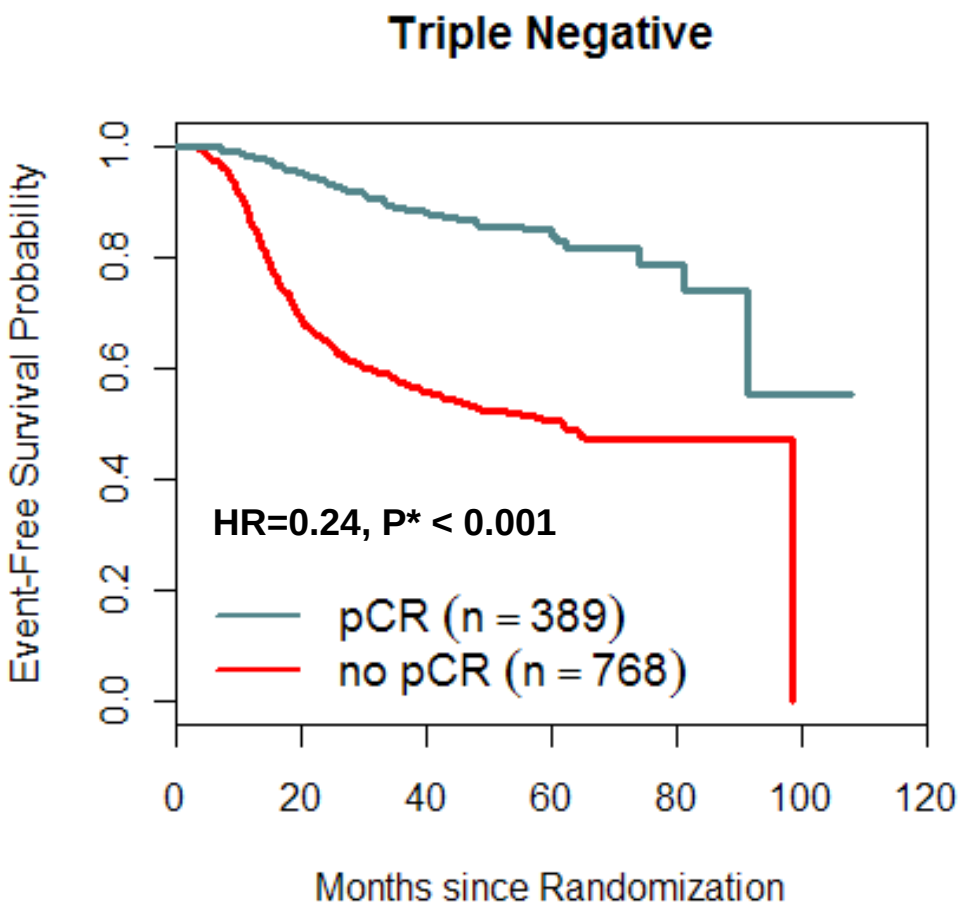
Association of pCR with EFS in Her2+ Subtype



pCR=ypT0/is ypN0

* Nominal p-value

Association of pCR with EFS in Triple Negative Subtype



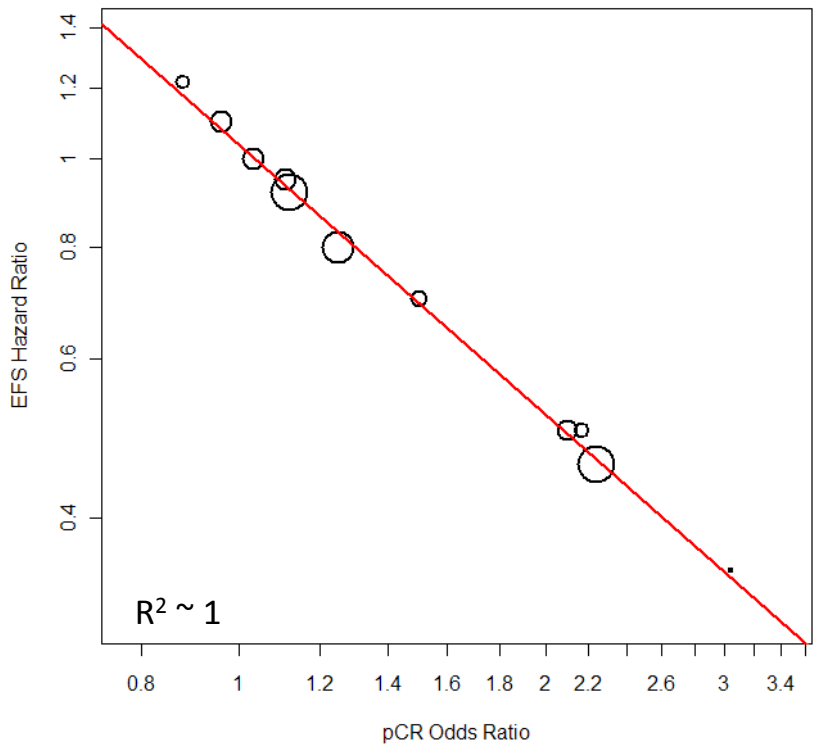
pCR=ypT0/is ypN0

* Nominal p-value

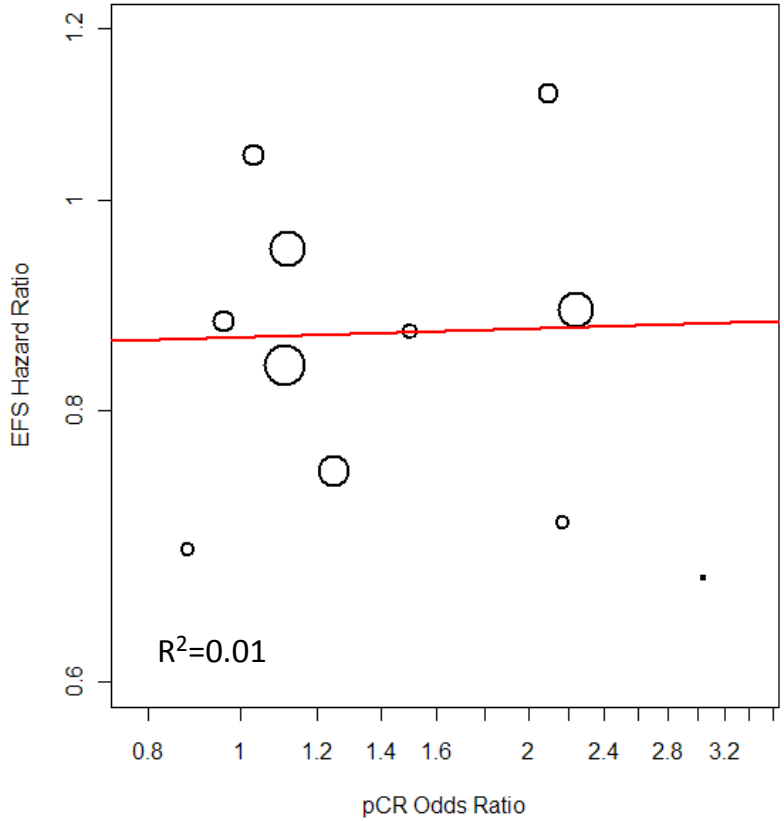
3. The meta-analysis could not establish the magnitude of pCR improvement that predicts long-term clinical benefit (EFS and OS improvement)

