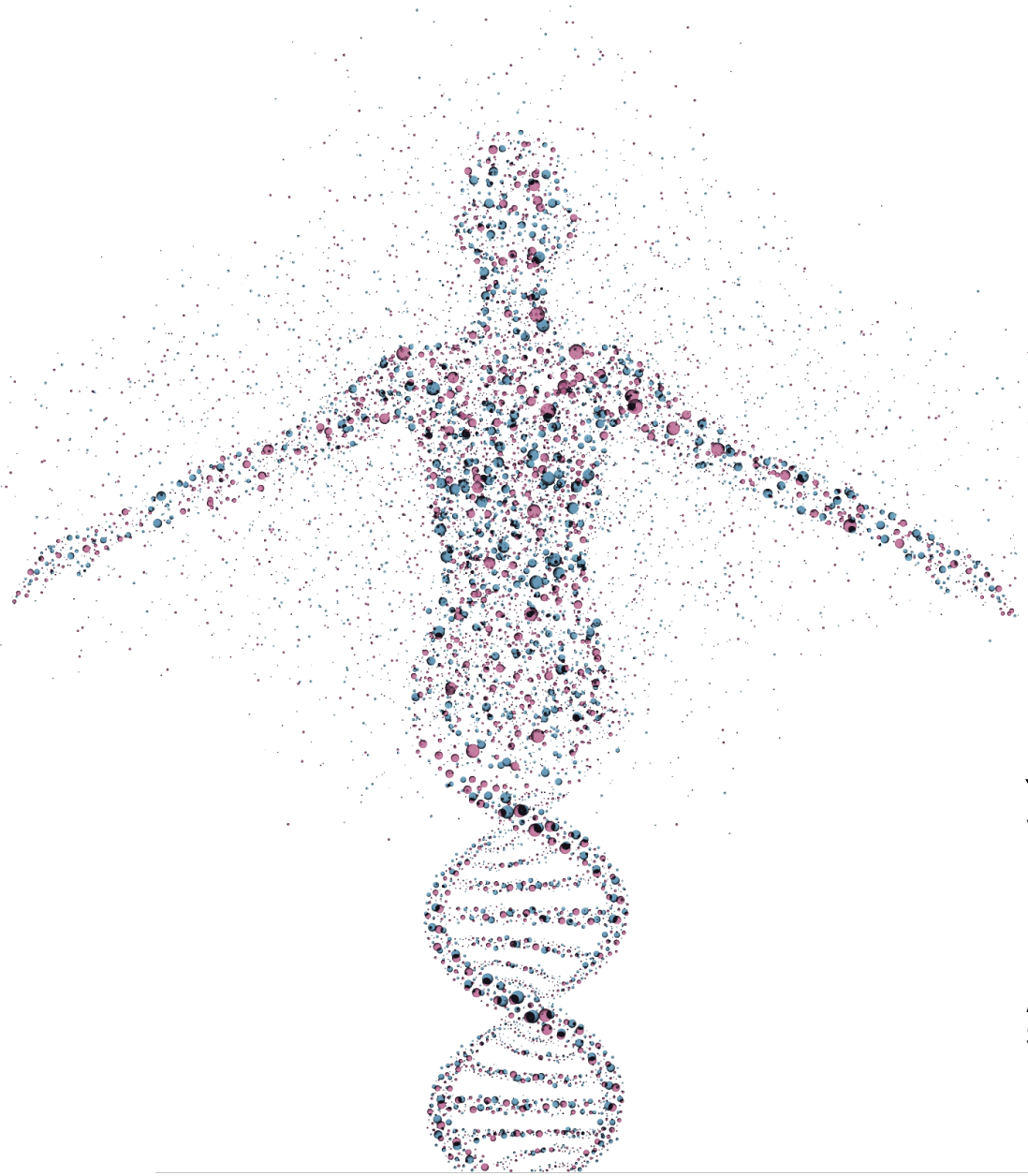
I have no financial relationship(s) with commercial interests to disclose.



Pathological Complete Response Predicts Event-Free and Distant Disease Free Survival in the I-SPY 2 TRIAL

Douglas Yee, MD
Masonic Cancer Center, University of Minnesota

On behalf of I-SPY2 Investigators and authors:

