A Bayesian Approach for Neoadjuvant/Adjuvant Oncology Trial

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Acknowledgement

- Inspiration of the Work
  - Bayesian Frame Work: ISPYII/III
  - 2-in-1 Study Design proposed by Co-author Cong Chen et al.

We also appreciate Yang Wang's (ex-Merck colleague) support on this work

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Outline

- Background and Introduction
  - Therapy development
  - Clinical Background
  - FDA Guidance on Early-Stage Breast Cancer
- Motivation Examples in Her2+ BC
- Meta-analysis
  - Relationship of pCR vs. EFS/DFS/OS
- Bayesian Framework
- Implementing 2-in-1design
- Summary

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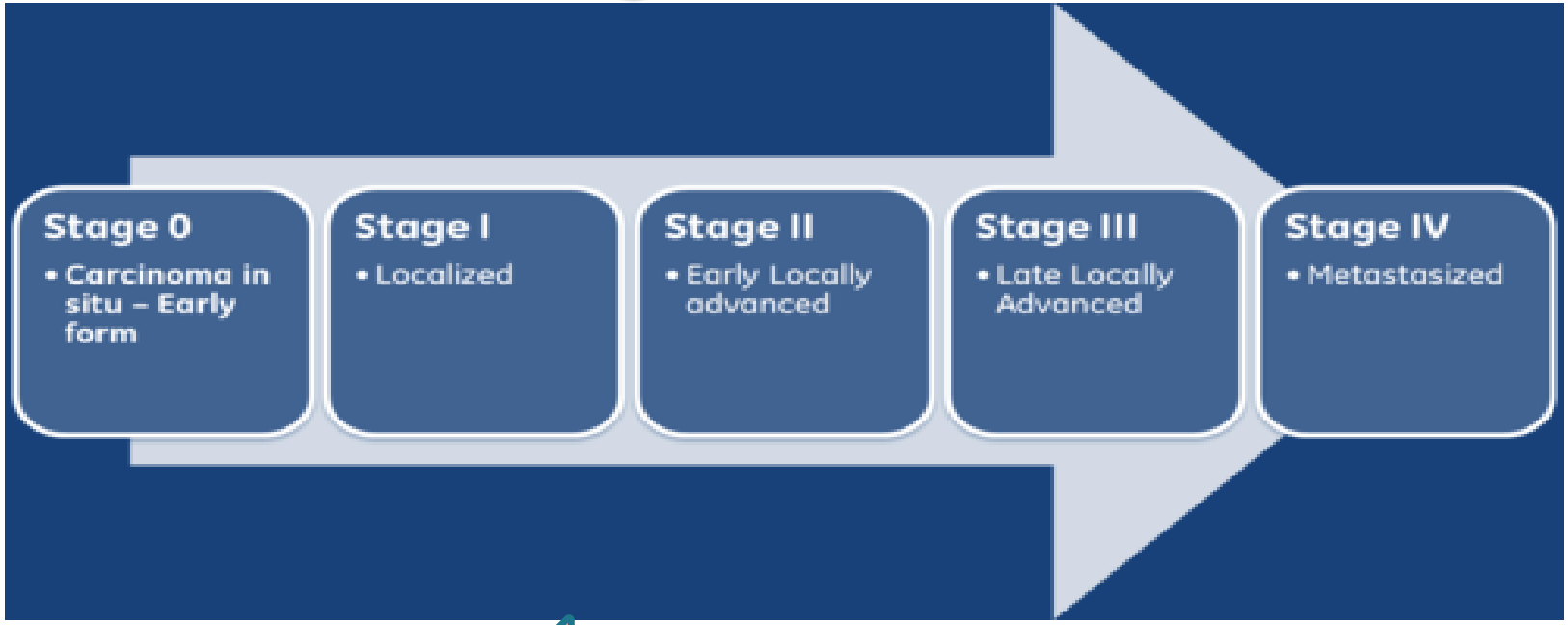
Therapy Development vs. Disease Progression



Early Stage Definitive Tx (Neoadjuvant/Adjuvant)

Recurrent and Metastatic Palliative Tx

Treatment Development

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Neoadjuvant/Adjuvant Therapy

- Neoadjuvant therapy: Medicines administered before surgery for the treatment of cancer. It may be recommended based on tumor size (T) and/or lymph node status (N).
- Adjuvant (meaning “in addition to”) therapy: Medicines administered after surgery. It is designed to prevent recurrence of the disease, particularly distant recurrence.

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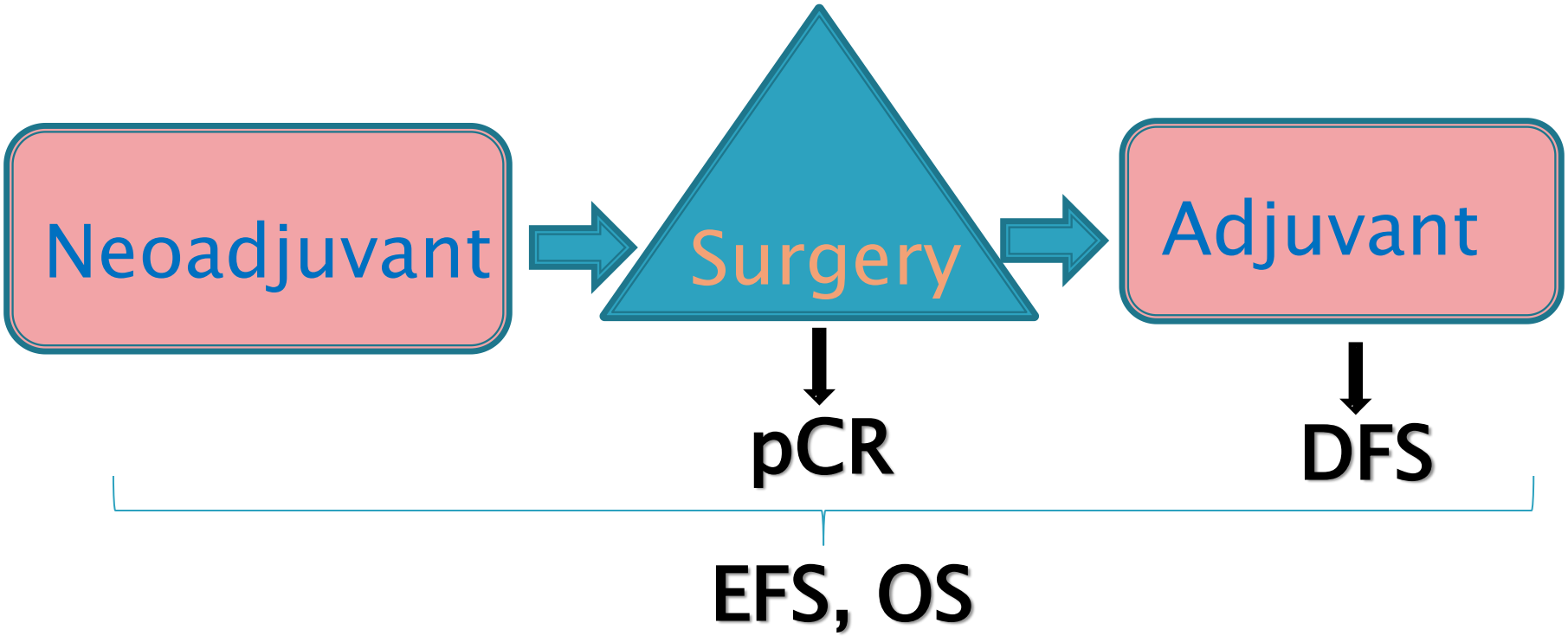
Neoadjuvant/Adjuvant Therapy--Clinical Endpoints



pCR: Pathological complete response; DFS: disease-free survival; EFS: event-free survival

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CTNeoBC Pool Analysis: pCR: Surrogate Endpoint for EFS and OS

- 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 Definition	Event-Free Survival HR (95% CI)	Overall Survival HR (95% CI)
ypT0 ypN0	0.44 (0.39-0.51)	0.36 (0.30-0.44)
ypT0/is ypN0	0.48 (0.43-0.54)	0.36 (0.31-0.42)
ypT0/is	0.60 (0.55-0.66)	0.51 (0.45-0.58)

Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-72.

