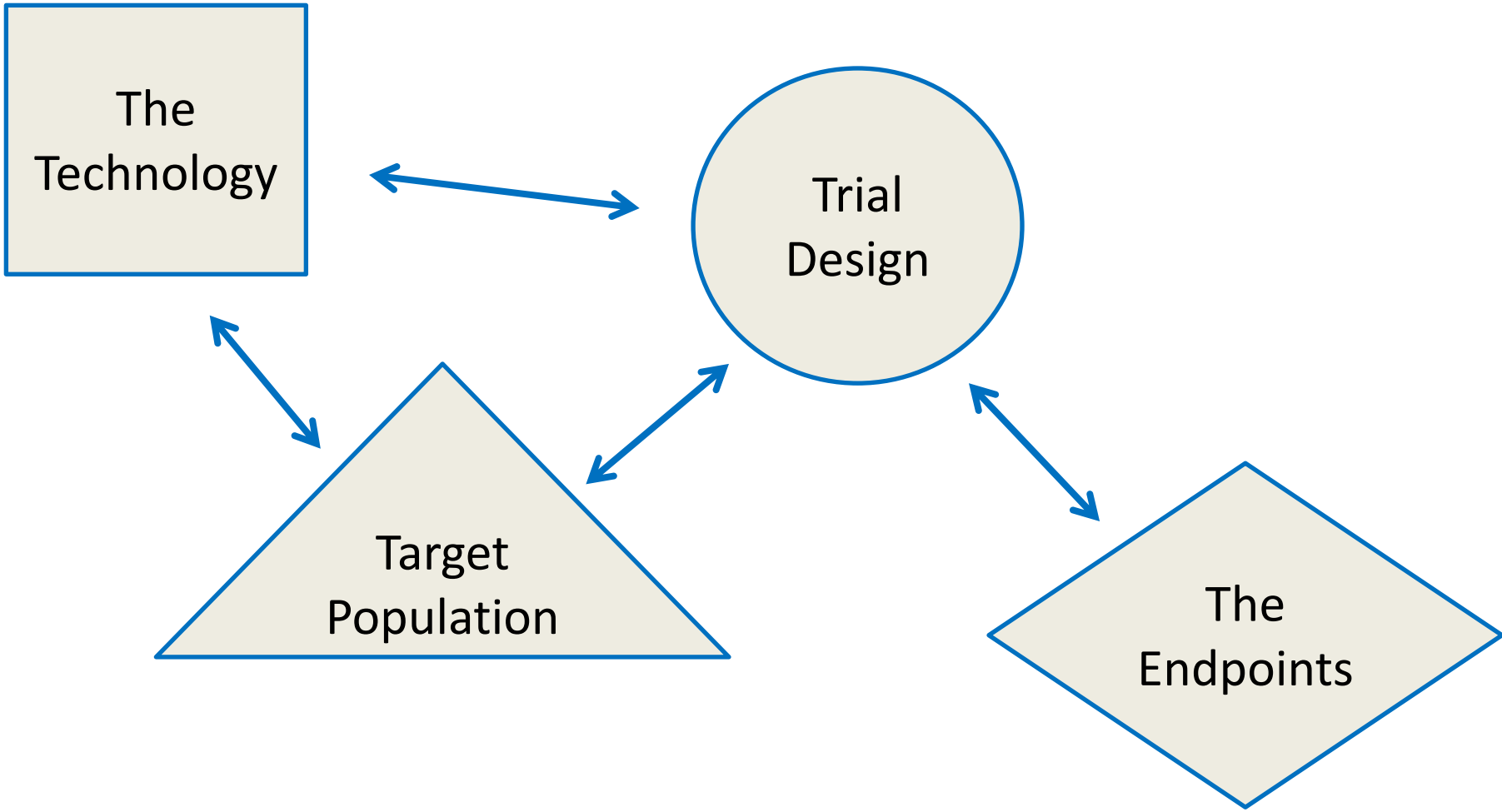
# Clinical Trial Design

COL (ret) George E Peoples, MD, FACS

# Clinical Trial Design

- Basic Elements of clinical trial design
- The interplay between these Elements
- Innovations in clinical trial design
- Special consideration for Immuno-oncology trials
- Discussion

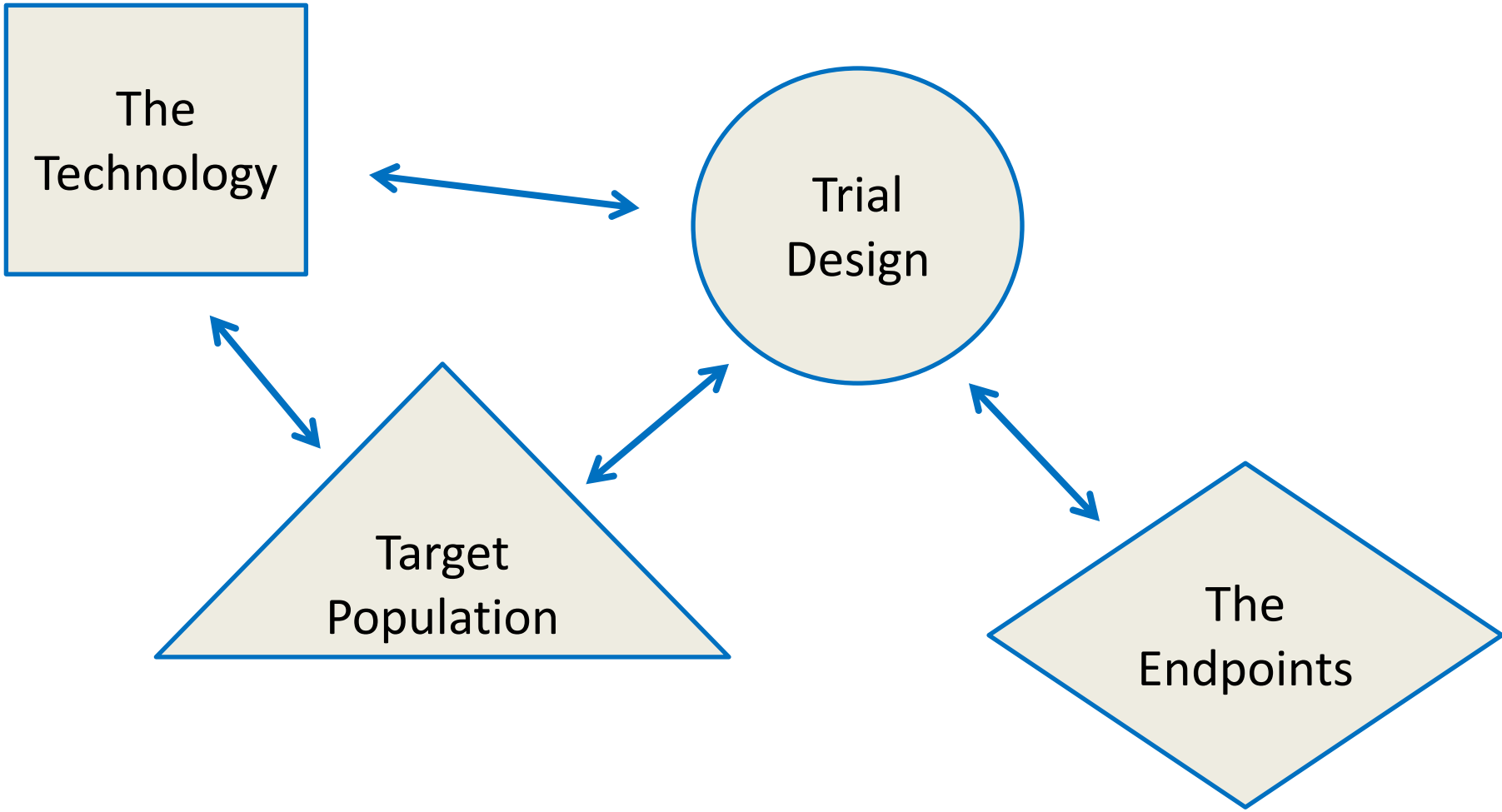
# The Trial Design Process



# The Technology

- What's known about it?
- The basics:
  - First in human?
  - Mechanism of action
  - Dosing and delivery
  - Expected toxicity
  - Expected outcome
- The answers will largely dictate the basic design
- Then the specifics

# The Trial Design Process



# Trial Design

- Matched to the technology
  - Based on MoA
  - Stage of development
- Type of trial
  - Safety
  - Efficacy
- The target population
- The endpoints

