Investigational Drug Steering Committee

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Welcome to the IDSC Newsletter

This is the seventeenth 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)

ANNOUNCEMENTS:

Dr. Amit Oza will be the new N01 IDSC co-chair beginning on January 1, 2014. We thank Dr. Miguel Villalona for his service over the past two years.

The next IDSC in-person meeting will be held on July 17th and 18th, 2014. We will hold webinars for the Winter and Spring 2014 meetings**.**

A pilot of the new Experimental Therapeutics Clinical Trials Network (ETCTN) is underway.

With the advent of the new ETCTN will come task force consolidation and changes. Dr. Steven Reeves will discuss on the IDSC Winter 2014 Webinar. (Friday, January 10th).

Please send any newsletter suggestions to: agravell@emmes.com

The IDSC Winter 2014 Webinar will be held on

Friday,

January 10th, 2014

From 11:00 AM-2:30 PM Eastern Time

Update from the IDSC Meeting – September 10, 2013

- The CTEP Early Drug Development (EDD) meeting will be held annually in the Fall (**starting in 2014; October 20-22nd**).
- ***Amit Oza will be the new IDSC N01 co-chair starting on January 1, 2014***. We thank Miguel Villalona for his service (term ends on December 31, 2013).
- **CTEP is planning to add the BER inhibitor; TRC-102 to its portfolio**. Dr. Alice Chen presented the drug development plan to the IDSC.
- **CTEP is planning to add the PARP 1 and 2 inhibitor; BMN-673 to its portfolio** . Dr. Alice Chen presented the drug development plan to the IDSC.
- **The Pharmacology Task Force requested authorization from the IDSC** to **form a writing committee** to draft a manuscript entitled, "Standardizing Metabolism and Transport Drug Interaction Assessment in Oncology Clinical Trials". **The IDSC approved the motion.**

Inside this issue:

UPCOMING IDSC/ EDD MEETINGS/ REMINDERS:

- **IDSC Winter 2014 Meeting**: Friday, January 10, 2014; **WEBINAR ONLY (11:00-2:30 PM ET)**
- **CTEP IDSC Spring 2014 Meeting**: Wednesday, April 2nd : **WEBINAR ONLY (1:00-3:00 PM ET)**
- **UM1 and N01 Annual Portfolio Presentation and IDSC Summer 2014 Meeting:** Thursday-Friday, July 17th-18th, 2014 **(NCI Shady Grove)**
- **CTEP EDD/IDSC Fall 2014 Meeting**: Monday-Wednesday, October 20-22nd, 2014 (NIH Campus; Natcher; Building 45)

Task Force Updates

Clinical Trial Design (CTD) and Biomarker TFs

- **Biomarker and CTD meeting— A Biomarkers in Phase 2 Trials** meeting was held on Monday-Tuesday, September 16-17th at the Bethesda North Marriott. Recommendations from this meeting and a synopsis will be discussed on the Winter IDSC webinar (January 10th).

- **LOI Benchmarking/ Concordance Project:** The control group project (2009 and 2010 approved protocols) has been completed and the recommendations in the original Phase 2 manuscript will be tweaked.

Manuscript underway or have been submitted for the CTD TF:

1. Phase 2 trial comparing adaptive design and Frequentist approach (Berry/Groshen) - re-submitted
2. Pancreatic manuscript for Historical Controls (LeBlanc) - submitted
3. Phase 1 Recommendations for Agent Combination Trials (Bradbury/Paller) - will be reviewed by the IDSC on January 10, 2014
4. CTEP Agent Combination Trial Data (upcoming manuscript by Channing Paller/ Percy Ivy)
5. Update to the Phase 2 Recommendations Manuscript (upcoming revision by Lesley Seymour)

Pharmacology TF

- The CTEP Drug-Drug Interaction (DDI) Process document is being finalized between the Pharmacology TF and CTEP PMB.

- The Pharmacology TF has developed a manuscript subcommittee to create a "best practices" DDI document. Dr. Jill Kolesar should present to the IDSC on the April 2nd (2014) webinar.

NOTE: Dr. Steven Reeves will discuss the transition to the new ETCTN model and changes for IDSC Task Forces on the Winter 2014 webinar (Friday, January 10th from 11:00 AM-2:30 PM Eastern Time)

SPOTLIGHT ON THE CTEP ETCTN (Experimental Therapeutics Clinical Trials Network)

Overview of the Coordination of the Experimental Therapeutics Clinical Trials Network:

To address the new opportunities and challenges in the development of novel targeted cancer therapeutics, the NCI has established a systematic approach with several interacting functional components. The NCI Experimental Therapeutics Program (NExT) is the portal through which NCI brings investigational agents into DCTD/CTEP for development. After a new agent is chosen for development, the Investigational Drug Branch (IDB) Project Team Leader will form an NCI Project Team from the various clinical, translational, and basic biology programs at NCI. Members of the Project Team will draft a preliminary drug/biomarker/assay development plan. Once this plan is reviewed and approved by the NCI Senior Advisory Committee (SAC), part of the NeXT approval process, NCI will send out a request for a Project Team Application (PTAs) to the ETCTN members, awardees of the NCI Phase 2 Contracts Program, NCTN awardees, and other appropriate investigators.

