Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 107 (2007) 173–176
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Clinical trial endpoints in ovarian cancer: Report of an FDA/ASCO/AACR Public Workshop☆

Robert C. Bast [a], J. Tate Thigpen [b,*], Susan G. Arbuck [c], Karen Basen-Engquist [a], Laurie B. Burke [d], Ralph Freedman [a], Sandra J. Horning [e], Robert Ozols [f], Gordon J. Rustin [g], David Spriggs [h], Lari B. Wenzel [i], Richard Pazdur [d]

[a] *M. D. Anderson Cancer Center, Houston, TX, USA*
[b] *University of Mississippi Medical Center, Jackson, MS, USA*
[c] *Schering-Plough Research Institute, Kenilworth, NJ, USA*
[d] *U.S. Food and Drug Administration, Rockville, MD, USA*
[e] *Stanford University Cancer Center, Stanford, CA, USA*
[f] *Fox Chase Cancer Center, Philadelphia, PA, USA*
[g] *Mount Vernon Cancer Center, Northwood, Middlesex, UK*
[h] *Memorial Sloan-Kettering Cancer Center, New York, NY, USA*
[i] *University of California-Irvine, Irvine, CA, USA*

Received 18 August 2007

Abstract

Objective. The unique characteristics of cancer, particularly issues involving the use of surrogate endpoints in clinical trials, present special challenges in the development of cancer drugs. In response, the U.S. Food and Drug Administration (FDA) has partnered with the American Society of Clinical Oncology, the American Association for Cancer Research, and the American Society of Hematology to conduct public workshops evaluating potential endpoints for drug approvals for the most common tumor types.

Methods. A workshop evaluating potential endpoints in ovarian cancer drug research was held in Bethesda, Maryland, in April 2006. Invited experts presented research findings and discussed endpoints in trials of drugs for treatment of Stage III and IV ovarian cancer.

Results. The panel responded to specific questions from FDA, discussing use of progression-free survival as a surrogate for overall survival and use of CA-125 levels as an indicator of response. Panel members also addressed endpoints in first-line therapy, second-line and subsequent therapy, and maintenance therapy.

Conclusion. Expert commentary provided by panel members will inform FDA's draft guidance on clinical endpoints for cancer drug approvals and will be discussed at meetings of the FDA's Oncologic Drugs Advisory Committee. FDA intends to develop a set of principles that can be used to define efficacy standards for drugs used to treat ovarian and other cancers.

Keywords: Approval; CA125; Cancer; Endpoints; FDA; Ovarian; Research; Therapy

Introduction

The U.S. Food and Drug Administration (FDA) has partnered with the American Society of Clinical Oncology, the American Association for Cancer Research, and the American Society of Hematology to hold a series of public workshops evaluating potential endpoints for cancer drug approvals in the most common tumor types. These workshops are designed to engage researchers at the forefront of cancer

☆ Disclaimers: The views expressed in this article are those presented at the workshop and do not necessarily represent the views or findings of the United States Food and Drug Administration or the sponsoring organizations.

* Corresponding author. Fax: +1 703 684 8364.
E-mail address: jtthigpen@att.net (J.T. Thigpen).

0090-8258/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2007.08.092

drug development in a thorough discussion of the advantages and disadvantages of various endpoints for clinical trials intended to support approval of new therapeutic agents. Issues highlighted at these workshops are subsequently brought to the Oncologic Drugs Advisory Committee (ODAC), FDA's statutory advisory body for review of oncology drugs. Discussions at both the workshops and ODAC will inform guidance that FDA is preparing on clinical endpoints for cancer drug approvals.

The most recent of these workshops was held on April 26, 2006, in Bethesda, Maryland, to consider clinical trial endpoints in ovarian cancer. The panel consisted of recognized experts in ovarian cancer along with FDA and NCI officials. The discussion was facilitated by Richard Pazdur, MD, director of the Office of Oncology Drug Products at FDA's Center for Drug Evaluation and Research.

The workshop focused on endpoints that are ready (or nearly ready) to incorporate into clinical trials testing of drugs for treatment of Stage III and Stage IV ovarian cancer. In addition, panelists identified key areas about which knowledge is limited and proposed areas that would benefit from further study.

Methods

The workshop consisted of a series of formal presentations by panel members followed by discussion. During the discussion periods, participants addressed several specific questions posed by FDA (Fig. 1), which focused on the accuracy, reproducibility, and clinical relevance of the endpoints about which data had been presented. The FDA questions also served as a starting point for a wide-ranging discussion. Time was allotted for members of the audience to provide comments and ask questions of the panel.

The workshop began with a review of regulatory terms, principles, and requirements as well as an overview of the types of endpoints that have been used to approve cancer drugs. Subsequent presentations covered the following topics:

- Issues related to the design of clinical trials for ovarian cancer therapies, including the unique features of ovarian cancer that must be taken into account when designing trials.

Use of CA-125 for Response/Progression Evaluation in Ovarian Cancer

- Should CA-125 be used as an endpoint in clinical trials intended to support drug approval?
- Should CA-125 be used as a marker of response, progression and/or relapse in clinical trials intended to support drug approval? If yes, are the CA-125 defined endpoints validated? If not, what data are needed to validate CA-125 as an endpoint?
- What differences in analytical performance characteristics among CA-125 measurement devices should be considered if the marker is used as a surrogate endpoint?

Clinical Trial Endpoints for Regulatory Approval

- Is PFS a reliable surrogate for overall survival in randomized front-line ovarian cancer trials? For second-line (or third-line) trials?
- If yes to either, how should progression be documented: objective measures and marker change using definitions from GCIG?
- If PFS is NOT a valid surrogate for overall survival in first or second-line treatment, can it stand alone as a reasonable endpoint on which to approve new agents? Is the answer to this dependent on the absolute gain in PFS? On changes in disease-related symptoms?
- Should an improvement in disease-free survival without an improvement in survival support approval of a new drug or indication in advanced ovarian cancer? If so, in what patient populations? First-line treatment? Second-line platinum sensitive? Second-line platinum refractory? Third-line and beyond?

Maintenance Therapy Setting

- Is PFS alone an acceptable endpoint to support regular approval in studies investigating the role of maintenance therapy following first-line therapy? Accelerated approval?

Second-Line and Subsequent Therapy Setting

- Could response rate with adequate duration of response in a single arm study support accelerated approval in 2nd line, platinum refractory setting?
- Could prolongation of TTP in a randomized study be sufficient for accelerated approval in second-line setting? Or regulatory approval?
- What is the role of CA-125 in clinical trials intended for licensure in 2nd line and beyond – setting in ovarian cancer?

Patient-Reported Outcomes

- What is the role of PROs as an endpoint in clinical trials intended to support ovarian cancer drug approval?
- How could PROs help support/validate PFS as a surrogate endpoint?
- What are the relative values of health-related quality of life (HRQL) measures compared to more specific symptom measures as endpoints?

Fig. 1. FDA questions for panel members.