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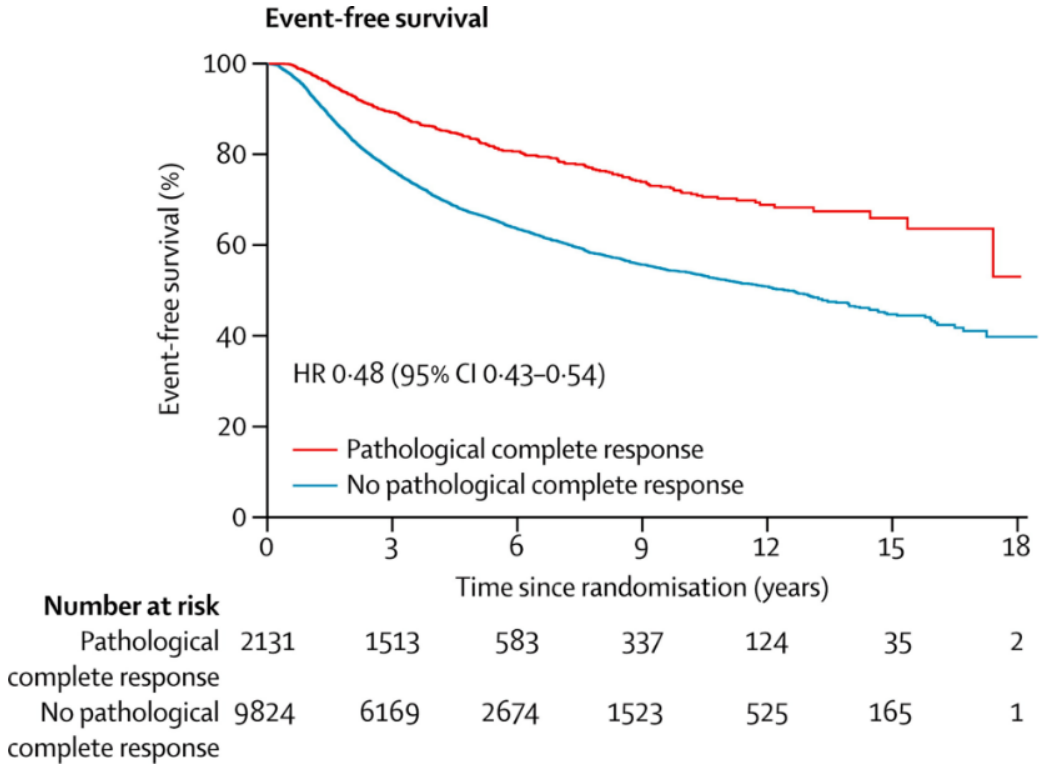
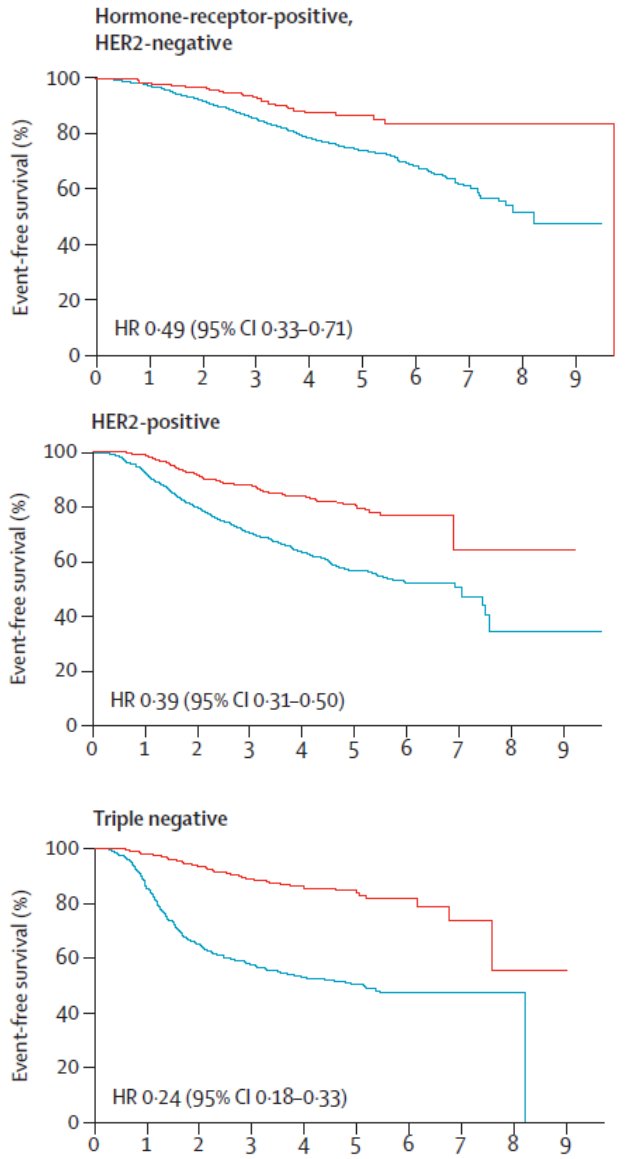
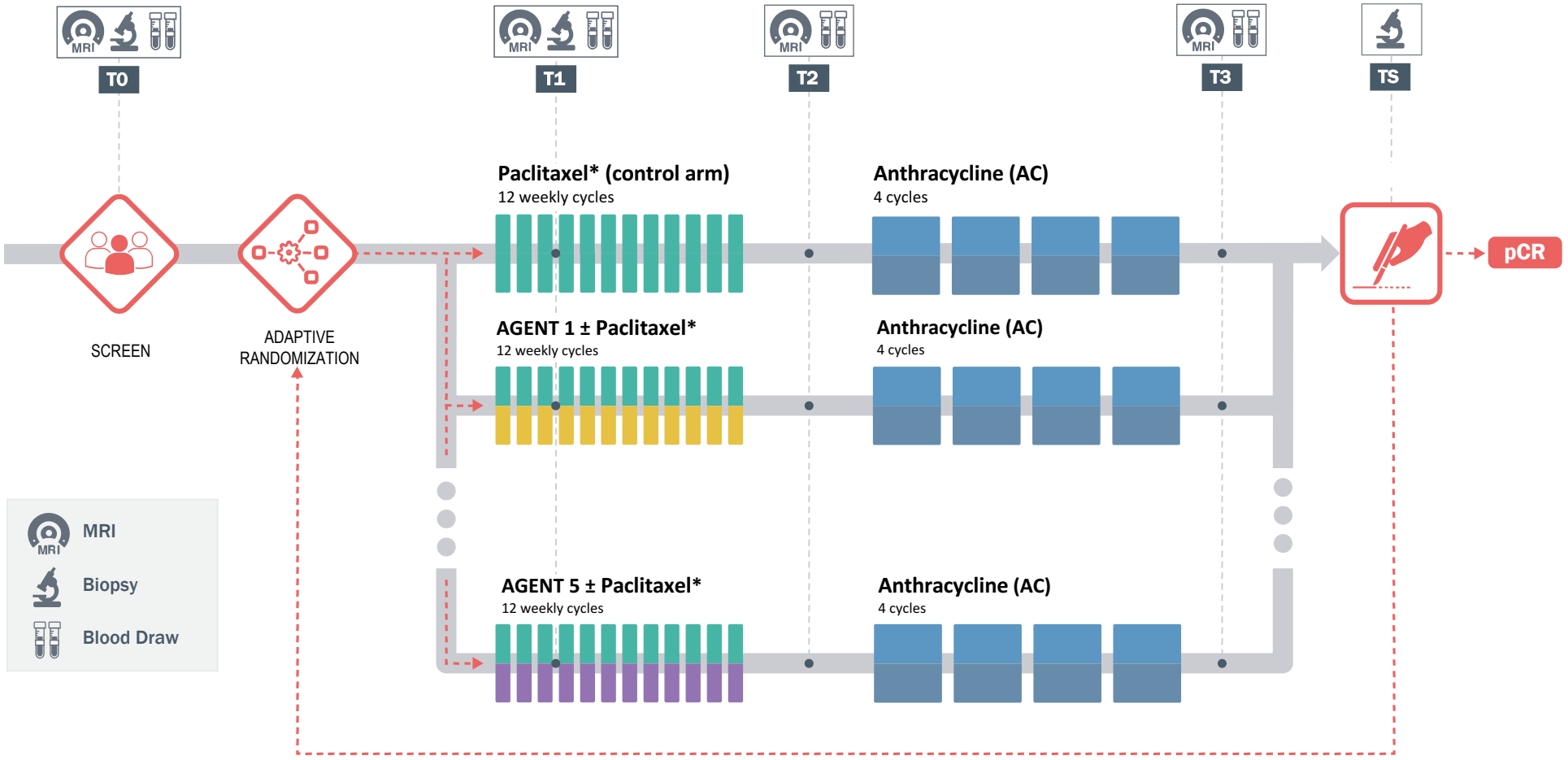
pCR and EFS

- FDA Meta Analysis (Cortazar et al, Lancet 2014)
  - >11K patients from 12 neoadjuvant trials
  - Median follow-up for EFS: 5.4 years





Study Design



HR+/HER2- patients with low-risk MammaPrint Scores are not enrolled in I-SPY2

Analysis

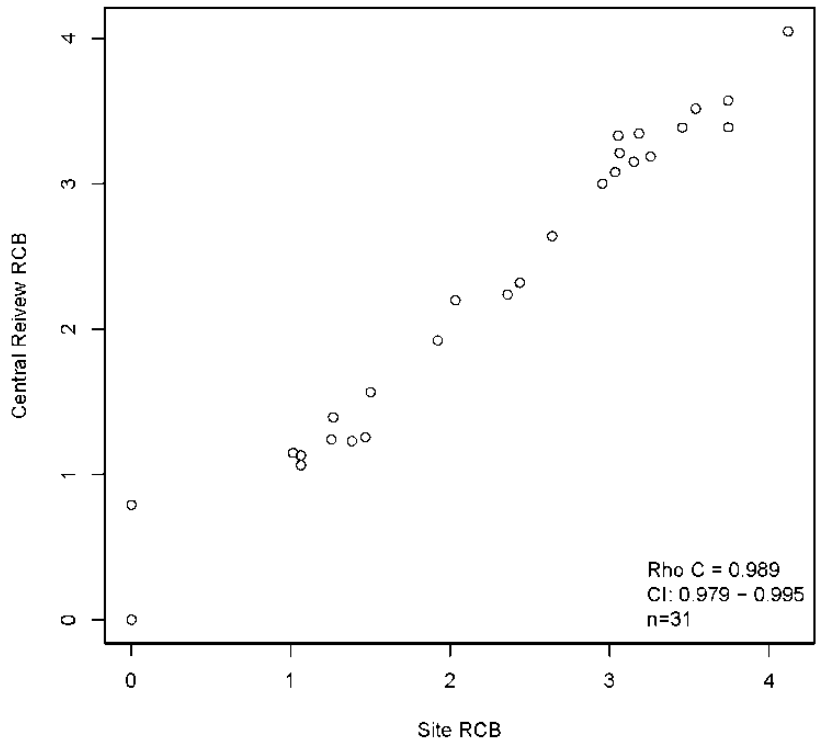
- **Primary Endpoint:**
  - Pathological complete response (pCR)
  - Defined as no residual invasive cancer in breast or lymph nodes
  - Assessed using the Residual Cancer Burden (RCB) method*
  - Highly reproducible between local and central pathologist review

- **Intent-to-treat:**
  - Patients who did not complete assigned therapy are considered non-pCR (withdrew, left the institution, received non-protocol therapy, or progressed).

