Investigational Drug Steering Committee

CCCT/EMMES
NCI Confidential

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February 2011

Welcome to the IDSC Newsletter

This is the ninth installment of a quarterly newsletter to IDSC members. As the task forces (TFs) and working groups (WGs) are becoming more active, it has become increasingly hard to keep track of progress. This newsletter highlights key announcements, accomplishments, schedules, publications and events of the IDSC.

Please feel free to provide input.

CCCT and EMMES staff,

LeeAnn Jensen (CCCT)

Amy Gravell (EMMES)

Pam West (EMMES)

ANNOUNCEMENTS:

- **Pat LoRusso** has become the new U01 IDSC co-chair as of January 1, 2011. We thank Mike Grever for his exceptional service.
- **Please NOTE** that the IDSC Spring 2011 meeting will ONLY be held on Tuesday, March 15th from 1:00-6:00 PM in Natcher Auditorium. The Wednesday morning portion has been canceled.
- **Publications:** The Adoptive Cell Therapy manuscript has been sent to CCR and comments were received.

See you at the IDSC Spring Meeting!

NIH Campus

Natcher Auditorium

March 15, 2011

From 1:00-6:00 PM

We welcome Dr. Glenn Liu as the new U01 PI for the University of Wisconsin and thank Dr. George Wilding for his service

Inside this issue:

UPCOMING IDSC MEETINGS:

- **Next call:** TBD
- **IDSC Spring Meeting** (2011): Tuesday, March 15th (Bethesda, MD)
- **IDSC Summer Meeting** (2011): TBD
- **IDSC Fall Meeting** (2011): Tuesday-Wednesday, October 4-5th (Bethesda, MD)

UPDATE from January 14th (2011) IDSC Meeting

- Mike Grever was presented with a plaque for his 2 year service as an IDSC co-chair.
- Developmental Therapeutics Program Combinatorial presentation by Dr. jerry Collins.
- IDB drug monitor, Helen Chen presented the TRC-105 (monoclonal antibody to CD105) CTEP Drug Development Plan to IDSC members.
- IDB drug monitor, Austin Doyle presented the SCH900776 (Chk1 inhibitor) and MK-1775 (Wee1 inhibitor) CTEP Drug Development Plans to IDSC members.
- Joanna Brell from the SxQOL Steering Committee discussed IDSC participation with identifying investigational agents that reduce treatment-related toxicities.
- The NCI Clinical Assay Development Program (CADP) was presented by Drs. Barbara Conley and Mickey Williams.

IDSC Task Force and Working Group Updates

Biomarker TF:

TBBA subcommittee call:

First or second Monday of the month at 11:00 AM ET

- This subcommittee has completed or is working on assay templates (IHC , FISH, and mutation assays) for early phase clinical trialists.
- NCI Case Report Forms for IHC and possibly FISH are underway, but need approval.

DNA Repair TF:

Accomplishments in 2010/2011:

- CTEP Early Drug Development (EDD) Session on Autophagy
- Autophagy manuscript to be submitted to Clinical Cancer Research (CCR)
- Autophagy P01 being devised
- Assisted in reviewing SCH900776 (Chk1) and MK-1775 (Wee1) in conjunction with the IDSC Signal Transduction Task Force.

Immunotherapy TF:

Adoptive Immunotherapy subcommittee:

- This subcommittee has completed the white paper involving adoptive immunotherapy.
- The white paper was presented to IDSC and NCI staff on July 19th (2010).
- White paper was sent to Clinical Cancer Research for publication.
- A CTEP Adoptive Cell Immunotherapy meeting will be held on February 16th.

IF YOU ARE INTERESTED IN JOINING ONE OF THE IDSC TASK FORCES

PLEASE CONTACT AMY GRAVELL (agravell@emmes.com)

Task Forces:

- **Angiogenesis**
- **Biomarkers**
- **Cancer Stem Cell**
- **Clinical Trial Design**
- **DNA Repair**
- **Immunotherapy**
- **Pharmacology**
- **PI3K/Akt/mTOR(PAM)**
- **Signal Transduction**

Working Groups:

- **COI**
- **Gap Analysis**
- **LOI Review**
- **Metrics**
- **Scientific Meeting Planning**

IDSC Task Force and Working Group Updates

Clinical Trial Design:

Accomplishments 2010:

- A CCR Focus series involving Phase 1 trials (March 15, 2010)
- Analysis of Phase 2 LOIs and compliance with the CTD TF approved recommendations.
- Working on or just completing Phase I Combination data, Historical controls, and Adaptive versus Frequentist designs.

