CTAC Meeting
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NCI Drug Development Project Teams:
Collaborative Efforts of Clinical, Translational and Basic Researchers to Generate Drug Development Plans

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Formation of Drug-Specific Project Teams

- NCI-CTEP procures an agent and solicits applications for team membership (PTMA)
- Invited participation of investigators with documented expertise (e.g. basic, translational)

- Investigators at ETCTN sites apply as basic, translational or clinical investigators
- Applications from junior investigators with senior mentors particularly encouraged

- Project Team is assembled
- Basic, Translational and Clinical Team Leaders are designated
- Members commit to a short-term, intense set of teleconference/web-based meetings with NCI-CTEP

Project Team Goals

- Arrive at pre-clinical/translational plan that addresses critical questions that will inform drug development
- Propose innovative disease-based or biomarker-based clinical trials incorporating appropriate safety, pharmacokinetic, pharmacodynamic and efficacy endpoints

Drug Development Plan presented to the Investigational Drug Steering Committee, after which full LOIs are written

Emphasis on Team Science and collaboration across ETCTN network

Drug-Specific Project Teams

Signal Transduction	DNA Repair	Immuno-Oncology	Other
AT13387 (HSP90)	**M6620** (ATR)	**Durva/Atezo** (PD-L1)	**anetumab ravtansine** (anti-mesothelin ADC)
osimertinib (EGFR)	**M3814** (DNA-PK)	**T-VEC** (Oncolytic Virus)	**AMG-232** (MDM2)
Rociletinib (EGFR)	**radium-223** α-emitter		**ixazomib/pevonedistat** (proteasome/NAE)
copanlisib (PI3K α/δ)			**CB839** (glutaminase)
rogaratinib (FGFR)			

- Drugs under study represent a broad portfolio; team membership is highly competitive.
- Teams generally propose 4-6 clinical trials for consideration by the IDSC.
- Trials are typically Phase 1 combinations or Phase 2 studies with a variety of designs.
- Phase 1s may involve a small number of sites; Phase 2s usually open to entire network.

Team Membership

- Mix of intramural and extramural membership
- Investigators from the ETCTN, NCTN and CITN may apply
- **Clinical Investigators**: typically junior investigators paired with a senior mentor from their institution; expected to design and ultimately submit Career Development LOIs and lead trials. This presents an enormous training opportunity for a junior investigator to play a leadership role.
- **Translational Investigators**: typically individuals interested in biomarker development to be incorporated across studies developed by the team
- **Basic Researchers**: individuals who have carried out research on biological principles surrounding the target
  - Translational and basic researchers may be invited on the team based on known expertise, publications, R01 grants
- **BRC member** joins telecons to provide guidance re: biomarker development
- **Statistician** provides input on study design and endpoints
- **Pharmacologist** provides input on pharmacokinetic endpoints and drug-drug interactions

Initial Development of Clinical Trials

- In the call for PTMAs, CTEP typically outlines suggestions for clinical trials that will be developed by the team
- The proposed trials do not overlap with industry-sponsored plans
- These preliminary suggestions encourage PTMAs from the most appropriate applicants
- CTEP has begun to request input from IDSC members, who can provide insight into the entire landscape of agents addressing the target and advise about ongoing competing trials
- The list of trials in the request for PTMAs is considered preliminary and may be changed or refined during the Project Team deliberations

Resources Available to Project Teams

- Project teams evaluate available preclinical data and identify any gaps; preclinical work can be completed by team members with supplements to UM1 funding
- Centralized, specialized preclinical and biomarker resources
  - CIMACs for IO endpoints
  - PADIS/NCLN lab network for pharmacodynamic endpoints
  - MoCha lab for sequencing
  - PDXNet for preclinical evaluation of NCI-IND agents
  - DRSN for drug resistance studies

M3814 (DNA-PK Inhibitor) Project Team

Call for PTMAs suggested the following studies:

- Combinations with radiation for liver metastases and GI malignancies, +/- avelumab
- Combination with oral etoposide for HGSOC
- Combination with anthracycline-containing regimen for AML
- Basket Study for patients with *BRCA* mutations, *TP53* mutations, *RAS* mutations

Name	Institution/Branch	Role
Clinicians		
Eileen O'Reilly	Memorial Sloan Kettering (JHU)	M3814 PT Co-Leader
Geoffrey Shapiro	Dana-Farber Cancer Center	M3814 PT Co-Leader
Eileen O'Reilly / Mike Pishvain	MSK-JHU-Georgetown University	CRDA Clinician-
Geoffrey Shapiro / Greg Cote	Dana-Farber Cancer Center	CRDA Clinician- Molecular
Sarah Gordon / Sarah Temkin	Virginia Commonwealth (PMH)	CRDA Clinician- Ovary
Rachel Grisham / Carol Aghajanian	Memorial Sloan Kettering (JHU)	CRDA Clinician- Ovary
Kristen Spencer / Janice Mehnert	Rutgers Cancer Institute	CRDA Clinician- Liver
S. Lindsey Davis / Karyn Goodman	University of Colorado (MDACC)	CRDA Clinician- Liver-SBRT
Brian Jonas / Bruno Medeiros	UC Davis / Stanford (COH)	CRDA Clinician- AML
Cancer Biologists	**Institution/Branch**	
Andrew Minchinton	BC Cancer Center (PMH)	Preclinical M3814 testing
Jonathan Brody / Karen Knudsen	Thomas Jefferson (JHU)	Gamma-H2AX
Apurva Srivastava	NCI-Frederick	Apoptosis - NCI PADIS lab
Translational Scientists	**Institution/Branch**	
Jan Beumer	University of Pittsburgh	Clinical Pharmacologist
Michael Andreeff	MD Anderson	AML translational science
Ranjit Bindra	Yale University	CyTOF Gamma-H2AX
Robert Kinders / Deborah Wilsker	NCI-Frederick	Biology - NCI PADIS lab
Nina Lukinova	NCI-CDP	NCI – Cancer Diagnosis Program
NCI CTEP Members	**Institution/Branch**	
Charles Kunos	IDB	IDB Drug Monitor/Co-leader
Percy Ivy	IDB	IDB Mentor
Carmen Allegra	CIB	Senior Scientist - GI
Elise Kohn	CIB	Senior Scientist - GYN
Rich Little	CIB	Senior Scientist - Leukemia
Naoko Takebe	DTC	Senior Investigator
Massimo Cardinali	RAB	Regulatory Affairs
Jared Foster	BRB	NCI Statistician
Support Staff	**Contractor**	
Michelle Hiser	EMMES	NCI CTEP IDB support
Tim Schulz	TRI	NCI CTEP IDB support

