Investigational Drug Steering Committee

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Welcome to the IDSC Newsletter

This is the thirteenth 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**: Charles Shapiro is the new SxQOL liaison to the IDSC.
- **Mark Ratain** will become the new Clinical Trial Design TF chair on June 1, 2012. We thank **Lesley Seymour** for her superb service!
- The PAM TF manuscript was **accepted by JCO**!
- **Please contact Amy Gravell** (agravell@emmes.com; 301-251-1161, ext. 216) if you have any additional topics for the newsletter, suggestions or questions.

See you at the IDSC Summer Meeting!

July 13, 2012

From 9:30-4:00 PM CDT

Hyatt Regency O'Hare

Chicago, IL

Inside this issue:

UPCOMING IDSC MEETINGS/ REMINDERS:

- **Next call:** TBD
- **IDSC Summer Meeting (2012):** Friday, July 13th (Chicago, IL)
- **IDSC Fall Meeting (2012**): Tuesday-Wednesday, October 16-17th (Bethesda, MD)
- **IDSC Winter Meeting (2013):** TBD
- **IDSC Spring Meeting (2013):** Monday-Tuesday, March 19th (Bethesda, MD)

UPDATE from March 13 (2012) IDSC Meeting

- The Biomarker TBBA subcommittee templates (IHC, DNA-based ISH, and mutational) were discussed with the IDSC by Kim Jessup.
- Richard Piekarz (IDB drug monitor) presented the CTEP Drug Development Plan for AZD1480 (JAK2) to IDSC members. The IDSC endorsed the development plan with minor modifications.
- Mark Ratain obtained IDSC endorsement for the Phase 1 combination recommendations; the subgroup will create a manuscript.
- Percy Ivy discussed the "Redesign of the NCI Early Experimental Therapeutics Program and requested further impute.
- Elad Sharon (IDB drug monitor) presented the CTEP Drug Development Plan for Moxetumomab pasudotox (HA22) to the IDSC as an FYI.

Task Force/WG Updates

Immunotherapy TF:

Upcoming calls:

June 22nd: The TF will review the CTEP and Cancer Immunotherapy Network (CITN) linkages (upcoming trials, ongoing trials, etc) and see how they can fill in any gaps.

Upcoming agents for TF:

MT-103 should be reviewed by the TF in the near future.

Pomalidomide will be reviewed by an ad hoc group of experts.

Signal Transduction/PAM TFs

Upcoming calls:

June 7th: The TF will review the CTEP Drug Development Plan for **MLN0128** (formerly INK-128; TORC 1/TORC 2) along with the **PAM TF**. Austin Doyle is the IDB drug monitor.

Upcoming agents for TF:

AMG-479 (IGF-1R) should be reviewed by the TF in the near future. Helen Chen is the IDB drug monitor.

DNA Repair TF:

Upcoming agents for TF:

ABT-263 (Bcl2) should be re-reviewed by the TF in the near future. This agent was reviewed by the IDSC in 2009 but due to CRADA issues was tabled.

The TF would like to review data on **ABT-199** (Bcl2) and potentially assist with obtaining for the CTEP portfolio.

Drug Development Criteria Checklist: A WG has been formed to create a checklist to assist IDB drug monitors and the IDSC.

Websites of Interest:

http://ccct.cancer.gov/

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

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

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/

Other Suggestions?

SPOTLIGHT ARTICLE: Poste, G., Jessup, JM, et al.,

Leveling the playing field: bringing development of biomarkers and molecular diagnostics up to the standards for drug development. Clin Cancer Res, 2012. **18**(6): p. 1515-23.

