Investigational Drug Steering Committee

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Welcome to the IDSC Newsletter

This is the fifteenth 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:

New IDSC U01 co-chair: Lillian Siu has become the new IDSC U01 co-chair. 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 Spring Meeting!

April 23, 2013

From 1:00-5:00 PM EDT

NIH Campus

Building 49

Inside this issue:

UPCOMING IDSC/ EDD MEETINGS/ REMINDERS:

- **Pharmacology Task Force meeting :** Monday, April 22nd from 6:00-8:00 PM (NIH Campus; Bldg 10, Room 2C116)
- **CTEP EDD/IDSC Spring Meeting (2013):** Monday-Tuesday, April 22nd-23rd (IDSC: NIH Campus; Bldg 49; CTEP EDD: Masur; Building 10)
- **IDSC Summer Meeting (2013):** Friday, July 26, 2013 (TBD)
- **CTEP EDD/IDSC Fall Meeting (2013**): Monday-Wednesday, September 9-11 (NIH Campus)

UPDATE from January 11th (2013) IDSC—NCI Special Symposium Meeting

- Lillian Siu became the new U01 IDSC co-chair on January 1, 2013.
- The TMSC Master Protocol Task Force has been working in a parallel effort with the Friends of Cancer (FOC) Task Force to finalize a Master Protocol design for NSCLC .
- Ed Harlow introduced the esteemed group of speakers to participants and outlined the session for the symposium .
- Ken Anderson (SPORE), Lewis Cantley (Stand Up to Cancer Dream Team), Levi Garraway (Broad Institute), Ken Turteltaub (Lawrence Livermore National Library), and L. Michelle Bennett (NHLBI) discussed team science strategies and obstacles.
- Recommendations for "successful" team – based science were provided (see next page).

Task Force/WG Updates

Clinical Trial Design (CTD) TF

- **Biomarker and CTD meeting—Biomarkers in Phase 2 Trials** will be held on Monday-Tuesday, May 20th-21st in the Neuroscience Building (6001 Executive Blvd).
- **Value of Information WG**: An additional call is scheduled for March 1st and the group aims to hold an educational session with discussing economic methods to prospectively evaluate clinical trials from a social and private perspective.
- **LOI Benchmarking/ Concordance Project** has been assessed through Q3 2012.

- **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) - to be submitted
3. Phase 1 Recommendations for Agent Combination Trials (Bradbury/Paller)
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)

Immunotherapy TF

An Immunotherapy Working Group has been formed to assist Drs. Elad Sharon and Howard Streicher with revision of the BMS-936558 and MK-3475 CTEP Drug Development Plans.

Calls for the Working Group: January 16th, February 12th, and March 13th.

The development plans will be presented at the IDSC Tuesday, April 23rd meeting. Drs. Jedd Wolchok and Michael Atkins will represent the Immunotherapy TF at the meeting.

Biomarkers TF

Janet Dancey (TF chair) and Percy Ivy will finalize the draft agenda for the "Biomarkers in Phase 2 Trials" meeting and discuss with Working Group.

RECOMMENDATIONS FOR SUCCESSUL TEAM-BASED SCIENCE (January11th, 2013)

1. Must have a clear goal that is achievable in the funding period.
2. Fosters partnerships of academia, pharmaceuticals, NCI, regulatory agencies, and advocacy to fast forward progress.
3. Must have clear, achievable **milestones with a timeline.** Frequent teleconferences and/or face-to-face meetings are required to verify that the milestones are being met.
4. May want to develop a "prenuptial" contract for scientist, which outlines what is expected of leadership, team members, and timelines.
5. Facilitates iterative bench to bedside and back research which has markedly improved patient outcome.
6. Leverages multiple resources. There must be sufficient funds to achieve the goal(s).
7. Deep and sustained collaborations are essential.
8. An escalating budget rather than fixed yearly budget is usually better. Some members of the team only become relevant at late stages of the project.
9. **The Leader is critical:** the Leader must be fully engaged in achieving the goal and must be willing to cede senior authorship on key papers to members of the team who achieve their assigned tasks (motivation). Ideally, the Leader should have a working knowledge of all aspects of technologies/ disciplines utilized by the team (or be willing to learn these at a level that allows evaluation of quality).
10. **The Leader (or leadership team) must have the ability to re-distribute resources** in a timely manner to solve unanticipated problems that arise or replace team members who, for whatever reason, are not meeting their milestones.
11. Model of team development includes: forming, storming, norming, and performing. This model is cyclical and arises each time the team is changed/altered.
12. Trust must be established with all team members.
13. Mentors should be available for new Team members.
14. Able to resolve conflict swiftly and effectively (developing ways to circumvent conflict).
15. All members of the team believe that the goal is a worthy one **AND** that it is achievable with the technology, expertise and funds available to the team.
16. Each member of the team must understand her/his role in achieving the goal, and must feel that she/he will get credit for making this contribution.
17. Metric of success is improved patient outcome.
18. Funds infrastructure for translational research and tissue banks.

Agents Reviewed by the IDSC (2006-2013)

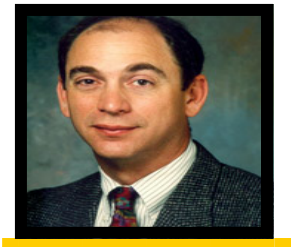
Agent Name	Target	IDSC Review	Mass Solicitation Status?
IMC-A12	IGF-1R	September 2006	Issued
IL-12	immune regulation	July 2008	Issued
SCH727965	CDK	February 2008	Issued
GDC-0449	sonic hedgehog	November 2008	Issued
RO4929097	notch	January 2009	Issued
OSI-906	IGF-1R	March 2009; June 2010	Issued
MK-2206	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	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 only
AMG-479	IGF-1R	July 13, 2012	Pending
MLN-0128	TORC1/TORC2	July 13, 2012	Issued
AMG-103	BiTE Bispecific Antibody	July 13, 2012	Pending
Pomalidomide	Immune regulation	October 16, 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: Wheeler HE, Maitland ML, Dolan ME, Cox NJ, Ratain MJ. Cancer pharmacogenomics: strategies and challenges. Nat Rev Genet 2013;14(1):23-34.

Genetic variation influences the response of an individual to drug treatments. Understanding this variation has the potential to make therapy safer and more effective by determining selection and dosing of drugs for an individual patient. In the context of cancer, tumours may have specific disease-defining mutations, but a patient's germline genetic variation will also affect drug response (both efficacy and toxicity), and here we focus on how to study this variation. Advances in sequencing technologies, statistical genetics analysis methods and clinical trial designs have shown promise for the discovery of variants associated with drug response. We discuss the application of germline genetics analysis methods to cancer pharmacogenomics with a focus on the special considerations for study design.



Mark Ratain, M.D.

Article 2: Seymour LK, Calvert AH, Lobbezoo MW, Eisenhauer E, and Giaccone G. Design and conduct of early clinical studies of two or more targeted anticancer therapies: commendations from the task force on Methodology for the Development of Innovative Cancer Therapies. European Journal of Cancer, 2013 (prepub).

The Methodology for the Development of Innovative Cancer Therapies (MDICT) task force considered aspects of the design and conduct of early (phase I and II) studies of combinations of molecular targeted agents during their 2012 meeting. The task force defined necessary non-clinical data, such as evidence of additive or synergistic effects in multiple molecularly credentialed and validated models, and appropriate pharmacodynamic marker development. A robust hypothesis was considered critical while non-clinical pharmacokinetic studies were also considered valuable.

Clinical trials should include clear objectives that will prove or disprove the hypothesis. Predictive biomarkers/classifiers should be explored in phase I studies, rather than used to select patients. Trial design should be efficient and flexible rather than based on a strict progression from phase I to II to III; researchers could consider phase I studies with an expansion cohort, Phase I/II designs or phase II studies with a safety run in. Pharmacokinetics are recommended when interactions or overlapping toxicity is expected. Pharmacodynamic evaluations should be considered especially in a subset of patients closest to the recommended dose; an attempt should be made to validate surrogate tissues to enable inclusion for all patients. Schedule and or dose should be formally explored for e.g. with a randomized or an adaptive design.

Lesley Seymour, M.D.

Upcoming Issue:

- **The next Publication Corner will focus on clinical trials with radiation therapy.**
- **A spotlight section will focus on genomics and the incorporation into multi-institutional clinical trials.**