Guidance for Industry

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

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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TABLE OF CONTENTS

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

I. INTRODUCTION

This guidance is intended to assist applicants in designing trials to support marketing approval of drugs to treat breast cancer in the neoadjuvant (preoperative) setting. The main focus of the guidance is to discuss the use of pathologic 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:

- Propose a uniform definition of pCR for regulatory purposes
- Briefly summarize what is currently known about the relationship between pCR and prognosis
- Describe trial designs and patient populations where pCR is reasonably likely to predict clinical benefit
- Provide guidance regarding trial designs that would permit confirmation of clinical benefit and support conversion to regular 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 breast cancer. This guidance describes one pathway to accelerated approval for promising drugs in early stages of development for breast cancer. Note that alternative approaches may be

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

acceptable for drugs with more extensive prior clinical data, existing breast cancer indications, those being studied in ongoing randomized adjuvant breast cancer trials, or those with unprecedented efficacy in early breast cancer trials. Applicants should consult the FDA as early as possible regarding trial designs intended to support 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 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 terms *drug* and *systemic therapy* refer to both drugs and biological products regulated by the Center for Drug Evaluation and Research

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 rationales for 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 enables the oncologist to evaluate tumor response and discontinue ineffective therapy or substitute an alternative systemic 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 receptor status. Finally, the neoadjuvant setting provides investigators the unique opportunity to examine modulation of tissue biomarkers from the time of biopsy to the time of definitive breast surgery following completion of 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 overall survival (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 facilitating development 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 populations of early-stage breast cancer patients. Developing highly effective new drugs for these populations is a priority of the FDA. We hope that this proposal to consider pCR an endpoint that would support accelerated approval in the neoadjuvant setting will encourage industry innovation and expedite the development of breakthrough therapies to treat high-risk early-stage breast cancer.

The accelerated approval regulations, at 21 CFR 314.510 and 21 CFR 601.41, provide that:

> FDA may grant marketing approval for a new drug [or biological] product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.

Section IV.A.2., Trials to Support Accelerated Approval, of this guidance discusses trial designs to support accelerated approval. The regulations further provide that:

> 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.

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

III. DEFINITION OF PATHOLOGIC COMPLETE RESPONSE

Pathologic 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, pathology outcomes in neoadjuvant trials have been termed not only pCR, but near pCR, quasi pCR, comprehensive pCR, strict pCR, and pCRinv (Kuroi et al. 2006).

Adoption of a single term with a standard definition would facilitate discussion of proposed trial designs and interpretation of clinical trial data to support accelerated approval. We propose the following definition for regulatory purposes:

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

This proposed definition reflects our current understanding of two important features of the underlying biology of early-stage breast cancer. First, neither ductal carcinoma in situ (DCIS) nor lobular carcinoma in situ (LCIS) is generally believed to regress with systemic therapy, nor does its persistence after neoadjuvant therapy appear to have prognostic significance; therefore, the presence of residual DCIS or LCIS at the time of surgery should not be used to judge the effectiveness of neoadjuvant systemic therapy (Mazouni et al. 2007). Second, regional nodal involvement at initial presentation is a well-established risk factor for breast cancer recurrence and death, and a goal of neoadjuvant systemic therapy is to eliminate it. Investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial and others have reported that patients with a pCR in the breast but residual regional nodal involvement have an inferior OS compared with patients with a pCR in both the breast and regional nodes (McCready et al. 1989; Fisher et al. 1998). We believe that the definition of pCR proposed in this guidance has the greatest likelihood of predicting clinical benefit for regulatory purposes in patients with early-stage breast cancer who achieve pCR following neoadjuvant systemic therapy.

The proposed definition also reflects 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 propose the phrase *sampled ipsilateral lymph nodes* for use in our standard definition of pCR. This definition permits flexibility in terms of the surgical approach to the

axilla, but reflects the assumption that the presence of any residual invasive cancer following neoadjuvant therapy is likely to portend a poorer prognosis. Given that the primary endpoint includes the pathologic status of the axilla and that an imbalance of ALND between arms has the potential to confound interpretation of pCR, an algorithm for surgical management of the axilla is critical and should be explicitly outlined in the protocol plans. These plans should minimize confounding by ensuring that the approach to local therapy is consistent across treatment arms.

