Guidance for Industry

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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I. INTRODUCTION (1, 1.1)

The purpose of this guidance is to provide information to assist in the design of an appropriate program of nonclinical studies for the development of anticancer pharmaceuticals. The guidance provides recommendations for nonclinical evaluations to support the development of anticancer pharmaceuticals in clinical trials for the treatment of patients with advanced disease and limited therapeutic options.

This guidance aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals, in accordance with the 3R principles (reduce/refine/replace), and other resources.

As appropriate, the principles described in other ICH guidances should be considered in the development of anticancer pharmaceuticals. Specific situations where recommendations for nonclinical testing deviate from other guidance are described in this document.

A. Background (1.2)

[1] This guidance was developed within the Expert Working Group (Safety) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This guidance has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, October 2009. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Because malignant tumors are life-threatening, the death rate from these diseases is high, and existing therapies have limited effectiveness, it is desirable to provide new, effective anticancer drugs to patients more expeditiously.

There have been no internationally accepted objectives or recommendations on the design and conduct of nonclinical studies to support the development of anticancer pharmaceuticals in clinical trials for the treatment of patients with advanced disease and limited therapeutic options. Nonclinical evaluations are conducted to:

(1) identify the pharmacologic properties of a pharmaceutical,

(2) establish a safe initial dose level for the first human exposure, and

(3) understand the toxicological profile of a pharmaceutical (e.g., identification of target organs, exposure-response relationships, and reversibility).

In the development of anticancer drugs, clinical studies often involve cancer patients whose disease condition is progressive and fatal. In addition, the dose levels in these clinical studies often are close to or at the adverse effect dose levels. For these reasons, the type, timing, and flexibility called for in the design of nonclinical studies of anticancer pharmaceuticals can differ from those elements in nonclinical studies for other pharmaceuticals.

B. Scope (1.3)

This guidance provides information for pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies. For the purpose of this guidance, this patient population is referred to as *patients with advanced cancer*. The guidance applies to both small molecule and biotechnology-derived pharmaceuticals (biopharmaceuticals), regardless of the route of administration. This guidance describes the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals in patients with advanced cancer and references other guidance as appropriate. It describes the minimal considerations for initial clinical trials in patients with advanced cancer whose disease is refractory or resistant to available therapy, or where current therapy is not considered to be providing benefit. The nonclinical data to support Phase 1 and the clinical Phase 1 data would normally be sufficient for moving to Phase 2 and into second or first line therapy in patients with advanced cancer. The guidance also describes further nonclinical data to be collected during continued clinical development in patients with advanced cancer. When an anticancer pharmaceutical is further investigated in cancer patient populations with long expected survival (e.g., those administered pharmaceuticals on a chronic basis to reduce the risk of recurrence of cancer), the recommendations for and timing of additional nonclinical studies depend upon the available nonclinical and clinical data and the nature of the toxicities observed.

This guidance does not apply to pharmaceuticals intended for cancer prevention, treatment of symptoms or side effects of chemotherapeutics, studies in healthy volunteers, vaccines, or cellular or gene therapy. If healthy volunteers are included in clinical trials, the ICH M3 guidance should be followed. Radiopharmaceuticals are not covered in this guidance, but some of the principles could be adapted.

C. General Principles (1.4)

The development of each new pharmaceutical calls for studies designed to characterize its pharmacological and toxicological properties according to its intended use in humans. Modification of "standard" nonclinical testing protocols generally is warranted to address novel characteristics associated with the pharmaceutical or with the manner in which it is to be used in humans.

The manufacturing process can change during the course of development. However, the active pharmaceutical substance used in nonclinical studies should be well characterized and should adequately represent the active substance to be used in the clinical trials.

In general, nonclinical safety studies that are used to support the development of a pharmaceutical should be conducted in accordance with Good Laboratory Practices.

II. STUDIES TO SUPPORT NONCLINICAL EVALUATION (2)

A. Pharmacology (2.1)

Prior to Phase 1 studies, preliminary characterization of the mechanism(s) of action and schedule dependencies, as well as anti-tumor activity of the pharmaceutical, should have been made. Appropriate models should be selected based on the target and mechanism of action, but the pharmaceutical need not be studied using the same tumor types intended for clinical evaluation.

These studies can:

- provide nonclinical proof of principle;
- guide schedules and dose-escalation schemes;
- provide information for selection of test species;
- aid in start dose selection and selection of investigational biomarkers, where appropriate; and,
- if relevant, justify pharmaceutical combinations.

Understanding the secondary pharmacodynamic properties of a pharmaceutical could contribute to the assessment of safety for humans, and those properties might be investigated as appropriate.

