Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer: Results from the I-SPY 2 Trial

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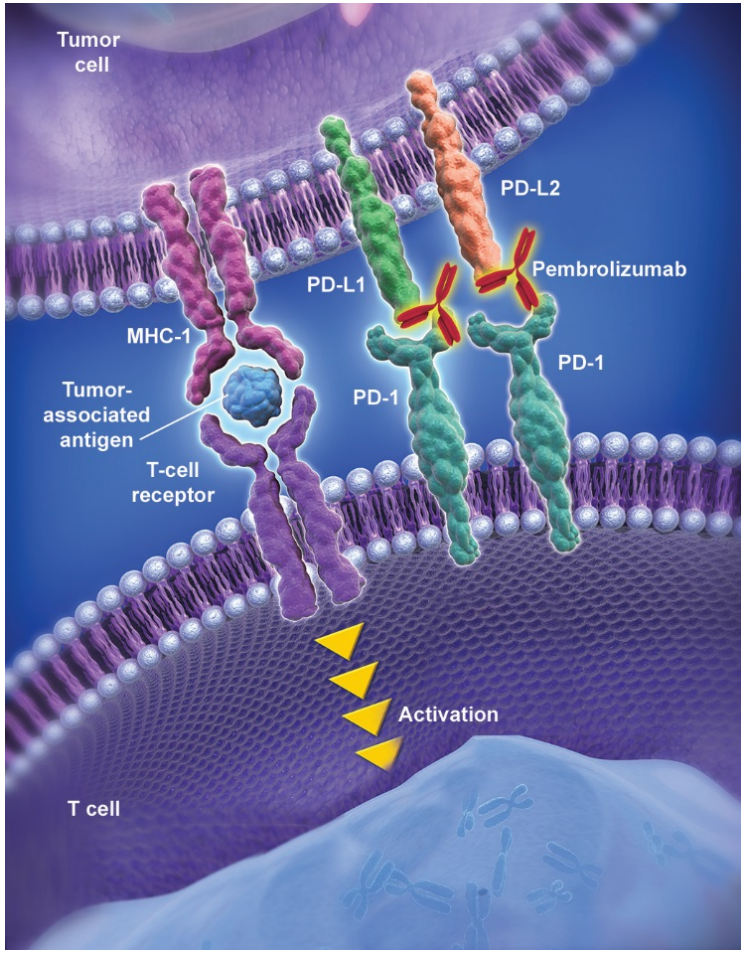
The Right Drug.
The Right Patient
The Right Time. Now.

Pembrolizumab and Breast Cancer

- Tumors can co-opt the PD-1 pathway to evade immune surveillance[1]
- Pembrolizumab is a humanized monoclonal antibody against PD-1; modest single agent activity in heavily pretreated breast cancer
  - RR in TNBC < 10%[2]; in HR+ disease 12.0% [3]
- Safety of pembrolizumab plus paclitaxel available prior to inclusion:
  - KEYNOTE 021 trial in advanced NSCLC[4]
- The I-SPY 2 Trial tested the ability of pembrolizumab to improve pathologic complete response (pCR) rates over standard therapy

