Supplementary Online Content

I-SPY2 Trial Consortium. Association of event-free and distant recurrence–free survival with individual-level pathologic complete response in neoadjuvant treatment of stages 2 and 3 breast cancer: three-year follow-up analysis for the I-SPY2 adaptively randomized clinical trial. *JAMA Oncol*. Published online July 23, 2020. doi:10.1001/jamaoncol.2020.2535

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

Bayesian modeling of EFS hazard ratio for pCR vs. non-pCR, adjusting for subtype.

We assume that EFS is exponentially distributed for both achieving pCR and not achieving pCR. The hazard rate is a function of subtypes defined by HR/HER2 status and treatment arm.

We denote the hazard rate of events for a non-pCR within patient subtype *s* by $\square_s$. The event hazard rate for a pCR on arm *a* in subtype *s* is assumed to be $\exp(\theta_a)\,\lambda_s$. In this parameterization, parameter θ_a is the log of the hazard ratio for achieving pCR on arm *a*; and is assumed to depend on treatment arm, but the same for each of the 4 subtypes.

The prior distribution for each of the hazard rate for non-pCR is a gamma distribution that is approximately non-informative:

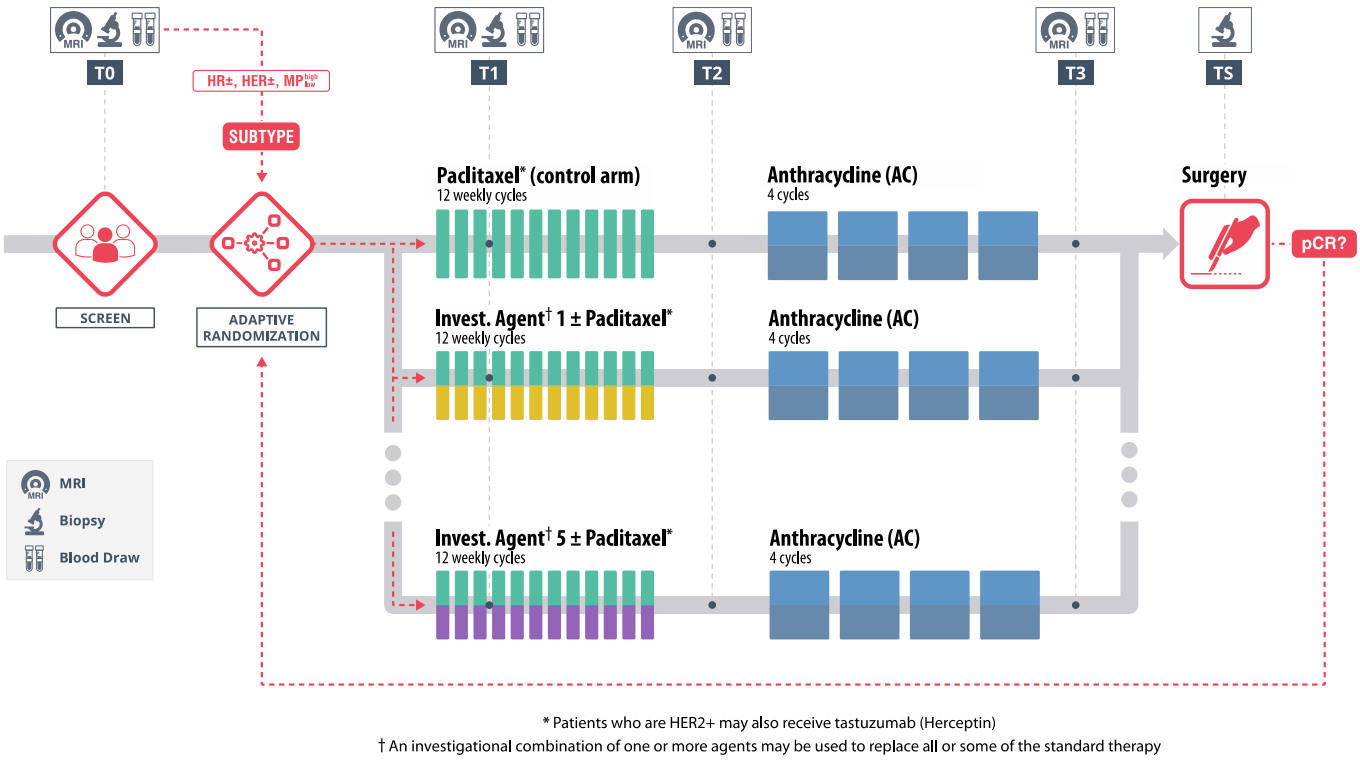
$$\lambda_s \sim gamma(0.01, 0.01),\ s = 1, 2, 3, 4$$

