“Experience with Building Sequential and Platform Precision Medicine Trials”

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Outline

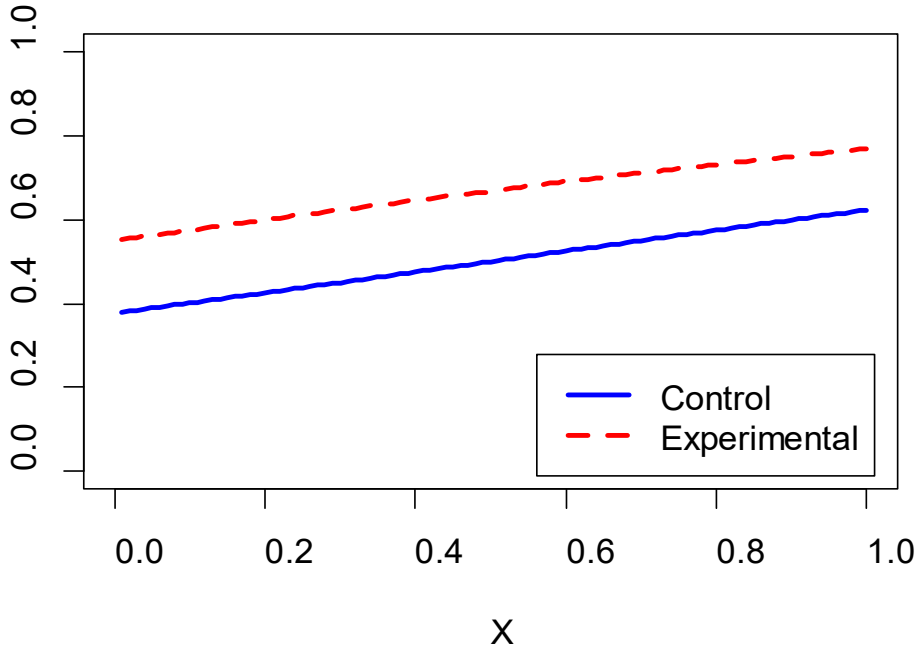
- Heterogeneous treatment efficacy in oncology
- Precision medicine targeted designs
- Efficiencies and costs of targeted studies
- Master Protocols (Umbrella and Basket) in the SWOG Cancer Research Network as part of the NCI National Clinical Trials Network

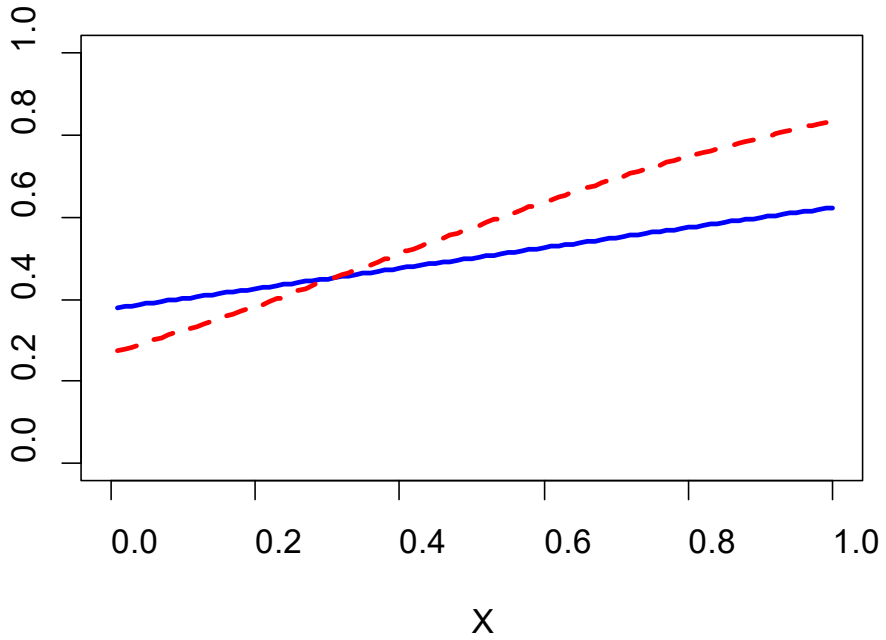
Some Precision Trial Observations

- Current evaluation of new treatments for cancer extensively utilizes designs that enrich outcomes for patients thought to be most impacted by new therapy
- Enrichment trials based on the criterion to maximize the treatment effect, and subsequently optimize the power of the trial
- Targeted group may be defined by mutation, or by utilizing more continuous biomarkers
- Often the targeted group can represent a relatively modest fraction of overall patients that could available for that clinical trial

Continuous Case: Treatment effect and marker value

- Two cases:
  1) Treatment is essentially equally effective regardless of marker
  2) The marker indicates where one treatment is preferred





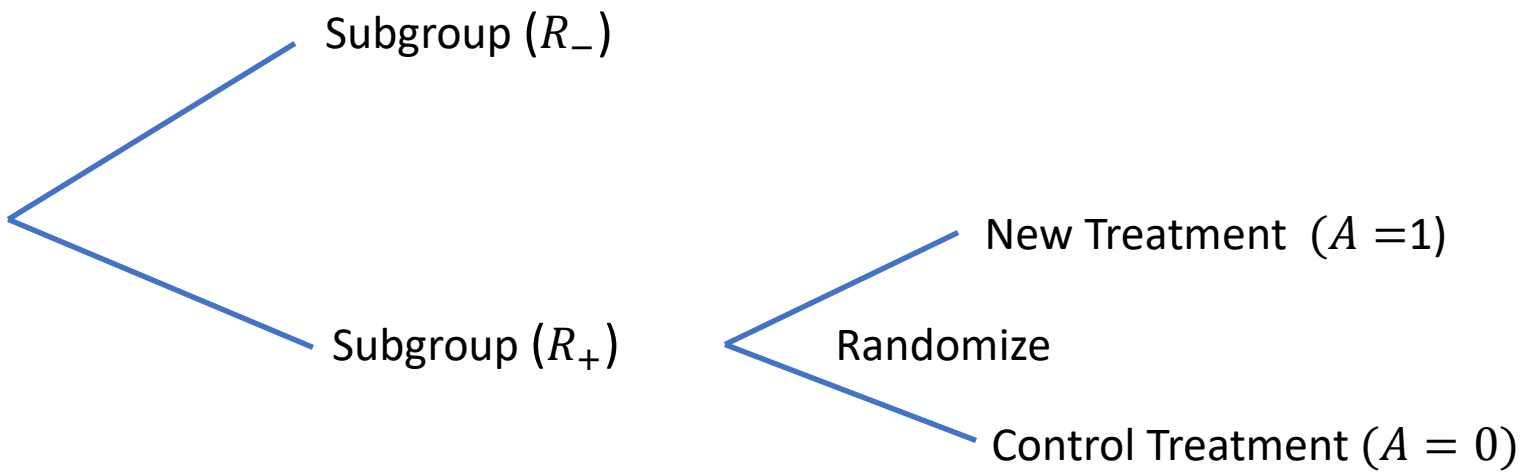
Recent SWOG Cancer Network Examples: Variation in treatment efficacy and targeted trials

