Fortrea

Is it time to go beyond classic design in oncology trials?

Use of healthy volunteers in first-in-human trials with oncology small molecules. Can an alternative approach expedite clinical development of small molecule oncology drugs and benefit patients?

Introduction

First-in-human (FIH) Phase I studies are designed to establish early safety and tolerability profiles of an IMP: Investigational Medicinal Product. While most Phase I trials are conducted in healthy volunteers, oncology studies typically enroll patients with cancer, for whom there is no other therapeutic option. This gives patients access to drugs in development that might offer some benefit. Also, it avoids the need to expose healthy volunteers to drugs that could have long-lasting adverse effects based on the drug's mechanism of action, such as cytotoxic oncology drugs, highly immunosuppressive or drugs with immunogenic activity.

However, this does not mean that healthy volunteers can be ruled out of all early phase oncology clinical trials. Trials with healthy volunteers or cancer patients both have their advantages and disadvantages, and healthy subjects can offer many benefits to a study with noncytotoxic therapeutic drugs with a favorable preclinical safety profile. Instead, it is about assessing what trial design would be best for the drug in development and determining whether to recruit healthy volunteers or cancer patients. This decision-making process is complex, and there is no one-size-fits-all approach when it comes to selecting the study population in FIH clinical trials with oncology therapeutics.

KEY TAKEAWAYS

Classically designed oncology clinical trials are reaching the limits of their potential

First-in-human (FIH) clinical trials for noncancer drugs are increasingly turning to enrolling healthy volunteers to expedite the drug development process

But is this feasible in oncology? What conditions determine whether FIH oncology trials should enroll healthy volunteers or cancer patients or use a hybrid design, and how should this recruitment decision be made?

Here, we discuss how FIH studies with healthy volunteers could open up new possibilities in cancer drug development and ultimately get therapies into the hands of doctors sooner

The sponsors and investigators making this decision should consider various characteristics of the study drug to successfully advance the IMP development process. They must weigh the benefits and risks, considering multiple factors such as the drug mechanism of action, toxicology findings and the safety pharmacology and pharmacokinetic (PK) profile of the drug. Here, we discuss the key advantages and disadvantages that should be considered when evaluating whether to include healthy volunteers versus cancer patients in FIH trials with oncology small molecule therapies. In some cases a hybrid design including healthy volunteers and cancer patients seems prudent.

Going beyond classical oncology trial design

The primary goal of a first-in-human clinical trial is to evaluate the safety and tolerability and characterize the PK of a novel drug candidate. Historically, FIH dose-finding studies in oncology were performed with classical rule-based designs, such as 3 + 3, and model-based designs like the continuous reassessment method. These are still used in some trials today, but innovators are turning to more innovative well-modeled designs that provide more precise and efficient ways to determine the recommended Phase II dose (e.g., Bayesian optimal interval or modified toxicity probability interval models). The benefits of these new design models include better criteria to mitigate risks, better methods for dose optimization and more sophisticated designs that expedite the trial process.

Regulators are actively supporting investigators to modernize clinical study design, particularly in determining how to manage risk in FIH clinical studies. The European Medicines Agency (EMA) published guidelines in 2007 (since revised in 2017) for conducting early clinical trials. The guidelines provide an overview of the requirements to move from nonclinical to early clinical development, including identification of the starting dose, dose escalation methods and definition of the maximum exposure and design of the FIH trial. The guidelines are a starting point to help answer the question of whether to include healthy volunteers or cancer patients in FIH small molecule oncology drug trials, but here, we take a closer look.

What conditions determine whether trials should be performed in healthy volunteers or cancer patients?

Deciding whether healthy volunteers or cancer patients are most suitable for an oncology FIH trial is a complex process. It involves weighing toxicology findings, pharmacokinetics/pharmacodynamics (PK/PD) profile, the mechanism of action plus the cost and time requirements. For example, a drug with genetic or epigenetic target would not be approved by the regulators to be dosed in healthy volunteers. Similarly, a drug with reported irreversible toxicology or adverse effects that cannot be readily monitored in the clinic, or compounds that must be administered intrauveally would not be acceptable for healthy volunteers.

In fact, the decision will be aligned by regulatory advice and requirements. For example, there are key regulatory differences in how FIH trials are conducted when using healthy volunteers or cancer patients based on data gathered from earlier preclinical work in animal models through to the Phase I trial in humans. In particular, the clinical process is highly dependent on the earlier studies, and aspects like calculating starting clinical doses from earlier animal model data differ strongly between patients and healthy volunteers.

Maximum exposure dose and dose escalation also differ in human volunteers vs cancer patients. Historically dose finding, escalation trials with cytotoxic drugs were designed to determine the maximum tolerated dose (MTD), where toxicity was related with drug exposure and efficacy. However, with the development of new cancer agents, the dose-relationship was generally not observed, meaning that doses below the MTD may have similar efficacy to the MTD and fewer toxicities. Therefore, the regulators have provided guidance to better define the dose, that is dose optimization, defining the recommended dose range for later testing in the next steps of the drug development.

However, dose escalation and maximum exposure dose are much stricter for healthy volunteers and must weigh PK, PD and toxicology findings from earlier animal studies. To enable testing small molecules in healthy volunteers, genotoxicity assessments must be conducted prior to the FIH clinical study using *in vitro* and *in vivo* testing, but only *in vitro* studies are essential and *in vivo* studies are desirable prior to initiating FIH in cancer patients.

