# UNDERSTANDING MULTI-COHORT TRIALS: BASKET, UMBRELLA, AND OTHERS

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**14th Annual California Cancer Conference Consortium**
**August 10-12, 2018**

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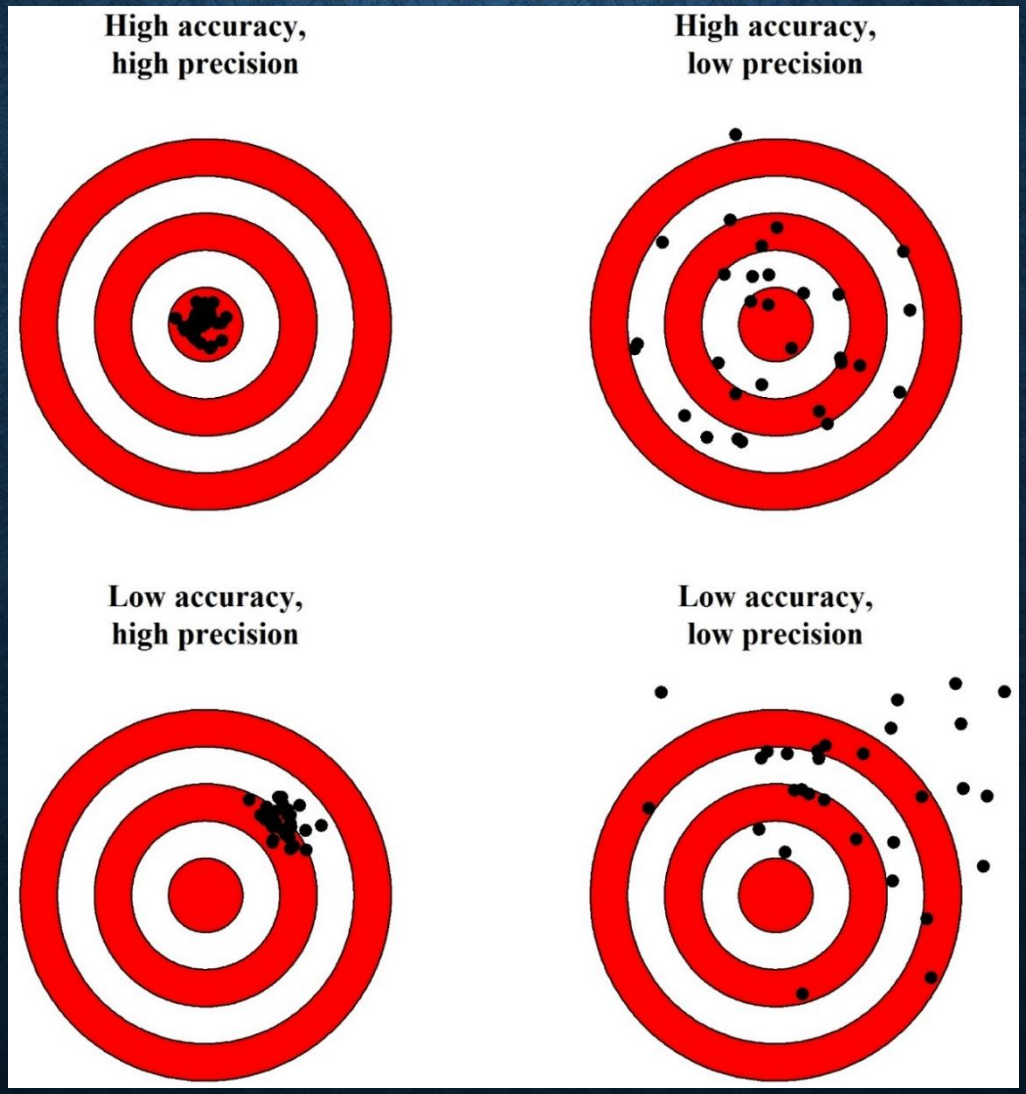
## UNDERSTANDING MULTI-COHORT TRIALS: BASKET, UMBRELLA, AND OTHERS