- Genetic or protein measurement
  - HER2 amplification [Herceptin]
  - tyrosine kinase enzyme (c-kit) [Imatinib]
  - BRAF mutation [Vemurafenib]
  - Pi3K [Taselisib]
  - CCGA [Palbociclib]
  - HRRD [Talazoparib]
  - c-MET [Teliso-V] (ABBV-399)
  - PDL-1 expression [Nivolumab,…]
  - …
- Multi-variable genetics predicting treatment efficacy
  - OncotypeDx recurrence score (breast cancer)
  - COXEN (bladder cancer)

Designs using biomarker subgroups

- Suppose we can define two subgroups of patients based on attributes measured at baseline
- Define two classes of individuals
  - Subgroup (R_+) - drug thought to most efficacious
  - Subgroup (R_-) - drug thought to lesser or not efficacious
- Examples of Targeted or Enrichment Designs – long literature
  - Maitournam and Simon, Statistics in Medicine 2005
  - Mandrekar and Sargent, Journal of Clinical Oncology, 2009
  - Hoering, LeBlanc and Crowley, Clinical Cancer Research, 2008
  - …
- Note: Many practical, technological, timing, cost, certification issues in actually defining (R_+) or (R_-)

Targeted or Enrichment Design (single study)



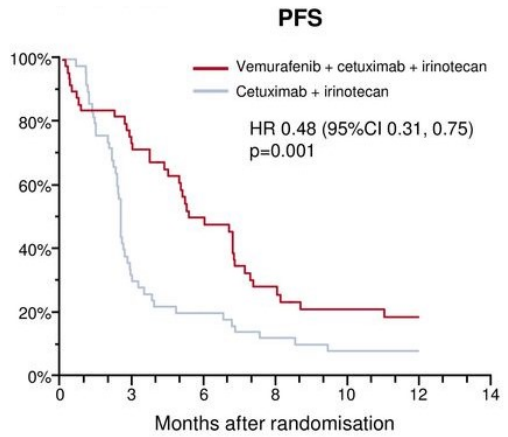
Advantages: If treatment is only effective (or more effective) in a subgroup this is a powerful strategy. However, if there is broader activity or if the goal is to assess a marker, then there is information loss.

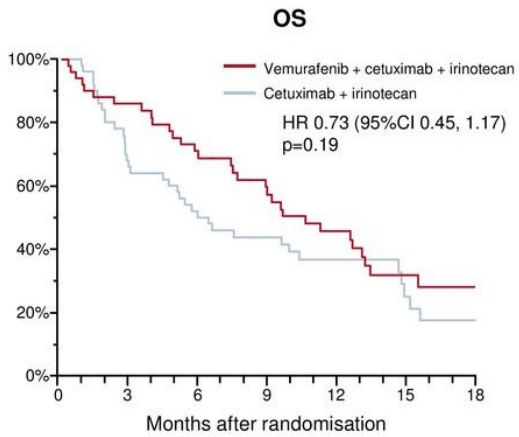
S1406 Randomized Phase II study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer

Unk/Not $BRAF^{V600E}$ mutation

$BRAF^{V600E}$

- Irinotecan and Cetuximab + Vemurafenib
- Irinotecan and Cetuximab





Notation

- Y denote the response and X the marker measure(s) used to select patient inclusion
- Let $A \in \{0,1\}$ denote the treatment options, where $A = 0$ represents standard care and $A = 1$ represents new treatment.
- The inclusion function of is defined

$$R_+ : f(X) > 0 \text{ describe enrolled patients}$$
$$R_- : f(X) \leq 0 \text{ describe not enrolled patients}$$

- Let $Y(a)$ be the potential outcome that would be observed were the subject to receive treatment $a, a = 0,1$
- Assume the power of the study is P_f under the alternative hypothesis, based on an enrollment criterion of $f(X) > 0$
- Recommend treatment for a new individual X^* based on the trial result as follows:

if the trial is successful, X^* with $f(X^*) > 0$ will receive new treatment

for X^* with $f(X^*) \leq 0$, they will receive standard care

Targeted Study Efficiency

- A key parameter is the frequency of the marker

$$v^+ = P(X \in R_+) \qquad v^- = P(X \in R_-) = (1 - v^+)$$

- Treatment effect as a function of the marker

$$\Delta(x) = E(Y|A = 1, X = x) - E(Y|A = 0, X = x)$$

- The effect within the maker group $\Delta^+ = E[\Delta(X^*)I\{X^* \in R_+\}]$
- Relative <u>randomized</u> sample size non-targeted/targeted

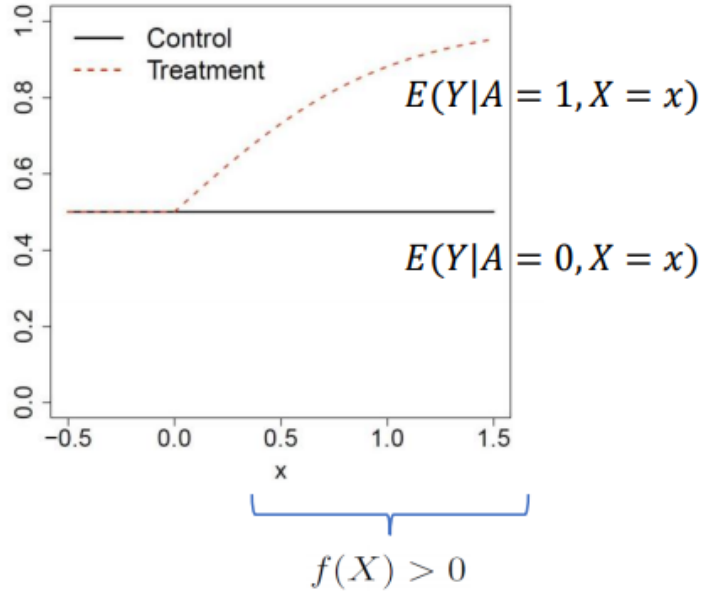
$$\frac{n}{n^T} = \left(\frac{\Delta^+}{(1 - v^+)\Delta^- + v^+\Delta^+}\right)^2$$