IV. CLINICAL TRIAL DESIGN AND STATISTICAL CONSIDERATIONS

We strongly encourage applicants to meet with the Office of Hematology and Oncology Products (OHOP) to discuss designs of all neoadjuvant trials intended to support accelerated approval and to submit all such protocols under the special protocol assessment mechanism for formal review prior to trial initiation.

A. Trial Designs in the Neoadjuvant Setting

1. Rationale for Use of Pathologic 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 who had an expected median OS of approximately 2 years or less. Trials to support adjuvant (postoperative) indications generally 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 prolonged follow-up in randomized trials is needed to demonstrate a difference in disease-free survival (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 is often well more than a decade.

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 effectiveness. 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 the investigational drug. We believe that use of pCR as an endpoint to support accelerated approval in high-risk populations in the neoadjuvant setting has the potential to help address unmet need in these 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 DFS or OS in patients with early-stage breast cancer treated with preoperative systemic therapy. In the 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 CI 0.33, 0.69) (van der Hage et al. 2007).

We acknowledge that these types of analyses, commonly referred to as *responder analyses*, have inherent limitations. We anticipate that both ongoing efforts led by the Breast Oncology Group in OHOP, as described below, as well as future neoadjuvant trials, will clarify prospectively the association between pCR and traditional breast cancer endpoints used for approval in the adjuvant setting.

We would emphasize that the analysis of neoadjuvant breast cancer trials for regulatory approval should compare pCR rates and DFS or OS between treatment arms, using the full intent-to-treat population, and should not be limited to those patients who achieve pCR, because this is a nonrandomized patient subset determined by outcome subsequent to randomization. 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). It is expected that a large difference in pCR rate between treatment arms will be needed to produce a statistically significant difference in DFS or OS in the overall trial population that is also clinically meaningful.

For example, in the Neoadjuvant Herceptin (NOAH) trial, patients with high-risk, human epidermal growth factor receptor 2- (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 rate of pCR was doubled in the trastuzumab arm compared with the chemotherapy-alone arm (38 percent versus 19 percent, p=0.001). With 3.2 years of median follow-up, the 3-year DFS 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).

In a smaller trial that was terminated early by the data monitoring committee because of superiority in terms of 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. The DFS was 100 percent in the trastuzumab arm and 85 percent in the chemotherapy-alone arm (unadjusted p=0.041) (Buzdar et al. 2007).

We have not previously approved any drugs for neoadjuvant treatment of early-stage breast cancer. Although pCR has been used as the primary endpoint in numerous neoadjuvant breast cancer trials, there remains a need to characterize more precisely the relationship between pCR and long-term clinical benefit measures such as DFS and OS. To this end, the Breast Oncology Group in OHOP has established an international working group with many of the investigators from these trials. This working group, known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC), has embarked upon a large meta-analysis of the relationship between pCR and DFS/OS using primary source data from more than 12,000 patients enrolled in published randomized neoadjuvant trials with long-term follow-up for DFS or OS available. Important topics that this meta-analysis will address include the correlation between pCR and DFS/OS and the subtypes of early-stage breast cancer in which pCR is most likely to predict clinical benefit.

The results of the CTNeoBC meta-analysis, as well as public commentary on this draft guidance, will help to inform the FDA's ultimate decision regarding use of pCR as an endpoint for accelerated approval in high-risk early-stage breast cancer. We expect that our thoughts on how to use pCR appropriately as an endpoint for approval will evolve as we gain additional experience with randomized neoadjuvant breast cancer trials designed with regulatory intent.

2. Trials to Support Accelerated Approval

To effectively assess the efficacy of the investigational drug, trials designed to support accelerated approval in the neoadjuvant treatment of high-risk early-stage breast cancer should be randomized, controlled trials designed to demonstrate superiority. The biological differences between the tumors of patients who achieve a pCR in response to neoadjuvant therapy and those who do not are 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 biologic characteristics of the tumors in the population enrolled, the efficacy of the investigational drug delivered, the efficacy of conventional therapy delivered, or, frequently, a combination of the above.

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). The preferred randomized trial design would be an *add-on design*, in which a standard adjuvant regimen delivered preoperatively is compared with the same regimen plus the investigational drug, also delivered preoperatively. 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. In all cases, pathologists interpreting surgical specimens for assessment of pCR should be blinded to treatment arm. The analysis should compare pCR rates and DFS or OS between treatment arms, using the full intent-to-treat population.