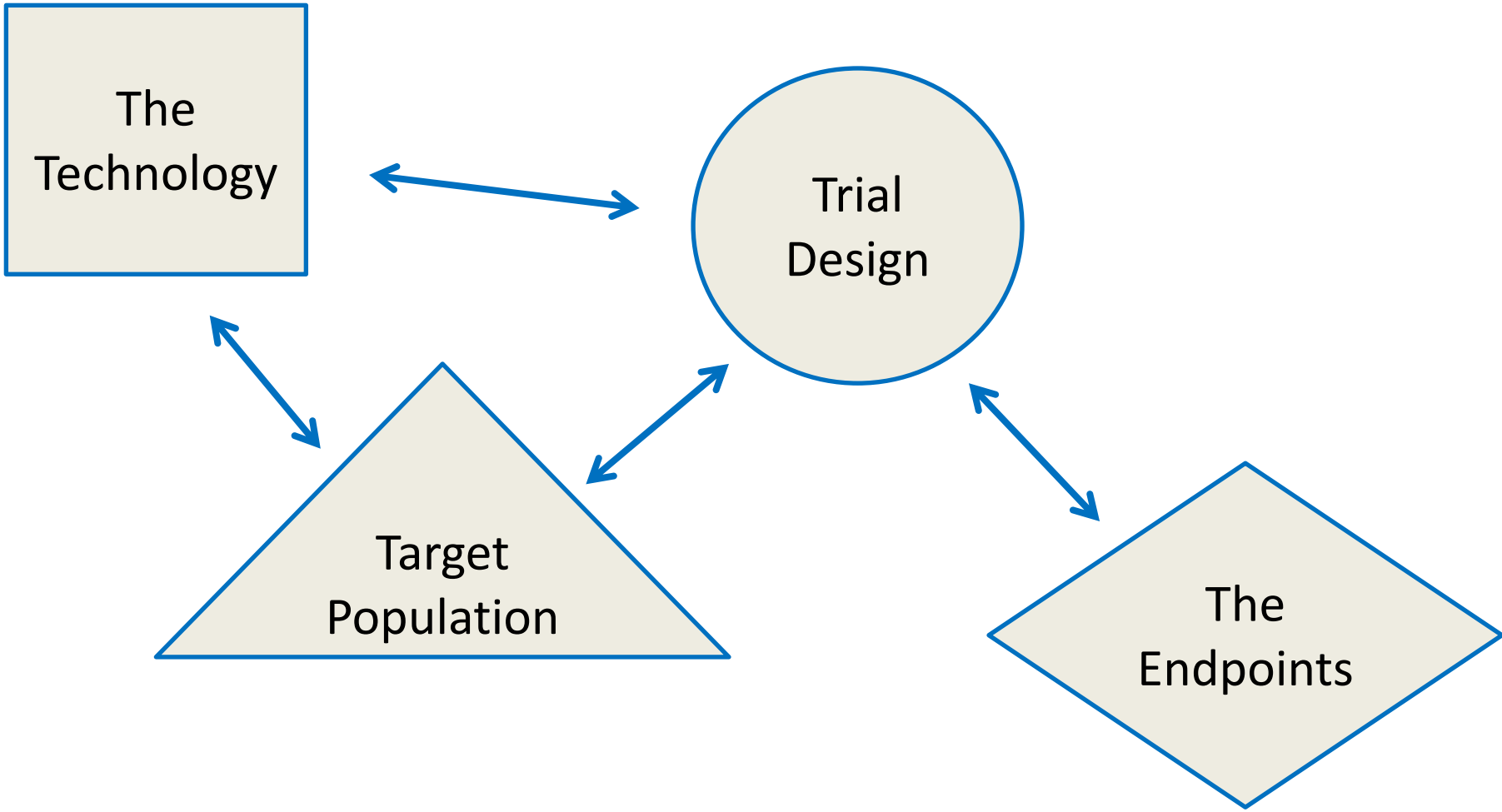
# The Target Population

- Which patients?
  - What tumor type, if any?
  - What stage?
  - Any specific biologic subset?
- Matched to the technology
  - Based on MoA
  - Stage of development
- Matched to the trial design
  - Safety
  - Efficacy
- Strategic vs tactical

# The Endpoints

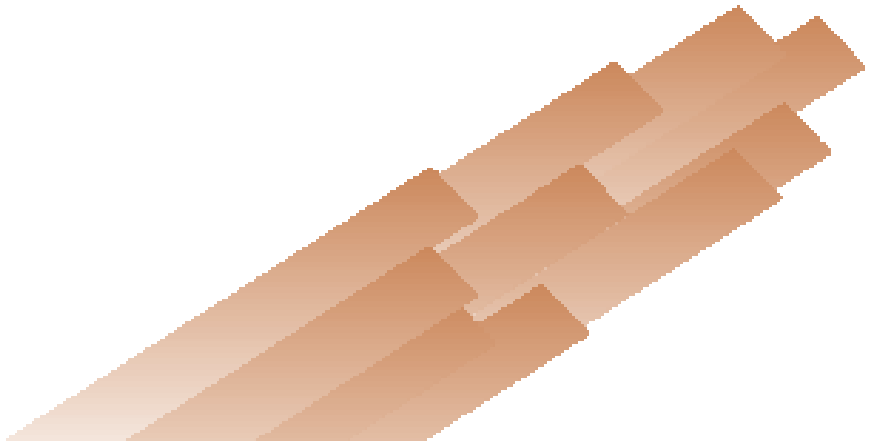
- Matched to the trial design
  - Safety (dosing and PK/PD)
  - Efficacy
- Matched to target patient population
  - Measureable disease
  - NED
- Approval Endpoints
  - Regular (OS)
  - Conditional
    - PFS vs DFS
    - ORR and DOR
    - RECIST 1.1 and/or iRECIST

