positive in genetic toxicology assays are assumed to be developmental toxicants, and therefore developmental toxicity studies do not need to be conducted. However, for this class of compounds, little information exists as to risks to the fetus from treating males. Thus, in the absence of such information, appropriate studies should be provided (mating treated males to untreated dams).

6. Genotoxicity

Genotoxicity studies are not necessary to support clinical trials for therapeutics intended to treat patients with late stage or advanced cancer.,. If a drug is clearly positive *in vitro* an *in vivo* study would not be needed. Genotoxicity studies should be performed to support a marketing application.

7. Carcinogenicity

Carcinogenicity studies are usually not necessary to support marketing for therapeutics intended to treat patients with late stage or advanced cancer. The need for carcinogenicity assessment for anticancer pharmaceuticals are described in ICH S1A guidance.

8. Immunotoxicity

For anticancer pharmaceuticals the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential and support marketing. In general additional studies defined in the ICH S8 guidance are generally not needed for pharmaceuticals intended to treat patients with late stage or advanced cancers.

The concepts outlined in ICH S8 should be taken into consideration, however the additional studies are usually not necessary given that the general toxicology evaluation is sufficient to evaluated the immunotoxicity of anticancer agents

9. Special considerations for biopharmaceuticals

Unless otherwise described the principles outlined in ICH S6, and the same considerations above apply to biopharmaceuticals used to treat cancer.

Assessment of pharmacological activity, target distribution and binding affinity are important in selection of a relevant test species for toxicity testing for biopharmaceuticals. These data should be provided prior to initiation of clinical trials.

Mass balance and excretion studies are not needed for chemically synthesized peptide drugs or biological products used to treat cancer.

In those cases where there is sufficient public information to scientifically justify a class effect, mechanistic studies

as outlined in ICH S6 may obviated the need for conducting full reproductive and developmental toxicity evaluation of biopharmaceuticals used to treat cancer.

For biotechnology derived pharmaceuticals genotoxicity and carcinogenicity studies are not needed..

C. Nonclinical data evaluation to support clinical trial design

1. Start dose for first administration in human

The goal of the start dose is to administer a pharmacologically active dose that is reasonably safe to use. This safety of the dose is determined from toxicology studies in the most sensitive species. The start dose should be scientifically justified and may employ various approaches. In case of compounds exhibiting low general toxicity it should be considered to set the starting dose in Phase I clinical trials on the basis of expected pharmacologically active dose. For anticancer small molecular weight drugs, the first-in-human maximal starting dose is usually determined from the appropriate general toxicology studies. (Note 2; see section C3). Doses that cause excessive lethality are not appropriate to select the safe start dose.. For most systemically administered therapeutics, this conversion should be based on the normalization of doses to body surface area. Although body surface area conversion is the standard way to approximate equivalent exposure if no further information is available, in some cases extrapolating doses based on other parameters may be more appropriate.

In certain circumstances, determined case-by-case, alternative approaches may be acceptable (e.g. cytotoxic drugs). In those cases a repeat-dose toxicity study of appropriate duration in two rodent species may be sufficient.

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

In general, nonclinical data do not limit the dose-escalation or highest dose investigated in a clinical trial for cancer patients. When a steep dose-response curve is observed in non-clinical toxicology studies, or 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 may be utilized in initial clinical trials, the design of non-clincial studies should be appropriately chosen. See Table 1 for example study designs and durations that may be used for drugs or biopharmaceuticals.

If a more intense schedule (e.g., going from weekly to 3X weekly) than those used in the toxicology studies used to support the initial clinical trial is to be used clinically, an appropriate toxicology study in a single species could suffice to support this new schedule and be limited to include clinical signs and clinical chemistry at a minimum..

4. Duration of toxicology studies to support continued development

In order to support continued development of a drug for patients with advanced disease, results from repeat dose studies of up to 3 months duration or 3-4 cycles, as appropriate, should be provided prior to initiating phase 3 studies. For most small molecular weight pharmaceuticals, these studies would be sufficient to support product registration. Longer-term studies may be requested in certain circumstances, on a case-by-case basis, to be provided at any phase in development. In Japan, if the indication is for a population without advanced disease, a more extensive evaluation (e.g six month studies in 2 species) should be conducted. In the case of biologic therapeutics, studies of 6 months duration in a relevant animal species are necessary prior to completion of the pivotal registration studies.

5. Combination of pharmaceuticals

Pharmaceuticals planned to be used in combination should be well studied individually in separate general toxicology evaluations. Data to support a pharmacologic rationale and an assessment for the potential for drug-drug interaction for the combination should be provided prior to starting the clinical study. Based on this information a determination is made whether or not a toxicity study should be conducted. In general, however, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced cancer are not needed.

