Phase I trial design considerations and CTEP clinical trial resources

Jeff Moscow, M.D.

Chief, Investigational Drug Branch, CTEP, DCTD, NCI

Phase 1 studies

Why are studies categorized into phases?

- Phase of study refer to the primary objective of the study
  - Phase 1: To determine the RP2D – the highest dose of a drug or drug combination to move forward to efficacy studies
  - Phase 2: To determine if the drug or drug combination delivered at the RP2D has activity against the targeted disease
  - Phase 3: To determine if the drug or drug combination is better than current conventional therapy

These are traditional concepts and many studies have combinations of these objectives built into their designs

What is a phase 1 study?

- The primary objective of a phase 1 study is to **define a safe and tolerable dose** to use in further studies designed to determine efficacy, ie the **Recommended Phase 2 Dose (RP2D)**
- A phase 1 study can be of a new single agent or agents in a new combination
- **Combination** phase 1 studies are generally conducted when the agents in a combination are predicted to have more toxicity when combined than when given alone
  - Overlapping toxicities
  - Drug:Drug interactions

Objectives of a phase 1 study

- **Primary:** Determination of the RP2D
- **Secondary:**
  - Pharmacokinetics (PK)- often the first opportunity to observe PK in humans, or to determine if there are significant DDI
  - Pharmacodynamics (PD)- often the first opportunity to develop an assay to determine whether a drug or drug combination has the anticipated on-target biological effect
- Incorporation of PK and PD objectives into phase 1 studies is extremely important in that it provides other data that can be used to determine the dose in future studies
  - Does the agent hit the intended target?
  - Is the purported mechanism of action correct?
  - Do agents interact with each other

Components of a phase 1 study

- A strong rationale **and** strong preclinical evidence supporting the commitment of study the agent or agent combination in cancer patients **and** a path to phase 2
- **Dose escalation scheme** – justification of starting dose(s) and definition of all dose levels to be explored
- Definition of **dose limiting toxicities (DLTs)** –toxicities that make the drug(s) intolerable or unsafe
- **Dose escalation statistical plan** – how many patients observed at each dose level for DLTs and when a dose can be escalated
- Definition of the **DLT observation period** – since dose escalation depends on the occurrence of toxicities, the observation window must defined so decisions can be made about increasing the dose
- **Eligibility** – inclusion and exclusion criteria
- **Expansion cohorts** to extend initial observations of tolerability and safety, and also for correlative objectives

The primary phase 1 objective: RP2D

- RP2D is the dose that does not exceed the DLT limit established by the dose escalation plan
  - Often it is exceeded during the course of a phase 1 study
- The dose escalation scheme is guided by the **DLTs that occur during the observation period**, but the safety and tolerability determinations also depend on whether subsequent dose reductions are required
- The **dose escalation scheme** that determines the RP2D, such as 3+3 or BOIN, have underlying assumptions about an **acceptable toxicity (DLT) rate**, and the designs can vary based on how much toxicity is considered to be acceptable
- **The R2PD is not necessarily the dose** that will be used in all subsequent studies – it is only the initial dose for the next studies determined by a small number of patients

Considerations for phase 1 studies

- Is the RP2D a tolerable dose?
  - The DLT observation window is usually brief, and does not take into account long term toxicities and subsequent dose reductions
- How long should the DLT observation window be?
  - Too short – miss toxicities that impact tolerability
  - Too long – too much time required before making dose escalation decisions
- Statistical plans make dose escalation decisions based on toxicity
  - How much toxicity should be allowed?

Expansion cohorts in a phase 1 study

- Expansion cohorts add additional patients treated at the RP2D
- CTEP does **not** support incorporating efficacy objectives for expansion cohorts in phase 1 studies
- CTEP **does** support other phase 1b objectives: PK, PD, additional safety observation
- Efficacy objectives are properly the subject of appropriately powered and designed phase 2 studies
- *Including small underpowered cohorts for preliminary efficacy objectives in phase 1 studies usually leads to results that are inconclusive and delay initiation of more definitive phase 2 studies*
- Every phase 1 study should be undertaken with the intention of subsequently conducting an appropriately powered and designed phase 2 study

CTEP clinical trial resources

What is CTEP? The CTEP-IND program? The ETCTN?