Team-based Science and the ETCTN:

The new Experimental Therapeutics – Clinical Trials Network (ETCTN) will employ a team science approach for drug development, while integrating research resources and programs across the NCI. Teams will work together to define the best path forward for the development of a new drugs. This team science approach should allow NCI-sponsored investigators to perform high impact clinical trials enriched with molecular characterization of patients and sophisticated scientific research. The goal is to move toward the more precise selection of patients for participation on clinical studies. Along the way we hope to enhance interaction and collaboration as well as improving the training of the next generation of drug developers.

Agents Reviewed by the IDSC (2006-2013)

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
ARQ-197	cMet	October 2009; July 2010	Issued
AT13387	HSP90	October 2009	Issued
MLN-8237	Aurora kinase	September 2010	Issued
AMG386	Ang 1/2	July 2010	Issued
TRC-105	mAB CD105	January 2011	Issued
MK-8776	Chk1	January 2011; July 15, 2011	Issued
MK-1775	Wee1	January 2011; July 15, 2011	Issued
Ipilimumab	antibody	June 15, 2011	Issued
TL32711	Smac mimetic; IAP	October 4, 2011	Pending—Phase 0
PCI-32765 (Ibrutinib)	BTK	October 4, 2011	Issued
XL-184 (Cabozantinib)	cMet; VEGFR2	October 5, 2011	Issued
GSK2118436	RAF	January 13, 2012	Issued
GSK1220212	MEK	January 13, 2012	Issued
AZD1480	JAK2	March 13, 2012	Presolicitation
AMG-479	IGF-1R	July 13, 2012	?
MLN-0128	TORC1/TORC2	July 13, 2012	Issued
AMG-103	BiTE Bispecific Antibody	July 13, 2012	Presolicitation
Pomalidomide	Immune regulation	October 16, 2012	No mass solicitation
Nivolumab (BMS-936558)	anti-PD-1	April 23, 2013	Pending
MK-3475	anti-PD-1	April 23, 2013	Pending
TRC-102	BER Inhibitor	September 10, 2013	Pending
BMN-673	PARP I and II	September 10, 2013	Pending

Agents previously presented to the IDSC as an FYI– SGN-35 and HA 22

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: Bedard PL, Hansen AR, Ratain MJ, Siu LL. Tumour heterogeneity in the clinic. Nature 2013;501 (7467):355-64.

Recent therapeutic advances in oncology have been driven by the identification of tumour genotype variations between patients, called interpatient heterogeneity, that predict the response of patients to targeted treatments. Subpopulations of cancer cells with unique genomes in the same patient may exist across different geographical regions of a tumour or evolve over time, called intratumour heterogeneity. Sequencing technologies can be used to characterize intratumour heterogeneity at diagnosis, monitor clonal dynamics during treatment and identify the emergence of clinical resistance during disease progression. Genetic interpatient and intratumour heterogeneity can pose challenges for the design of clinical trials that use these data.

Mark Ratain, M.D.

Article 2: Sleijfer S, Bogaerts J, Siu LL. Designing transformative clinical trials in the cancer genome era. J Clin Oncol 2013;31(15):1834-41.

The incorporation of molecular profiling into routine clinical practice has already been adopted in some tumor types, such as human epidermal growth factor receptor 2 (HER2) testing in breast cancer and KRAS genotyping in colorectal cancer, providing a guide to treatment selection that is not afforded by histopathologic diagnosis alone. It is inevitable that over time, with rapid advances in scientific knowledge, bioinformatics, and technology to identify oncogenic drivers, molecular profiling will complement histopathologic data to influence management decisions. Emerging technologies such as multiplexed somatic mutation genotyping and massive parallel genomic sequencing have become increasingly feasible at point-of-care locations to classify cancers into molecular subsets. Because these molecular subsets may differ substantially between each other in terms of sensitivity or resistance to systemic agents, there is consensus that clinical trials should be more stratified for or be performed only in such molecularly defined subsets. This approach, however, poses challenges for clinical trial designs because smaller numbers of patients would be eligible for such trials, while the number of novel anticancer drugs warranting further clinical exploration is rapidly increasing. This article provides an overview of the emerging methodologic challenges in the cancer genome era and offers some potential solutions for transforming clinical trial designs so they can identify new active anticancer regimens in molecularly defined subgroups as efficiently as possible

Lillian Siu, M.D.

Upcoming Issue:

- **ET-CTN Pilot will be highlighted in the next issue.**