Efficacy of T-DM1+Pertuzumab over Standard Therapy for HER2+ Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

Angela M. DeMichele[1], Stacy Moulder[2], Meredith Buxton[3], Douglas Yee[4], Anne Wallace[5], Jo Chien[3], Claudine Isaacs[6], Kathy Albain[7], Judy Boughey[8], Kathleen Kemmer[9], Barbara Haley[10], Julie Lang[11], Henry Kaplan[12], Susan Minton[13], Andres Forero[14], Anthony Elias[15], Rita Nanda[16], Larissa Korde[17], Richard Schwab[5], Michelle Melisko[3], Ashish Sanil[18], Michael Hogarth[19], Nola Hylton[3], Melissa Paoloni[20], Fraser Symmans[2], Jane Perlmutter[21], Julia Lyandres[3], Christina Yau[3], Don Berry[2], Laura Esserman[3], I-SPY 2 TRIAL Investigators.

COI

- Dr. DeMichele receives institutional research support from Pfizer, Novartis, Johnson & Johnson, Calithera, Incyte and Genentech, and has participated in scientific advisory boards for Pfizer and Novartis.

Therapeutic Landscape for Her2+ Breast Cancer

- Her2+ breast cancer is curable with chemotherapy plus Her2-directed therapy
- In the neoadjuvant setting
  - pCR (pathologic complete res
    an excellent surrogate for lon
  - Not all patients achieve a pCF
- **Goal: To determine if new Her2-directed therapies can improve pCR rate over standard chemotherapy plus trastuzumab**

(This is a bold statement. Could be interprete
HER2+ BC which is not true. Could be interpr
some HER2 which may be true. There is no qu
that therapy dramatically improves outcomes
distinguishing between "cure" and "greatly sl
the course of disease" is almost impossible in
BC, including in HER2+ BC. The statement is a
certainly wrong in metastatic BC. And there's
good evidence that it's correct in early BC.

The I-SPY2 TRIAL Platform

- **Phase II, adaptively randomized trial of multiple agents/combinations**
  - Patients are randomized to ~~receive~~ one of several experimental arms ~~for Her2+ disease~~
  - Comparator is **standard neoadjuvant therapy**
  - Endpoint is pathologic complete response (pCR)
- **Match therapies with breast cancer subtypes**
  - Reduce ~~the~~ cost, time, and number of patients needed to get effective drugs to **market**

[[Important to sa
"neoadjuvant"
somewhere]]

We are reporting *one* ~~of the~~ experimental arm~~s~~ of I-SPY 2:

T-DM1 + Pertuzumab in HER2+ disease

T-DM1 + Pertuzumab

T-DM1 (ado-trastuzumab emtansine)

- Antibody-drug conjugate: trastuzumab linked to DM-1 (maytansine)
- Inhibits microtubules>cell cycle arrest and cell death
- Toxicities: Thrombocytopenia, transaminitis

Pertuzumab

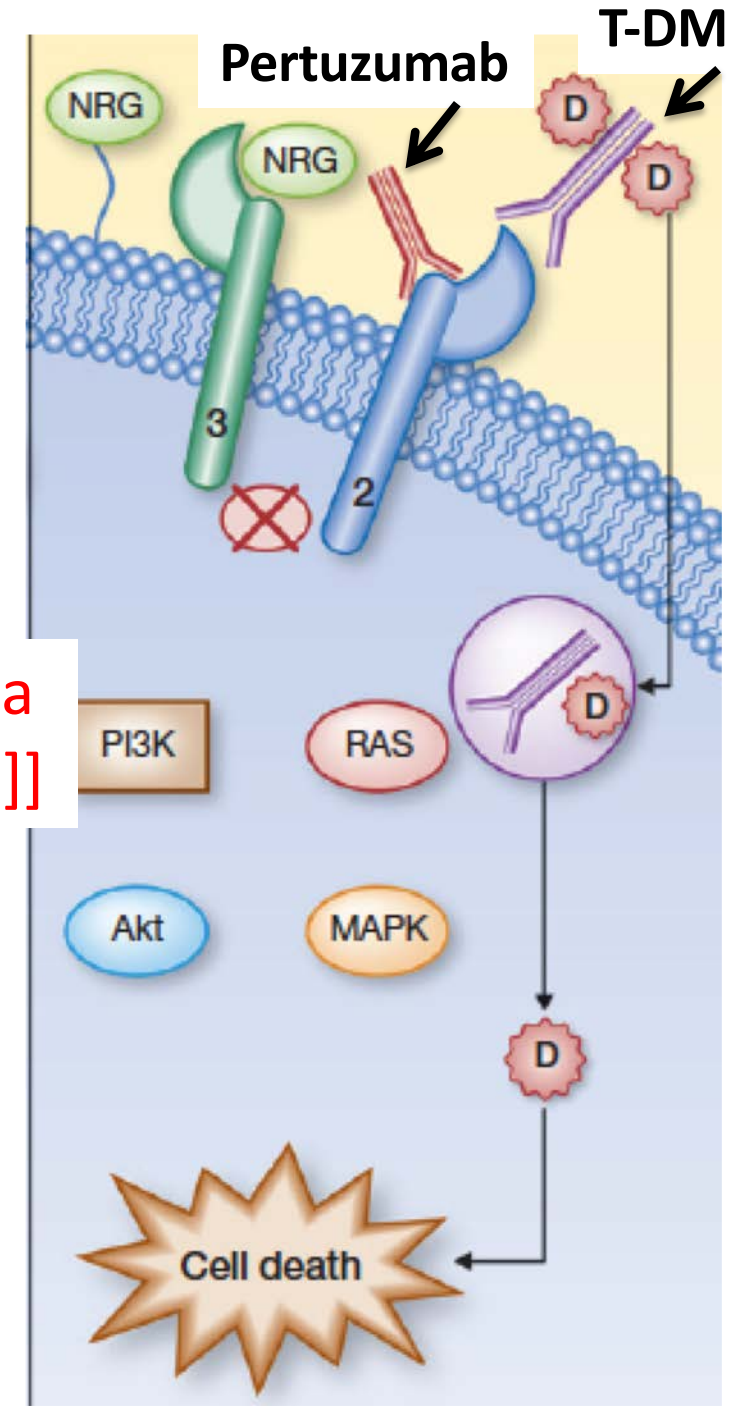
- Monoclonal antibody to HER2
- Binds at critical heterodimerization site, different site from trastuzumab
- Toxicities: Diarrhea, fatigue, rash, nausea

[[Seems like a lot of words.]]

Rationale for I-SPY2 Entry

- T-DM1 superior to docetaxel/trastuzumab in front-line metastatic setting
- T-DM1+ Pertuzumab safe, high response rate in front-line metastatic setting

TDM 4450 and 4373 Trials



Gwin and Spector, CCR, 2014

[[Every time I see this slide I think of Poseidon with his trident.]]

I-SPY2 TRIAL Schem

SCREENING

TREATMENT

Adaptive Randomization

NEW PATIENT

Paclitaxel* (control)

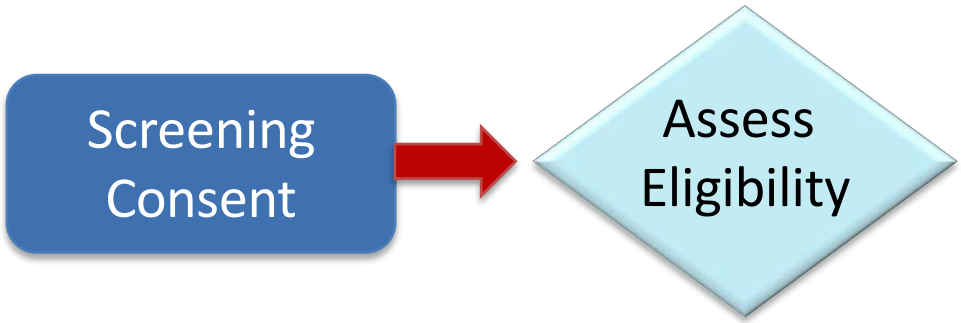
Paclitaxel* + **Agent A**

12 weeks

[[Some of the labels on this slide will be very confusing because they don't apply to the T-DM1 arm. Maybe just drop the trident and the "AC Chemotherapy pentagon" and replace them with a box saying "Adaptively Randomized to Neoadjuvant Therapy." A later slide describes the treatment & comparison for T-DM1 arm.]]

[[10% of U.S. males are red colorblind. It's hard for us to see the "Adaptive Randomization" and "12 weeks" because they're on a dark background.]]

I-SPY2 TRIAL Eligibility



Screening

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

I-SPY2 TRIAL Eligibility

[[You seem to be talking about the overall trial here ....]]

