Neoadjuvant/Adjuvant Standards of Care and Experimental Approaches in Breast Cancer

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#MelanomaNeoadjuvant

Disclosures

- Scientific Consulting: Pfizer, Novartis, Calithera

- Institutional Support of Research Trials: Pfizer, Novartis, Calithera, Menarini, Genentech

The I-SPY Platform Trial

A Multicenter Consortium to Optimize Therapy in Early Breast Cancer

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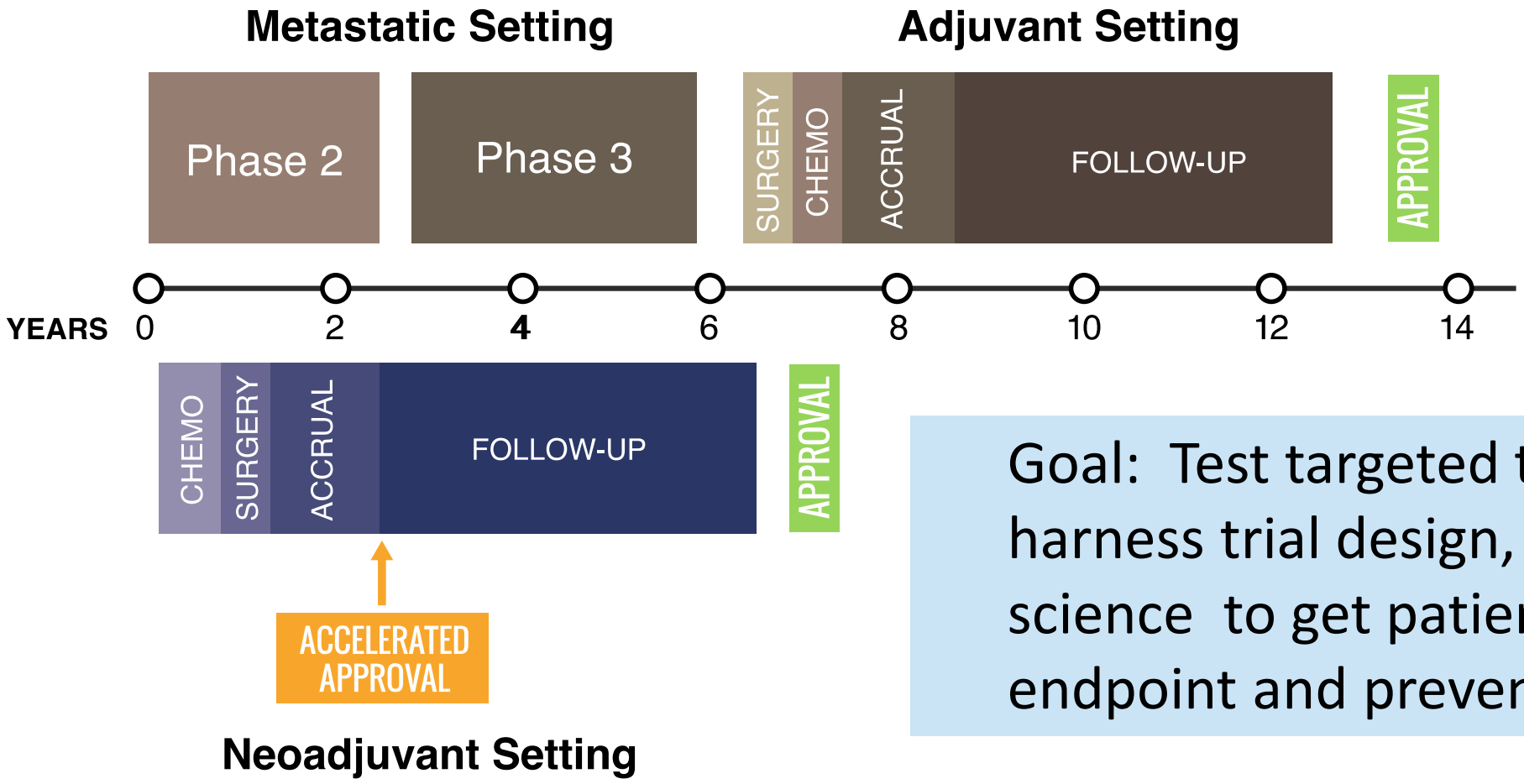
Thank you to the remarkable **patients and families,** our amazing advocates, all of the investigators, staff, and our DSMB for supporting the trial

An inflection point

- Breast Cancer has evolved from one disease to many
  - Molecular subtyping revealed different outcomes
    - Informed better use of ER, PR, Her2, proliferation (grade/Ki-67)
  - Multigene assays have enabled us to refine patient populations and treatment
  - *How much risk and when . . . .*
- Screening has changed the spectrum/ distribution of tumor types
  - Atypia, DCIS, Earlier stage cancers
  - But aggressive cancers still persist- in spite of “awareness” and access
- Trials, agents are evolving
  - Large trials with small benefit for all → smaller trials focused on larger benefit for subsets; better drugs have less toxicity

The Opportunity: Use early endpoints to enable interventions to rapidly evolve



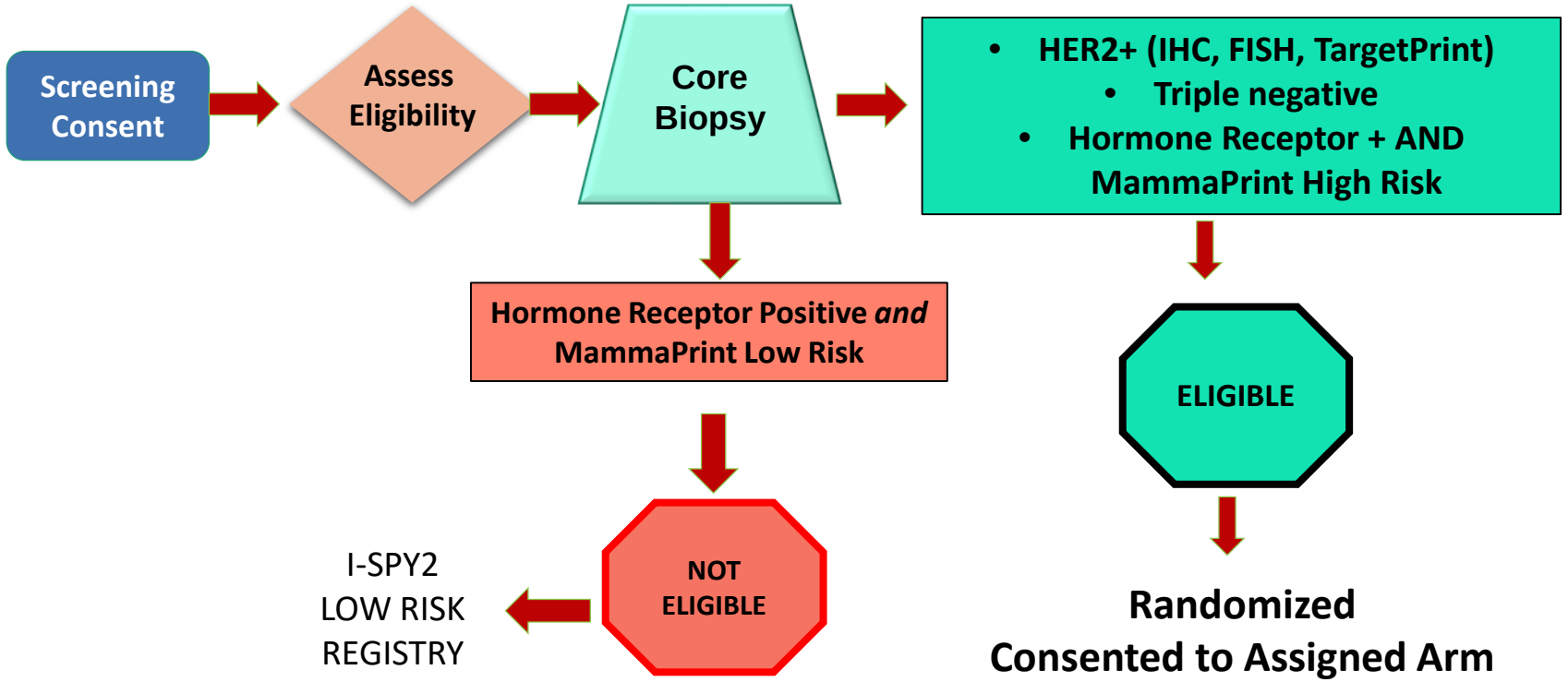
Goal: Test targeted therapeutics, harness trial design, and regulatory science to get patients to the optimal endpoint and prevent recurrence