If no off-target effect $\frac{n}{n^T} = \left(\frac{1}{v^+}\right)^2$

- Relative <u>screened</u> sample size targeted/non-targeted

$$\frac{n}{n_s^T} = (1 - v^+)\left(\frac{\Delta^+}{(1 - v^+)\Delta^- + v^+\Delta^+}\right)^2$$

If no off-target effect $\frac{n}{n_s^T} = \frac{1}{v^+}$



For same power, smaller randomized and screen sample sizes

Some Precision Trial Challenges

- Often the targeted group or marker positive group is a very small fraction of overall patients that could available for that clinical trial
- Cost or feasibility issues to develop (or open) a clinical trial with such a low chance of finding a eligible patients
- May be limited patient interest, depending on the up front screening timing and costs
- If it is a rare subgroup, limited the overall impact to patients with the disease

Alternative Targeted Methods

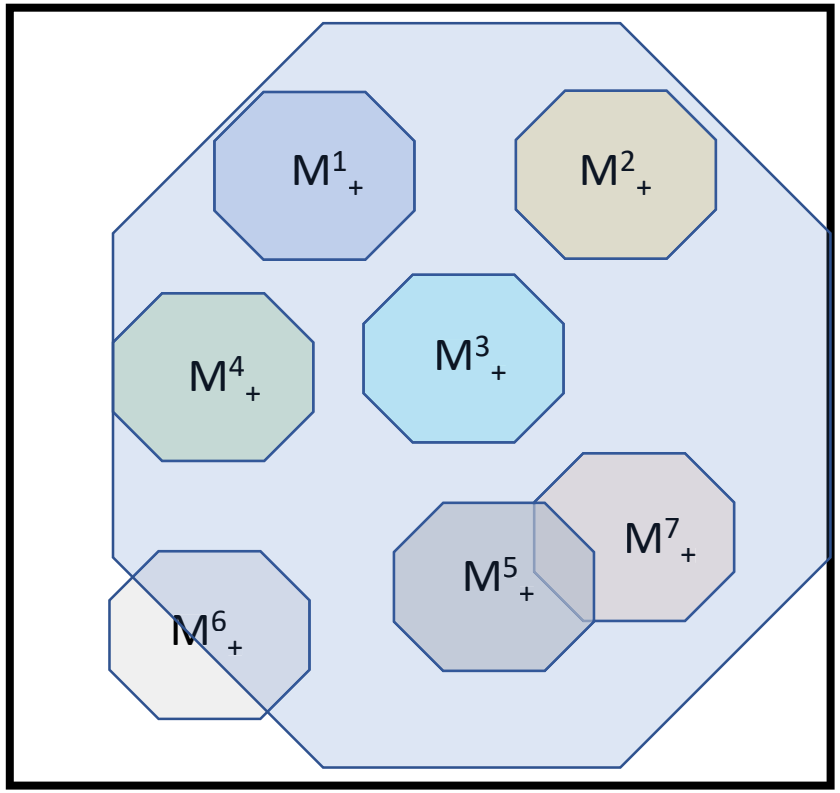
- A new targeted design strategy to focus on treatment broader population impact rather than just study power
- Makes assumption that future new treatment is to only patients in the assignment rule $\{f(X^*) > 0\}$
- Can include cost/toxicity constraints or fraction of patients in target group
- Typically increases number of patients under study, yields better population impact

Zhao Y, LeBlanc M. Designing precision medicine trials to yield a greater population impact, Biometrics, 2019.

Master Protocols

- A strategy to evaluate multiple therapeutic questions in at the same time
- Typical structure to include multiple sub-studies with different patient groups/treatment's
- Goals: Efficiency in patient availability and assessment of new regimens
- FDA Guidance: *In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, master protocols use a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple sub-studies, allowing for efficient and accelerated drug development.*

Master Protocol – multiple sub-group sub-studies



Let M^j_+ be a marker subgroup (or disease)

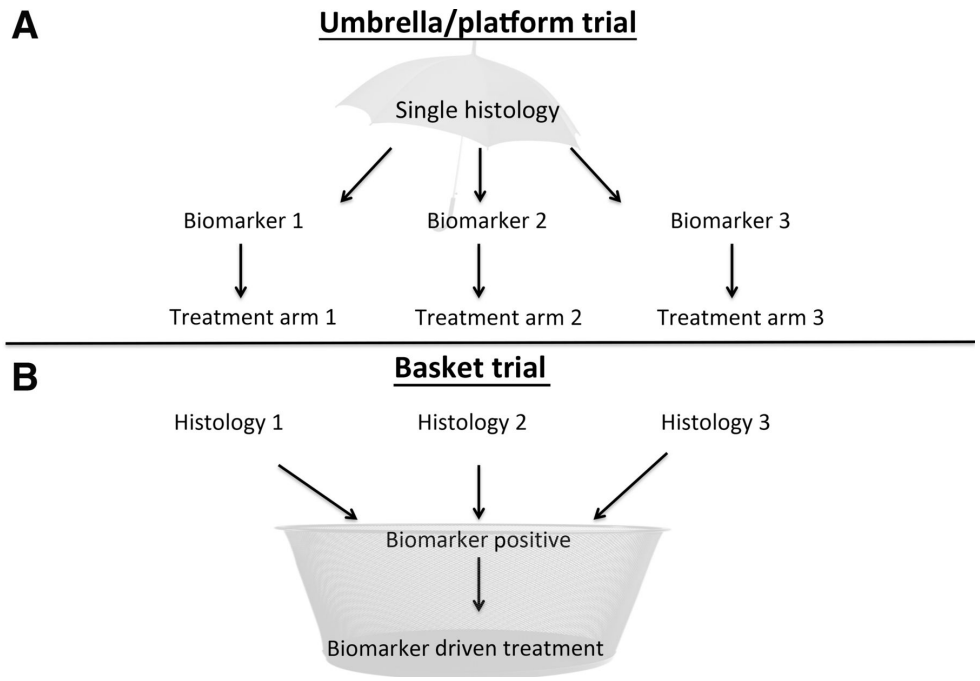
More targeted subgroups lead to higher overall eligible “hit” rate. That is the number of patients Actually registered to sub-study trials

