NCI’s Experimental Therapeutics Clinical Trials Network (ETCTN) & FNLCR’s PD Biomarker Program

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Program Director, PDXNet
CTEP/DCTD
NExT program and clinical drug development

- NExT Special Emphasis Panel selects agents for **clinical** development assistance
  - These agents are assigned to the **Investigational Drug Branch (IDB)**, CTEP for clinical development in the *Experimental Therapeutics Clinical Trials Network (ETCTN)*

- Pharmaceutical companies apply to NExT for NCI-sponsored development for several reasons:
  - CTEP has **access to novel agents from competitors**
  - Potential **therapeutic indications that do not compete** for limited corporate resources
  - CTEP has a **network of experienced early-phase clinical trialists**
  - NCI will **invest in correlative science** studies that expand knowledge of the agent

- NCI supports clinical development of Pharma agents because:
  - There is a **significant public interest** in finding indications for new oncology drugs beyond those that may be the most profitable
  - NCI can **advance the understanding of cancer biology and treatment** through carefully designed clinical trials and **through correlative biomarker studies**
NCI’s Experimental Therapeutics Clinical Trials Network (ETCTN)

- **The ETCTN mission** is to design and perform the early-phase clinical studies of agents that are approved through NExT

- For NExT-selected agents, NCI
  - **Negotiates CRADAs** with Pharma applicant for clinical trial development
  - Assumes the **regulatory responsibility** for the trials (IND holder)
  - Sponsors clinical trials of NCI-IND agents through **cooperative grants** (UM1) to ETCTN clinical trial sites
  - Works with ETCTN investigators and pharma partners to formulate the **clinical and biomarker development plan** for the agent
  - NCI IDB physician staff **monitor ETCTN trials for safety**

- The **Investigational Drug Steering Committee** is the external advisory committee to IDB
NCI’s Experimental Therapeutics Clinical Trials Network (ETCTN)

- ETCTN size and scope
  - 11 awards and 41 trial sites in US and Canada
  - 75 agents currently under CRADA
  - Currently 70 active phase 1 and early phase 2 studies
  - Expected to accrue 1000 patients to clinical trials in 2018
  - Extensive **centralized clinical trial support** for network functionality
    - Dedicated early therapeutics CIRB
    - Centralized Identity and Access Management (IAM), regulatory support services (RSS), document management services (CTSU), patient registration (OPEN), data collection (Theradex RAVE), adverse event reporting (CTEP-AERS)

- ETCTN clinical trial proposal review (LOIs)
  - **Protocol** Review Committee for study concept and design
  - **Biomarker** Review Committee for biomarker assay qualification
High impact NCI/IND agent clinical trials

- **Agents that have achieved FDA approval based in part on early development in CTEP collaborative early phase programs**
  - Azacytidine – Myelodysplastic syndrome
  - Bortezomib- Mantle Cell Lymphoma
  - Ipilimumab- Melanoma
  - Lenalidomide and bortezomib- Multiple Myeloma
  - Oxaliplatin- Colorectal Cancer
  - Romidepsin- Peripheral T cell Lymphoma
  - Sorafenib- Thyroid Cancer
  - Ziv-aflibercept- Colorectal Cancer

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

- **Orphan Drug indications**
  - Triapine- Advanced uterine cervical cancer
  - Selumetinib- NF1
Validated biomarkers for the ETCTN

- ETCTN studies almost always incorporate biopsies and correlative studies to determine the relationship of tumor biology and target engagement with clinical response.

- However numerous factors affect reliability and reproducibility of these studies
  - Biopsy quality is variable
  - Pre-analytic variables are variable
  - Assays that are lab-developed tests have not been analytically validated and demonstrated to be fit-for-purpose

- FNLCR’s PD Biomarker Program staff play a major role in clinical trial development in ETCTN by
  - Demonstrating the need for rigor in biomarker assay development through its own assay development activities – the scientific process starts long before the biopsy material enters the lab
  - Providing the laboratory science expertise for incorporating a new level of rigor in ETCTN biospecimen acquisition and analysis
FNLCR’s PD Biomarker Program impact on ETCTN

- Provided the impetus to **involve of research pathologists and interventional radiologists** at the site level to improve biopsy quality
  - PD Biomarker evaluation of biopsy quality from ETCTN trials demonstrated the **need for a comprehensive quality effort**
  - Prompted and supported ETCTN to provide supplemental funding for interventional radiologists who are now developing SOP’s for adoption at all ETCTN sites

- Provided the **expertise for scientific review of biomarker assays** that are incorporated into ETCTN studies
  - The Biomarker Review Committee now reviews integral and integrated assays for ETCTN studies, **utilizing the expertise of FNLCR’s PD Biomarker Program staff**
  - PD program staff **provide consultation** to recipients of ETCTN UM1 Biomarker Assay Development supplements to support development of validated assays

- FNLCR’s PD Biomarker Program **directly performs PD assays** on biopsy material obtained in ETCTN studies
Novel agents accepted into the NExT pipeline from Pharma/Biotech in the past year

- M6620 (VX-970; ATRi)
- M3814 (DNA-PKi)
- Venetoclax (BCL2)
- TAK-243 (UAEi-ubiquitin-activating enzyme)
- GMI-1271 (E-selectin)
- **Radium-223**
- Hu5F9-G4 (anti-CD47 Ab)
- Rogaratinib (pan-FGFRi)
# FNLCR PD Assays for Recent ETCTN Trials

<table>
<thead>
<tr>
<th>CTEP #</th>
<th>Tumor biopsies?</th>
<th>CTCs?</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>8880</td>
<td>yes (baseline, C1D8)</td>
<td>no</td>
<td>Phase Ib Study of the Combination of Pazopanib, an Oral VEGFR Inhibitor, and ARQ 197 (Tivantinib), an Oral MET Inhibitor, in Patients with Refractory Advanced Solid Tumors</td>
</tr>
<tr>
<td>9350</td>
<td>yes (baseline, C1D3/C1D8)</td>
<td>yes</td>
<td>A Phase I Study of Single-agent MK-1775 (AZD1775), a Wee1 Inhibitor, in Patients with Advanced Refractory Solid Tumors</td>
</tr>
<tr>
<td>9284</td>
<td>no</td>
<td>yes</td>
<td>A Phase 2 Study of Cabozantinib (XL184), a Dual Inhibitor of MET and VEGFR, in Patients With Metastatic Refractory Soft Tissue Sarcoma</td>
</tr>
<tr>
<td>9483</td>
<td>yes (baseline, C1D4)</td>
<td>yes</td>
<td>A Phase I Trial of TRC102 (methoxyamine HCl) in Combination with Temozolomide in Patients with Relapsed Solid Tumors and Lymphomas</td>
</tr>
<tr>
<td>9510</td>
<td>yes (baseline, C1D8)</td>
<td>yes</td>
<td>Pilot Trial of BMN 673, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Deleterious BRCA Mutations</td>
</tr>
<tr>
<td>9762</td>
<td>no</td>
<td>yes</td>
<td>Phase I Trial of the Combination of Bortezomib and Clofarabine in Adults with Refractory Solid Tumors</td>
</tr>
<tr>
<td>9659</td>
<td>yes (baseline, C1D2, C1D28)</td>
<td>yes</td>
<td>Phase I Trial of the Combination of Nilotinib and Paclitaxel in Adults with Refractory Solid Tumors</td>
</tr>
<tr>
<td>9883</td>
<td>no</td>
<td>yes</td>
<td>Phase I Trial of 4'-thio-2'-deoxycytidine (TdCyd) in Patients With Advanced Solid Tumors</td>
</tr>
<tr>
<td>10002</td>
<td>yes (baseline, C1D2)</td>
<td>yes</td>
<td>A Phase I Study of Indenoisoquinoline LMP744 in Adults With Relapsed Solid Tumors and Lymphomas</td>
</tr>
<tr>
<td>10005</td>
<td>yes (baseline, C3D1)</td>
<td>yes</td>
<td>A Phase 2 Study of Anti-PD-L1 Antibody (Atezolizumab) in Alveolar Soft Part Sarcoma</td>
</tr>
<tr>
<td>10145</td>
<td>yes (baseline, C1D8, C2D15)</td>
<td>yes</td>
<td>Phase Ib Combination Study of Copanlisib and Nivolumab in Advanced Solid Tumors and Lymphomas</td>
</tr>
<tr>
<td>10114</td>
<td>no</td>
<td>yes</td>
<td>Phase I Trial of 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC) in Patients With Advanced Solid Tumors</td>
</tr>
</tbody>
</table>
Pharmacodynamic Biomarkers - POM of MET-TKIs: Impact on CTEP portfolio development of MET inhibitors

