
Guidance for Industry

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

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**October 2014
Clinical/Medical**

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Guidance for Industry¹

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I. INTRODUCTION

This guidance is intended to assist applicants in designing trials to support marketing approval of drugs and biological products for the treatment of 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 breast cancer as a potential endpoint to support approval under the accelerated approval regulations (21 CFR part 314, subpart H, for drugs and 21 CFR part 601, subpart E, for biological products). 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 design strategies that would permit confirmation of clinical benefit and support conversion to regular approval

¹ This guidance has been prepared by the Breast and Gynecological Oncology Groups, Office of Hematology and Oncology Products, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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

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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 breast cancer. This guidance primarily describes potential pathways to accelerated approval for promising drugs in early stages of development for breast cancer. An alternate approach is also outlined for drugs with more extensive prior clinical data, existing breast cancer or other oncologic indications, those being studied in ongoing randomized adjuvant breast cancer trials, or those with unprecedented efficacy observed in early breast cancer trials. Applicants 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 (i.e., American Joint Committee on Cancer (AJCC) Stage I-III)
- The phrase *high-risk* refers to patients with early-stage breast cancer who 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 and statistically significant improvement in event-free survival (EFS), disease-free survival (DFS), or overall survival (OS)

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

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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.

A meta-analysis of approximately 4,000 patients enrolled in 9 trials of neoadjuvant versus adjuvant chemotherapy or endocrine therapy found no evidence that the sequencing of adjuvant systemic therapy and surgery alters distant disease recurrence or OS (Mauri et al. 2005). Of note, there was an increased risk of locoregional recurrence in patients who received neoadjuvant therapy compared with those who received postoperative adjuvant therapy, which has been attributed to omission of definitive local therapy in some of the neoadjuvant trials (Mauri et al. 2005). Assuming that definitive local therapy will be provided, preoperative systemic therapy appears to be an acceptable alternative to standard postoperative systemic therapy of early-stage breast cancer, and pursuing development and approval of new drugs for use in the neoadjuvant setting is a worthwhile objective.

B. The Accelerated Approval Regulations

The FDA's accelerated approval regulations are 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. Developing highly effective new drugs for these populations is a priority of the FDA. It is our hope that considering pCR as an endpoint for accelerated approval in the neoadjuvant setting will 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.”

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Section IV.B.1., Clinical Trials to Support Accelerated Approval, of this guidance discusses trial design strategies to support accelerated approval. The accelerated approval regulations further provide that:³

Approval under this section will be subject to the requirement that the applicant 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 applicant shall carry out any such studies with due diligence.⁴

Section IV.B.3., Clinical Trials to Verify and Describe Clinical Benefit (Confirmatory Trials), of this guidance discusses options for trial designs to verify and describe clinical benefit, commonly referred to as confirmatory trials.

III. ENDPOINTS FOR NEOADJUVANT TRIALS

Pathological complete response has been used as an endpoint in numerous trials of neoadjuvant systemic therapy for breast cancer. To date, however, there has not been a uniform definition of pCR, which has made reporting and interpretation of data from neoadjuvant trials challenging. For example, some investigators have defined pCR as the absence of both in situ and invasive cancer following neoadjuvant chemotherapy, whereas others have considered only the invasive component in the definition. Some investigators have defined pCR as absence of residual cancer in the breast and regional lymph nodes at the time of definitive surgery, whereas others have defined pCR as a complete response in the breast, irrespective of axillary nodal involvement (Buzdar et al. 2005; von Minckwitz et al. 2010; Bear et al. 2006; Wolmark et al. 2001). Furthermore, multiple variations on the term pCR have been used to describe similar pathological outcomes in neoadjuvant trials (Kuroi et al. 2006).

Recognizing that greater understanding of endpoints for neoadjuvant trials would be necessary to design and interpret clinical trial data to support accelerated approval, 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 pCR clearly defined and long-term follow-up available, 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

³ See 21 CFR 314.510.

⁴ See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*, 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 <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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ypN0 (absence of invasive and in situ cancer in the breast and axillary nodes)) and their relationship with long-term patient outcome. These increasingly stringent definitions of pCR not surprisingly resulted in decreasing average pCR rates: 22 percent, 18 percent, and 13 percent, respectively, in the trials included in the pooled analysis. 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 anticipate that future clinical trials probably will not mandate ALND for all patients with positive sentinel lymph nodes. To address this issue proactively, we recommend using the phrase *sampled regional lymph nodes* 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 regular approval should be termed EFS or OS. We recommend that EFS be defined, for regulatory purposes, 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 regular approval should be termed DFS or OS.