- NCI's Cancer Therapy Evaluation Program (**CTEP**) is in the NCI Division of Cancer Treatment and Diagnosis
  - **CTEP administers all NCI extramural clinical research networks**, including the adult and pediatric cooperative groups (NCTN)
- The **CTEP IND** program allows CTEP to **act as sponsor of clinical trials** within its funded networks
  - **Creates 3-way partnerships** between pharma, academic investigators and NCI where pharma provides agents for trials and CTEP provides regulatory support and safety oversight
  - Research agreements (CRADAs) between CTEP and pharma partners define relationship
  - **All** and **only** CTEP-funded networks can run trials with CTEP-IND agents
- The Experimental Therapeutics Clinical Trials Network (**ETCTN**) is one of the CTEP networks, and the only network **devoted only to the development of CTEP IND agents**

NCI/CTEP IND program– a highly successful platform for public-private partnerships

- Over **134** collaborative agreements (CRADAs, CTAs, Agent-CRADAs and Material-CRADAs) with pharmaceutical companies
- **199** Investigational New Drug Applications (INDs) for trials including **150** agents.
- Over **300** actively accruing cancer clinical trials as of May 19, 2021
- Approximately **80** treatment trials were opened/year between 2018 and 2020 many of which included combinations that involve more than one CTEP IND agent
- Approximately **18,000** registered investigators at approximately **2,000** institutions in the US and internationally

Why do pharmaceutical companies apply to NExT for NCI-sponsored development of their agents?

- CTEP has **access to novel agents from competitors-** can act as an honest broker for drug combination studies – with an agreements platform that is transparent to all
- Companies realize that there are potential therapeutic indications that do not have high enough priority to compete for limited corporate resources
- CTEP can expend public funds for clinical trials and regulatory support to advance the development of agents owned by Pharma
- CTEP supports several large **networks of experienced clinical trialists** and centralized clinical trial support systems
- CTEP will **invest in correlative science** studies to explore the pharmacodynamics of agents in clinical studies, especially in early phase studies in the ETCTN

Why does NCI help pharmaceutical companies develop their agents?

- NCI recognizes that there is a **significant public interest** in finding indications for new oncology drugs beyond those that may be the most profitable.
- NCI can **advance the understanding of cancer biology and treatment** through carefully designed clinical trials and **through correlative studies** that are extensively incorporated into ETCTN trials

NExT –entry portal for drugs into the NCI/IND program

- Most agents eligible for NCI/CTEP IND development are selected through NExT: next.cancer.gov
- Administered by the Development Therapeutics Program (DTP) in DCTD, not by CTEP, even though agents selected in the program can be assigned to CTEP/IDB for clinical development
- DTP manages peer review (Special Emphasis Panel; SEP) of applications for NCI-assistance in product development – all phases of clinical and pre-clinical assistance
- Applications for CTEP-sponsored clinical development are most commonly from Pharma, although products generated from academia can also apply
- No funding provided, only services
- Three review cycles per year -4 month cycle from application deadline to outcome

CTEP roles in study development and implementation

- CTEP – acting in its role as the **funder** of clinical trials networks:
  - **Provides funding** for network operations offices and investigators
  - **Provides infrastructure support** for all clinical trials networks

- CTEP – may also act in its role as **sponsor** for IND studies:
  - The **Investigational Drug Branch (IDB)** oversees the CTEP-IND program
  - IDB physicians are primary contacts for pharma and investigators and function as lead scientific reviewers
  - IDB physicians are the official **medically-responsible physicians** for **safety oversight of all CTEP IND studies**
  - Other CTEP branches also play significant roles in the IND program, including Regulatory Affairs Branch, Pharmaceutical Management Branch and Clinical Investigations Branch