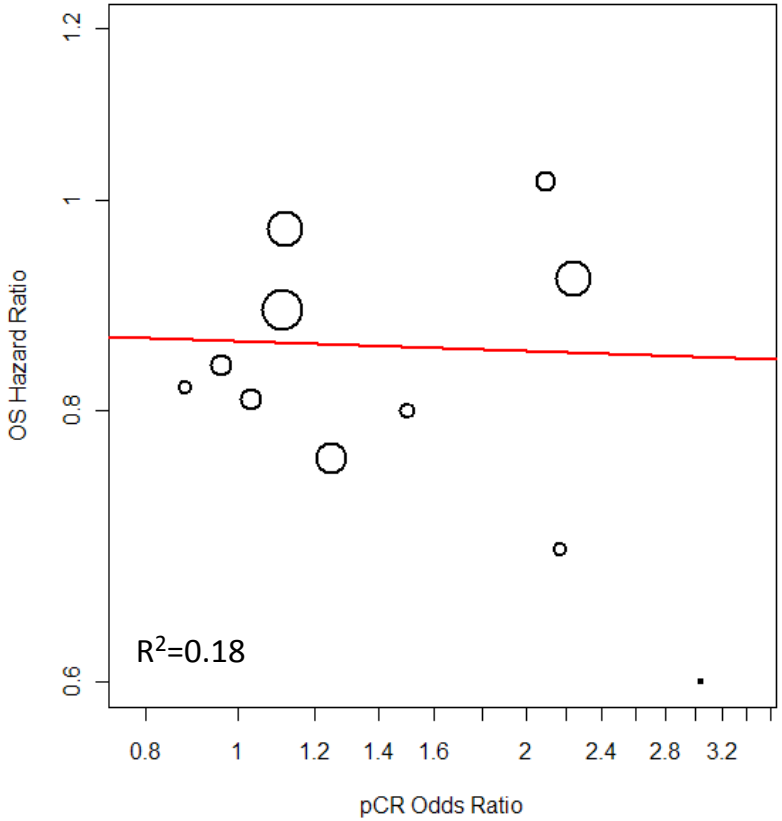
Trial level correlation between pCR and EFS

A perfect scenario example (simulated-data)

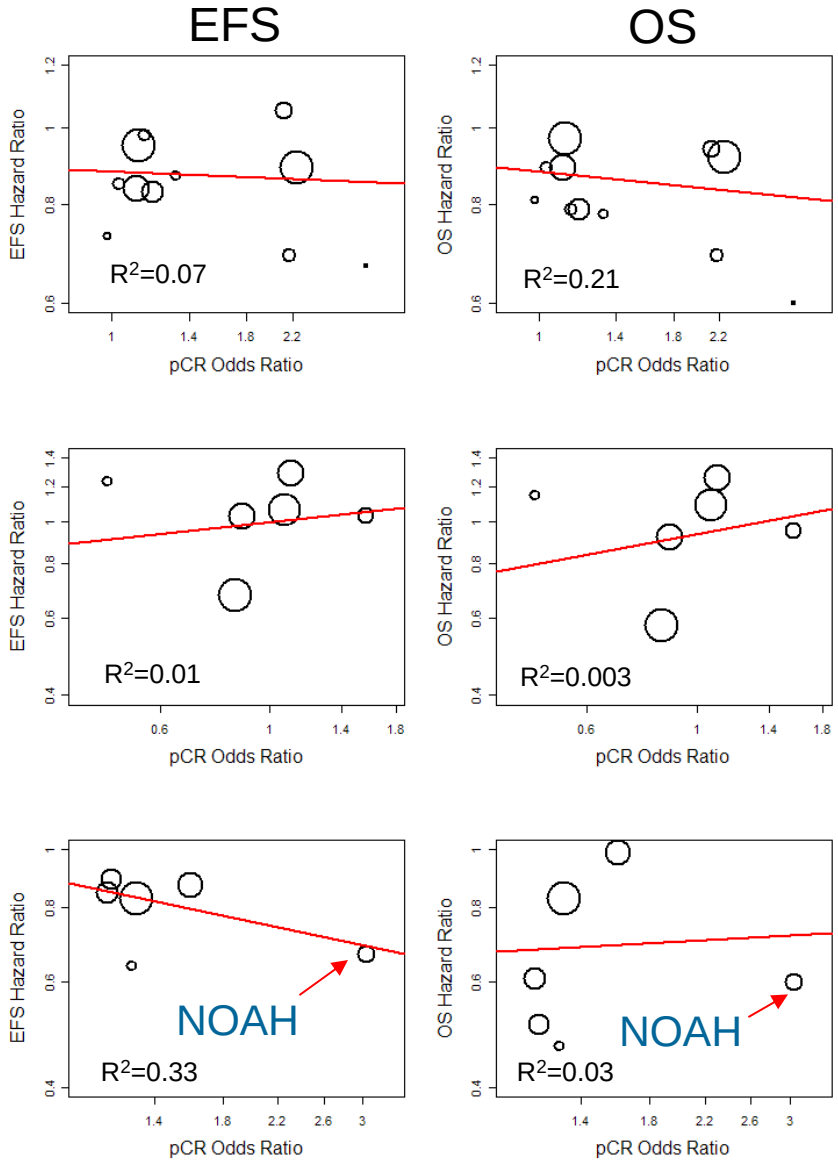


The magnitude of improvement in pCR rate did not predict EFS and OS effect





Subgroup analysis



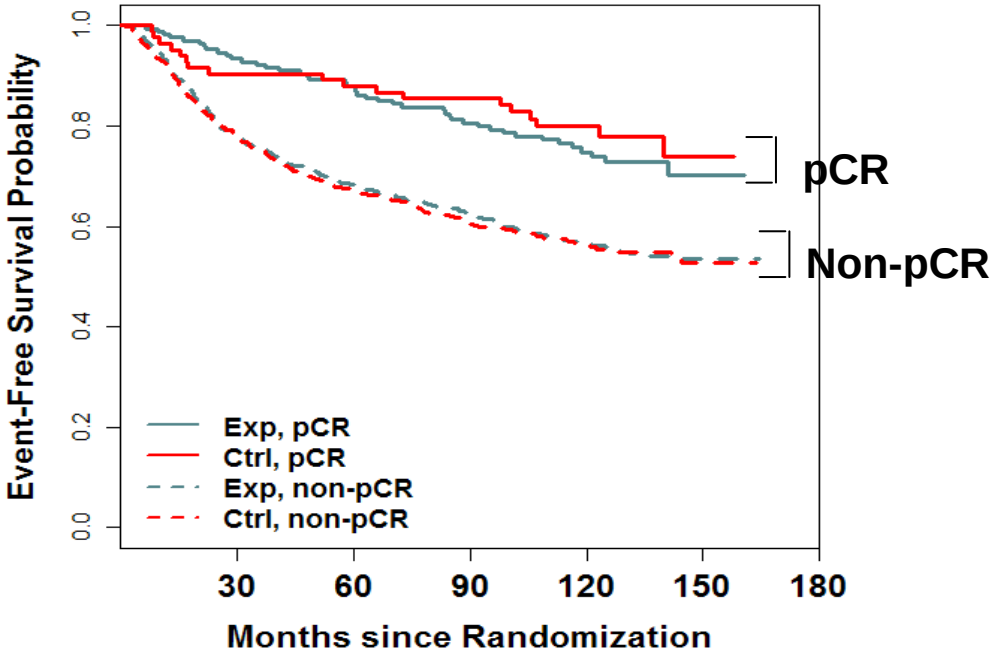
Excluding patients with HR+ Grade 1 or 2