Screening

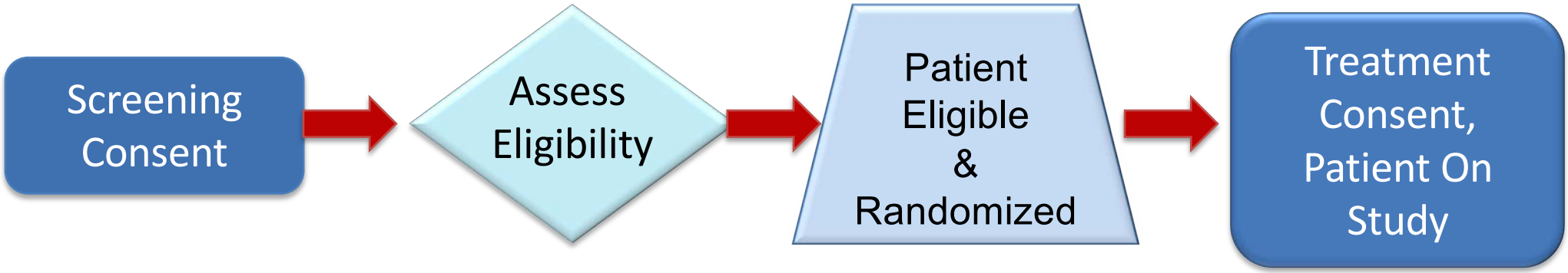
- Tumor size ≥ 2.5 cm
- Candidate for preoperative chemotherapy
- Able to have MRI and biopsy
- Adequate organ function, PS<2

Treatment

- If HR**- or HER2+ or** Mammaprint high-risk
- Meet all agent-specific eligibility criteria

I-SPY2 TRIAL Eligibility

[[You seem to be talking about the overall trial here ....]]



Screening

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

Treatment

- If HR**- or HER2+ or** Mammaprint high-risk
- Meet all agent-specific eligibility criteria

I-SPY2 TRIAL Treatment Plan

here you're talking about the T-DM1 comparison only. It's not
:hat what's on this slide is the "I-SPY 2 TRIAL Treatment Plan."
he "R" for randomization is misleading in at least 3 ways.]]

Experimental regimen

- **T-DM1:** 3.6 mg/kg iv
  Pertuzumab: 840 mg load, followed by 420 mg
- Every 3 weeks x 4
- AC x 4 > Surgery

Control regimen

- **Paclitaxel** 80 mg/m2
- **Trastuzumab** 4 mg/kg load, then 2 mg/kg
- Weekly x 12
- AC x 4 > Surgery

Accelerated Approval of Pertuzumab

- 9/2013: FDA granted accelerated approval to pertuzumab in the neoadjuvant setting
- THP was already an open arm of the trial
- I-SPY2 Executive Committee determined that paclitaxel/trastuzumab was no longer an appropriate clinical option
- Randomization to the paclitaxel/trastuzumab arm stopped (randomization probability set to zero)
- Time adjusted analysis was utilized to compare enrolling Her2+ arms to all prior trial control patients receiving paclitaxel/trastuzumab moving forward

[[See notes.]]

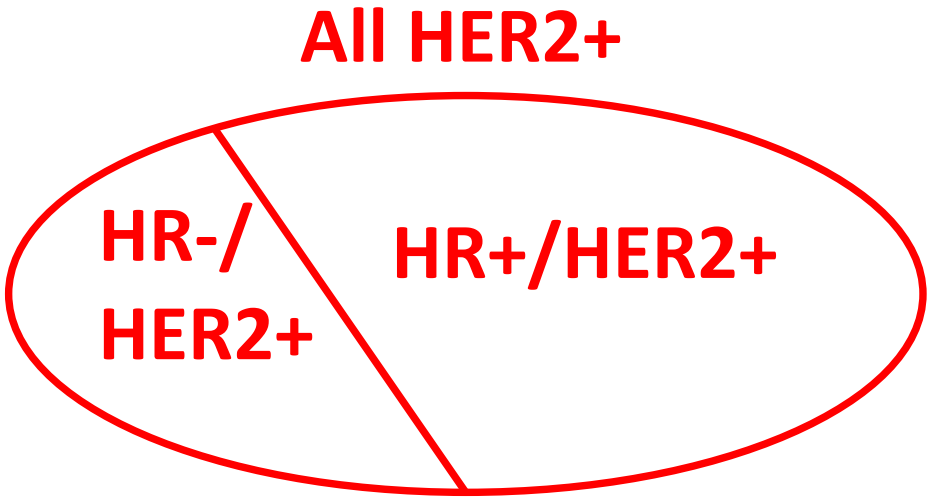
Primary Endpoint: pCR

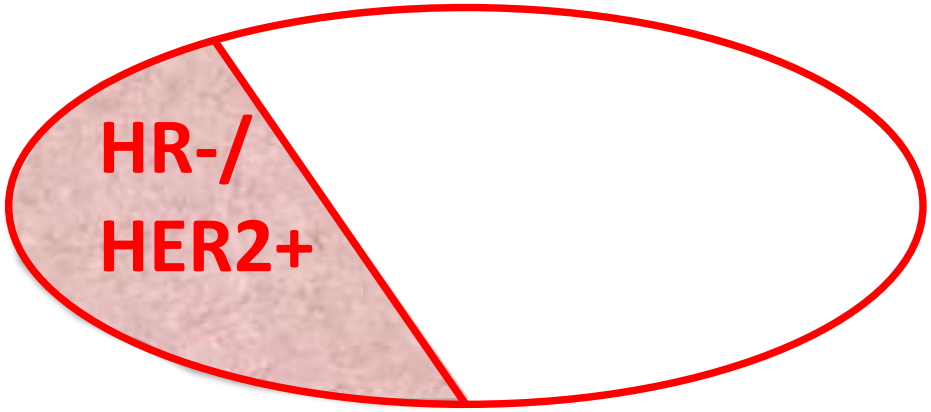
- Defined as **no residual invasive cancer in the breast or lymph nodes (ypT0/is and ypN0)**
  - If do not **have** surgery: "non-pCR" by ITT
    or receive non-protocol therapy
- Endpoint ~~is~~ assessed ~~in~~ overall ~~group and~~ within ~~up to~~ 10 pre-specified **"biomarker signatures"**
  - By receptor subtype (HR, Her2) and Mammaprint Score
- 3 signatures **applicable for** ~~patients with~~ Her2+ disease:
  - **All Her2+, HR+/Her2+, HR-/Her2+**

[other places you use all caps: HER]

[[Added slide for commenting. I suggest using a diagram such as the below on the previous slide. You could also consider a very quick transition through the next 3 slides. This issue of “signatures” is difficult to grasp. “An animation is worth 1000 words,” and certainly worth the 6 seconds these three slides will take.]]

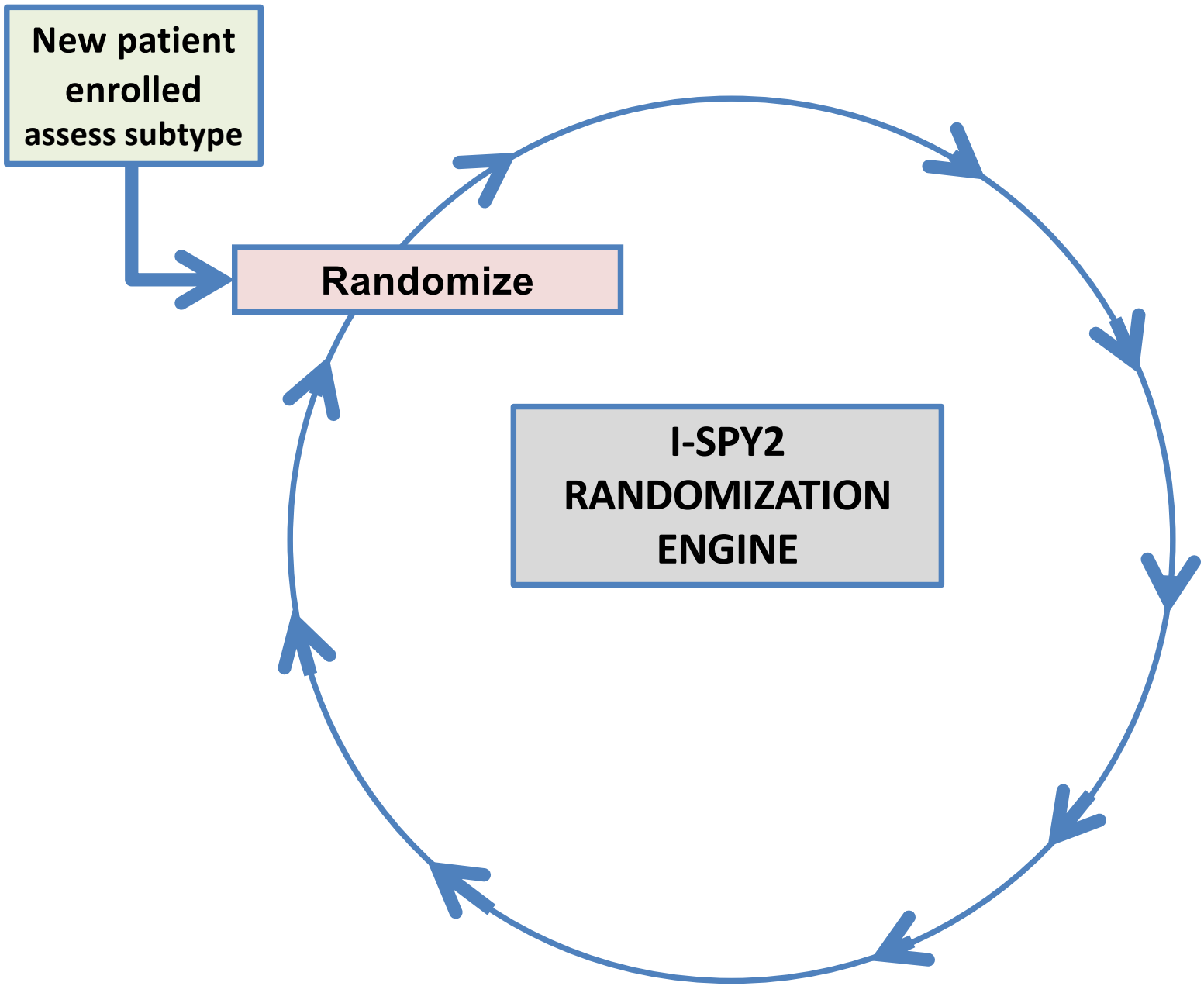
- 3 signatures applicable for HER2+ disease:

