NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

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Experimental Therapeutics Clinical Trials Network (ETCTN)

≈ 41 enrolling North American sites

UM1 network first renewal RFA/FOA
• 12 Lead Academic Organization (LAO) sites (includes NCI-Clinical Center)
• 29 Affiliated Organizations (AO) sites
• 2120 patients enrolled through Q4 2017

Clinical trials
• Activated studies: 82
• Ongoing studies: 132
• Closed studies: 37
• Completed/Admin Completed studies: 11

ETCTN Sites (UM1)
Bio-Repository at Nationwide (U10)
Centralized Support Services
EDDOP-Leadership/Accrual

≈ 41 enrolling North American sites
Goals and Objectives of Experimental Therapeutics Clinical Trials Network

**Research, development and improvement of cancer treatments**
- Advance the clinical development of NCI-IND agents with early phase studies
  - *Complementary collaboration with pharma partners*
- Determine dose, schedule and sequence for NCI-IND agents and combination regimens
- Perform disease-specific activity studies of NCI-IND agents and combinations
  - *Prioritize cancers and cancer subsets where industry is not investing*

**Biomarker and cancer biology-driven studies using patient derived specimens**
- Acquire high quality patient tumor specimens for correlative studies
- Incorporate fit-for-purpose PD/biomarker assays into ETCTN trials

**Career enhancement for early career investigators**
- Experience leading clinical trials in the ETCTN
- Play a significant role on the drug development Project Teams
ETCTN – Transformation to a Network Structure

• Collaborative approach to clinical trial development and implementation
  – Moved from mass solicitations to extramural project teams early in clinical development planning
  – Involve disease-specific clinical expertise from all sites
  – Enhance study participation across the network

• Assuring Reproducible Translational Science
  – Transformed the approach to biomarkers from laboratory developed tests (LDTs) to analytically validated, fit for purpose bioassays

• Site Re-Organization and Infrastructure Support
  – Moved from siloed sites to a unified trials network with centralized infrastructure support
  – Further enhanced GCP principles in all aspects of ETCTN trials
Experimental Therapeutics Clinical Trials Network: Lead Academic (12) and Affiliated Organizations (41); Experimental Drug Development Opportunities Program (15)
ETCTN central infrastructure support

Secure investigator access
(Identity and Access Management)

Other Tasks:
CTEP monitoring and reporting

Document access and Regulatory check
(Cancer Trials Support Unit)

Central IRB

Regulatory Support Services (RSS)
Track ICDs, amendments, protocol versions, FDA filings

Enroll Patients
(Oncology Patient Enrollment Network)

Safety reporting and protocol authoring
(Technical Resources International)

CTEP Enterprise

Patient DB

Safety DB

Specimen tracking

Auditing

ETCTN Biorepository and Accessioning Center

Patient DB

Specimen tracking Auditing
External review of Agents and Trials in the ETCTN

- **All agents come from the NExT (NCI Experimental Therapeutics) Pipeline**
  
  Review of applications by external experts


- **All trials proposed by drug development project teams are reviewed by Investigational Drug Steering Committee**
  
  - IDSC is composed of ETCTCN PIs, external experts and NCTN members
ETCTN drug development project teams

Drug development project teams (14):
- AT13387 (onalespib) (HSP90i)
- Osimertinib (AZD9291, T790M EGFRi)
- M3814 (DNA-PKcs i)
- VX970 (ATRi)
- Durvalumab (PD-L1i)
- Atezolizumab (PD-L1i)
- T-VEC (Talimogene laherparepvec, oncolytic virus)
- AMG-232 (mdm2i)
- Anetumab ravtansine (BAY 94-9343, anti-mesothelin)
- Copanlisib (BAY 80-6946, PI3Ki)
- CB839 (glutaminase i)
- Ixazomib (proteasome i)
- Pevonedistat (NEDD8i)
- M3814 (DNA-PKi)
- 3 others starting

- Extensive extramural involvement
- Reflects heavy emphasis on early career development
- Drug development and CRADA negotiations occur in parallel
- Unsolicited LOIs accepted after Project Team deliberations
High impact NCI/CTEP IND agent clinical trials

- **FDA approval**
  - Dinutuximab (ch14.18)- Neuroblastoma

- **Orphan Drug and Breakthrough Designation application**
  - Triapine- Advanced uterine cervical cancer (11.08.2017)
  - Selumetinib- NF1 (02.14.2018)
Ipilimumab in Relapsed Hematologic Malignancies post-Allogeneic HSCT (9204)

- 28 patients enrolled to 3 or 10 mg/kg
- Among 22 receiving 10 mg/kg:
  - 5 CR (4 extramedullary AML and 1 AML evolving from MDS)
  - 2 PR
  - 6 with reduced tumor burden
  - 4 patients with durable response > 1 year
- Responses associated with:
  - *In situ* infiltration of cytotoxic CD8+ T cells
  - Decreased activation of regulatory T cells
  - Expansion of subpopulations of effector cells in peripheral blood

Follow-up studies: evaluation of nivolumab and ipilimumab/decitabine in the same population (CTEP 10026)

*Davids et al., NEJM, 2016  (Career Development Award; Mentor R. Soiffer)*
Olaparib and Cediranib in Platinum-Sensitive High-Grade Serous Ovarian Cancer (8348)

- Based on pre-clinical data indicating that VEGFR inhibition can establish a PARP-dependent microenvironment
- 46 patients randomized to olaparib alone and 44 randomized to cediranib + olaparib
- Improvement noted in **BRCA carriers as well as non-carriers** (effect size greater in non-carriers)
- Has led to an extensive follow-up program and phase 3 and 2/3 pivotal trials in platinum sensitive & resistant patients