NO RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

# PRECISION MEDICINE ??

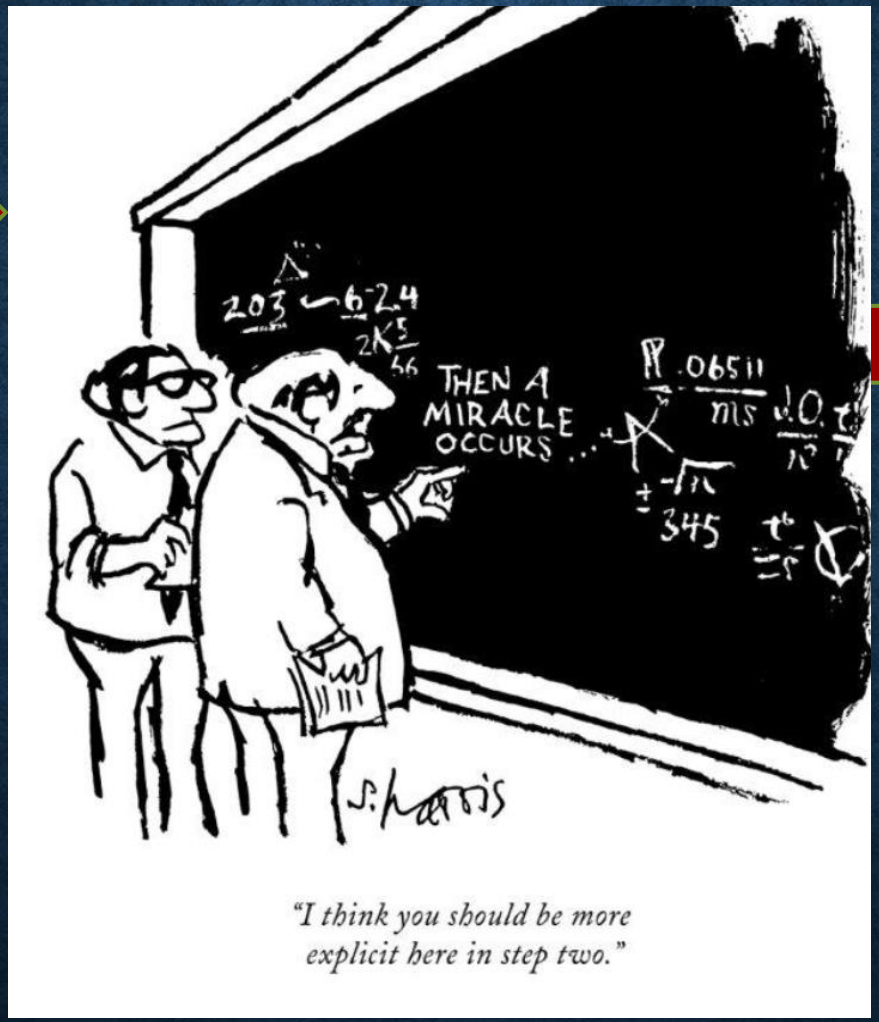


- **Personalized Medicine:**
  - standard of care / evidence based medicine
  - patient specific characteristics
  - medical experience

- **Precision Medicine Research:**
  - research to better define **cohorts** of patients who will benefit from specific treatment strategies
    (David Magnus, MD; Stanford Center for Biomedical Ethics (School of Medicine))
  - not "N of 1"

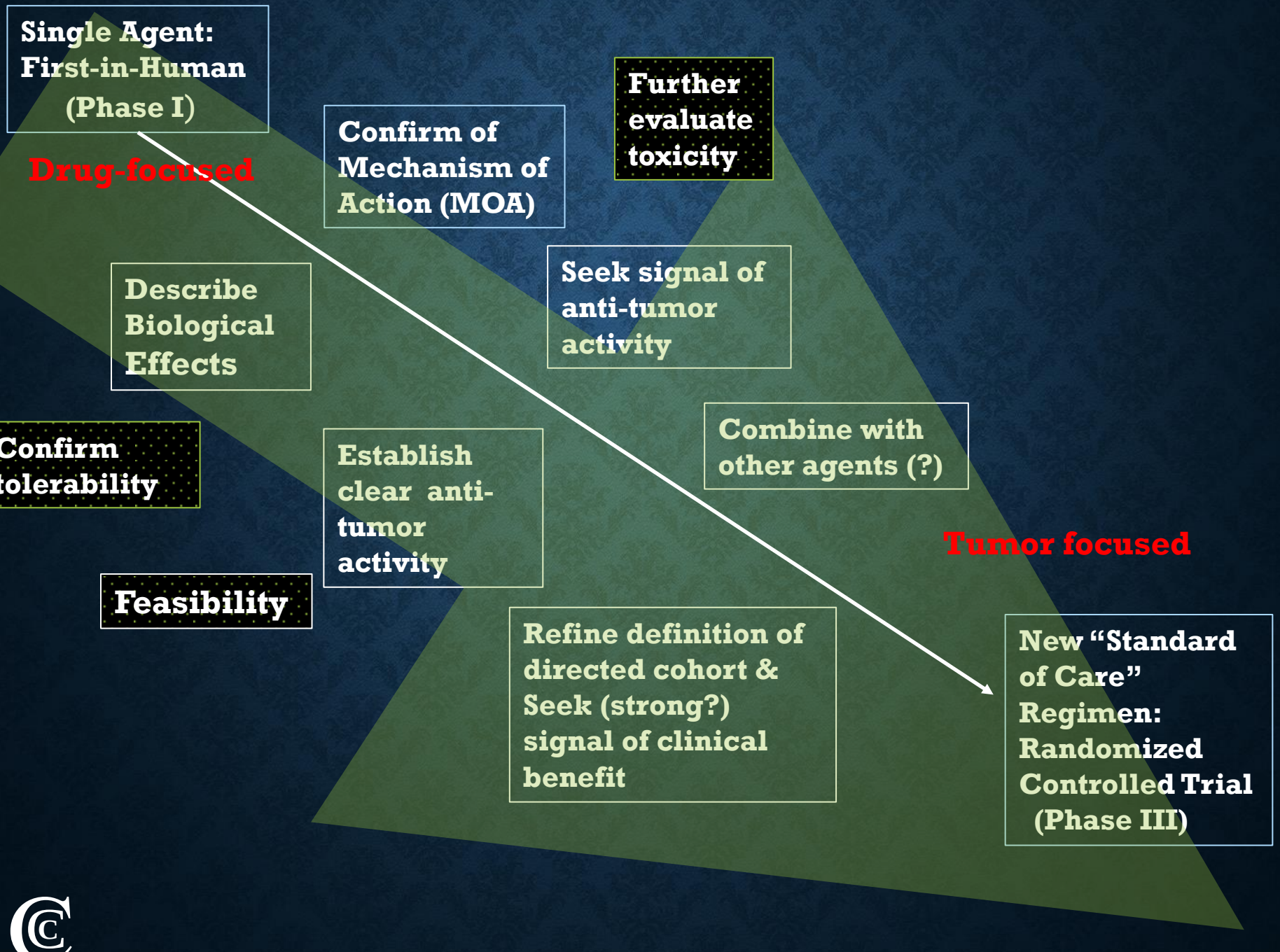
# Role of Phase II Testing

Single Agent: First-in-Human (Phase I)




