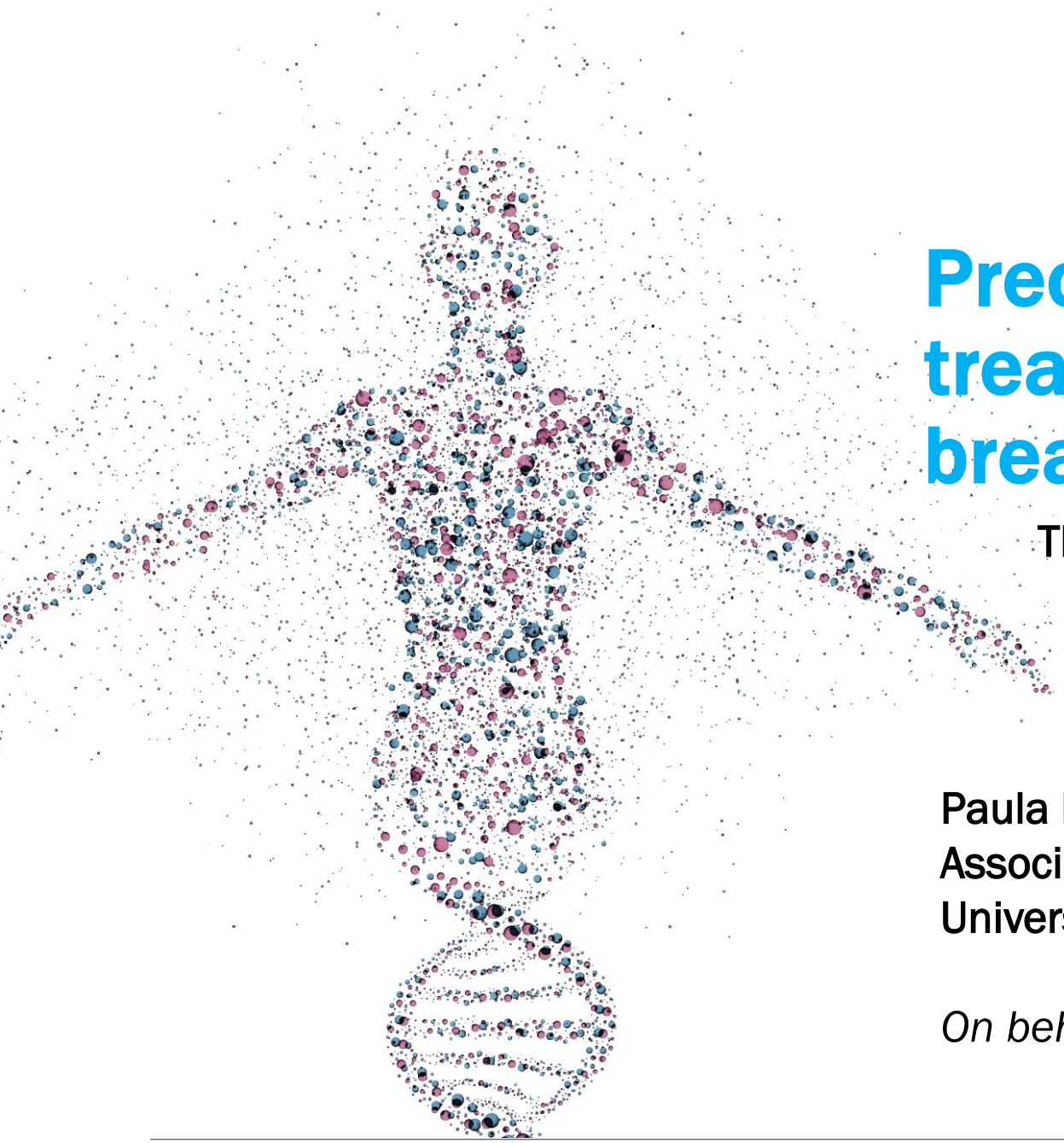

Precision medicine in the treatment of patients with breast cancer

The I-SPY 2 trial's experience

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On behalf of I-SPY2 Investigators

Disclosures

(1) Current honoraria from Frontiers (Editorship) and unpaid trial steering committee (SEAGEN);

(2) Past leadership and stock ownership in Immunonet BioSciences; past honoraria from ASCO, Dava Oncology, OncLive and Genentech/Roche (Courses); past consulting for Personalized Cancer Therapy, Immunonet BioSciences, Sirtex, CARIS Lifesciences, OncoPlex Diagnostics, Pfizer, Heron, Puma, AbbVie, BOLT, SEAGEN.

Outline

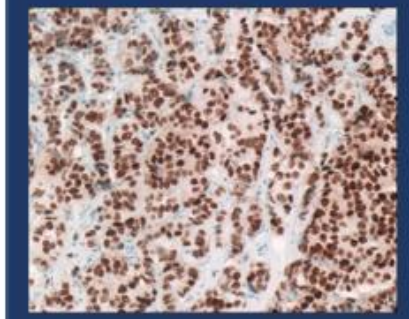
- Breast cancer
- Treatment of early stage breast cancer
- I-SPY 2 clinical trial
- I-SPY 2.2 clinical trial
- Conclusion

