Investigational Drug Steering Committee

IDSC Co-Chairs: Michael Carducci
Johns Hopkins University
Primo "Lucky" Lara
University of California at Davis
Investigational Drug Steering Committee (IDSC)

- The IDSC was created at the recommendation of the NCI’s Clinical Trials Working Group to assist with the **design and prioritization of early phase** drug development trials with agents for which the Cancer Therapy Evaluation Program (CTEP) holds an Investigational New Drug application (IND).

- Established in 2005
IDSC Membership Composition

- **2 Co-Chairs**
- **33 Principal Investigators of CTEP’s UM1 early drug development grants**
- **2 Consortia Representatives**
  - CITN
  - ABTC
- **6 Subject Matter Experts**
  - Radiation
  - Cell Signaling
  - Omics
  - Imaging
  - SxQOL
  - Pediatrics
- **2 Biostatisticians**
- **2 Patient Advocates**
- **1 FDA**
- **NCI Staff**
Role of the IDSC in NCI Early Therapeutics Program

- Provide input regarding Drug/Clinical Development Plans prepared by the NCI CTEP Project Teams for new drugs and selected current drugs within the CTEP portfolio.

- Foster and prioritize a “team approach” to function as a Network by inclusion of scientific and disease specific expertise

- Evaluation of scientific issues of importance to the NCI as well as the larger early phase clinical trial community through the development of Task forces (TFs)
  - Clinical Trial Design TF
  - Biomarkers TF
  - Pharmacology TF
  - Immunotherapy TF
Linkages between the IDSC and CTEP
IDSC Involvement and CTEP
Drug Development Process
IDSC Review Meeting
Occurs 4 times per year:
Face-to-Face in conjunction with CTEP EDD meeting (fall) and ETCTN Annual Portfolio Presentation meeting (spring) and twice as WebEx teleconferences (winter and summer)

*Proposals outside the initial DDP for this agent(s)
The IDSC has reviewed and provided scientific input into the drug development plans of 45 new investigational agents within the CTEP portfolio:

- 30 CTEP Drug Development Plans developed by IDB senior staff (prior to the launch of the ETCTN)
- 13 ETCTN Project Team Drug Development Plans (15 agents); 62 trial concepts proposed with 4 trial projects disapproved
- All drug development plans take into account IDSC recommendations prior to moving forward with LOI submission.
- ETCTN disease portfolio diagrams have been developed to assist with decreasing duplicative projects ([https://ctep.cancer.gov/initiativesPrograms/etctn_trials.htm](https://ctep.cancer.gov/initiativesPrograms/etctn_trials.htm)).
- LOI appeals process for unsolicited LOIs was recently instituted and 2 LOIs went through the process smoothly.
ETCTN Disease Diagram – Landing Page

CTEP Cancer Therapy Evaluation Program

ETCTN Trials

NCI Experimental Therapeutics Clinical Trials Network (ETCTN) is conducting early-stage trials of cancer treatment therapies in the areas listed below. To see trials that are in review, approved, and active for a specific disease/treatment area, please click that area from the following list.

Note: For full functionality, it is recommended that users download the PDF file, and open with a PDF reader.

Cancer trials by disease/treatment area:
- Brain (PDF)
- Breast (PDF)
- Gastrointestinal (PDF)
- Genitourinary (PDF)
- Gynecological (PDF)
- Head and neck (PDF)
- Leukemia (PDF)
- Lung (PDF)
- Lymphoma (PDF)
Example of an ETCTN Disease Diagram - Gynecologic
IDSC and CTEP Early Drug Development Sessions
IDSC and CTEP Early Drug Development (EDD) Sessions

CTEP EDD

- Cancer Stem Cell
- Phase II Clinical Trial Recs
- ALK
- C-Met
- Biomarker Recs
- JAK-STAT
- Autophagy
IDSC Task Forces and Publications
IDSC Task Force Publications

**Clinical Trial Design TF**
- Phase 1 Recommendations (CCR Focus 2010)
- Design of Phase 1 Combination Trials (CCR 2014)
  - Lead to the Factors Affecting Combination Trial Success (FACTS) project (ASCO 2018)
- Phase 2 Recommendations (CCR Focus 2009)
  - Lead to Concordance of Phase 2 Recommendations (CCR 2015)
- Immuno-oncology Agents and Clinical Trial Design (CCR Focus 2017)

**Immunotherapy TF**
- Adoptive Cell Therapy using Tumor-infiltrating Lymphocytes Recommendations (CCR 2014)
- Current Understanding of the Endocrine Effects from Immune Checkpoint Inhibitors (JNCI-CS; prepub 2018)

