

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

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1 Nonclinical evaluation for anticancer pharmaceuticals

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35 A. Introduction

36 1. Objectives of the Guideline

37
38 There have been no internationally accepted objectives or recommendations on the design and
39 conduct of nonclinical studies to support the development of anticancer pharmaceuticals in
40 patients with advanced disease and limited therapeutic options. The purpose of this guidance is
41 to provide information to assist in the design of an appropriate program of nonclinical studies for
42 the development of anticancer pharmaceuticals. This guideline aims to facilitate and accelerate
43 the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse
44 effects, while avoiding unnecessary use of animals and other resources.

45
46 As appropriate, the principles described in other ICH guidelines should be considered in the
47 development of anticancer pharmaceuticals. Specific situations where recommendations for
48 nonclinical testing deviate from other guidance are described in this document.

49
50 2. Background

51
52 Since malignant tumors are life-threatening, the death rate from these diseases is high, and
53 existing therapies have limited effectiveness, it is desired to provide new effective anticancer
54 drugs to patients more expeditiously. Nonclinical evaluations are intended to 1) identify the
55 pharmacologic properties of a pharmaceutical, 2) establish a safe initial dose level for the first
56 human exposure, and 3) understand the toxicological profile of a pharmaceutical, e.g.,
57 identification of the target organ, estimation of the safety margin, and reversibility. In the
58 development of anticancer drugs, most often the clinical studies involve cancer patients whose
59 disease condition is often progressive and fatal. In addition, the clinical dose levels often are
60 close to or at the adverse effect dose levels. For these reasons, the type and timing and flexibility
61 called for in designing of nonclinical studies of anticancer pharmaceuticals can have a different
62 pattern from those for other pharmaceuticals.

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66 3. Scope

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

73
74 This guideline does not apply to pharmaceuticals intended for patients with long life expectancy,
75 cancer prevention, treatment of symptoms or side effects of chemotherapeutics, studies in healthy
76 volunteers, vaccines, or cellular or gene therapy. If healthy volunteers are included in clinical
77 trials, the ICH M3 guideline should be followed. Radiopharmaceuticals are not covered in this
78 guideline but some of the general principles could be adapted.

79
80 4. General Principles

81

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

87
88 The manufacturing process can change during the course of development. However, the active
89 pharmaceutical substance used in nonclinical studies should be well characterized and
90 representative of the clinical material.

91
92 In general, non-clinical safety studies that are used to support the development of a
93 pharmaceutical should be conducted in accordance to Good Laboratory Practices.

94
95 B. Studies to support nonclinical evaluation
96
97 1. Pharmacology (description of mechanism of action)
98
99 Prior to phase I studies, preliminary characterization of the mechanism(s) of action,
100 resistance, and schedule dependencies as well as anti-tumor activity should have been
101 made. Appropriate models should be selected based on the target and mechanism of action
102 but need not be studied using the same tumor types intended for clinical evaluation.

103
104 These studies can provide preclinical proof of principle, guide schedules and dose-
105 escalation schemes, provide information for selection of test species, aid in starting dose
106 selection, and in some cases justify pharmaceutical combination where clinical
107 information cannot be obtained.

108
109 Secondary pharmacodynamic or off target effects should be investigated as appropriate.

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111
112 2. Safety Pharmacology
113
114 An assessment of vital organ function, including cardiovascular, respiratory and central
115 nervous systems, should be available before the initiation of clinical studies; such
116 parameters could be included in general toxicology studies. Stand-alone safety
117 pharmacology studies need not be conducted to support studies in patients with late stage
118 cancer or advanced disease. In case of concern appropriate safety pharmacology studies,
119 core battery described in ICH S7A and/or follow up or supplemental studies should be
120 considered.

121
122 3. Pharmacokinetics
123
124 The evaluation of limited kinetic parameters, e.g., peak plasma levels, AUC, and half-life,
125 in the animal species used for non-clinical studies can facilitate dose escalation during
126 Phase I studies. Further information on absorption, distribution, metabolism and excretion
127 in animals should normally be generated in parallel with clinical development.

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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

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

179
180 7. Carcinogenicity

181
182 Carcinogenicity studies are usually not warranted to support marketing for therapeutics
183 intended to treat patients with late stage or advanced cancer. The appropriateness of a
184 carcinogenicity assessment for anticancer pharmaceuticals is described in ICH S1A
185 guideline.

186
187 8. Immunotoxicity

188
189 For anticancer pharmaceuticals the design components of the general toxicology studies
190 are considered sufficient to evaluate immunotoxic potential and support marketing.

191
192
193 C. Nonclinical data to support clinical trial design and marketing

194
195 1. Start dose for first administration in human

196
197 The goal of selecting the start dose is to administer a pharmacologically active
198 dose that is reasonably safe to use. The start dose should be scientifically justified
199 using all available nonclinical data (e.g., pharmacokinetics, pharmacodynamics,
200 toxicity), and its selection based on various approaches (Note 2; see section C3).
201 For most systemically administered therapeutics, interspecies scaling of the animal
202 doses to an equivalent human dose should be based on normalization to body
203 surface area (allometric scaling). Although allometric scaling by body surface
204 area is the standard way to approximate equivalent exposure if no further
205 information is available, in some cases (e.g., biopharmaceuticals) extrapolating
206 doses based on other parameters (e.g., body weight) might be more appropriate.

