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GUIDELINES

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Guidelines for clinical evaluation of anti-cancer drugs

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Abstract

Clinical studies intended for regulatory approval must demonstrate the clinical benefits of the drug in a target population. Clinical development of a drug proceeds by stepwise clinical studies; after safety and pharmacokinetics are evaluated and the recommended dosage and administration are determined, efficacy and safety are evaluated in an exploratory manner, and finally clinical benefits are compared with conventional standard therapies. Guidelines for the clinical evaluation of anti-cancer drugs in Japan were established in 1991 and amended in 2006 after molecular-targeted drugs were introduced. Recent progress in the development of drugs acting on the immune system and cancer genomic medicine targeting rare but important

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; CAR-T, chimeric antigen receptor T cells; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; HNSTD, highest non-severely toxic dose; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; irAEs, immune-related adverse events; MABEL, minimally anticipated biological effect level; MRD, minimal residual disease; MTD, maximum tolerated dose; QOL, quality of life; RD, recommended dose; STD10, severely toxic dose in 10% of animals.

These guidelines are the English translation of the original guidelines in Japanese issued from the Ministry of Health, Labor and Welfare.

molecular subtypes have altered the strategy for development of anti-cancer drugs. It is often difficult to conduct a confirmatory randomized controlled study using overall survival as the primary endpoint in rare molecular subtypes, and the primary evaluation of the efficacy of some drugs and subsequent approval is based on the tumor response. As conducting clinical studies for rare subtypes solely within Japan is difficult, drug development needs to be conducted within a global study. However, this requires robust monitoring to detect possible ethnic differences in pharmacokinetics and drug efficacy. Development using the conditional approval system for drugs enforced in 2020 may be considered, when clinical utility is evaluated based on surrogate endpoints. Because of these changes, we have revised the guidelines for the clinical evaluation of anti-cancer drugs in Japan. To promote global development of anti-cancer drugs involving Japan, the guidelines have been translated into English.

KEYWORDS

anti-cancer drugs, clinical trials, developmental therapeutics, guidelines, regulatory science

1 | INTRODUCTION

These guidelines describe the basic principles regarding the design, conduct, and evaluation methods of clinical studies, which are performed to evaluate the clinical benefits of anti-cancer drugs for approval in Japan (clinical trials defined by Article 2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices [Act No. 145 in 1960]). In clinical studies, it is necessary to scientifically determine the appropriateness of a method to evaluate clinical benefits based on the relevant drug, target disease, clinical status, and accumulation of scientific evidence.

2 | BACKGROUND

Traditionally anti-cancer drugs have been clinically developed after evaluation of safety and efficacy in phase I, II, and III studies.[1] The first guidelines for the clinical evaluation of anti-cancer drugs were established in February 1991 when cytotoxic drugs were the main focus of clinical development. Subsequently, molecular-targeted drugs including antibody drugs have been developed, to which the second guidelines have been applied since April 2006. In recent years, drugs acting on the immune system such as immune checkpoint inhibitors have become a major part of the development of novel anti-cancer drugs. The effects and adverse events associated with these drugs are different from those of conventional cytotoxic drugs and molecular-targeted drugs, thereby making it necessary to update points to consider on clinical studies.[2,3]

There have been major changes in the development of molecular-targeted drugs since the release of the previous guidelines. Certain drugs targeting driver mutations particularly important for cancer development have proven highly effective, leading to the development of drugs against functional changes based on less frequent gene mutations.[4] In the clinical development of anti-cancer drugs for these rare molecular subtypes (see Section VI), it is often difficult to conduct a confirmatory randomized controlled study using overall survival as the primary endpoint, and the primary evaluation of the efficacy of some drugs and subsequent approval is based on the tumor response observed in a phase II study.[5,6]

As it is often difficult to conduct clinical studies for rare subtypes solely within Japan, drug development needs to be proactively conducted as a global study even in early clinical studies.

In addition, cancer genomic testing has been introduced in clinical practice as part of a 'cancer precision medicine' to identify rare molecular subtypes,[7-9] and many drugs will be also developed for tumors based on less frequent gene changes in the future. If there is strong biological support for a driver role of an infrequent genomic alteration, some anti-cancer drugs can be approved for use across cancer types with the genomic alteration in a 'tumor agnostic' manner after demonstrating efficacy and safety in a single clinical study enrolling different types of cancer.[10-13] When an anti-cancer drug is approved across different types of cancer, the drug may be utilized even for cancer types for which efficacy data are lacking. Therefore, it is necessary to carefully determine whether or not the use of the drug is scientifically appropriate and to promote the proper use of drugs based on the available knowledge, which includes information obtained in a post-marketing setting.

There has been development of immune checkpoint inhibitors and molecular-targeted drugs for rare subtypes based on cancer genomic tests.[5,14,15] In some cases, clinical development has been conducted with different perspectives from conventional approaches.[16] Regulatory approval has been granted based on the efficacy of the

drug in clinical studies at the early stage of development[5,6,11,12,17]; this trend may be accelerated in the future.

In response to these changes in drug development, the guideline committee has deemed it necessary to revise the guidelines for the clinical evaluation of anti-cancer drugs in Japan. We expect that drug development will be actively promoted by using the guidelines. Indeed, with increased globalization of drug development, international collaboration is essential for Japanese cancer patients to benefit from new drugs at the same time as their overseas counterparts. However, attention should be paid to ethnic differences in pharmacokinetics and pharmacodynamics between Japan and other countries. We aimed to develop practical guidelines that take into account the opinions of researchers, regulatory authorities, pharmaceutical industries, and cancer patients.

3 | OUTLINE

3.1 | Definition of anti-cancer drugs

The guidelines cover anti-cancer drugs that are intended for approval by the regulatory authority once they demonstrate clinical usefulness such as inhibition of growth/metastasis/recurrence of malignant tumors leading to prolongation of survival and improvement of symptoms and QOL. There are various types of anti-cancer drugs such as small molecular compounds, antibodies, cell therapies, and vaccines. The guidelines do not cover treatments using cell therapy and gene therapy products, including chimeric antigen receptor T cells (CAR-T). This is because these products require a different consideration from that of other drugs due to the different nature of the products; however, some principles described in the guidelines may be useful as reference.