Breast Cancer: not all the same

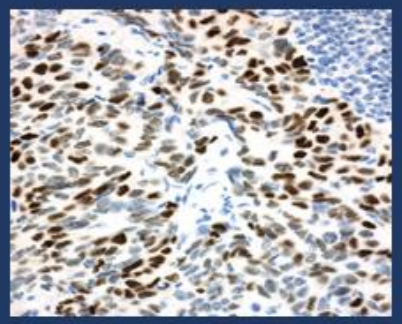
Diagnosis

Mammogram, Breast US, Breast MRI
Breast biopsy with receptor status

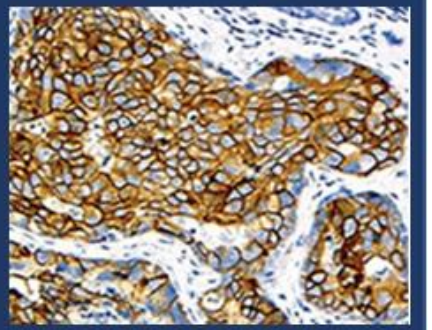
ER



PR



HER2

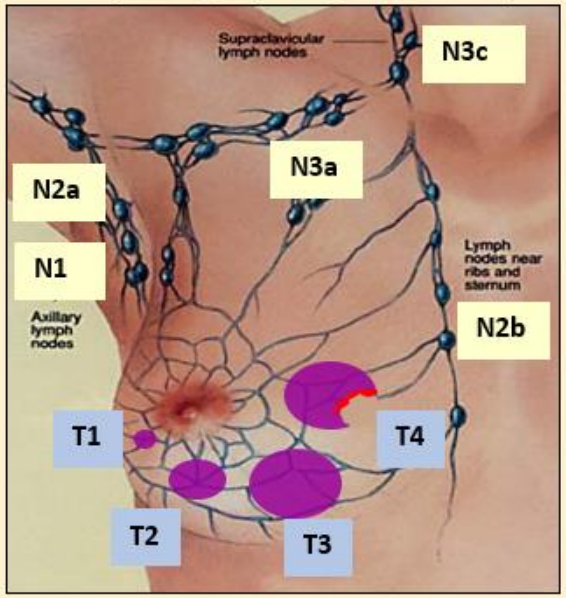


General subtypes

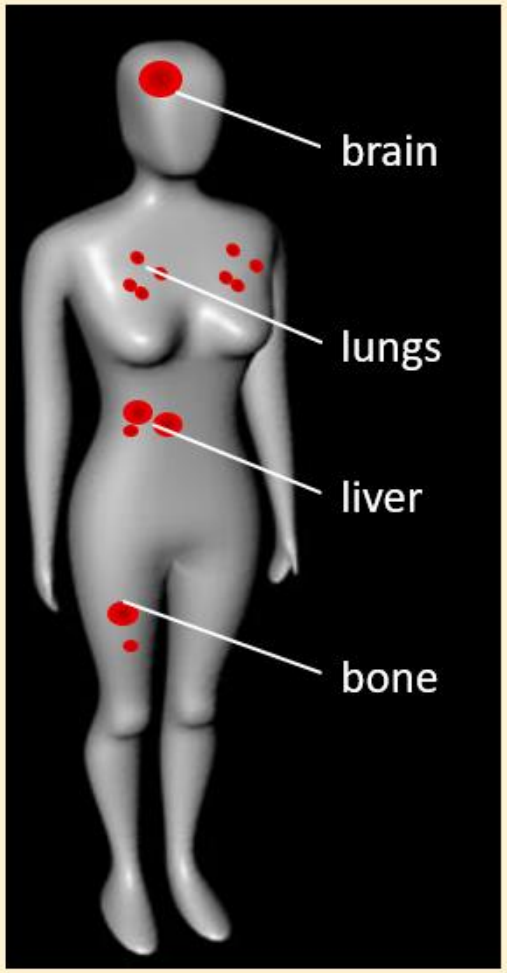
HER2+ **HR+** **TNBC**

Clinical Staging

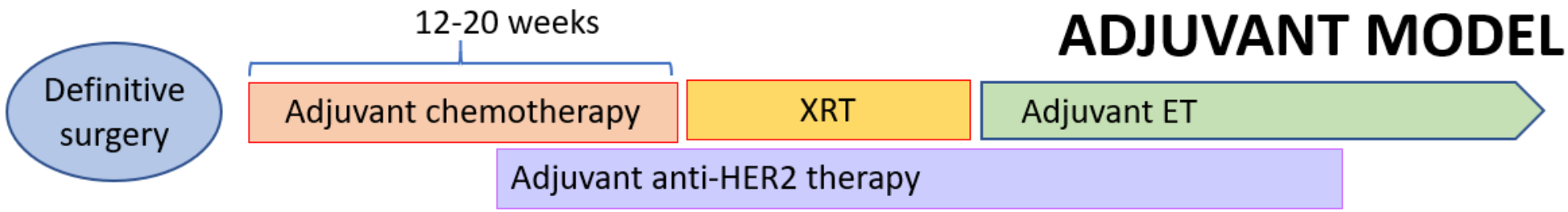
Early stage (Stages I to III)



