NCI Experimental Therapeutics Clinical Trials Network (ETCTN):
Clinical/Translational Researcher Perspective

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Co-PI, Dana-Farber/Harvard Cancer Center ETCTN Site
Primary reasons why participation in the ETCTN is essential for the vitality of Early Drug Development programs:

- Creation of **Drug-Specific Project Teams** affords opportunity to contribute to a collaborative network with substantial input into drug development plans that is inclusive of junior investigators.

- Ability of NCI-CTEP to foster the development of **novel drug combinations** allows leveraging of preclinical results that otherwise may not be translated to clinical trial.
Legacy Program vs. Project Team Model

**Legacy Program**

- NCI-CTEP procured an agent and solicited LOIs for pre-defined trials that were not already incorporated into industry’s drug development plan (“mass solicitations”)
- Investigators at individual institutions submitted competitive LOIs, including extensive preclinical data justifying the clinical proposal (if available), details of the trial execution and biostatistical considerations
- Process had a high failure rate because only a small number of LOIs were approved, resulting in substantial investigator frustration, especially at the junior level

**Project Teams**

- Investigators apply for project team membership as basic, translational or clinical scientists
- Assembled project team works with CTEP to (1) assess preclinical package and determine if other work is needed to inform clinical development and (2) propose innovative disease-based or biomarker-based clinical trials incorporating appropriate safety, pharmacokinetic, pharmacodynamic and efficacy endpoints
- Drug Development Plan is presented to the IDSC, after which full LOIs are written
Astex development plan includes ALK+ NSCLC (+crizotinib), GIST (+imatinib) and CRPC (+abiraterone)

Critical disease-based and scientific areas not addressed:

- Activity of a potent HSP90 inhibitor in NHL, where ALK, CDK4 and BCL6 are all HSP90 clients
- Activity of HSP90 inhibition in TNBC in which multiple pathways involving HSP90 clients are activated
- Activity of the agent in EGFR-mutated NSCLC, especially true for mutant EGFRs with *de novo* resistance to quinazoline TKIs
- Ability of HSP90 inhibition to modulate DNA damage responses (e.g. chemoradiation in SCCHN)
<table>
<thead>
<tr>
<th>Basic Science</th>
<th>Translational</th>
<th>Clinical</th>
<th>Other</th>
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<tbody>
<tr>
<td>L. Neckers (NCI)</td>
<td>G. Shapiro (Leader; DFCI)</td>
<td>L. Siu (Leader; PMH)</td>
<td>B. Vikram (Rad Onc; NCI)</td>
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<tr>
<td>M. Nyati (U Mich)</td>
<td>D. Carbone (OSU)</td>
<td>A. Hope (SCCHN; PMH)</td>
<td>E. Bernhard (Rad Onc; NCI)</td>
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<td></td>
<td>G. Mills (MDACC)</td>
<td>C. Jacobson (NHL; DFCI)</td>
<td>K. Camphausen (Rad Onc; NCI)</td>
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<td></td>
<td>C. Van Waes (NCI)</td>
<td>D. Weinstock (NHL; DFCI)</td>
<td>F.-F. Liu (Rad Onc; PMH)</td>
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<td></td>
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<td>J. Reiss (NSCLC; UC-Davis)</td>
<td>F. Lin (Imaging; NCI)</td>
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<tr>
<td>Alice Chen, Senior Investigator, NCI-CTEP</td>
<td></td>
<td>K. Reckamp (NSCLC; UC-Davis)</td>
<td>M. Knopp (Imaging; OSU)</td>
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<tr>
<td>Jamie Zwiebel, IDB Chief, NCI-CTEP</td>
<td>R. Wesolowski (Breast; OSU)</td>
<td></td>
<td>P. Choyke (Imaging; NCI)</td>
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<tr>
<td>Amy Gravell (Administrative)</td>
<td></td>
<td>B. Ramaswamy (Breast; OSU)</td>
<td>L. Rubinstein (Biostats; NCI)</td>
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<tr>
<td>Steven Reeves (IDSC)</td>
<td>A. Eisbruch (SCCHN; U Mich)</td>
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<td></td>
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<td>K. Rao (SCCHN; UCHIC)</td>
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**Bold denotes Career Development Investigator**