We would 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).

As previously mentioned, this guidance 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 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) may in some cases be appropriate in lieu of an add-on design.

3. 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 DFS or OS. The confirmatory trial should be ongoing at the time of accelerated approval. One acceptable approach would be to follow the patients entered into the original randomized neoadjuvant trial that supported the accelerated approval until DFS or OS data are mature. This approach may enable a single 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 breakthrough therapies for high-risk early-stage breast cancer. Alternatively, clinical benefit may be able to be confirmed in another breast cancer setting. 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 the sample size needed to demonstrate a clinically and statistically significant improvement in pCR may be considerably smaller than that needed to demonstrate a clinically and statistically significant improvement in DFS or OS. Thus a single neoadjuvant trial designed and powered to demonstrate both an improvement in pCR rate and an improvement in either DFS or OS may be *overpowered* (i.e., able to detect differences that may be statistically significant without being clinically meaningful) for the endpoint of pCR. In this scenario, the statistical analysis plan for evaluating pCR should be prespecified, with the target 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 DFS/OS. All patients should be enrolled in the trial before any efficacy analyses, including analyses of pCR, are performed. Although interim analyses for DFS 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 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, DFS or OS, to support regular approval. Because the effect size on DFS 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 alpha is allocated to the comparisons of direct measure(s) of clinical benefit (i.e., DFS or OS), and a lesser portion to the pCR endpoint.

It is important to note that many patients with high-risk early-stage breast cancer enrolled in neoadjuvant trials will not achieve pCR. The benefit of delivering additional cytotoxic therapy to patients with residual invasive cancer at the time of surgery following preoperative therapy is unclear. Given that DFS and OS may be confounded by additional systemic therapy delivered postoperatively to patients enrolled in a neoadjuvant trial, neoadjuvant trials with regulatory intent generally should avoid postoperative cytotoxic therapy intended to treat residual disease found at the time of surgery. If postoperative systemic therapy is needed (e.g., completion of 52 weeks of trastuzumab in patients with early-stage HER2+ breast cancer), the protocol should include a detailed and uniform approach to ensure that postoperative systemic therapy is delivered consistently across treatment arms. Designs that permit patients on the control arm to receive the investigational drug in the postoperative setting generally should be avoided because this will confound DFS and OS.

B. 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 populations judged to have a high risk of distant disease recurrence and mortality despite use of optimal modern local and systemic therapy. Patients may be classified as high risk for recurrence on the basis of conventional histologic features or by appropriately validated genomic measures. The decision to pursue accelerated approval via the neoadjuvant pathway should be made on the basis of a 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 in terms of DFS or OS 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 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 estrogen, progesterone, 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 a few 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 estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor negative (i.e., triple-negative) breast cancer are currently regarded as having the poorest prognosis, the subset of those patients who achieve pCR may have a comparable OS to patients with non-triple-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). Despite the infrequency of pCR 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). Furthermore, the majority of patients with hormone receptor-positive breast cancer will receive postoperative endocrine therapy, the delivery of which could make it more difficult to demonstrate an effect of a new drug on DFS for confirmation of clinical benefit.

We wish to emphasize that we are concerned about 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 acceptable in populations of breast cancer patients with significant unmet medical need (e.g., patients with high-grade ER, PR, and HER2-negative breast cancer), 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 generally not be enrolled in neoadjuvant trials intended to support accelerated approval.

C. 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 be the result of 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 support a phase 3 neoadjuvant trial. Before designing a randomized neoadjuvant trial, applicants should plan to collect and provide to the FDA at least 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 needed to initiate a randomized, neoadjuvant trial with marketing intent.

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 would 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 studies as postmarketing requirements under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.

REFERENCES

Bear, H et al., 2006, Sequential Preoperative or Postoperative Docetaxel Added to Preoperative Doxorubicin Plus Cyclophosphamide for Operable Breast Cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27, J Clin Oncol, 24:2019-2027.

Bottini, A et al., 2005, Cytotoxic and Antiproliferative Activity of the Single Agent Epirubicin Versus Epirubicin Plus Tamoxifen as Primary Chemotherapy in Human Breast Cancer: A Single-Institution Phase III Trial, Endocr Relat Cancer, 12:383-392.

