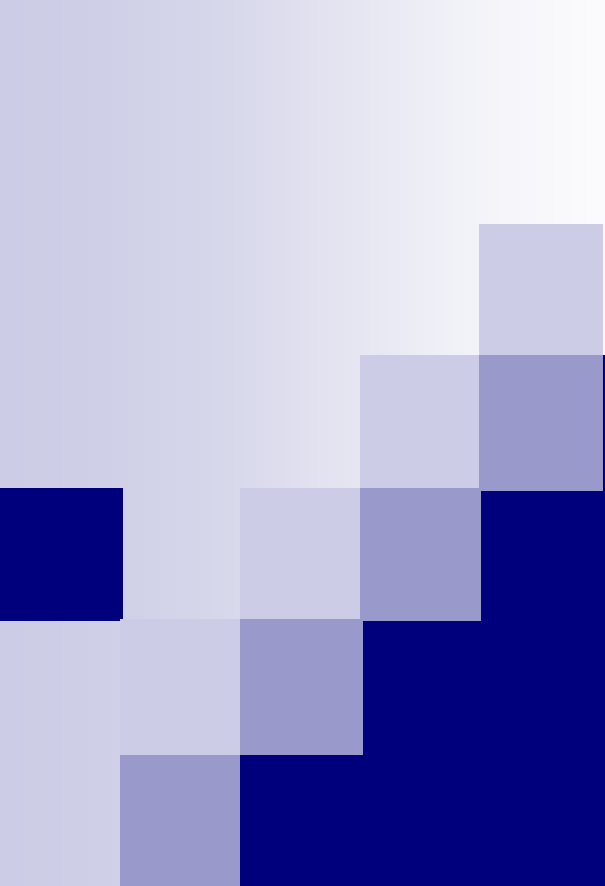




Nonclinical evaluation for anticancer pharmaceuticals - Step 2 - Klaus Olejniczak

International Conference on Harmonisation of Technical
Requirements for Registration of Pharmaceuticals for Human Use





Scope

Pharmaceuticals that are intended only to treat cancer in patients with late stage or advanced disease including both small molecule and biotechnology derived pharmaceuticals

Recommendations on type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals

Not apply to pharmaceuticals intended for patient with long life expectancy, cancer prevention, treatment of symptoms or side effects of chemotherapeutics, studies in healthy volunteers, vaccines, 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



Characterisation of Primary Pharmacodynamics

Prior to Phase I

- Mechanism(s) of action
- Resistance
- Anti-tumor activity
- Schedule dependency



Safety Pharmacology

An assessment of vital organ function, including cardiovascular, respiratory and central nervous system should be available before the initiation of clinical studies and such parameters could be included in general toxicology studies

Stand alone safety pharmacology studies are not required in patients with late stage cancer or advanced disease

In case of concern appropriate safety pharmacology studies, core battery and/or follow up or supplemental studies should be considered



Principles of Phase I Clinical Trials

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

For protein therapeutics with agonistic properties, minimally anticipated biologic effect level (MABEL) should be considered

Duration and schedule of toxicology studies to support initial clinical trials

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



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

Duration of toxicology studies to support continued development and marketing

For continued development 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 pharmaceuticals, these studies would be considered sufficient to support marketing



Reproduction toxicology / Embryofetal toxicity

Embryofetal toxicity studies of anticancer pharmaceuticals should be available for marketing

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

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. This will be reviewed in further development of this ICH S9 guideline



Fertility studies / Peri- and postnatal studies

A fertility study is generally not warranted to support the treatment of patients with late stage or advance 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 advance cancer



Genotoxicity, Carcinogenicity, Immunotoxicity, Combinations, Juvenile animals studies

Genotoxicity studies should be performed to support a marketing application

Carcinogenicity studies are usually not warranted

General toxicology studies are considered sufficient to evaluate the immunotoxicological potential

Based on available information, a determination should be made whether or not a toxicology study of the combination should be conducted Normally a toxicology study is not warranted

Conduct of studies in juvenile animals should be considered when human safety data and previous animal studies are considered insufficient



Other Considerations

Conjugated agents

Liposomal products

Evaluation of drug metabolites

Evaluation of impurities



Specific accomplishments leading to a reduction of animal use

No need for 6/9 month studies

No need for fertility and peri- and postnatal studies

Only 1 embryofetal study if a positive is observed

Recovery only to a single species prior to phase I

Safety pharmacology assessments could be conducted within the general toxicology studies

No need for non - rodent studies for initiation of clinical trials with cytotoxic drugs



THANK YOU