NCI's Precision Medicine Clinical Trials
A Learning Process

Jeffrey S. Abrams M.D.
Acting Director for Clinical Research, DCTD
Associate Director, CTEP, DCTD
National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

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A Modified Definition of Precision Medicine

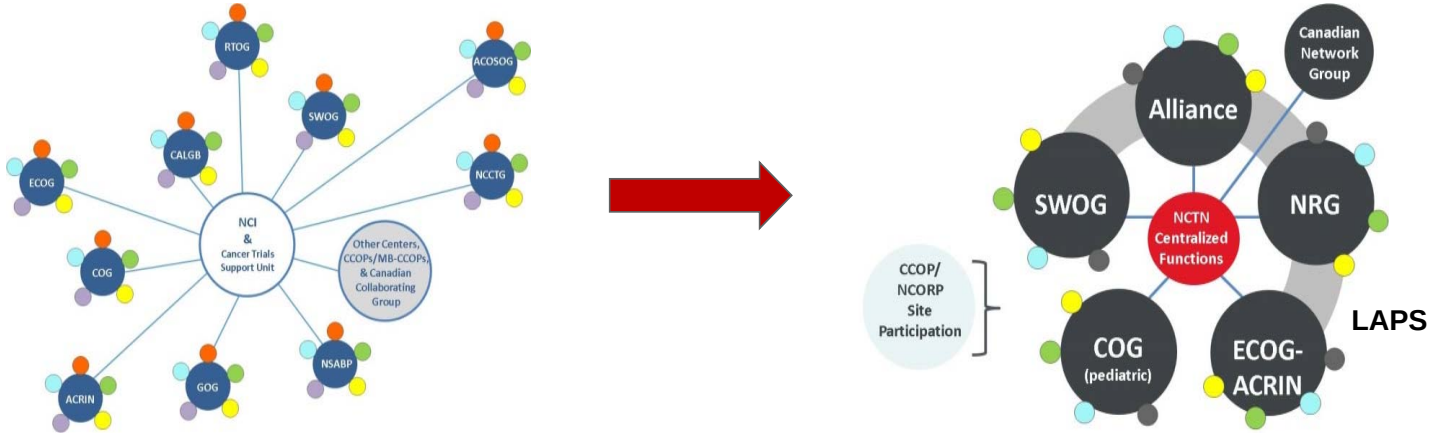
Interventions to prevent, diagnose, or treat a disease (e.g., cancer), based on a molecular and/or mechanistic understanding of the causes, pathogenesis, and/or pathology of the disease. Where the individual characteristics of the patient are sufficiently distinct, interventions can be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Modified by D. Lowy, M.D. from: IOM's Toward Precision Medicine, 2011

Unique features/goals of the NCI's Precision Medicine Trials

- Requires screening of large numbers of cancer patients to find those with the appropriate molecular abnormality
- Demands sophisticated high throughput testing with rapid turnaround for labs
- Is logistically challenging for sites as multiple treatment arms are included in a single trial or testing platform
- **Overarching goal:** With more precisely defined and limited molecular subgroups in each tumor phenotype, precision medicine trials should enable more rapid discovery of therapeutic signals and hence the ability to move from early phase trials to definitive trials expeditiously.

NCTN as a Network in the Era of Precision Medicine



Activated:

- **Lung-MAP (S1400) – led by SWOG**
- **ALCHEMIST (A151216) – led by Alliance and ECOG-ACRIN**
- **NCI MATCH – led by ECOG-ACRIN**

In development:

- **NCI Pediatric MATCH – led by COG**

… It takes a network

…

Molecular Analysis for Therapy CHoice

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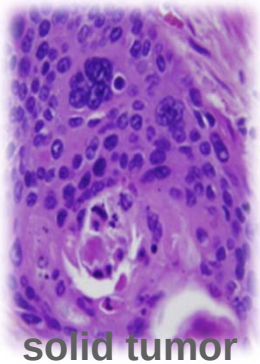
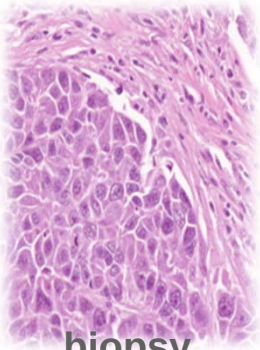
ECOG-ACRIN cancer research group
Reshaping the future of patient care

