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AACR, ASA, and FDA Outline Considerations for Overall Survival Analyses in Clinical Trials

New article in Clinical Cancer Research lists best practices, novel statistical methods, and suggestions for improving benefit-risk assessments

PHILADELPHIA – *Clinical Cancer Research*, a journal of the American Association for Cancer Research (AACR), today published an article outlining considerations for clinical trial design to enhance the collection and analysis of overall survival (OS) in the context of modern-day treatments.

OS measures how long a patient survives after treatment and is an important metric of a drug's efficacy and safety. It has long been considered the gold standard for oncology clinical trials.

The article—coauthored by researchers, clinicians, statisticians, industry representatives, patient advocates, and experts from the AACR, the American Statistical Association (ASA), and the U.S. Food and Drug Administration (FDA)—builds on discussions from the July 2023 FDA-AACR-ASA Workshop on Overall Survival in Oncology Clinical Trials, which convened stakeholders across drug development to explore how to overcome hurdles associated with traditional analyses of OS.

"Although overall survival has been a good endpoint in the past for new drug approval, its utility has become difficult in recent decades," said senior author and workshop co-chair Kenneth C. Anderson, MD, FAACR, in an interview with *Cancer Research Catalyst*, the official blog of the AACR. "It quite simply takes too long to measure now due to the remarkable progress we've made in the treatment of many cancers."

While early endpoints, such as progression-free survival, can offer early insight into a drug's efficacy, Anderson noted that these do not always align with OS. "There are examples where patients who received the study treatment had longer progression-free survival than patients in the control arm, but subsequent overall survival in larger trials was not any different between the arms," he said. In some cases, the study treatment has led to worse OS, despite promising progression-free survival results.

Attendees of the July 2023 workshop discussed this issue and others, including how unequal randomization, crossover from one trial arm to another, subsequent lines of therapy, subgroup considerations, and adverse effects might impact the interpretation of OS.

"The questions surrounding overall survival measures must be addressed in order to continue with new drug development and approvals at such a rapid pace," said Anderson.

The *Clinical Cancer Research* article consolidates discussions from workshop attendees and session working groups and includes:

- Best practices in the clinical trial design and planning, including considerations for when OS should be a primary efficacy endpoint;
- a recommendation that all trials with registrational intent be designed to collect and assess OS to inform patient safety, regardless of its role in evaluating efficacy;
- a recommendation to prespecify a measure of harm including OS and other safety endpoints to rule out specific safety concerns when OS is not the primary efficacy endpoint;
- acknowledgement that trials with crossover elements could complicate analysis of OS but, in certain cases, may be appropriate;

- acknowledgement that unequal randomization may reduce statistical power of OS analyses but may be used in certain situations;
- the importance of planning adequate follow-up time, informed by disease setting, patient population, and expected survival time, among other factors;
- a recommendation that independent Data Monitoring Committees have access to OS data for futility and safety analyses;
- considerations for prespecified analyses of OS, post hoc analyses of OS, and subgroup planning and analyses; and
- considerations and regulatory implications for incorporating early or limited OS results into benefit-risk assessments for drug reviews and approvals.

"The focus on OS is often as an efficacy endpoint in oncology clinical trials, but OS is also an important safety endpoint. Prespecified statistical analyses of OS as a safety endpoint provide valuable information on a product's benefit-risk profile when relying on earlier endpoints such as progression-free survival or overall response rates," said Nicole Gormley, MD, associate director of endpoint development in the Oncology Center of Excellence, FDA. "Robust assessments of OS as a safety measure are critical for the FDA's use of earlier endpoints to support approval."

"The significant efforts showcased in the article and throughout the workshop exemplify a successful cross-disciplinary collaboration," said article coauthor and workshop cochair Ruixiao Lu, PhD, FASA, who serves as the chair of the ASA's Partnership for Clinical Research and Statistics (PCRS) and is a former treasurer and board member of the ASA. "These endeavors will ultimately improve the quality of cancer research and lead to better patient care."

"I extend my sincere appreciation to all involved for their dedication to promoting scientific excellence and advancing public health outcomes," said Ron Wasserstein, PhD, executive director of ASA. "We look forward to the continued dialogues in driving innovations in the field of oncology and beyond."

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About the American Association for Cancer Research
Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 58,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 141 countries and territories around the world. Presently, 32% of members live outside the United States and 22% of AACR's international members are located in countries with emerging economies. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting. The AACR publishes 10 prestigious, peer-reviewed scientific journals. Other AACR publications include *Cancer Today,* a magazine for cancer patients and caregivers; the annual *AACR Cancer Progress Report*; *AACR Cancer Disparities Progress Report*; *AACR Annual Impact Report*; *Leading Discoveries*, the AACR's awareness and donor magazine; and the blog, *Cancer Research Catalyst*. In addition, the AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.

About the American Statistical Association
The American Statistical Association is the world's largest community of statisticians, the "Big Tent for Statistics" and the country's oldest scientific association. Since it was founded in Boston in 1839, the ASA has supported excellence in the development, application, and dissemination of statistics, the science of learning from data. Our members serve in industry, government, and academia in more than 90 countries, advancing research and promoting sound statistical practice to inform public policy and improve human welfare.