NCI Experimental Therapeutics Clinical Trials Network (ETCTN)
NCAB 9 September 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
High Priority Targets and DCTD/CTEP Agents

- EGF-R
- VEGF-R
- Ras
- Raf
- Bcr
- Abl
- Akt
- MEK
- Btk
- CDKs
- Raf
- P13K
- src
- abl
- sorafenib
dasatinib
tipifarnib
erlotinib
AZD9291
MK-2206
AT-101
obatoclax
navitoclax
TL32711
fenretinide
Ceramide

- Apoptosis
- Survival/Proliferation
- Angiogenesis
- Protein turnover
- Migration/invasion
- Mitosis
- Other receptors
- Surface antigens
- SGN 35 (CD30)
- HA 22 (CD22)
- CDX-011
- IGF-1R
- ganitumab
cixutumumab
- sorafenib
- Lapatinib
- Pertuzumab
- trastuzumab
- c-Kit
- imatinib
- sunitinib
- dasatinib
- saracatinib
dinaciclib
- pazopanib
- sorafenib
cediranib
- pazopanib
- sunitinib
- cediranib
- vandetanib
- bortezomib
- belinostat
- vorinostat
- temsirolimus
- AMG386
- Hsp90
- AT13387
- PU-H71
- Proteasome
- bortezomib
- belinostat
- vorinostat
- LMP400/776
- Topoisomerase
- Alkylating
- Dimethane sulfonate
- Methylation inh.
- FdCyd
- TRC102
- DNA repair epigenetics

- Immuno-modulation
- Notch
- Hedgehog
- Vismodegib
- R04929097
- PARP
- veliparib
- BMN673
- olaparib
- HDAC
- belinostat
- entinostat
- vorinostat
- PD1
- pembrolizumab
- nivolumab
- iMID
- thalidomide
- lenalidomide
- pomalidomide
- CTLA4
- ipilimumab
- tremelimunab
- 1-Methyl-[D]-tryptophan
- FO200/776
- TRC102
- Immuno-modulation
- Notch
**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 ETCTN: Scientific Changes

<table>
<thead>
<tr>
<th>Scientific Elements</th>
<th>Legacy Program</th>
<th>ETCTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Characterization</td>
<td>Occasional</td>
<td>Expected</td>
</tr>
<tr>
<td>Team Science</td>
<td>Infrequent</td>
<td>Required</td>
</tr>
<tr>
<td>Drug Development Plan</td>
<td>Trials not on industry’s development plan</td>
<td>Tackle critical unanswered questions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Disease-based</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Biomarker-based</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drug combinations</td>
</tr>
</tbody>
</table>
NCI Team Science-Drug Development Project Teams

- Clinical
  (Experimental Therapeutics Clinical Trial Network)
- NCI Team Science-Drug Project Teams
  - Translational
  - Centralized Support
  - Cancer Biology
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
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
ETCTN Program Portfolio Management Portal

Provides the ability to manage and track experimental therapies from application submission through protocol accrual.
New Development Cycle for NCI Experimental Therapeutics

1. New Drug
   → Company proposal
   → Special Emphasis Panel
   → NCI Development Committee

2. Request for Projects
   → Important questions
   → Clinical
   → NCI Project Team
   → Translational Support
   → Cancer Biology
   → Division of Cancer Treatment
   → And Diagnosis/Cancer Therapy Evaluation Program meeting
   → Preliminary Drug Development Plan
   → Senior Advisory Committee
   → Scientific Agreements

3. Scientific
   → Translational
   → Drug Project Team
   → Centralized Support
   → Cancer Biology
   → Drug and Assay/Biomarker Development Plan
   → Investigational Drug Steering Committee Review of Important Questions and Drug Development Plan
   → Cooperative Research and Development Program- Development
   → Projects
   → Cooperative Research and Development Program-Signed

4. Projects
   → Letters of intent submitted
   → DCTD Reviews
   → Senior Advisory Committee
   → Protocol development
   → Protocol Activation
New Development Cycle for NCI Experimental Therapeutics

NExT Special Emphasis Panel and Development Committee Reviews

**NCI Project Team** and CTEP Program Meeting: Preliminary Development Plan

**SAC I Review**

CRADA negotiation

**Extramural Project Team**: Finalized Development Plan & IDSC Review

**Sac II Review**

**LOI/Protocol submission**
### NCI ETCTN: Operational Changes

<table>
<thead>
<tr>
<th>Operational Elements</th>
<th>Legacy Program</th>
<th>ETCTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organization</td>
<td>In Silos (14 sites)</td>
<td>Integrated Network (10 sites)</td>
</tr>
<tr>
<td>Centralized Support</td>
<td><strong>Limited:</strong> Safety, Auditing</td>
<td><strong>Comprehensive:</strong> Safety, Auditing, Data capture/monitoring, Central Institutional Review Board, Registration/Roster/Regulatory, Project management, Pharmacokinetics</td>
</tr>
<tr>
<td>Timeline-LOI approval</td>
<td>~21 months</td>
<td>~15 months</td>
</tr>
<tr>
<td>Resources for Molecular Characterization and Sample Acquisition</td>
<td>Limited</td>
<td>• Fewer sites, fewer trials, more extensive characterization</td>
</tr>
</tbody>
</table>
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

CTSU

CTEP Enterprise

CIRB

OPEN IWRS

Regulatory Support Services (RSS)