*"I think you should be more explicit here in step two."*

New "Standard of Care" Regimen: Randomized Controlled Trial (Phase III)


Single Agent: First-in-Human (Phase I)
Drug-focused
Confirm of Mechanism of Action (MOA)
Further evaluate toxicity
Describe Biological Effects
Seek signal of anti-tumor activity
Confirm tolerability
Establish clear anti-tumor activity
Combine with other agents (?)
Tumor focused
Feasibility
Refine definition of directed cohort & Seek (strong?) signal of clinical benefit
New "Standard of Care" Regimen: Randomized Controlled Trial (Phase III)

# PRECISION MEDICINE RESEARCH USES BIOMARKERS TO DEFINE COHORTS

- Still use tumor site, tumor histology, stage, underlying organ function, prior treatment, etc.
- Consider tumor DNA, RNA, protein, tumor environment
  - challenges in establishing biomarkers to assess these tumor features
  - develop companion biomarkers
- Defining the appropriate cohort (target population) is part of the Phase II stage of development
  - single new agent or combination or regimen

# MULTI-COHORT TRIAL DESIGNS

- Defining tumor groups that will respond to the proposed treatment

- Phase II trial trials – signal seeking / evidence of anti-tumor activity
  - sufficient clinical activity to allow transition into Phase III

- **Basket Trial**: focus is on a drug and its target
  - agnostic of anatomical site and histology

- **Umbrella Trials**: focus is on cohorts within a diagnosis

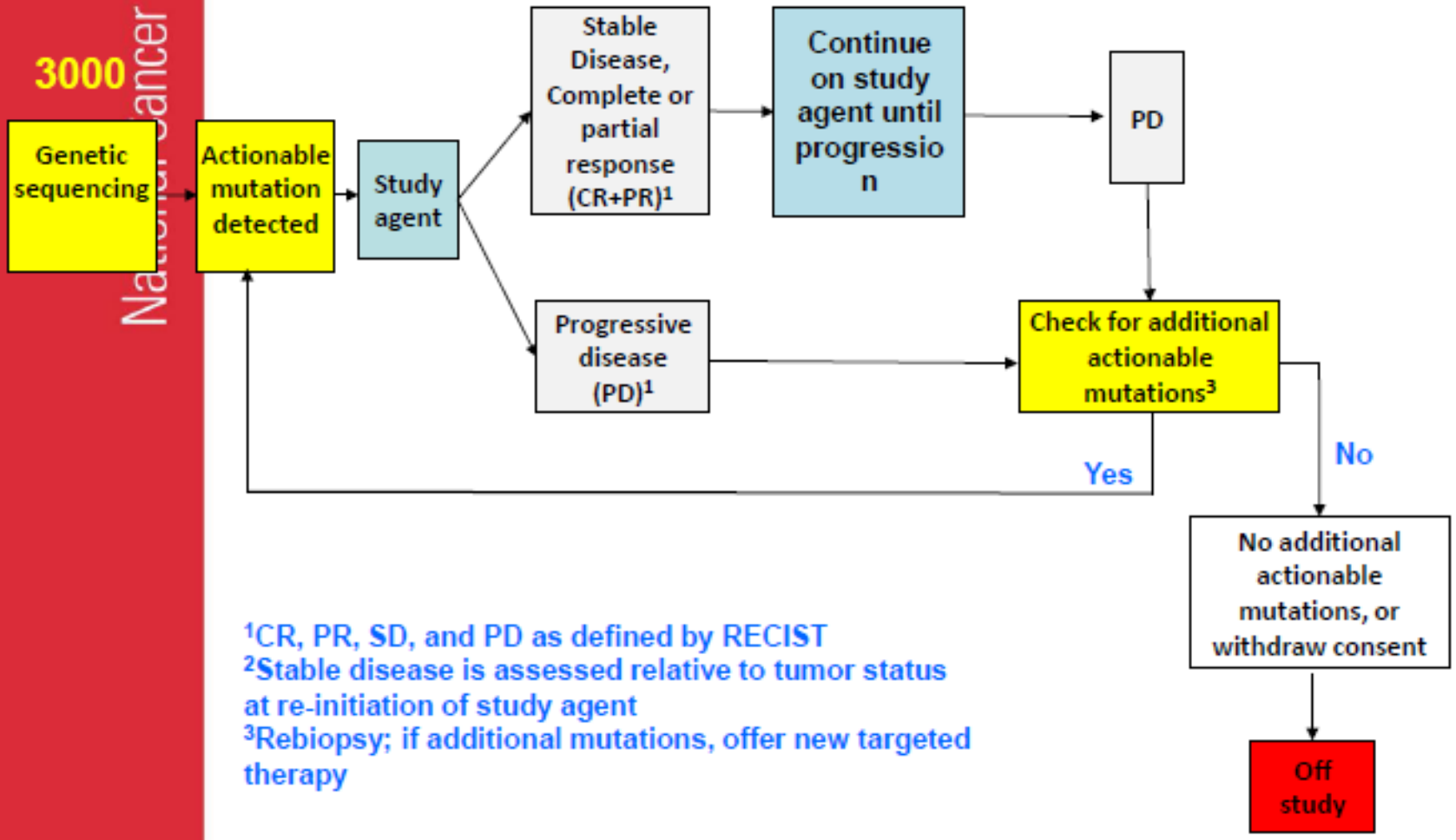
# Example of **Basket Trial**: NCI Molecular Analysis for Therapy Choice (MATCH)