- **Secondary endpoints:**
  - RCB
  - EFS

- **I-SPY 2 To Date**
  - >1000 patients completed surgery
  - 11 investigational agents/combinations

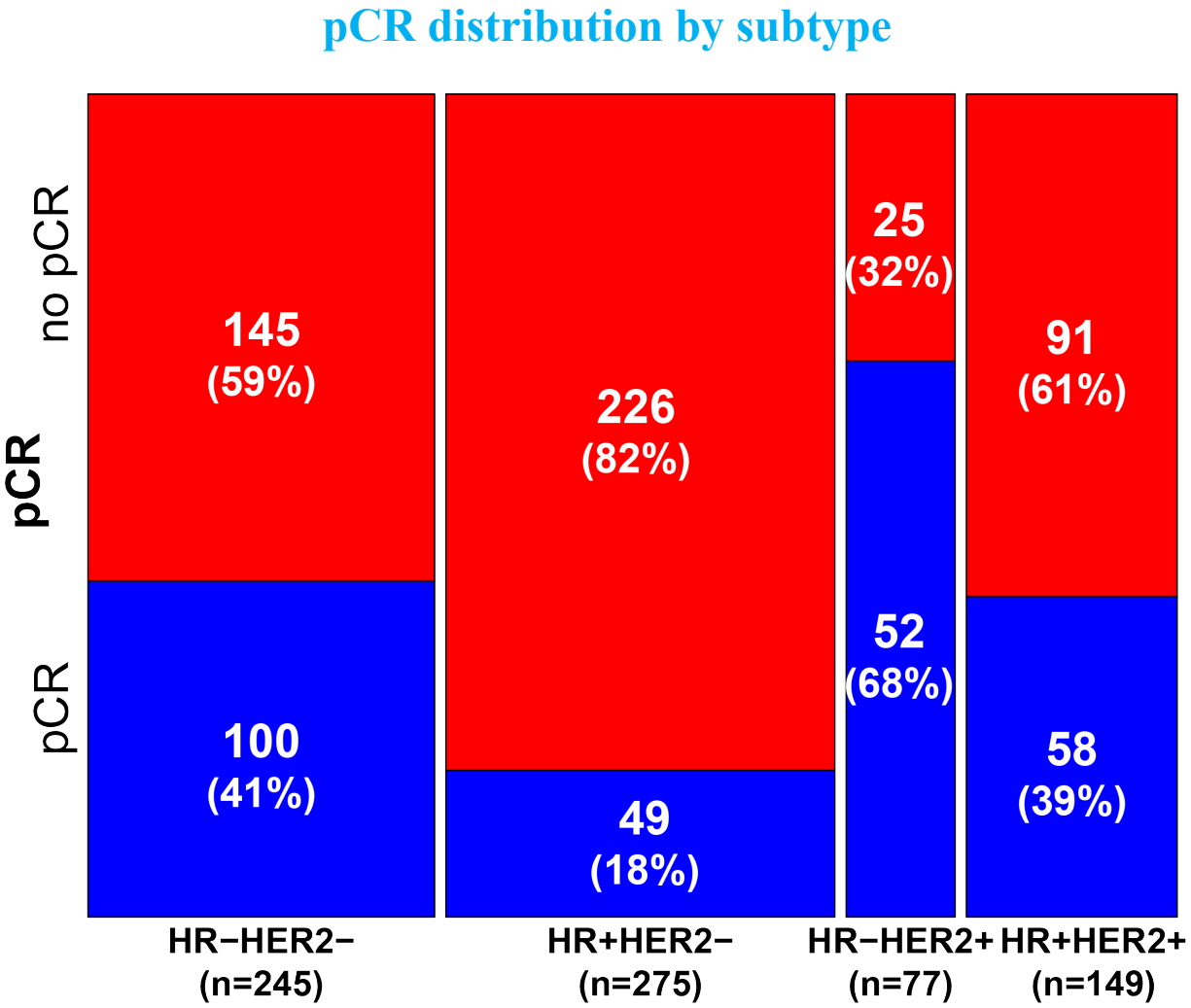
Scatterplot of RCB index entered by Site vs. Central Review



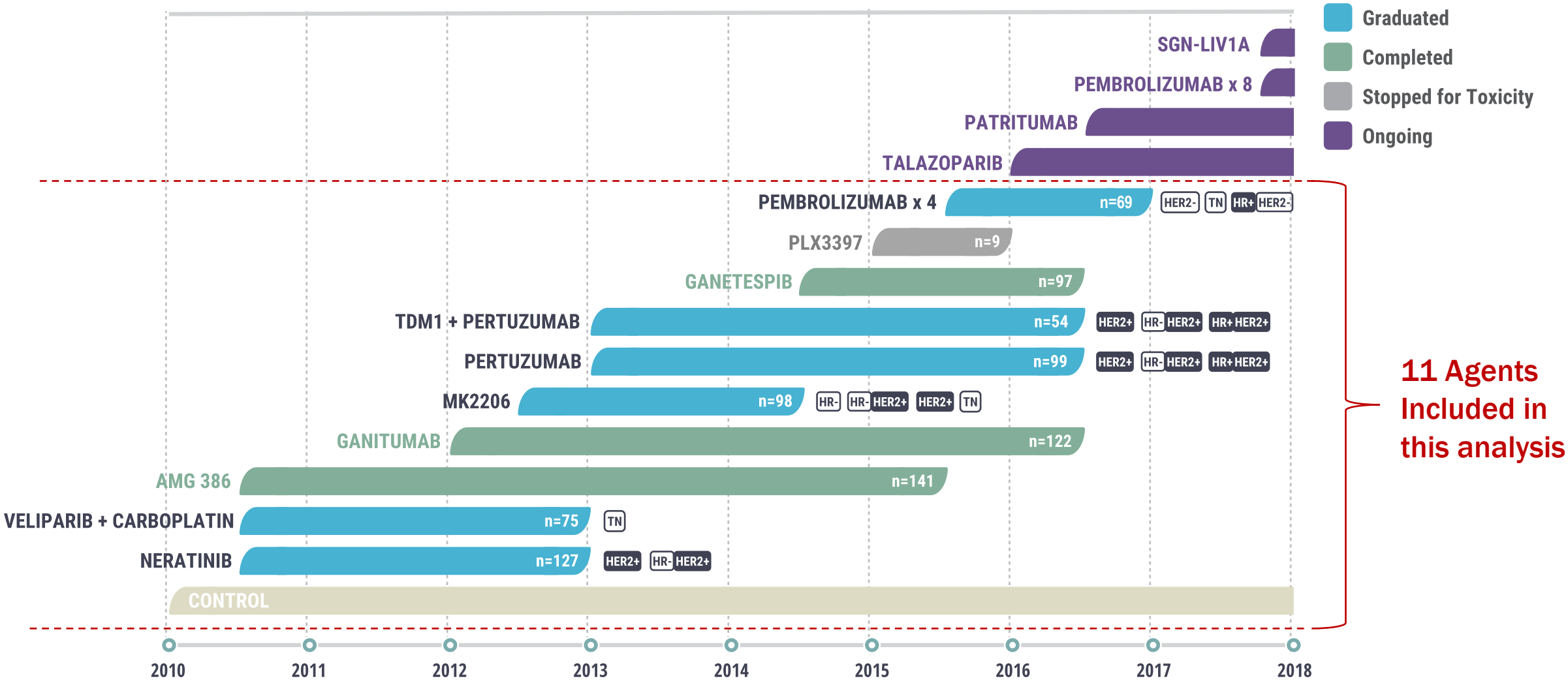
*Symmans, et al. J Clin Oncol 25:4414 2007 PMID: 17785706

EFS Dataset

- Evaluable population: 746
  - 259 (35%) pCR, 487 (65%) non-pCR
  - Median follow-up: 2.7 yrs (0.02-7.2)
  - 126 EFS events, 109 DRFS events
- 12 patients did not go to surgery
  - considered non-pCR per protocol

