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SGO guidance document for clinical trial designs in ovarian cancer: A changing paradigm

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HIGHLIGHTS

- Clinical trials demonstrating a benefit in progression-free survival frequently fail to preserve that effect in overall survival.
- Ovarian cancer is a heterogeneous disease defined by histologic subtypes and activated biologic pathway aberrations, which are impacting drug development.
- Alternative clinical trial endpoints should be explored in regulatory strategies this should be its own section as in the instructions.

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ABSTRACT

Objective. To explore and facilitate the multifaceted process of drug development and regulatory approval in ovarian cancer.

Methods. The Society of Gynecologic Oncology (SGO) recently sought and received input from multiple stakeholders including the National Cancer Institute's (NCI) Clinical Therapy Evaluation Program (CTEP), the Food and Drug Administration (FDA), pharmaceutical industry, and patient advocates. This whitepaper is the work product and opinion solely of the SGO.

Results. This document summarizes the SGO's interpretation of these meetings and the current regulatory environment where there has been a paucity of recent approvals in the United States. It provides guidance in clinical trial design with the express purpose of encouraging novel drug development in ovarian cancer. Points of emphasis include: ovarian cancer heterogeneity (histologic subtypes and molecular genetic alterations), clinical trial design elements, surrogate as well as composite endpoints, and the four principles of clinical drug development (unmet medical need, discovery, safety, and efficacy).

Conclusions. There has been an evolution in the acceptance of surrogate endpoints depending upon the clinical setting in ovarian cancer. While overall survival (OS) remains the most objective clinical trial endpoint, there is now realization that demanding OS as the primary endpoint has many obstacles. Ovarian cancer is a heterogeneous disease that is now divided by histologic subtypes. Future registration strategies will need to address disease heterogeneity. The exploration of currently acceptable clinical trial endpoints and alternative regulatory strategies will hopefully stimulate interest in novel drug development for patients with ovarian cancer.

Introduction

The Society of Gynecologic Oncology (SGO) recognizes the evolving challenges in cancer drug development. These challenges, particularly in ovarian cancer, have adversely influenced the portfolio expansion of approved agents. The perception that overall survival (OS) is the only acceptable clinical trial endpoint has challenged the interpretation of

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several recent trials and has deterred drug development in ovarian cancer. As ovarian, fallopian tube and peritoneal cancers, collectively known as epithelial ovarian cancer, are characterized by a long initial post progression survivorship, the unbalanced and frequent use of active treatment, including frequent crossover treatment, as well as the length and cost of clinical trials may make OS an imprecise and impractical endpoint [1].

To address this problem, the SGO first sought to better understand the key issues responsible for this dynamic paradigm whereby no new ovarian cancer drug approvals have occurred in the United States since 2006. Thus a task force was formed to examine the issues. The role of clinical trial endpoints was seen as one of the contributory factors, and an SGO white paper was published by the task force to provide insight into pivotal regulatory issues, the patients' perspective, the unique features of ovarian cancer, and the potential role of surrogate clinical trial endpoints in clinical trials designed for new drug approvals [1] (Table 1).

One of the most significant developments influencing drug development and therefore drug regulatory approval in oncology is the rapid growth and discovery in cancer biology. The molecular and/or genetic etiologies of many cancers are now known, and the molecular-genetic characteristics of others are well established. Innovation to develop targeted agents to leverage these molecular–genetic aberrations has advanced rapidly. The discovery of actionable mutations has outpaced our ability to clinically validate many of these intriguing targets.

In many solid tumors, including ovarian cancer, these developments have prompted the division of relatively homogenous populations into smaller and even more homogenous subgroups. For instance, most epithelial ovarian cancers were initially considered biologically similar. However, it has become apparent that certain histologic subtypes are more clinically diverse than previously thought based upon origin and response to chemotherapeutics [2]. More recently, it has been noted that even more heterogeneity exists, even within the same histology, and gene signatures that demonstrate both prognostic and predictive roles for therapy and survivorship are emerging [3]. Further complicating our understanding of this process is the role of varying host responses within the tumor microenvironment and the critical role of poorly understood immunologic variables. Together, these rapidly changing forces will have significant implications on the design of future clinical trials in ovarian cancer.

