Public Summary
Investigational Drug Steering Committee (IDSC)
Tuesday-Wednesday, September 28-29th, 2010

1) **Call to Order/Introductions, and Review of Minutes**
   a) **In remembrance of Dr. Merrill Egorin, M.D., FACP** for his vast contributions to the IDSC and oncology community as an esteemed colleague, friend, mentor, and teacher.
   b) **Motion 1**: The IDSC meeting minutes from July 19, 2010 were approved.
   c) **Announcements:**
      i) Dr. Pat LoRusso will become the new U01 IDSC co-chair on January 1st, 2011. We thank Dr. Michael Grever for his exceptional service.
      ii) The IDSC-Coordination Team and Signal Transduction TF co-chairs (Drs. Grant and Perentesis) have approved Dr. Ravi Salgia (University of Chicago) as a new TF member.
      iii) The IDSC-Coordination Team and Angiogenesis TF chair (Chandra Belani) have approved Ben Haines (Angiogenesis Patient Advocate) as a new member.
   d) **Coordinating Center for Clinical Trials (CCCT) update**: The next IDSC Winter meeting will be held on January 14, 2011 in Chicago, IL at the O'Hare Hyatt.
   e) **Cancer Therapy Evaluation Program (CTEP) update**: James Zwiebel (IDB Chief) discussed ongoing/pending CTEP solicitations (OSI-906 and ARQ-197) and CRADA statuses (*confidential information*).

2) **Lessons Learned from the OSI-906 Presolicitation** *(LoRusso)*
   a) Because U01 and N01 holders have an obligation to perform a certain number of studies with NCI agents, presolicitations for clearly defined studies withOSI-906 and ARQ-197 (*agents previously reviewed by the IDSC*) have been sent to U01/N01 holders.
   b) **Next steps**: Track approved U01-N01 LOI presolicitations as to how well and expediently the phase I/II protocols are written, submitted, evaluated, and implemented.

3) **Pharmacology Task Force – Creatinine Methodology Issue** *(Newman/Collins)*
   a) The IDSC approved Michelle Rudek (JHU) as the new Pharmacology TF co-chair.
   b) The Pharmacology Task Force held an evening meeting on Monday, September 27th to discuss new methodology for serum creatinine measurement and the impact on carboplatin dose determinations.
   c) **Key Points**:
      i) Serum creatinine used as surrogate for renal function (GFR) to adjust chemotherapy dose for renally-cleared agents (carboplatin)
      ii) Earlier serum creatinine measurements were not standardized across laboratories
      iii) Formulas for estimating GFR were developed using patients with renal disease
      iv) Variability exists in serum creatinine measurements and leads to poor concordance with GFR estimations
      v) New serum creatinine methodology (isotope dilution mass spectrometry, IDMS) recommended in 2005
      vi) Uses NIST reference standards
      vii) All US clinical chemistry labs will use new method by end of 2010
      viii) No linear correlation between previous values and new values

ix) Not possible to convert IDMS creatinine values to compare with FDA-approved labeling for carboplatin

d) **TF Recommendations**:

i) The IDSC recommends that a correction factor should NOT be used to calculate carboplatin doses based on IDMS serum creatinine.

ii) The IDSC recommends that each CTEP-sponsored protocol using carboplatin must have a maximum dose based on the target AUC or mandate measured GFR for patients with serum creatinine below the lower limit of normal.

iii) The IDSC recommends that studies of serum creatinine, GFR, carboplatin clearance, AUC, and toxicity in patients with normal and near-normal renal function are needed.

4) CTEP Drug Development Plan – MLN-8237 (Aurora Kinase A; *Piekarz)*

a) CTEP is planning to add the Aurora kinase A inhibitor, MLN-8237 to its portfolio (*further information is confidential).*

b) Signal TF recommendations on CTEP's clinical development plan were presented to the IDSC and approved with minor modifications.

c) The mass solicitation and pre-solicitation will be sent to IDSC members when available

5) Cardiovascular Toxicities Panel (CTP) – Recommendations for Project # 2 *(Steingart and Maitland)*

a) The IDSC reviewed the updated CTP's bulleted recommendations and offered a few minor edits. See recommendations document in Appendix I*; next step is condensing original manuscript for publication in JACC*).

b) A report on hypertension and VEGF inhibitors was recently published: Maitland ML, et al, J Natl Cancer Inst. 2010 May 5;102(9):596-604.)

6) NCI Experimental Therapeutics Program (NExT) update *(Doroshow)*:

a) James Doroshow (DCTD Director) provided an overview of NExT and projects that are under review or approved. http://next.cancer.gov/

b) Mission: The mission of the NExT Program is to advance clinical practice and bring improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects. The NExT Program is not a grant mechanism; applications with exceptional science cannot be accepted without a clear path to the clinic or potential benefit to patients. Awardees will not necessarily receive direct funding; rather, the NCI may allocate various contracts and grant resources toward the implementation and development of submitted projects. The NCI will partner with successful applicants to facilitate the milestone-driven progression of new anticancer drugs (small molecules, biologics) and imaging agents towards clinical evaluation and registration.

c) The NCI's Experimental Therapeutics (NExT) Program, a partnership between NCI's Division of Cancer Treatment and Diagnosis (DCTD) and the Center for Cancer Research (CCR), consolidates NCI's anticancer drug discovery and development resources in support of a robust, balanced, goal-driven therapeutics pipeline. Combined, these resources are capable of supporting a discovery and development continuum from

initial discovery through Phase II clinical trial evaluation. *The NCI is focused on moving high-priority discovery and development projects through to proof-of-concept clinical trials and, when warranted, will continue non-commercial research and development activities (up through and including clinical trials) on any discovery project in the NExT Program.*

d) The discovery engine of this program is the **Chemical Biology Consortium (CBC)**. The NCI has established this collaborative network comprising 12 of the top Specialized and Comprehensive Screening and Chemistry Centers with world-class capabilities covering high-throughput methods, bioinformatics, medicinal chemistry, and structural biology. Additionally, the highly successful Developmental Therapeutic Program (DTP) provides the resources needed to facilitate discovery and late-stage preclinical development through the final steps of development to first-in-human studies. Concurrent molecular imaging and/or pharmacodynamic assay development provided by the **Cancer Imaging Program (CIP)**, **National Clinical Target Validation Laboratory (NCTVL)**, and CCR allow early assessment of potential clinical biomarkers. These coordinated and focused R&D processes enable continued incorporation of new data and disease insights into every step of the discovery and development process, thereby increasing the potential for successful clinical evaluation of agents.

e) Clinical evaluation is supported by the **Cancer Therapy Evaluation Program (CTEP)**, NCI. The development program will be a collaborative effort between NCI and industry for agents in the late preclinical stage or early clinical stage to further develop the clinical program in the niche area that is outside the pharmaceutical industry's scope. Agents requiring IND-directed toxicology data or agents already in Phase I or II clinical trials are of interest. Companies seeking NCI collaboration are encouraged to apply to the NExT Program.

f) Recognizing the importance of an integrated approach to therapeutics development, NCI Senior Leadership has organized a unified governance structure for the NExT Program responsible for coordinating and integrating available resources. With a goal of reaching go/no-go decisions as efficiently as possible, the purpose of **NExT governance** is to ensure a pragmatic approach to drug discovery and development and a clear path to market. With the governance structure and unified **NExT Program Mission**, NCI will make data-driven decisions following NExT **Stage Gate** guidelines to maximize the potential for success at each consecutive stage. As such, the NExT Program is envisioned to streamline the development and testing of promising new anticancer drugs and expedite their delivery to bedside.

7) Biomarker Task Force *(Dancey/Stadler/True)*:

a) The Biomarker TF held an evening meeting on Monday, September 27th to discuss strategic initiatives that have been ongoing and planned.

b) A Tissue-based Biomarker Assays (TBBA) subcommittee lead by Larry True (UWASH) has been working on an IHC and DNA-based ISH template for early phase clinical trialists.

c) **TF Recommendations**:

i) Biomarker resources should be collated and links provided on the resources page on the CTEP website.
ii) Ask investigators who are proposing tissue based IHC biomarkers in context of proposed trial to complete template and for CTEP to share anonymized data with IDSC.

8) IDSC 2010 Survey Results *(Collyar)*:

a) The IDSC 2010 survey results were presented to the members by Metrics Working Group chair, Deborah Collyar.

9) Future Plans/Calls/Meetings:

a) Next call: TBD

b) IDSC Winter 2011 Meeting: Friday, January 14th, 2011 (Chicago, IL; O'Hare Hyatt)

c) Spring 2011 CTEP EDD/IDSC Meeting: Monday-Wednesday, March 14-16th, 2011 (Bethesda, MD)

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

ADDENDIX I

The primary recommendations of this panel regarding cardiac toxicity of VSP inhibitors are:

1) To endorse the principles outlined in the prior guidance on Initial Assessment, Surveillance, and Management of Blood Pressure in Patients Receiving Vascular Endothelial Growth Factor Signaling Pathway Inhibitors. A key element of that guidance was to reduce the risk of secondary cardiac toxicity associated with VSP-inhibition –induced hypertension. Consequently the same basic principles apply to reducing and managing cardiac toxicity. The key elements of that guidance were:

a) **Conduct and document a formal risk assessment for potential cardiovascular complications prior to VSP inhibitor treatment.**

b) **Recognize that pre-existing hypertension will be common in cancer patients and should be identified and addressed prior to initiation of VSP inhibitor therapy.**

c) Actively monitor blood pressure throughout treatment with more frequent assessments during the first cycle of treatment.

d) The goal for hypertension control in patients receiving VSP inhibitor therapy is a maximum blood pressure of 140/90 mmHg and efforts to reach this goal should begin before initiation of VSP inhibitor therapy. This numerical goal should be set lower in specific populations.

e) Manage blood pressure elevations aggressively to avoid the development of complications associated with excessive/prolonged elevations

2) A baseline 12-lead electrocardiogram (ECG) should be strongly considered for all persons who will receive VSP inhibitor therapy. This panel encourages this to become a standard of care.

Quantitative risk for adverse consequences of elevated blood pressure is associated with the independent factors listed in Table 1. Item 5, subclinical organ damage, can only be evaluated by ECG or more expensive imaging techniques. For those patients in whom none of these procedures has been performed, the ECG is the least expensive option. ECG is a non-invasive test with numerous and varied indications likely to apply to (and to already have been performed in) cancer patients for whom VSP inhibitor therapy is considered. A baseline EKG can prove useful even for cancer patients with none of the risk factors in Table 1 as they can still experience, acute, high magnitude, elevations in blood pressure and present with symptoms consistent with myocardial ischemia. Similar to otherwise healthy individuals undergoing routine moderate risk surgical procedures, a baseline ECG can be a useful tool in the later evaluation of a patient presenting with acute, non-specific, signs and symptoms. For administration of some commonly used drugs in non-cancer patient populations, such as antihypertensives (described in JNC 7 recommendations) and -methadone, a baseline ECG is considered a standard of care. Likewise, for other anticancer agents with associated cardiovascular toxicities (eg. anthracyclines, trastuzumab) a baseline ECG is standard.

3) The risk for cardiovascular events is increased in patients who have:

a) 2 or more bolded categories of risk factors for cardiovascular disease (as defined in Table 1)

b) Known cardiovascular disease consistent with elevated risk for myocardial ischemia [history of myocardial infarction, abnormal cardiac catheterization (including any intervention), abnormal exercise/perfusion stress test results, or history of signs/symptoms consistent with angina].

c) Known ventricular dysfunction. The safety of VSP inhibitor therapy in New York Heart Association class I or II (symptom-controlled) patients with left ventricular systolic dysfunction or valvular heart disease has not been established and warrants attentive management if VSP inhibitor therapy is planned.

d) Known cerebrovascular disease (history of transient ischemic attacks, cerebrovascular occlusion/hemorrhage)

e) Known peripheral vascular disease (history of claudication and any history of intervention including arterial bypass or stent and graft procedures)

f) An abnormal baseline ECG consistent with possible ischemia, ventricular hypertrophy, or uncontrolled rhythm or conduction abnormality

g) History of cancer-specific risk for adverse cardiac events such as prior or current exposure to anthracyclines or chest radiation that included the heart in the irradiated field

4) VSP inhibitor therapy should not be administered in the face of unstable or poorly controlled angina, uncontrolled heart failure or arrhythmia.

5) Monitor for the development of heart failure and LV dysfunction:

During the course of VSP inhibitor therapy, patients may develop dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cough, pleural effusions, ascites, peripheral edema, unexplained weight gain, or sinus tachycardia. Treatment-related left ventricular dysfunction should be in the differential diagnosis and if the patient is planned to continue VSP inhibition therapy, should be ruled out in timely fashion. Early satiety, fatigue, nausea and vomiting, abdominal discomfort, wheezing and confusion are other non-specific symptoms of heart failure. These non-specific findings should stimulate a search for more specific symptoms or clinical signs of cardiac toxicity before proceeding to more advanced confirmatory testing. For oncologist, urgent consultation with a cardiovascular medicine specialist might support rapid evaluation and expedite further testing and effective management if ventricular dysfunction or another cardiac abnormality is identified. VSP inhibitors should be held in patients with symptomatic heart failure. The safety of resuming VSP inhibition upon recovery of heart failure has not been established, and the risk-benefit should be carefully assessed on an individual basis.

6) Monitoring for myocardial ischemia.

Table 2 describes recommendations from NCI-sponsored clinical trials on management of cardiac ischemia during therapy with VSP inhibitors.

- Cardiology consultation can be useful in patients with asymptomatic ECG changes and in patients with symptoms suggesting myocardial ischemia.
- If there is documented myocardial ischemia, VSP inhibitor therapy should be discontinued.
    - A collaborative decision should then be made as to whether more advanced cardiac testing (eg, stress testing, coronary angiography) is needed, and whether the benefits of resuming therapy with aggressive supportive care outweigh the risk.
    - The panel believes that documented myocardial infarction while a patient is receiving VSP inhibitor therapy is a possible indication for permanent discontinuation of that therapy. Again, risk and benefit must be weighed on an individual patient basis.

7) Recommendations for imaging studies: Baseline and follow up.

a) Baseline imaging studies (either MUGA or echocardiogram) are not mandatory in all patients receiving VSP inhibitors, but should be considered in accord with local standards of care for patients with history or clinical findings of LV dysfunction or those at high risk for a cardiac event

When available, echocardiography may be preferred as it can provide the opportunity to evaluate left ventricular wall motion, valve function, right heart structure and function, and left atrial and pulmonary artery pressures concurrent with the ejection fraction assessment.

b) There is also no evidence-based guideline for follow-up echocardiogram or MUGA scans in asymptomatic patients. While a few LVEF-based dose modification algorithms have been used in clinical trials that called for periodic echo/MUGA assessments, at the time of writing this document there are no carefully collected data on which to base general guidance for VSP inhibitor dose adjustment or supportive medical management for VSP-inhibitor associated ventricular dysfunction or other cardiac events. This is an important area worthy of further investigation in future NCI-sponsored trials of VSP inhibitor therapy.