Signal Transduction TF:

Call held on December 15th and January 5th (2010)

IDB drug monitor, Austin Doyle presented SCH900776 and MK-1775 to TF members. Presented to IDSC on January 14th, 2011.

TF members previously reviewed in 2010

- ARQ-197
- OSI-906
- MLN-8237

Cancer Stem Cell TF:

Accomplishments in 2010:

- GDC-0449 and RO4929097 CTEP trials were reviewed by drug monitors
- New Wnt/Notch inhibitors for the CTEP portfolio were discussed
- EMT and CSC targets were discussed. Axl may be presented at a future CTEP EDD meeting.

IDSC Task Force and Working Group Updates

Pharmacology TF

Accomplishments from 2010:

Estimating Renal Function for Chemotherapy Dosing

- Creatinine clearance methodology changed in 2005
- Calculation method impacts carboplatin dose
- How should CTEP address this in its protocols?
- Recent CTEP Action Letter for protocols containing carboplatin
- Mass solicitation to address this issue is being developed by CTEP

Angiogenesis TF:

- Reviewed the TRC-105 limited CTEP drug development plan for CTEP.
- Helen Chen presented TRC-105 to the IDSC on January 14, 2011 and was approved.
- Chandra Belani and Roy Herbst (TF co-chairs) presented the Angiogenesis TF recommendations to the IDSC.

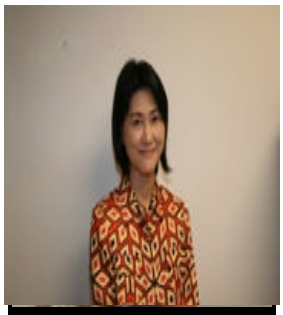
Agents Reviewed by the IDSC (2006-2011)

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	Pending
SCH900105	cMet	October 2009	WITHDRAWN
MK-8033	cMet	October 2009	WITHDRAWN
AT13387	HSP90	October 2009	Pending
MLN-8237	Aurora kinase	September 2010	Pending
AMG386	Ang 1/2	July 2010	Issued
TRC-105	mAB CD105	January 2011	Pending
SCH900776	Chk1	January 2011	Pending
MK-1775	Wee1	January 2011	Pending

Publication Corner: *this section will highlight 3 articles written by IDSC investigators per issue (within the IDSC or outside publications of relevance)*

Article I: Takebe, N., Ivy, S.P., et al., *Targeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways.* Nat Rev Clin Oncol. **8**(2): p. 97-106

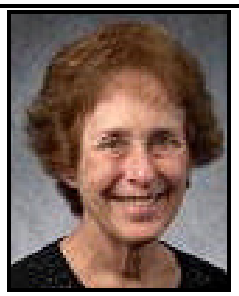
Tumor relapse and metastasis remain major obstacles for improving overall cancer survival, which may be due at least in part to the existence of cancer stem cells (CSCs). CSCs are characterized by tumorigenic properties and the ability to self-renew, form differentiated progeny, and develop resistance to therapy. CSCs use many of the same signaling pathways that are found in normal stem cells, such as Wnt, Notch, and Hedgehog (Hh). The origin of CSCs is not fully understood, but data suggest that they originate from normal stem or progenitor cells, or possibly other cancer cells. Therapeutic targeting of both CSCs and bulk tumor populations may provide a strategy to suppress tumor re-growth. Development of agents that target critical steps in the Wnt, Notch, and Hh pathways will be complicated by signaling cross-talk. The role that embryonic signaling pathways play in the function of CSCs, the development of new anti-CSC therapeutic agents, and the complexity of potential CSC signaling cross-talk are described in this Review.



Naoko Takebe, M.D., Ph.D.

Article 2: Karp JE, et. al. Phase I and pharmacokinetic study of bolus-infusion flavopiridol followed by cytosine arabinoside and mitoxantrone for acute leukemias. Blood. 2011.

