# Supplementary Appendix

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

Supplement to: Park JW, Liu MC, Yee D, et al. Adaptive randomization of neratinib in early breast cancer. N Engl J Med 2016;375:11-22. DOI: 10.1056/NEJMoa1513750

# Supplementary Appendix

**Supplement to Park, J, Liu, M, Yee, D *et al*. "*I-SPY 2 TRIAL Adaptive Randomization of Neratinib in Breast Cancer"***

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## Additional Study Design Details

To determine treatment assignment probabilities for patients entering the trial population is categorized into 8 disease subtypes defined by a 2 x 2 x 2 arrangement of the 3 biomarkers HR (ER/PgR), HER2, and MP (Table S1). Each week during the trial the current probability distribution of each regimen's pCR rate is updated based on the data available in the trial. These distributions are found for each of these 8 subtypes based on a multivariate analysis with covariates HR, HER2, and MP. In each subtype 20% of the patients are assigned to control therapy. The remaining 80% is apportioned to the available experimental regimens in proportion to each regimens current probability of being the most effective therapy for that subtype.

Primary endpoint pCR is assessed at surgery approximately 6 months after initiation of therapy. To improve the efficiency of the adaptive randomization algorithm the design uses a longitudinal model of tumor burden during therapy to predict each patient's pCR result. MRI measurements are made 3 weeks and 12 weeks after initiation of therapy, with the latter timepoint coinciding with the end of the paclitaxel-based cycles. The prior distribution for this longitudinal model was based on MRI results from I-SPY 1 [1] and was updated based on results accruing in the present I-SPY 2 trial. Each patient in the trial who has not yet had surgery has a probability of experiencing a pCR based on MRI measurements of her tumor. To account for uncertainty in predicting each result calculations use multiple imputation.[2] Though these interim MRI results helped in determining the randomization assignment probabilities the results reported here are based only on the actual pCR results in the trial, and on tumor biomarkers.

Deciding to graduate or drop a regimen for futility is based on its performance in 10 prospectively defined subsets of tumor subtypes called "signatures." These are defined in Supplementary Table 3 and also in the Results section. Each regimen is compared with its concurrently randomized control group, which differs across regimens because they have different periods of tenure in the trial. Each month the probability distribution of each regimen's pCR rate in each of the 10 signatures is found and reported to the trial's DSMB. These probability distributions are standardized to the proportions of patients in the various biomarker subtypes across the entire trial and not based on the proportions of patients assigned to the regimen in question. Also reported to the DSMB by signature are (i) the current probabilities for each regimen that its pCR rate is greater than that of control and (ii) the current predictive probabilities that the regimen will show a statistically significance improvement in pCR rate in

comparison with control in a subsequent equally randomized 300-patient phase 3 trial with patients having tumors with the signature in question.

An experimental regimen with having been assigned to a total of at least 60 patients and a predictive probability greater than or equal to 85% in any signature graduates in that signature. A regimen with predictive probability less than 10% in all 10 signatures drop for futility with as few as 20 patients having been assigned. The maximum total number of patients assigned to any regimen is 120.

Operating characteristics for the trial were found using simulations. Many types of error are possible in a multiarm trial for which there are many possible conclusions for each arm. For example, one may conclude that an arm's signature is HR-negative/HER2-positive when its true signature is HER2-positive, and the same when the signatures are reversed. In both cases the conclusion is partly correct and partly incorrect. In addition, error rates for a particular regimen depend on which other regimens are in the trial. We set the type I error to be less than 10% when there are a small number of experimental regimens in the trial and the regimen in question has no effect for any signature and the design concludes that it does. And the trial design typically has at least 80% power when a signature has at least a log odds ratio of 1.5 in comparison with control. In terms of sample size in the simulations, the average ranged from 60 to 90 depending on the scenario assumed.

1. Esserman LJ, Berry DA, Cheang MC, et al. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast Cancer Res Treat 2011.

