Guidance for Industry

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2010
ICH

Par Pharm., Inc.
Exhibit 1122
Par Pharm., Inc. v. Novartis AG
Case IPR2016-00084

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I. INTRODUCTION (1, 1.1)

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. The guidance provides recommendations for nonclinical evaluations to support the development of anticancer pharmaceuticals in clinical trials for the treatment of patients with advanced disease and limited therapeutic options.

This guidance aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals, in accordance with the 3R principles (reduce/refine/replace), and other resources.

As appropriate, the principles described in other ICH guidances 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.

A. Background (1.2)

[1] This guidance was developed within the Expert Working Group (Safety) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This guidance has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, October 2009. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

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Because malignant tumors are life-threatening, the death rate from these diseases is high, and existing therapies have limited effectiveness, it is desirable to provide new, effective anticancer drugs to patients more expeditiously.

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 clinical trials for the treatment of patients with advanced disease and limited therapeutic options. Nonclinical evaluations are conducted 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 target organs, exposure-response relationships, and reversibility).

In the development of anticancer drugs, clinical studies often involve cancer patients whose disease condition is progressive and fatal. In addition, the dose levels in these clinical studies often are close to or at the adverse effect dose levels. For these reasons, the type, timing, and flexibility called for in the design of nonclinical studies of anticancer pharmaceuticals can differ from those elements in nonclinical studies for other pharmaceuticals.

B. Scope (1.3)

This guidance provides information for pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies. For the purpose of this guidance, this patient population is referred to as *patients with advanced cancer*. The guidance applies to both small molecule and biotechnology-derived pharmaceuticals (biopharmaceuticals), regardless of the route of administration. This guidance describes the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals in patients with advanced cancer and references other guidance as appropriate. It describes the minimal considerations for initial clinical trials in patients with advanced cancer whose disease is refractory or resistant to available therapy, or where current therapy is not considered to be providing benefit. The nonclinical data to support Phase 1 and the clinical Phase 1 data would normally be sufficient for moving to Phase 2 and into second or first line therapy in patients with advanced cancer. The guidance also describes further nonclinical data to be collected during continued clinical development in patients with advanced cancer. When an anticancer pharmaceutical is further investigated in cancer patient populations with long expected survival (e.g., those administered pharmaceuticals on a chronic basis to reduce the risk of recurrence of cancer), the recommendations for and timing of additional nonclinical studies depend upon the available nonclinical and clinical data and the nature of the toxicities observed.

This guidance does not apply to pharmaceuticals intended for 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 guidance should be followed. Radiopharmaceuticals are not covered in this guidance, but some of the principles could be adapted.

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