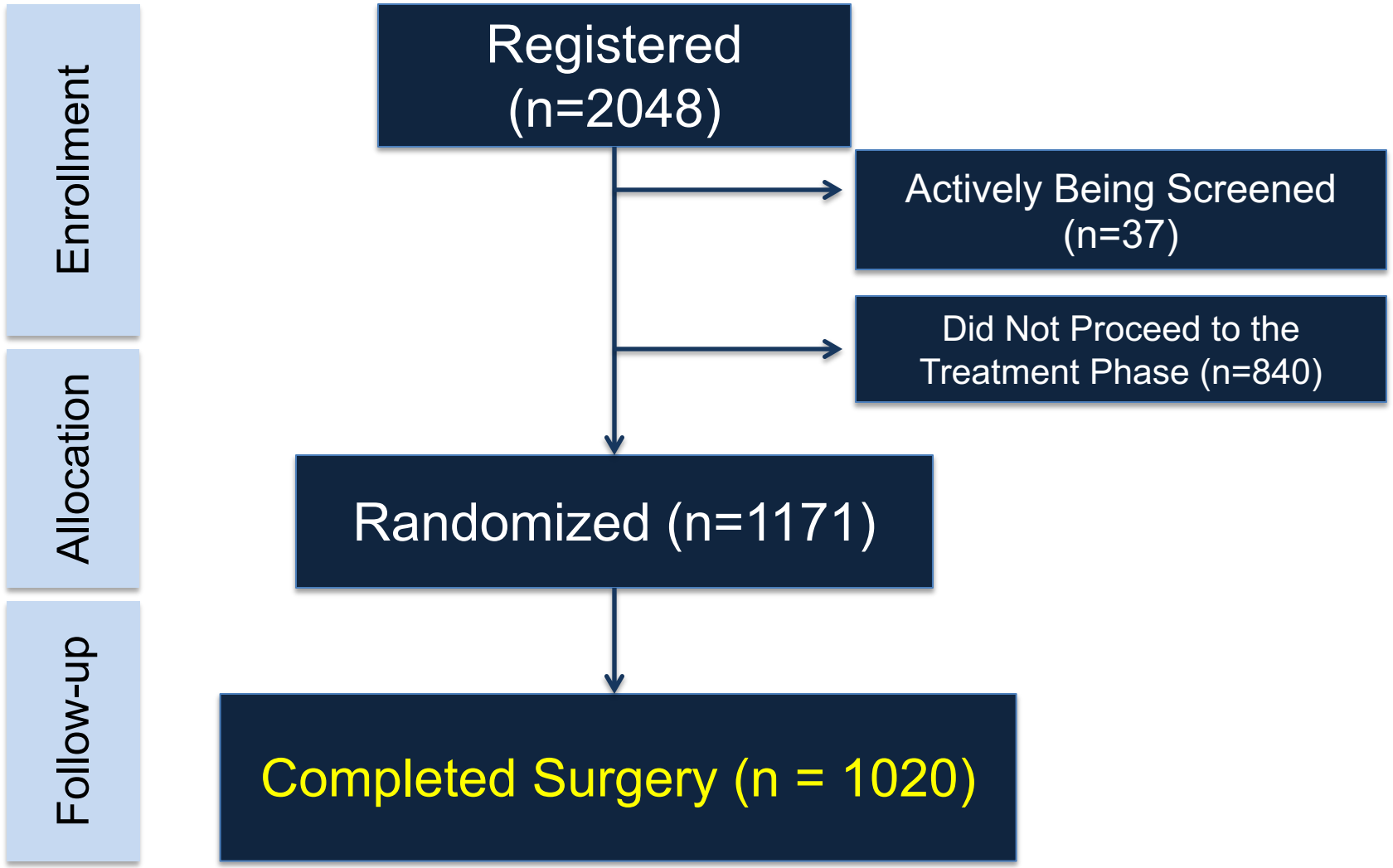


1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64; 2.. Adams S, et al. ASCO 2017; 3. Rugo H, et al. Cancer Res. 2016;76(4 suppl):Abstract nr S5-07; 4. Langer CJ, et al. Lancet Oncol. 2016;17(11):1497-508.

The I-SPY 2 TRIAL Standing Platform

- Phase II, adaptively-randomized neoadjuvant trial
  - Goal: efficiently identify promising agents to take to phase III
- Multiple concurrent experimental arms; 13 agents to date
- Adaptive randomization minimizes number of patients needed to determine efficacy
- “Graduation” for efficacy = reach an 85% predicted probability of success in a 1:1 randomized 300 patient phase III trial