2. Little RJA, Rubin, D.B. Statistical Analysis with Missing Data. 2nd ed: J Wiley & Sons: New York; 2002.

## Figure S1

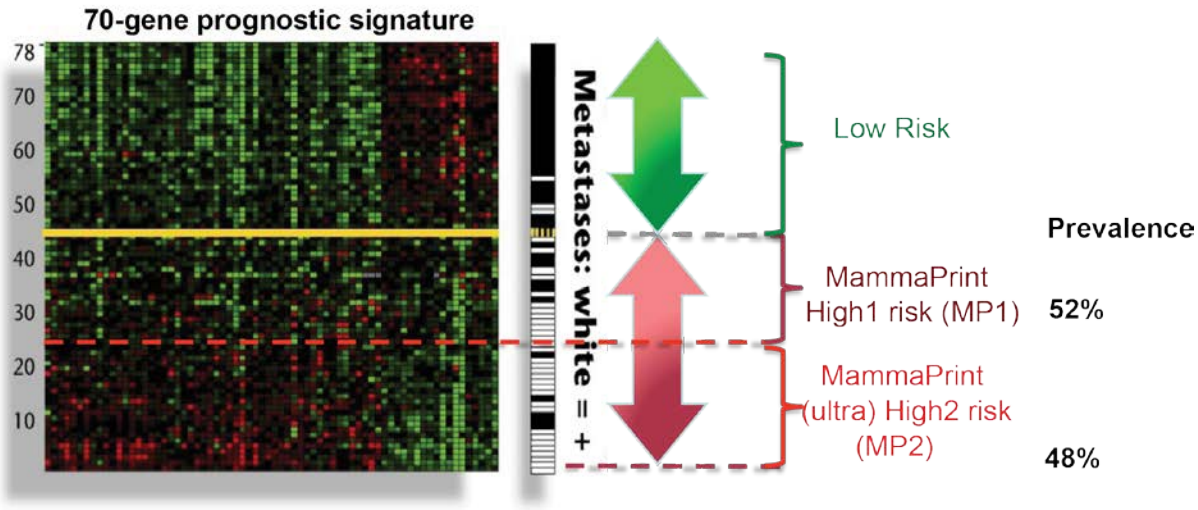


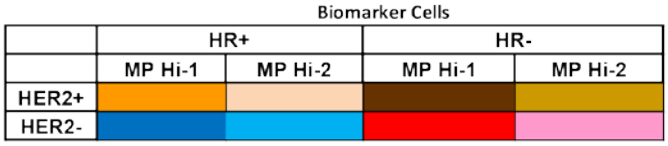

**Figure S1**

**Definition of MP1 and MP2 subtype:** The figure depicts a heat map representation of the 70 genes in the MammaPrint score. The rows are the patients, and the columns are each of the 70 genes. The cut point of -0.154 for MP1 vs MP 2 is the midpoint of I-SPY 1 patient MammaPrint results that would have been eligible for I-SPY 2. The MP1 to MP2 threshold on the current commercially available MP test translates to –0.569, after an adjustment of the high versus low threshold to 0.00 (numerical subtraction of 0.415). The prevalence for each of the subtypes (as of August 2015) in the I–SPY 2 TRIAL is listed along the right hand border of the figure.

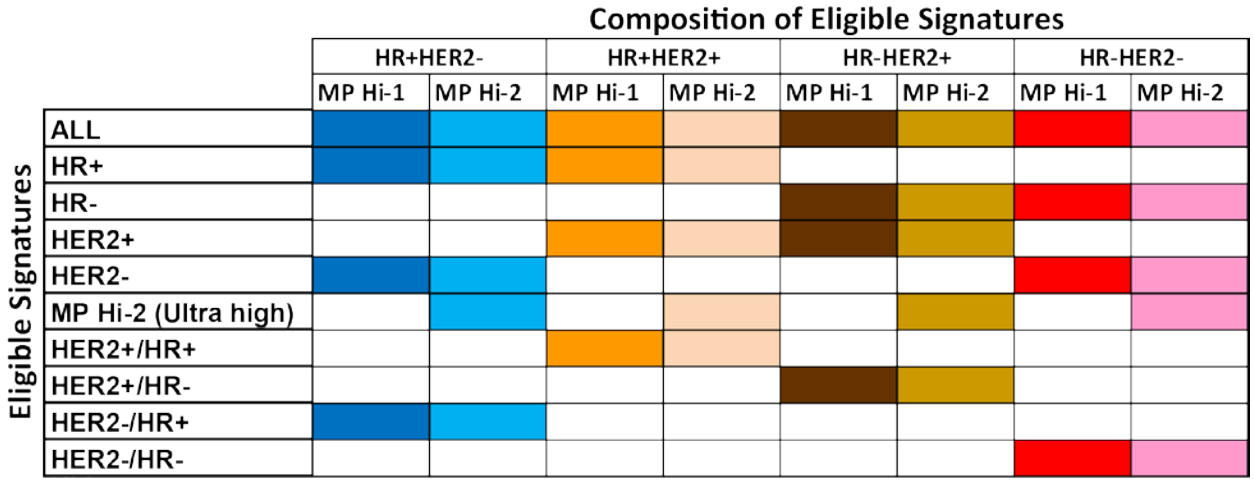
## Table S1: Eligible signatures and their biomarker subtypes composition