B. Safety Pharmacology (2.2)

An assessment of the pharmaceutical's effect on vital organ functions (including cardiovascular, respiratory, and central nervous systems) should be available before the initiation of clinical studies; such parameters could be included in general toxicology studies. Detailed clinical observations following dosing and appropriate electrocardiographic measurements in nonrodents are generally considered sufficient. Conducting stand-alone safety pharmacology studies to support studies in patients with advanced cancer is not called for. In cases where specific concerns have been identified that could put patients at significant additional risks in clinical trials, appropriate safety pharmacology studies described in ICH S7A and/or S7B should be

considered. In the absence of a specific risk, such studies will not be called for to support clinical trials or for marketing.

C Pharmacokinetics (2.3)

The evaluation of limited pharmacokinetic parameters (e.g., peak plasma/serum levels, area under the curve (AUC), and half-life) in the animal species used for nonclinical studies can facilitate dose selection, schedule, and escalation during Phase 1 studies. Further information on absorption, distribution, metabolism, and excretion of the pharmaceutical in animals should normally be generated in parallel with clinical development.

D. General Toxicology (2.4)

The primary objective of Phase 1 clinical trials in patients with advanced cancer is to assess the safety of the pharmaceutical. Phase 1 assessments can include dosing to a maximum tolerated dose (MTD) and dose limiting toxicity (DLT). Toxicology studies to determine a no observed adverse effect level (NOAEL) or no effect level (NOEL) are not considered essential to support clinical use of an anticancer pharmaceutical. As the toxicity of the pharmaceutical can be greatly influenced by its schedule of administration, an approximation of its clinical schedule should be evaluated in toxicology studies. This is further discussed in sections III.C and III.D (3.3 and 3.4).

Assessment of the potential to recover from toxicity should be provided to understand whether serious adverse effects are reversible or irreversible. A study that includes a terminal nondosing period is called for if there is severe toxicity at approximate clinical exposure and recovery cannot be predicted by scientific assessment. This scientific assessment can include the extent and severity of the pathologic lesion and the regenerative capacity of the organ system showing the effect. If a study of recovery is called for, it should be available to support clinical development. The demonstration of complete recovery is not considered essential.

For small molecules, the general toxicology testing usually includes rodents and nonrodents. In certain circumstances, determined case-by-case, alternative approaches can be appropriate (e.g., for genotoxic drugs targeting rapidly dividing cells, a repeat-dose toxicity study in one rodent species might be considered sufficient, provided the rodent is a relevant species). For biopharmaceuticals, see ICH S6 for the number of species to be studied.

Toxicokinetic evaluation should be conducted as appropriate.

E. Reproduction Toxicology (2.5)

An embryofetal toxicology assessment is conducted to communicate potential risk for the developing embryo or fetus to patients who are or might become pregnant. Embryofetal toxicity studies of anticancer pharmaceuticals should be available when the marketing application is submitted, but these studies are not considered essential to support clinical trials intended for the treatment of patients with advanced cancer. These studies are also not considered essential for the purpose of marketing applications for pharmaceuticals that are genotoxic and target rapidly dividing cells (e.g., crypt cells, bone marrow) in general toxicity studies or belong to a class that has been well characterized as causing developmental toxicity.

For small molecules, embryofetal toxicology studies are typically conducted in two species as described by ICH S5(R2). In cases where an embryofetal developmental toxicity study is positive for embryofetal lethality or teratogenicity, a confirmatory study in a second species is usually not warranted.

For biopharmaceuticals, an assessment in one pharmacologically relevant species should usually be sufficient. This assessment might be done by evaluating the toxicity during the period of organogenesis or study designs as described by ICH S6. Alternative approaches might be considered appropriate if scientifically justified. The alternative approaches might include a literature assessment, assessment of placental transfer, the direct or indirect effects of the biopharmaceutical, or other factors.

A study of fertility and early embryonic development is not warranted to support clinical trials or for marketing of pharmaceuticals intended for the treatment of patients with advanced cancer. Information available from general toxicology studies on the pharmaceutical's effect on reproductive organs should be used as the basis of the assessment of impairment of fertility.

A pre- and postnatal toxicology study is generally not warranted to support clinical trials or for marketing of pharmaceuticals for the treatment of patients with advanced cancer.

F. Genotoxicity (2.6)

Genotoxicity studies are not considered essential to support clinical trials for therapeutics intended to treat patients with advanced cancer. Genotoxicity studies should be performed to support marketing (see ICH S2). The principles outlined in ICH S6 should be followed for biopharmaceuticals. If the in vitro assays are positive, an in vivo assay might not be warranted.

