

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

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ETCTN Innovations for Early Phase Drug Development

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

First Drug-Specific Project Team: HSP90 inhibitor AT13387

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)

AT13387 Project Team

Basic Science	Translational	Clinical	Other
L. Neckers (NCI)	<i>G. Shapiro (Leader; DFCI)</i>	L. Siu (Leader; PMH)	B. Vikram (Rad Onc; NCI)
M. Nyati (U Mich)	D. Carbone (OSU)	A. Hope (SCCHN; PMH)	E. Bernhard (Rad Onc; NCI)
	<i>G. Mills (MDACC)</i>	C. Jacobson (NHL; DFCI)	K. Camphausen (Rad Onc; NCI)
	C. Van Waes (NCI)	D. Weinstock (NHL; DFCI)	F.-F. Liu (Rad Onc; PMH)
		J. Reiss (NSCLC; UC-Davis)	F. Lin (Imaging; NCI)
Alice Chen, Senior Investigator, NCI-CTEP		K. Reckamp (NSCLC; UC-Davis)	M. Knopp (Imaging; OSU)
Jamie Zwiebel, IDB Chief, NCI-CTEP		R. Wesolowski (Breast; OSU)	P. Choyke (Imaging; NCI)
Amy Gravell (Administrative)		B. Ramaswamy (Breast; OSU)	L. Rubinstein (Biostats; NCI)
Steven Reeves (IDSC)		<i>A. Eisbruch (SCCHN; U Mich)</i>	
		K. Rao (SCCHN; UCHIC)	
Bold denotes Career Development Investigator		S. Kummar (NCI)	
<i>Italics denotes SPORE investigator</i>		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

Priority #1: Proof-of-Mechanism

- Induction of HSP70 in tumor as canonical marker for HSP90 inhibition
- Depletion of clients likely required to produce response or clinical benefit
 - Reduced expression of DNA repair proteins in combination with chemoRT
 - Reduced mutant EGFR expression
 - Plasma-based detection of mutant EGFR
 - Reduced expression of lymphoma drivers
 - Reduced expression of TNBC drivers or determinants that could affect response to taxane

Priority #2: Genomics

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

Priority #3: Non-invasive assessments

- FLT-PET scans in lymphoma and TNBC studies

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

Potential Problems	Solutions/ Mitigating Factors
Project Team Size (attempt to be inclusive)	Careful selection of members based on prior experience, publications, peer-reviewed grants in the field
Too selective (not all ETCTN sites can be represented)	Engagement of other investigators who may join ETCTN studies once initial plans are reaching maturity
Heavy time investment for project team members without guarantee of leading a trial	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)
Varied priorities of project team members; can't develop all ideas	Strong team leadership required from CTEP and project team leaders; ability to submit unsolicited LOIs after plan presented by project team is approved

Novel Drug Combinations Facilitated by NCI-CTEP/ETCTN

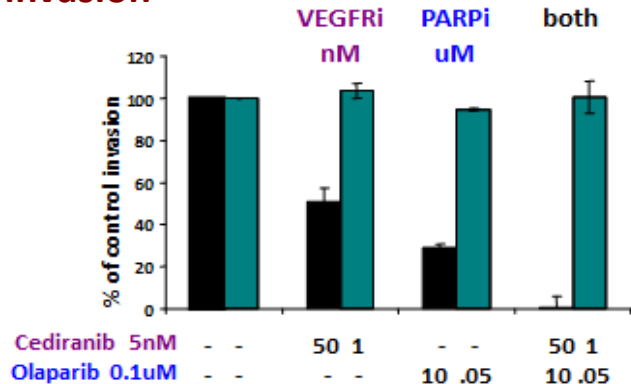
- **Trametinib/Navitoclax (CTEP 9525)** in KRAS mutated cancers (NSCLC, CRC, pancreatic), based on synthetic lethal interaction of MEK and Bcl-xL inhibition
- **Pembrolizumab/Aflibercept (CTEP 9676)**, based on favorable modulation of the immune microenvironment by VEGF inhibition in the setting of PD-1-blockade
- **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