6. Studies in pediatric populations

The general paradigm that exists for most pharmaceuticals that are investigated in pediatric patients is first to define an MTD in adult populations and to assess some fraction of that dose in initial pediatric studies. Studies in juvenile animals are not usually needed to support inclusion of pediatric populations for the treatment of cancer. The requirements 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 aniamal studies are considered insufficient for a safety evaluation in the intended pediatric age group.

7. Special considerations for biologics

The principles described in ICH S6 for dose schedule apply for Oncology. However, a dose schedule of weekly X5 for products with a long-half administered on an intermittent schedules is usually sufficient to provide support for phase I clinical trials. Similar to small molecules molecules doses on a continuous daily basis would be expected to be dosed daily in a nonclinical study as outlined in Table 1

For non-agonist biologics the starting dose should be based on the same principles as described above for small molecules. For agonist antibodies, however, a minimally biologic active dose should be considered.

D.Other Considerations

1. Conjugated agents

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

2. Liposomal

Likely to be deleted and discussed under change in formulation

The safety assessment should include a complete evaluation of the drug product and a more limited evaluation of the unencapsulated drug and carrier.

3. Evaluation of drug metabolites

In some cases, metabolites have been identified in humans that have not been qualified in safety studies. For these drugs, a separate general toxicology evaluation may not be necessary for patients with late stage or advanced cancer as the metabolite is not likely to contribute significantly to the overall toxicity profile and the human safety would have been assessed in phase I clinical trials. If the parent compound is considered positive in an evaluation for embryo-fetal and reproductive toxicity, *in vitro* and *in vivo* for genetic toxicity, or in carcinogenicity studies (if necessary), then separate studies for the disproportionate metabolite may not be needed in any cancer indication.

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 may not be appropriate for antineoplastic drugs intended to treat advanced stage patients The limits on impurities in other ICH guidance may be exceded as justified on a case by case basis.

Table 1:Example Study schedules for Drugs and Biopharmaceuticals to support initial clinical trials

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

[1] Schedules described in the table does not specify recovery periods, which should be incorporated into the study design. Timing of recovery sacrifices should be scientifically justified on the basis of either time for drug clearance, or other important criteria

[2] Nonclinical schedule includes rodents and non rodents

Notes

1- Appropriate *in vitro* and *in vivo* models should be selected based on the target and mechanism of action.Without a clear understanding that the cell line characteristics are related to the pharmacology of the drug it is not required that the same tumor types/models intended for clinical evaluation be studied in these models.]

2 A common approach is to set a start dose at 1/10 the STD 10 in rodents. If the non-rodent is the most sensitive species then 1/6 the HNSTD is considered an appropriate start dose. The HNSTD is defined as the dose level below that in which observations of lethality, life-threatening toxicities or irreversible findings were observed This approach may continue to be followed.

A note to consider

Special attention should be made in clinical trails since non-target tissue binding may result in serious clinical outcomes, particularly with antibodies that mediate antibody or complement-dependent cytotoxicity (ADCC and CDCC, respectively) and will not be sufficiently characterized in nonclinical studies when pharmacologically active antibodies or cytotoxic immunoconjugates are used.

NOT TO BE INCLUDED IN GUIDANCE _ THIS IS ONLY FOR REFERENCE

Timing of nonclinical studies in relation to clinical development in patients (for small molecules)

Nonclinical studies	Prior to first administration	During Clinical development	Marketing Application Approval
Primary Pharmacodynamics	Preliminary characterization of antitumor activity	Follow-up and supplemental studies	Submitted with filing
Safety Pharmacology	Preliminary characteristics	Follow-up/supplemental, as appropriate	Submitted with filing
Pharmacokinetics	Preliminary characterization	Evaluation of ADME	Submitted with filing
General Toxicology including toxicokinetics including local tolerance/safety pharmacology, and reversibilty, as appropriate See data need in footnote	Up to 28 days in two species	Options: Option 1 – 3 month studies in two species rodent and non-rodent provided prior to initiating phase III studies Option 2-6 month studies in two species rodent and non-rodent following new M3 guidance	Rationale Option 1- Over last 10 years the utility of 6 mo studies has not been demonstrated – 6 mo studies submitted with filing have not impacted clinical development in Oncology Option 2 & 3–Current experience with all drug classes
Genotoxicity	Not needed	Not needed	ICH battery submitted with filing, as appropriate
Reproduction Toxicology	Not needed	Prior to long term clinical trials – pending M3 - specific studies needed will be discussed in the text	Submitted with filing
Carcinogenicity	Not needed	Not needed	May be needed under certain circumstances and/or cause for concern- may be requested post-approval - see S1A
Immunotoxicity	Not needed	Deferred discussion	

Data need – findings in 6/9 mo studies that impacted on clinical development that were not observed in 3 month studies

［別添５］S9ガイドラインstep 2文書

Nonclinical evaluation for anticancer pharmaceuticals

Table of contents

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.