There can be a sub-study for the non-match patients

Master Protocols: Basket and Umbrella

- Common feature – scientifically address small subgroups of patients
- Umbrella: Single disease(usually), multiple biomarkers matched to treatments
- Basket Trials: Multiple diseases placed into cohorts and a single regimen (usually) is evaluated

A Simplified View



Cecchini et al. CCR, 2019

Study Efficiency and Cost

- Targeting subgroups can involve direct and indirect screening costs
- Cost per sub-study trial patient where there are costs per patient for screening and costs per patient registered/randomized to the targeted sub-study

$$C_i = cost_s \times n_s + cost_r$$

As the number needed screened (n_s) increases cost per patient can also increase substantially

- By bundling multiple sub-studies in a Master Protocol the number screened, n_s per patient registered to a sub-study should decrease

$$C_i = cost_s \times n_s + cost_r + \frac{study\_cost}{n_r}$$

However, there can be significant costs to develop a master protocol

Hopefully, the cost to develop one master protocol is less than the sum of individual sub-study costs

SWOG Cancer Research Network

- Network of 1,200+ sites, including:
  - 35 NCI-designated cancer centers
  - Multiple member sites and collaborations outside U.S.

- Members included:
  - 6,000+ researchers/clinicians
  - 7,000+ research nurses, clinical research associates, pharmacists, patient advocates and others

Lung-MAP Master Protocol for advanced non-small cell lung cancers

Mary Redman, Lead Lung-MAP Statistician

Improve screening

- Screening large numbers of patients for multiple targets
- Reduce screen failure rate
- Provide a sufficient “hit rate” to engage patients & physicians

Increase speed of drug evaluation and development

- Provide an infrastructure to open new sub-studies faster
- Rapid drug/biomarker testing for detection of “large effects”
- Facilitate FDA approval of new drugs and bring safe & effective drugs to patients faster

Lung-MAP is a public/private partnership including many pharma and:

FNIH Foundation for the National Institutes of Health

NCI National Clinical Trials Network a National Cancer Institute program

FRIENDS of CANCER RESEARCH

SWOG CANCER RESEARCH NETWORK

Biomarker-Driven Platform: Design Considerations

Biomarker Considerations:

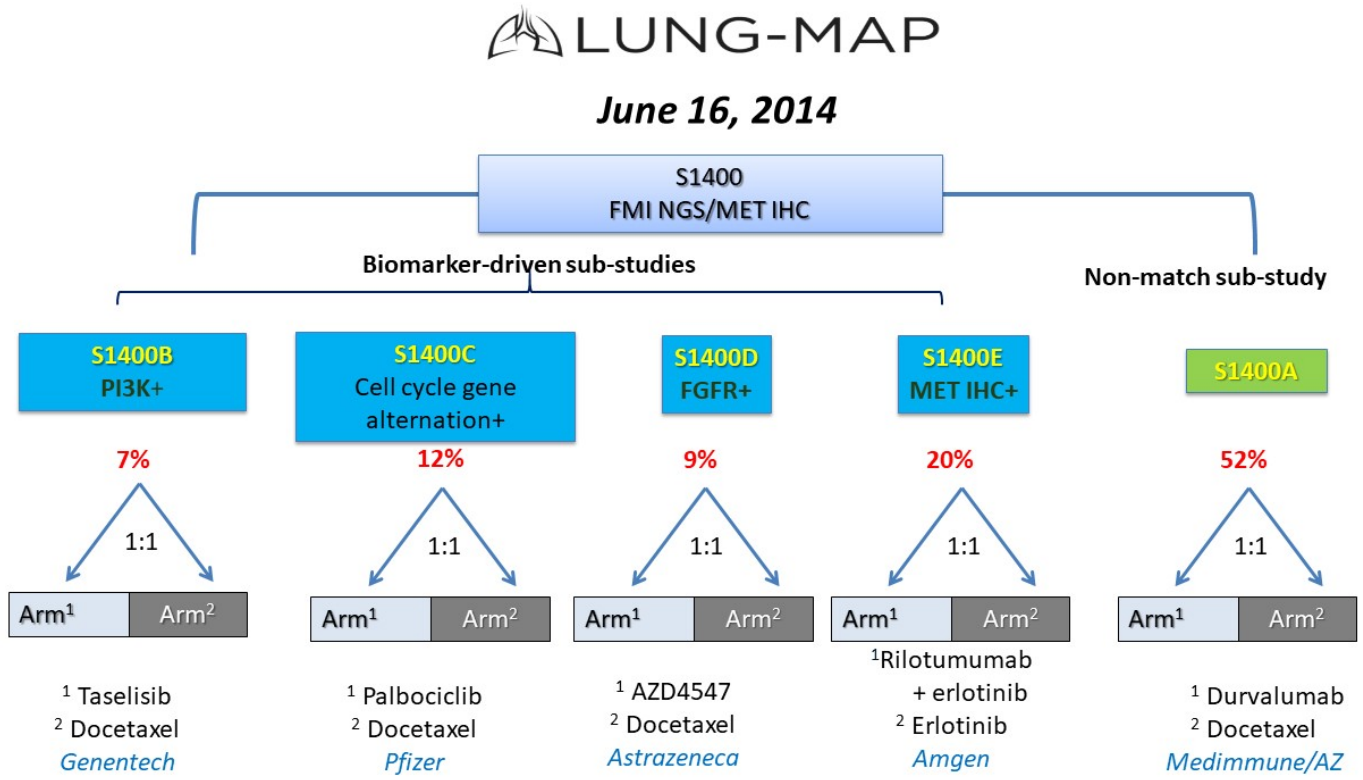
- Are biomarkers sufficiently developed/validated to guide treatment
  - Is the biomarker test reliably detecting what it should be?
- What does it mean to be biomarker positive?
  - If a continuous biomarker, how well established is the cut-off
  - If binary, is it truly binary?
- Are there data to estimate prevalence of the biomarker?

