



6 Key Questions to Ask in Assessing Early Phase Oncology Trial Design

The answer to how to best design an early phase oncology clinical trial depends on a variety of factors, and, ultimately, there is not a one-size-fits-all design. Conversations should occur early and often among scientists, clinical leads, and statisticians during protocol development to determine which design would be best utilized for a certain protocol.

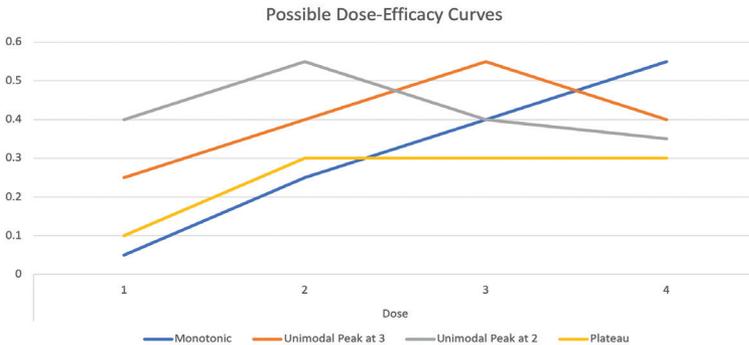
Following are 6 important questions that need to be asked in the process:

1. What type of agent is the drug?

- a. Cytotoxic
- b. Targeted
- c. Immunotherapy
- d. Being offered in combination with another drug
 - Is the dose of the other drug being held constant or can it vary?

2. What are the assumptions on the dose-efficacy curve?

- a. Always non-decreasing (i.e. monotonic)
 - $Efficacy_{d_1} \leq Efficacy_{d_2} \leq \dots \leq Efficacy_{d_{highest}}$
 - Cytotoxic agents typically follow this assumption. Targeted agents may/may not follow this assumption.
- b. Unimodal, can increase to a point and then may decrease at an unknown point.



3. What is the time to observe toxicity? Efficacy?

- a. If either are long, consider the use of a design that utilizes the time to event.

□ 4. What is the expected enrollment?

- a. Is it reasonable to think that subjects in a cohort can be enrolled on the same day?
- b. Or, is the disease/population more difficult to find and, therefore, enrollment for a cohort may take several weeks?

□ 5. How many doses will be under consideration?

- a. How many subjects are to be enrolled in each cohort?

□ 6. What is a realistic scenario for the dose-toxicity curve? Dose-efficacy curve?

Utilizing this information, we may conduct simulations on a variety of designs to show how each may behave under the assumptions and what may happen if those assumptions are incorrect. In each scenario of the simulation, the chance of identifying the true MTD, average number of subjects treated at doses above the MTD, average trial duration (if applicable), average sample size, and average number of subjects treated at ineffective dose levels (defined as either very minimal toxicity for cytotoxic agents or minimal efficacy when efficacy is taken into account).

As an example, if the agent is cytotoxic, monotonic, there are 4 doses under consideration, and toxicity and efficacy are followed for three 28-day cycles before escalation decisions are made.

After that, the following should also be considered to determine which design to use:

- a. Trial Duration
 - i. It would take at least 9 months to reach the highest dose level in the 3+3 design. The 9 months also assumes that all subjects in each cohort are enrolled on the same day which may/may not be fair.
 - i. Simulations can present the average duration of a trial under various assumptions including subject accrual.
- b. Long follow-up would mean having a design that utilizes the partial information on toxicity and efficacy that you gathered on subjects while waiting for the remaining subjects in a cohort to complete the full observation period, in order to make faster dose escalation decisions.
- c. Since toxicity and efficacy take the same amount of time to observe, how would a design which utilizes both outcomes into dose decisions fare?

**Need assistance assessing your early phase oncology clinical trial design?
[Contact us to find out how we can help.](#)**

Synteract.com

BRINGING CLINICAL TRIALS TO LIFE™