Trial Enrollment Overview



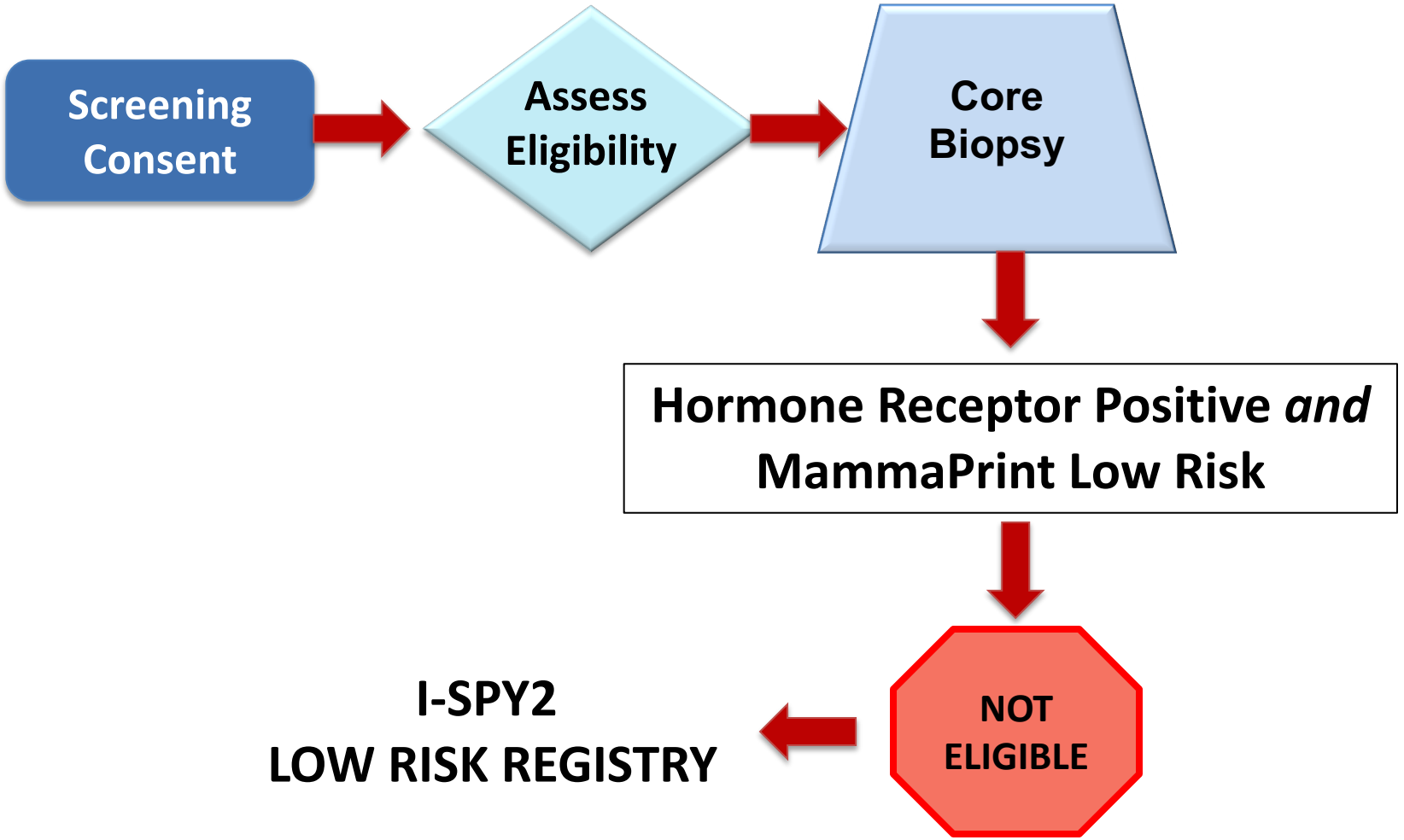
Status as of June 1st, 2017

I-SPY 2 TRIAL Eligibility

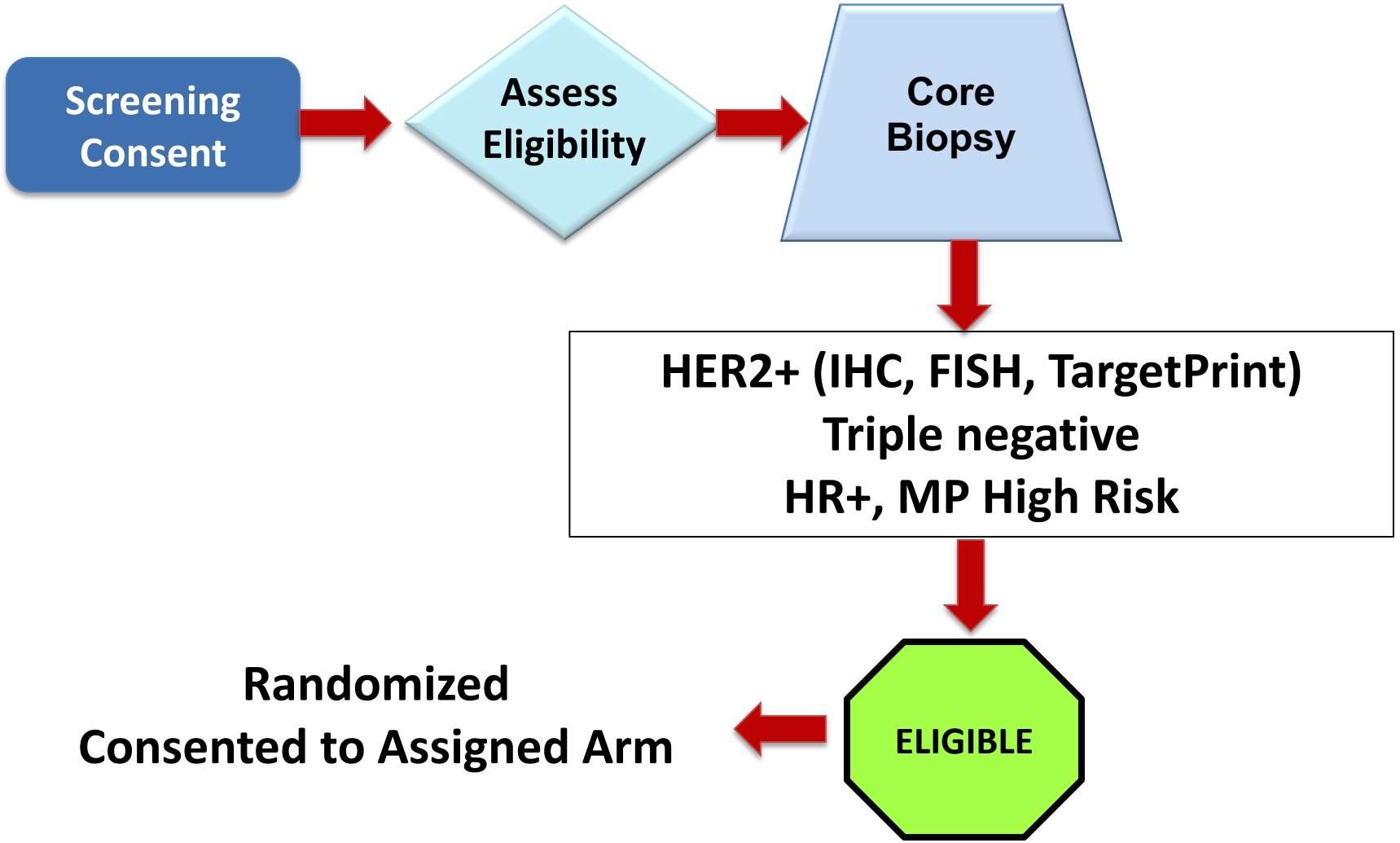
Screening

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

I-SPY 2 TRIAL Eligibility



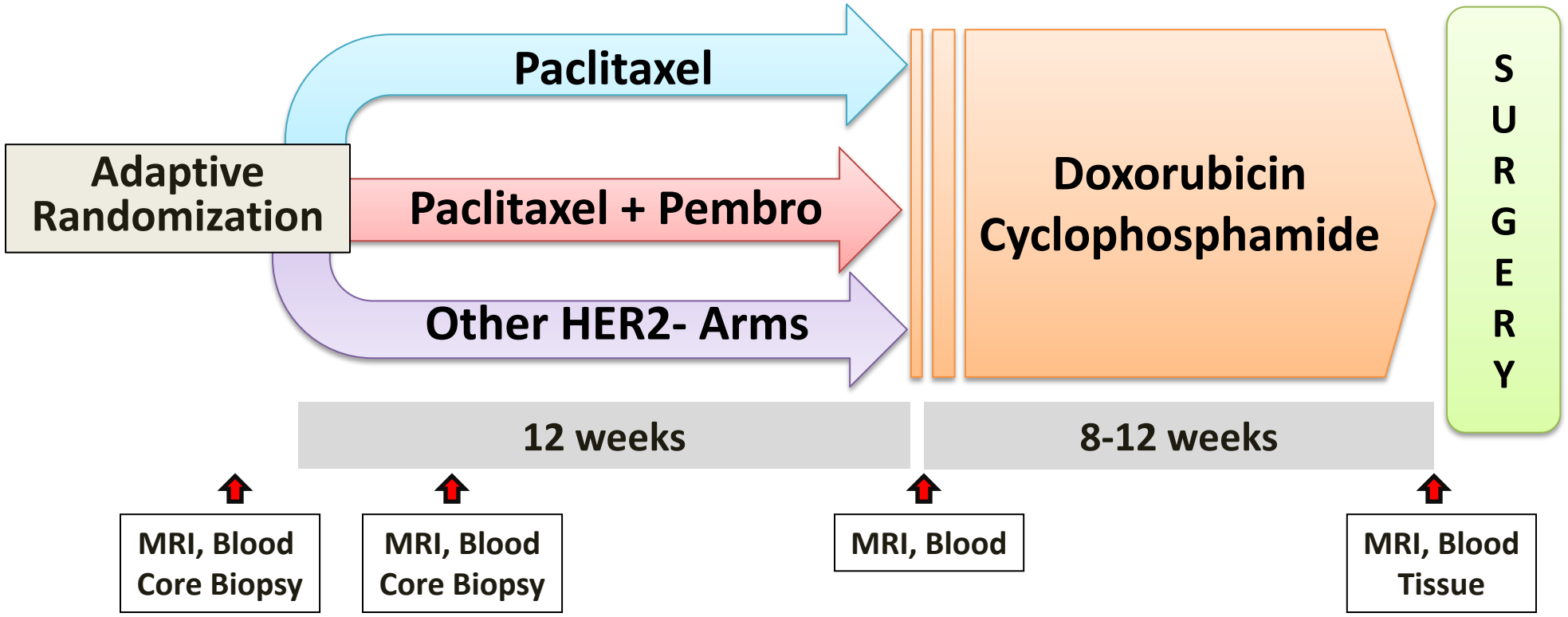
I-SPY 2 TRIAL Eligibility



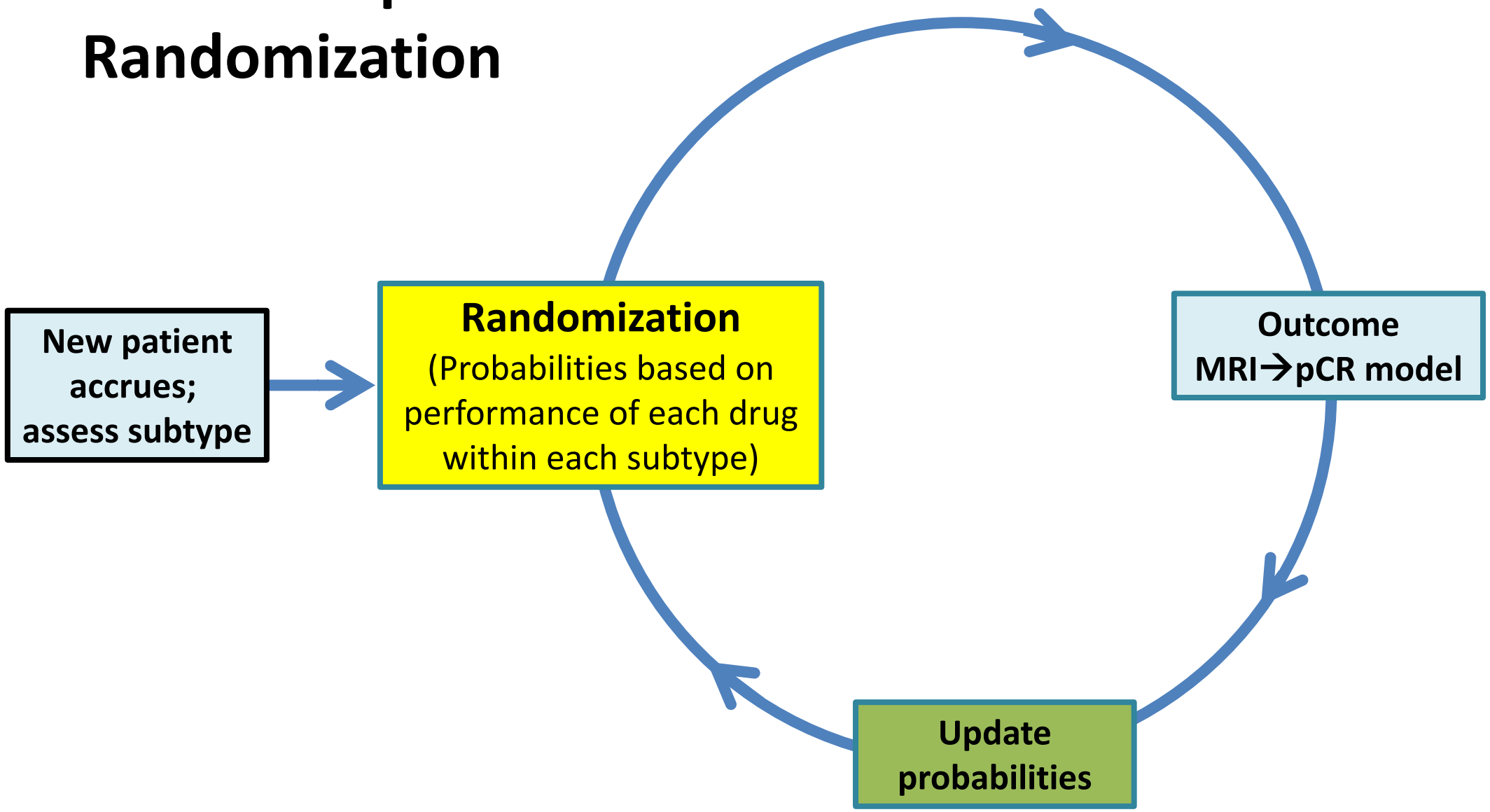
Primary Endpoint: pCR

- Defined as no residual invasive cancer in the breast or lymph nodes (ypT0/is and ypN0)
  - Intent-to-treat
  - Protocol-defined non-pCR:
    - Switch to non-protocol assigned therapy (e.g. addition of carbo)
    - No surgery
    - Withdrawal from the trial
- Pembrolizumab was studied in 3 HER2 negative “biomarker signatures”
  - All HER2-
  - HR+/HER2-
  - HR-/HER2- (triple-negative breast cancer; TNBC)

