Investigational Drug Steering Committee

CCCT/EMMES
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Welcome to the IDSC Newsletter

This is the eleventh 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,

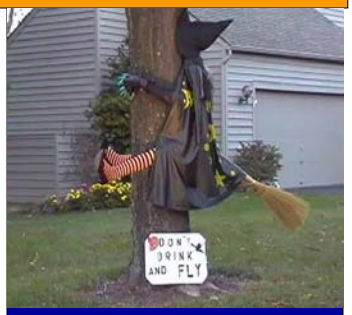
Steven Reeves (CCCT)

Amy Gravell (EMMES)

Pam West (EMMES)

ANNOUNCEMENTS:

- **We welcome new IDSC Subject Experts**: Steven Larson (Imaging), Gary Rosner (Biostatistician), and Jedd Wolchok (Immunotherapy).
- **Additional subject experts in the following categories will be sought**: Pharmacogenomic/Pharmacometric; Preclinical Experimental Therapeutics; Genomic - Early Drug Development; and Lymphoma.
- **Miguel Villalona** has been nominated as the new N01 IDSC co-chair. His term will begin 1/1/2012. We thank Dan Sullivan for his service!
- **Publications:** The PAM TF manuscript has been submitted to JCO.



See you at the IDSC Winter Meeting!

January 13, 2012
From 9:30-4:00 PM CDT
O'Hare Hilton
O'Hare Airport

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UPCOMING IDSC MEETINGS:

- **Next call:** TBD
- **IDSC Winter Meeting (2012):** Friday, January 13, 2012 (Chicago, IL)
- **IDSC Spring Meeting** (2012): Tuesday-Wednesday, March 13-14th (Bethesda, MD)
- **IDSC Summer Meeting** (2012): TBD
- **IDSC Fall Meeting (2012**): Tuesday-Wednesday, October 16-17th (Bethesda, MD)

UPDATE from October 4-5 (2011) IDSC Meeting

- Mario Sznol, Anthony Shields and Don Berry were provided with letters of gratitude from the NCI.
- **New IDSC subject experts were introduced**: Steven Larson (Imaging), Gary Rosner (Biostatistician), and Jedd Wolchok (Immunotherapy).
- Naoko Takebe presented the CTEP drug development plan for **TL32711** (Smac mimetic, IAP inhibitor) to the IDSC.
- Pam Harris presented the CTEP drug development plan for **PCI-32765** (BTK inhibitor) to the IDSC.
- John Wright presented the CTEP drug development plan for **XL-184** (c-Met and VEGFR2) to the IDSC.
- A NExT update was presented by Barbara Mroczkowski.
- A Cooperative Group update was presented by Jeff Abrams.

IDSC Task Force and Working Group Updates

Biomarker TF

TBBA subcommittee:

Congratulations to Larry True and the subcommittee for completing the IHC and DNA-based ISH templates. They are currently nearing completion on a single gene DNA mutation template.

These templates will be placed on the DCTD/CTEP websites and also the IHC template will be piloted by CTEP.

Clinical Trial Design TF

The **Phase 2 Benchmarking project** has completed two cycles to prospectively track concordance of trial design elements between the IDSC Phase 2 Recommendations and recently approved Phase 2 CTEP-sponsored protocols. Results from review of Phase 2 trials approved in the first quarter of 2011 was presented at the Summer IDSC meeting in Chicago. The project group is continuing to conduct reviews on a quarterly basis for 2011.

Related to the Agent Combination Trials project, a **new project group is being developed to prepare Investigator Guidelines for Designing Trials of Agent Combinations**. This project is beginning to draft ideas for a document that would eventually be published to provide investigators with tips for designing trials investigational agent combinations, taking into consideration important scientific criteria for development of investigational agents as well as recent changes to the IND process and procedures .

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**

Working Groups:

- **COI**
- **LOI Review**
- **Metrics**
- **Scientific Meeting Planning**

SPOTLIGHT ON THE NEW SUBJECT EXPERTS

STEVEN LARSON, M.D. (MSKCC) - IMAGING

Steven Larson is a nuclear medicine physician whose clinical interests focus on the use of positron emission tomography (PET) for diagnostic and molecular imaging. He has special expertise in the care and management of patients who receive radio-targeted therapy, particularly for thyroid cancer.

In addition to being Chief of the Nuclear Medicine Service, he is the Director of the Laurent and Alberta Gerschel Positron Emission Tomography Center and Head of the Nuclear Medicine Research Laboratory. He is a member of the Executive Council for the Molecular Pharmacology and Therapeutics Program of the Sloan-Kettering Institute. Research interests involve PET and targeted therapy in oncology. I have had a long-term interest in radiopharmaceuticals for oncologic applications in nuclear medicine and have been working in various aspects of PET since 1979.

GARY ROSNER, ScD (Johns Hopkins) - BIOSTATISTICIAN

Gary Rosner's primary academic research interests are in population pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenetics (PGx), Bayesian inference, and clinical trial methodology. Much of this work shares the common theme of applying Bayesian inferential methods, particularly Bayesian nonparametric models, to aid inference and decision-making. These models find applicability in population-based studies concerning anticancer drugs' PK, PD, and PGx. He also works on methodology related to optimal study designs for use in clinical cancer studies, particularly optimal sequential designs. In this research, optimal design means that the study's design includes decision rules that consider possible outcomes of decisions (e.g., stop the study or continue it) and associated utilities. One chooses actions to maximize the expected utility (or minimize the expected loss).