Investigational Therapy Considerations

- Are there sufficient/appropriate agents to test to warrant master protocol?
- Are there safety data on the investigational therapy or combination?
- Is there any evidence that “biomarker-negative” patients may benefit?
- Is there evidence that the biomarker could also be prognostic?

Original Lung-MAP Design

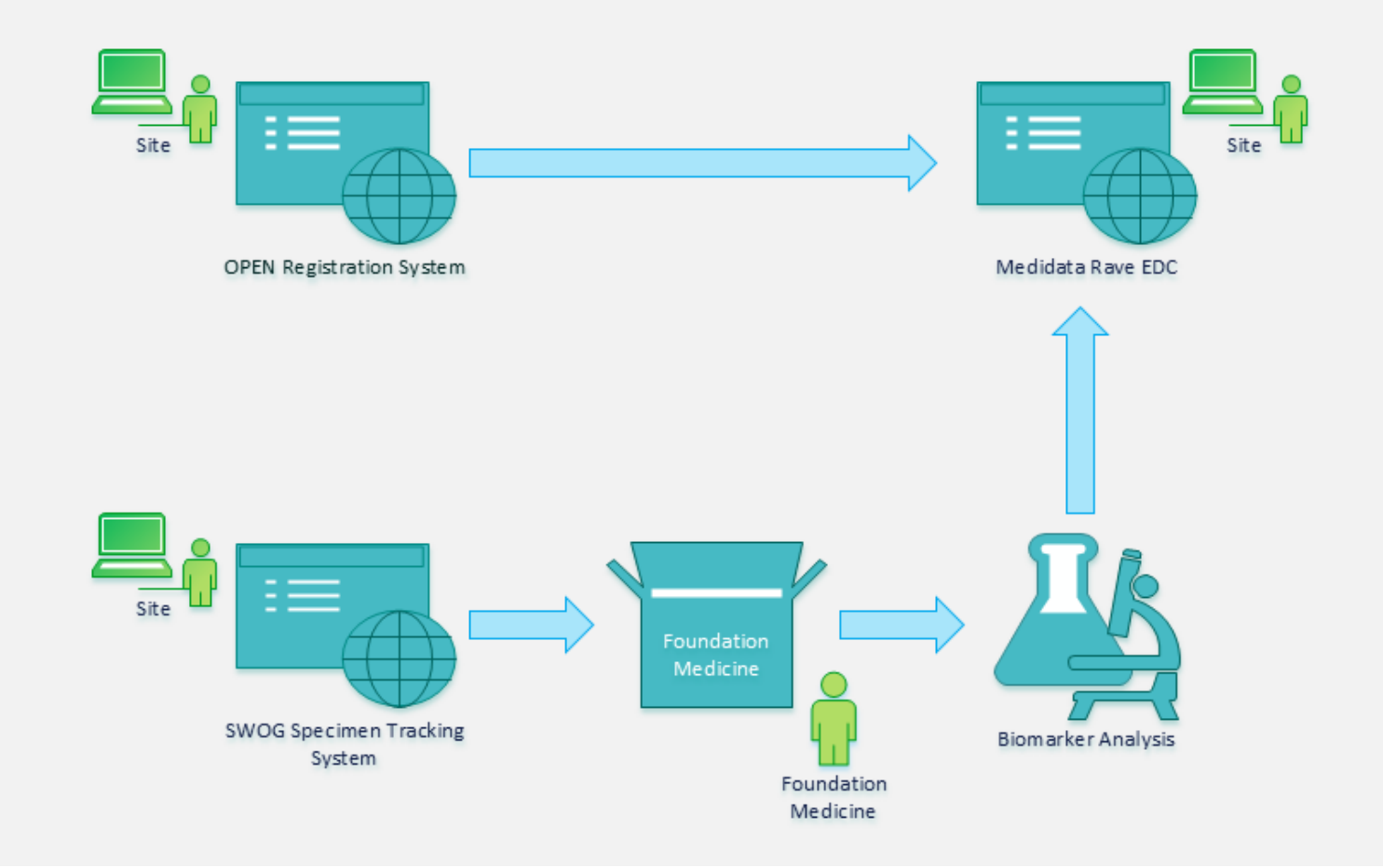
- Study included 5 sub-studies. (4 marker driven and non-match Study)
- Eligibility for both screening and sub-studies
- Specialized registration and randomization (to address multiple biomarkers)
- Design <u>standardized</u> to be Randomized Phase II/III design within each marker subgroup.

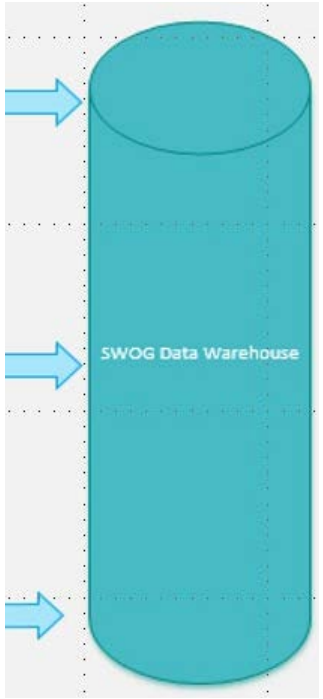


Biomarker-Driven Platform: Design Considerations

- Sub-study assignments
  - Will the study use prioritization or randomization for patients eligible for multiple sub-studies
  - If randomization, will the weights be equal?
- Biomarker Testing Results and Reporting
  - Will the study return results to patients and if so, how?
  - Will the study provide any interpretation of biomarker results?