IV. CLINICAL TRIAL DESIGN AND STATISTICAL CONSIDERATIONS

We strongly encourage applicants to meet with the Office of Hematology and Oncology Products to discuss all neoadjuvant trial designs intended to support accelerated approval.

A. Rationale for Use of Pathological Complete Response as a Surrogate Endpoint in Neoadjuvant Trials

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 phase 3 trial of a drug in metastatic breast cancer to approval for its use in an adjuvant population has historically 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 the best available adjuvant therapy. Unfortunately, novel postoperative systemic therapies for these patients can be assessed only in multiyear trials, and there is no early marker of potential efficacy in the adjuvant setting. In contrast, when systemic therapy is given in the preoperative setting, a pCR endpoint that may be reasonably likely to predict clinical benefit can be assessed within several months of initiation of an investigational drug. We believe that use of pCR as an endpoint to support accelerated approval in the neoadjuvant setting has the potential to help address unmet need in high-risk populations in a far shorter time frame than would be required via the conventional approach to breast cancer drug development.

Randomized neoadjuvant trials comparing the same treatment administered either preoperatively or postoperatively have suggested that pCR may predict long-term outcome in patients with early-stage breast cancer treated with preoperative systemic therapy. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, which compared preoperative versus postoperative delivery of 4 cycles of doxorubicin plus cyclophosphamide (AC), patients in the preoperative AC arm who attained pCR had a markedly reduced risk of death (hazard ratio (HR) 0.32, $p < 0.0001$) at 16 years of follow-up compared with those who did not (Rastogi et al. 2008). Similarly, in the NSABP B-27 trial, which compared the addition of preoperative or postoperative docetaxel to preoperative AC, patients who achieved a pCR also had a significantly improved OS (HR 0.33, $p < 0.0001$) (Bear et al. 2006).

A Cochrane meta-analysis of 14 trials of preoperative versus postoperative chemotherapy enrolling 5,500 patients with a median follow-up of 18 to 124 months reported that the risk of death in patients who attained pCR was reduced by almost half compared with patients who had residual tumor present at the time of surgery (HR 0.48; 95 percent confidence interval (CI) 0.33, 0.69) (van der Hage et al. 2007). Similarly, in the CTneoBC pooled analysis, patients who achieved a pCR, defined as absence of invasive cancer in the breast and axillary nodes (ypT0/Tis

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ypN0), had a marked reduction in the risk of death (HR 0.36; 95 percent CI 0.31, 0.42) compared to those with residual invasive cancer (Cortazar et al. 2012).

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 long-term outcome at a trial level. Some trials that have shown a difference in pCR rate between arms have nonetheless failed to show a significant difference between arms in DFS 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).

In the NOAH trial, which was the only trial in the pooled analysis to enroll a more homogeneous patient population and include a therapy targeted to that breast cancer subtype, patients with high-risk, HER2-positive locally advanced or inflammatory breast cancer were randomly allocated to receive preoperative chemotherapy plus trastuzumab followed by completion of a total of 1 year of adjuvant trastuzumab versus the same regimen of preoperative chemotherapy alone. The pCR rate was doubled in the trastuzumab arm compared with the chemotherapy-alone arm (38 percent versus 19 percent, $p=0.001$). Though the relationship between pCR and long-term outcome is confounded by the postoperative use of trastuzumab in the investigational arm, at 3.2 years of median follow-up, the 3-year EFS was 71 percent in the trastuzumab arm and 56 percent in the chemotherapy-alone arm (HR 0.58, adjusted $p=0.013$). There was no statistically significant difference in OS, but fewer deaths occurred in the trastuzumab arm (18 versus 26; HR 0.62) (Gianni et al. 2010).

Similarly, in a smaller trial not included in the pooled analysis that was terminated early by the data monitoring committee because of superiority in pCR rate, patients with HER2-positive operable breast cancer were randomized to preoperative chemotherapy with or without preoperative trastuzumab. The pCR rate was 67 percent in the trastuzumab arm compared with 25 percent in the chemotherapy-alone arm (Buzdar et al. 2005). With a median follow-up of 3 years, only 3 of the original 42 patients had experienced disease recurrence, one of whom had died. All events were in the chemotherapy-alone arm (Buzdar et al. 2007).

