INCREASE EFFICACY

I-SPY with my little eye

your best matched treatment

Laura van ‘t Veer, PhD

University California San Francisco

Inspire2Live 2020

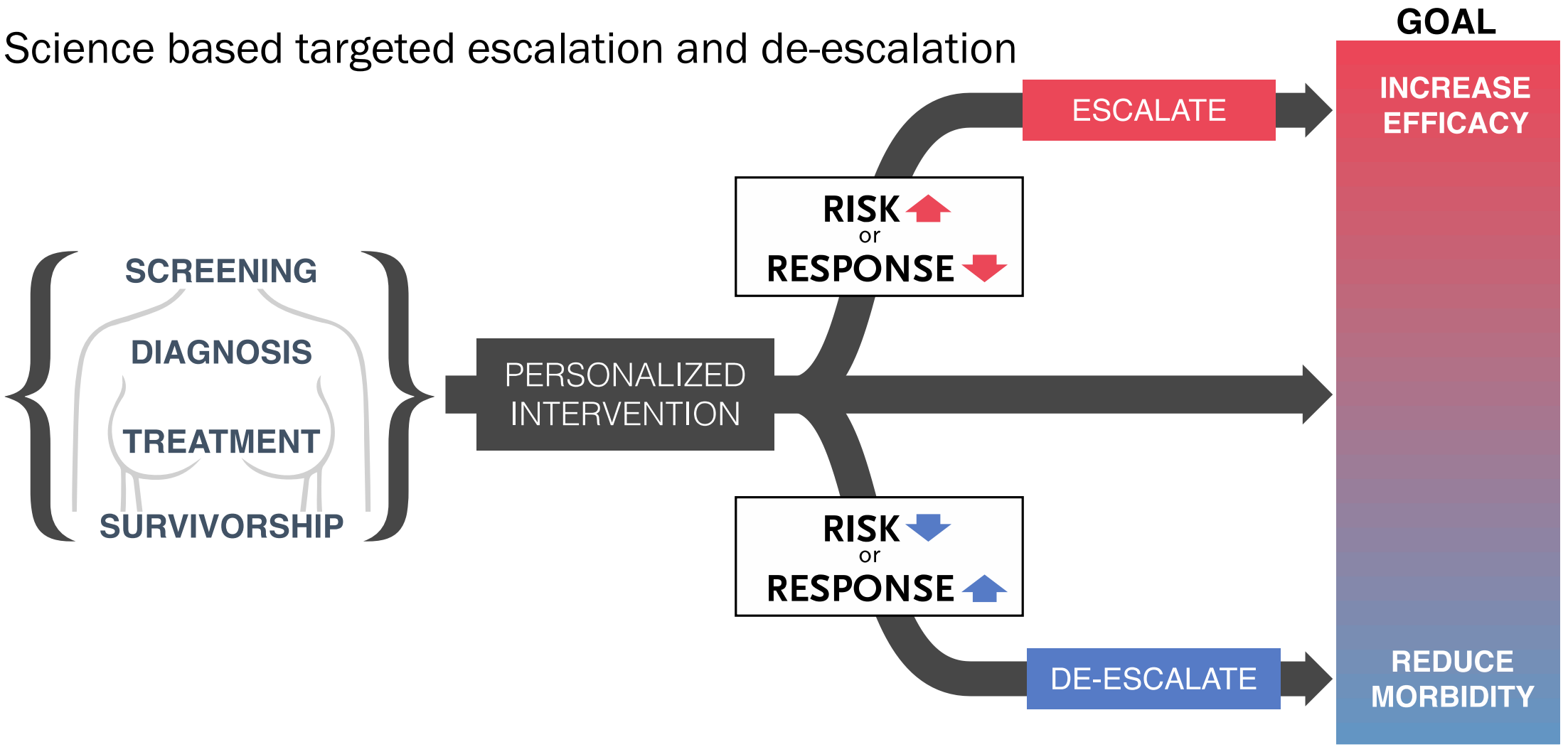
REDUCE MORBIDITY

Disclosure

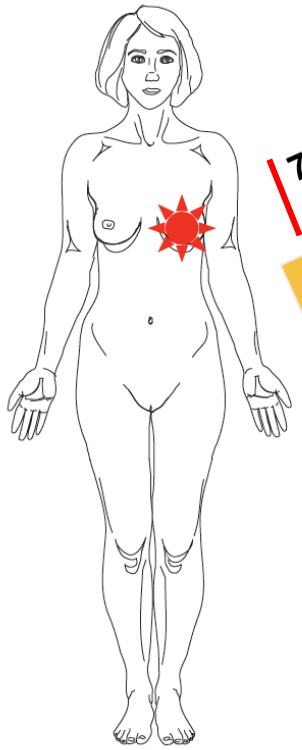
- *Co-Founder, part-time employee and stock holder Agendia NV (MammaPrint)*
- *No off-label use will be discussed*

Personalized Healthcare - Precision Oncology

Science based targeted escalation and de-escalation



Breast Cancer Therapy – early 2000's

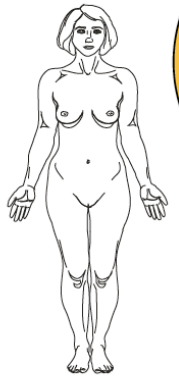


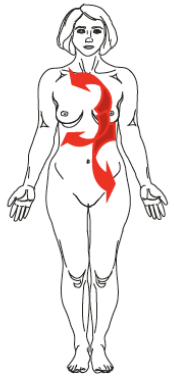
70% cured by surgery and radiotherapy

70 % of them are offered CTX

30% develop distant metastases

90% of them are offered CTX





Overtreatment

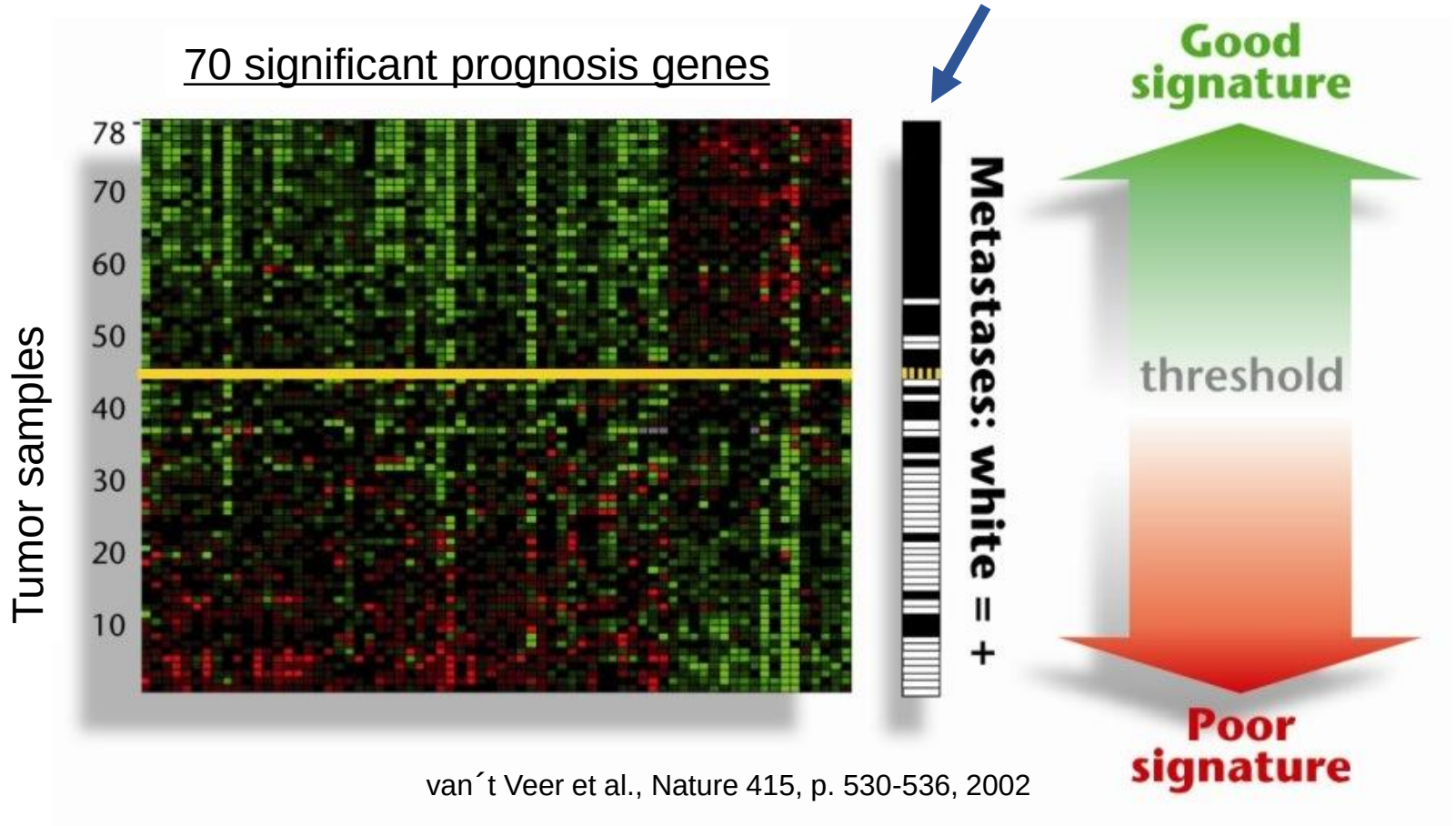
High socio-economical burden

Undertreatment

Node negative BC

70 Gene Prognosis Signature - MammaPrint

MammaPrint: ‘07 FDA cleared IVDMIA for prognosis assessment technology – microarray



van´t Veer et al., Nature 415, p. 530-536, 2002

MINDACT Trial : Study Objective

- **M**icroarray **I**n **N**ode negative and 1-3 positive node **D**isease may **A**void **C**hemo**T**herapy (**MINDACT**)

- Designed to provide evidence for the clinical utility of MammaPrint:
  - Use of the **70-gene signature (MammaPrint)**
  - In addition to **standard clinical-pathological criteria**
- **Goal:** more accurate selection of patients for adjuvant chemotherapy
- "Precision Medicine/Personalized Medicine"

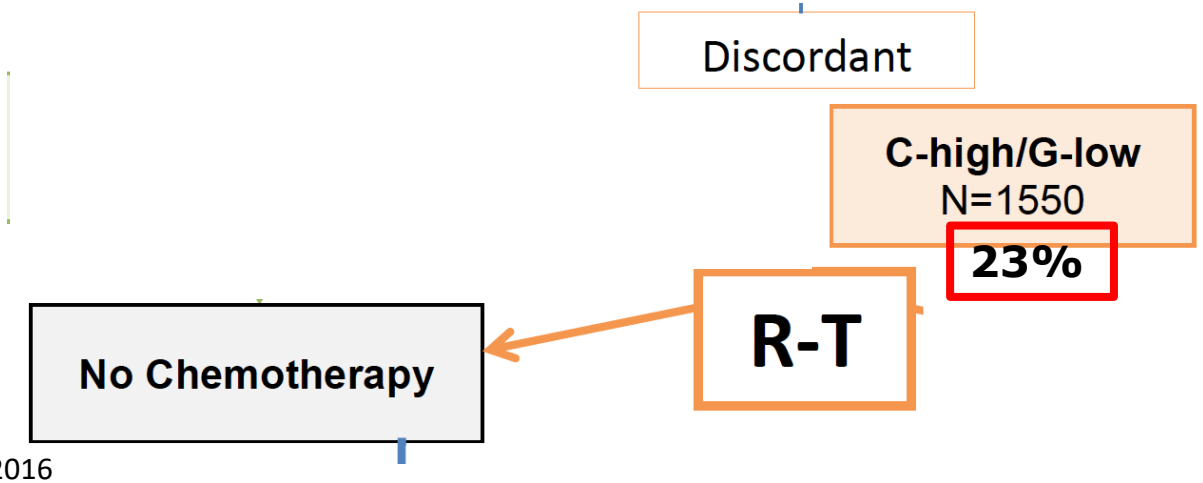
MINDACT Primary Test and End Point

Primary endpoint:

- Distant Metastasis Free Survival (DMFS) at 5 years

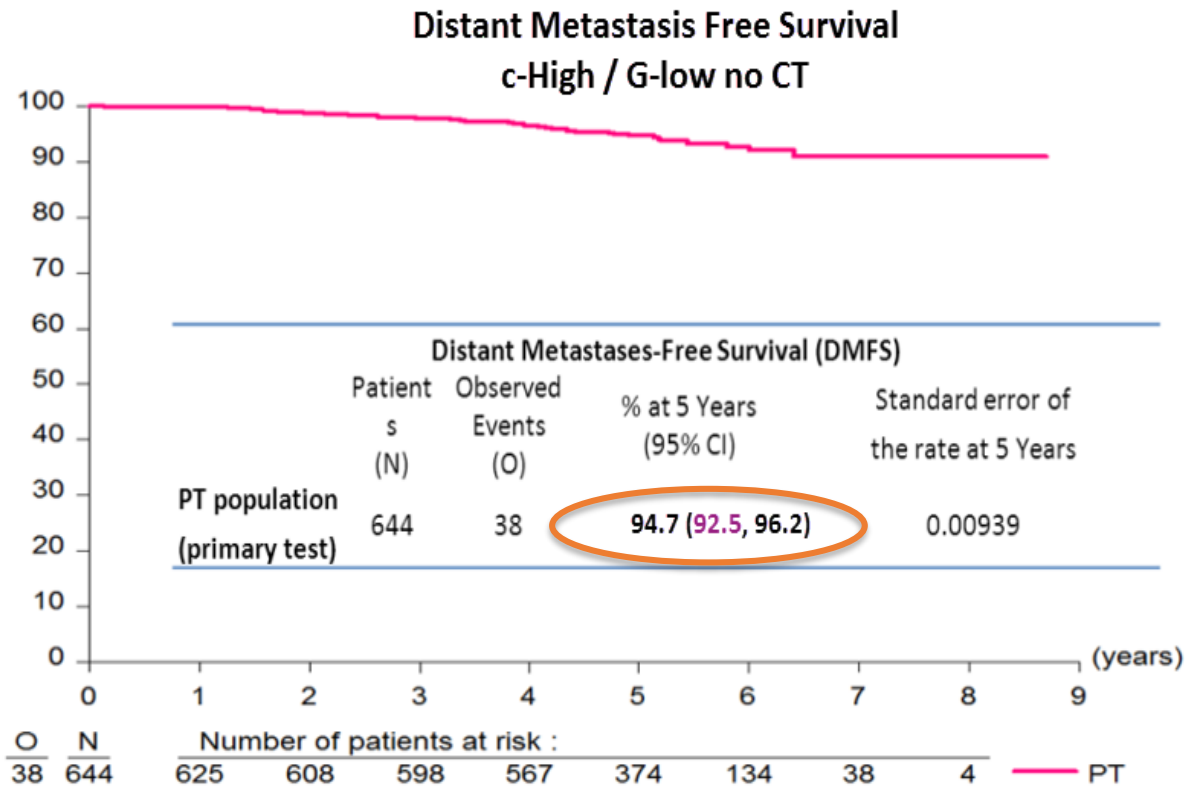
Primary test:

- To assess whether patients with clinical high risk features and a genomic Low Risk profile who did not receive CT would have a 5-year DMFS of ~95%.
  - A **non-inferiority** boundary of **92%** (lower limit confidence) interval)



NEJM, 2016

MINDACT Trial Primary Test Analysis: Clin-High / MP Low group- No Chemo (100% compliance)



Primary Test Population, C-high / G-low tumors:

- 58% >2cm
- 93% Grade II or III
- 48% LN+ 1-3
- 98% HR+

Primary Endpoint met!

- 5-Year DMFS for the C-high / G-low (MP Low) group with no CT= **94.7%** (CI: 92.5 – 96.2%).
- Excludes 92%, positive outcome met.

