New Initiatives to Accelerate Development of Cancer Therapies in the Era of Precision Medicine

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National Cancer Institute
Overview of Presentation

- Overview of NCI-sponsored Drug Development in CTEP/DCTD
- Focus of NCI/CTEP Clinical Trials Programs in the Era of Precision Medicine & Structure for Public/Private Collaborative Agreements
- Example of National Precision Medicine Trial - NCI MATCH
- Process for Partnering in Drug Development - NExT
- New Initiative: NCI Formulary
Overview of Clinical Treatment Trials Programs at NCI – CTEP/DCTD
Cancer Therapy Evaluation Program (CTEP) 
Division Cancer Treatment & Diagnosis (DCTD)

Mission is to improve the lives of cancer patients by finding better ways to treat, control and cure cancer

- Extensive national program of cancer research
- Sponsor clinical trials to evaluate new anti-cancer agents and establish new standard of care
- *Particular emphasis on translational research to elucidate molecular targets/biomarkers and mechanisms of drug effects and using this information to use targeted agents to provide clinical benefit for patients*
Doing Battle Against Cancer: A Collaborative Effort

DCTD-NCI
- Expedite Pivotal Trials
- Exploratory Studies
- Other indications:
  - Combination regimens of investigational agents from two or more sources
  - Alternative Methods of Drug Administration

Pharmaceutical/Biotech Company
- Pilot Studies & Pivotal Trials Leading to Licensing

Investigational Anti-Cancer Agents

Clinical Investigators

IND & Clinical Trials

Novel Cancer Therapies
Full Spectrum of Clinical Trials

- **Phase 0**: exploratory IND studies that facilitate targeted therapies being tested in patients earlier in the drug development process
- **Phase 1**: small trials to define the appropriate dose and schedule for further testing in humans and identify toxicities and determine pharmacokinetics
- **Phase 2**: slightly larger trials to show promising antitumor activity in specific tumor types
- **Phase 3**: large, definitive, randomized trials to establish efficacy compared to standard treatment
- **Phase 4**: post-marketing studies
CTEP/DCTD Clinical Trials
Clinical Trials Programs

- Basic Resources
  - Pediatric Phase 1 Program
  - Experimental Therapeutics Clinical Trials Network (ETCTN)
  - National Clinical Trials Network (NCTN)

- Other / Specialty Resources
  - Adult & Pediatric Brain Tumor Consortia (ABTC & PBTC)
  - Cancer Immunology Clinical Trials Network (CITN)
  - Bone Marrow Transplant Clinical Trials Network (BMCTN)*
  - Other: SPORES, R21, R01, P01, Grants, etc.

*BMCTN overseen by NHLBI with collaborative support from NCI/CTEP
Focus of NCI/CTEP Clinical Trials Programs in the Era of Precision Medicine & Structure for Public/Private Collaborative Agreements
CTEP’s Role in Drug Development

- Combinations of targeted agents a high priority
  - Based on evidence that resistance to initially effective single agents often develops quite rapidly in many adult tumors
  - More than 100 combination trials initiated since 2000
  - Facilitated by the Intellectual Property (IP) language in CTEP-industry agreements
- Molecular-targeted effects:
  - Mechanism of Action/Proof of Principle
  - Biomarker assessment and evaluation, assay development and qualification
CTEP’s Role in Drug Development (continued)

- Alternative methods of drug administration, schedule and sequence
- Investigational/Novel imaging
- Evaluate drug effects in children, elderly, rare diseases and special populations, e.g. hepatic and renal dysfunction, HIV+
- Agents under evaluation include small molecules, antibodies, vaccines, targeted toxins, oligonucleotides, and gene transfer agents
- Ability to move promising early phase results into later phase, definitive trials
Recently developed NCI IND agents

- Agents that have achieved FDA approval based *in part* on early development in CTEP collaborative early phase programs
  - Bortezomib - Mantle Cell Lymphoma
  - Ipilimumab - Melanoma
  - Lenalidomide and bortezomib - Multiple Myeloma
  - Romidepsin - Peripheral T cell Lymphoma
  - Sorafenib - Thyroid Cancer
  - Ziv-aflibercept - Colorectal Cancer
  - Dinutuximab (ch14.18) - Neuroblastoma
- Pending FDA approval
  - Nivolumab - Anal and Nasopharyngeal Cancer
  - Pembrolizumab - Merkel Cell, Mycosis Fungoides
- In pivotal trials based on development in CTEP program: Cediranib and Oliparib - Ovarian Cancer
CTEP by Numbers

- Currently uses 99 agents sponsored throughout 140 Investigational New Drug Applications (INDs)
- Approx. 20,000 registered investigators (clinical & pre-clinical) at over 2,771 institutions in the US and internationally
- Over 750 active protocols
- 140 new protocols/year
- Approx. 20,000 patients accrued/year on CTEP-sponsored treatment trials
- One of the largest sponsors of cancer related combination studies in the world - Approximately 2/3rds of all combination studies in clinicaltrials.gov are CTEP-sponsored studies
- Over 100 collaborative agreements (CRADAs, CTAs, Agent-CRADAs and CSAs) with pharmaceutical companies
Why does NCI/CTEP do combinations of novel agents?

NCI is uniquely positioned to perform novel agent combination trials by overcoming regulatory, intellectual property, and risk aversion hurdles because of its extensive collaborations with industry and academia.

- Molecularly targeted combination studies are the future of personalized medicine.
- Combination strategies are critical to improving therapeutic outcomes
  - Rational combination of agents
  - Properly selected patient population
- Trials designed to maximize inhibition of a critical target or target multiple cellular pathways in cells
  - Tumor cell eradication
Molecularly Targeted Combinations: Accrual Data

- Active Studies 2011-2016: 263
  - 97 Investigational/Investigational
  - 127 Investigational/Commercial
  - 39 Commercial New indication
  - 29 Trials in review using investigational combinations

- Total Accrual: 11,432 across all histologies (phase 1, phase 2, and pilot studies only - ETCTN and NCTN clinical trials programs)
CTEP Regulatory Affairs Branch: Agent Coordination Group

- Clinical Agreements
  - Development of Program-Specific Template Language
  - Negotiation & Review of international agreements
  - Total number of Clinical Agreements Active = 105
  - Total Number of Agents = ~80

- Executed in 2014
  - Cooperative Research and Development Agreements (CRADAs): 10
  - Clinical Trial Agreements: 11; Material Transfer Agreements: Basic Research (~64)
Regulatory Affairs Branch (RAB): Drug Regulatory Group

- CTEP-held INDs = 128 (DCTD is the legal Sponsor)
  - NCI-developed agent
  - Company-developed agent (phase 1-3, post-marketing)
  - Combination studies
- INDs Filed per Year = ~20
- Sponsor Responsibilities
  - Safety Reporting (expedited and annual)
  - New Protocols and Amendments
  - Response to FDA Queries
CTEP Regulatory Affairs Branch: Agent Coordination Group

Company

NCI

Clinical Group

Supplemental Funding

Intellectual Property
Option & Data Rights

Drug & Trial Data

Sponsorship/Oversight

Agent & Funding

Data
Clinical Trials Provisions for All CTEP Collaborative Agreements

- IND Sponsor
- Drug Supply
- Protocols
- AE Reports
- Monitor
- IP
- Pubs
- Data Rights

NCI Collaborative Agreements
Invention Categories in the IP Option

Section A - Clinical Inventions

The IP Option described in Section A would apply to inventions that are described in patent disclosures that claim the use and/or the composition of the Agent(s) and that are conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the NCI CTEP provided Agent(s).

Section B- Biomarker-Related Inventions

The IP Option described in Section B applies to inventions not covered by Section A conceived or first actually reduced to practice pursuant to clinical or non-clinical studies utilizing the CTEP-provided Agent(s). It also applies to inventions that are conceived or first actually reduced to practice pursuant to NCI CTEP-approved studies that use non-publicly available clinical data or specimens from patients treated with the CTEP-provided Agent (including specimens obtained from NCI CTEP-funded tissue banks).
IP Option Section A - Clinical Inventions
(Inventions using the agent)

Offers:
(i) a **royalty-free**, worldwide, **non-exclusive license for commercial purposes**; and
(ii) a time-limited **first option to negotiate an exclusive, or co-exclusive**, if applicable, world-wide, **royalty-bearing license for commercial purposes**

Covers:
- Alternate uses for agents, the “Minoxidil and Viagra” scenarios.
- Dosing schedules, unique administration techniques that improve efficacy.
- In general, inventions that would fall under the scope of Section A would be very rare
IP Option Section B – Biomarker-related Inventions (“Assay” inventions)

Offers:

(i) **Nonexclusive**, nontransferable, **royalty-free**, world-wide license to all Institution Inventions for **research purposes only**; and

(ii) A grant of a **label/regulatory use license** of any invention for development of the provided agent

Covers:

- Assays/Diagnostics - Possibly broad in array
- New scientific methods or techniques

The scope of inventive material is much broader under Section B, however the license grant is much narrower
NCI: Evolving a National Strategy for Precision Medicine

- Precision Medicine uses genetic information from a person’s cancer to determine a patient’s treatment with a treatment targeted to that particular genetic abnormality

- Genomics of Exceptional Responders (Phenotype to Genotype Evaluation)
  - Tumor from patients who had an exceptional response to a drug that did not go forward to clinical use

