Premenopausal Women with Breast Cancer: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (OCE) Jennifer Gao at 240-402-4683; (CDER) Julia Beaver at 240-402-0489; or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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I. INTRODUCTION

This guidance provides recommendations to sponsors developing drugs or biological products[2] regulated by CDER and CBER for the treatment of breast cancer. Specifically, this guidance includes recommendations regarding the inclusion of premenopausal women, as defined by serum hormonal levels (including but not limited to follicle-stimulating hormone and estradiol), in breast cancer clinical trials. The issues of fertility and fertility preservation when treating premenopausal women with breast cancer are outside the scope of this guidance and are not addressed.

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II. BACKGROUND

Historically, premenopausal women have been excluded from some trials that have investigated the efficacy of certain drugs that rely upon manipulation of the hormonal axis for the treatment of hormone receptor (HR)-positive breast cancer. In some cases, separate studies have been conducted to confirm the benefit in this patient population, which has resulted in delays in the availability of these therapies for premenopausal women with HR-positive breast cancer.

[1] This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drugs* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

Certain groups of drugs such as chemotherapy, immunotherapy, and targeted therapy (which act independent of the hormonal axis) have similar efficacy in pre- and post-menopausal women with breast cancer.

In patients with HR-positive breast cancer, where drugs are targeting or being combined with drugs targeting the hormonal axis, FDA believes hormonal drugs administered to premenopausal women with adequate estrogen suppression are likely to have generally the same efficacy and safety profile as in postmenopausal women, based on a review of the nonclinical, clinical pharmacology, and clinical literature. The inclusion of premenopausal women in breast cancer oncology product development programs will result in more complete clinical information to inform clinical decision making and bring safe and effective therapies in a timely manner to this patient population.

III. RECOMMENDATIONS

Consideration should be given to including premenopausal women in breast cancer drug development programs.[3] FDA encourages sponsors to discuss their breast cancer drug development plan with CDER and CBER, as applicable, early in development. FDA recommends:

- Menopausal status should not be the basis of exclusion from any breast cancer clinical trial.

- Premenopausal women[4] with adequate estrogen suppression[5] and postmenopausal women should be equally eligible and included in clinical trials for drugs or combinations manipulating the hormonal axis.

- Stratification of randomization based on menopausal status at study entry may be appropriate if there are efficacy and/or safety concerns.

[3] See the final guidance for industry *Male Breast Cancer: Developing Drugs for Treatment* (August 2020) for FDA's recommendations regarding including another patient population (i.e., males) in breast cancer clinical trials. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See the draft guidance for industry *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation* (January 2003). When final, this guidance will represent the FDA's current thinking on this topic.

[5] We acknowledge challenges with defining a cut-off level for estrogen suppression given differences in assays, patient demographics such as weight, medical comorbidities (e.g., polycystic ovarian syndrome), etc.

- An assessment of the weight of evidence that includes published literature and existing nonclinical data for reproductive toxicity should be provided to allow FDA to determine if reproductive toxicity studies may be necessary for an indication that will include premenopausal women.[6]

- Information on long-term clinical effects (e.g., bone health, cardiac health) of breast cancer drugs in premenopausal women should be collected during the trial.

- A gynecologist should be consulted during trial planning and monitoring, as needed.

[6] For recommendations regarding nonclinical data needed to support clinical trial design and marketing applications, refer to ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010), ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018), and guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* (May 2019).