The prior distribution for each of the log-hazard ratios is standard normal:

$$\theta_a \sim N(0, 1),\ a = 1, \ldots, 10$$

We update this distribution based on the data within each of the 10 treatment arms considered separately. Calculation method is Markov chain Monte Carlo (MCMC) with 50,000 observations and a burn-in of 10,000. The 10 posterior distributions (for $\exp(\theta_a)$) are summarized in a forest plot in Supplemental Figure 4, where the solid rectangle is the distribution's median and the horizontal line extends from lower to upper 2.5 percentiles.

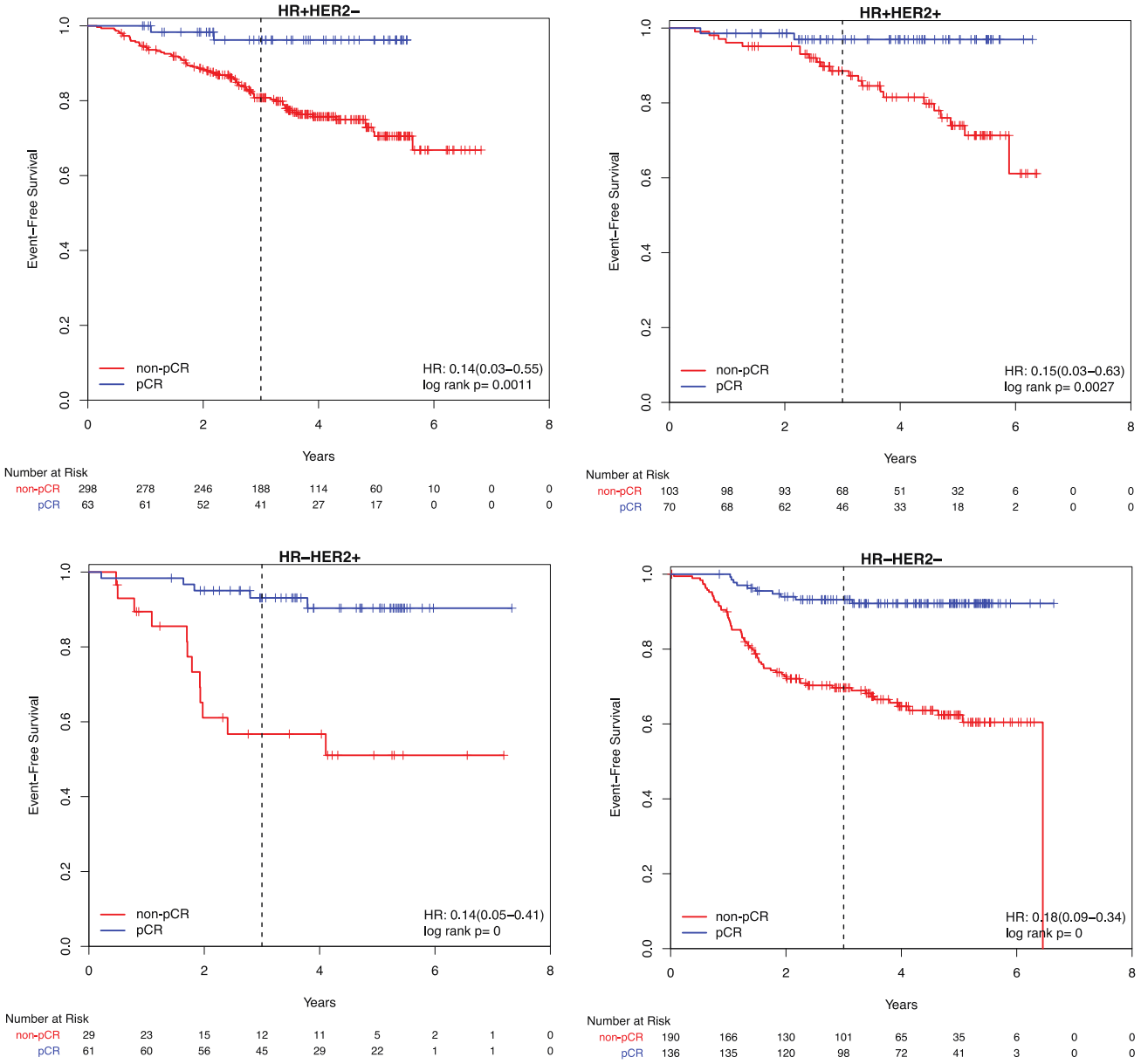
eFigure 1. I-SPY2 study schema, illustrating multiple experimental arms compared with a common control, adaptive randomization and schedule of assessments.