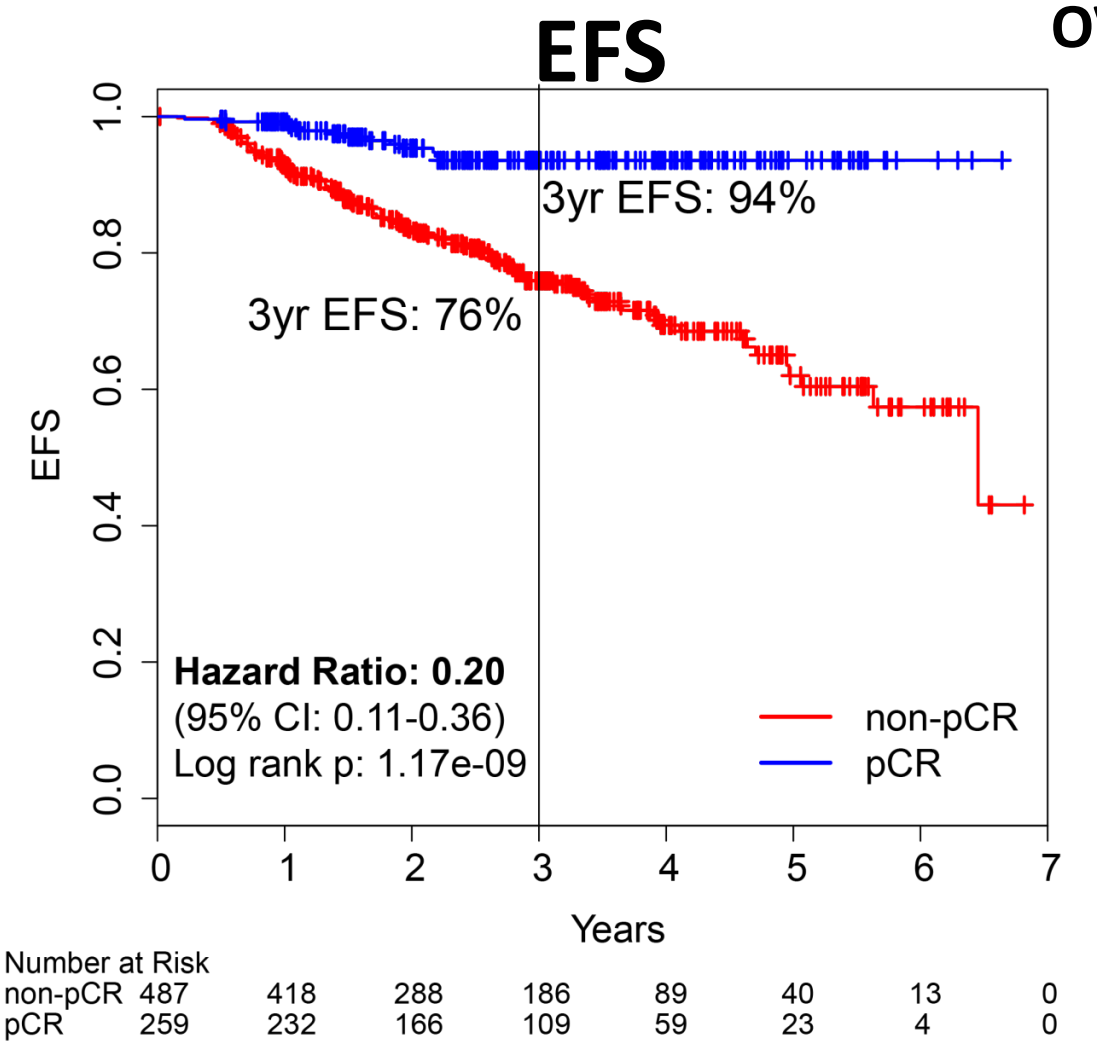


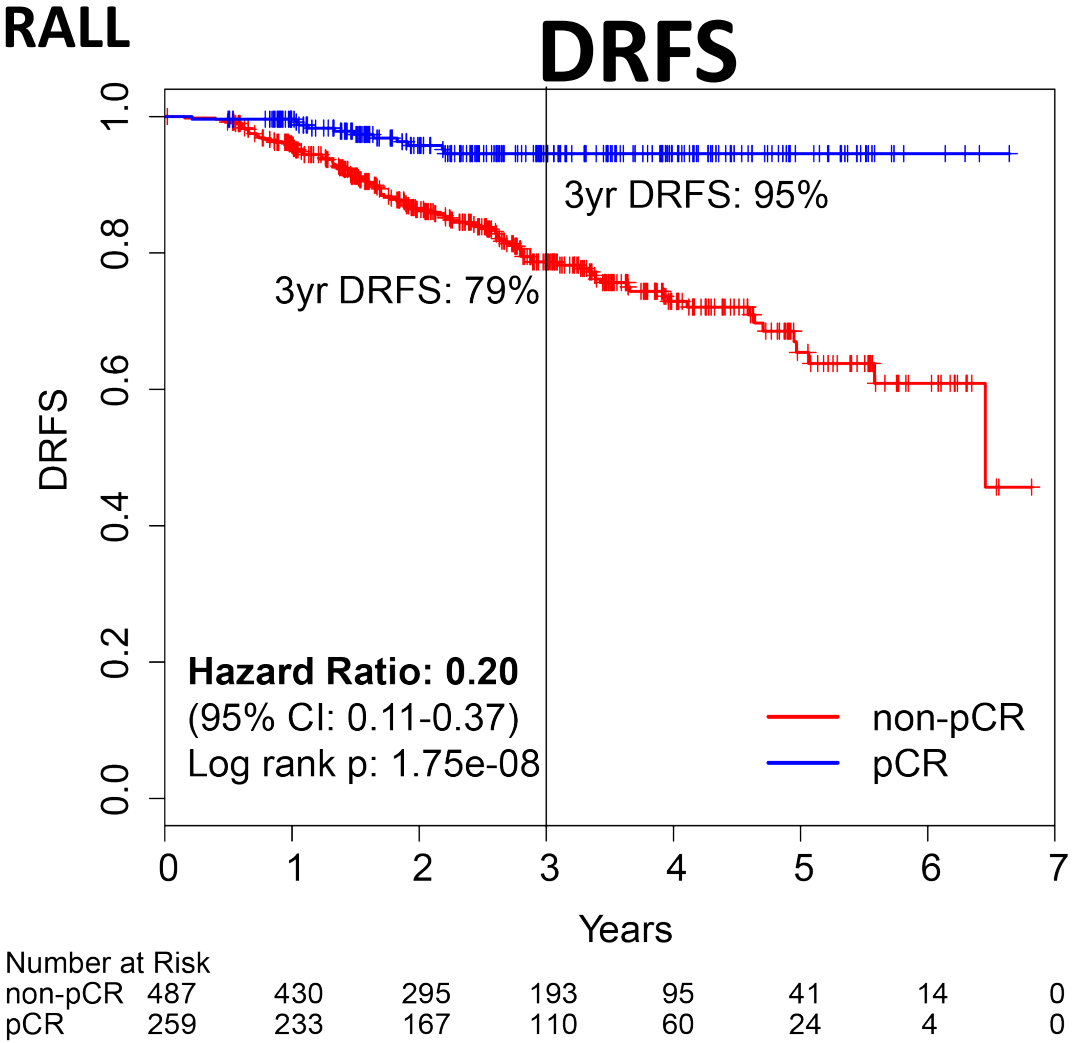
Agent Timeline



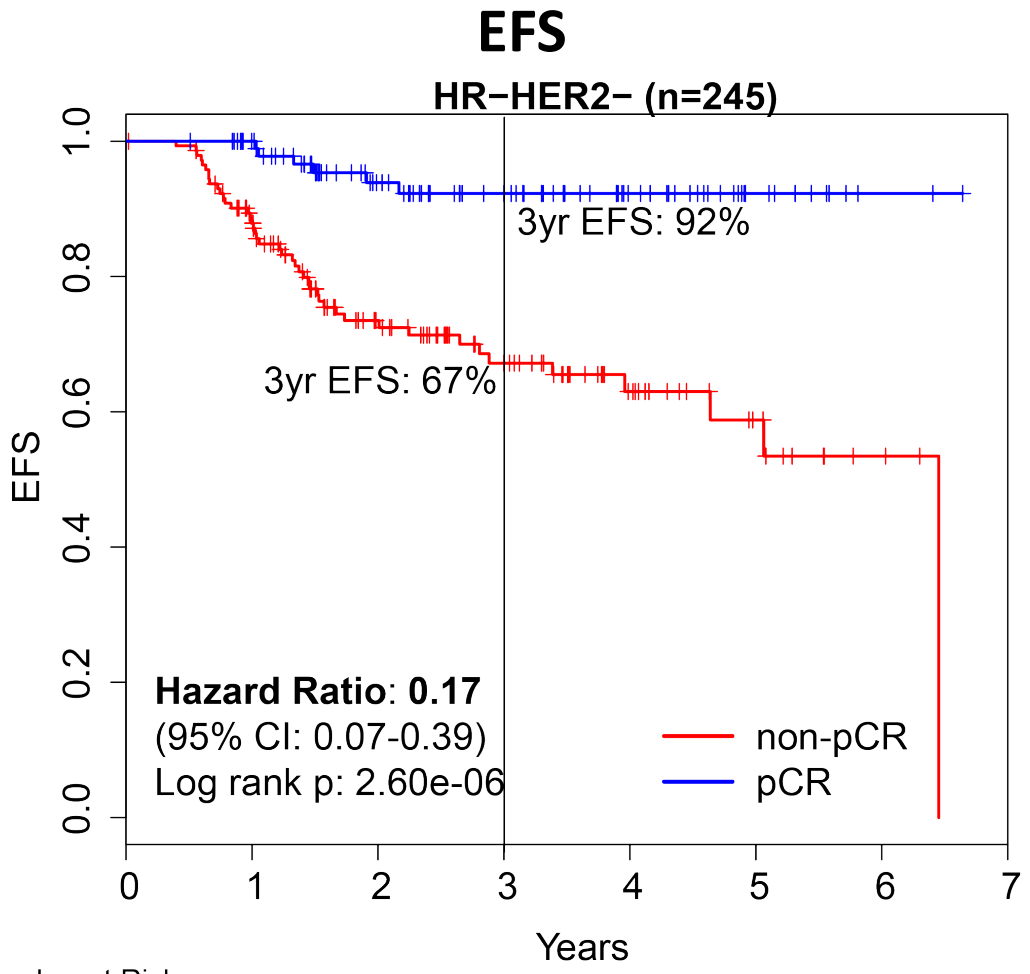
pCR is a highly significant predictor of EFS and DRFS

