S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

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Nonclinical evaluation for anticancer pharmaceuticals

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A. Introduction

1. Objectives of the Guideline

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 patients with advanced disease and limited therapeutic options. 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. This guideline aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals and other resources.

As appropriate, the principles described in other ICH guidelines 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.

2. Background

Since malignant tumors are life-threatening, the death rate from these diseases is high, and existing therapies have limited effectiveness, it is desired to provide new effective anticancer drugs to patients more expeditiously. Nonclinical evaluations are intended 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 the target organ, estimation of the safety margin, and reversibility. In the development of anticancer drugs, most often the clinical studies involve cancer patients whose disease condition is often progressive and fatal. In addition, the clinical dose levels often are close to or at the adverse effect dose levels. For these reasons, the type and timing and flexibility called for in designing of nonclinical studies of anticancer pharmaceuticals can have a different pattern from those for other pharmaceuticals.

3. Scope

This guideline provides information for pharmaceuticals that are only intended to treat cancer in patients with late stage or advanced disease regardless of the route of administration, including both small molecule and biotechnology-derived pharmaceuticals. This guideline describes the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals and references other guidance as appropriate.

This guideline does not apply to pharmaceuticals intended for patients with long life expectancy, 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 guideline should be followed. Radiopharmaceuticals are not covered in this guideline but some of the general principles could be adapted.

4. General Principles

The development of each new pharmaceutical calls for studies designed to characterize its pharmacological and toxicological properties specifically as it is proposed to be used in humans. This might require modification of "standard" nonclinical testing protocols in order to address novel characteristics associated with either the pharmaceutical or 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 representative of the clinical material.

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

B. Studies to support nonclinical evaluation

1. Pharmacology (description of mechanism of action)

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

These studies can provide preclinical proof of principle, guide schedules and dose-escalation schemes, provide information for selection of test species, aid in starting dose selection, and in some cases justify pharmaceutical combination where clinical information cannot be obtained.

Secondary pharmacodynamic or off target effects should be investigated as appropriate.

2. Safety Pharmacology

An assessment of vital organ function, 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. Stand-alone safety pharmacology studies need not be conducted to support studies in patients with late stage cancer or advanced disease. In case of concern appropriate safety pharmacology studies, core battery described in ICH S7A and/or follow up or supplemental studies should be considered.

3. Pharmacokinetics

The evaluation of limited kinetic parameters, e.g., peak plasma levels, AUC, and half-life, in the animal species used for non-clinical studies can facilitate dose escalation during Phase I studies. Further information on absorption, distribution, metabolism and excretion in animals should normally be generated in parallel with clinical development.

4. General Toxicology

The primary objective of Phase I clinical trials in patients with cancer is to assess the safety of the pharmaceutical. This can include dosing to a maximum tolerated dose (MTD) and dose limiting toxicity (DLT). Therefore, determination of a no observed adverse effect level (NOAEL) or no effect level (NOEL) in the toxicology studies is not considered essential to support clinical use of an anticancer pharmaceutical. Toxicology studies should be designed to support the clinical schedule as exemplified by the examples in Table 1. Evaluation of reversibility and delayed toxicity should be addressed. The demonstration of complete reversibility from all pharmaceutical induced effects is not considered essential. (See Note 1). To support Phase I clinical trials at least one nonclinical study should incorporate a recovery period at the end of the study to assess for reversibility of toxicity findings or the potential that toxicity continues to progress after cessation of drug treatment. Toxicokinetic evaluation should be conducted as appropriate.

5. Reproduction toxicology

An embryofetal toxicology assessment is warranted 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 late stage or advanced cancer. These studies are also not considered essential for pharmaceuticals which target rapidly dividing cells in general toxicity studies or belong to a class which has been well characterized in causing developmental toxicity.

Embryofetal toxicology studies are typically conducted in two species. In cases where an embryofetal developmental toxicity study is positive for embryofetal lethality or is teratogenic, a confirmatory study in second species is usually not warranted.

For biopharmaceuticals an embryofetal toxicity study might not always be feasible. Since this is now under discussion in ICH S6, this will be reviewed in further development of this ICH S9 guideline.

Generally no fertility study is warranted to support the treatment of patients with late stage or advanced cancer. Information available from general toxicology studies on reproductive organs should be incorporated into the assessment of reproductive toxicology.

A peri- and postnatal toxicology study is generally not warranted to support the treatment of patients with late stage or advanced cancer.

6. Genotoxicity

Genotoxicity studies are not considered essential to support clinical trials for therapeutics intended to treat patients with late stage or advanced cancer. Genotoxicity studies should be performed to support marketing (see ICH S2). The principles outlined in ICH S6 should be followed for biopharmaceuticals.

7. Carcinogenicity

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

8. Immunotoxicity

For anticancer pharmaceuticals the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential and support marketing.
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C. Nonclinical data to support clinical trial design and marketing

1. Start dose for first administration in human

The goal of selecting the start dose is to administer a pharmacologically active dose that 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 (Note 2; see section C3). For most systemically administered therapeutics, interspecies scaling of the animal doses to an equivalent human dose should be based on normalization to body surface area (allometric scaling). Although allometric scaling by body surface area is the standard way to approximate equivalent exposure if no further information is available, in some cases (e.g., biopharmaceuticals) extrapolating doses based on other parameters (e.g., body weight) might be more appropriate.