3.2 | Types of clinical studies of anti-cancer drugs

Clinical development has been generally performed in a stepwise manner and includes 3 phases: phase I, phase II, and phase III studies.[1] Phase I studies evaluate the tolerability, safety, and pharmacokinetics, and determine the dosage and administration. Phase II studies then evaluate the efficacy and safety in an exploratory manner. Finally, phase III studies compare the clinical benefits with conventional standard therapies. In recent years, however, a phase II study may be substituted with an expansion cohort in a phase I study and evaluating the efficacy and safety in an exploratory manner depending on the several parameters including drug characteristics.[18,19] Additionally, a phase II study and a phase III study may be conducted continuously as a single study.[20,21] In any case, the basic principle is that, after tolerability, safety, and pharmacokinetics are evaluated and recommended dosage and administration are determined, efficacy and safety are evaluated in an exploratory manner, and finally clinical benefits are compared with conventional standard therapies.

In these guidelines, an exploratory study corresponding to phases I and II above and a confirmatory study corresponding to phase III are described separately.

3.3 | Basic principles on the clinical development of anti-cancer drugs

In the clinical development of a drug, studies should be conducted based on guidelines issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The concept of accepting overseas clinical study data is shown in ICH E5 ("Handling of Clinical Study Data on Pharmaceuticals Conducted in Foreign Countries" [PMSB Notification No. 739; August 11, 1998]). However, as it is often difficult to conduct clinical studies on rare subtypes only in Japan, the conduct of global studies should be considered more proactively. The following documents also refer to global clinical studies.

- ICH E17 ("Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials" [PSEHB/ PED Notification No. 0612-1; June 12, 2018])
- "Basic Principles on Global Clinical Trials" [PFSB/ELD Notification No. 0 928 010; September 28, 2007]
- "Basic Principles on Global Clinical Trials (Reference Cases)" [Administrative Notice; September 5, 2012]
- "Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials" [Administrative Notice; October 27, 2014]

Clinical studies (clinical trials) intended for regulatory approval need to demonstrate the clinical benefits of the drug in a target population. Clinical benefits are determined by a comprehensive evaluation of treatment effects and adverse events. During this evaluation, a range of factors including the characteristics of the target disease, presence or absence of other treatment, and QOL are considered, and a study design that can appropriately evaluate the endpoints is adopted.

In clinical studies for cancer types with a large number of patients, a clear efficacy based on an endpoint such as survival prolongation must be demonstrated. However, this is not the case for rare cancers. If the number of patients who are expected to respond to the drug based on scientific evidence is markedly small (eg, patients with a rare molecular subtype based on genetic abnormality), it may be difficult or require a long time to conduct a confirmatory study evaluating overall survival.

Cancer is a serious life-threatening disease for which standard therapy has not been sufficiently effective, and there are few effective therapies after treatment with standard therapies fail. To increase the treatment options for cancer patients, development using the conditional approval system for drugs enforced in September 2020 may also be considered. When using a conditional approval system for drugs, clinical utility is evaluated based on surrogate endpoints that should reflect clinical efficacy.

When an application for approval is filed based on data from a small number of subjects (eg, when using the conditional approval system for drugs), attention should be paid to the necessity of continuous and appropriate evaluation of efficacy, safety, and ethnic differences after marketing authorization. There may be ethnic differences in pharmacokinetics and drug efficacy.[22,23] However, when a drug is developed for a rare subtype, it may be approved and used in clinical practice based on data that include only a small number of Japanese patients. In such cases, ethnic differences should also be evaluated after marketing authorization, and it is important to collect and evaluate post-marketing information and then provide the information necessary for the proper use to medical institutions.

For anti-cancer drugs that act on the immune system, adverse events may occur more than several months after the start of treatment, and the immune system may remain activated even after the end of treatment.[2,24-26] Therefore, it is important to collect long-term safety data including data after the end of treatment in clinical studies. In instances when other anti-cancer drugs that may affect the immune system have been used or are concomitantly used, their effects and interactions should be considered. It may be efficient to evaluate efficacy with low tumor volume in maintenance therapy following standard therapy or adjuvant therapy.[27,28] In such cases, sufficient scientific evidence and the ethical nature of the study design should be guaranteed.

If high clinical utility is expected by selecting patients using biomarkers (genomic changes, for example) based on their mode of action or non-clinical study results, clinical evaluation may be performed in patients with first-line or postoperative therapy as opposed to previously treated patients even at an early stage of development. In such cases, there should be sufficient scientific evidence, and ethics must be built into the study design.

It is important to investigate the pharmacokinetics of the drug under development in patients with specific backgrounds, and drug-drug interactions throughout the clinical development after the characteristics of the drug including pharmacokinetics are fully understood.[29,30] It is also useful to identify factors that affect the pharmacokinetics of the drug based on methods including population pharmacokinetic analysis.[31-33] If possible, population pharmacodynamic analyses should also be performed to simulate the pharmacokinetic and pharmacodynamic responses in various situations expected in the clinical practice. In addition, exposure-response analyses for efficacy and safety should be conducted to assess the appropriateness of dosage and administration. There is potential that oral preparations may be affected by food.[34,35] Therefore, it is necessary to examine the effect of food on the dosage form to be marketed by referring to the "Clinical Pharmacokinetic Studies on Pharmaceuticals" (PMSB/ELD Notification No. 796; June 1, 2001). It is desirable to evaluate the food effect prior to commencing a phase III study.