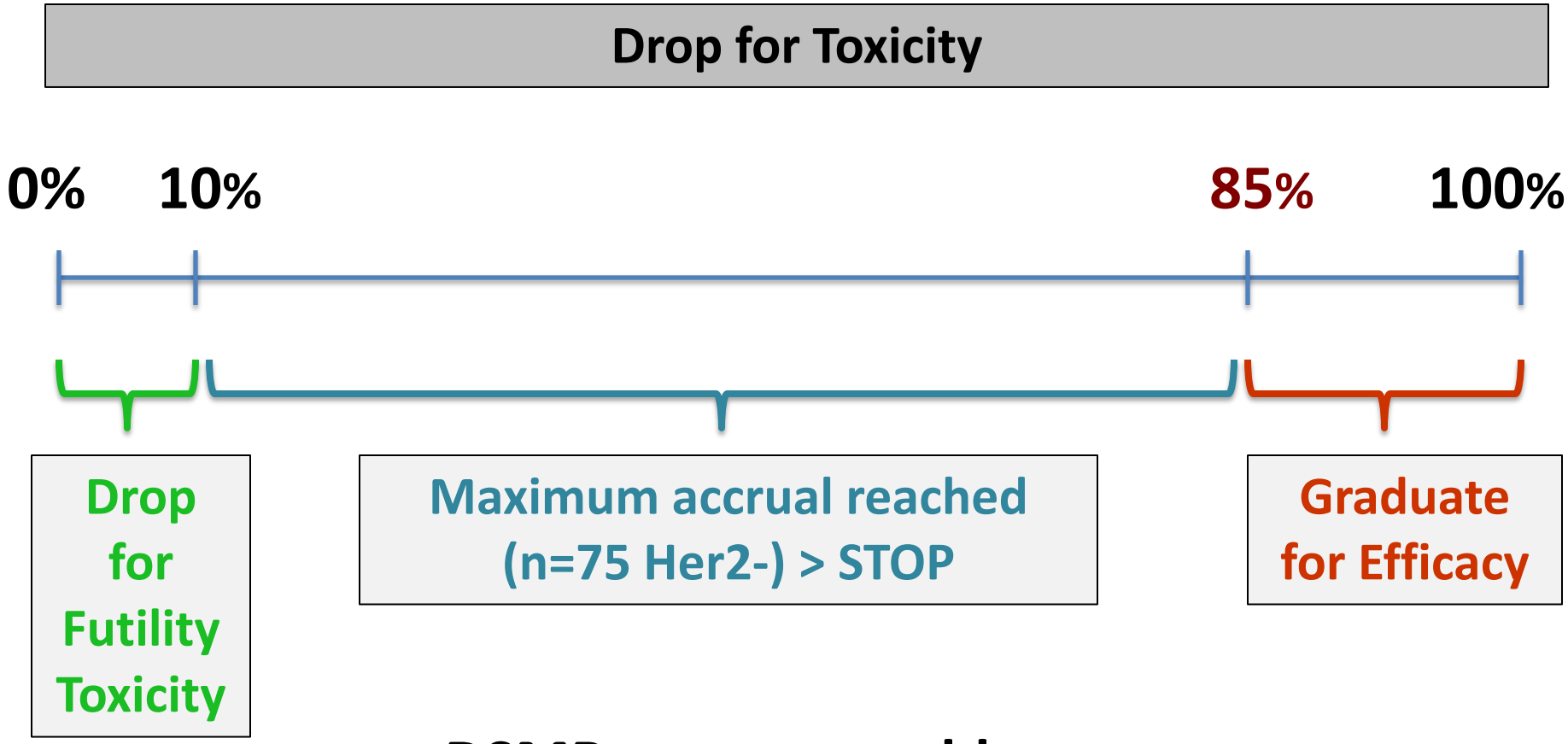
I-SPY 2 TRIAL Schema: HER2- Signatures



I-SPY 2 Adaptive Randomization



Not Every Regimen Graduates for Efficacy



DSMB meets monthly

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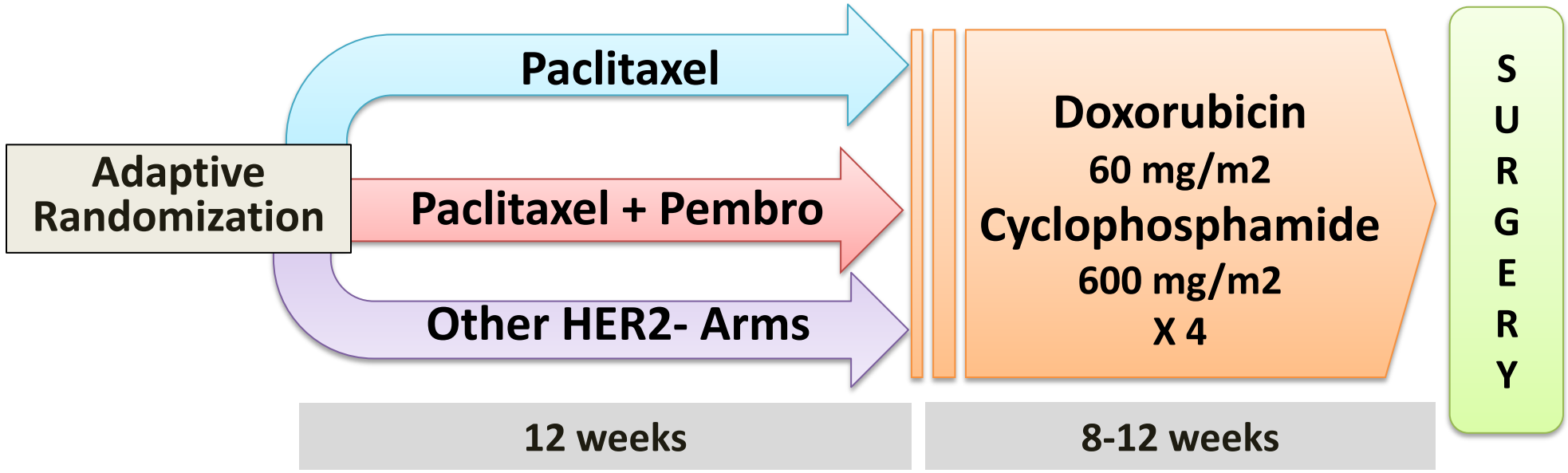


Control

Paclitaxel 80 mg/m2 every wk x 12

Experimental

Paclitaxel 80 mg/m2 every wk x 12

Pembro 200 mg every 3 wks x 4

