Precision Medicine Initiative for Oncology
Including Development of Improved Preclinical Cancer Models

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National Cancer Institute, NIH
### Precision Medicine Initiative

**Proposed FY16 Support**

<table>
<thead>
<tr>
<th>Agency</th>
<th>$ Million</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td></td>
</tr>
<tr>
<td>• <em>Cancer</em></td>
<td>200</td>
</tr>
<tr>
<td>• <em>Cohort</em></td>
<td>70</td>
</tr>
<tr>
<td>• <em>Cohort</em></td>
<td>130</td>
</tr>
<tr>
<td>FDA</td>
<td>10</td>
</tr>
<tr>
<td><strong>Office of the National Coordinator for Health Information Technology</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>$215</strong></td>
</tr>
</tbody>
</table>
What Problems Are We Trying to Solve?

• For most of its 70-year history, systemic cancer treatment has relied on drugs marginally more toxic to malignant cells than to normal tissues.

• Molecular markers to predict benefit or understand therapeutic resistance in the clinic have usually been lacking.

Proposed Solution to These Problems

• Use genomics to identify and target molecular vulnerabilities of individual cancers.
Precision Medicine/Oncology in Practice

<table>
<thead>
<tr>
<th>Non-clinical models for targets</th>
<th>Translational research with clinical models</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Mouse" /></td>
<td><img src="image" alt="Sequencing" /></td>
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<td></td>
<td><img src="image" alt="Methylation" /></td>
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<td></td>
<td><img src="image" alt="FISH" /></td>
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<td></td>
<td><img src="image" alt="IHC" /></td>
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<tr>
<td></td>
<td><img src="image" alt="Expression array" /></td>
</tr>
</tbody>
</table>

**Patients eligible for early or late phase clinical trials**

**Analysis of tumor and other tissues for pathway activation or resistance**

**Patient assigned to trial based on molecular characterization of tumor**

**Patient monitoring**

**Patient monitoring: post-treatment molecular re-analysis**

**Clinical observations:**

- Clinical response
- PK
- Functional imaging
- CTCs, CECs

- Tumor and normal tissue PD markers
- Tumor-initiating cells

**Goal:** Increase Genomics-Based Clinical and Preclinical Studies of Cancer Treatment

1. Expand genomics-based clinical trials

2. Understand & overcome resistance to targeted drugs; drug combinations; and mechanistic understanding of immunotherapy

3. Build repository of patient-derived pre-clinical models for evaluating targeted therapeutics

4. Create national cancer database to integrate genomic information with clinical response and outcome
2014:
- MPACT
- Lung MAP
- ALCHEMIST
- Exceptional Responders

2015:
- NCI-MATCH

Pending:
- ALK Inhibitor
- MET Inhibitor
- Pediatric MATCH
NCI-MATCH: Features

[Molecular Analysis for Therapy Choice]

• Foundational treatment/discovery trial; assigns therapy based on molecular abnormalities, not site of tumor origin for patients without standard therapy

• Regulatory umbrella for phase II drugs/studies from > 20 companies; single agents or combinations

• Validated gene sequencing at 4 sites; >98% concordance for “locked down” analysis of mutations in 143 genes; fresh biopsies at study entry

• Available nationwide (2400 sites); CIRB

• Accrual began mid-August 2015; 160 patients accrued first 4 weeks
**NCI MATCH**

- Conduct across 2400 NCI-supported sites
- Pay for on-study and at progression biopsies
- Initial estimate: screen 3000 patients to complete 20 phase II trials; target 25% ‘rare’ tumors; primary endpoint RR 5% vs. 25%

1. CR, PR, SD, and PD as defined by RECIST
2. Stable disease is assessed relative to tumor status at re-initiation of study agent
3. Rebiopsy; if additional mutations, offer new targeted therapy

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**Flowchart Description**

- Genetic sequencing
- Actionable mutation detected
- Study agent
- Stable Disease, Complete or partial response (CR+PR)$^{1,2}$
  - Continue on study agent until progression
  - Check for additional actionable mutations$^3$
    - Yes
      - No additional actionable mutations, or withdraw consent
    - No
      - Off study