Molecular diagnostics are becoming increasingly important in clinical research to stratify or identify molecularly profiled patient cohorts for targeted therapies, to modify the dose of a therapeutic, and to assess early response to therapy or monitor patients. Molecular diagnostics can also be used to identify the pharmacogenetic risk of adverse drug reactions. The articles in this *CCR Focus* section on molecular diagnosis describe the development and use of markers to guide medical decisions regarding cancer patients. They define sources of preanalytic variability that need to be minimized, as well as the regulatory and financial challenges involved in developing diagnostics and integrating them into clinical practice. They also outline a National Cancer Institute program to assist diagnostic development. Molecular diagnostic clinical tests require rigor in their development and clinical validation, with sensitivity, specificity, and validity comparable to those required for the development of therapeutics. These diagnostics must be offered at a realistic cost that reflects both their clinical value and the costs associated with their development. When genome-sequencing technologies move into the clinic, they must be integrated with and traceable to current technology because they may identify more efficient and accurate approaches to drug development. In addition, regulators may define progressive drug approval for companion diagnostics that requires further evidence regarding efficacy and safety before full approval can be achieved. One way to accomplish this is to emphasize phase IV postmarketing, hypothesis-driven clinical trials with biological characterization that would permit an accurate definition of the association of low-prevalence gene alterations with toxicity or response in large cohorts. *Clin Cancer Res; 18(6); 1515–23. ©2012 AACR .*

Kim Jessup, M.D. (NCI liaison to the Biomarker Task Force)

Please see page 4 for other articles in this CCR FOCUS SERIES

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	Issued
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	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	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: Hewitt, S.M., S.S. Badve, and L.D. True, *Impact of preanalytic factors on the design and application of integral biomarkers for directing patient therapy.* Clin Cancer Res, 2012. **18**(6): p. 1524-30.

Molecular assays have been routinely applied to improve diagnosis for the last 25 years. Assays that guide therapy have a similar history; however, their evolution has lacked the focus on analytic integrity that is required for the molecularly targeted therapies of today. New molecularly targeted agents require assays of greater precision/quantitation to predict the likelihood of response, i.e., to identify patients whose tumors will respond, while at the same time excluding and protecting those patients whose tumors will not respond or in whom treatment will cause unacceptable toxicity. The handling of tissue has followed a fit-for-purpose approach focused on appropriateness for diagnostic needs, which is less rigorous than the demands of new molecular assays that interrogate DNA, RNA, and proteins in a quantitative, multiplex manner. There is a new appreciation of the importance and fragility of tissue specimens as the source of analytes to direct therapy. By applying a total test paradigm and defining and measuring sources of variability in specimens, we can develop a set of specifications that can be incorporated into the clinical-care environment to ensure that a specimen is appropriate for analysis and will return a true result. *Clin Cancer Res; 18(6); 1524–30. ©2012 AACR*

Stephen Hewitt, M.D. , Ph.D. (Biomarker Task Force)

Article 2: Williams, P.M., Conley, B.A., et al., *Bridging the gap: moving predictive and prognostic assays from research to clinical use.* Clin Cancer Res, 2012. **18**(6): p. 1531-9.

The development of clinically useful molecular diagnostics requires validation of clinical assay performance and achievement of clinical qualification in clinical trials. As discussed elsewhere in this Focus section on molecular diagnostics, validation of assay performance must be rigorous, especially when the assay will be used to guide treatment decisions. Here we review some of the problems associated with assay development, especially for academic investigators. These include lack of expertise and resources for analytical validation, lack of experience in designing projects for a specific clinical use, lack of specimens from appropriate patient groups, and lack of access to Clinical Laboratory Improvement Amendments-certified laboratories. In addition, financial support for assay validation has lagged behind financial support for marker discovery or drug development, even though the molecular diagnostic may be considered necessary for the successful use of the companion therapeutic. The National Cancer Institute supports a large number of clinical trials and a significant effort in drug development. In order to address some of these barriers for predictive and prognostic assays that will be used in clinical trials to select patients for a particular treatment, stratify patients into molecularly defined subgroups, or choose between treatments for molecularly defined tumors, the National Cancer Institute has begun a pilot program designed to lessen barriers to the development of validated prognostic and predictive assays.

Barbara Conley, M.D. (NCI CADP)

Other articles in the CCR FOCUS Series (not listed on Page 2 or above):

- Schilsky, R.L., et al., *Development and use of integral assays in clinical trials.* Clin Cancer Res, 2012. **18**(6): p. 1540-6.
- Meshinchi, S., et al., *Lessons learned from the investigational device exemption review of Children's Oncology Group trial AAML1031.* Clin Cancer Res, 2012. **18**(6): p. 1547-54.