Investigational Drug Steering Committee

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Welcome to the IDSC Newsletter

This is the twelfth 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,

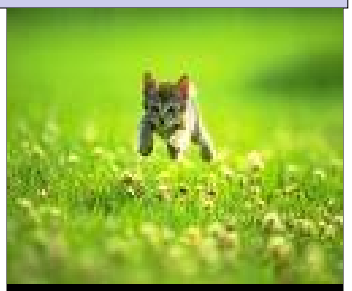
Steven Reeves (CCCT)

Amy Gravell (EMMES)

Pam West (EMMES)

ANNOUNCEMENTS:

- **We welcome new IDSC Members**: John Carpten (Genomic - Early Drug Development); Steven Grant (Lymphoma IDSC Liaison); Brenda Weigel (replacing Susan Blaney as the COG Phase 1 Representative).
- **Miguel Villalona** is the new N01 IDSC co-chair. His term began on 1/1/2012. We thank Dan Sullivan for his service!
- **Publications:** The PAM TF manuscript has been resubmitted to JCO. Naifa Busaidy (co-lead author) is to tentatively scheduled to present this paper at the CTEP Early Drug Development (EDD) meeting on March 13th.



See you at the IDSC Spring Meeting!
March 13, 2012
From 1:30-5:30 PM EDT
Rockville Hilton
Rockville, MD

Inside this issue:

UPCOMING IDSC MEETINGS:

- **Next call:** TBD
- **IDSC Spring Meeting** (2012): Tuesday, March 13th (Rockville, MD)
- **IDSC Summer Meeting** (2012): Friday, July 13th (Chicago, IL)
- **IDSC Fall Meeting (2012**): Tuesday-Wednesday, October 16-17th (Bethesda, MD)

UPDATE from January 13th (2012) IDSC Meeting

- New N01 co-chair is Miguel Villalona (we thank Dan Sullivan for his 2-years of service)
- New IDSC Disease-specific Steering Committee Liaisons: Steven Grant (Lymphoma); Robert DiPaola (GU)
- The Pharmacology and Immunotherapy Task Forces have undergone membership review and rotation. The Biomarker and Clinical Trial Design Task Forces will be the next to be reviewed .
- Redesign of the U01 Program – Introductory Discussion (Ivy)
- Helen Chen presented the CTEP drug development plan for **GSK2118436** (RAF inhibitor) to the IDSC members.
- Helen Chen presented the CTEP drug development plan for **GSK1220212** (MEK inhibitor) to the IDSC members.
- Mark Ratain updated the group on the Clinical Trial Design LOI Benchmarking project Q2-Q3 2011.
- Jedd Wolchok discussed his research and results from the Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center with IDSC members.

IDSC ACCOMPLISHMENTS (2008–2012)

Transparency and enhanced scientific input into NCI drug development process

- Reviewed 24 Clinical Development Plans (20 have moved forward)
- Assisted with Presolicitation efforts for U01 and N01 investigators (LOI Review Working Group)
- Recommended Career Development LOI (CrDL) Program for New Investigators

Identify niches for NCI involvement complementary to industry

Transition from IDSC to Disease-specific Steering Committees (DSSCs) facilitated by designated liaisons

Have published or are in the process of publishing 23 manuscripts (21 published and 2 in process)

Highlights:

- Phase 2 clinical trial design - 5 CCR FOCUS papers (March 2009)
- Phase 1 clinical trial design - 5 CCR FOCUS papers (March 2010)
- Management of blood pressure in patients receiving VEGF inhibitors (JNCI 2010)
- Management of the common cardiovascular toxicities associated with angiogenesis inhibitors ventricular dysfunction (AHJ 2012)
- Management of hyperglycemia/hyperlipidemia in patients treated with PI3K/Akt/mTOR agents (JCO – pre-pub)

Educational Sessions at CTEP Early Drug Development (EDD) Meeting

- Cancer stem cell educational session (Cancer Stem Cell TF)
- Phase II recommendations (Clinical Trial Design TF)
- Biomarker TF recommendations (Biomarker TF)
- Autophagy (DNA Repair TF)
- JAK-STAT educational session (Signal Transduction)
- c-Met educational session (Signal Transduction)
- ALK educational session (Signal Transduction)
- PIM Kinase educational session (Signal Transduction)
- PI3K educational session (Signal Transduction/PAM)

Miguel Villalona, M.D.