**Biomarker TF**
- Guidelines for Incorporation of Biomarkers into Early-Phase Trials (CCR 2010)
  - Lead to Biomarker Assay Templates for CTEP CDP (IHC, DNA-based ISH, and Mutation Assays)
  - Gateway to Biomarker Review Committee (BRC)
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Cancer Cancer Res September 1 2017 33 (17) 4955-4960; DOI: 10.1158/0008-5472.CAN-17-3025

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Cancer Cancer Res September 1 2017 33 (17) 4961-4966; DOI: 10.1158/0008-5472.CAN-17-3076

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Valentina Ambrusato, Mark Yorkston, Aaron R. Hansen, Hao Wang, Francois Verde, Elad Sharon, Deborah Cibulsky, Laura O.M. Choe, and Patrick M. Forte

Cancer Cancer Res September 1 2017 33 (17) 4968-4989; DOI: 10.1158/0008-5472.CAN-16-3305

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Jenica M. Mehner, Ari M. Menyeras, Joanna M.T. Berthoupin, Deborah Cibulsky, Larry Ruben, and Lindsay H. Harris

Cancer Cancer Res September 1 2017 33 (17) 4970-4979; DOI: 10.1158/0008-5472.CAN-16-3303

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Cancer Cancer Res September 1 2017 33 (17) 4982-4991; DOI: 10.1158/0008-5472.CAN-16-3504

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**Immmuno-oncology Clinical Trial Design: Limitations, Challenges, and Opportunities**

Christina S. Ball, Eric H. Rubin, Patrick M. Forte, Jenica M. Mehner, Deborah Cibulsky, Marco O. Butler, Eric L. Doxan, and Laura O.M. Choe

Cancer Cancer Res September 1 2017 33 (17) 4993-5002; DOI: 10.1158/0008-5472.CAN-16-3306
FACTS: Factors Affecting Combination Trial Success

1The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD; 2National Cancer Institute; 3The Grove Corporation; 4Yale Berglund School of Public Health

ABSTRACT

Background: Experimental therapeutic oncology agents are often combinatory, in an effort to assure tumor resistance in individual agents, yield combination trials, or test for known or unknown effects. Combining agents requires sufficient safety and efficacy to advance to later phase trials. The FACTS study collected survey data on phase 1 clinical trials regarding the design and conduct of early phase combination trials to: 1) raise awareness of the best approaches and Investigational Drug Steering Committee (IDSC) Clinical Trial Design Task Force (CTD-TF) Guidelines; 2) describe study design characteristics that affect combinations achieving regulatory approval; and 3) describe combinations with successful clinical outcomes. The present analysis investigated approaches to the design of phase 1 combination studies, and identified gaps between current approaches and Investigational Drug Steering Committee (IDSC) Clinical Trial Design Task Force (CTD-TF) Guidelines recommendations.

Objectives: Identify boundaries of concordance between guidelines and practice; describe study design characteristics that affect combinations achieving regulatory approval; and describe combinations with successful clinical outcomes.

Methods: A 15-question survey collected data on phase 1 trial design, primary and secondary objectives, eligibility criteria, dose escalation strategies, study duration, and investigator's familiarity with CTD-TF Guidelines. Probability of achieving each milestone toward regulatory approval was estimated using the logistic model with a full interaction model. The study design of combinations achieving regulatory approval was compared to those that did not achieve regulatory approval using a logistic regression model. Monte Carlo simulation using a Bayesian network model was used to quantify the impact of key study characteristics on regulatory success.

Results: Probability of achieving each milestone toward regulatory approval was estimated using the logistic model with a full interaction model. The study design of combinations achieving regulatory approval was compared to those that did not achieve regulatory approval using a logistic regression model. Monte Carlo simulation using a Bayesian network model was used to quantify the impact of key study characteristics on regulatory success.

CONCLUSIONS

- Data provide evidence that observation of clinical promise of a combination in the phase 1 trial is associated with progress toward regulatory approval.
- Although concordance between study design of phase 1 trial of combination therapies and CTD-TF Guidelines was relatively high, a greater number of investigators used formal phase 1 trial designs for combination trials.
- Future support of outcome studies on clinical trial design and conduct may help improve the rate of regulatory success.