**MET-TKI treatment of SNU5 XG**
- EMD1214063 (NSC 758244, tepotinib)
- ARQ197 (NSC 758242, tivantinib)
- XL184 (NSC 761068, cabozantinib)
- XL880 (NSC 755775, GSK1363089, foretinib)

Demonstration of lack of METi activity contributed to discontinuation of ETCTN development of ARQ197
Pharmacodynamic Biomarkers - POM of PARPi’s: Impact on CTEP portfolio development of PARP inhibitors

Ji et al, AACR Annual Meeting 2011

Demonstration that treatment with ABT-888, MK-4827, and AZD2281 decreased PAR levels in A375 xenografts, but treatment with BSI-201 did not, contributed to discontinuation of CTEP sponsorship of BSI-201
Scheduling of Veliparib (PARPi) for Constant Control of PARP 1/2

First-ever phase 0 trial in oncology justified by preclinical modeling
- PD biomarker as the Primary Objective of CTEP-sponsored trial at NIH Clinical Center
- POM and kinetics of molecular target control
- Exploratory IND filing

### Time-Course of PD Biomarker Response (% of vehicle group) in model system

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>2-hr</th>
<th>5-hr</th>
<th>24-hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>8%</td>
<td>57%</td>
<td>180%</td>
</tr>
<tr>
<td>3.2</td>
<td>3%</td>
<td>66%</td>
<td>60%</td>
</tr>
<tr>
<td>6.3</td>
<td>2%</td>
<td>53%</td>
<td>55%</td>
</tr>
<tr>
<td>12.5</td>
<td>1%</td>
<td>40%</td>
<td>44%</td>
</tr>
<tr>
<td>25</td>
<td>1%</td>
<td>20%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Kummar et al. *JCO* 2009, 27, 2705-2711
Reproducible inhibition of PARP activity: Phase 1 study of veliparib and temozolomide in AML

"Veliparib at all dose levels suppressed PAR formation in peripheral blood cells with different percentages of circulating blasts... but no clear difference between responders and nonresponders"
<table>
<thead>
<tr>
<th>Pathway Target</th>
<th>Molecular Target</th>
<th>Agents</th>
<th>DDR PD Biomarker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single/Double Strand Break</td>
<td>multiple TOP1i</td>
<td>any chemoRx agents, irinotecan, topotecan, indenoisoquinolines, AZD1775 (Wee1i)</td>
<td>pNBS1, γH2Ax, RAD51, ERCC1, γH2Ax w/cCasp3 (apoptosis)</td>
</tr>
<tr>
<td>Induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Strand Break Response: BER</td>
<td>PARP1/2i</td>
<td>veliparib, olaparib, talazoparib</td>
<td>PAR polymer</td>
</tr>
<tr>
<td></td>
<td>APE blockade w/TO</td>
<td>TRC102 (methoxyamine)</td>
<td>Late DNA damage (pNBS1, γH2Ax, RAD51)</td>
</tr>
<tr>
<td>p sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Strand Break Response: TMB, MSI</td>
<td>PD1/L1 blockade</td>
<td>pembrolizumab, nivolumab, durvalumab, atezolizumab</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDR Sensors</td>
<td>ATRi</td>
<td>M6620 (formerly VX-970)</td>
<td>pS1989 autophosphorylation</td>
</tr>
<tr>
<td></td>
<td>DNA-PKi</td>
<td>M3814, M9831 (aka VX-984)</td>
<td>γH2Ax, pKAP1 (recent project plan)</td>
</tr>
</tbody>
</table>
Multiplex Immunofluorescence DDR assays for ETCTN trials

