Public Summary
Investigational Drug Steering Committee (IDSC)
Friday, July 15th, 2011

1) **Call to Order, Introductions and Review of Minutes**
   a) **Motion 1**: The IDSC meeting minutes from June 15, 2011 call were approved.
   b) **New IDSC Members**: Mac Cheever (Cancer Immunotherapy Network PI), Diana Chingos (patient advocate), Patrick Wen (Adult Brain Tumor Consortium), and James Yao (new MDA N01 PI)
   c) **Coordinating Center for Clinical Trials (CCCT) update** *(Reeves):*
      i) IDSC subject expert rotation for biostatistics, imaging, and immunotherapy were discussed. IDSC Subject Matter Experts serve a term of three years with a possible renewal of another three years.
      ii) Mario Sznol (immunotherapy), Don Berry (biostatistics) and Anthony Shields (imaging) will serve until the end of 2011. Susan Groshen's (biostatistics) term will be extended until the end of 2012.
      iii) Deb Barton (IDSC liaison to SxQOL SC) is departing but will serve until the end of 2011; SxQOL SC will be asked to propose replacement.
   d) **Cancer Therapy Evaluation Program (CTEP) update** *(Zwiebel):* James Zwiebel (IDB Chief) discussed the U01/N01 pre-solicitations (ARQ-197, MLN-8237, and OSI-906), mass solicitations recently released (ARQ-197, AMG-386, and TRC-105), and the additional planned solicitation schedule for 2011-2012.

2) **CTEP Drug Development Plan – SCH900776 (Chk1;** *Doyle)*
   a) CTEP is planning to add the Chk1 inhibitor, SCH900776 to its portfolio (*further information is confidential*). Dr. Austin Doyle presented a reprioritized plan to the IDSC.
   b) The IDSC endorsed the reprioritized SCH900776 development plan with some modifications.

3) **CTEP Drug Development Plan – MK-1775 (Wee1;** *A. Chen)*
   a) CTEP is planning to add the Wee1 inhibitor, MK-1775 to its portfolio (*further information is confidential).* Dr. Alice Chen presented a reprioritized plan to the IDSC.
   b) The IDSC endorsed the reprioritized MK-1775 development plan with some modifications.

4) **CTEP Drug Development Plan – SGN-35 (monoclonal antibody to CD30;** Espinoza-Delgado*)*
   a) CTEP is planning to add the monoclonal antibody to CD30 (SGN-35) to its portfolio (*further information is confidential).* A limited testing plan has been developed for this agent upfront.
   b) No mass solicitation will be developed for this agent. This was presented as an FYI to IDSC members.

5) **Presentation of the Cancer Immunotherapy Network** *(CITN; Cheever):*
   a) **Goals for the CITN:**

i) Establish a productive network of leading investigators/institutions to implement early phase cancer immunotherapy trials.
ii) Design & conduct novel biologically dictated early phase trials using agents/combinations to demonstrate proof of concept essential to proceed to Phase III pivotal trials.
iii) Provide high quality immunogenicity & biomarker data that elucidate mechanism of response.

b) CITN Mission

i) The CITN is an NCI funded network of highly experienced immunotherapy investigators
ii) Mission: To select, design and conduct early phase trials using priority agents with known and proven biologic function and to provide the high-quality research data essential to develop effective treatments for patients.
iii) Strategy:
(1) Focus on trials likely to achieve the optimal/quickest route to
(a) Proof of Concept
(b) Demonstration of patient benefit
(c) Regulatory approval
(2) To focus on agents & formulations likely to achieve commercialization

c) Categories of Immunotherapy

i) Vaccines
(1) To activate and expand the number of patient T cells capable of specifically killing cancer cells
ii) Autologous T cell therapy
(1) To treat with large numbers of cultured autologous T cells
iii) Antibody therapy
(1) To augment the efficacy of “standard” antibody therapy
iv) Combinations of Immune Modifier Agents
(1) To activate and expand nascent or ongoing immune responses

d) THE MAJOR BARRIER for development of effective & curative cancer immunotherapy

i) Immunotherapy agents with profound & proven function & high potential to benefit cancer patients are not broadly available for testing.