- Multiple Basket Trials
  - Each molecular subgroup is matched to a targeted agent
    - Master protocol for screening & genetic sequencing, and then common CTEP template for each subgroup
  - Subgroups can be added or deleted without affecting others
    - Will consider combinations in the future
  - Initial design will enroll 35 patients in each subgroup which will be expanded to 70 in selected subgroups– no interim analysis
  - Anticipate about 50 subgroups

# NCI-MATCH SCHEMA

National Cancer Institute

3000




[1]CR, PR, SD, and PD as defined by RECIST
[2]Stable disease is assessed relative to tumor status at re-initiation of study agent
[3]Rebiopsy; if additional mutations, offer new targeted therapy

# NCI MATCH TRIAL – CURRENTLY OPEN (BASKET) SUBGROUPS

| Targeted Genetic Change | Drug(s) |
|---|---|
| EGFR mut | Afatinib |
| MET ex 14 sk | Crizotinib |
| EGFR T790M | AZD9291 |
| ALK transloc | Crizotinib |
| ROS1 transloc | Crizotinib |
| HER2 amp | Trastuzumab, Pertuzumab |
| FGFR amp | Erdafitinib |
| FGFR mut or fusions | Erdafitinib |
| mTOR mut | TAK-228 (formerly MLN0128) |
| TSC1 or TSC2 mut | TAK-228 (formerly MLN0128) |
| GNAQ/GNA11 mut | Trametinib |
| SMO/PTCH1 mut | Vismodegib |
| cKIT mut | Sunitinib |
| CDK4 or CDK6 amp and Rb exp | Palbociclib |
| NTRK fusions | Larotrectinib (LOXO-101) |
| PIK3CA | Copanlisib |
| PTEN loss without PIK3CA mut | Copanlisib |
| PTEN (deleterious) seq result & PTEN exp | Copanlisib |

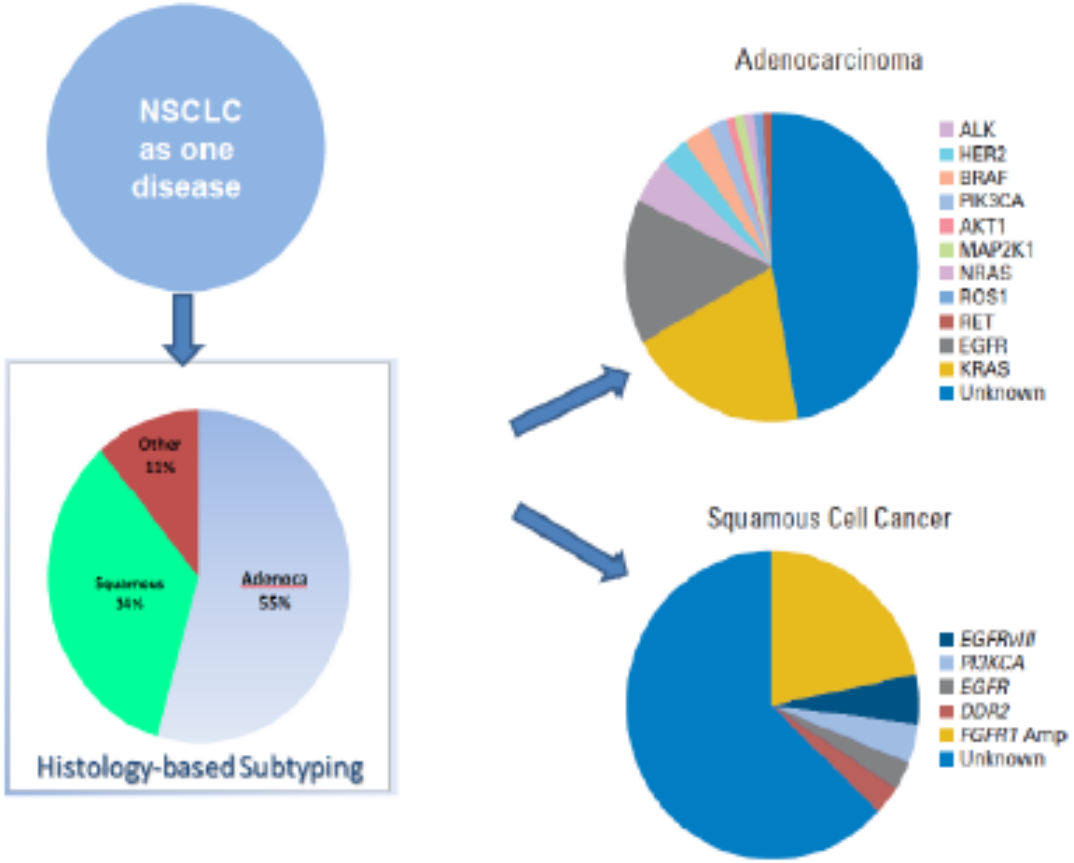
# Example of Umbrella Trial: SWOG S1400 for Squamous Cell Carcinoma (SCC) of the Lung

- Rationale for multi-cohort master protocol
  - Homogeneous patient population and consistent eligibility from cohort to cohort
  - Common broad-based NGS screening platform
  - Each cohort is independent
  - Can add and drop cohorts
  - Phase II/III design allows rapid drug/biomarker testing for detecting "large" effects
  - Designed to bring safe & effective drugs to patients faster / expedite FDA drug-biomarker approval

Roy S. Herbst, David R. Gandara, Fred R. Hirsch, et al. Lung Master Protocol (Lung-MAP)--A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. *Clin Cancer Res* 2015:1514-1524.