REFERENCES


ACKNOWLEDGMENTS

The authors acknowledge the support of the principal investigators of early phase combination phases who took the time to respond to the questions, and especially the members of the project review group who met at the 2013 CTEP spring meeting and provided project review for these data. The authors thank E. Huang, A. Gravell, H. Massett, C. Williams, J. Zhao, A. Ivy, R. Rosner, M. Carducci, L. Rubinstein, and S. Reeves for data collection and analysis. NCI/CTEP provided grant support under grant U01 CA186401. Support was also provided by NCI under U01CA69683.
IDSC New and Planned Activities

- **New in 2017:**
  - Integration of the IDSC into the CTEP drug development process at the CTEP Program meeting level and in the development of Project Team Member Application (PTMA) announcements in order to increase ETCTN-wide engagement in trials.
  - Updated LOI IDSC Arbitration process
  - Tasked Clinical Trials Design TF to review feasibility of alternative trial designs within ETCTN
- **New in 2018:** Addition of *ad hoc* experts to IDSC drug development plan review
- **2018/2019** – Continued scientific and clinical input into strategic directions for CTEP-funded phase I and II trials and in CTEP’s Drug Development process of new investigational drugs.
Additional Information
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ABSTRACT

Background: Experimental therapeutic oncology agents are often considered in a series to ascertain tumor resistance in individual agents, dual or combination trials. This necessitates careful planning to support sufficient safety and efficacy to advance to later phase. The FACTS study collected survey data on phase 1 design through questionnaires to assess success, limit errors, and clarify information and questions about the trial’s results and progress. The phase 1 studies were concordant with Clinical Trial Design Task Force (CTD-TF) recommendations.

Methods: 13-question survey collected data on phase 1 trial design, predefined expectations and criteria to assess success, biomarking, and statistical analysis. Conclusions and recommendations, and questions about the trial’s results and progress were answered in the survey. The FACTS study was commissioned by the Investigational Drug Steering Committee (IDSC) Clinical Trial Design Task Force of the NCI to design and conduct of early phase combination trials present.

RESULTS: Past phase 3 (34%) and past phase 1 (21%) were commonly selected as a past phase. The design and conduct of early phase combination trials present. Those that exhibit clinical promise have higher probabilities of achieving all milestones toward regulatory approval outcome. Figure 1 illustrates the achievement of milestones toward regulatory approval at time of data acquisition.

CONCLUSIONS: Future trials combining agents with overlapping dose-limiting toxicities should have overlapping dose-limiting toxicities. Those that do not. Those that exhibit clinical promise have higher probabilities of achieving all milestones toward regulatory approval outcome. For the above-mentioned factors, which are related to the overall analysis for the association with achievement of milestones toward regulatory approval was less than 0.1: No further study beyond phase 1 (e.g. unacceptable toxicity) and Regulatory approval achieved.

METHODS

Eligibility criteria

Primary Objective:
• Develop, implement and administer a survey to PI's of phase 1 clinical trials regarding combination trial design decisions and success, biomarker interactions, biomarker response, and regulatory approval. Consider whether the design of phase 1 combination clinical trials were concordant with CTD-TF recommendations.

Secondary Objectives:
• Develop a survey delivery platform for ongoing collection, distribution, analysis and discussion of clinical trial success.
• Develop a database of the results of the survey that can serve as the foundation for future projects to gather additional data and trial results and integrates that data with relevant external events and literature databases.

Study design:
1. Randomize 114 surveys completed (43%). Two independent coders validated 10% of the surveys (n = 11). Revisions were made to earlier versions of non-concordant surveys identified in red.

Mann-Whitney U Test statistic:
• Proportion of studies in which study design and CTD-TF recommendations were concordant was (95% CI: 72.2%, 87.1%); most trials. The guidelines (Fig. 1) suggest investigators select the most promising combination study design.

Statistical analysis:
• Maximum likelihood estimation was used to estimate the probabilities of achieving each milestone.

Table 2: Summary of achievement of all milestones

Table 3: Concordance of study design with CTD-TF recommendations

Table 2: Associations between achievement of all milestones and study characteristics

Table 3: Concordance of study design with CTD-TF recommendations

CONCLUSIONS

• Data provide evidence that observation of clinical milestone is related to the phase of trial is associated with progress toward regulatory approval.
• Although concurrence between study design of phase 1 trial of combination therapies and CTD-TF Guidelines was relatively high, a formal phase 1 design was used in 1168 of which a design was not achieved.
• Additional benefit may be gained by raising more awareness of the best study design to use when pharmacokinetic/pharmacodynamic interactions are expected.
• Future superior design of data on trial clinical trials may help to achieve the goals.

ACKNOWLEDGMENTS

The authors acknowledge the support of the principal investigators of early phase combination trial who took the time to re-look at the questionnaires, and especially the members of the project review group who met at the 2015 CTEP meeting to provide project review and consultation on the topic of the questionnaires.

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Facts: Factors Affecting Combination Trial Success

Nilo Azad, Lesley Seymour (CNCI), Lillian Siu (Princess Margaret), Geoffrey Shapiro (Dana Farber) 2015-09-28

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