- NCI-MATCH Clinical trial (Master protocol for Genotype to Phenotype Evaluation)
  - Screen for molecular features that may predict response to a drug with a given mechanism of action
Biomarkers in Clinical Trials

**• Integral**
- Used for patient selection
- Used to determine patient treatment
- Performed in a CLIA environment
- May require an IDE

**• Integrated**
- Used for patient description
- Provide evidence of pathway activation
- CLIA ready
- IDE not required

**• Exploratory**
- Descriptive biomarkers
- Not validated or fit for purpose

**Prioritization**
- Possibly phase dependent
- Proof of mechanism
- Proof of principal
- Pharmacokinetics
- Pharmacodynamics
- Propose innovative disease- or biomarker-based trials incorporating appropriate endpoints

**Emphasis on fit for purpose, qualified assays**
Example of National Precision Medicine Trial: NCI MATCH
Molecular Analysis for Therapy Choice

NCI MATCH: Example of National Precision Medicine Clinical Trial
Overview of NCI MATCH Clinical Trial

- Molecularly profile $\approx 6,000$ patients with a multi-analyte validated targeted NGS assay to identify up to $\approx 1,000$ to $1,200$ patients with tumor that has mutations/amplifications in pathways targetable by existing agents.

- Patients will be assigned to receive one of the agents/regimens defined to work on one of their identified mutations/amplifications in a phase II setting.

- Assess response/PFS to treatments targeting the particular molecular abnormality in a patient’s malignancy.
Collaboration Mechanism: Clinical Trial Agreement (CTA)

- Umbrella CTA for NCI-MATCH with each participating company for agents not already in CTEP portfolio. For agents with existing CRADAs, the agent may be utilized under that agreement (all CRADAs amended to account for additional research plan scope and agreement for NCI to fund).

- Agents in MATCH trial can be listed in an appendix to the CTA that will allow for easy additions and deletions.

- NCTN Group-led study (by ECOG-ACRIN for NCTN Network) so CTA most efficient in this case and no funding to CTEP.

- DCTD IND sponsorship; agent distribution, AE reporting.
Matching Targeted Drugs to Molecular Lesions

- **Umbrella** for **multiple** single-arm phase II trials across different types of cancers (multiple histologies within each trial)
  - Each molecular subgroup matched to a targeted agent
  - Rules based assignment

- Agents could be commercially available or experimental but would have at minimum *dose/safety established* in phase 1 trials
  - Level 1: FDA approved different tumor
  - Level 2: Data from trials in similar molecular abnormality; investigational drug
  - Level 3: plausible preclinical evidence that drug works against a given tumors with a given molecular abnormality
NCI-MATCH / EAY131 SCHEMA

- Genetic sequencing
  - PTEN IHC
  - Actionable mutation detected
  - Study agent
  - Stable disease, complete or partial response (CR+PR)^1
    - Continue on study agent until progression
    - Progressive disease (PD)^1
      - Check for additional actionable mutations^2
        - Yes
          - No additional actionable mutations, or consent withdrawn
            - Repeat biopsy and sequencing
          - No
            - 3 year follow-up or off study
        - No
          - Continue on study agent until progression

^1CR, PR, SD, and PD as defined by RECIST
^2Rebiopsy if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH
NCI-MATCH Assay System & Work Flow
~ 14 Day Turnaround Time

NCI / Cancer Therapy Evaluation Program (CTEP)
Status and History of NCI-MATCH Trial

- Trial opened August 12, 2015, with 10 treatment arms
- Trial temporarily closed to new accrual November 11, 2015 for built-in interim analysis to assess operational efficiency and match rate
- Trial re-opened in May 2016 with a total of 24 treatment arms
- Original estimate of 50 screens per month greatly surpassed (100+/week now)
- Active Sites Across: 2/3 Community sites, 1/3 Academic sites
- Current Enrollment Jan. 1 2017: 4,110 patients; assay completion rate ≈ 93%; 368 patients enrolled on treatment arm (≈ 21% to 24% match rate since May ‘16)
NCI-MATCH Expanded to 24 Arms May 2016

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NCI Pediatric MATCH structured in a similar way and led by the Children’s Oncology Group should open in Spring/Summer 2017
Process for Partnering in Drug Development:

NExT
Access to NExT

Who: Researchers in academia, government and industry, nationally and internationally

http://next.cancer.gov/

About NExT

How NExT Works

How To Apply

NExT Resources

Imaging

The NCI Experimental Therapeutics (NExT) Program

A Unique Partnership with the NCI to Facilitate Oncology Drug Discovery and Development

Do you need

- A partner to complete development of an orphan drug for a pediatric or rare cancer?
- Exploratory screen development and optimization?
- Preclinical development for an agent with a specific molecular target?
- A different formulation of your agent for it to be clinically useful?
- Pharmaceutical-grade investigational drug to conduct clinical studies?