- Progressive disease (PD)$^1$

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$^1$CR, PR, SD, and PD as defined by RECIST
$^2$Stable disease is assessed relative to tumor status at re-initiation of study agent
$^3$Rebiopsy; if additional mutations, offer new targeted therapy
## NCI-MATCH: Initial Ten Studies

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Molecular Target(s)</th>
<th>Estimated Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>ALK Rearrangement (non-lung adenocarcinoma)</td>
<td>4%</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ROS1 Translocations (non-lung adenocarcinoma)</td>
<td>5%</td>
</tr>
<tr>
<td>Dabrafenib and Trametinib</td>
<td>BRAF V600E or V600K Mutations (non-melanoma)</td>
<td>7%</td>
</tr>
<tr>
<td>Trametinib</td>
<td>BRAF Fusions, or Non-V600E, Non-V600K BRAF Mutations (non-melanoma)</td>
<td>2.8%</td>
</tr>
<tr>
<td>Afatinib</td>
<td>EGFR Activating Mutations (non-lung adenocarcinoma)</td>
<td>1 – 4%</td>
</tr>
<tr>
<td>Afatinib</td>
<td>HER2 Activating Mutations (non-lung adenocarcinoma)</td>
<td>2 – 5%</td>
</tr>
<tr>
<td>AZD9291</td>
<td>EGFR T790M Mutations and Rare EGFR Activating Mutations (non-lung adenocarcinoma)</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>TDM1</td>
<td>HER2 Amplification (non breast cancer)</td>
<td>5%</td>
</tr>
<tr>
<td>VS6063</td>
<td>NF2 Loss</td>
<td>2%</td>
</tr>
<tr>
<td>Sunitnib</td>
<td>cKIT Mutations (non GIST)</td>
<td>4%</td>
</tr>
</tbody>
</table>

Agents and targets below grey line are pending final regulatory review; economies of scale—larger number of agents/genes, fewer overall patients to screen ≈ 35%
MATCH Assay: Workflow for 10-12 Day Turnaround

Biopsy Received at Quality Control Center

- **3-5 DAYS**
  - Tissue Fixation
  - Path Review

- **1 DAY**
  - Nucleic Acid Extraction

- **1 DAY**
  - Library/Template Prep

- **1 DAY**
  - Sequencing, QC Checks

- **1 DAY**
  - Centralized Data Analysis

- **3 DAYS**
  - Clinical Laboratory aMOI Verification

**10-12 days**

- Tumor content > 70%
- DNA/RNA yields > 20 ng
- Library yield > 20 pM
- Test fragments
  - Total read
  - Reads per BC
  - Coverage
  - NTC, Positive, Negative Controls

**aMOIs Identified**

**Rules Engine Treatment Selection**
PMI-O: Expanding Genomically-Based Cancer Trials (FY16-FY20)

- Accelerate Launch of NCI-Pediatric MATCH
- Broaden the NCI-MATCH Umbrella:
  - Expand/add new Phase II trials to explore novel clinical signals—mutation/disease context
  - Add new agents for new trials, and add new genes to panel based on evolving evidence
  - Add combination targeted agent studies
  - Perform Whole Exome Sequencing, RNAseq, and proteomic studies on quality-controlled biopsy specimens—extent of research based on resource availability
  - Add broader range of hematologic malignancies
- Perform randomized Phase II studies or hand-off to NCTN where appropriate signals observed
- Apply genomics resources to define new predictive markers in novel immunotherapy trials
- Expand approach to ‘exceptional responders’: focus on mechanisms of response/resistance in pilot studies
Mechanisms of Resistance To Targeted Cancer Therapeutics

- Broad range of mechanisms
- Until recently, tools to interrogate possibilities in vivo quite limited
- Resistance to single agents inevitable: 1° or acquired; requires combinations but data to provide molecular rationale for the combination (both therapy & toxicity) not often available
PMI-O: Understanding and overcoming resistance to therapy (FY16-FY20)