# Unmet Needs in Clinical Trial Designs for NSCLC when viewed as a Multitude of Genomic Subsets

Evolution of NSCLC → Histologic Subsets → Genomic Subsets

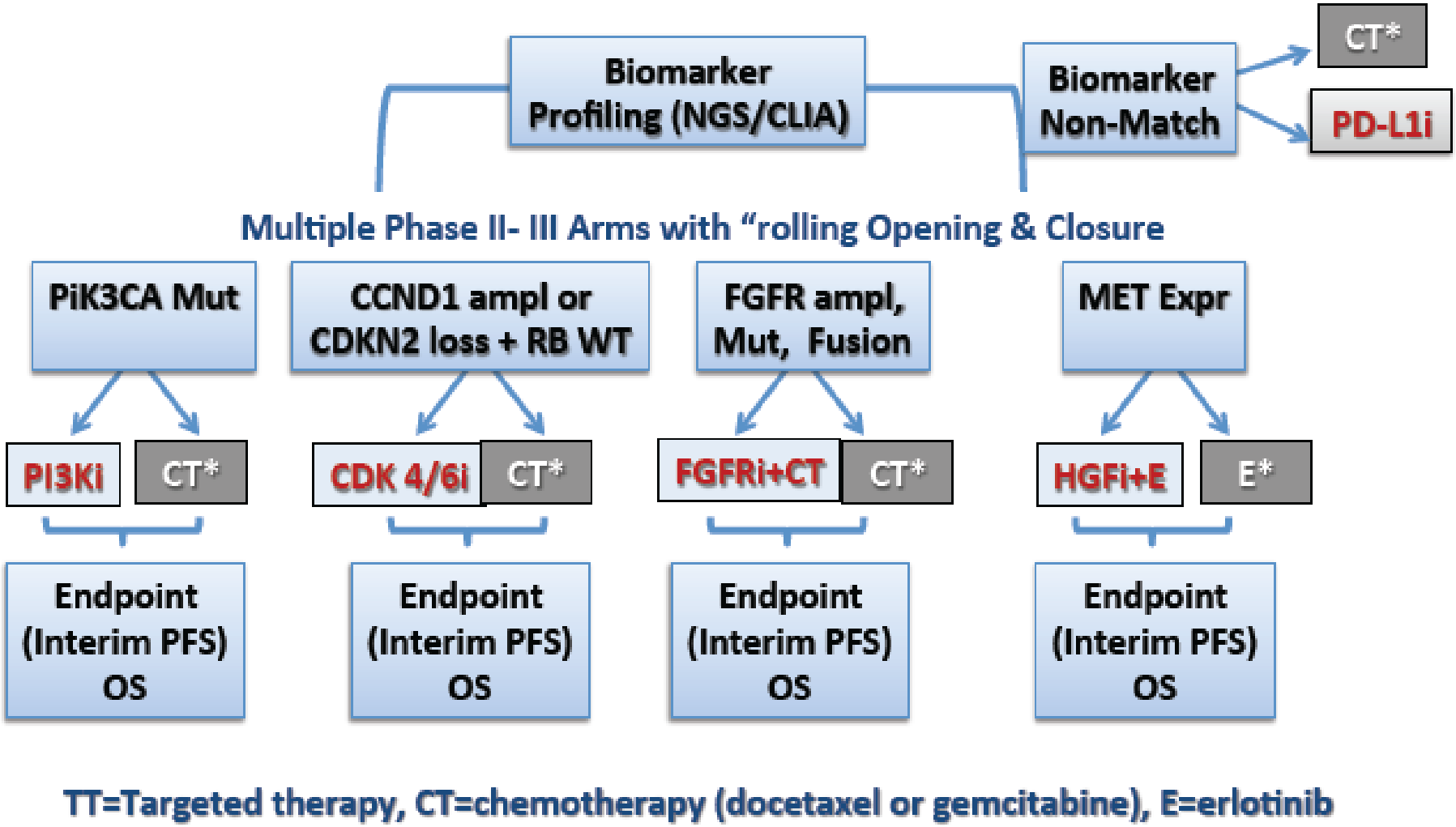



Unmet Needs in Clinical Trials:

- How to develop drugs for uncommon-rare genotypes?
- How to apply broad-based screening (NGS)?
- How to achieve acceptable turn-around times for molecular testing for therapy initiation? (<2 weeks)
- How to expedite the new drug-biomarker FDA approval process? (companion diagnostic)

*Li, Mack, Kung, Gandara: JCO 2013*

# S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy




The trial was modified from a phase II/III trial to one that includes both phase II and phase III substudies. The phase II studies allow investigational agents to be evaluated in single-arm trials.
http://www.lungcancernews.org/2018/06/01/the-lung-master-protocol-results-and-updates/ June 2018