Recognizing the multifaceted process of drug development and regulatory approval both inside the United States as well as abroad, the SGO recently sought and received input from multiple stakeholders including the National Cancer Institute's (NCI) Clinical Therapy Evaluation Program (CTEP), the Food and Drug Administration (FDA), pharmaceutical industry, and patient advocates. This document summarizes the SGO's interpretation of the current regulatory environment and provides guidance in clinical trial design with the express purpose of encouraging novel drug development in ovarian cancer. This document is the work product and opinion solely of the SGO. Official endorsement or approval from any governmental, industry, or advocacy groups has not been sought and/or independently provided.

Methods

Subsequent to the publication of the SGO White Paper on Clinical Trial Endpoints in Ovarian Cancer, an SGO task force was assembled and a meeting with the FDA was convened in March of 2014. During this meeting, information about the SGO professional organization and its mission, as well as the unique features of ovarian cancer was discussed. Several key agenda items, such as factors associated with extending median survival in advanced ovarian cancer and the continued poor long-term outcomes associated with advanced stage ovarian cancer were reviewed and discussed. In addition, the task force asked for input and response to the SGO White Paper emphasizing clinical trial endpoints (OS, PFS, response rate, CA125 levels, quality of life and patient reported outcomes). Deliberations of this meeting were discussed by the SGO task force at the 2014 SGO Annual Meeting on Women's Cancers, and the outline and content for the current manuscript were formulated. The final document was reviewed by the SGO's Publication Committee and its Executive Board prior to submission and represents the opinions of the SGO task force after careful consideration and input from a number of stakeholders in ovarian cancer drug development.

Statistical considerations in clinical trial design

Clinical drug development focuses on four principles: unmet medical need, discovery, safety and efficacy. In traditional development strategies, these are interrogated generally in sequence with increasingly more restricted sample populations. The central tenet guiding the ongoing dialog with the FDA and industry partners has been to identify and establish a definition of “meaningful clinical benefit” linked to a particular therapy and a cohort of ovarian cancer patients. This issue is difficult to globally define because, while the magnitude of effect is relatively equipoise (as quantified by Hazard Ratios), the context impacts the size of this effect. For instance, a hazard ratio of 0.67 may represent a median survival outcome delta between two regimens ranging from 3 to 12 months, depending on the sample size and whether PFS or OS is the focus of the analysis. However, this conundrum does not mean to imply that there are no standards against which to establish a meaningful precedent of effect.

With efficacy usually being evaluated in phase III randomized, placebo-controlled trials, involving unselected large numbers of patients with multiple stratifications to account for post-randomization effects that may affect the trial's endpoints, preserving power to evaluate both OS and PFS endpoints generally lead to large sample sizes. This results in over-powering for the PFS endpoint (risking a clinically unimpressive significant effect) and wasting valuable resources and time. In addition, given that survival endpoints are dependent on

Table 1
Endpoints and study settings. In addition to statistically significant difference, other means of benefit would need to be demonstrated such as significant difference in time off therapy or at least an OS trend. Opportunities to develop metrics of clinical benefit that integrate response elements with context to better define treatment effect. Modified from Herzog TJ, Armstrong DK, Brady MF, Coleman RL, Einstein MH, Monk BJ, Mannel RS, Thigpen JT, Umpierre SA, Villella JA, and Alvarez RD. Gynecol Oncol. 2014 Jan; 132 (1):8–17.doi: 10.1016/j.ygyno.2013.11.008. Reproduced with permission of Elsevier.

	Frontline	Platinum-sensitive	Platinum-resistant
OS	Approve	Approve	Approve
PFS (statistically significant) + other (QoL/PRO)	Approve	Approve	Consider
PFS (statistically significant) with clinically meaning MOE	Consider	Consider	Consider
Response Rate/CBR	No	No	Consider
Overall- high grade serous			
Response rate/CBR	Consider	Consider	Consider
selected histologies			
(eg. clear cell, mucinous, and low grade serous)			

MOE = magnitude of effect; QOL = quality of life; PRO = patient reported outcomes; CBR = clinical benefit rate.