Triple negative subgroup

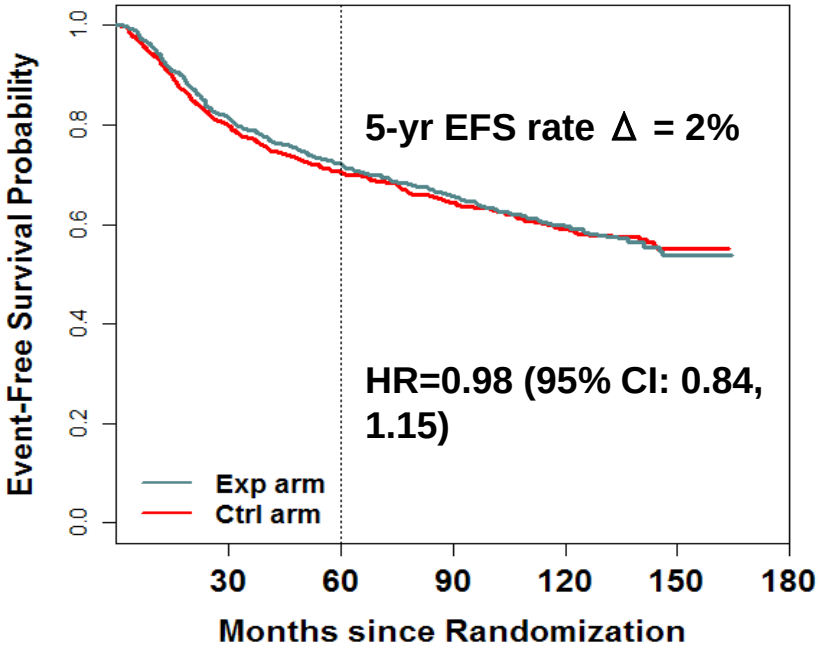
Her2+ subgroup

A Hypothetical Example Limitations of Responder Analysis

Patient level



Trial level



	Exp	Ctrl
pCR	21%	10%
No pCR	79%	90%

Although patients with pCR have better EFS irrespective of treatment.
There is no difference on EFS between the two randomized treatment arms.

Summary

1. pCR association with long term outcomes (EFS and OS):

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

2. Association of pCR with EFS by breast cancer subtype:

- Larger Association in patients with aggressive breast cancer tumor subtypes
- Smaller Association in patients with less aggressive tumors

Summary

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

Where do we stand?

- We need a validated endpoint for regular approval
- pCR is not yet an established surrogate endpoint and we do not have sufficient experience to validate it
- Uncertainty regarding the ultimate outcome:
  - Long-term efficacy (EFS and OS)
  - Long-term safety

We will need long term follow-up and confirmation of ultimate outcome

The Neoadjuvant Regulatory Path could be opened through Accelerated Approval

Accelerated Approval Regulations

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**

- Should pCR be considered reasonably likely to predict for clinical benefit?
- AA requires confirmation of benefit

Accelerated Approval Process

- Allows earlier approval of products to become available for patients
- Risks:
  - of approving a product that will not show ultimate clinical benefit
  - of exposing patients to the toxicity of therapy without certainty of benefit

Select High-Risk Early Breast Cancer Population to Justify Accelerated Approval

Reasons for Selecting a High-Risk Early Breast Cancer Population

- To justify Accelerated Approval
- Enough risk to see an effect in pCR as well as long-term outcome (EFS, OS)

How should “high-risk” be defined for regulatory purposes in designing neoadjuvant trials intending to use pCR to support an accelerated approval?

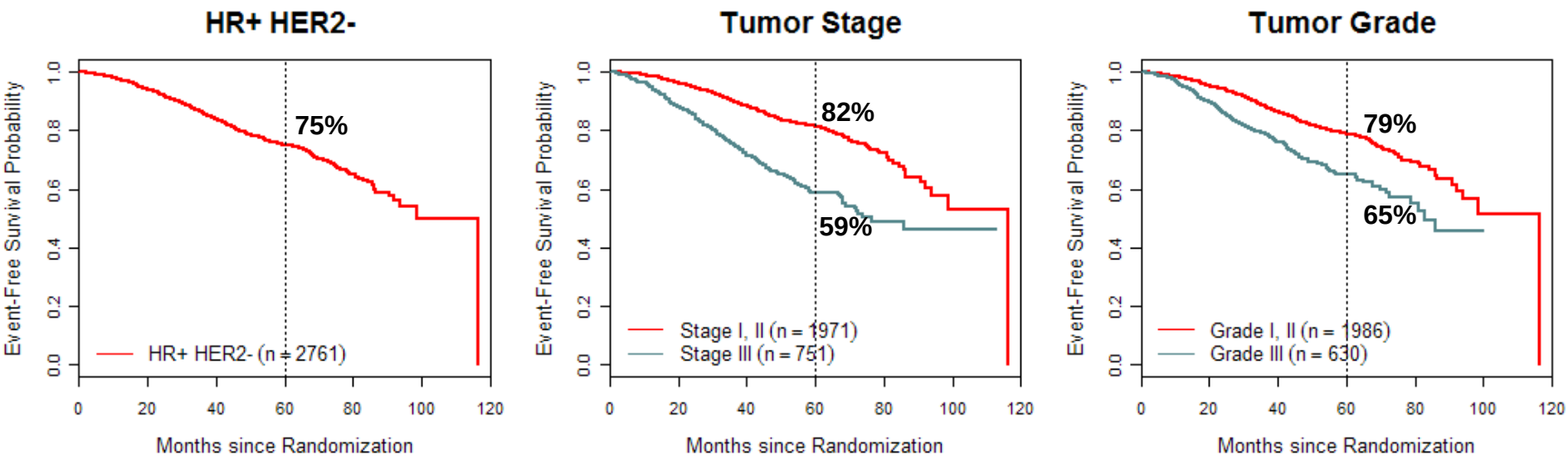
How Should We Define "High Risk Population"?

Factors that affect the risk of relapse:

- Staging (tumor and lymph node)
- Tumor Grade?
- Clinical/molecular subtype?
- Age
- Other?

How should we define “high-risk” in hormone receptor-positive patients?

