Investigational Drug Steering Committee

IDSC Co-Chairs: *Michael Carducci*

Johns Hopkins University

Primo “Lucky” Lara

University of California at Davis

NIH NATIONAL CANCER INSTITUTE

July 10, 2018

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

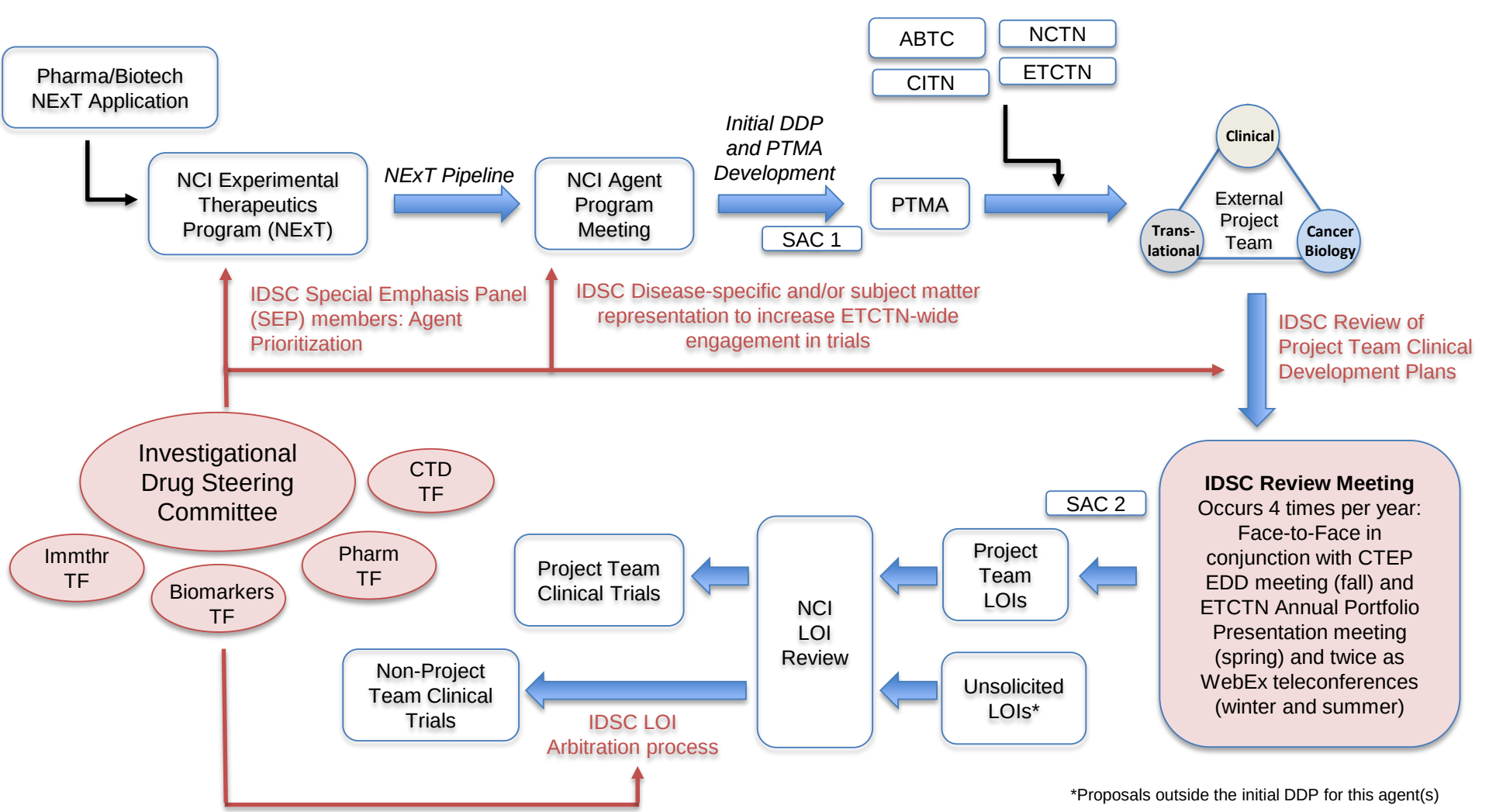
- 2 **Co-Chairs**
- 33 **Principal Investigators of CTEP's UM1 early drug development grants**
- 2 **Consortia Representatives**
  - CITN
  - ABTC
- 6 **Subject Matter Experts**
  - Radiation
  - Cell Signaling
  - Omics
  - Imaging
  - SxQOL
  - Pediatrics
- 2 **Biostatisticians**
- 2 **Patient Advocates**
- 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

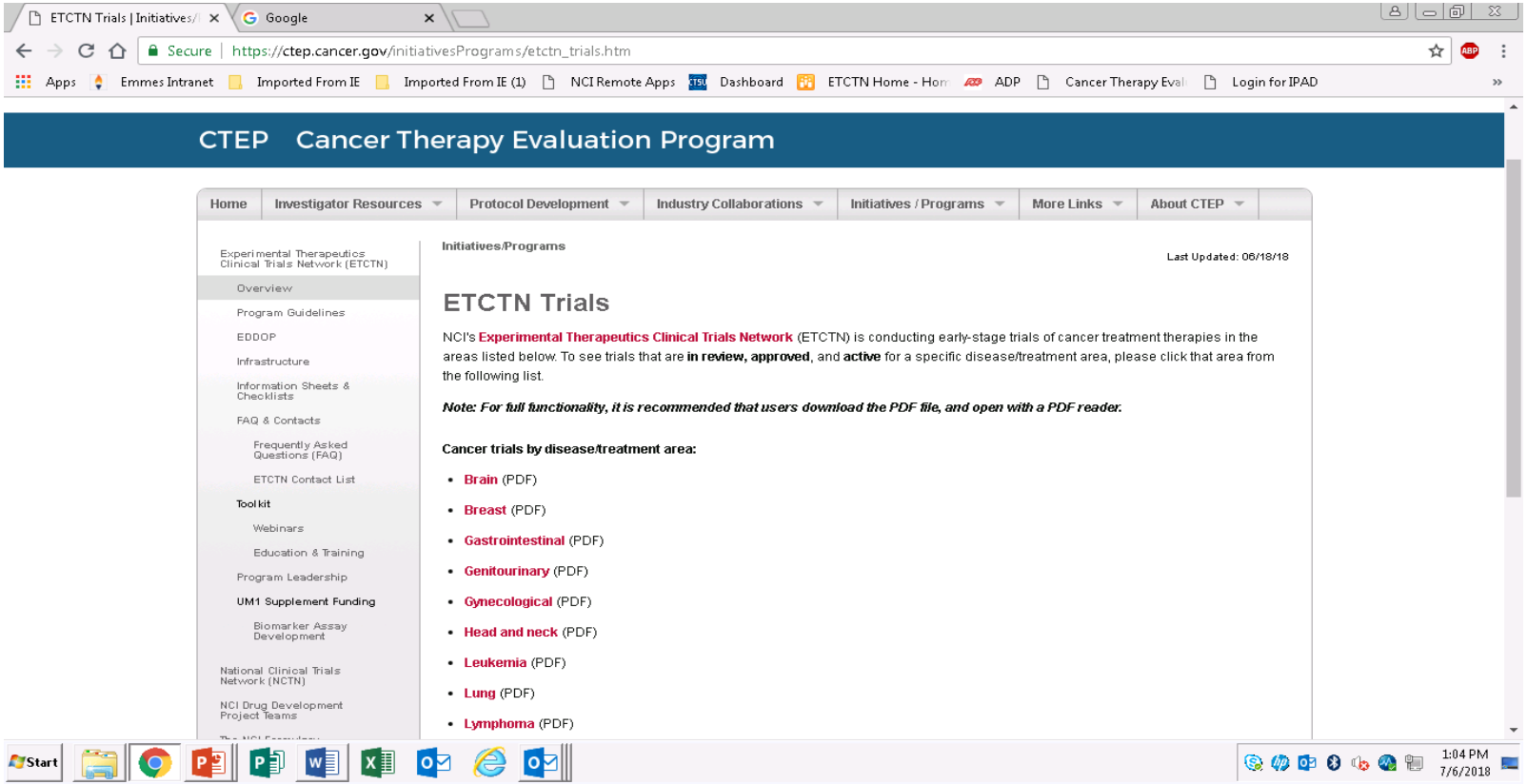
IDSC Involvement and CTEP Drug Development Process


Pharma/Biotech NExT Application
NCI Experimental Therapeutics Program (NExT)
NExT Pipeline
NCI Agent Program Meeting
Initial DDP and PTMA Development
SAC 1
PTMA
ABTC
CITN
NCTN
ETCTN
Clinical
External Project Team
Trans-lational
Cancer Biology
IDSC Special Emphasis Panel (SEP) members: Agent Prioritization
IDSC Disease-specific and/or subject matter representation to increase ETCTN-wide engagement in trials
IDSC Review of Project Team Clinical Development Plans
Investigational Drug Steering Committee
CTD TF
Immthr TF
Pharm TF
Biomarkers TF
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)
SAC 2
Project Team LOIs
Unsolicited LOIs*
NCI LOI Review
Project Team Clinical Trials
Non-Project Team Clinical Trials
IDSC LOI Arbitration process
*Proposals outside the initial DDP for this agent(s)