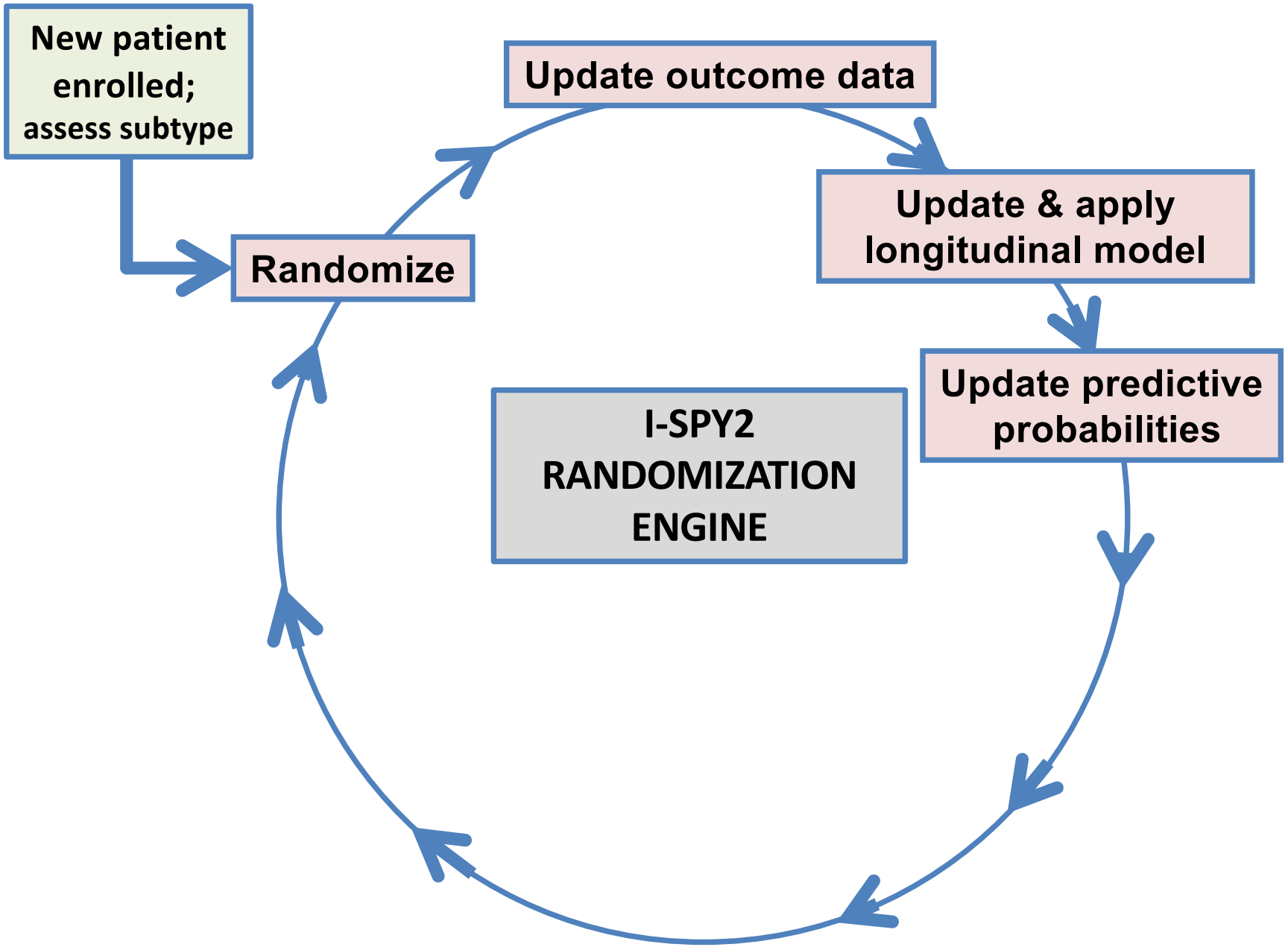


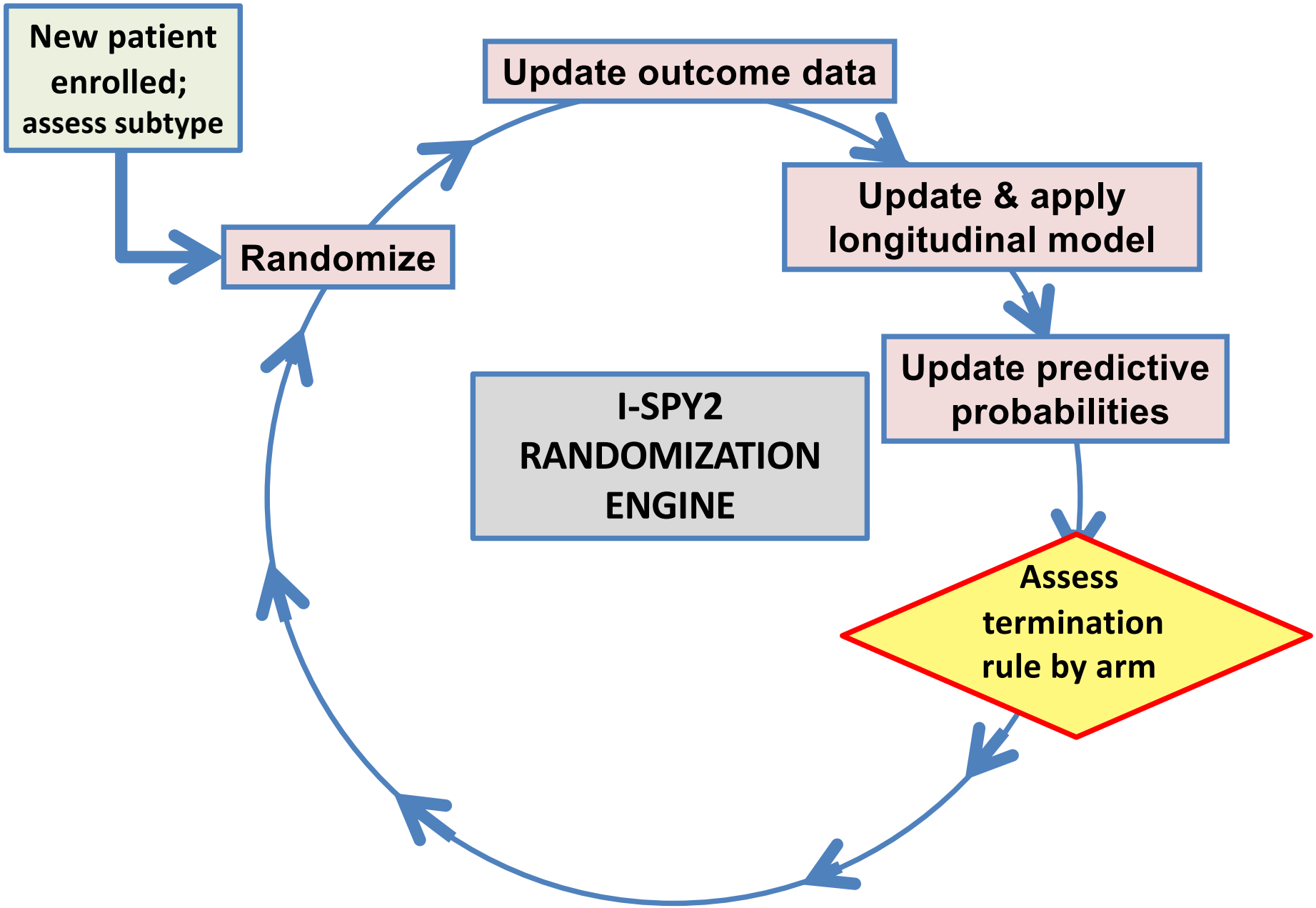

HR-/
HER2+

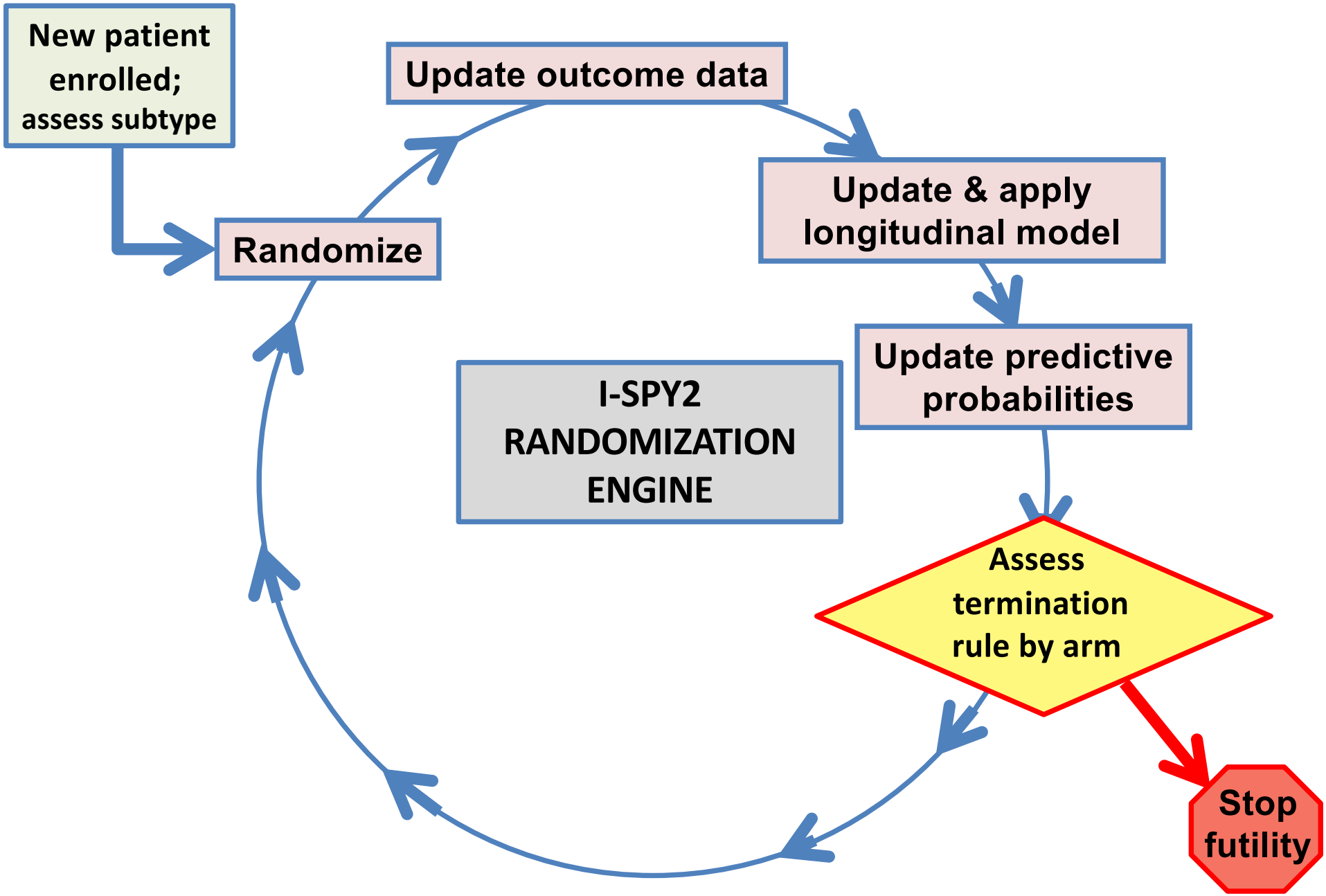

HR+/HER2+

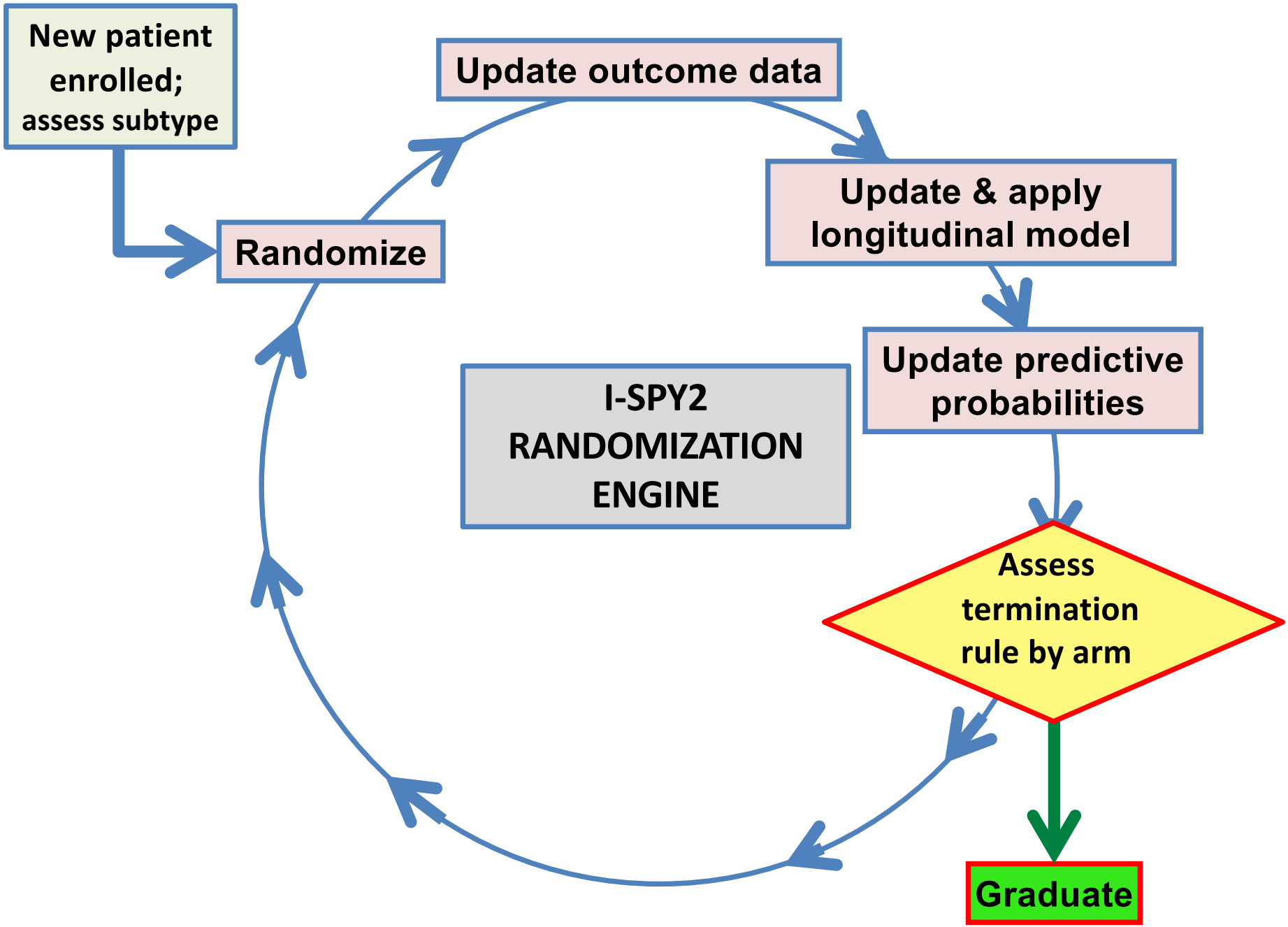
All HER2+

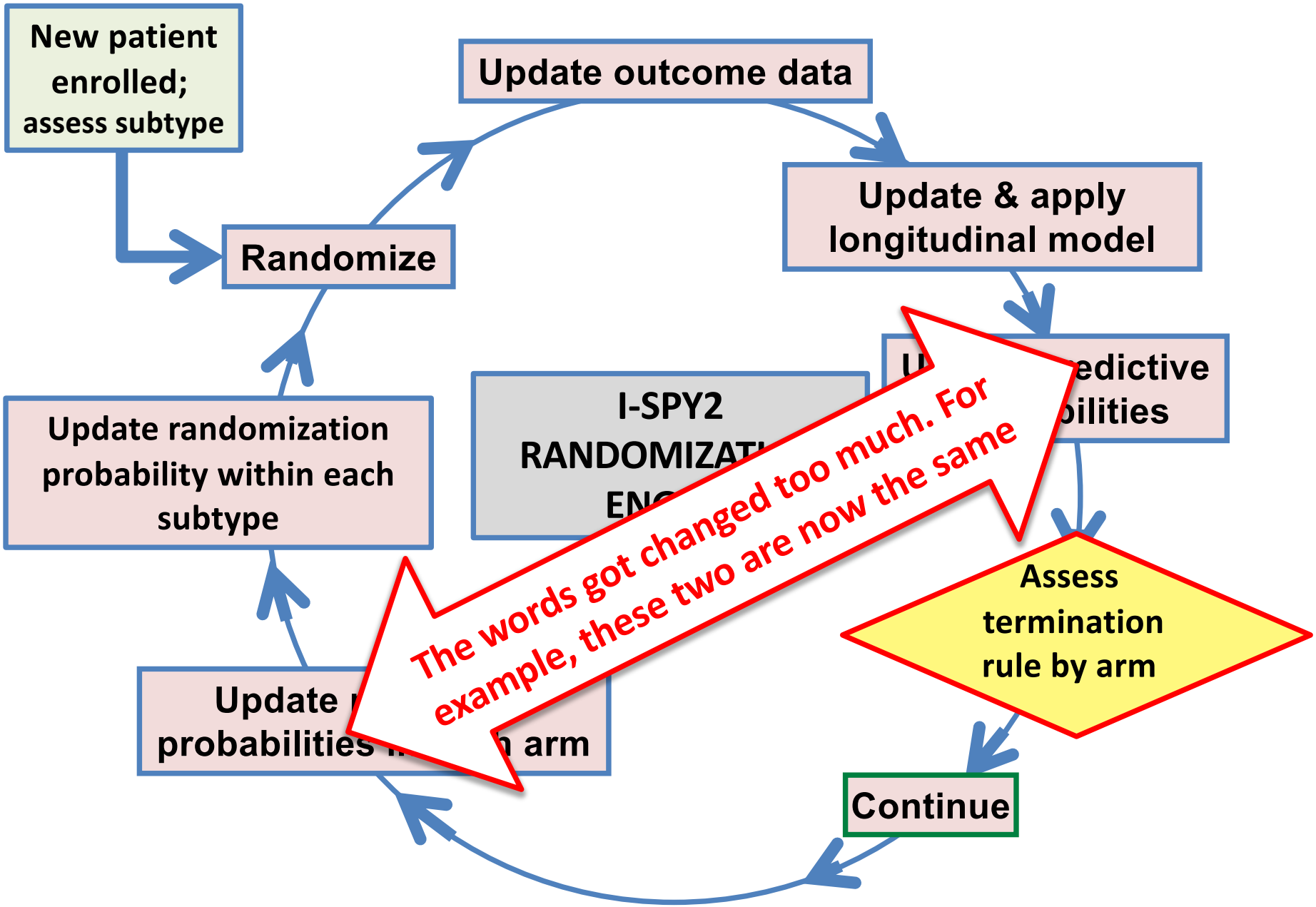

New patient enrolled
assess subtype
Randomize
I-SPY2 RANDOMIZATION ENGINE


New patient enrolled; assess subtype
Randomize
Update outcome data
Update & apply longitudinal model
