NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

Clinical Trials Advisory Committee (CTAC) November 12th, 2014

Percy Ivy, MD

Associate Chief, Investigational Drug Branch Cancer Therapy Evaluation Program

Program Director, Experimental Therapeutics Clinical Trials Network
Goals and Objectives of The ETCTN

Research and Development for New Treatments
- Dose and schedule in early treatment trials
- Novel combination therapies

Tumor Characterization in Biomarker-driven studies
- Molecular characterization: expression, sequence and epigenetics
- Validated biomarker assays in qualified labs
- Functional imaging

Enhanced understanding of cancer biology
- Bedside to bench and back

Education and Training for young investigators
Challenges for the Experimental Therapeutics Clinical Trials Network

Accrual
- Smaller patient populations due to molecularly-defined diseases
- A scalable/flexible program that can rapidly adapt to accrual needs

Biomarkers
- Often requires biopsies
- Fit for purpose, validated assays
- Functional imaging

More Facile Mechanisms for Translation
- To and From Bench to Bedside Collaborations
- More predictive animal models to evaluate tumor heterogeneity
Clinical Translational Research and Cancer Biology: Bedside to Bench and Back

**Clinical observations:**
- Clinical response
- PK
- Functional imaging
- Tumor and normal tissue PD markers
- CTCs, CECs
- Tumor-initiating cells

**Patients eligible for early phase clinical trials**

**Analysis of tumor and Other tissues for pathway activation or biomarker**

**Patient assigned to trial Based on molecular characterization of tumor**

**Patient monitoring**

**Patient monitoring: Post-treatment molecular re-analysis for response/resistance**

**Non-clinical models for targets**

**Translational research with clinical models**
- Sequencing
- Methylation
- FISH
- IHC
- Expression array
NCI Team Science-Project Development: Step 2 – NCI Division/Programs Project Team

Step 2

- Request for Projects
- Important questions

Preliminary Drug Development Plan

Division of Cancer Treatment and Diagnosis/Cancer Therapy Evaluation Program meeting

NExT Senior Advisory Committee I

Scientific

Regulatory/Agreements

3

Drug Project Team

Clock starts ticking
NCI Team Science-Project Development: Step 3 - Extramural Project Team

**Step 3**

- NExT Program ➔ NCI Project Team ➔ Drug “X” Project Team ➔ Protocol development

**Scientific**

- Translational
- Drug "X" Project Team
- Centralized support
- Cancer Biology
- Clinical

**Drug Project Team**

- Drug Development Plan
- Investigational Drug Steering Committee Review of Important Questions and Drug Development Plan

**Regulatory/Agreements**

- Cooperative Research and Development Program-Development
- Cooperative Research and Development Program-Signed

6 months to send out PTMA, select team and develop plans

Drug Project Team is dissolved

Projects
AZD9291 Project Team Timeline

- AZD9291 approved by NDeC on Jan 17, 2014
- AZD9291 drug project team formation approved by SAC1 on April 3, 2014
- AZD9291 PTMA issued May 20, 2014
- AZD9291 project team selected by PRC July 9, 2014
- AZD9291 team had 17 meetings over 10 weeks- required commitment
  - 7 meetings of full team
  - 10 meetings of subgroups of full team
- CRADA signed September, 2014
- IDSC presentation and unanimous (27-0) approval: October 22, 2014

