Clinical Trial Design – Phase I

Clinical Trial Design – Considerations for Phase I

Clinical trials are a fundamental part of the drug development process. Clinical trial design is a critical factor of interventional, first-in-human (Phase I) trials that serves to optimize safety and efficacy endpoints for new therapeutic agents based on translational science. These initial hypotheses are used to craft key trial objectives, formulate risk mitigation strategies, determine appropriate statistical methods to interpret data outcomes, and estimate economic feasibility.

The clinical trial designs outlined below describe four strategies used to enroll patients into Phase I therapeutic trials for new drug products. These clinical trials may compare a novel therapeutic agent to other treatments such traditional standard of care therapy or a placebo, or compare the same novel therapeutic agent within various tumor indications.

During the design process, researchers will plan various risk mitigation strategies to maximize therapeutic benefit for patients. However, researchers are unaware of all potential risks, benefits, or outcomes. Thoughtful consideration of various design strategies is imperative to maximize clinical trial success.

Common Clinical Trial Designs

Randomized Clinical Trial: Patients are randomized often into two groups: 1) the group that receives the interventional drug product, and 2) the group that receives standard of care therapy or placebo. Randomization allows researchers to collect and interpret data without bias. Randomized clinical trials are not typically used for rare or advanced tumor indications as it is unethical to provide treat these groups of patients with placebo.

Non-randomized Clinical Trial: Patients are selected and placed into cohorts without randomization. Patient selection is predictable and bias is evident. Data validity is a key concern. Statistical analyses are critical to ensure data collection and outcomes are accurate, reliable, and complete.

Cross-over Clinical Trial: Patients receive the same type of drug product at different timepoints in the study. Therefore, each group is considered a control for the other currently undergoing treatment.

Factorial Clinical Trial: Patients are placed into multiple groups typically within the same population yet provided different combinations of drug products. Therapeutic outcomes are compared amongst the groups.

Phase I Design

Phase I clinical trials are often described as Phase Ia or Phase Ib cohorts. Phase Ia typically refers to dose escalation studies in which ascending cohorts of patients receive higher doses of

drug product until a maximum tolerated dose is reached. Phase Ib typically describes cohort expansion which means the appropriate dose has been identified and will be provided to additional patients or patients with specific tumor indications.

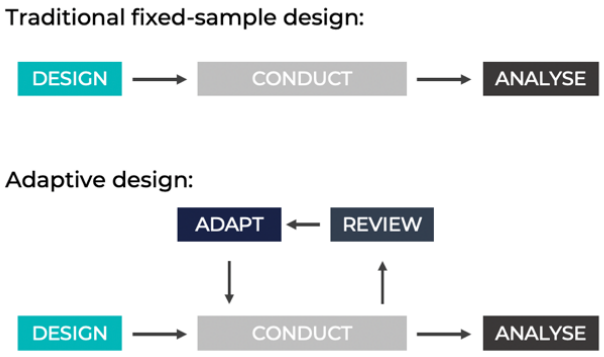
InnovoTEX – Clinical Trial Design

The Phase Ia clinical trial will provide information related to regimen, safety, tolerability, and pharmacokinetics (PK). Phase Ia dose escalation will establish the maximum tolerated dose and cohort indication for dose expansion.

Since the pandemic of 2020, innovative clinical trial strategies, such as adaptive or modified trial designs, have been implemented to ease the burden of data collection and monitoring on patients and administrative staff. The adaptive model is often more efficient and informative as it provides opportunities to streamline and optimize interim data outcomes, and the flexibility to modify the trial course in accordance with the pre-specified methodology.

InnovoTEX will plan to use an innovative, adaptive trial design with a modified treatment regimen for dose escalation in Phase I. Pre-clinical data has shown that OxaliTEX is well-tolerated, tumor localizing, and overcomes platinum resistance in multiple solid tumor indications including ovarian cancer.

Figure 1. Adaptive Trial Design

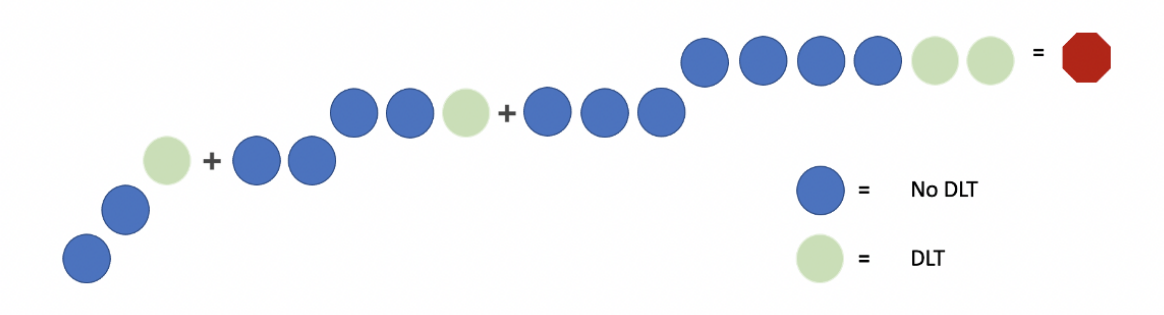


A modified 3+3 design will be used to minimize the number of subjects treated at potentially sub-therapeutic doses. The initial cohorts in Phase I will enroll a single subject until a subject has a > Grade 2 AE considered possibly related to drug product during the DLT period (i.e., the subject's initial 28-day cycle). Dose escalations up to 100% of the prior dose will be permitted until the occurrence of a > Grade 2 AE considered possibly related to drug product during the DLT period. Once a DLT has occurred, cohorts will be expanded to enroll 3 subjects at a dose level. If none of the 3 subjects experience a DLT, the dose will be escalated to the next highest dose level. If 1 of the 3 subjects in a cohort experiences a DLT, up to 3 additional subjects will be enrolled and treated at the same dose. If none of the additional 3 subjects

experiences a DLT (i.e., only 1 of 6 subjects in the cohort experiences a DLT) the dose will be escalated to the next highest dose level. If 2 or more of up to 6 subjects experiences a DLT, enrolment to that cohort will stop and the dose will be considered above the maximum tolerated dose (MTD). The dose will then be decreased to the previous dose level or to a level intermediate to the dose previously evaluated at which < 1 of 6 (or less than 1/3rd of subjects are enrolled in a cohort) have a DLT. A minimum of 6 DLT-evaluable subjects will be enrolled to any dose level being evaluated as the possible MTD.

Anticipated cohort management outline is provided in the figure below. After each DLT period, the Safety Review Committee (SRC) will convene to review patient safety and drug efficacy of the prior cohort. Upon approval from the SRC, the next dose level and cohort will open, and will continue until the maximum tolerated dose is reached.

Figure 2. Cohort Management



The safety and efficacy data from dose escalation will be reviewed once MTD is reached. This data will confirm the recommended dose for continued treatment and provide further confirmation of the target indication.