Update predictive probabilities
I-SPY2 RANDOMIZATION ENGINE

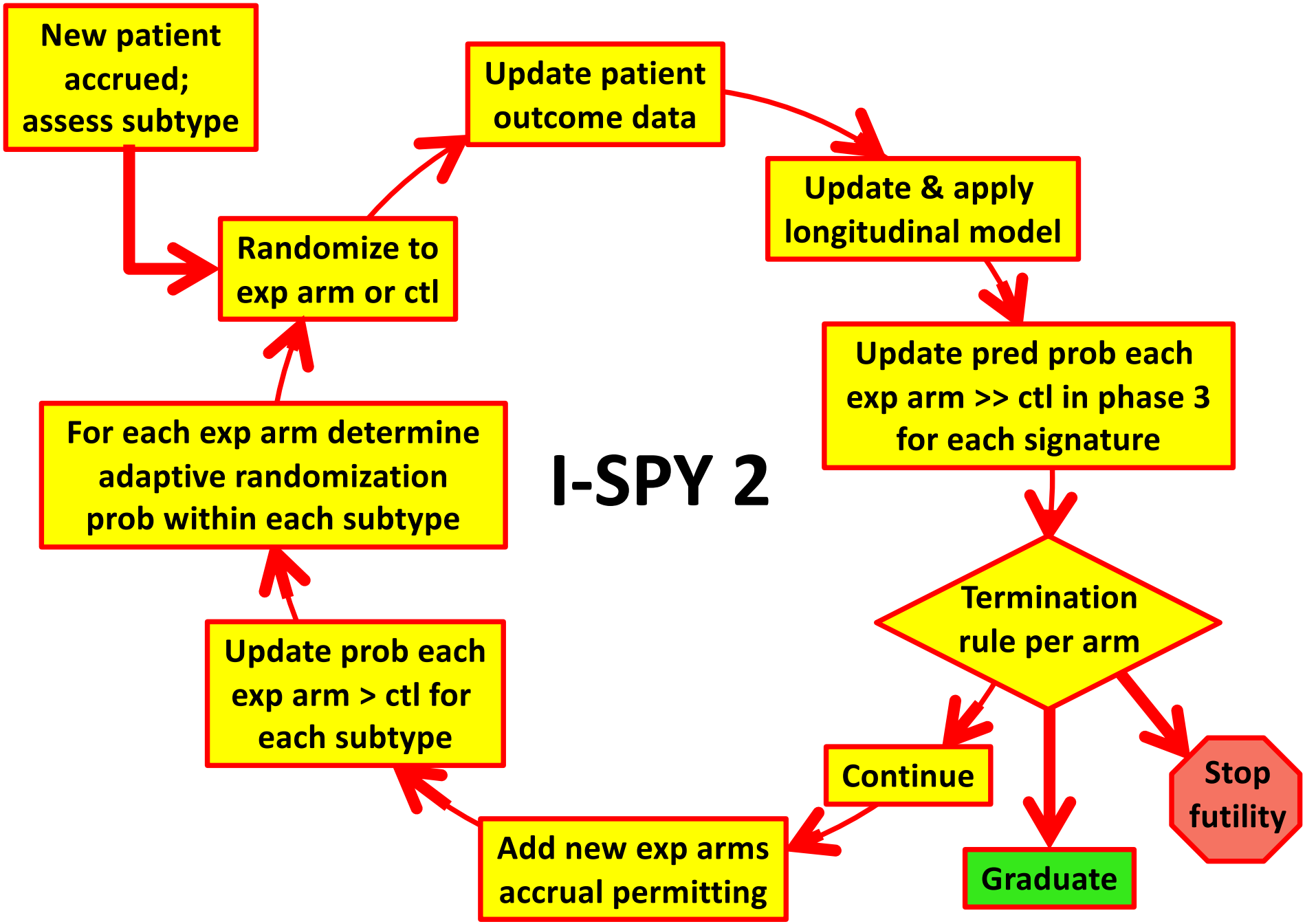

New patient enrolled; assess subtype
Update outcome data
Update & apply longitudinal model
Update predictive probabilities
Assess termination rule by arm
Randomize
I-SPY2 RANDOMIZATION ENGINE


New patient enrolled; assess subtype
Update outcome data
Update & apply longitudinal model
Update predictive probabilities
Assess termination rule by arm
Stop futility
Randomize
I-SPY2 RANDOMIZATION ENGINE


New patient enrolled; assess subtype
Update outcome data
Update & apply longitudinal model
Update predictive probabilities
Assess termination rule by arm
Graduate
Randomize
I-SPY2 RANDOMIZATION ENGINE



[[I'll insert the original diagram on the next slide. I'm not sure what boxes you want to show but I agree there's too many words on the original slide.]]