Given the substantial improvements in survival for individual patients who attain pCR, a novel agent that produces a marked absolute increase in pCR rate compared with standard therapy alone in the full intent-to-treat population may be reasonably likely to result in long-term improvements in EFS or OS. Although it is possible that different breast cancer subtypes may require different magnitudes of improvement in pCR rate to translate into superior EFS or OS,

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therapies that modestly increase pCR rate are unlikely 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 full 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 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, controlled trial intended to demonstrate superiority. The preferred design is an add-on trial comparing the investigational drug plus standard adjuvant therapy to standard adjuvant therapy alone.

- **Randomized, controlled trial**

To effectively assess the efficacy of an investigational drug, trials designed to support accelerated approval in the neoadjuvant treatment of high-risk early-stage breast cancer should be randomized, controlled trials. 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 some investigators have expressed concern about the use of pCR as an endpoint to evaluate an investigational drug in nonrandomized trials. We share these concerns. A high pCR rate in a single-arm trial may reflect the biological characteristics of the tumors in the population enrolled, the efficacy of the investigational drug delivered, the efficacy of conventional therapy delivered as part of neoadjuvant therapy, and most likely a combination of the above.

- **Superiority design**

Neoadjuvant trials for marketing approval should be designed to demonstrate superiority. The goal of a noninferiority design is to demonstrate that an investigational drug has similar efficacy to that of an established treatment. More precisely, a noninferiority trial seeks to demonstrate that the investigational drug results in a loss of efficacy no greater than a certain percentage of the treatment effect achieved with the control therapy, a value known as the noninferiority margin.

Within the context of oncology, noninferiority designs are most commonly used when a new drug is likely to produce a comparable effect on survival but with less toxicity than standard therapy. The rationale for proposing pCR as an endpoint for accelerated approval is that there are breast cancer patients who remain at considerable risk of distant metastases and death despite the best currently available therapy, and the FDA is seeking to expedite the development of drugs that will have a substantial effect on long-term outcome for those patients. Therefore, this pathway is *not* intended for development of therapies for which no improvement in efficacy in these patient populations is expected and indeed some loss of efficacy may even be anticipated. Furthermore, although pCR

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has prognostic value for individual patients, an association between pCR and long-term outcome has not been confirmed at a trial level. Until such validation has occurred, it is not clear how one would select an appropriate noninferiority margin for pCR rate. For both of these reasons, we do not consider noninferiority designs to be appropriate at this time for neoadjuvant trials using pCR as an endpoint for accelerated approval.

- **Add-on design**

Many individuals with early-stage breast cancer, including those identified as high risk at initial presentation, can be cured with currently available therapy, and 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, we consider the preferred randomized trial design to be an *add-on design*, in which a standard adjuvant regimen is compared with the same regimen plus the investigational drug. Such a design ensures that high-risk patients are not denied standard effective therapy with curative potential and also permits isolation of the effect of the investigational drug. A double-blind, placebo-controlled design is preferred, if blinding the investigators and patients is feasible in view of the toxicities of the investigational drug.

As previously mentioned, this guidance primarily describes one pathway to accelerated approval, focusing on promising drugs in early stages of development for breast cancer. Alternative approaches may be acceptable for drugs with extensive prior clinical data, existing breast cancer or other oncologic indications, those being studied in ongoing randomized adjuvant breast cancer trials, or those with unprecedented efficacy in early breast cancer trials. For example, when there are more substantive prior data supporting the activity of the drug in breast cancer, a randomized superiority trial comparing standard adjuvant therapy delivered preoperatively versus an investigational therapy delivered preoperatively (i.e., omitting the standard therapy from the investigational arm) in some cases may be appropriate in lieu of an add-on design. Such proposals would be the exception and should be discussed in advance with the FDA.

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 be provided to the study pathologist that includes a general overview of the trial, including a statement that pathologists are to remain blinded to treatment arm. The note also 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 purpose of this summary note would be to avoid the need for pathologists to access clinic notes and other documents that may result in their inadvertent unblinding to treatment arm. The statistical analysis should compare pCR rates and EFS or OS between treatment arms, using the full intent-to-treat population.

Although we appreciate that practices for identifying and evaluating the axillary nodes may vary in different centers and geographical regions, the nature and timing of nodal assessment should

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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.

For trials being conducted with U.S. regulatory intent, 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.