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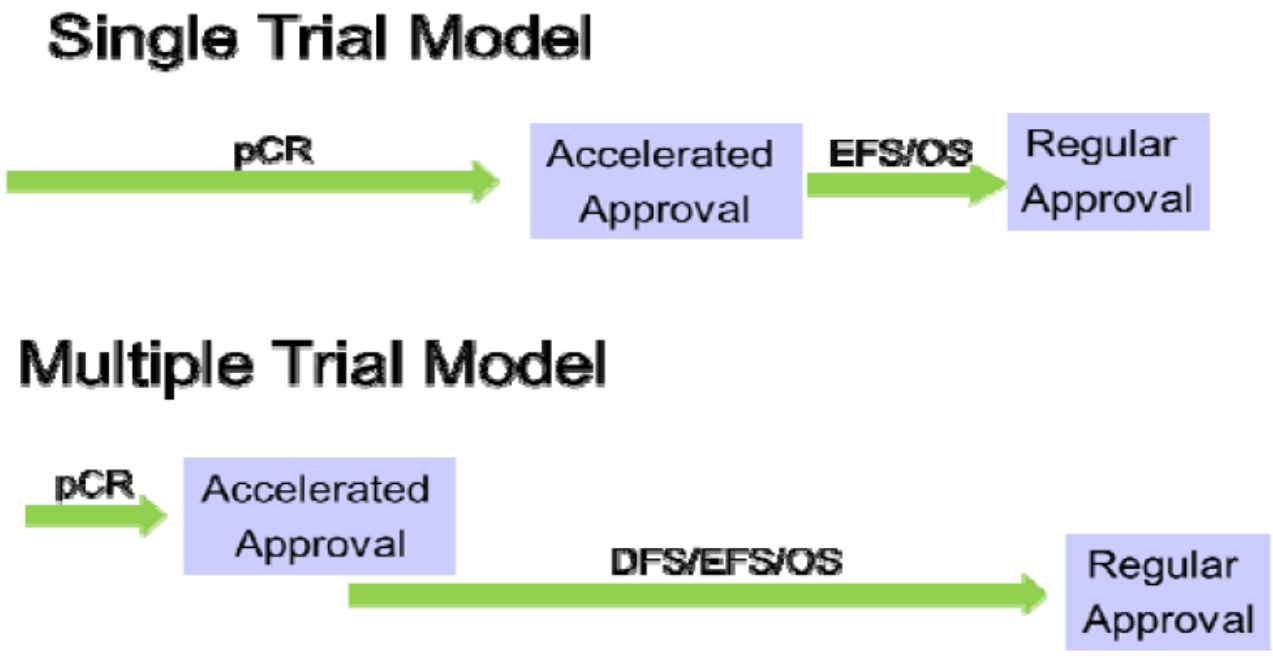
FDA Guidance for Accelerated Approval (AA)-- A Breast Cancer Example

cancer over the past few decades, there remains a significant unmet medical need for certain high-risk or poor prognosis subsets of early-stage breast cancer patients. Developing highly effective new drugs for these populations is a priority of the FDA. It is our hope that considering pCR as an endpoint for accelerated approval in the neoadjuvant setting will encourage industry innovation and expedite the development of novel therapies to treat high-risk early-stage breast cancer.



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Multi-Trial Model: Examples in Early Her2+ Breast Cancer

Neoadjuvant Study			Adjuvant Study		
Study	**Trt**	**ΔpCR (%)**	**Study**	**Trt**	**3 (4.5) yr IDFS (%) & HR**
NeoSphere (2012) N=~420 Ph II	PTH vs. TH	~16.8%	APHINITY (2017) N=4800 Ph III	PHC vs. HC	94.1% vs. 93.2% HR=0.81 (p=0.045)
NeoALTTO (2012) N=~455 Ph III	Lap+H vs. H	~19.3%	ALTTO 2016 N=8381 Ph III	Lap+ H vs. H	88% vs. 86% HR=0.84 (p=0.048*)

- Pertuzumab: AA approval of neoadjuvant Her2+ in 2013 (w/ mHer2+ data in CLEOPATRA)
- In Sep 2017, FDA grants Priority Review for Perjeta (pertuzumab) based on APHINITY

T=docetaxel, H=trastuzumab, P=pertuzumab, C=chemotherapy, Lap=Lapatinib

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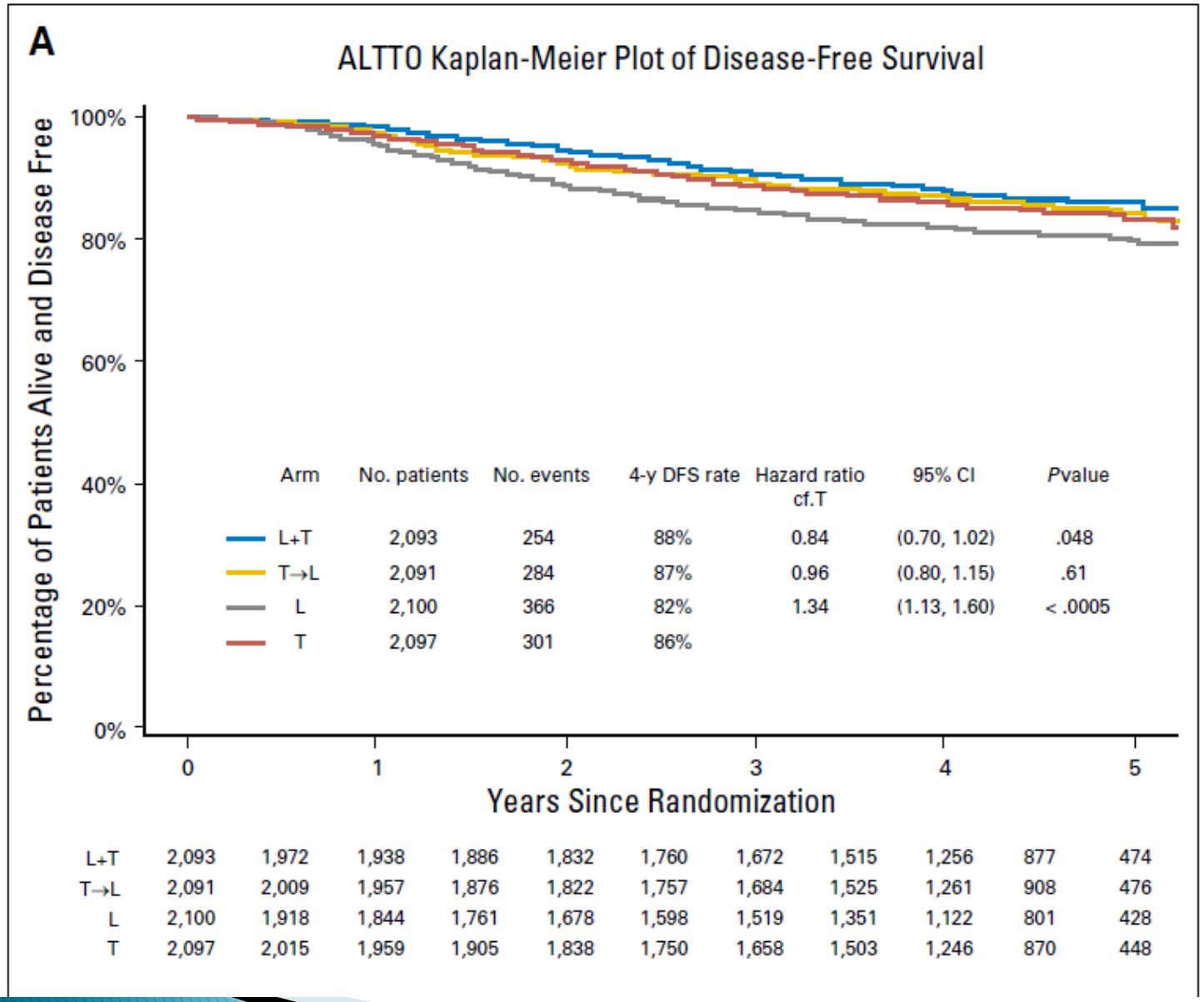