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

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.

［別添６］S9ガイドライン骨子文書和訳版

ICH抗悪性腫瘍薬の非臨床試験に関するガイドライン

目次

A．緒言

1．ガイドラインの目的

抗悪性腫瘍薬開発の裏づけとなる非臨床試験のデザインと実施に関して、これまで国際的に受け入れられている方針や勧告はない。本ガイドラインの目的は、抗悪性腫瘍薬開発に向けた非臨床試験プログラムの適切なデザインに資する情報を提供することにある。本ガイドラインで提示する勧告は、ほとんどの開発プログラムがクリアできる最低限のものである。従来より、臨床試験開始に必要とされる十分な非臨床データを得るためのアプローチはこれ以外にも提供されており、それらを必要に応じて具体的な治療法開発プログラムの参考にするものとする。本ガイドラインは、動物及びその他の資源の不必要な使用を避ける一方、開発を促進・加速し、かつ患者を抗悪性腫瘍薬によって生じる不必要な有害作用から守るために作成された。

本ガイドラインに収載された勧告は、発行時点で入手可能であった科学的情報や規制情報をもとに作成されている。薬剤開発に関連する生物医学分野の学問の進歩の結果、将来的には修正が加えられることが予想される。抗悪性腫瘍薬の開発では、他のガイダンスに記された指針も考慮するものとする。

2．背景

悪性腫瘍は生命を脅かすものであり、この疾患による死亡率は高く、既存の治療法の効果は限定的であることから、一刻も早く腫瘍患者への効果的な新規抗悪性腫瘍薬の提供が求められている。一般的に非臨床安全性評価を実施する目的は、1）ヒトに対する初回臨床試験のための安全な初回用量レベルを確立すること、2）標的器官の特定、安全域の見積もり、可逆性などの薬剤の毒性プロファイルを明確にすること、そして3）臨床において有害反応モニタリングを実施する際の評価項目を見出すことである。しかし、抗悪性腫瘍薬開発の特徴とも言えるが、第Ⅰ相臨床試験に参加する悪性腫瘍患者の疾患状態は進行性で致死的であることが非常に多い。さらに、臨床用量レベルが毒性量と非常に近い又は同じであることがしばしばある。このような理由から、抗悪性腫瘍薬の安全性試験のデザインに必要とされる試験の種類と実施時期、そして柔軟性は、その他の薬品の場合とは異なるパターンとなる可能性がある。開発された個々の抗悪性腫瘍薬が使用される具体的な状況を踏まえ、科学的見地から安全性試験の種類と実施時期を個別に決定した上で非臨床安全性を適切に評価しなければならない。

3．範囲

本ガイドラインは、低分子医薬品やバイオテクノロジー応用医薬品（バイオ医薬品）などを含め、投与経路にかかわらず、悪性腫瘍患者の治療を目的としたすべての医薬品に関する情報を提供する。本ガイドラインでは、抗悪性腫瘍薬の開発に関連した安全性試験の種類と実施時期の基本概念を規定する。

本ガイドラインは、副作用軽減又は悪性腫瘍予防を目的とした医薬品、健康被験者における試験、ワクチン、細胞、或いは遺伝子療法には適用されない。臨床試験に健康被験者を含める場合には、ICH M3ガイドラインに従うものとする。放射線医薬品は本ガイドラインの対象ではないが、一般原則の中には適用できるものもある。

4．一般原則

個々の新規医薬品の開発においては、ヒトへの使用を想定して具体的にその薬品の薬理と毒性を明らかにするための試験をデザインすることが求められる。この際、医薬品又はその医薬品をヒトで使用する方法に関連して生じる新たな特性に対処するために、「標準的な」非臨床試験プロトコルの変更が必要となる可能性がある。

開発過程で製造工程に変更が生じることもある。したがって、非臨床試験を行う医薬品はGMPに従って製造される必要はない。しかし、非臨床試験で用いられる有効成分の特性は十分に明らかにされていなければならず、分析方法及び純度は試験報告書に記載されるものとする。