Biomarker assessments (HER2, HR, MammaPrint) performed at baseline are used to classify patients into 2 x 2 x 2 = 8 prospectively defined subtypes for randomization purposes. To assess efficacy, ten clinically relevant biomarker 'signatures' were defined in the protocol: All; HR+; HR-; HER2+; HER2-; MP Hi-2; HER2+/HR+; HER2+/HR-; HER2-/HR+; HER2-/HR-.

**A**




**B**




**(A)** The 2 x 2 x 2 color table shows the 8 biomarker subtypes as defined by HR, HER2, and MP status. Biomarker subtypes are color-coded as follows: HR+HER2+ MP-1 (orange); HR+HER2+ MP-2 (beige); HR+HER2- MP-1 (dark blue); HR+HER2- MP-2 (light blue); HR-HER2+ MP-1 (brown); HR-HER2+ MP-2 (tan); HR-HER2- MP1 (red); HR-HER2- MP2 (pink).

**(B)** This color table shows the biomarker subtype composition of the 10 eligible signatures in which an experimental agent can 'graduate' in the I-SPY 2 TRIAL. Subtypes within the eligible signature are colored (HR+HER2+ MP-1 (orange); HR+HER2+ MP-2 (beige); HR+HER2- MP-1 (dark blue); HR+HER2- MP-2 (light blue); HR-HER2+ MP-1 (brown); HR-HER2+ MP-2 (tan); HR-HER2- MP1 (red); HR-HER2- MP2 (pink)); and subtypes not within eligible signatures are left white.

## Table S2: Randomization probabilities to neratinib for the various biomarker subtypes in the latter part of its tenure in the trial

| | MP1 (Hi-1) | | MP2 (Hi-2, Ultra High) | |
|---|---|---|---|---|
| | **HR+** | **HR-** | **HR+** | **HR-** |
| **HER2+** | + | ++ | + | ++ |
| **HER2-** | 0 | 0 | + | + |

Table S2

**Table Legend:** The probability of being randomized, at the end of the trial, at the time of graduation, for the given tumor biomarker subtype, is indicated in the table (0= zero probability of randomization, + moderate probability of randomization, ++ high probability of randomization). This demonstrates that non-Her2 positive MP1 patients were not being randomized to Neratanib at the time of graduation.

**Table S3: Change in diarrhea management protocol and prevalence of Grade 2-3 diarrhea over the course of the study**

| Time Period | Diarrhea Management | Patients in Treatment Arm (n) | Prevalence, n (%) | | |
|---|---|---|---|---|---|
| | | | Grade 2 Diarrhea | Grade 3 Diarrhea | Neratinib dose modifications (reductions/holds/ discontinuation) |
| Before 4/6/2011 | Dose holds and reductions for Grade 2/3 diarrhea | 21 | 13 (61.9%) | 10 (47.6%) | 13 (61.9%) |
| 4/6/2011 - 1/16/2012 | Patient material for diarrhea management | 52 | 31 (59.6%) | 22 (42.3%) | 36 (69.2%) |
| After 1/16/2012 | Prophylactic loperamide | 72 | 40 (55.6%) | 26 (36.1%) | 48 (66.7%) |

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