Implementation: User workflow diagram

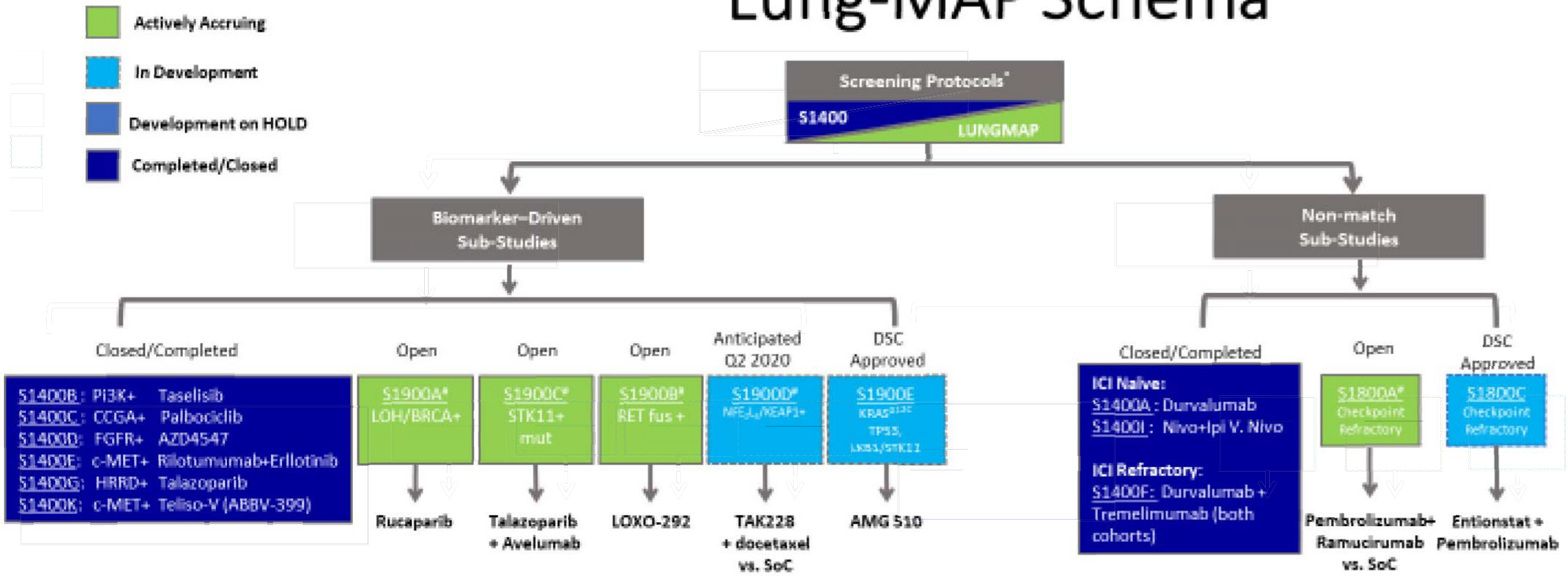




The data for the Lung-MAP comes into the SWOG database as would any other study in SWOG portfolio

Standardized coding conventions allow standardized management, and statistical analysis tools

Lung-MAP Schema



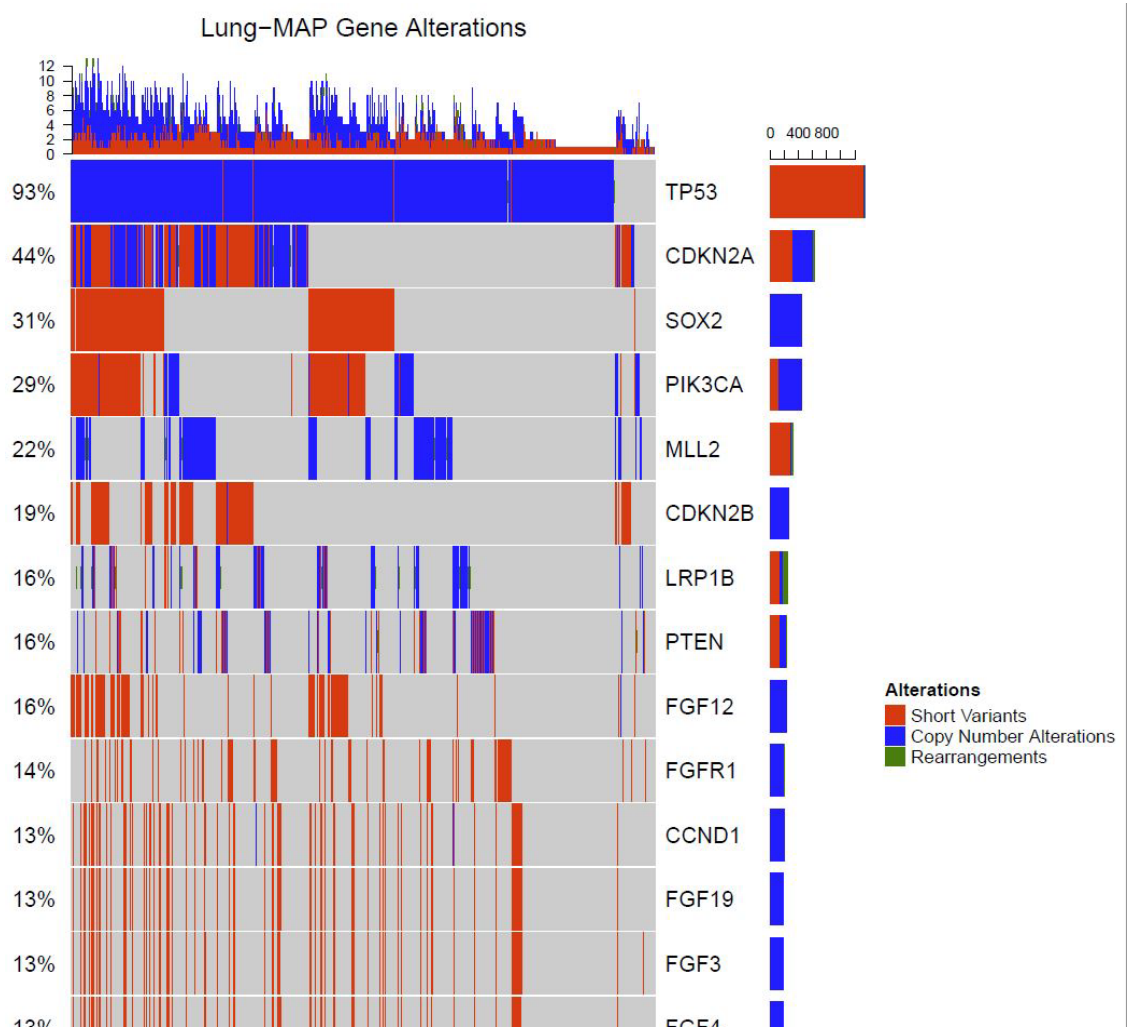
*LUNGMAP screening protocol (activated 1/28/19) allows all histologic types of NSCLC. S1400, the original screening/umbrella protocol included only squamous lung cancer. S1400 accrued patients between 6/16/2014 and 1/28/2019. While S1400 is closed to accrual, patients enrolled to S1400 may participate in sub-studies they are eligible for.