一般的に医薬品の開発を裏付けるための非臨床安全性試験は、GLP（医薬品の安全性に関する非臨床試験の実施の基準）の記載に従わなければならない。

B．安全性評価を裏付けるための非臨床試験

1．薬理（作用機序の説明）

第Ⅰ相臨床試験前に、予備的に作用機序、耐性、スケジュール依存性、及び*in vivo*での抗腫瘍活性の特性を明らかにしておかなければならない。必要に応じ、これらの特性を第Ⅱ相及び第Ⅲ相臨床試験と並行してより詳しく調査すべきである。

これらの試験によって、前臨床において原理検証を行うことができるとともに、スケジュール及び用量漸増スキームの指針、試験動物種の選択に必要な情報、開始用量選択の支援、そして時として臨床的情報が入手できない場合における適切な医薬品の組み合わせの正当性を提供することができる。

必要に応じ、副次的薬理効果や目的とする薬理作用以外の効果についても調査するものとする。

これらの医薬品が腫瘍促進因子として作用する可能性があるか、腫瘍増殖を増強する可能性があるか、又は効果的な治療を妨げる可能性があるかどうかについても慎重に考慮しなければならない。このため、これらのパラメータに対する医薬品の影響を評価することは不可欠である。併用化学療法の有無における*in vitro*及び*in vivo*のデータ（異種移植、遺伝子組み換えモデルなど）は、これらの製品の有害な影響について貴重な洞察を与えると考えられ、したがってそのような情報は初回臨床試験の裏づけとして提供されるべきである。注釈1を参照のこと。

a．*In vitro*試験

*In vitro*試験の主な目的は、試験物質に関するメカニズム情報を得ること及び活性プロファイルの特性を明確にすることである。

i．活性プロファイルと作用機序

特定の標的構造が示唆される場合、可能であればこの構造を様々なレベルで発現する細胞系で研究を行うべきである。その際、遺伝子型や生化学についてその特性がよく知られている細胞系の使用が奨励される。

ii．耐性機序

作用機序の特性の解析と並行して、それに対応した耐性発現のメカニズムについても情報を得ることができる場合がある。細胞系を新薬に長期曝露することにより起こりうる耐性誘導の調査や、さらに耐性機序の特性を解析することが奨励される。

b．*In vivo* 試験

*In vivo*試験の主な目的は、抗腫瘍活性、治療指数、スケジュール依存性に関するより詳しい情報を得ることである。

動物での試験は通常、可能であれば薬物動態／薬力学において生じうるヒトとの差異を十分に考慮し、主にマウスなどのげっ歯類において行われる。適切な動物モデル（種、系統、腫瘍タイプなど）の選択は、その抗悪性腫瘍薬の特性や提案されている治療適応、そして様々な腫瘍細胞系の反応に関して入手可能な情報によって決まってくる。

適切な抗腫瘍活性の評価基準は、腫瘍増殖、生存期間、寛解又は治癒の程度などである。

2．安全性薬理

心血管系、呼吸系、中枢神経系など生命維持に欠かせない臓器の機能に対する評価は、第Ⅰ相試験前の一般毒性評価に含めてもよい。安全性薬理試験は、末期がん又は進行がん患者の治療には必要ないこともある。懸念がある場合には適切な安全性薬理試験、コアバッテリー試験（core battery）及びフォローアップ試験、又は補足的安全性薬理試験を考慮すべきである。

3．ADMEを含む薬物動態／トキシコキネティクス

非臨床試験で用いられる動物種における最高血漿中濃度や血中濃度曲線下面積（AUC）などの限定された速度論的パラメータの評価は第Ⅰ相試験の用量増加を容易にする可能性がある。通常、動物におけるADMEについてのより詳しい情報は、臨床開発と並行して入手すべきである。

4．全身毒性

悪性腫瘍患者を対象とした第Ⅰ相臨床試験の主要目的は、最大耐量（MTD）と用量規定毒性（DLT）を求めることである。可能であれば、一般毒性試験は標的器官毒性を求めるために行うべきであるが、無毒性量（NOAEL）又は無影響量（NOEL）を求めることは必須ではない。毒性試験は表1に要約した臨

床スケジュールをサポートするようにデザインされるべきである。回復性、蓄積効果、及び遅発毒性の評価も考慮すべきである。とはいえ、非げっ歯類での試験については、用量群は最低３匹／性別／群とし、回復性に関しては対照群及び高用量群でさらに２匹／性別／群を追加すべきである。一般的には雌雄ともに用いなければならず、そうでない場合には具体的にそうしなかった理由がなければならない。第Ｉ相臨床試験を支持するために、毒性所見の可逆性又は毒性が薬物治療中止後に持続又は進行する可能性を評価する目的で、少なくとも１つの非臨床試験で回復期間を取り入れるべきである。第Ｉ相臨床試験では、患者への治療はその患者の反応によっては継続される可能性もある。この場合、継続治療の裏づけとして新たな毒性試験の必要性はないと思われる。臨床開発の継続のためには、本項で言及した原則を取り入れた追加的毒性試験を実施すべきである。