Fig 2. (A) Kaplan-Meier of DFS intention-to-treat population for study arms. (B) Kaplan-Meier of O intention-to-treat population for study arms. ALTTO, Adjuvant L

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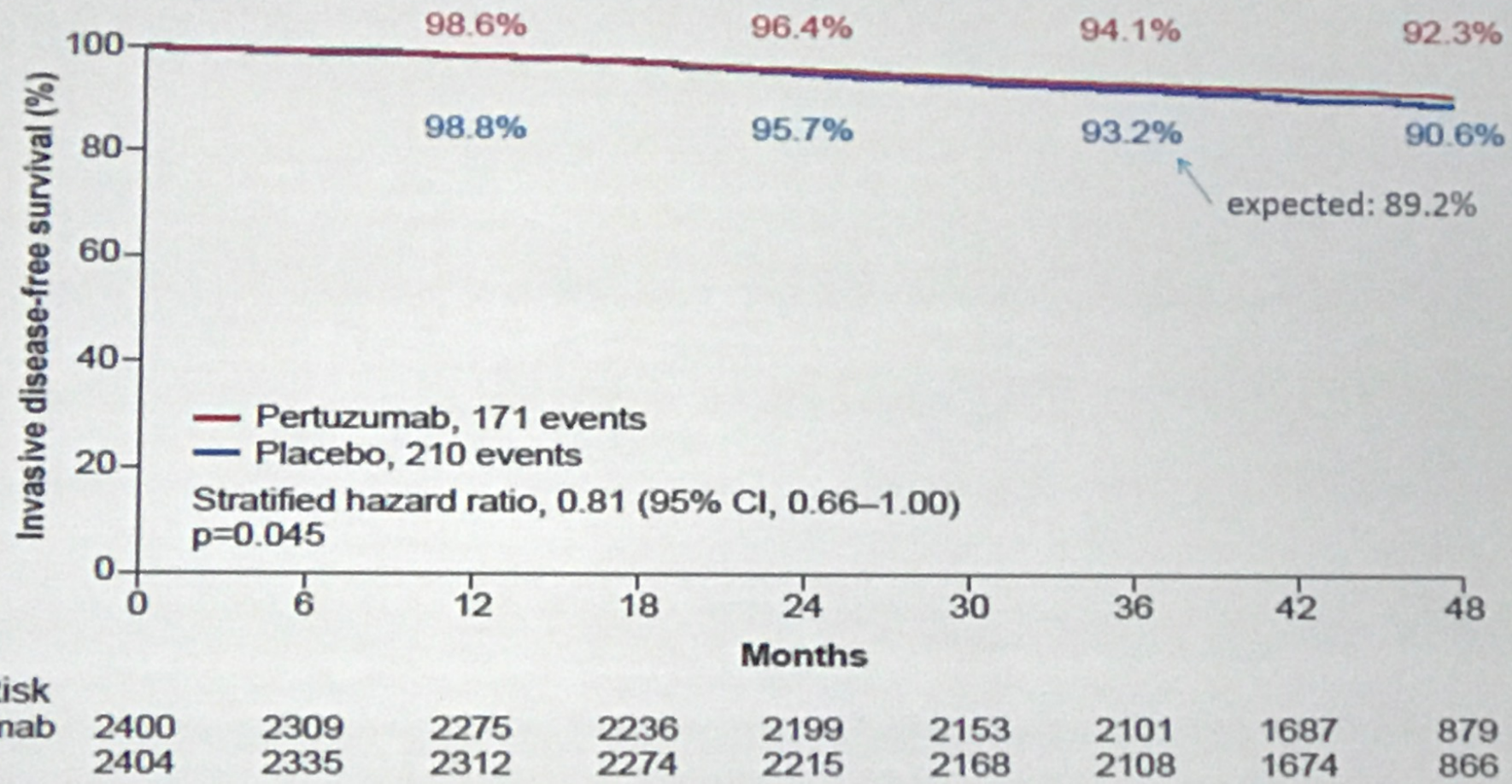
ITY: Intent-to-Treat Primary Endpoint Analysis
Invasive Disease-free Survival



isk									
nab	2400	2309	2275	2236	2199	2153	2101	1687	879
	2404	2335	2312	2274	2215	2168	2108	1674	866

mission required for reuse

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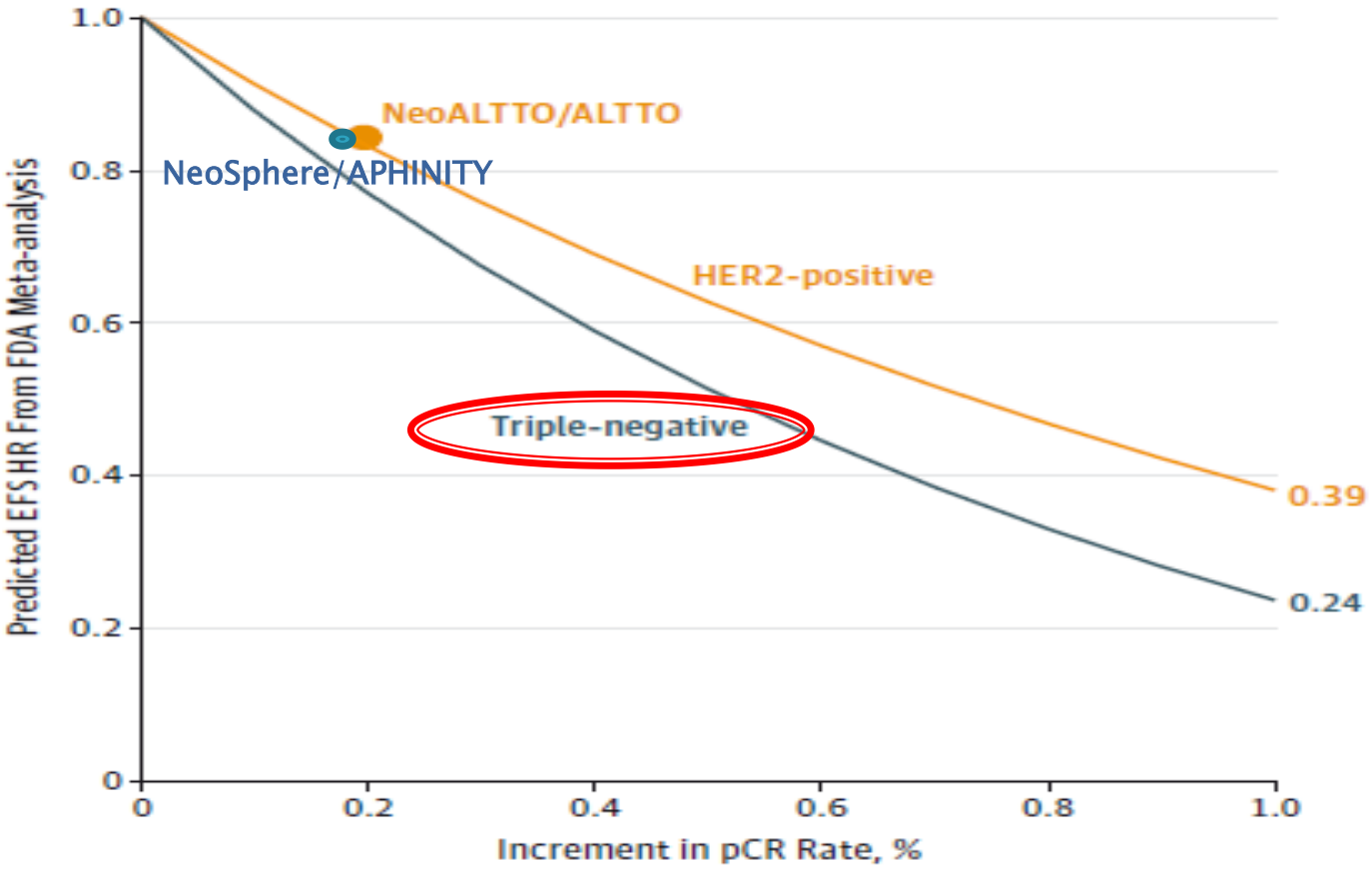
Neoadjuvant Therapy in Breast Cancer as a Basis for Drug Approval

By Don Barry Based on Cortazar 2014 meta-analysis

Figure. Association Between Incremental Improvement in Pathologic Complete Response (pCR) Rate and Event-Free Survival Hazard Ratio (EFS HR) for Experimental Arm in Comparison With Control



We calculated the 2 curves in this graph based on the results in the FDA's meta-analysis: one curve applies for triple-negative disease and the other for

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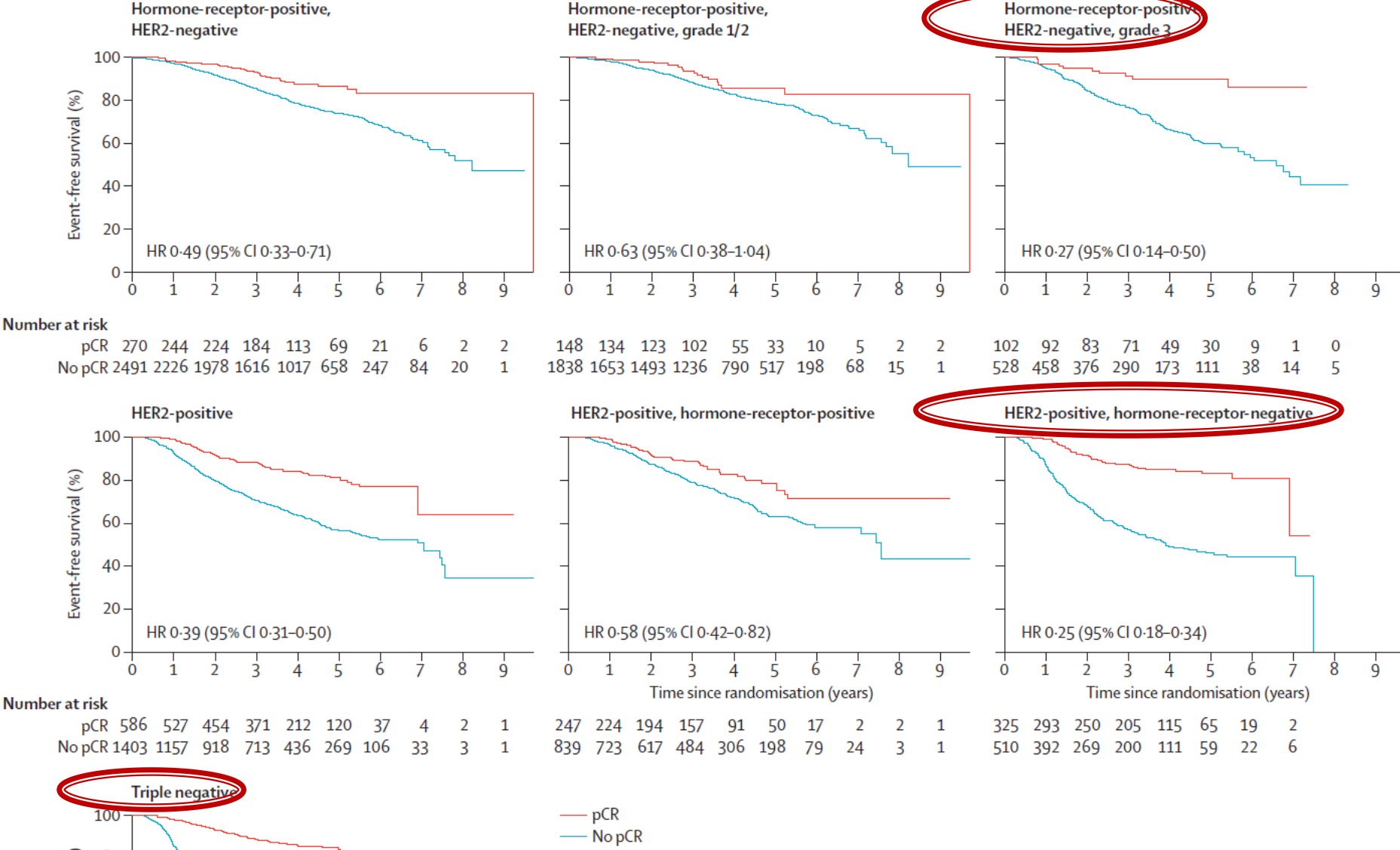

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Era after ALTTO and APHINITY

- Uncertainty of observation from pCR improvement
- Huge sample size of adjuvant study in multi-trial model after AA (successful neoadjuvant trials)
- Long term survival results in adjuvant study on the boundary (disappointing after tremendous cost and long time waiting)

How to mitigate the risk ??