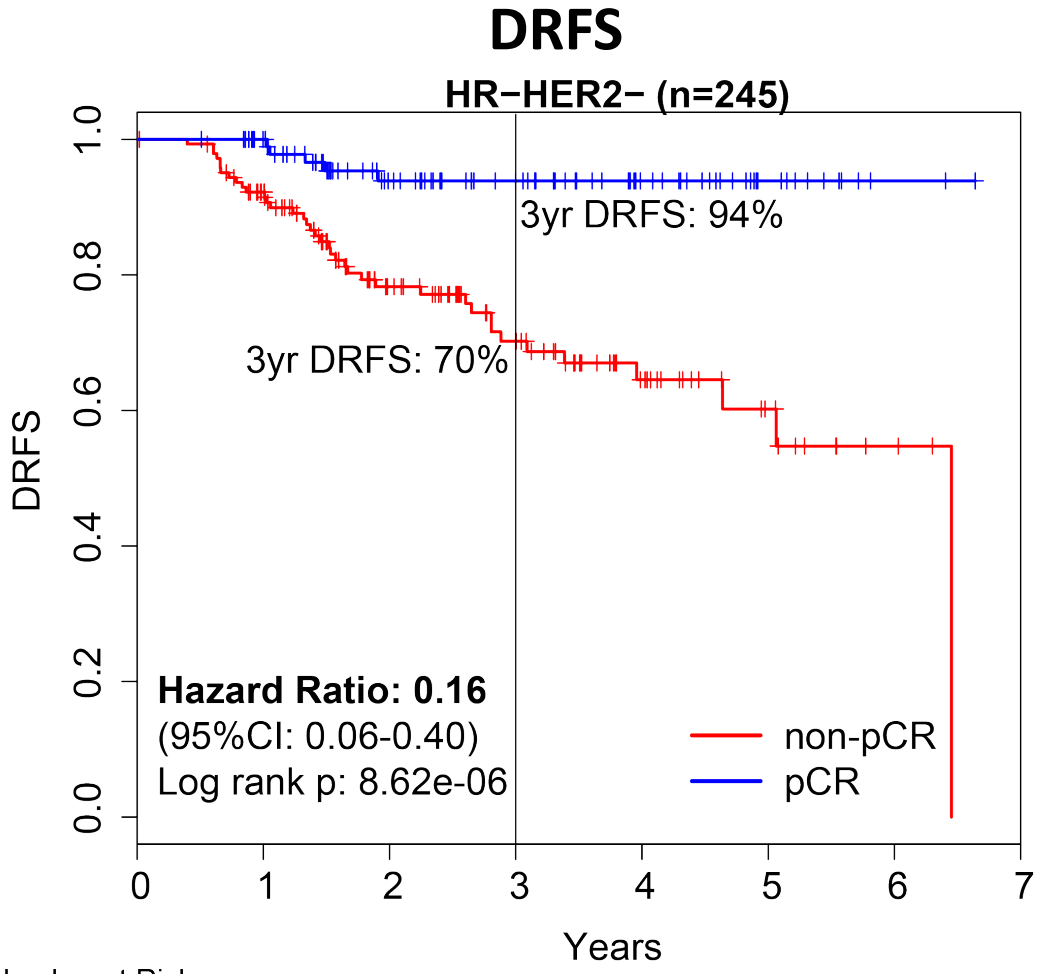
OVERALL



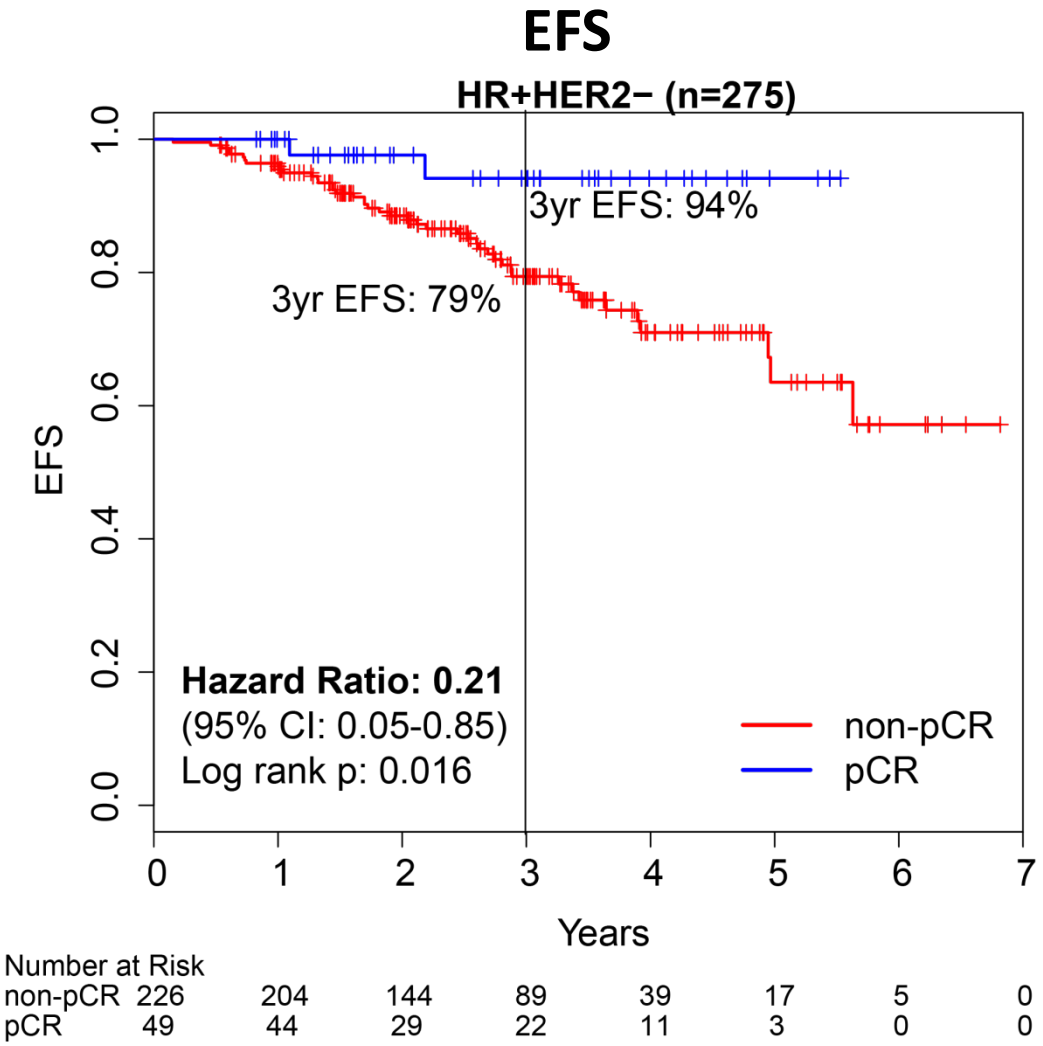


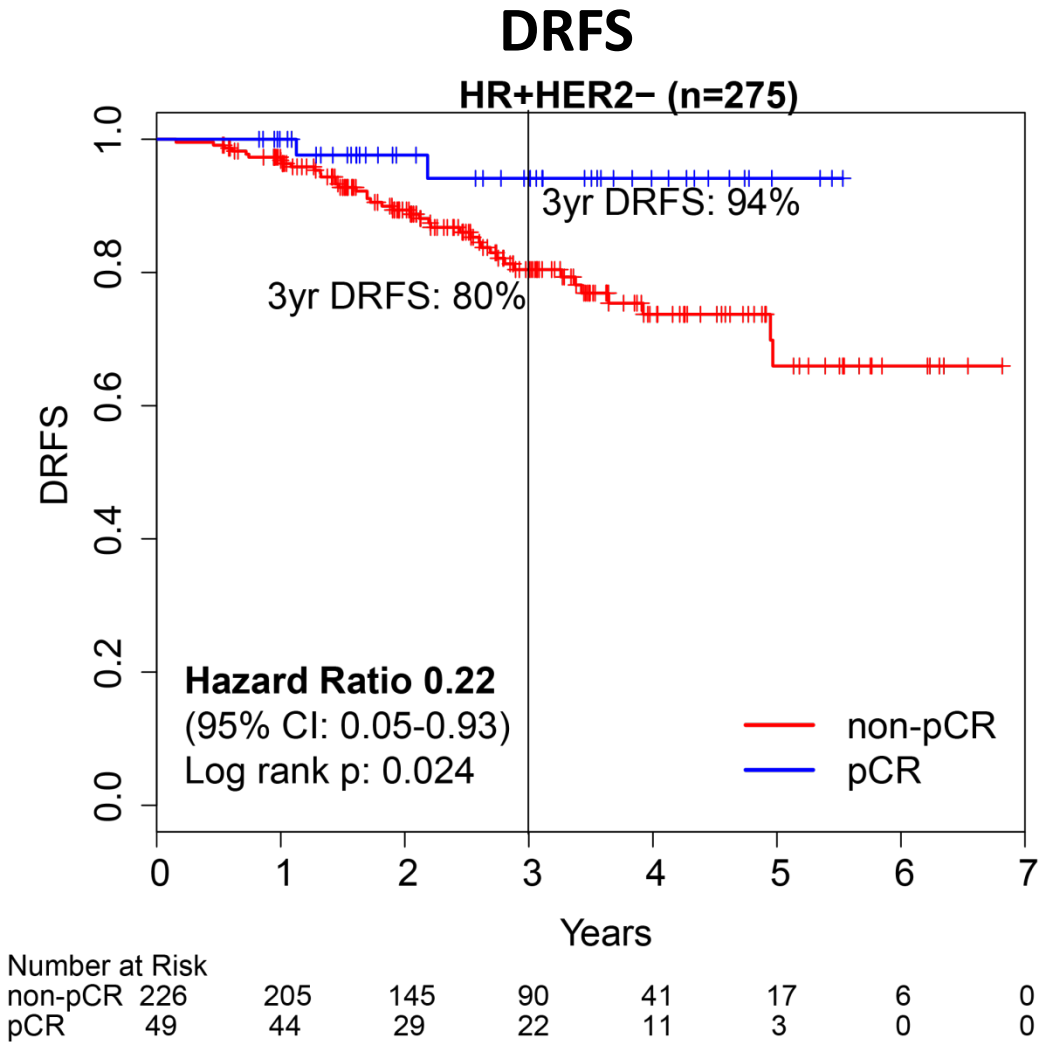
