

Ovarian Cancer National Alliance Clinical Trials Endpoints Policy Position

The Ovarian Cancer National Alliance is the nation's leading ovarian cancer advocacy organization. As the advocacy arm of the ovarian cancer movement, the Alliance works to save women's lives through advocacy, education and awareness.

One of the current controversies concerning ovarian trials is the relative merit of different trial endpoints. Thus, the Alliance has deemed it necessary to promulgate a clinical trials endpoints policy.

Background

To be useful, ovarian cancer trials must be developed in the context of what we know about the disease. The complexity and deadliness of ovarian cancer illustrates the need for significant improvement in our nation's clinical trial processes. There is a great deal we do not know about the origin, biology and genetics of ovarian cancer. However, the high mortality rate -- fewer than 50 percent of women with ovarian cancer survive five years from diagnosis and that seventy-five percent of women who attain remission from initial treatment will have at least one recurrence -- underlines the need for accelerating our understanding and trial results. Thus, the focus of current trials is on finding an early detection test and improved treatments. As we are looking for these answers, emphasis must be on improving the quality and length of life for women with ovarian cancer.

The nature of ovarian cancer itself also argues for more refined trial designs. Response to treatment among ovarian cancer patients ranges from no response to very long term response, even with advanced disease. Recently, The Cancer Genome Atlas has been used to show that ovarian cancer is a genetically heterogeneous disease; early results from TCGA show approximately 200 genetic variations in ovarian cancer. This heterogeneity may help to explain the far ranging variation in response among women with ovarian cancer. Regardless of the cause, ovarian cancer is extremely complicated to treat due to multiple genetic mutations, potential pathways and target interventions. Thus, isolating the causal effect of a specific intervention is difficult. And an inability to test multiple agents against multiple targets simultaneously hampers the speed with which we can uncover better treatments. However, we can determine the additions to quality and length of life by identifying a variety of trial endpoints.

Clinical Trial Endpoints

Clinical trials are designed to measure specific endpoints, which can include Overall Survival (OS), Progression Free Survival (PFS), Patient Reported Outcomes (PRO) or CA 125 response or progression.

Overall Survival (OS)

An increase in OS is the goal of any new treatment. However, this endpoint may be hard to obtain or accurately measure in the population of women with ovarian cancer. For example, measuring the impact of a potential new frontline therapy on OS would require that no additional treatment beyond standard of care be given to women in the trial in order to isolate the effect of the new therapy. Because so many women with ovarian cancer have a recurrence, denying further treatment in order to validate the results of a trial would be impossible. In addition, if OS is used as the endpoint for a trial in women with a recurrence, their prior treatments may confound the effect of the single agent

being studied. During the years it would take to measure outcome in terms of OS, other newer therapies may become available and used by patients in the trial. It would be difficult to determine which treatment(s) actually affected OS.

Progression Free Survival(PFS)

Due to the difficulty of measuring OS in women with ovarian cancer, PFS is often used as a proxy. The data are not clear that PFS is directly related to OS. Nonetheless, PFS can be a reliable and useful measure in and of itself. The time that a woman does not progress—is either in remission or has stable disease—is important both clinically and personally. Progression must be measured at the same interval for women in both arms of the trial in order to eliminate evaluation time bias. An independent review committee may be helpful in confirming results of the trial.

CA-125

Measuring the serum levels of CA-125 is also used as a proxy for OS. The Gynecologic Cancer Intergroup (GCIg) recommends using CA-125 progression for evaluating front-line therapies. For trials in the recurrent setting, GCIg recommends using CA-125 response. A rise in CA-125 may precede imaging evidence of tumor progression.

Patient Reported Outcomes (PRO)

PRO is another potential endpoint; however, this is not used very often. These data take into account patient functioning and quality of life, such as side effects from the treatment. Measuring quality of life is difficult since standards are not widely accepted. In addition, what might be meaningful to one patient might not be meaningful to another. However, good measures of adverse events and other non-cancer related outcomes must be developed

Relative Usefulness of Varying Endpoints

Measuring only outcomes such as PFS and OS while only analyzing a single new agent is too simplified for our current understanding of cancer. Trials should include information about correlative science so patients can be appropriately matched to treatments. As we move into an age of increased genetic information, it appears that there are hundreds of types of ovarian cancer and that an individual patient may have multiple genetic mutations. If ovarian cancer trials must evaluate interventions only in terms of PFS and OS in large groups, we are limited to studying only one new single agent at a time.

Ovarian Cancer National Alliance Position on Clinical Trial Endpoints

Given the challenges of measuring other endpoints, the Alliance believes that PFS is a useful endpoint in clinical trials for ovarian cancer therapies. In addition, the Alliance urges development of a valid and useful measure to determine quality of life for PRO trials. Lastly, the Alliance urges the integration of correlative data into trials whenever possible.

Sources:

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