Who: Researchers in academia, government, and industry, nationally or internationally. A list of highly ranked applications can be found here.

What: Drug discovery and development projects will enter an NCI pipeline focused on unmet needs in therapeutics that are not adequately addressed by the private sector. The NCI is committed to moving high-priority discovery and development projects through to proof-of-concept clinical trials. For more information, visit About NExT.

When: Submission deadlines occur three times per year.

Where: Online submission of NExT application.

How: Entry into NExT can occur at any stage of the drug discovery and development process.
NExT Process

- Three submission deadlines per year
  - February 15th
  - June 15th
  - October 15th
- Applicants apply with their discovery/development programs and proposals for collaboration with DCTD
- Special Emphasis Panel prioritizes applicant agents
- Plans are endorsed or rejected by senior NCI leadership (SAC)
- Once SAC approves plan:
  - Project Teams are formed
  - Company has 6 month timeline to negotiate CRADA for clinical projects
NExT Pipeline: Current Status

86 NExT-initiated Projects

19 Active

26 NExT-initiated projects closed

41 Active
NExT Applications Received Since Inception

- 569 Applications to Date

**Sector**
- Biotech: 34%
- Government: 3%
- Academic: 42%
- Non-Profit: 14%
- Pharma: 7%

**Agent**
- Small Molecule: 64%
- Biologic: 33%
- Natural Product: 1%
- Imaging: 2%
- Academic: 42%
- Government: 3%
- Non-Profit: 14%
- Pharma: 7%
- Biotech: 34%
New Initiative: NCI Formulary
The Challenge

- Access to investigational drugs for academic investigator-initiated studies is time consuming for industry and for the investigators, as the entire apparatus for conducting the trial must often be “re-invented”

- Multi-agent combination studies, that use investigational agents from different development teams within a company or especially ones that use agents from different companies, are especially labor-intensive
Aspirational Goals for NCI Formulary Initiative

- Large “formulary” of novel agents for investigators to access
- Agents will be provided for both clinical and pre-clinical (PDX, cell line, etc.) studies
- INDs will be held by investigators/institutions, not NCI/CTEP
- Companies, not NCI, will review proposals scientifically and decide on their merit
- NCI will facilitate the process by providing infra-structure to assure a consistent review and reporting format
Industry-NCI/CTEP-Investigator Agreements

Common Data Sharing and IP Option Agreement Language

- Agreements encompass multiple trials/studies of mutual interest
- Framework accepted by Collaborators and Cancer Centers

Collaborative Agreements

Funding Agreement/Protocol Language or MTA (for non-clinical studies)

NCI/DCTD

Collaborator A
Investigational Agent A

Collaborator B
Investigational Agent B

Institutions
Network Groups
Consortia
Proposed: Agreement Structure

- Sites will be bound by the terms of a clinical or pre-clinical MTA
- Pharmaceutical collaborators will sign a single agreement with the NCI, either as a CRADA amendment or a stand alone agreement (CTA or CRADA) covering all pledged agents
  - Data use and transfer will be handled according to the terms present in current agreements
  - IP will follow the terms of the CTEP IP Option to Collaborator found here: http://ctep.cancer.gov/industryCollaborations2/guidelines_for_collaboration.htm
    These terms have already been agreed to by all parties in existing funding agreements
- NCI will provide its standard support structure at no charge to companies
Proposed: “Virtual Formulary”

- Create a system that leverages existing NCI mechanisms to provide Collaborator Investigational and/or newly marketed agents for investigator-held INDs

- The program will have the following characteristics:
  - Easy to access with a “menu” of agents to choose from
  - Quick and simple process that ensures rapid turn-around times
  - Utilizes pre-existing agreements/infrastructure that current Pharmaceutical Collaborators are already familiar with
Potential Advantages of NCI Formulary

- **For Industry:**
  - Centralized data and distribution mechanism that utilizes NCI existing resources that many companies are already familiar with existing agreement structure
  - Uniformity among investigator initiated studies: data are collected in a centralized, standard system with consistent IP and other agreement terms
  - NCI takes on cost of drug distribution and provides data submission support systems to fulfill FDA requirements for investigators

- **For Investigators:** Existing agreement structure that significantly reduces the transactional costs of agreement negotiation & Access to a wide tableau of agents, with the potential for novel combinations

- **For Public:**
  - Provides a mechanism to quickly initiate trials in both common & rarer indications
  - Provides access at major centers to investigator-initiated combination studies
  - Private-public sector collaboration in interest of speeding potential treatments to patients
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