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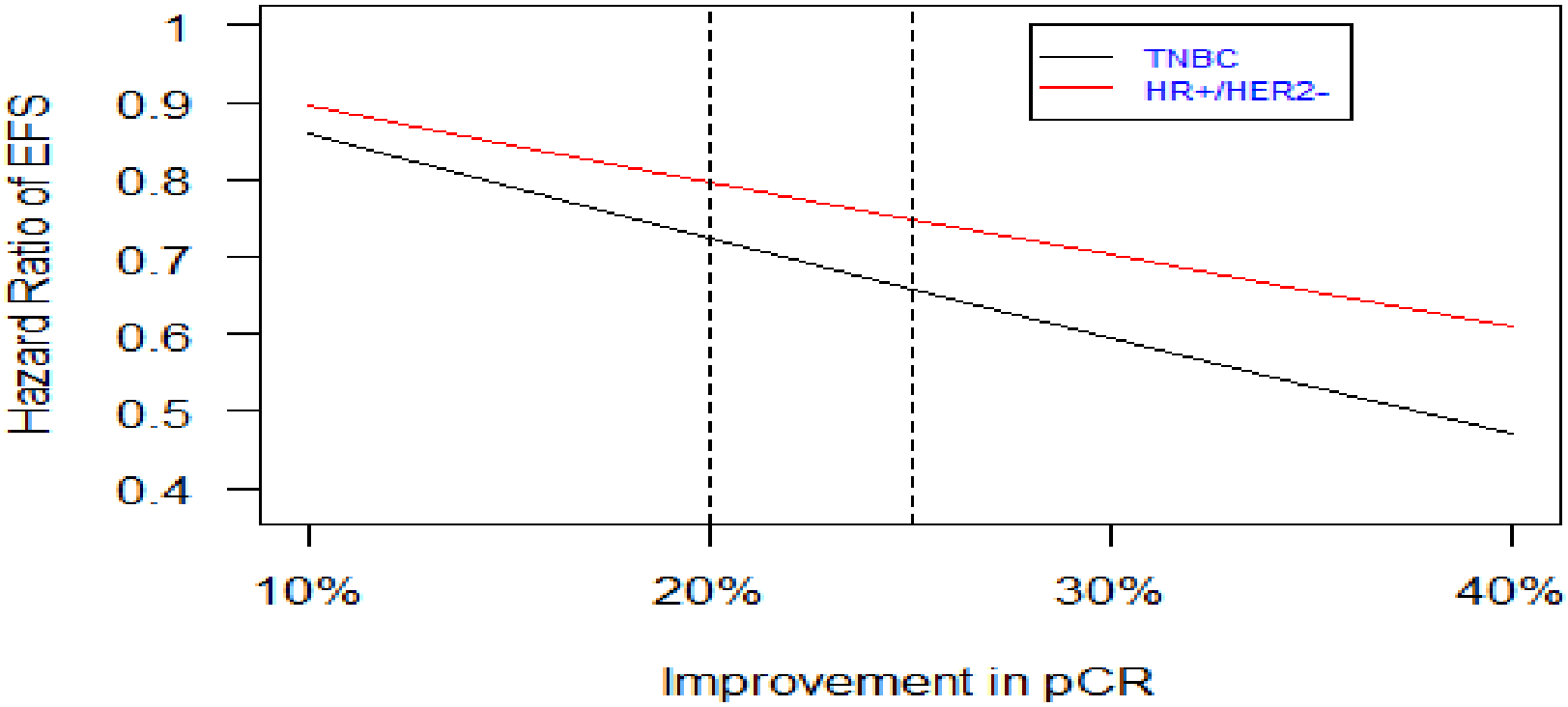
The Association of pCR improvement vs. EFS HR in TNBC (ref. Cortazar 2014)



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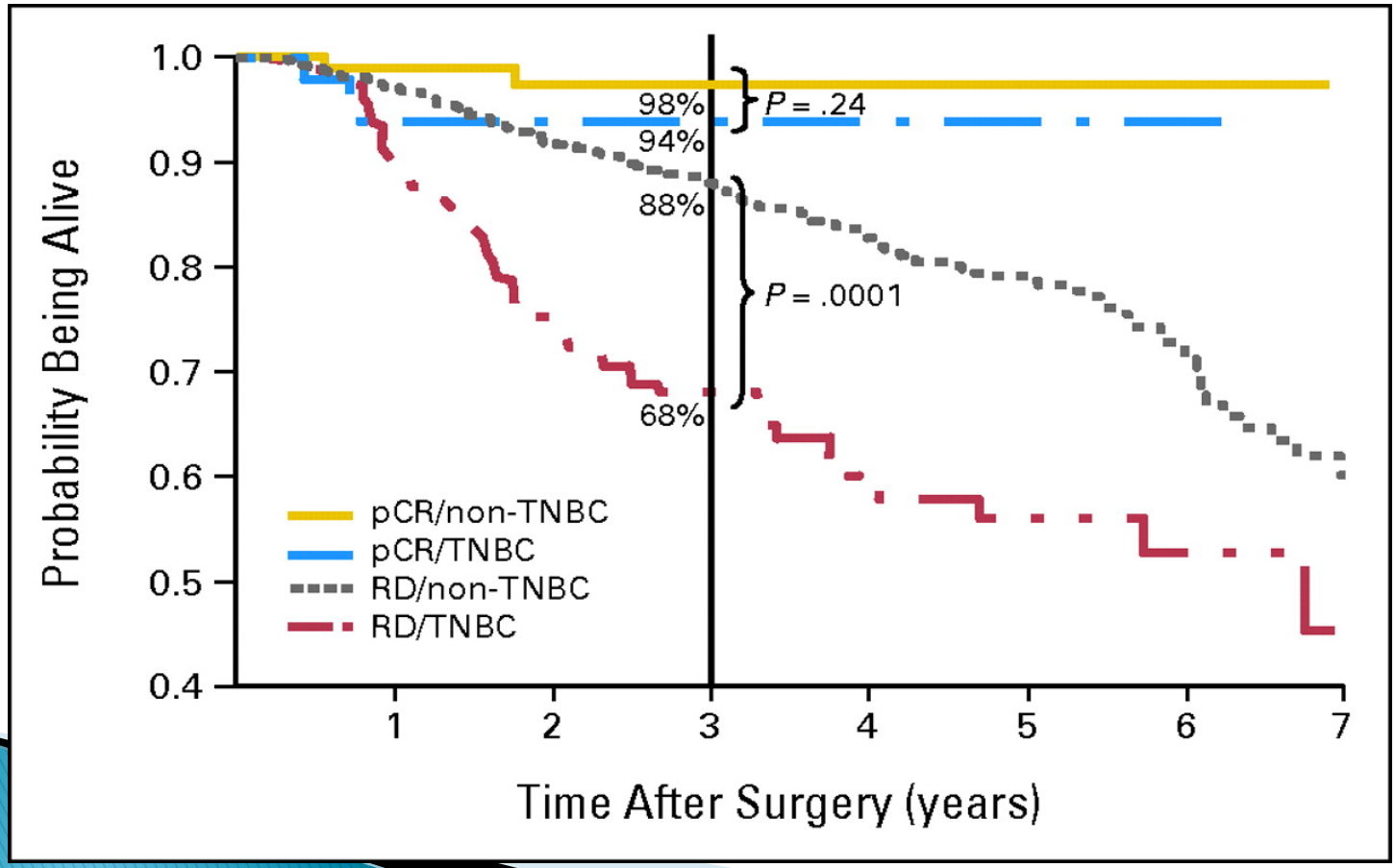
The Association between pCR and Longer Term Survival is Stronger in Triple Negative BC than other subtypes



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Neoadjuvant/Adjuvant Development Strategy

- Single-Study over Multiple-Study Model
  - Improved study rigorous and data integrity
  - Shorter development period
- pCR and EFS as dual-primary for **2-in-1** Design
- pCR for Accelerated Approval (Phase II Part) and EFS for Final Approval (Phase III Part)
- Focus on the cancer subtype which has highest correlation between pCR and EFS
- Go/NoGo Decision-Making Based on Bayesian Predictive Power