IF YOU ARE INTERESTED IN JOINING ONE OF THE IDSC TASK FORCES

PLEASE CONTACT AMY GRAVELL (agravell@emmes.com)

Task Forces:

- **Angiogenesis**
- **Biomarkers**
- **Cancer Stem Cell**
- **Clinical Trial Design**
- **DNA Repair**
- **Immunotherapy**
- **Pharmacology**
- **PI3K/Akt/mTOR(PAM)**
- **Signal Transduction**

SPOTLIGHT ON NEW SUBJECT EXPERTS

JOHN CARPTEN, Ph.D. (TGen) - GENOMICS

Prior to joining TGen, Dr. Carpten was an intramural tenure track investigator with the Cancer Genetics Branch of the National Human Genome Research Institute (NHGRI).

He has made a number of seminal discoveries in cancer genetics and genomics. While a fellow and later a tenure track investigator at NHGRI/NIH, he co-led the first published genome wide scan for prostate cancer susceptibility genes published in 1996 in *Science*. His lab subsequently discovered germ-line mutations in the *RNASEL* gene in HPC1-linked hereditary prostate cancer families. His contigs of the 1q24-q31 region of the human genome became the framework and template for sequencing of that 20 megabase region by the Human Genome Project. These data were also used for the subsequent discovery of two other disease genes.

Has an intense focus on understanding the role of biology in disparate cancer incidence and mortality rates seem among minority populations. Through his leadership, the African American Hereditary Prostate Cancer Study (AAHPC) Network was conceived.

Has a very active research program in sporadic tumor research. His research team has applied high throughput genomic technologies such as CGH, gene expression profiling and mutational analysis to discover important genomic alterations in cancer. One such study resulted in the identification of somatic inactivating mutations in the *EphB2* gene in prostate cancer, the results of which were published in *Nature Genetics.*

More recently, he has begun to apply Next Generation Sequencing (NGS) technologies for deep genomic profiling of tumors. These technologies offer the opportunity to sequence entire cancer genomes to discovery of mutations, copy number changes, and rearrangements such as translocations. This work has led to the discovery of genomic alterations in lethal prostate tumors, which was published in *Genome Research*.

John Carpten, Ph.D.

Agents Reviewed by the IDSC (2006-2012)

Agent Name	Target	IDSC Review	Mass Solicitation Status?
IMC-A12	IGF-1R	September 2006	Issued
IL-12	immune regulation	July 2008	Issued
SCH727965	CDK	February 2008	Issued
GDC-0449	sonic hedgehog	November 2008	Issued
RO4929097	notch	January 2009	Issued
OSI-906	IGF-1R	March 2009; June 2010	Issued
MK-2206	AKT	March 2009	Issued
ABT-263	bcl2, BH3 mimetic	April 2009	Issued
AZD8055	mTOR	May 2009	ON-HOLD
ARQ-197	cMet	October 2009; July 2010	Issued
SCH900105	cMet	October 2009	WITHDRAWN
MK-8033	cMet	October 2009	WITHDRAWN
AT13387	HSP90	October 2009	Pending
MLN-8237	Aurora kinase	September 2010	Issued
AMG386	Ang 1/2	July 2010	Issued
TRC-105	mAB CD105	January 2011	Issued
SCH900776	Chk1	January 2011; July 15, 2011	Pending
MK-1775	Wee1	January 2011; July 15, 2011	Pending
Ipilimumab	antibody	June 15, 2011	Issued
TL32711	Smac mimetic; IAP	October 4, 2011	Pending
PCI-32765	BTK	October 4, 2011	Issued
XL-184	cMet; VEGFR2	October 5, 2011	Issued
GSK2118436	RAF	January 13, 2012	Pending
GSK1220212	MEK	January 13, 2012	Pending
AZD1480	JAK2	March 13, 2012	Pending

Publication Corner: *this section will highlight 2-3 articles written by IDSC investigators per issue (within the IDSC or outside publications of relevance)*

Article I: Steingart, R. M., G. L. Bakris, et al. "Management of cardiac toxicity in patients receiving vascular endothelial growth factor signaling pathway inhibitors." Am Heart J **163**(2): 156-63 .

