Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval
Guidance for Industry

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

July 2020
Clinical/Medical
Revision 1

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Guidance for Industry[1]

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## I.	INTRODUCTION

This guidance is intended to assist sponsors in designing trials to support marketing approval of drugs and biological products for the treatment of high-risk early-stage breast cancer in the neoadjuvant (preoperative) setting.[2] The main focus of the guidance is to discuss the use of pathological complete response (pCR) in high-risk early-stage breast cancer as a potential endpoint to support approval under the accelerated approval regulations (21 CFR part 314, subpart H, for new drug applications and 21 CFR part 601, subpart E, for biologics license applications). The objectives of the guidance are to:

- Describe acceptable definitions of pCR for regulatory purposes

- Briefly summarize what is currently known about the relationship between pCR and prognosis

- Describe trial designs and patient populations in which pCR may be accepted as reasonably likely to predict clinical benefit

- Provide guidance regarding trial designs to verify clinical benefit in support of traditional approval

This guidance does not address trials of neoadjuvant endocrine therapy for breast cancer, nor does it address use of pCR as an endpoint for approval of drugs to treat tumor types other than

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[1] You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2012-D-0432.

[2] The terms *drug* and *systemic therapy* refer to both drugs and biological products regulated by CDER and CBER.

breast cancer. This guidance primarily describes potential pathways to accelerated approval for drugs for the treatment of high-risk early-stage breast cancer. Sponsors should consult the FDA as early as possible regarding their development strategy when seeking a neoadjuvant breast cancer indication.

Specific terms and phrases used in this guidance are defined as follows:

- The phrase *early-stage breast cancer* refers to invasive breast cancer without distant metastases

- The phrase *high-risk* refers to patients with early-stage breast cancer who continue to have a high risk of distant disease recurrence and death despite use of optimal modern local and systemic adjuvant therapy

- The terms *neoadjuvant* and *preoperative* are used interchangeably to refer to systemic therapy that is given before lumpectomy or mastectomy to reduce the risk of breast cancer recurrence

- The term *clinical benefit* in an early-stage breast cancer population refers to a clinically meaningful and statistically significant improvement in event-free survival (EFS), disease-free survival (DFS), or overall survival (OS)

This guidance is a revision of the final guidance of the same title that published in October 2014. This guidance replaces the October 2014 guidance of the same title.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II.   BACKGROUND

A.   Rationale for Neoadjuvant Therapy

Adjuvant systemic therapies for breast cancer (i.e., drugs given to reduce the risk of breast cancer recurrence) historically have been administered following definitive breast surgery. Preoperative or *neoadjuvant* systemic chemotherapy, once reserved for patients with locally advanced breast cancer in whom the goal was to render large breast cancers operable, has become increasingly common. There are several potential reasons to consider neoadjuvant treatment for early-stage breast cancer. Giving chemotherapy preoperatively permits breast conservation in some patients who would otherwise require mastectomy and may improve cosmesis in existing candidates for breast conservation. Preoperative therapy also provides a *real-time* evaluation of tumor response to permit discontinuation of ineffective therapy. Further, a patient's response to neoadjuvant chemotherapy may provide prognostic information that can supplement conventional prognostic

data, such as initial staging, tumor grade, and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. Finally, the neoadjuvant setting offers investigators the unique opportunity to examine modulation of tissue, imaging, and other biomarkers from the time of biopsy to the time of definitive breast surgery following preoperative systemic therapy.

B.   The Accelerated Approval Program

The FDA's accelerated approval program is intended to facilitate development of drugs for treatment of a serious or life-threatening disease that provide meaningful therapeutic benefit over available therapy. We recognize that, despite advances in adjuvant systemic therapy of breast cancer over the past few decades, there remains a significant unmet medical need for certain high-risk or poor prognosis subsets of early-stage breast cancer patients. Consideration of pCR as an acceptable study endpoint for accelerated approval in the neoadjuvant setting may encourage industry innovation and expedite the development of novel therapies to treat high-risk early-stage breast cancer.

Section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 356(b), as amended by the Food and Drug Administration Safety and Innovation Act of 2012, provides that:

> The FDA may grant accelerated approval ". . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

The accelerated approval regulations further provide that:[3]

> Approval under this section will be subject to the requirement that the sponsor study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The sponsor shall carry out any such studies with due diligence.[4]

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[3] See 21 CFR 314.510.

[4] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014), section VII.D. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA drugs guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

C. Implementation of the Guidance

Since the draft version of this guidance was published in May 2012, the FDA has participated in public discussions regarding this pathway for drug development. In March 2013, the FDA and the American Society of Clinical Oncology co-sponsored a public neoadjuvant breast cancer workshop to discuss the use of pCR to support accelerated approval.[5] The panel concluded that a large improvement in pCR rate based upon analysis of a full intent-to-treat population was reasonably likely to predict clinical benefit, and that the potential advantages of granting accelerated approval based upon pCR from a neoadjuvant randomized controlled trial generally outweighed risks. The panel emphasized that such trials should be limited to high-risk patients, and that a confirmatory trial should be ongoing at the time of accelerated approval.

The first drug to be granted accelerated approval in the neoadjuvant setting for high-risk, early breast cancer was discussed at an Oncologic Drugs Advisory Committee (ODAC) meeting in September 2013.[6] The favorable review of this application, both by the ODAC and the FDA, was based upon results of the submitted trials in the neoadjuvant setting taken in the context of the robustness of the development program. The submitted application demonstrated a significant absolute improvement in pCR rate in the intent-to-treat population with acceptable safety. Importantly, this application was supported by a statistically and clinically significant effect on OS in a separate trial in the metastatic setting, an extensive body of safety data from treatment of several thousand patients with metastatic breast cancer and an adjuvant confirmatory trial that was fully accrued at the time of accelerated approval in the neoadjuvant setting.[7] The adjuvant confirmatory trial subsequently met its primary endpoint of disease-free survival, and the drug subsequently received regular approval for use in early breast cancer in both the neoadjuvant and adjuvant setting.

The 2014 final guidance was revised to discuss the challenge that use of additional therapy in the setting of post neoadjuvant residual disease has the potential to confound interpretation of long-term outcomes supporting confirmation of clinical benefit. The revision also streamlines the guidance by removing information that is no longer current and information that is not specific to the focus of the guidance, as well as by including revised language to improve clarity.

III. ENDPOINTS FOR NEOADJUVANT TRIALS

Randomized neoadjuvant trials comparing the same treatment regimen administered either preoperatively or postoperatively have suggested that pCR may predict long-term outcome in individual patients with early-stage breast cancer treated with preoperative systemic therapy (Cortazar et al. 2012, van der Hage et al. 2007, Rastogi et al. 2008, and Bear et al. 2006). While pathological complete response has been used as an endpoint in numerous trials of neoadjuvant

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[5] https://www.fdalive.com/agendas/PM032213/Agenda.pdf.
[6] http://wayback.archive-it.org/7993/20170113054202/http:/www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM371011.pdf (January 13, 2020).
[7] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125409Orig1s051SumR.pdf.

systemic therapy for breast cancer, historically, there was not a uniform definition of pCR, which created challenges in reporting and interpreting data from neoadjuvant trials (Buzdar et al. 2005, von Minckwitz et al. 2010, Bear et al. 2006, Wolmark et al. 2001).

To address these limitations, the FDA established a working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTneoBC). Primary source data was obtained from nearly 13,000 patients enrolled in large-scale neoadjuvant trials with clear definitions of pCR and available long-term follow-up, including U.S. and international trials. Using these data, the FDA performed a pooled analysis to assess the relationship between pCR and long-term outcome (Cortazar et al. 2012). The FDA compared the three most commonly used definitions of pCR (ypT0/Tis (absence of invasive cancer in the breast), ypT0/Tis ypN0 (absence of invasive cancer in the breast and axillary nodes), and ypT0 ypN0 (absence of invasive and in situ cancer in the breast and axillary nodes)) and their relationship to long-term patient outcome. As expected, use of increasingly stringent definitions of pCR resulted in decreasing average pCR rates: 22 percent, 18 percent, and 13 percent, respectively, in the trials included in the pooled analysis. Persistent nodal involvement following neoadjuvant therapy was associated with an increased risk of recurrence and death, whereas residual ductal carcinoma in situ did not have prognostic value. Therefore, we recognize either of the following two definitions of pCR for the purposes of designing trials for U.S. marketing approval:

1. ***Pathological complete response (pCR)*** is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 in the current AJCC staging system)

   or

2. ***Pathological complete response (pCR)*** is defined as the absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0 in the current AJCC staging system)

The definitions reflect an evolving paradigm in surgical management of the axilla. Axillary lymph node dissection (ALND) may not be required for patients with sentinel lymph node-positive breast cancer in whom local and systemic therapies are unlikely to be affected by the finding of additional positive lymph nodes. We therefore recommend using the phrase *sampled regional lymph nodes,* as indicated in our standard definitions of pCR. These definitions permit flexibility in terms of the surgical approach to the axilla, but reflect the fact that the presence of any residual invasive cancer following neoadjuvant therapy portends a poorer prognosis. Given that the primary endpoint includes the pathological status of the axilla and that an imbalance of ALND between arms has the potential to confound interpretation of pCR, an algorithm for surgical assessment of the axilla should be explicitly outlined in the protocol and discussed with the FDA before trial initiation.

For neoadjuvant trials, in which all patients by definition will have invasive cancer at the time of randomization, the long-term clinical benefit endpoints for traditional approval should be termed event free survival (EFS) or OS (see section IV).

EFS should be defined as time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence, or death due to any cause.

For confirmatory trials conducted in the adjuvant setting, in which patients are presumed to be free of disease at the time of randomization, the long-term clinical benefit endpoints for traditional approval should be termed disease-free survival (DFS) or OS (see section IV).

DFS should be defined as time from randomization until local or distant recurrence or death due to any cause.

IV. CLINICAL TRIAL DESIGN AND STATISTICAL CONSIDERATIONS

We strongly encourage sponsors to meet with the FDA to discuss all neoadjuvant trial designs intended to support accelerated approval.

A. Rationale for Use of Pathological Complete Response in Neoadjuvant Trials as an Endpoint for Accelerated Approval

Historically, new drugs for breast cancer have been developed and approved initially in the metastatic setting, with patients whose expected median OS was generally 2 years or less. Trials to support adjuvant (postoperative) indications have followed development and approval in the metastatic setting and are much lengthier. Existing adjuvant therapy for breast cancer will effectively delay or eliminate recurrence for many patients so that large sample sizes and prolonged follow-up in randomized trials are needed to demonstrate a difference in DFS or OS adequate to support drug approval in the adjuvant setting. As a result, the time from initiation of a pivotal trial of a drug in metastatic breast cancer to approval for its use in an adjuvant population has often been a decade or more.

The effectiveness of adjuvant therapy for breast cancer is well-established, but certain subpopulations of breast cancer patients continue to be at substantial risk of recurrence and death, even with optimal adjuvant therapy. There is currently no early marker of potential efficacy in the adjuvant setting. In contrast, when systemic therapy is given in the preoperative setting, pCR can be assessed within several months of initiation of an investigational drug. Use of pCR as an endpoint to support accelerated approval in the neoadjuvant setting may help address unmet medical needs in high-risk populations in a far shorter time frame.

Randomized neoadjuvant trials comparing the same treatment regimen administered either preoperatively or postoperatively have suggested that pCR may predict long-term outcome in individual patients with early-stage breast cancer treated with preoperative systemic therapy (Cortazar et al. 2012, van der Hage et al. 2007, Rastogi et al. 2008, and Bear et al. 2006).

An important limitation of these types of analyses, commonly referred to as *responder analyses*, is that they compare outcomes between two subpopulations (e.g., those who had a pCR and those who did not) irrespective of treatment assignment. Although such data are informative at a patient level, indicating a more favorable prognosis for those with complete eradication of invasive tumor by preoperative therapy, they do not necessarily establish that a difference in pCR rates between treatment arms will predict a difference in efficacy endpoints, such as DFS, EFS, or OS, between two treatments. Some trials that have shown a difference in pCR rate between arms have nonetheless failed to show a difference between arms in EFS when the entire intent-to-treat population is considered (Kaufmann et al. 2006). The CTneoBC pooled analysis found no correlation between magnitude of difference in pCR rates between treatment arms and EFS or OS at a trial level (Cortazar et al. 2012). A variety of potential explanations for this finding exist. The trials included in the pooled analysis enrolled heterogeneous patient populations and, with one exception, compared various cytotoxic regimens to one another. As a result, the absolute differences in pCR rate between treatment arms in the included trials ranged from 1 to 20 percent, but no trial other than the Neoadjuvant Herceptin (NOAH) trial had an absolute difference in pCR rate between arms of greater than 10 percent (Cortazar et al. 2012). The relationship between pCR and long-term outcome for immunotherapy and other targeted agents is an area of ongoing investigation.

Given the substantial improvements in survival for individual patients who attain pCR, a novel agent administered with standard therapy that produces a marked absolute increase in pCR rate compared with standard therapy alone in the intent-to-treat population (i.e., all randomized patients) may be reasonably likely to result in long-term improvements in EFS or OS. Different breast cancer subtypes may require different magnitudes of improvement in pCR rate to achieve clinically meaningful improvement in EFS or OS. Therapies that modestly increase pCR rate are less likely to improve long-term outcomes in any subtype. We emphasize that the analysis of neoadjuvant breast cancer trials for regulatory approval should compare pCR rates and long-term outcomes between treatment arms, using the intent-to-treat population, and should *not* be limited to those patients who achieve pCR, given that this is a nonrandomized patient subset determined by an outcome subsequent to randomization.

B. Trial Designs in the Neoadjuvant Setting

1. *Clinical Trials to Support Accelerated Approval*

A trial to support accelerated approval should be a randomized, well-controlled trial intended to demonstrate superiority. An add-on trial comparing the investigational drug plus standard neoadjuvant therapy to standard neoadjuvant therapy alone may be the most appropriate option when the standard of care regimen involves a limited number of agents. For situations in which the standard of care for neoadjuvant therapy involves a large number of agents, alternatives to an add-on design may be considered.

- **Randomized, well-controlled trial**

  The biological differences between the tumors of patients who achieve a pCR in response to neoadjuvant therapy and those who do not are still poorly understood, and there is

uncertainty about the use of pCR as an endpoint to evaluate an investigational drug in nonrandomized trials. A high pCR rate in a single-arm trial may reflect the known and unknown biological characteristics of the tumors and other factors in the enrolled population, the efficacy of the investigational drug, the efficacy of conventional therapy delivered as part of neoadjuvant therapy, or some combination of the above. Randomized clinical trials are therefore necessary to establish treatment effects of the investigational drug.

- **Superiority design**

   Neoadjuvant trials intended to support marketing approval should be designed to demonstrate superiority of the investigational drug over the standard of care for the trial population.

   Noninferiority trials are not appropriate for accelerated approval based on pCR. Since an association between the absolute or relative increase in pCR that correlates with an improvement in long-term outcome has not been determined at a trial level, there is no basis for selection of an appropriate noninferiority margin for pCR rate. Thus, such trials would expose patients to an unacceptable risk of inferior OS or EFS.

- **Add-on design**

   Many individuals with early-stage breast cancer, including those identified as high risk at initial presentation, can be cured with available therapy; at present there appears to be no advantage, in terms of survival, to earlier (i.e., preoperative) administration of systemic therapy (Mauri et al. 2005). Therefore, an *add-on design*, in which a standard adjuvant regimen is compared with the same regimen plus the investigational drug, is preferred when a standard of care treatment involves a limited number of agents. Such a design ensures that high-risk patients are not denied effective therapy with curative potential and also permits isolation of the effects of the investigational drug. In situations when there is substantial evidence of anti-tumor activity that is large in magnitude observed with an investigational drug in metastatic breast cancer, or when a standard of care regimen involves a large number of agents, a randomized superiority trial directly comparing standard neoadjuvant therapy with an investigational agent delivered preoperatively (i.e., omitting the standard therapy from the investigational arm) may be acceptable in lieu of an add-on design. In these circumstances, omission of part or all of the standard therapy from the investigational arm may be acceptable because the risk of the investigational agent being inferior to standard therapy is relatively low and, in certain cases, may be offset by the benefit of avoiding the need for multiple agents.

   2.   *Outcome Assessment*

In all cases, pathologists interpreting surgical specimens for assessment of pCR should be blinded to treatment assignment. We recommend that a summary note for each subject be provided to the blinded study pathologist that includes a general overview of the trial but no patient-level treatment information. The note should include the major clinical, radiographic,

and operative findings, including a description or diagram of the original size and location of the tumor, the presence or absence of multifocality, the extent of preoperative lymph node involvement, the number of clips in the breast or nodes, hormone and HER2 receptor status, presence of calcifications if any, and type of surgery. The summary note should also include a statement that pathologists are to remain blinded to treatment arm. This summary note is intended to avoid the need for pathologists to access clinic notes and other documents that may result in their inadvertent unblinding to treatment arm.

Although we appreciate that practices for identifying and evaluating the axillary nodes may vary between clinical centers and geographical regions, the nature and timing of nodal assessment should be standardized within a given trial to avoid confounding the primary endpoint. We recommend an axillary ultrasound and pretreatment fine needle aspiration or core biopsy of any clinically or radiographically suspicious nodes before administration of any preoperative systemic therapy. Any involved nodes should be marked with a metallic indicator or other standard approach before systemic therapy to ensure their removal at the time of definitive surgery.

We strongly recommend that sentinel lymph node biopsy, using dual blue dye and radioisotope tracers, be performed at the time of definitive surgery and include resection of at least two nodes whenever possible (Boughey et al. 2012, Kuehn et al. 2012). For global trials inclusive of geographic regions where the sentinel lymph node assessment is commonly performed before administration of systemic therapy, randomization may be stratified accordingly. The protocol should provide guidelines for axillary lymph node dissection in patients found to have axillary nodal involvement. Finally, the protocol should outline under what circumstances cytokeratin staining of the axillary nodes should be performed and state how patients found to have isolated tumor cells will be classified in terms of the primary endpoint.

Since it is common for patients without any remaining palpable tumor in the breast or axilla after neoadjuvant therapy (i.e., those who have a clinical complete response (cCR)) to nonetheless have residual invasive breast cancer detected by pathology at the time of definitive breast surgery (von Minckwitz et al. 2001), a patient who has achieved *cCR* cannot be assumed to have achieved *pCR*. Neoadjuvant trials intended to support a marketing application should require that all patients must receive local therapy consistent with current standards of care, at the completion of neoadjuvant systemic therapy (Davidson 2005).

3. *Postoperative Therapy*

Criteria for radiotherapy should be prespecified in the protocol, and details of all radiation treatment should be captured in standardized manner in case report forms given the potential for local therapy to affect the risk of local and distant recurrence, as well as survival.

It is important to recognize that many patients with high-risk early-stage breast cancer enrolled in neoadjuvant trials will not achieve pCR. Patients with postneoadjuvant residual disease are at increased risk of distant recurrence (Cortazar et al. 2012).

The high rate of distant recurrence in patients with postneoadjuvant residual disease is of concern and underscores the need for future randomized trials in this patient population comparing novel therapies to one another or to the current standard of care.

4.   *Clinical Trials to Verify and Describe Clinical Benefit (Confirmatory Trials)*

To verify and describe the clinical benefit of a drug granted accelerated approval on the basis of pCR, the confirmatory trial should demonstrate a clinically meaningful and statistically significant improvement in EFS, DFS, or OS. The confirmatory trial should be ongoing at the time of accelerated approval. One acceptable approach, referred to as the *single trial model*, would be to follow the patients entered into a randomized neoadjuvant trial that supported the accelerated approval until EFS or OS data are mature. This approach may enable a single, well-controlled randomized trial, if adequately powered and with sufficiently compelling results, to serve as the basis for both accelerated and traditional approval, saving time and resources in drug development and expediting patient access to highly effective therapies for high-risk early-stage breast cancer. The applicant should ensure adequate collection of long-term safety data and be prepared to provide interim safety data to the FDA on an ongoing basis so that serious safety signals can be quickly identified and mitigated.

A single large neoadjuvant trial designed and powered to demonstrate both an improvement in pCR rate and an improvement in either EFS or OS may be capable of detecting pCR differences that are statistically significant without being clinically meaningful. In this scenario, the statistical analysis plan for evaluating pCR should be prespecified, with the target magnitude of effect calculated based upon the sponsor's best estimate of the magnitude of the difference in pCR rate between arms needed to result in a clinically and statistically significant difference in EFS or OS. All patients should be enrolled in the trial before any efficacy analyses, including analyses of pCR, are performed. Although prespecified interim analyses for EFS and/or OS performed for futility or for efficacy at the time of the definitive analysis of pCR are acceptable, interim efficacy analyses of pCR, which could impair the ability of the trial to complete accrual, should be avoided. Interim analyses for futility with regards to the pCR endpoint would be acceptable.

If a single trial is intended to support both accelerated and traditional approval, the statistical analysis plan should include a plan for controlling the false positive rate (type I error) for the primary endpoint, pCR, to support accelerated approval, as well as a plan for controlling the false positive rate for either of the primary endpoints, EFS or OS, to support traditional approval. Because the effect size on EFS or OS is likely to be smaller than the effect size on pCR rate, the statistical analysis plan for controlling the overall false positive rate (type I error) for all key efficacy objectives should be structured such that a greater portion of level of significance (alpha) is allocated to the comparisons of direct measure(s) of clinical benefit (i.e., EFS or OS), and a lesser portion to the pCR endpoint.

An alternate development approach, referred to as the *multiple trial model*, would rely upon separate trials to support accelerated approval and traditional approval. In this model, sponsors would conduct one or more neoadjuvant randomized trial(s), powered to detect a substantial absolute improvement in pCR rate between arms, to support accelerated approval. A subsequent

larger trial, which may be conducted in either the neoadjuvant or adjuvant setting, powered for EFS (neoadjuvant), DFS (adjuvant), and/or OS (either disease setting), would be used to confirm clinical benefit and provide the basis for traditional approval in early breast cancer.

> 5.   *Selecting a Development Strategy: Single Trial Model vs. Multiple Trial Model*

There are advantages and disadvantages to both the single trial and the multiple trial models.

>   a.   Single Trial Model

A single trial, which should be powered for both pCR and EFS or OS, will require a larger sample size than a trial intended only to support accelerated approval and may take longer to complete accrual. A single large trial provides for an improved estimate of treatment effect on pCR, a better understanding of how pCR effect impacts long-term outcome in the same trial population, and a larger body of safety data from an early-stage high-risk breast cancer population at the time of initial accelerated approval, which will more fully characterize the toxicity of the drug. Given that the trial should be fully accrued by the time of the pCR analysis, the single trial model also avoids the feasibility issues of conducting a separate confirmatory trial. Furthermore, long-term outcome data is likely to be available earlier than if a separate trial to verify and describe clinical benefit had to be designed, conducted, and analyzed, which would shorten the time to satisfaction of the confirmatory study obligation, or withdrawal of the neoadjuvant breast cancer indication if clinical benefit is not confirmed. The disadvantages of the single trial model include exposure of a large number of patients to potentially less effective and/or more toxic therapy, a potentially longer wait to initial U.S. approval compared with the multiple trial model, a lack of data on use of the drug in a strictly postoperative setting, and the potential for confounding by postoperative systemic therapy.

A substantial challenge for confirmation of clinical benefit is the increasing use of drugs in the setting of postneoadjuvant residual disease, which has the potential to confound long-term outcomes such as EFS and OS. For example, in the KATHERINE trial, patients with HER2 positive breast cancer who had residual invasive cancer after neoadjuvant chemotherapy and trastuzumab had improved DFS if they switched to receive T-DM1 postoperatively rather than continuing trastuzumab (von Minckwitz et al. 2019). In addition, there are ongoing randomized trials of multiple drug classes in patients with residual invasive cancer following preoperative therapy. This issue should be anticipated and addressed proactively in the protocol and statistical analysis plan. Designs that permit patients on the control arm to receive the investigational drug under study in the trial in the postoperative setting will confound EFS and OS and generally should be avoided. Postoperative systemic therapy for all randomized patients irrespective of treatment arm that represents the current standard of care (e.g., HER2-directed therapy in patients with early-stage HER2+ breast cancer or endocrine therapy for women with hormone receptor-positive breast cancer) is acceptable. The protocol should include a detailed and uniform plan to ensure that the approach to postoperative therapy is pre-specified and recorded in the case report form to assess the potential for confounding of long-term clinical outcomes. Sample size calculations should take into consideration this potential for confounding of the endpoint used to verify and describe the long-term clinical benefit by postoperative therapy, and sensitivity analyses to assess the effect of postoperative therapy should be pre-planned. If

response-adaptive treatments are considered, a second randomization is recommended. Given that EFS and OS results may be impacted by postoperative treatment, sponsors are encouraged to meet early with FDA to discuss selection of single versus multiple trial model, approach to use of postoperative systemic therapy in the setting of residual invasive cancer, and the details of the statistical analysis plan.

b. Multiple Trial Model

The multiple trial model also has advantages and disadvantages. The multiple trial model permits widespread access to highly effective drugs earlier because fewer patients need to be accrued before potentially granting accelerated approval based on the pCR endpoint. Demonstrating the efficacy of a drug provides greater assurance that the results are not due to chance alone. The results of the neoadjuvant trial also may help to inform the design of the confirmatory trial. In addition, there is less concern about confounding of results due to postneoadjuvant residual disease additional therapies. Finally, the multiple trial model may facilitate study of the new drug combined with, or compared to, other standard therapy, or in a different patient population (e.g., lower risk patients, postoperative setting, or post-neoadjuvant residual disease setting), in the confirmatory trial. The multiple trial model has as its principal disadvantage the feasibility issues involved in designing and conducting a second trial. Confirmatory trials that recapitulate the design and patient populations enrolled in the trial that supported accelerated approval would be expected to accrue poorly in the United States, and patient dropout or recommendations for patient cross-over are likely to occur following accelerated approval. The effect of these issues may be mitigated by having a global adjuvant trial well underway at the time of accelerated approval.

c. Additional Considerations for Selecting a Development Strategy

There is no single best development strategy for all drugs to treat high-risk, early breast cancer in the neoadjuvant setting. Factors that can help to determine whether the single trial or the multiple trial model is more appropriate include: the extent of prior clinical data with the drug, knowledge of efficacy and safety of the drug class, regulatory status of the drug (e.g., existing approvals for breast cancer, other malignancies, or non-oncologic indications), and the status of any ongoing development program in early-stage breast cancer. In general, the multiple trial approach, in which accelerated approval would be granted on the basis of one or more small neoadjuvant randomized trials followed by a postapproval trial, is most appropriate for drugs with evidence of substantial efficacy in the metastatic setting, safety profiles that are well characterized and acceptable for the patient population in question, and ongoing or fully accrued large randomized adjuvant trials. The multiple trial model also may be appropriate for drugs with evidence of unprecedented efficacy in breast cancer subtypes with significant unmet medical need. Finally, the multiple trial model may be preferable in settings where use of standard of care systemic therapy to treat postneoadjuvant residual disease is expected, as this would confound the endpoints used to verify and describe the long-term clinical benefit in a single large neoadjuvant trial. Selection of a neoadjuvant development plan should be tailored to the drug and patient population in question and should take place in consultation with the FDA.

C.   Patient Populations for Neoadjuvant Breast Cancer Trials to Support Accelerated Approval

Patient populations appropriate for trials of neoadjuvant systemic therapy for breast cancer with marketing intent are those judged to have a high risk of distant disease recurrence and mortality despite use of optimal therapy. This is primarily because of excellent outcomes in patients without high-risk disease with available therapy where the potential risks of inferior DFS, EFS, or OS would be unacceptable. Patients may be classified as high risk for recurrence on the basis of conventional histologic features or by appropriately validated genomic measures, but in general should have a 5-year EFS of less than 75 percent. The decision to pursue accelerated approval via the neoadjuvant pathway should be made on the basis of strong biological and clinical rationale for a drug's activity in high-risk subtypes of breast cancer.

The median follow-up in a neoadjuvant trial with pCR as its primary endpoint will be relatively immature at the time of accelerated approval. Data that verify and describe, or fail to verify and describe, effects on DFS, EFS, or OS may require several years of additional follow-up to reach maturity. It is also conceivable that the initial trial supporting the approval of an investigational drug, as an add-on to standard neoadjuvant chemotherapy, may be conducted in a development program that does not include large trials in the metastatic setting, further limiting supportive data on the anti-tumor activity or efficacy of the investigational drug in breast cancer at the time of approval. Therefore, it is possible that a drug approved in the neoadjuvant setting could remain on the market for a prolonged period of time and subject patients with potential alternative options to a risk of inferior DFS, EFS, or OS.

We recognize the risk of granting an initial approval in the setting of limited long-term efficacy and safety data from a neoadjuvant trial. Although it is possible that such a risk may be appropriate in populations of breast cancer patients with significant unmet medical need, it is unlikely to be acceptable for populations having more favorable prognoses with existing therapy. For all of these reasons, we strongly recommend that patients with hormone receptor-positive tumors lacking high-risk features not be enrolled in neoadjuvant trials with pCR as the endpoint to support accelerated approval.

D.   Characterization of Drug Safety

In a neoadjuvant trial relying upon pCR as the primary endpoint to support accelerated approval, long-term safety data will be limited. Conventional adjuvant trials include several years of follow-up and, in addition, have historically been conducted only after one or more randomized trials in the metastatic setting have been performed. The resultant safety database characterizes not only the incidence and severity of acute treatment-emergent adverse events, but also provides long-term data on the outcome of acute or cumulative adverse events, such as neuropathy, and the incidence of rare or late toxicities, such as secondary malignancy or heart disease. Such a comprehensive safety assessment is critical in an early-stage breast cancer population, in whom long-term survival is common and indeed may result from local therapy alone.

Given that a neoadjuvant trial to support accelerated approval could potentially occur in a development program that does not include a completed randomized trial or drug approval in the

metastatic setting, sponsors should discuss with the FDA the amount of safety data needed to proceed to a randomized neoadjuvant trial intended to support accelerated approval. Before embarking on a such a neoadjuvant trial, sponsors should provide to the FDA at a minimum the same level of safety data on the investigational drug, administered alone and in combination with the regimen for which it will be studied, as would currently be needed to launch a trial intended to support approval in the metastatic setting. Such data should be sufficient to establish that the dosage regimen(s) are reasonably safe and that preliminary pharmacology assessments have been conducted characterizing the pharmacokinetic profile with an emphasis on specific populations based on age and ethnicity, and the potential for drug interactions, QT prolongation, and food effects (for orally administered drugs). The results of chronic nonclinical toxicology studies and preliminary assessments for effects on embryofetal development should have been submitted to FDA. Based on the safety profile and extent of prior clinical experience with the investigational drug or other drugs in the same class, and the proposed trial population, additional safety or efficacy data may be required prior to the initiation of the randomized neoadjuvant trial.[8]

Regulatory decisions on accelerated approval in the neoadjuvant setting would take into consideration the known, and potentially unknown, risks of a drug in the context of the observed improvement in pCR for the population under study. Given these long-term safety considerations, the neoadjuvant setting should be designed to collect long-term safety data from a number of patients comparable to traditional adjuvant breast cancer trials.[9] At the time of accelerated approval, applicants also may be required to conduct additional safety trials as postmarketing requirements under section 505(o)(3) of the FD&C Act.

E. Recommendations for Pathology Standard Operating Procedures

All protocols for neoadjuvant trials conducted to support a marketing application should include a detailed set of standard operating procedures (SOP) for collection, handling, and interpretation of pathology specimens, comparable to imaging charters for oncology trials with radiographic primary endpoints (see IV.B.2). All neoadjuvant trial pathologists should receive formal training provided by the sponsor via webinar or on-site in a small number of centralized geographic locations. A pathologist principal investigator with extensive prior experience interpreting postneoadjuvant specimens should be identified for each country or region to serve as an adjudicator for cases in which the study site pathologist is uncertain whether a given patient has achieved pCR.

The SOP should include an approach to ensure localization of the tumor bed, including placement of a clip in the tumor bed and any involved lymph nodes at the time of biopsy, postoperative specimen radiographs to verify excision, and use of colored sutures or other approaches to orient the specimen (see also IV.B.2). Pathological findings that may aid identification of the tumor bed, such as absence of glandular tissue, hyalinized vascular stroma, cell vacuolization, or foci of lymphocytic infiltration, should be described and illustrated. Acceptable standards for specimen handling and processing, such as a 1-hour maximum time of

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[8] See section 505(o)(3) of the FD&C Act.
[9] See the guideline for industry *ICH-E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995).

specimen transit to the laboratory and a 24-hour minimum formalin fixation, also should be defined.

The SOP should provide explicit guidelines for evaluation of specimens, particularly for those patients with cCR. After entire specimens are inked for orientation, specimens from such patients should have a minimum of 1 block prepared per centimeter of pretreatment tumor size, or at least 10 blocks in total, whichever is greater, with 3 to 5 millimeter (mm) slices. Review of both the radiologist's interpretation of the specimen radiograph(s) and the pathologist's assessment of the gross specimen(s) should be used to target areas deemed suspicious for potential residual disease. Areas of concern identified by either discipline should be subjected to more extensive sectioning. Given that tumors may shrink concentrically or irregularly, patients with no evidence of residual disease identified on initial evaluation should have additional blocks examined to ensure that no residual disease has been overlooked, and in particular, that no positive margins have been missed that may be surgically improved.

All lymph nodes collected at the time of surgery should be assessed via serial gross sectioning. Nodes without residual disease apparent on gross inspection should be paraffin-embedded and cut in 2 to 3 mm slices. At least one representative section per paraffin block should be analyzed after staining with hematoxylin and eosin. The most reliable indicator of pCR in a lymph node is the presence of a well-defined scar in the absence of identifiable tumor cells.

Both the SOP and the formal training for study pathologists should include guidance for situations when the presence of residual disease in the breast, lymph nodes, or lymphatics is in question. Although cytokeratin staining should not be routinely performed on lymph nodes that are negative by gross inspection and hematoxylin and eosin staining, it may be helpful to assess lymph nodes where there are suspicious cells that preclude a final determination of nodal status by the pathologist. Immunohistochemical staining also can help to distinguish epithelial cells (CK AE1/AE3, or CK7) from histiocytes (CD68). If final determination of overall pCR status cannot be made by the site's study pathologist, the complete case should be submitted to the country/region's pathology principal investigator for formal adjudication.

V.   POTENTIAL FOR UNINTENDED EFFECT ON DRUG DEVELOPMENT

Although this pathway has the potential to provide high-risk early-stage breast cancer patients with earlier access to highly effective drugs compared to historical oncology drug development, there are potential limitations to this approach.

First, long-standing practice involves characterizing the safety of oncology drugs first in patients with incurable disease. Although investigational drugs are expected to continue to be studied initially in dose-finding and anti-tumor activity-estimating studies of patients with refractory metastatic cancer, the first large-scale randomized trials of an investigational drug under this pathway may be conducted in a curable population where the benefit/risk assessment differs from patients with incurable disease, particularly long-term risks, and the tolerance of physicians and patients for emerging serious safety signals will be lower. Second, it is possible that a neoadjuvant trial could fail to demonstrate a significant difference in pCR rates and result in

abandoned development of an investigational drug that is, in fact, active in the adjuvant or metastatic breast cancer setting. Finally, of concern to both patient advocacy groups and the FDA, there is a risk of failure to investigate investigational drugs in patients with metastatic breast cancer if companies assume that an approval for early-stage high-risk disease will result in widespread off-label use for patients with advanced breast cancer. For all of these reasons, we wish to emphasize that formal study of new drugs in patients with metastatic breast cancer will continue to be important.

VI.   CONCLUSION

The FDA acknowledges that important regulatory questions persist regarding use of pCR to support accelerated approval in high-risk early-stage breast cancer. A trial-level relationship between improvement in pCR and improvement in long-term outcome has not been established. If such a relationship exists, it is unknown whether the necessary magnitude of improvement in pCR will differ according to breast cancer subtype or drug class. Hence, we recommend that sponsors pursuing a neoadjuvant indication meet early with the FDA to discuss their plans for designing a neoadjuvant trial in the context of a robust breast cancer drug development program. These discussions should include a justification for the proposed magnitude of improvement in pCR rate and long-term outcome, additional trials that would provide supporting evidence of clinical benefit in breast cancer, and the anticipated safety database to support the drug's use in a curative intent setting.

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