I-SPY 2 Goals

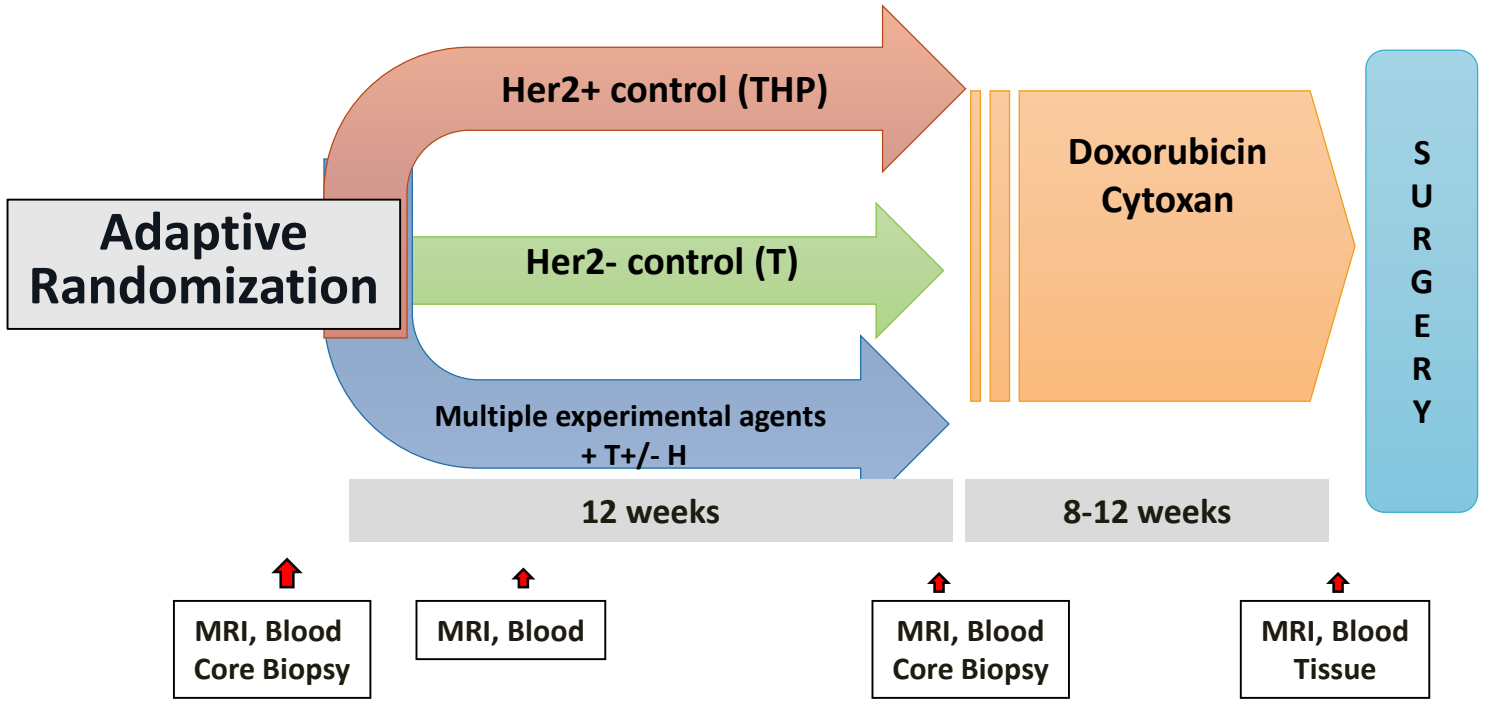
- Improve the efficiency of testing new agents:
  - Platform trial
  - Adaptive randomization
  - Testing against common controls and historic controls as the standards change
- Incorporate standards for:
  - Qualifying biomarkers
  - “Biomarker platforms”
  - Patient reported adverse endpoints
- Transform care at all participating sites→ Learning system
  - Knowledge continues to increase as the trial proceeds

I-SPY 2 TRIAL Eligibility

- Tumor size ≥ 2.5 cm
- Candidate for preoperative chemotherapy
- Study MRI and biopsy
- Adequate organ function, PS<2