pCR is predictive of EFS and DRFS in TNBC





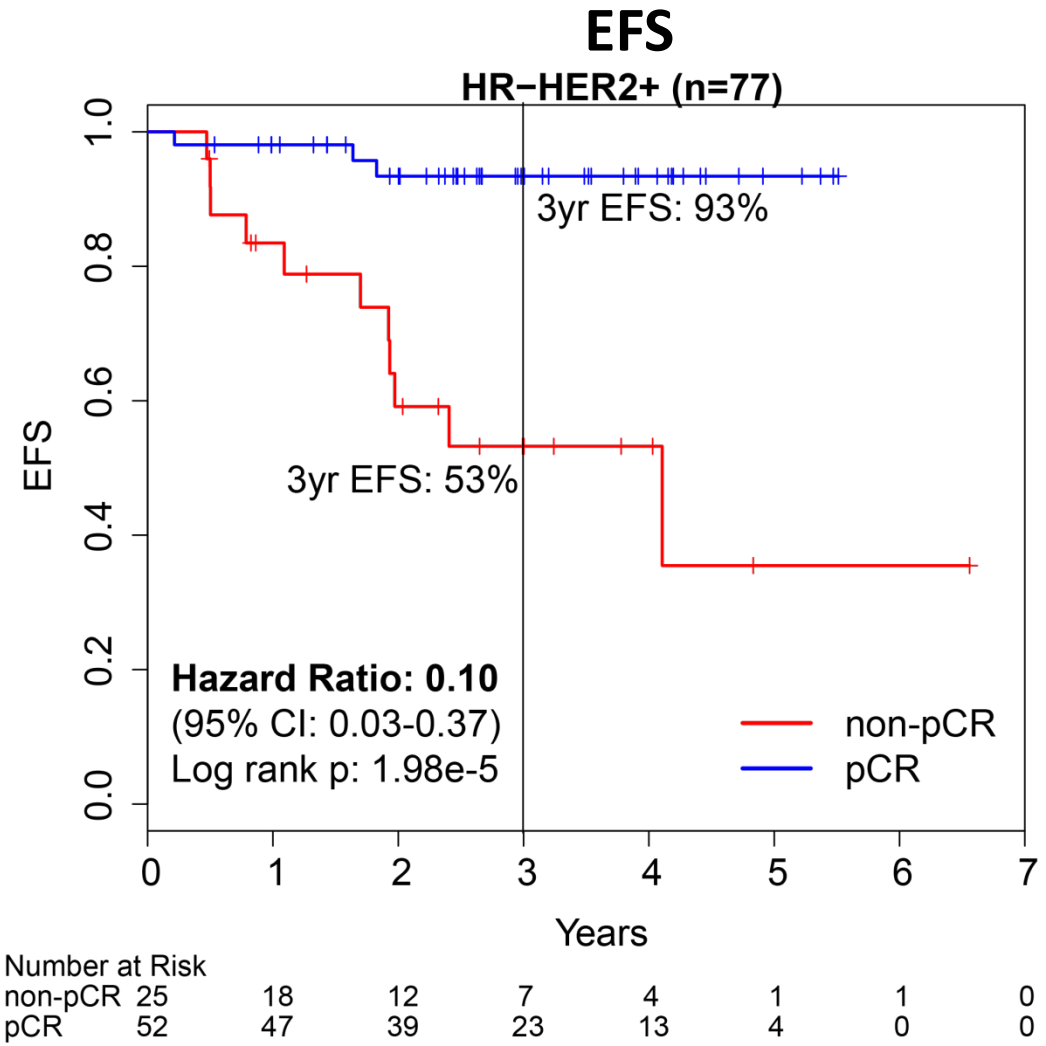
pCR is predictive of EFS and DRFS in HR+/HER2–