**Italics denotes SPORE investigator**

- S. Kummar (NCI)
- K. Do (NCI)
- G. Shapiro (DFCI)
Work Conducted by the AT13387 Project Team

- Leadership and Team Orientation Calls
- Proposals for Lymphoma and TNBC, with biomarker discussion
- Proposals for SCCHN and NSCLC, with biomarker discussion
- 4 Disease-based calls during which clinical investigators from other ETCTN sites with relevant expertise were invited
- Additional preclinical calls (SCCHN, radiation biology)
- Additional preclinical discussions of strategies to abrogate HSP70 induction in response to HSP90 inhibition and of other combinations exploiting effects of HSP90 inhibition on DNA repair (PARP inhibition)
- Overall, 12 teleconferences over a 4-week period culminated in 4 proposals presented to the IDSC encompassing clinical trials with associated pharmacodynamic and genomic components
Clinical Proposals Emanating from the AT13387 Project Team Deliberations

- **NHL**: Monotherapy Phase 2 study in ALK-positive ALCL, Mantle Cell Lymphoma and BCL6-positive DLBCL
- **TNBC**: Phase 1/1b Monotherapy followed by taxane combination
- **NSCLC**: Phase 1b Erlotinib/AT13387 following erlotinib run-in; patients with tumors harboring exon 20 insertion mutations also to be evaluated
- **SCCHN**: Phase 1 study of AT13387 with standard dose chemoradiation
### Biomarker Prioritization

<table>
<thead>
<tr>
<th>Priority #1: Proof-of-Mechanism</th>
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<td>• Induction of HSP70 in tumor as canonical marker for HSP90 inhibition</td>
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<td>• Depletion of clients likely required to produce response or clinical benefit</td>
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<td>– Reduced expression of DNA repair proteins in combination with chemoRT</td>
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<td>– Reduced mutant EGFR expression</td>
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<tr>
<td>– Plasma-based detection of mutant EGFR</td>
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<tr>
<td>– Reduced expression of lymphoma drivers</td>
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<tr>
<td>– Reduced expression of TNBC drivers or determinants that could affect response to taxane</td>
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<th>Priority #2: Genomics</th>
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<td>• WES assessments separating responders from non-responders</td>
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<td>• RNA-seq/WES analysis of mechanisms of pathway adaptation and resistance</td>
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<th>Priority #3: Non-invasive assessments</th>
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<td>• FLT-PET scans in lymphoma and TNBC studies</td>
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Additional Preclinical Recommendations

• Additional work to confirm safety of cisplatin and AT13387 in preclinical SCCHN models
• *In vivo* assessment of AT13387 with
  – AT7519 (CDK9 inhibitor, to disrupt HSP70 induction)
  – veliparib or BMN673, PARP inhibitors within the CTEP portfolio
• AT13387/AT7519 and AT13387/PARPi to be submitted as unsolicited LOIs at a later date
## Drawbacks of the Project Team Model and Solutions

<table>
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<tr>
<th>Potential Problems</th>
<th>Solutions/ Mitigating Factors</th>
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<tbody>
<tr>
<td>Project Team Size (attempt to be inclusive)</td>
<td>Careful selection of members based on prior experience, publications, peer-reviewed grants in the field</td>
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<tr>
<td>Too selective (not all ETCTN sites can be represented)</td>
<td>Engagement of other investigators who may join ETCTN studies once initial plans are reaching maturity</td>
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<td>Heavy time investment for project team members without guarantee of leading a trial</td>
<td>Ability to engage junior mentees and participate in network-wide studies; ability for basic and translational investigators to crystallize experiments that will inform drug development (with possible support)</td>
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<td>Varied priorities of project team members; can’t develop all ideas</td>
<td>Strong team leadership required from CTEP and project team leaders; ability to submit unsolicited LOIs after plan presented by project team is approved</td>
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Novel Drug Combinations Facilitated by NCI-CTEP/ETCTN