Indicators from the patient perspective, including patient-reported outcomes, are increasingly important in the design of cancer treatment strategies.[36-39] In the development of anti-cancer drugs, it is desirable to gather such information considering the potential for the use of perceived benefits described by patients as endpoints in future clinical studies. Generally, drugs need to be evaluated in actual medical settings and the use of real-world data is also considered.[40]

The efficacy and safety of anti-cancer drugs acting on the immune system may be influenced by the nature of cancer cells including genetic abnormalities, and patient constitution based on genetic factors, lifestyle, and environmental factors. In addition, ethnic differences may exist in these factors.[41,42] Drugs should be developed considering these factors and depending on the best available scientific knowledge.

3.4 | General principles for exploratory study

If the dose is restricted due to adverse events, regardless of whether it is a cytotoxic drug or a molecular-targeted drug, the DLT should be identified and the MTD and RD should be determined. If no DLT is observed in a molecular-targeted drug with well defined target molecules and high selectivity, the dosage and administration to be used in the next phase are determined based on pharmacokinetic/pharmacodynamic findings in non-clinical studies, observed tumor response, dose-response relationships, and pharmacokinetic/pharmacodynamic findings in clinical studies. If a biological response such as target engagement is observed in tumors despite no clear evidence of tumor shrinkage, the dosage and administration may be determined with reference to the biological response, and the efficacy may be evaluated with the relevant dosage and administration.

For antibody drugs, the characteristics of the target molecule including its expression in human normal tissues should be examined prior to the beginning of clinical studies to assess possible risks in humans. In exploratory studies of molecular-targeted drugs including antibody drugs and anti-cancer drugs acting on the immune system, pharmacological and immunological analyses before and after administration may provide useful information for clinical development.[43-46]

If pharmacological action cannot be appropriately evaluated after standard therapy, and if the drug is expected to be effective and confirmed to be well tolerated, it may be administered only for a short period of time prior to standard therapy with due consideration to ethical aspects. Pharmacodynamic evaluation and biomarker exploration using clinical samples including tumors before and after administration may be informative for subsequent clinical development.[47,48]

When drug development is conducted using biomarkers, an explanation that therapeutic effects of the drug are associated with the relevant biomarkers must be given based on scientific evidence. In the conduct of clinical studies, it must be documented that clinical trial assays that detect biomarkers have achieved an adequate level of analytical performance. It is important to identify patient populations by biomarkers for which clinical benefits are expected, but care should be taken not to exclude populations that may clinically benefit from the drug before clinical studies are conducted. In early

clinical studies, biomarkers are often evaluated in an exploratory manner. In confirmatory studies, it is important to examine the appropriateness of the clinical cut-off value and the clinical usefulness of the assays.

As cancer rarely results in spontaneous regression to the extent that it meets the definition of a response, the response rate is considered the most appropriate endpoint to evaluate tumor response in single-arm clinical trials. For the evaluation of endpoints requiring the measurement of tumor size such as tumor shrinkage and progression-free survival, the timing of the evaluation should be specified in the protocol in advance and strictly followed.

With the recent globalization of drug development, a global study may be conducted from the phase I stage for investigational drugs for diseases with low frequency.[49,50] In such cases, accurate information should be shared rapidly and possible ethnic differences should be considered in study designs. In some cases, tolerability in Japanese patients may be evaluated as the initial part of a global phase II or phase III study.

3.5 | General principles for confirmatory study

In principle, the dosage and administration in the global confirmatory study should be identical for all participating ethnic groups. However, data from early clinical studies may reveal clear differences in the dose-response or exposure-response relationship between ethnic groups. In such cases, it may be appropriate to use different dosage and administration strategies. The dosage and administration schedule should be expected to provide a similar therapeutic effect within the acceptable safety range, and scientific validity to use the different dosages and administrations should be described in the protocol. In addition, the evaluation method for different dosages and administrations should be carefully planned in advance for each case and clearly described in the analysis plan.

Cancer is a life-threatening disease, and overall survival is the most meaningful endpoint for patients. However, progression-free survival, disease-free survival, or QOL can also be used as efficacy endpoints depending on the clinical condition if they are meaningful indicators for patients. However, as these endpoints may introduce bias into the evaluation if treatments are not double-blinded, clinical studies should be designed to minimize bias. When the relief of symptoms caused by a local tumor is important for patients, its control may also be an efficacy endpoint. As MRD may be a surrogate endpoint in the future, it is desirable to collect data based on a clear definition of MRD.[51] Nonetheless, the principle in confirmatory studies for cancers in incurable condition is to evaluate the efficacy by endpoints that directly reflect clinical benefits such as overall survival.

The efficacy of a drug is evaluated based on tumor response and its duration in some rare subtypes in a tumor agnostic study using a biomarker.[10-13] However, for cancer types with a certain frequency, phase III studies should be conducted to evaluate the effect of prolonging survival, in a randomized controlled study. It is conceivable that indices from the patients' feeling/perception will become important in the future. It is important to include assessment of efficacy and safety by means of patient-reported outcomes or QOL in which therapeutic effects and adverse events are evaluated by the patients themselves.

It should be noted that anti-cancer drugs acting on the immune system may have characteristics different from those of conventional anti-cancer drugs; for example, immune oncology drugs may be associated with an increased probably of extended overall survival.[52] In addition, it is desirable to perform a study treatment with an appropriate study design that can infer patients in whom the effect is expected.

It is not ethically acceptable to use placebo as a control in a comparative study in a disease status for which a standard therapy is available. The exception to this is when the clinical benefits of the investigational drug are investigated as an add-on to standard therapy. Conversely, when verifying the clinical benefits of an add-on to standard therapy, it is desirable to use placebo in combination with the standard therapy as the control group whenever possible.

Combination therapy with novel agents such as those acting on the immune system or combination therapies that induce synthetic lethality may be considered as a study treatment. In these instances, the contribution of each individual drug to the combination and their interaction need to have been confirmed in the previous clinical studies.

A randomized, active-controlled, non-inferiority study is acceptable for treatments that obviously reduce the burden on patients and/or the adverse events they experience to a clinically significant extent.