**Cediranib Aims for a Comeback**
*J Natl Cancer Inst, 2015, Vol. 107, No. 3*

*Liu et al., Lancet Oncol, 2014*  
(Career Development Award; Mentor U. Matulonis)

2014 Award from the Research Foundation of the Columbia Hospital

<table>
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<tr>
<th></th>
<th>Olaparib</th>
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<tr>
<td>PFS events</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Median PFS</td>
<td>9.0 mo</td>
<td>17.7 mo</td>
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<tr>
<td>p</td>
<td>0.005</td>
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<tr>
<td>HR</td>
<td>0.42 (95% CI: 0.23-0.76)</td>
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Increasing Number of ETCTN Studies

- Activated Cumulative Studies
- Closed Studies Cumulative

- 2014: 4
- 2015: 0
- 2016: 4
- 2017: 11
- 2018 (3/31/2018): 82

- 2014: 4
- 2015: 2
- 2016: 47
- 2017: 74
- 2018 (3/31/2018): 82
Quarterly ETCTN Accrual (Limited, Wide, Legacy and Total) Q2 2014 – Q1 2018
<table>
<thead>
<tr>
<th>Activity</th>
<th>Number of LOIs (% of total)</th>
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<tr>
<td>LOIs from Project Teams with early career PI’s</td>
<td>45 (90)</td>
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<tr>
<td>Unsolicited/pre-solicitation LOIs with early career PI</td>
<td>60 (31)</td>
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<tr>
<td>Activated or transitioned ETCTN protocol with early career PI</td>
<td>44 (60)</td>
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ETCTN External Program Review

- Reviewers were recruited from government and pharma, both nationally and internationally in January 2018
  
  Greg Reaman, FDA, USA  Janet Dancey, NCIC & ORI, Canada
  Eric Rubin, Merck & Co., USA  Ian Walker, CRUK, UK

- Review questions included:
  
  - Have **phase 1/2 trials opened** at an adequate rate?
  - Are trials answering **important questions and optimally designed**?
  - Were steps taken to adapt to cancer **precision medicine** challenges?
  - Does the program conform to **GCP standards**?
  - Is **team science** promoted? Is this a collaborative, interactive research network?
  - Are adequate clinical research opportunities provided for **early career investigators**?

- Reviewers **responded positively to all questions**, thought the program achieved its goals and objectives, and provided additional **input for future endeavors**.
ETCTN transformation during the 2020-2025 award period: Leveraging NCI resources to enhance drug development & productivity

1. Address the need to find rare or uncommon, molecularly defined subsets of patients – a challenge for phase 2 studies

2. Enhance requirements for high quality biopsy material for correlative studies

3. Improve ability to perform validated biomarker assays to characterize and monitor molecularly defined subsets of common or uncommon tumors (validation of integral/integrated biomarkers)
1. Recruit rare or uncommon, molecularly defined subsets of patients

- **Lead and Affiliate Organizations will apply as teams**
  - Encourage multiple PI applications
  - Leads to have a minimum of **one Phase 1 investigator**
  - Leads and Affiliates to have a minimum number of **identified key investigators** responsible for **disease-specific** accrual
    - **4** distinct disease-specific investigators **for each Lead**
    - **2** distinct disease-specific investigators **for each Affiliate**
  - Award will provide **partial salary support** for each team member- NCI can provide academic credit through grant salary support
  - Funded co-investigators will have **performance criteria outlined in Terms of Award** for performance opening studies and accrual
2. Improve the quality of biopsy specimens

- **Organize ETCTN-wide initiatives with ETCTN-funded investigators to improve biopsy quality**
  - Partial salary support for these team members will be provided
  - Funded investigators will have **performance criteria in the Terms of Award**

- **Lead academic organization teams to include:**
  - An **Interventional Radiologist and Research Pathologist** for acquisition of high quality specimens

- **Each Affiliate team to include**
  - An **Interventional Radiologist** for acquisition of high quality specimens; **Research Pathologist** optional
3. Enhance use of biomarker assays to achieve Precision Medicine goals

- **Increase use of biomarker assay resources developed through NCI resources**
  - Pharmacodynamic Assay Development and Implementation Section (PADIS) lab and network
  - Cancer Immune Monitoring and Analysis Centers (CIMACs) for Immuno-Oncology (IO) studies
  - Molecular Characterization (MoCha) lab for genomic and transcriptomic evaluation
  - ETCTN biorepository and accessioning center

- **Scale back UM1 Biomarker Assay Development supplements**

- **Consolidate ETCTN PK activities**
  - Two U24-funded PK consortia
  - **Remove funding** for PK assays from core ETCTN UM1 awards
Experimental Therapeutics Clinical Trials Network (ETCTN)

- Bio-Repository at Nationwide (U10)
- ETCTN Sites (UM1)
- Centralized Support Services
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Proposed updates/changes to ETCTN Network

- Affiliated organizations
- New ETCTN initiatives
- ETCTN biorepository (U10)
- Early drug development opportunities programs in NCI CCs (EDDOP) for accrual and leadership
Additional goals for the ETCTN 2020-2025

• **Use of Moonshot networks/centers** for preclinical work in support of clinical trials (e.g., PDxNet, DRSN)

• **Broaden classes of agents** under NCI development (e.g., radiopharmaceuticals, cellular therapies)

• Include **ePRO’s** in early phase ETCTN studies for safety and tolerability determinations

• Further development of **risk-based monitoring approaches**