New patient accrued; assess subtype
Update patient outcome data
Update & apply longitudinal model
Randomize to exp arm or ctl
Update pred prob each exp arm >> ctl in phase 3 for each signature
For each exp arm determine adaptive randomization prob within each subtype
I-SPY 2
Termination rule per arm
Update prob each exp arm > ctl for each subtype
Continue
Stop futility
Add new exp arms accrual permitting
Graduate

Threshold for Graduation

- Graduation Threshold = 85% predict**ive** probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)
  - Probability is calculated from estimated pCR rates per signature
  - If pCR data is not available, use MRI volume response

- A drug "graduates" when the probability threshold is reached -> accrual to that arm then stops
  - *Final probabilities* are recalculated when all patients have gone to surgery and pathology data are complete

Not Every Drug Graduates for Efficacy

Based upon predicted probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)

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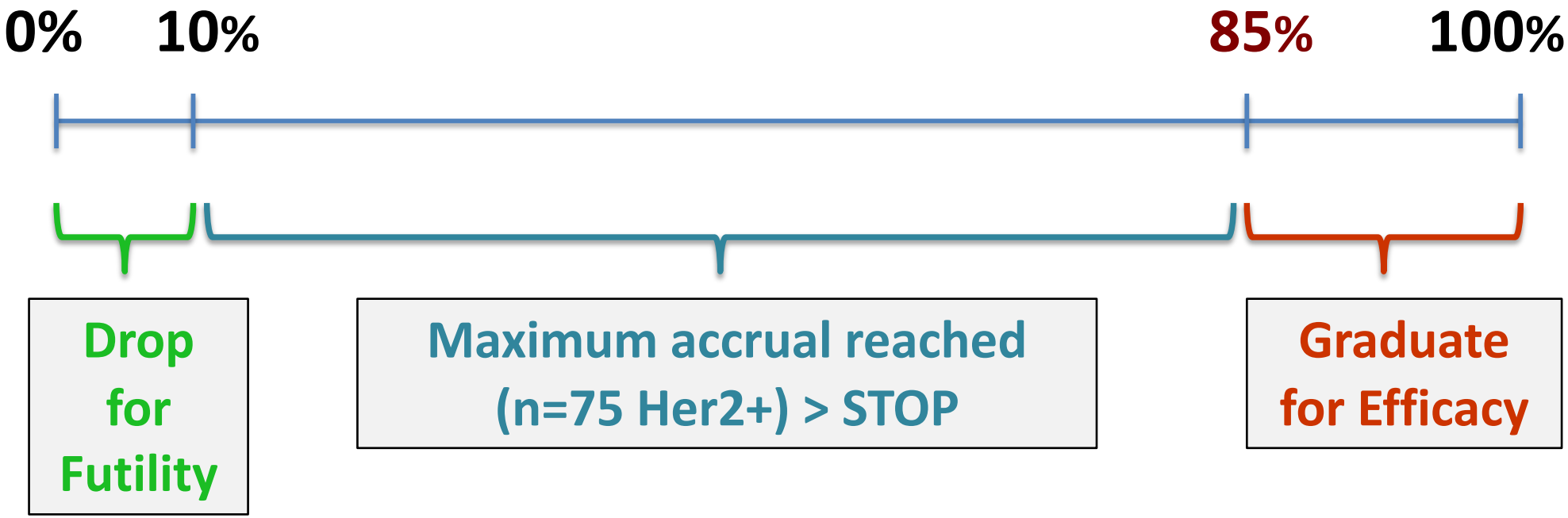
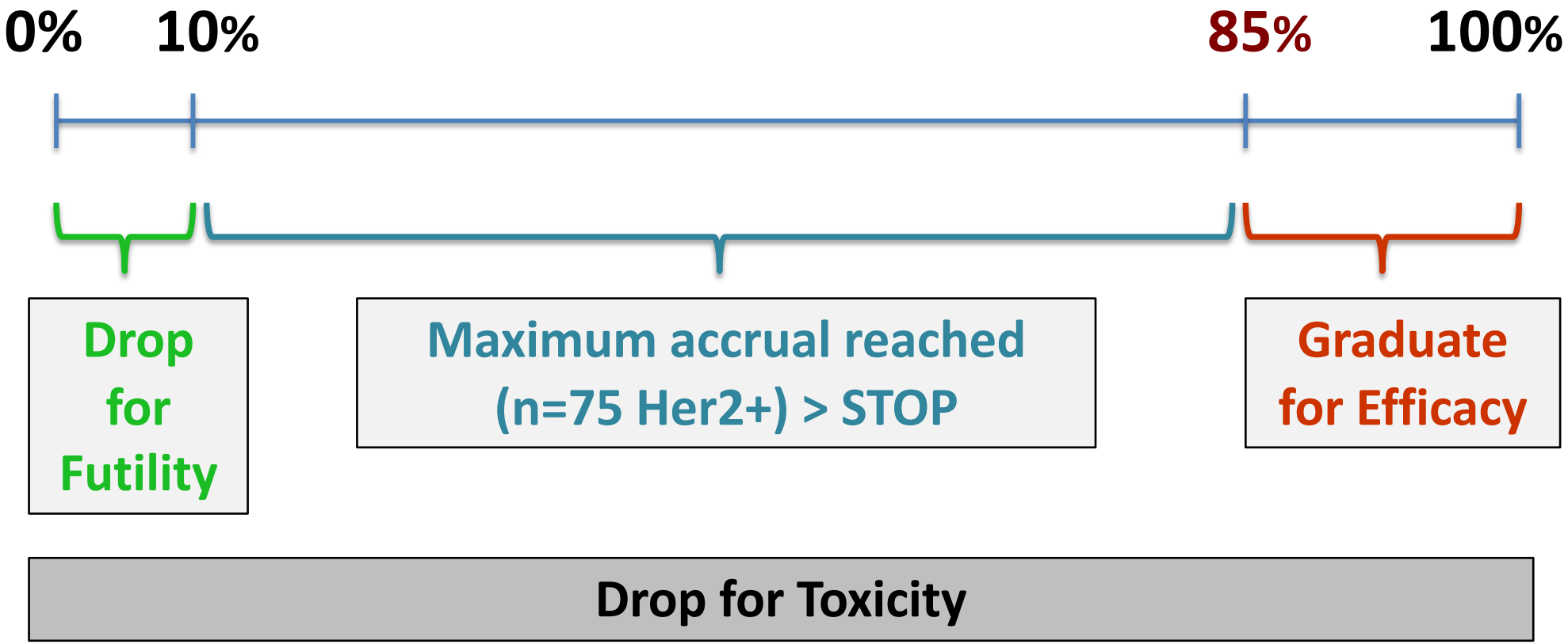


Not Every Drug Graduates for Efficacy

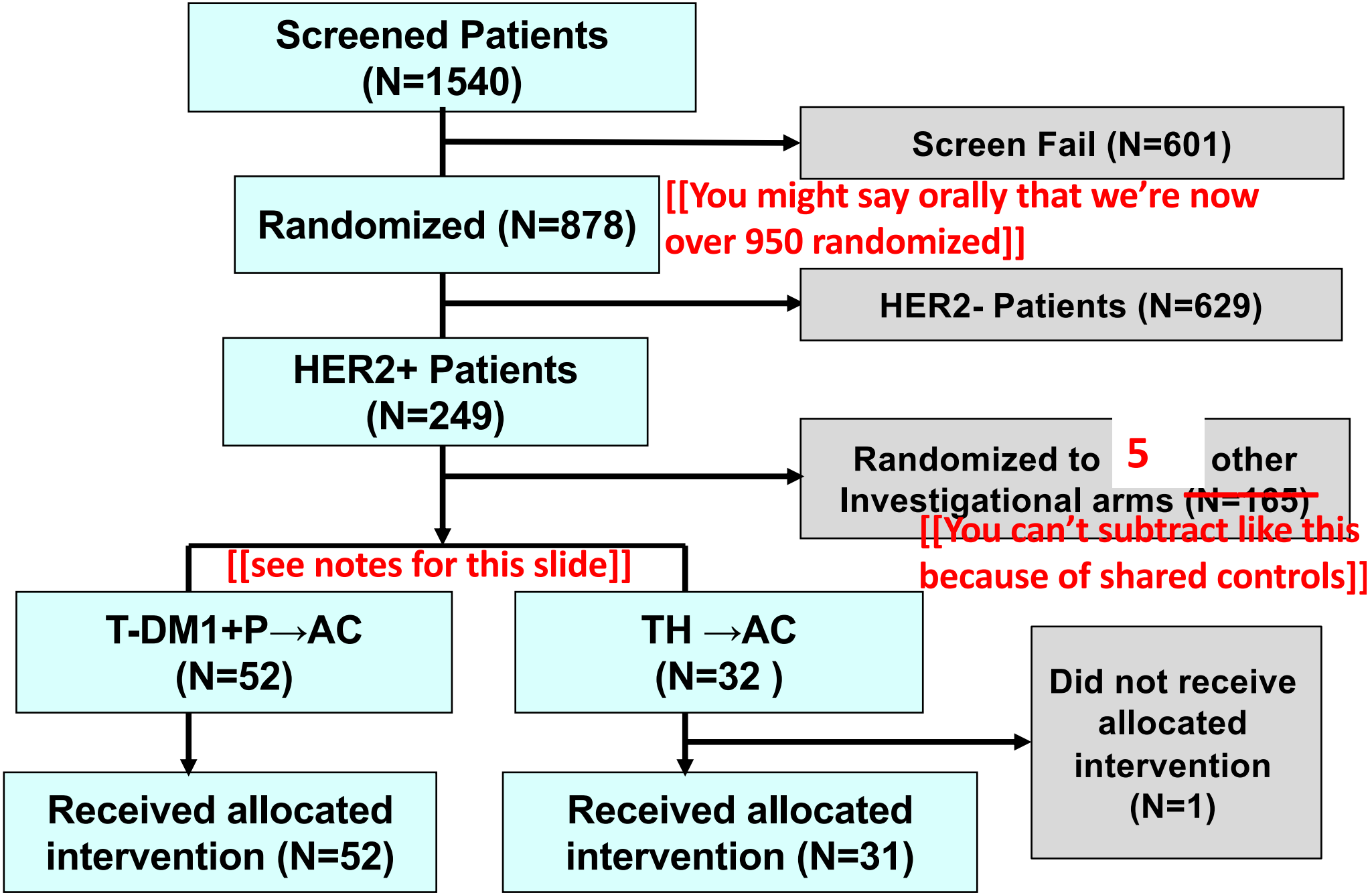
Based upon predicted probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)