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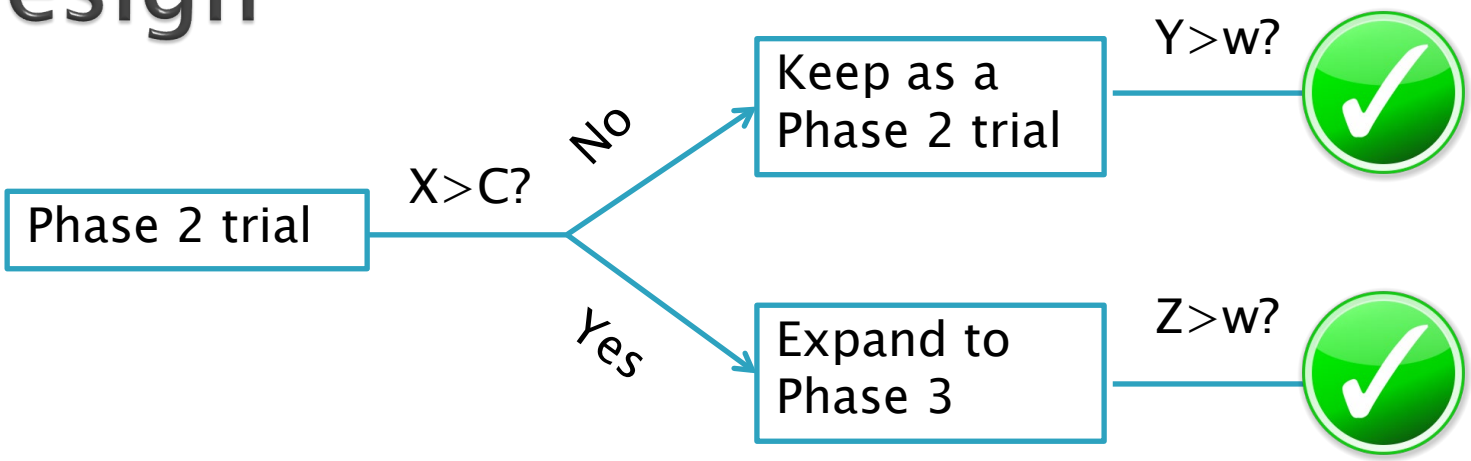
Introducing A Generic 2-in-1 Design



- The three endpoints that the standardized test statistics are based upon can be different from each other
- No penalty needs to be paid for multiplicity control as long as the correlations for the 3 test statistics satisfy $\rho_{XY} \geq \rho_{XZ}$
  - i.e., w=1.96 to keep overall Type I error at 0.025

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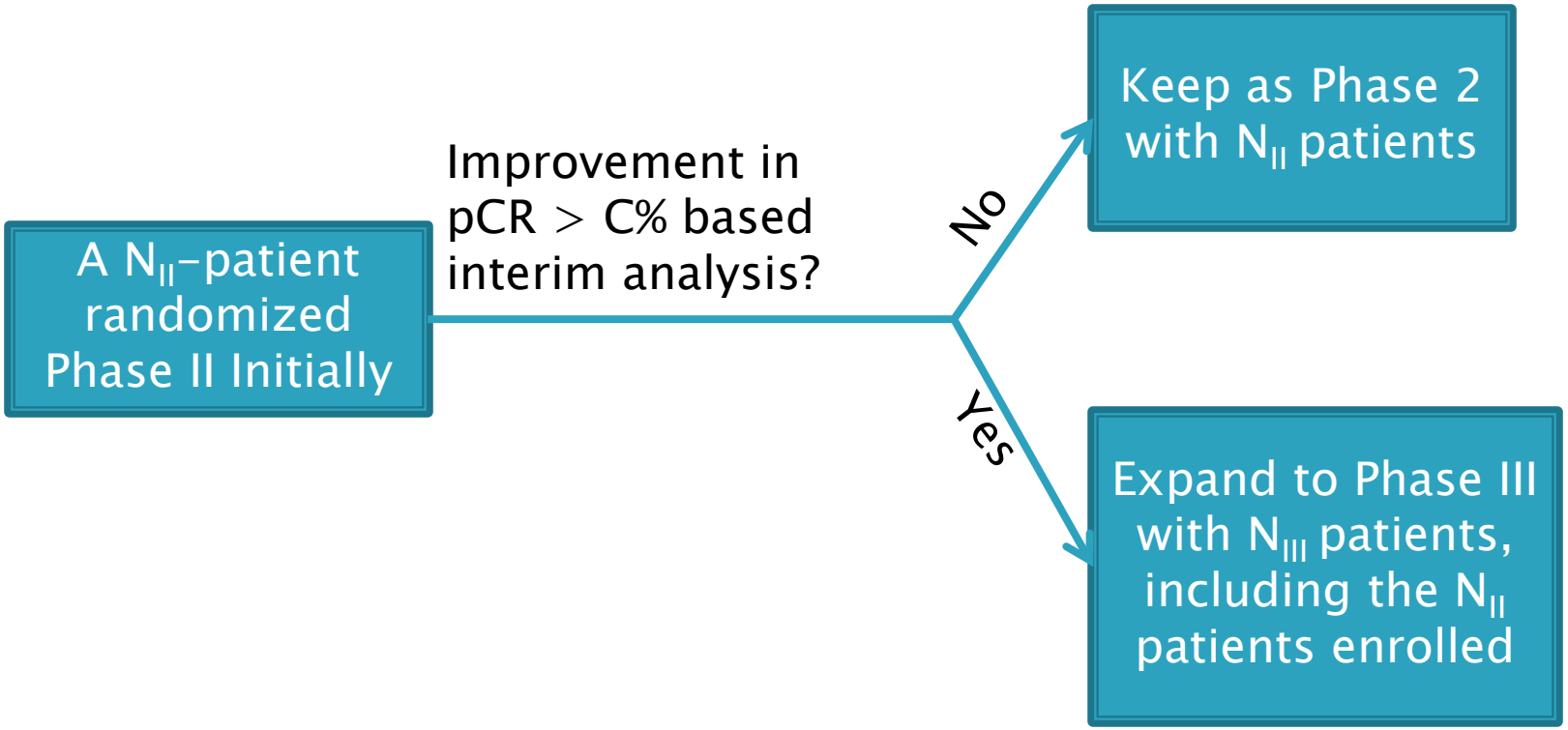
Single-Trial Model: 2-in-1 Design



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Bayesian Predictive Power

- Consider Dual-primary pCR (X) and EFS (Z) follows a bivariate asymptotic normal distribution:
  - $\begin{pmatrix} X \\ Z \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_x \\ \mu_z \end{pmatrix}, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}\right)$
- Correlation model between pCR and EFS:
  - $HR_{n^{th}}(\Delta_{pCR}) = log(R_{n^{th}}(p0 + \Delta_{pCR}) + nR_{n^{th}}(1 - (p0 + \Delta_{pCR})))/ log(R_{n^{th}} * p0 + nR_{n^{th}}(1 - p0))$
  - Derive μ_z, ρ based on the above model
- Calculate phase III power based on Survival endpoint: $HR_{n^{th}}(\Delta_{pCR})$
- Predictive probability is obtained by repeating the above procedure