トキシコキネティクスに関する評価は適宜実施するものとする。ヒトと動物モデルとの間に関連する生理学的、生化学的、動態学的差異がわかれば、用いるべき最も適切な動物種の決定が容易になる。

５．生殖発生毒性

臨床試験前に生殖発生毒性試験を行う必要はない。

一般的には、製造販売承認申請を提出する際に生殖発生毒性評価が入手可能な状態であることが望まれる。特定の患者集団（補助療法の場合など）では、このような生殖発生毒性試験は第Ⅲ相臨床試験計画の提出前に行われなければならない。

低分子医薬品に関しては、従来からの細胞毒性型薬剤を除き、胚・胎児発生に関する試験と出生前及び出生後の発生並びに母体機能に関する試験が必須である。

一般的に受胎能及び着床までの初期胚発生に関する試験は必要とされないが、反復投与毒性試験に評価項目を追加すべきである。しかし、治療が本質的に治癒的なものであり、かつ患者集団がその試験を必要とする場合には、さらに詳細な受胎能評価を実施しなければならない。

胚・胎児発生に関する試験は通常２種類の動物種で実施される。胚・胎児発生に関する試験が催奇形性に関して疑いなく陽性である場合には、第二の動物種での確認試験は通常必要ない。

一般毒性試験において、急速に分裂している細胞（胃腸管や骨髄など）を標的としていると評価され、かつ遺伝毒性試験において陽性である薬剤は、発生毒性物質であると推定されるため、発生毒性試験は実施する必要はない。しかし、この種類の化合物に関しては、処置を受けた雄性から胎児へのリスクに関する情報はほとんどない。したがって、そのような情報がない場合には適切な試験を行うべきである（処置を受けた雄性動物と処置を受けていない雌性動物の交配）。

６．遺伝毒性

遺伝毒性試験は、末期又は進行がん患者の治療を目的とした医薬品の臨床試験の実施のためには必要な

い。*In vitro*試験において薬剤が明らかに陽性であれば、*in vivo*試験は必要ではないと思われる。遺伝毒性試験は製造販売承認申請を行うために実施が必要である。

7．がん原性

がん原性試験は通常、末期又は進行がんの患者の治療を目的とした医薬品の製造販売承認申請のためには必要ない。抗悪性腫瘍薬に関するがん原性評価の必要性についてはICH S1Aガイドラインに記載されている。

8．免疫毒性

抗悪性腫瘍薬に関しては、一般毒性試験のデザイン構成要素で十分に製造販売承認に必要な免疫毒性の可能性を評価することができると考えられる。末期又は進行がん患者の治療を目的とした医薬品に関しては、ICH S8ガイドラインに規定された追加試験は一般的に必要ではない。

ICH S8に概説された概念は考慮に入れるべきであるが、一般毒性評価が抗悪性腫瘍薬の免疫毒性評価には十分であることを考えれば、追加試験は通常は必要とされない。

9．バイオ医薬品に関して特別に考慮する事項

他に記載がない限り、がん治療に用いられるバイオ医薬品に対して、ICH S6に概説された原則及び上記同様の考慮事項が適用される。

薬理活性、標的の分布、結合親和性の評価は、バイオ医薬品のための毒性試験に適切な動物種を選択する上において重要である。これらのデータは臨床試験開始前に得ておく必要がある。

マスバランス試験及び排泄試験は、悪性腫瘍治療に用いられる化学合成ペプチド医薬品やバイオ医薬品については必要ではない。

公開情報が十分にあり、クラス効果の正当性を科学的に論証できる場合、悪性腫瘍治療に用いられるバイオ医薬品の生殖発生毒性の詳細な評価は、ICH S6に概説されている機序研究によって必要ではないこともある。

バイオ医薬品については、遺伝毒性及びがん原性試験は必要ない。

C．臨床試験デザインを裏付けるための非臨床データ評価

1．ヒトでの初回投与における開始用量

開始用量の目標は、使用が安全であると合理的に考えられる薬理学的活性用量を投与することにある。この用量の安全性は、最も感受性の高い動物種に対する毒性試験から求められる。開始用量は科学的妥