• Create a repository of molecularly analyzed samples of resistant disease
• Expand the use of tumor profiling methods such as circulating tumor cells (CTCs) and fragments of tumor DNA in blood to understand and monitor disease progression
• Develop new cancer models to identify the heterogeneity of resistance mechanisms
• Use preclinical modeling to determine the effectiveness of new combinations of novel molecularly targeted investigational agents
PMI-O: Developing new models for preclinical studies (FY16-FY20)

• Launch the Human Cancer Models Initiative (HCMI) and develop representative human cancer model systems for the research community
• Expand the number and availability of novel human cell lines and patient-derived xenographs
• Enhance the ability to predict the success of immunotherapy through the examination of malignancies that have shown response to immune checkpoint therapy in novel model systems
Modeling the Diversity of Human Cancer: An Unmet Need

- Genetic analysis has identified recurrent genetic lesions in cancer that range in frequency from 1% - >50% of cases.
- Most cancer cell lines have not been directly compared to the primary tumor using current genomic methods.
- Existing cell line models of common cancer types are suspect biologically and genetically (e.g. prostate CA)
- Models of rare cancer subtypes may be nonexistent or underrepresented
- Models do not exist for many recurrent genetic lesions in human cancer, and for common combinations of lesions
- Existing models do not recapitulate hierarchical relationships of tumor subpopulations (i.e. tumor propagating cells, stroma)
- Baseline clinical data and response to treatment are typically not available for existing cancer cell lines
PMI-O: Developing a national cancer knowledge system to support precision medicine (FY16-FY20)

• Establish NCI’s Genomic Data Commons (GDC) to facilitate the identification of subtypes of cancers and potential new drug targets
• Develop secure, flexible, meaningful, interoperable interfaces to provide for the analysis of large-scale cancer genomic and clinical data
• Establish a sustainable infrastructure for cancer genomic data to allow for the analysis of multiple data types, multi-scalar data, and temporal data
The NCI Genomic Data Commons (GDC): Rationale

- The Cancer Genome Atlas (TCGA) project and many other NCI funded cancer genomics projects each currently have their own data coordinating center
  - Raw data and results stored in many different repositories; confusing to users, inefficient, barrier to research
- GDC will be a single repository for all NCI cancer genomics data
  - Will include data from existing and new NCI cancer genomics efforts
  - Will allow researchers to upload, analyze, and share their own cancer genomic data
  - Store all data including raw data
  - Harmonize the data as appropriate
  - Will be the authoritative reference data set
Recent & Ongoing Input from Extramural Community

- Joint meeting of NCI Board of Scientific Advisors & National Cancer Advisory Board., June 2015
- Organoids & Reprogrammed Cell Lines: Lou Staudt, M.D., Ph.D., July 2015
- Exceptional Responders Workshop—Next Steps: Barbara Conley, M.D., March 2016
- Immunotherapy—Combination Approaches and NGS: Helen Chen, M.D., January 2016
- PDX Models, Combination Therapy, and Drug Resistance: J. Doroshow, M.D. and Dinah Singer, Ph.D., January 2016
- Genomic Data Commons workshop: W. Kibbe, Ph.D. and Lou Staudt, M.D., Ph.D., Fall, 2016
Patient-Derived Models Repository to Support Cancer Discovery & Therapeutics Development

September 2015

**Goal**: Develop a program attractive to academia and industry to create and produce clinically-annotated, patient-derived mouse and cell-based model systems for cancer discovery and therapeutics development in support of extramural investigators
FNLCR Patient Derived Cancer Models Repository: Issues for Consideration

- Development of PDM Repository—update since February 2014
- Novel cancer models
- Considerations for future use
NCI Patient-Derived Models (PDM) Repository

- A national repository of PDMs to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery comprised of:
  - clinically-annotated patient-derived xenografts (PDXs),
  - patient-derived tumor cell cultures (PDCs, including conditionally-reprogrammed tumor cell cultures) developed from 1º or metastatic tumors and/or PDXs,
- NCI to provide long-term home for >1000 PDX and PDC models each produced from tissues and blood supplied by NCI-designated Cancer Centers, NCTN & ETCTN
  - Target collections of tumors less prevalent in current resources (eg., Small Cell Lung, Pancreatic, Head/Neck, Ovarian & Bladder cancers; Prostate, Kidney, Sarcomas, Melanomas)