I-SPY 2 TRIAL Master Schema

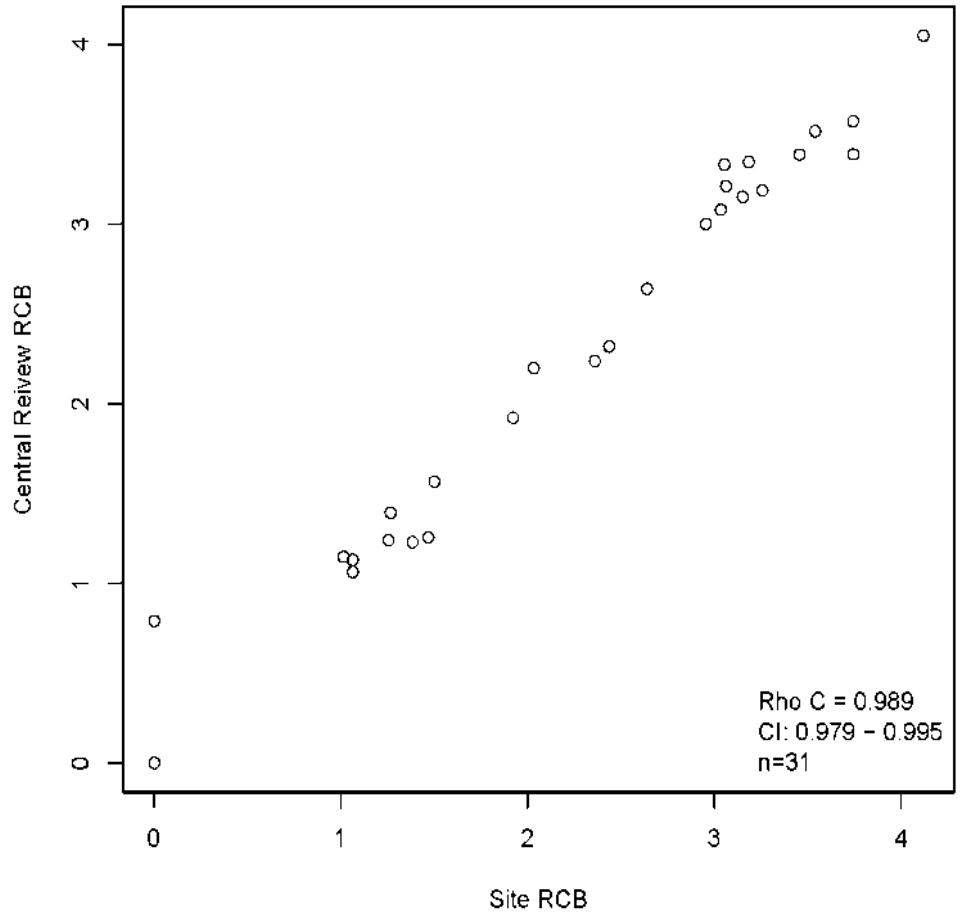


T=Paclitaxel, H=Trastuzumab, P=Pertuzumab

I-SPY 2 Statistical Analysis

- **Primary Endpoint:**
  - Pathological complete response (pCR)
  - Defined as no residual invasive cancer in breast or lymph nodes (pyT0pyN0)
  - Assessed using the Residual Cancer Burden (RCB) method*
  - Highly reproducible between local and central pathologist review
- **Intent-to-treat:**
  - Patients who received therapy, but later withdrew, leave the institution, went to non-protocol therapy, or progressed are considered non-pCR
- **Secondary endpoints:**
  - RCB, EFS, DRFS at 3, 5 and 10 years

Scatterplot of RCB index entered by Site vs. Central Review



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

Categories of Biomarkers in I-SPY 2

STANDARD

1. **ER/HER2 IHC; FISH**
2. **Mammaprint**
   - FDA cleared 70 gene assay (used to determine randomization eligibility)
   - IDE (filed with FDA) for 44K array
2. **MR volume**
   - used to determine response to treatment
   - IDE (filed with FDA)

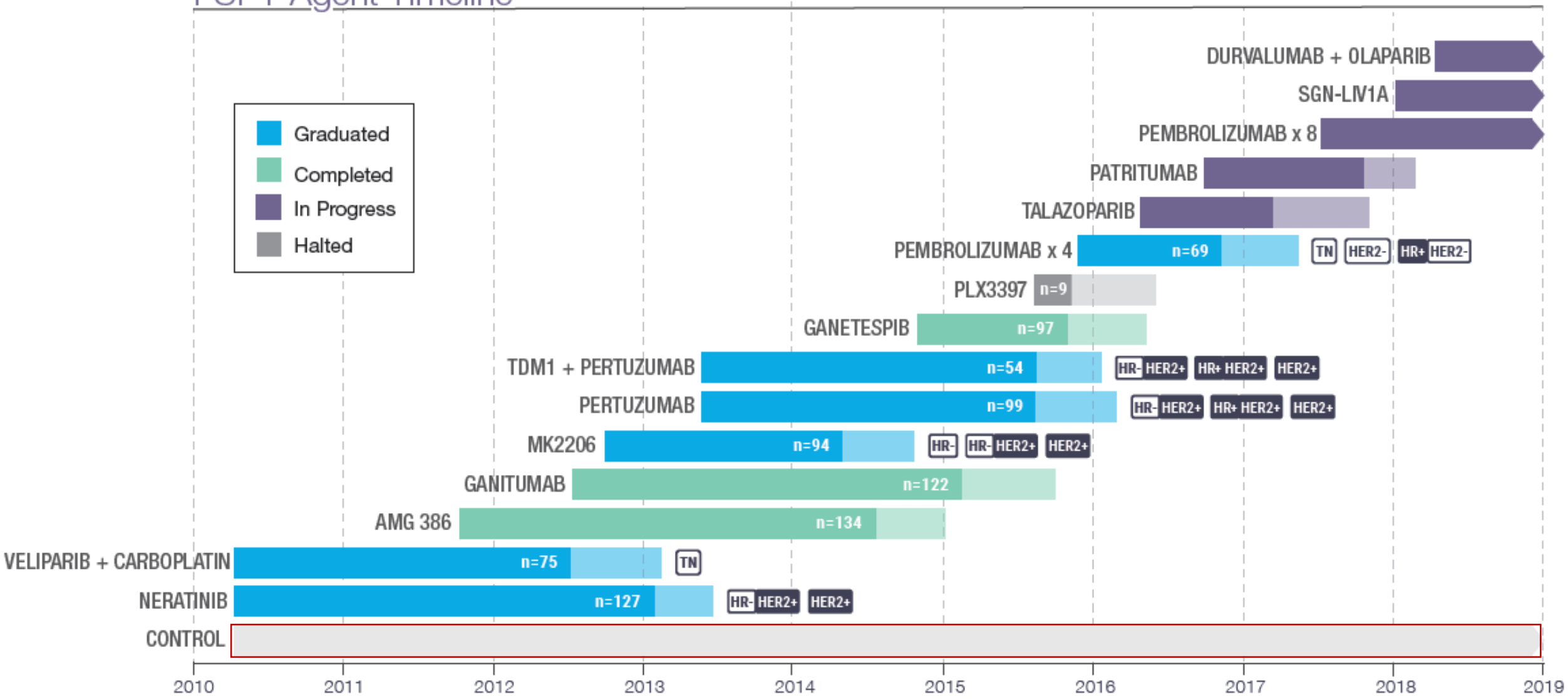
QUALIFYING

1. **Signatures**
   1. DNA Repair Deficiency
   2. AKT pathway
   3. HER pathway
   4. Hi-2 (Mammaprint)
   5. Immune Signatures
2. **Platforms**
   1. 44k Agilent Array
   2. Reverse Phase Protein Arrays
   3. Vectra Multiplex Staining Environment