Flavopiridol is a protein bound, cytotoxic, cyclin-dependent kinase inhibitor. Flavopiridol given by one hour bolus at 50 mg/m(2) daily x 3 followed by ara-C and mitoxantrone (FLAM) is active in adults with poor-risk acute leukemias. A pharmacologically-derived "hybrid" schedule (30 minute bolus followed by 4 hour infusion) of flavopiridol was more effective than bolus administration in refractory chronic lymphocytic leukemia. Our Phase I trial "hybrid FLAM" in 55 adults with relapsed/refractory acute leukemias began at a total flavopiridol dose of 50 mg/m(2)/day x 3 (20 mg/m(2) bolus, 30 mg/m(2) infusion). Dose limiting toxicity occurred at level 6 (30 mg/m(2) bolus, 70 mg/m(2) infusion) with tumor lysis, hyperbilirubinemia and mucositis. Death occurred in 5 patients (9%). Complete remission (CR) occurred in 22 (40%) across all doses. Overall and disease-free survivals for CR patients are > 60% at > 2 years. Pharmacokinetics demonstrated a dose-response for total and unbound plasma flavopiridol unrelated to total protein, albumin, peripheral blast count or toxicity. Pharmacodynamically, flavopiridol inhibited mRNAs of multiple cell cycle regulators, but with uniform increases in bcl-2. "Hybrid FLAM" is active in relapsed/refractory acute leukemias, with a recommended "hybrid" dose of bolus 30 mg/m(2) followed by infusion 60 mg/m(2) daily for 3 days. This clinical study is registered at www.clinicaltrials.gov as: #NCT00470197



Judith Karp, M.D.

Article 3: Messersmith WA, et. al. Phase I trial of oxaliplatin, infusional 5-fluorouracil, and leucovorin (FOLFOX4) with erlotinib and bevacizumab in colorectal cancer. Clin Colorectal Cancer. 2010;9(5):297-304

This phase I study was conducted to determine the maximum tolerated dose (MTD) of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, with 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX4) in patients with advanced colorectal cancer (CRC). Bevacizumab was later included as standard of care at the MTD. PATIENTS AND METHODS: Patients received FOLFOX4 with escalating doses of erlotinib: dose level (DL) 1, 50 mg; DL 2, 100 mg; and DL 3, 150 mg once daily continuously. Bevacizumab 5 mg/kg days 1 and 15 was added at the MTD upon Food and Drug Administration approval. Correlative studies included pharmacokinetics, pharmacodynamics was assessed in paired skin biopsies, and fluorodeoxyglucose positron emission tomography scans. RESULTS: Fifteen patients received 60 cycles (120 FOLFOX treatments). Two dose-limiting toxicities (DLTs) were seen at DL 3: intolerable grade 2 rash (Common Terminology Criteria for Adverse Events version 2) lasting > 1 week, and grade 4 neutropenia. Dose level 2 was expanded to 6 more patients, this time adding bevacizumab, and 1 DLT of grade 3 mucositis occurred. As expected, the primary toxicities were cytopenias, diarrhea, rash, and fatigue. There were 2 occurrences of pneumatosis. One patient experienced an unrelated grade 4 myocardial infarction before starting chemotherapy. No pharmacokinetic drug interactions were observed. The Response Evaluation Criteria in Solid Tumors response rate was 11 of 14 (78%), median progression-free survival was 9.5 months, and median overall survival was 30 months. Three patients are currently alive > 3 years, with 1 having no evidence of disease. CONCLUSION: The MTD of erlotinib with FOLFOX4 with or without bevacizumab is 100 mg daily. The regimen appeared to increase toxicity but showed activity in CRC.

Michael Carducci, M.D.

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NEW IDSC website: https://idsc.sharepointsite.net/default.aspx

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Please contact me with any suggestions for the IDSC Newsletter!

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Websites of Interest:

http://ccct.cancer.gov/

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

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

https://cancersteeringcommittees.sharepointsite.net/default.aspx

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/

REMINDERS:

Next IDSC meeting:
Tuesday, March 15, 2011 at Natcher Auditorium on NIH Campus

Agenda:

- **Reprioritization of the SCH900776 and MK-1775 CTEP clinical development plans.**
- **FDA perspective on 2NMEs**
- **Clinical Trial Design TF—Phase 1 Combinations, Historical Control, and Adaptive versus Frequentist Projects**

Other Upcoming IDSC meetings:

IDSC Summer Meeting: TBD

Tuesday-Wednesday; October 4-5th, 2011 (Bethesda, MD)

Next call: TBD

Please send any new topics for the IDSC newsletter to
Amy Gravell
(agravell@emmes.com)