Welcome to the IDSC Newsletter

This is the tenth installment of the newsletter to IDSC members. The newsletter highlights key announcements, accomplishments, schedules, publications and events of the IDSC.

Please feel free to provide input.

CCCT and EMMES staff,
Steven Reeves (CCCT)
LeeAnn Jensen (CCCT)
Amy Gravell (EMMES)
Pam West (EMMES)

ANNOUNCEMENTS:

- We **welcome new IDSC members**: Mac Cheever (Cancer Immunotherapy Network PI), Diana Chingos (patient advocate), Patrick Wen (Adult Brain Tumor Consortium), and James Yao (MDA N01 PI replacing David Stewart).
- Welcome **to Steven Reeves** as the new NCI IDSC Project Officer.
- The **rotation of subject experts** will be reviewed by NCI CCCT with advisement from IDSC Coordination Team (CT) members.
- **Publications:** The PAM TF hyperglycemia and hyperlipidemia manuscript will be submitted to JCO.

See you at the IDSC Summer Meeting!
July 15, 2011; From 9:30-4:00 PM CDT
O'Hare Hilton

UPDATE from March 15th (2011) IDSC Meeting

- Diana Chingos and Patrick Wen were selected as new IDSC members.
- Robert Temple provided the FDA perspective on 2 new molecular entity (2NME) INDs.
- Austin Doyle provided a brief update on the SCH900776 (Chk1) and MK-1775 (Wee1) inhibitors.
- Peter Adamson provided an overview of the impending CTWG evaluation process of the IDSC.
- The Clinical Trial Design (CTD) Task Force presented an update on several projects: Historical Controls Database (Mike LeBlanc); Bayesian multiple histology trials in phase II versus separate trials for each histology (Don Berry and Susan Groshen); and Phase I Combination Database (Percy Ivy)

IDSC Task Force and Working Group Updates

Clinical Trial Design TF

The **Historical Controls Database project** is nearing completion. Existing data has been collected from over 1500 pancreatic cancer patients and over 5000 NSCLC patients from clinical trials of 5 Cooperative Groups from 1995-2005.The database was

created to facilitate more reliable use of historical controls data in Phase II for single arm study comparison. A manuscript of the analyses and discussion of the database has been prepared. Submission for publication is expected to occur by Fall 2011.

The **Simulation project** is nearing completion. The project has performed simulation studies to compare trial designs and evaluate these approaches for indication finders. Data has examined differences between conducting individual trials for each tumor type compared to conducting a single trial with multiple tumor types (examining effectiveness of an agent across tumor types and, where similar, identifying where borrowing across types might be employed).

The **Phase 2 Benchmarking project** is currently completing its first cycle to prospectively track concordance of trial design elements between the IDSC Phase 2 Recommendations and recently approved Phase 2 CTEP sponsored protocols. A pilot review for this project was reported in July 2010. Results from review of Phase 2 trials approved in the first quarter of 2011 will be presented at the Summer IDSC meeting in Chicago. The project group will continue to conduct reviews on a quarterly basis for 2011.

A **database is being developed to analyze data and trial design elements from Phase 1 Agent Combination Trials**. Data has already been abstracted from more than 150 clinical trials; a project group is currently working to prioritize analysis questions to be explored as well as identifying expanded data elements needed to answer specific questions. The database intends to examine questions on trial design efficiency, dose escalation schemes, and preclinical data contributions which may be indicative for successful combination of novel therapeutic agents.

Currently this project group is working to include representation of international studies combining experimental agents. Related to the Agent Combination Trials project, a **new project group is currently in development to begin formulating Recommendations for Designing Trials of Agent Combinations**. This project would draft ideas for a document that would eventually be published as guidelines for investigators designing trials investigational agent combinations, taking into consideration recent changes to the IND process for the U.S. FDA.

Immunotherapy TF

- **April 15th call:** TF discussion of CDX-110, Ipilimumab and IL-15 CTEP status.
- **May 23rd call:** Howard Streicher presented the Ipilimumab CTEP Drug Development Plan (DDP) to Task Force members for comment.
- **June 15th call:** Howard Streicher presented the Ipilimumab CTEP DDP to the IDSC and it was endorsed to move to mass solicitation.

Signal Transduction and DNA Repair TFs:

- **June 27th call:** TF leadership will review the reprioritized SCH900776 (Chk1) and MK-1775 (Wee1) CTEP DDPs.
- **July 6th call:** TF members will review the Chk1 and Wee1 reprioritized plans. These agents will be represented to the IDSC in July 15thin Chicago, IL.

Biomarker TF:

- Larry True and Kim Jessup will present the IHC, DNA-ISH and draft mutation assay templates to IDSC members on July15th.