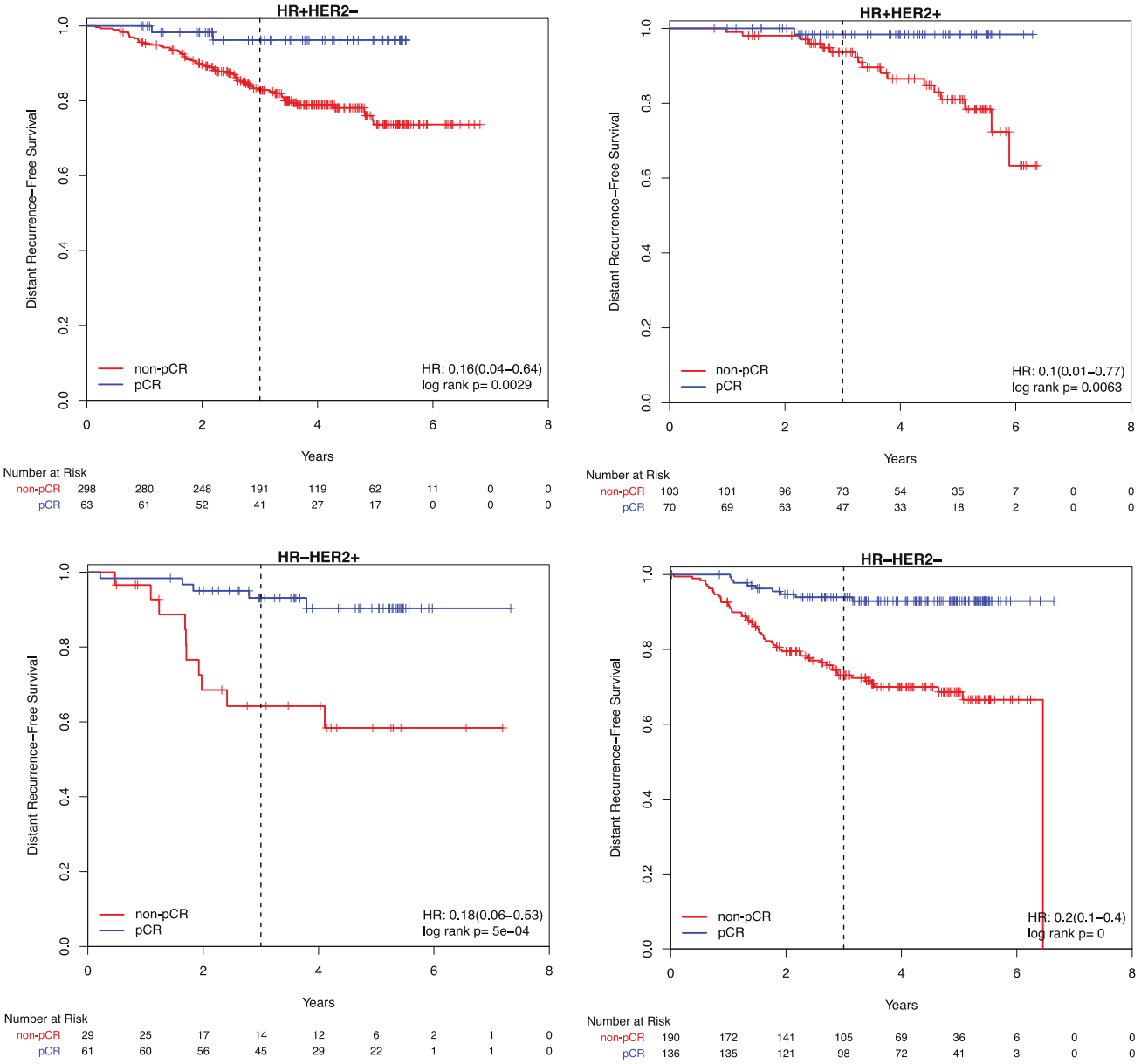
* Patients who are HER2+ may also receive tastuzumab (Herceptin)

† An investigational combination of one or more agents may be used to replace all or some of the standard therapy

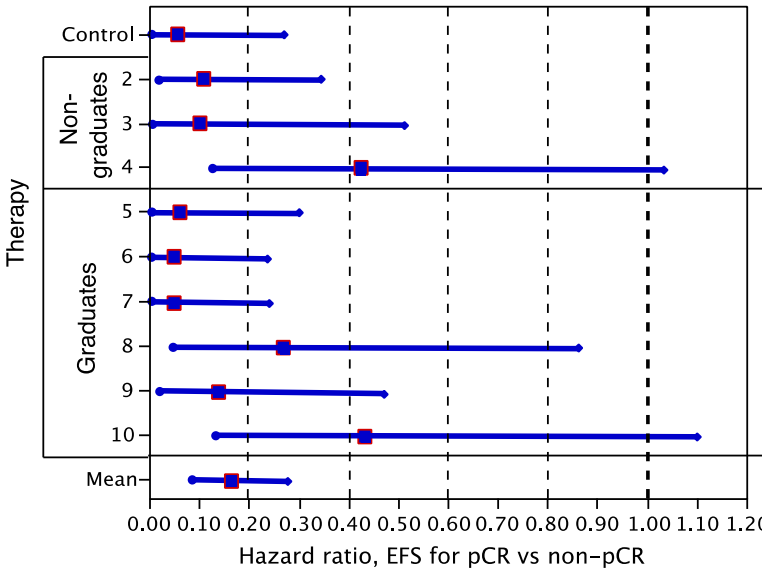
eFigure 2. Kaplan-Meier survival curves for Event-free Survival for each molecular subtype.



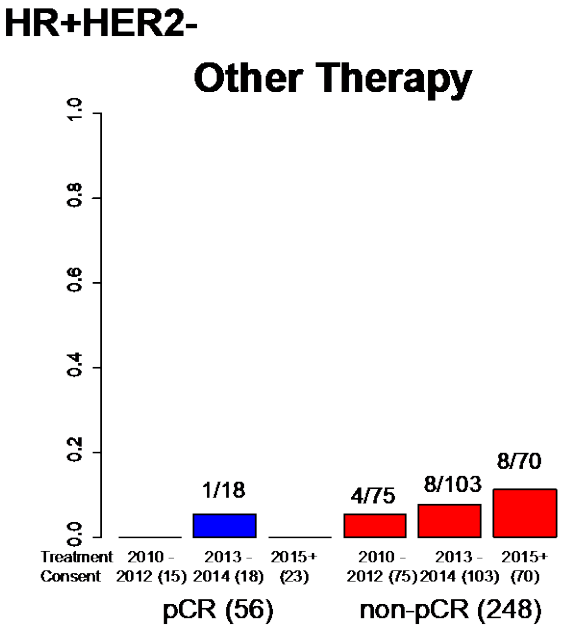
eFigure 3. Kaplan-Meier survival curves Distant Relapse-free Survival for each molecular subtype.



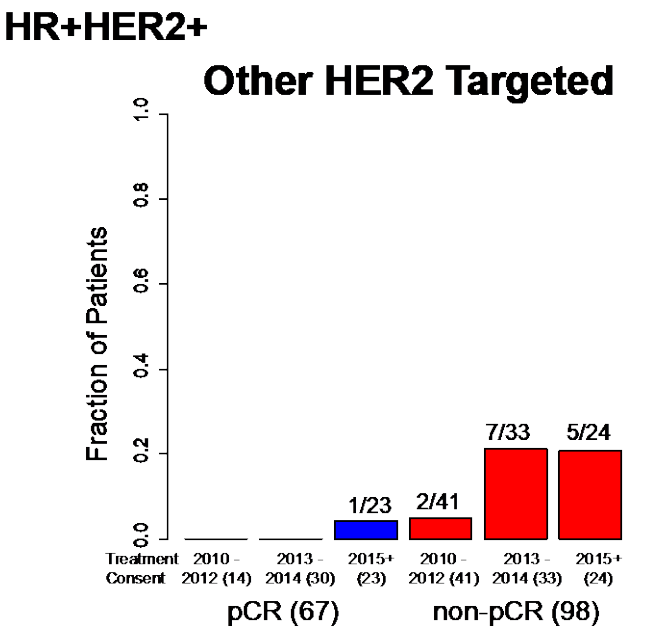
eFigure 4. Forest plot showing Bayesian modeled EFS hazard ratios by pCR vs non-pCR for each therapy, adjusting for molecular subtype. The solid rectangle is the median of exponent of the posterior distribution of log-hazard ratio in each treatment arm and the horizontal line extends from lower to upper 2.5 percentiles. Therapies are organized into 3 groups: control, those that did not graduate and those that did.