Format for Reporting I-SPY 2 Results

- **The I-SPY 2 Bayesian model finds the probability distribution of pCR rates by signature**
  - Actual pCR rates are biased by the adaptive randomization and are *not* **provided**
- **3 analyses presented**
  - Estimated $\hat{pCR}$ (mean) rates by signatures
  - Probability ~~that the~~ drug ~~is~~ better than ~~the~~ control for ~~a~~ **each** signature
  - Predicted probability of success in ~~a~~ 300 patient phase 3 trial ~~based on estimated pCR rates (Threshold)~~

Consort Diagram for T-DM1 + Pertuzumab



Study Population

Characteristic	T-DM1+P->AC (n=52)	TH->AC (n=31)
Age, median years (range)	48 (33-72)	50 (29-71)
Race (%)		
White	42 (80.7%)	25 (81%)
African American	4 (7.7%)	2 (6%)
Asian	5 (9.6%)	4 (13%)
Other	1 (1.9%)	0 (0%)
Ethnicity (%)		
Hispanic or Latina	8 (15%)	3 (10%)
HR Status (%)		
Positive	35 (67%)	19 (61%)
MRI Tumor Diameter (cm), median (range)	3.25 (1.5 – 12.0)	3.5 (1.3 – 11.7)

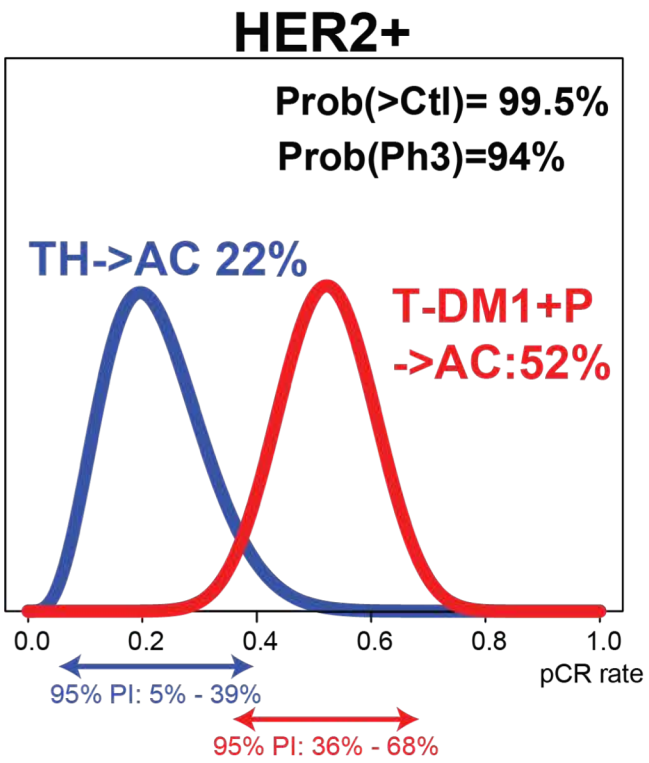
T-DM 1 + Pertuzumab Graduated in all 3 HER2+ Signatures: All HER2+, HR+/HER2+, and HR-/HER2+

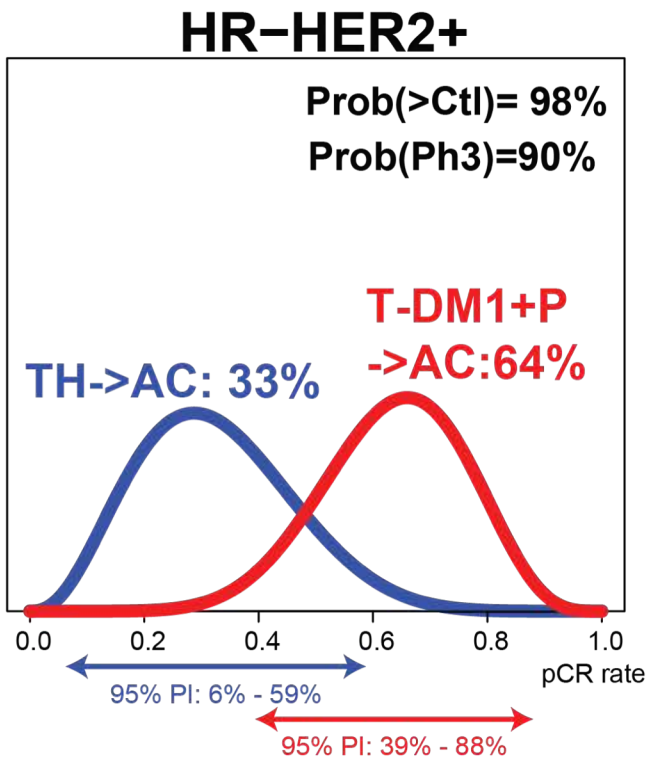
Arm	Estimated pCR Rate (95% PI)	Prob(>Ctrl)	Prob(Ph3)
All HER2+			
TH->AC	0.22 (0.05 – 0.39)		
T-DM1+P->AC	0.52 (0.36 – 0.68)	0.995	0.94
HR- HER2+			
TH->AC	0.33 (0.06 – 0.59)		
T-DM1+P->AC	0.64 (0.39 – 0.88)	0.98	0.90
HR+ HER2+			
TH->AC	0.17 (0.00 – 0.34)		
T-DM1+P->AC	0.46 (0.26 – 0.66)	0.991	0.93

