Public Summary
Investigational Drug Steering Committee (IDSC)
Tuesday, March 15, 2011

1) Call to Order, Introductions and Review of Minutes

a) **New IDSC members**:
   i) Diana Chingos (USC) has been selected as the new IDSC patient advocate. Deborah Collyar will be retained as an advocate emeritus. We welcome Diana and are glad that Deborah will continue to work with the IDSC.
   ii) Dr. Patrick Wen (Dana-Farber Cancer Institute) has joined the IDSC as the new Adult Brain Tumor Consortium (ABTC) representative. He replaced Dr. Myrna Rosenfeld. We welcome Dr. Wen.

b) **Motion 1**: The IDSC meeting minutes from January 14, 2011 were approved.

c) **Coordinating Center for Clinical Trials (CCCT) update**: LeeAnn Jensen introduced new CCCT staff, Drs. Steven Reeves and Wolf Lindwasser.

d) **Cancer Therapy Evaluation Program (CTEP) update**: Dr. James Zwiebel (IDB Chief) discussed the upcoming U01/N01 presolicitations (ARQ-197 in combination, etc.), mass solicitations from 2010 (OSI-906, AFP-464, and AMG-386), and planned solicitation schedule for 2011.

2) Clinical Trial Design Task Force *(Berry/Groshen/Ivy/LeBlanc/Seymour)*

a) FDA Perspective – 2 New Molecular Entities (2NME) INDs (Ivy/*Temple*)
   i) Dr. Percy Ivy provided some background information for 2NME and introduced Robert Temple, FDA.
   ii) FDA Guidance
      (1) Noting the considerable interest in simultaneous development of 2 novel NMEs, especially in ID and oncology, as well as uncertainty as to FDA requirements, we wrote, in December, Guidance on Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination.
      (2) The guidance is very much a discussion of possible approaches and is relatively non-directive, essentially taking the view that exact pathways will depend on the situation. It appears likely, however, that success in phase 1-2 trials will often allow the phase 3 trials to compare the combination, with a control (i.e., not be a factorial study.
      (3) ***Complete FDA Guidance is listed in Appendix I.***

b) Historical Controls Database – Pancreatic and Advanced Non-Small Cell Lung Cancer (NSCLC) *(LeBlanc)*
   i) **Goal of Project**:
      (1) Provide historical control data for planning phase II trials in advanced non-small cell lung cancer and metastatic pancreatic cancer. Patient level outcome and covariate data from cooperative groups in North America (and possibly from the EORTC), will provide web-based tools for sample size and power calculations based on the relevant covariates and their expected distribution. Endpoints to be considered include OS and PFS, but could also include response rate, and disease control rate if available.
   ii) **Summary of findings**:

(1) Less time variation for outcome for Pancreas data set than Lung.
(2) Focusing (or reducing) data to "relevant" group of patients was substantial with alternatives possible.
(3) In both cases – more than an overall target benchmark would be required to inform design or analysis of new Phase II.

c) Bayesian multiple histology trials in phase II versus separate trials for each histology (*Berry*)

i) Using data from Susan Groshen's simulation trial plus some from Don Berry's studies, they found that borrowing data across trials was beneficial in some circumstances, and not in others. Hierarchical borrowing across subtypes (biomarker or histologic) was of benefit if a drug was consistently effective (or ineffective) across the tumor types, strengthening the result when combining data from like tumors. However, in situations where a drug is active in 1 tumor type but not in others, borrowing would weaken the result – i.e., lead to incorrect conclusions regarding drug activity in the tumor types. This could also be applied within multiple subtypes in a tumor type, such as sarcoma, where a drug might be effective in 2 or more subtypes, but not in others (suggesting other mechanisms of disease). In general, these types of designs could be combined, and could be used for "indication finding".

d) Brief Update on Phase I Combination Database (*Ivy*)

i) The IDSC Clinical Trial Design (CTD) TF held a Phase I Workshop on July 8, 2008. One of the topics covered was "Phase I trials in agent combinations". Several questions raised at this meeting remained unanswered regarding patient selection (hypothesis driven or preclinical), prioritization of potential combinations (empiric recommendations), schedule and sequence, and trial design (escalation, endpoints). The CTD and NCI were asked by FDA representatives at this Workshop to comment on guidelines for combinations. A database of Phase I combination trials was developed (novel-novel and standard novel-combinations; 151 protocols) and key data extracted from CTEP-sponsored protocols. Analysis is currently ongoing.