We caution that 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). Thus, a patient who has achieved cCR should not be assumed to have achieved pCR. This observation underscores the need for standard local therapy in all patients who are treated with preoperative systemic therapy. Neoadjuvant trials conducted with regulatory intent should specify that all patients must receive lumpectomy and radiotherapy, or mastectomy with or without postmastectomy radiotherapy, consistent with current standards of care, at the completion of neoadjuvant systemic therapy (Davidson 2005).

3. 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 a trial with pCR as the primary endpoint, 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 the original randomized neoadjuvant trial that supported the accelerated approval until EFS or OS data are mature. This approach may enable a single, well-conducted randomized trial, if adequately powered and with sufficiently compelling results, to serve as the basis for both accelerated and regular approval, saving time and resources in drug development and expediting patient access to highly effective therapies for high-risk early-stage breast cancer. Applicants should plan to collect long-term safety data and provide this to the FDA on an ongoing basis so that serious safety signals can be quickly identified and managed.

We recognize that 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

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magnitude of effect calculated based upon the applicant's best estimate of the difference in pCR rate between arms needed to produce 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 interim analyses for EFS and/or OS would be appropriate, 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.

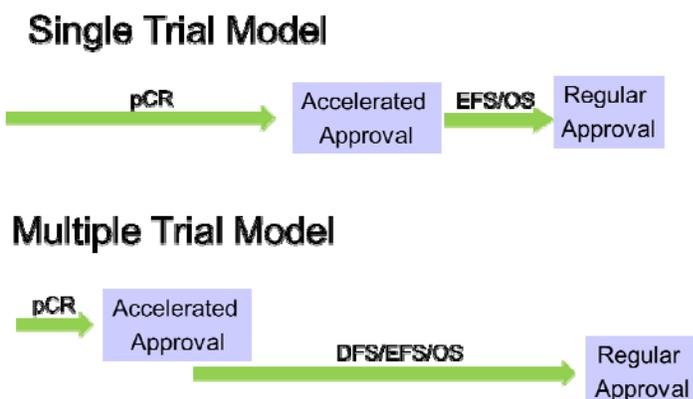
If a single trial is intended to meet the two objectives stated above, the statistical analysis plan should include a plan for controlling the false positive rate (type I error) for the primary endpoint, pCR, to support accelerated approval, as well as a plan for controlling the false positive rate for either of the primary endpoints, EFS or OS, to support regular 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 trial 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 regular approval. In this model, applicants 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 regular approval.

4. 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, as shown in Figure 1. A single trial, which should be powered for both pCR and EFS or OS, will need a larger sample size. This provides for an improved estimate of treatment effect size and a larger body of safety data from an early-stage patient population at the time of initial approval, which will more fully characterize the toxicity of the drug. Given that the trial will 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 will be available earlier than if a separate trial had to be designed, conducted, and analyzed, which would enable faster conversion to regular approval, or withdrawal of the breast cancer indication if clinical benefit is not confirmed. The disadvantages of the single trial model include the potential to expose a large number of patients to less effective and/or more toxic therapy, the longer wait to initial U.S. approval compared with the multiple trial model, and the lack of data on use of the drug in the postoperative setting.

Figure 1. Single Trial Model vs. Multiple Trial Model



The multiple trial model also has its advantages and disadvantages. Demonstrating the efficacy of a drug in multiple trials provides greater assurance that the results are not caused by chance alone. The multiple trial model permits widespread access to highly effective drugs earlier because fewer patients would need to be accrued before analyzing the pCR endpoint. The results of the neoadjuvant trial also may help to inform the design of the confirmatory trial. 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 or postoperative 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 multinational adjuvant trial well underway at the time of accelerated approval.

It is clear that there is not one best approach for all drugs. Because of safety concerns when enrolling a patient population being treated with curative intent, the single large trial model, which provides a larger safety database at the time of initial approval and a shorter time spent in accelerated approval status while awaiting long-term clinical benefit data, should be considered the default for most drugs. 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, 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. 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.

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5. Postoperative Local and Systemic Therapy

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). Presently, there is no evidence to support use of additional postoperative cytotoxic therapy in patients with residual invasive cancer following a complete standard course of preoperative therapy (Kaufmann et al. 2006). Given that EFS and OS results may be confounded by postoperative treatment, neoadjuvant trials with regulatory intent generally should avoid postoperative cytotoxic therapy intended to treat residual disease found at the time of surgery.