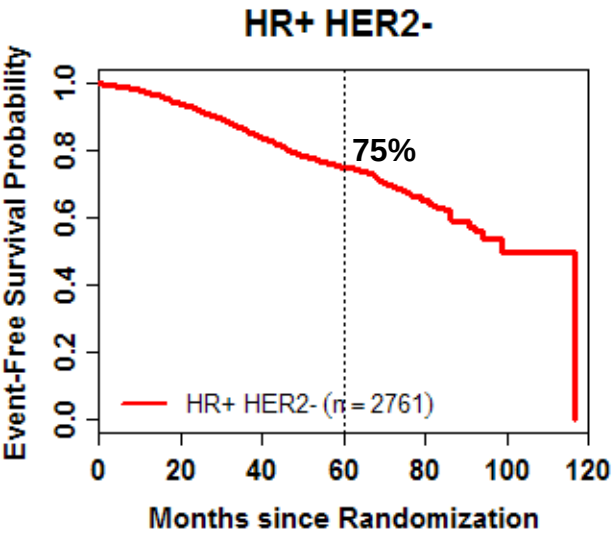
HR+ HER2-, 5-yr EFS Rate

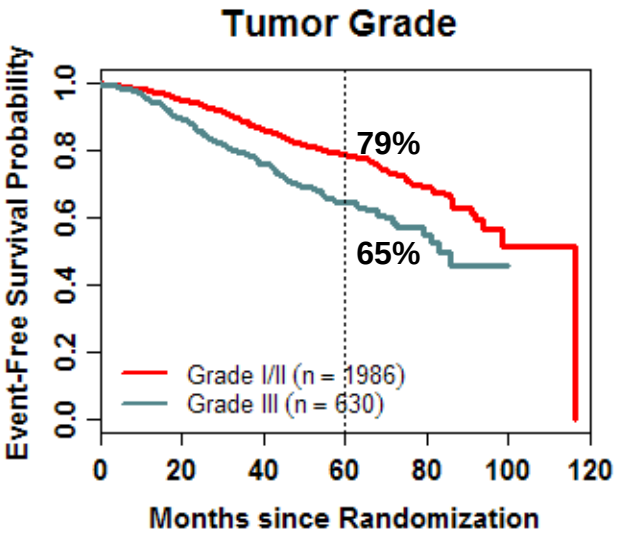


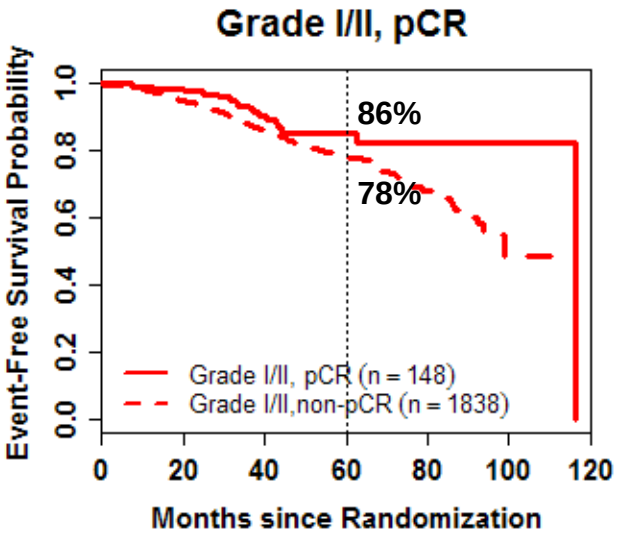
Grade I/II pCR= **7%**

Grade III pCR= **16%**

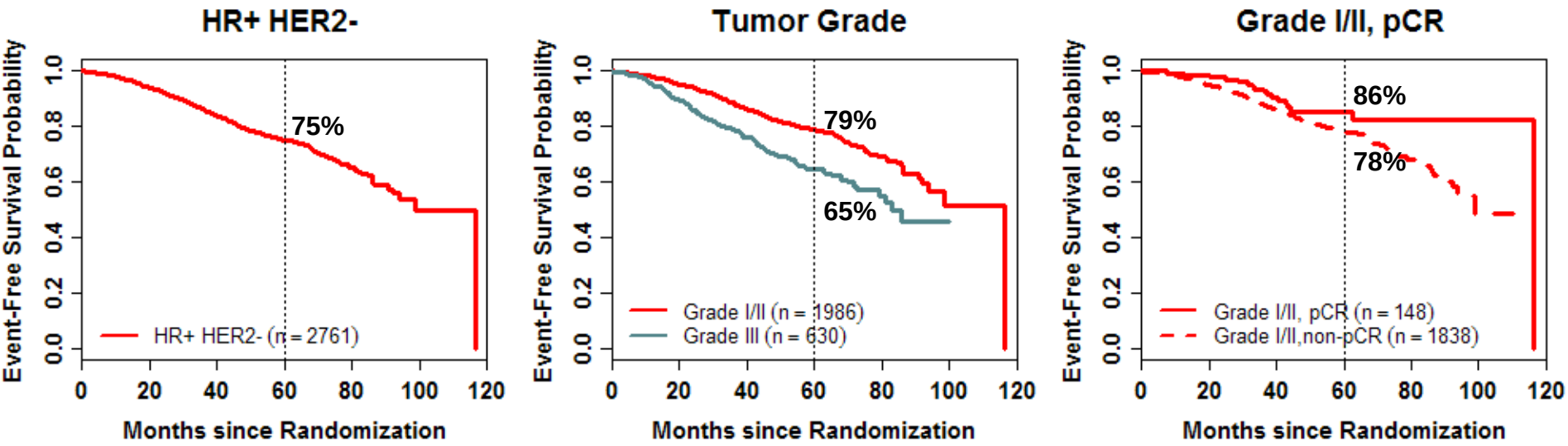
HR+ HER2-, 5-yr EFS Rate





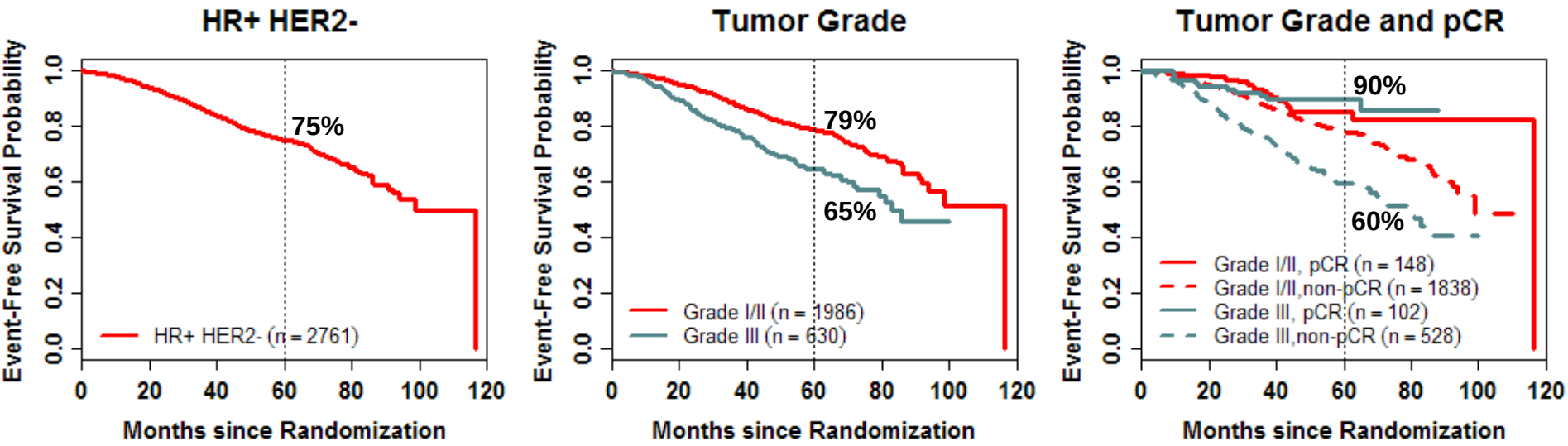


HR+ HER2-, 5-yr EFS Rate