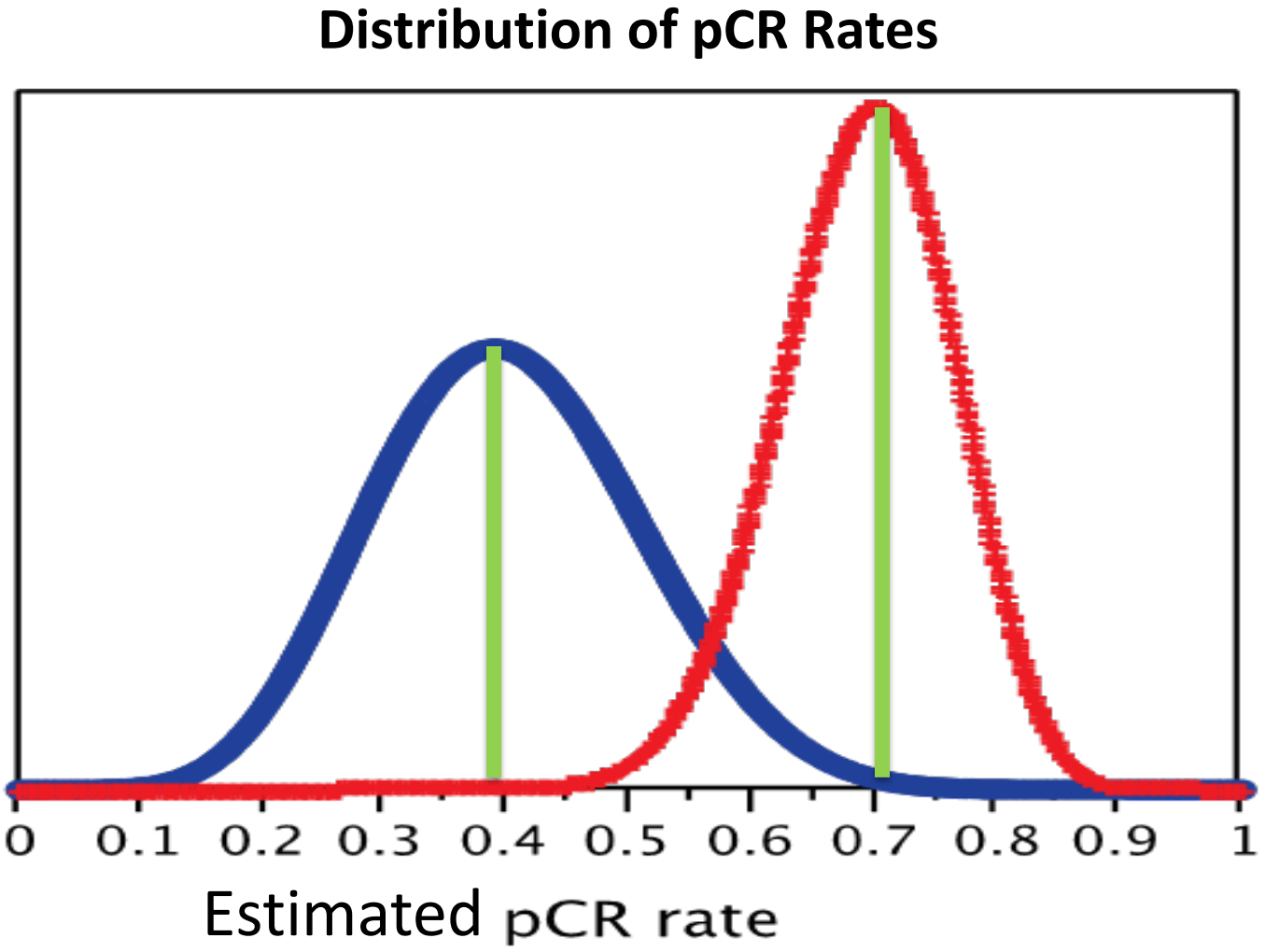
Demographics

Patient Characteristic	Pembrolizumab (n=69)	Control (n=180)
Median Age, yrs (range)	50 (27-71)	47 (22-77)
Race, %		
White	81.2	76.7
African American	8.7	14.4
Asian	4.3	7.2
Other	5.8	1.7
HR Status, %		
Positive	58.0	52.8
Negative	42.0	47.2
Median tumor size, cm (range)	3.6 (1.9-13.0)	3.95 (1.2-15.0)
Nodal Status		
Positive	37.7	43.9
Negative	52.2	50.5
Missing	10.1	5.6