# The Trial Design Process



# Guidance for Industry

## E6 Good Clinical Practice: Consolidated Guidance



ICH
April 1996

# Special Consideration

- Immuno-oncology products
- Accelerated safety designs
- Adaptive designs
- Accelerated approval endpoints
- More than one active agent
- Unmet need/Orphan

# Guidance for Industry

## Clinical Considerations for Therapeutic Cancer Vaccines

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2011

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# Accelerated Titration Designs for Phase I Clinical Trials in Oncology

*Richard Simon, Boris Freidlin, Larry Rubinstein, Susan G. Arbuck, Jerry Collins, Michaele C. Christian**

*Background:* Many cancer patients in phase I clinical trials are treated at doses of chemotherapeutic agents that are below the biologically active level, thus reducing their chances for therapeutic benefit. Current phase I trials often take a long time to complete and provide little information about interpatient variability or cumulative toxicity. *Purpose:* Our objective was to develop alternative designs for phase I trials so that fewer patients are treated at subtherapeutic dose levels, trials are of reduced duration, and important information (i.e., cumulative toxicity and maximum tolerated dose) needed to plan phase II trials is obtained. *Methods:* We fit a stochastic model to data from 20 phase I trials involving the study of nine different drugs. We then simulated new data from the model with the parameters estimated from the actual trials and evaluated the performance of alternative phase I designs on this simulated data. Four designs were evaluated. Design 1 was a conventional design (similar to the commonly used modified Fibonacci

tients required for a phase I trial was reduced from 39.9 for design 1 to 24.4, 20.7, and 21.2 for designs 2, 3, and 4, respectively. The average number of patients who would be expected to have grade 0-1 toxicity as their worst toxicity over three cycles of treatment is 23.3 for design 1, but only 7.9, 3.9, and 4.8 for designs 2, 3, and 4, respectively. The average number of patients with grade 3 toxicity as their worst toxicity increases from 5.5 for design 1 to 6.2, 6.8, and 6.2 for designs 2, 3, and 4, respectively. The average number of patients with grade 4 toxicity as their worst toxicity increases from 1.9 for design 1 to 3.0, 4.3, and 3.2 for designs 2, 3, and 4, respectively. *Conclusion:* Accelerated titration (i.e., rapid intrapatient drug dose escalation) designs appear to effectively reduce the number of patients who are undertreated, speed the completion of phase I trials, and provide a substantial increase in the information obtained. [J Natl Cancer Inst 1997;89:1138-47]

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Review Article

# Adaptive clinical trial designs in oncology

Yong Zang, J. Jack Lee

Department of Biostatistics, the University of Texas MD Anderson Cancer Center, Houston, TX, USA

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**Abstract:** Adaptive designs have become popular in clinical trial and drug development. Unlike traditional trial designs, adaptive designs use accumulating data to modify the ongoing trial without undermining the integrity and validity of the trial. As a result, adaptive designs provide a flexible and effective way to conduct clinical trials. The designs have potential advantages of improving the study power, reducing sample size and total cost, treating more patients with more effective treatments, identifying efficacious drugs for specific subgroups of patients based on their biomarker profiles, and shortening the time for drug development. In this article, we review adaptive designs commonly used in clinical trials and investigate several aspects of the designs, including the dose-finding scheme, interim analysis, adaptive randomization, biomarker-guided randomization, and seamless designs. For illustration, we provide examples of real trials conducted with adaptive designs. We also discuss practical issues from the perspective of using adaptive designs in oncology trials.