BACKGROUND: Interfering with angiogenesis is an effective, widely used approach to cancer therapy, but antiangiogenic therapies have been associated with important systemic cardiovascular toxicities such as hypertension, left ventricular dysfunction, heart failure, and myocardial ischemia and infarction. As the use of vascular endothelial growth factor signaling pathway (VSP) inhibitors broadens to include older patients and those with existing cardiovascular disease, the adverse effects are likely to be more frequent, and cardiologists will increasingly be enlisted to help oncologists manage patients who develop adverse cardiovascular effects. The Cardiovascular Toxicities Panel of the National Cancer Institute reviewed the published literature and abstracts from major meetings, shared experience gained during clinical development of VSP inhibitors, and contributed extensive clinical experience in evaluating and treating patients with cancer with cardiovascular disease. This report was edited and approved by the National Cancer Institute Investigational Drug Steering Committee. It presents the panel's expert opinion on the current clinical use and future investigation for safer, more expansive use of these drugs. **CONCLUSIONS:** The panel recommends that physicians (1) conduct and document a formal risk assessment for existing cardiovascular disease and potential cardiovascular complications before VSP inhibitor treatment recognizing that preexisting hypertension and cardiovascular disease are common in patients with cancer, (2) actively monitor for blood pressure elevations and cardiac toxicity with more frequent assessments during the first treatment cycle, and (3) aggressively manage blood pressure elevations and early symptoms and signs of cardiac toxicity to prevent clinically limiting complications of VSP inhibitor therapy.

Richard Steingart, M.D. (Cardiovascular Toxicities Panel Co-leader)

Article 2: Ulmert, D., R. Kaboteh, S.M. Larson, et al. "A Novel Automated Platform for Quantifying the Extent of Skeletal Tumour Involvement in Prostate Cancer Patients Using the Bone Scan Index." Eur Urol.

BACKGROUND: There is little consensus on a standard approach to analysing bone scan images. The Bone Scan Index (BSI) is predictive of survival in patients with progressive prostate cancer (PCa), but the popularity of this metric is hampered by the tedium of the manual calculation. **OBJECTIVE:** Develop a fully automated method of quantifying the BSI and determining the clinical value of automated BSI measurements beyond conventional clinical and pathologic features. **DESIGN, SETTING, AND PARTICIPANTS**: We conditioned a computer-assisted diagnosis system identifying metastatic lesions on a bone scan to automatically compute BSI measurements. A training group of 795 bone scans was used in the conditioning process. Independent validation of the method used bone scans obtained </=3 mo from diagnosis of 384 PCa cases in two large population-based cohorts. An experienced analyser (blinded to case identity, prior BSI, and outcome) scored the BSI measurements twice. We measured prediction of outcome using pretreatment Gleason score, clinical stage, and prostate-specific antigen with models that also incorporated either manual or automated BSI measurements. **MEASUREMENTS:** The agreement between methods was evaluated using Pearson's correlation coefficient. Discrimination between prognostic models was assessed using the concordance index (C-index). **RESULTS AND LIMITATIONS:** Manual and automated BSI measurements were strongly correlated (rho=0.80), correlated more closely (rho=0.93) when excluding cases with BSI scores >/=10 (1.8%), and were independently associated with PCa death ($p<0.0001$ for each) when added to the prediction model. Predictive accuracy of the base model (C-index: 0.768; 95% confidence interval [CI], 0.702-0.837) increased to 0.794 (95% CI, 0.727-0.860) by adding manual BSI scoring, and increased to 0.825 (95% CI, 0.754-0.881) by adding automated BSI scoring to the base model. **CONCLUSIONS**: Automated BSI scoring, with its 100% reproducibility, reduces turnaround time, eliminates operator-dependent subjectivity, and provides important clinical information comparable to that of manual BSI scoring.

Steven M. Larson, M.D. (IDSC Imaging Subject Expert)

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NEW IDSC website: https://idsc.sharepointsite.net/default.aspx

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Please contact me with any suggestions for the IDSC Newsletter!

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Websites of Interest:

http://ccct.cancer.gov/

http://ctep.info.nih.gov/

http://www.research.ucsf.edu/chr/Guide/chrCLIA.asp

https://cancersteeringcommittees.sharepointsite.net/default.aspx

https://idsc.sharepointsite.net/default.aspx

http://proteomics.cancer.gov/

http://www.nci-bestpractices-forum.com/

http://www.biomarkersconsortium.org/

http://www.cancer.gov/trwg/

REMINDERS:

Next IDSC meeting:

Tuesday, March 13, 2012 at the Rockville Hilton (Rockville, MD).

Agenda:

- **CTEP Drug Development Plan for AZD1480 (JAK2)**
- **U01 Redesign Discussion—Part 2**
- **Discussion of HA22 (FYI to IDSC members)**

Other Upcoming IDSC meetings:

Friday, July 13th (Chicago, IL)

Tuesday-Wednesday; October 16-17th, 2012 (Bethesda, MD)

Next call: TBD

Please send any new topics for the IDSC newsletter to
Amy Gravell
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