I-SPY 2 Results Reporting

- The I-SPY 2 Bayesian model generates predictive probability distributions of pCR rates by signature
  - Estimated pCR rates
  - Actual pCR rates not reported; biased by the adaptive randomization
- Format of results presented
  - Estimated mean pCR rates by signature
  - Probability that experimental arm is superior to the control for a given signature
  - Predicted probability of success in a 1:1 randomized 300 patient phase 3 trial

Results Format: Estimated Probabilities for pCR



- Curves: probability distribution of pCR rate
- Blue=control; Red=experimental arm
- Midpoint of curves: estimated pCR rate
- Separation: strength
- Width: certainty

Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pembro Superior to Control	Predictive Probability of Success in Phase 3
	Pembro	Control		
HER2-	**0.44** (0.33 – 0.55)	**0.17** (0.11 – 0.23)	**>0.999**	**0.985**
HR-HER2-	**0.60** (0.44 – 0.75)	**0.22** (0.13 – 0.30)	**>0.999**	**0.996**
HR+HER2-	**0.30** (0.17 – 0.43)	**0.13** (0.07 – 0.19)	**0.996**	**0.834**

The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population.
The raw pCR rates (not shown) are higher than the model estimate of 0.604 in TNBC.

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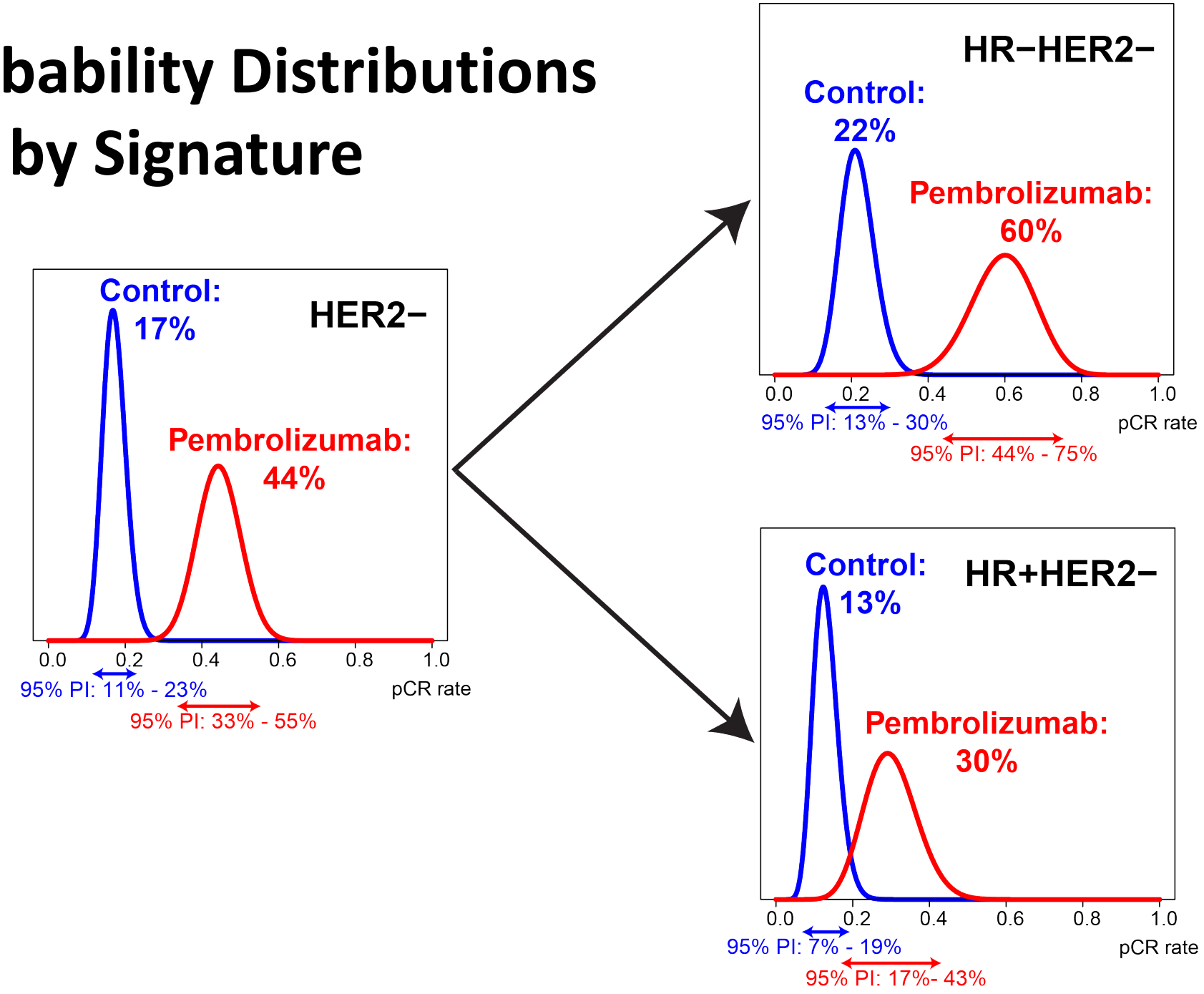
pCR Probability Distributions by Signature



