Public Summary
Investigational Drug Steering Committee (IDSC)
Friday, January 14, 2011

1) Call to Order, Introductions and Review of Minutes

a) **Presentation of a plaque to Michael Grever** for his contributions as IDSC U01 co-chair over the past 2 years. Pat LoRusso has replaced Michael Grever starting January 1, 2011.
b) **Motion 1**: The IDSC meeting minutes from September 28-29, 2010 were approved.
c) **Coordinating Center for Clinical Trials (CCCT) update**: The next IDSC Spring meeting will be held on March 15-16, 2011 in Bethesda, MD at Natcher Auditorium.
d) **Cancer Therapy Evaluation Program (CTEP) update**: The CTEP recent and pending solicitation schedule for 2010/2011 (pending: ARQ-197, MLN8237, TRC-105, etc.), Operational Efficiency Working Group (OEWG) Phase I and II timelines, and presolicitation statistics (OSI-906, ARQ-197, and MLN8237) were discussed by James Zwiebel (IDB Chief).

2) Developmental Therapeutics Program (DTP) Combinatorial Presentation *(Collins)*

a) The rapid development of new therapeutic agents that target specific molecular pathways involved in tumour cell proliferation provides an unprecedented opportunity to achieve a much higher degree of biochemical specificity than previously possible with traditional chemotherapeutic anticancer agents. However, the lack of specificity of these established chemotherapeutic drugs allowed a relatively straightforward approach to their use in combination therapies. Developing a paradigm for combining new, molecularly targeted agents, on the other hand, is substantially more complex. The abundance of molecular data makes it possible, at least in theory, to predict how such agents might interact across crucial growth control networks. Initial strategies to examine molecularly targeted agent combinations have produced a small number of successes in the clinic. However, for most of these combination strategies, both in preclinical models and in patients, it is not clear whether the agents being combined actually hit their targets to induce growth inhibition. Here, we consider the initial approach of the US National Cancer Institute (NCI) to the evaluation of combinations of molecularly targeted anticancer agents in patients and provide a description of several new approaches that the NCI has initiated to improve the effectiveness of combination-targeted therapy for cancer (Kummar, S., Collins, J., Chen, H.X., Wright, J., Holbeck, S., Millin, M., Tomaszewski, J., Zwiebel, J., and Doroshow, J.H., *Utilizing targeted cancer therapeutic agents in combination: novel approaches and urgent requirements.* Nat Rev Drug Discov. **9**(11): p. 843-56)
b) **This initiative is unquestionably "big" but <u>why</u> should it be attempted?**
    i) Creation of public database can stimulate improvements in the art and science of choosing combinations.
    ii) The truly unexpected discovery of a successful empiric combination can bring full attention to understanding molecular basis. NCI-60 has extensive characterization.

iii) In some cases, immediate translation into a clinical trial of the combination provides the fastest route from an "interesting" lab finding to direct evaluation of patient benefit.

3) CTEP Drug Development Plan – SCH900776 (Chk1; *Doyle)*

a) CTEP is planning to add the Chk1 inhibitor, SCH900776 to its portfolio (*further information is confidential).*

b) Signal Transduction and DNA Repair TF recommendations on CTEP's clinical development plan were presented to the IDSC and a smaller portfolio with reprioritization of trials was requested for the March 15-16th (2011) meeting.

4) CTEP Drug Development Plan – MK-1775 (Wee1; *Doyle)*

a) CTEP is planning to add the Wee1 inhibitor, MK-1775 to its portfolio (*further information is confidential).*

b) Signal Transduction and DNA Repair TF recommendations on CTEP's development plan were presented to the IDSC and a smaller portfolio with reprioritization of trials was requested for the March 15-16th (2011) meeting.

5) CTEP Drug Development Plan – TRC-105 (monoclonal antibody to CD105; H. *Chen)*

a) CTEP is planning to add the monoclonal antibody to CD105, TRC-105 to its portfolio (*further information is confidential).* A limited testing plan has been developed for this agent upfront.

b) Angiogenesis TF recommendations on CTEP's development plan were presented to the IDSC and approved.

c) The mass solicitation will be sent to IDSC members when available.

6) NCI Toxicity and Symptom Management Drug Development Task Force *(Brell)*

a) Task Force goal:

i) Agents to reduce treatment-related toxicity or cancer disease-related symptoms

ii) Evaluate agents for clinical trials in Community Clinical Oncology Program (CCOP)

b) Importance: Toxicities (CIPN) and symptoms (pain, weight loss) impair ability to give cancer therapy

i) Toxicity mitigation best included cancer therapy evaluation plan

ii) Process to evaluate new cancer therapy toxicities (HTN)

iii) Regulatory processes melded CTEP and DCP

iv) Capacity depends on interest – few agents at start

v) Supplement funds, credits structure arrangement in process

c) U01 and N01 grant/contract holders to assist with this effort?

i) IDSC members were interested and Joanna Brell should discuss further at the March 15-16th IDSC meeting.

d) **Contact Joanna M. Brell, M.D. with questions - brelljm@mail.nih.gov** (office phone: 301-496-8541)

7) **NCI Clinical Assay Development Program (CADP;** *Conley and Williams)*
   a) **Rationale:**
      i) Advances in understanding cancer biology and the advent of technologies to characterize individual tumors promise to change the practice of medicine.
      ii) Many promising "biomarkers" have been identified, assays developed, clinical correlations found.
      iii) Unfortunately, the translation of these findings to improved clinical assays has been inefficient. A large number of markers are reported but very few have entered practice.
      iv) A failure to appropriately validate assays is a common cause for the disappointing record.
   b) **Goal:** The goal of the NCI's new Clinical Assay Development Program (CADP) is to create a process to efficiently develop diagnostic tests that will address clinical needs in oncology, including co-development of targeted agents and predictive markers. It aims to identify promising predictive and prognostic assays, assess the needs for further development, and provide services to facilitate optimization of analytical performance and to establish clinical validity so that the clinical utility of the assay can be evaluated in well-designed clinical studies. The CADP will aim to deliver analytically validated clinical assays to the submitting laboratory, including documentation of good performance with the intended clinical specimen type.
   c) **Specimen Retrieval System**
      i) Provides paraffin embedded and annotated specimens from community.
      ii) NLP tool (Harvard) to scrub identifiable data
      iii) Institutions of the NCI-funded Cancer Research Network
      iv) Large health plans with stable membership
      v) Automated data systems
      vi) Pathology specimens dating back 30-40 years
      vii) Specimens closely reflect the type of cancers diagnosed and managed in the community setting.
   d) **Application Deadlines for 2011:**
      i) Jan 21
      ii) May 15
      iii) Sept 15
      iv) Anticipate start of approved projects June 2011

8) **Future Plans/Calls/Meetings:**
   a) **Next call: TBD**
   b) **Spring 2011 CTEP EDD/IDSC Meeting**: Monday-Wednesday, March 14-16th, 2011 (Bethesda, MD at Natcher Auditorium)
   c) **Summer IDSC meeting:** TBD
   d) **Fall 2011 CTEP EDD/IDSC Meeting:** Monday, Wednesday, October 3-5th, 2011 (tentative dates; Bethesda, MD)