

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## The Importance of Dose Optimization Prior to Initiation of a Registration Trial



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### **H&O** What is the current process for establishing dosages of new pharmaceutical agents?

**NR** The aim of a clinical development program is to identify the right dose, as too high a dose can result in unacceptable toxicity and too low a dose decreases the chance of obtaining a clinically meaningful response from a therapy. The dosages of new drugs are established based on the optimal rate of administration of a dose that provides the maximum benefit in terms of balancing the efficacy and safe use of a product. Although the current oncology drug products are predominantly targeted therapies, the traditional dose-escalation scheme of a “3 + 3” design to assess the safety of chemotherapies is still being implemented in the development of targeted therapies. In this design, a cohort of 3 subjects (mostly patients with advanced cancer) is tested to establish a safe starting dose. Subsequently, a new cohort of 3 patients receives the next higher dose. The objective of the dose-escalation trial is to assess the dose-limiting toxicity and establish a maximum-tolerated dose of the drug. This approach may not be suitable for targeted therapy. The dose-escalation trials of targeted therapy assess not only the safety of the drug, but also the preliminary activity using sensitive and reliable biomarkers or clinical endpoints in phase 1 safety trials. Based upon the dose-escalation trial, a single dose or a limited number of doses are then tested in a phase 2 trial to establish effectiveness of the drug using surrogate endpoints. Usually, a single dose is then tested in the confirmatory registration trial.

In vitro and animal data, and sometimes modeling and in silico data, are used to provide insight into the selection of the target starting dose and expected target concentration in human trials.

### **H&O** In what ways do targeted therapies complicate the process of establishing dosages?

**NR** The targeted drugs are expected to be continuously used until relapse or disease progression, unlike the non-targeted drugs, which are administered for a particular number of cycles within a defined time frame. Therefore, short-term follow-up in clinical trials of targeted agents during development may not reflect the chronic toxicity that may appear after long-term use of these drugs. In some patients, the dosage may need to be tailored based on tolerability of the targeted therapies for chronic use.

Targeted therapies may provide similar activity across a wide range of dosages with similar toxicity. Selecting the optimal dose that balances the benefits and risks of the drug without compromising the effectiveness may be challenging.

### **H&O** What are some other limitations to the current process?

**NR** There are several other limitations of the “3 + 3” design. Sensitive and relevant biomarkers are needed in early development programs to reliably assess the activity

of the drug in terms of both safety and efficacy. Early-phase clinical trials are performed in a relatively limited number of patients, and therefore true variations in exposure and in patient response are not discovered until later, through larger trials. In oncology, phase 2 programs are often abbreviated. Selection of the dose is frequently empirical and rarely scientifically sound. The dose exposure response is poorly characterized, owing to the limited dose range tested in phase 2 programs. Therefore, dose evaluation for various scenarios may continue after the drug is brought to market.

### **H&O** Do clinical trials in oncology have a high rate of dose reductions?

**NR** Trials of chemotherapeutic agents typically start with a maximum tolerated dose that may be lowered for some patients based on tolerability and response. A toxicity-based dose reduction algorithm is commonly implemented in clinical trials in oncology. If the drug is approved, instructions for protocol-based dose reduction are included in the “Dosage and Administration” section of the package insert. Dose reduction in the oncology setting is therefore planned and usually performed in a prospective manner.

The rates of dose reduction in oncology clinical trials vary among drug classes and mechanisms of action. Cytotoxic therapies may require dose reductions under various conditions, mostly to reduce toxicity. Targeted therapies, including biologics, are expected to have less frequent dose reductions.

### **H&O** Does it appear that some approved oncology drugs are labeled for use at doses that are either too high or too low, at least for some patients?

**NR** Clinical trials establish a dose or range of doses that provide a favorable benefit-risk ratio for the average patient population. Because of the variability in drug exposure and patient tolerability, a prescribed dose may be too high or too low for patients who are at the extreme ends of the normal distribution curve of the patient population. This is expected. If a prescribed dose causes toxicity in a patient, the next dose is usually reduced after the toxicity is adequately managed. Sometimes with therapies that are approved for unmet medical needs or for conditions that have no approved therapy and that do not respond well to off-label therapies, the prescribed dose may be high to ensure that patients achieve effective exposure and hopefully respond to the therapy.