EXPLORATORY

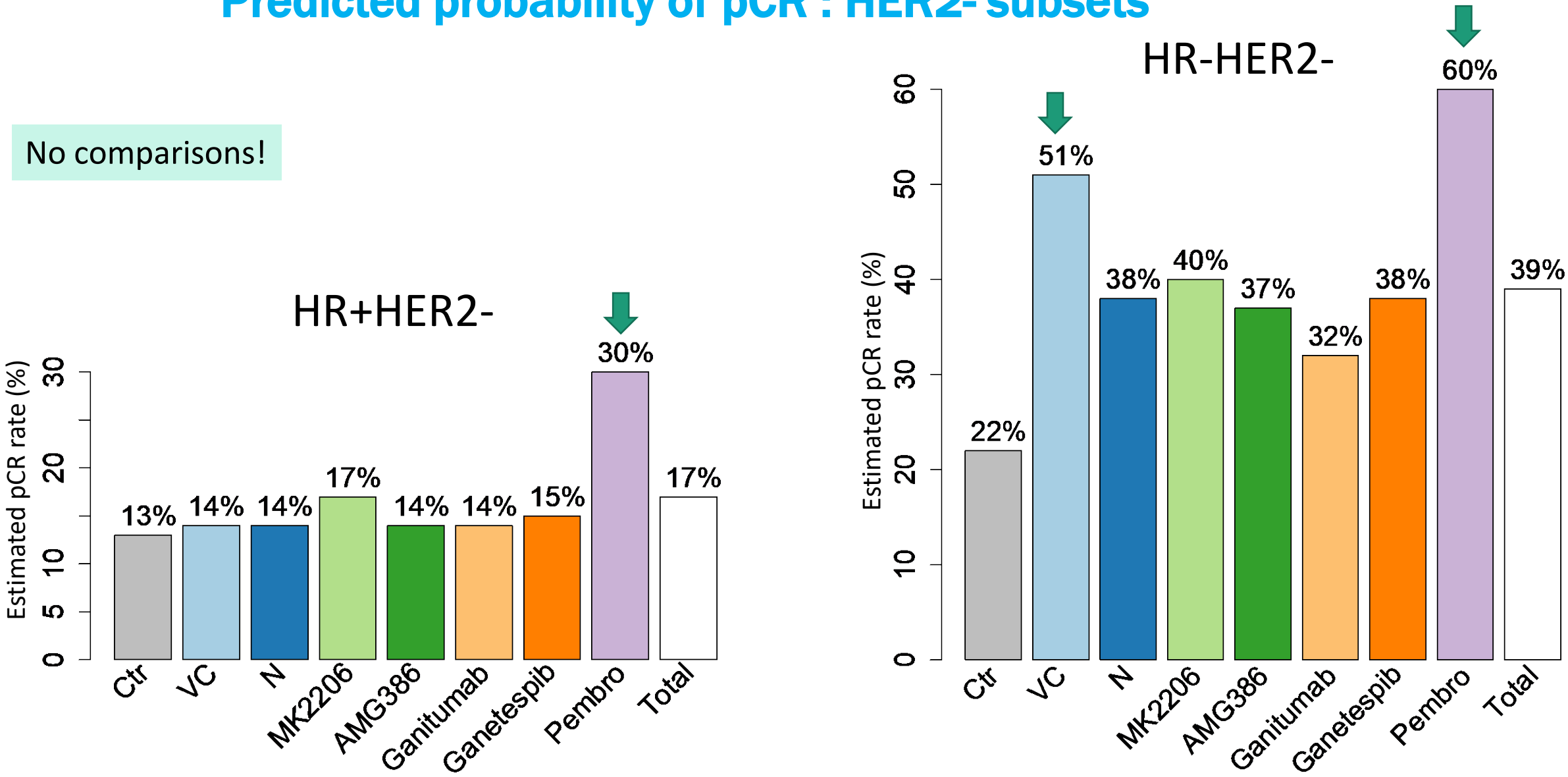
1. RNA seq
2. DNA seq
3. Circulating DNA
4. Circulating tumor cells

I-SPY Agent Timeline



Predicted probability of pCR : HER2- subsets

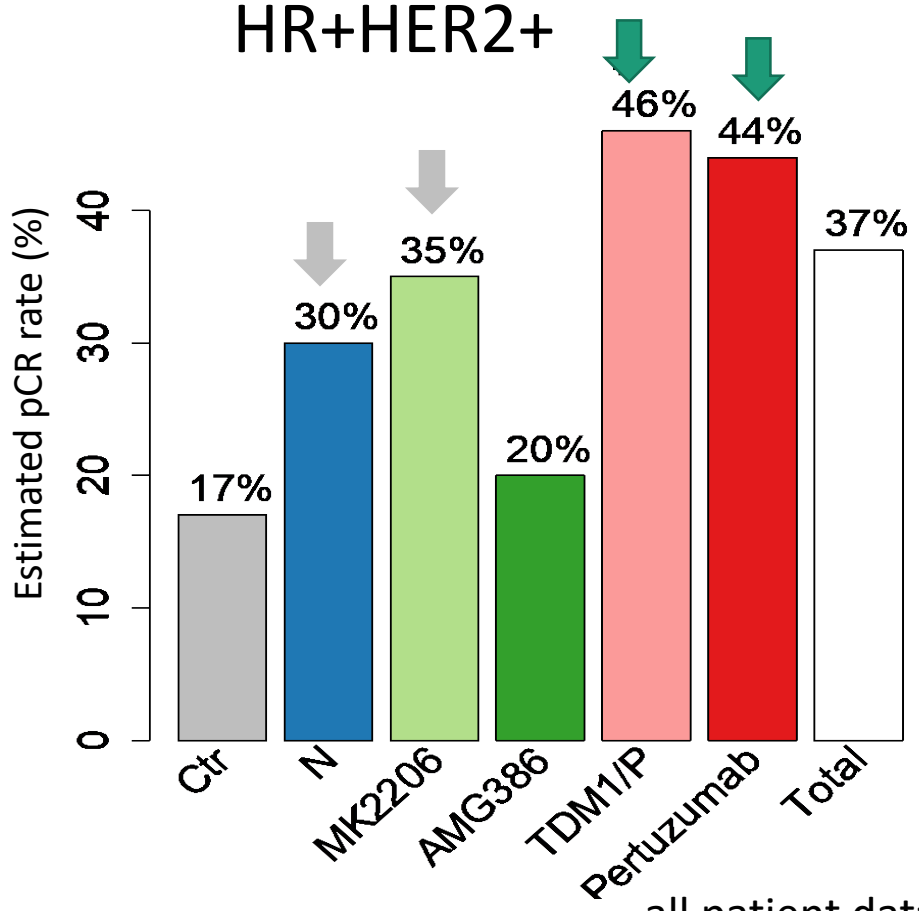
No comparisons!