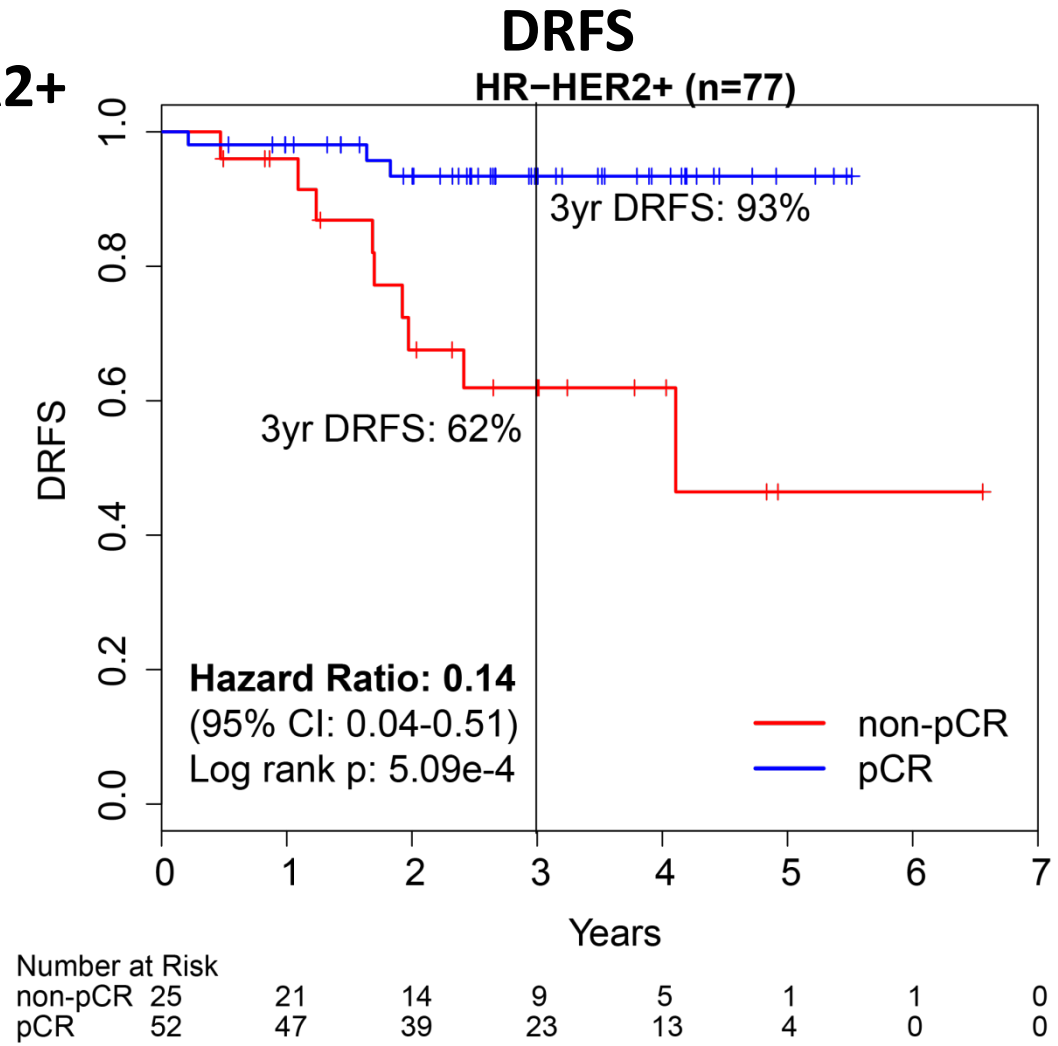




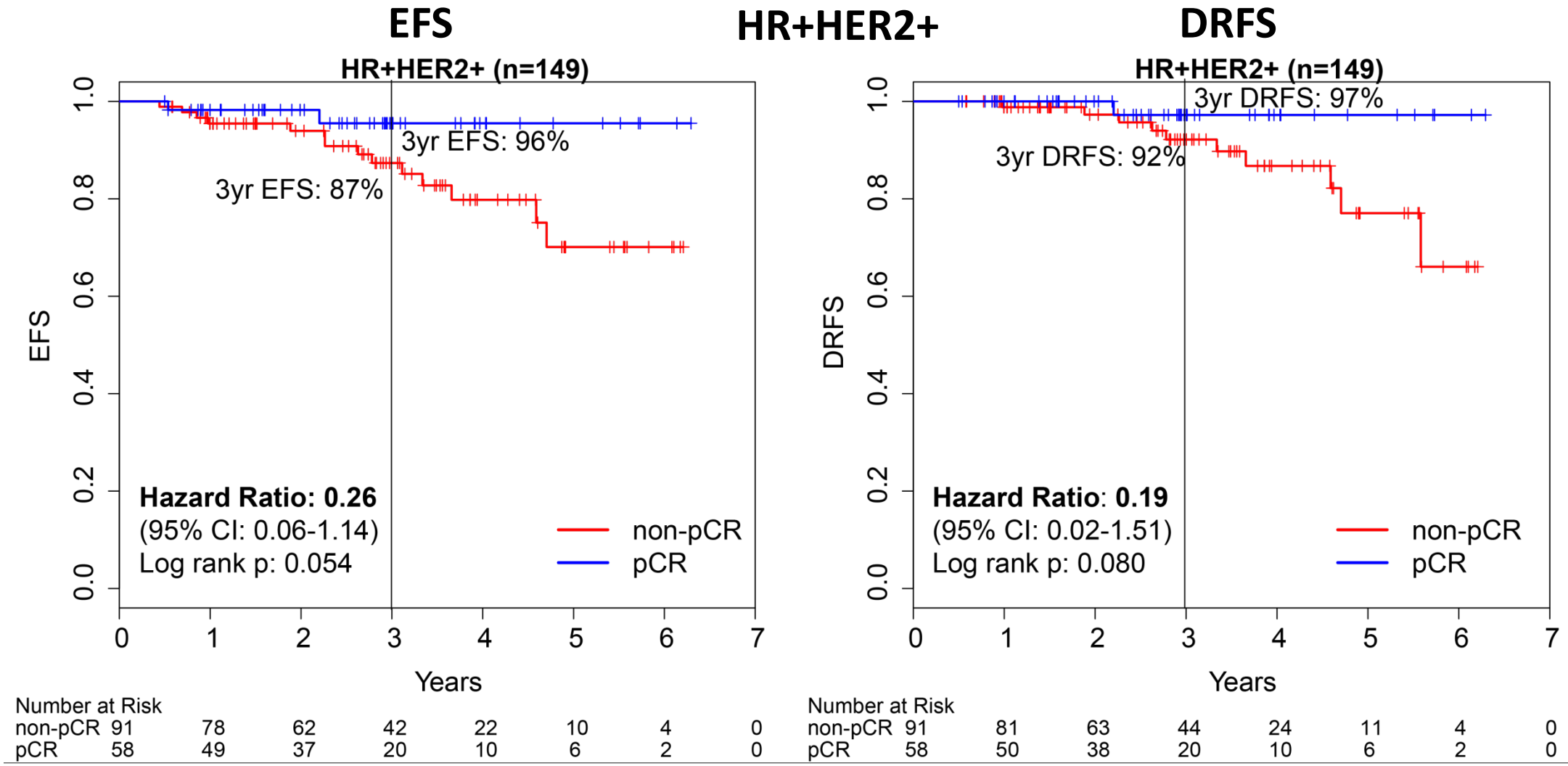
pCR is predictive of EFS and DRFS in HR–/HER2+

HR-HER2+

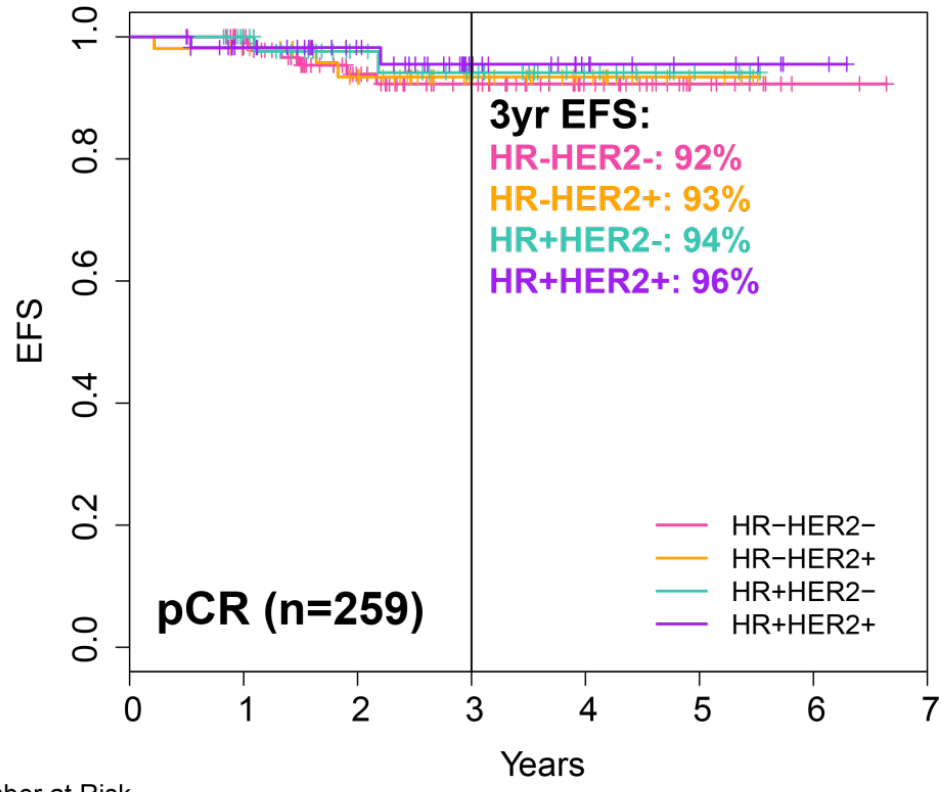




pCR is predictive of EFS and DRFS in HR+/HER2+

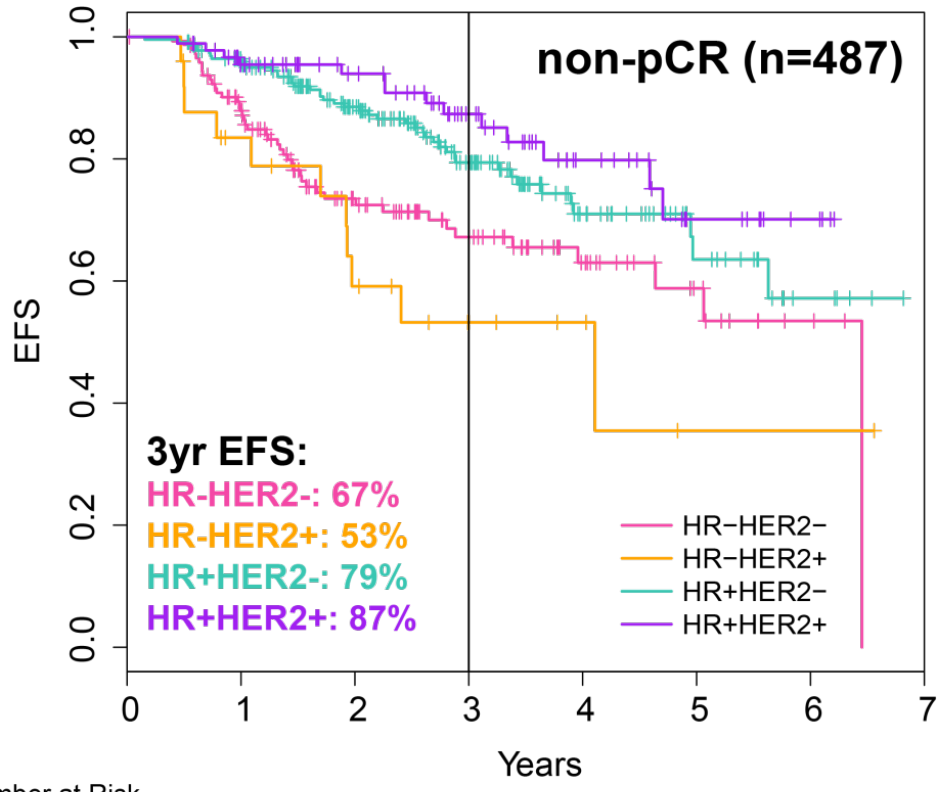


EFS by pCR & non-pCR by Subtype



Number at Risk

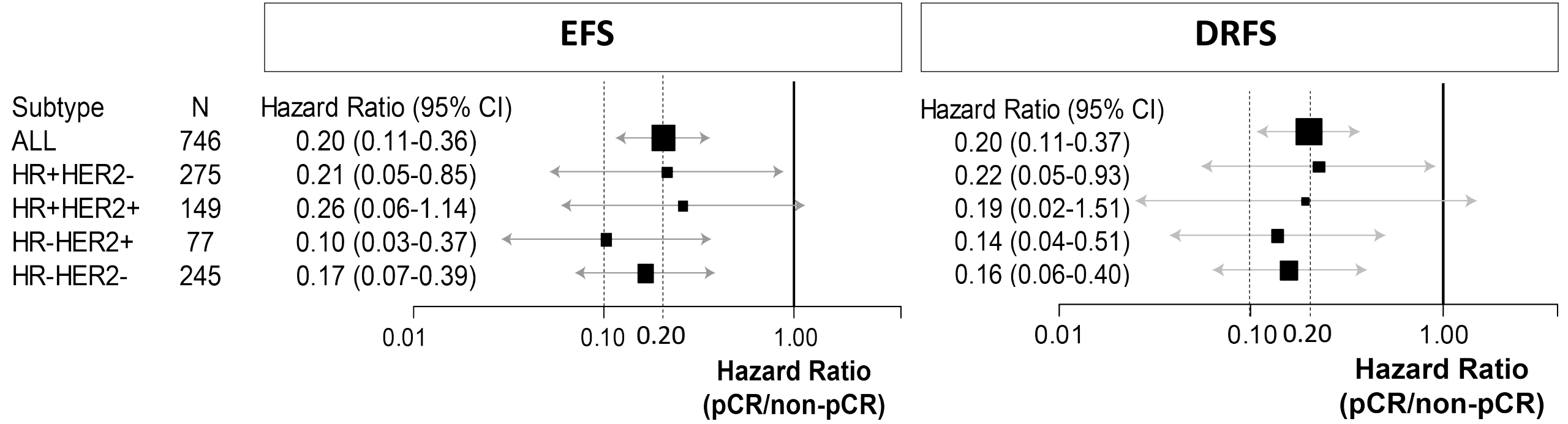
HR−HER2−	100	92	61	44	25	10	2	0
HR−HER2+	52	47	39	23	13	4	0	0
HR+HER2−	49	44	29	22	11	3	0	0
HR+HER2+	58	49	37	20	10	6	2	0



Number at Risk

HR−HER2−	145	118	70	48	24	12	3	0
HR−HER2+	25	18	12	7	4	1	1	0
HR+HER2−	226	204	144	89	39	17	5	0
HR+HER2+	91	78	62	42	22	10	4	0

EFS and DRFS Hazard Ratio for pCR vs non-pCR



I-SPY2 EFS Hazard Ratio for pCR/non-pCR compared to FDA meta-analysis and cooperative group results

	I-SPY 2	Cortazar Meta-analysis	Cooperative Group CALGB 40603
Overall	0.20 (0.11-0.36)	0.48 (0.43-0.54)	
*HR+HER2-	0.21 (0.05-0.85)	0.49 (0.33-0.71)	
HER2+	0.21 (0.08-0.55)	0.39 (0.31-0.50)	
HR-HER2-	0.17 (0.07-0.39)	0.24 (0.18-0.33)	0.30 (0.19-0.45)

*Mammaprint low patients excluded

Summary

- pCR is a strong predictor of EFS and DRFS in the setting of a multiple agent platform trial that includes:
  - Standards for eligibility
    - *high risk for early recurrence (MP low risk, HR+Her2- excluded)*
    - *exclusion of metastatic disease*
  - All chemotherapy given before pCR determination
  - Standards for pathology assessment and multidisciplinary identification (surgeons, radiologists, pathologists)
  - Long term follow-up of patients over time (correlation of early, intermediate, and late endpoints)

- pCR is equally predictive across all tumor subsets

- pCR as an endpoint enables rapid evaluation of novel therapy combinations and can accelerate the identification of effective and potentially less toxic regimens

The Future of I-SPY 2

- Achieving pCR through any therapy for any subtype is a sufficient endpoint

- Develop minimally invasive techniques (MRI and biopsy) to identify pCR prior to definitive surgery
  - Validate robust MRI and tissue predictors of pCR
  - Deescalate toxic therapy (AC) if pCR obtained early

- Re-assign patients to new therapies if pCR is not predicted
  - Validate robust MRI and tissue predictors of non-PCR
  - Assign new therapies based on molecular profiling of tumor and link to investigational agents

Acknowledgements

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