Phase III clinical trials: objectives, hypothesis and design considerations
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Abstract
Phase III trials are conducted in large patient populations (typically, the number of subjects range from 1,000 to 3,000). They can either be controlled or uncontrolled, unblinded, single-blinded or double blinded. Phase III trial participants are assigned to treatment groups by randomization. Building on the data from Phase I and II studies, Phase III trials aim to gather efficacy and safety data of a new treatment intervention in comparison with the current standard of care. These trials may also examine the clinical benefit of the intervention in different patient populations, using different dosages and in combination with other drugs.

While the endpoints of Phase III oncology trials are commonly overall survival (OS) or time to progression (TTP), progression-free survival (PFS) is often selected as a surrogate endpoint OS in oncology trials as it reflects the true measure of first-line drug activity. However, controversy exists regarding the use of PFS as an endpoint. Even when supported by strong results from Phase II trials, failed Phase III oncology trials are quite common. In most of these cases, a statistically significant difference in PFS between treatment groups fails to translate into OS benefit. In the placebo-controlled Phase III AVADO and E2100 trials, which investigated the efficacy of bevacizumab as a first-line therapy for HER2-negative metastatic breast cancer, combination bevacizumab was shown to significantly increase PFS. However, in July 2010, the Oncology Drug Advisory Committee (ODAC) voted that the breast cancer indication be removed from the bevacizumab label. One of the reasons for the removal was that while bevacizumab increased PFS in the Phase III trials, the magnitude of benefit did not translate into improved survival. The pros and cons of the use of PFS as a surrogate endpoint will be addressed in this session.

At the end of this presentation, participants should have an improved understanding of the essential elements of a Phase III trial. This will include defining the study objectives and primary endpoints, as well as the choice of study population.

Key messages
• Phase III trials begin if evidence of effectiveness is shown in Phase II studies.
• The primary objective of Phase III clinical trials is to compare the effectiveness of a new treatment intervention with the current standard of care. If the new intervention is more effective than the usual treatment and/or is better-tolerated, it may become the new standard of care.
• The primary endpoints of Phase III oncology trials are often overall survival (OS) or time to progression (TTP). Progression-free survival (PFS) can be selected as a surrogate endpoint for OS.
• PFS remains a debatable surrogate endpoint in oncology trials.

References