In these settings, adequate dose-reduction schemes are included in the label to manage toxicities. Occasion-

ally, dose-optimization trials are required in the postmarket setting to further refine the dose.

### **H&O** Why should a dose be optimized before initiation of a registration trial?

**NR** I cannot overemphasize enough the importance of optimizing the dose and dosing regimen prior to initiation of a registration trial. It is key to a successful overall development program for a product. Dose optimization through nonclinical studies and phase 1 and phase 2 trials will ensure that the selected dose and dosing regimen of a registration trial demonstrate the maximum benefit from the therapy with acceptable toxicity. In some instances, a drug has failed to demonstrate adequate efficacy or acceptable toxicity in the registration trial because the dose was not optimized in early trials. Establishing the dose before a registration trial will also help to avoid the need to conduct dose-optimization trials in the postmarket setting. There are several challenges associated with the conduct of postmarketing trials, such as the ethical issues raised, the need for timely enrollment of patients, and the burdens placed on drug manufacturers regarding the design and conduct of such trials.

### **H&O** What types of strategies are used to improve assessment of drug doses in clinical trials?

**NR** In a phase 1 development program, the exposure and variability in exposure should be adequately assessed to select a dose range that is safe and demonstrates preliminary activity for further development. When a “3 + 3” design is used, especially for the targeted therapies, the selected dose or range of doses should be evaluated in an expansion cohort to obtain a reliable estimate of the exposure variability and to better assess the toxicity. This approach should provide a reliable estimate of a dose or range of doses that demonstrate reasonable activity with acceptable toxicity.

In phase 2 development, more than one dose should be tested for effectiveness, and drug exposure should be assessed in every patient through the sparse plasma sampling technique. The sparse sampling technique allows estimation of a patient’s overall exposure to a drug by collecting 2 to 3 blood samples within a reasonable time frame. An exposure-response analysis should be performed on data from phase 1 and phase 2 trials. Modeling and simulation of the data should be helpful to generate an optimal dose, dosing regimen, and the best study design for the registration trial. In phase 3 trials, sparse sampling of plasma should be collected from all patients to further conduct exposure response analysis and refine

the dose for the average population. The analysis of the data from sparse sampling should be helpful to tailor the dose for specific patient populations that are otherwise not enrolled in the clinical trial, such as patients with comorbidities, patients using concomitant medications, or patients with organ dysfunction. This strategy should help development of both nontargeted (cytotoxic) therapy and targeted therapy.

The relationship between a target expression and drug response should be evaluated in the early phase of development so that an appropriate dose and, if necessary, a selected target population, are evaluated in the phase 2 setting. This will be particularly helpful for targeted therapy.

### **H&O** How can trials identify patients who might benefit from a higher dose?

**NR** Based on the dose-response analysis, if the dose or exposure response curve is flat, and a lower than maximum tolerated dose is selected for the registration trial, the protocol should consider including a provision for up-dose titration based on tolerability and the patient's response. If a response is not observed after a reasonable duration of treatment and the patient has no toxicity, a higher dose may be administered. This provision should be built in and tested in the registration trial. This strategy may be helpful in the development of targeted therapy and biologics, in which the maximum tolerated dose may not be tested in the registration trial. This will be the reverse of down-dose titration, which is routinely built into oncology registration trials for cytotoxic agents.

Based on genetic predisposition, subsets of patients may benefit from higher doses of a drug. For example, if an active drug is cleared by a polymorphic enzyme, patients who are rapid metabolizers and carry higher levels of the enzyme and clear the drug faster may benefit from a higher dose than the recommended average dose. The safety of a higher dose that may benefit a patient must be established in an early-phase clinical trial before up-titration is included in a registration trial.

### **H&O** What are the advantages and disadvantages of randomized dose-comparison studies?

**NR** I will start with the advantages. A randomized dose-comparison trial provides a sensitive measure of dose and exposure response to allow selection of an optimum dose for testing in a registration trial. A randomized dose-comparison trial will provide a better estimate of the drug's effect compared with a single-dose trial. In the setting of an unmet medical need, accelerated approvals

may be granted based on dose-comparison trials when a therapy achieves a response that is robust and better than any existing treatment for that condition. Another benefit is that a dose-comparison trial provides wider exposure data, enabling a tailored dose for patients with comorbidities and other conditions. These trials also provide a response profile for up-dose or down-dose titration based on various intrinsic and extrinsic factors that may impact drug response.