JEDD WOLCHOK, M.D., Ph.D. (MSKCC) - IMMUNOTHERAPY

Jedd Wolchok is a medical oncologist who specializes in the treatment of melanoma. He is interested in finding new and improved ways to prevent melanoma from recurring after surgery, as well as more effective treatments for the disease when it does recur. His research is focused on the development of innovative ways to use the immune system to treat cancer.

Research Summary: Cancer vaccines, Immunotherapy (Ipilimumab), targeted therapies.

Agents Reviewed by the IDSC (2006-2011)

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	Pending
XL-184	cMet; VEGFR2	October 5, 2011	Pending

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

Article I: Chau, N. G., A. Florescu, Siu, L. L., et al. "Early mortality and overall survival in oncology phase I trial participants: can we improve patient selection?" BMC Cancer **11**(1): 426

Patient selection for phase I trials (PIT) in oncology is challenging. A typical inclusion criterion for PIT is 'life expectancy >3 months', however the 90 day mortality (90DM) and overall survival (OS) of patients with advanced solid malignancies are difficult to predict. METHODS: We analyzed 233 patients who were enrolled in PIT at Princess Margaret Hospital. We assessed the relationship between 17 clinical characteristics and 90DM using univariate and multivariate logistic regression analyses to create a risk score (PMHI). We also applied the Royal Marsden Hospital risk score (RMI), which consists of 3 markers (albumin <35g/L, >2 metastatic sites, LDH >ULN). RESULTS: Median age was 57 years (range 21-88). The 90DM rate was 14%; median OS was 320 days. Predictors of 90DM were albumin <35g/L (OR=8.2, p=0.01), >2 metastatic sites (OR=2.6, p=0.02), and ECOG >0 (OR=6.3, p=0.001); all 3 factors constitute the PMHI. To predict 90DM, the PMHI performed better than the RMI (AUC=0.78 vs 0.69). To predict OS, the RMI performed slightly better (RMI [greater than or equal to]2, HR=2.2, p=0.002 vs PMHI [greater than or equal to]2, HR=1.6, p=0.05). CONCLUSIONS: To predict 90DM, the PMHI is helpful. To predict OS, risk models should include ECOG >0, >2 metastatic sites, and LDH >ULN. Prospective validation of the PMHI is warranted.

Lillian Siu, M.D.

Article 2: Cheever, M. A. and C. S. Higano "PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine." Clin Cancer Res **17**(11): 3520-6.

Sipuleucel-T (PROVENGE; Dendreon) is the first therapeutic cancer vaccine to be approved by the U.S. Food and Drug Administration. In men who have metastatic castration-resistant prostate cancer with no or minimal symptoms, sipuleucel-T prolongs median survival by 4.1 months compared with results in those treated with placebo. At 3 years, the proportion of patients in the vaccine group who were alive was 50% higher than that in the control group (31.7% versus 21.7%, respectively). Sipuleucel-T, which is designed to elicit an immune response to prostatic acid phosphatase, uses the patient's own immune system to recognize and combat his cancer. Currently, no other agents are available that offer a survival benefit for this population of asymptomatic patients who have not been treated with chemotherapy, except for docetaxel (whose inherent toxicities often lead patients and physicians to delay administration until symptoms develop). Straightforward strategies to increase the efficacy of sipuleucel-T are likely to provide even greater benefit. The preclinical and clinical development of sipuleucel-T is reviewed, and approaches to enhance efficacy are considered herein.

Mac Cheever, M.D.

Article 3: Postow, M., M. K. Callahan, Wolchok, J. D., et al. (2011). "Beyond cancer vaccines: a reason for future optimism with immunomodulatory therapy." Cancer J **17**(5): 372-8.

Despite significant scientific knowledge in the field of cancer immunology, therapeutic strategies using cancer vaccines to generate anti-tumor immunity have historically resulted in only modest clinical benefit. Disappointing results from prior cancer vaccine trials are likely due to multifactorial causes. Perhaps the most important is the role of inherent tumor-induced immune suppression and enhanced immunologic tolerance. Current research directed toward understanding the mechanisms of immunologic tolerance has led to the development of promising therapeutic immune regulatory antibodies that inhibit immunologic checkpoints and subsequently enhance immunologic antitumor activity. This review discusses the prior challenges associated with cancer vaccines and describes how, by breaking immune inhibition and facilitating immune stimulation, immune regulatory antibodies show great promise in the treatment of a variety of tumors.

Jedd Wolchok, M.D., Ph.D.

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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:

Friday, January 13, 2012 at the O'Hare Hilton in Chicago, IL

Agenda:

- **GSK RAF CTEP DRUG DEVELOPMENT PLAN**
- **GSK MEK CTEP DRUG DEVELOPMENT PLAN**
- **Task Force Updates**

Other Upcoming IDSC meetings:

Tuesday-Wednesday; March 13-14th, 2012 (Bethesda, MD)

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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