Statistical Considerations When Planning Phase I Clinical Trials in Oncology
- From the Safety Perspective
（Early Consideration）

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1. Introduction

From a healthcare and hygiene perspective, regarding drugs for which a thorough understanding of the actual situation of clinical trials is considered essential, their clinical trial plans must be submitted to the Pharmaceuticals and Medical Devices Agency. If an investigational drug is a new active ingredient, a new route of administration, or a new combination drug, and it is the first time that the drug has been administered to Japanese participants, its clinical trial plan will be subject to the 30-day-CTN Review.[1), 2)] The 30-day-CTN Review is necessary to prevent healthcare and hygiene hazards, and it is often conducted for the clinical trial plan for Phase I trials.

Phase I trials in general drug development are conducted on healthy volunteers to evaluate initial safety, tolerability, and pharmacokinetics, etc., and in the subsequent Phase II trials, the dosage and administration are explored using patients with the target disease. On the other hand, in the development of oncology drugs, there are concerns about strong toxicity. Therefore, the purpose of phase I trials of oncology drugs is often to evaluate tolerability, safety, pharmacokinetics, etc. in cancer patients, and to further investigate and determine the dosage and administration. For Phase I trials of oncology drugs, it is necessary to carefully consider the design of the clinical trial to ensure patient safety.

In traditional phase I trials of oncology drugs, the concept is that the maximum tolerated dose (MTD) is defined as the highest dose within an acceptable range of toxicity and that the maximum efficacy is expected at the MTD, based on the assumption that efficacy and toxicity will increase in a dose-dependent manner. In addition to estimating the MTD while evaluating for tolerability in patients, the recommended dose for Phase II and later trials is determined based on the estimated MTD. In recent years, various designs have been adopted for the dose-escalation design of phase I trials of oncology drugs, and there are also various methods for estimating the MTD. In the 30-day-CTN review, it is necessary to review whether the dose-escalation design adopted in the clinical trial plan is preventing healthcare and hygiene hazards, along with, if necessary, the evaluation results of the operating characteristics of the dose-escalation design.

To reduce the burden on the Pharmaceuticals and Medical Devices Agency (PMDA) of preparing

inquiries and on the sponsor of preparing responses to those inquiries, a "Check List for Inquiries on Initial Clinical Trial Notification" has been made public. [3)] The checklist also mentions minimum information that should be included to explain the appropriateness of the dose-escalation design, particularly regarding tolerability evaluation. The purpose of this document is to further reduce the burden mentioned above by specifically introducing factors and points to consider that could affect the operating characteristics of the dose-escalation design based on statistical considerations, particularly from a safety perspective. These points for consideration are not intended to indicate the characteristics of various dose-escalation designs or the pros and cons of their MTD selection performance. The selection of a dose-escalation design for individual clinical trial planning is assumed to be considered in accordance with the development status and is not necessarily based solely on the MTD selection performance and safety assurance. If a discussion is needed regarding a specific dose-escalation-design, please use the pre-Phase I consultation meeting at the PMDA.

In addition, this document introduces points to consider when conducting dose-finding based on statistical considerations in Phase I trials involving Japanese participants, and these points may not necessarily apply when planning Phase I trials involving Japanese participants based on the results of dose-finding conducted overseas.

Please note that the approaches outlined in this document have been developed based on tolerability evaluation methods as of the time of publication and may change in the future based on new findings and other information.

2. Basic principles of evaluation of dose-escalation designs in 30-day-CTN review

The purpose of conducting a 30-day-CTN review is to confirm that appropriate measures are being taken to ensure patient protection is given top priority in all circumstances in terms of safety, before the initiation of a clinical trial.

The operating characteristics of the dose-escalation design adopted in the clinical trial plan can be evaluated by simulating the behavior of dose escalation and dose selection under multiple conditions (see Chapter 3). When evaluating operating characteristics, it is important to consider a variety of scenarios based on the anticipated situation and then examine whether safety can be ensured.

Also, considering the purpose of conducting a 30-day-CTN review, it is important to evaluate the operating characteristics of the dose-escalation design while giving sufficient consideration to the content for which specific trial plans have not yet been decided at the initiation of the clinical trial. Even when there are limitations to the preliminary investigation, it is necessary to explain whether the adopted dose-escalation design ensures safety. When adopting a dose-escalation design that allows for flexible measures according to the situation during the clinical trial, it is necessary to fully consider the impact of selected measures on safety. For example, when considering dose finding in combination therapy after dose finding in monotherapy, the evaluation of the operating characteristics of dose

escalation in combination therapy should also be conducted at the time of submitting the clinical trial notification (see Section 3.3).

