Public Summary
Investigational Drug Steering Committee
Friday, July 24th 2009

1. **Call to Order, Announcements, and Review of Minutes**
    a. **Welcome to new IDSC member**: David Spriggs, M.D. (MSKCC U01)
    b. **Michaele Christian Award Nominees**: The selection committee is reviewing nominations.
    c. **Update on the October 2009 EDD/IDSC meeting**: The next CTEP Early Drug Development (EDD) meeting will be held on Monday-Tuesday, October 5-6th (2009) at the Sheraton National Hotel in Arlington, VA (near Washington Reagan National airport and Pentagon). cMet and Wnt educational sessions will be highlighted along with CTEP-sponsored clinical trial updates. Lesley Seymour (Clinical Trial Design TF Phase 2 recommendations) and/or Janet Dancey (Biomarker TF recommendations) may the IDSC update.
    d. **CTEP update:** Mass solicitations are expected for inhibitors for IGF-1R, akt, and bcl2.
    e. **CCCT update**: The Request for Information (RFI) for the Immune Response Modifiers Translational Research Opportunity has just been issued. This RFI is part of NCI's Process to Accelerate Translational Science as recommended by the Translational Research Working Group (TRWG). The complete RFI may be found at http://grants.nih.gov/grants/guide/notice-files/NOT-CA-09-031.html
2. **Update on the ABT-888 CTEP Drug Development Plan**
    a. CTEP is considering a new clinical development plan for this agent.
3. **Metrics Working Group**
    a. IDSC Publication Principles Flow Diagram: Lesley Seymour presented a flow diagram for IDSC publication principles. The IDSC approved the diagram with minimal changes. See Attachment 1.
    b. A non-confidential meeting summary will be written after each meeting/teleconference for IDSC members to share with non-IDSC members.
4. **PI3K/Akt/mTOR (PAM) Task Force**
    a. Naifa Busaidy (MD Anderson) and Azeez Farooki (Memorial Sloan-Kettering) provided an overview of mTOR-related hyperglycemia and hyperlipidemia on behalf of PAM TF Subgroup 3.
    b. See Attachment 2 for a summary of their presentation.
    c. Screening, treatment, and management of hyperglycemia/hyperlipidemia were discussed in regards to PAM agents.
    d. The IDSC applauded their effort and requested more defined guidance related to patients in early phase clinical trials from PAM TF Subgroup 3.
5. **Clinical Trial Design (CTD) Task Force**
    a. The CTD Task Force Phase 2 recommendations were approved by the IDSC.
    b. See Attachment 3 for the recommendations
6. **Immunotherapy TF**
    a. The Immunotherapy Task Force held a face-to-face meeting in Denver, CO on April 17, 2009 and considered the following:
        i. CTEP/DCTD Portfolio of immunotherapy agents
        ii. Cancer Immunotherapy Trials Network (CITN) structure

iii. Clinical endpoints in phase 1 and 2 trials
iv. Predictive biomarkers
v. CTEP role: new clinical developments

b. Discussion of phase III multi-institutional randomized study of immunization with the gp100:209-217(210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma and NCI next steps.
c. Future work will be done on 2 CTEP Drug Development Plans.

7. Cancer Stem Cell Task Force

a. Update on GDC-0449 and RO4929097 LOIs was provided.
b. The Task Force is planning a Wnt educational session for the Fall CTEP EDD meeting on Monday, October 5th (location: Sheraton National Hotel near Washington, DC).

8. CTCAE 4.0 CTEP Presentation and IDSC Motion

a. Steve Friedman (NCI) provided background on the NCI Common Toxicity Criteria for Adverse Events (CTCAE) and discussed the pros and the cons of converting all NCI-sponsored protocols to CTCAE 4.0.
b. **IDSC Motion**: The IDSC recommended in an email vote following the meeting that implementation of CTC version 4.0 should be performed in a selective manner. All studies in which treatment is completed and studies in follow-up only should not be revised to version 4.0. All studies which have not been initiated should use CTC version 4.0. Studies in the accrual and/or treatment phases should be assessed for cost/benefit effect including impact on scientific integrity, patient safety, and effort required to change to CTC version 4.0. Additional funding to offset the resource impact on grant and contract holders should be made available.

9. Signal Transduction Task Force

a. Targets being considered by this Task Force include:
i. Proteasome
ii. JAK
iii. STAT3

10. Biomarker Task Force

a. The IDSC was interested in having FDA representatives come to an IDSC meeting and discuss biomarker development.
b. The Biomarker Task Force manuscript will be submitted to Clinical Cancer Research (CCR).

