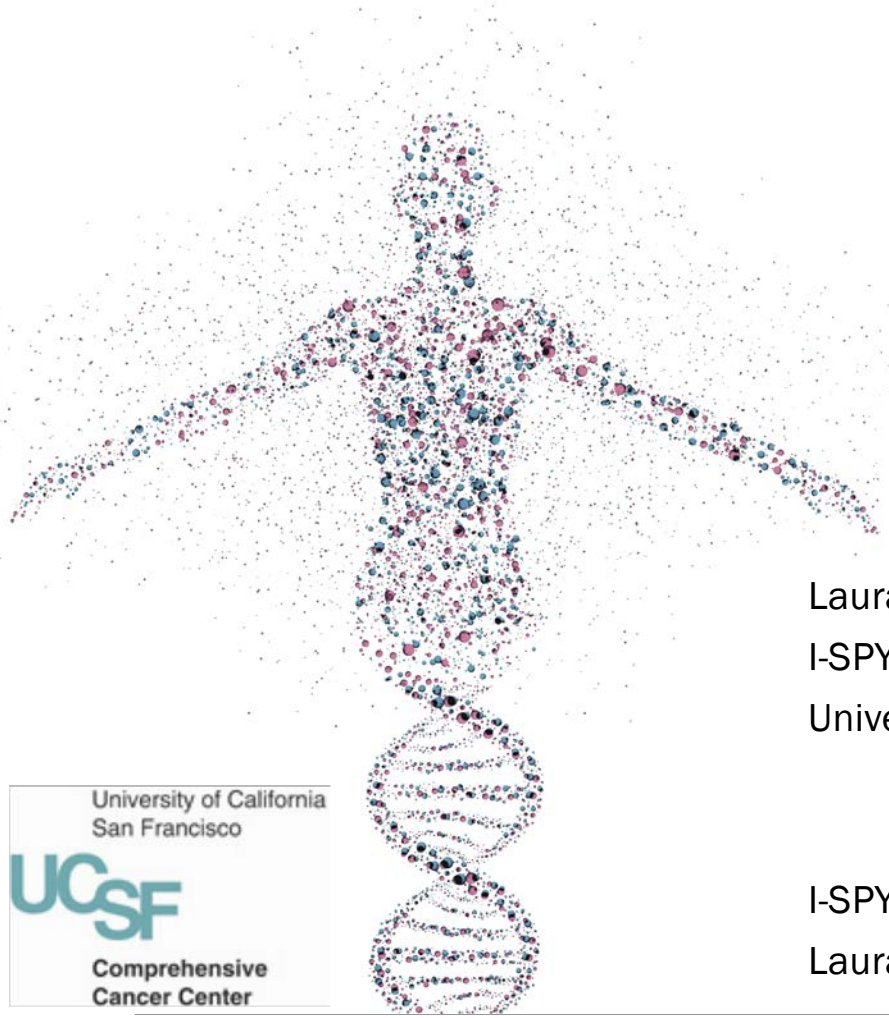


I SPY 2: The right drug, the right patient, the right time

Using Biology to Adaptively Guide Treatment for Early Breast Cancer and Predict Response

Laura van ‘t Veer, PhD

I-SPY 2 co-Principal Investigator and Biomarker Chair

University of California San Francisco

University of California San Francisco
UCSF
Comprehensive Cancer Center

I-SPY 2 TRIAL PI’s:

Laura Esserman, MD MBA, UCSF & Don Berry, PhD, MD Anderson

Disclosure

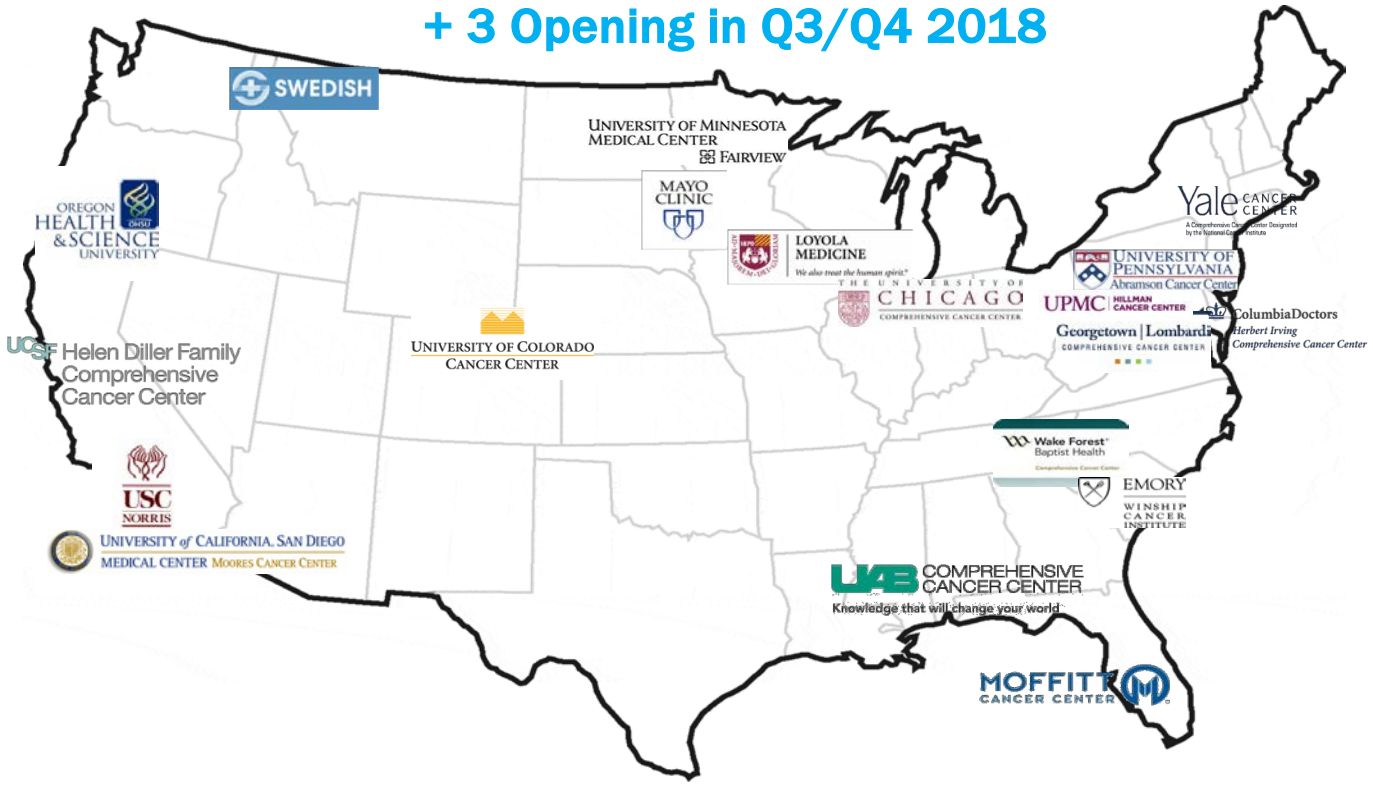
- Co-founder & stockholder Agendia BV
- No other disclosures

Basic Principles of I-SPY

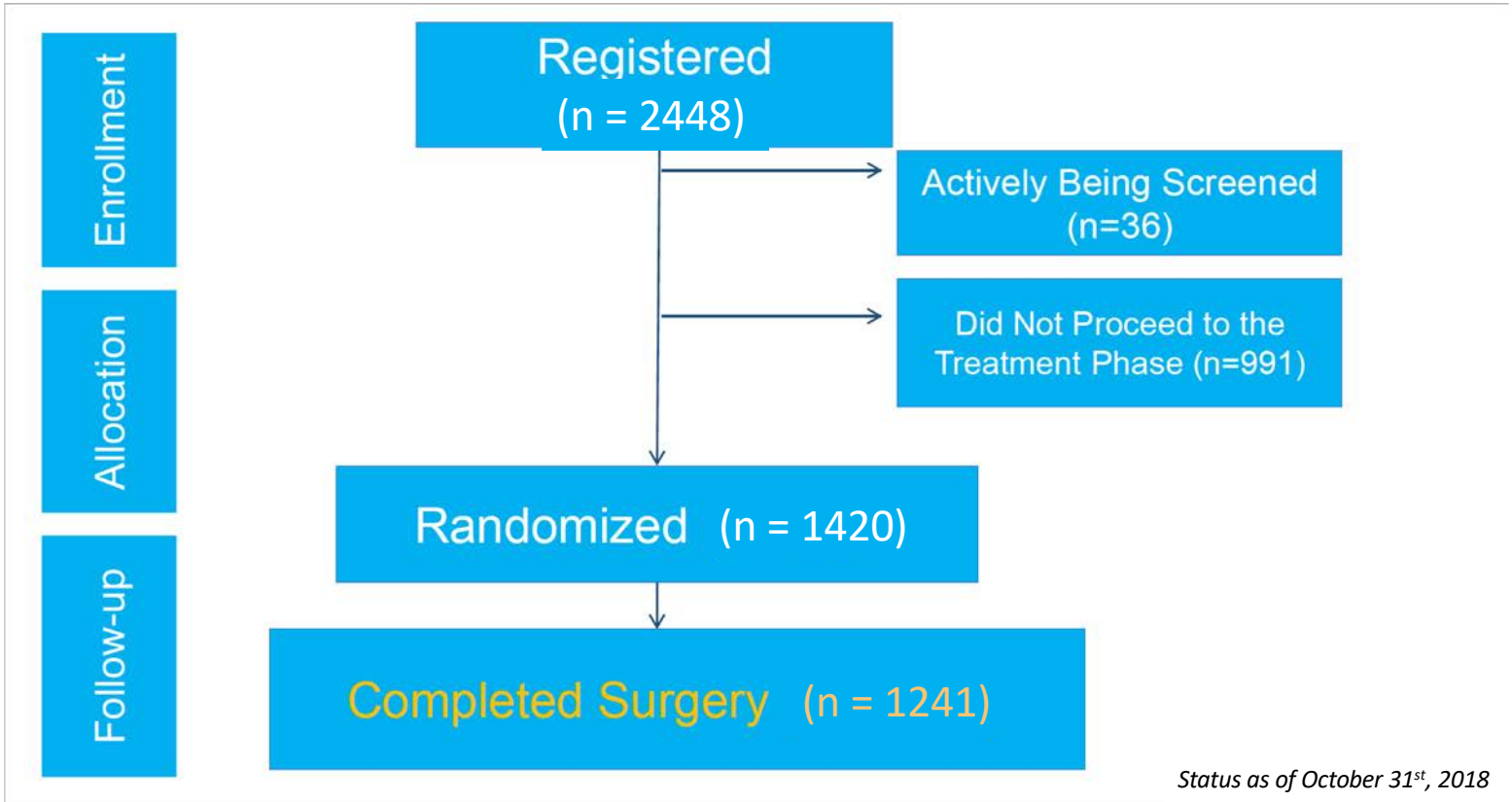
- Test new drugs where they matter most
  - **Early stage** rather than metastatic disease
- Change the order of therapy: learn about response early in the course of care
  - Neoadjuvant setting (**systemic therapy before surgery**)
  - Primary Endpoint is complete response to therapy (**pCR**)
- Build an efficient engine to evaluate drugs, accelerate knowledge turns
  - Master Protocol, Adaptive Design
- Use imaging and biomarker guidance
  - Focus on the population of patients who are at high risk for EARLY recurrence
  - Insights about who responds to what agents
  - "Graduation" for efficacy = threshold predictive probability of success in next phase III trial
- Collaborative by Design:
  - FDA, IRBs, Pharma, Biotech, Academics, Community Cancer Ctrs, Advocates

I-SPY 2 Participating Sites

16 Sites Open and Enrolling
+ 3 Opening in Q3/Q4 2018



Trial Patient Enrollment Overview



Status as of October 31st, 2018

I-SPY 2 Investigational Agents

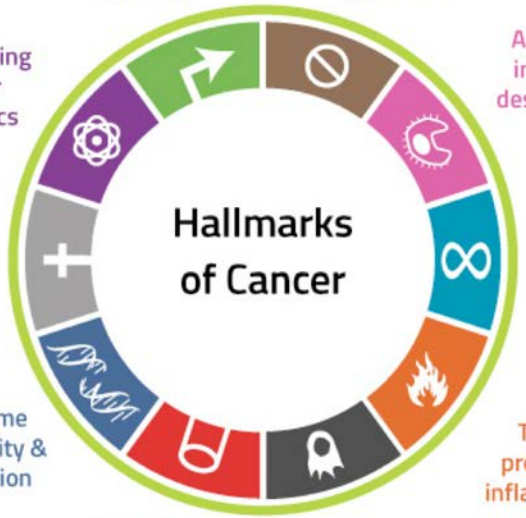
Anti-HER family signaling
- Neratinib
- trastuzumab/pertuzumab
- TDM1/pertuzumab
- trastuzumab/patritumab

Anti-IGF1R
- Ganitumab

AKT inhibition
- MK2206

Immune checkpoint inhibition
- Pembrolizumab

Unfolded protein response inhibition
- ganetespib (HSP90i)



PARP inhibition + DNA damage
- Talazoparib/irinotecan
- veliparib/carboplatin

TIE1/2 inhibition
- AMG386

Agents Developed Targeting Hallmarks of Cancer

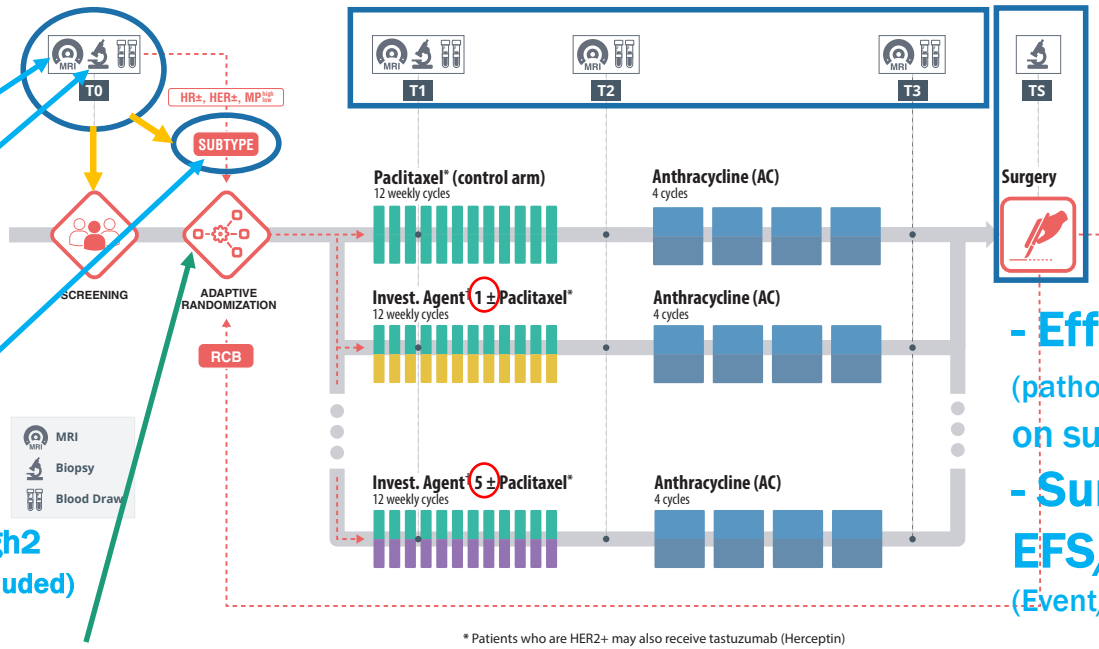
I-SPY 2 Framework for Early High Risk Breast Cancer:

Biomarkers Guide Enrichment of Neoadjuvant Drug Arm with Responding Subtype

Diagnosis → 5 Investigational Drug Arms + Control → Surgery

MRI - tumor volume
biopsy - biological subtype

serial MRI (volume change) & pathology at surgery (residual cancer burden)
informs adaptive randomization by subtype



Biomarkers:

- **Imaging**
- **Pathology**
- **Molecular Biology**
  - **8 subtypes by:**
    - **Hormone Receptor +/-**
    - **HER2 +/-**
    - **MammaPrint High1/High2**
      (HR+/MammaPrint low excluded)

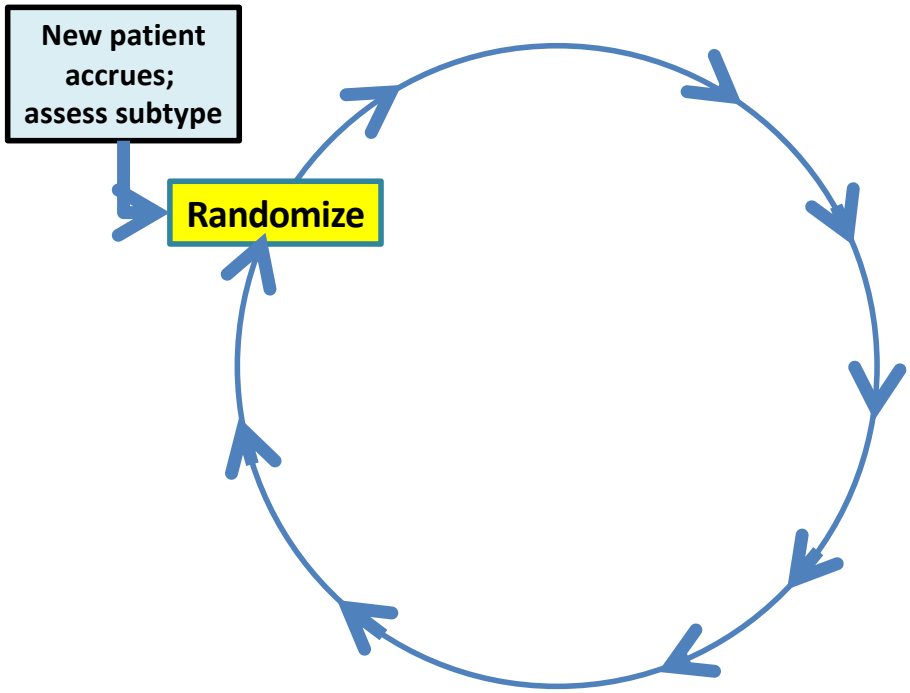
- Efficacy endpoint: pCR
(pathological Complete Response)
on surgery specimen

- Survival endpoint:
EFS/DRFS at 3y & 5y
(Event/Distant Recurrence Free survival)

Adaptive Randomization

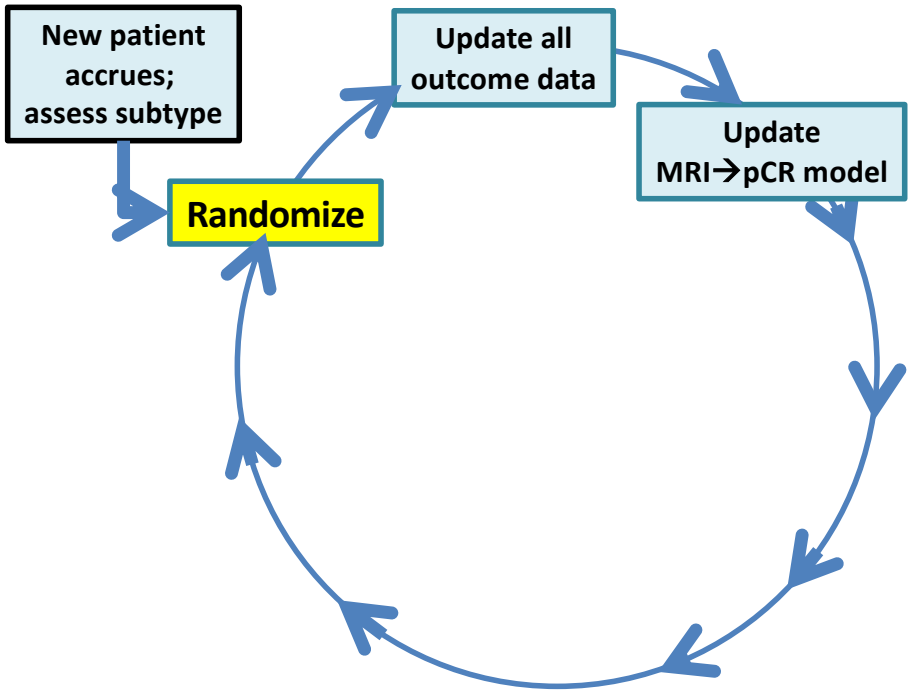
* Patients who are HER2+ may also receive tastuzumab (Herceptin)
† An investigational combination of one or more agents may be used to replace all or some of the standard therapy

I-SPY 2 Adaptive Randomization



Adaptive randomization based on 8 subtypes
(hormone receptor (HR) +/-, HER2 +/-, MammaPrint-High 1 or High 2; 2^3=8)

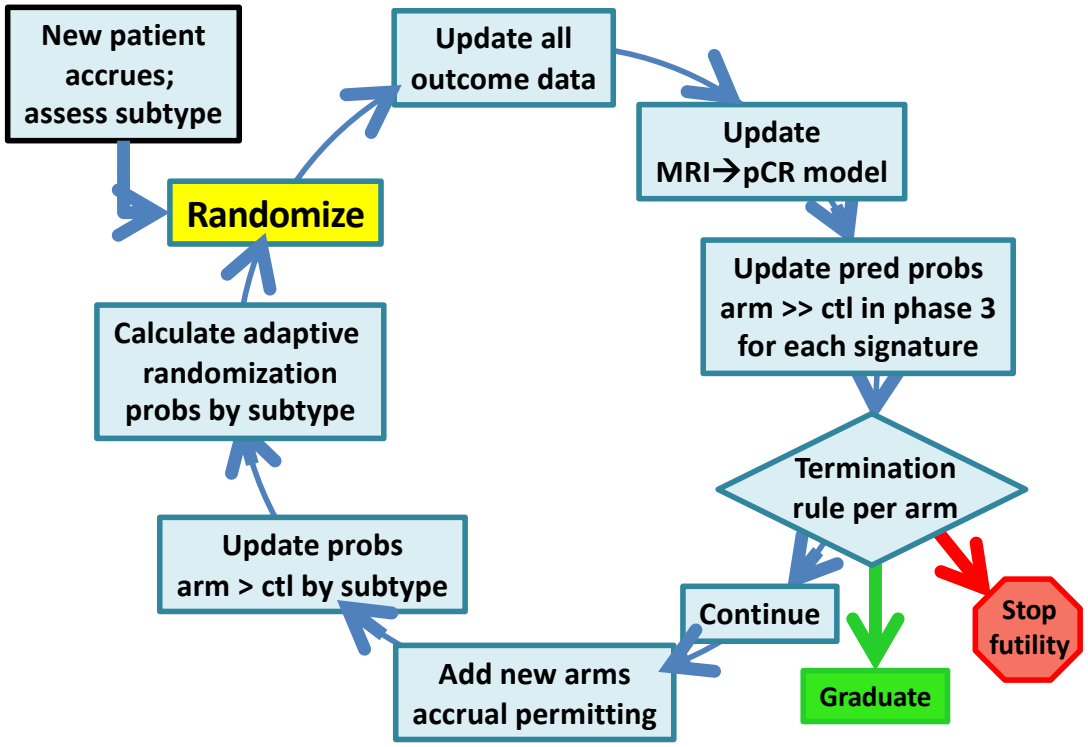
I-SPY 2 Adaptive Randomization



Adaptive randomization based on 8 subtypes
(hormone receptor (HR) +/-, HER2 +/-, MammaPrint-High 1 or High 2; 2^3=8)

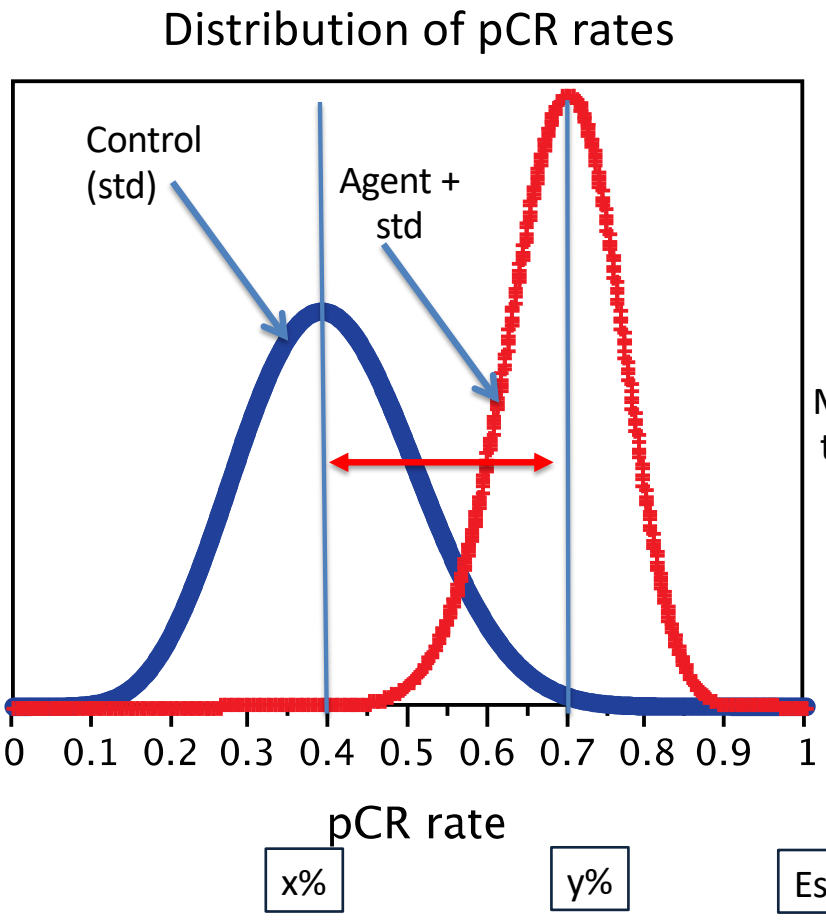
I-SPY 2 Adaptive Randomization

Adaptive randomization based on 8 subtypes



Graduation based on 10 signatures (combinations of subtypes)

Methods for Estimating Response Probability (pathological Complete Response = pCR)



Mean of distribution is the Point Estimate for pCR (estimated pCR)

I-SPY 2 Framework:

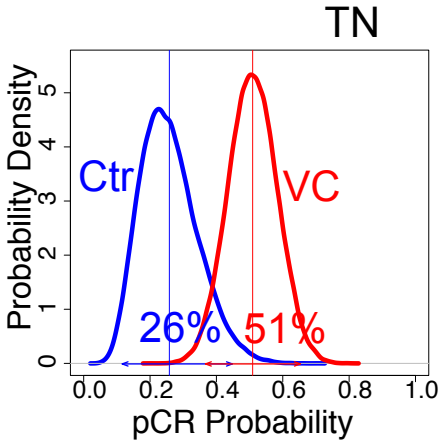
Biomarkers Guide Enrichment of Drug Arm with Responding Subtype

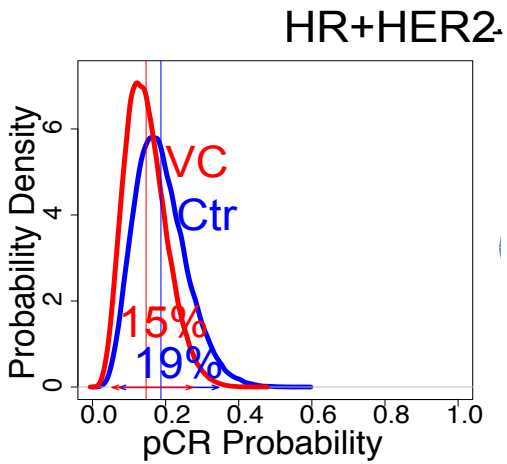
Example: Veliparib (PARP-inhibitor)/Carboplatin

Biomarkers indicated while arm was ongoing:

- response in Triple-Negative (TN) Breast Cancer > 'graduation'
- no response in Hormone receptor positive Breast cancer (HR+/HER2-)

and the adaptive randomization enriched the VC arm with TN Breast Cancer





VC response ~50%!

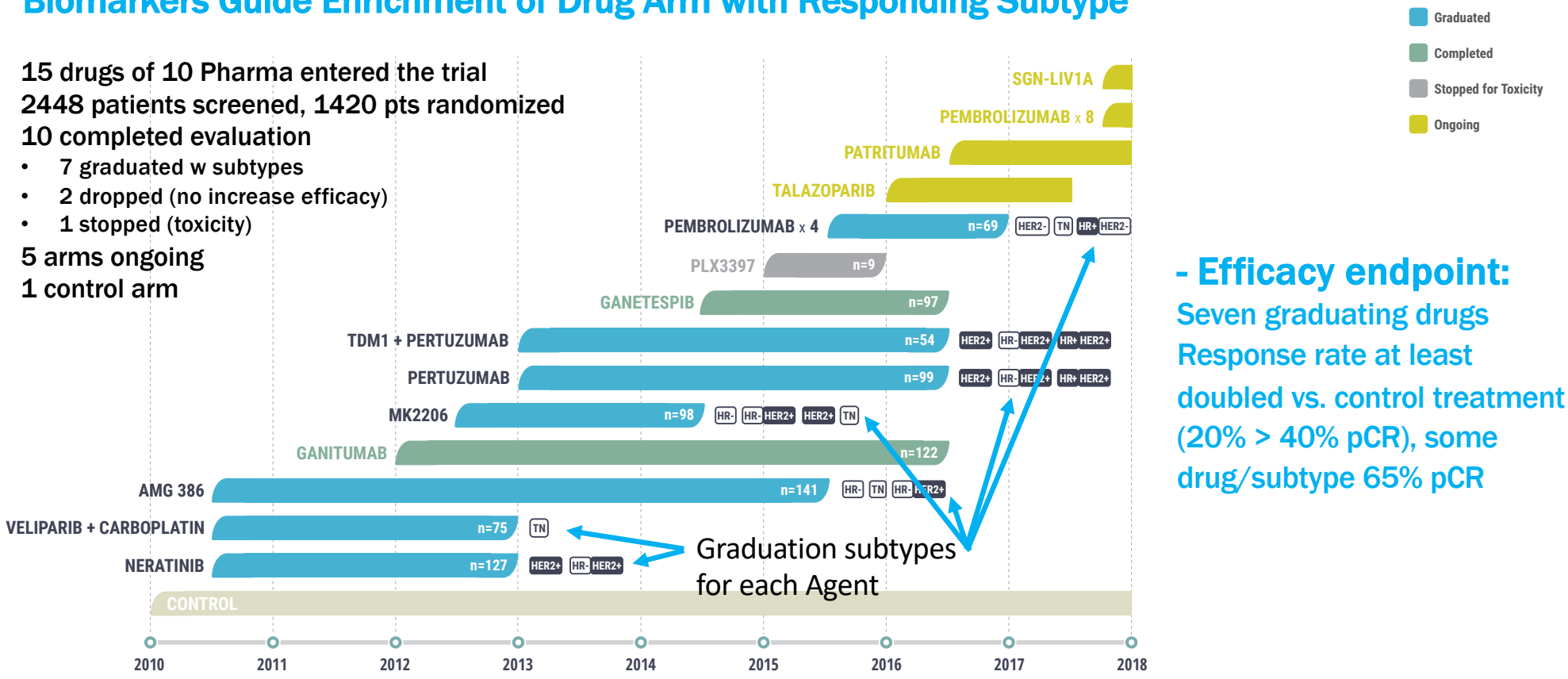
Timeline of Investigational Drugs and Graduating Subtypes

Biomarkers Guide Enrichment of Drug Arm with Responding Subtype

15 drugs of 10 Pharma entered the trial
2448 patients screened, 1420 pts randomized
10 completed evaluation

- 7 graduated w subtypes
- 2 dropped (no increase efficacy)
- 1 stopped (toxicity)

5 arms ongoing
1 control arm



- Efficacy endpoint:

Seven graduating drugs
Response rate at least doubled vs. control treatment (20% > 40% pCR), some drug/subtype 65% pCR

pCR relates to survival regardless of treatment

10 treatment arms, 741 patients, minimal 2 yr and median 2.7 yr follow-up

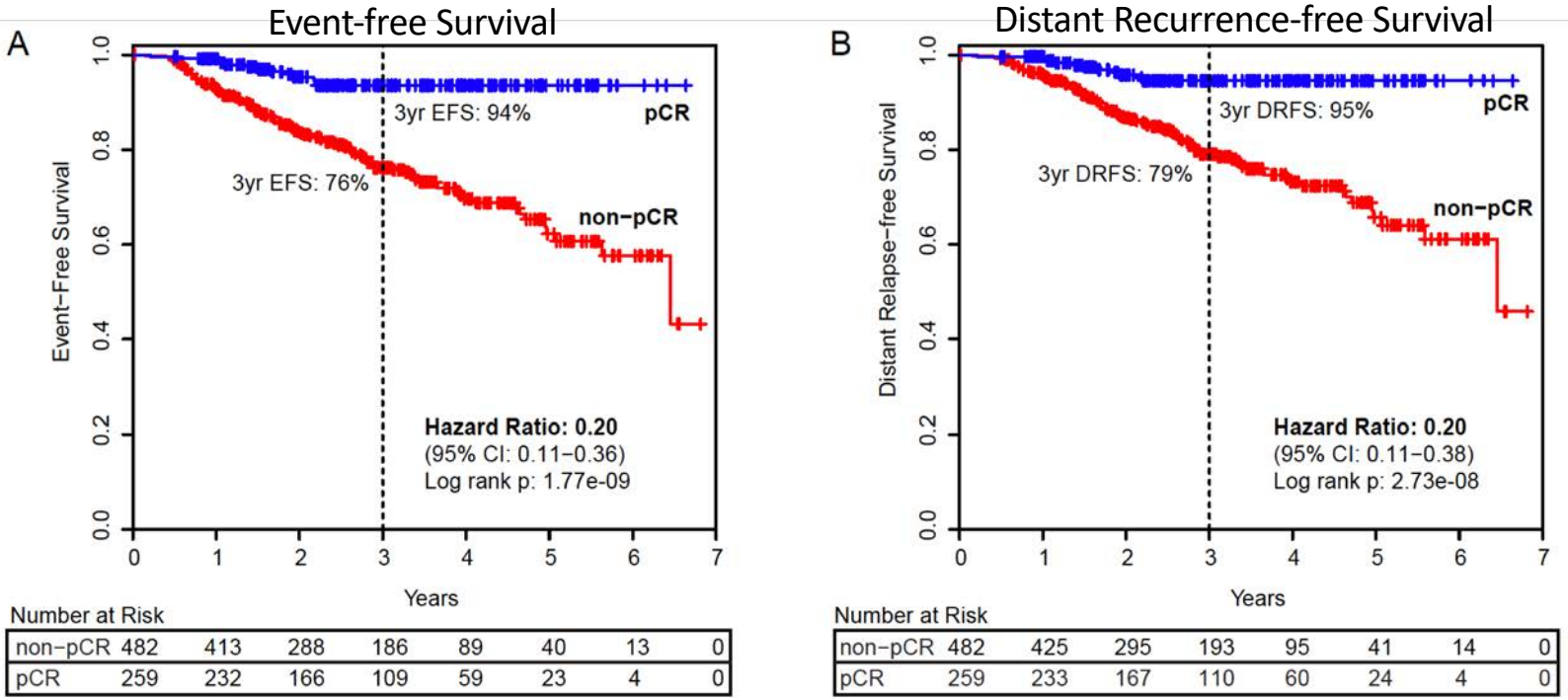


Figure 3: Association between pCR and Survival Outcomes (A) Kaplan Meier curves of EFS by pCR; (B) Kaplan Meier curves of DRFS by pCR.

(poster PB-11 DeMichele et al)

pCR gives 94-95% 3 yr survival, regardless of drug vs. no-pCR 76-79% 3 yr survival

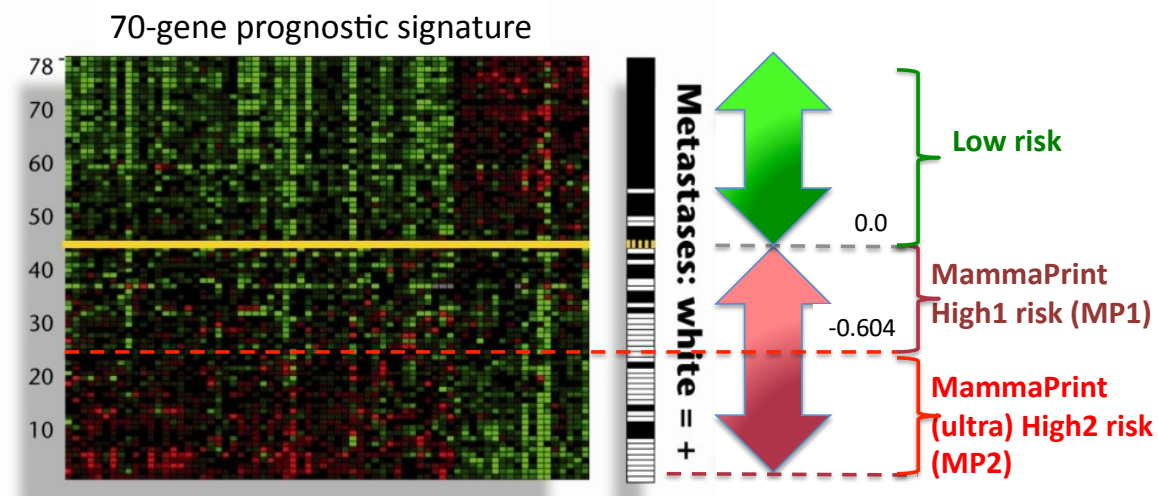
Yee et all, SABCS 2017; DeMichele et all, ENA 2018 abstract 160

Qualifying Biomarkers to improve response prediction

- Important to get every patient to pCR (increased probability of survival)
- I-SPY 2 randomizes by 8 subtypes (HR +/-, HER2+/-, MammaPrint High1/High 2)
- How can biology further identify responders?

- I-SPY 2 tests ‘Qualifying Biomarkers’, which have existing evidence for response prediction
  - Biology of Targeted agent, eg DNA repair deficiency, HER2 signaling, immune signatures, biology subtyping
- Presented here: 70-gene signature (MammaPrint) High1 versus High2 (high risk and very high risk for recurrence, and 80-gene molecular subtyping signature (BluePrint) which identifies luminal-, basal- and HER2-type

70-gene High1 and High2 risk as biomarker of response prediction



MammaPrint 70-gene expression signature identifies patients at low risk and high risk for recurrence.
Here we use a High-risk1 and High-risk2 (ultra-high) sub-classification

986 patients I-SPY 2 patients with MPHigh1/High2 class assessments (49% MP1, 51% MP2)

Control arm: paclitaxel (with trastuzumab (H) in HER2+), followed by doxorubicin/cytoxan (AC) (ctr treatment)

9 Experimental arms: veliparib/carboplatin (VC); neratinib (N); MK2206; Ganitumab; Ganetespib; AMG386; TDM1/pertuzumab(P); H/P; and Pembrolizumab; + ctr treatment

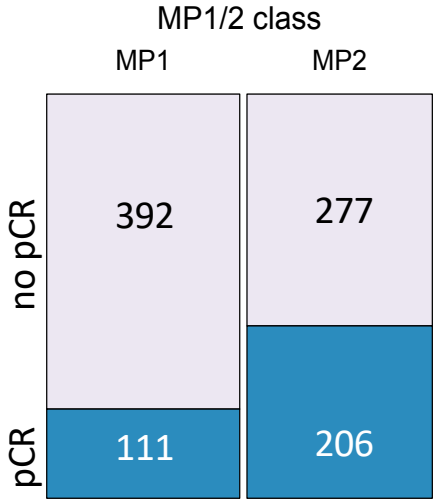
Assessment of association of MP1/2 class and pCR:

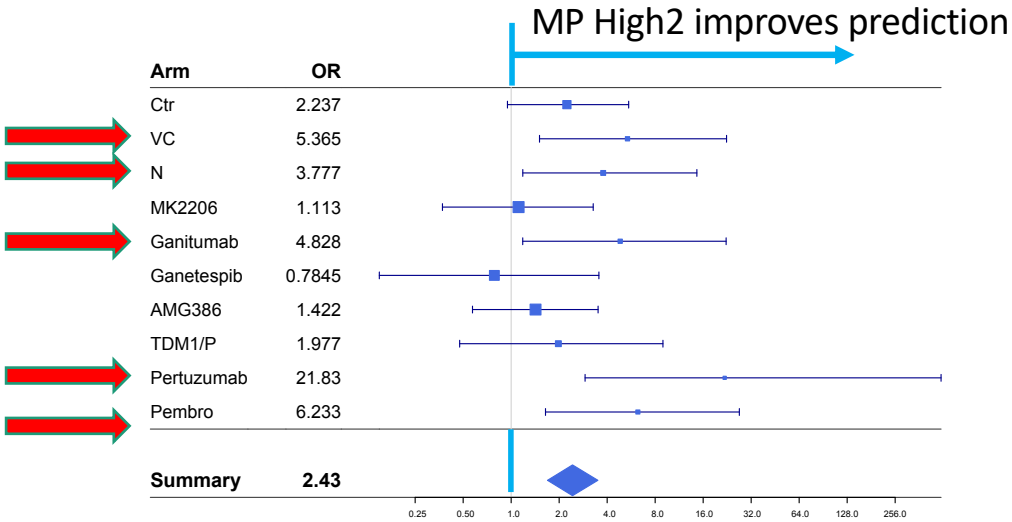
Univariate: Logistic model and **Multivariate:** Logistic model adjusting for HR and HER2 status, and treatment arm as covariates. Significance threshold: p value < 0.05

Denise Wolf, PhD
Computational Scientist

MPHigh1/High2 predicts 'chemo-sensitivity'

- 986 I-SPY 2 patients across and within 10 treatment arms
- Association of MP High1/High2 with pCR across all, and within 5 arms





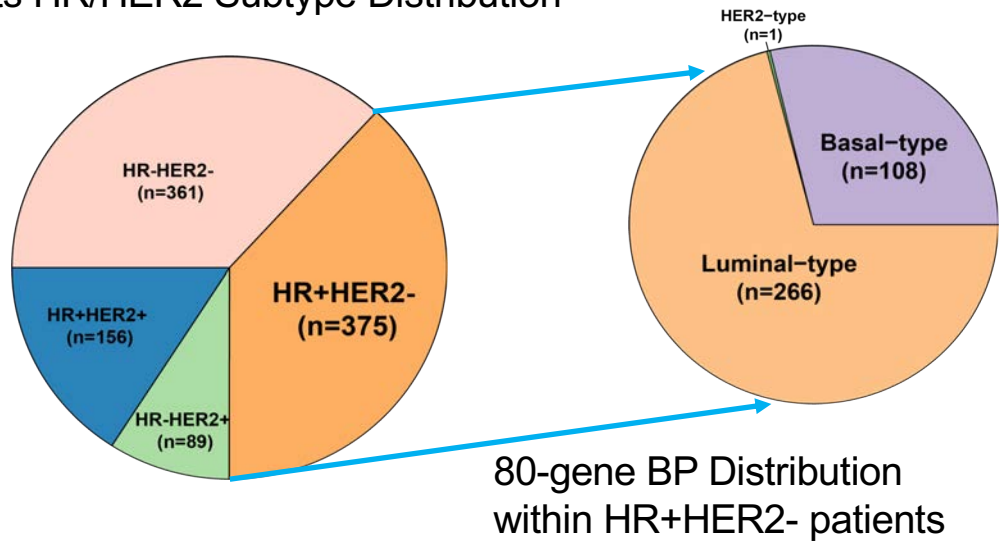
Across all arms combined, **MP High2 associates with pCR** (OR=2.43; p=1.31E-06) **in a model adjusting for treatment arm, HR, and HER2 status**

MP High2 associated with pCR in half the arms (*Veliparib-carbo, Neratinib, Ganitumab, Trastuzumab/Pertuzumab and Pembrolizumab*) in a model adjusting for HR and HER2 status (OR 2.43)
- most strongly in HR+/HER2- (OR 3.62; p=1.18E-0.5) (data not displayed)

80-gene Molecular subtype 'basal' as biomarker of response prediction

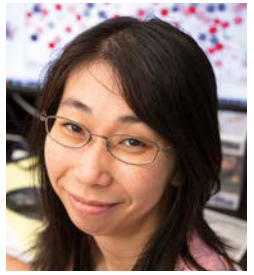
- BluePrint molecular subtype identifies functional luminal-, basal- and HER2-type

986 patients HR/HER2 Subtype Distribution



80-gene BP Distribution
within HR+HER2- patients

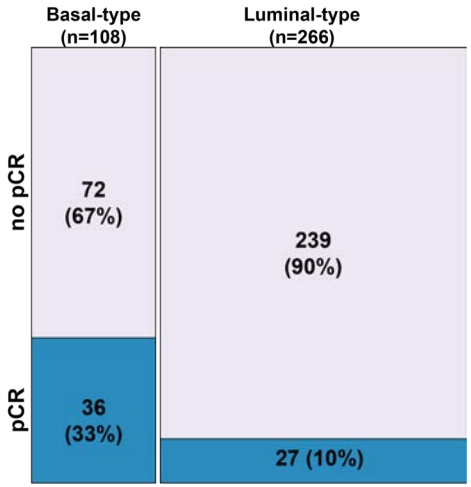
While the majority of **HR+HER2- patients** are Luminal (71%), **29% are Basal-type**



Christina Yau, PhD
Computational Scientist

HR+/HER2- with Basal subtype predicts 'chemo-sensitivity'

- 375 I-SPY 2 HR+/HER2- patients across 8 treatment arms
- Association of molecular BluePrint basal subtype with pCR



Across all arms combined, **BP basal associates with pCR** (OR= 4.98, p<0.0001) **in a model adjusting for treatment arm, HR, and HER2 status**

Estimated pCR Rate (95% CI) by Subtype By Arm

Arm	BP-Luminal	BP-Basal
A	10% (4%-16%)	32% (20%-44%)
B	7% (0%-15%)	34% (18%- 50%)
C	9% (2%-15%)	35% (21%-50%)
D	10% (2%-17%)	29% (15%-43%)
E	10% (3%-17%)	32% (9%- 46%)
F	15% (1%- 29%)	31% (16%-46%)
G	9% (0%-19%)	32% (17%- 48%)
H	17% (5%- 29%)	41% (21%-62%)

Within treatment arms, the estimated **pCR rates** among **HR+HER2- Basal** patients ranged from **29%-41%,** compared to **7%-17% in HR+HER2- Luminal** patients

I SPY 2: Learning, Innovating, and Evolving

- **Patient Centered**
  - Adaptive randomization, they get the best agent for their subtype
- **Maximizes chance of pCR and cure for each patient**
  - pCR results in 95% 3 yr disease-free survival (no-pCR 76-79%)
- **Qualifies predictive biomarkers to identify responders (ENA 2018)**
  - MammaPrint High1/High2, BluePrint molecular subtypes
  - Can prioritize treatment in subsequent trials (I-SPY 2.2 trial design)
- **Increases chance of pCR and cure for the high risk population**
  - Learn, approve drugs and combinations that are effective and less toxic
- A **design that patients like**, that investigators like, where industry will participates- speeds the chance that patients will survive
- **Advances regulatory science**

I-SPY 2 TRIAL Study Team

Working Group Chairs

PI:	Laura Esserman	**Operations:**	Angie DeMichele
PI:	Don Berry	**Biomarkers:**	Laura van 't Veer
Imaging:	Nola Hylton	**Pathology:**	Fraser Symmans
Agents:	Doug Yee	**Advocates:**	Jane Perlmutter
Safety:	Hope Rugo	**PRO/QOL:**	Michelle Melisko

Site PIs

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Denver:	Anthony Elias	**UChi**:	Rita Nanda
Gtown:	Claudine Isaacs	**UCSD**:	Anne Wallace
Loyola:	Kathy Albain	**UCSF**:	Jo Chien
Mayo:	Judy Boughey	**UMinn**:	Doug Yee
Moffitt:	Heather Han	**UPenn**:	Amy Clark
OHSU:	Kathleen Kemmer	**USC**:	Julie Lang
Swedish:	Erin Ellis	**Yale**:	Tara Sanft

Sponsor:

Quantum Leap Healthcare Collaborative

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I-SPY 2 Biomarkers/Specimens:
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I-SPY Imaging Lab:
Jessica Gibbs, Melanie Regan
Business Development:
Julie Sudduth-Klinger, Dan Dornbusch
Grants:
Jeff Matthews

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Biomarkers: Denise Wolf, Christina Yau, Chip Petricoin, Julia Wulfkuhle, Lamorna Swigert, Gill Hirst & Collaborators NKI: Sabine Linn, Tessa Severson, Daniel Vis, Lodewyk Wessels, Rene Bernards, Emile Voest

Qualifying Biomarker Process: Denise Wolf, Christina Yau et al, Nature Partner Journals Breast Cancer, 2017

I-SPY 2 Participating Organizations

NIH I-SPY 2.2 Program Project 2017-2010