This issue should be anticipated and addressed proactively via patient education during the informed consent process. Applicants who remain concerned about the potential for dropout or protocol violations related to this concern can design trials reserving a small portion of the standard systemic therapy (e.g., the last 4 weeks of paclitaxel in the dose-dense doxorubicin/cyclophosphamide + paclitaxel regimen) to be delivered postoperatively to all patients in both arms, regardless of whether or not a patient has achieved pCR. Designs that permit patients on the control arm to receive the investigational drug in the postoperative setting will confound EFS and OS and generally should be avoided. Postoperative systemic therapy for all randomized patients that represents the current standard of care (e.g., completion of 52 weeks of trastuzumab in patients with early-stage HER2+ breast cancer or 5 to 10 years of endocrine therapy for women with hormone receptor-positive breast cancer) is acceptable. The protocol should include a detailed and uniform approach to ensure that postoperative therapy is prespecified and delivered consistently across treatment arms to avoid confounding long-term clinical outcomes.

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 placebo. We emphasize that this initiative has the potential to promote drug development in two important areas of unmet need: neoadjuvant treatment of high-risk early-stage breast cancer and treatment of breast cancer patients with postneoadjuvant residual disease.

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.

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 modern local and systemic therapy. This is primarily because of risk-benefit considerations, but also the need to observe sufficient events in a trial to be able to demonstrate a significant difference in long-term outcome between treatment arms. Patients can

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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 for efficacy in a neoadjuvant trial with pCR as its primary endpoint will be brief at the time of accelerated approval. Data that confirm, or fail to confirm, clinical benefit will need several years of additional follow-up to reach maturity. It is also conceivable that a trial adding a new drug to standard adjuvant chemotherapy delivered preoperatively could be conducted without a prior large randomized trial in the metastatic setting, further limiting available data on the activity of the drug in breast cancer at the time of initial U.S. approval. Therefore, there is a risk that a drug approved in the neoadjuvant setting could remain on the market for a prolonged period of time, exposing a large number of patients with a curable disease and potentially normal longevity to the short- and long-term risks of an ultimately ineffective therapy.

To mitigate this risk, randomized neoadjuvant trials intended to support a marketing application should be limited to populations of breast cancer patients with an unmet medical need and designed to detect increases in pCR rate over available therapy that are of substantial magnitude. Populations with an unmet medical need can be generally defined as patients having a poor prognosis despite receipt of the most effective adjuvant systemic therapy currently available (e.g., patients with high-grade tumors lacking ER, PR, and HER2 receptors). What constitutes an appropriate magnitude of benefit depends on the prognosis of the patient population under study and the effectiveness of existing therapy for that patient population.

Highly variable pCR rates have been reported from trials of neoadjuvant therapy, ranging from less than 10 percent to more than 65 percent (Mauri et al. 2005; Buzdar et al. 2005). Multiple investigators have reported that the patients most likely to achieve pCR with neoadjuvant chemotherapy are those with high-grade, hormone receptor-negative breast cancers (Kuerer et al. 1999; Rouzier et al. 2005) and those with HER2-positive breast cancer (Buzdar et al. 2005; Gianni et al. 2010). Although patients with triple negative breast cancer currently are regarded as having the poorest prognosis, the subset of those patients who achieve pCR have a comparable OS to patients with nontriple negative breast cancer (Liedtke et al. 2008).

Likewise, pCR is uncommon in patients with low-grade, hormone receptor-positive tumors treated with preoperative systemic therapy (Rouzier et al. 2005; Cortazar et al. 2012). Despite the low pCR rates in this population, patients with low-grade, hormone receptor-positive tumors nonetheless have a more favorable long-term prognosis and are more likely to be cured with currently available therapy, rendering pCR a poor predictor of clinical benefit in this population (Bottini et al. 2005; Cortazar et al. 2012). Furthermore, the majority of patients with hormone receptor-positive breast cancer will receive a prolonged course of postoperative endocrine therapy, the delivery of which could make it more difficult to demonstrate an effect of a new drug on EFS or OS for timely confirmation of clinical benefit.

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We wish to emphasize that 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 deemed 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 followed one or more randomized trials in the metastatic setting. The resultant safety database characterizes not only the incidence and severity of acute treatment-emergent adverse events, information that will be available in a neoadjuvant trial as well, but also provides long-term data on the outcome of acute or cumulative adverse events, such as neuropathy, as well as on 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 without a prior randomized trial or drug approval in the metastatic setting, applicants should discuss with the FDA the amount of safety data needed to proceed to a large, randomized neoadjuvant trial. Before embarking on a phase 3 neoadjuvant trial, applicants should plan to collect and provide to the FDA, at a minimum, as much safety data on the investigational drug, alone and in combination, as would currently be needed to launch a phase 3 trial in the metastatic setting. Based on the safety profile and extent of prior clinical experience with the investigational drug(s) or other drugs in the same class, as well as the proposed trial population, additional safety data may be required.⁵

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, we emphasize that trials in the neoadjuvant setting should be designed to collect long-term safety data from a number of patients comparable to traditional adjuvant breast cancer trials. In addition to conducting trials adequate to confirm clinical benefit to support conversion to regular approval, applicants also may be required to conduct additional safety trials as postmarketing requirements under section 505(o)(3) of the FD&C Act.

⁵ See section 505(o)(3) of the FD&C Act.

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E. Recommendations for Pathology Standard Operating Procedures

All protocols for neoadjuvant trials conducted with regulatory intent should include a detailed set of standard operating procedures (SOP) for collection, handling, and interpretation of pathology specimens, comparable to imaging charters in oncology trials with radiographic primary endpoints. All neoadjuvant trial pathologists should receive formal training provided by the applicant 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. 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 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

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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.⁶

V. POTENTIAL FOR UNINTENDED EFFECT ON DRUG DEVELOPMENT

Although we believe that this pathway has the potential to provide high-risk breast cancer patients widespread access to highly effective drugs several years sooner than historical approaches to oncology drug development, we must acknowledge the potential to negatively affect drug development as well.

First, we are accustomed to characterizing the safety of oncology drugs first in patients with incurable disease. Although new drugs will continue to be studied initially in phase 1 and phase 2 studies of patients with refractory metastatic cancer, the first large-scale randomized trials of a new drug under this pathway may be conducted in a curable population where the safety profile, particularly long-term, may differ and the tolerance for emerging safety signals will be lower. Second, given the uncertain relationship between pCR and long-term outcome, it is possible that a neoadjuvant trial could fail to demonstrate a significant difference in pCR rates and result in abandoned development of a drug that is, in fact, active in the adjuvant or metastatic setting. Finally, of concern to both patient advocacy groups and the FDA, there is a risk of diminished drug development for metastatic breast cancer if companies assume that an approval for early-stage disease will result in widespread off-label use for patients with advanced breast cancer, even absent any data to support the efficacy of the new drug in a more extensively pretreated population. 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 and necessary.

VI. IMPLEMENTATION OF THE GUIDANCE

Since the release of the draft version of this guidance 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 with an international panel of breast cancer experts seeking to discuss the use of pCR to support accelerated approval.⁷ 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 concerns. 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.

⁶ For additional information on pathological evaluation of postneoadjuvant specimens, applicants may wish to refer to the most current version of the College of American Pathologists' "Protocol for the Examination of Specimens From Patients With Invasive Carcinoma of the Breast" available at <http://www.cap.org> and the "Protocol for Pathologists" on the MD Anderson Web site at <http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3>.

⁷ <http://www.fda.gov/Drugs/NewsEvents/ucm339396.htm>

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The first supplemental biologics license application for a neoadjuvant breast cancer indication has also been submitted. This application was discussed at the September 5, 2013, meeting of the Oncologic Drugs Advisory Committee (ODAC), whose members ultimately voted unanimously, with one abstention, in favor of approval.⁸ The application was recently granted accelerated approval. The favorable review of the application, both by ODAC and the FDA, was based upon the robustness of the development program and the totality of the evidence. This included not only the absolute improvement in pCR rate in the intent-to-treat population, but importantly a statistically and clinically significant effect on OS in the metastatic setting, an extensive body of safety data from treatment of several thousand breast cancer patients, and a fully accrued adjuvant confirmatory trial.⁹

The FDA acknowledges that important regulatory questions remain at this time regarding use of pCR to support accelerated approval. A relationship between magnitude of improvement in pCR and improvement in long-term outcome has not been established at a trial level. Assuming that such a relationship exists, it is unknown whether the necessary magnitude of improvement in pCR will differ according to breast cancer subtype. Hence, we recommend that applicants pursuing a neoadjuvant indication meet early with the FDA to discuss their plans for designing a neoadjuvant trial in the context of a breast cancer 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.

⁸ <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM371011.pdf>

⁹ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125409Orig1s051SumR.pdf

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