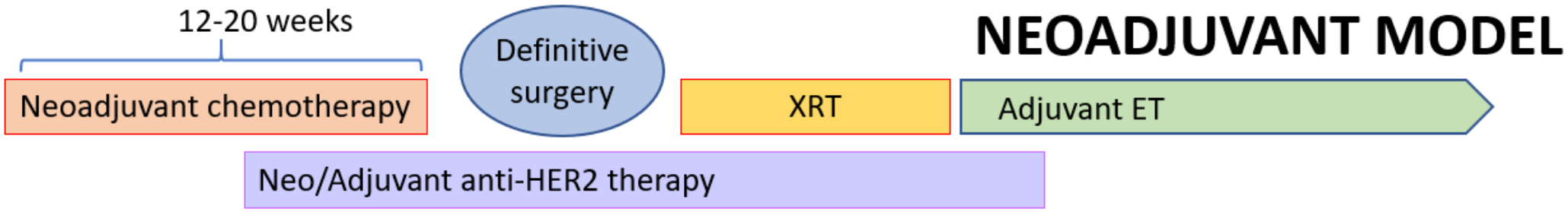
Metastatic disease



Treatment of early stage breast cancer



Added adjuvant treatments over 40 years of clinical studies led to progressive OS increments, but after tumor is removed, we cannot tell if individual patient is benefiting or will benefit from interventions. Treatment cannot be escalated or de-escalated individually.



Tumor is on site when systemic therapy starts, and depending on result at surgery, today we can change adjuvant therapy and attempt to rescue non responders. But again, after tumor is removed, we cannot tell if individual patient is benefiting or will benefit from adjuvant interventions.

Treatment of early stage breast cancer

- Neoadjuvant chemotherapy (NAC) has become a standard-of-care for early breast cancer patients diagnosed with locally advanced disease [1].
- Since NAC is administered prior to surgical resection of the primary tumor, it offers a unique window for real-time monitoring of tumor response during treatment [2-4].
- Approximately 10-65% of patients—depending on subtype and treatment—achieve pathologic complete response (pCR) after NAC [5].
- pCR is characterized by the complete eradication of invasive cancer in the breast and regional nodes.
- A pooled analysis by Spring and colleagues has shown that achieving pCR provides a significant survival advantage [6]. This has been confirmed by the I-SPY 2 TRIAL[7].

1. Wang, M. *et al. Sci Rep* **7**, 44673, (2017); 2. Tromberg, B. J. *et al. Cancer Res* **76**, 5933-5944, (2016).; 3. DeMichele, A. *et al. Clin Cancer Res* **21**, 2911-2915, (2015). 4. Berry, D. A. & Hudis, C. A. *JAMA Oncol* **1**, 875-876, (2015). 5. Cortazar, P. *et al. Lancet* **384**, 164-172 (2014). 6. Spring, L. M. *et al. Clin Cancer Res* **26**, 2838-2848, (2020). 7. Yee, D. *et al.* SABCS 2017.

Treatment of early stage breast cancer

- The absence of tumor after neoadjuvant chemotherapy was established as an optimal endpoint
- A major challenge faced by clinicians in the neoadjuvant setting is how to enable each patient to achieve pCR while minimizing exposure to treatment-related toxicities.
- Biomarkers that accurately predict response to NAC early during treatment are key to this objective
  - Non-responders could be eligible for an early switch to a more effective therapy to increase the likelihood of achieving a pCR and
  - Responders could potentially be sent to surgery early (de-escalation).

I-SPY 2 clinical trial [NCT01042379]

- I-SPY 2 is an ongoing, multicenter, open-label, adaptive phase 2 platform trial with multiple experimental groups to evaluate new agents combined with standard neoadjuvant therapy in patients with high risk early stage breast cancer
- Main Aim: to identify agents that improve the chance of pCR in combination with standard chemotherapy in molecularly high risk stage II/III breast cancer
- Overall GOAL: Improve the Way We Evaluate New Treatments
  - To accelerate knowledge: driving urgency and innovation
  - Trial design incorporates disease heterogeneity
  - Identify additional early endpoints that can be captured in the course of care
  - Look for big signals (screening phase 2)
- Demand - willingness of patients to try a new approach

I-SPY 2 clinical trial: Methods & Statistics

- Primary endpoint is pCR rate
- Five new drugs may be tested simultaneously, with no more than 120 patients tested for each experimental arm
- Multiple biopsies and MRI are obtained throughout the trial to assess response and to discover new predictive biomarkers.
- Bayesian methods of adaptive randomization are applied in I-SPY 2 to achieve a higher probability of efficacy: the likelihood of assignment to a given agent or combination increases with pCR cases as the trial continues
- Enrollment in the experimental group is stopped when:
    1) Bayesian predictive probability of success reaches a prespecified threshold (usually 85%) for any biomarker signature in a confirmatory 300-patient phase 3 trial of neoadjuvant therapy (Experimental drug or combination “graduates”)
    2) Futility criteria met: if the probability falls to below 10% for all biomarker signatures
    3) There is unexpected toxicity
- The I-SPY 2 trial has strict safety monitoring process to ensure patient safety.

pCR predicts EFS for patients

Original Investigation

February 13, 2020

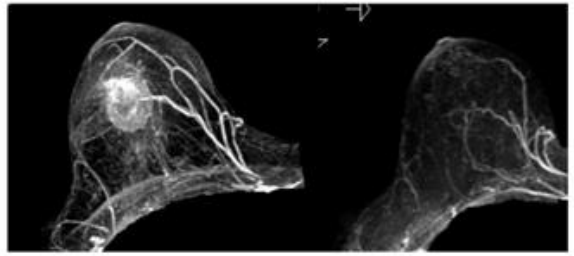
Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer

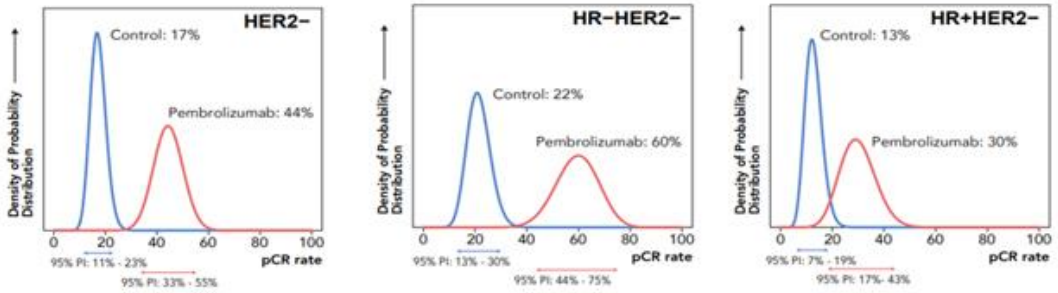
An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial

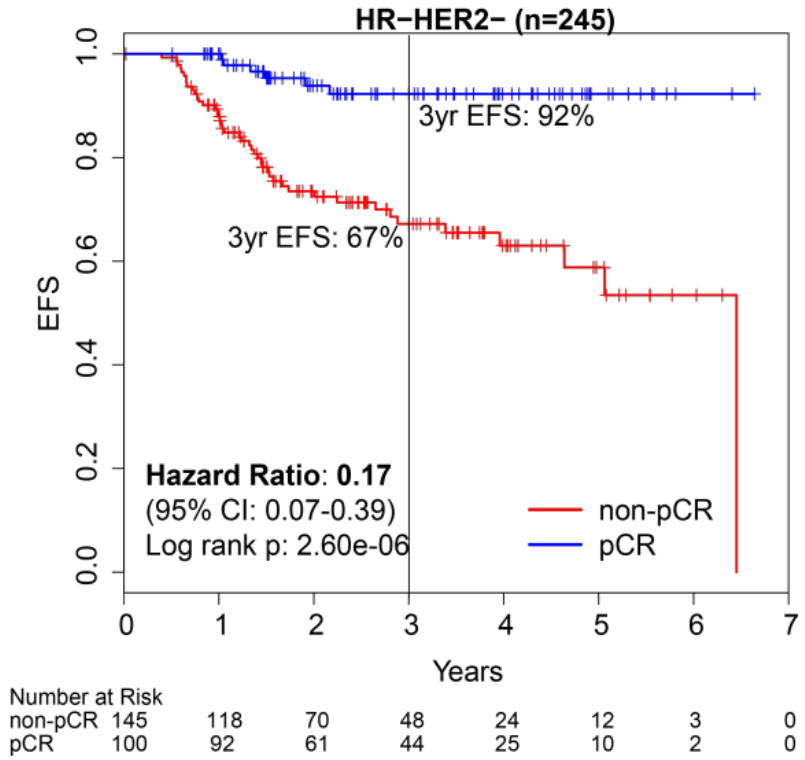
Rita Nanda, MD[1]; Minetta C. Liu, MD[2]; Christina Yau, PhD[3]; et al

Author Affiliations | Article Information

JAMA Oncol. 2020;6(5):676-684. doi:10.1001/jamaoncol.2019.6650







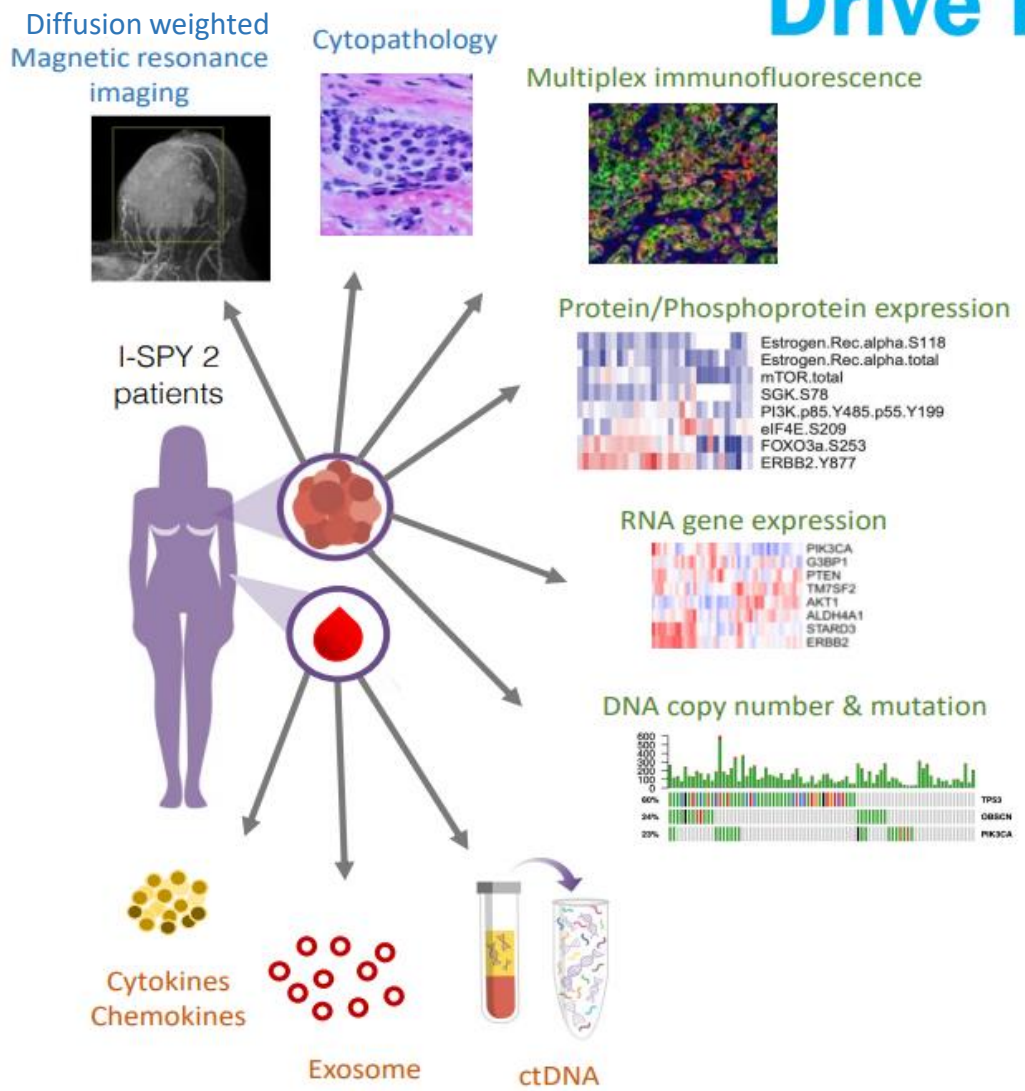
Yee et al 2020

JAMA Oncology | Original Investigation

Correlation of Event-Free and Distant Recurrence-Free Survival With Individual-Level Pathologic Complete Response in Neoadjuvant Treatment of Stages 2 and 3 Breast Cancer

The I-SPY2 Adaptively Randomized Clinical Trial

Biomarkers of Response and Non-response will Drive Progress



The I SPY repository
has over 90,000 specimens
annotated with short and long-term response

Power of a long-standing Platform Trial:
Inform our approach to prevention of metastatic disease AND complications

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 (CLIA)

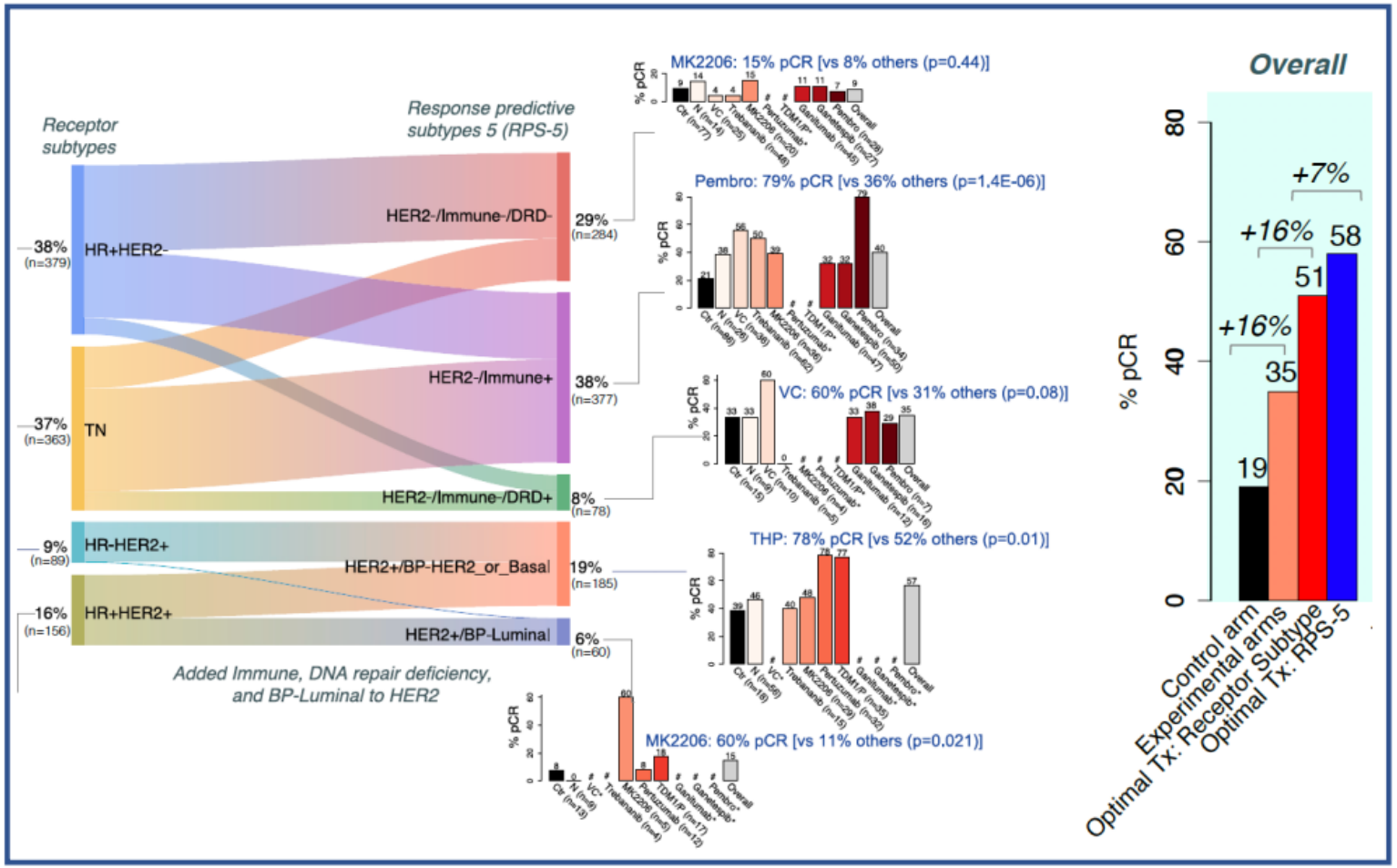
1. **Signatures**
   1. DNA Repair Deficiency
   2. AKT pathway
   3. HER pathway
   4. Hi-2 (Mammaprint)
   5. Immune Signatures
2. **Platforms**
   1. 44k Agilent Array
   2. Reverse Phase Protein Arrays
   3. Vectra Multiplex Staining Environment
   4. DNA mutation panel