3) Update on SCH900776 (Chk1) and MK-1775 (Wee1) *(Doyle)*

a) CTEP is currently reprioritizing the SCH900776 (Chk1) and MK-1775 (Wee1) development plans. When this internal process is complete, the Signal Transduction and DNA Repair TFs will assist in finalizing the recommended reprioritization.

4) Assessing Implementation of the CTWG Recommendations *(Adamson)*

a) CTWG Evaluation Process

i) Completed baseline study October 2008

(1) Determined feasibility of data collection
(2) Reported on certain measures of the state of system (data from 2005-2006
(3) http://transformingtrials.cancer.gov/initiatives/ctwg/evaluation

ii) Baseline study included measures and methodologies for a proposed future evaluation plan

iii) CCCT constituted the CTWG Evaluation Working Group under CTAC to advise on the proposed evaluation plan

iv) Investigational Drug Steering Committee Evaluation Methodology

(1) Predominantly qualitative approaches
(2) Expert panel review of IDSC impact
(3) Database analyses of timeline performance in approving protocols
(4) Qualitative analysis via stakeholder interviews
  (a) IDSC members
  (b) Investigators who submitted LOIs
  (c) NCI staff
  (d) Industry
  (e) Steering Committee members
(5) Bibliometrics and document review

v) Investigational Drug Steering Committee Evaluation Topics

(1) Clinical Development Plan (CDP) quality pre- and post-IDSC review (expert panel and stakeholder interviews
(2) Process for developing CDPs (stakeholder interviews)
(3) Quality/balance of CTEP early drug development trial portfolio (expert panel)
(4) Transparency and quality of early drug development trial prioritization (stakeholder interviews)
(5) Collaboration in accrual to CTEP EDD trials (database analyses)
(6) Collaboration among IDSC members (stakeholder interviews)
(7) Impact of IDSC Reports/Guidelines (database/document analyses and stakeholder interviews)

b) Discussion Questions

i) Should the evaluation be a high priority for initiation in 2011?
ii) Are there alternatives to expert judgment for assessing the scientific importance and clinical relevance of trial results?
iii) Are there alternatives to stakeholder interviews for addressing Steering Committee and IDSC performance?
iv) Is the extent of qualitative measures appropriate to achieve the goals of the evaluation?

5) PD Assay Update (*Tomaszewski)*

a) Dr. Joe Tomaszewski updated the IDSC on the DCTD Pharmacodynamic (PD) program; please see the website below for more information.
b) PD Biomarker SOPs available on DCTD website: http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm

6) Task Force Updates

a) Biomarkers TF:

i) FDA-reviewed version of the IHC Case Report Form (CRF) template

(1) IHC Template Intent
  (a) Annotate the development of assays for NCI-supported clinical trials
  (b) Allow assessment of analytical performance of assay
  (c) Contribute to a database of molecular diagnostics for the CTRP

(d) Facilitate the pre-IDE review of integral assays that the FDA is now requiring for all trials with integral markers

ii) DNA-based ISH (latest version; almost finalized) - should be converted into a template

iii) New templates: mutation assay template

iv) Future Plans:

(1) Genetic Templates to cover somatic mutations

(2) Need to consider how best to represent integral markers for targeted therapy

(3) Also consider ELISA's and similar assays

(4) Also important to link to the high level molecular diagnostics module that is now incorporated into the trial summary report to *ClinicalTrials.gov* and *Cancer.gov*

b) Immunotherapy TF:

i) Recent Focus on Adoptive Immunotherapy

(1) White paper accepted for publication – CCR

(2) Assisted in planning of CTEP-sponsored meeting Feb 16, 2011, with investigators, Surgery Branch, and FDA representatives

ii) Future Task Force Activities

(1) IL-15 development plans

(2) Other agents?

(a) Vaccines and adjuvants

(b) Anti-GITR

(c) Anti-OX40

(d) Anti-CD200

iii) Discussion of involvement in ipilimumab post approval development

iv) Interactions with CITN?

v) Review exclusion criteria for trials

(1) Brain metastases

vi) Position on conducting studies in special populations

(1) Abnormal organ function

(2) Prior autoimmunity

vii) Consider development issues and hurdles for key predicted combinations

viii) How to design phase 1 combination studies when autoimmunity is DLT?

ix) Address questions re: severe autoimmunity as DLT - if easily controlled with steroids?

x) Trials to develop and validate predictive biomarkers (CRP, VEGF, lymphocyte counts)

xi) Develop proposals for NCI development of key IHC assays in tumor microenvironment (markers of inflammatory and immunosuppressive environments)

xii) Develop proposals for NCI development of multiplex serum assays of potential predictive and PD biomarkers

(1) MICA, MICB, VEGF, serologic responses, etc

c) Pharmacology TF:

i) Dr. Percy Ivy is working on a carboplatin dosing mass solicitation, which the TF will review.