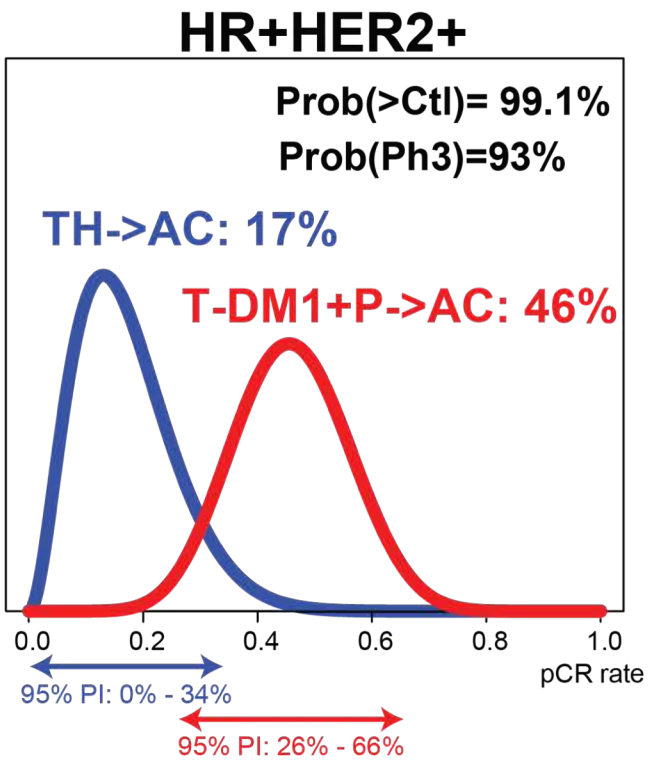
P= pertuzumab

TH = paclitaxel + trastuzumab

pCR Probability Distributions by Signature







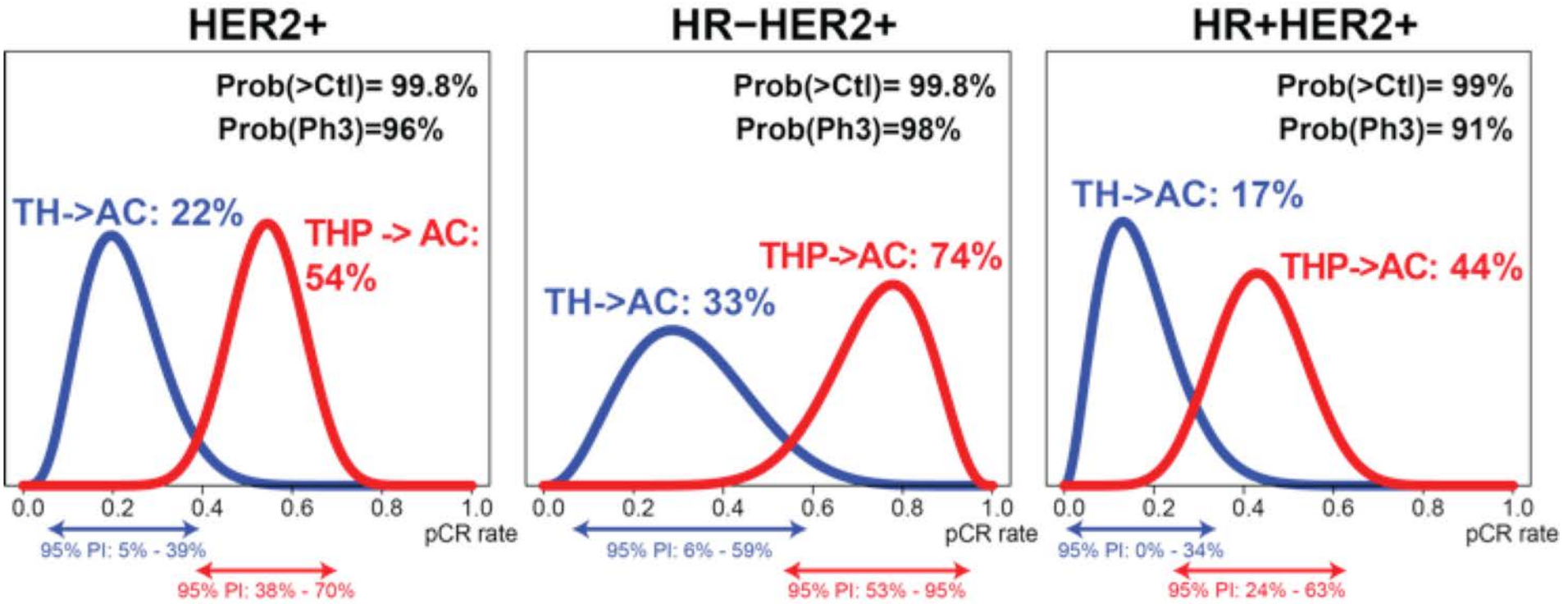
To be updated

Adverse Events Grade ≥ 3

	T-DM1+P->AC (n=52)	TH->AC (n=31)
Available for Evaluation, n	36	31
Neutropenia	5 (14%)	2 (6%)
Febrile neutropenia	4 (11%)	3 (10%)
Anemia	2 (6%)	1 (3%)
Diarrhea	2 (6%)	1 (3%)
Hypertension	3 (8%)	4 (13%)
Neuropathy		
Alopecia		

- Data summarized from files “Output_AE_Paclitaxel_Trastuzumab.txt” and “Output_AE_T-DM1_Pertuzumab.txt” received from Amy 4/1/2016
- 16 patients missing AE data in TDM1 arm
- Summary excludes baseline adverse events (3 patients on the TDM-1+Pertuzumab arm have no on-treatment events)
- CTCAE Term experienced by >5% of patients on the TDM-1+Pertuzumab Arm are listed

The THP regimen also graduated in I-SPY2
(paclitaxel/trastuzumab/pertuzumab)



(Abstract # XX, Poster Tuesday 4/19/16)

Conclusions

To Be Updated

- I-SPY 2 adaptive trial has identified biomarker signatures for T-DM 1 + pertuzumab:
  - T-DM1 + Pertuzumab has graduated in all HER2+ signatures, including the HR+ and HR- subsets of HER2+
- T-DM 1 + pertuzumab is well tolerated, with only minor toxicity reported
  - **Details….**
- I-SPY 2 is a biomarker rich trial; additional response predictors are under investigation
- Based on these strong efficacy results, tolerability and favorable toxicity profile, additional combinations with T-DM1 are being explored

(Passive voice is a problem here.
Who's doing the exploring?)

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
Meredith Buxton: Co-PI, Project Management
Jane Perlmutter: Lead Advocate

I-SPY Program Management Office (PMO)
Meredith Buxton: Exec Director, I-SPY Program
Julia Lyandres Clennell: Operations Director
Ashish Sanil, Christina Yau, Denise Wolf: Data Analysis
Karen Kimura, Garry Peterson, Amy Wilson: IT
Gillian Hirst: Biomarkers / Lamorna Brown-Swigart: I-SPY 2 Lab
Ruby Singrao, Tayeba Maktabi, John Nespeco, Mamta Shah, Brigitte Cronier, Julia Chambers: PMO Office

Site PIs:
UCSD: Anne Wallace**; USC:** Julie Lang; **Swedish:** Hank Kaplan; **MDAnderson:** Stacey Moulder; **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 **British Columbia CA:** Stephen Chia; **Moffitt**: Susan Minton

I-SPY 2 Agents Committee
Kathy Albain, Christopher Benz, Stephen Chia, Jo Chien, 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, Debu Tripathy, Doug Yee, Amy Clark, Paula Pohlmann, Richard Schwab, Patricia LoRusso, Anthony Elia, Melissa Paoloni, Patricia Haugen

Sponsor: QuantumLeap Healthcare Collaborative: Melissa Paoloni, Cabot Brown
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

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

I-SPY 2 Participating Organizations

Sponsors and Managers

QuantumLeap
A Healthcare Collaborative

Funders, Operations

UCSF
University of California
San Francisco

Novella
CLINICAL
A Quintiles Company

SAFEWAY
Ingredients for life.

William K. Bowes, Jr.
Foundation

Foundation for the National Institutes of Health
THE biomarkers CONSORTIUM

Investigational Agent Providers

abbvie

AMGEN

Genentech
A Member of the Roche Group

MEDIVATION

Plexxikon

MERCK
Be well

SYNTA
PHARMACEUTICALS®

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Biomarker Device Providers

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

salesforce

UCSF
University of California
San Francisco

sentinelle MEDICAL

HOLOGIC
The Women's Health Company

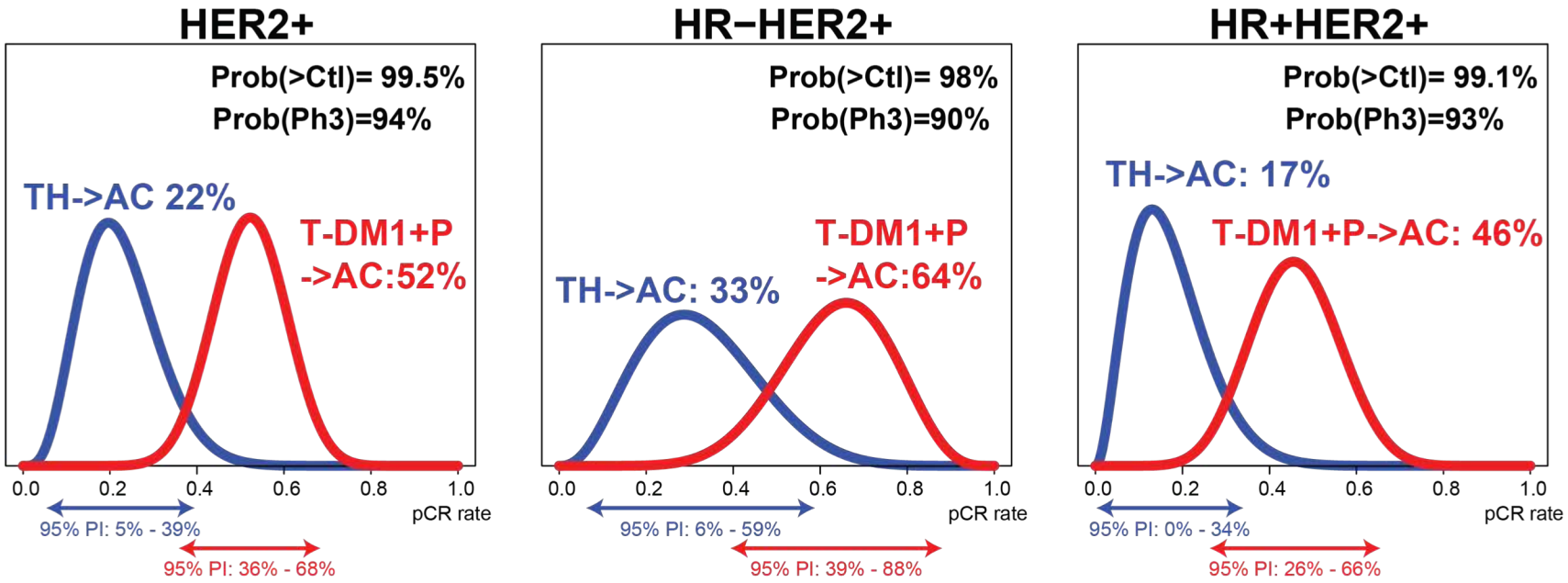
GEORGE MASON UNIVERSITY

THERANOSTICS HEALTH
The Partner of Choice for Personalized Medicine

agendia
decoding cancer

BERKELEY LAB
LAWRENCE BERKELEY NATIONAL LABORATORY

T-DM1 + Pertuzumab vs. Paclitaxel + Trastuzumab



THP vs. Paclitaxel + Trastuzumab