e) Agents needed to overcome biological restrictions have been invented

i) Dendritic cell activators
ii) Dendritic cell growth factors
iii) Vaccine adjuvants
iv) T-cell stimulators
v) T-cell growth factors
vi) Genetically modified T cells
vii) Immune checkpoint inhibitors
viii) Agents to neutralize or inhibit suppressive cells, cytokines and enzymes

f) Why aren’t curative cancer vaccines standard therapy

i) Historical challenge

(1) Biological limitations

ii) Current challenge

(1) Agents to overcome biologic limitations have been invented, but are not broadly available

(2) Limitations are funding, organization & vision

g) Conclusion:

i) Immunotherapy agents needed to treat and possibly cure cancers have been invented & manufactured

ii) Methods to prioritize immunotherapy agents, target antigens & regimens have been piloted.

iii) The CITN will provide an organized effort to conduct early phase trials with a focus on trials likely to achieve the optimal/quickest route to

(1) Proof of Concept

(2) Demonstration of patient benefit

(3) Regulatory approval

iv) CITN Vision – To have many immunotherapy agents with proven biologic function broadly available for cancer therapy.

6) Clinical Trial Design TF LOI Benchmarking Project *(Ratain):*

a) Approved Project: Perform quarterly reviews to track concordance between trial design elements of Approved Phase II CTEP trials and the IDSC Phase II Recommendations**.**

b) Review Process:

i) Participants: 3 reviewers from TF plus 2 ex-officio members

ii) Document Review: Approved Phase II CTEP-sponsored protocols identified and documents provided to reviewers electronically

iii) Rating: For each protocol, reviewers submit an overall assessment of “concordant” or “not concordant.” Where review results are not unanimous for a trial, protocols are discussed by conference call.

c) Results reported for Phase II Protocols Approved January 1-March 31, 2011

d) Summary of Q1 2011 Analysis

i) >60% are consistent with the Phase II Recommendations

ii) Trials that are Not Concordant employ single arm designs and use of alternate endpoints

(1) 3 trials employed composite endpoints, often as single arm trials

(2) biomarker endpoints may need to be addressed in greater detail if Recommendations are revised, or referred to Biomarker TF;

(3) Patient selection criteria employing biomarkers used in several trials

e) Next steps:

i) Conduct reviews for subsequent quarters in 2011;

ii) Categorize selected trials for discussion with TF to address potential gaps in Recommendations for possible revision.

7) Biomarker TF (Tissue-based Biomarker Assays Subcommittee - *True***):**

a) Develop **guidelines** for tissue-based biomarker assays (integral, integrated, or research) used in early phase clinical trials.
b) The TBBA has developed IHC (Case Report Form approved by the FDA), DNA-based ISH (Case Report Form under review by FDA), and now is working on a mutation assay template for early clinical/translational trialists.
c) The IDSC approved the following two motions:
   i) Templates be made publicly available on the CDP and CTEP websites and promoted by CDP and CTEP as appropriate at high profile stakeholder meetings (AACR Molecular Targets, NCI-EORTC-AACR, Early Drug Development, Cooperative Group meetings.)
   ii) CTEP should use these templates for LOI's, concepts and protocols that contain integral and integrated markers and develop a mechanism for them to be tested, to determine their value and utility to CTEP investigators.

8) Pharmacology TF: An IDSC teleconference should be scheduled for Percy Ivy to present the carboplatin dosing research questions to IDSC members (*update: conference call held on August 8th*).

9) Future Plans/Calls/Meetings:
a) Next call: Monday, August 8th at 12:00 PM ET
b) **Fall 2011 CTEP EDD/IDSC Meeting:** Monday, Wednesday, October 3-5th, 2011 (Bethesda, MD)
c) **Spring 2012 CTEP EDD/IDSC Meeting:** Monday-Wednesday, March 12-14th, 2012 (Bethesda, MD)
d) **Fall 2012 CTEP EDD/IDSC Meeting:** Monday-Wednesday, October 15-17th, 2012 (Bethesda, MD)