G. Carcinogenicity (2.7)

The appropriateness of a carcinogenicity assessment for anticancer pharmaceuticals is described in ICH S1A. Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

H. Immunotoxicity (2.8)

For most anticancer pharmaceuticals, the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential and support marketing. For immunomodulatory pharmaceuticals, additional endpoints (such as immunophenotyping by flow cytometry) might be included in the study design.

I. Photosafety testing (2.9)

An initial assessment of phototoxic potential should be conducted prior to Phase 1, based on photochemical properties of the drug and information on other members in the class. If assessment of these data indicates a potential risk, appropriate protective measures should be taken during outpatient trials. If the photosafety risk cannot be adequately evaluated based on

nonclinical data or clinical experience, a photosafety assessment consistent with the principles described in ICH M3 should be provided prior to marketing.

III. NONCLINICAL DATA TO SUPPORT CLINICAL TRIAL DESIGN AND MARKETING (3)

A. Start Dose for First Administration in Humans (3.1)

The goal of selecting the start dose is to identify a dose that is expected to have pharmacologic effects and is reasonably safe to use. The start dose should be scientifically justified using all available nonclinical data (e.g., pharmacokinetics, pharmacodynamics, toxicity), and its selection based on various approaches (see Note 2). For most systemically administered small molecules, interspecies scaling of the animal doses to an equivalent human dose is usually based on normalization to body surface area. For both small molecules and biopharmaceuticals, interspecies scaling based on body weight, AUC, or other exposure parameters might be appropriate.

For biopharmaceuticals with immune agonistic properties, selection of the start dose using a minimally anticipated biologic effect level (MABEL) should be considered.

B. Dose Escalation and the Highest Dose in a Clinical Trial (3.2)

In general, the highest dose or exposure tested in the nonclinical studies does not limit the dose-escalation or highest dose investigated in a clinical trial in patients with cancer. When a steep dose- or exposure-response curve for severe toxicity is observed in nonclinical toxicology studies, or when no preceding marker of severe toxicity is available, smaller than usual dose increments (fractional increments rather than dose doubling) should be considered.

C. Duration and Schedule of Toxicology Studies to Support Initial Clinical Trials (3.3)

In Phase 1 clinical trials, treatment can continue according to the patient's response, and in this case, a new toxicology study is not called for to support continued treatment beyond the duration of the completed toxicology studies.

The design of nonclinical studies should be appropriately chosen to accommodate different dosing schedules that might be utilized in initial clinical trials. It is not expected that the exact clinical schedule always will be followed in the toxicological study, but the information provided from the toxicity studies should be sufficient to support the clinical dose and schedule and to identify potential toxicity. For example, one factor that can be considered is the half-life in the test species and the projected (or known) half-life in humans. Other factors could include exposure assessment, toxicity profile, saturation of receptors, etc. Table 1 provides examples of nonclinical treatment schedules that are commonly used in anticancer pharmaceutical development and can be used for small molecules or biopharmaceuticals. In cases where the available toxicology information does not support a change in clinical schedules, an additional toxicology study in a single species is usually sufficient.

D. Duration of Toxicology Studies to Support Continued Clinical Development and Marketing (3.4)

The nonclinical data to support Phase 1 and the clinical Phase 1 data would normally be sufficient for moving to Phase 2 and into second or first line therapy in patients with advanced cancer. In support of continued development of an anticancer pharmaceutical for patients with advanced cancer, results from repeat dose studies of 3 months' duration following the intended clinical schedule should be provided prior to initiating Phase 3 studies. For most pharmaceuticals intended for the treatment of patients with advanced cancer, nonclinical studies of 3 months' duration are considered sufficient to support marketing.

When considering a change in the clinical schedule, an evaluation of the existing clinical data should be conducted to justify such change. If the clinical data alone are inadequate to support the change in schedule, the factors discussed in section III.C (3.3) above should be considered.

E. Combination of Pharmaceuticals (3.5)

Pharmaceuticals planned for use in combination should be well studied individually in toxicology evaluations. Data to support a rationale for the combination should be provided prior to starting the clinical study. In general, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced cancer are not warranted. If the human toxicity profile of the pharmaceuticals has been characterized, a nonclinical study evaluating the combination is not usually warranted. For studies in which at least one of these compounds is in early stage development (i.e., the human toxicity profile has not been characterized), a pharmacology study to support the rationale for the combination should be provided. This study should provide evidence of increased activity in the absence of a substantial increase in toxicity on the basis of limited safety endpoints, such as mortality, clinical signs, and body weight. Based on available information, a determination should be made whether or not a dedicated toxicology study of the combination is warranted.