NEJM, 2016

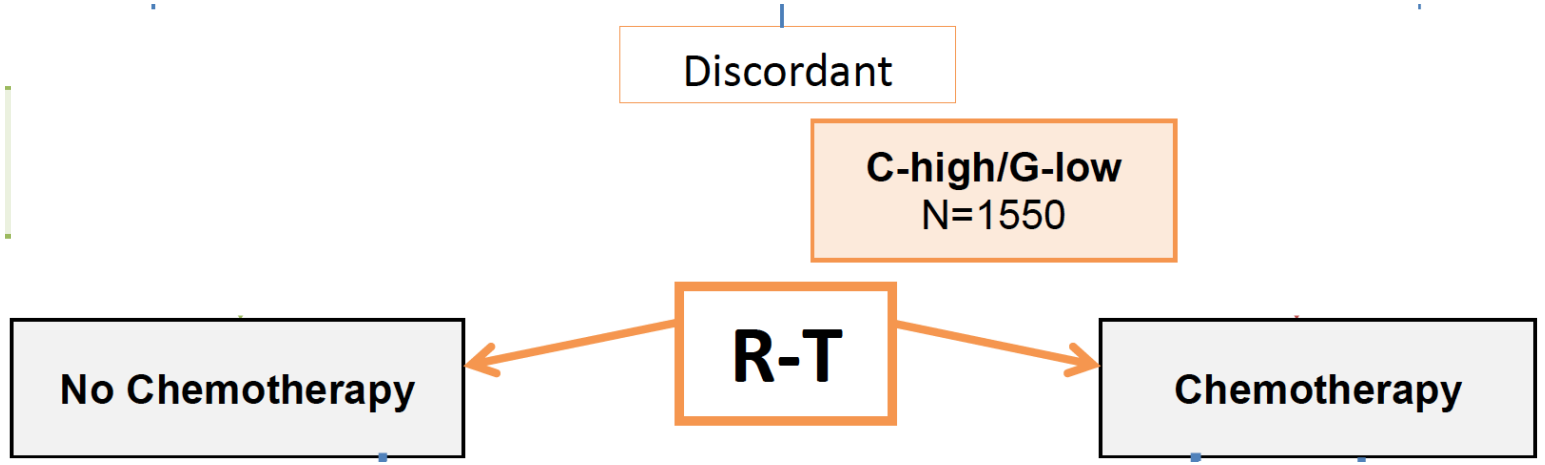
MINDACT Secondary Test

Secondary endpoint:

- Distant Metastasis Free Survival of *noCT vs CT*

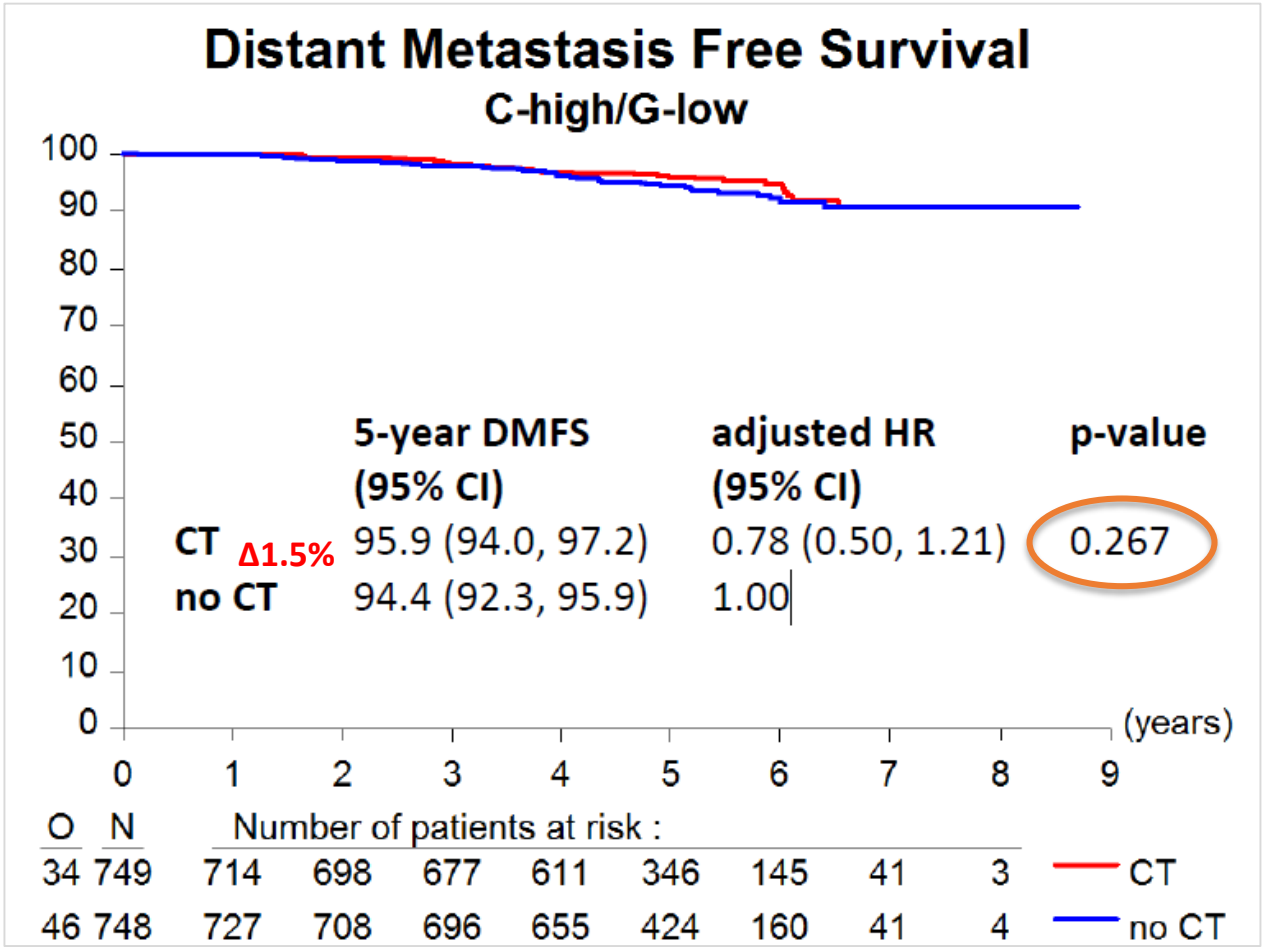
Secondary test:

- To assess significance of survival difference, *added clinical benefit of chemotherapy*, for patients with clinical high risk features and a genomic Low Risk



NEJM, 2016

Chemo efficacy in Clin-High / MP Low (DMFS)



Adapted from Figure 2

DMFS:
distant relapses
deaths all causes

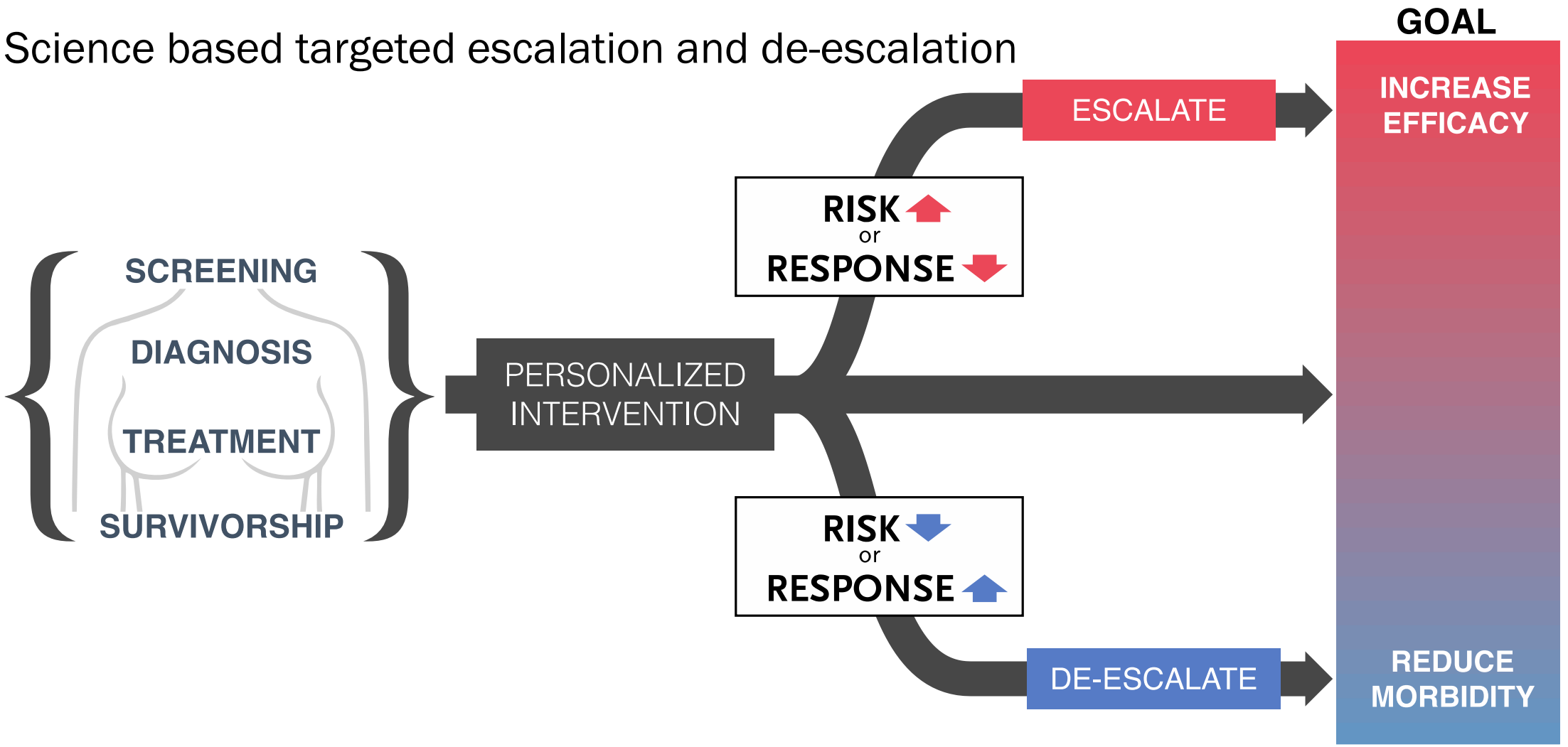
- **No statistical difference** between CT vs no CT arms
- Excellent survival with no chemotherapy for patients with clinically high risk features **(94.4%)**

Secondary Endpoint met!

NEJM, 2016

Personalized Healthcare - Precision Oncology

Science based targeted escalation and de-escalation



Early Breast Cancer
High risk for recurrence – Unmet need

Standard Chemotherapy Only 20% Response

New Targeted Drugs Need Companion Diagnostics

use case: early stage breast cancer - high risk

(stage 2 and 3)

EU: 100K and US: 60K patients/year

Breast cancer molecular subtypes to predict response in a modern treatment landscape

lessons from ~1000 patients across 10 arms of the I-SPY 2 TRIAL

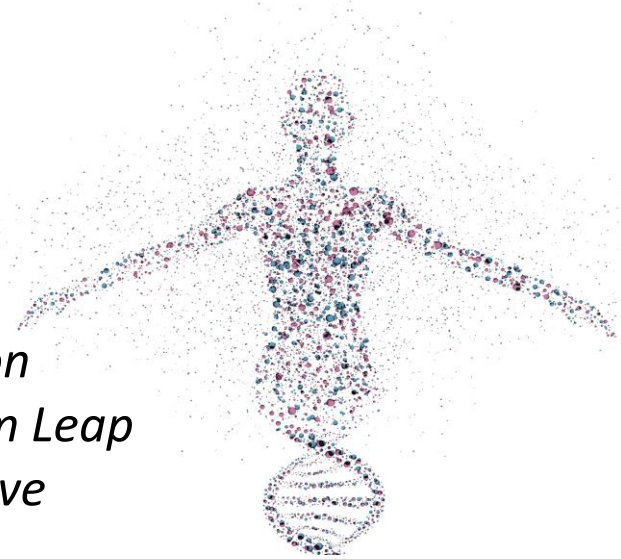
the 'right bins'

Laura van 't Veer, PhD - University California San Francisco

University of California San Francisco
UCSF
Comprehensive Cancer Center

I-SPY Scientists:
Christina Yau, Denise Wolf, Michael Campbell, Chip Petricoin, Julia Wulfkuhle, Mark Magbanua, Lamorna Swigart, Gillian Hirst
and Concept holder scientists

I-SPY 2 Trial PI's:
Laura Esserman, UCSF
Don Berry, MDAnderson
Trial Sponsor: Quantum Leap Healthcare Collaborative

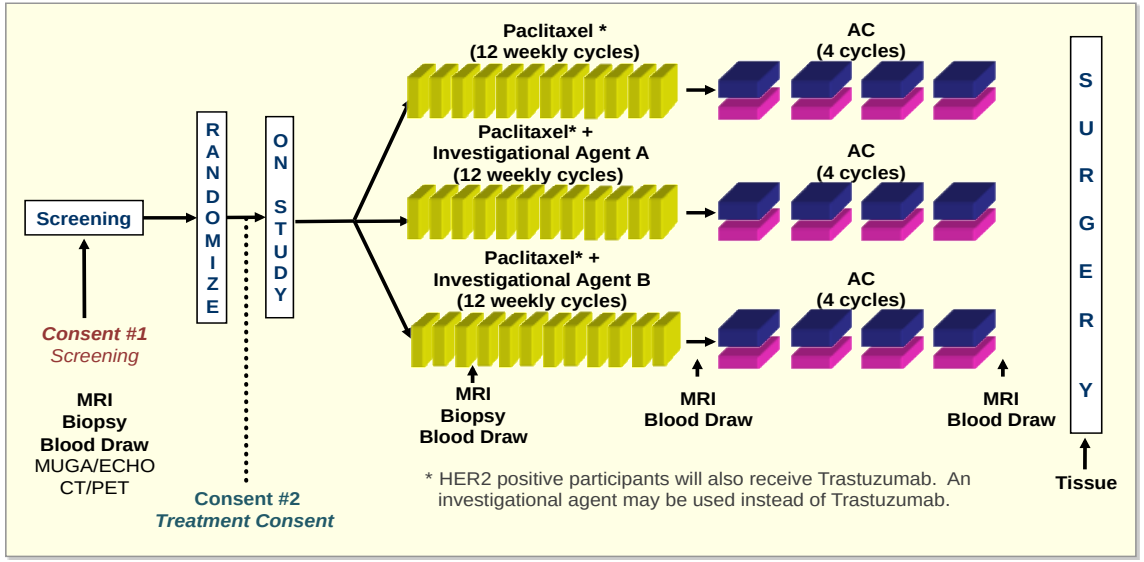


Basic Principles of I-SPY Platform Clinical Trial

- Test new drugs where they matter most
  - **Early stage (primary diagnosis)** 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 pathology complete response to therapy (**pCR, evaluated at surgery**)
- 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 Centers, Advocates

The I-SPY 2 TRIAL Standing Platform for High Risk Early Stage Breast Cancer

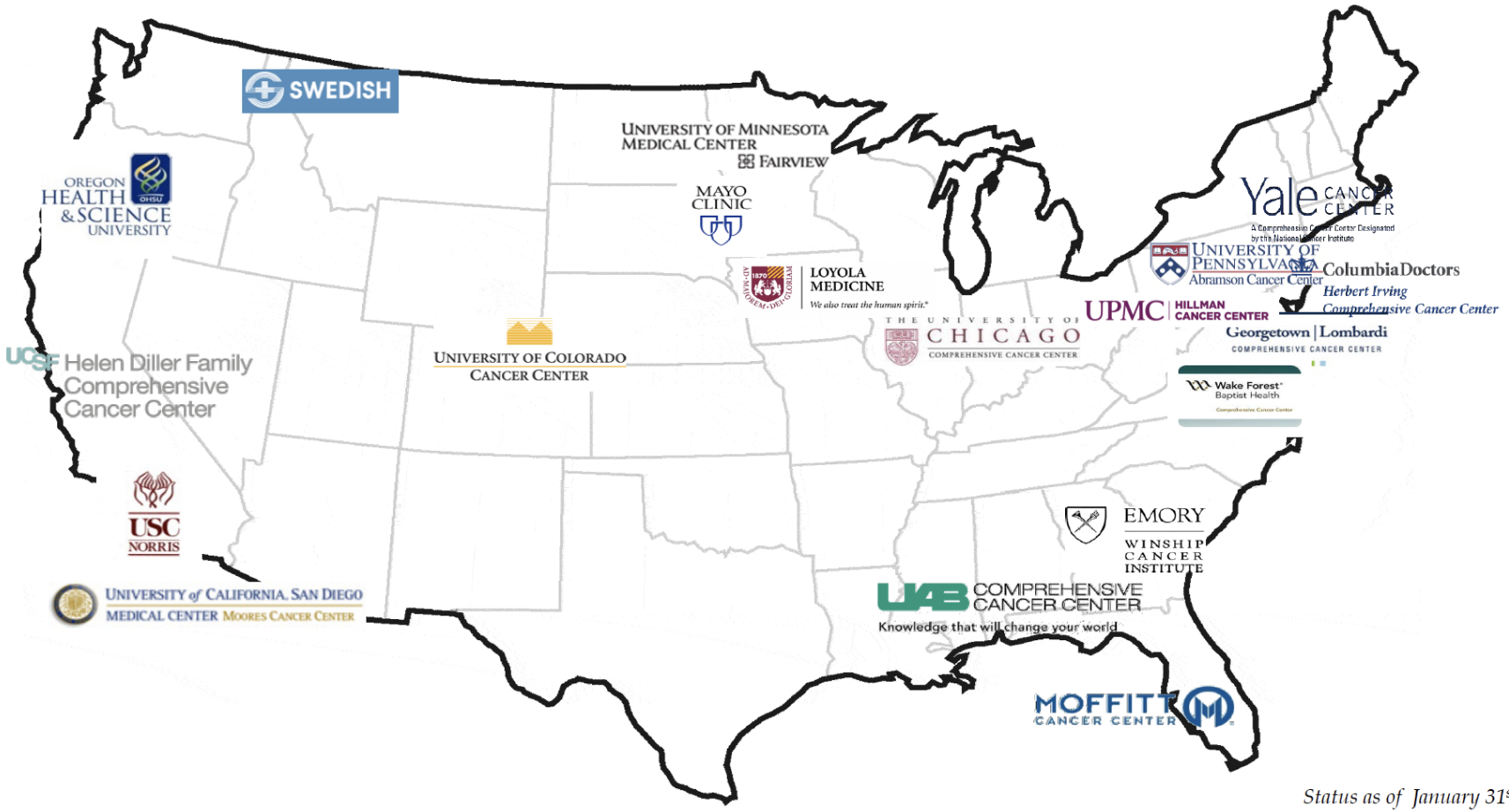
- **Phase II, adoptively randomized neoadjuvant trial**
  - Phase II drugs added to standard chemo
  - High-risk disease: MammaPrint high risk, plus all HER2+
- **Shared control arm**
  - Standard neoadjuvant chemotherapy
  - HER2+ also gets standard of care for targeted agents
- **Simultaneous experimental arms**
  - Up to five
- Primary endpoint: pathologic complete response (pCR)
  - Defined as no residual invasive cancer in the breast or lymph nodes
- Match therapies (adaptively) with most responsive subtypes
  - Defined by HR+/-, HER2+/-, MammaPrint High1/(ultra) High 2 (MP1/2) status



- **Agents/combinations "graduate" for efficacy** = reaching >85% predictive probability of success in a subsequent phase III trial in the most responsive patient subset (HR/HER2/MPh1-2)

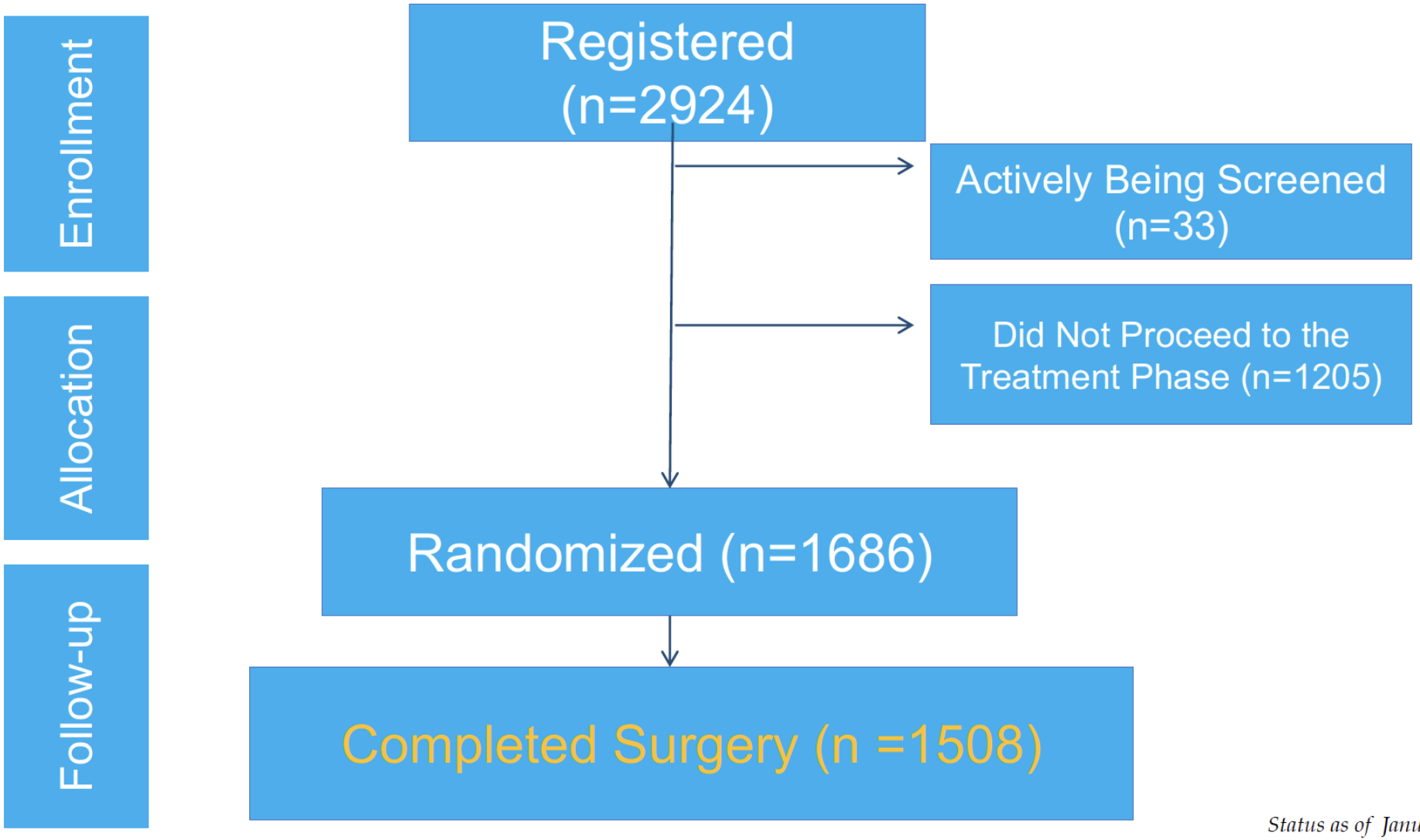
I-SPY 2 Participating Sites

18 Sites Open and Enrolling, Opening 3 sites Q1 and 3 sites Q2 2020



Status as of January 31st, 2020

Trial Patient Enrollment Overview



Status as of January 31, 2020

I-SPY 2 Investigational Drugs

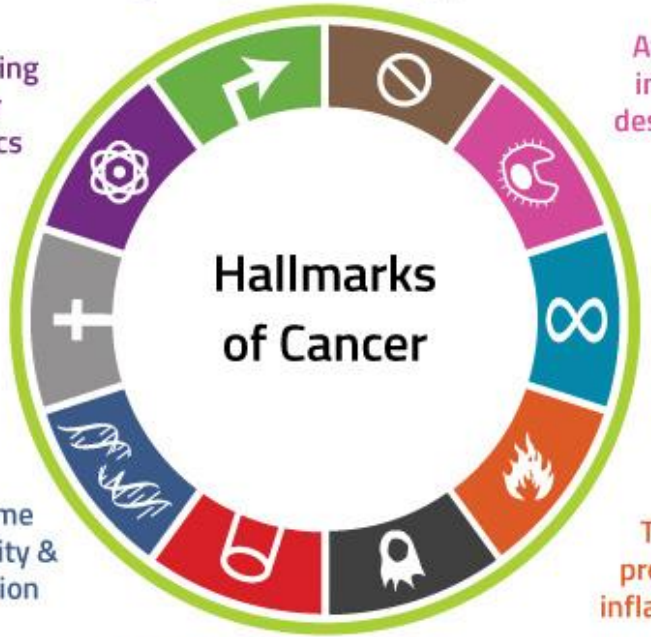
Anti-HER family signaling
- Neratinib
- trastuzumab/pertuzumab
- TDM1/pertuzumab
- trastuzumab/patritumab

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

Drugs Developed Targeting Hallmarks of Cancer

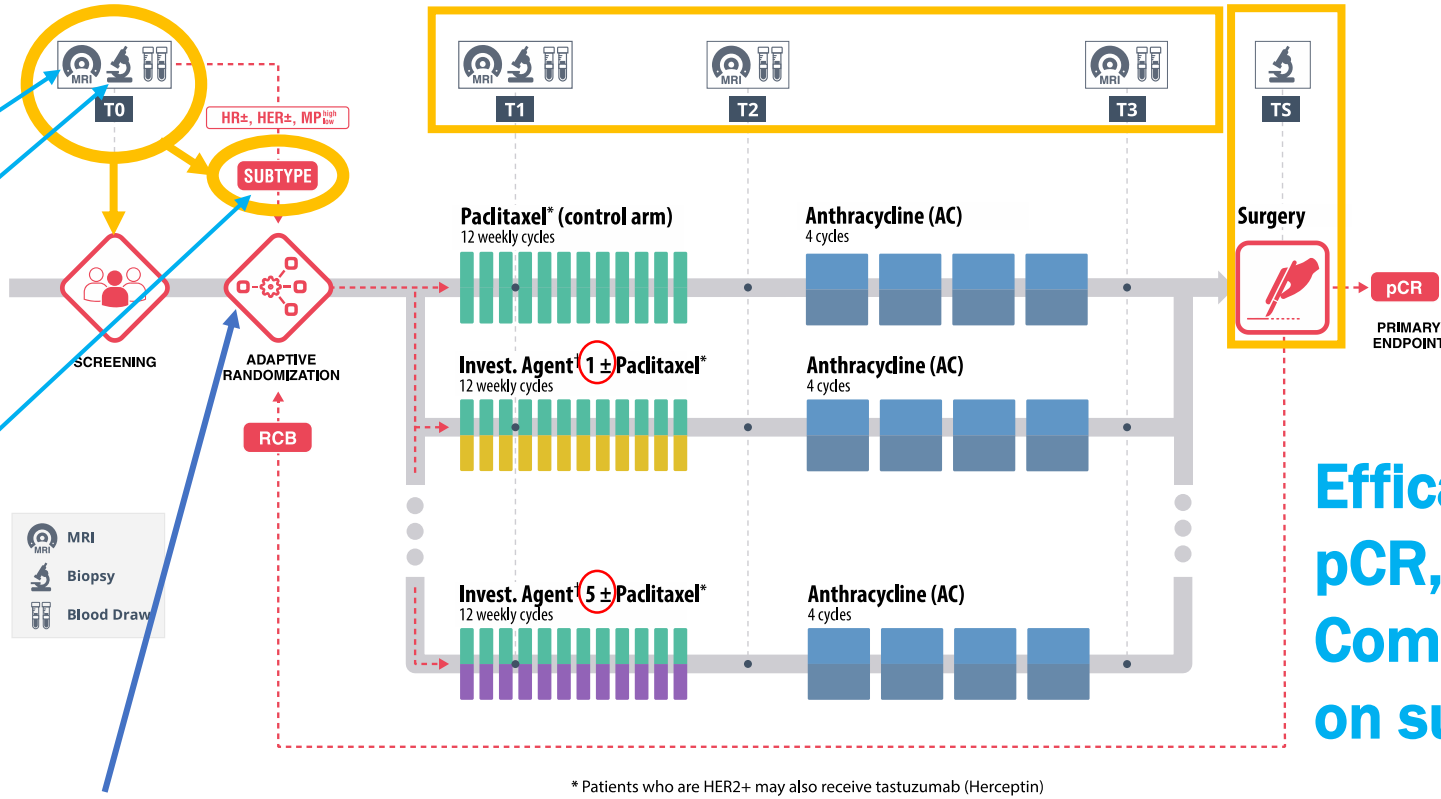
I-SPY 2 Framework:

Biomarkers Guide Enrichment of Drug Arm with Responding Subtype

Diagnosis | Drug Treatment | Surgery

MRI to assess tumor volume
Biopsy to assess biological subtype

Serial MRI (volume change) & Pathology (pCR) at surgery informs adaptive randomization by biological subtype



Biomarkers:

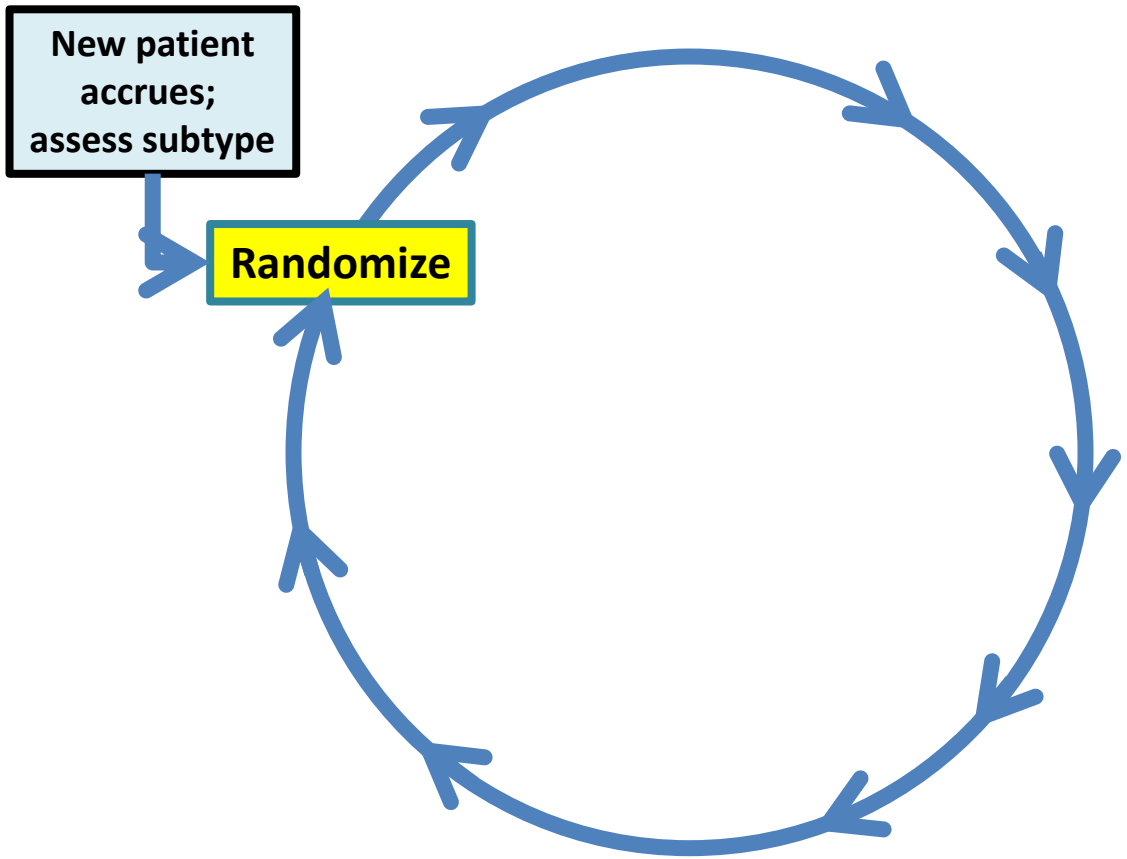
- **Imaging**
- **Pathology**
- **Molecular Biology**
  - 8 subtypes (current) by:
    - Hormone Receptor +/-
    - HER2 +/-
    - MammaPrint high1/2

Efficacy endpoint: pCR, pathological Complete Response, on surgery specimen

Adaptive Randomization

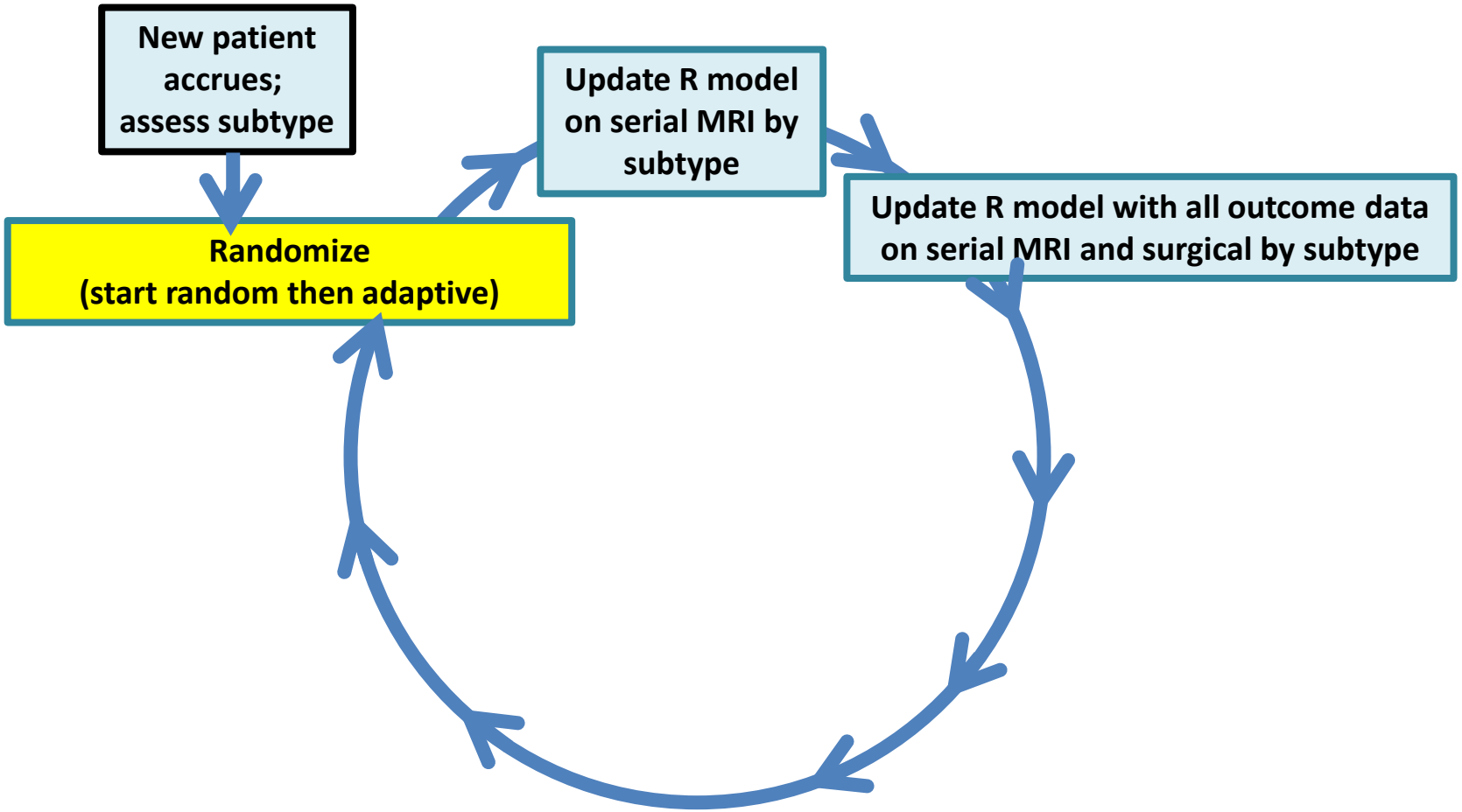
* Patients who are HER2+ may also receive tastuzumab (Herceptin)
† An investigational combination of one or more agents may be used to replace all or some of the standard therapy

I-SPY 2 Adaptive Randomization



1) Randomization of a drug starts randomly across 8 subtypes

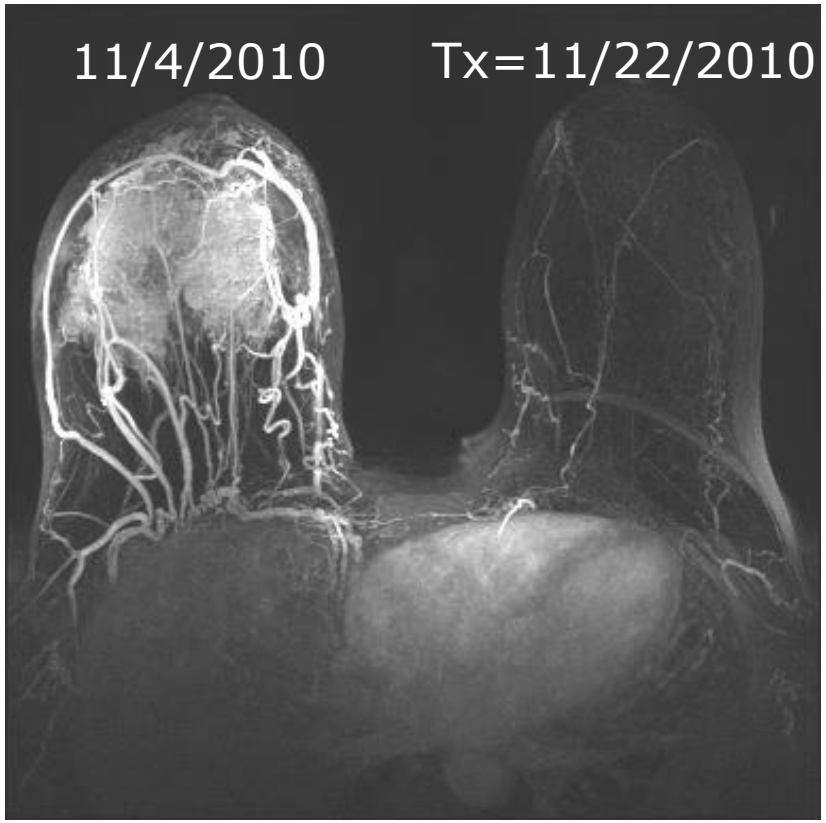
I-SPY 2 Adaptive Randomization



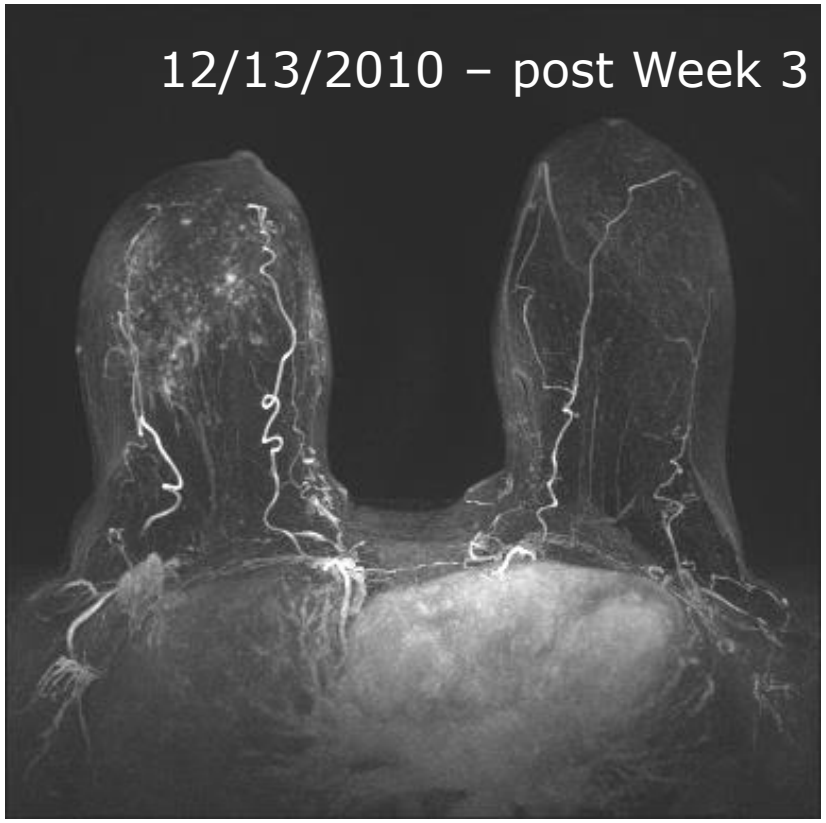
2) Adaptive randomization to 1 of 5 'investigational' arms based on serial MRI response and surgical endpoint seen for each of 8 subtypes (hormone receptor +/-, HER2 +/-, MammaPrint-high 1 or 2), plus 1 in 5 to control

MRI: Rapid Response in TN-BC to Veliparib, Paclitaxel, Carboplatin

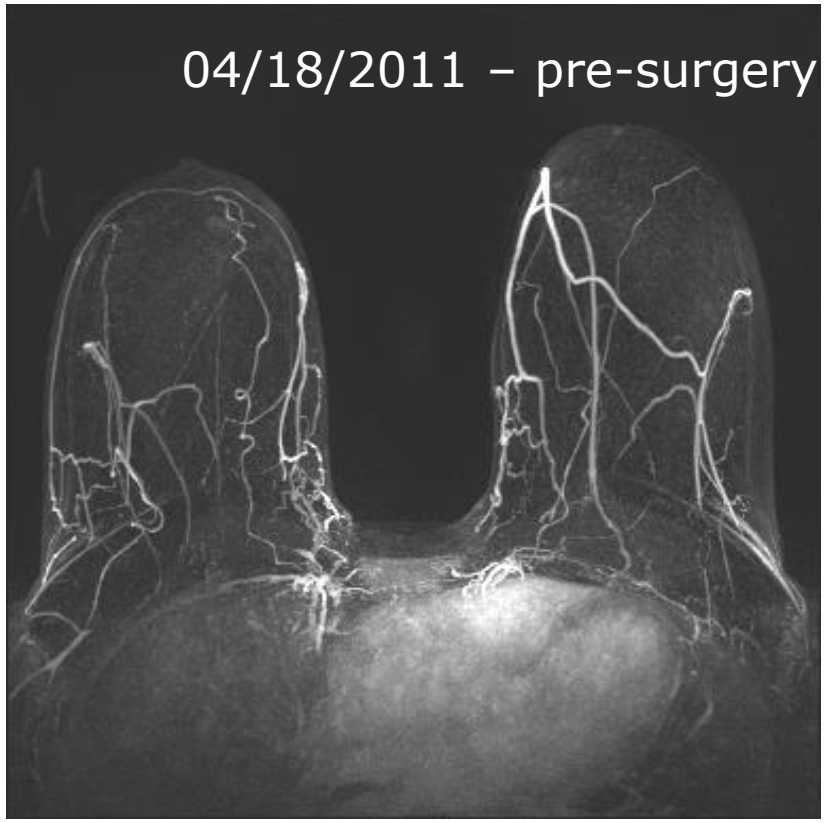
MRI imaging volume change at every time point informs adaptive randomization



At Diagnosis



After 3 cycles/weeks of treatment

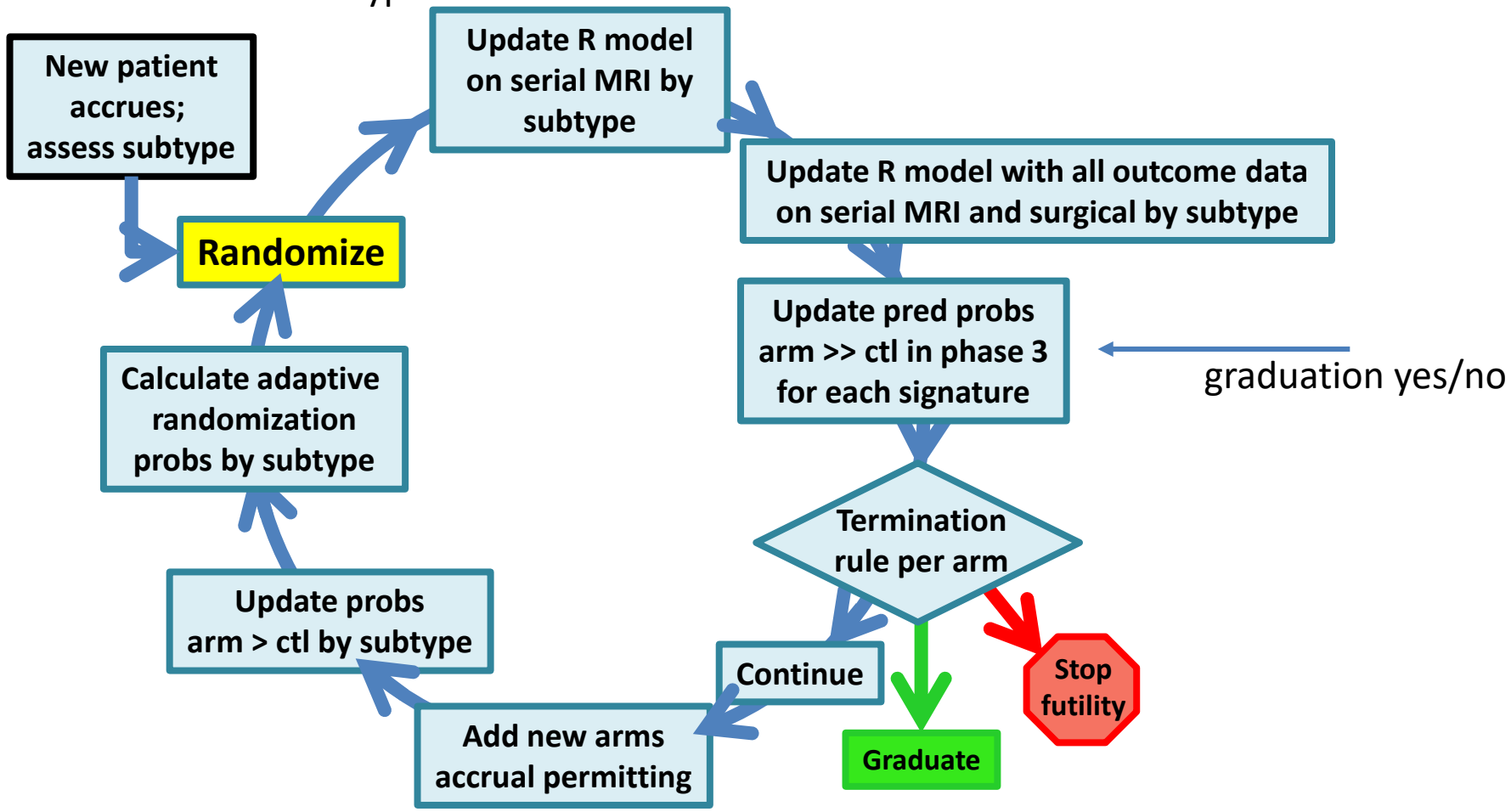


At treatment completion 6 months

Example of 3 week response - (full treatment is ~ 6 months! De-escalate?)

I-SPY 2 Adaptive Randomization and Graduation

Adaptive randomization on 8 subtypes



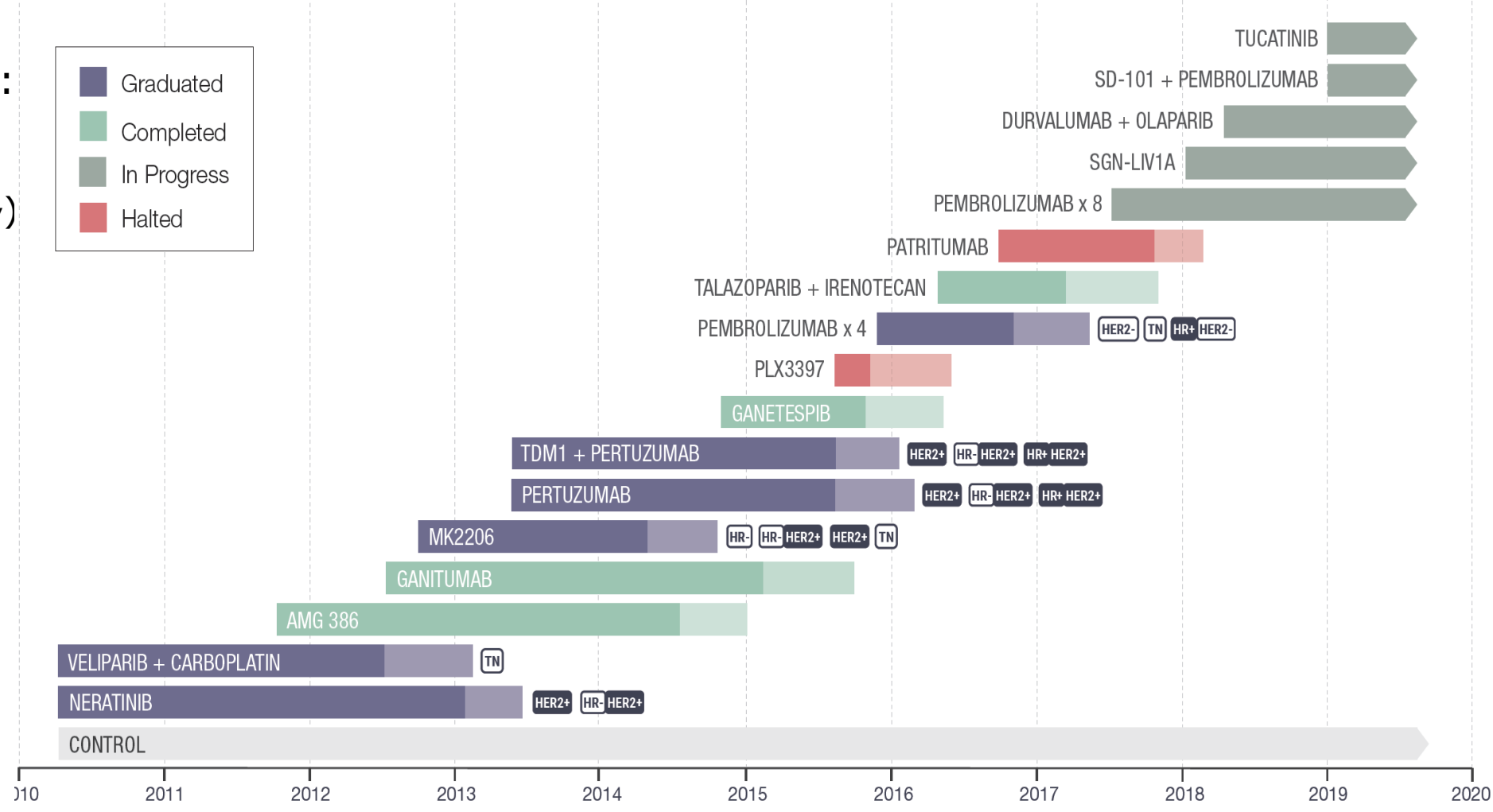
3) Drug Graduation based on 10 signatures (single or combinations of 8 subtypes) and 85% success in Phase 3

Timeline of Investigational Drugs and Graduating Signatures

Biomarkers Guide Enrichment of Drug Arm with Responding Subtype-Signature

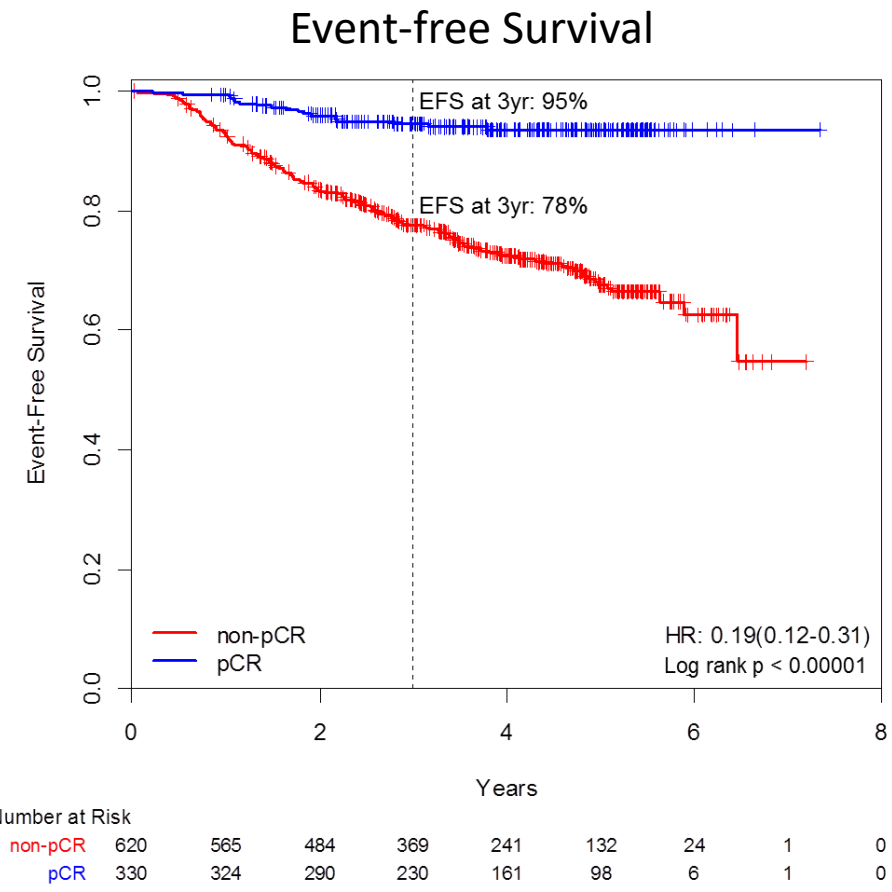
17 drugs entered the trial:
- 12 completed
- 6 graduated w signatures
- 4 dropped (no increase efficacy)
- 2 halted/stopped (toxicity)
- 1 control arm
- 5 arms ongoing

Overall for graduating signatures for each Drug the pCR response rates Doubled or Tripled



pCR at surgery relates to survival regardless of treatment

10 treatment arms, 950 patients, median 3.8 yr follow-up



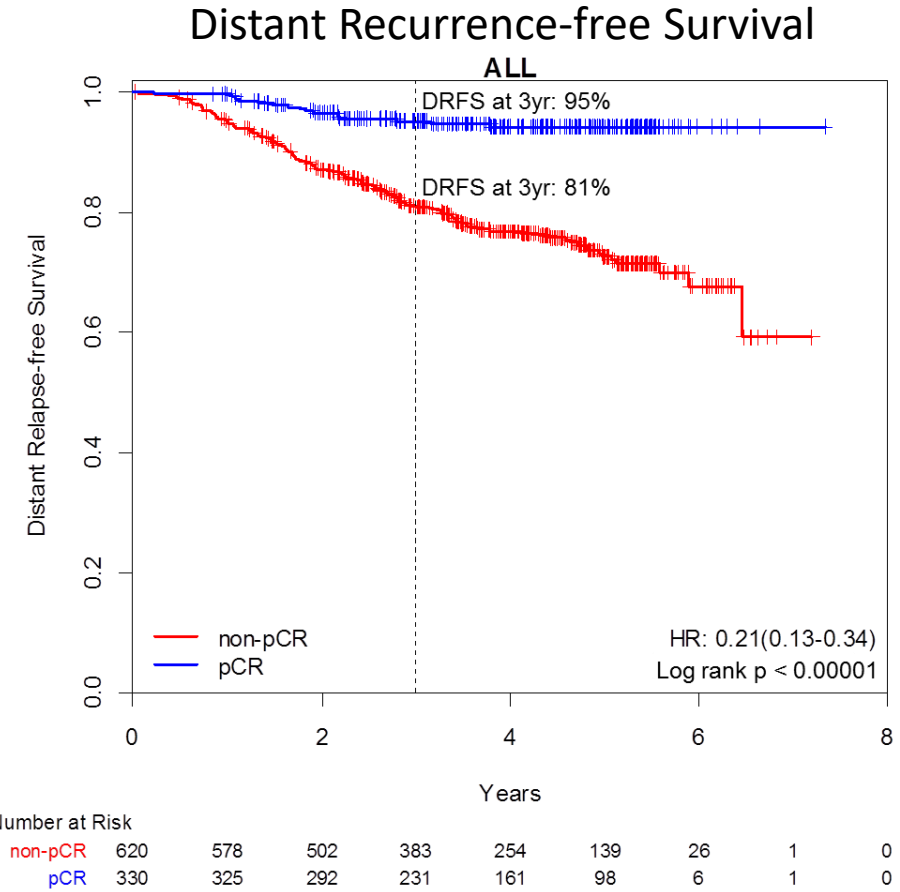


Figure 3: Association between pCR and Survival Outcomes (A) Kaplan Meier curves of EFS by pCR; (B) Kaplan Meier curves of DRFS by pCR.

3 yr survival (EFS)
pCR is 95%
vs.
no-pCR 78%

Across high-risk subtypes, agents

pCR = pathological complete response at surgery

Yee et all, SABCS 2017; DeMichele et all, ENA 2018; manuscript in revision

I-SPY 2 is a biomarker rich trial

STANDARD

- **Level 1 evidence**
- **FDA cleared or approved or IDE filed**
- **Used in clinical decision**

HR, HER2, MammaPrint, MR volume

QUALIFYING

- **Level 2 evidence**
- **Have existing evidence for response prediction**
- **Based on mechanism of action**
- **Evaluated in CLIA setting**
  - **Agilent 44K array (FDA IDE)**
  - **Phospho-protein array (CLIA)**
  - **DNA mutation panel (CLIA)**
- **Hypothesis testing**
  - Pre-defined biomarkers
  - Pre-specified rigorous

EXPLORATORY

- **Biomarker discovery**
- **Hypothesis generation**

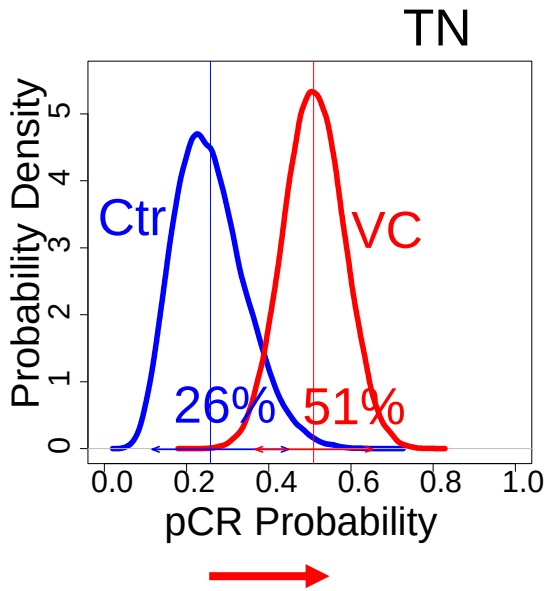
I-SPY 2 Framework – 'Standard Biomarkers' (level 1):
Biomarkers Guide Enrichment of Drug Arm with Responding Subtype (example 1)

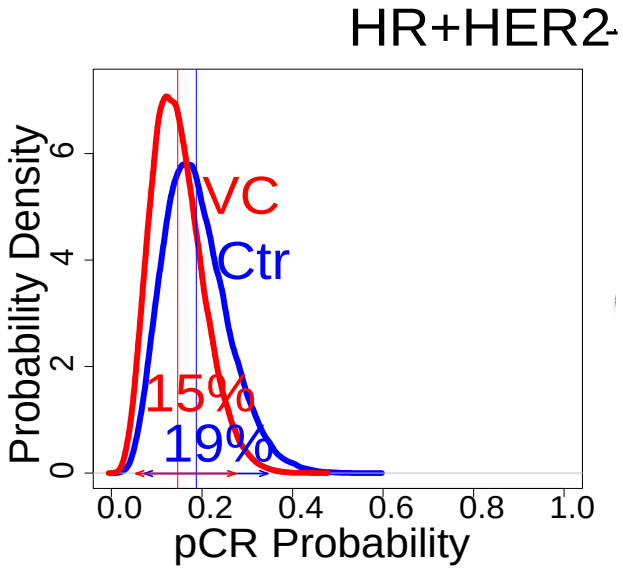
Example: Veliparib (PARP-inh)/Carboplatin (tested in HER2neg subtypes)

Adaptive Biomarker Subtypes indicated:

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

and the adaptive randomization enriched the VC arm and graduated in TN Breast Cancer



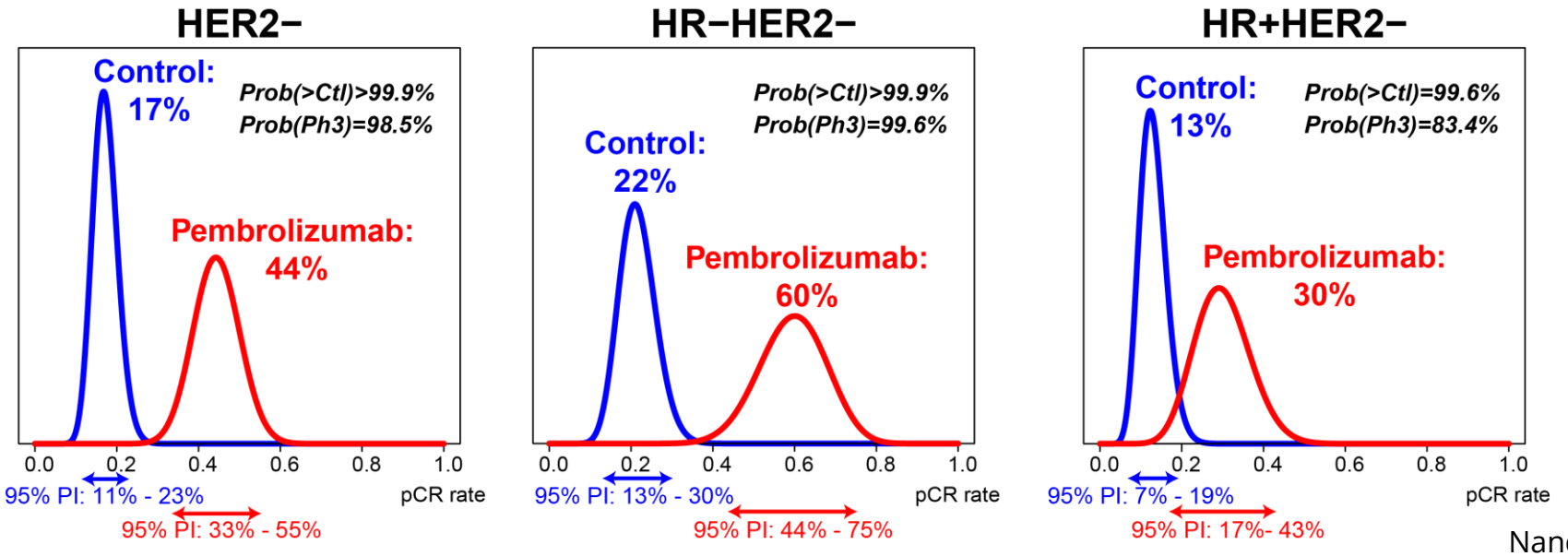


VC response ~50%!

I-SPY 2 Framework – 'Standard Biomarkers' (level 1):

Biomarkers Guide Enrichment of Drug Arm with Responding Subtype (example 2)

Example: Pembroluzimabx4 (anti-PD1) (tested in HER2neg subtypes)
Adaptive randomization indicated:
response and graduated in three biomarker subtypes/signatures



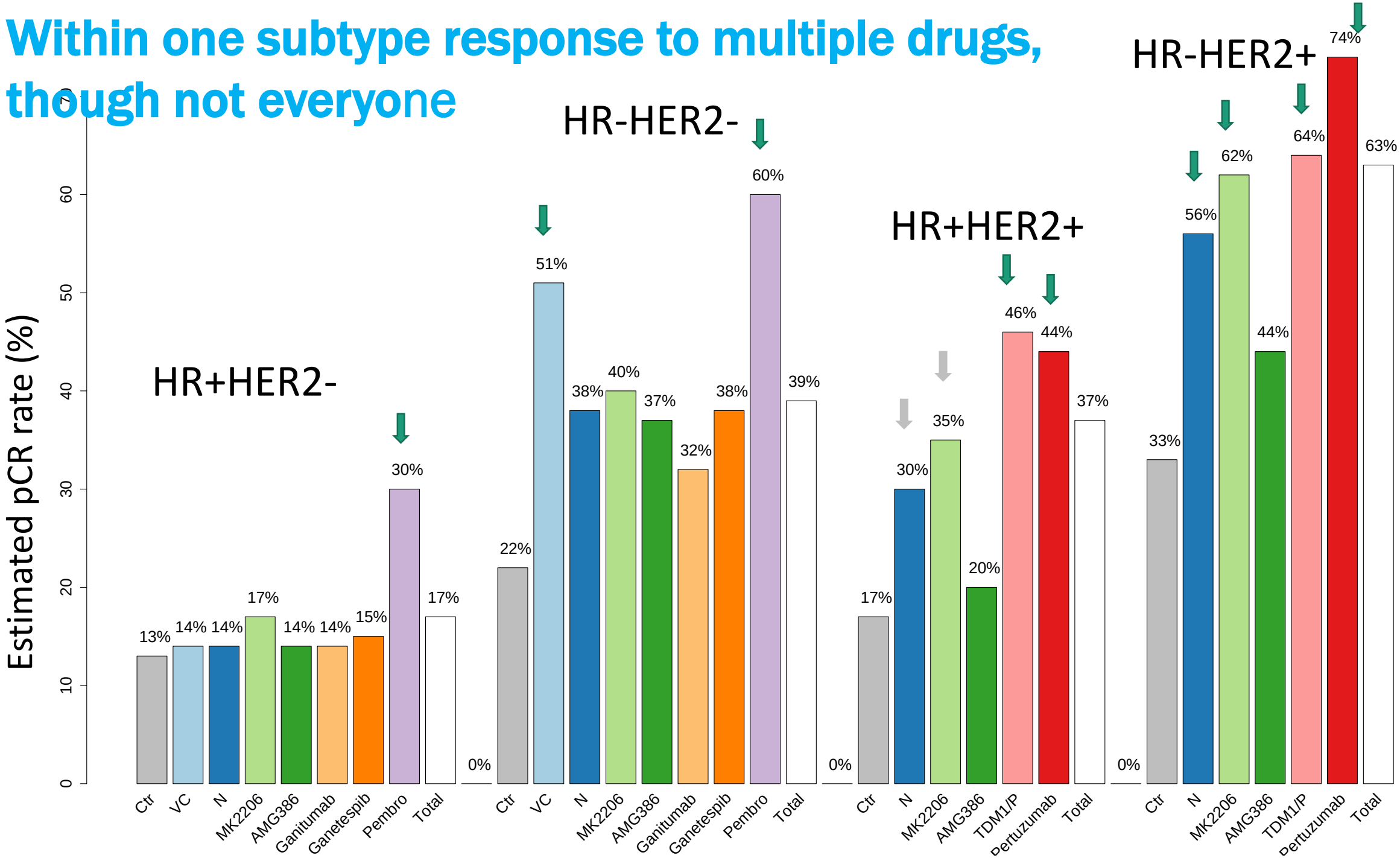
Nanda et al ASCO 2017

~ doubled response
all HER2-

~ tripled response
TN

~ doubled response
HR+/HER2-

Within one subtype response to multiple drugs, though not everyone



Response Biomarkers to improve response prediction
(Biomarkers level 2)

- Important to get every patient to pCR (increased probability of survival)
- I-SPY 2 randomizes by 8 subtypes (HR +/-, HER2+/-, MammaPrint High1/High 2; 2^3=8)
- How can biology further identify responders?

- I-SPY 2 tests 'Qualifying Biomarkers', which have existing evidence for response prediction (Biomarkers level 2)
  - Biology of Targeted agent, eg DNA repair deficiency, HER2 signaling, immune signatures, biology subtyping (gene expression, phosphor protein, some DNA mutation)
- Presented here: Individual and Integrated Qualifying Biomarkers

I-SPY 2 is a biomarker rich trial

STANDARD

- **Level 1 evidence**
- **FDA cleared or approved or IDE filed**
- **Used in clinical decision**

HR, HER2, MammaPrint, MR volume

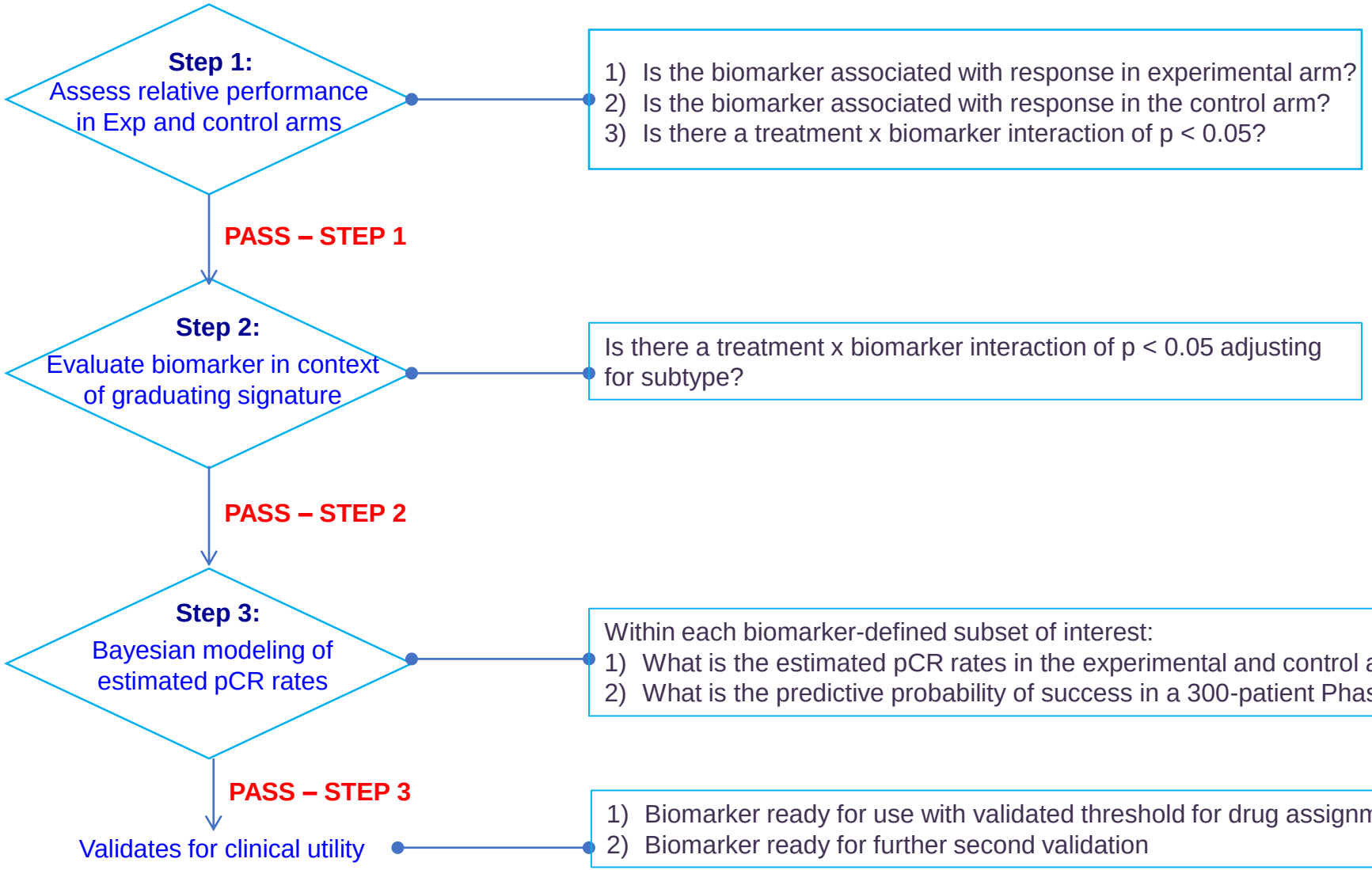
QUALIFYING

- **Level 2 evidence**
- **Have existing evidence for response prediction**
- **Based on mechanism of action**
- **Evaluated in CLIA setting**
  - **Agilent 44K array (FDA IDE)**
  - **Phospho-protein array (CLIA)**
  - **DNA mutation panel (CLIA)**
- **Hypothesis testing**
  - Pre-defined biomarkers
  - Pre-specified rigorous