- Goals:
  ✓ ~50 unique patient models (solid & derived tumor line) per disease (min) with sufficient size of each molecularly-characterized subgroup to power validation and/or efficacy studies
  ✓ Comprehensive pre-competitive molecular characterization of samples and earliest passage PDXs: MPACT mutation panel, WES, RNAseq, copy number, histology, growth curves, and proteomics/phospho-proteomics (pilot study)
  ✓ All models and associated data made available through a publicly available website
NCI Patient-Derived Models Repository: Multiple Avenues for Discovery

Tumor/Patient Heterogeneity

- Blood/CTCs
- Tumor
- Blood/CTCs
- Tumor

Develop PDX Models and PDC (Tumor & Fibroblast) Lines
DNA, RNA, Protein, WES, RNASeq, Targeted Sequencing

3D Culture, 3D Pharmacodynamics

2D Culture, Spheroid growth

Increasing Drug Concentration

Preclinical Trial Modeling

Live Tumor Imaging
Specimen Acquisition for Model Development

- Currently receiving tissue (resections, biopsies) and blood samples for CTC enrichment from two separate tissue procurement protocols (06-C-0213 [NCI] and 9846 [CIRB])
- Clinical centers include 2 NCI clinics, 16 NCI comprehensive cancer centers, and 23 ETCTN/NCORP LAO/LPOs with >140 participating sites.
NCI Patient-Derived Models Repository

Patient Tumor Types by Disease Location

As of Sept, 21 2015

Total Number of Specimens (tissue and blood) Received: 1502
Total Number of Patients: 1083
# PDX Take-Rate from Tumor Tissue Implantations

<table>
<thead>
<tr>
<th>Body Location</th>
<th>Total Received</th>
<th>Total Assessable Specimens (&gt;P0)</th>
<th>%Take-Rate of Assessable Specimens</th>
<th>Passageable Tumor*</th>
<th>Discontinued†</th>
<th>Not Yet Assessable: P0 tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>16</td>
<td>3</td>
<td>0%</td>
<td>0</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Digestive/ Gastrointestinal</td>
<td>103</td>
<td>59</td>
<td>78%</td>
<td>46</td>
<td>13</td>
<td>44</td>
</tr>
<tr>
<td>Endocrine/ Neuroendocrine</td>
<td>24</td>
<td>7</td>
<td>43%</td>
<td>3</td>
<td>4</td>
<td>17</td>
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<tr>
<td>Genitourinary</td>
<td>108</td>
<td>48</td>
<td>54%</td>
<td>26</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>1</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Gynecologic</td>
<td>23</td>
<td>18</td>
<td>50%</td>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>97</td>
<td>70</td>
<td>79%</td>
<td>55</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Hematologic/Blood</td>
<td>1</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>86</td>
<td>31</td>
<td>58%</td>
<td>18</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td>Neurologic</td>
<td>4</td>
<td>1</td>
<td>0%</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory/Thoracic</td>
<td>44</td>
<td>25</td>
<td>80%</td>
<td>20</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Skin</td>
<td>31</td>
<td>15</td>
<td>87%</td>
<td>13</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Unknown Primary</td>
<td>8</td>
<td>4</td>
<td>50%</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>546</strong></td>
<td><strong>281</strong></td>
<td><strong>68%</strong></td>
<td><strong>192</strong></td>
<td><strong>89</strong></td>
<td><strong>265</strong></td>
</tr>
</tbody>
</table>

*Passageable Tumor: Includes any PDX where a palpable tumor has been passed to at least P1 as well as Distributable PDXs. One or more of QC steps for PDX confirmation are pending for earlier passages.

†Discontinued: (1) Did not successfully grow palpable tumor in P0 (monitored 300 days), (2) Passaged tumor failed to grow in subsequent passages, (3) Mouse found dead/tumor not passageable, (4) Palpable tumors were 100% murine content, (5) xenograft-associated lymphoproliferative disease (XALD: host-versus-graft disease or human lymphoma out-growth)
PDC Patient Tumor Types by Disease Location

Total number of cultures that have either been (1) Completed or are (2) In Progress for initial *in vitro* growth: **416**

Discontinued no-growth models not included in chart
**In vitro Culture of Patient-Derived Tissue**

Primary culture expanded in F12+Y+P/S (7-8 passages) → FACs separation of patient tumor and CAFs for in vitro culture → QC and stock vial preparation

3-10 vials cryopreserved (~P4)

<table>
<thead>
<tr>
<th></th>
<th>Grown to P4</th>
<th>Tumor Material Present After FACs</th>
<th>CAFs Present After FACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Attempted Cultures</td>
<td>578</td>
<td>341</td>
<td>341</td>
</tr>
<tr>
<td># In Initial or Post-FACS Culture</td>
<td>52</td>
<td>69</td>
<td>33</td>
</tr>
<tr>
<td>Total Assessable Cultures</td>
<td>526</td>
<td>272</td>
<td>308</td>
</tr>
<tr>
<td># Successful</td>
<td>341</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td># Discontinued (no growth)</td>
<td>185</td>
<td>79</td>
<td>30</td>
</tr>
<tr>
<td># Discontinued (cell type not present)</td>
<td>--</td>
<td>118</td>
<td>87</td>
</tr>
<tr>
<td>Sorted, Tumor Cells Present*</td>
<td>--</td>
<td>75</td>
<td>N/A</td>
</tr>
<tr>
<td>Sorted, CAF Present*</td>
<td>--</td>
<td>N/A</td>
<td>191</td>
</tr>
</tbody>
</table>

- *After initial isolation of tumor cells or CAFs by FACs, cultures are expanded and may be resorted to achieve >99% pure cultures.
- Cultures then undergo final QC including: Genomic studies, Identifiler, karyotyping, tumorigenicity testing, growth rate assessment, and verification that distribution lots will grow for up to 20 passages from freeze.

9/28/2015
TPP, JAX, GBM Models
Salivary Gland Adenocarcinoma

In vitro

Fibroblast Culture
CD90+ EPCAM-

Tumor Cell Culture
CD90- EPCAM+

Passage 0 in Mice

P0 Growth Curve
PDM Quality Control Steps

Patient-Derived Xenografts (PDX)

• **Initial QC**
  - Verify pathology matches patient diagnosis
  - Human:Mouse DNA ratio

• **Distribution Lot (DL) QC**
  - Verify pathology of all PDXs contributing to DL
  - Identifiler comparison to Passage 0
  - Whole Exome Sequencing, MPACT assay, and RNASeq of 6 PDXs performed; 1 deep sequence and 5 shallow sequence. Reviewed for concordance with primary and/or P0.
  - Verify regrowth of cryopreserved fragment

Patient-Derived Cell (PDC) Cultures

• **Initial QC**
  - Use FACs sorting to isolate tumor cultures and cancer-associated fibroblast cultures
  - Determine doubling time, and optimal growth conditions
  - Perform qRT-PCR for tumor versus fibroblast cell phenotype
  - Human:mouse DNA ratio if tumor cells originated from a PDX rather than directly from human donor

• **Distribution Lot (DL) QC**
  - FACS and qRT-PCR analysis to verify purity
  - Identifiler comparison to early passage in vitro culture, and when possible to PDX
  - Whole Exome Sequencing, MPACT assay, and RNASeq of 6 PDXs performed; 1 deep sequence and 5 shallow sequence. Reviewed for concordance with PDX
  - Karyotyping performed
  - Verify growth of cryopreserved vial for tumor lines and lack of growth for CAF lines as PDXs
Preclinical trial dosing modeled after the **CLINICAL TRIAL**:

- Patients with specified mutations of interest will be assigned to receive one of the following study drugs or drug combinations at the assigned dose.
- **ABT-888** 40 mg orally BID qd days 1-7 plus **temozolomide** 150 mg/m2 orally qd days 1-5 (no food restrictions) in 28-day cycles
- **Everolimus** 10 mg orally each day (no food restrictions) in 28-day cycles
- **Trametinib DMSO**: 2 mg orally each day either one hour before or two hours after a meal in 28-day cycles
- **MK-1775** 225 mg orally BID for 5 doses either at least two hours before or two hours after a meal plus **carboplatin** (AUC 5) IV on day 1 every 3 weeks (21-day cycle)
Preclinical MPACT Bladder Models

<table>
<thead>
<tr>
<th>(Group) NSC</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>(G1)</td>
<td>vehicle</td>
</tr>
<tr>
<td>(G2) 733504</td>
<td>Everolimus</td>
</tr>
<tr>
<td>(G4) 758246</td>
<td>Trametinib</td>
</tr>
<tr>
<td>(G6) 752840</td>
<td>ABT-888</td>
</tr>
<tr>
<td>362856</td>
<td>Temazolomide</td>
</tr>
<tr>
<td>(G8) 754352</td>
<td>MK-1775</td>
</tr>
<tr>
<td>241240</td>
<td>Carboplatin</td>
</tr>
</tbody>
</table>

**BL0382**
- Bladder Cancer, transitional cell ca
- MPACT aMOI: TP53-E336 (stop codon)
- Assign: MK1775+Carboplatin
- Of interest: BRCA2-R2034C (cosegregated in a male breast ca family in the Dutch BRCA1/2 database)

**BL0269**
- Bladder Cancer, invasive
- MPACT aMOI: PIK3C-H1074R
- Assign: Everolimus

**BL0293**
- Bladder Cancer, sarcomatoid differentiation
- MPACT aMOI: TP53-R248Q
- Assign: MK1775+Carboplatin
Planned Analysis of Preclinical MPACT

- To date 12 models have completed the Preclinical NCI-MPACT study, 3 are ongoing and an additional 7 models are in the queue for tumor growth and treatment.
- Whole exome sequencing and RNASeq are being performed at baseline and at pre-defined times during the study.
- In a PDX model, what correlates with response to drug? While complete regressions and no response can be categorized fairly easily; what is/can be called a drug response in between those two extremes can be difficult to define.
  - We currently evaluating different criteria for tumor doubling times and event-free survival to assign a numerical value for the relative survival of different treatment groups.
  - Once criteria have been established, comparison of RNASeq data for models that survive statistically longer than others within a treatment cohort will begin.
Bladder Model BL0293: *In Vitro* and *In Vivo* Response

**In vitro** data confirmed that BL0293 was more sensitive to ABT-888 + Temozolomide than MK1775 + Carboplatin.

**Cl values: MK1775 + Carboplatin**
- ED50 3.52 = antagonistic
- ED75 2.19 = antagonistic
- ED90 1.4 = antagonistic

**Cl values: ABT-888 + Temozolomide**
- ED50 5.04 = antagonistic
- ED75 0.65 = synergistic
- ED90 0.47 = synergistic
BL-0293 Bladder PDX Implanted in 3 NSG mice on 6/8/2015
MRI 7/30/2015

T2 Image of Primary In Place

Multiple Liver Metastases
BL-0293 Bladder Tumor:
Single Cycle of ABT-888 + TMZ Begun 8/12/2015 (Daily X 5d)

8/12/2015: Pre-Dose
8/27/2015: CR
9/04/2015: CR
Nude Rat PDXs: Implanted from Human PDXs Grown in NSG Mice