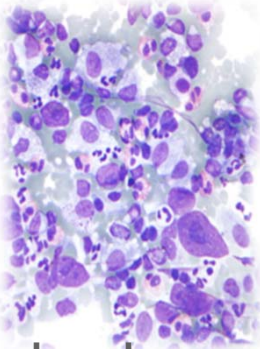


solid tumor

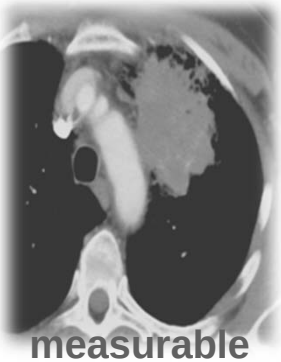
prior therapy



biopsy



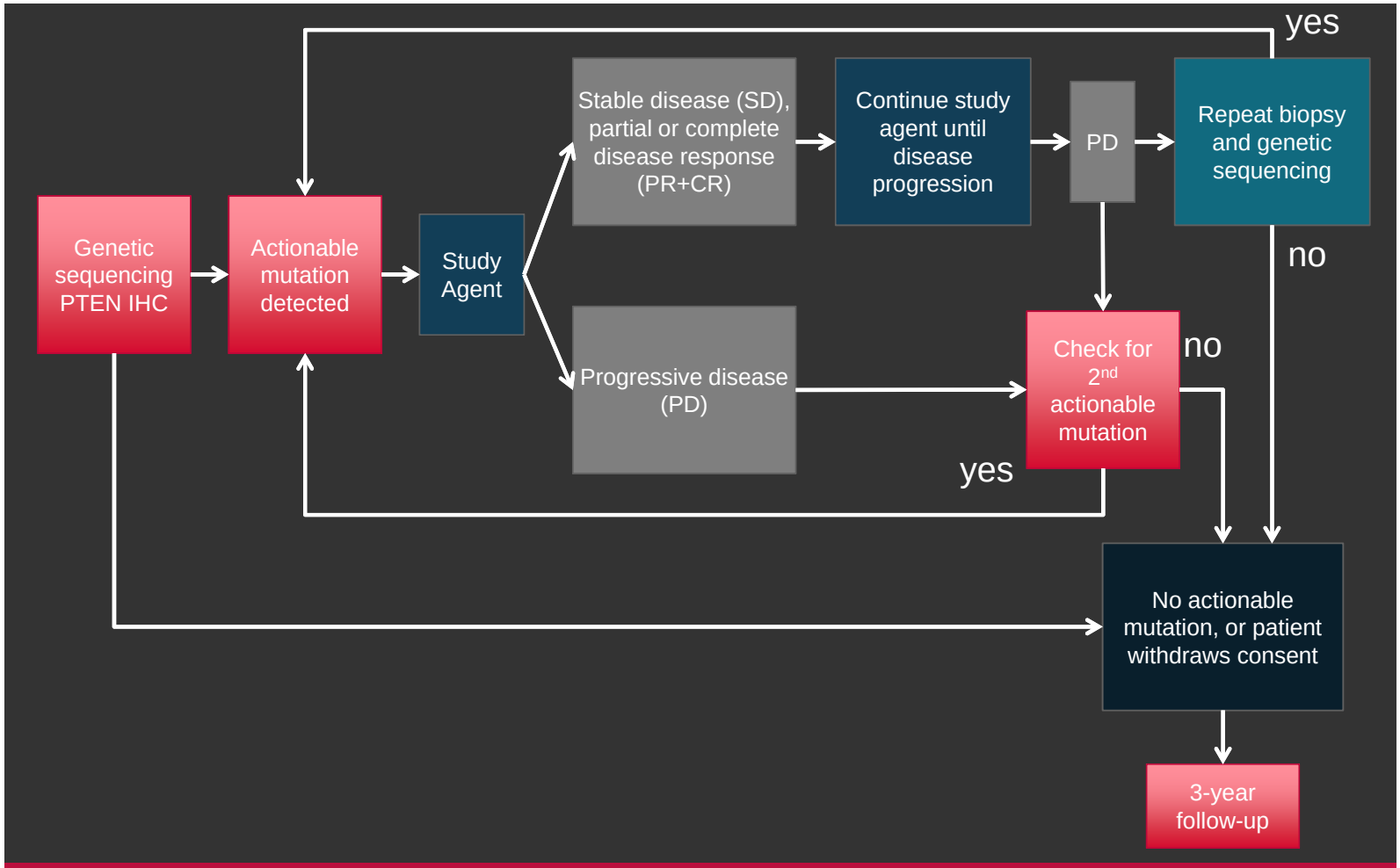
lymphoma



measurable

ECOG PS 0,1

Eligibility


yes
Stable disease (SD), partial or complete disease response (PR+CR)
Continue study agent until disease progression
PD
Repeat biopsy and genetic sequencing
Genetic sequencing PTEN IHC
Actionable mutation detected
Study Agent
no
Progressive disease (PD)
Check for 2nd actionable mutation
no
yes
No actionable mutation, or patient withdraws consent
3-year follow-up

SCHEMA

Gene variant is credentialed for selection of an approved anticancer drug

Gene variant is an eligibility criterion for an ongoing clinical trial for that drug, or the variant was identified in an N-of-1 response

Preclinical inferential data:

- **Models with variant respond; without variant do not respond;**
- **Gain of function mutation demonstrated in preclinical model;**
- **Loss of function or stop codon in a pre-clinical model (such as a tumor suppressor gene or molecular pathway inhibitor)**

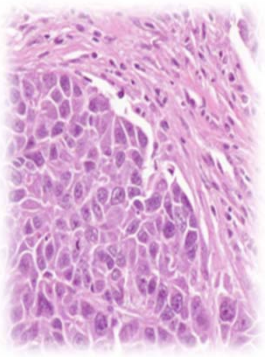
TARGET LEVELS of EVIDENCE

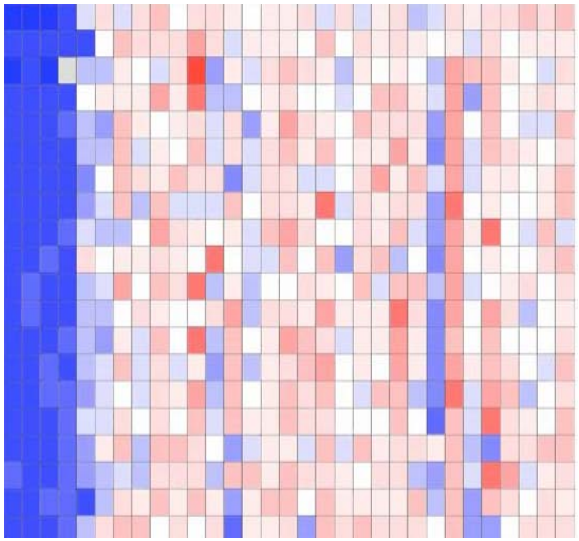
Agent has Food & Drug Administration approval for any indication for that target

Agent has met an actionable clinical endpoint (objective response or survival) with evidence of target inhibition

Agent has shown evidence of clinical activity with evidence of any level target inhibition

DRUG SELECTION





Hotspot genes, n=73

ABL1	GNA11	MYD88
AKT1	GNAQ	NFE2L2
ALK	GNAS	NPM1
AR	HNF1A	NRAS
ARAF	HRAS	PAX5
BRAF	IDH1	PDGFRA
BTK	IDH2	PIK3CA
CBL	IFITM1	PPP2R1A
CDK4	IFITM3	PTPN11
CHEK2	JAK1	RAC1
CSF1R	JAK2	RAF1
CTNNB1	JAK3	RET
DDR2	KDR	RHEB
DNMT3A	KIT	RHOA
EGFR	KNSTRN	SF3B1
ERBB2	KRAS	SMO
ERBB3	MAGOH	SPOP
ERBB4	MAP2K1	SRC
ESR1	MAP2K2	STAT3
EZH2	MAPK1	U2AF1
FGFR1	MAX	
FGFR2	MED12	
FGFR3	MET	
FLT3	MLH1	
FOXL2	MPL	

Full-gene coverage, n=26

APC
ATM
BAP1
BRCA1
BRCA2
CDH1
CDKN2A
FBXW7
GATA3
MSH2
NF1
NF2
NOTCH1
PIK3R1
PTCH1
PTEN
RB1
SMAD4
SMARCB1
STK11
TET2
TP53
TSC1
TSC2
VHL
WT1

Copy Number Variants, n=49

ACVRL1	IGF1R
AKT1	IL6
APEX1	KIT
AR	KRAS
ATP11B	MCL1
BCL2L1	MDM2
BCL9	MDM4
BIRC2	MET
BIRC3	MYC
CCND1	MYCL
CCNE1	MYCN
CD274	MYO18A
CD44	NKX2-1
CDK4	NKX2-8
CDK6	PDCD1LG2
CSNK2A1	PDGFRA
DCUN1D1	PIK3CA
EGFR	PNP
ERBB2	PPARG
FGFR1	RPS6KB1
FGFR2	SOX2
FGFR3	TERT
FGFR4	TIAF1
FLT3	ZNF217
GAS6	

Fusion drivers, n=22

ALK
RET
ROS1
NTRK1
NTRK3
FGFR1
FGFR2
FGFR3
BRAF
RAF1
ERG
ETV1
ETV4
ETV5
ABL1
AKT3
AXL
EGFR
ERBB2
PDGFRA
PPARG

ONCOMINE

Status and History of NCI-MATCH Trial

- **Trial opened August 12, 2015, with 10 treatment arms.**
- **Trial temporarily closed to new accrual November 11, 2015 for built-in interim analysis.**
- **795 patients screened between August 2015 opening and November 2015 temporary closure (3 month period).**
- **Original estimate of 50 screens per month greatly surpassed (100/week during latter period).**
- **Approx. 900 approved sites**
- **192 active sites (at least 1 patient)**
  - **Active : 2/3 community, 1/3 academic**
- **Trial re-opened May 31, 2016, with 24 treatment arms.**

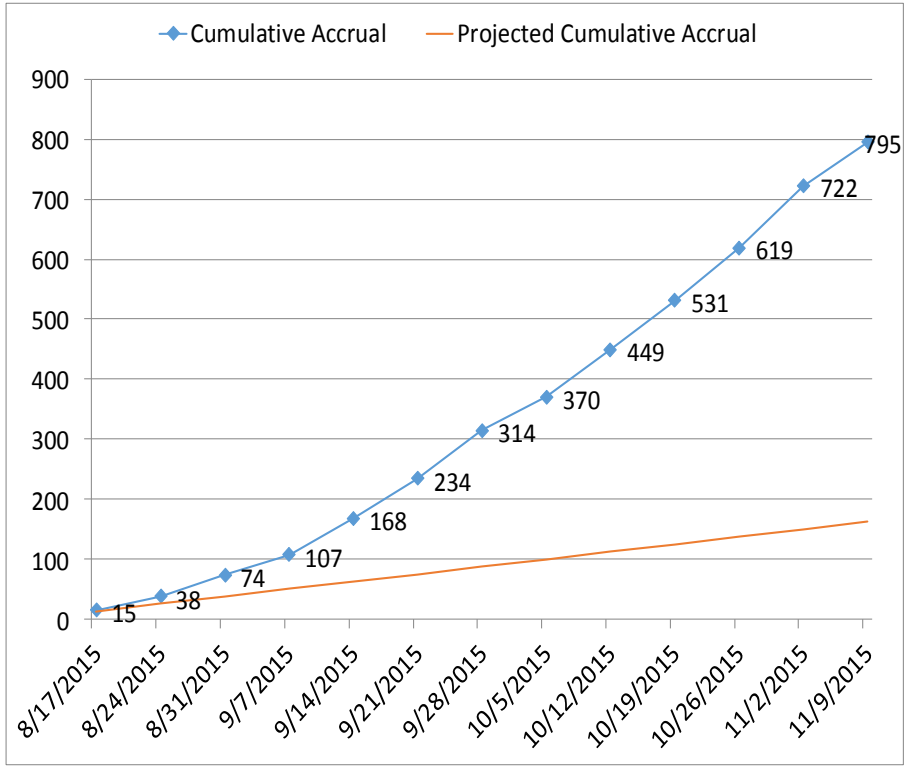
NCI-MATCH Primary Disease Sites

Common Cancers	Enrolled for Screening (N=795)	Screened (N=645)	Assigned to Rx (N=33)
Colorectal	104 (13.1%)	84 (13.0%)	6 (18.2%)
Breast	96 (12.1%)	84 (13.0%)	2 (6.1%)
Non-Small Cell Lung	62 (7.8%)	48 (7.4%)	5 (15.2%)
Prostate	20 (2.5%)	17 (2.6%)	1 (3.0%)
Common Cancers Subtotal	**282 (35.47%)**	**233 (36.12%)**	**14 (42.42%)**

Uncommon Cancers			
Ovarian	89 (11.2%)	72 (11.2%)	6 (18.2%)
Pancreas (Adeno/NOS)	43 (5.4%)	34 (5.3%)	--
Head and Neck[1]	38 (4.8%)	34 (5.3%)	--
Endometrial/Uterine (Non-Sarcoma)	34 (4.3%)	27 (4.2%)	--
Esophageal/GE Junction/Gastric	31 (3.9%)	28 (4.3%)	4 (12.1%)
Neuroendocrine[2]	27 (3.4%)	20 (3.1%)	2 (6.1%)
Cholangio	24 (3.0%)	22 (3.4%)	1 (3.0%)
Bladder/UT	21 (2.6%)	14 (2.2%)	1 (3.0%)
Endometrial/Uterine Sarcoma[3]	20 (2.5%)	16 (2.5%)	--
Small Cell Lung	16 (2.0%)	14 (2.2%)	--
Other[4]	151 (19.0%)	116 (18.0%)	3 (9.1%)
Primary Site Not Specified	19 (2.4%)	15 (2.3%)	2 (6.1%)
Uncommon Cancers Subtotal	**513 (64.53%)**	**412 (63.87%)**	**19 (57.57%)**

[1] Salivary Gland = 3
[2] NOS = 18, Pancreas = 6, Carcinoid = 3
[3] Uterine Carcinosarcoma = 7
[4] Key Other Types: Lymphoma = 9, Brain Tumor = 9, Melanoma = 9

NCI-MATCH Weekly Accruals Far Exceeded Projections



Projected 50 Cases/Month at Start and

Gradual Ramp-up in Year 1

NCI-MATCH Expanded to 24 Arms May 31, 2016

Arm / Target	Drugs(s)
A EGFR mut	Afatinib
B HER2 mut	Afatinib
C1 MET amp	Crizotinib
C2 MET ex 14 sk	Crizotinib
E EGFR T790M	AZD9291
F ALK transloc	Crizotinib
G ROS1 transloc	Crizotinib
H BRAF V600	Dabrafenib+trametinib
I PIK3CA mut	Taselisib
N PTEN mut	GSK2636771
P PTEN loss	GSK2636771
Q HER 2 amp	Ado-trastuzumab emtansine

Arm / Target	Drug(s)
R BRAF nonV600	Trametinib
S1 NF1 mut	Trametinib
S2 GNAQ/GNA11	Trametinib
T SMO/PTCH1	Vismodegib
U NF2 loss	Defactinib
V cKIT mut	Sunitinib
W FGFR1/2/3	AZD 4547
X DDR2 mut	Dasatinib
Y AKT1 mut	AZD 5363
Z1A NRAS mut	Binimetinib
Z1B CCND1,2,3 amp	Palbociclib
Z1D dMMR	Nivolumab

National Cancer Institute

MATCH STATUS: SINCE MAY 30, 2016
24 arms (expected match rate 23%)

- **Enrolled: 2141 (as of 10/23)**
- **Median time to specimen receipt 7 days**
- **Specimens submitted 1884 (88%)**
- **Assays completed: 1374/1460 (94%); median TAT 14 days (13% > 28 days)***
- **Assigned to one of 24 arms: 311 (23%)**
- **Enrolled on arm: 217; 77% of assigned (exclude most recent 3 weeks)**
- **2 arms at enrollment cap (follow-on arms drafted)**
- **6 arms awaiting submission**
- **4 additional arms in development for next "wave"**
- **Expect 11-12 current arms to complete with screening 5000-6000 (based on past experience)**
- **Rare variants initiative will add from FoundationOne, Caris, MDACC, MSKCC assays with MATCH confirmation (next amendment) for the other and potentially future arms**

*sample insufficient; inadequate documentation

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What we know - On the plus side:

- **MATCH is popular**
- **Match rate of successful biopsies is 23% (as predicted for 24 arms)**
- **Rare variants and rare tumors are out there, only successfully screened in large scale trial**
- **Labs are working well; 93% of biopsies are successful**
- **Academic sites can propose arms - open**
- **Sites are learning how to do these trials (80% biopsies successful, 77% enrollment of assigned patients)**
- **More patients are able to get profiling done**

What we know - On the minus side:

- **20% of Biopsies as currently done are not really fit for rapid turnaround (slows entire process)**
- **It takes several months to add arms, even though we thought we designed a "nimble trial"**
- **Rare variants are rare – need help finding them**
- **The rapid pace of accrual on MATCH means we won't have results for awhile**
- **Need combinations to be tested**

Logistics

- **MATCH, as one trial, frequently requires considerable work, every time something is changed**
- **Current processes make it difficult to be “nimble”**
- **Would basket trials be more efficient in this way? They would have about 3 dedicated tissue arms, and an “other”; but not changes in drugs.**

