CTEP/NCI’s Role in Registration Trials

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Implementing a National Cancer Clinical Trials System for the 21st Century:
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February 12, 2013
Overview of the Current Program

- 3,100 Institutions
- 14,000 Investigators
- 20,000+ pts enrolled on clinical treatment trials annually

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</tr>
</thead>
<tbody>
<tr>
<td>All Phases: Treatment Trials</td>
<td>27,263</td>
<td>24,289</td>
<td>25,540</td>
<td>29,063</td>
<td>23,299</td>
<td>19,462</td>
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</table>

Accrual Distribution FY2006 - FY2010:
- Phase 3: 82.0%
- Phase 2: 15.3%
- Phase 1/Pilot: 2.6%
Interventional Clinical Trials in U.S.

- Cancer Incidence – 1.6 million cancers annually in U.S.
- NCI-Network treatment trials - ~20,000
- NCI- Network control/prevention - ~5,000
- NCI – Investigator-initiated trials - ~ 20,000
- Industry - ~ 50,000
- Other funders - ~ 5,000
- About 6% of patients dx’d with cancer annually go on trial in U.S.
Selected NCI/CTEP-sponsored Trials Contributing to FDA-approved Indications for New Oncology Agents

- **1991 - 1994**
  - Fludarabine phosphate (SWOG)
  - Pentostatin (CALGB, SWOG)
  - Paclitaxel (GOG, CALGB, ECOG, NCCTG, SWOG)
  - Melphalan IV (CALGB)
  - Pegasparaginase (POG)

- **2001 - 2004**
  - Imatinib mesylate (COG, SWOG)
  - Letrozole (NCIC, Intergroup)
  - Oxaliplatin (NCCTG, Intergroup)
  - Taxotere (SWOG)

- **2005 - 2008**
  - Nelarabine (COG, CALGB)
  - Bevacizumab (ECOG, Intergroup)
  - Herceptin (NSABP, NCCTG, Intergroup)
  - Imatinib mesylate/GIST-adjuvant (ACOSOG)
  - Rituximab (ECOG, Intergroup)
  - Bortezomib (Memorial Sloan-Kettering)

- **2009 – 2012**
  - Bevacizumab/RCC (CALGB)
  - Romidepsin (CCR)
  - Dasatinib (SWOG)
  - Imatinib mesylate (ACOSOG)
<table>
<thead>
<tr>
<th>Year FDA Approval of Indication in Agent Label</th>
<th>Agent</th>
<th>Supplemental Indication Unless Otherwise Noted</th>
<th>Related Cooperative Group Trial Number(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA Currently in Preparation</td>
<td>Anti-GD2 Antibody ch14.18</td>
<td>Use in &quot;high-risk&quot; neuroblastoma (Primary indication for the agent)</td>
<td>COG: ANBL0032</td>
</tr>
<tr>
<td>2009</td>
<td>Bevacizumab</td>
<td>Use in 1st-line therapy in advanced renal cell carcinoma in combination with interferon alpha</td>
<td>CALGB-90206</td>
</tr>
<tr>
<td>2008</td>
<td>Imatinib mesylate</td>
<td>Use as adjuvant therapy after resection of primary GIST</td>
<td>ACOSOG-Z9001</td>
</tr>
<tr>
<td>2006</td>
<td>Bevacizumab</td>
<td>Second-line therapy in advanced colorectal cancer in combination with FOLFOX</td>
<td>E3200</td>
</tr>
<tr>
<td>2006</td>
<td>Bevacizumab</td>
<td>Use in 1st-line therapy in advanced NSCLC in combination with chemotherapy</td>
<td>E4599</td>
</tr>
<tr>
<td>2006</td>
<td>Imatinib mesylate</td>
<td>Use in pediatric newly diagnosed CML</td>
<td>COG: AAML0123</td>
</tr>
<tr>
<td>2006</td>
<td>Rituximab</td>
<td>Use in Diffuse Large B-cell Lymphoma</td>
<td>E4494</td>
</tr>
<tr>
<td>2006</td>
<td>Rituximab</td>
<td>Use in Non-Hodgkins Lymphoma</td>
<td>E1496</td>
</tr>
<tr>
<td>2006</td>
<td>Thalidomide</td>
<td>Use in newly diagnosed Multiple Myeloma</td>
<td>E1A00</td>
</tr>
<tr>
<td>2006</td>
<td>Trastuzumab</td>
<td>Use in combination with adjuvant chemotherapy in operable HER2-positive breast cancer</td>
<td>NSABP-B-31 and NCCTG-N9831</td>
</tr>
<tr>
<td>2005</td>
<td>Nelarabine</td>
<td>Use in T-cell ALL and T-cell lymphoblastic lymphoma that has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens (Primary indication for the agent)</td>
<td>P9673 and CALGB-59901</td>
</tr>
<tr>
<td>Year Publication (or Abstract or Announcement) of Negative Results</td>
<td>Cancer Site</td>
<td>Trial Number</td>
<td>Experimental Agent or Regimen</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-------------</td>
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<td>-------------------------------</td>
</tr>
<tr>
<td>2011</td>
<td>Brain Cancer: Glioblastoma</td>
<td>RTOG-0525</td>
<td>Dose-dense temozolomide</td>
</tr>
<tr>
<td>2011</td>
<td>Head &amp; Neck Cancer (SCCA)</td>
<td>RTOG-0522</td>
<td>Concurrent accelerated RT plus cisplatin with cetuximab</td>
</tr>
<tr>
<td>2010</td>
<td>Colon Cancer</td>
<td>N0147</td>
<td>Cetuximab in combination with adjuvant chemotherapy</td>
</tr>
<tr>
<td>2010</td>
<td>Colon Cancer</td>
<td>NSABP-C-08</td>
<td>Bevacizumab in combination with adjuvant chemotherapy</td>
</tr>
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</table>
Overview of Changes to the NCI Clinical Trials System for Registration Trials

- National Clinical Trials Network (NCTN)
  - Trial Efficiency and Quality
- NCI Central IRB
- CRADA and Intellectual Property Agreements
- New Trial Designs for Registration
Recommendation 1: Facilitate some consolidation of Group “front-office” operations by reviewing & ranking Groups with defined metrics on similar timetable & by linking funding to review scores

Progress:

- New Program with up to 4 adult & 1 pediatric Network Groups
- Peer-review focused on overall research strategy, collaboration, & operational efficiency
- Support for trials designed with integral molecular screening
- Integrated translational science & Lead Academic Participating Site awards
- Core RT/Imaging services
- Strategic planning & trial prioritization at national level
- Adult and pediatric Central IRBs
- Common IT data mgt system
- Centralized 24/7 patient registration

New Program: NCI National Clinical Trials Network (NCTN)
Cancer Trials Support Unit (CTSU) has expanded centralized administrative & regulatory functions for clinical trials

- Over 57,000 patients enrolled via CTSU since 2002
- Cross-Group accrual available for all phase 3 & select phase 2 tx trials
- Expansion of services to other NCI trial networks & collaborative trials
- Provides a range of critical services in support of the national system

- Patient registration
- Accrual reimbursement
- Protocol Coordination
- Clinical Data Operations
- Regulatory Support Service
- Financial Management
- Site Auditing
- Site QA
- CTSU Help Desk
- CTSU Web Site
- Education & Trial Promotion

As of 2011, 24/7 enrollment for all Group Tx trials
Common IT Data Management System (CDMS)

- **Electronic tool(s) or processes that support**
  - Data collection: Remote Data Capture (RDC)
  - Data coding: Standard libraries - Common Toxicity Criteria
  - Data management: Discrepancy, delinquency, communication, correction & preparation of data for analysis

- **Core benefits of CDMS on NCI-supported multicenter trials**
  - Reduces training costs & cost of overall cost of data management
  - Reduces risk of data delinquency and/or discrepancy
  - Reduces time/effort to correct/complete data
  - Reduces delays in obtaining Science and Safety results & improves trial management & decision-making

- **Other Benefits to NCI-supported multicenter trials**
  - Supports/complements transformation of Groups into new ‘Network’ program
  - Meets FDA & other Federal requirements for e- data capture, security & transfer
  - Promotes data sharing
  - Sets stage for further infrastructure improvements such as integration with expedited Serious AE reporting, remote auditing, electronic filing for FDA reports
Record all Grade 3 or higher AEs. Record only Unexpected Grade 2 AEs. Record Grades 1 and higher for all events listed in protocol section 8.1.1. Record each event only one time per cycle of treatment, identifying the highest grade of the event.