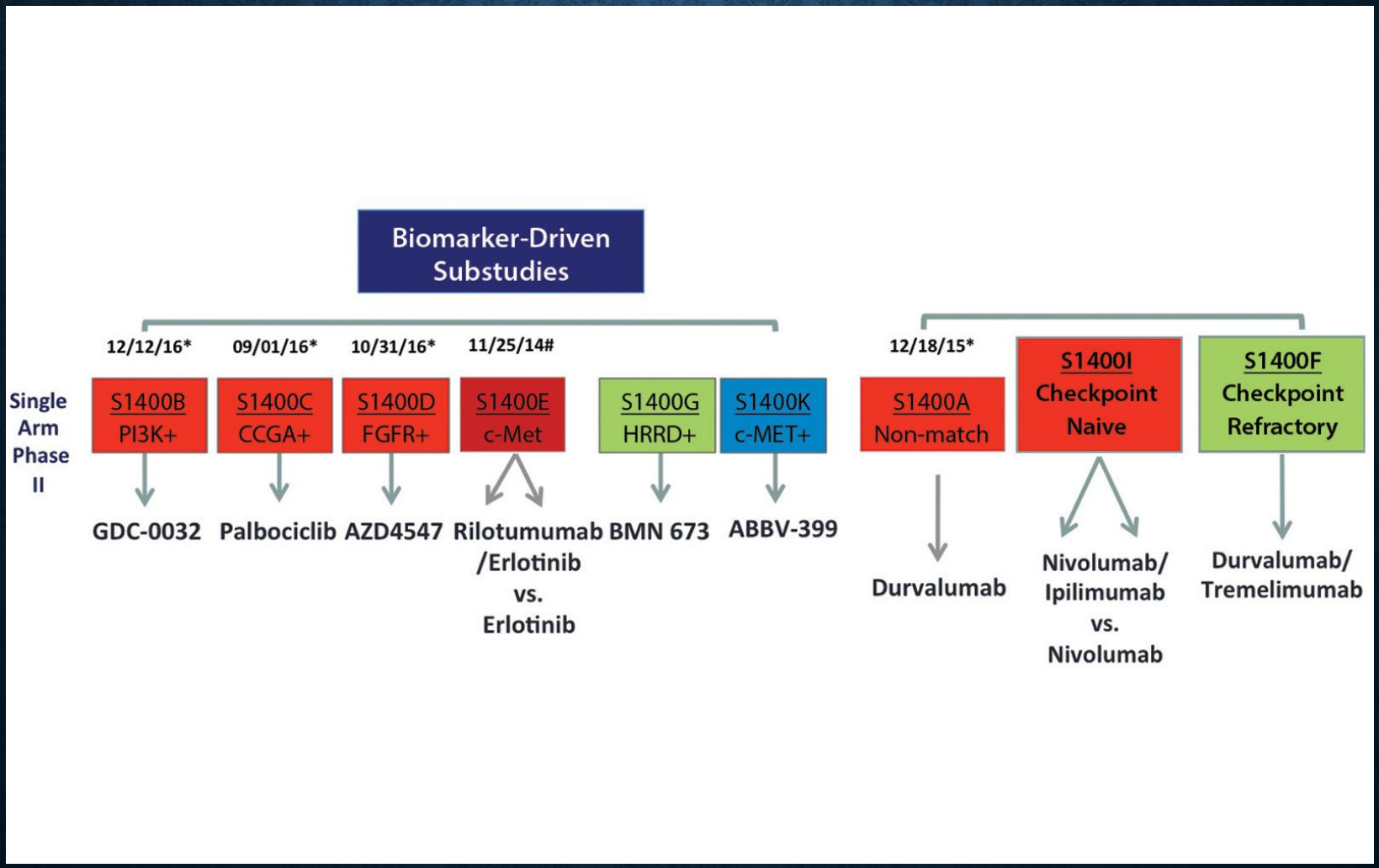
# LUNG MASTER PROTOCOL TRIAL (LUNG-MAP) - RESULTS

**Table. Updated Results of Completed Lung-MAP Substudies**

| Substudy Closure Date | Final Accrual | Response: Patients (%) | PFS Median (95% CI) | OS Median (95% CI) |
|---|---|---|---|---|
| S1400A (non-match) 12/18/15 | Total: 116<br>Durvalumab: 78<br>Docetaxel: 38 | 11 (16%) | 2.9 (1.8, 4.1) | 11.6 (10.1, 15.4) |
| S1400B PI3K 12/12/16 | Total: 39<br>Taselisib: 31<br>Docetaxel: 8 | 1 (4%) | 2.8 (1.7, 4.0) | 5.9 (4.1, 11.5) |
| S1400C (CCGA+) 9/1/16 | Total: 54<br>Palbociclib: 37<br>Docetaxel: 17 | 2 (6%) | 1.8 (1.6, 2.9) | 7.2 (4.0, 14.6) |
| S1400D (FGFR+) 10/31/16 | Total: 45<br>AZD4547: 35<br>Docetaxel: 10 | 2 (7%) | 2.7 (1.4, 4.5) | 7.5 (3.6, 9.3) |
| S1400E (MET+) 11/26/14 | Total: 9<br>Rilotumumab + Erlotinib: 4<br>Erlotinib only: 5 | 3 (5%) | 2.7 (1.9, 2.9) | 7.7 (6.7, 9.2) |

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; CCGA, cell cycle genetic alterations.