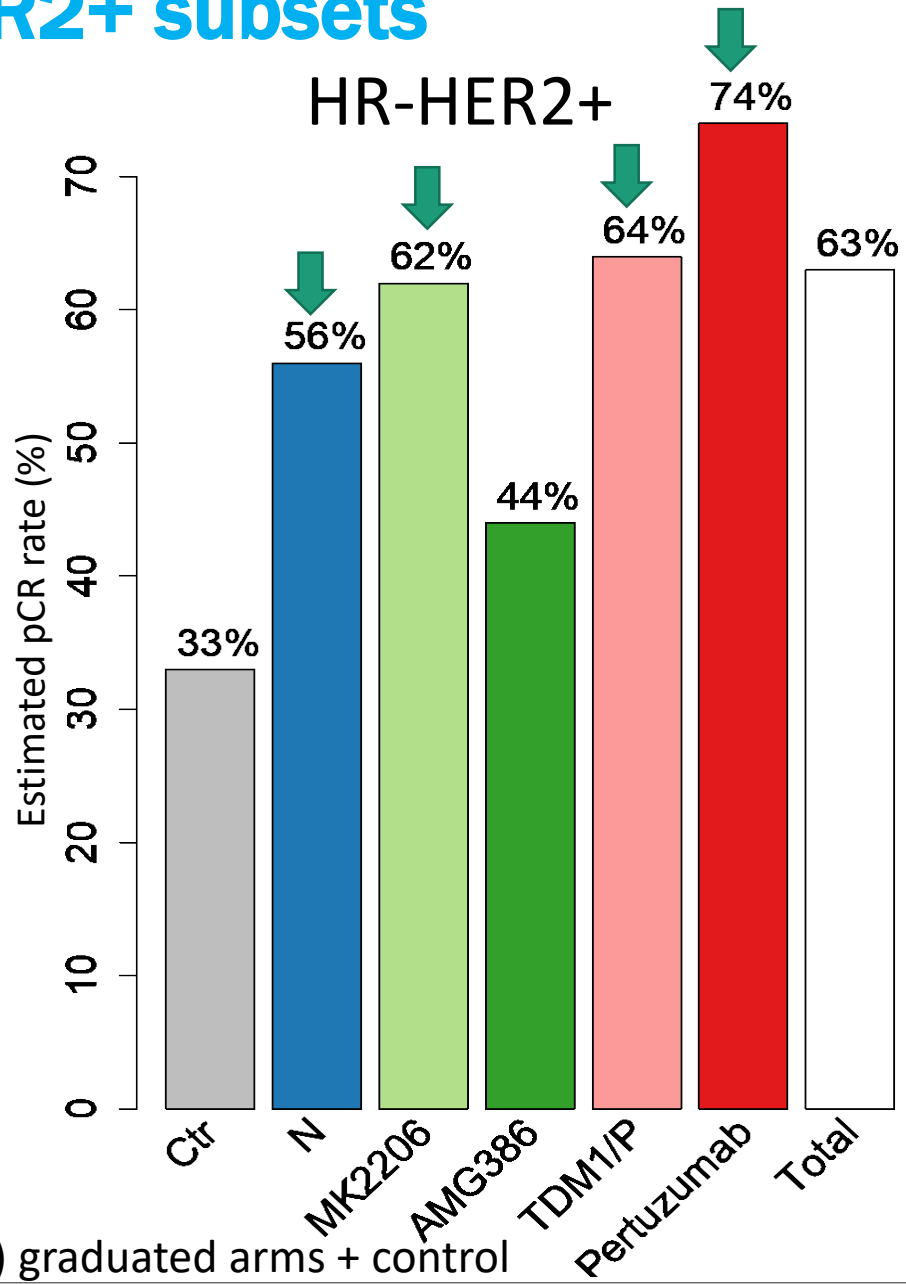


all patient data from 7 graduated arms + control

Predicted probability of pCR: HER2+ subsets

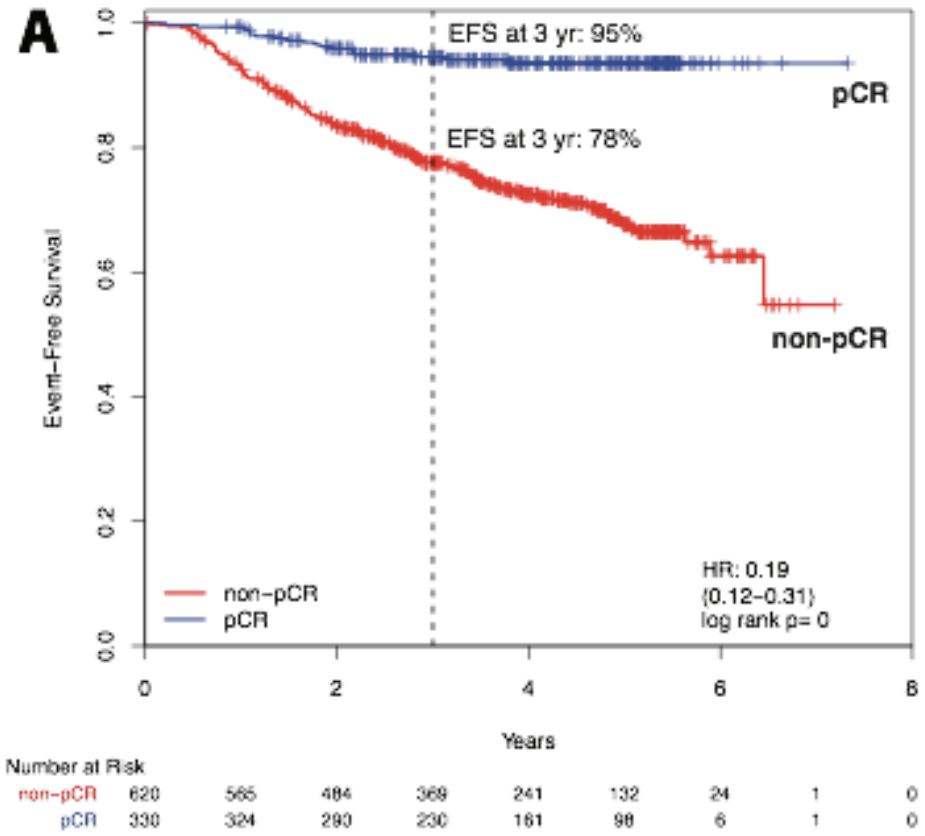
No comparisons!

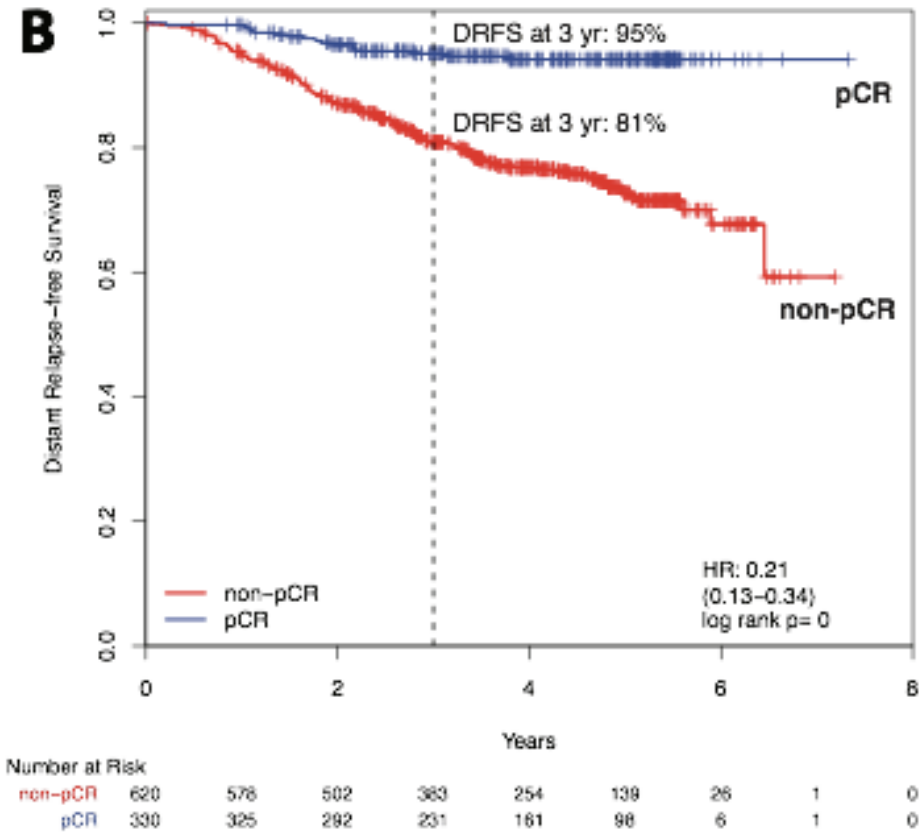




all patient data from 4 HER+ (4/7) graduated arms + control

pCR status as predictor of DRFS and EFS
All subtypes combined

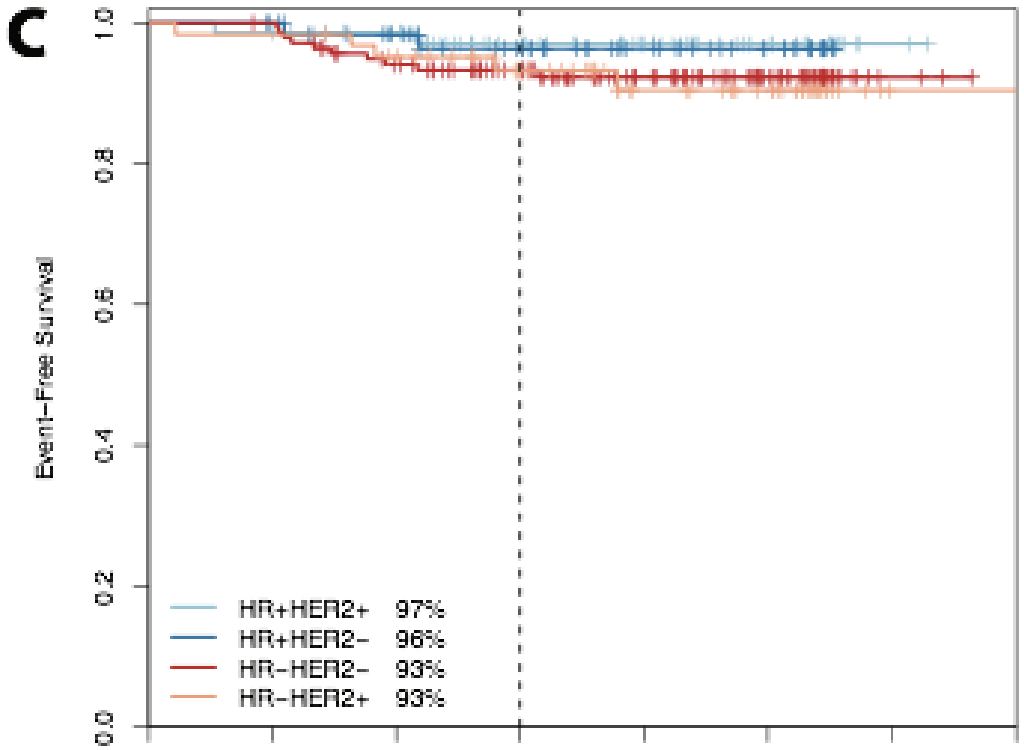




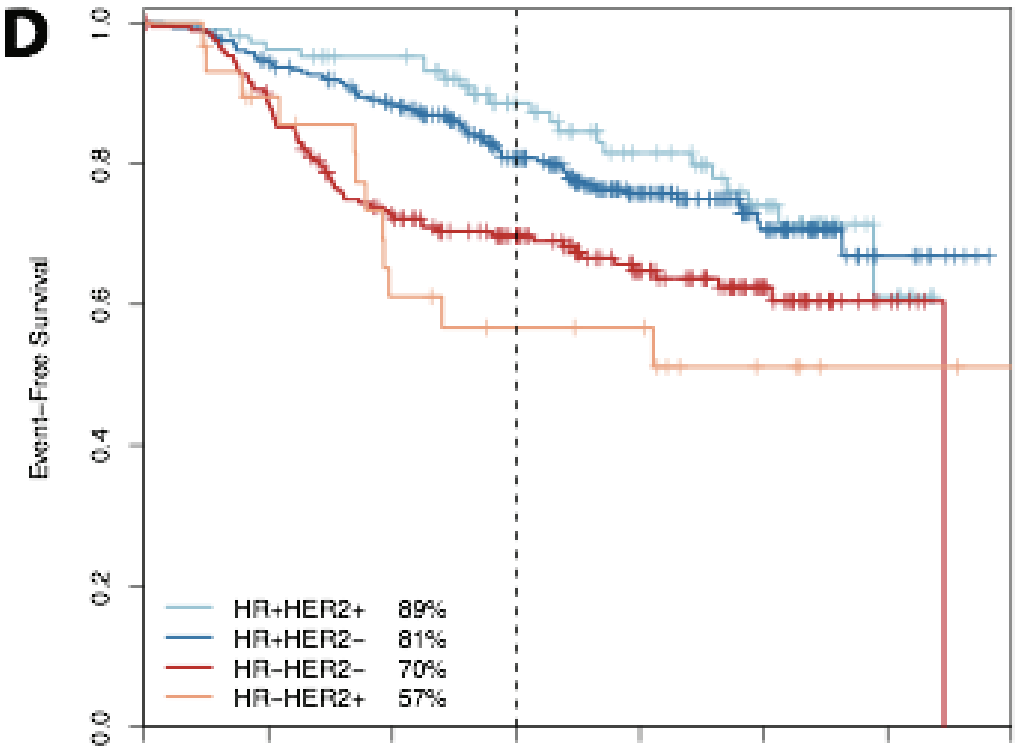
19 events in 1265 woman- years for those achieving pCR (0.0150/yr) and 169 events in 2125 woman-years for those not achieving pCR (0.0795/yr).