11. Future Calls/Meetings/Plans

a. IDSC Winter 2010 meeting: Friday, January 15th (Chicago, IL)
b. EDD/IDSC Spring 2010 meeting: Monday-Wednesday, March 22-24th (Bethesda, MD)

mTOR-related Hyperglycemia and Hyperlipidemia

Dyslipidemia

mTOR inhibitors have been associated with dyslipidemias in the post-renal and post-cardiac transplantation settings, and dyslipidemia has also been seen with mTOR inhibitors in the oncologic setting. They have been shown to increase total cholesterol and especially triglycerides. As mTOR is a downstream component of the PI3K/Akt/mTOR (PAM) pathway, drugs which affect earlier steps are likely to create similar affects.

The likely pathophysiologic mechanism involves impaired clearance of lipids from the bloodstream**.** Rapamycin has been shown in primary cultures of rat hepatocytes to affect hepatic fatty acid metabolism. It promoted β-oxidation while decreasing flux into anabolic storage pathways (Brown NF, Metabolism 2007). Since glucose uptake and glycogen synthesis were decreased, the authors suggested that rapamycin induced a fasting metabolic phenotype, which is characterized by preference for fatty acids as a metabolic fuel and a high rate of lipolysis (high serum levels of fatty acids and triglycerides). In this study, rapamycin affected the transcription of key metabolic enzymes involved in hepatic lipid metabolism.

Another pathophysiologic mechanism of mTOR inhibitor induced hyperlipidemia, as shown in rats, is inhibition of insulin-stimulated lipoprotein lipase (Kraemer FB, Metabolism 1998.) Lipoprotein lipase (LPL) hydrolyzes the triacylglycerol component of circulating lipoprotein particles, mediating the uptake of fatty acids into adipose tissue and muscle. Insulin is the principal factor responsible for regulating LPL activity to deposit triglycerides in adipose tissue. A rapamycin-sensitive phosphorylation pathway, most likely ribosomal protein P70S6K, appears to be one important downstream component in the insulin signaling pathway through which LPL is regulated (Kraemer FB, Metabolism 1998).

Another study, in renal transplant patients, also supports impaired clearance of trigclycerides from the bloodstream as a mechanism of PAM mediated hyperlipidemia. In kidney transplant recipients with rapamycin-related hypertriglyceridemia, a significant reduction (rather than an increase) in the fractional catabolic rate of apoB100, a triglyceride-rich very low-density lipoprotein, was observed (Hoogeveen RC, Transplantation 2001).

Hyperglycemia

Skeletal muscle is a major target for insulin-stimulated glucose disposal and suppression of fatty acid oxidation after a meal. Long-term rapamycin treatment in L6 muscle cells was shown to affect fuel metabolism, promoting β-oxidation while diminishing basal glucose transport and glycogen synthesis (Sipula IJ, Metabolism 2006). Also, in the presence of rapamycin, the effects of insulin on glucose and fatty acid metabolism were diminished. An increase in fatty acid oxidation at the expense of glucose utilization is characteristic of the fasted metabolic state. Metabolic switching between fatty acids and glucose for energy production is a normal physiologic response; the effect of rapamycin is to induce a behavior suitable for the fasted environment regardless of circumstances. Rapamycin increased fatty acid oxidation by 60% accompanied by increased activity of carnitine palmitoyltransferase I (the primary intracellular regulatory enzyme of the fatty acid oxidation pathway). Glucose transport capacity, glycogen synthesis, and glycolysis were reduced by approximately 40%. Rapamycin reduced basal glucose uptake whereas the short-term response to insulin was unaffected-- the authors postulated this might involve transcriptional/translational regulation of basal glucose transporters (i.e., those not subject to rapid, short-term regulation by insulin) and as yet undefined direct effects on other steps in glucose metabolism. The reduction in

basal glucose uptake may partially explain the observed decreases in glucose utilization and glycogen synthesis.

Sirolimus (another name for rapamycin) also appears to interfere with insulin signaling and causes an insulin resistant picture in vivo. In renal transplant recipients on sirolimus, in vivo expression and activation of 3-kinase, AKT and insulin receptor substrates (IRS-1 and IRS-2) was investigated (Di Paolo S, J Am Soc Nephrol. 2006). A decrease of basal and insulin-stimulated AKT phosphorylation, which correlated with the increase of patients' insulin resistance, was demonstrated. In addition, an increase of IRS total protein expression, together with a smaller (IRS-2) or absent (IRS-1) increase of insulin-induced tyrosine phosphorylation were found, which closely mimics the naturally occurring pattern found in type 2 diabetes.

