Phase 2 Clinical Trials Component of the ETCTN

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Role of NCI/DCTD in Early Clinical Development of New Cancer Therapies

- NCI/DCTD forms collaborations with Pharma and academic medical centers to develop new anticancer agents and new combinations of agents.

- Underlying concept is that important public health needs are not met by Pharma activities alone – role of NCI/DCTD is to expand indications of novel agents as well as the understanding of their biology.
Recently developed NCI IND agents

Agents that have achieved FDA approval based *in part* on early development in CTEP collaborative early phase programs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacytidine</td>
<td>Myelodysplastic syndrome (secondary)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Mantle Cell Lymphoma (secondary)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Melanoma (primary)</td>
</tr>
<tr>
<td>Lenalidomide and bortezomib</td>
<td>Multiple Myeloma (secondary)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Colorectal Cancer (primary)</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>Peripheral T Cell Lymphoma (secondary)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Thyroid Cancer (secondary)</td>
</tr>
<tr>
<td>Ziv-aflibercept</td>
<td>Colorectal Cancer (secondary)</td>
</tr>
</tbody>
</table>

*Pending* FDA approval

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinutuximab (ch14.18)</td>
<td>Neuroblastoma (primary)</td>
</tr>
</tbody>
</table>

In pivotal trials based on development in CTEP program

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Cediranib and Oliparib</td>
<td>Ovarian Cancer</td>
</tr>
<tr>
<td>Selumetinib</td>
<td>Uveal Melanoma (secondary)</td>
</tr>
</tbody>
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Role of NCI / DCTD in Early Clinical Development of New Cancer Therapies

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- Underlying concept is that important public health needs are not met by Pharma activities alone – role of NCI/DCTD is to expand indications of novel agents as well as the understanding of their biology.

- Many interrelated NCI programs are devoted to this effort, from initial evaluation of proposed collaborations and preclinical development through initial clinical evaluation.
New Development Cycle for Early Experimental Therapeutics

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

2. Translational → NCI Project Team → Centralized Support → Clinical → Cancer Biology
   - Division of Cancer Treatment and Diagnosis/Cancer Therapy Evaluation Program meeting
   - Senior Advisory Committee
   - Recruit Scientific Project Team
   - Regulatory/Agreements

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

4. Projects → Letters of intent submitted → DCTD Reviews → Senior Advisory Committee
   - Protocol development → Protocol Activation
Role of ETCTN in NCI Drug Development

- The Experimental Therapeutics Clinical Trials Network (ETCTN) is the network of clinical trial sites and infrastructure that is solely devoted to the conduct of the earliest clinical studies of Investigational New Drugs (INDs) sponsored by NCI.

- Assures the development of NCI IND agents up to the point of hand-off to NCTN and/or back to Pharma: defining dose, schedule, target engagement, biomarkers of response, and demonstration of clinical activity.

- Involves a community of extramural experts in the CTEP drug development strategy for NCI IND agents.

- Maintains an experienced network of investigators focused on mechanism-based early phase studies that require intensive monitoring for safety and intensive intervention for correlative studies.
Centralized clinical trial support services to support ETCTN

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

CTEP Enterprise

Regulatory Support Services (RSS)

IAM

CTSU

CIRB

OPEN

IWRS

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Consolidating the NCI ETCTN initiative

- The ETCTN is currently composed of two distinct clinical components: Phase 1 UM1 grant program and Phase 2 N01 contract program.
- Both the phase 1 and phase 2 programs consist of lead organizations, either the grant or contract holders, and multiple affiliated centers that contribute to accrual and scientific goals.
- The Phase 1 program was recently re-competed as part of the formation of ETCTN.
- The expiration of contracts for the phase 2 program is an opportunity to develop ETCTN into a unified grant program to adapt to the era of targeted therapies.
- As clinical science has evolved, current programmatic separation of phase 1 and 2 activities is not desirable.
Evolution of the science of early phase trials

Requirements for early phase trials have evolved:

• Disease-focused context traditionally associated with phase 2 trials now frequently required in phase 1 studies

• Disease-specific biomarker incorporation into trials, both for eligibility and proof of target engagement, are now almost always required for early stage drug development

• Pharma has already adopted flexible early phase study design, quickly building phase 2 endpoints into phase 1 studies when signal of activity is detected
Phase 2 Program goals: How do we make the program fit the science?

Program goals reflecting new realities:

- Shorter duration from phase 1 initiation through proof-of-activity by placing pharmacology-focused investigators (phase 1) with disease-focused investigators (phase 2) in the same program to quickly explore signals of activity.