In confirmatory studies, early termination is acceptable if sufficient efficacy is demonstrated in an interim analysis. Alternatively, futility stop may occur if it is highly unlikely that efficacy will be demonstrated. In such cases, the termination criteria should be determined in advance. Futility stop can minimize the number of patients receiving ineffective treatment, while early termination due to efficacy can lead to the early approval of useful investigational drugs.

For early termination based on an interim analysis of efficacy, sufficient scientific and ethical rigor must be demonstrated. For example, crossover should be allowed, as it will provide patients enrolled in the control group with an opportunity to benefit from a novel experimental therapy. Statistical analysis methods, including interim analyses, should be determined prior to beginning the study and described in the protocol.

4 | EXPLORATORY STUDY

4.1 | Phase I study

4.1.1 | Objectives

A phase I study is a clinical study in which an investigational drug is administered to humans for the first time based on the results of

non-clinical studies or an equivalent study. The primary objective is to investigate the dose-dependent safety of the investigational drug with reference to observations in non-clinical studies. In general, the following are carried out.

1. Evaluation of DLT, and determination of MTD and RD
2. Examination of pharmacokinetics
3. Observation of therapeutic effect
4. Search for predictive biomarkers for response (eg, molecular-targeted drugs)

4.1.2 | Study investigators and study sites

It is desirable that investigators with sufficient knowledge and experience of anti-cancer drugs conduct a clinical trial in cooperation with researchers with sufficient knowledge of results of non-clinical studies and those with expertise in clinical pharmacology. As unexpected toxicity may occur in a phase I study, the study should be conducted in a single center or the least possible number of institutions that have similar capability to evaluate the drug under investigation; study investigators should also communicate closely so that the study is safely performed.

4.1.3 | Study population

Phase I studies evaluating anti-cancer drugs with a certain level of toxicity should be conducted in patients with cancer instead of healthy individuals. Cancer patients who would benefit from prolonged survival or relief of symptoms with generally accepted standard therapies should not be enrolled on phase I trials. Phase I studies of drugs that are predicted to cause no significant toxicity in humans based on non-clinical studies or pharmacological action may be conducted in healthy individuals.

Hospitalization is not uniformly required. However, due to the potential for unknown and unexpected adverse events, evaluation and management should be performed in an environment in which emergency medical care is available. If it is difficult to ensure sufficient safety, the study should be performed under inpatient management.

The target patients should meet the following criteria.

1. In principle, a malignant tumor should have been confirmed by histology or cytology.
2. Patients with a malignant tumor who are not expected to respond to standard treatments or for whom no standard therapeutic option is available in the clinical practice guidelines of the academic societies at the time of enrolling to the study. If exploratory studies are conducted in patients with cancer for which standard therapies are available, scientific and ethical validity should be fully examined. It is not always necessary to have measurable lesions depending on the objective of the study, status of the target disease, or characteristics of the drug. If it is obvious that a particular type of cancer will be included in a future clinical study due to the characteristics of the drug or the development plans, the study may be limited to that type of cancer.
3. Patients with adequate physiological compensation with no significant impairment in the bone marrow, cardiac, lung, hepatic, and renal functions or serious complications, ie, patients whose organ functions and performance status have been maintained allowing for the appropriate evaluation of adverse events at the time the investigational drug is administered.
4. Toxicities of prior therapy are not carried over, or are mild enough to allow an adequate evaluation of adverse events at the time the investigational drug is administered, ie patients are in a stable physiological state at the start of the study. A clinically appropriate interval is required from prior therapy.
5. Sufficient life expectancy (eg, at least 3 mo) to observe tumor response and adverse events.
6. No factors that make it difficult to evaluate adverse events, such as complications that affect pharmacokinetics.

4.1.4 | Phase I study design

Route of administration

The expected route of administration and dosage for phase II study are examined based on the results of non-clinical studies, and an appropriate scientific rationale is necessary for the selected administration route and dosage and administration. For combination therapy, interactions between the combined drugs are examined by investigating pharmacokinetics/pharmacodynamics; information from such studies is used to determine the timing of administration.

Evaluation criteria for adverse events

Adverse events are evaluated for the term and severity according to the internationally acknowledged CTCAE.[53]

Endpoints

- Presence or absence of DLT

The causal relationship between the investigational drug and adverse events should be evaluated. Those events that have a causal relationship or for which a causal relationship cannot be ruled out are adverse reactions. Adverse reactions leading to dose restrictions are DLTs. The definitions of DLT (type, severity, and frequency) and MTD as well as the criteria for decision should be clearly specified in the protocol in advance.

Molecular-targeted drugs are often administered daily over long periods of time. In such cases, toxicities equivalent to DLT may appear after several courses of administration. In this case, it is desirable to comprehensively evaluate the toxicities to make a final decision on RD. Furthermore, toxicity can be persistent for drugs that are continuously administered over a long period of time, such as oral drugs. Therefore, it is necessary to define DLT according to

the characteristics of the drug (ie, persistent toxicity should be defined as DLT even if the grade is lower than that of intermittently administered cytotoxic drugs).

- Pharmacokinetics and pharmacokinetic/pharmacodynamic evaluation
  Required to determine dosage and administration.
- Tumor response
  May be evaluated to select cancer types or to explore biomarkers.

Determination of initial dose

The initial dose and administration schedule for the first-in-human study are based on the results of non-clinical studies. With reference to ICH S9 (Nonclinical Safety Evaluation of Anti-cancer Pharmaceuticals [PFSB/ELD Notification No. 0604-1; June 4, 2010]) and "Guidance for Establishing Safety in First-in-Human Studies during Drug Development" [PFSB/ELD Notification No. 0402-1; April 2, 2012], in principle, the initial dose is set at 1/10 of the severely toxic dose in 10% of animals (STD10) in rodents or 1/6 of the HNSTD in non-rodents. The initial dose is set after converting the dose in animals (mg/kg) to body surface area (mg/m^2), depending on parameters such as the route of administration and characteristics of the drug.