NCI-Pediatric MATCH
APEC1621

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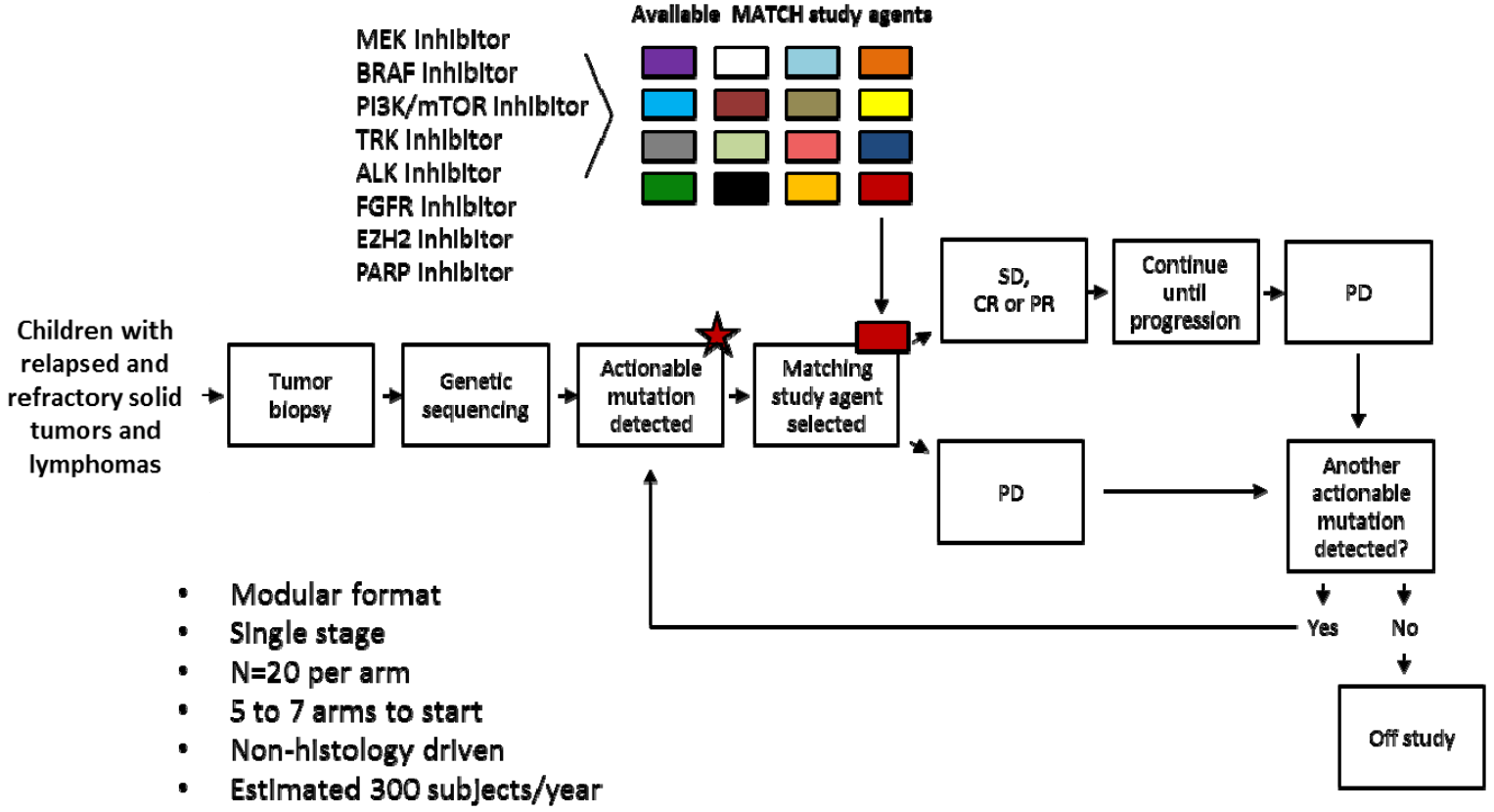
NCI-Pediatric MATCH Study



- Modular format
- Single stage
- N=20 per arm
- 5 to 7 arms to start
- Non-histology driven
- Estimated 300 subjects/year

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Hypothesis

By identifying genetic changes affecting pathways of interest in refractory and recurrent pediatric cancers, we will be able to deliver targeted anticancer therapy that produces a clinically meaningful objective response rate.

NCI-Pediatric MATCH Treatment Arms

Agent Class	aMOI Frequency	Subarm Chair	Protocol ID
LOXO 101	2-3%	Katie Janeway	APEC1621-A
Erdafitinib	2-3%	Jae Cho	APEC 1621-B
Tazemetostat	2-3%	Susan Choi	APEC 1621-C
LY3023414	5-10%	Ted Laetsch	APEC 1621-D
Selumetinib	10-20%	Carl Allen	APEC 1621-E
Ensartinib	2-3%	Meredith Irwin	APEC 1621-F
Vemurafenib	5%	Aerang Kim	APEC 1621-G
Olaparib	2-3%	Julia Glade Bender	APEC 1621-H

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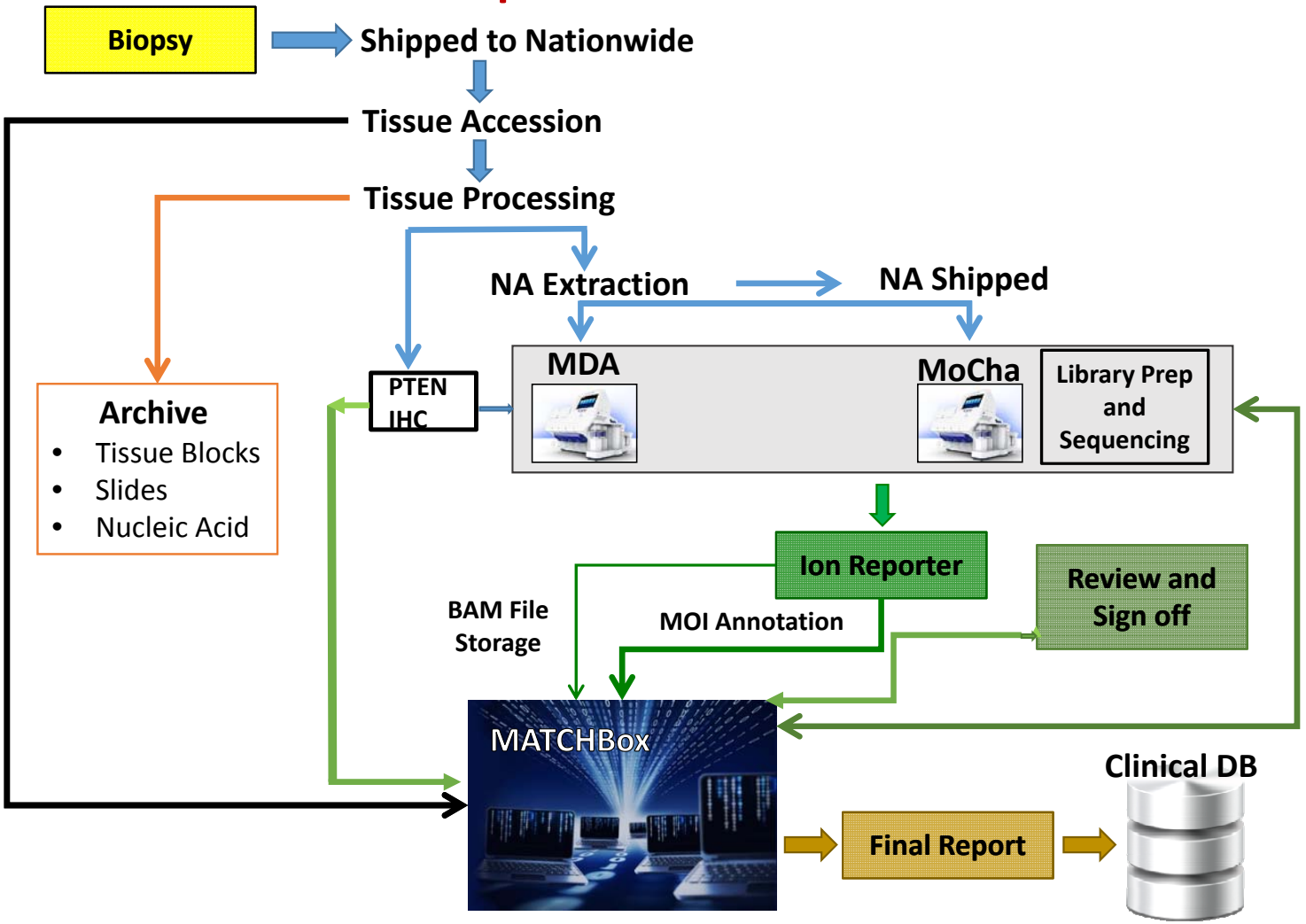
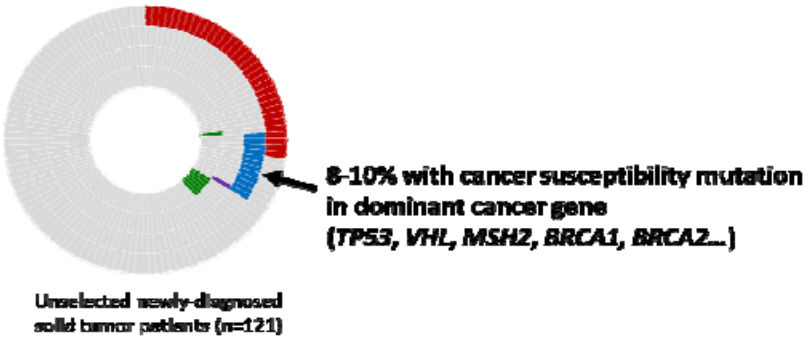
NCI-MATCH Specimen Work Flow Schema