EXPLORATORY

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

I-SPY 2 randomized/graduated agents on Receptor Subtypes
I-SPY 2.2 will randomize/graduate on Response Predictive Subtypes

Evaluation 9 drugs in 990 I-SPY 2 patients – Response Predictive Subtypes



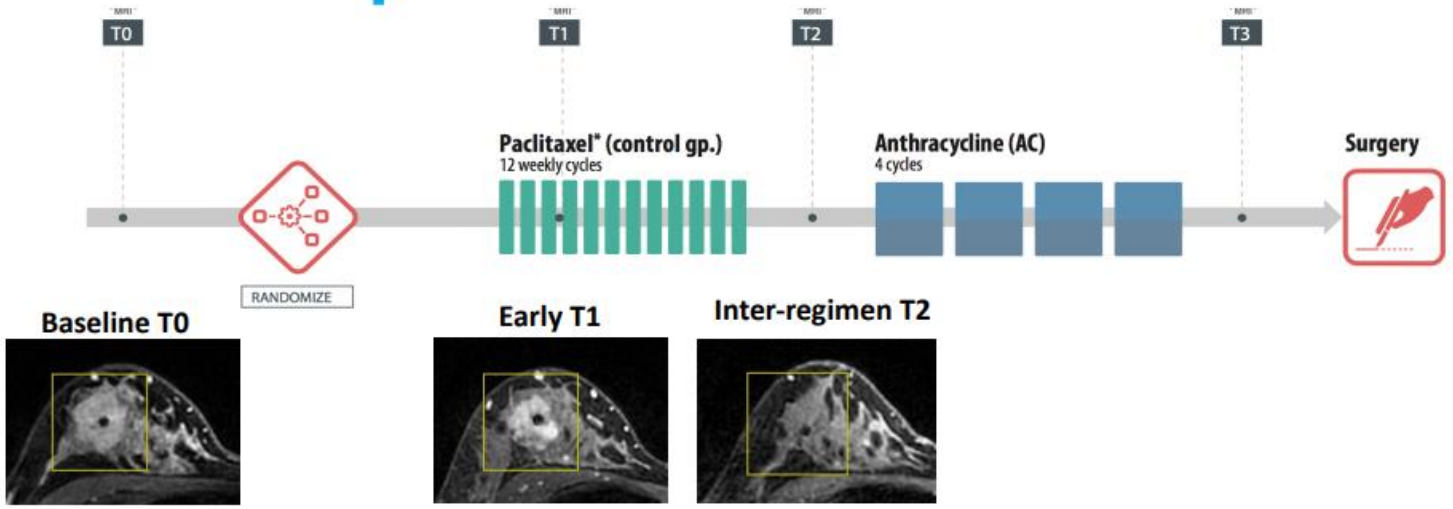
Wolf, Yau, van 't Veer et al; 2022 Cancer Cell 40, p1-15

Alternative **Breast Cancer Response Predictive Subtyping (RPS)** schema **better predicts** response in modern treatment landscape

RPS includes relevant drug response pathways; more can be added as new drugs/ mechanisms are found. *(RPS components were validated in newer I-SPY 2 arms or other trials)*

Using RPS should optimize the chance of achieving a pCR and will be used for randomization in ISPY2.2 **under an IDE**

De-escalation: Skip AC based on combined MRI/biopsy



MRI-predicted pCR
No invasive tumor on core biopsy

abstracts and articles can be found on the ISPYTRIALS.org website under *Manuscripts* or *meeting abstract*

We introduced optional de-escalation in 2020 in I-SPY 2

Patients who meet threshold for predicted pCR: 100% have RCB0 (85%) or RCB1 (15%)

→ **Skip AC**
Go directly to surgery

Greater Personalization: Toward optimal early endpoints

I-SPY 1

Measure outcomes by subtype

- Standardize imaging, pathology, biomarkers, data collection

GOAL: create collaborative framework

1

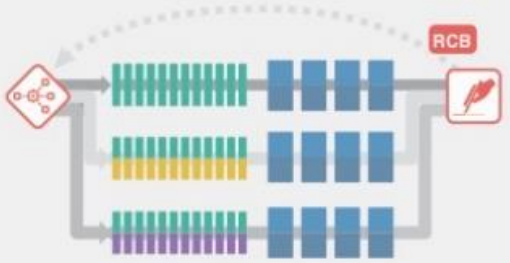
- (pCR) is optimal early endpoint
  - for molecularly high risk
  - Better by subtype

I-SPY 2

Adapt therapy within trial

- pCR regulatory endpoint (accelerated approval)
- Test multiple novel agents adaptively
- Operational efficiencies, platform trial, culture of innovation