For immune oncology antibody drugs with high specificity to human epitopes, it is assumed that there are no animal models that exhibit pharmacological effects, and it is difficult to set the initial dose for first-in-human studies. However, it is recommended to conduct pharmacological and toxicological evaluation as much as possible. If this is difficult, it is desirable to evaluate toxicity based on in vitro pharmacological effects using human cells and human tissue cross-reactivity studies. For antibody drugs that may have agonistic effects on the immune system, the initial dose is determined based on scientific evidence such as the MABEL in consideration of the risk of unexpected adverse effects based on the results of non-clinical studies.[54,55]

Dose escalation plan and observation period

In cytotoxic anti-cancer drugs, the dose range expected to be effective is generally close to the toxic range. This should be fully noted when considering the method for dose escalation of the investigational drug. A 3 + 3 cohort design using a modified Fibonacci sequence may be used as a general dose escalation method.[56,57] Alternatively, an appropriate design such as Bayesian design may be adopted according to scientific progress.[58,59] In any case, there should be careful consideration when the dose of the investigational drug is increased based on the slope of the dose-toxicity curve in non-clinical studies and the results of pharmacological studies. In doing so, the slope of the dose-exposure-response curve and heterogeneity among patients should also be taken into consideration. The historical non-clinical and clinical data from trials that used a similar agency-approved drug can be used as references. Based on the above, the dose is carefully increased until the MTD is determined or to the dose level at which the biological effect is obtained.

In principle, each dose escalation should be appropriately determined, and MTD is evaluated based on adverse events with a causal relationship to the investigational drug or adverse events for which a causal relationship cannot be ruled out during the DLT evaluation period. Adverse events that occur after the DLT evaluation period should also be examined, and the dose escalation and MTD evaluation then modified accordingly. The RD is finally determined by taking these into consideration. If the investigational drug has delayed toxicity in non-clinical studies, it is necessary to set a sufficient observation period to protect patients from toxicity.

Intra-patient dose escalation

In principle, the dose should not be increased in the same patient. However, it may be increased in the same patient if the following conditions are met.

- The investigational drug is tolerable in the relevant patient and higher efficacy can be expected by dose escalation.
- There is no effective therapeutic drug other than the investigational drug.
- The patient agrees to continue treatment at an increased dose.
- The tolerability of the investigational drug at the increased dose has already been confirmed.

While information on the tolerability of the patients at the increased dose is used to evaluate safety, it should not be used to determine the DLT.

Investigational drugs with prior results in overseas

For investigational drugs for which reliable clinical results have been available and parameters such as the efficacy, safety, MTD, and pharmacokinetics/pharmacodynamics have been demonstrated overseas, the initial dose, dosage and administration, and dose escalation plan in the Japanese phase I study can be set using the results of the overseas studies based on the ICH E5 guidelines. However, it is necessary to carefully evaluate the applicability of information on pharmacokinetics/pharmacodynamics from the beginning of the study.

If it is possible to predict that there are no ethnic differences in pharmacokinetics/pharmacodynamics and safety of the investigational drug in the phase I study, efficient conduct of subsequent clinical trials should be discussed according to the ICH E5 guidelines.

Pharmacokinetic examination

Before starting the study, it is necessary to establish a measurement system for drug concentration, identify active metabolites, and investigate metabolic pathways. Parameters (eg, clearance, volume of distribution, bioavailability, half-life, metabolites, protein binding) related to ADME of the investigational drug are evaluated, and the possibility of accumulation of the unchanged drug or metabolites, the relationship with the onset of toxicity, slope of the dose-exposure-response curve and so on are investigated. These parameters are

used to determine the appropriate administration route, dose, and dosing schedule.

Pharmacodynamic evaluation

Blood and/or tumor tissue samples obtained during the study are evaluated for expected pharmacological effects (for example, signs of an immune response for immunotherapy).

Determination of RD

The RD to be used in the next phase study is determined through a comprehensive consideration of DLT, the type and frequency of adverse events observed throughout the study, pharmacokinetics, antitumor effects, and dose intensity. For some anti-cancer drugs such as immunotherapy, the setting of RD based on the concept of MTD may not be appropriate. In such cases, it may be appropriate to use the evaluation of biomarkers based on presumed pharmacological action or immune response to determine the RD.

Exploratory investigation

Following dose escalation in a phase I study, the exploratory evaluation of tumor response in specific types of cancer and assessment of alternative dosage and administration of the relevant drug (including combinations with other anti-cancer drugs) may be undertaken in a single cohort or multiple cohorts as an expansion cohort. However, when tumor response in a particular cancer type is evaluated in an exploratory manner, the principles underpinning a phase II study should be applied. Appropriate termination criteria should be established based on efficacy and safety.

4.2 | Phase I/II study

Due to the limited number of patients who receive the drug at the RD in phase I studies, sufficient information on safety, pharmacokinetics, and therapeutic effect may not be available. In the phase I/II study, the RD is determined during the phase I component, and the safety, pharmacokinetics, and therapeutic effects of the drug administered at the RD in an additional target population may be acquired during phase II component.

In terms of the study population and study design, the phase I component should be conducted according to the principles for the phase I study, while the phase II component should be conducted according to the principles for the phase II study.

4.3 | Phase II study

4.3.1 | Objectives

The objectives of phase II studies are to evaluate the clinically significant efficacy and safety of the investigational drug in the target cancer type and population according to the dosage and administration determined in the phase I study, and to decide whether further evaluation should be conducted (eg, a phase III study comparing the new treatment that incorporates the investigational drug with existing standard therapy).

At times, a randomized, controlled study may be conducted, but this is a non-confirmatory study designed to plan subsequent phase III studies.[60] Infrequent adverse reactions that were not detected in the phase I study or had occurred in a subacute or accumulated manner are also further evaluated.

4.3.2 | Study sites

Studies are performed at multiple or single sites.

4.3.3 | Study population

The target patients should meet the following criteria in principle.