From NExT approval to SAC2: 9.5 months

Goal was to decrease this interval from 21 months to 15 months
# AZD9291 Project Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Role</th>
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<tbody>
<tr>
<td><strong>External Members</strong></td>
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<tr>
<td>Clinicians</td>
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<tr>
<td>Geoffrey Oxnard</td>
<td>Dana-Farber Cancer Institute</td>
<td>CRDL investigator</td>
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<tr>
<td>Pasi Janne</td>
<td>Dana-Farber Cancer Institute</td>
<td>Mentor/Team co-leader</td>
</tr>
<tr>
<td>Jonathan Riess</td>
<td>UC Davis</td>
<td>CRDL investigator</td>
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<tr>
<td>David Gandara</td>
<td>UC Davis</td>
<td>Mentor/Team co-leader</td>
</tr>
<tr>
<td>Penelope Bradbury</td>
<td>University Health Network-Princess Margaret Hospital</td>
<td>Clinician scientist</td>
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<tr>
<td><strong>Translational scientists</strong></td>
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<tr>
<td>Jill Marie Kolesar</td>
<td>University of Wisconsin Hospital and Clinics</td>
<td>Pharmacology</td>
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<td>Phil Mack</td>
<td>UC Davis</td>
<td>Genomics</td>
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<tr>
<td>Eric Haura</td>
<td>Moffitt Cancer Center</td>
<td>Kinome</td>
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<td><strong>Basic scientists</strong></td>
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<tr>
<td>Katerina Politi</td>
<td>Yale University</td>
<td>Preclinical mEGFR models</td>
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<tr>
<td>Jeffrey Engelman</td>
<td>Massachusetts General Hospital Cancer Center</td>
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<td>Trever Grant Bivona</td>
<td>UCSF-Mount Zion</td>
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<td><strong>Internal members</strong></td>
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<tr>
<td>Jeff Moscow</td>
<td>IDB</td>
<td>Drug Monitor/Team co-leader</td>
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<tr>
<td>Helen Chen</td>
<td>IDB</td>
<td>Drug monitor</td>
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<tr>
<td>Shakun Malik</td>
<td>CIB</td>
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<tr>
<td>Udayan Guha</td>
<td>TOB</td>
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<tr>
<td>Lokesh Agrawal</td>
<td>CDP</td>
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<tr>
<td>Bhanu Ramineni</td>
<td>RAB</td>
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<tr>
<td>Ed Korn</td>
<td>BRB</td>
<td>Biostatistician</td>
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Biomarkers in ETCTN Trials

**Integral**
- Primary study endpoint
- Used for patient selection
- Used to determine patient treatment
- Performed in a CLIA environment
- May require an IDE

**Integrated**
- Used for patient description
- Hypothesis generating
- Provide evidence of pathway activation
- CLIA ready
- IDE not required

**Exploratory**
- Descriptive biomarkers
- Not validated or fit for purpose

**Prioritization**
- Possibly phase dependent
  - Proof of mechanism
  - Proof of principal
  - Pharmacokinetics
  - Pharmacodynamics
- Propose innovative disease-based or biomarker-based clinical trials incorporating appropriate endpoints

Emphasis on fit for purpose, qualified assays
Biomarker Prioritization

**Proof-of-Mechanism**
- Tumor biomarkers
- Mechanism based studies to correlate with response or clinical benefit
  - Reduced expression of target proteins
  - Reduced mutant DNA expression
  - Plasma-based detection of mutated protein
  - Reduced expression driver mutations

**Genomics**
- WES assessments separating responders from non-responders
- RNA-seq/WES analysis of mechanisms of pathway adaptation and resistance

**Non-invasive assessments**
- MRI scans
- PET scans
Agents currently on track for PTA/PTMA or solicitation

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<tr>
<th>Agent</th>
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NCI-Sponsored Infrastructure for ETCN Trials

1. Investigators and Associates register with CTEP. CTEP IAM accounts required for access to applications.

2. Access Protocol Documents and Check Regulatory Status

3. Obtain CIRB Approval

4. Enroll Patients

5. Enter and Manage Patient Data

6. Other Tasks: CTEP-AERS, Agent Ordering, Monitoring/Audits, OEWG Reporting

- IAM
- CTSU
- CIRB
- Regulatory Support Services (RSS)
- OPEN IWRS
- medidata RAVE
- CTEP Enterprise
Theradex Instance of Medidata Rave: Web-based Reporting

August 1, 2014 NCI/CTEP
Moved from paper to web-based reporting for early clinical trials

* Real time, interactive, web-based, data summaries for monitoring and data mining/analysis

Compliance Overall for a Protocol
Protocol: 5582

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NCI Drug Development Programs: ETCTN Phase 1
Goals:
- Document ETCTN’s implementation
- Identify course corrections if needed
- Provide data to guide decision making for program’s subsequent funding cycle

Assess Four Key ETCTN Domains
- Adoption/Implementation
- Team Science Approach
- Clinical Trial Performance
- Network Synergy
New Development Cycle for NCI Experimental Therapeutics

1. NExT
   NCI Experimental Therapeutics

2. Division/Programs Drug Project Team
   - Clinical
   - Translational
   - NCI Project Team
   - Centralized Support
   - Cancer Biology
   - Preliminary Drug Development Plan
   - DCTD/Programs Meeting
   - Senior Advisory Committee
   - Scientific
   - Regulatory/Agreements