7) Future Plans/Calls/Meetings:

a) Next Call: TBD

b) Summer IDSC meeting: Tentatively July 15th (2011) in Chicago, IL

c) **Fall 2011 CTEP EDD/IDSC Meeting:** Monday, Wednesday, October 3-5th, 2011 (Bethesda, MD)

d) **Spring 2012 CTEP EDD/IDSC Meeting:** Monday-Wednesday, March 12-14th, 2012 (Bethesda, MD)

APPENDIX I

I. Overview

Inevitably, developing 2 drugs in combination will give less information about the S & E of each than would individual development. This may be unavoidable (rapid resistance means you just can't use the drug alone) but there needs to be a good reason to accept the risk. Co-development is therefore for special situations

- Combination is for a serious disease
- There is a compelling biological rationale for use of the combination (drugs hit distinct targets, inhibit a primary and compensatory pathway, avoid important toxicity by allowing lower doses)
- Have support from pre-clinical or short-term clinical biomarker of synergy
- A good reason why the agents can't be developed individually (early resistance, limited solo activity)

II. Non-Clinical

Very helpful to have a non-clinical in vivo (or in vitro) model showing activity of separate drugs and the combination on a relevant pathophysiologic process (animal model of disease nice but not essential).

Safety - see ICH M3 (R2), section on Combination Drug Toxicity Testing.

III. Clinical

Always consult Review Division

A. Early Human Studies

1. Safety of components
Generally, phase 1 safety studies should be of individual components, identifying MTD, dose-limiting toxicity, and PK, generally in normal volunteers. If relevant PD, getting PK/PD information is very desirable.

If pre-clinical data show use in NV is not possible, studies would be done in patients, or, if this is not possible (monotherapy unacceptable), the combination would be studied in animals to guide initial human dosing.

2. Safety of the combination
Doses generally based on phase 1 single agent studies. Could use sequential approaches (drug A, then B, then AB; then increase A, add B, increase B, add A, etc).

3. Clinical Pharmacology

Generally same as if drugs were developed separately, including PK, drug-drug interaction (in vitro and follow-up).

If possible, and a good measure, PK/PD (concentration-response) studies are very desirable to develop dosing strategies.

Notes (here and elsewhere) the desirability of using > 1 dose in phase 3.

If drugs must be given together, use of various doses in combination can allow assessments of components.

B. Proof of Concept (phase 2)

Should:

- Show contribution of each component (if still needed)
- Show effectiveness of combination
- Optimize doses for phase 3 trials

Very variable, depending on the situation. Often, e.g., not possible to give monotherapy more than briefly at most, so usual AB vs A vs B will not be possible. Three scenarios, each using a PD or short-term endpoint (e.g., tumor response):

1. Can't use drugs individually, e.g., because monoRx clearly ineffective. Can only do AB vs placebo (SOC) or AB + SOC vs SOC.

In some cases could use brief monoRx using a short-term outcome.

2. Each drug active and can be given individually. These can use 4 arm (or 3 arm)

AB vs A vs B (vs SOC/placebo)
AB + SOC vs A + SOC vs B + SOC vs plbo + SOC

Note the 3-arm is useful if successful but placebo (SOC alone) is very helpful in interpreting (e.g., if AB, A and B are all equal but > SOC).

An interim examination plan could allow dropping A and/or B if they were clearly less active.

3. One drug active; other inactive

In vitro or animal mechanistic data could make it clear that one drug is inactive alone. In that case probably study active drug (A) alone, generally as

AB vs A vs SOC (or as add-on)

It is possible that no trial is needed if only effect of B is to raise A blood levels.

4. Dosing

The more active component should be studied at multiple doses to get best dose for phase 3 (a more toxic component also should be). In general, better dose-finding lowers risk of phase 3 surprises.

C. Phase 3

If the phase 2 trials show the contribution of each component in a clinically credible way, phase 3 should test only the combination

AB vs SOC, or
AB + SOC vs SOC

If phase 2 is <u>not</u> clear, may need factorial, again, with interim assessments planned. If doubts affect only one component (B) and A is clearly active, could test only

AB vs A,

to establish the contribution of B, but would not need

AB vs B,

as effect of A is clear.

Co-development should ordinarily be done under a single IND, although early studies could have separate INDs.