<table>
<thead>
<tr>
<th>Adverse Event Text Name (CTCAE v4.0)</th>
<th>MedDRA Adverse Event Code (v12.0)</th>
<th>Adverse Event Grade</th>
<th>Adverse Event Description</th>
<th>CTC Adverse Event Attribution Scale</th>
<th>Has an event ever been reported before?</th>
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</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
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<tr>
<td>Bone marrow hypopcellular</td>
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<td>Disseminated intravascular coagulation</td>
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<tr>
<td>Febrile neutropenia</td>
<td></td>
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<td></td>
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<tr>
<td>Hemolysis</td>
<td></td>
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<tr>
<td>Hemolytic uremic syndrome</td>
<td></td>
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<tr>
<td>Leukocytosis</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Lymph node pain</td>
<td></td>
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<tr>
<td>Spleen disorder</td>
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<tr>
<td>Thrombotic thrombocytopenic purpura</td>
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</tbody>
</table>
Implementation of Operational Efficiency Timelines

- **Group Phase 3 Trials**
  - Historical Median Time to Activation (2006 - 2008) = 830 days
  - OEWG Target & Absolute Deadlines as of 2013:
    - Absolute = 540 days
  - Protocol terminated if absolute timelines not achieved

- **CTEP Early Phase Trials (Groups & Other)**
  - Historical Median Time to Activation (2006 - 2008) = 550 days
  - OEWG Target & Absolute Deadlines as of 2013:
    - Absolute = 450 days
  - Protocol terminated if absolute timelines not achieved

**Protocol terminated if absolute timelines not achieved**
Breakdown of Study Development Stages

Early Phase Trials

- LOI submission to LOI approval: Target = 60 days
  - Pre-OEWG data: 110 days
  - Post-OEWG data: 78 days
- LOI approvals to protocol submission: Target = 60 days
  - Pre-OEWG data: 60 days
  - Post-OEWG data: 60 days
- Protocol submission to trial activation: Target = 90 days
  - Pre-OEWG data: 303 days
  - Post-OEWG data: 247 days
Timeline Comparison Early Phase Trials

Historical vs Post-OEWG (Apr 2010 – Aug 2012)
Timeline Comparison Phase 3 Trials
Historical vs Post-OEWG (Apr 2010 – Aug 2012)
NCI CIRB Profile - Enrollment

- Enrollment of Institutions/IRBs reviewing Group Studies
  - Number of Signatory Institutions Enrolled: 330
    - Number of Institutions using Adult CIRB only: 183
    - Number of Institutions using Pediatric CIRB only: 42
    - Number of Institutions using both Adult & Pediatric CIRB: 105
  - Total Number of Enrolled Signatory Institutions, Affiliates, and Components: 1,023

- Number of NCI Designated Cancer Centers: 43
- Number of CCOPs: 35
- Number of MBCCOPs: 10

As of 4/30/2012
NCI CIRB: Changes in Initial Review Timeline

Timeline to Adult CIRB Approval of Initial Reviews
(Median Number of Days)

- Time from CIRB Receipt to Review
- Time from CIRB Review to Approval
- Time from CIRB Receipt to Approval

Number of Days

- 2008
- 2009
- 2010
- 2011
- 2012
NCI Adult & Pediatric CIRB Independent Model

- Received full accreditation by Association for Accreditation of Human Research Participant Protection Programs (AAHRPP) in December 2012
- New institutions being added and current institutional members of CIRB being transitioned to independent model
- Participation in NCTN trials will require use of CIRB (with waiver exemption possible for sites demonstrating similar local IRB review timelines)
- Being expanded to include study review of other NCI-supported clinical trials networks & potential expansion to other types of studies
  - Experimental Therapeutics Clinical Trials Network
  - DCP-supported cancer control & prevention studies
**Single Agent Studies**

- Collaborator receives a non-exclusive, royalty-free license for internal research purposes only.
- Collaborator has first rights to negotiate an exclusive or non-exclusive royalty-bearing license.

**Combination Agent Studies**

- Each Collaborator receives a non-exclusive, royalty-free license for all purposes, including commercial purposes, to any combination IP.
- Still can negotiate a co-exclusive or exclusive license for Collaborator agent IP.
Entrance of molecularly targeted agents into clinical trials has changed relationships among parties. Trials depend more on defining targets and developing biomarkers.

Prior IP Option and most of our collaborative agreements (and funding agreements) were silent as to the disposition of agent-treated human tumor samples and rights related to them. The IP framework surrounding agent-treated samples and the associated clinical data have become increasingly important.
Revised IP Option for CTEP-sponsored Trials

A. The IP Option described in this Section A would apply to inventions that would be described in patent disclosures that claim the use and/or the composition of the Agent(s) and that are conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the NCI CTEP provided Agent(s) ("Section A Inventions"): 

(i) a **royalty-free**, worldwide, **non-exclusive** license for commercial purposes; and

(ii) a time-limited **first option** to negotiate an exclusive, or **co-exclusive**, if applicable, world-wide, royalty-bearing license for commercial purposes.
What are examples of Section A Inventions?

- Alternate uses for agents, the “Minoxidil and Viagra” scenarios.
- Dosing schedules, unique administration techniques that improve efficacy.
- In general, inventions that would fall under the scope of Section A would be very rare.
B. The IP Option described in this Section B would apply to inventions not covered by Section A, but are nevertheless conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the CTEP-provided Agent(s). It also applies to inventions that are conceived or first actually reduced to practice pursuant to NCI CTEP-approved studies that use non-publicly available clinical data or specimens from patients treated with the CTEP-provided Agent (including specimens obtained from NCI CTEP-funded tissue banks) (“Section B Inventions”).
Revised IP Option (continued)

- (i) **Nonexclusive**, nontransferable, **royalty-free**, world-wide license to all Institution Inventions for **research purposes only**; and

- (ii) “A nonexclusive, royalty-free, world-wide license to disclose and to promote Section B Inventions that are necessary or required by a regulatory authority for marketing authorization of the Agent or required to be on a product insert or other promotional material regarding the Agent or useful for informing Healthcare providers and patients regarding use of the Agent”
What are examples of Section B Inventions?

- Assays/Diagnostics – Possibly broad in array
- New scientific methods or techniques
- The scope of inventive material is much broader under Section B, however the license grant is much narrower.
Vision for Transformed Network

• Provide essential infrastructure for NCI trials in treatment, control, screening, diagnosis, & prevention across all NCI clinical research programs

• Launch trials rapidly and complete accrual according to defined guidelines through integrated national network of performance sites

• Promote user-friendly, harmonized processes to extramural community (investigators, patients, advocates, & industry)

• Provide functional platform to perform large scale testing of increasingly smaller subsets of molecularly-defined cancers & focus on questions not well supported in a commercial environment
Molecular Profiling in NCI-sponsored Clinical Treatment Trials

DCTD, CCG, CBIIT, OD
Presentation Overview

- ALCHEMIST
- Master Protocol in Advanced Lung Cancer
ALChEMIST

Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial
### Lung Cancer Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>New Cases / Yr</th>
<th>Deaths / Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>116,470</td>
<td>87,750</td>
</tr>
<tr>
<td>Female</td>
<td>109,690</td>
<td>72,790</td>
</tr>
<tr>
<td>Total</td>
<td>226,100</td>
<td>160,340</td>
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</table>

<table>
<thead>
<tr>
<th>Stage at Dx</th>
<th>Local</th>
<th>Regional</th>
<th>Distant</th>
<th>Unstaged</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16%</td>
<td>22%</td>
<td>56%</td>
<td>7%</td>
</tr>
<tr>
<td>5 year survival</td>
<td>52%</td>
<td>24%</td>
<td>4%</td>
<td>--</td>
</tr>
</tbody>
</table>

5 year survival after lobectomy (Stage IA, IB): **45-63%**
Drug Biomarkers in Lung Adenocarcinoma

TKI-sensitizing EGFR mutations:
- **10%** in Western population
- Up to **50%** in Asian population

Enriched in:
- females
- non-smokers
- younger patients

Multiple tests in clinical use
No FDA-approved clinical assay

ALK Rearrangement
- **5-7%** in Western population

FDA approved companion diagnostic:
Vysis Break Apart FISH probe
National Trial for Molecular Characterization of Early Stage, Adenocarcinoma of the Lung

Eligibility:
• Diagnosis of Adenocarcinoma
• Clinical stage I, II, or III deemed resectable
• Pathologic stage I, II, or III that:
  • has been successfully resected
  • adequate tissue available
  • +/- local test for EGFR mutation or ALK rearrangement
• Patient Consent to allow
  • donation of de-identified cancer information for research
  • performance of central testing for adjuvant study referral
  • 5 year follow-up: treatment and outcome
  • contact regarding follow-up biopsy if cancer recurs
  • (optionally) re-contact if no recurrence at end of study
Consent & Register: A151216 Screening & Follow-up Protocol

Pre-op Cohort
- SOP-driven FF/FFPE
- After resection, buffy coat

Post-op Cohort
- Assess FFPE
- buffy coat

CLIA-approved LAB
- EGFR mutation test (sequencing)
- ALK rearrangement (FISH)

TCGA
- Genomic sequencing
- Transcriptome
- Methylation

E4512: Erlotinib
A081105: Crizotinib

Other Adjuvant Studies
Data Flow

Consent & Register

Pre-op Cohort
  CLIA-approved Lab Marker Analysis
    EGFR activating mutation
    E4512
    ALK+
    A081105
    Screen
    Neg.
    5 year follow-up cohort