Key Study Considerations

- Requirement for biopsy: must obtain tissue post-relapse for study eligibility except for brain stem glioma patients
  - Rationale: Tumor genomes evolve. To identify potential targets for therapy a "current" relapsed sample is needed
- Most patients screened will be biomarker negative and will not match to a treatment arm
- Evaluation of germline DNA



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NCI-Pediatric MATCH Milestones

- **Clinical sequencing plan in place; pipeline validation using pediatric samples to begin**
- **Detailed plan for collection, processing, QC, distribution of clinical and research tissue and blood**
- **Customized informatics system based on the MATCHBox program from the adult NCI MATCH to assign patients to treatment based on gene mutation, disease, and patient characteristics**
- **Procedures for analysis of germline DNA (using patient's peripheral blood) to see if any of the molecular changes identified in the tumor are present in the patient's germline**
- **First six concepts approved and subprotocols in various stages of development after individual calls with pharmaceutical companies to finalize actionable mutations of interest; additional two concepts under development**
- **Contract agreements with pharmaceutical companies for best drugs available to most effectively target childhood cancer mutations**
- **CDRH device determination completed (NSR); Presubmission call with CDRH**
- **Education and discussion with advocates**

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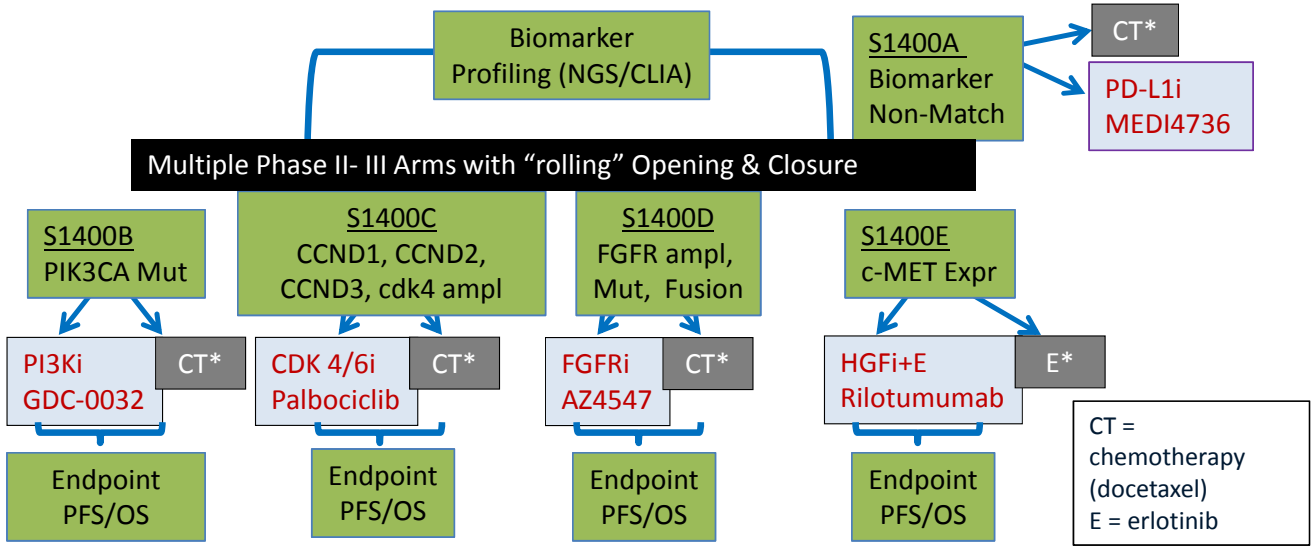
Master Lung Protocol: A Biomarker-Driven Master Protocol for Previously-Treated Squamous Cell Lung Cancer

Vali Papadimitropoulou, Roy Herbst, Mary Redman, David Wholley, Stacey Adam, Ellen Sigal, Jeff Allen, Shakun Malik, Holly Massett

Original Trial Schema (Activated Jun 16, 2014)



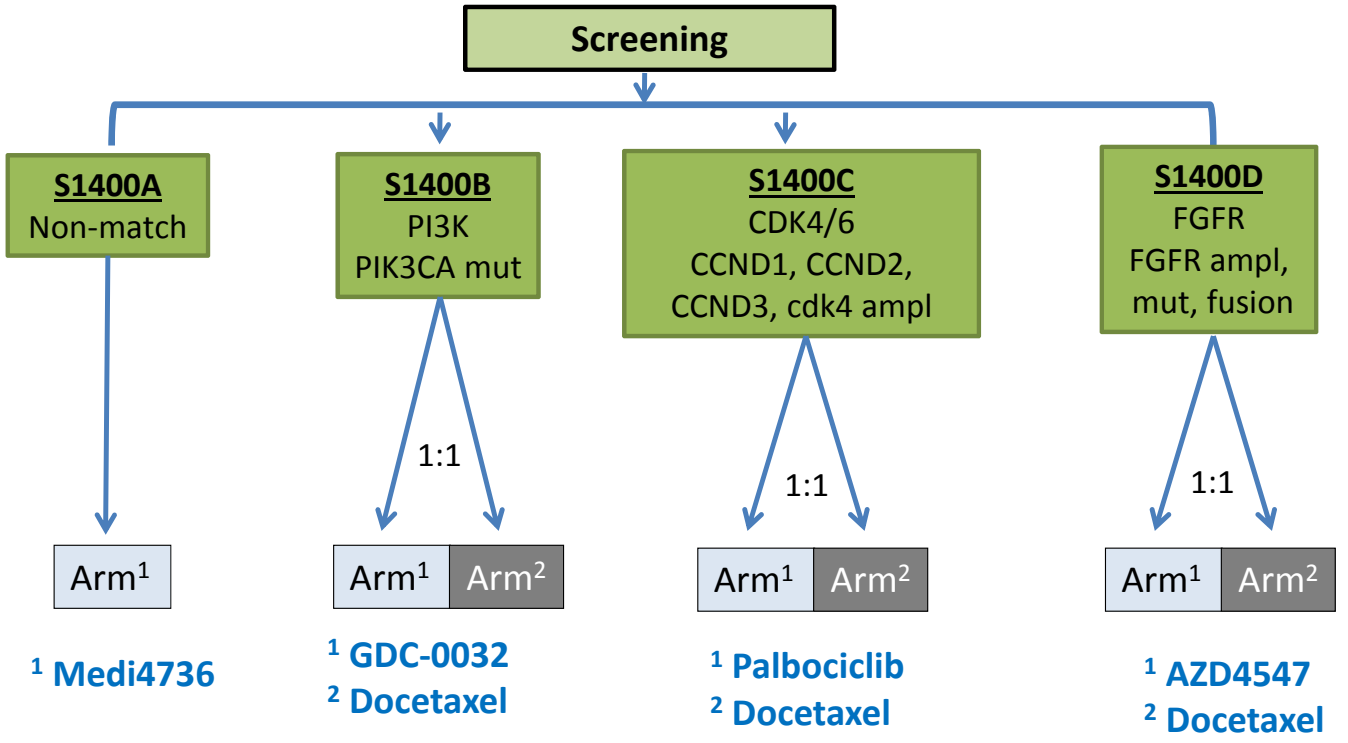
Sub-studies assigned based on biomarker results, patients with multiple biomarkers randomly assigned to sub-study. Investigators/patients will only be notified of sub-study assignment

Overview of Changes Through Revision #2

- **Closure of S1400E (November 2014)**
- **Revision # 1 (January 2015)**
  - Eligibility clarifications
  - Relaxation of timing from study assignment to registration
- **Revision # 2 (May 2015)**
  - Allow 2nd and greater lines of therapy
  - Add in pre-screening during 1st line therapy
  - S1400A design modification to single arm

LUNG-MAP

Modified Trial Schema
[Revision # 2 Activated 5/26/15]



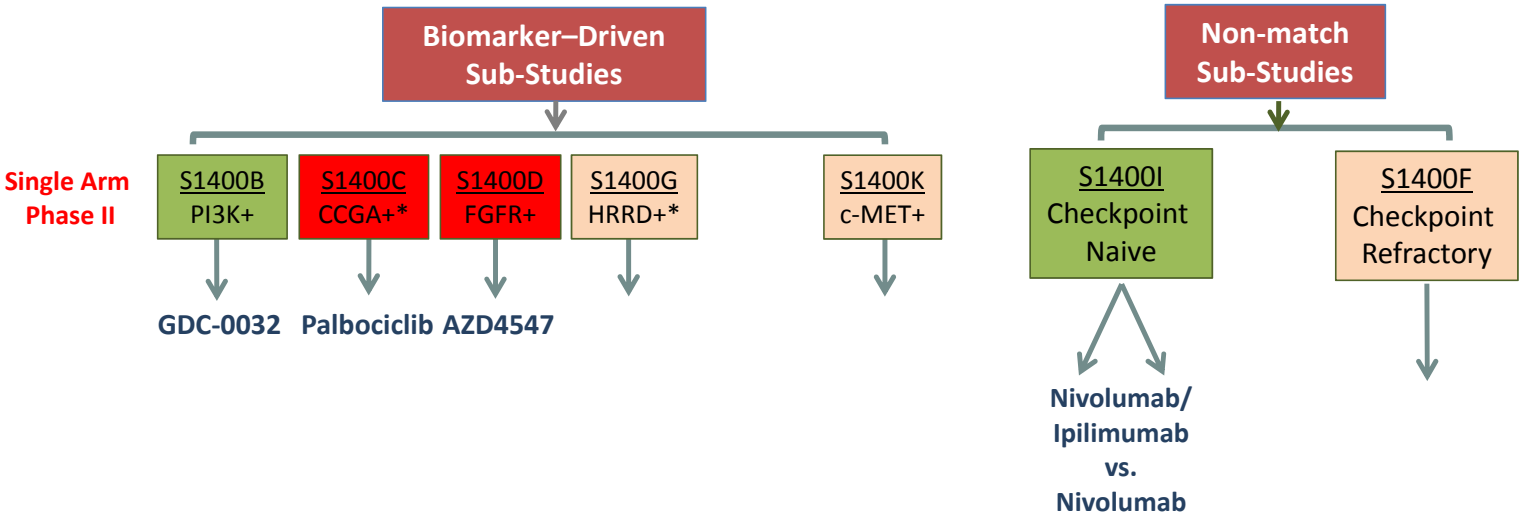
LUNG-MAP

Responsive Revisions to Lung MAP Revisions #3 and #4

- **Immunotherapy is changing the landscape in lung cancer**
  - **Nivolumab approved for 2nd line**
- **Revisions # 3 and #4 (Fall 2015/Early 2016)**
  - Add checkpoint inhibitor combinations: S1400I (nivolumab + ipilimumab)
  - S1400B, S1400C, S1400D modified to single-arm Phase II sub-studies to be followed by randomized Phase III studies if relevant and feasible

LUNG-MAP

Current Protocol Schema



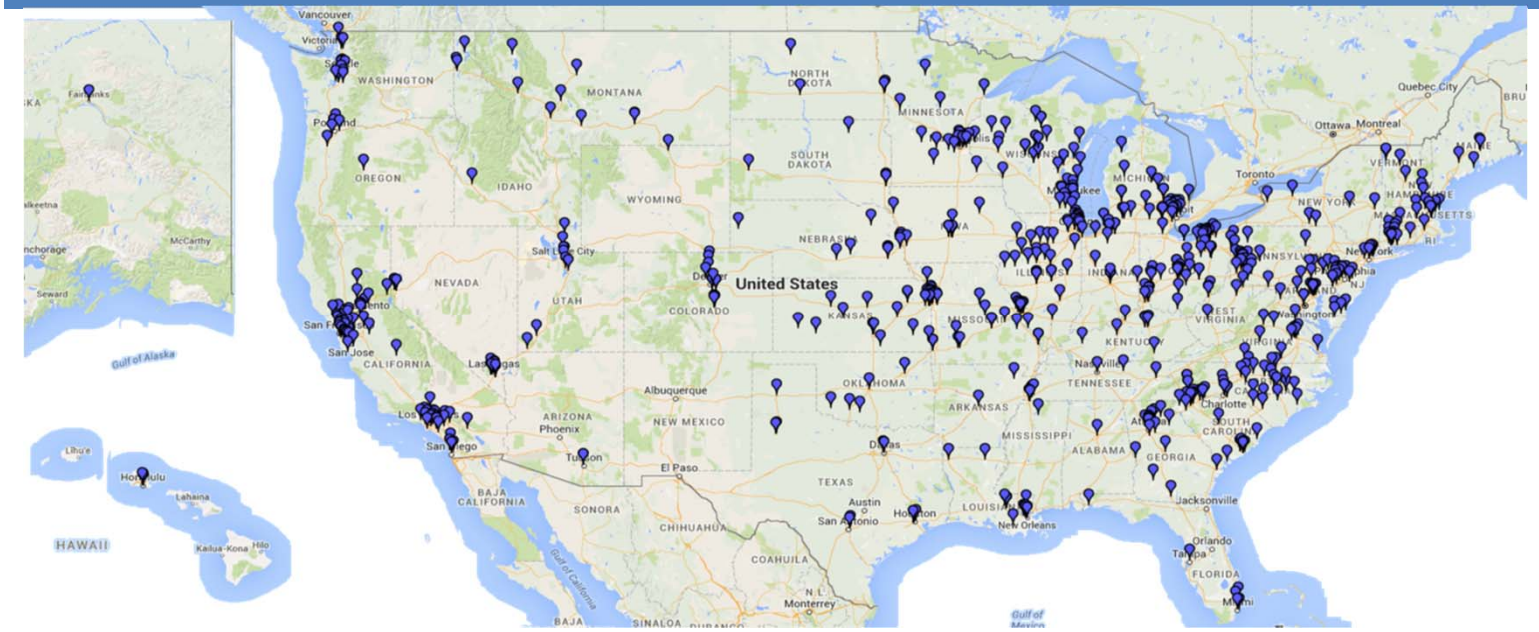
Two new sub-studies – S1400G and S1400F – added within 6 months
Additional Sub-studies – S1400J and S1400K expected within 6-9 month period
*CCGA = Cell Cycle Gene Alternation, HRRD = Homologous Recombinant Repair Deficiency,

Design Option #2: Single Arm Phase 2, Followed by Randomized Phase 3, if Feasible

- Primary objective of the Phase II component is to evaluate ORR. The sample size is 40-50 patients; a response rate of 25% is needed to qualify for further evaluation.
- A follow-on randomized Phase III trial will be considered feasible if the expected duration of accrual is approximately ≤3 years – about 140-190 pts with a HR=0.57 for OS.
- If the Phase II data meet the definition of a positive Single Arm Phase II, but a Phase III trial is not feasible, accrual to the Single Arm Phase II may be expanded

Where Are We Now?

(As of 10/21/16)



IRB Approvals:

- **702 sites**
- **270 sites with at least 1 patient accrued**

Patient registrations/status:

- **1052 patients enrolled in screening phase (<u>S1400</u> registrations)**
  - **703 screened at PD**
  - **349 pre-screened**
- **771 patients notified of sub-study assignment**
  - **619 screened at PD**
  - **152 pre-screened**
- **385 patients registered to a sub-study**

Overview of Upcoming Changes

- **Revision #6 - S1400G – Targeting 11/16 Activation**
  - **S1400G: a biomarker-driven study including a PARP inhibitor**
- **Drug shipping to Canada resolved – Canada Ready to be Fully Activated**
- **Pembrolizumab first-line approval 10/25/16 in PD-L1+ NSCLC (KEYNOTE-024)**
  - **Potential impact on Lung-MAP accrual**
- **Proposed Revision #7 – S1400F – Targeting 01/01/17 Activation**
  - **S1400F: a non-match study for patients whose tumors progressed on prior nivolumab**
- **Proposed Revision #7 (Submit Early 2017) –S1400K: a biomarker-driven study including a cMet antibody**

ALCHEMIST

Adjuvant **L**ung **C**ancer Enric**h**m**e**nt
Marker **I**dentification and **S**equencing
Trial

ALCHEMIST

- A group of four clinical trials for patients with completely resected early stage non-small cell lung cancer

1. Screening trial (A151216): Eligible patients will have their tumor tissue tested for genetic changes in ALK or EGFR, and will have additional tissue submitted for investigational genomic analysis
2. Erlotinib tx trial (A081105): Erlotinib vs. placebo will be evaluated in patients with activating EGFR mutations following standard of care adjuvant therapy
3. Crizotinib tx trial (E4512): Crizotinib vs. placebo will be evaluated in patients harboring the Anaplastic Lymphoma Kinase (ALK) fusion protein following standard of care adjuvant therapy
4. Nivolumab vs. observation will be evaluated in all comers despite their PDL1 status which will only be used as a stratification factor. In addition a cohort of squamous cell lung cancer patients are added

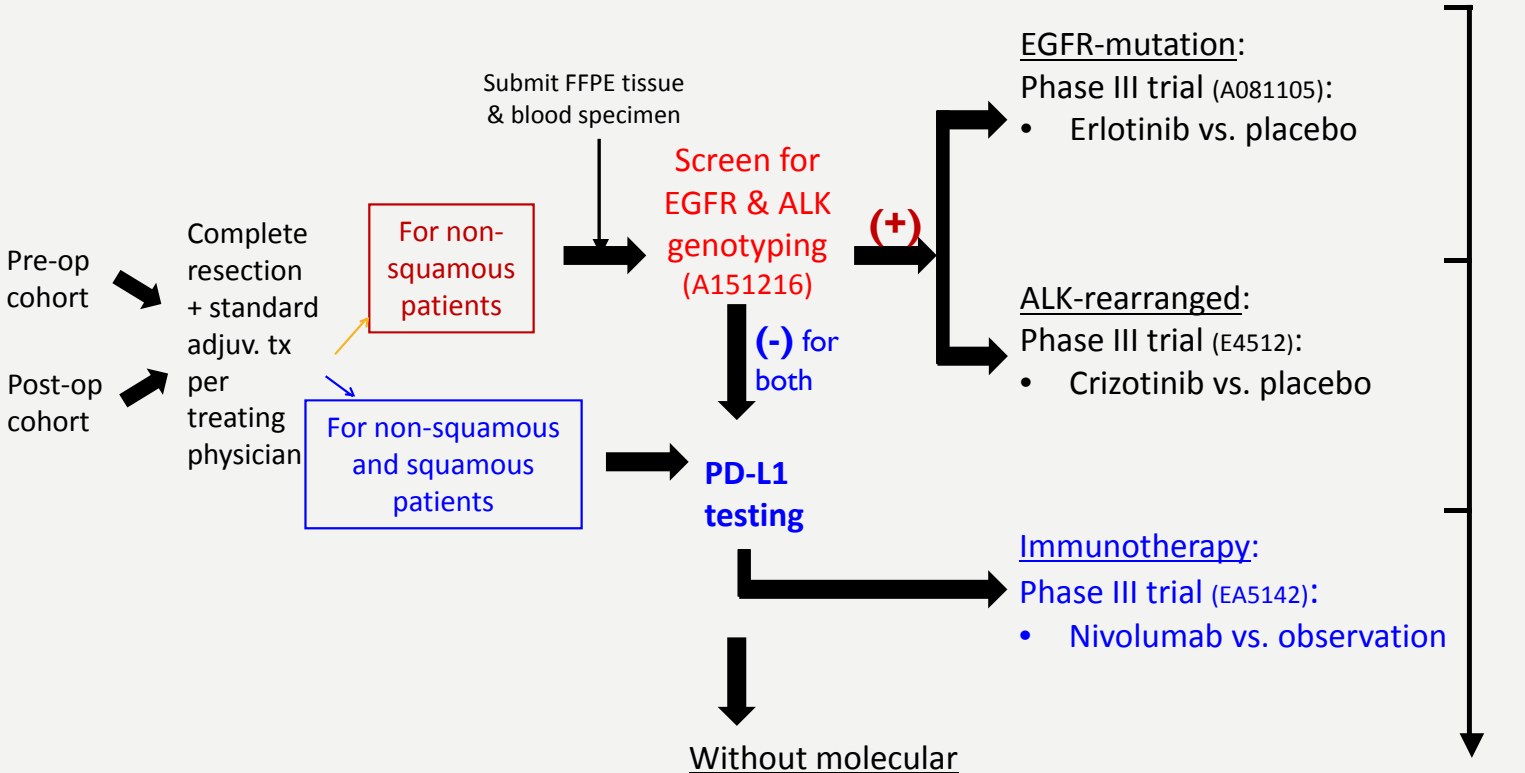
ALCHEMIST RATIONALE

- Molecularly targeted therapy has improved outcomes within NSCLC advanced disesase:
  - erlotinib in NSCLC (target: EGFR activating mutation)
  - crizotinib in NSCLC (target: EML4-ALK)
- Immunotherapy has improved outcomes as well for advanced NSCLC
  - PD-1 inhibitors in front-line and second-line NSCLC
- This has lead to routine testing of EGFR mutations and ALK rearrangements…However, in advanced diseases, patients treated with Tyrosine Kinase Inhibitors eventually develop resistance.
- ALCHEMIST is studying whether or not treatment based on genotype improves cure rates in earlier stage NSCLC for those with mutations, and whether PD-1 checkpoint inhibition can do the same for those w/o mutations