Novel CTEP Combinations: Integration with SPOREs and R01's and Involvement of Junior Investigators

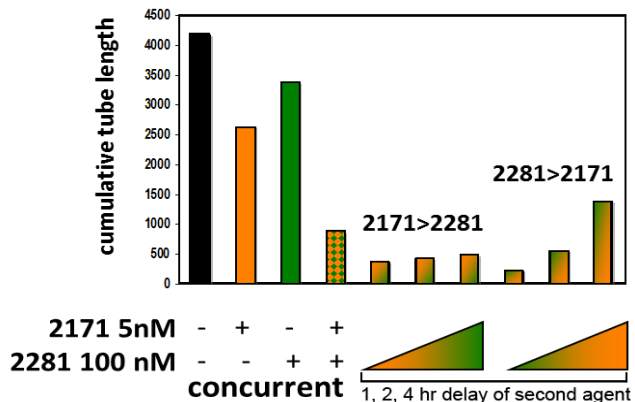
Combination	Collaborative Disease Based Program (s)	SPORE or other Funding	Career Development Investigator
Trametinib/Navitoclax	GI, Thoracic	GI SPORE	Yes
Pembrolizumab/ ziv-Aflibercept	Melanoma, Immuno- oncology	Melanoma Research Alliance (for ipi + bev)	No
Dinaciclib/Veliparib	Breast	Breast SPORE R01	Yes
Cediranib/Olaparib	Gyn	ARRA supplement	Yes

CTEP 8348: Phase 1/2 Study of Cediranib/Olaparib in EOC and TNBC

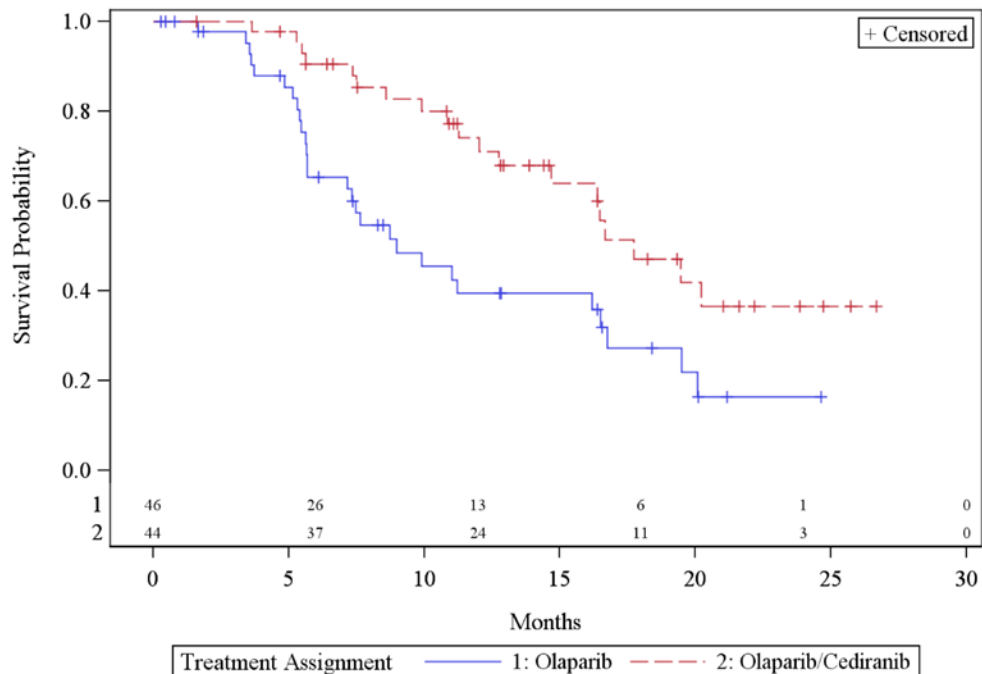
Effect of cediranib/olaparib on cell invasion