Post-op Cohort
  Collect local test info
  TCGA Data

A151216 Registry

Sequencing Database

E4512 Trial Database

A081105 Trial Database
## Trial Protocol Details

<table>
<thead>
<tr>
<th></th>
<th>E4512</th>
<th>A081105</th>
<th>A151216</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>ALK+</td>
<td>EGFRmut</td>
<td>Registry</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>~5%</td>
<td>~10%</td>
<td>all comers</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>360</td>
<td>410</td>
<td>7000 – 8000</td>
</tr>
<tr>
<td><strong>Primary Endpt</strong></td>
<td>OS</td>
<td>OS</td>
<td>--</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>80%</td>
<td>85%</td>
<td>--</td>
</tr>
<tr>
<td><strong>One-sided α</strong></td>
<td>0.05</td>
<td>0.05</td>
<td>--</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.67</td>
<td>0.67</td>
<td>--</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>5 yrs accrual; 3.6 yrs f/u</td>
<td>4.1 yrs accrual; 3.2 yrs f/u</td>
<td></td>
</tr>
<tr>
<td><strong>Adjunct</strong></td>
<td>Peripheral screening for ALK; RTPCR to identify fusion partners</td>
<td>Targeted sequence and kinome analysis; PRO and QOL</td>
<td>Extended sequencing for additional targets; correlation with local testing</td>
</tr>
</tbody>
</table>
ALChEMIST – Beyond Treatment Endpoints

- Opportunity to collect epidemiologic info spanning tobacco, diet, alcohol and work exposures
- TCGA (GDAC centers) to perform molecular profiling studies on large cohort (~ 7000 pts) with ability to re-profile at relapse in about 50% (“natural genomic history”)
- Opportunity to develop a molecular profiling report for physicians that will meet with FDA approval
- Development of approach to sharing unexpected germline mutations for cancer risk with patients screened in this trial
Master Protocol: Advanced NSCLC

- Multi-arm, multi-marker/drug “master protocol”
- Phase 2-3 trial
  - Randomized, Controlled
  - Multiple new therapies are tested simultaneously in a specific disease setting
  - Designed to allow FDA approval of new therapeutics
  - Assigns patients to experimental treatment vs standard-of-care control arm on the basis of specific biomarkers
Advantages of Master Protocol Multi-Drug Registration Trial Design

- Grouping multiple studies reduces the overall screen failure rate
- Single master protocol will result in process and operational efficiency gains
  - Provides consistency
  - Trial infrastructure will be in place
  - Bring safe and effective drugs to patients faster
A trial steering committee will evaluate each application to determine whether a drug/biomarker pair can enter the trial.

**Drugs**
- Ready to enter a phase 2-3 confirmatory trial
- Each drug must have clinical data demonstrating activity in a responsive patient group
- Patient group can be identified by assessment of biomarker in patient tumor biopsies
Trial Design – Biomarkers and Screening

- Each compound’s biomarker is based on analytically validated test/platform suitable for a pivotal trial
- This trial could use common screening platform that assays multiple biomarkers
  - If predictive biomarker is in a CLIA-approved platform, it could be considered adequate for patient selection and randomization
    - Would require Investigational Device Exemption (IDE) prior to trial start
    - If new drug shows clinical benefit in selected patient population the biomarker could be analyzed and given FDA clearance
# Lung Cancer: Example Squamous Cell Carcinoma Mutation Incidence

<table>
<thead>
<tr>
<th>Gene</th>
<th>Event Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>20-25%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Mutation</td>
<td>5%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>9%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation-Deletion</td>
<td>18%</td>
</tr>
<tr>
<td>CCND1</td>
<td>Amplification</td>
<td>8%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Deletion/Mutation</td>
<td>45%</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Amplification-Mutation</td>
<td>9%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>10%</td>
</tr>
<tr>
<td>MCL1</td>
<td>Amplification</td>
<td>10%</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>3%</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>4%</td>
</tr>
<tr>
<td>MET</td>
<td>High copy-amplification</td>
<td>11%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>2%</td>
</tr>
</tbody>
</table>
Use of a Multi-marker Platform

• Advantages
  - Conserves tumor samples
  - Testing protocols easier to standardize
  - Sponsors would not be responsible for designing their own diagnostic

• Considerations
  - Have not yet been used in registration trial
  - The process would require close communication with the FDA to determine its applicability
Advanced NSCLC patients, multiple experimental drugs with matching predictive biomarker

Phase 2 Endpoint, PFS

Meets pre-specified endpoint
- Continue experimental arm
- Phase 3, OS endpoint

Does not meet pre-specified endpoint
- Withdrawn from trial