Investigational Drug Steering Committee

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Welcome to the IDSC Newsletter

This is the sixteenth 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:

We will be looking for a new N01 IDSC co-chair, since Dr. Miguel Villalona's term will conclude on December 31, 2013 (We thank him!). Amy Gravell will send ballots in July 2013 to N01 holders.

The Summer 2013 IDSC meeting for Friday, July 26th has been **canceled.**

Good luck to all current U01 holders with the ET-CTN RFA. The **applications are due on August 23, 2013**.

A pilot of the new Experimental Therapeutics—Clinical Trials Network (ET-CTN) should take place by 2014.

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

See you at the IDSC Fall Meeting!

September 10, 2013

From 1:00-5:30 PM EDT

NIH Campus

Building 45—Natcher (RM D)

Update from the ET-CTN Meeting -April 21, 2013

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 ET-CTN members, awardees of the NCI Phase 2 Contracts Program, NCTN awardees, and other appropriate investigators.

Inside this issue:

UPCOMING IDSC/ EDD MEETINGS/ REMINDERS:

- **CTEP EDD/IDSC Fall Meeting (2013)**: Monday-Tuesday September 9-10th, 2013 (NIH Campus— Natcher; Building 45)
- **IDSC Winter 2014 Meeting**: Friday, January 10, 2014; NIH Campus (TBD)
- **CTEP EDD/IDSC Spring 2014 Meeting**: Monday -Tuesday; March 10-11th , 2014 (NIH Campus—Natcher; Building 45)
- **IDSC Summer 2014 Meeting:** Friday, July 18th, 2014 (NIH Campus; Building 31; Room 6C)
- **CTEP EDD/IDSC Fall 2014 Meeting**: Monday -Wednesday, October 20-22nd, 2014 (NIH Campus; Natcher; Building 45)

Task Force/WG Updates

Clinical Trial Design (CTD) TF

- **Biomarker and CTD meeting—Biomarkers in Phase 2 Trials** will be held on Monday-Tuesday, September 16-17th at the Bethesda North Marriott.
- **Value of Information WG**: Rena Conti is currently working on updating the example.
- **LOI Benchmarking/ Concordance Project** has been assessed through Q3 2012. Q4 2012 will be completed after the "baseline concordance rate" from 2010 has been assessed (will assist with the update of the Phase 2 recommendations manuscript).

- **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)
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

Two anti-PD-1 development plans were presented at the IDSC Tuesday, April 23rd meeting. Drs. Jedd Wolchok and Michael Atkins represented the Immunotherapy TF at the meeting.

Pharmacology TF

The TF held a meeting on April 22nd to discuss the Drug-Drug Interaction Guidance developed for CTEP.

Signal Transduction TF

The educational session on Target Resistance from the CTEP Spring 2013 EDD meeting will be transformed into a manuscript by the TF.

SPOTLIGHT ON GENOMICS: Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497(7447):67-73.

We performed an integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas using array- and sequencing-based technologies. Uterine serous tumours and approximately 25% of high-grade endometrioid tumours had extensive copy number alterations, few DNA methylation changes, low oestrogen receptor/progesterone receptor levels, and frequent TP53 mutations. Most endometrioid tumours had few copy number alterations or TP53 mutations, but frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A and KRAS and novel mutations in the SWI/SNF chromatin remodeling complex gene ARID5B. A subset of endometrioid tumours that we identified had a markedly increased transversion mutation frequency and newly identified hotspot mutations in POLE. Our results classified endometrial cancers into four categories: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high. Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas. We demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may affect post-surgical adjuvant treatment for women with aggressive tumours.

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 (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 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
BMS-936558	anti-PD-1	April 23, 2013	Pending
MK-3475	anti-PD-1	April 23, 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: Chakravarti A, Wang M, Robins HI, Lautenschlaeger T, Curran WJ, Brachman DG, **Dicker, A. P.,** et al. RTOG 0211: a phase 1/2 study of radiation therapy with concurrent gefitinib for newly diagnosed glioblastoma patients. Int J Radiat Oncol Biol Phys 2013;85(5):1206-11.

PURPOSE: To determine the safety and efficacy of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in combination with radiation for newly diagnosed glioblastoma (GBM) patients. **METHODS AND MATERIALS**: Between March 21, 2002, and May 3, 2004, Radiation Therapy Oncology Group (RTOG) 0211 enrolled 31 and 147 GBM patients in the phase 1 and 2 arms, respectively. Treatment consisted of daily oral gefinitnib started at the time of conventional cranial radiation therapy (RT) and continued post RT for 18 months or until progression. Tissue microarrays from 68 cases were analyzed for EGFR expression. **RESULTS:** The maximum tolerated dose (MTD) of gefitinib was determined to be 500 mg in patients on non-enzyme-inducing anticonvulsant drugs (non-EIAEDs). All patients in the phase 2 component were treated at a gefitinib dose of 500 mg; patients receiving EIADSs could be escalated to 750 mg. The most common side effects of gefitinib in combination with radiation were dermatologic and gastrointestinal. Median survival was 11.5 months for patients treated per protocol. There was no overall survival benefit for patients treated with gefitinib + RT when compared with a historical cohort of patients treated with RT alone, matched by RTOG recursive partitioning analysis (RPA) class distribution. Younger age was significantly associated with better outcome. Per protocol stratification, EGFR expression was not found to be of prognostic value for gefitinib + RT-treated patients. **CONCLUSIONS:** The addition of gefitinib to RT is well tolerated. Median survival of RTOG 0211 patients treated with RT with concurrent and adjuvant gefitinib was similar to that in a historical control cohort treated with radiation alone.

Adam Dicker, M.D., Ph.D.

Article 2: Lawrence YR, Vikram B, Dignam JJ, Chakravarti A, Machtay M, Freidlin B, **Dicker, A. P.,** et al. NCI-RTOG translational program strategic guidelines for the early-stage development of radiosensitizers. J Natl Cancer Inst 2012;105(1):11-24.

The addition of chemotherapeutic agents to ionizing radiation has improved survival in many malignancies. Cure rates may be further improved by adding novel targeted agents to current radiotherapy or radiochemotherapy regimens. Despite promising laboratory data, progress in the clinical development of new drugs with radiation has been limited. To define and address the problems involved, a collaborative effort between individuals within the translational research program of the Radiation Oncology Therapy Group and the National Cancer Institute was established. We discerned challenges to drug development with radiation including: 1) the limited relevance of preclinical work, 2) the pharmaceutical industry's diminished interest, and 3) the important individual skills and institutional commitments required to ensure a successful program. The differences between early-phase trial designs with and without radiation are noted as substantial. The traditional endpoints for early-phase clinical trials-acute toxicity and maximum-tolerated dose-are of limited value when combining targeted agents with radiation. Furthermore, response rate is not a useful surrogate marker of activity in radiation combination trials. Consequently, a risk-stratified model for drug-dose escalation with radiation is proposed, based upon the known and estimated adverse effects. The guidelines discuss new clinical trial designs, such as the time-to-event continual reassessment method design for phase I trials, randomized phase II "screening" trials, and the use of surrogate endpoints, such as pathological response. It is hoped that by providing a clear pathway, this article will accelerate the rate of drug development with radiation.

Upcoming Issue:

- **Will focus on the new CTEP ET-CTN and common questions.**