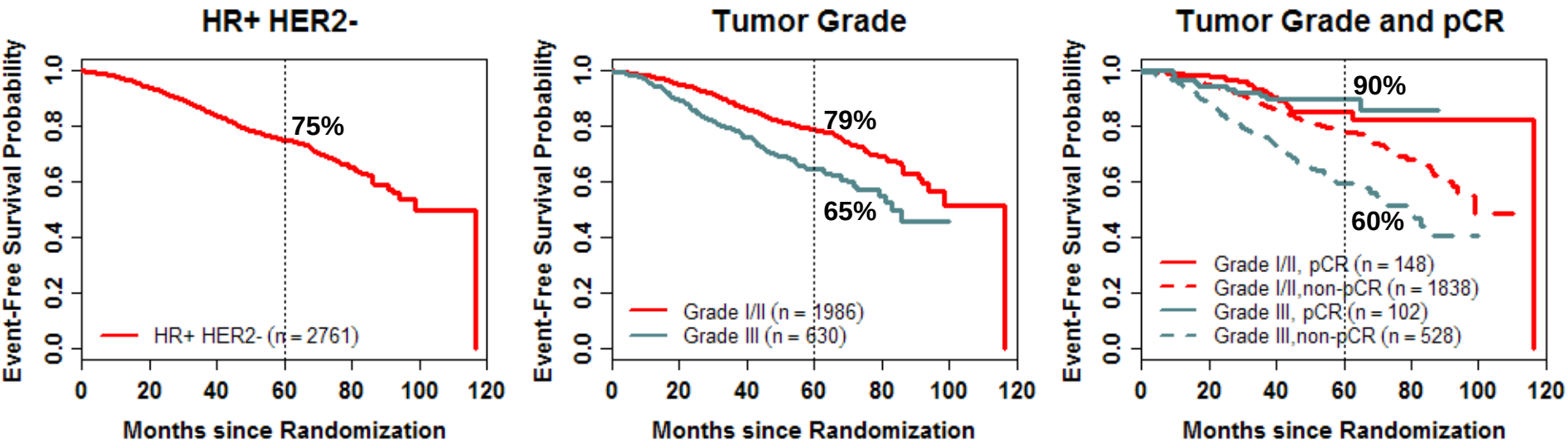


Patients with HR+ HER- low grade tumors have a lower risk of relapse regardless of pCR

HR+ HER2-, 5-yr EFS Rate



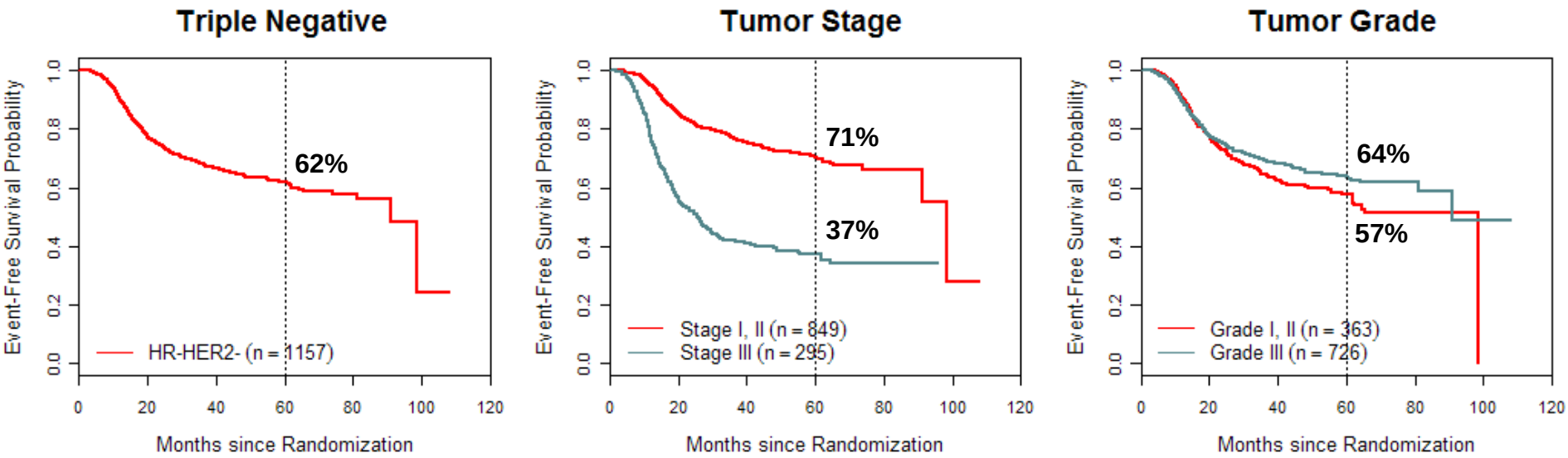
HR+ HER2-, 5-yr EFS Rate



- Patients with HR+ HER- high-grade tumors have a higher risk of relapse
- pCR is associated with improved 5 yr EFS

