Guideline ICH S9:
“Non-clinical evaluation for anticancer pharmaceuticals”

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Guidance Timeline

- Business plan proposed by PhRMA
- Endorsed by ICH Steering Committee May 2007
  - Driver for guidance:
    - separate regional oncology guidances were being developed
    - in the absence of an oncology guidance, recommendations outlined in ICH M3 and S6 were being requested
- First meeting Yokohama Japan Oct 2007
  - Japan, EU, and US discussed current and proposed approaches to anticancer drug and biological development
- Milestones
  - Additional meetings Portland OR (June 2008) and Brussels (Nov 2008)
  - Planned release:
    - Step 2: October 2008
    - Step 4: 29 October 2009
    - Date for coming into operation: May 2010
• Nonclinical evaluations are intended to
  – identify the pharmacologic properties of a pharmaceutical
  – establish a safe initial dose level for the first human exposure
  – understand the toxicological profile of a pharmaceutical, e.g., identification of the target organs, exposure-response relationship and reversibility.
  • For anticancer pharmaceuticals, the clinical dose level is often close to or at an adverse effect level.
Background

• Rationale
  – malignant tumors are life-threatening,
  – death rate from diseases are high
  – existing therapies have limited effectiveness
  – desire to provide new effective anticancer pharmaceuticals to patients more expeditiously.

• The type, timing and flexibility in the design of nonclinical studies for anticancer pharmaceuticals can differ from other pharmaceuticals
Objectives

• Nonclinical studies to support the development of anticancer pharmaceuticals in patients with advanced disease and limited therapeutic options
• Protect patients from unnecessary adverse effects
• Avoiding unnecessary use of animals in accordance with the 3 R principles (reduce/refine/replace)
Scope

• Patient population is referred to as patients with advanced cancer
• Includes both small molecule and biotechnology-derived pharmaceuticals
• Provide recommendations on type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals
• The nonclinical data to support Phase I and the clinical Phase I data would normally be sufficient for moving to Phase II and into second or first line therapy in patients with advanced cancer
Scope

• **Further Investigation**
  - cancer patient populations with long expected survival, the recommendations for and timing of additional nonclinical studies depend upon the available nonclinical and clinical data and the nature of the toxicities observed

• **Excludes pharmaceuticals intended for**
  - cancer prevention
  - treatment of symptoms or side effects of chemotherapeutics
  - studies in healthy volunteers (follow ICH M 3)
  - vaccines, cellular or gene therapy
  - Radiopharmaceuticals are not covered in this guideline but some of the principles could be adapted
Content of Guidance

• Pharmacology
  – Prior to Phase I
  – Preliminary characterization to include
    • Mechanism(s) of action
    • Anti-tumor activity
    • Schedule dependency
  – Justify combinations when needed
Content of Guidance

• Pharmacology

  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.
• Safety Pharmacology
  – An assessment of vital organ function, including cardiovascular, respiratory and central nervous systems should be available before the initiation of clinical studies
  – Assessment could be included in general toxicology studies. Conducting stand-alone safety pharmacology studies to support studies in patients with advanced cancer is not needed
  – In case where specific concerns have been identified, appropriate safety pharmacology studies described in ICH S7A and/or S 7B should be considered
  – In the absence of a specific risk, such studies will not be called for to support clinical trials or for marketing
Content of Guidance

- Pharmacokinetics
  - 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 I studies.
  
  - Further information (ADME) can be generated in parallel with clinical studies
Content of Guidance

• General Toxicology
  – *Identification of a NOEL/NOAEL not essential*
  – *Should use a schedule to support the clinical trial*
    • Examples are provided in the guidance
  – *For small molecules studies usually conducted in both rodent and non-rodent*
    • Exception: for genotoxic drugs targeting rapidly dividing cells, one rodent species might be considered sufficient
    • For biopharmaceuticals see ICH S6
  – *Reversibility*
    A study that includes a terminal non-dosing period is called for if there is severe toxicity at approximate clinical exposure and recovery cannot be predicted by scientific assessment.
    *The demonstration of complete recovery is not considered essential.*
Reproduction Toxicology

- Embryofetal toxicity studies of anticancer pharmaceuticals should be available for marketing
- Exceptions
  - 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
  - If a pharmaceutical is positive for embryofetal lethality or is teratogenic, a confirmatory study in second species is usually not warranted
- For biopharmaceuticals, the 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.
Content of Guidance

• Reproduction Toxicology (continued)
  – A fertility study is generally not warranted to support the treatment of patients with 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 advance cancer
Content of Guidance

• Genotoxicity
  – Studies should be performed to support marketing. 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.

• Carcinogenicity
  – Studies are usually not warranted based on scope of the guidance

• Immunotoxicology
  – General toxicology studies are considered sufficient to evaluate the immunotoxicological potential
Content of Guidance

• Photosafety testing
  - An initial assessment of phototoxic potential should be conducted prior to Phase I, 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.
Content of Guidance

• Start dose
  – Goal 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)
  – Interspecies scaling of the animal doses to an equivalent human dose is usually based on normalization to body surface area. Interspecies scaling based on body weight, AUC, or other exposure parameters might be appropriate
  – For biopharmaceuticals with agonistic properties, minimally anticipated biologic effect level (MABEL) should be considered
Determine Severely Toxic Dose to 10% of rodents (STD10)

Convert from mg/kg to mg/m^2

Is 1/10 Rodent STD10 (mg/m^2) Severely toxic to Non-rodents?

NO
Start Dose = 1/10 Rodent STD10

YES
Determine non-rodent Highest Non-Severely Toxic Dose (HNSTD)

Convert from mg/kg to mg/m^2

Start Dose = 1/6 Non-Rodent HNSTD

Example of starting dose in patients
Content of Guidance

- Clinical Trials
  - Highest clinical dose not limited by nonclinical data
  - In Phase I 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.
  - Examples of duration and schedule of toxicology studies to support initial clinical trials are provided (Table 1)
  - 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.
Examples of Treatment Schedules for Anticancer Pharmaceuticals to Support Initial Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Schedule</th>
<th>Examples of Nonclinical Treatment Schedule&lt;sup&gt;1,2,3,4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once every 3-4 weeks</td>
<td>Single dose</td>
</tr>
<tr>
<td>Daily for 5 days every 3 weeks</td>
<td>Daily for 5 days</td>
</tr>
<tr>
<td>Daily for 5-7 days, alternating</td>
<td>Daily for 5-7 days, alternating weeks (2-dose cycles)</td>
</tr>
<tr>
<td>weeks</td>
<td></td>
</tr>
<tr>
<td>Once a week for 3 weeks, 1 week</td>
<td>Once a week for 3 weeks</td>
</tr>
<tr>
<td>off</td>
<td></td>
</tr>
<tr>
<td>Two or three times a week</td>
<td>Two or three times a week for 4 weeks</td>
</tr>
<tr>
<td>Daily</td>
<td>Daily for 4 weeks</td>
</tr>
<tr>
<td>Weekly</td>
<td>Once a week for 4-5 doses</td>
</tr>
</tbody>
</table>
Content of Guidance

• For continued pharmaceutical 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
Content of Guidance

• Toxicology studies of drug combinations
  - Pharmacologic rationale for the combination should be provided
  - Toxicology studies of combinations of pharmaceuticals are not warranted

• Pediatric Population
  - Define a relatively safe dose in adult patient
  - Studies in juvenile animals are not usually conducted
Content of Guidance

- Consideration is given in the guidance to specific issues or product classes, including:
  - Conjugated agents
  - Liposomal products
  - Evaluation of drug metabolites
  - Evaluation of impurities
Conjugated Agents

- 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
A complete evaluation of the liposomal product is not warranted if the unencapsulated material has been well characterized.

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).

Toxicokinetics should assess both the liposomal product and the free compound after administration of the liposomal product.
Metabolites

- 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.
Exceeding the established limits for impurities identified in the ICH guidelines Q3A & Q3B 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.
Genotoxic impurities limits based on increase in lifetime risk of cancer are not appropriate for pharmaceuticals intended to treat patients with advanced cancer.
Phase 0 trials for anticancer drug development

The results of the first ‘Phase 0’ clinical trial in oncology of a therapeutic agent under the Exploratory Investigational New Drug Guidance of the US FDA have recently been reported. (Kummar et al J. Clin. Oncol. Vol 27, (16) 2705 - 2711).

• Phase 0 clinical trial:
  - A first-in-human clinical trial conducted under an exploratory IND that has no therapeutic or diagnostic intent and involves very limited human exposure.
  - The results of a Phase 0 trial can provide essential pharmacodynamic, pharmacokinetic and/or imaging data at the initial stage of the clinical trials process to inform and expedite the subsequent development of promising new agents.
First in patient phase 0

~13 months

Phase I combination trial

Median time for conventional evaluation 30 months

First in patient

Phase I combination trial

Modified from Kummar et.al.
Conclusion

- Highlights of accomplishments
  - 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
  - No in vivo if in vitro gentoxicity assays are positive
  - 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
  - Studies to be conducted in late stage development to conserve resources and reduce animal use
  - Limited recommendation for impurities
Find the formula, optimize the drug development and cure the cancer

THANK YOU