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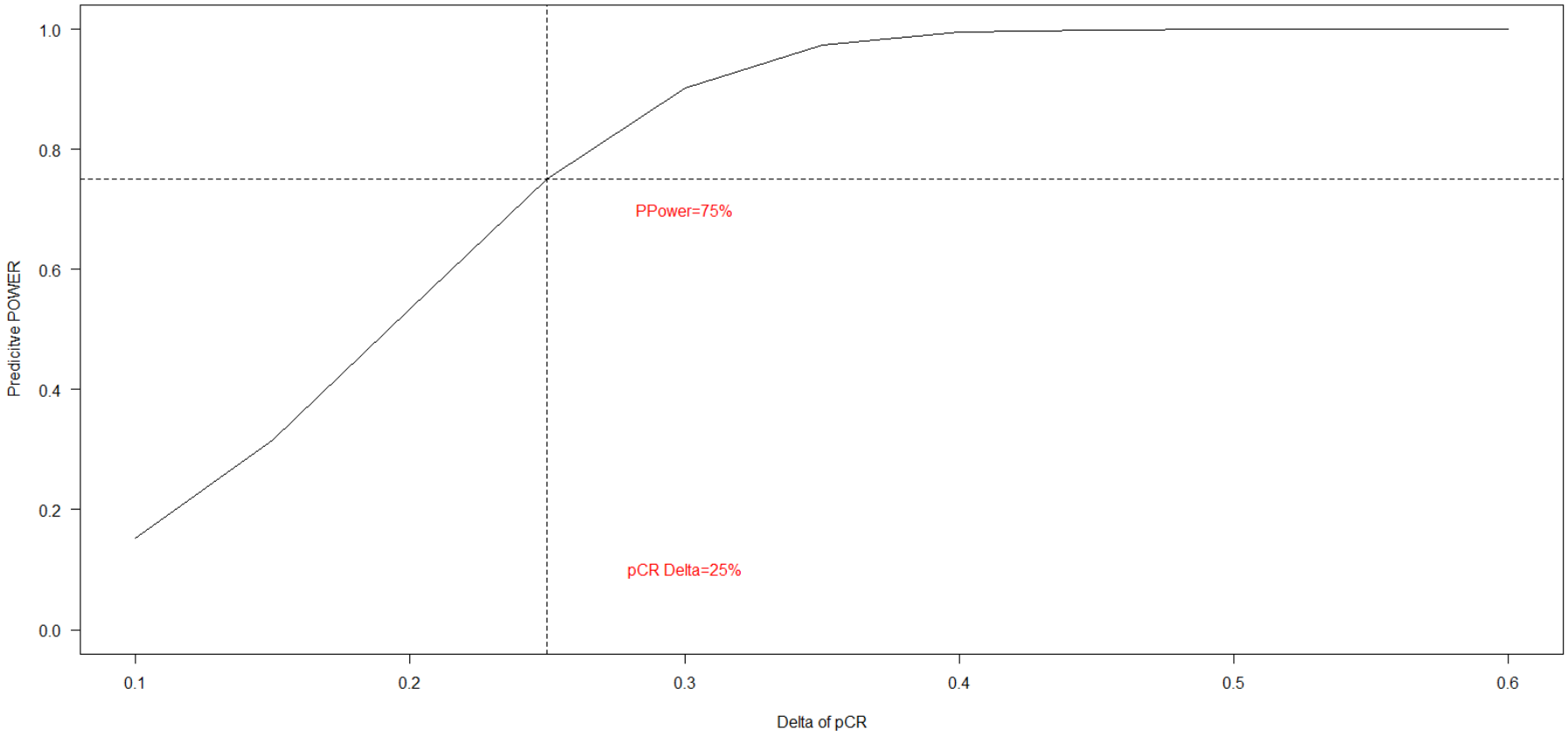
pCR Improvement vs. Phase III Study Predictive Power (N_{sim}=10000)



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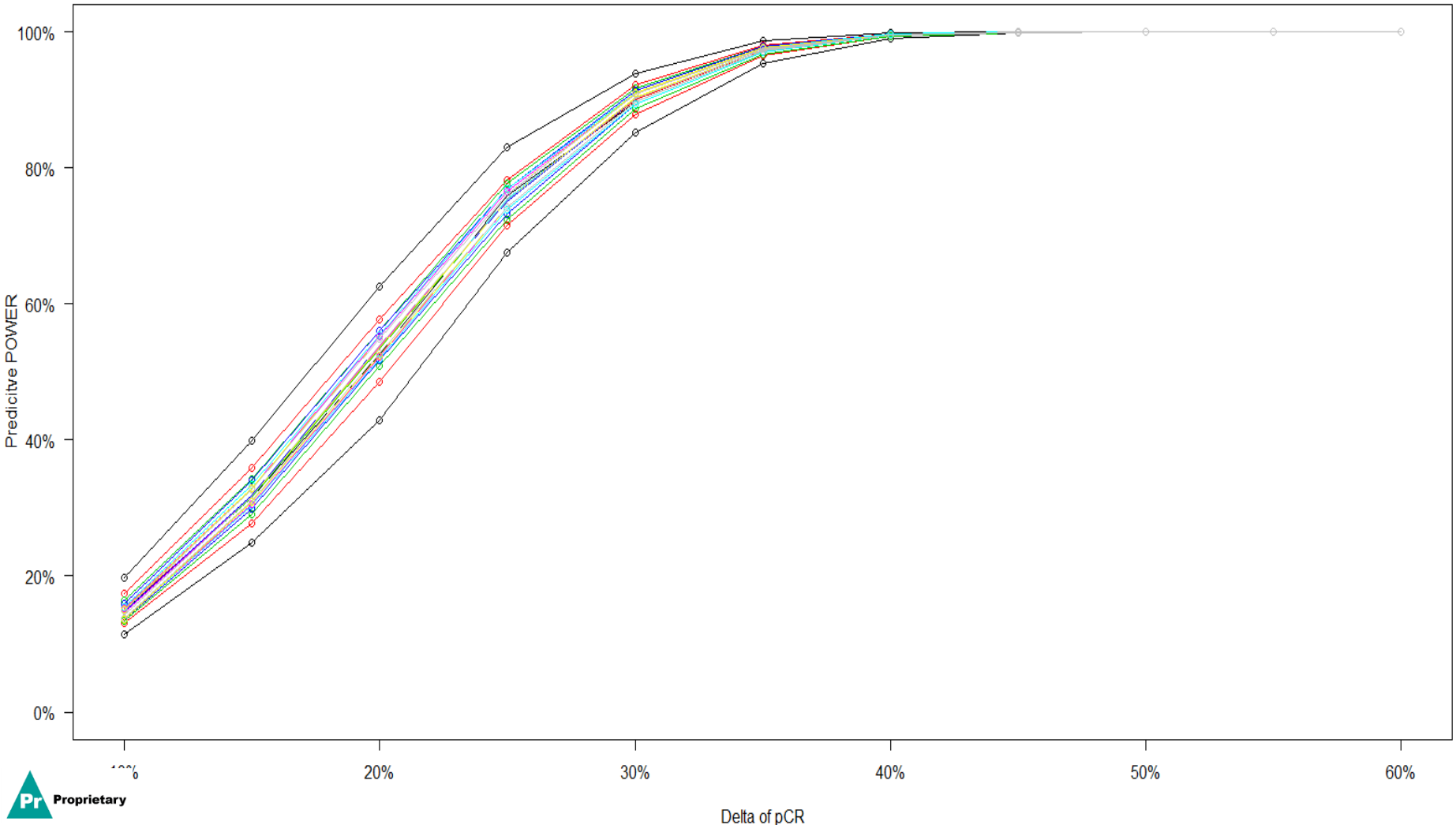
Predictive Power w/ 90% Band by diff. N of pCR size.