Access to CTEP resources

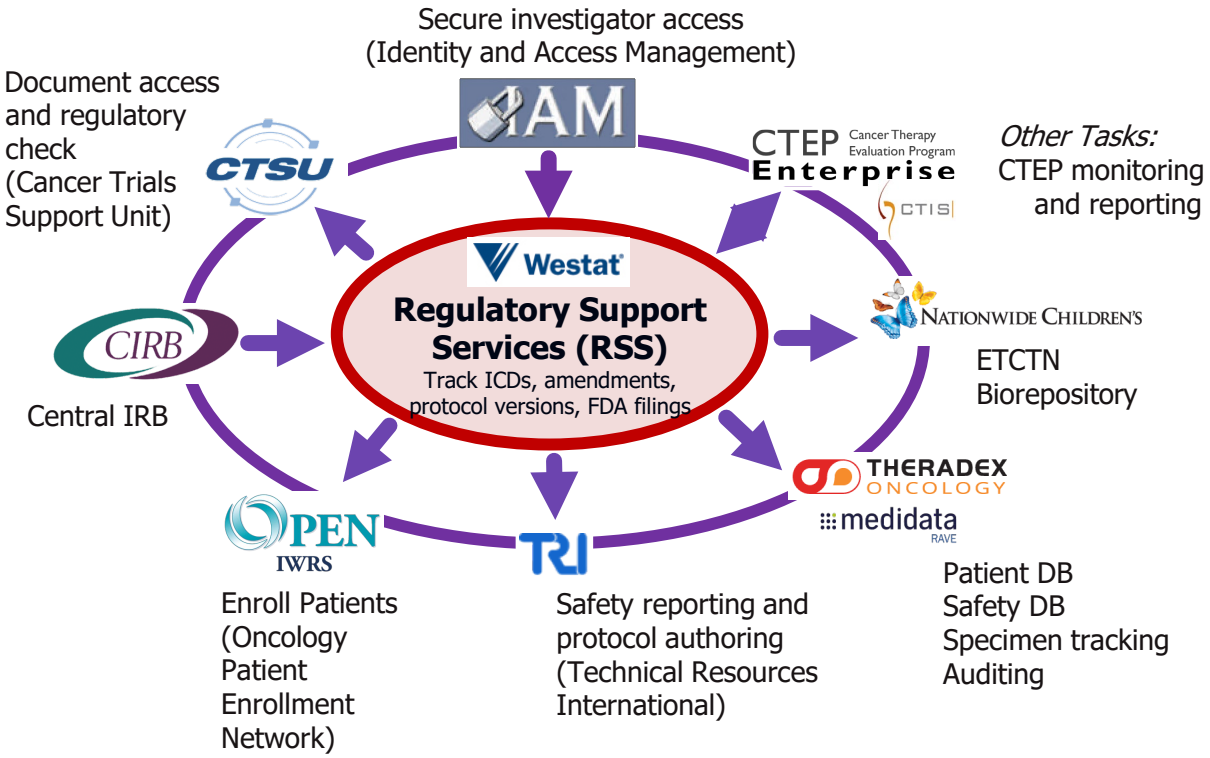
- Most CTEP clinical trial resources are available through its grant-funded networks – **not open access**
  - NCTN groups – have scientific committees that advance clinical trial proposals (LOIs or Concepts) to CTEP for review and approval
  - ETCTN
    - ETCTN grant PI's can submit LOIs for review and approval
    - EDDOP program allows investigators from **non-ETCTN NCI-CCs** to submit LOIs for ETCTN trials
  - Other small CTEP-funded networks have access to CTEP-IND agents, e.g. CITN
  - All clinical trial proposals for NCI networks must be submitted to CTEP Protocol Information Office (PIO) by the PI of an eligible grant
- Resources available outside grant-funded networks
  - NCI formulary – investigational agents (without funding) for preclinical or clinical studies

Resources available for ETCTN studies

- **CTEP expertise** – scientific input during review process adds to the rigor of trial design and value of study
- **Investigator expertise** – ETCTN investigators are highly experienced early phase clinical trialists provide input and understand how to conduct these studies within their own institutions
- **Clinical trial infrastructure** that supports early phase trials in a network setting for enhanced accrual and full regulatory compliance
- **National Clinical Laboratory Network** provides exceptional correlative science resources for molecular characterization of patient tumors and pharmacodynamic analysis of on study biopsy specimens

CTEP/ETCTN centralized clinical trial support

All IND studies receive centralized support from CTEP so that the individual sites can function together as a national network and so that CTEP can meet its obligation as sponsor