207
208 For biopharmaceuticals without agonistic activity or that are antagonists of the
209 intended target/ligand, selection of the starting dose should employ the same
210 principles as described above. For protein therapeutics with agonistic properties,
211 however, selection of the starting dose using an identified, minimally anticipated
212 biologic effect level (MABEL) should be considered.

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214
215 2. Dose escalation and the highest dose in a clinical trial

216
217 In general, the dose-escalation or highest dose investigated in a clinical trial in
218 patients with cancer should not be limited by the highest dose tested in the
219 nonclinical studies. When a steep dose-response curve is observed in nonclinical
220 toxicology studies, or when no preceding marker of toxicity is available, a slower
221 escalation should be considered.

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

223
224 Since different dosing schedules might be utilized in initial clinical trials, the
225 design of nonclinical studies should be appropriately chosen. See Table 1 for
226 examples of study designs and durations that can be used for drugs or
227 biopharmaceuticals. In phase I clinical trials, the treatment of patients can
228 continue according to the patient's response, and in this case, a new toxicology
229 study would not be called for in order to support continued treatment beyond the
230 duration of the completed toxicology studies.

231
232 An appropriate toxicology study in a single species could suffice to support a more
233 intense clinical schedule (e.g., going from weekly to 3X weekly) than originally
234 supported by previously completed nonclinical studies.

235
236 4. Duration of toxicology studies to support continued clinical development and marketing

237
238 In support of continued development of an anticancer pharmaceutical for patients
239 with late stage or advanced disease, results from repeat dose studies of 3 months
240 duration following the intended clinical schedule should be provided prior to
241 initiating phase III studies. For most anticancer pharmaceuticals, nonclinical
242 studies of 3 months duration would also be considered sufficient to support
243 marketing.

244
245 5. Combination of pharmaceuticals

246
247 Pharmaceuticals planned for use in combination should be well studied
248 individually in toxicology evaluations. Data to support a pharmacologic rationale
249 for the combination should be provided prior to starting the clinical study. Based
250 on available information, a determination should be made whether or not a
251 toxicology study of the combination should be conducted. In general, however,
252 toxicology studies investigating the safety of combinations of pharmaceuticals
253 intended to treat patients with advanced or late stage cancer are not warranted.

254
255 6. Nonclinical studies to support trials in pediatric populations

256
257 The general paradigm that exists for most anticancer pharmaceuticals that are
258 investigated in pediatric patients is first to define a relatively safe dose in adult
259 populations, and then to assess some fraction of that dose in initial pediatric
260 clinical studies. Studies in juvenile animals are not usually conducted in order to
261 support inclusion of pediatric populations for the treatment of cancer. The
262 recommendations for nonclinical testing outlined elsewhere in this document also
263 apply to this population. Conduct of studies in juvenile animals should be
264 considered when human safety data and previous animal studies are considered
265 insufficient for a safety evaluation in the intended pediatric age group.

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268 D. Other Considerations

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270 1. Conjugated agents

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272 Conjugated agents are pharmaceuticals covalently bound to carrier molecules,
273 such as to proteins, lipids, or sugars. The safety assessment of the conjugated
274 material is the primary concern. The safety of the unconjugated material including
275 the linker used can have a more limited evaluation. Stability of the conjugate in
276 the test species and human plasma should be provided. A toxicokinetic evaluation
277 should assess both the conjugated and the unconjugated compound.
278

279 2. Liposomal products

280 A complete evaluation of the liposomal product is not warranted if the
281 unencapsulated material has been well characterized. As appropriate, the safety
282 assessment should include a toxicological evaluation of the liposomal product and
283 a limited evaluation of the unencapsulated drug and carrier (e.g., a single arm in a
284 toxicology study). The principle described here might also apply to other similar
285 carriers.
286

287 3 Evaluation of drug metabolites

288

289 In some cases, metabolites have been identified in humans that have not been
290 qualified in nonclinical studies. For these metabolites, a separate general
291 toxicology evaluation might not be warranted for patients with late stage or
292 advanced cancer, as the human safety of the metabolite would have been assessed
293 in phase I clinical trials. If the parent compound is considered positive in an
294 evaluation for embryofetal toxicity or genotoxicity then separate studies for the
295 disproportionate metabolite might not be warranted. Unless there is a specific
296 cause for concern, nonclinical testing of the metabolite is not warranted.
297

298 4. Evaluation of impurities

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

306 Table 1: Example schedules for anticancer pharmaceuticals to support initial clinical trials
 307

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

308
 309 ¹ Schedules described in the table do not specify recovery periods, which should
 310 be incorporated into the study design. Timing of recovery sacrifices should be
 311 scientifically justified (also see Note 1).
 312

313 ² Nonclinical schedule includes rodents and nonrodents. In certain circumstances,
 314 determined case-by-case, alternative approaches can be appropriate (e.g. genotoxic
 315 drugs targeting rapidly dividing cells). In those cases, a repeat-dose toxicity study
 316 in two rodent species might be considered sufficient.
 317

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

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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.