Investigational Drug Steering Committee Update

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Outline

- Background
- Goals of IDSC
- Achievements of IDSC
- Future Directions

Background: Clinical Trials Working Group Recommendations (2005)

- **Involve all stakeholders in design and prioritization of clinical trials** that address the most important questions, using the tools of modern cancer biology

- Led to the **formation of the Investigational Drug Steering Committee** (IDSC; which makes recommendations to NCI regarding agents for early phase trials)

- Led to the **formation of the Disease-specific Steering Committees** (which develop later phase trials)

IDSC Goals

- Provide external strategic input into the prioritization of phase I and II trials for new agents with NCI CTEP
- Increase transparency of process
- Give input to NCI's Investigational Drug Branch (IDB) on drug development plans
- Optimize clinical trial designs to improve effectiveness of early phase therapeutics
- Increase the predictive value of early phase trials, resulting in the design of more successful phase III trials
- Develop a new forum for interaction among grant and contract holders and with CTEP

IDSC: Membership

- **PI's of all NCI Phase I U01 grants and Phase II N01 contracts**
- **Current Co-chairs**: Pat LoRusso (U01); Miguel Villalona (N01)
- Former Co-chairs: U01: Mark Ratain (served 3 years), Michael Grever; N01: David Gandara, Charles Erlichman, and Dan Sullivan
- **Representatives from Cooperative Groups**
- **Liaisons with other Steering Committees**
- **Content/Subject experts**: Biostatistics, Biomarkers, Imaging, Radiation Oncology, Clinical and Preclinical Pharmacology, Patient Advocates, NCI Staff
  - **Recently Add Expertise**: Genomics and Preclinical Drug Development Experts

IDSC: Task Forces

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

IDSC Accomplishments

- **Transparency and enhanced scientific input into NCI drug development process**
  - Reviewed 24 Clinical Development Plans (20 have moved forward)
  - Assisted with Presolicitation efforts for U01 and N01 investigators (LOI Review Working Group)
  - Recommended Career Development LOI (CrDL) Program for New Investigators
    - Dozens of Junior Investigators have become PI's through this mechanism
- **Identify niches for NCI involvement complementary to industry**
- **Transition from IDSC to Disease-specific Steering Committees (DSSCs) facilitated by designated liaisons**
  - Membership discussion to invite two DSSC members to present to IDSC during in-person meetings
  - Target DSSC members to attend IDSC CTEP agent reviews, when specific diseases are being discussed for trials

IDSC Accomplishments

- **Have published or are in the process of publishing 23 manuscripts (21 published and 2 in process) –** *see citation listing on slides 18-20*

  - **Highlights**
    - Phase 2 clinical trial design - 5 CCR FOCUS papers (March 2009)
    - Phase 1 clinical trial design - 5 CCR FOCUS papers (March 2010)
    - Management of blood pressure in patients receiving VEGF inhibitors (JNCI 2010)
    - Management of the common cardiovascular toxicities associated with angiogenesis inhibitors ventricular dysfunction (AHJ 2012)
    - Management of hyperglycemia/hyperlipidemia in patients treated with PI3K/Akt/mTOR agents (JCO – prepub)

IDSC Accomplishments - Recommendations

- **Toxicity management of antiangiogenic agents:**
  - Cardiovascular Toxicities Panel (CTP) was developed as a subcommittee of the Angiogenesis Task Force
  - Identified need and developed guidance to manage hypertension and cardiac toxicity related to antiangiogenic agents
  - **Two manuscripts emerged from this effort**:
    - Maitland, M.L., et al., ***Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors***. J Natl Cancer Inst, 2010. **102**(9): p. 596-604.
    - Steingart, R. M., G. L. Bakris, et al. **Management of cardiac toxicity in patients receiving vascular endothelial growth factor signaling pathway inhibitors**. Am Heart J, 2012. **163**(2): 156-63.

IDSC Accomplishments - Recommendations

- ***Novel Phase 1 and Phase 2 clinical trial designs*:**
  - A Phase 1 Workshop was held in 2008 - several opinion papers were published in CCR March 2010
    - An overview of the optimal planning, design, and conduct of phase I studies of new therapeutics
    - Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations
    - Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents
  - Currently working on Phase 1 agent combinations and recommendations (*draft to be presented to IDSC in March 2012*)
  - A series Phase 2 of opinion papers were published in Clinical Cancer Research (CCR) in 2009 (*see citations section)*
    - Introduction on Phase 2 Trial Designs
    - Imaging Endpoints
    - Randomized Phase 2 Designs
    - Biomarkers in Phase 2
    - Predictive Analysis of Alternative Endpoints

IDSC Accomplishments - Recommendations

- ***Adoptive Immunotherapy White Paper*:**
  - Adoptive transfer of immune effector cells against metastatic melanoma is a clinically promising and complex procedure
  - Substantial activity noted in phase II trials
  - Needed confirmation:
    - Multi-institution phase II trial
    - Adequately-powered, randomized, and controlled
    - Central facility for cell growth
  - Pharma is currently conducting study based on Immunotherapy Task Force subcommittee white paper
  - **Citation**: Weber, J., M. Atkins, et al. (2011). *White paper on adoptive cell therapy for cancer with tumor-infiltrating lymphocytes: a report of the NCI CCCT subcommittee on adoptive cell therapy.* Clin Cancer Res **17**(7): 1664-73.

IDSC Accomplishments - Recommendations

- **Hyperglycemia and hyperlipidemia guidelines for PAM inhibitors:**
  - **The PAM Task Force 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
    - provide management guidance and therapeutic goals upon 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.
  - Dose modifications or discontinuation of PAM pathway inhibitors should only be considered in situations of severe events, or if progressive metabolic derangement persists despite adequate therapeutic interventions.
  - Specialty consultation should be sought to aid clinical trial planning and the management of these metabolic adverse events
  - **Citation:** resubmitted to JCO and is pending (as of February 2012)

IDSC Accomplishments - Recommendations

- **Guidelines for incorporation of biomarkers into early phase trials**:
  - The IDSC charged the Biomarker Task Force to develop recommendations to improve the decisions regarding incorporation of biomarker studies in early investigational drug trials.
  - The Task Force members reviewed biomarker trials, the peer-reviewed literature, NCI and FDA guidance documents, and conducted a survey of investigators to determine practices and challenges to executing biomarker studies in clinical trials of new drugs in early development.
  - This document provides standard definitions and categories of biomarkers, and lists recommendations to sponsors and investigators for biomarker incorporation into such trials.
  - **Citation:** Dancey, J.E., et al., *Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents.* Clin Cancer Res, 2010. **16**(6): p. 1745-55.

IDSC Accomplishments

- **Educational Sessions at CTEP Early Drug Development (EDD) Meeting**:
  - Cancer stem cell educational session (Cancer Stem Cell TF)
    - CTEP agents: GDC-0449 (Hedgehog) and RO4929097 (GSI)
  - Phase II recommendations (Clinical Trial Design TF; manuscripts)
    - Lead to Phase 2 LOI benchmarking project (concordance)
  - Biomarker TF recommendations (Biomarker TF; manuscript)
    - Lead to Biomarker Assay Templates for CTEP/DCTD:
      - IHC, DNA-based ISH, and Mutation Assays
  - Autophagy (DNA Repair TF; manuscript)
    - CTEP agent: Chloroquine
  - JAK-STAT educational session (Signal Transduction)
    - CTEP agent: AZD1480 (under review currently by IDSC)
  - c-Met educational session (Signal Transduction)
    - CTEP agents: ARQ-197; Cabozantinib (XL-184)
  - ALK educational session (Signal Transduction)
  - PIM Kinase educational session (Signal Transduction)
  - PI3K educational session (Signal Transduction/PAM)

CTEP Drug Development Plans Reviewed by IDSC (2006 – 2012)

Agent Name	Target
IMC-A12	IGF-1R
IL-12	immune regulation
SCH727965	CDK
GDC-0449	sonic hedgehog
RO4929097	Notch
MK-2206	Akt
ABT-263	bcl2, BH3 mimetic
ARQ-197	cMet
OSI-906	IGF-1R
AMG386	Ang 1 / 2 Inhibitor
MLN-8237	Aurora kinase A
TRC-105	mAb to CD105
SCH-900776	Chk1
MK-1775	Wee1
Ipilimumab	antibody
PCI-32765	BTK
TL32711	Smac mimetic
XL184	c-MET; VEGFR2
GSK2118436	RAF
GSK1220212	MEK

Future Directions

- Continue to assist CTEP with Phase I Redesign effort
- Increase expertise on IDSC agent-based Task Forces and Ad Hoc Groups to improve/better assist CTEP with Drug Development Plan reviews.
- Increase trials opportunities with agents already in CTEP portfolio.
- Continue to develop an effective communication effort in collaboration with disease-specific steering committees to inform them of early drug development

Websites

- CTEP active agreements: http://ctep.cancer.gov/protocolDevelopment/default.htm
- IDSC website for NCI CCCT http://transformingtrials.cancer.gov/steering-committees/investigational-drug

IDSC Publications – Citation Listing (1)

- Adjei, A.A., M. Christian, and P. Ivy, *Novel designs and end points for phase II clinical trials.* Clin Cancer Res, 2009. **15**(6): p. 1866-72.
- Amaravadi, R.K., et al., *Principles and Current Strategies for Targeting Autophagy for Cancer Treatment.* Clin Cancer Res, 2011. **17**(4): p. 654-666.
- Dancey, J.E., et al., *Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents.* Clin Cancer Res, 2010. **16**(6): p. 1745-55.
- Dhani, N., et al., *Alternate endpoints for screening phase II studies.* Clin Cancer Res, 2009. **15**(6): p. 1873-82.
- Forster, M.D., et al., *Performing phase I clinical trials of anticancer agents: perspectives from within the European union and Japan.* Clin Cancer Res, 2010. **16**(6): p. 1737-44.
- Ivy, S.P., et al., *Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the national cancer institute investigational drug steering committee.* Clin Cancer Res, 2010. **16**(6): p. 1726-36.
- LaBarge, M.A., *The difficulty of targeting cancer stem cell niches.* Clin Cancer Res, 2010. **16**(12): p. 3121-9.

IDSC Publication –Citation Listing (2)

- LoRusso, P.M., S.A. Boerner, and L. Seymour, *An overview of the optimal planning, design, and conduct of phase I studies of new therapeutics.* Clin Cancer Res, 2010. **16**(6): p. 1710-8.
- Maitland, M.L., *Cardiovascular toxicity of new agents.* Clin Adv Hematol Oncol, 2008. **6**(9): p. 657-9.
- Maitland, M.L., et al., *Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors.* J Natl Cancer Inst, 2010. **102**(9): p. 596-604.
- McShane, L.M., S. Hunsberger, and A.A. Adjei, *Effective incorporation of biomarkers into phase II trials.* Clin Cancer Res, 2009. **15**(6): p. 1898-905.
- Merchant, A.A. and W. Matsui, *Targeting Hedgehog--a cancer stem cell pathway.* Clin Cancer Res, 2010. **16**(12): p. 3130-40.
- O'Brien, C.A., A. Kreso, and C.H. Jamieson, *Cancer stem cells and self-renewal.* Clin Cancer Res, 2010. **16**(12): p. 3113-20.
- Pannuti, A., et al., *Targeting Notch to target cancer stem cells.* Clin Cancer Res, 2010. **16**(12): p. 3141-52.
- Rubinstein, L., et al., *Randomized phase II designs.* Clin Cancer Res, 2009. **15**(6): p. 1883-90.

IDSC Publications – Citation Listing (3)

- Sargent, D.J. and J.M. Taylor, *Current issues in oncology drug development, with a focus on Phase II trials.* J Biopharm Stat, 2009. **19**(3): p. 556-62.
- Seymour, L., *Controversies in the Design of Phase II Clinical Trials.* Clinical Advances in Hematology & Oncology, 2010. **8**(2): p. 95-97.
- Seymour, L., et al., *The design of phase II clinical trials testing cancer therapeutics: consensus recommendations from the clinical trial design task force of the national cancer institute investigational drug steering committee.* Clin Cancer Res, 2010. **16**(6): p. 1764-9.
- Shankar, L.K., et al., *Considerations for the use of imaging tools for phase II treatment trials in oncology.* Clin Cancer Res, 2009. **15**(6): p. 1891-7.
- Steingart, R. M., G. L. Bakris, et al. "Management of cardiac toxicity in patients receiving vascular endothelial growth factor signaling pathway inhibitors." Am Heart J **163**(2): 156-63.
- Takebe, N. and S.P. Ivy, *Controversies in cancer stem cells: targeting embryonic signaling pathways.* Clin Cancer Res, 2010. **16**(12): p. 3106-12.
- Weber, J., M. Atkins, et al. (2011). *White paper on adoptive cell therapy for cancer with tumor-infiltrating lymphocytes: a report of the NCI CCCT subcommittee on adoptive cell therapy.* Clin Cancer Res **17**(7): 1664-73

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