**Keywords:** Adaptive design; adaptive randomization; interim analysis; seamless design; biomarker-guided design

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# Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics

## Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2015
Clinical/Medical

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# Guidance for Industry

## Codevelopment of Two or More New Investigational Drugs for Use in Combination

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**June 2013**
**Clinical Medical**

Ott et al. Journal for ImmunoTherapy of Cancer (2017) 5:16
DOI 10.1186/s40425-017-0218-5

Journal for ImmunoTherapy of Cancer

REVIEW Open Access

# Combination immunotherapy: a road map

Patrick A. Ott[1*], F. Stephen Hodi[1], Howard L. Kaufman[2], Jon M. Wigginton[3] and Jedd D. Wolchok[4]

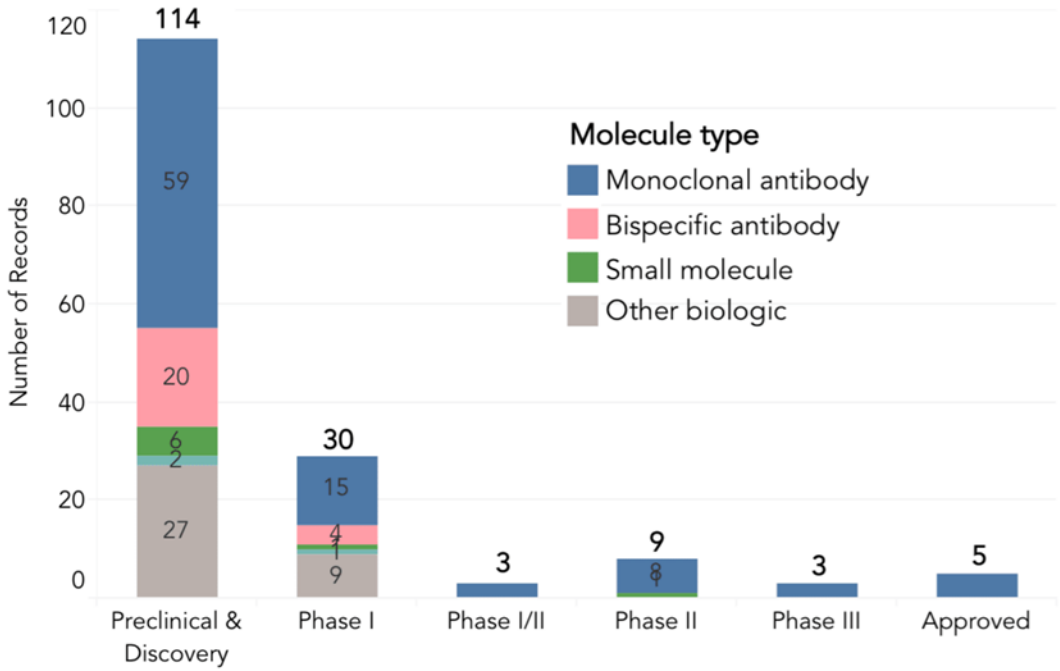
**Abstract**

Cancer immunotherapy and in particular monoclonal antibodies blocking the inhibitory programed cell death 1 pathway (PD-1/PD-L1) have made a significant impact on the treatment of cancer patients in recent years. However, despite the remarkable clinical efficacy of these agents in a number of malignancies, it has become clear that they are not sufficiently active for many patients. Initial evidence, for example with combined inhibition of PD-1 and CTLA-4 in melanoma and non-small cell lung cancer (NSCLC), has highlighted the potential to further enhance the clinical benefits of monotherapies by combining agents with synergistic mechanisms of action. In order to address the current progress and consider challenges associated with these novel approaches, the Society for Immunotherapy of Cancer (SITC) convened a Combination Immunotherapy Task Force. This Task Force was charged with identifying and prioritizing the most promising prospects for combinatorial approaches as well as addressing the challenges associated with developing these strategies. As a result of the extensive clinical benefit and tolerable side effects demonstrated with agents inhibiting the PD-1 pathway, an overview of current evidence to support its promising potential for use as a backbone in combination strategies is presented. In addition, key issues in the development of these strategies including preclinical modeling, patient safety and toxicity considerations, clinical trial design, and endpoints are also discussed. Overall, the goal of this manuscript is to provide a summary of the current status and potential challenges associated with the development and clinical implementation of these strategies.

**Keywords:** Immunotherapy, Combination, Checkpoint inhibitors, Preclinical models, Clinical trial, Endpoints

# Presented at SITC 2017

## 164 PD-1/L1-TARGETED AGENTS, 50 IN CLINICAL DEVELOPMENT




### Studies

- **164 Agents (clinical+ preclinical)**
- **PD-1/L1: Clinical Trials: 1,502**
- **PD-1/L1 Combos: 1,105**
- **50 in clinical phase**
- **34 MoAb Clinical Development**

Tang, Shalabi, Lucey (submitted)


Email: ClinicalAcceleratorIO@cancerresearch.org

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# Clinical Trial Design Summary

- Basic Elements of clinical trial design
- The interplay between these Elements
- Special consideration in trial design
  - FDA guidance(s)
  - I-O products
  - Combination trials
- Discussion