3. EXTRAMural Drug Project Team
   - Scientific
   - Translational
   - Drug Project Team
   - Centralized Support
   - Cancer Biology
   - Cooperative Research and Development Agreement-
     Development
   - Drug and Assay/Biomarker Development Plan
   - Investigational Drug Steering Committee Review
   - Cooperative Research and Development Agreement-
     Signed
   - Projects

4. DCTD/CTEP
   - Projects
   - Senior Advisory Committee
   - DCTD Reviews
   - Letters of intent submitted
   - Protocol development
   - Protocol Activation
Backup Slides
Division and Programs Project Team

Team members

- Clinical scientists- IDB and CIB
- Translational scientists with biomarker and imaging expertise- PADIS, MoCha, CDP, Others
- Cancer biologists- other NCI Divisions and Programs

Tasks

- Draft NCI development plan
- Review of company clinical projects/protocols
- Overview of other competitive agents and molecules
- Biomarkers appropriate for agent development
- Outline of preclinical studies- preliminary or concurrent

Presentation

- Initial NCI development plan to Division of Cancer Treatment and Diagnosis
- Input from Senior Advisory Committee (SAC I)
Extramural Project Team

Team members
- Clinical scientists
- Translational scientists with biomarker and imaging expertise
- Cancer biologists

Tasks
- Initial NCI agent drug development plan
- Description of clinical projects/protocols
- Biomarkers appropriate for agent development
- Outline of preclinical studies- preliminary or concurrent

Presentation
- Initial NCI agent drug development plan
- Input from the Investigational Drug Steering Committee
# ETCTN Phase 1 Principal Investigators

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<tr>
<th>Institutions</th>
<th>PIs</th>
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<tr>
<td>City of Hope/Beckman Res. Inst.</td>
<td>Newman, Edward</td>
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<td></td>
<td>Lenz, Heinz-Joseph</td>
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<td>Dana-Farber/Harvard Cancer Center</td>
<td>Kufe, Donald</td>
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<td>Flaherty, Keith</td>
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<td>Shapiro, Geoffrey</td>
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<td>Duke</td>
<td>Hurwitz, Herbert</td>
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<td>U. North Carolina Wash. U.</td>
<td>Dees, Elizabeth</td>
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<td>Carducci, Michael</td>
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<td>Gocke, Christopher</td>
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<td>Erlichman, Charles</td>
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<td>Huluska, Paul</td>
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<td>Sausville, Ed</td>
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<td>Kummar, Shivaani</td>
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<td>Ohio State U.</td>
<td>Grever, Michael</td>
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<td>Rutgers-Cancer Inst. NJ</td>
<td>DiPaola, Robert</td>
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<td>U. Wisconsin</td>
<td>Liu, Glenn</td>
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<td>Siu, Lillian</td>
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<td>Chu, Edward</td>
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<td>Yao, James</td>
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<td>U. Colorado – Denver</td>
<td>Eckhardt, Gail</td>
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<td>Meric-Bernstam, Funda</td>
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<td>Yale University</td>
<td>Lorusso, Patricia</td>
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<td>Eder, Paul</td>
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<td>Berlin, Jordan</td>
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Transformed NCI
Experimental Therapeutics
Clinical Trials Program

Phase 1
- Basic Resources:
  - Adult Phase 1 Program (UM1)
  - Pediatric Phase 1 Consortium
- Resources /Other:
  - NCI Developmental Therapeutics Clinic
  - Cancer Centers, NCIC CTG

Phase 2
- Basic Resources:
  - Adult Phase 2 Program (N01)
- Resources /Other:
  - Specialty Consortia: ABTC, CITN, other
  - *Other (Centers, SPORES, R21, R01, P01, etc.)

Phase 3
- National Clinical Trials Network

Legend:
- ETCTN
- NCTN
- Other Phase 1
ETCTN Organization Structure

Roster Level

Org Type

Roster Owners
Grantees

Treating Sites*

LAO
Site Name
CTEP Site Code

LAO MM
Site Name
CTEP Site Code

LAO IC
Site Name
CTEP Site Code

LAO AO
Site Name
CTEP Site Code

P2C
Site Name
CTEP Site Code

P2C MM
Site Name
CTEP Site Code

P2C Affiliate
Site Name
CTEP Site Code

P2C Affiliate
Site Name
CTEP Site Code

P2C Sub affiliate
Site Name
CTEP Site Code

*For LAO, the treating site roster is defined by the LAO grant (i.e., updates require an amendment to the grant and to the LAO package in CTEPESYS).