Yee D, DeMichele A, Isaacs C, et al, SABCS, 2017; updated

EFS by pCR & non-pCR: By subtype



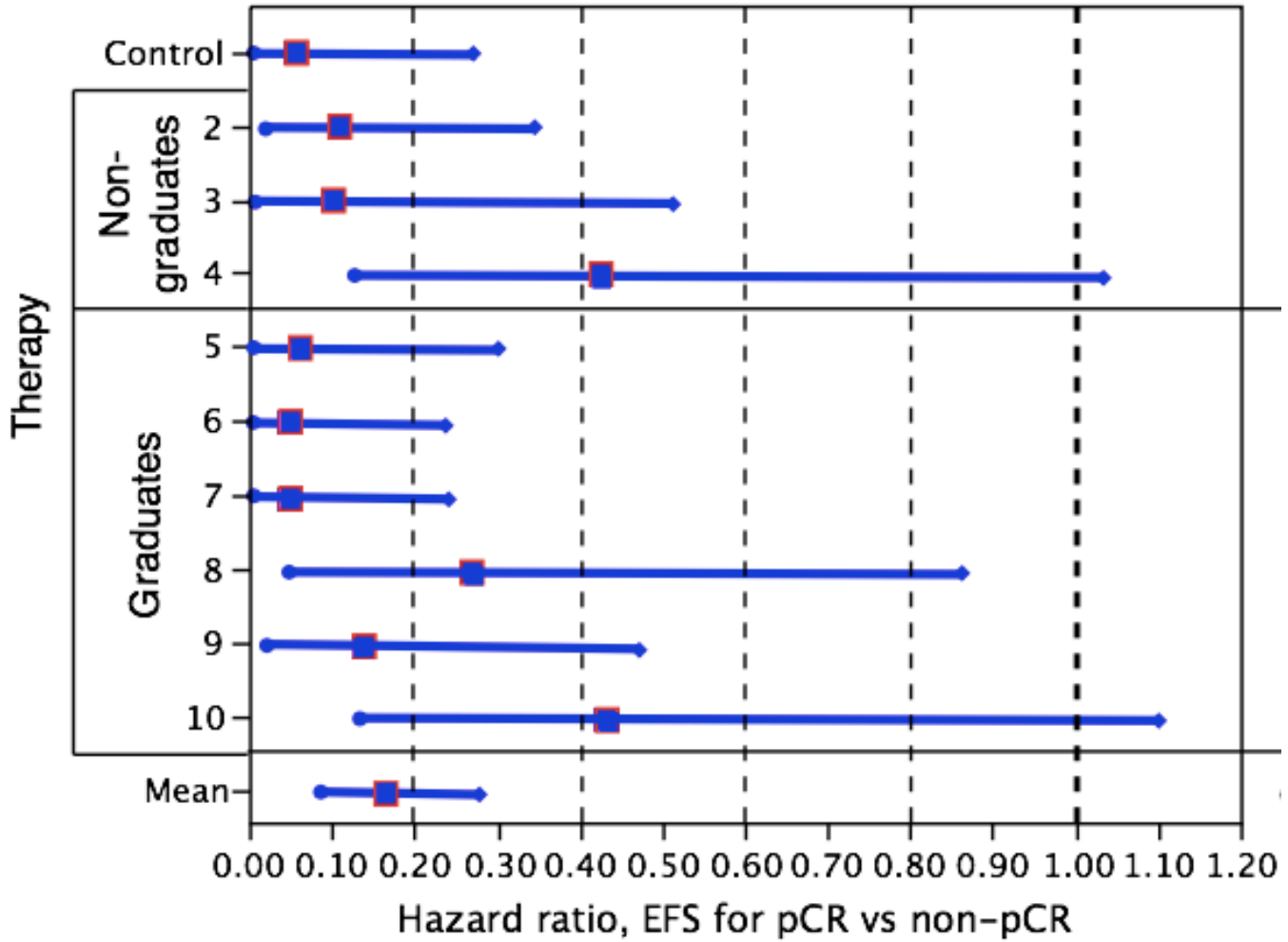
pCR



Non pCR

Yee D, DeMichele A, Isaacs C, et al, SABCS, 2017; updated

EFS Hazard Ratio for pCR/non-pCR: By Treatment Arm



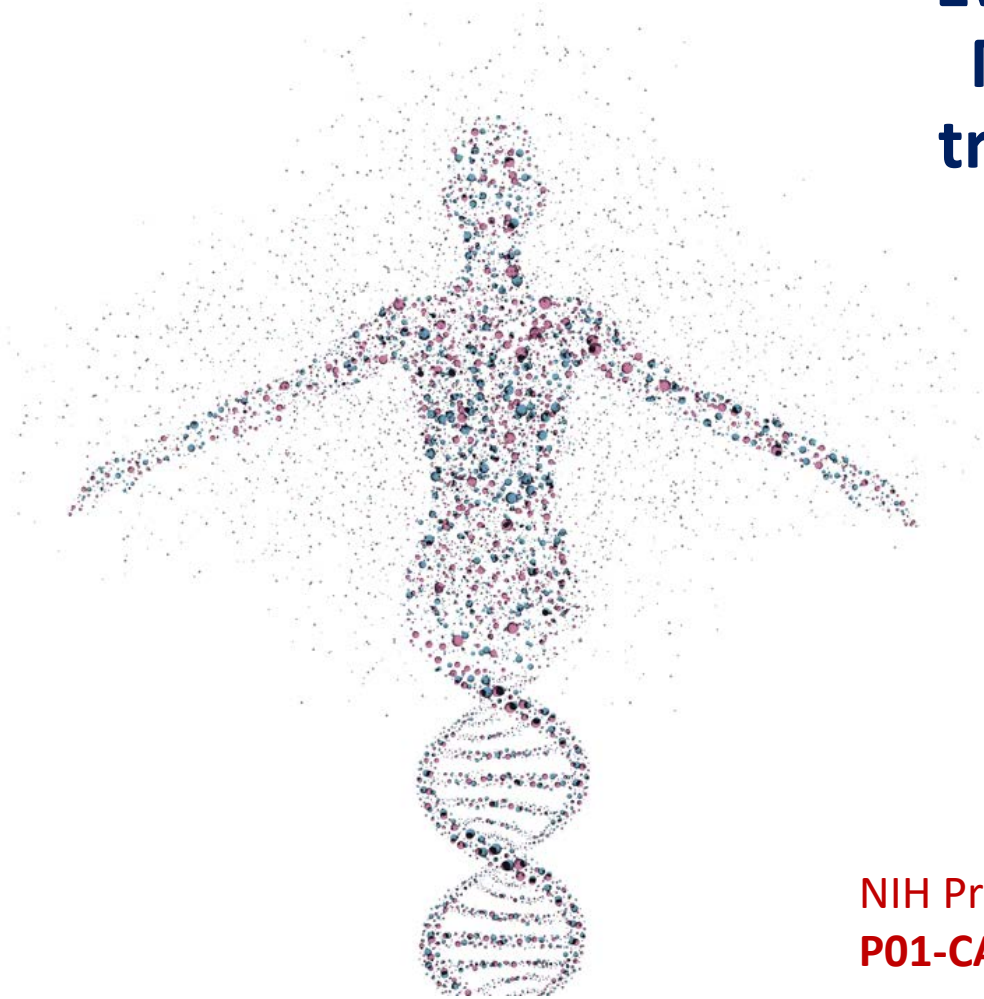
EFS Analysis Summary

Subtype	N	pCR Rate (95% CI*)	EFS Hazard Ratio (95% CI)	DRFS Hazard Ratio (95% CI)
HR+HER2-	361	17% (14%-22%)	0.14 (0.03 – 0.55)	0.16 (0.04 – 0.64)
HR+HER2+	173	40% (33%-48%)	0.15 (0.03 – 0.63)	0.10 (0.01 – 0.77)
HR-HER2+	326	42% (36%-47%)	0.18 (0.09 – 0.34)	0.20 (0.10 – 0.40)
HR-HER2-	90	68% (57%-77%)	0.14 (0.05 – 0.41)	0.18 (0.06 – 0.53)
ALL	950	35% (32%-38%)	0.19 (0.12 – 0.31)	0.21 (0.13 – 0.34)

*Based on binomial exact (Clopper-Pearson) confidence interval method.