Effect of cediranib/olaparib on microvascular cell tube organization

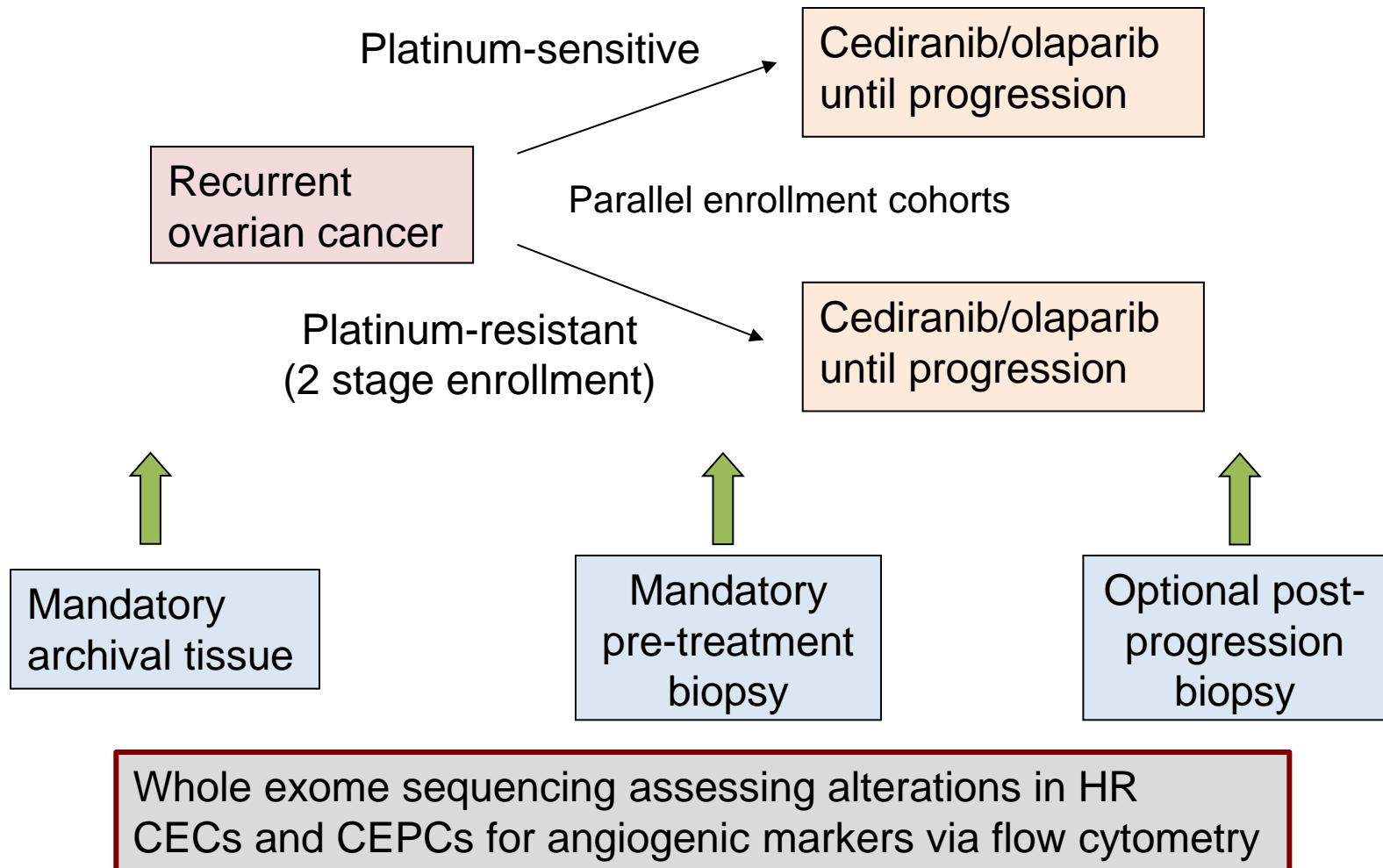


Platinum-sensitive EOC



	Olaparib	Ced/Olap
PFS events	28	19
Median PFS	9.0 mo	17.7 mo
p=0.005		
HR 0.42 (95% CI: 0.23-0.76)		

CTEP 9825: Phase 2 Biomarker Study of Cediranib/Olaparib



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.