ALCHEMIST SCHEMA – NEW

Non-squamous & Squamous NSCLC

Clinical/Pathologic Stage IB (≥ 4cm), II, IIIA, Post-Op neg. surgical margins



Red = same as current schema

Blue = changes to schema

TRIAL PROTOCOL DETAILS – STATS DESIGN

Trial Category	ALCHEMIST SCREEN Component A151216	ALCHEMIST - ALK E4512	ALCHEMIST – EGFR A081105	ALCHEMIST Nivo vs Obs EA5142
Target	Registry/Intervention with biopsy at recurrence	ALK+	EGFRmut	PDL-1 for stratification
Prevalence	all comers	~5%	~10%	all comers
Total Sample Size	6000 – 8000	378 (5% ineligible)	430 (5% ineligible)	714
Primary Endpoint	N/A	Overall Survival	Overall Survival	Co-primary OS & DFS
Power	N/A	80%	85%	81%
One-sided α	N/A	0.025	0.05	0.025
Hazard Ratio	N/A	0.67	0.67	0.70

ALCHEMIST: SCREENED POPULATION

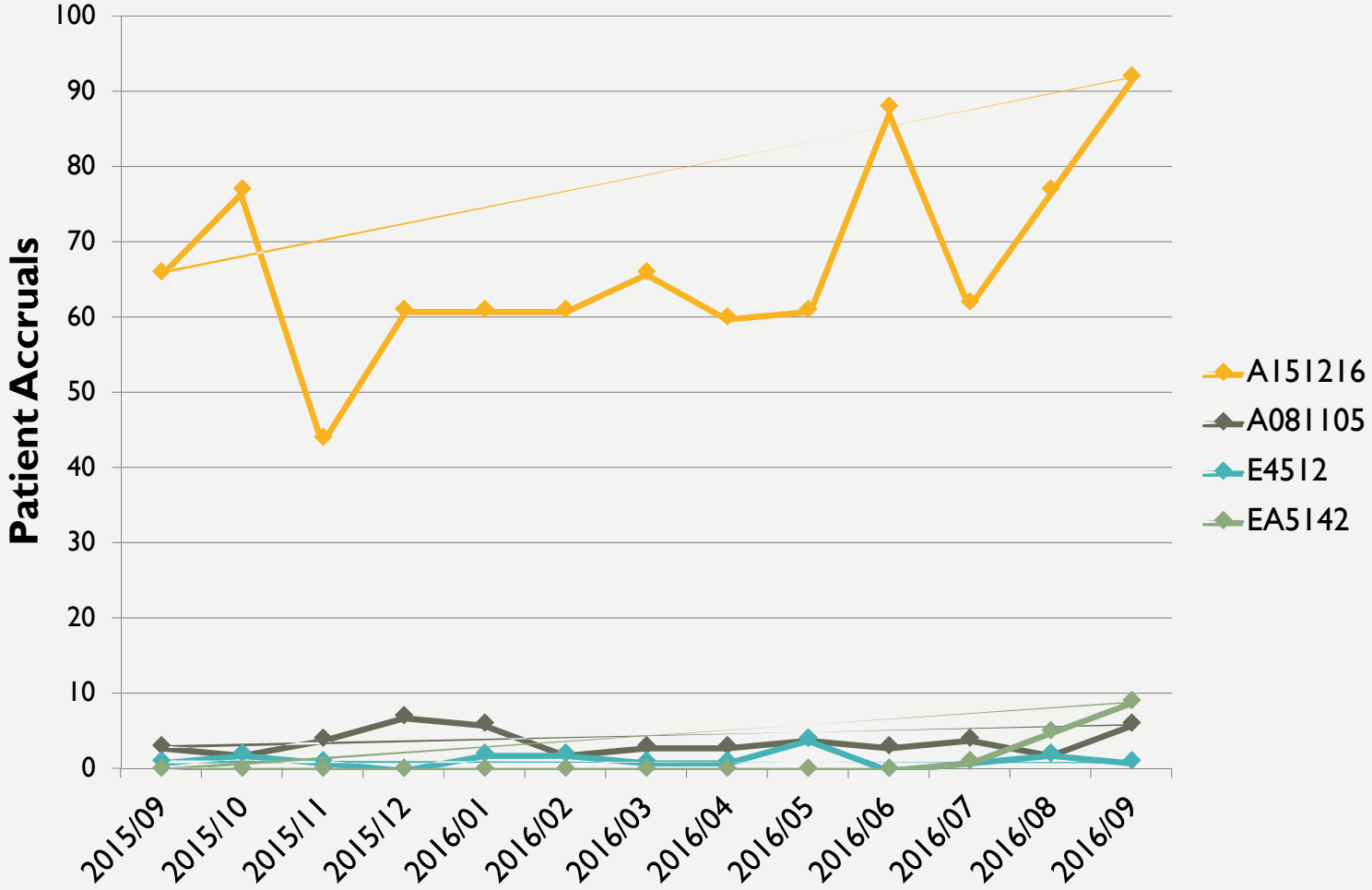
- Research component addressing both screen positive and negative patients
  - Screen positive: Directed to marker-specified clinical trial
  - Screen negative: Minimal follow-up on standard therapy
- All:
  - Epidemiological questionnaire
  - DNA sampling from tumor (preop or postop) and buffy coat
  - Collection of plasma for circulating DNA
  - Follow for clinical outcome
  - Biopsy at progression – research genomics

- Provide public resource w/ genomic characterization tied to detailed clinical annotation & longterm f/u data

Trial Metrics: ALCHEMIST

Metric	Value
Total # sites open for A151216	1059
Total pts registered to A151216	1288
Total pts registered to A081105	71
Total pts registered to E4512	25
Total pts registered to EA5142	21

Monthly ALCHEMIST Accruals



ENROLLMENT TO A081105 BY EGFR POSITIVE STATUS BY CENTRAL TESTING AS OF 10/19/2016

A081105 Enrollment Status	N (%)
Enrolled	70* (38%)
Not Enrolled	**~50-60%**
Ineligible: outside of enrollment window	8 (4%)
Ineligible: recurrent disease	5 (3%)
Ineligible: other reason**	9 (5%)
Not interested: concern with randomization	4 (2%)
Not interested: does not want further treatment	19 (10%)
Not interested: other reason**	25 (13%)
Other reason**	11 (6%)
Pending (Potentially eligible / have not yet completed adjuvant therapy)	35 (19%)
Total	**186/1059= 17.5%**

*1 pt had other EGFR mutation;
**Other includes more than one reason from the above, and/or ones not included above

ENROLLMENT TO E4512 BY ALK REARRANGEMENT STATUS BY CENTRAL TESTING AS OF 10/19/2016

E4512 Enrollment Status	N (%)
Enrolled	25* (46%)
Not Enrolled	**~50%**
Ineligible: recurrent disease	2 (4%)
Ineligible: other reason**	4 (7%)
Not interested: does not want further treatment	4 (7%)
Not interested: other reason**	4 (7%)
Other reason**	6 (11%)
Pending (Potentially eligible / have not yet completed adjuvant therapy)	9 (17%)
Total	**54/1059=5%**

*2 pts with no results yet

**Other includes more than one reason from the above, and/or ones not included above

POSSIBLE CORRECTIVE PLANS

- **Remove Placebo for targeted therapies**
- **Change endpoint to DFS for targeted therapies**
- **Increase outreach to thoracic surgeons**
- **Increased screening is likely with addition of nivo**

- **IF screening does not improve dramatically: Change the trial design**

Considerations for CTAC

- Suggestions for improving the conduct of these trials?
- Recommendations regarding future directions for such trials?
- Are there high throughput platforms that are ready to be introduced into precision medicine trials beyond tissue-based, NGS DNA testing?
- If therapeutic signals are found in adult or pediatric MATCH, how should the trials be conducted to f/u on these signals?
- Is there a preference for histology agnostic approaches in early phase trials or should discovery occur in specific cancer type settings?
- OTHERS?