1. Malignant tumor confirmed by histology or cytology.
2. Patients showing no response to standard therapies or having no standard or equivalent therapies. However, if the study treatment is expected to be as effective (or more effective) than standard therapies or if combination with existing therapy is considered scientifically and ethically appropriate, patients who have not received standard therapies are allowed to participate.
3. Appropriate physiological function (bone marrow, cardiac, lung, hepatic, renal, etc.) and performance status.
4. No remaining toxicities of prior therapy or toxicities that are mild enough to allow an adequate evaluation of adverse events at the time the investigational drug is administered, ie, patients in a stable physiological state at the start of the study. A clinically appropriate interval is required from prior therapy.
5. Life expectancy for a sufficient period of time (eg, at least 3 mo) to observe tumor shrinkage and adverse events.
6. No factors that make it difficult to evaluate effects or adverse events, such as serious complications, multiple primary cancers, or complications that affect pharmacokinetics.
7. Objectively measurable lesions for the quantitative measurement of tumor response if the primary endpoint is the response rate.

4.4 | Endpoints

4.4.1 | Tumor response

A clinically meaningful treatment effect in a phase II study is usually a tumor shrinkage that is evaluated using certain criteria. However, in the development of anti-cancer drugs that act on the immune system, the effect on the tumor may be delayed, and therefore the endpoints should be set considering the possibility that the true effect and toxicity may be overlooked when the effect is evaluated

based only on the conventional tumor response. The duration of the response is also clinically important and should be evaluated.

4.4.2 | Overall survival, progression-free survival

If efficacy is to be demonstrated using time-dependent measures such as overall survival as the primary endpoint, a randomized, controlled study should be carried out.

4.4.3 | Type, severity, and frequency of adverse events

It is desirable to prepare guidelines summarizing the recommendations to control adverse reactions.

4.4.4 | QOL

If an evaluation of QOL is planned in a phase III study, exploratory evaluation should also be considered in a randomized phase II study as this would serve as reference for the design of a phase III study.

4.4.5 | Biomarkers

Biomarkers that predict the efficacy of molecular-targeted drugs are further explored.

4.4.6 | Pharmacokinetics and exposure-response relationship (efficacy and safety)

Safety in each population is investigated based on risk factors identified from ADME characteristics. Evaluation should focus on the relationships between exposure and efficacy endpoints and between exposure and safety endpoints, and the appropriateness of each dosage and administration.

If the phase I study suggests a relationship between pharmacokinetics and specific adverse reactions, a phase II study should further investigate and evaluate this potential relationship. There should also be an investigation into drugs that may induce immune-related adverse events (irAEs),[61,62] including cytokine release syndrome, in terms of their presence, severity, and methods to resolve them.

4.5 | Selection of target cancer type and number of patients

The study should be conducted for specific cancer types for which the treatment is expected to be effective based on observations in the phase I study, or based on similarities with existing anti-cancer drugs, or results of pharmacological studies using human cancer cells and cell lines.

The expected efficacy level of the anti-cancer drug should be clarified beforehand, and if the primary endpoint is the response rate, the expected response rate is carefully determined considering the effect of prior treatment (the development of cross-resistance, for example). If the drug does not show a response higher than the acceptable threshold response rate, it is not accepted as an effective anti-cancer drug. The threshold response rate and expected response rate may differ depending on multiple factors including the type of cancer and target population, and therefore it is essential to scientifically clarify the rationale for the expected and threshold response rates for each setting.

The number of patients is determined based on statistical inference to evaluate the treatment effect with scientifically sufficient accuracy.

The study should be planned based on sufficient ethical considerations so that it can be terminated early for investigational drugs that do not elicit the expected effects.

4.6 | Dosage and administration

The study should begin based on the dosage and administration, and duration of administration determined appropriate from the results of the phase I study. It is particularly important to carefully consider the function of organs that are involved in pharmacokinetics. In principle, drugs that interfere with the evaluation of the safety and efficacy of the investigational drug or drugs that may interact with the investigational drug should not be used concomitantly.

In addition, to determine an appropriate dosage and administration, multiple candidates of dosage and administration may be investigated.

4.7 | Statistical analysis

If the primary endpoint is the response rate, this should be estimated in a clearly defined target patient population, and the precision (confidence interval, etc.) of the estimate is calculated. In such a case, the response rate is determined for all eligible patients regardless of administration of the investigational drug or, when appropriate, for eligible patients who received the investigational drug.

4.8 | Response evaluation criteria

RECIST are used as the standard for solid tumors.[63] It is desirable to confirm response evaluation in individual patients by a third party organization such as an independent radiological review committee. Criteria appropriate for investigational drugs are used according to current scientific progress. For example, a delayed onset of

effect may be presumed due to the specific mechanism of action in immunotherapy. Response evaluation criteria that take into account the delayed onset of effect have been proposed.[64,65] If the clinical response is therefore evaluated according to the proposed criteria in addition to RECIST, retrospective investigation of such immunotherapy-specific evaluation methods may be possible in future.

In principle, treatment should be terminated if tumor progression occurs. However, it may not be appropriate to immediately terminate a treatment in cases of pseudoprogression, slow tumor growth, or the appearance of new lesions in drugs that are expected to have a delayed effect (eg, drugs acting on the immune system). In such cases, it is necessary to clarify criteria to allow treatment continuation and termination in advance. It may be assumed that the time to progression taking this into consideration is used as the primary endpoint in an exploratory study. However, even in such cases, the definition of the endpoint needs to be clarified.

4.9 | Evaluation criteria for adverse events

The nature and severity of adverse events are evaluated using internationally acknowledged criteria (eg, CTCAE).[53] The relationship between adverse events and investigational drugs must be evaluated. Adverse events for which a causal relationship with the investigational drug is confirmed (or cannot be ruled out) are defined as treatment-related adverse events. For irAEs in immunotherapy, it is desirable to evaluate toxicities for a certain period of time considering the possibility of delayed toxicity onset even after completion of treatment.[3,62]

The observation items include various general laboratory tests and test items considered to be specific to the investigational drug identified by the time of planning the phase II study.