Select treatment-related adverse events

	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	**Grades 3-5**	**All grades**	**Grades 3-5**
Febrile neutropenia	7.2 (5)	7.2 (5)	6.7 (12)	6.7 (12)
Neutropenia w/o fever	5.8 (4)	1.4 (1)	1.7 (3)	0 (0)
Anemia	27.5 (19)	4.3 (3)	18.9 (34)	3.9 (7)
Fatigue	79.7 (55)	5.8 (4)	81.1 (146)	0.6 (1)
Nausea	73.9 (51)	4.3 (3)	71.7 (129)	0 (0)
Vomiting	34.8 (24)	1.4 (1)	18.3 (33)	0 (0)
Diarrhea	49.3 (34)	7.2 (5)	37.8 (68)	2.2 (4)
Peripheral motor neuropathy	13.0 (9)	1.4 (1)	4.4 (8)	0 (0)
Peripheral sensory neuropathy	50.7 (35)	1.4 (1)	59.4 (107)	1.1 (2)

From start of treatment to 30 days after surgery (3 months after last dose of pembrolizumab)
Up to 60 days after treatment for those not undergoing surgery

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Adverse Events of Special Interest (including immune-related toxicities)

	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hypothyroidism	8.7 (6)	1.4 (1)	0.6 (1)	0 (0)
Hyperthyroidism	4.3 (3)	0 (0)	0 (0)	0 (0)
Adrenal Insufficiency^	8.7 (6)	7.2 (5)	0 (0)	0 (0)
Hepatitis	2.9 (2)	2.9 (2)	0 (0)	0 (0)
Pneumonitis	2.9 (2)	0 (0)	1.1 (2)	0.6 (1)
Colitis	1.4 (1)	1.4 (1)	0.6 (1)	0.6 (1)
Pruritis	24.6 (17)	0 (0)	11.1 (20)	0.6 (1)

*includes both hyperthyroidism and hypothyroidism
^includes primary and secondary causes of AI

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Primary and Secondary Adrenal Insufficiency

- Adrenal insufficiency reported in 6 patients
  - At least 3 were related to hypophysitis (secondary AI)
  - 5 presented after completion of AC (10-12 weeks after last pembro dose)
  - 1 presented during pembro treatment (5 weeks after 1st pembro dose)
  - Variable presentation (N/V, fatigue, weakness)
  - Patients on replacement therapy
- Primary and secondary AI are known toxicities of pembrolizumab
  - Rates across all studies are 0.8% and 0.6%
- Due to the toxicities observed, serial screening AM cortisol levels have been incorporated into trial, in addition to ongoing serial thyroid function testing

Conclusions

- Pembrolizumab x 4 cycles plus paclitaxel has graduated for all HER2- signatures studied
  - Near Tripling of the estimated pCR rate in TNBC (60% vs 20%)
  - More than doubling of the estimated pCR rate in HR+/HER2- (34% vs 13%)
  - First agent to graduate in HR+/HER2- signature

- Adrenal insufficiency was observed at a higher rate than previously reported in advanced cancer; pts are doing well on replacement therapy; follow-up of patient outcomes is ongoing

- This is the first report regarding the incidence and time course of immune-mediated toxicities in early stage breast cancer

Future Work

- An experimental arm where pembrolizumab is continued for the anthracycline-based portion of the I-SPY 2 will begin enrollment soon (8 cycle arm)

- I-SPY2 is a biomarker-rich clinical trial with multiple platforms and serial tumor specimens
  - Studies to identify those most likely to benefit or have complications are ongoing

I-SPY 2 TRIAL Study Team

I-SPY 2 Working Group Chairs:
Laura Esserman: Principal Investigator
Don Berry: Principal Investigator, Study Statistician
Angela DeMichele: Co-PI, Site Operations
Doug Yee: Co-PI, Agents
Laura van 't Veer: Co-PI, Biomarkers
Fraser Symmans: Co-PI, Pathology
Nola Hylton: Co-PI, Imaging
Michael Hogarth: Co-PI, Informatics
Jane Perlmutter: Lead Advocate, Advocates
Hope Rugo & Richard Schwab: PI/Co-PI, Safety
Michelle Melisko: Co-PI, Quality of Life

Site PIs:
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UMinn: Doug Yee **Mayo:** Judy Boughey**; UCSF:** Jo Chien**;**
Georgetown: Claudine Isaacs **U.Chicago:** Rita Nanda;
Loyola Chicago: Kathy Albain**; U.Colorado:** Anthony Elias**;**
U.Penn: Amy Clark **Oregon HSU:** Kathleen Kemmer**;**
UTSouthwestern: Barbara Haley **U Alabama:** Andres Forero-Torres
Columbia: Kevin Kalinsky; **Moffitt**: Heather Han;

Sponsor: Quantum Leap Healthcare Collaborative: Dave Mandelkern, Nancy Lisser, Mike Bankert, Adam Asare, Smita Asare
Funding: Safeway, Bill Bowes, Quintiles, J&J, Genentech, Amgen, Give Breast Cancer the Boot, Harlans, Side-Out, Avon, Alexandria
Oversight: Anna Barker/ASU, Gary Kelloff/NCI
FDA: Janet Woodcock, Richard Pazdur

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Business Development: Daniel Dornbusch

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Kathy Albain, Christopher Benz, Jo Chien, Amy Clark, Angela DeMichele, Laura Esserman, Andres Forero-Torres, Teresa Helsten, Claudine Isaacs, Brian Leyland-Jones, Minetta Liu, Stacy Moulder, Rita Nanda, Funmi Olopade, John Park, Barbara Parker, Hope Rugo,, Doug Yee, Paula Pohlmann, Richard Schwab, Patricia LoRusso, Anthony Elias, Patricia Haugen, Pamela Miunster, Lajos Pusztai; Heather Beckwith, Larissa Korde (CTEP)

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

I-SPY 2 Participating Organizations

Sponsors and Managers

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A Healthcare Collaborative

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