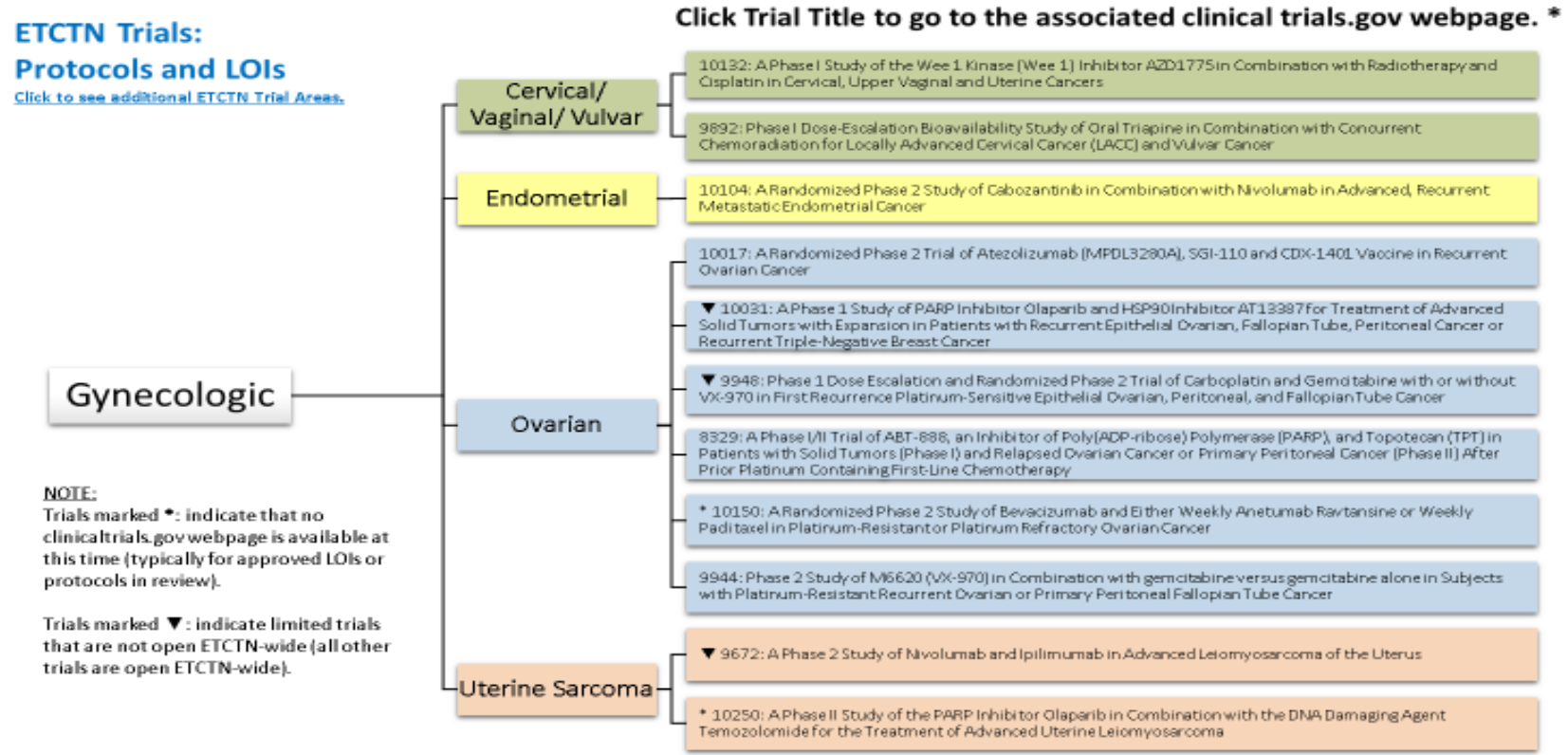
IDSC review of CTEP IND agents

- 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).
- LOI appeals process for unsolicited LOIs was recently instituted and 2 LOIs went through the process smoothly.

ETCTN Disease Diagram – Landing Page

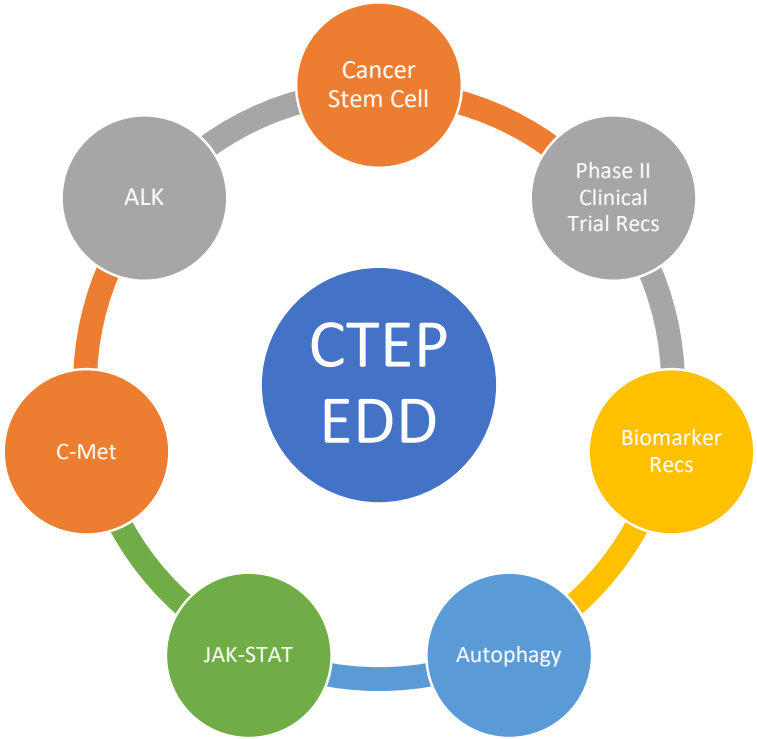


Example of an ETCTN Disease Diagram - Gynecologic



IDSC and CTEP Early Drug Development Sessions

IDSC and CTEP Early Drug Development (EDD) Sessions



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)