5 | CONFIRMATORY STUDY

5.1 | Phase III study

5.1.1 | Objectives

Phase III studies are conducted to establish better standard therapies. This is a study to compare study treatments with the current standard therapies. Study treatment includes a new drug or treatment method, or a new dosage and administration of approved drugs that have been suggested to have some clinical usefulness, such as safety, tumor shrinkage, and symptomatic relief.

This randomized controlled study must be designed to clearly demonstrate the clinical benefits of the study treatment. Therefore, in the phase III study, the primary endpoint should directly reflect clinical benefits such as overall survival. Other endpoints include relief of symptoms and improvement in QOL, but a well validated evaluation method should be used.[66,67]

In a phase III study, it is necessary to appropriately allocate a well defined patient population among treatment arms considering important prognostic factors, and appropriate data management practices must be in place. Particularly in global studies, it is useful to identify important factors related to ethnic differences at the time of planning, and such information should also be collected in confirmatory studies so that the impact on efficacy and safety can be evaluated later.

5.1.2 | Study sites

Studies are generally performed at multiple sites.

5.1.3 | Study population

The target patients should meet the following criteria in principle.

1. A specific malignant tumor has been confirmed by histology or cytology.
2. Patients fulfilling certain criteria for prior therapy.
3. Patients with appropriate physiological function (bone marrow, cardiac, lung, liver, kidney, etc.) and performance status.
4. Life expectancy long enough to evaluate the therapeutic effect.
5. No factors that make it difficult to evaluate the efficacy, such as serious complications, multiple primary cancers or complications that affect the pharmacokinetics.

5.1.4 | Endpoints

The standard endpoints are indices regarding survival (typically overall survival). If the study is conducted in a population with very good prognosis, the primary endpoint may be progression-free survival or disease-free survival, considering that many patients and extended follow-up periods are necessary if overall survival is used as the primary endpoint.[18]

If progression-free survival or disease-free survival is used as a primary endpoint, it should be confirmed by a third party organization such as an independent radiological review committee. In immunotherapy, pseudoprogression or delayed onset of effect is presumed,[65] and therefore it is desirable to evaluate endpoints considering these as an exploratory endpoint, so that an evaluation method specific to immunotherapy can be investigated later.

5.1.5 | Selection of target disease and study design

If efficacy and safety are observed in a phase II study, the clinical benefits of the study treatment for the target tumor type are compared with an appropriate control group using endpoints such as overall survival.

In a phase III study, patients are randomly assigned to the study treatment group and the control group, and a double-blind method should be used if it is appropriate and possible according to parameters such as the characteristics of the drug.

5.1.6 | Control group

The control group is a standard therapy for the target tumor type. Best supportive care only or standard anti-cancer drug therapy can be used as controls depending on the target tumor, the patient's condition, and characteristics of the investigational drug. The use of such therapies as a control requires medical, scientific, and ethical validity.

The use of a placebo control is not ethically acceptable for diseases with established treatments, except when it is used in combination with standard therapies. When the study treatment is used in combination with standard therapy, the scientific basis for the combination must be clarified or the rationale supporting the combination should be provided by previous clinical and/or non-clinical studies. The use of placebo as a control should be considered for diseases that are refractory to standard therapies.

The control treatment does not necessarily have to be single. Standard therapies may vary by region in global studies, and different treatments may be used as a control depending on the past treatment history and clinical condition. If different treatments are used as a control, it is assumed that there are no clear differences in efficacy and safety among these treatments. In addition, different timing of evaluation for efficacy will impact on time-dependent endpoints such as progression-free survival. Therefore, it is desirable to use a control therapy with the same treatment interval as a study treatment whenever possible.

5.1.7 | Statistical analysis

For statistical analysis of the primary endpoint, such as survival period, a robust and appropriate statistical method should be used. To verify the superiority or non-inferiority of the study treatment to the control group, the target number of patients is determined by using an appropriate power and significance level based on a previously reported treatment effect of the control group and the expected treatment effect of the study treatment. Prognostic factors that may affect treatment effects should be stratified at the randomization stage. If heterogeneous distribution of known prognostic factors occurs or new potentially important prognostic factors are identified during the study, appropriate statistical methods should be applied to examine the robustness of the primary analysis results.

5.1.8 | Evaluation criteria for adverse events

Adverse events are evaluated for their nature and severity using internationally acknowledged criteria (eg, CTCAE).[53] For irAEs in immunotherapy, it is desirable to evaluate toxicity over a certain period of time, considering the potential for delayed onset or onset after completion of treatment.

5.2 | Phase II/III study

A phase II study (an exploratory study to evaluate the efficacy and safety for a specific type of cancer) and a phase III study (a confirmatory study to establish a standard therapy) may be conducted continuously as a single study. Efficacy and safety are analyzed during the phase II component to determine whether it is appropriate to proceed to the phase III component. The dosage and administration in the phase III component are determined based on the efficacy and safety data that were derived from the phase II component.

6 | CLINICAL EVALUATION OF ANTI-CANCER DRUGS FOR RARE CANCERS AND RARE SUBTYPES

6.1 | Basic concept

Rare cancers and rare subtypes are recognized as distinct disease groups. Rare cancers are a group of diseases with very few numbers of patients, which presents greater practical and therapeutic challenges than other cancers.[68] Among clinicopathologically defined (relatively common) cancers, rare subtypes are considered a group of diseases for which there is a common characteristic and biologically significant genomic alteration (such as a fusion gene, mutation, or gene amplification) that occur only in a very few patients[69]; however, there is no clear definition of a rare subtype. It is not defined purely based on the estimated prevalence, and comprehensive analyses must be used to determine whether the target disease corresponds to a rare subset. Rare cancer is defined by prevalence, while the term rare subtype is used to describe a cancer with specific genomic changes.

For drugs developed for rare cancers or rare subtypes with a very small number of patients, it is difficult to conduct a confirmatory randomized controlled study, and they may therefore be evaluated in a single-arm phase II study. In such cases, it is important to explain the clinical benefits in comparison with historical data, and the use of data sources such as a disease registry may be considered if necessary. When using historical data, there should be a focus on their reliability and relevance. Considering that spontaneous regression of cancer rarely occurs, tumor shrinkage is thought to reflect the pharmacological activity of anti-cancer drugs, whereby tumor shrinkage (response rate) should be the primary endpoint in principle. Such cases must be evaluated by an independent radiological review committee. In addition, because sustained tumor shrinkage is considered beneficial for patients, it is considered appropriate to evaluate it in a single-arm disease specific study with a small number of patients. It is also necessary to evaluate not only the response rate

but also the degree of tumor shrinkage, complete response rate, and duration of response. It is also important to evaluate overall survival and progression-free survival.

Some drugs prolong overall survival or progression-free survival even if the response rate is low,[70,71] while the evaluation of tumor shrinkage is difficult in some tumor types.[72] The evaluation method for the development of such drugs for diseases with a small number of patients remains a challenge. Future studies in this area should select appropriate endpoints considering the mechanism of action of the drug and the disease characteristics.

6.2 | Rare cancers

Because of their low incidence, an appropriate endpoint should be selected when performing clinical trials in rare cancers. This is because it will take time to enroll patients, and it is unlikely that a randomized controlled study will be possible. A global study is also recommended, but a certain number of patients should be registered in Japan as well. For rare cancers for which it is difficult to conduct a comparative study, evaluation in a single-arm clinical study and comparison with historical data should be considered, but in addition to tumor shrinkage (response rate), overall survival and progression-free survival should also be added to endpoints whenever possible. High-quality, adequate, and appropriate data should be collected after marketing authorization.

6.3 | Rare subtypes

In a general clinical study, evaluation is performed with a single drug for a single cancer type, but for rare subtypes, a study design based on a master protocol in which evaluation is conducted for multiple drugs and/or multiple types of cancer in parallel in a single protocol with various study designs may be used. Global studies are also recommended, but a certain number of patients should also be enrolled from Japan.

Tumor shrinkage (response rate) can be the primary endpoint. In such cases, overall survival, progression-free survival, and duration of response should be secondary endpoints whenever possible. It is desirable to examine proof-of-concept using biomarkers. If a relevant biomarker to select target patient populations is available based on the mechanism of action of the drug or results of non-clinical studies, the clinical performance of a companion diagnostic should also be evaluated in clinical studies in principle. Performance of clinical trial assays with regard to analytical parameters such as accuracy and precision should be evaluated prior to major efficacy trials.

If the biological significance of a genomic alteration is common among different types of cancer, it may be used as a biomarker to evaluate efficacy and safety in one clinical study across cancer types.[10] If biomarkers are used to define a target tumor type, they should be scientifically validated and clearly defined. It is also recommended that the regulatory authorities are consulted in advance regarding the development strategy. For a drug for which an application for approval is filed with tumor agnostic indications based on a biomarker, high-quality, adequate, and appropriate data are required after marketing authorization, including for cancer types that have not been evaluated in clinical trials.

6.4 | Master protocol

6.4.1 | Basic concept

The master protocol is a study design in which multiple investigational drugs or multiple cancer types are evaluated in parallel using a single protocol.[73] It is not necessary to develop a new protocol for each drug or cancer type, and such a trial is expected to promote the development of anti-cancer drugs for rare cancers and rare subtypes. Among master protocols, study designs such as basket, umbrella, and platform studies are used to evaluate multiple investigational drugs or cancer types concurrently using a single protocol with flexibility. In principle, investigational drugs with known RDs are used for evaluation.

6.4.2 | Basket study

This is a study involving multiple diseases using a single treatment method. Clinical evaluation of a single investigational drug is performed across multiple cancer types with a specific genomic alteration, for example.[69,74] A basket study is exploratory in nature and is based on a single-arm study in which the response rate is the primary endpoint.

6.4.3 | Umbrella study

This is a study of multiple treatments for a single disease. Clinical evaluation is performed for a type of cancer with various molecular abnormalities (gene mutations, for example) or histological types.[69,74] In each sub-study, clinical evaluation of drugs according to parameters such as the presence of genetic abnormalities is performed for molecularly defined subtypes.

6.4.4 | Platform study

This is a continuous study involving multiple therapies for a single disease in which the addition or removal of a new drug or target patients is permitted during the study based on a prespecified algorithm.[75,76] The flexible addition or deletion of new drugs or target patients enables efficient transfer to confirmatory studies. However, studies of this type may be complicated and prolonged, and are associated with an increased management burden.

7 | CONCLUSION

The guidelines have been developed and published with the support of the research fund of the Research on Regulatory Science of Pharmaceuticals and Medical Devices, in the Japan Agency for Medical Research and Development. Methods for the clinical development of anti-cancer drugs are expected to change in response to future science advances. As such, the guidelines will be revised in response to scientific progress.

RELATED GUIDELINES/NOTIFICATIONS

ICH E5(R1): "Handling of Clinical Trials Data on Drugs Conducted in Foreign Countries" (PMSB Notification No. 739; August 11, 1998).

ICH E17: "General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1; June 12, 2018).

ICH S9: "Nonclinical Safety Evaluation for Anticancer Pharmaceuticals" (PMSB/ELD Notification No. 0604-1; June 4, 2010).

"Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010; September 28, 2007).

"Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice; September 5, 2012).

"Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials" (Administrative Notice; October 27, 2014).

"Clinical Pharmacokinetics Studies on Pharmaceuticals" (PMSB/ELD Notification No. 796; June 1, 2001).

"Guidance for Establishing Safety in First-in-Human Studies during Drug Development" (PFSB/ELD Notification No. 0402-1; April 2, 2012).

"Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis" (PSEHB/ELD Notification No. 0515-1; May 15, 2019).

DISCLOSURES

None.

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