Key Lessons Learned: pCR> EFS/DRFS in I-SPY2

- **pCR is a robust early endpoint in the setting of a well run platform trial set up as a learning system with:**
  - Standards for eligibility (high risk for early recurrence)
  - Screening for metastatic disease
  - Standards for pathology assessment and multidisciplinary identification (surgeons, radiologists, pathologists)
  - Long term follow-up of all patients over time (correlation of early, intermediate and late endpoints)
- **Achieving a pCR is equally prognostic across all tumor subsets**
  - Enable targeted de-escalation and escalation of therapy, to *both* decrease toxicity and improve overall chance of survival



I-SPY2 +:
Evolving the I-SPY 2 TRIAL to include MRI-directed, adaptive sequential treatment to optimize breast cancer outcomes

NIH Program Project Grant
P01-CA210961

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Requirements for “multi- line” neoadjuvant trials

Identify patients who are ***not*** on the course to pCR

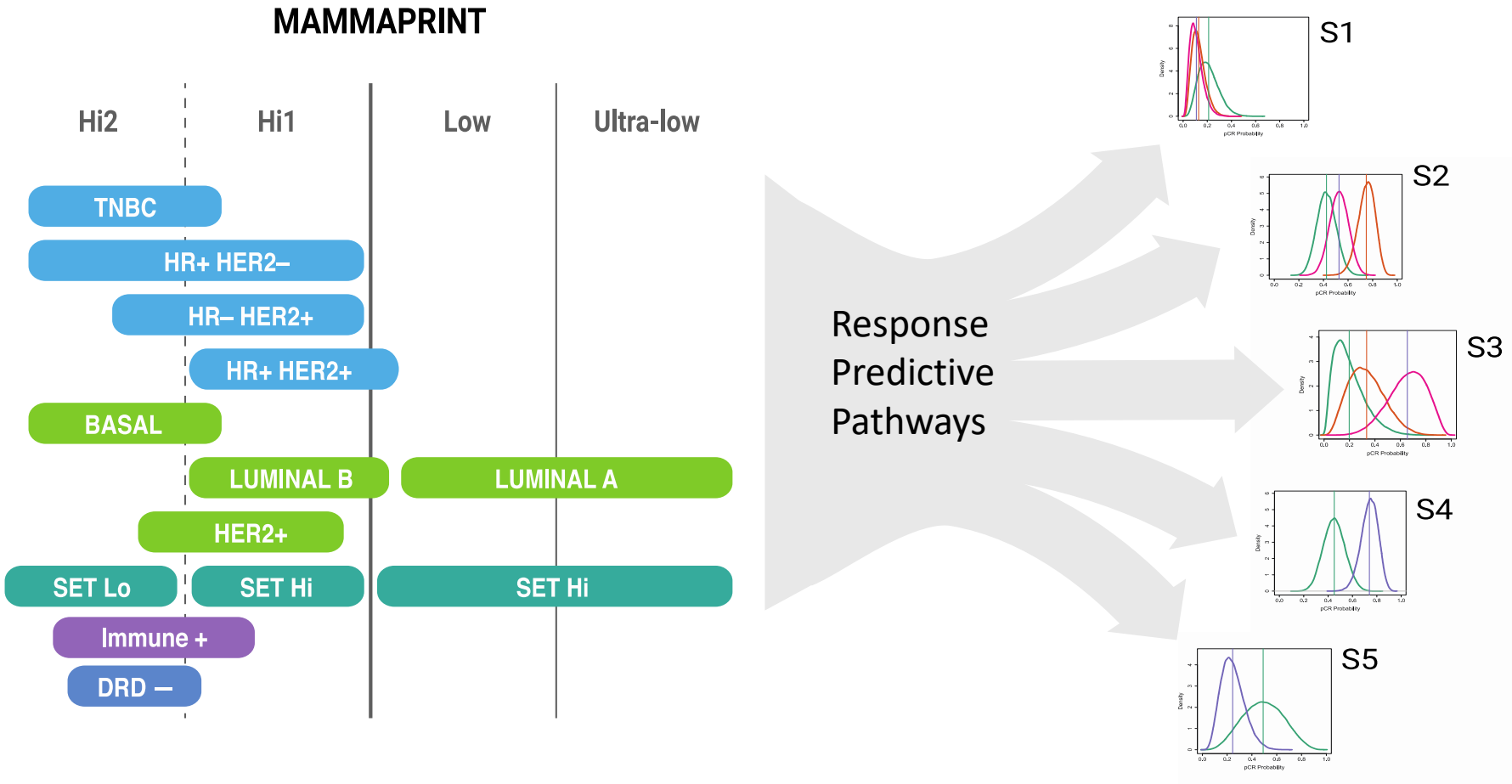
- Determine failure **non-invasively**
- Assess when to call failure and **switch**

Escalate to second line therapy to achieve pCR

- Rational selection of second-line therapy
- Determine whether “switching” strategies are effective

Biomarker Profiles for Prospective Treatment Assignment

Identify the Right Population to Optimize Treatment



The I-SPY Platform is Evolving

- Surrogates and endpoints are validated for the individual
- Accumulating data that combination imaging/biopsy can tell us when we have reached pCR
- Biomarker/drug combinations exist for real-time drug selection based upon individual's tumor biology
- We can test these strategies for precision treatment in platform trials of continuous learning
  - Optimizing outcomes for individuals
  - Assessing benefits of drugs in patient subsets
  - Reducing the burden of metastatic disease

Participating Organizations

FUNDING PARTNERS

William K Bowes, Jr. Foundation
Give Breast Cancer the Boot
University of California San Francisco (UCSF)
The Biomarkers Consortium
IQVIA tm (formerly known as Quintiles Transnational Corporation)
The Breast Cancer Research Foundation
Safeway Foundation, an Albertsons Company
Stand Up to Cancer Netherlands
University of Pennsylvania

INVESTIGATIONAL AGENT PROVIDERS

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UCSF
The Translational Genomics Research Institute (TGen)