Investigational Drug Steering Committee

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Welcome to the IDSC Newsletter

This is the fourteenth 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:

New IDSC U01 co-chair: Lillian Siu has been nominated as the new IDSC U01 co-chair and will begin her term on January 1, 2013. We thank Pat LoRusso for her service!

We welcome new IDSC member: Elizabeth Garrett-Mayer as a new Biostatistics member.

Last meeting for IDSC members (October 2012): Deborah Collyar (Patient Advocate), Peter Adamson (Pediatric Subject Expert), and Susan Groshen (Biostatistician). We thank them for their effort over the past 6 years!

Please send any newsletter suggestions to:

agravell@emmes.com

See you at the IDSC Fall Meeting!

October 16, 2012

From 1:00-5:00 PM EDT

Natcher Auditorium

NIH Campus

Inside this issue:

UPDATE from July 13 (2012) IDSC Meeting

- Helen Chen (IDB drug monitor) presented the CTEP Drug Development Plan for AMG-479 (IGF-1R) to the IDSC.
- Austin Doyle (IDB drug monitor) presented the CTEP Drug Development Plan for MLN0128 (TORC 1/2) to the IDSC .
- Elad Sharon (IDB drug monitor) presented the CTEP Drug Development Plan for AMG-103 (BiTE bispecific antibody) to the IDSC.
- Ned Newman presented the CYP drug interaction guidance .
- James Zwiebel discussed the "Redesign of the NCI Early Experimental Therapeutics Program and requested further impute.
- John Carpten presented findings from Translational Genomics Research Institute (TGen) studies .

UPCOMING IDSC/ EDD MEETINGS/ REMINDERS:

- **Next call:** TBD
- **IDSC Fall Meeting (2012)**: Monday-Tuesday, October 15-16th (Natcher; NIH Campus)
- **IDSC Winter Meeting (2013):** Friday, January 11th (Building 31; NIH Campus)
- **IDSC Spring Meeting (2013):** Monday-Tuesday, March 18-19th (Natcher; NIH Campus)
- **IDSC Fall Meeting (2013)**: Monday-Wednesday, September 9-11 (NIH Campus)

Task Force/WG Updates

Recent Agents Reviewed:

July 2012:

AMG -479 (IGF-1R) was reviewed by the **Signal Transduction TF** and endorsed by the IDSC in July 2012 . Helen Chen is the IDB drug monitor.

AMG-103 (BiTE bispecific antibody) was **reviewed by an ad hoc expert group** and endorsed by the IDSC on July 13th, 2012 . Elad Sharon is the IDB Senior Investigator.

July 2012:

MLN0128 (TORC1/TORC2) was reviewed by the **Signal Transduction and PAM TF** and endorsed with modifications by the IDSC on July 13, 2012. Austin Doyle is the IDB Senior Investigator.

September/October 2012:

Pomalidomide was **reviewed by an ad hoc expert group**. This agent will be reviewed by the IDSC on October 16th., 2012 (Howard Streicher IDSC Senior Investigator).

A **Drug Development Checklist** has been created to assist IDB Senior Investigators and the IDSC. A copy of this checklist will be available in the meeting packets for the Tuesday, October 16th meeting. **We thank the Working Group members and Ed Harlow** for their time devising the checklist.

The **DNA Repair TF** recently had Abbott Representatives attend a call to consider ABT-199 for the NExT Program and further ABT-263 studies for the CTEP Portfolio.

HAPPY HALLOWEEN!

SPOTLIGHTARTICLE:

Busaidy, N.L., Siu, L.L. et al., *Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway.* J Clin Oncol. **30**(23): p. 2919-28.

Agents inhibiting the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin (PAM) pathway are currently in various stages of clinical development in oncology, ranging from some in early-phase evaluations to others that have already received regulatory approval for treatment in advanced cancers. The administration of PAM pathway inhibitors has been associated with metabolic toxicities of hyperlipidemia and hyperglycemia. **The PAM Task Force of the National Cancer Institute Investigational Drug Steering Committee** convened an interdisciplinary expert panel to review the pathophysiology of hyperlipidemia and hyperglycemia induced by PAM pathway inhibitors, summarize the incidence of these metabolic toxicities induced by such agents in the current literature, advise on clinical trial screening and monitoring criteria, and provide management guidance and therapeutic goals on occurrence of these toxicities. The overarching aim of this consensus report is to raise awareness of these metabolic adverse events to enable their early recognition, regular monitoring, and timely intervention in clinical trials. Hyperglycemia and hyperlipidemia are generally not acutely toxic and most often reversible with therapeutic intervention. Dose modifications or discontinuation of PAM pathway inhibitors should only be considered in situations of severe events or if progressive metabolic derangement persists after therapeutic interventions have been attempted for a sufficient duration. Specialty consultation should be sought to aid clinical trial planning and the management of these metabolic adverse events.

Lillian Siu, M.D. (PAM Task Force co-chair)

More publications are listed on page 4.

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
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	BTK	October 4, 2011	Issued
XL-184	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	Pending
MLN-0128	TORC1/TORC2	July 13, 2012	Pending
AMG-103	BiTE Bispecific Antibody	July 13, 2012	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: Freidlin, B., et al., *Randomized Phase II Trial Designs With Biomarkers.* J Clin Oncol. **30**(26): p. 3304-9.

Efficient development of targeted therapies that may only benefit a fraction of patients requires clinical trial designs that use biomarkers to identify sensitive subpopulations. Various randomized phase III trial designs have been proposed for definitive evaluation of new targeted treatments and their associated biomarkers (eg, enrichment designs and biomarker-stratified designs). Before proceeding to phase III, randomized phase II trials are often used to decide whether the new therapy warrants phase III testing. In the presence of a putative biomarker, the phase II trial should also provide information as to what type of biomarker phase III trial is appropriate. A randomized phase II biomarker trial design is proposed, which, after completion, recommends the type of phase III trial to be used for the definitive testing of the therapy and the biomarker. The recommendations include the possibility of proceeding to a randomized phase III of the new therapy with or without using the biomarker and also the possibility of not testing the new therapy further. Evaluations of the proposed trial design using simulations and published data demonstrate that it works well in providing recommendations for phase III trial design.

Boris Freidlin, Ph.D. (NCI Biometrics Research Branch)

author of both papers on this page

Article 2: Freidlin, B., L.M. McShane, and E.L. Korn, *Randomized clinical trials with biomarkers: design issues.* J Natl Cancer Inst. **102**(3): p. 152-60.

Clinical biomarker tests that aid in making treatment decisions will play an important role in achieving personalized medicine for cancer patients. Definitive evaluation of the clinical utility of these biomarkers requires conducting large randomized clinical trials (RCTs). Efficient RCT design is therefore crucial for timely introduction of these medical advances into clinical practice, and a variety of designs have been proposed for this purpose. To guide design and interpretation of RCTs evaluating biomarkers, we present an in-depth comparison of advantages and disadvantages of the commonly used designs. Key aspects of the discussion include efficiency comparisons and special interim monitoring issues that arise because of the complexity of these RCTs. Important ongoing and completed trials are used as examples. We conclude that, in most settings, randomized biomarker-stratified designs (ie, designs that use the biomarker to guide analysis but not treatment assignment) should be used to obtain a rigorous assessment of biomarker clinical utility.

We thank Pat LoRusso for her IDSC U01 co-chair service!

MORE TASK FORCE NEWS:

The Biomarker and Clinical Trial Design Task Forces are currently putting together a meeting to discuss Predictive/Selective Biomarkers in Phase II Trials for Winter/ Spring 2013. The meeting still needs to be approved by NCI CTROC.