Buzdar, A et al., 2005, Significantly Higher Pathologic Complete Remission Rate After Neoadjuvant Therapy With Trastuzumab, Paclitaxel, and Epirubicin Chemotherapy: Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2-Positive Operable Breast Cancer, J Clin Oncol, 23:3676-3685.

Buzdar, A et al., 2007, Neoadjuvant Therapy With Paclitaxel Followed By 5-Fluorouracil, Epirubicin, and Cyclophosphamide Chemotherapy and Concurrent Trastuzumab in Human Epidermal Growth Factor Receptor 2-Positive Operable Breast Cancer: An Update of the Initial Randomized Study Population and Data of Additional Patients Treated With the Same Regimen, Clin Cancer Res, 13:228-233.

Davidson, N., 2005, Sometimes a Great Notion — An Assessment of Neoadjuvant Systemic Therapy for Breast Cancer, J Natl Cancer Inst, 97:159-161.

Fisher, B et al., 1998, Effect of Preoperative Chemotherapy on the Outcome of Women With Operable Breast Cancer, J Clin Oncol, 16:2672-2685.

Gianni, L et al., 2010, Neoadjuvant Chemotherapy With Trastuzumab Followed by Adjuvant Trastuzumab Versus Neoadjuvant Chemotherapy Alone, in Patients With HER2-Positive Locally Advanced Breast Cancer (The NOAH Trial): A Randomized Controlled Superiority Trial With a Parallel HER2-Negative Cohort, Lancet, 375:377-384.

Kaufmann, M et al., 2006, Recommendations From an International Expert Panel on the Use of Neoadjuvant (Primary) Systemic Treatment of Operable Breast Cancer: An Update. J Clin Oncol, 24:1940-1949.

Kuerer, H et al., 1999, Clinical Course of Breast Cancer Patients With Complete Pathologic Primary Tumor and Axillary Lymph Node Response to Doxorubicin-Based Neoadjuvant Chemotherapy, J Clin Oncol, 17:460-469.

Kuroi, K et al., 2006, Issues in the Assessment of the Pathologic Effect of Primary Systemic Therapy for Breast Cancer, Breast Cancer, 13:38-48.

Liedtke, C et al. 2008, Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer, J Clin Oncol, 26:1275-1281.

Mauri, D et al., 2005, Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis, J Natl Cancer Inst, 97:188-194.

Mazouni, C et al., 2007, Residual Ductal Carcinoma In Situ in Patients With Complete Eradication of Invasive Breast Cancer After Neoadjuvant Chemotherapy Does Not Adversely Affect Patient Outcome, J Clin Oncol, 25:2650-2655.

McCready, D et al., 1989, The Prognostic Significance of Lymph Node Metastases After Preoperative Chemotherapy for Locally Advanced Breast Cancer, Arch Surg, 124:21-25.

Rastogi, P et al., 2008, Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27, J Clin Oncol, 26:778-785.

Rouzier, R et al., 2005, Breast Cancer Molecular Subtypes Respond Differently to Preoperative Chemotherapy, Clin Cancer Res, 11:5678-5685.

van der Hage, J et al., 2007, Preoperative Chemotherapy for Women With Operable Breast Cancer, Cochrane Database of Systematic Reviews, Issue 2, Art. No: CD005002.

von Minckwitz, G et al., 2001, Dose-Dense Doxorubicin, Docetaxel, and Granulocyte Colony-Stimulating Factor Support With or Without Tamoxifen as Preoperative Therapy in Patients With Operable Carcinoma of the Breast: A Randomized, Controlled, Open Phase IIb Study, J Clin Oncol, 19:3506-3515.

von Minckwitz, G et al., 2010, Capecitabine in Addition to Anthracycline- and Taxane-Based Neoadjuvant Treatment in Patients With Primary Breast Cancer: Phase III Geparquattro Study, J Clin Oncol, 28:2015-2023.

Wolmark, N et al., 2001, Preoperative Chemotherapy in Patients With Operable Breast Cancer: Nine-Year Results From National Surgical Adjuvant Breast and Bowel Project B-18, J Natl Cancer Inst Monogr, 30:96-102.