ETCTN — Experimental Therapeutics Clinical Trials Network
LAO — Lead Academic Organization; MM — Main Member; IC — Integrated Component; AO — Affiliated Organization; P2C — Phase 2 Consortium
Project Team Announcement and the Project Team Member Application

• Project Team Announcement (PTA)
  • Replaced the Mass Solicitation

• Project Team Member Application (PTMA):
  • Investigator applies as a clinical or translational project team member
  • NIH biosketch with statement indicating pertinent expertise
  • Specify affiliation (UM1, U01, NCTN, Consortium)
  • PRC review to select PT members

• Clinician Project Team (PT) members
  • Principal Investigators on the trials
  • Identified by the PT for the agent development plan
# Drug Project Teams vs Mass Solicitation

<table>
<thead>
<tr>
<th>Drug Project Teams (DPTs)</th>
<th>Mass Solicitation</th>
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</thead>
<tbody>
<tr>
<td>Drug development plan designed by team of intramural and extramural scientists</td>
<td>Drug development ideas proposed by extra-mural investigators and selected by intramural staff</td>
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<tr>
<td>Limited number of LOI’s generated as a result of DPT deliberations</td>
<td>Many LOI’s generated that compete for placement</td>
</tr>
<tr>
<td>Application by individuals to be on DPTs</td>
<td>Application by teams to execute proposed studies</td>
</tr>
<tr>
<td>Nationally-recruited team members from multiple institutions work together</td>
<td>Institution-based teams compete with other institution-based teams</td>
</tr>
<tr>
<td>Drug development planning occurs during CRADA negotiations</td>
<td>Mass solicitation occurs after CRADA negotiations have been completed</td>
</tr>
<tr>
<td>Brief application for membership</td>
<td>LOI forms require extensive preparation</td>
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ETCTN Program Portfolio Management Portal

Provides the ability to manage and track experimental therapies from application submission through protocol accrual
Educational Materials

- Educational Materials on the ETCTN-CTSU website includes: links to the webinar recordings, checklists, and information sheets on 14 different topics:
  - Protocol Development
  - Protocol Amendments
  - Person Registration & CTEP-IAM
  - Rosters & Roles
  - The CTSU
  - Protocol Access & Communications
  - Regulatory Processing
  - The NCI CIRB
  - Patient Enrollment
  - Agent Ordering
  - Data Management
  - SAE Reporting
  - CDUS Reporting
  - Auditing and Monitoring

- All documents will be posted to the ETCTN pages on the CTEP website once development is complete
ETCTN Education and Training

Since program launch, we have held a number of educational webinars for ETCTN members:

- **For Leadership:**
  - Kick-off and Overview
  - Rosters and Roles
  - Patient Enrollment
  - NCI CIRB
  - PIO Updates
  - Data Management
  - Biomarkers
  - Implementing Drug Project Teams
  - Web Reporting

- **For Site Staff:**
  - Introduction to the ETCTN, Centralized Services, and the CTSU Website
  - Patient Enrollment
  - Regulatory Processes
  - Data Management
**Team Formation for Drug-Specific Project**

- NCI-CTEP acquires an agent through NExT and announces a drug-specific project team will form (PTA)
  - Investigators with documented expertise (e.g. basic, translational)
- ETCTN Investigators apply as basic, translational or clinical investigators (PTMA)
  - Junior investigators along with senior mentors particularly encouraged (CRDL)
- Project Team is assembled
  - Basic, Translational and Clinical Team Leaders are designated
  - Members commit to a short-term, intense set of teleconference/web-based meetings with NCI-CTEP

**Project Team Goals**

- Arrive at pre-clinical/translational plan that addresses critical questions that will inform drug development
- Propose innovative disease-based or biomarker-based clinical trials incorporating appropriate safety, pharmacokinetic, pharmacodynamic and efficacy endpoints

Drug Development Plan presented to the Investigational Drug Steering Committee, after which full LOIs are written

**Emphasis on Team Science and collaboration across ETCTN network**
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<thead>
<tr>
<th>Basic Science</th>
<th>Translational</th>
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<th>Other</th>
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<tbody>
<tr>
<td>Basic Scientist</td>
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<td>Clinical Leader</td>
<td>Radiation Oncology</td>
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<tr>
<td>Basic Scientist</td>
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<td><strong>Career Development Investigator</strong></td>
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**Bold denotes Career Development Investigator**

**Italics denotes SPORE investigator**