GOAL: Increase pCR in each biomarker signature



2

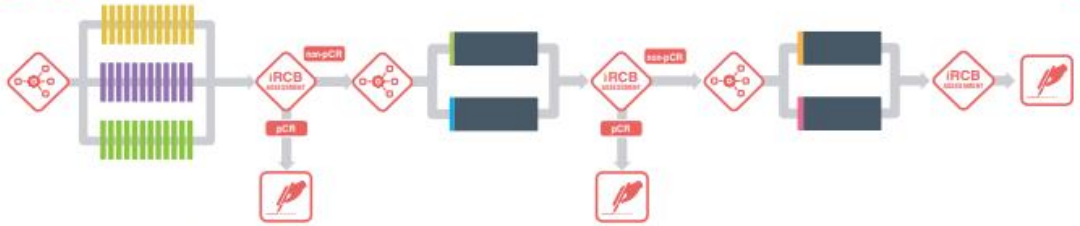
- pCR predicts DRFS HR 0.18 regardless of subtype, therapy
- RCB adds critical information
- Many agents improve subtype specific pCR
- Outcomes better using Molecular markers for treatment assignment

I-SPY 2+

Adapt therapy within patients

- iRCB, Imaging as a regulatory endpoint for poor responders
- SMART approach
- Compare pathways vs receptors to select agents

GOAL: Increase chance of pCR for each patient

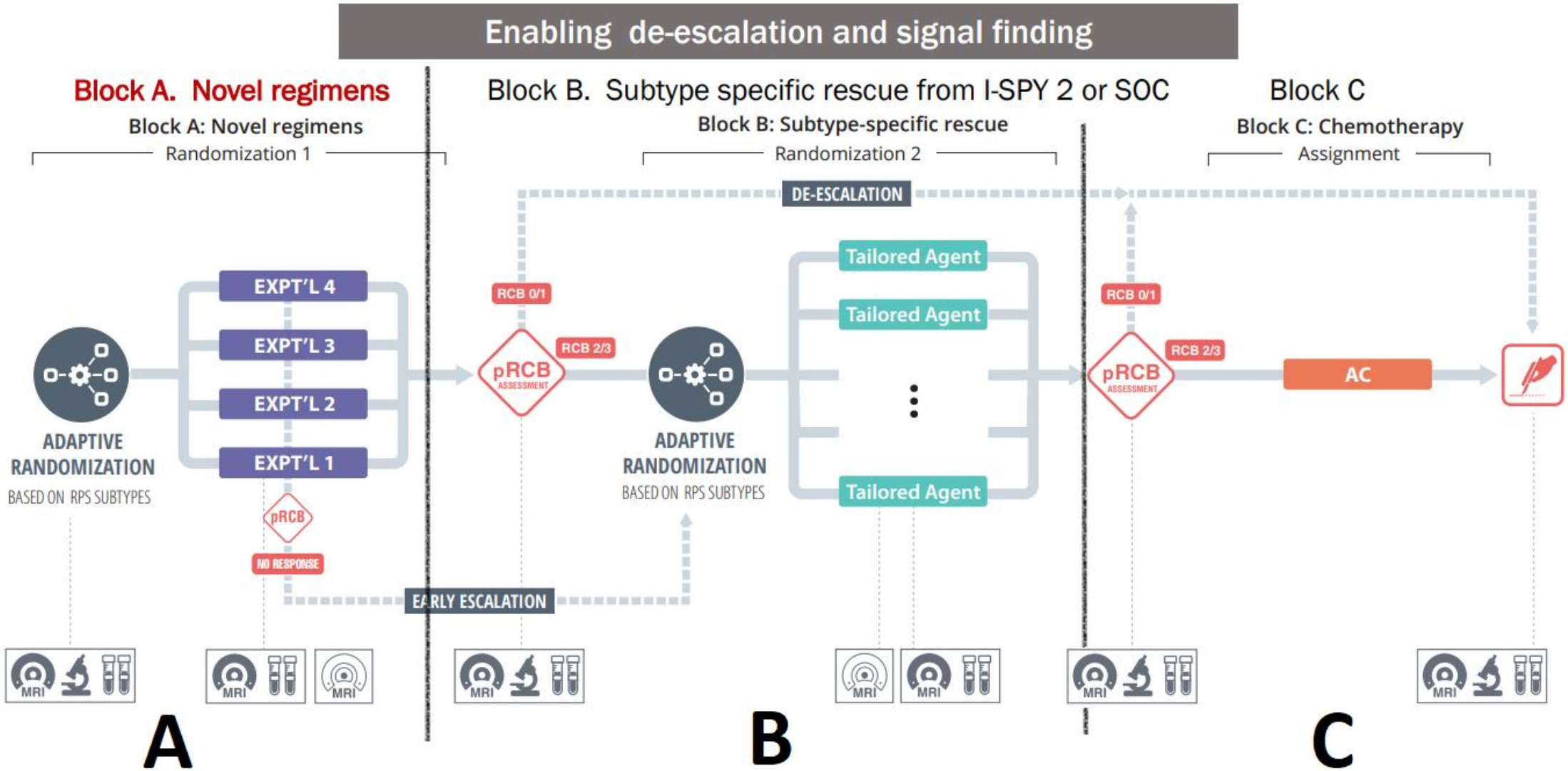


2+

- Optimize pCR for each patient
- Tailor regimens to response
  - Stop at pCR, continue if not
- Accelerated approval for agents that generate optimal pCR rates
- Confirm DRFS at 3 years ≥92%