TRIAL POINTS OF INTEREST:

- *Each of* sub-study operates independently of the others
- Prescreening can be performed while the patient is on any line of therapy for stage IV disease
- Repeat or fresh biopsy necessary for tissue screening is paid by the trial
- ***Biomarker-driven sub-studies may progress to Phase III if study meets endpoint and Phase III is feasible, at which point the standard of care arm will be determined.**

Master Protocol Secondary Analyses

- Genomic data from screening step available for cross sub-study analysis
- Key design feature for correlative studies that there is follow-up for non-sub-study registered patients.
- Analyses currently ongoing



Statistical Design Considerations for sub-studies

- While standardization is important – we learned that variation of designs were needed for sub-study objectives
- For Lung-MAP (sub-study designs include)
  - Single arm Phase II (two stage) → Randomized Phase III
  - Single arm Phase II (with targeted subgroup)
  - Randomized Phase II
  - Randomized Phase II with interim looks at response
  - Randomized Phase II/III designed for delayed treatment effects (seen in some immunotherapy studies)

Rare Tumor Trials

Megan Othus, Lead DART Statistician

- Rare Tumor Challenges
  - Recruitment & Accrual Barriers
  - Study Design Limitation Small Sample Size
  - Difficult for institutions
- One way to address some challenges
  - Bundle many disease into one, unified protocol; evaluate separately
  - Basket Trial

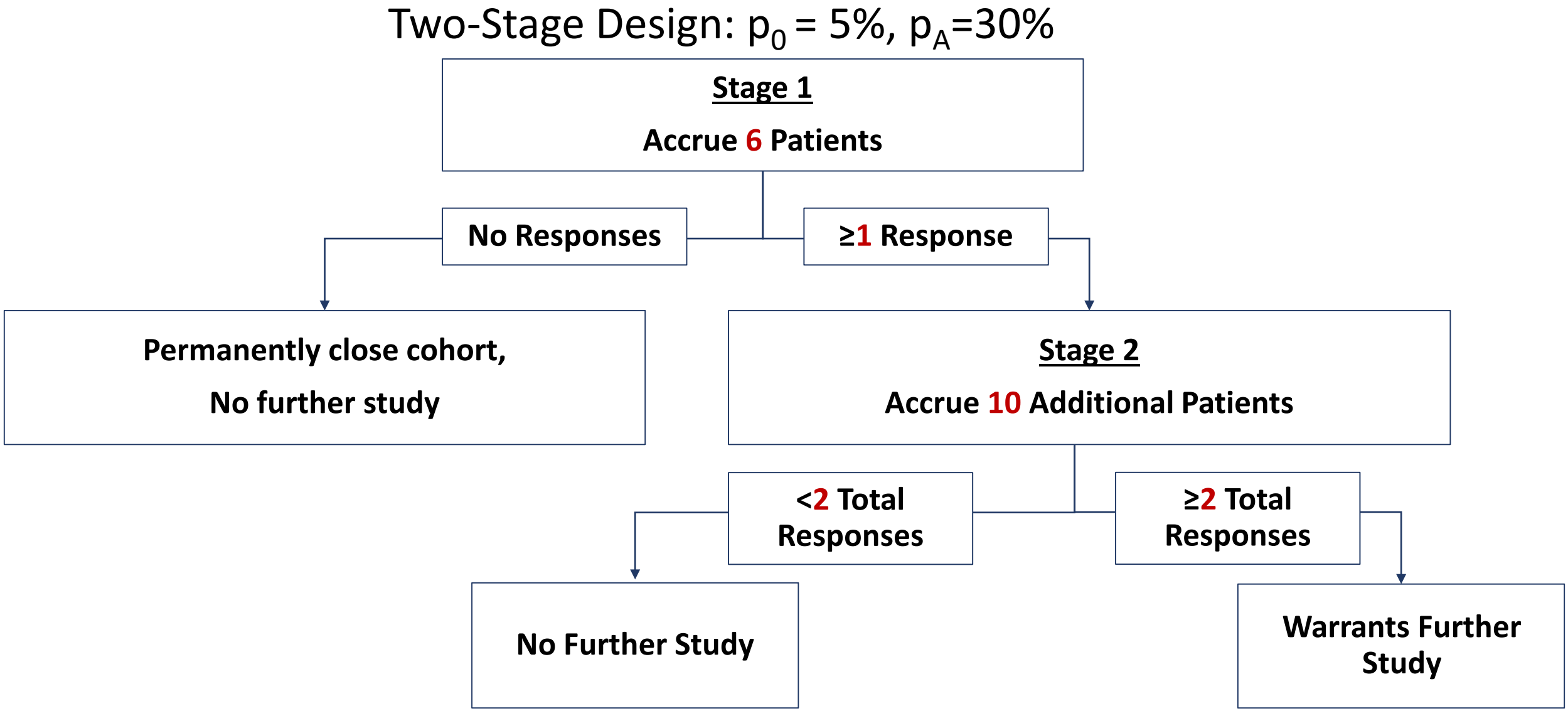
The DART Trial – Overview

- Trial opened Jan. 13, 2017 through NCI National Clinical Trials Network
- Initial protocol specifications
  - Maximum sample size of 334 patients
  - 31 histological cohorts of 16 patients each
  - 1 ‘Tumor of unknown primary’ cohort
  - 33rd Cohort (Other Rare Cancers)

DART

The Cancer Letter 2017

DART Statistical Design: Standardization across cohorts



Rare Tumor (many) cohort challenges

- New Cohort Level Challenges
  - Identifying histology groups in real-time is extremely challenging
  - Real-time monitoring required to ensure no over accrual of a histology
    - Difficult to adhere to DART's standard (and very small) two-stage design for cohorts
- Statistical Design Challenge
  - Is there a way to borrow information across cohorts
  - Shrinkage estimation or Bayes solution (a plan for a secondary analysis) using biomarkers such as tumor mutational burden, immune factors.

New DART Cohorts added over time

Jan 13, 2017

Cohort Number	Histologic Cohort
1	Epithelial tumors of nasal cavity, sinuses, nasopharynx
2	Epithelial tumors of major salivary glands
3	Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location
4	Undifferentiated carcinoma of gastrointestinal (GI) tract
5	Adenocarcinoma with variants of small intestine
6	Squamous cell carcinoma with variants of GI tract (stomach small intestine, colon, rectum, pancreas)
7	Fibromixoma and low grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary
8	Rare Pancreatic tumors including acinar cell carcinoma, mucinous cystadenocarcinoma or serous cystadenocarcinoma
9	Intrahepatic cholangiocarcinoma
10	Extrahepatic cholangiocarcinoma and bile duct tumors
11	Sarcomatoid carcinoma of lung
12	Bronchoalveolar carcinoma lung (a.k.a. adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, or invasive mucinous adenocarcinoma)
13	Non-epithelial tumors of the ovary
14	Trophoblastic tumor
15	Transitional cell carcinoma other than that of the renal, pelvis, ureter, or bladder
16	Cell tumor of the testes and extragonadal germ tumors
17	Epithelial tumors of penis - squamous adenocarcinoma cell carcinoma with variants of penis
18	Squamous cell carcinoma variants of the genitourinary (GU) system
19	Spindle cell carcinoma of kidney, pelvis, ureter
20	Adenocarcinoma with variants of GU system (excluding prostate cancer)
21	Odontogenic malignant tumors
22	Pancreatic neuroendocrine tumor (PNET)
23	Neuroendocrine carcinoma including carcinoid of the lung
24	Pheochromocytoma, malignant
25	Paraganglioma
26	Carcinomas of pituitary gland, thyroid gland parathyroid gland and adrenal cortex
27	Desmoid tumors
28	Peripheral nerve sheath tumors and NF1-related tumors
29	Malignant giant cell tumors
30	Chordoma
31	Adrenal cortical tumors
32	Tumor of unknown primary (Cancer of Unknown Primary; CuP)
33	Not Otherwise Categorized (NOC) Rare Tumors

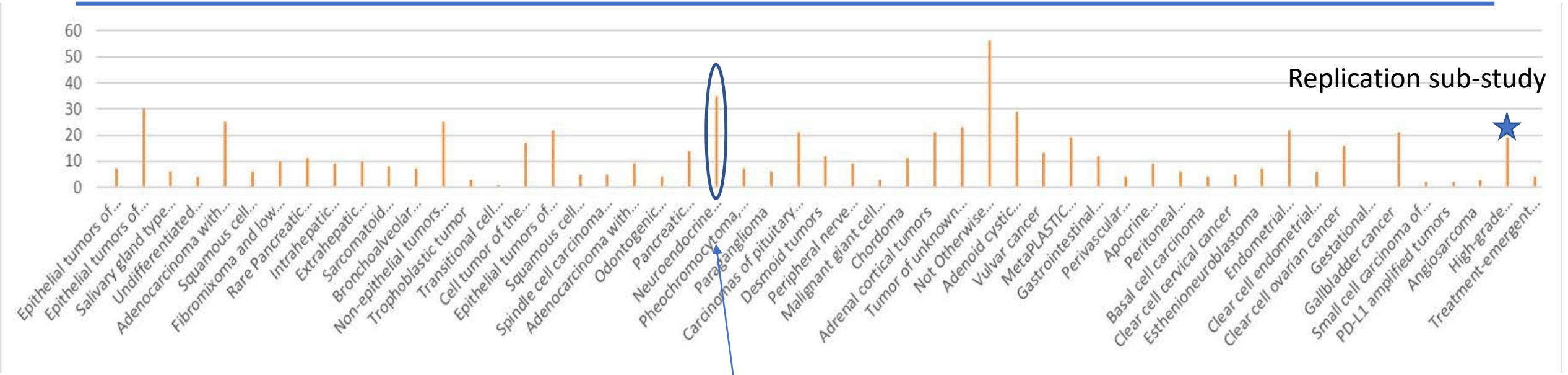
Sept 11, 2017

Cohort Number	Histologic Cohort
34	Adenoid cystic carcinoma
35	Vulvar cancer
36	MetaPlastic carcinoma (of the breast)
37	Gastrointestinal stromal tumor (GIST)

June 11, 2019

Cohort Number	Histologic Cohort
38	Perivascular epithelioid cell tumor (PEComa)
39	Apocrine tumors/Extramammary Paget's Disease
40	Peritoneal mesothelioma
41	Basal cell carcinoma
42	Clear cell cervical cancer
43	Esthenioneuroblastoma
44	Endometrial carcinosarcoma (malignant mixed Mullerian tumors)
45	Clear cell endometrial cancer
46	Clear cell ovarian cancer
47	Gestational trophoblastic disease (GTD)
48	Gallbladder cancer
49	Small cell carcinoma of the ovary, hypercalcemic type
50	PD-L1 amplified tumors
51	Angiosarcoma
52	High-grade neuroendocrine carcinoma
53	Treatment-emergent small-cell neuroendocrine prostate cancer (t-SCNC)

Cohort accrual to DART



<u>COMPLETED COHORT</u>: High grade neuroendocrine tumors response rate >40% in high-grade subgroup, 0% in non-high grade subgroup.

Even within DART a subgroup analysis!

General Observations

- Goal of Master protocols is typically to increase efficiency over a single targeted study
- Plan extensively for the initial launch
- But be flexible to necessary design changes – while still retaining sound statistical principles in the sub-cohorts. In Lung-MAP we moved from uniform statistical design to sub-study specific designs (but a still a limited menu to increase efficiency of development)
- Likely there will be reporting out of sub-study results prior to completion of other sub-studies
- The non-match (Lung-MAP) and the “Other Cancer” (NOC) cohort (DART) were critical in providing options to patients and to adapt to new knowledge about marker frequencies

Lung-MAP and DART

- Lung-MAP
  - Mary Redman PhD *(Lead Statistician Lung-MAP, SWOG Lung)*
  - Katie Minichiello MS, Jim Moon MS,
  - Jieling Miao MS, Michael Wu PhD.
- DART
  - Megan Othus PhD *(Lead Statistician DART, SWOG Leukemia and Rare Tumors)*
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