3. Evaluation of operating characteristics

3.1. Contents that require consideration and explanation

When evaluating the operating characteristics of a dose-escalation design, the following points should be considered and explained at least.

- Dose-escalation design

  In addition to the design-specific settings (prior distributions, parameters, etc.), the number of doses (dose levels), cohort size, etc., the following points also need to be explained.

  - Rules for dose escalation

    The criteria for determining dose escalation (including stay, de-escalation, and elimination) should be explained, with the target dose-limiting toxicity (DLT) rate, the boundary for de-escalation and escalation, the number of participants with DLT experience, etc. Using tables and flowcharts may be useful for the explanation.

  - Stopping rules of tolerability evaluation

    It is necessary to explain rules, such as the maximum number of overall participants and participants in each dose, and the cutoff probability for controlling overdose. If rules that differ from those for other doses applied to specific doses, this must also be clearly stated.

  - Definition of MTD

    The method for selecting the MTD needs to be explained, including the minimum number of cases required to select the MTD, and whether isotonic regression is performed. The examples of the definition of MTD are the highest dose not determined to require de-escalation, the highest dose that the estimated DLT rate is below the target DLT rate, and the dose that the estimated DLT rate is closest to the target DLT rate; however, it is not limited to these definitions.

    In addition, if there is a possibility that a dose determined to require de-escalation (especially at the starting dose) will be selected as the MTD, the appropriateness of the selection should also be explained from the safety perspective.

- Evaluation metrics for operating characteristics

  The following metrics are particularly important when evaluating the operating characteristics of a dose-escalation design from a safety perspective.

  - Proportion of MTD selection: The proportion of which each dose is selected as the MTD
  - Average number of participants at each dose
  - Average number of participants with DLT at each dose
  - Proportion of the trial termination: The proportion of cases where none of the doses are

selected as the MTD

In a design that determines the escalation based on the target interval of the DLT rate, it is possible to present multiple doses together corresponding to the range, but even within the target range, the proportion of the selection of each dose according to the MTD definition and the proportion of the selection of each dose in the range of excessive toxicity is also important. Therefore, it is necessary to present the proportion of MTD selection, the average number of participants, and the average number of participants with DLT at each dose.

- Scenarios based on the assumption of a dose-toxicity relationship

  When evaluating operating characteristics, it is necessary to consider multiple scenarios that assume dose-toxicity relationships. From the safety perspective, it is important that the trial can be appropriately terminated without any doses being selected as the MTD in scenarios where all doses should not be selected as the MTD (hereafter referred to as "excessive-toxicity scenarios"). For example, if the dose with an estimated DLT rate of 33% or less is to be selected as the MTD, a scenario in which the true DLT rate exceeds 33% for all doses is an excessive-toxicity scenario.

  In addition, if a scenario with extreme toxicity or sharp rise of toxicity is set as the excessive-toxicity scenario, there is a possibility that the proportion of termination will be overestimated. Therefore, it is desirable to assume a moderate dose-toxicity relationship in which the true DLT rate at the lowest dose is slightly higher than the excessive-toxicity threshold.

3.2. Key points in evaluating operating characteristics

When evaluating operating characteristics of a dose-escalation design, the following three points are the main key points from the safety perspective.

(ⅰ) The selection proportion of the dose that should be selected as the MTD is the highest.
(ⅱ) The number of participants receiving doses with high toxicity has been kept low.
(iii) The trial will be appropriately terminated in case all doses should not be selected as the MTD.

In the 30-day-CTN review, the safety is evaluated comprehensively, not only based on the entire trial plan including the dose-escalation design, but also on a toxicological and clinical perspective for each drug. Therefore, it is difficult to set general criteria as specific values for the proportion and number of participants in (ⅰ) to (iii) above. However, for (ⅰ) and (iii) above, <u>at least</u> the proportion of appropriate decisions (dose selection or trial termination) in each scenario should be the highest.

It is also useful to consider the pros and cons of the dose-escalation design adopted compared to other dose-escalation designs (e.g., 3+3 design), and to explain what measures can be taken to ensure safety if there are any safety-related disadvantages.

3.3. Items requiring further evaluation and consideration of operating characteristics

Regardless of the dose-escalation design adopted, if the following options will be involved, these options should be pre-specified, and it is necessary to evaluate and consider the operating characteristics including these options. Even if the options are not pre-specified, it is necessary to evaluate and consider the operating characteristics when adding the options, and to consider whether it is possible to ensure the safety. It would be useful to evaluate the impact of adding options on the operating characteristics by comparing them with the case where the options are not added.

- Change in cohort size or minimum number of participants to be evaluated

  If the cohort size or minimum number of participants to be evaluated is changed for doses with accelerated escalation during the trials, the impact of the change on the operating characteristics must be explained based on simulations.

  It is also necessary to explain the cohort size when additional inclusion is made for the same dose.

  Example

  In the case of a dose-escalation design with accelerated escalation, where the cohort size is 3 but escalation is possible if no DLTs are experienced in the first participant at the starting dose, it is necessary to explain whether the number of participants to be added to the same dose after DLT is experienced in the first participant at the starting dose falls under any of the following:

  - ✧ 2 participants (3 participants in total together with the first participant. The total is same as the cohort size)
  - ✧ 3 participants (4 participants in total together with the first participant. The size of the cohort to be added is 3.)

- Additional dose

  If any of the following doses may be added during the trial, the conditions for transitioning to the added dose must be explained, and the impact of the settings on operating characteristics must be explained based on simulations.

  - ➢ A dose lower than the minimum dose specified in advance
  - ➢ Intermediate dose

  If a detailed plan has not yet been decided, it is necessary to set tentative doses and evaluate both scenarios that the added dose can be selected as the MTD and scenarios that the added dose should not be selected, and to explain the impact of adding doses on the operating characteristics based on simulations.

- Change in dosing interval/schedule

  If the dosing interval or dosing schedule may be changed during the trial, the impact of the change on the operating characteristics must be explained, along with an explanation of the

content of the change and the measures taken.

The following are possible measures but are not limited to them.

- Terminate the dose escalation before the change and start dose escalation from the starting dose
- Suspend the dose escalation before the change, and continue dose escalation considered as an additional dose

In addition, the same approach is also necessary in the case of a dose-escalation design in which multiple dosing intervals or dosing schedules are assumed, and the information from the different regimens is integrated for the decision to escalate the dose.

- Backfill cohort

After the dose has been confirmed as tolerable and the escalation from the dose is determined, the dose may be expanded (known as backfilling) and participants added at a given dose, to collect further information for determining the recommended dose and optimizing the dose, in parallel with the dose escalation. When evaluating tolerability in the backfill cohort and using information on DLT experience in the additional participants for dose escalation based on a dose-escalation design, it is necessary to explain the impact of the settings on operating characteristics based on simulations. If the maximum number of additional participants is fixed but the actual number of additional participants may vary, it is also necessary to clarify the simulation settings in the explanation.

- Dose exploration in combination therapy

When exploring the dose for combination therapy following the monotherapy, the dose-escalation design for combination therapy may be determined based on the results of the monotherapy. When designing the trial, it is possible that the detailed plan for dose-finding in combination therapy has not yet been decided, but even in this case, the operating characteristics should be evaluated based on simulations to the extent possible in advance. If the details of the design differ from the preliminary assumptions when they are decided, additional investigation of the impact on operating characteristics will be needed and efforts should be made to ensure safety.

Regarding combination therapy, when considering the dose or dosing schedule of both drugs simultaneously, rather than fixing the dose of one drug and conducting the dose escalation of the other, it is needed to fully consider the necessary scenarios based on the order of the combinations and to explain the impact on operating characteristics based on simulations.

References:

1） Notification: PSB/PED No. 0820/1: Handling of Notifications of Clinical Trial Plan by Person Intended to be Sponsor, 20-Aug-2024 (in Japanese)

2） Notification: PSB/PED No. 0820/2: Handling of Notifications of Clinical Trial Plan by Person Intended to be Sponsor-investigator, 20-Aug-2024 (in Japanese)

3） Check List for 30-day-Clinical Trial Notification Review on an Initial Clinical Trial Notification (Oncology Drugs), (in Japanese) https://www.pmda.go.jp/files/000252155.pdf