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
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.
**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
Eligibility

- solid tumor
- lymphoma
- prior therapy
- measurable
- biopsy
- ECOG PS 0,1
SCHEMA

Genetic sequencing PTEN IHC

Actionable mutation detected

Study Agent

Stable disease (SD), partial or complete disease response (PR+CR)

Continue study agent until disease progression

PD

Repeat biopsy and genetic sequencing

Progressive disease (PD)

Check for 2nd actionable mutation

No actionable mutation, or patient withdraws consent

3-year follow-up

Yes

No

Yes

No

No

Yes
TARGET LEVELS of EVIDENCE

Level 1
Gene variant is credentialed for selection of an approved anticancer drug

Level 2
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

Level 3
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)
DRUG SELECTION

Level 1
Agent has Food & Drug Administration approval for any indication for that target

Level 2
Agent has met an actionable clinical endpoint (objective response or survival) with evidence of target inhibition

Level 3
Agent has shown evidence of clinical activity with evidence of any level target inhibition
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

<table>
<thead>
<tr>
<th>Common Cancers</th>
<th>Enrolled for Screening (N=795)</th>
<th>Screened (N=645)</th>
<th>Assigned to Rx (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>104 (13.1%)</td>
<td>84 (13.0%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Breast</td>
<td>96 (12.1%)</td>
<td>84 (13.0%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Non-Small Cell Lung</td>
<td>62 (7.8%)</td>
<td>48 (7.4%)</td>
<td>5 (15.2%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>20 (2.5%)</td>
<td>17 (2.6%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td><strong>Common Cancers Subtotal</strong></td>
<td><strong>282 (35.47%)</strong></td>
<td><strong>233 (36.12%)</strong></td>
<td><strong>14 (42.42%)</strong></td>
</tr>
<tr>
<td>Uncommon Cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>89 (11.2%)</td>
<td>72 (11.2%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Pancreas (Adeno/NOS)</td>
<td>43 (5.4%)</td>
<td>34 (5.3%)</td>
<td>--</td>
</tr>
<tr>
<td>Head and Neck(^1)</td>
<td>38 (4.8%)</td>
<td>34 (5.3%)</td>
<td>--</td>
</tr>
<tr>
<td>Endometrial/Uterine (Non-Sarcoma)</td>
<td>34 (4.3%)</td>
<td>27 (4.2%)</td>
<td>--</td>
</tr>
<tr>
<td>Esophageal/GE Junction/Gastric</td>
<td>31 (3.9%)</td>
<td>28 (4.3%)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Neuroendocrine(^2)</td>
<td>27 (3.4%)</td>
<td>20 (3.1%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Cholangio</td>
<td>24 (3.0%)</td>
<td>22 (3.4%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Bladder/UT</td>
<td>21 (2.6%)</td>
<td>14 (2.2%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Endometrial/Uterine Sarcoma(^3)</td>
<td>20 (2.5%)</td>
<td>16 (2.5%)</td>
<td>--</td>
</tr>
<tr>
<td>Small Cell Lung</td>
<td>16 (2.0%)</td>
<td>14 (2.2%)</td>
<td>--</td>
</tr>
<tr>
<td>Other(^4)</td>
<td>151 (19.0%)</td>
<td>116 (18.0%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Primary Site Not Specified</td>
<td>19 (2.4%)</td>
<td>15 (2.3%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td><strong>Uncommon Cancers Subtotal</strong></td>
<td><strong>513 (64.53%)</strong></td>
<td><strong>412 (63.87%)</strong></td>
<td><strong>19 (57.57%)</strong></td>
</tr>
</tbody>
</table>

---

\(^1\) 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

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

<table>
<thead>
<tr>
<th>Arm / Target</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>BRAF nonV600 Trametinib</td>
</tr>
<tr>
<td>S1</td>
<td>NF1 mut Trametinib</td>
</tr>
<tr>
<td>S2</td>
<td>GNAQ/GNA11 Trametinib</td>
</tr>
<tr>
<td>T</td>
<td>SMO/PTCH1 Vismodegib</td>
</tr>
<tr>
<td>U</td>
<td>NF2 loss Defactinib</td>
</tr>
<tr>
<td>V</td>
<td>cKIT mut Sunitinib</td>
</tr>
<tr>
<td>W</td>
<td>FGFR1/2/3 AZD 4547</td>
</tr>
<tr>
<td>X</td>
<td>DDR2 mut Dasatinib</td>
</tr>
<tr>
<td>Y</td>
<td>AKT1 mut AZD 5363</td>
</tr>
<tr>
<td>Z1A</td>
<td>NRAS mut Binimetinib</td>
</tr>
<tr>
<td>Z1B</td>
<td>CCND1,2,3 amp Palbociclib</td>
</tr>
<tr>
<td>Z1D</td>
<td>dMMR Nivolumab</td>
</tr>
</tbody>
</table>
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
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
NCI-Pediatric MATCH Study

Available MATCH study agents

MEK Inhibitor
BRAF Inhibitor
PI3K/mTOR Inhibitor
TRK Inhibitor
ALK Inhibitor
FGFR Inhibitor
EZH2 Inhibitor
PARP Inhibitor

Children with relapsed and refractory solid tumors and lymphomas

- Tumor biopsy
- Genetic sequencing
- Actionable mutation detected
- Matching study agent selected
- SD, CR or PR
- Continue until progression
- PD

- PD
- Another actionable mutation detected?
  - Yes
    - Off study
  - No

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

<table>
<thead>
<tr>
<th>Agent Class</th>
<th>aMOI Frequency</th>
<th>Subarm Chair</th>
<th>Protocol ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOXO 101</td>
<td>2-3%</td>
<td>Katie Janeway</td>
<td>APEX1621-A</td>
</tr>
<tr>
<td>Erdafitinib</td>
<td>2-3%</td>
<td>Jae Cho</td>
<td>APEX 1621-B</td>
</tr>
<tr>
<td>Tazemetostat</td>
<td>2-3%</td>
<td>Susan Choi</td>
<td>APEX 1621-C</td>
</tr>
<tr>
<td>LY3023414</td>
<td>5-10%</td>
<td>Ted Laetsch</td>
<td>APEX 1621-D</td>
</tr>
<tr>
<td>Selumetinib</td>
<td>10-20%</td>
<td>Carl Allen</td>
<td>APEX 1621-E</td>
</tr>
<tr>
<td>Ensartinib</td>
<td>2-3%</td>
<td>Meredith Irwin</td>
<td>APEX 1621-F</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>5%</td>
<td>Aerang Kim</td>
<td>APEX 1621-G</td>
</tr>
<tr>
<td>Olaparib</td>
<td>2-3%</td>
<td>Julia Glade Bender</td>
<td>APEX 1621-H</td>
</tr>
</tbody>
</table>
NCI-MATCH Specimen Work Flow Schema

- **Biopsy** shipped to Nationwide

  - Tissue Accession
  - Tissue Processing
    - NA Extraction
    - NA Shipped

  - Archive
    - Tissue Blocks
    - Slides
    - Nucleic Acid

  - PTEN IHC

  - **MDA**

  - **MoCha**
    - Library Prep and Sequencing

  - **Ion Reporter**
    - MOI Annotation
    - Review and Sign off

  - **MATCHBox**
    - BAM File Storage

  - **Clinical DB**
    - Final Report
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
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
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
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 2^{nd} and greater lines of therapy
  - Add in pre-screening during 1^{st} line therapy
  - S1400A design modification to single arm
Modified Trial Schema
[Revision #2 Activated 5/26/15]

Screening

**S1400A**
Non-match

Arm¹

1Medi4736

**S1400B**
PI3K PIK3CA mut

Arm¹

1:1

1 GDC-0032
2Docetaxel

**S1400C**
CDK4/6 CCND1, CCND2, CCND3, cdk4 ampl

Arm¹

1:1

1Palbociclib
2Docetaxel

**S1400D**
FGFR FGFR ampl, mut, fusion

Arm¹

1:1

1AZD4547
2Docetaxel

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
**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 ($1400 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 Lung Cancer Enrichment Marker Identification and Sequencing 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 disease:
  - 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

Pre-op cohort
Complete resection + standard adjuv. tx per treating physician

Post-op cohort
Submit FFPE tissue & blood specimen

For non-squamous patients
Screen for EGFR & ALK genotyping (A151216)
(+)

For non-squamous and squamous patients
PD-L1 testing
(-) for both

EGFR-mutation:
Phase III trial (A081105):
• Erlotinib vs. placebo

ALK-rearranged:
Phase III trial (E4512):
• Crizotinib vs. placebo

Immunotherapy:
Phase III trial (EA5142):
• Nivolumab vs. observation

Without molecular alterations and patient in no treatment category:
Followed q6 months x 5 years after any adj tx

FFPE tissue from biopsy submitted at recurrence

Red = same as current schema
Blue = changes to schema
## TRIAL PROTOCOL DETAILS – STATS DESIGN

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

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # sites open for A151216</td>
<td>1059</td>
</tr>
<tr>
<td>Total pts registered to A151216</td>
<td>1288</td>
</tr>
<tr>
<td>Total pts registered to A081105</td>
<td>71</td>
</tr>
<tr>
<td>Total pts registered to E4512</td>
<td>25</td>
</tr>
<tr>
<td>Total pts registered to EA5142</td>
<td>21</td>
</tr>
</tbody>
</table>
Monthly ALCHEMIST Accruals

Patient Accruals

- A151216
- A081105
- E4512
- EA5142
ENROLLMENT TO A081105 BY EGFR POSITIVE STATUS BY CENTRAL TESTING AS OF 10/19/2016

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

*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

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

*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?