Clinical Trial Design TF Recommendations for Phase 2 Clinical Trial Design

Phase II trials evaluate the activity, and toxicity, of a new agent either as monotherapy or in combination. Trial designs with a single arm, based on response, are acknowledged as having limitations, especially when agents are used in combination or to study molecularly targeted agents - which may have significant clinical activity but low complete or partial response rates.

The CTD-TF has attempted to provide guidance by developing these general recommendations. These recommendations primarily focus on trial designs to demonstrate activity but may include secondary objectives exploring toxicity, scheduling or biomarkers.

The recommendations are intended to be general guidelines that may be used to inform the development of a robust phase II study design, rather than rigid rules dictating the design of all trials irrespective of the agent under study. The trial design should always be tailored to the specific agent or combination under study, and the most appropriate endpoint.

Recommendations

The first and critical decision point for the design of a phase II trial is based on the choice of the most appropriate primary endpoint, which should be tailored to the disease and drug(s) under investigation.

- Response-based endpoints such are that defined by RECIST, are standard, especially in early phase II trials. Other qualified biomarkers, such as molecular imaging or tumor markers, may be appropriate in select circumstances. Response based endpoints are appropriate primary endpoints if unambiguous and clinically relevant direct anti-tumor activity (such as tumor shrinkage) is hypothesized.
- If a response-based endpoint is not appropriate, especially in later phase II trials, progression-free survival is recommended as the primary endpoint. Other biomarker endpoints (such as tumor burden, tumor markers, novel imaging, tumor response, molecular biomarkers) and Patient Reported Outcomes (PROS) are always encouraged as secondary endpoints, especially in the context of studies that aim to qualify such endpoints. It is acknowledged that once qualified, these biomarker endpoints will become appropriate primary endpoints.

1) Study Design

a) <u>If 'Tumor Response' is the primary endpoint</u>

1) Monotherapy trials

Single arm designs are acceptable. However, randomization should be encouraged to optimize dose and schedule or to benchmark activity against known active therapies.

2) Combination trials

With some exceptions (e.g. availability of a well validated robust control database), randomization is usually required for trials testing combinations of agents to establish efficacy. An example is standard therapy ± novel agent or combinations of novel agents.

b) <u>If Progression Free Survival or another qualified biomarker is the primary endpoint (monotherapy or combinations)</u>

(1) With some exceptions (e.g. availability of a robust control database), randomization is required
(2) For randomized trials, blinded designs are encouraged where feasible. While placebo controlled trials are challenging, they are encouraged whenever possible. Alternatives include dose ranging, randomization vs. active controls or other novel agents, and randomized discontinuation and other crossover designs.
(3) It may be informative to prospectively incorporate crossover to the standard therapy + novel agent for those patients initially assigned to the standard therapy alone, although careful consideration should be given to the timing of crossover (for e.g., only after the primary endpoint has been observed). Such cross-over designs increase the access of patients to investigational agents, and also provide additional information about the activity of the study arms.

2) Patient Selection/Enrichment Strategies (all trial designs)

a) A goal of Phase (I and) II development should be to define biomarkers predictive of efficacy and/ or toxicity. Where feasible and appropriate, molecular biomarkers should be explored in order to identify subsets of patients of interest for future study.
b) However, enrollment should in general not be limited by biomarker status unless there are strong confirmatory and supportive *clinical* data justifying the enrichment strategy. Adaptive statistical designs may be used to allow modification of enrollment if data suggest a biomarker is predictive.
c) In an un-selected trial, the patient population of primary interest (i.e. defined by a biomarker) should be predefined and the study powered accordingly to detect an effect in that subset.
d) Multi-disease phase II designs should be considered, especially if the objective is to test a biomarker-focused hypothesis.

3) Statistical Designs

Prospective designs that adapt to what is learned during the trial can improve the efficiency of drug development and provide greater precision. Available adaptations include stopping early, continuing longer than anticipated, dropping arms (or doses), adding arms, focusing on patient subsets, assignment of better performing treatment arms with greater probability, and seamlessly moving from Phase I to II or Phase II to III during a single trial.