EXPLORATORY

- **Biomarker discovery**
- **Hypothesis generation**

Our Pre-specified Qualifying Biomarker Evaluation Methodology is a 3-Step Process



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

Qualifying Biomarkers for all I-SPY 2 Drugs

top predictive biomarkers

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

Anti-IGF1R
- Ganitumab

AKT inhibition
- MK2206

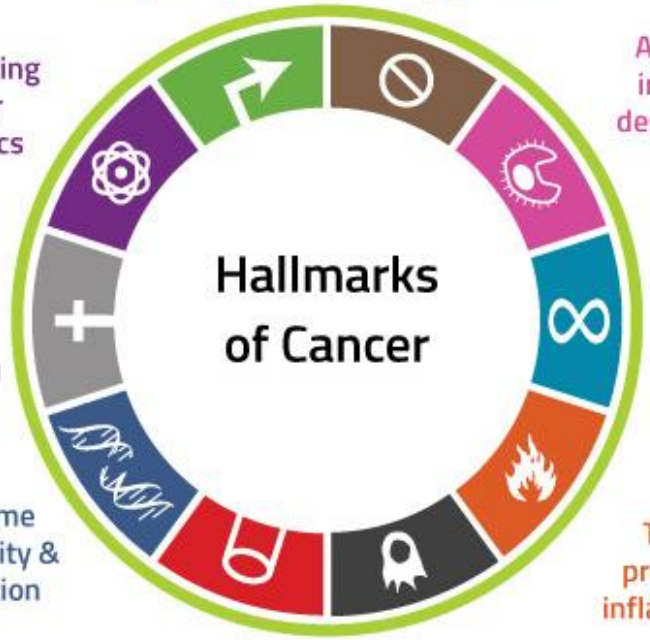
N: BP HER2 subtype in HR+HER2+
EGFR Y1173, ERBB2 Y1248, STMN1 in HER2-

TP and TDM1: BP HER2 subtype & Immune

M: PIK3CA, FOXO2a.S253 and SGK.S78 in TN
FOX01.S256 and Immune in HER2+; BP Luminal in HR+HER2+

P: Dendritic Immune and DNA damage sensing in TN
MP2, B cell and Mast cells in HR+HER2-

Immune checkpoint inhibition
- Pembrolizumab



Unfolded protein response inhibition
- ganetespib (HSP90i)

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

VC: MP2/PARPi7-high

TIE1/2 inhibition
- AMG386

AMG386: ANGPT1 and phospho-PI3K overall; immune in TN; Phospho-TIE2 in HER2+; Phospho-PI3K in HR+HER2-

Top Qualifying predictive biomarkers by platform
- Gene expression 44K array
- Phospo-protein array
- (few) DNA NGS panel

Exploratory by platform
- IHC multiplex

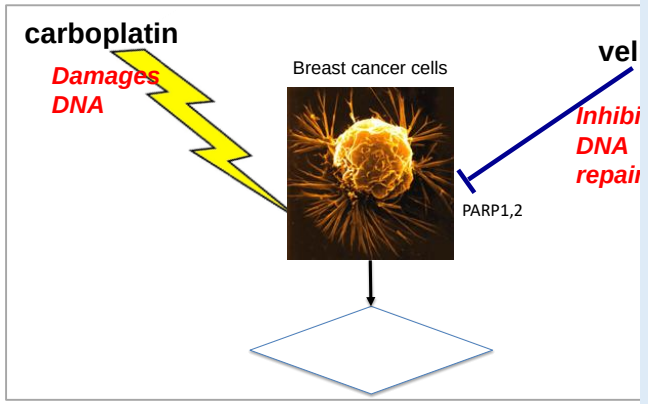
- 10 drugs/combinations tested, plus control
- 5 pathways/hallmarks: DNA repair deficiency, HER2, Immune, AKT, angiogenesis

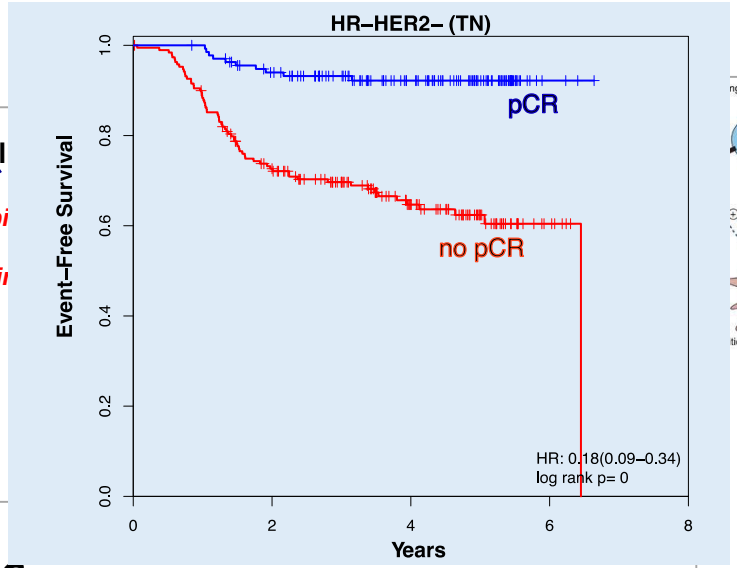
Evaluation by receptor subtype: TNBC

- BOTH veliparib/carboplatin (VC) combination therapy AND pembrolizumab (P) graduated in the triple negative (TN) subset
  - *Plan to include pembro in Block B; carbo in Block B; more immunotherapy & DRD agents in Block A*

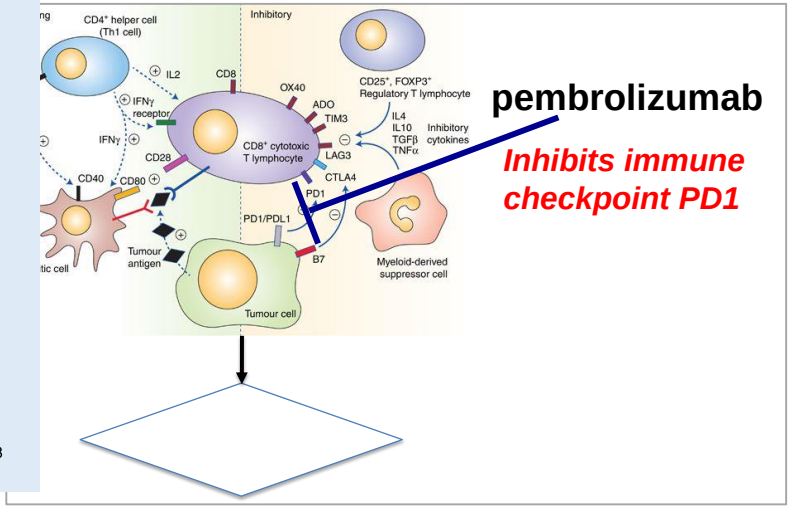
- Who should get what and can we prioritize based on biomarkers to improve outcome?

Platinum-based





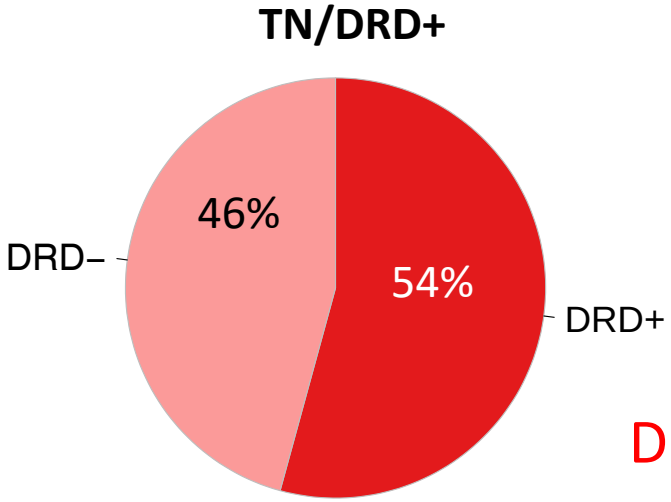
Immunotherapy

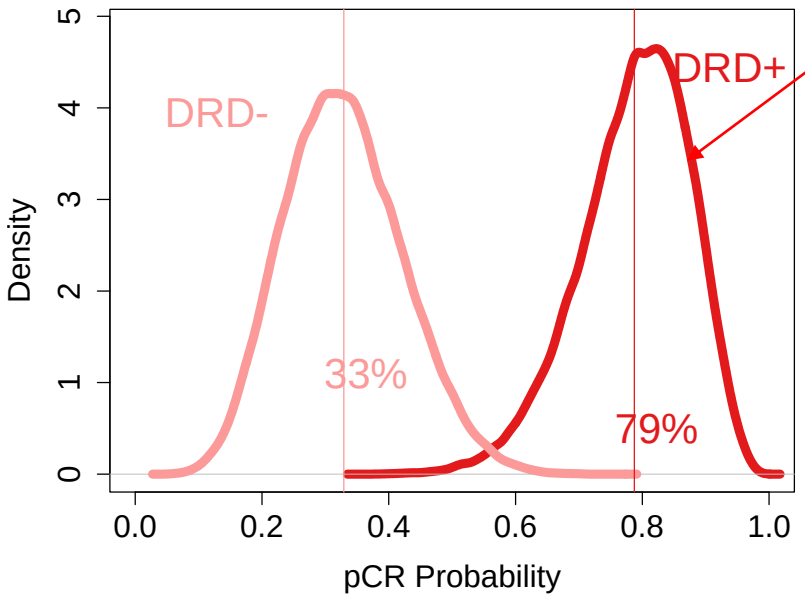


51% estimated pCR rate in VC
(vs 26% in control)

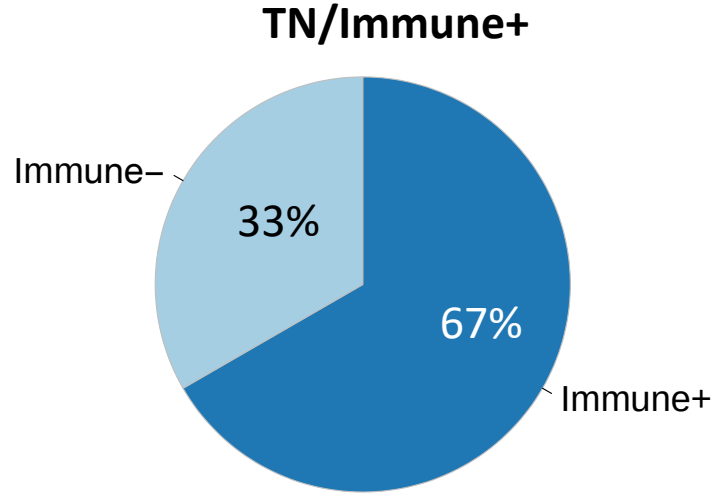
60% estimated pCR rate in P
(vs 22% in control)

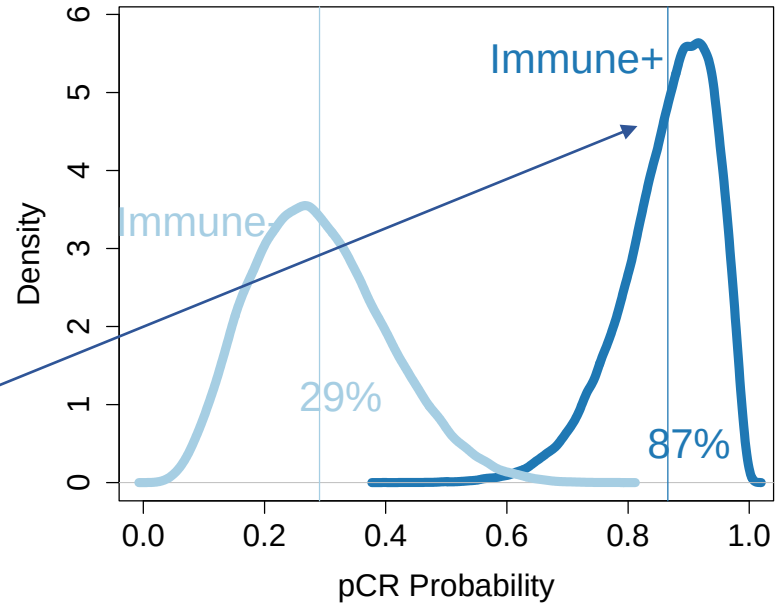
Immune and DRD biomarkers in TNBC, viewed individually





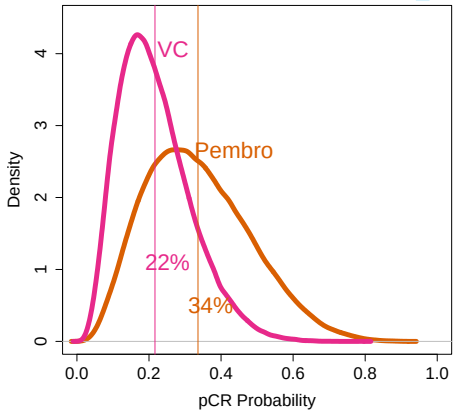
DRD+ patients have a high estimated pCR rate to VC (79%)





Immune+ patients have a high estimated pCR rate to Pembro (87%)

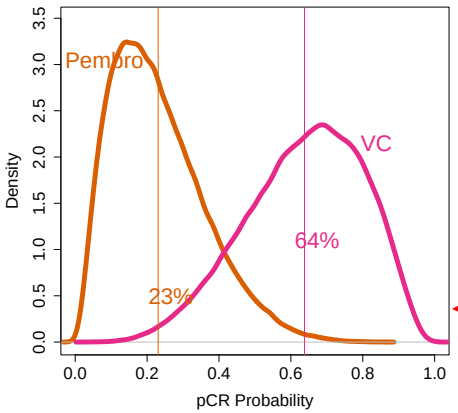
Which drug should be prioritized for whom in TNBC?



Lower pCR in both
(22%, 34%)

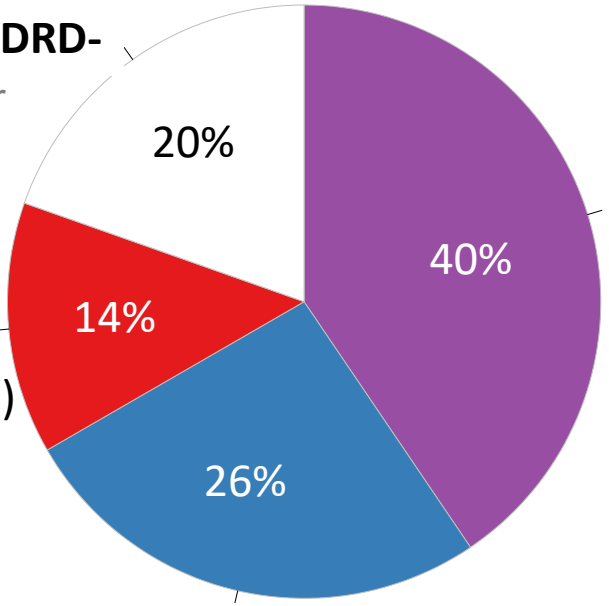
Immune-/DRD-

Biomarker negative



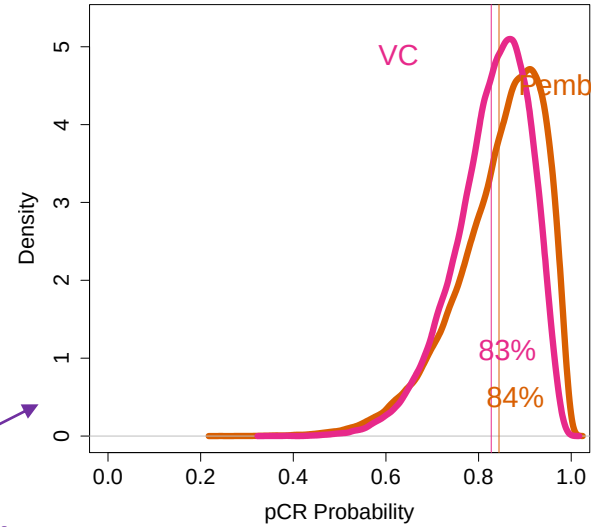
Immune-/DRD+

higher pCR in VC (64%)

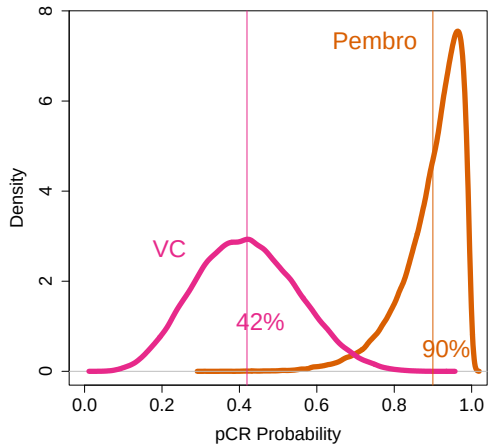


Immune+/DRD+

positive for both biomarkers



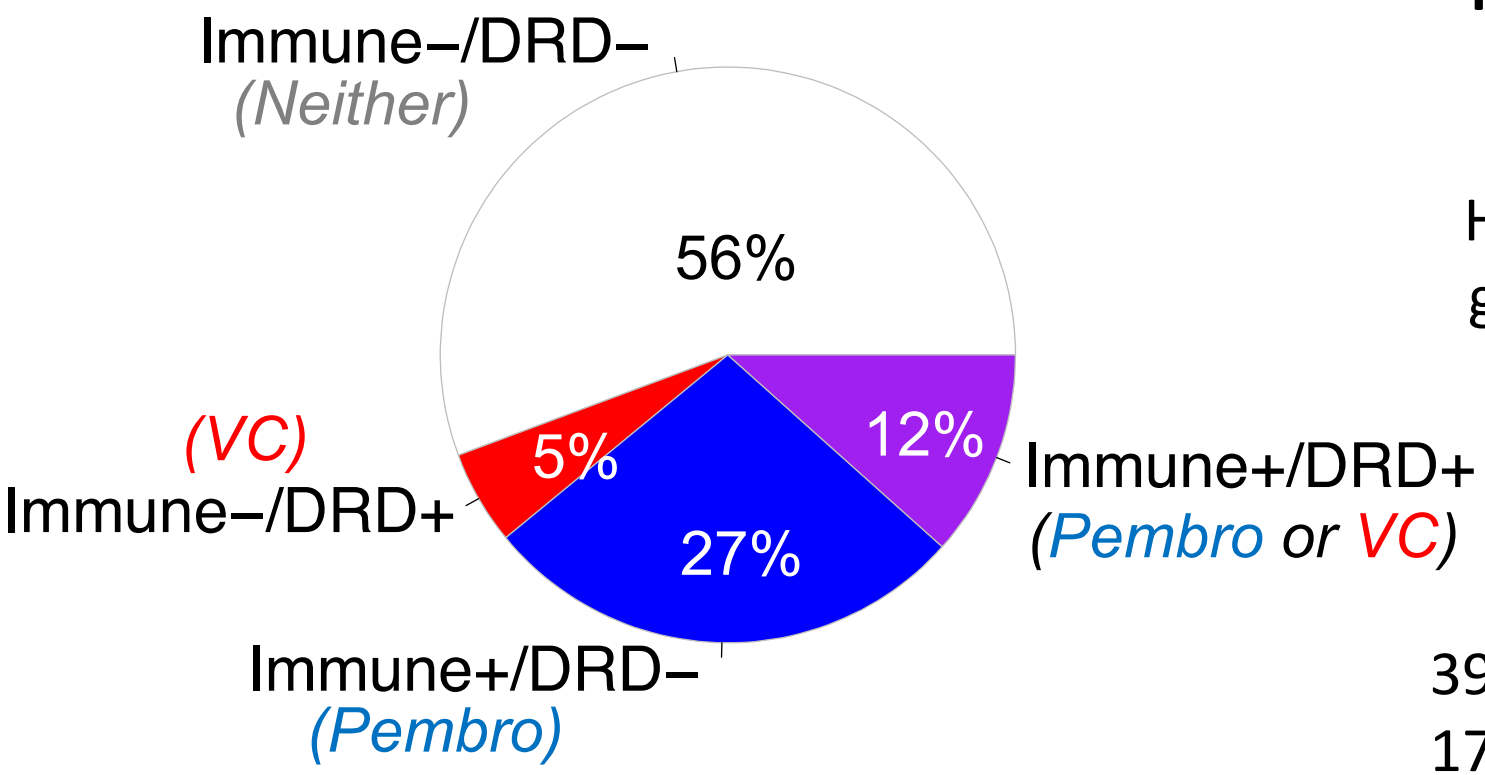
high pCR in Pembro
(84%) ***and*** VC (83%)



Immune+/DRD-

higher pCR in Pembro (90%)

Immune and DRD biomarkers associate with pCR in HR+HER2- as well, though prevalence differs



HR+/HER2- Pembro4 graduated w 30% estimated pCR rate in P
(vs 13% in control)
HR+/HER2- Veliparib/Carbo did not graduate, but qualifying biomarker DRD+ patients showed increased response

39% are Immune+
17% are DRD+
HR+HER2- (I-SPY 2 all MammaPrint High Risk)

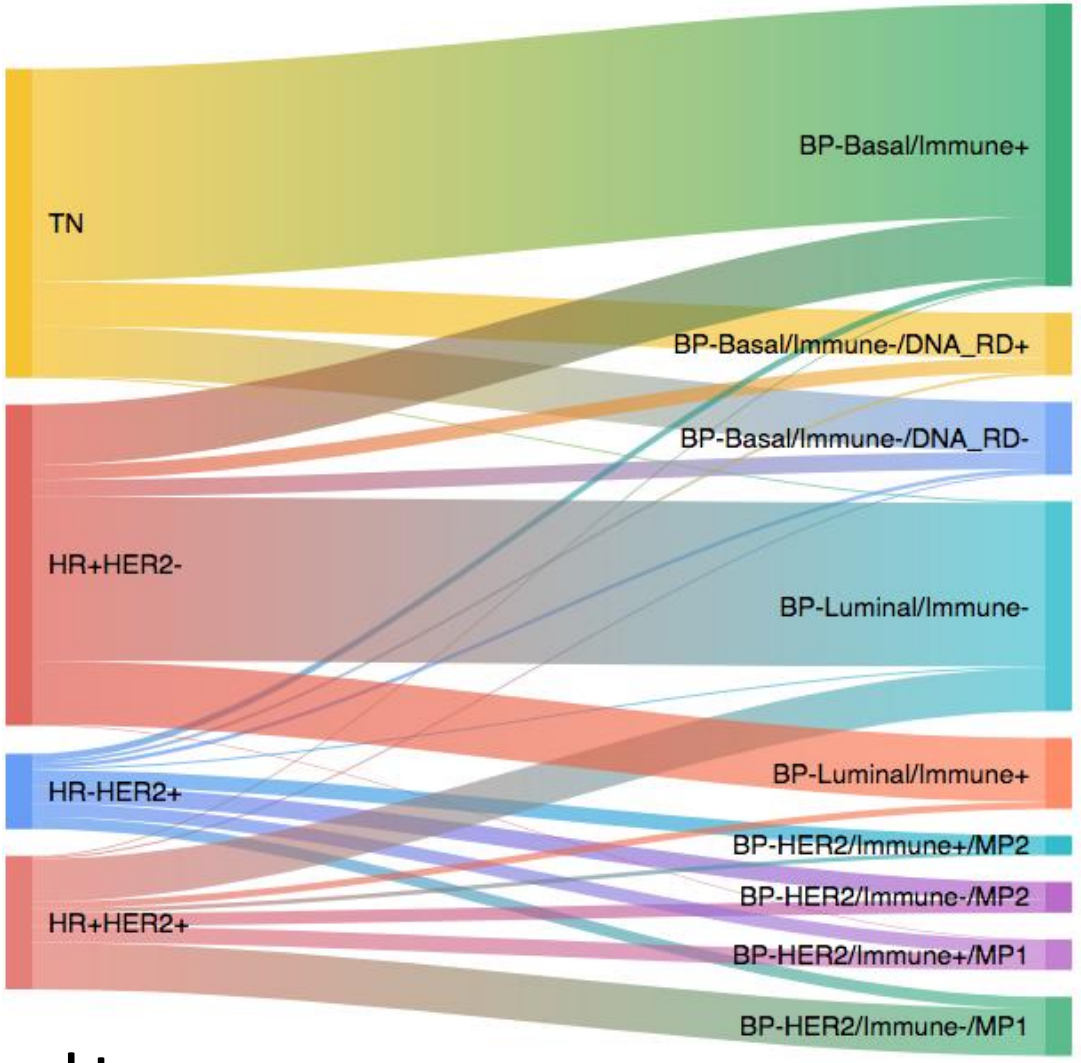
How do we integrate all this information?

(Our current status based om pre-treatment tumor biomarkers)

From Breast Cancer Receptor Subtypes to Drug Sensitivity Subtypes

~1000 I-SPY 2 patients

Pre-treatment biopsy



Receptor subtypes

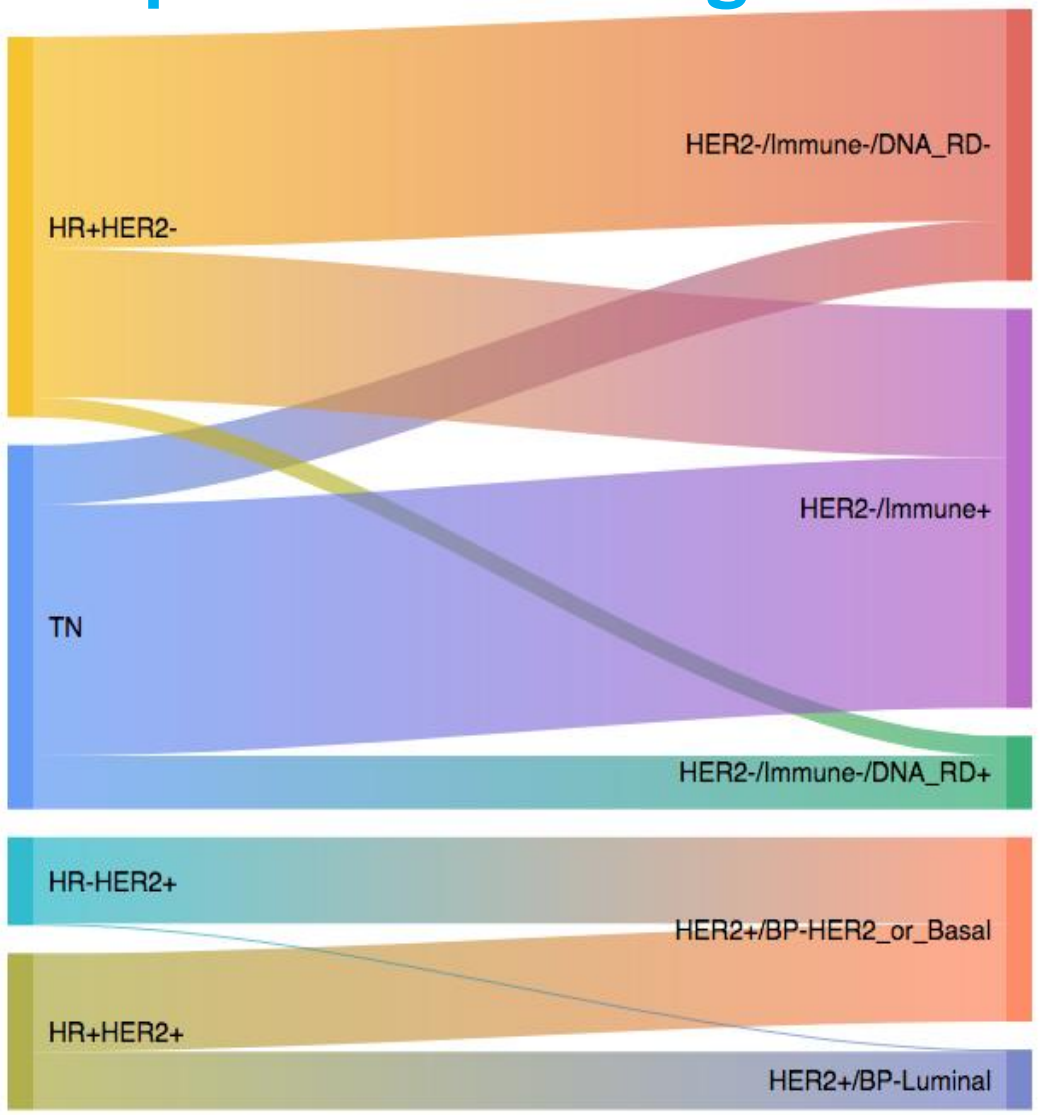
Qualifying Biomarkers-based subtypes

Denise Wolf, Christina Yau ao

Integrated Qualifying Biomarkers

~1000 I-SPY 2 patients –> 5 Drug Sensitivity subtypes

Receptor subtypes



Hybrid-5
Drug Sensitivity subtypes

S1 (27.5%)

S3 (40%)

S2 (7.4%)

S4 (18.7%)

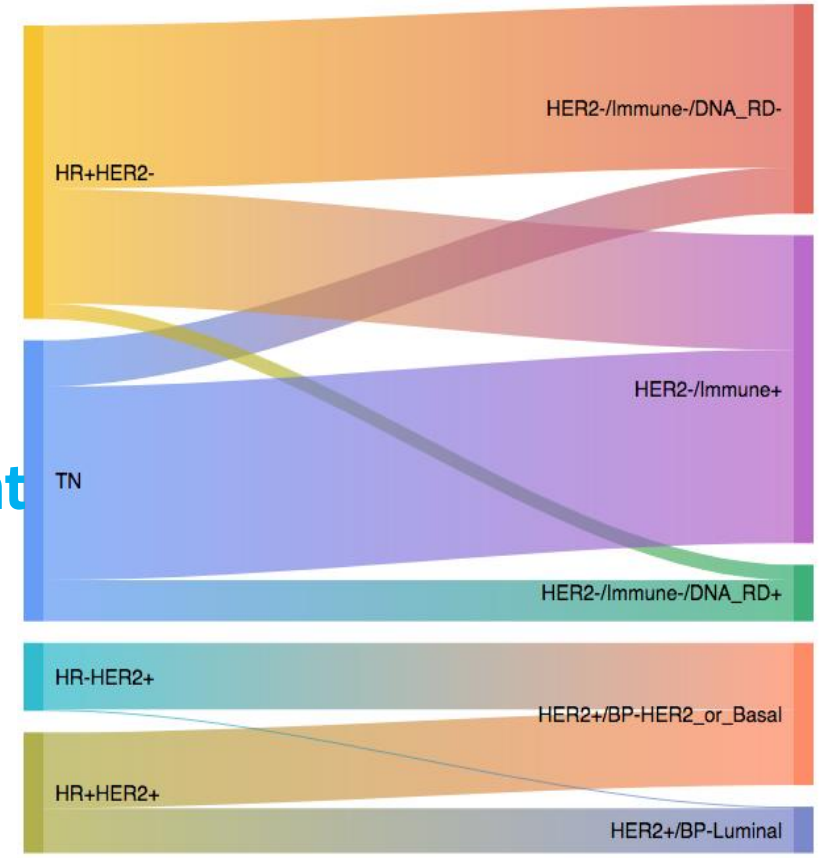
S5 (6.1%)

Denise Wolf, Christina Yau ao

Prioritizing Agents per Hybrid Response Subtype

~1000 I-SPY 2 patients

Pre-treatment biopsy



Receptor subtypes ***Hybrid-5 Response subtypes***

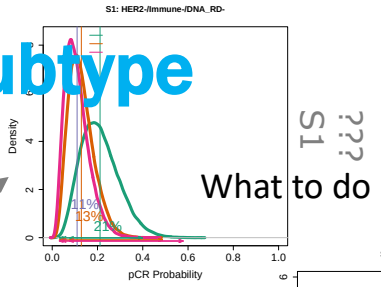
S1 (27.5%)

S3 (40%)

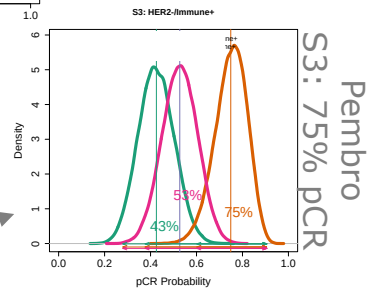
S2 (7.4%)

S4 (18.7%)

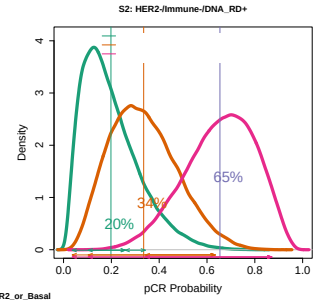
S5 (6.1%)



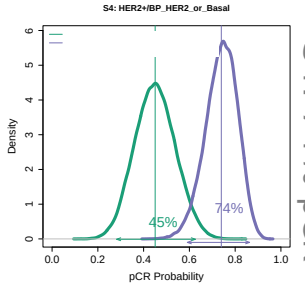
S1 ??? What to do here?



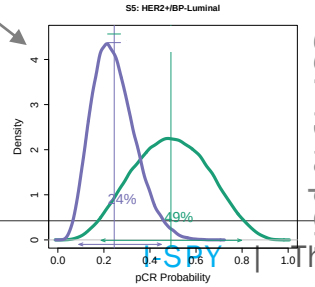
S3: 75% pCR Pembro



S2: 65% pCR VC



S4: 74% pCR TDM1/Pertz



S5: 49% pCR MK2206

some have multiple options, some not yet

hallmarks for other agents?

for each Hybrid subtype based in I-SPY 2 responses

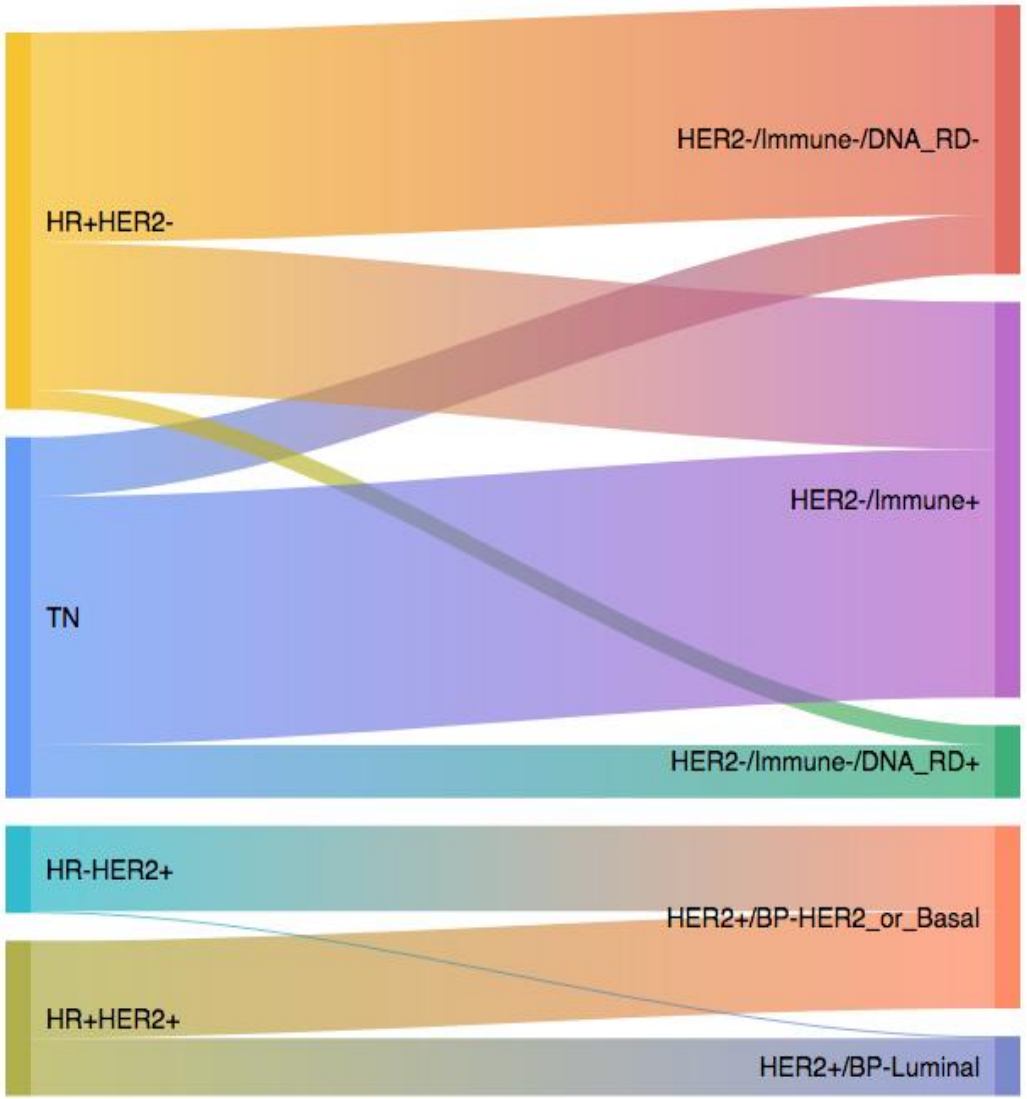
Denise Wolf, Christina Yau ao

From Breast Cancer Receptor Subtypes to Drug Response Subtypes

~1000 I-SPY 2 patients

Pre-treatment biopsy: standard receptor subtypes (left) to best qualifying biology (right), based on 24 per drug qualified biomarkers combined (work in progress)

Denise Wolf, Christina Yau ao



4 Receptor subtypes

5 Response subtypes

Increase of Response prediction:

1) Standard Chemotherapy No subtype selection 20-25%
2) I-SPY 2 Standard chemo with targeted agents on optimal receptor subtype 40%
3) Predicted Response subtypes w preferred targeted agent estimated ~60-70% (ongoing)
4) Next: Test in I-SPY 2.2

I-SPY 2 is a biomarker rich trial

STANDARD

- **Level 1 evidence**
- **FDA cleared or approved or IDE filed**
- **Used in clinical decision**

HR, HER2, MammaPrint, MR volume

QUALIFYING

- **Level 2 evidence**
- **Have existing evidence for response prediction**
- **Based on mechanism of action**
- **Evaluated in CLIA setting**
  - **Agilent 44K array (FDA IDE)**
  - **Phospho-protein array (CLIA)**
  - **DNA mutation panel (CLIA)**
- **Hypothesis testing**
  - Pre-defined biomarkers
  - Pre-specified rigorous

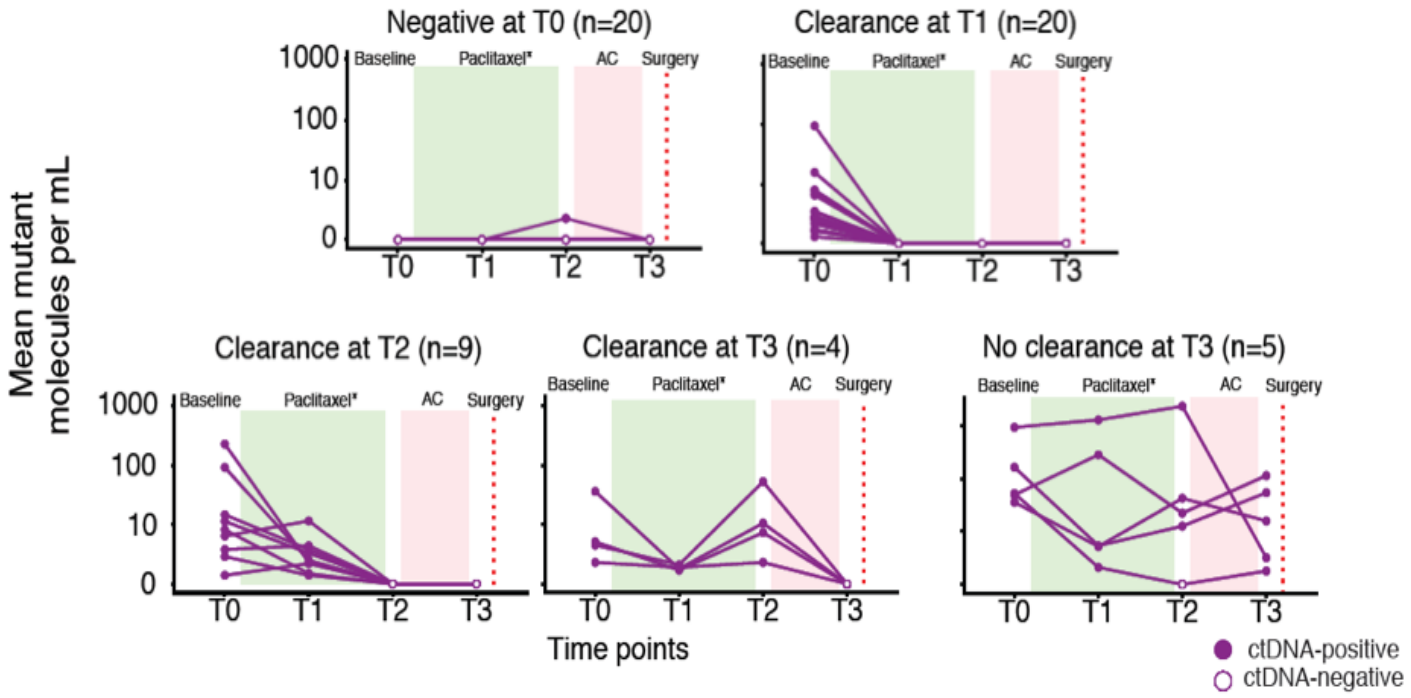
EXPLORATORY

- **Biomarker discovery**
- **Hypothesis generation**

ctDNA and increased risk of metastatic recurrence

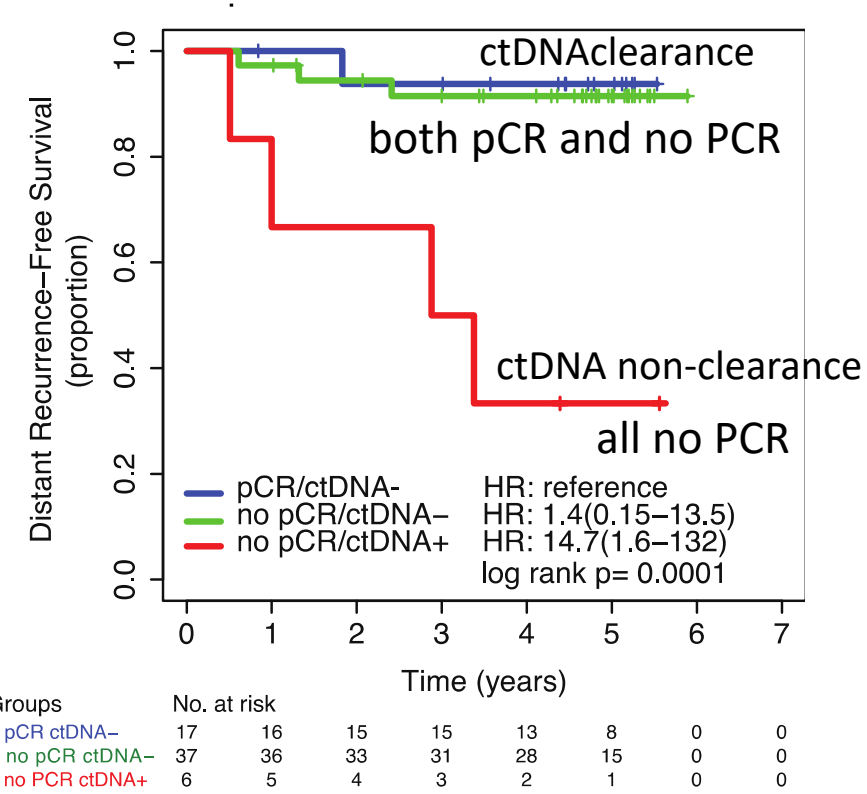
Exploratory Biomarker – ctDNA in plasma - MK2206(AKT-inh)

Circulating Tumor DNA (exploratory biomarker):
Personalized 16 tumor mutated specific fragments
Serial liquid biopsies: MK2206 (Akt-inh) plus controls



Signatera platform – Natera Inc

pCR/no pCR and ctDNA status at surgical timepoint



Mark Magbanua et al, SABCS 2018/2019, submitted

Evolution to I-SPY 2.2

Permit de-escalation or escalation of therapy as needed

- Adapt treatment on the individual patient level to maximize pCR and further increase survival probability
- Make use of MRI volume change early
- Guidance by ctDNA (high need: validation, sequencing)*
- Immune blood marker changes (high need: sequencing)*
- Integrate all our qualifying biomarker knowledge to guide drugs
  - 24 predictive biomarkers across 10 drugs evaluated on 1000 I-SPY 2 patient
- Introduce 'window of opportunity' drug treatment in trial to find signal of response

I-SPY 2 Platform Trial: Learning, Innovating, and Evolving

- **The I-SPY 2 trial**
  - adaptive randomization of targeted drugs to responding subtypes optimizes complete response and survival for high risk breast cancer
- **Patient Centered**
  - the best drug for their subtype
- **Maximize chance of pCR and cure for each patient**
  - pCR results in 95% 3 yr disease-free survival (no-pCR 76-79%)
- **Increase 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 participate - speeds the chance that patients will survive
- **Advances regulatory science**

I-SPY 2 Data and Biospecimen Access Process

- Platform Data available for access proposals
- Biospecimen available for proposals

By Data Access and Publication Policy and Concept sheet submission

Acknowledgements

WORKING GROUP CHAIRS

Study PIs:	Laura Esserman, Don Berry	**Operations:**	A. DeMichele/C. Isaacs
Imaging:	Nola Hylton	**Biomarkers:**	Laura van 't Veer
Agents:	Doug Yee	**Pathology:**	Fraser Symmans
Safety:	Hope Rugo/R. Schwab	**Advocates:**	Jane Perlmutter
		PRO/QOL:	Michelle Melisko

SITE PRINCIPAL INVESTIGATORS: 19 sites

Columbia:	Kevin Kalinsky	**UCSF:**	A. Jo Chien
Denver:	Anthony Elias	**UMinn:**	Doug Yee
Gtown:	Claudine Isaacs	**UPenn:**	Amy Clark
Loyola:	Kathy Albain	**USC:**	Julie Lang
Mayo:	Judy Boughey	**Yale:**	Tara Sanft
Moffitt:	Heather Han	**Emory:**	Jane Meisel
OHSU:	Kathleen Kemmer	**Wake:**	Alexandra Thomas
Swedish:	Erin Ellis	**UPMC:**	Adam Brufsky
UChi:	Rita Nanda	**UAB:**	Erica Stringer-Reasor
UCSD:	Anne Wallace		

SPONSOR

Quantum Leap Healthcare Collaborative

QLHC Board, James Palazzolo, Adam Asare, Kathryn Watson-Feiner, Tracey Heather, Smita Asare, Paul Henderson, Dan Dornbusch, Karyn DiGiorgio, Brendan Raven

PROJECT OVERSIGHT

Anna Barker/ASU, Gary Kelloff/NCI, Janet Woodcock/FDA, Richard Pazdur/FDA, Robert Becker/FDA, ShaAvhree Buckman/FDA,CDER, Steve Gutman, David Wholley/FNIH

DSMB & Independent Agent Selection Committee (IASC) members

PROGRAM MANAGEMENT

Executive Director: Smita Asare

Operations Manager: Ruby Singhrao

Program Administration:
Stig Kreps, Meera Bose, Lorena K., Julie L., Jill P., Janelle J., Aminat A., Laura G., Carlos B., Andrea W.

Safety & Regulatory:
Danielle Zaragoza, Snigdha Bezawada, and Beverly Smolich (CCS Assoc.)

Manuscripts/Strategy:
Laura Sit, Jeff Matthews

Biomarkers/Specimens:
Michael Campbell, Chip Petricoin, Julie Wulfkuhle, Denise Wolf, Lamorna Brown-Swigart, Gillian Hirst, Sara Venters, Aye Aye Ma, Elizabeth Bergin, Mark Magbanua & Collaborators

Imaging Lab:
Wen Li, David Newitt, Jessica Gibbs, Melanie Regan, Margarita Watkins

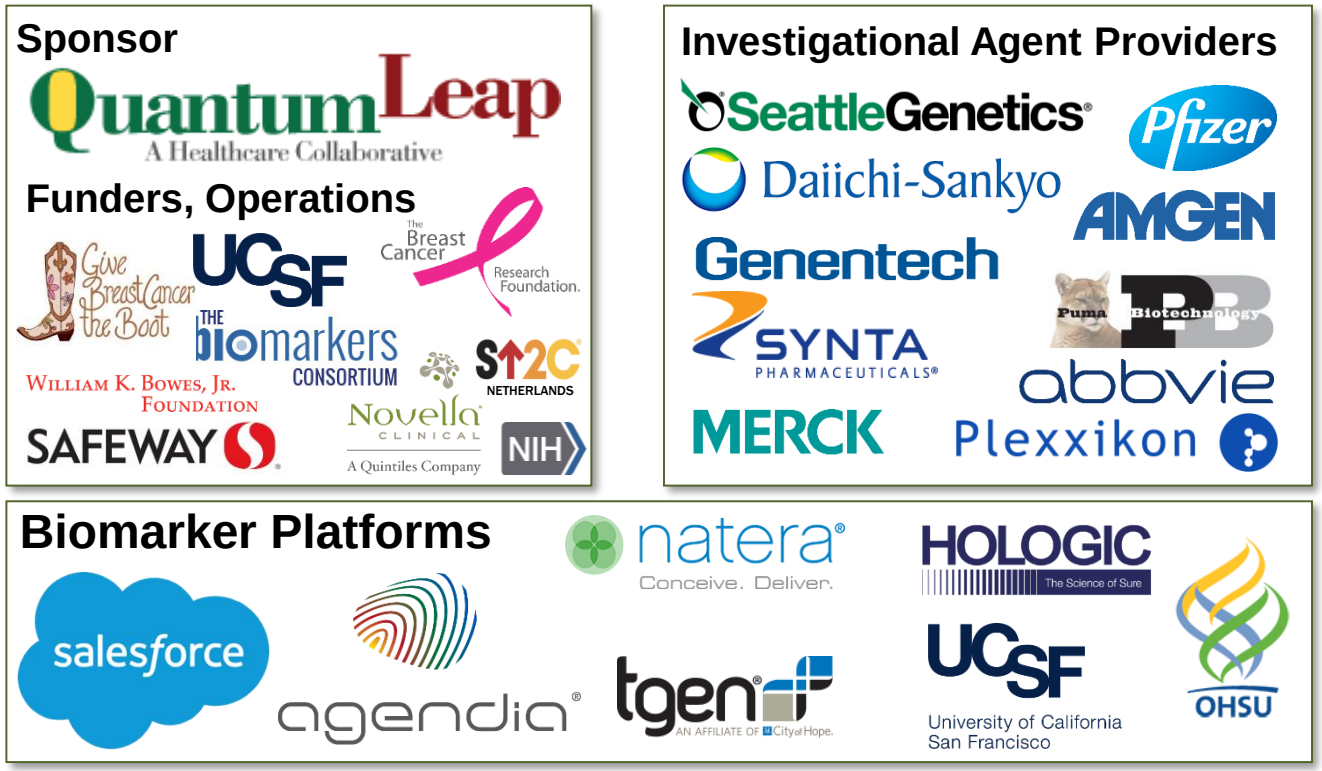
Data Analysis, Data Management & IT:
Ashish Sanil (Berry Consultants), Christina Yau, Amrita Basu, Garry Peterson, Amy Wilson, Sruthi Samineni, Nick O'Grady

PRIOR COLLABORATORS and STAFF

Andres Forero-Torres, Larissa Korde, Rashmi Murthy, Donald Northfelt, Qamar Khan, Kirsten Edmiston, Rebecca Viscusi, Barbara Haley, Amelia Zelnak, Julie Sudduth-Klinger, Nancy Lisser, Meredith Buxton, Melissa Paolini, and Julia Lyanderes

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

I-SPY 2 Participating Organizations and Funders



"Here are my genes..."