Patient Centered Design

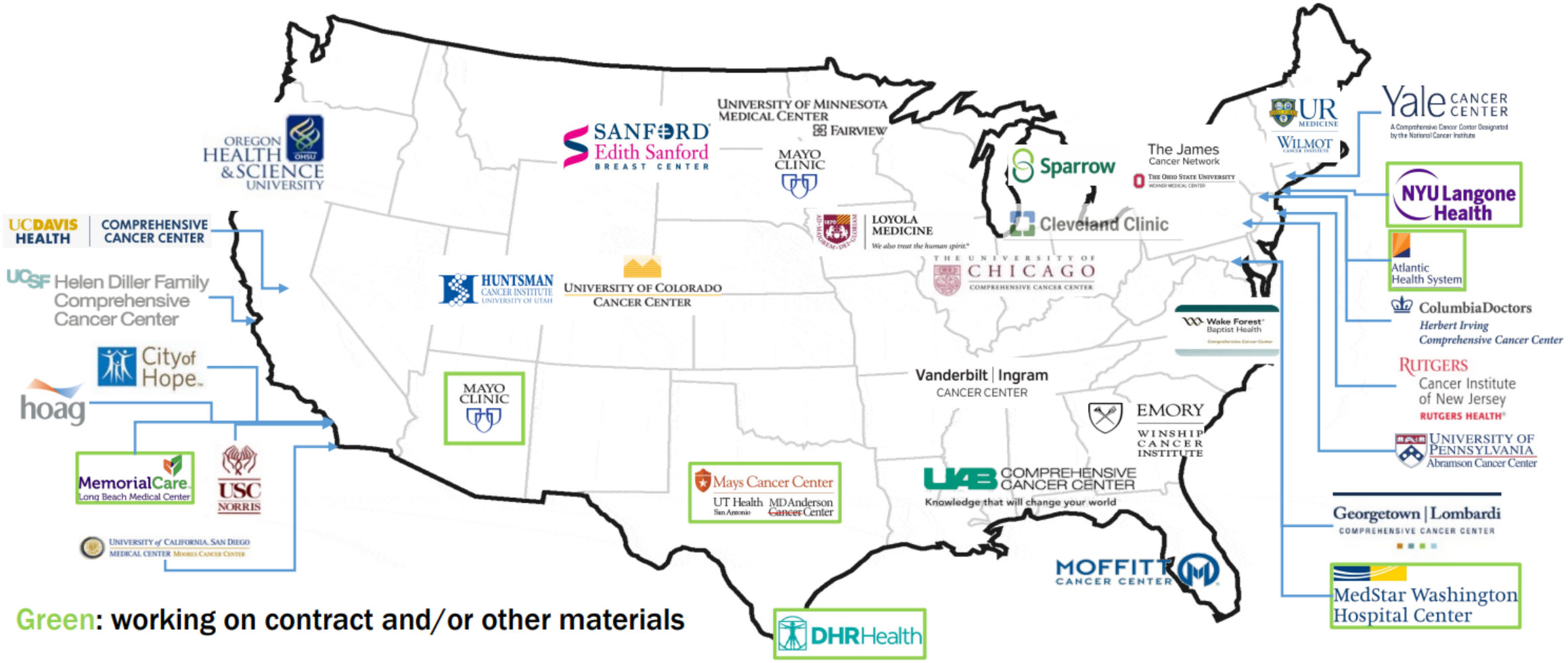
Transition to I-SPY 2.2 June 23, 2022 (A.28)



I-SPY 2.2 Clinical Trial: the plan to implement change

- We need better understanding of the biology of responders and non-responders
- There are new targeted agents that might be effective for all or some subtypes and allow patients to skip traditional chemotherapy
- We have good tools to identify lack of response to trigger escalation of Tx
  - We know 3 weeks is not sufficient (there can be lack of response at 3 wks and good response at 6)
  - 6 weeks is sufficient time to make that decision, and 90% chance of RCB 2/3
- We have tools to predict absence of tumor with good specificity (>90%)
- I-SPY2 was amended in 2020 to allow going to the OR after each regimen if pCR predicted
- Clinicians and patients are excited about testing new regimens
- But they want the rescue therapy to be taxane based optimal therapy, not AC
- Thus Block A is novel targeted therapies, Block B is the prior optimal I-SPY2, Block C contains the anthracycline rescue regimen

I-SPY 2: 32 sites activated (28 Main sites, 4 Satellite)



Green: working on contract and/or other materials

Updated 07/15/2022

Conclusions

- pCR is a good surrogate for 3 and 5 year EFS and DRFS
- Prediction is improved when looking by subtype
- Additional information is gained by looking at residual cancer burden
- The strategy of using biomarkers for adaptation and graduation, and testing qualifying biomarkers has led to the identification of a new way to characterize tumors that improves the chance of getting each patient to pCR
- Functional Tumor Volume (FTV) by MRI has been shown to be a good predictor of response, and has led to graduation decisions that have stood the test of time
- Using pCR as the surrogate primary endpoint can significantly shorten the evaluation process of promising drugs. In I-SPY 2, the average time for a drug to “graduate” is only about 18 months and is much shorter than the duration of a traditional phase 2 trial

I-SPY2.2 VISION

“Make new, better and more personalized treatments, available faster, at a time when patient’s need them most”

Better:	**Higher Distant Disease -Free Survival AND less toxic**
Personalized:	**Matching patient’s biology**
Faster:	**Use early endpoints; Continuous learning**

I-SPY 2 Participating Organizations and Funders