American Association for Cancer Research

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Chief Executive Officer

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Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2012-D-0432, "Draft Guidance for Industry: "Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval"

To whom it may concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the May 2012 draft guidance, "Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval."

We congratulate the FDA for its willingness to foster innovative approaches to accelerating drug development. The FDA's forward-looking consideration of pathologic complete response (pCR) as an endpoint for accelerated approval creates new hope for speeding the delivery of new therapies to cancer patients.

In general, the AACR is very supportive of the draft guidance and applauds the FDA for a clear guide to using pCR as an endpoint. The AACR respectfully asks FDA to provide further clarity on the FDA's current thinking with respect to two areas: 1) defining "high-risk" and the level of flexibility with respect to identifying populations based on emerging information such as biomarkers, and 2) clarifying the FDA's expectations with respect to investigational treatment given post-surgery.

**Define "high-risk" with more specific parameters**

The utility of the guidance is dependent on the appropriate interpretation of the FDA's definition of "high-risk." The draft guidance states: "The phrase *high-risk* refers to patients with breast cancer who have a high risk of distant disease recurrence and death despite use of optimal modern local and systemic adjuvant therapy." We feel that it is clear that the FDA intends to identify those patients with greater need for new therapeutics and the higher risk of an accelerated approval is acceptable; however, additional clarity on what the FDA considers "high-risk" is necessary for developers to take full advantage of this new approach. While there has been some discussion within the oncology community to develop a consensus around high-risk, an open discussion between FDA and multiple

stakeholders would be ideal to appropriately define "high-risk." A threshold figure such as 25-30% risk of recurrence within 3-4 years might be a starting point for discussion.

We are hopeful that gaining clarity on how the FDA defines "high-risk" will also help alleviate concerns about how the FDA will determine which patient populations are appropriate for trials to support accelerated approval, specifically with respect to ER+ subgroups and newly identified biomarker populations.

The draft guidance focuses on triple negative (ER- PR- HER2-) and HER2+ breast cancers because these diseases have a higher likelihood of pCR and more evidence that pCR predicts clinical benefit, as well as a clear unmet medical need. While we agree that the ER+ group, as a whole, is more likely to have long-term survival with available therapy, we know there are as yet unidentified subgroups within this population that are at high risk of recurrence. As new high-risk subgroups are identified, there should be a pathway to eligibility for a pCR accelerated approval endpoint. We feel that the draft guidance language suggests a willingness on the part of the FDA to consider ER+ positive patients with high-risk features for such accelerated trials, but it would be helpful for this to be stated outright, if indeed this is the case.

We would also like clarification about how the FDA would approach populations defined by biomarkers where historical data for recurrence in the particular biomarker-defined group is not available from prospective clinical trials. Consider the following hypothetical example: A population with high expression of biomarker X results in a large increase in pCR compared to the biomarker-negative population after exposure to the investigational therapy. The sponsor is interested in a potential registration trial based on pCR but is unsure how to proceed. It would be helpful to understand what level of evidence linking the biomarker-positive population to risk of recurrence is needed and whether the relationship between pCR and disease recurrence in the overall population would suffice when such information for the biomarker-positive population is lacking. Understanding the extent to which FDA will require evidence of the link between pCR and clinical outcomes for potential new biomarker populations will be helpful.

**Clarify post-operative treatment component**

There remains some confusion with respect to how the use of investigational therapies after surgery will impact the ability to use pCR as an endpoint for accelerated approval. The draft guidance states: "If postoperative systemic therapy is needed… the protocol should include a detailed and uniform approach to ensure that postoperative systemic therapy is delivered consistently across treatment arms." It is important to clarify this statement: does "delivered consistently" mean that the post-surgical treatment is identical in both treatment groups or does it mean that the treatment is the same pre- and post-surgery in a given arm? This is particularly relevant for the HER2+ setting, where an investigational therapy may be administered with a protocol similar to 52 weeks of trastuzumab, thus requiring pre- and postoperative therapy. As written, we feel the guidance is subject to interpretation and we respectfully ask for clarity on the issue of postoperative investigational therapy.

The AACR commends FDA for its commitment to incorporating scientific advances into its regulatory framework and is pleased to extend its resources and broad expertise as the FDA further considers the use of pCR as an endpoint for accelerated approval as well as other critical issues.

If you have any further questions or require follow up, please contact Pamela Bradley, Ph.D., Director of Science Policy, at (202) 898-6499 or pamela.bradley@aacr.org.

Sincerely,

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AACR President
Chair, Task Force on Regulatory Science & Policy

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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's membership includes 34,000 laboratory, translational and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in more than 90 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 17,000 attendees. In addition, the AACR publishes seven peer-reviewed scientific journals and a magazine for cancer survivors, patients and their caregivers. 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 individual and team science grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and policymakers about the value of cancer research and related biomedical science in saving lives from cancer.