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When Are "Positive" Clinical Trials in Oncology Truly Positive?

Ocana A, Tannock IF.

Affiliations of authors: Medical Oncology Department-AECC unit, Albacete University Hospital, Albacete, Spain (AO); Division of Medical Oncology and Hematology, Princess Margaret Hospital and University of Toronto, Toronto, ON, Canada (IFT).

Abstract

The approval of a new drug for cancer treatment by the regulatory authorities, such as the United States Food and Drug Administration or European Medicines Agency, is usually based on the positive results of one or more randomized phase III clinical trials comparing the investigational treatment with the standard treatment. A clinical trial is presented as positive if the new drug tested on an experimental group shows a statistically significant difference with the control group ($P < .05$) in the primary endpoint, which is usually a time-to-event endpoint (overall survival or progression-free survival). Such apparently positive clinical trials disregard whether the final value of the difference in the primary endpoints between the experimental and control groups (δ) meets the criterion that was predefined in the protocol. Currently, the trend is to design large trials that may detect statistically significant, but often trivial, differences in survival endpoints. However, recent appeals have been made in the oncology literature for the design of smaller clinical trials to detect or exclude only larger, clinically important, values of δ . Here, we have evaluated 18 randomized phase III clinical trials that were used for the approval of molecular-targeted anticancer drugs by the United States Food and Drug Administration. Results showed that in some of the articles the magnitude of the reported values of δ were lower than the values predefined in the protocol. We suggest that trials should not be declared positive based only on a statistically significant P value, but should also require detection of a difference in survival outcome that equals or exceeds a clinically important value that is specified in the protocol.

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