Publication Corner: *this section will highlight 3 articles written by IDSC Investigators per issue (within the IDSC or outside publications of relevance):*

Article I: Gaddipati, H., Dowlati, A. et al. (2011). "Phase I Clinical Trials in Patients >/=80." J Geriatr Oncol **2**(2): 142-146.

Phase 1 clinical trials play a crucial role in development of therapeutics for cancer patients. During phase I clinical trials common toxicities are delineated, dose limiting toxicities (DLT) are determined and a dose for phase II studies is recommended. However, reviews of the phase I population indicate a younger group of participants with a median age of 50-55. No data exists on the performance of octogenarians on phase I trials. Concerns for enrollment of this patient population, relates to presence of comorbidities and possibly altered pharmacokinetics in the setting of unknown potential toxicities. We present herein the largest review of octogenarians on phase I trials. Twenty-two octogenarian patients with a median age of 83 were enrolled on phase I clinical trials. More than 50% of them were chemotherapy naive most likely indicative of the fact that treating physicians believed standard therapy to be potentially toxic to this population. These 22 patients were otherwise matched in terms of performance status and other parameters to a control group of participants < 80. This includes a similar number of cycles administered. Patients >/=80 had a 3 fold higher rate of achieving DLT (p=0.06) compared to the control group enrolled at the same dose level. The toxicities observed include cardiovascular, gastrointestinal and infectious complications. Three patients were enrolled on molecular targeted treatments with no significant toxicities. We conclude that enrollment of patients >/=80 on phase I trials of chemotherapy agents is most likely associated with higher risk of DLT.

Article 2: Weber, J. S., M. B. Atkins, et al. (2011). "White Paper on Adoptive Cell Therapy for Cancer with Tumor Infiltrating Lymphocytes: a report of the CTEP Subcommittee on Adoptive Cell Therapy." Clin Cancer Res.

Adoptive T-cell therapy (ACT) using expanded autologous tumor infiltrating lymphocytes (TIL) and tumor antigen-specific T cell expanded from peripheral blood are complex but powerful immunotherapies directed against metastatic melanoma. A number of nonrandomized clinical trials using TIL combined with high-dose (HD) IL-2 have consistently found clinical response rates of 50% or more in metastatic melanoma patients accompanied by long progression free survival. Recent studies have also established practical methods for the expansion of TIL from melanoma tumors with high success rates. These results have set the stage for randomized Phase II/III clinical trials to determine whether ACT provides benefit in stage IV melanoma. Here, we provide an overview of the current state-of the art in T-cell based therapies for melanoma focusing on ACT using expanded TIL and address some of the key unanswered biological and clinical questions in the field. Different Phase II/III randomized clinical trial scenarios comparing the efficacy of TIL therapy to HD IL-2 alone are described. Finally, we provide a roadmap describing the critical steps required to test TIL therapy in a randomized multicenter setting. We suggest an approach using centralized cell expansion facilities that will receive specimens and ship expanded TIL infusion products to participating centers to ensure maxial yield and product consistency. If successful, this approach will definitively answer the question of whether ACT can enter mainstream treatment for cancer.

Article 3: Dowlati, A., M. Kundranda, et al. "Temporal evolution of patient characteristics enrolled on phase I trials." Invest New Drugs **29**(2): 312-5.

Phase I trials serve a crucial role in anticancer drug development. Given the explosion in the number of both approved anticancer therapies and agents in development, we hypothesized that the characteristics of patients enrolling on phase I clinical trials is evolving. We reviewed 476 published phase I trials over the past decade encompassing 15,100 patients and determined the following characteristics for patients enrolled: age; percentage with ECOG PS of 0, 1, or 2; sex; race; and number of prior chemotherapeutic therapies received: 0, 1, 2 or >/= 3. We also identified the major tumor types enrolled: colorectal, lung, renal, breast, head/neck or "other". The change of patient characteristics over time as well as between the first half of studied period (period 1 = 1998-2001) and the second half period (period 2 = 2002-2006) was analyzed. Colorectal and lung cancer patients together comprise ~35% of all patients enrolled on phase I trials and this has not changed over the past decade. The contribution of "other" malignancies has however significantly increased over time. The proportion of patients with PS2 has declined while that of PS1 has increased. The pro- portion of patients with >/=3 prior therapies prior to study enrollment has also significantly increased. The shifting of patient characteristics especially as related to tumor types enrolled and number of prior therapies has important implications for future design of studies and inadequate attention to these issues may slow the accrual process.

UPCOMING IDSC MEETINGS:

- **Next call:** TBD
- **IDSC Summer Meeting:** (2011): Friday, July 15th in Chicago, IL (O'Hare Hilton)
- **IDSC Fall Meeting:** (2011): Tuesday-Wednesday, October 4-5th (Bethesda, MD)
- **IDSC Spring Meeting:** (2012): Tuesday-Wednesday, March 11-12th (Bethesda, MD)