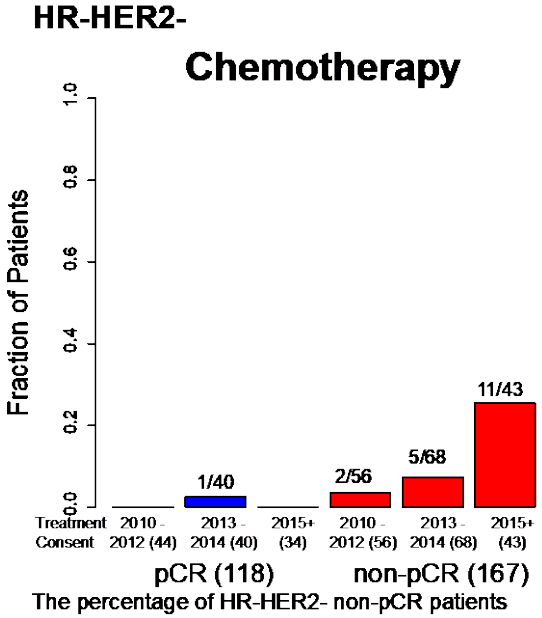
eFigure 5. Trends in use of adjuvant therapy in patients with residual disease following neoadjuvant treatment and surgery since I-SPY2 opened in 2010. over time in I-SPY2. Adjuvant treatment is not mandated, rather left to the discretion of the treating physician in I-SPY2.



The percentage of HR+HER2- non-pCR patients receiving other therapies adjuvantly appears to be higher in those who enrolled in the trial later



The percentage of HR+HER2- non-pCR patients receiving other HER2-targeted therapies adjuvantly appears higher in those who enrolled after 2012



The percentage of HR-HER2- non-pCR patients receiving chemotherapies adjuvantly appears to be higher in those who enrolled in the trial later

eTable 1. Baseline characteristics of participants in the analysis set who achieved pCR prior to surgery and those with residual disease at surgery.

	pCR (n=330)	No pCR (n=620)	p
Age			0.5947
Median (Range)	49 (25 - 73)	49 (23 - 77)	
Race			0.9814
White	266 (81%)	493 (80%)	
Black or African American	35 (11%)	73 (12%)	
Asian	23 (7%)	44 (7%)	
Native Hawaiian or Pacific Islander	2 (1%)	3 (0%)	
American Indian or Alaska Native	1 (0%)	3 (0%)	
Mixed Race	3 (1%)	4 (1%)	
Ethnicity			0.0213
Hispanic or Latino	46 (14%)	55 (9%)	
Not Hispanic or Latino	284 (86%)	565 (91%)	
HR status			<0.0001
HR-negative	197 (60%)	219 (35%)	
HR-positive	133 (40%)	401 (65%)	
HER2 status			<0.0001
HER2-negative	199 (60%)	488 (79%)	
HER2-positive	131 (40%)	132 (21%)	
Pre-treatment longest diameter by MRI*			<0.0001
Median (Range)	3.7 (0.44-14.7)	3.9 (0.8 - 22)	
Palpable Nodes			0.3212
No	173 (52%)	305 (49%)	
Yes	108 (33%)	233 (38%)	
Missing	49 (15%)	82 (13%)	
Time to Surgery, days			0.9249
Median (Range)	169 (97 - 265)	169 (64 - 351)	
Length of Follow-up, years			0.0611
Median (Range)	4.0 (0.8 – 7.3)	3.7 (0.2 - 7.6)	

eTable 2. Use of adjuvant therapy in the I-SPY2 population, by subtype and pCR result.

	HR+HER2- (n=304)		HR+HER2+ (n=165)		HR-HER2- (n=285)		HR-HER2+ (84)	
	pCR (56)	**non-pCR (248)**	**pCR (67)**	**non-pCR (98)**	**pCR (118)**	**non-pCR (167)**	**pCR (57)**	**non-pCR (27)**
Endocrine Therapy*	50 (89%)	209 (84%)	61 (91%)	91 (93%)	5 (4%)	16 (10%)	4 (7%)	4 (15%)
Trastuzumab	1 (2%)	5 (2%)	60 (90%)	83 (85%)	0 (0%)	5 (3%)	53 (93%)	23 (85%)
Other HER2-Targeted Therapy	0 (0%)	3 (1%)	1 (1%)	14 (14%)	1 (1%)	2 (1%)	1 (2%)	1 (4%)
Chemotherapy	0 (0%)	11 (4%)	1 (1%)	7 (7%)	1 (1%)	18 (11%)	0 (0%)	0 (0%)
Other Therapy	1 (2%)	20 (8%)	1 (1%)	5 (5%)	3 (3%)	7 (4%)	0 (0%)	0 (0%)