There are potential limitations. Randomized dose-comparison trials require longer time for follow-up and more patients, and the cost is higher. Some patients may not receive optimal therapy in some dose cohorts, unless the trial design includes inpatient dose escalation or dose de-escalation based on both safety and efficacy. Randomized dose-comparison trials may be difficult to conduct for rare diseases, and they may lack the statistical power to test a hypothesis.

### **H&O** What types of factors can impact a patient's response to a drug?

**NR** There are both intrinsic and extrinsic factors that may alter drug exposure in a given patient receiving a prescribed dose, which can impact response to a drug. Intrinsic factors include age, race, sex, genetics, and organ dysfunction. For example, patients with severe renal impairment not requiring dialysis should take 250 mg of crizotinib (Xalkori, Pfizer) once daily instead of twice daily, which is the prescribed dosage for a patient with normal renal function. In the oncology setting, organ dysfunction is a critical intrinsic factor that influences drug clearance and requires lower doses for patients with such dysfunction. (Crizotinib is approved for patients with non-small cell lung cancer who have ALK-positive tumors.)

Extrinsic factors include food intake, concomitant medications, smoking habits, and alcohol consumption. As an example, the dosage of venetoclax (Venclexta, AbbVie/Genentech), which is approved for chronic lymphocytic leukemia, should be reduced by 75% when strong cytochrome 450 3A enzyme inhibitors are used concomitantly, after the ramp-up phase of treatment, to avoid overexposure and toxicity.

Another important factor is that oncology patients are usually receiving polypharmacy. As a result, they may require dose modification of a cancer drug or the other concomitant medications to achieve the target exposure of all therapies.

### **H&O** How might pharmacodynamic endpoints be used?

**NR** Pharmacodynamic endpoints can be used for various

purposes. For example, they can be used to assess exposure response to select a dose or dosing regimen. Tumor response may be a pharmacodynamic endpoint for assessment of drug activity and selection of a dose or range of doses. For example, the relationship between dose and overall response rate (a surrogate of drug activity) assessed in the dose-escalation trial was used to select the dose of nivolumab (Opdivo, Bristol-Myers Squibb) used in further development.

A pharmacodynamic endpoint may be a surrogate measure for accelerated approval of drugs pending verification and description of clinical benefit in a confirmatory trial. A demonstration of improvement in progression-free survival led to the approval of palbociclib (Ibrance, Pfizer) in combination with letrozole for patients with advanced or metastatic breast cancer that is negative for the human epidermal growth factor receptor 2.

A pharmacodynamic endpoint may also help to evaluate a new formulation of an approved product. In particular, they are being used for the assessment of biosimilar products. The similarity of the first approved biosimilar product, filgrastim-sndz (Zarxio, Sandoz/Novartis), was based on demonstration of no significant difference in the absolute neutrophil counts (a pharmacodynamics endpoint) between filgrastim-sndz and the originally approved filgrastim.

### **H&O** Do you have any other recommendations on how to optimize the dose prior to initiation of a registration trial?

**NR** The data from nonclinical studies and early clinical trials should be adequately assessed to optimize the dose for registration trials. In a fast-paced development program, all of the generated data may not be evaluated before moving onto the next phase of development.

The understanding of the mechanism of action is important. This should include data on target engagement and factors that may contribute both in target and nontarget interactions to select a dose for the phase 1 trial. Influence of food on oral medications should be assessed early to adequately incorporate provision for food intake in registration trials. The impact of concomitant medications and organ impairment should be evaluated during drug development, so that we can adequately select doses for these populations and include them in the registration trial.

The traditional phases of drug development may not be applicable for therapies that demonstrate remarkable efficacy in early studies and receive a breakthrough designation from the US Food and Drug Administration. We therefore need to rethink the entire paradigm of oncology product development for these breakthrough therapies. For these drugs, optimizing the dose for testing in clinical trials will be a critical issue that should be addressed using all nonclinical and clinical data generated during drug development.

### **Disclosure**

*The views expressed in this interview represent Dr Rahman's personal perspectives and do not reflect the official position of the US Food and Drug Administration.*

### **Suggested Readings**

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