F. Nonclinical Studies to Support Trials in Pediatric Populations (3.6)

The general paradigm for investigating most anticancer pharmaceuticals in pediatric patients is first to define a relatively safe dose in adult populations and then to assess some fraction of that dose in initial pediatric clinical studies. The recommendations for nonclinical testing outlined elsewhere in this document also apply for this population. Studies in juvenile animals are not usually conducted in order to support inclusion of pediatric populations for the treatment of cancer. Conduct of studies in juvenile animals should be considered only when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended pediatric age group.

IV. OTHER CONSIDERATIONS (4)

A. Conjugated Products (4.1)

Conjugated products are pharmaceuticals covalently bound to carrier molecules, such as proteins, lipids, or sugars. The safety of the conjugated material is the primary concern. The safety of the unconjugated material, including the linker used, can have a more limited evaluation. Stability of the conjugate in the test species and human plasma should be provided. A toxicokinetic evaluation should assess both the conjugated and the unconjugated compound after administration of the conjugated material.

B. Liposomal Products (4.2)

A complete evaluation of the liposomal product is not warranted if the unencapsulated material has been well characterized. As appropriate, the safety assessment should include a toxicological evaluation of the liposomal product and a limited evaluation of the unencapsulated pharmaceutical and carrier (e.g., a single arm in a toxicology study). The principle described here might also apply to other similar carriers. A toxicokinetic evaluation should be conducted as appropriate. If possible, such an evaluation should assess both the liposomal product and the free compound after administration of the liposomal product.

C. Evaluation of Drug Metabolites (4.3)

In some cases, metabolites that have been identified in humans have not been qualified in nonclinical studies. For these metabolites, a separate evaluation is generally not warranted for patients with advanced cancer.

D. Evaluation of Impurities (4.4)

It is recognized that impurity standards have been based on a negligible risk, as discussed in ICH Q3A and Q3B. Exceeding the established limits for impurities identified in these ICH guidances could be appropriate for anticancer pharmaceuticals, and a justification should be provided in the marketing application. The justification could include the disease being treated and the patient population, the nature of the parent pharmaceutical (pharmacologic properties, genotoxicity and carcinogenic potential, etc.), duration of treatment, and the impact of impurity reduction on manufacturing. Further, the qualification assessment could include consideration of either the dose or concentration tested in nonclinical study relative to clinical levels. For genotoxic impurities, several approaches have been used to set limits based on increase in lifetime risk of cancer. Such limits are not appropriate for pharmaceuticals intended to treat patients with advanced cancer, and justifications described above should be considered to set higher limits. Impurities that are also metabolites present in animal and/or human studies are generally considered qualified.

Table 1: Examples of Treatment Schedules for Anticancer Pharmaceuticals to Support Initial Clinical Trials

Clinical Schedule	Examples of Nonclinical Treatment Schedule[1,2,3,4]
Once every 3-4 weeks	Single dose
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5-7 days, alternating weeks	Daily for 5-7 days, alternating weeks (2-dose cycles)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Two or three times a week	Two or three times a week for 4 weeks
Daily	Daily for 4 weeks
Weekly	Once a week for 4-5 doses

[1] Table 1 describes the dosing phase. The timing of the toxicity assessment(s) in the nonclinical studies should be scientifically justified based on the anticipated toxicity profile and the clinical schedule. For example, both a sacrifice shortly after the dosing phase to examine early toxicity and a later sacrifice to examine late onset of toxicity should be considered.

[2] For further discussion regarding flexibility in the relationship of the clinical schedule and the nonclinical toxicity studies, see section III.C (3.3).

[3] The treatment schedules described in the table do not specify recovery periods (see section II.D (2.4) and Note 1 regarding recovery).

[4] The treatment schedules described in this table should be modified as appropriate for molecules with extended pharmacodynamic effects, long half-lives or potential for anaphylactic reactions. In addition, the potential effects of immunogenicity should be considered (see ICH S6).

V. NOTES (5)

1. For nonrodent studies, dose groups usually consist of at least 3 animals/sex/group, with an additional 2/sex/group for recovery, if appropriate (see section II.D (2.4)). Both sexes should generally be used, or justification should be given for specific omissions.

2. A common approach for many small molecules is to set a start dose at 1/10 the severely toxic dose in 10% of the animals (STD 10) in rodents. If the nonrodent is the most appropriate species, then 1/6 the highest non-severely toxic dose (HNSTD) is considered an appropriate starting dose. The HNSTD is defined as the highest dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings.