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:
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.

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)
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.

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)

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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

- IDSC website for NCI CCCT http://transformingtrials.cancer.gov/steering-committees/investigational-drug
IDSC Publications – Citation Listing (1)


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