Project Team Deliberations and Mechanics

- Team had 28 telecons over a 12-week period
- First 8 telecons included the entire team
  - Reviewed basic biology of DNA-PK inhibition
  - Reviewed M3814 pharmacology and potential drug-drug interactions
  - Reviewed pharmacodynamic biomarkers of DNA-PK inhibition
  - Reviewed Merck/EMD Serono preclinical/clinical data supporting radiotherapy combinations and Merck/EMD Serono clinical plan
  - Established that there was only limited evaluation of chemotherapy combinations
  - Reviewed that no molecularly pre-specified subset had yet emerged from preclinical data
  - Established PADIS support for γ-H2AX/pKAP1 multiplex assay
  - Established MoCHA support for WES and RNA-seq
  - Discussed CIMAC support for avelumab combination
  - Reviewed early iterations of clinical trial proposals
  - Subgroups defined for remaining 20 telecons: (1) AML; (2) ovarian; (3) GI; and (4) Molecular subsets; CTEP monitor, one project leader, BMC representative, statistician, pharmacologist attended every telecon

AML	Ovarian	GI	Molecular
Phase 1 study with MEC in r/r disease 2 x 2 dose escalation design 12-patient expansion Biomarker heavy trial with assessment of PD endpoints at multiple timepoints after MEC alone and after MEC/M3814 Study team to carry out preliminary work on AML blasts to ensure markers work in Western blots	HGSOC: Phase 1 study of M3814 + oral etoposide; lead-in cycle of etoposide alone to facilitate PK/PD comparisons Randomized Phase 2 of etoposide/placebo vs. etoposide/M3814 LGOC: Safety lead-in with doxil followed by randomized Phase 2 of doxil/placebo vs. doxil/M3814	Study 1: M3814 + hypofractionated RT + avelumab in advanced solid tumors, with Phase 2 in HCC and cholangio-carcinoma cohorts Biopsies planned to correlated DNA damage induction of SBRT/M3814 with changes in immune microenvironment Study 2: pancreatic study: neoadj chemo f/b SBRT/placebo vs. SBRT/M3814; R0 resection rates to be compared; pre-post biopsies will assess contribution of M3814 to DNA damage induction	DNA-PK inhibition recognized as a back-up pathway to ATR inhibition ATM mediated pathways can circumvent ATR inhibition as well Study team conducted in vitro studies to demonstrate synergism of combined DNA-PK and ATR inhibition in ATM-deficient cells Phase 1 of M3814/M6620 in ATM-deficient cancers and in cancers with replication stress Molecular biomarker driven study developed over the 12 weeks of the project team meetings
	Supplement awarded to study combinations in ovarian cancer xenografts	Supplement awarded to study radiobiology preclinical science in pancreatic cancer models	Supplement submitted to confirm tolerability and efficacy of combination in ATM-deficient models *in vivo*

Outcomes

- All 6 trials approved by the IDSC
- Six career-development LOIs solicited from the junior clinical investigators
- LOIs from the ovarian and molecular groups will require review of preclinical data developed via supplemental funding
- Within 12 weeks, 6 trials developed that would not be done by Merck/EMD Serono that leverage DNA-PK inhibition in combination with with SBRT, topoisomerase II inhibition, immune checkpoint blockade and with ATR inhibition in a molecularly-defined patient population (i.e. ATM-deficiency)

Potential Problems 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; many PTMAs are not accepted)	Engagement of other investigators who may join ETCTN studies once initial plans are reaching maturity; ability to develop unsolicited LOI after plan presented by project team is approved
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

Summary

- Project teams are a compelling innovation by NCI-CTEP
- Teams promote collaboration between clinical, translational and basic investigators
- There is far greater engagement of the extramural community in generation of drug development plans compared to the system in place prior to implementation of project teams, when investigators responded to a competitive RFA to lead a trial already specified by CTEP
- Substantial NCI resources are supporting the teams to enhance clinical trials
- Although the M3814 example utilized Merck EMD Serono combinations (Avelumab, M6620), NCI-CTEP can facilitate combinations utilizing drugs from different companies, when scientifically supported
- The Project Teams provide rich training ground for junior investigators to garner skills in clinical trial development and leadership. Many junior investigators subsequently graduate to mentorship roles in their institutions.