Therefore, the preclinical package is essential to plan the FIH study design. Likewise, although it can be easier to manage adverse effects in healthy volunteers with no comorbid disease(s), it has to take into consideration that the threshold for acceptable toxicities is lower for healthy volunteers than for cancer patients. This means that higher doses, which in cancer patients may be efficacious enough to outweigh side effects, cannot be tested in healthy volunteers. Ultimately, the choice of recruiting healthy volunteers versus cancer patients involves weighing the advantages and disadvantages of which participant cohorts are best suited for each individual Phase I trial.

Advantages of recruiting healthy volunteers for Phase I oncology trials

1. **Rapid subject accrual**
   It's much quicker and easier to recruit healthy volunteers in the early startup of the program. This can speed up the overall progress of the phase 1 trial and ultimately the entire clinical development program. This efficiency can also help reduce trial costs.
2. **Accelerated timelines of the clinical development program**
   In healthy volunteers, the minimum data required for dose escalation review are determined on the half-life of the compound, which can be relatively short for small molecules. In contrast, dose escalation for trials with cancer patients requires a review of the safety data from all patients of the cohort up to the completion of the last day of cycle 1 to determine whether a dose-limiting toxicity was encountered plus the review of the pharmacokinetic and pharmacodynamic available data. Each cohort cycle can last up to three to four weeks in trials with cancer patients, meaning that the safety review process can slow down the clinical development program.
3. **Limit unnecessary exposure of cancer patients to low, subtherapeutic doses**
   During early dose escalation, participants will receive subtherapeutic doses, which may pose ethical concerns at the early first doses. In contrast, administer subtherapeutic doses with oncology drugs to healthy volunteers, if the nonclinical package allows, it is permissible, meaning that cancer patients can be allocated to higher doses, which may offer increasing benefit to cancer patients.
4. **Evaluation of the safety and PK profile in the absence of comorbid conditions and concomitant medications**
   When testing in cancer patients, the safety and PK/PD profile of the drug might be affected by factors such as comorbidities and interactions with drugs that the patient is taking. While these data are important for future stages of the trial, it might introduce confounding factors

when evaluating the safety of the therapeutic in humans for the first time.

It is more accurate to evaluate the safety profile of a new therapeutic in healthy volunteers in the absence of confounding factors such as comorbid disease and concomitant medications. Secondly, it is easier to manage adverse events in healthy volunteers compared to cancer patients. Intensive PK blood sample collection is more straightforward in healthy volunteers than in cancer patients, allowing frequent and accurate measurements of the drug's PK parameters. These parameters are crucial for determining dose-exposure relationship and dosing regimen of the study drug.

5. **Integration of single-dose clinical studies in the FIH study testing aspects like food-drug interactions, drug-drug interactions, age, gender and ethnicity effects**
   Testing in human volunteers also allows early assessment of aspects like food-effect drug interactions or drug-drug interactions as well as age, gender and ethnicity on the PK of the drug. It can be easier to test these interactions in healthy volunteers than in cancer patients due to potential confounding factors such as drug-drug interactions. These data can help guide dose adjustment and dosing regimen in larger-scale future trials.

Disadvantages of recruiting healthy volunteers for Phase I oncology trials

1. **Absence of pathology in the healthy tissue, which may render the model irrelevant to the patient**
   Obviously, the drug target in the tumor is not present in most healthy tissue; therefore, PD and efficacy cannot be monitored at the first dose levels. Testing in healthy volunteers can thus provide only an indication of effectiveness in cancer patients for some drugs if the target is present, and early efficacy information relies on biopsies from cancer patients.
2. **Uncertainty about translatability of PK and PD findings to cancer patients**
   There could also be differences in the PK profile of a small molecule drug in cancer patients versus healthy volunteers, which largely depends on the different expression levels of the drug target in healthy and tumor tissue underlying medical conditions in cancer patients. For example, many cancer patients might have altered hepatic metabolic function due to liver malignancies or hepatotoxicity from previously administered chemotherapies (e.g., the antimetabolite fluorodeoxyuridine). As such, the liver metabolism of the drug and active metabolites might differ between healthy volunteers and cancer patients. Thus, dose adjustments in the patient population might be needed for drugs tested in healthy volunteers, considering side effects and efficacy variability in cancer patients.
3. **Risk of unexpected serious side effects, which may lead to life-threatening or long-term adverse effects**
   As with any other new investigational drug, some oncology small molecule drugs have adverse toxicology effects that are too risky and potentially life-threatening for testing on healthy volunteers. For healthy volunteers who stand to gain no benefit from the treatment, the threshold of acceptable risk is lower than it is for cancer patients. Dosage escalation and testing will therefore be less extensive than in cancer patients.

Weighing the choice

Ultimately, the choice of whether to start an FIH clinical trial for oncology small molecule drugs in healthy volunteers or cancer patients depends on a wide range of aspects, but the preclinical package and the mechanism of action are the key decision drivers. Anyway, each study must be judged on a case-by-case basis, as no "**one-size-fits-all**" approach exists to define HVs as a population for a FIH oncology trial. Benefits and risks need to be balanced and all the stakeholders involved (sponsor, regulators, investigators, even CRO organizations) have to determine the most appropriate approach.

LEARN MORE at fortrea.com

Fortrea