.medidata RAVE
Theradex Instance of Medidata Rave: Web-based Reporting

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

Enrollment by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dana-Farber</td>
<td>7</td>
</tr>
<tr>
<td>National Cancer</td>
<td>30</td>
</tr>
<tr>
<td>Scripps Clinic</td>
<td>0</td>
</tr>
<tr>
<td>UCSF Thornton Ho</td>
<td>11</td>
</tr>
<tr>
<td>UCSF-Mount Zion</td>
<td>1</td>
</tr>
<tr>
<td>Univ of California</td>
<td>34</td>
</tr>
</tbody>
</table>

Event Count by Course and Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Event Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Compliance Overall for a Protocol
Protocol: 5582

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Number of Courses</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Investigator Eligible Patients</td>
<td>50</td>
<td>98.6%</td>
</tr>
<tr>
<td>Investigator Ineligible Patients</td>
<td>1</td>
<td>2.0%</td>
</tr>
<tr>
<td>Monitor Eligible Patients</td>
<td>49</td>
<td>96.1%</td>
</tr>
<tr>
<td>Monitor Ineligible Patients</td>
<td>2</td>
<td>3.9%</td>
</tr>
<tr>
<td>Monitor Missing Info</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Courses Evaluable</td>
<td>96</td>
<td>95.6%</td>
</tr>
<tr>
<td>Courses Complete</td>
<td>85</td>
<td>84.2%</td>
</tr>
<tr>
<td>Courses with Dose Modifications</td>
<td>47</td>
<td>46.5%</td>
</tr>
<tr>
<td>Courses with Significant Toxicities</td>
<td>70</td>
<td>69.3%</td>
</tr>
<tr>
<td>Average Lab Delay (Days)</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Labs Completed per Protocol</td>
<td>9644</td>
<td>81.3%</td>
</tr>
</tbody>
</table>

* Real time, interactive, web-based, data summaries for monitoring and data mining/analysis
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
NCI Drug Development Programs: ETCTN
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
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
Evaluation of the ETCTN

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
Backup Slides
# ETCTN Principal Investigators

<table>
<thead>
<tr>
<th>Institutions</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dana-Farber/Harvard Cancer Center</td>
<td>Kufe, Donald Flaherty, Keith Shapiro, Geoffrey</td>
</tr>
<tr>
<td>Duke</td>
<td>Hurwitz, Herbert Dees, Elizabeth Lockhart, Albert</td>
</tr>
<tr>
<td>U. North Carolina Wash. U.</td>
<td>Carducci, Michael Gocke, Christopher Gojo, Ivana Rudek, Michelle</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>Erlichman, Charles Huluska, Paul Sausville, Ed</td>
</tr>
<tr>
<td>Mayo - Rochester</td>
<td>Kummar, Shivaani</td>
</tr>
<tr>
<td>Ohio State U.</td>
<td>Grever, Michael</td>
</tr>
<tr>
<td>Rutgers-Cancer Inst. NJ U. Wisconsin</td>
<td>DiPaola, Robert Liu, Glenn</td>
</tr>
<tr>
<td>U. Chicago</td>
<td>Ratain, Mark Maitland, Michael</td>
</tr>
<tr>
<td>U. Health Network</td>
<td>Siu, Lillian Sullivan, Dan</td>
</tr>
<tr>
<td>U. Pittsburgh</td>
<td>Chu, Edward Beumer, Jan</td>
</tr>
<tr>
<td>U. Texas – MDACC U. Colorado – Denver</td>
<td>Yao, James Eckhardt, Gail Meric-Bernstam, Funda</td>
</tr>
<tr>
<td>Yale University</td>
<td>Lorusso, Patricia Eder, Paul Berlin, Jordan</td>
</tr>
</tbody>
</table>
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
# Agents currently tracked for PTA/PTMA

<table>
<thead>
<tr>
<th>Agent</th>
<th>NSC/IND</th>
<th>MOA</th>
<th>CRADA/CDA</th>
<th>PTA/PTMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT13387</td>
<td>749712/109876</td>
<td>Hsp90i</td>
<td>11/02/2009</td>
<td>To IDSC</td>
</tr>
<tr>
<td>BMN 673</td>
<td>771561/119558</td>
<td>Oral PARPi</td>
<td>06/21/2013</td>
<td>Mass Solicitation</td>
</tr>
<tr>
<td>AZD9291</td>
<td>781254/--------</td>
<td>EGFRi, 3rd Gen</td>
<td>04/03/2014</td>
<td>In prep</td>
</tr>
<tr>
<td>VX-970</td>
<td>780162/--------</td>
<td>ATRi</td>
<td>05/29/2014</td>
<td>In prep</td>
</tr>
<tr>
<td>SGI-110</td>
<td>780463/--------</td>
<td>DNMTi</td>
<td>11/20/2011*</td>
<td>In prep</td>
</tr>
<tr>
<td>AMG-337</td>
<td>779337/--------</td>
<td>cMeti</td>
<td>08/09/2013</td>
<td>In prep</td>
</tr>
</tbody>
</table>
Glossary

- **IAM** – Identity and Access Management
- **Regulatory Support System (RSS)** - An application created within the CTSU Enterprise system to create and manage institution, person, and regulatory data for CTEP-supported Cooperative Groups, contractors, and grantees. It is also used to manage CTSU-specific enrollment and delinquency tracking data.
- **Oncology Patient Enrollment Network (OPEN)** - The web-based registration system for patient enrollments onto NCI-sponsored clinical trials. The system is integrated with the CTSU Enterprise System for regulatory and roster data, and with each of the Cooperative Groups' registration/randomization systems for patient registration/randomization. OPEN provides the ability to enroll patients on a 24/7 basis.