# LUNG MASTER PROTOCOL TRIAL (LUNG-MAP) – CURRENT STATUS



## NCI-MATCH - Basket

- Independent cohorts
- Can add and delete cohorts
- Adaptive design – can expand
- Common genetic profiling
- Potential drugs based on genetic results
- Many solid tumors, lymphoma
- No other therapeutic options
- **No randomization**
- **Single agents**
- **Signal seeking**

## LUNG-MAP - Umbrella

- Independent cohorts
- Can add and delete cohorts
- Adaptive design – go to Phase III
- Common genetic profiling
- Potential drugs based on genetic results
- Lung: squamous cell carcinoma
- 2nd line therapy
- **Randomization (in initial design)**
- **New agent added to backbone**
- **Evidence of improved outcome**

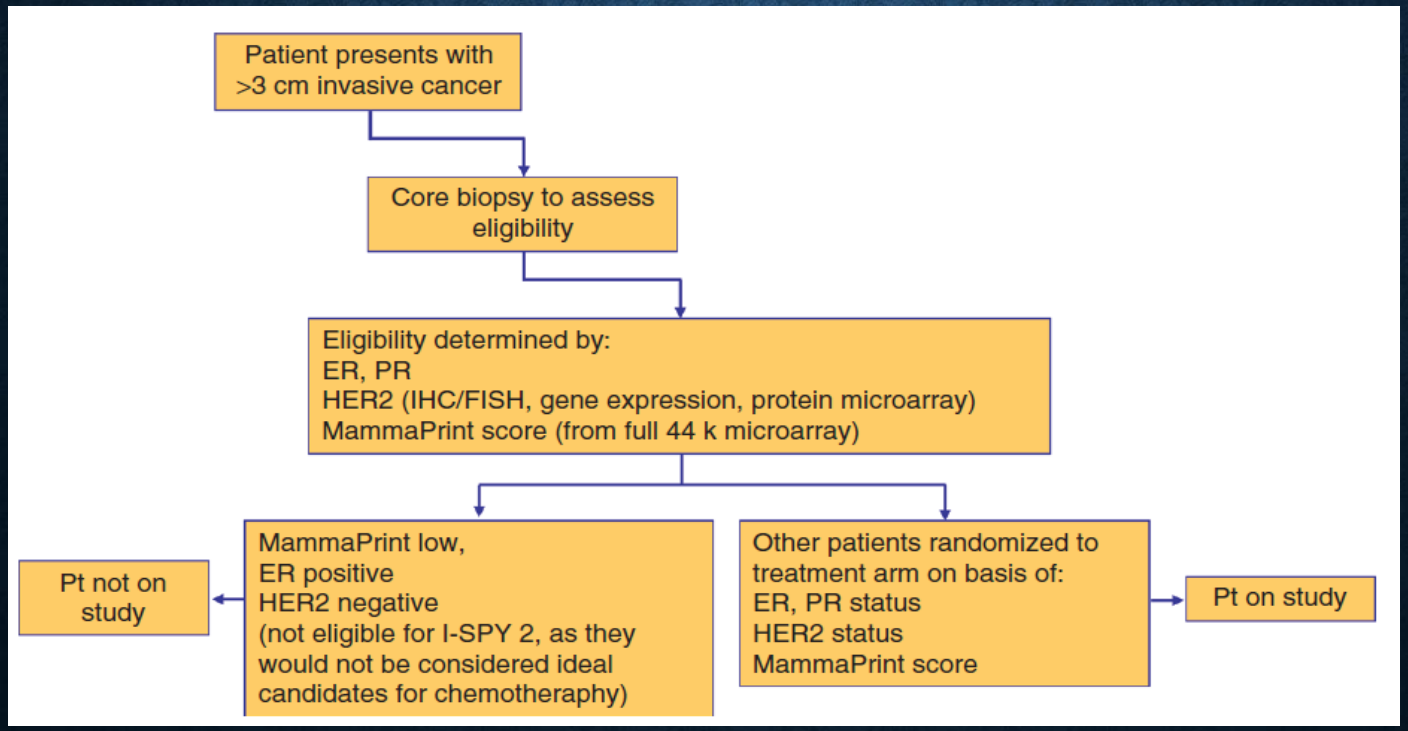
# VARIATIONS OF MULTI-COHORT TRIALS

I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

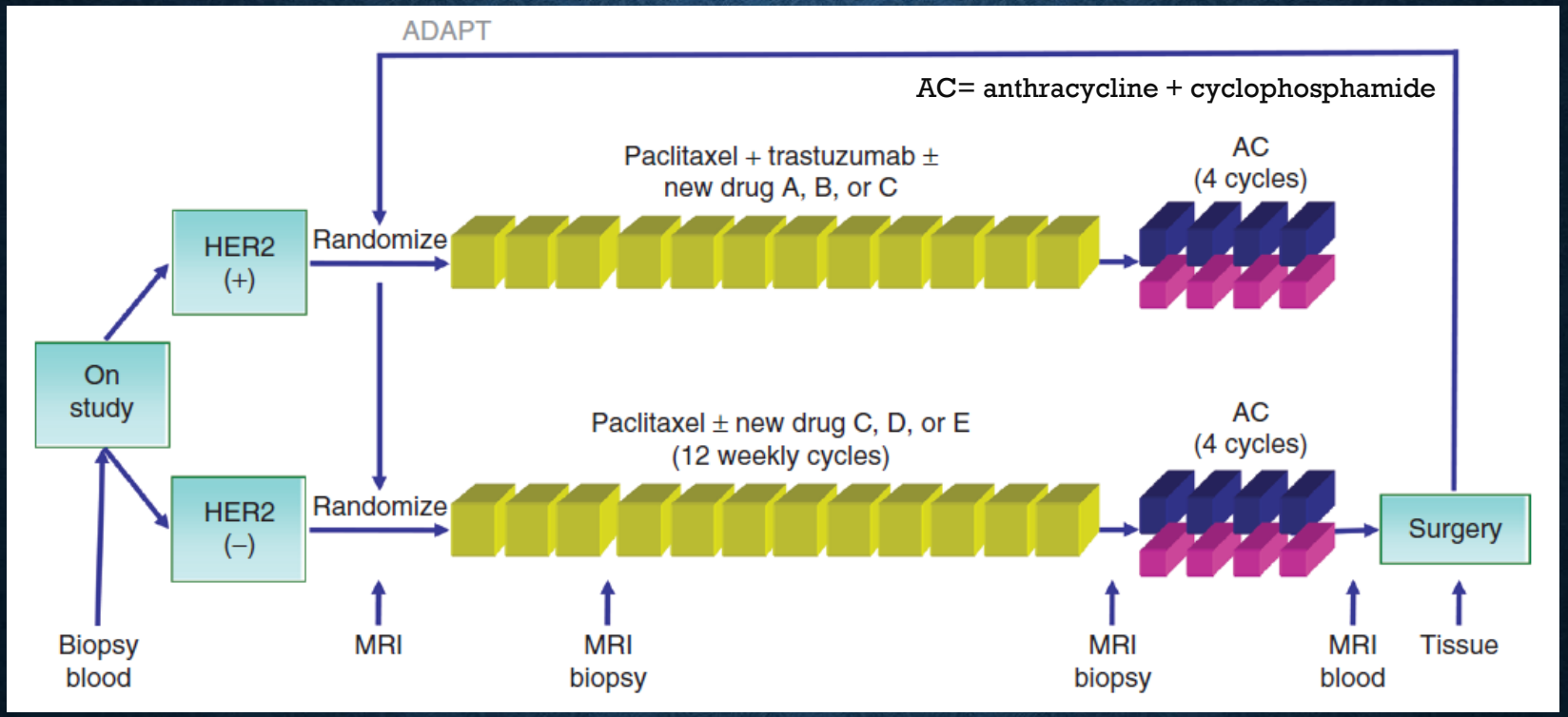
AD Barker[1], CC Sigman[2], GJ Kelloff[1], NM Hylton[3], DA Berry[4] and LJ Esserman[3]