- Enhance biomarker incorporation into phase 2 study design

- Maintain experienced phase 2 investigators in ETCTN and on ETCTN project teams that develop early phase studies

- Expand pool of eligible patients for rare tumor subtypes

- Further leverage ETCTN centralized clinical trial support resources
Separate vs unified ETCTN structure

Current

Phase 1
(n=12 plus 10 NCI CC affiliates)

Phase 2
(n=7 plus 16 NCI CC affiliates)

Proposed
ETCTN Core Grant Program

- Current phase 1 grantees will compete for supplements to expand phase 2 expertise
  - May include current NCI phase 2 programs or qualified experimental therapeutics programs at other NCI CC’s
  - Opportunity to redistribute the 23 NCI CCs currently affiliated with the phase 2 contract program into more streamlined alignments
    - 7 NCI CC’s affiliated with different UM1 and N01 LAO’s
    - Flexibility in number of supplements requested to optimize network
- A limited-competition RFA is soon to be published for UM1 supplements; focus will be on scientific leadership/expertise for ETCTN phase 2 studies
ETCTN Pilot Collaboration with NCI CC Program

Phase 1
(n=12 plus 10 NCI CC affiliates)

Phase 2
(n=7 plus 16 NCI CC affiliates)

NCI Early Therapeutics Opportunity Program
(P30 supplement)
(NCI CC’s without ETCTCN affiliation = 29)

Current

Proposed

NCI CCs with ETCTN affiliation = 27
NCI CC’s without ETCTN affiliation = 29
NCI Early Therapeutics Opportunity Program - Pilot collaboration with NCI cancer centers program

- Proposal designed to greatly expand participation in early drug development studies for both physician-scientists and patients
  - Study leadership proposal
  - Phase 2 study participation proposal
In the NCI Early Therapeutics Opportunity Program, an investigator from any clinical NCI-designated cancer center could submit an Letter of Intent (LOI) to CTEP and, if approved by the Protocol Review Committee (PRC), the PI could receive:

- Full ETCTN clinical trial support for the study – including CI RB, registration and data management support, and accrual from ETCTN sites
- Funds for salary reimbursement (% effort)
- Funds for accrual to the study at the PI’s home institution

LOIs must be approved and submitted by cancer center

Administered as a P30 administrative supplement after LOI approved by PRC
NCI Cancer Centers and ETCTN Phase 2 study accrual

- NCI Cancer Centers would be able to open selected ETCTN phase 2 studies that require screening for rare tumor subsets.
- Reimbursement via P30 supplement with some restricted funding.
- Approximately 30 of the non-ETCTN NCI CC’s after the revised UM1 grants are awarded can compete for approximately 15 phase 2 accrual supplements.
- Supplements intended to offset per-patient research study costs, not screening costs.
NCI Cancer Centers and ETCTN Phase 2 study accrual

- Review criteria will include: Relevant patient accrual history, molecular screening practices, investigator qualifications, access to special populations

- Annual renewal of supplements will depend on demonstration of minimum accrual during previous year.

- New supplements may be awarded to additional cancer centers after the first year using funds not spent on renewals.
Study Leadership: Announcement soon after UM1 revisions announced (Jan, 2016)
  - Will accept LOI’s anytime after that date

Phase 2 accrual: Announcement soon after UM1 revisions announced
  - Dates for acceptance of supplement applications TBD

Overall additional accrual to ETCTN trials with both proposals is up to 91 patients per year
  - Study leadership n=16
  - Rare population accrual n=75
Metrics for Pilot NCI CC collaboration

- Number of accepted LOI’s
- Accrual to studies opened through leadership supplement
- Number of NCI CC’s participating in both programs
- Accrual to studies for rare tumors

Renewal would depend on performance of pilot program
## Total budget request

**Total Proposed Annual Allocation of Funds** $10,000,000 per year  
**Proposed Annual Allocation of Funds for UM1 supplements:** $9,000,000 per year

<table>
<thead>
<tr>
<th>UM1 Phase 2 Supplements</th>
<th>$9,000,000</th>
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<tbody>
<tr>
<td>Unrestricted Funding</td>
<td>$7,200,000</td>
</tr>
<tr>
<td>Salary support and travel</td>
<td>$1,000,000</td>
</tr>
<tr>
<td>Per-case patient accrual and biopsy acquisition</td>
<td>$6,200,000</td>
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**Restricted funding – For Biomarker Studies**  
$1,800,000  
20%

**NCI Cancer Centers Pilot Collaboration with ETCTN**  
$1,000,000

- Study leadership supplements (n=4 @ $62,500/supplement)  
  $250,000
- Supplements for study accrual (n=15 @ $50,000/supplement)  
  $750,000
Open for discussion
Questions for CTAC:

How can we increase participation in ETCTN clinical trials?

How can we generate more phase 2 trial concepts (with supporting data) for testing NCI-IND agents?

What other initiatives could be undertaken to develop NCI-IND agents?