Clinical Cancer Research

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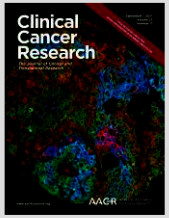
CCR Focus



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Genome-wide DNA Methylation Analysis Reveals *GABBR2* as a Novel Epigenetic Target for *EGFR* 19 Deletion Lung Adenocarcinoma with Induction Erlotinib Treatment

In Vivo Hemin Conditioning Targets the Vascular and Immunologic Compartments and Restrains Prostate Tumor Development

MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory $HR^+/HER2^-$ Metastatic Breast Cancer

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Personalized Medicine and Imaging
Cancer Therapy: Preclinical
Biology of Human Tumors
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FACTS: Factors Affecting Combination Trial Success

C. J. Paller[1], E. Huang[2], T. Luechtefeld[4], H. Massett[2], C. Williams[3], J. Zhao[3], A.E. Gravell[3], S. Reeves[2], G. Rosner[4], M. A. Carducci[1], L. Rubinstein[2], S. P. Ivy[2]

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD; [2]National Cancer Institute; [3]The Emmes Corporation; [4]Johns Hopkins Bloomberg School of Public Health

Time: Monday June 4, 8:00 AM to 11:30 AM. Location: Hall A. Abstract No: 2544. Poster Board Number: 370.

ABSTRACT

Background: Experimental therapeutic oncology agents are often combined in an effort to circumvent tumor resistance to individual agents; most combination trials, however, fail to demonstrate sufficient safety and efficacy to advance to a later phase. The FACTS study collected survey data on phase 1 combination therapies to: 1) assess rates of advancement and regulatory approval, 2) identify factors associated with these rates, and 3) assess the degree that phase 1 trials were concordant with Clinical Trial Design Task Force (CTD-TF) Guidelines.[1]

Methods: A 13-question survey collected data on phase 1 trial design, predefined expectations and criteria to assess success, biomarker information, and questions about the trials' results and progress. Online surveys (N = 289, July-Dec. 2017) were emailed to PIs of early-phase NCI and/or industry trials; 263 emails (91%) were received and 114 surveys completed (43%). Two independent coders validated 10% of survey responses (N = 12) against manuscript publications (intercoder reliability = 99%).

Results: Phase 1 results indicated further investigation was warranted for 39.8% of combinations (95% CI: 30.8%, 48.8%). 24.9% of combination trials (95% CI: 15.3%, 34.4%) progressed to phase 2 or further. 18.7% (95% CI: 5.90%, 31.4%) progressed to phase 3 or FDA approval. 12.4% (95% CI: 0.00%, 25.5%) achieved regulatory approval. Trial results where "clinical promise was observed" in phase 1 of the combination study were associated with higher rates of progression past each milestone toward regulatory approval (cumulative OR = 11.9; p = 0.0002). The phase 1 study designs were concordant with CTD-TF Guidelines for 79.6% of the combinations (95% CI: 72.2%, 87.1%); most discordances occurred where no plausible pharmacokinetic or pharmacodynamic interactions were expected.

Conclusion: "Clinical promise" of a combination is associated with progress toward regulatory approval. Although concordance between study designs of phase 1 trials of combination therapies and CTD-TF Guidelines was relatively high, raising more awareness of the best

BACKGROUND

- Experimental therapeutic agents are often combined in an effort to circumvent tumor resistance to individual agents, but trials of most combinations fail to demonstrate sufficient safety and efficacy to move to later phases of development.[2]
- The design and conduct of early phase combination trials present specific challenges such as optimum selection of agents to combine, an appropriate dose and schedule (including which agent to escalate) as well as drug-drug interactions and overlapping toxicities.
- The NCI Investigational Drug Steering Committee appointed a Clinical Trial Design Task Force to develop pragmatic clinical guidelines for the design of phase 1 combination clinical trials.[1]
- The guidelines (Fig. 1) suggest investigators select the most effective trial design by using a biologic or pharmacologic rationale to justify the combination, describing next steps and potential clinical results and taking into account overlapping dose limiting

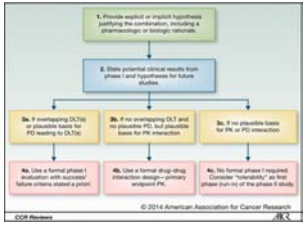


Figure 1: Consensus recommendations for the design of phase 1 combination clinical trials.

OBJECTIVES

Primary Objective

- Develop, implement and administer a survey to PIs of phase 1 clinical trials regarding combination trial design decisions and success (progression toward regulatory approval), determine how investigators approach the design of phase 1 combination studies, and identify gaps between current approaches and Investigational Drug Steering Committee (IDSC) Clinical Trial Design Task Force recommendations.

Secondary Objectives

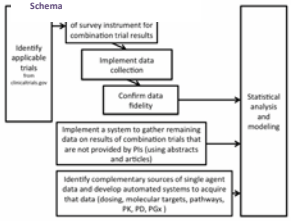
- Develop a survey delivery platform for ongoing collection, distribution, analysis and discussion of clinical trial results.
- Develop a database of the results of the survey that can serve as the foundation for future projects to gather preclinical data and trial results and integrate that data with relevant drug, adverse event and literature databases.

Outcomes

- Probability of a combination achieving each milestone toward regulatory approval.
- Percent of combinations for which the study design of the phase 1 trial and CTD-TF

METHODS

Schema



Eligibility criteria

- Phase 1, Phase 1b, or Phase 1/2 drug intervention trial.
- Trial evaluates combinations of two or more of the 450 pre-selected therapeutic agents.
- Are cancer clinical trials.

Study design

- Survey of 113 Combination Trials.
- Evaluates trial success in phase 1-3 and regulatory approval.
- 29 questions asked.
- Questions assess trial design:
  - overlapping DLTs
  - response biomarkers
  - dose schedule
  - clinical promise

Achievement of Milestones Toward Regulatory Approval at Time of Data Acquisition

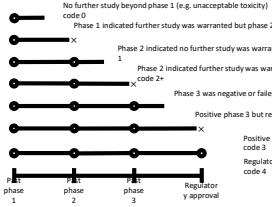


Figure 2: Illustration of the achievement of milestones toward regulatory approval outcome. X indicates failure at that phase, and O indicates successful advancement beyond that phase. An open line indicates that the highest milestone ultimately achieved is not known at time of data acquisition. Add the number of O's to obtain the numerical coding. Studies of some combinations may be in progress at time of data acquisition and the highest milestone ultimately achieved is not currently known. Outcomes of such combinations are indicated by a "+".

Statistical analysis

Probabilities of achieving milestones toward regulatory approval

- Maximum likelihood estimation was used to estimate the probabilities of achieving each milestone.
- Likelihood ratio tests were used to assess associations between individual study characteristics and probabilities of achieving each milestone.
- Benjamini-Hochberg procedure was used to adjust for multiple testing.

Concordance of study design with CTD-TF recommendations

- Proportion of studies in which study design and CTD-TF recommendations were concordant was estimated along with a 95% confidence interval.
- Mann-Whitney U test was used to assess concordance with the study PI's familiarity with CTD-TF guidelines.

RESULTS

Trial Selection

- Start with all 198,056 clinical trials from clinicaltrials.gov as of September 1, 2015.
- Select cancer trials with at least two of 450 preselected experimental therapeutic agents (3,974).
- Select phase 1 and phase 1/2 trials (745).
- Initiate project with 113 CTEP-sponsored trials to maximize response rate.

Table 1: Summary statistics of achievement of each milestone

Milestone	Probability estimate with 95% confidence intervals	Number of combinations in data known to have achieved this milestone
Past phase 1	39.8% (30.8%, 48.8%)	45
Past phase 2	24.9% (15.3%, 34.4%)	15
Past phase 3	18.7% (5.90%, 31.4%)	3
Regulatory approval	12.4% (0.00%, 25.5%)	2

Although most of the 113 combinations had achieved regulatory approval at the time of data acquisition, more combinations may also do so in the future. The probability estimates take this into account.

Table 2: Associations between achievement of each milestone and study characteristics

Milestone	Probability estimates for combinations that do not show clinical promise (71/113 or 62.8% of all combinations)	Probability estimates for combinations that show clinical promise (42/113 or 37.2% of all combinations)
Past phase 1	23.9%	66.7%
Past phase 2	16.0%	40.0%
Past phase 3	10.6%	40.0%
Regulatory approval	5.32%	40.0%

Probabilities of achieving each milestone for combinations that exhibit clinical promise in phase 1 and in those that do not. Those that exhibit clinical promise have higher probabilities of achieving all subsequent milestones (adjusted p-value of likelihood ratio test 0.0049).

Other characteristics for which the adjusted p-value for the association with achievement of milestones toward regulatory approval was less than 0.1:

- Observation of results other than establishment of safe or optimal doses and schedules,
- establishment of sequence of drug administration, or observation of any pharmacodynamic or pharmacokinetic interactions (associated with lower probabilities of achieving all subsequent milestones, adjusted p-value of likelihood ratio test 0.052)

Figure 3: Bayesian Network Describes Survey Relationships

A Bayesian network describing dependencies between survey answers was constructed. This network identified strong relationships (arrows) that satisfy intuitions about survey answers. For instance, trials where adverse events were expected and overlapping DLTs were expected also frequently test for interactions (upper right).