CLINICAL PHARMACOLOGY & THERAPEUTICS. 86: 97-100 (2009) | www.nature.com/cpt

- Adaptive randomization (probability of assignment to an arm depends on outcome of previous patients – overall and within biomarker signature)
- Bayesian methodology



# I-SPY 2: ADAPTIVE RANDOMIZATION



# I-SPY 2: RESULTS

**RESULTS**

Neratinib reached the prespecified efficacy threshold with regard to the HER2-positive, hormone-receptor–negative signature. Among patients with HER2-positive, hormone-receptor–negative cancer, the mean estimated rate of pathological complete response was 56% (95% Bayesian probability interval [PI], 37 to 73%) among 115 patients in the neratinib group, as compared with 33% among 78 controls (95% PI, 11 to 54%). The final predictive probability of success in phase 3 testing was 79%.

**CONCLUSIONS**

Neratinib added to standard therapy was highly likely to result in higher rates of pathological complete response than standard chemotherapy with trastuzumab among patients with HER2-positive, hormone-receptor–negative breast cancer. (Funded by QuantumLeap Healthcare Collaborative and others; I-SPY 2 TRIAL ClinicalTrials.gov number, NCT01042379.)

N ENGL J MED 375;1 NEJM.ORG JULY 7, 2016

Neratinib: tyrosine kinase inhibitor, an irreversible inhibitor of the ErbB and the human epidermal growth factor receptor (HER) kinase family (epidermal growth factor receptor, HER2, and HER4).

# VARIATIONS OF MULTI-COHORT TRIALS

New drug alone or added to backbone in a limited number of tumors (by anatomic or histologic type or other feature)

- An "indication seeking" design
- Multiple independent Phase II trials of *a priori* defined cohorts
- Underlying hypothesis: drug is effective in many tumor types
  - May design to assess overall activity, as well as in individual cohorts (hierarchical modeling)
- Example: a new specific checkpoint inhibitor in lung, breast, bladder, lymphoma

# VARIATIONS OF MULTI-COHORT TRIALS

PHI-77: A Phase I Trial of Osimertinib and Necitumumab After Prior EGFR-TKI: Focus on T790M Negative and C797S Positive EGFR Mutant NSCLC

- Jonathan Riess, PI

- Phase I trial with 4 expansion cohorts

**For Expansion Cohorts A, B, and C:**

- Must harbor at least one of the following EGFR activating mutations: Exon 21 L858R, Exon 19 deletion, Exon 18 G719X, Exon 21 L861Q.
- No EXON 20 Insertion.
- Must have progressed during or after treatment with an EGFR-TKI.
- Must anti-EGFR antibody naïve.

**For Expansion Cohort D**:

- EGFR EXON 20 Insertion required.
- Progression on or after platinum-based chemotherapy required. Must anti-EGFR antibody naïve.
- Must be EGFR-TKI naïve.

| Expansion Cohort | Progression During or After Prior | EGFR T790M Status |
|---|---|---|
| **A** (n=18) | 1st or 2nd Generation (i.e. gefitinib, erlotinib, afatinib) & must be **last** trt received / Must be 3rd generation EGFR-TKI naive | Negative |
| **B** (n=18) | 3rd Generation: i.e. AZD9291, rociletinib, HM61813 | Negative |
| **C** (n=18) | 3rd Generation: i.e. AZD9291, rociletinib, HM61813 | Positive |
| **D** (n=18) | Platinum-based chemotherapy | EGFR EXON 20 Insertion |

# THANK YOU!!

- CCC Leadership:  Drs. Gandara, Lara, Lenz, Morgan, Newman
- CCC Operations / DCC:  Ms. Calcanas-Perez & Ms. Khoo
- All the CCC Clinical Trialists
- All the patients (trial participants)
- COH Statisticians:  Drs. Blanchard, Frankel, Longmate, Chris Ruel, and Nora Ruel