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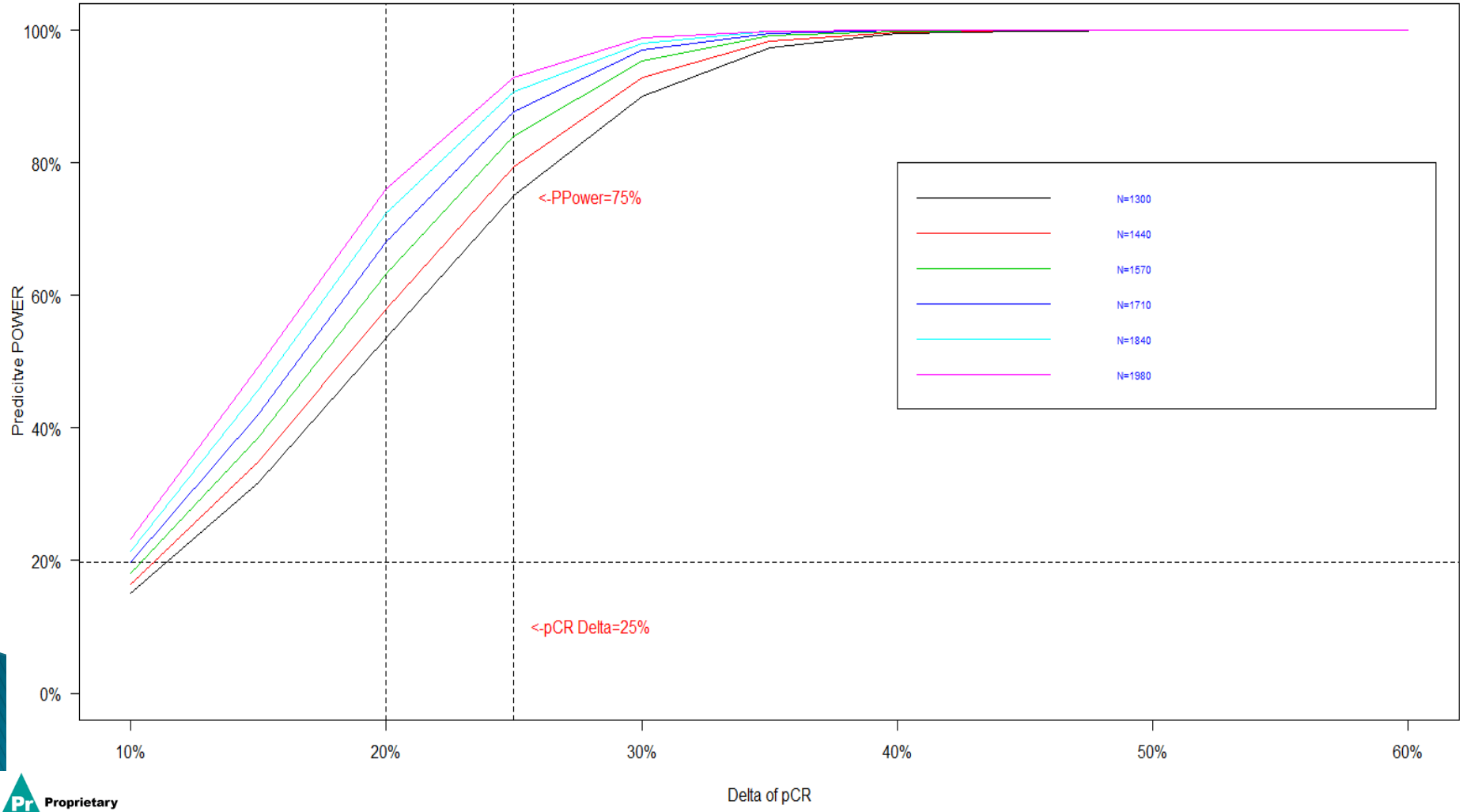
pCR Improvement vs. Predictive Power w/ Diff. size of Phase III



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2-in-1 Design vs. Traditional Ph III

- Reduced false positive: reduce the chance of a failed phase III study due to insufficient sample size to properly power the EFS endpoint
- More informed decision at "Go/No-go" point with actual observed pCR improvement
- Increased false negative: uncertainty in new therapy if EFS effect size of new therapy is better than reported in FDA pooled analysis (CTNeoBC: chemo)
- Operationally, additional sites are not initiated until after an expansion decision is made

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Go-NoGo Decision Making

A higher cutoff C (i.e. larger pCR improvement) in the Go/No-go decision

- More confidence in the Phase III outcome with "Go decision"
- Better chance of getting accelerated approval (AA) with pCR
- Trial could be stopped for efficacy at early Interims of EFS endpoint by building GSD property
- Increased the chance of No-go decision

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Go-NoGo Decision Making

After No-go decision: plan additional adjuvant study (as opposed to no follow-up study)

- Informed decision on study design and sample size based on phase II portion:
  - additional adjuvant study (as opposed to no follow-up study) ➔ multi-study model
  - a full approval (FA) potential
- A much larger study with moderate pCR improvement
- Due to moderate pCR, it has lower probability of AA and requires prolonged follow up of DFS to see a treatment effect.

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Benefit vs. Risk Assessment

- Due to huge investment on a large phase III study with lack of phase II data to support decision making
- The benefit of **2-in-1** design may get reduced if enrollment is too fast while waiting for Go/No-go decision.
- A proper cutoff of C is critical with the help of the relationship between predictive power of EFS vs. C% pCR improvement
  - Operating characteristics (OC) evaluation by simulation
- Depending on the observed pCR improvement, and additional data accumulated externally, predictive power incorporated from the observed pCR may guide the decision.

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Backup

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Proof of Type I Error Control

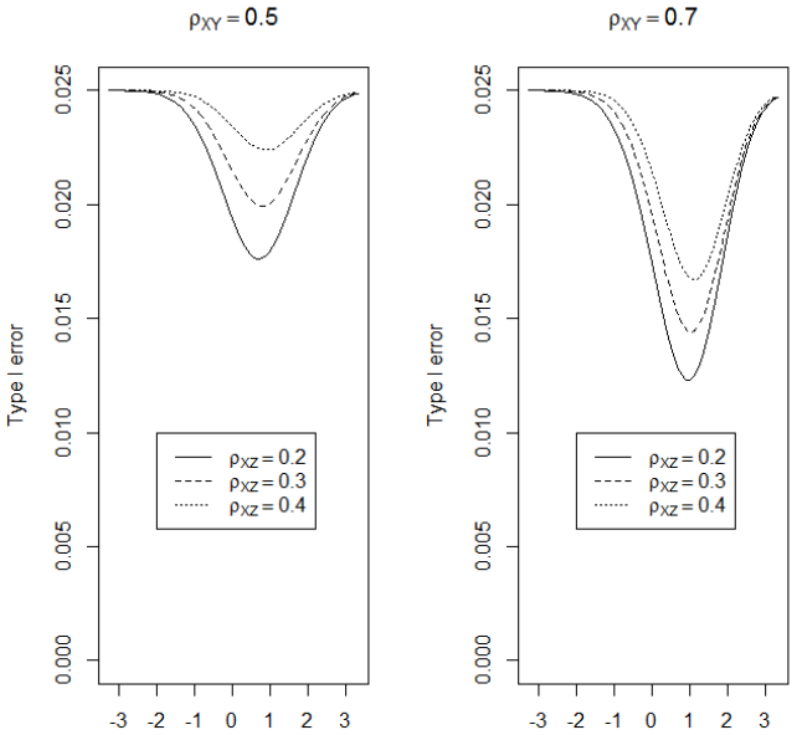
Given that bivariate normal quadrant increases with correlation coefficient, we have the following:

$$\Pr(X<C,\ Y>Z_{1-\alpha})+\Pr(X\geq C,\ Z>Z_{1-\alpha})$$

$$\leq \Pr(X<C,\ Y>Z_{1-\alpha})+\Pr(X\geq C,\ Y>Z_{1-\alpha})$$

$$=\Pr(Y>Z_{1-\alpha})$$

$$=\alpha$$



No assumption is made about E{X} under null hypothesis for Y and Z

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