- **Trametinib/Navitoclax (CTEP 9525)** in KRAS mutated cancers (NSCLC, CRC, pancreatic), based on synthetic lethal interaction of MEK and Bcl-xL inhibition
- **Pembrolizumab/Aflibercept (CTEP 9676)**, based on favorable modulation of the immune microenvironment by VEGF inhibition in the setting of PD-1-blockade
- **Dinaciclib/Veliparib (CTEP 8484)**, based on CDK inhibitor-mediated disruption of HR repair and sensitization to PARP inhibition
- **Cediranib/Olaparib (CTEP 9348)**, based on greater PARP dependence in a hypoxic environment
<table>
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<tr>
<th>Combination</th>
<th>Collaborative Disease Based Program (s)</th>
<th>SPORE or other Funding</th>
<th>Career Development Investigator</th>
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<tbody>
<tr>
<td>Trametinib/Navitoclax</td>
<td>GI, Thoracic</td>
<td>GI SPORE</td>
<td>Yes</td>
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<tr>
<td>Pembrolizumab/ziv-Aflibercept</td>
<td>Melanoma, Immunology</td>
<td>Melanoma Research Alliance (for ipi + bev)</td>
<td>No</td>
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<tr>
<td>Dinaciclib/Veliparib</td>
<td>Breast</td>
<td>Breast SPORE R01</td>
<td>Yes</td>
</tr>
<tr>
<td>Cediranib/Olaparib</td>
<td>Gyn</td>
<td>ARRA supplement</td>
<td>Yes</td>
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CTEP 8348: Phase 1/2 Study of Cediranib/Olaparib in EOC and TNBC

Effect of cediranib/olaparib on cell invasion

![Graph showing cell invasion inhibition by cediranib/olaparib](image)

- **VEGF receptor inhibition** (nM): 50, 1
- **PARP inhibition** (uM): 10, 0.05
- **Both**

Effect of cediranib/olaparib on microvascular cell tube organization

![Graph showing microvascular cell tube organization](image)

- **2171 5nM**
- **2281 100nM**
- **Concurrent**

Platinum-sensitive EOC

![Survival curve graph](image)

- **Median PFS**
  - Olaparib: 9.0 mo
  - Ced/Olap: 17.7 mo

- **PFS events**
  - Olaparib: 28
  - Ced/Olap: 19

- **HR**
  - Olaparib: 0.42
  - Ced/Olap: 0.42

- **95% CI**: 0.23-0.76

- **p-value**: 0.005

Liu et al. J Clin Oncol 2014;32:5s:LBA5500
CTEP 9825: Phase 2 Biomarker Study of Cediranib/Olaparib

Platinum-sensitive

Recurrent ovarian cancer

Platinum-resistant (2 stage enrollment)

Parallel enrollment cohorts

Cediranib/olaparib until progression

Cediranib/olaparib until progression

Mandatory archival tissue

Mandatory pre-treatment biopsy

Optional post-progression biopsy

Whole exome sequencing assessing alterations in HR CECs and CEPCs for angiogenic markers via flow cytometry

Joyce Liu, PI
ETCTN Molecular Characterization Hubs

**DFCI/BWH/Broad Institute**
- Neal Lindeman, MD
- Levi Garraway, MD, PhD
- Agilent hybrid capture and Illumina-based Targeted NextGen sequencing (305 gene panel)
- Whole exome and whole transcriptome sequencing on selected cases

**Yale Cancer Center**
- Jeffrey Sklar, MD
- David Rimm, MD
- Ion Torrent 409 gene panel
- Protein-based profiling

Gene panel to be decided relevant for AZD9291, AT13387, BMN673 with cross-validation between the sites
Summary

- Project Team model facilitates a **highly collaborative and interactive process** for proposing a drug development plan. This is superior to the legacy system in which there was far less engagement of U01 sites in trial prioritization and design for particular agents.
- Highly advantageous for ETCTN to draw on a **multidisciplinary team** of senior leaders and **junior investigators early** in the process.
- NCI-CTEP portfolio is poised to promote development of **innovative combinations** from different pharmaceutical companies based on strong preclinical rationale.
- NCI-CTEP **operational improvements** (CIRB, patient registration, data management) will facilitate more rapid activation of studies and engagement of the network when required for robust accrual.