NCLN Genomics assays available for ETCTN trials

Biomarker Name	Laboratory
Whole Exome Sequencing (WES) • **Tumor** • **Blood, Germline Control for WES**	NCLN Genomics Laboratory
RNAseq	NCLN Genomics Laboratory
Oncomine Panel	NCLN Genomics Laboratory
circulating tumor DNA (ctDNA)	NCLN Genomics Laboratory

- **Available if approved without cost; no BRC review required**

NCLN PD assays available for ETCTN trials

Biomarker Name	Assay	Laboratory
γH2AX, pNBS1 IFA with βCATN segmentation	Multiplex Immunofluorescence Assay (mIFA)	NCLN PD Assay Laboratory at MD Anderson
Apoptosis Multiplex Immunoassay, Luminex	Luminex, • Panel 1: BAK, BAX, Lamin-B, Smac dimer • Panel 2: BIM, BAD, BAX-Bcl-2 heterodimer, Bcl-xL, Mcl-1 • Panel 3: BAK-Mcl-1 heterodimer, BAK-Bcl-xL heterodimer, Active Caspase 3 (cleaved), Survivin	NCLN PD Assay Laboratory at Molecular Pathology Laboratory Network, Inc.
AKT Multiplex Immunoassay Panels 1-3	Luminex, • Panel 1: AKT1, AKT2, AKT3, rpS6 • Panel 2: pS473-AKT1, pS474-AKT2, pS472-AKT3, pS235-rpS6 • Panel 3: pT308-AKT1, pT309-AKT2, pT305-AKT3, pS240/244-rpS6	NCLN PD Assay Laboratory at Molecular Pathology Laboratory Network, Inc.
ERK/MEK Multiplex Immunoassay Panels 4-5	Luminex, • Panel 4: ERK1, ERK2, MEK1, MEK2 • Panel 5: pS218/S222-MEK1, pS222/S226-MEK2, pT202/Y204-ERK1, pT185/Y187-ERK2	NCLN PD Assay Laboratory at Molecular Pathology Laboratory Network, Inc.

- **Available if approved without cost; no BRC review required**

CTEP scientific review

- **Pre-clinical or clinical evidence** to support proposed study
  - **Rationale is not enough**
  - Higher priority proposals have strong preclinical evidence
- Fills a need
  - **No duplicative studies** ongoing or in planning stages
- Sound statistical design
  - Will study endpoint advance the development of the agent or agent combination
- Sound clinical plan for future development
- Biomarker plan
  - Assays validated and relevant to MOA of the agents
- Feasibility
  - Is accrual plan reasonable

Why does CTEP require preclinical evidence to prioritize clinical trial concepts?

- Insufficient number of patients and insufficient resources to fund every clinical trial proposal – so evidence of in vivo tumor response is used to prioritize trials
  - 'No resources to conduct preclinical studies' is not a justification to test novel therapies on patients without supporting evidence of therapeutic benefit
  - 'Unmet medical need' is also not a substitute for strong supporting data
- Clinical studies are much more costly – in both dollars and human terms – than preclinical studies
- No models are perfect and no evidence is absolutely predictive
- *Every patient enrolled on a study deserves our best effort to ensure that the study is rigorously scientifically supported and soundly designed,* ***so that their experience will have meaning*** *even if the trial is negative*
- Strength of preclinical evidence is only one of many factors in LOI evaluation

CTEP contacts

- Investigational Drug Branch – Jeff Moscow, M.D.
  - jeffrey.moscow@nih.gov
- ETCTN – Percy Ivy, M.D
  - ivyp@ctep.nci.nih.gov

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What factors are important in evaluation of in vivo experiments to support an LOI for non-IO agents or agent combinations?

- ***Significance of effect size*** not statistical significance
- **Depth of response:** Strength in descending order: Tumor regression vs prolonged growth inhibition vs slowing rate of growth
- **Durability of response:** Strength in descending order: Effect continues after therapy vs effect ends at end of therapy
- K-M and growth curves **much better than one point in time**
- **Duration** of experiment – the longer the better – to show durability of response
  - No need to stop observation of treated animals for response because control animals have been sacrificed
- The in vivo evidence of response should be analogous to measures of clinical benefit