<table>
<thead>
<tr>
<th>PDX ID</th>
<th>CTEP SDC Diagnosis</th>
<th>Growth in Rat (Passageable tumor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>172845-121-B</td>
<td>Adenocarcinoma - colon</td>
<td>No Growth</td>
</tr>
<tr>
<td>CN0330F216</td>
<td>Adenocarcinoma - colon</td>
<td>No Growth</td>
</tr>
<tr>
<td>CN0375F725</td>
<td>Adenocarcinoma - colon</td>
<td>Yes</td>
</tr>
<tr>
<td>CN0428F1126</td>
<td>Adenocarcinoma - colon</td>
<td>No Growth</td>
</tr>
<tr>
<td>CN0446F447</td>
<td>Adenocarcinoma - colon</td>
<td>Yes</td>
</tr>
<tr>
<td>466732-252-T</td>
<td>Adenocarcinoma - small intest.</td>
<td>Yes</td>
</tr>
<tr>
<td>ST0110F1568</td>
<td>GIST, poorly differentiated</td>
<td>No Growth</td>
</tr>
<tr>
<td>295223-140-R</td>
<td>H &amp; N squamous cell car.</td>
<td>Yes</td>
</tr>
<tr>
<td>SA0426F1136</td>
<td>Leiomyosarcoma - not uterine</td>
<td>Yes</td>
</tr>
<tr>
<td>692163-330-T</td>
<td>Leimyosarcoma - uterus</td>
<td>Yes</td>
</tr>
<tr>
<td>941425-263-T</td>
<td>Mesothelioma</td>
<td>Yes</td>
</tr>
<tr>
<td>LG0904F1496</td>
<td>Neuroendocrine cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>LG0703F948</td>
<td>NSCLC, Adenocarcinoma</td>
<td>No Growth</td>
</tr>
<tr>
<td>LG0807F1297</td>
<td>NSCLC, Adenocarcinoma</td>
<td>Yes</td>
</tr>
<tr>
<td>LG1189F1952</td>
<td>NSCLC, Adenocarcinoma</td>
<td>Yes</td>
</tr>
<tr>
<td>114551-080-T</td>
<td>Salivary gland cancer, acinic</td>
<td>No Growth</td>
</tr>
<tr>
<td>275155-148-R</td>
<td>Salivary gland cancer, adenocarcinoma</td>
<td>Yes</td>
</tr>
<tr>
<td>LG0520F434</td>
<td>Squamous cell lung carcinoma</td>
<td>No Growth</td>
</tr>
<tr>
<td>LG0830F1385</td>
<td>Squamous cell lung carcinoma</td>
<td>Yes</td>
</tr>
<tr>
<td>41634-122-T</td>
<td>Transitional cell car. - uroth.</td>
<td>Yes</td>
</tr>
<tr>
<td>BL0269F402</td>
<td>Urothelial/bladder cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>BL0293F563</td>
<td>Urothelial/bladder cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>BL0382F1232</td>
<td>Urothelial/bladder cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>BL0470F1820</td>
<td>Urothelial/bladder cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>SA0350F605</td>
<td>Uterine cancer, undifferentiated sarcoma</td>
<td>Yes</td>
</tr>
</tbody>
</table>

A total of 54 models have been implanted into nude rats
- Of the 25 assessable models (table) there is a 72% success rate growing PDXs.
- 29 additional models are still in P0 growth
- Possible now to assess CTCs

Of interest: Previous less successful attempts to grow traditional xenografts in nude rats have been started from in vitro culture and required a larger cell number implanted than normal to grow a xenograft.
Similar Pathology in Mouse and Rat PDXs

**Mouse PDX**

- **275155-148-R**
  - Salivary Gland adenocarcinoma

- **LG0904-F1496**
  - Neuroendocrine carcinoma

- **295223-140-R**
  - H & N squamous cell carcinoma

**Rat PDX**

- **P0**
Enhancing Immunotherapy Models

- Develop complementary models of spontaneous tumors amenable to pre-clinical tissue sampling and clinical trials: COTC
- For pre-clinical modeling of immunotherapy combinations using species specific reagents
FNLCR Patient Derived Cancer Models Repository: Future Possibilities

- Distribution of models: PDXs, conditionally-reprogrammed cell lines, DNA, RNA, whole cell lysates first quarter 2016
- Use as core resource in support of extramural SCLC consortium
- Support development of extramural early phase pre-clinical clinical trials consortium
- Novel models to develop immunotherapy combinations and PD, for example in comparative oncology trials
- Support extramural studies that require in vivo use of investigational agents—performed at FNLCR with PI
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