DNA damage response of MX-1, a BRCA-deficient breast cancer model, to 7.5 mg/kg irinotecan; 40x

FNLCR PD Biomarker Assays in Development of the Wee1 Inhibitor AZD1775 by ETCTN

Proof of Mechanism: Reduction in pTyrCdk and Concurrent Increase in γH2AX Signaling by AZD1775 in Paired Tumor Biopsies

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FNLCR PD Biomarker Assays in M3814 drug development:
A phase I study of M3814 + mitoxantrone/etoposide/cytarabine (MEC)
in refractory acute myeloid leukemia (AML)

A phase I/II study of M3814 + avelumab + hypofractionated radiation (SBRT) in Solid Tumors and Hepatobiliary Malignancies

**Treatment:**
oral M3814 twice daily D2-D21 +
MEC (8 mg / 50-100 mg / 1g / m^2) D1-5

**Correlatives:**
pharmacokinetics (UPITT UM1)
pDNA-PK assay (UCDavis UM1 supplement)
H2AX/pKap1 (PADIS)
WES & RNA-seq (MoCha)

**Phase I 3+3 design (**A5 / A6 open if left & below cohort clear**)
oral M3814 twice daily D1-D28 (dose escalation) +
IV avelumab 10mg/kg q2wk
SBRT (10Gy x 5) QOD

**Correlatives:**
pharmacokinetics (UPITT UM1)
H2AX/pKap1 (PADIS)
WES & RNA-seq (MoCha)
perfusion CT (Rutgers)
Future of FNLCR PD Program & ETCTN

- The ETCTN effort to provide supplemental funding to ETCTN investigators for biomarker assay development has had limited success
  - There is a big gulf between laboratory science discipline and the approach of basic scientists in clinical sample analysis

- **ETCTN will increasingly rely on the FNLCR PD Biomarker Program** for the development of PD assays to be used in clinical trials
  - Involve FNLCR PR Biomarker Program staff in the initial review of biomarker plans, for input into sampling strategy as well as in the technical assay development

- FNLCR PR Biomarker Program assays anticipated to be used in upcoming ETCTN studies include: EMT, MMR, DDR
Questions?
ETCTN accomplishments

- Evaluate new molecular entity
  - Z-endoxifen for ER-positive breast cancer
  - MEDI570 for ICOS-positive peripheral T-cell lymphomas
  - PARP inhibitor veliparib for leukemia
  - Fluorodeoxycytidine, a novel DNA methyltransferase inhibitor

- First in human, combinations and studies demonstrating activity
  - Eribulin/gemcitabine in bladder cancer
  - Cediranib/olaparib in high grade serous ovarian cancer
  - Osimertinib combinations in EGFR-mut NSCLC (necitumumab/MTORC1 & MTORC2/navitoclax)
  - HDAC/proteasome inhibitors in multiple myeloma

- Immuno-oncology agents
New Development Cycle for NCI Experimental Therapeutics

**NEXT Processes**
- NExT: NCI Experimental Therapeutics
- NExT Pipeline

**Drug Plan Internal Development**
- Clinical
- Preliminary Drug Development Plan
  - DCTD / Program Meetings
- Preliminary Biomarker/Assay Development Plan
- Senior Advisory Committee
- Regulatory Agreements

**Drug Plan External Development**
- Clinical
- Drug Development Plan
  - IDSC Review
- Biomarker/Assay Development Plan
  - BRC Review
- Regulatory Agreements – CRADA Development
  - CRADA Signed
- Projects

**LOI & Protocol Development**
- Projects
- Senior Advisory Committee
- CTEP Reviews
  - BRC Review
- LOIs
- LOI Development
- LOI Approval
- Collaborative Protocol Development
- Protocol Activation

**Abbreviations**
- CRADA: Cooperative Research and Development Agreement
- IDSC: Investigational Drug Steering Committee
- BRC: Biomarker Review Committee
PD Biomarkers in Clinical Translation of Novel Drug Combinations: EMT assays for ETCTN trials

Kinders, Navas, 2018
unpublished
Reproducible inhibition of PARP activity: Phase 1 study of veliparib and irinotecan in solid tumors

"There was no analogous positive association between the degree of PARP inhibition and best response"