Surprisingly, 'Trial passed phase 1' is not strongly dependent on the queried trial results (in red). For instance, trials finding optimal dose (outcome 3) did not strongly increase odds of success (odds ratio = 1.8).

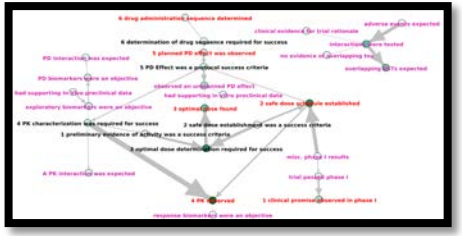


Figure 3: A Bayesian network was constructed using structural expectation maximization algorithm available in the BNLearn R package. The above Bayesian network identifies strong dependencies (dark nodes/large arrows) between question answers. Red labels identify phase 1 results. Black labels identify requirements for trial success. Pink labels are other (non-outcome or criteria) trial properties. Related criteria and outcomes share the same preceding number.

Table 3: Concordance of study design with CTD-TF recommendations (shown in Figure 1)

	Formal phase 1 evaluation with pre-determined success criteria	Drug-drug interaction design with PK primary endpoint	No formal phase 1
Overlapping DLTs or plausible PD leading to DLTs	90	3	0
No overlapping DLTs, no plausible PD, plausible PK	1	0	0
No plausible PK or PD interaction	19	0	0

Although concordance occurred in 79.6% (90/113) of the cases, formal phase 1 designs were used in 110/113 cases, including in all 20 cases in which the CTD-TF would not have recommended this design. This indicates an overwhelming number of investigators using formal phase 1 designs even when expected interactions indicate that it is not ideal (p-value of test of independence of expected interactions and design: 0.956).

Familiarity with CTD-TF guidelines	Design of phase 1 study not concordant with CTD-TF guidelines	Design of phase 1 study concordant with CTD-TF guidelines
Not familiar	9	27
Somewhat familiar	11	44
Very familiar	3	19

Mann-Whitney U Test statistic: 1168 (p = 0.304).

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 designs of phase 1 trials of combination therapies and CTD-TF Guidelines was relatively high, a formal phase 1 design was used in all 20 cases where such a design was not needed.
- Additional benefit may be gained by raising more awareness of the best study design to use when no plausible pharmacokinetic or pharmacodynamic interactions are expected.
- Future curation of structure data on clinical trials may help to

REFERENCES

1. Paller CJ, Bradbury PA, Ivy SP, et al: Design of Phase I Combination Trials: Recommendations of the Clinical Trial Design Task Force of the NCI Investigational Drug Steering Committee. Clin Cancer Res 20:4210-4217, 2014.
2. Yap TA, Omlin A, de Bono JS Development of therapeutic combinations targeting major cancer signaling pathways. J Clin Oncol

ACKNOWLEDGEMENTS

The authors acknowledge the support of the principal investigators of early phase combination trials who took the time to respond to the questionnaire, and especially the members of the project review group who met at the 2015 CTEP meeting to provide project review and feedback on the design of the questions:

- Pat LoRusso (Yale)
- Geoffrey Shapiro (Dana Farber)
- Lillian Siu (Princess Margaret)
- Lesley Seymour (CNCI)
- Nilo Azad
- Roisin Connolly
- Other Johns Hopkins faculty members who participated in subsequent testing of the data collection instrument.

NCI/NIH/CTEP provided grant support under grant 5UM1CA186691. Support was also provided by NCI under grant P30CA006973.

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

IDSC UM1 Principal Investigators/ ETCTN sites

ETCTN Lead UM1	UM1 PI	LAO and Associated Clinical Sites
DFCI	Donald Kufe	Dana-Farber Cancer Institute
	Geoffrey Shapiro	Dana-Farber Cancer Institute
	Keith Flaherty	Massachusetts General Hospital
MD Anderson	Funda Meric-Bernstam	MD Anderson Cancer Center
	James Yao	MD Anderson Cancer Center
	S. Gail Eckhardt	University of Texas Austin
	Wells Messersmith	University of Colorado Cancer Center
CCC	Edward Newman	City of Hope Comprehensive Cancer Center
	Primo Lara	UC Davis Comprehensive Cancer Center
	Heinz-Josef Lenz	USC Norris Comprehensive Cancer Center
OSU	Michael Grever	OSU Comprehensive Cancer Center
	William Carson	OSU Comprehensive Cancer Center
	Jennifer Eads	Case Western Reserve University
	Robert DiPaola (Susan Arnold)	University of Kentucky College of Medicine
Mayo	Alex Adjei	Mayo Clinic Cancer Center
	Brian Costello	Mayo Clinic Cancer Center
Pittsburgh	Edward Chu	University of Pittsburgh Cancer Institute
	Jan Beumer	University of Pittsburgh Cancer Institute
JHU	Michael Carducci	Sidney Kimmel Comprehensive Cancer Center - JHU
	Ivana Gojo	Sidney Kimmel Comprehensive Cancer Center - JHU
	Chris Gocke	Sidney Kimmel Comprehensive Cancer Center - JHU
	Michelle Rudek	Sidney Kimmel Comprehensive Cancer Center - JHU
	Noah Hahn	Sidney Kimmel Comprehensive Cancer Center - JHU
Duke	James Abbruzzese	Duke Cancer Institute
	Elizabeth Claire Dees	UNC Lineberger Comprehensive Cancer Center
	Andrea Wang-Gillam	Washington University
Yale	Pat LoRusso	Yale Cancer Center
	Jordan Berlin	Vanderbilt-Ingram Cancer Center
Rutgers	Janice Mehnert	Rutgers-CINJ
	Glenn Liu	University of Wisconsin - Madison
PMH	Lillian Siu	Princess Margaret Hospital - UHN
	Amit Oza	Princess Margaret Hospital - UHN
	Dan Sullivan	H. Lee Moffitt Cancer Center

IDSC NCTN and Subject Matter Experts

Name	Position	Institution
Carol Aghajanian	**NRG** Representative	Memorial Sloan-Kettering Cancer Center
Chandra Belani	**ECOG-ACRIN** Representative	Pennsylvania State University
Gary K. Schwartz	**Alliance** Representative	Columbia University
David Gandara	**SWOG** Representative	University of California, Davis
Lesley Seymour	**CCTG** Representative	Queen's University
Mac Cheever	**CITN** Representative	Fred Hutchinson Cancer Research Center
Patrick Wen	**ABTC** Representative	Dana-Farber Cancer Institute
Wayne Bernstein	**Patient Advocate**	
Mary Scroggins	**Patient Advocate**	Pinkie Hugs, LLC; In My Sister's Care
Adam Dicker	**Radiation** Subject Matter Expert	Thomas Jefferson University
Steven Grant	**Cell Signaling** Subject Matter Expert	Virginia Commonwealth University
Jeffrey Sklar	**Omics** Subject Matter Expert	Yale University
Steven Larson	**Imaging** Subject Matter Expert	Memorial Sloan-Kettering Cancer Center
Charles Shapiro	**SxQOL** Subject Matter Expert	MSSN
John Perentesis	**Pediatric** Subject Matter Expert	Cincinnati Children's Hospital
Gary Rosner	**Statistical** Subject Matter Expert	Johns Hopkins
Elizabeth Garrett-Mayer	**Statistical** Subject Matter Expert	ASCO CENTRA
Gregory Reaman	**FDA** Representative	FDA

FACTS: Factors Affecting Combination Trial Success

C. J. Paller[1], E. Huang[2], T. Luechtefeld[4], H. Massett[2], C. Williams[3], J. Zhao[3], A.E. Gravell[3], S. Reeves[2], G. Rosner[4], M. A. Carducci[1], L. Rubinstein[2], S. P. Ivy[2]

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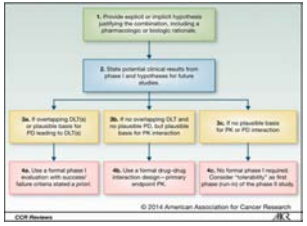

Figure 1: Consensus recommendations for the design of phase 1 combination clinical trials.

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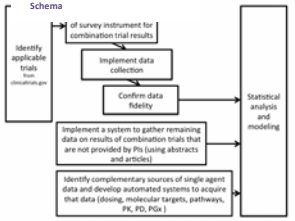

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  - clinical promise

Achievement of Milestones Toward Regulatory Approval at Time of Data Acquisition

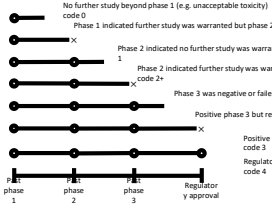

Figure 2: Illustration of the achievement of milestones toward regulatory approval outcome. X indicates failure at that phase, and O indicates successful advancement beyond that phase. An open line indicates that the highest milestone ultimately achieved is not known at time of data acquisition. Add the number of O's to obtain the numerical coding. Studies of some combinations may be in progress at time of data acquisition and the highest milestone ultimately achieved is not currently known. Outcomes of such combinations are indicated by a "+".

Statistical analysis

Probabilities of achieving milestones toward regulatory approval

- Maximum likelihood estimation was used to estimate the probabilities of achieving each milestone.
- Likelihood ratio tests were used to assess associations between individual study characteristics and probabilities of achieving each milestone.
- Benjamini-Hochberg procedure was used to adjust for multiple testing.

Concordance of study design with CTD-TF recommendations

- Proportion of studies in which study design and CTD-TF recommendations were concordant was estimated along with a 95% confidence interval.
- Mann-Whitney U test was used to assess concordance with the study PI's familiarity with CTD-TF guidelines.

RESULTS

Trial Selection

- Start with all 198,056 clinical trials from clinicaltrials.gov as of September 1, 2015.
- Select cancer trials with at least two of 450 preselected experimental therapeutic agents (3,974).
- Select phase 1 and phase 1/2 trials (745).
- Initiate project with 113 CTEP-sponsored trials to maximize response rate.

Table 1: Summary statistics of achievement of each milestone

Milestone	Probability estimate with 95% confidence intervals	Number of combinations in data known to have achieved this milestone
Past phase 1	39.8% (30.8%, 48.8%)	45
Past phase 2	24.9% (15.3%, 34.4%)	15
Past phase 3	18.7% (5.90%, 31.4%)	3
Regulatory approval	12.4% (0.00%, 25.5%)	2

Although most of the 113 combinations had achieved regulatory approval at the time of data acquisition, more combinations may also do so in the future. The probability estimates take this into account.

Table 2: Associations between achievement of each milestone and study characteristics

Milestone	Probability estimates for combinations that do not show clinical promise (71/113 or 62.8% of all combinations)	Probability estimates for combinations that show clinical promise (42/113 or 37.2% of all combinations)
Past phase 1	23.9%	66.7%
Past phase 2	16.0%	40.0%
Past phase 3	10.6%	40.0%
Regulatory approval	5.32%	40.0%

Probabilities of achieving each milestone for combinations that exhibit clinical promise in phase 1 and in those that do not. Those that exhibit clinical promise have higher probabilities of achieving all subsequent milestones (adjusted p-value of likelihood ratio test 0.0049).

Other characteristics for which the adjusted p-value for the association with achievement of milestones toward regulatory approval was less than 0.1:

- Observation of results other than establishment of safe or optimal doses and schedules,
- establishment of sequence of drug administration, or observation of any pharmacodynamic or pharmacokinetic interactions (associated with lower probabilities of achieving all subsequent milestones, adjusted p-value of likelihood ratio test 0.052)

Figure 3: Bayesian Network Describes Survey Relationships

A Bayesian network describing dependencies between survey answers was constructed. This network identified strong relationships (arrows) that satisfy intuitions about survey answers. For instance, trials where adverse events were expected and overlapping DLTs were expected also frequently test for interactions (upper right).

Surprisingly, 'Trial passed phase 1' is not strongly dependent on the queried trial results (in red). For instance, trials finding optimal dose (outcome 3) did not strongly increase odds of success (odds ratio = 1.8).

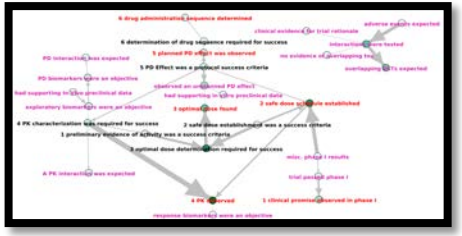

Figure 3: A Bayesian network was constructed using structural expectation maximization algorithm available in the BNLearn R package. The above Bayesian network identifies strong dependencies (dark nodes/large arrows) between question answers. Red labels identify phase 1 results. Black labels identify requirements for trial success. Pink labels are other (non-outcome or criteria) trial properties. Related criteria and outcomes share the same preceding number.

Table 3: Concordance of study design with CTD-TF recommendations (shown in Figure 1)

	Formal phase 1 evaluation with pre-determined success criteria	Drug-drug interaction design with PK primary endpoint	No formal phase 1
Overlapping DLTs or plausible PD leading to DLTs	90	3	0
No overlapping DLTs, no plausible PD, plausible PK	1	0	0
No plausible PK or PD interaction	19	0	0

Although concordance occurred in 79.6% (90/113) of the cases, formal phase 1 designs were used in 110/113 cases, including in all 20 cases in which the CTD-TF would not have recommended this design. This indicates an overwhelming number of investigators using formal phase 1 designs even when expected interactions indicate that it is not ideal (p-value of test of independence of expected interactions and design: 0.956).

Familiarity with CTD-TF guidelines	Design of phase 1 study not concordant with CTD-TF guidelines	Design of phase 1 study concordant with CTD-TF guidelines
Not familiar	9	27
Somewhat familiar	11	44
Very familiar	3	19

Mann-Whitney U Test statistic: 1168 (p = 0.304).

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 designs of phase 1 trials of combination therapies and CTD-TF Guidelines was relatively high, a formal phase 1 design was used in all 20 cases where such a design was not needed.
- Additional benefit may be gained by raising more awareness of the best study design to use when no plausible pharmacokinetic or pharmacodynamic interactions are expected.
- Future curation of structure data on clinical trials may help to

REFERENCES

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2. Yap TA, Omlin A, de Bono JS Development of therapeutic combinations targeting major cancer signaling pathways. J Clin Oncol

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