Triple Negative
High-Risk Population

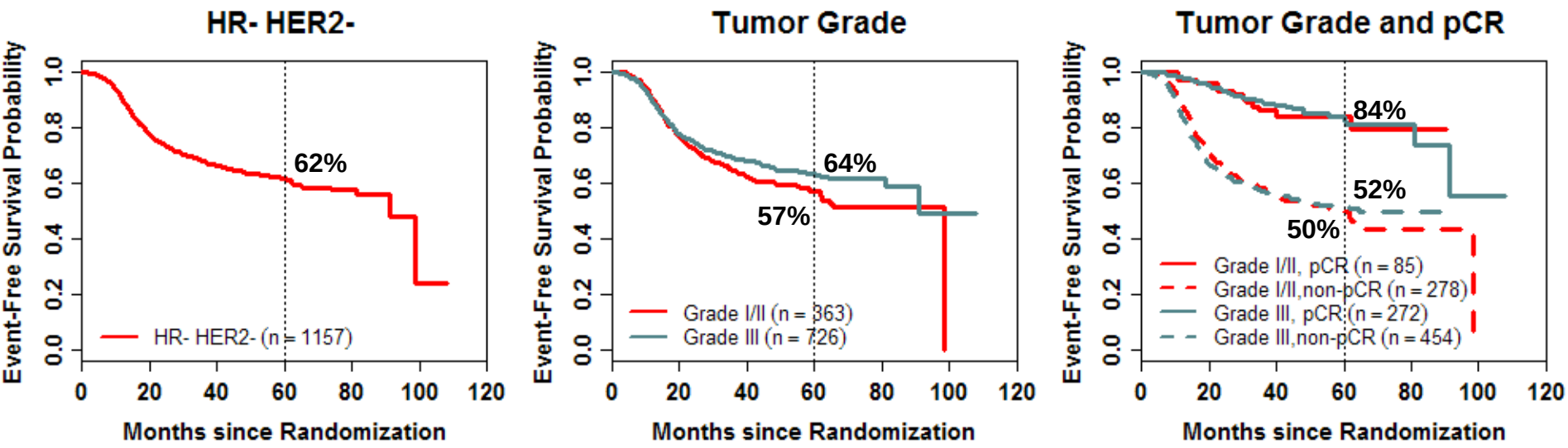
Triple Negative, 5-yr EFS Rate



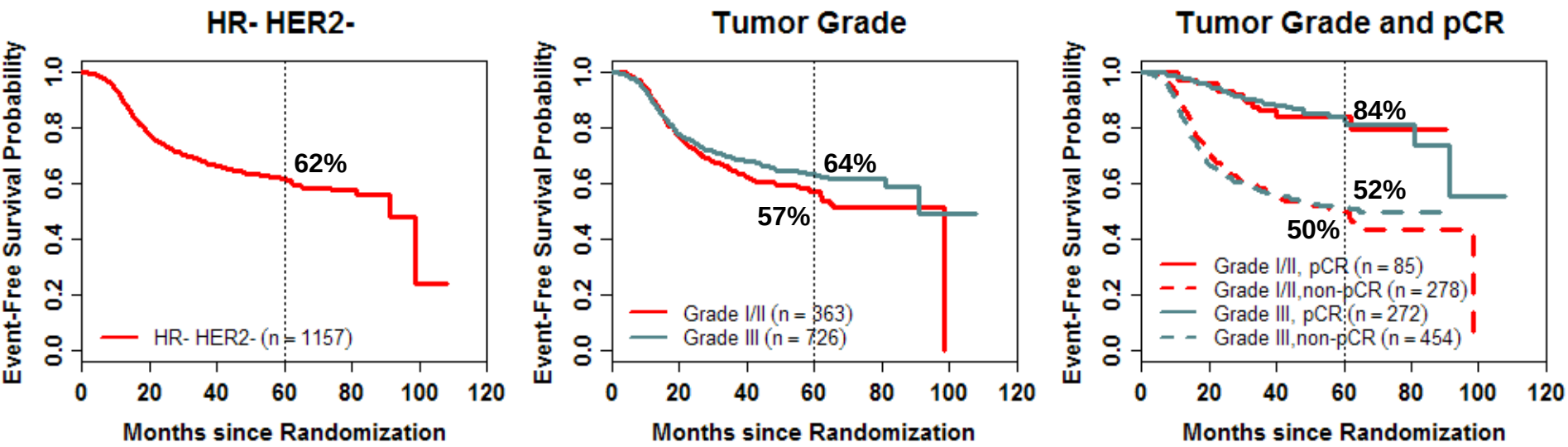
Grade I/II pCR= **23%**

Grade III pCR= **37%**

Triple Negative, 5-yr EFS Rate



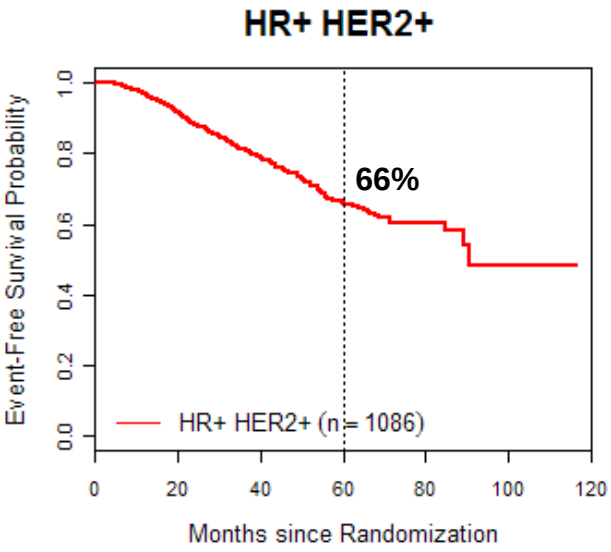
Triple Negative, 5-yr EFS Rate

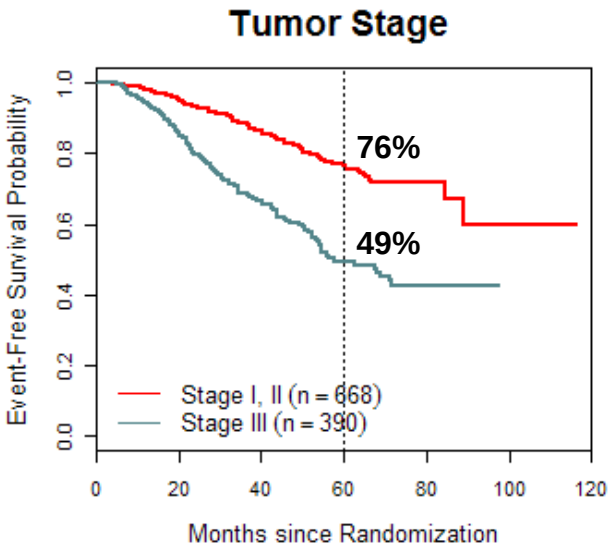


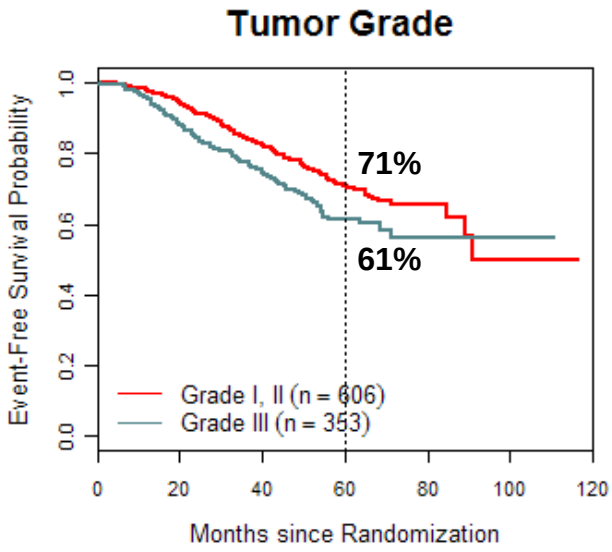
- **Overall patients with TNBC have a high risk of relapse**
- **pCR is associated with improved 5 yr EFS**

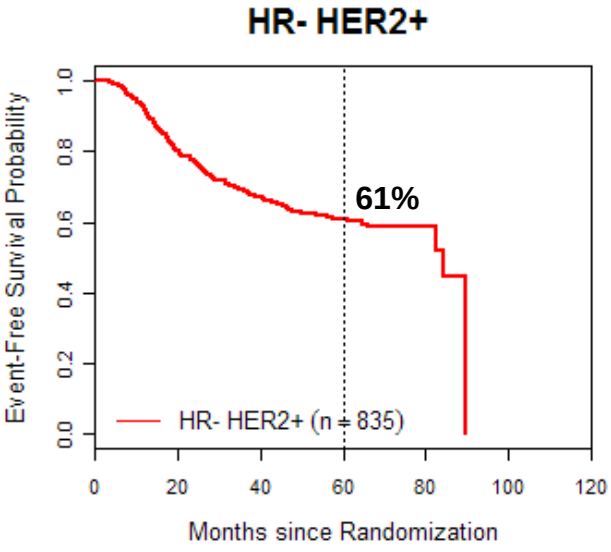
How should we define “high-risk” in HER2-positive?

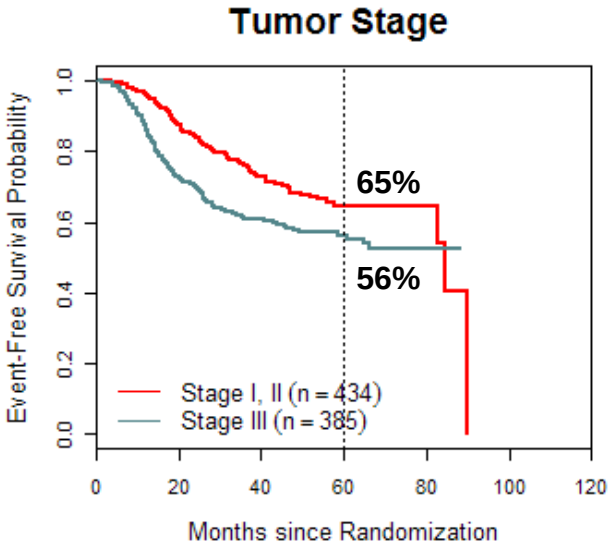
HER2+, 5-yr EFS Rate

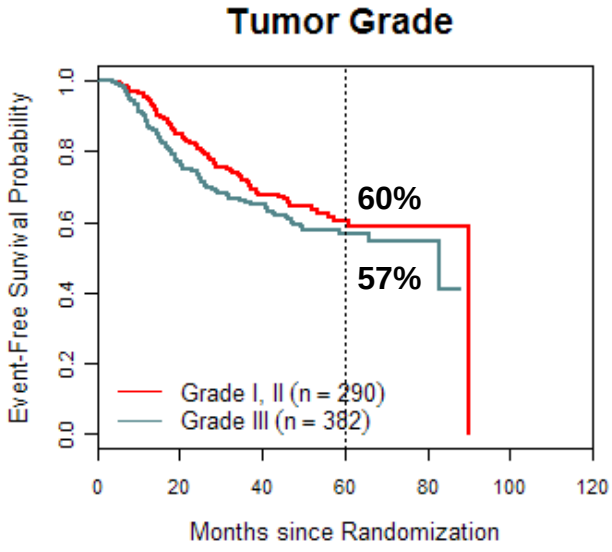












What absolute risk of relapse should be considered “high-risk” for regulatory purposes?

What absolute risk of relapse should be defined "high-risk" for regulatory purposes?

≥ 20% - 25% absolute risk of relapse?

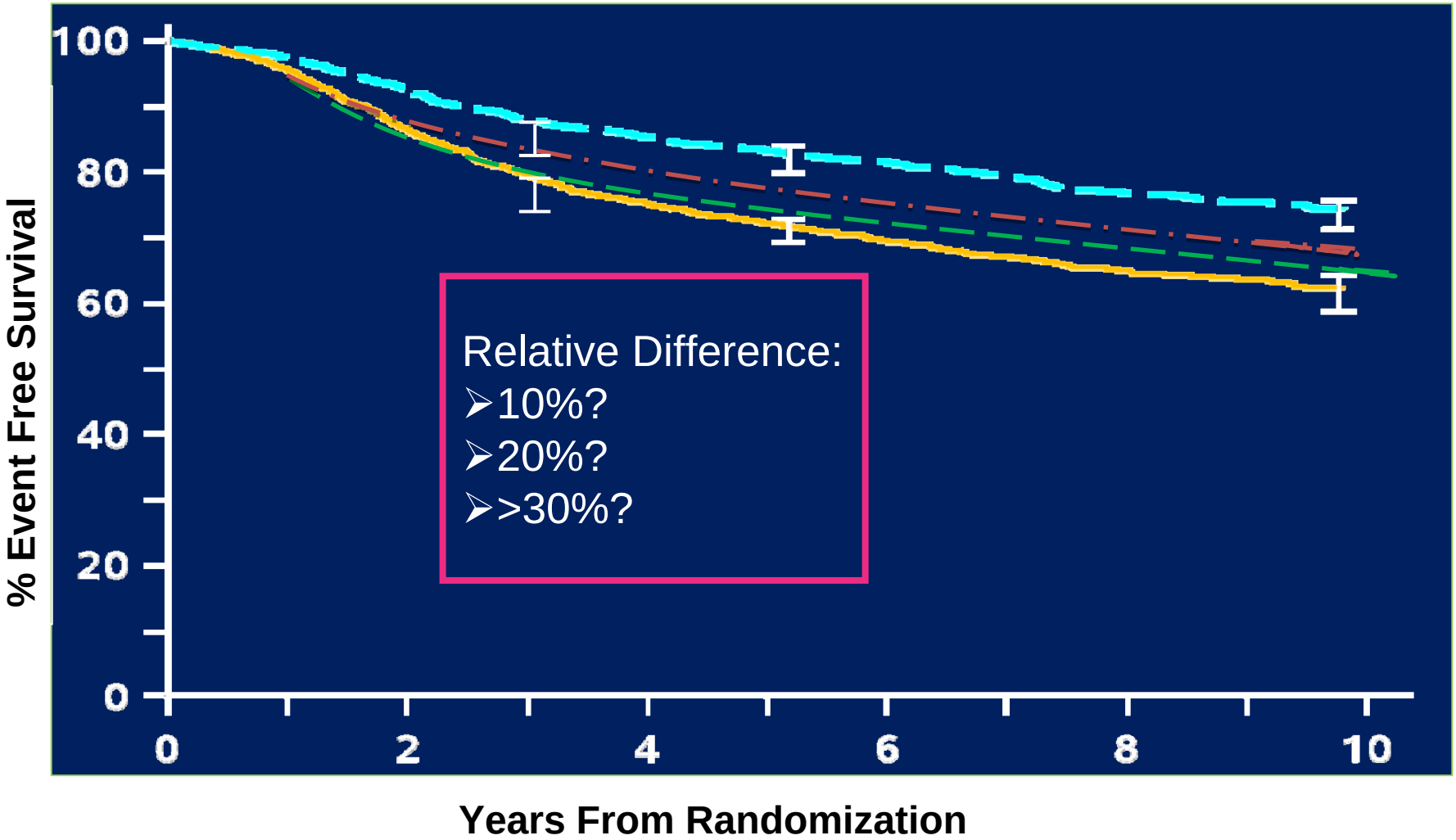
	5 year Event Free Survival Rate (EFS)			
TNM	**Stage II**		**Stage III**	
	Grade II	**Grade III**	**Grade II**	**Grade III**
Hormone Receptor + HER2-	83%	71%	63%	51%
HER2+ HR+	81%	69%	50%	48%
HER2+ HR-	61%	66%	58%	46%
Triple Negative	66%	72%	38%	37%

What magnitude of improvement in EFS should be considered clinically meaningful?

DFS improvement in Adjuvant Breast Cancer Approvals

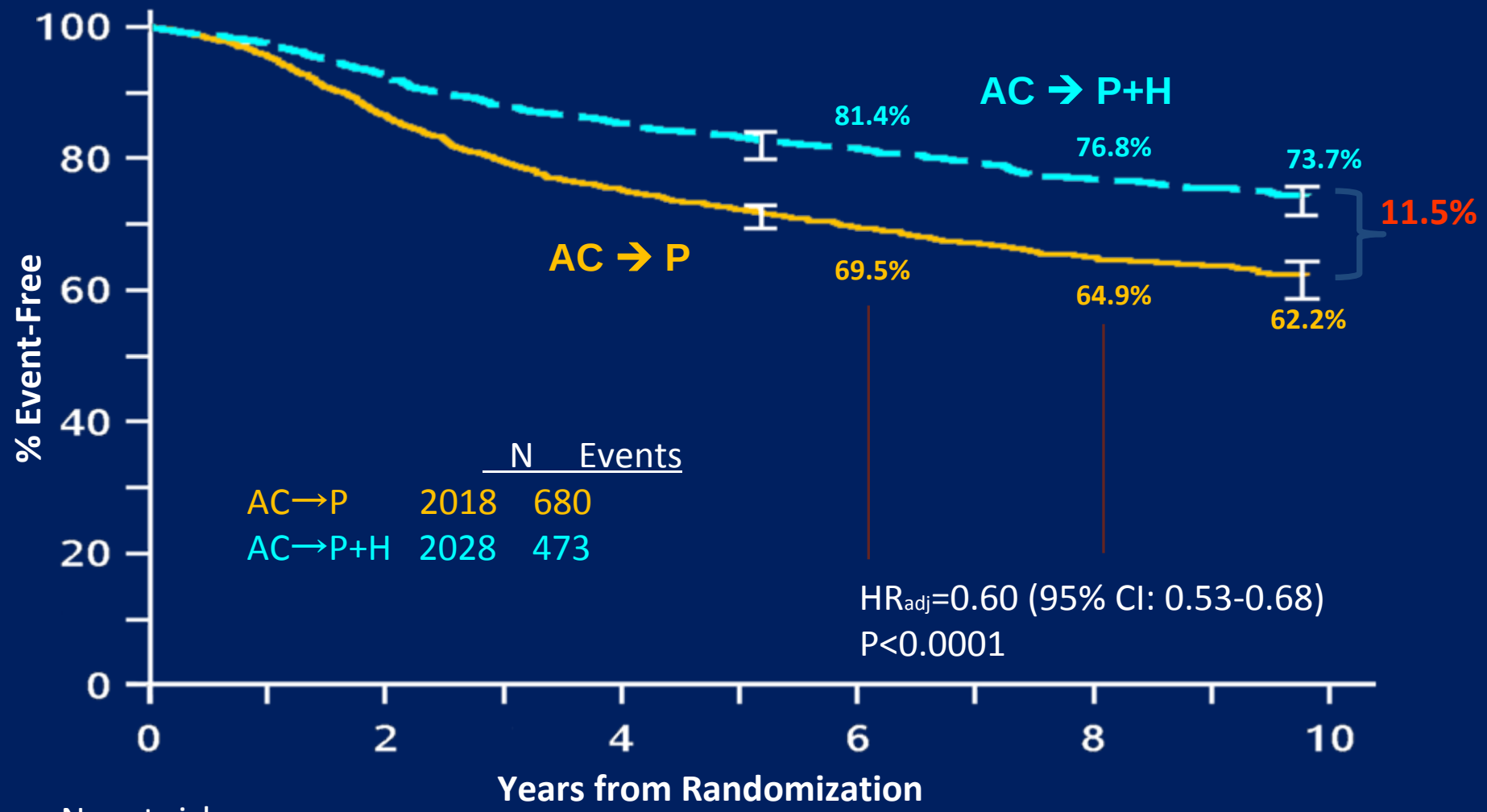
Drug (n)	Regimen	DFS		
		HR	Relative Risk Reduction	Absolute Difference
Paclitaxel 3170	AC vs. AC+T	0.78	22%	5% (5-yr)
Trastuzumab 3752 3386 2148 2147	AC→ T+/-H Chemo→+/-H TCH vs AC→ T AC→ T+/-H	0.48 0.54 0.67 0.60	52% 46% 33% 40%	12% (4-yr) 6.4% (4-yr) 6% (5-yr) 9% (5-yr)
Docetaxel 1491	TAC vs FAC	0.74	26%	7% (5-yr)
Epirubicin 716	CEF vs CMF	0.76	24%	9% (5-yr)
Anastrozole 6241	Ana vs Tam	0.87	13%	2.8% (5-yr)
Letrozole 5100	Let vs Tam	0.62	38%	4.6% (4-yr)
Exemestane 4724	Exe vs Tam	0.69	31%	3.4% (5-yr)

What magnitude of improvement in EFS should be considered clinically meaningful?



What is the feasibility of improving EFS in HER 2-positive breast cancer, where the EFS improvement is already high?

N9831/B-31 Disease-Free Survival



No. at risk

2028	1959	1848	1747	1675	1611	1514	1293	910	619	350
2018	1887	1689	1529	1423	1329	1232	1027	705	449	255

EH Romond et al SABCS 2012

Thank You!

Acknowledgments

- All patients who made this study possible
- Co-authors and all investigators participating in these trials
- All participating biostatisticians
- All participating cooperative groups
- NCI
- FDA staff involved in this project
- CDER Center Director

Panel Discussion

- Should pCR be considered reasonably likely to predict for clinical benefit?
- How should “high-risk” be defined for regulatory purposes in designing neoadjuvant trials intending to use pathologic complete response (pCR) to support an accelerated approval?
- What absolute risk of relapse should be considered “high-risk” for regulatory purposes?
- What magnitude of improvement in EFS should be considered clinically meaningful?
- What is the feasibility of improving EFS in HER 2-positive breast cancer, where the EFS improvement is already high?