For biopharmaceuticals without agonistic activity or that are antagonists of the intended target/ligand, selection of the starting dose should employ the same principles as described above. For protein therapeutics with agonistic properties, however, selection of the starting dose using an identified, minimally anticipated biologic effect level (MABEL) should be considered.

2. Dose escalation and the highest dose in a clinical trial

In general, the dose-escalation or highest dose investigated in a clinical trial in patients with cancer should not be limited by the highest dose tested in the nonclinical studies. When a steep dose-response curve is observed in nonclinical toxicology studies, or when no preceding marker of toxicity is available, a slower escalation should be considered.

3. Duration and schedule of toxicology studies to support initial clinical trials

Since different dosing schedules might be utilized in initial clinical trials, the design of nonclinical studies should be appropriately chosen. See Table 1 for examples of study designs and durations that can be used for drugs or biopharmaceuticals. In phase I clinical trials, the treatment of patients can continue according to the patient's response, and in this case, a new toxicology study would not be called for in order to support continued treatment beyond the duration of the completed toxicology studies.

An appropriate toxicology study in a single species could suffice to support a more intense clinical schedule (e.g., going from weekly to 3X weekly) than originally supported by previously completed nonclinical studies.

4. Duration of toxicology studies to support continued clinical development and marketing

In support of continued development of an anticancer pharmaceutical for patients with late stage or advanced disease, results from repeat dose studies of 3 months duration following the intended clinical schedule should be provided prior to initiating phase III studies. For most anticancer pharmaceuticals, nonclinical studies of 3 months duration would also be considered sufficient to support marketing.

5. Combination of pharmaceuticals

Pharmaceuticals planned for use in combination should be well studied individually in toxicology evaluations. Data to support a pharmacologic rationale for the combination should be provided prior to starting the clinical study. Based on available information, a determination should be made whether or not a toxicology study of the combination should be conducted. In general, however, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced or late stage cancer are not warranted.

6. Nonclinical studies to support trials in pediatric populations

The general paradigm that exists for most anticancer pharmaceuticals that are investigated 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. Studies in juvenile animals are not usually conducted in order to support inclusion of pediatric populations for the treatment of cancer. The recommendations for nonclinical testing outlined elsewhere in this document also apply to this population. Conduct of studies in juvenile animals should be considered when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended pediatric age group.

D. Other Considerations

1. Conjugated agents

Conjugated agents are pharmaceuticals covalently bound to carrier molecules, such as to proteins, lipids, or sugars. The safety assessment 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.

2. Liposomal products

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 drug and carrier (e.g., a single arm in a toxicology study). The principle described here might also apply to other similar carriers.

3 Evaluation of drug metabolites

In some cases, metabolites have been identified in humans that have not been qualified in nonclinical studies. For these metabolites, a separate general toxicology evaluation might not be warranted for patients with late stage or advanced cancer, as the human safety of the metabolite would have been assessed in phase I clinical trials. If the parent compound is considered positive in an evaluation for embryofetal toxicity or genotoxicity then separate studies for the disproportionate metabolite might not be warranted. Unless there is a specific cause for concern, nonclinical testing of the metabolite is not warranted.

4. Evaluation of impurities

It is recognized that impurities are not expected to have any therapeutic benefit, that impurity standards have been based on a negligible risk (e.g., an increase in lifetime risk of cancer of one in 10^5 or 10^6 for genotoxic impurities), and that such standards might not be appropriate for anticancer pharmaceuticals intended to treat advanced stage patients. The limits on impurities in other ICH guidance might be exceeded as justified on a case by case basis.

Table 1: Example schedules for anticancer pharmaceuticals to support initial clinical trials

Clinical schedule	Nonclinical study schedule[1,2,3]
Once every 3 weeks	Single dose
Daily for 3 days every 3 weeks	Daily for 3 days
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 every 2 weeks	2 doses 14 days apart
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks,
Twice or three times a week	Two or three times a week for 4 weeks
Continuous daily	Daily for 28 days
Continuous weekly	Once a week for 4-5 doses

[1] Schedules described in the table do not specify recovery periods, which should be incorporated into the study design. Timing of recovery sacrifices should be scientifically justified (also see Note 1).

[2] Nonclinical schedule includes rodents and nonrodents. In certain circumstances, determined case-by-case, alternative approaches can be appropriate (e.g. genotoxic drugs targeting rapidly dividing cells). In those cases, a repeat-dose toxicity study in two rodent species might be considered sufficient.

[3] The schedules described in this table should be modified as appropriate with molecules with extended pharmacodynamic effects or long half-lives e.g., monoclonal antibodies. In addition, the potential effects of immunogenicity should be considered (see ICH S6).

Notes
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1- For non-rodent studies, dose groups usually consist of at least 3 animals/sex/group, with an additional 2/sex/group for recovery. However, there can be instances where recovery groups are either not warranted or should be included at some or all dose levels, but this should be scientifically justified. 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 non-rodent is the most sensitive species then 1/6 the Highest Non- Severely Toxic Dose (HNSTD) is considered an appropriate start dose. The HNSTD is defined as the highest dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings.