Neoadjuvant Therapy as a Platform for Drug Development and Approval in Breast Cancer

Aditya Bardia and José Baselga

Abstract

The traditional drug development process in breast cancer based on large phase III studies has serious limitations and needs a major overhaul. Searching for new approaches, the testing of novel agents in the preoperative (neoadjuvant) setting approach offers a potentially rapid and efficient strategy for drug development utilizing pathologic complete response (path CR), a surrogate marker for survival, as the primary endpoint. In addition, neoadjuvant studies allow the assessment of drug effects on the target (pharmacodynamic response) and the development of predictive biomarkers of response. Molecular profiling of the residual tumor in the surgical specimen may also provide insights into actionable mechanisms of resistance. Recognizing the potential of neoadjuvant trials for drug development, the U.S. Food and Drug Administration (FDA) recently announced consideration of neoadjuvant trials for accelerated drug approval in early breast cancer, particularly for tumors with high risk of recurrence and unfavorable prognosis, and provided accelerated approval to neoadjuvant pertuzumab in September 2013. The FDA has emphasized that while improvement in path CR could be utilized for "accelerated" approval, improvement in survival will still need to be demonstrated for "regular" approval. Key considerations in conduct of such neoadjuvant drug development trials include (i) study design such as utilization of biomarker stratified design to evaluate a biomarker that could enrich response, (ii) definition of path CR, (iii) distribution of factors that influence path CR between the treatment arms, (iv) prespecified plan for follow-up to obtain data on survival, and (v) safety as it involves a patient population with curable disease. In the years to come, we anticipate an increase in the number of neoadjuvant trials testing novel therapies that hopefully will open a new path in bringing efficacious new therapies to patients with breast cancer.

Introduction

Neoadjuvant therapy, also known as preoperative therapy or primary systemic therapy, refers to the administration of systemic therapy in patients with early breast cancer before surgery, as opposed to after surgery (adjuvant). The concept of neoadjuvant therapy was initially introduced in the 1970s for the treatment of patients with unresectable locally advanced breast cancer as a strategy to convert them to operable (1–3). Subsequent studies, including the landmark NSABP 18 (National Surgical Adjuvant Breast and Bowel Project) trial, demonstrated neoadjuvant therapy increased breast conservation surgery and had similar clinical outcomes as adjuvant therapy (4–6). In addition to neoadjuvant therapy now being used as one of the conventional treatment approaches, clinical trials in the neoadjuvant setting are increasingly being utilized for the study of new agents and novel therapeutic strategies in breast cancer.

In this review, we provide an overview of the ongoing initiatives in the neoadjuvant space and analyze the key considerations and challenges involved in utilizing neoadjuvant trials as a platform for drug development and approval in breast cancer.

Rationale for drug development in the neoadjuvant setting

Rapid assessment of efficacy and triage. The traditional drug development process based on large phase III trials to show statistical incremental benefit from standard therapy is slow, expensive, and inefficient. It takes more than 10 years, on an average, from drug entry into clinical trials to eventual approval by regulatory authorities, and this occurs at a cost of more than $1 billion (7, 8). In contrast, the neoadjuvant trial model provides rapid assessment of short-term drug efficacy and triage utilizing pathologic complete response (path CR) as the primary endpoint.

Various studies have shown that achieving a path CR after neoadjuvant chemotherapy is a strong surrogate marker of improved disease-free survival (DFS) and overall survival (OS). A recent systematic review and meta-analysis of 30 published neoadjuvant studies has shown that path CR after neoadjuvant chemotherapy was associated with improved survival (9). Triple-negative breast cancer (TNBC) and HER2-positive breast cancers were more likely to achieve...
path CR than hormone receptor (HR\(^+\)) breast cancers, but when present, path CR was associated with significantly improved outcomes in all three subtypes. Another large meta-analysis based on pooling of individual patient data from 12 neoadjuvant randomized controlled trials reported that path CR after neoadjuvant chemotherapy was a strong predictor of improved DFS and OS (10). Moreover, the improved outcomes with path CR were in all the three breast cancer subtypes: HR\(^+\) (hazard ratio, 0.49; \(P < 0.001\)), HER2\(^+\) (hazard ratio, 0.39; \(P < 0.001\)), and TNBC (hazard ratio, 0.24; \(P < 0.001\)), though for HR\(^+\) tumors, the association was stronger for grade 3 tumors (hazard ratio, 0.27; \(P < 0.001\)) than grade 1/2 tumors (hazard ratio, 0.63; \(P = 0.07\)). Thus, path CR is a powerful predictor of survival for many patient populations and a robust surrogate biomarker for clinical outcomes in breast cancer.

With the use of path CR as the primary endpoint, the time and cost required for a neoadjuvant trial is much smaller than in a conventional adjuvant trial. This issue is perhaps best exemplified in the development of HER2-directed therapies. The neoadjuvant trial of lapatinib (a small-molecule tyrosine kinase inhibitor of HER2), NeoALTTO, and the adjuvant trial, ALTO, were launched together. The NeoALTTO trial randomized patients with localized HER2\(^+\) breast cancer and successfully demonstrated path CR improvement with lapatinib plus trastuzumab combination (51.3%) as compared with trastuzumab (29.5%) or lapatinib (24.7%; ref. 11). In contrast, in the adjuvant counterpart, the ALTO trial (NCT00490139), the last patient was randomized in July 2011 and the results are still pending at this time. If the results of the ALTO trial are similar to those of the much smaller NeoALTTO study, it would strongly validate the neoadjuvant model. Similarly, the neoadjuvant study with pertuzumab (a novel monoclonal antibody against HER2), NeoSphere, completed enrollment in 2 years (\(N = 417\)) and demonstrated that dual combination of trastuzumab and pertuzumab was associated with significantly higher path CR (45.8% vs. 29%) as compared with trastuzumab (12). On the other hand, the adjuvant pertuzumab clinical trial, APHINITY (NCT01358877), is currently ongoing with a planned enrollment of 4,800 patients and participation of more than 500 sites worldwide. In fact, results from the NeoSphere trial suggest that trastuzumab and pertuzumab would be an effective combinatorial therapy for HER2\(^+\) breast cancer around the same time that the pivotal metastatic trial, CLEOPATRA, demonstrated that pertuzumab and trastuzumab combination improved survival (hazard ratio, 0.62; \(P < 0.001\)) as compared with trastuzumab (13). Indeed, considering these issues, the U.S. Food and Drug Administration (FDA) recently granted accelerated approval to pertuzumab for neoadjuvant treatment of women with early-stage HER2\(^+\) breast cancer on September 30, 2013 (14). Pertuzumab is the first FDA-approved drug for the neoadjuvant treatment of breast cancer based on path CR as the primary outcome.

Path CR can be utilized as an endpoint for rapid triage of drugs and to facilitate go/no-go decisions. For example, gene-expression profiling of breast cancer in the early 2000s suggested that TNBC shares molecular features with basal-like BRCA-1 tumors, and TNBC is likely to be sensitive to DNA cross-linking agents such as cisplatin (15). Subsequently, various small neoadjuvant trials testing cisplatin observed a high path CR rate with platinum therapy suggesting it merits further evaluation (16, 17). More recently, results of the neoadjuvant randomized clinical trial GeparSixto (\(N = 595\)) demonstrated that addition of carboplatin to standard neoadjuvant chemotherapy was associated with a significant improvement in path CR for TNBC (58.7% vs. 37.9%, \(P < 0.05\)), but not for HER2\(^+\) disease (33.1% vs. 36.3%; ref. 18). Results of other large randomized neoadjuvant trials comparing platinum-containing chemotherapy to non–platinum-based chemotherapy such as CALGB 40603 (NCT00861705) are eagerly awaited to confirm these findings and potentially validate the observations.

**Smaller sample size.** In contrast with neoadjuvant trials, adjuvant trials require a large sample size to evaluate a significant difference between the study arms. For example, the adjuvant clinical trials evaluating efficacy of adjuvant trastuzumab had a sample size of more than 3,000 patients: the NCCTG (North Central Cancer Treatment Group) N9831 and NSABP-B31 trial enrolled 3,351 patients, the BCIRG006 (Breast Cancer International Research Group) enrolled 3,222 patients, and the HERA (Herceptin Adjuvant) trial enrolled 5,081 patients (19–21). In contrast, the phase III neoadjuvant trastuzumab trial, NOAH, enrolled 334 patients and successfully demonstrated that neoadjuvant trastuzumab in combination with chemotherapy resulted in a significantly higher path CR rate (43% vs. 23%, \(P = 0.002\)) than chemotherapy alone (22). Moreover, the magnitude of benefit observed in the neoadjuvant trial (hazard ratio, 0.56; \(P = 0.006\) for DFS) was similar to that observed in the large adjuvant trials (hazard ratio, 0.54; \(P = 0.0001\) for DFS in the HERA trial) suggesting that trastuzumab can be started in the neoadjuvant setting. The results of the NOAH trial led to the approval of neoadjuvant trastuzumab by the European Medicines Agency. While the sample size needed for the neoadjuvant trial is smaller than that of adjuvant trials, the exact number obviously depends on a number of factors, including the magnitude of correlation (i.e., the larger the correlation the fewer the number of patients needed to prove the correlation).

**Biomarker development and validation.** To develop effective and successful targeted therapies, predictive markers of response need to be developed early in translational trials. Neoadjuvant trials provide an ideal platform for biomarker development and validation for a number of reasons. First, a pretreatment breast cancer biopsy allows for the potential identification of biomarkers predictive of response to treatment. For example, based on massive parallel whole-genome and exome sequencing of pretreatment tumor biopsies obtained from a preoperative neoadjuvant hormone phase II trial, mutations in GATA3 have been identified to correlate with response to neoadjuvant aromatase inhibitor therapy (23). Similarly, based on mRNA gene expression analysis from pretreatment core biopsies using the Affymetrix GeneChip platform, microtubule-
associated protein tau and a 10-gene penalized logistic regression model have been identified to be predictors of response to the neoadjuvant chemotherapy agent ixabepilone (24). Thus, neoadjuvant trials can help discover novel predictive biomarkers that can then be validated by additional studies in the neoadjuvant and adjuvant setting before appropriate adoption in clinical practice. Second, midtreatment biopsy obtained during a neoadjuvant trial allows correlation of changes of biomarkers with outcomes. For example, presence of high Ki67 expression at day 15 after 2 weeks of neoadjuvant endocrine therapy for HR+ breast cancer is significantly associated with higher relapse-free survival ($P = 0.004$; ref. 25) and can provide early insights about therapeutic potential of a drug. In a neoadjuvant trial evaluating everolimus and letrozole, versus letrozole and placebo, higher reduction in Ki67 at day 15 was observed in the everolimus arm as compared with the placebo arm (57% vs. 30%; $P < 0.01$; ref. 26). The superior efficacy of mTOR in combination with aromatase inhibitor was subsequently confirmed in the pivotal randomized phase III BOLERO-2 trial (hazard ratio, 0.36; $P < 0.001$ for DFS; ref. 27). Third, analysis of the tumor sample while on therapy allows the ascertainment of pharmacodynamic effect at the dose utilized (28). Finally, a neoadjuvant clinical trial provides a platform for validation of a biomarker hypothesis identified in other settings. For example, biomarker analyses from neoadjuvant trials and the CLEOPATRA trial have identified PIK3CA mutation to be associated with poor prognosis in HER2+ breast cancer treated with HER2 therapies, suggesting PI3K inhibitor in combination with HER2 therapy to be a promising therapeutic strategy (29, 30). This hypothesis can be rapidly tested in a neoadjuvant trial by comparing path CR rates between PI3K inhibitor combination with HER2 therapy versus HER2 therapy alone, stratified by PIK3CA status. Indeed, neoadjuvant clinical trials testing a combination of trastuzumab with PI3K inhibitors are under way (NCT01816594). Similarly, neoadjuvant trials can be utilized to test the efficacy of biomarker-driven targeted therapies in the various molecular subtypes of TNBC (discussed elsewhere in this CCR Focus series; ref. 31).

Besides discovery of biomarkers from tumor tissue, imaging studies performed in a neoadjuvant trial allow development of noninvasive predictive biomarkers. As part of a substudy within the NeoALTTO trial, patients who do not have FDG-PET response at week 6 had a lower chance of achieving path CR (19% vs. 44%; $P = 0.05$; ref. 32). Similarly, characterization of molecular changes in circulating tumor cells and circulating cell-free DNA is a promising strategy for identification of key biologic processes such as epithelial-to-mesenchymal transition and genomic evolution of tumor in response to therapy (33–35).

**Discovery of mechanisms of resistance to therapy.** In a neoadjuvant trial, patients who do not achieve a path CR have residual tumor in the resected surgical specimen. The residual tumor is a valuable resource for discovery of mechanisms contributing to resistance, identification of activation of compensatory pathways, and development of novel therapeutic strategies. For example, for TNBC, utilizing NanoString technology for gene expression profiling in residual disease after neoadjuvant therapy, low expression of DUSP4, a negative regulator of ERK (extracellular-regulated kinase), has been associated with high tumor proliferation ($P = 0.001$), worse survival ($P = 0.02$), and potential sensitivity to MEK inhibition (36). Similarly, utilizing next-generation sequencing on residual tumors after neoadjuvant therapy (37), molecular aberrations in five distinct targetable pathways have been discovered that could potentially be modulated by targeted therapies: PI3K/mTOR (PI3K/mTOR inhibitors), DNA repair (PARP inhibitors), Ras/MAPK (MEK/ERK inhibitors), cell cycle (CDK inhibitors), and growth factor receptors (tyrosine kinase inhibitors). For HR+ tumors, utilizing massive parallel sequencing and pathway analysis software, certain activity “hubs” have been identified to be associated with resistance to endocrine therapy (high Ki67), including TP53, MYC, HDAC1, and actionable mutations such as PIK3CA and MAP3K1 have been identified that could potentially be targeted with therapies to improve outcomes (23).

### Key considerations for neoadjuvant drug development

Recognizing the importance of neoadjuvant trials for drug development, the FDA recently announced the consideration of neoadjuvant randomized trials for accelerated drug approval in early breast cancer (38). The FDA has stated that while improvement in path CR could be utilized for “accelerated” approval, improvement in DFS or OS will still need to be demonstrated for “regular” approval. The FDA clearly stated that the goal of the neoadjuvant accelerated approval pathway is to make highly effective drugs available sooner and is not intended to be an “easy” route for approval. In line with this approach based on path CR as the primary outcome, the FDA granted accelerated approval to pertuzumab for neoadjuvant treatment of women with early-stage HER2+ breast cancer on September 30, 2013 (14).

In the coming years, we anticipate a marked increase in the number of neoadjuvant clinical trials testing novel therapies. Figure 1 depicts an approach for development of novel therapies and biomarkers utilizing neoadjuvant trials. The key considerations in designing a neoadjuvant trial for drug approval are discussed below. We focus predominantly on HER2+ and TNBC in line with the FDA position statement.

#### Trial design considerations.

**Classical two-arm and multi-arm study designs.** A neoadjuvant randomized two-arm add-on design is outlined in Fig. 2, similar to the NeoALTTO and CALGB 40601 trial design (11, 39). While NeoALTTO and CALGB 40601 had three arms (trastuzumab, lapatinib, trastuzumab and lapatinib), a two-arm design is presented for simplicity. Eligible women with invasive breast cancer, who are candidates for neoadjuvant therapy, are randomized to receive novel therapy with standard therapy (experimental arm), or standard therapy only (control arm). A short lead-in phase with novel therapy is built in for pharmacodynamic evaluation. After this “biologic window,” patients continue on the same novel therapy, plus...
standard therapy up to definitive surgery. A midtreatment imaging study is usually built in to allow for noninvasive pharmacodynamic evaluation and for identification of nonresponders (who could potentially be switched to other therapies depending on study design). The primary endpoint is difference in rate of path CR. Such a neoadjuvant trial design is best suited to assess the efficacy of a novel agent in addition to standard therapy.

A multi-arm design builds on a two-arm design and is particularly suited for assessing the efficacy of targeted therapy combinations. For example, the NeoSphere trial had four arms: trastuzumab plus docetaxel, pertuzumab plus docetaxel, trastuzumab plus pertuzumab plus docetaxel, and trastuzumab plus pertuzumab without docetaxel (12). Such a design allows direct comparison of multiple therapies, facilitates identification of predictive biomarkers for individual agents, and aids the discovery of mechanisms of resistance. A similar multi-arm clinical trial design is anticipated with the novel anti-HER2 antibody drug conjugate T-DM1.

In an add-on design, the choice of neoadjuvant chemotherapy backbone is critical as it has a significant impact on the primary outcome. For example, in NeoALTTO the neoadjuvant chemotherapy backbone was Adriamycin–cyclophosphamide followed by weekly paclitaxel (11, 40). Not surprisingly, the path CR rate in the trastuzumab arm (control arm) was much higher in the NSABP41 trial (52.5%) as compared with NeoALTTO (29.5%). Note that in the NeoALTTO trial, all patients did receive the anthracycline-based chemotherapy that was omitted in the neoadjuvant setting in the adjuvant setting. Table 1 outlines the path CR rates with different regimens from the key neoadjuvant trials in HER2" breast cancer (41). From a biomarker discovery perspective, trial designs like NeoALTTO are preferred because (i) they allow better assessment of the specific contribution of the novel agent, and because (ii) they help in identification of biomarkers that predict path CR with no/less chemotherapy, which could then be validated in confirmatory biomarker stratified trials.

**Biomarker-stratified design** A biomarker-stratified neoadjuvant trial design needs to be considered when initial studies identify a biomarker that could potentially enrich for response to targeted therapy, but there is some uncertainty about benefit in an overall population as opposed to marker-defined subgroups. In the trial, the patient enrollment is stratified on the basis of the biomarker. The primary endpoint, path CR is analyzed separately in the biomarker-positive and -negative groups. Such a design can answer multiple questions. First, if positive results with novel therapy are seen only in the biomarker-positive group, but not the biomarker-negative arm, it confirms that the biomarker is indeed a predictive biomarker for novel therapy response. Second, this design allows for assessment of interaction between the biomarker and control therapy by evaluating the association between biomarker positivity and path CR rates in the control arm. Third, this design allows for assessment of prognostic significance of the biomarker by evaluating the association between biomarker positivity and
outcomes. An example of biomarker-stratified design evaluating a novel inhibitor of apoptosis protein (IAP) inhibitor, LCL161 (NCT01617668), is outlined in Fig. 3.

The key issues involved in design of biomarker trials include reliability and validity of the assay, turnaround time, and biomarker prevalence (41). To address the issue of a turnaround time and delay in initiation of therapy, a run-in treatment phase before randomization can be built into the trial design. If the biomarker prevalence is uncertain or there are multiple biomarkers, an adaptive biomarker trial design is better because it allows for change in biomarker arms based on the results observed during the trial (42, 43). An example of adaptive biomarker trial design is the ongoing I-SPY 2 neoadjuvant trial (44).

Genome-driven neoadjuvant trials are also reviewed in this CCR Focus series (45).

Path CR considerations. To advance the concept of path CR, it is imperative to agree on a definition of path CR that is accurate and uniform for cross-trial comparisons. It is best to consider evaluation of both breast and lymph nodes for path CR because the presence of residual tumor in lymph nodes after neoadjuvant therapy could affect DFS or OS. On the other hand, absence of ductal carcinoma in situ (DCIS) need not be required for path CR because the presence of residual DCIS after neoadjuvant trials does not affect DFS or OS (46). The FDA released a regulatory guideline in March 2013 defining path CR 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 preoperative systemic therapy (i.e., ypT0ypN0 in the current AJCC staging system)." The FDA purposefully used the term "all sampled" lymph nodes as not all patients with positive lymph nodes require axillary dissection and it is important that plans for axillary management are clearly specified in the protocol. Finally, while the treatment arms in the trial could be open label (not blinded), it is crucial that the pathologist(s) assessing path CR is blinded to the treatment allocation.

Patient population and treatment considerations. Neoadjuvant trials should be considered for patients who would otherwise meet criteria for adjuvant therapy. Tumor size (T), lymph node status (N), grade, and HR status, are all important predictors of path CR, and need to be well balanced between the treatment arms. For trials testing HER2 therapies, use of neoadjuvant endocrine therapy needs to be prespecified, because the combination can inhibit the cross-talk between estrogen receptor and HER2 and result in synergistic therapeutic efficacy (47). A detailed plan for follow-up after surgery needs to be incorporated to allow assessment for potential late toxicity and for survival data. Consequently, factors that affect DFS or OS, including postoperative chemotherapy, radiotherapy, and adjuvant endocrine therapy need to be clearly specified in the protocol and administered uniformly to all the arms to avoid bias.

Safety considerations. Safety is a key issue for neoadjuvant trials because these trials involve a patient population with curable disease. While the amount of safety data needed before neoadjuvant trials are launched is dependent on the novel agent being considered and the study context, in general the safety in neoadjuvant trials
Table 1. Summary of the major neoadjuvant randomized controlled trials for HER2-positive breast cancer

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Regimen</th>
<th>Sample size</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td><strong>Trastuzumab</strong></td>
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<tr>
<td>NOAH (22)</td>
<td>A) Doxorubicin and paclitaxel $\times$ 3, followed by paclitaxel $\times$ 4, and then cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) $\times$ 3, with trastuzumab</td>
<td>235 path CR</td>
<td>38% in A vs. 19% in B $P &lt; 0.01$</td>
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<tr>
<td></td>
<td>B) Doxorubicin and paclitaxel $\times$ 3, followed by paclitaxel $\times$ 4, and then cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) $\times$ 3, without trastuzumab</td>
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<tr>
<td><strong>MDACC (41)</strong></td>
<td>A) Paclitaxel $\times$ 4, followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) $\times$ 4, with trastuzumab</td>
<td>42 path CR</td>
<td>66.7% in A vs. 26% in B $P = 0.02$</td>
</tr>
<tr>
<td></td>
<td>B) Paclitaxel $\times$ 4, followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) $\times$ 4, without trastuzumab</td>
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<tr>
<td><strong>Trastuzumab and lapatinib</strong></td>
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<tr>
<td>NeoALTTO (12)</td>
<td>A) Trastuzumab with weekly paclitaxel $\times$ 12 weeks</td>
<td>455 path CR</td>
<td>29.5% in arm A vs. 24.7% in arm B $P = 0.032$ A vs. C $P = 0.0001$ A vs. C</td>
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<td></td>
<td>B) Lapatinib with weekly paclitaxel $\times$ 12 weeks</td>
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<td></td>
<td>C) Trastuzumab and lapatinib with weekly paclitaxel $\times$ 12 weeks</td>
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<tr>
<td>GeparQuinto (41)</td>
<td>A) Trastuzumab with epirubicin, cyclophosphamide (EC) $\times$ 4 cycles, followed by docetaxel q3 weeks $\times$ 4 cycles.</td>
<td>620 path CR</td>
<td>30.3% in A vs. 22.7% in B $P &lt; 0.05$</td>
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<tr>
<td></td>
<td>B) Lapatinib with epirubicin, cyclophosphamide (EC) $\times$ 4 cycles, followed by docetaxel q3 weeks $\times$ 4 cycles.</td>
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<tr>
<td>NSABP41 (40)</td>
<td>A) Doxorubicin plus cyclophosphamide (AC) $\times$ 4 followed by trastuzumab with weekly paclitaxel $\times$ 16 weeks</td>
<td>522 path CR</td>
<td>49.1% in Arm A vs. 47.4% in Arm B $P = 0.74$ A vs. C</td>
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<tr>
<td></td>
<td>B) Doxorubicin plus cyclophosphamide (AC) $\times$ 4 followed by lapatinib with weekly paclitaxel $\times$ 16 weeks</td>
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<td></td>
<td>C) Doxorubicin plus cyclophosphamide (AC) $\times$ 4 followed by trastuzumab and lapatinib with weekly paclitaxel $\times$ 16 weeks</td>
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<tr>
<td>CALGB40601 (39)</td>
<td>A) Trastuzumab with weekly paclitaxel $\times$ 16 weeks</td>
<td>305 path CR</td>
<td>46% in Arm A vs. 37% in Arm B $P = 0.04$ A vs. C</td>
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<tr>
<td></td>
<td>B) Lapatinib with weekly paclitaxel $\times$ 16 weeks</td>
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<td></td>
<td>C) Trastuzumab and lapatinib with weekly paclitaxel $\times$ 16 weeks</td>
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<tr>
<td><strong>Trastuzumab and pertuzumab</strong></td>
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<tr>
<td>NeoSphere (13)</td>
<td>A) Trastuzumab with docetaxel q3 weeks $\times$ 4 cycles</td>
<td>417 path CR</td>
<td>29% in arm A vs. 24% in arm B $P = 0.01$ A vs. D</td>
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<tr>
<td></td>
<td>B) Pertuzumab with docetaxel q3 weeks $\times$ 4 cycles</td>
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<td>C) Trastuzumab and pertuzumab with docetaxel q3 weeks $\times$ 4 cycles</td>
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<tr>
<td></td>
<td>D) Trastuzumab and pertuzumab q3 weeks $\times$ 4 cycles</td>
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should follow the same principles as in adjuvant trials, i.e., careful monitoring, interim look at safety, and prolonged follow-up. Important issues to consider before initiating a neoadjuvant trial include whether the study agent has been approved for advanced breast cancer or other cancers (safety data are likely to be present), whether there are data on compounds with a similar mechanism of action (the class effect of blocking a pathway would be known), potential for interaction between novel agent and standard therapy (at least phase Ib data need to be available), and careful assessment of risk–benefit ratio (TNBC versus HR\textsuperscript{+} disease; ref. 48).

Limitations of neoadjuvant model

Despite the significant advantages of utilizing the neoadjuvant model as a strategy for drug development, there are a few limitations that need to be considered. First, while in general, path CR results observed among the neoadjuvant trials with similar arms have been consistent (such as with trastuzumab and lapatinib in NeoALTTO and CALGB 40601), and therapies that have shown path CR improvement in the neoadjuvant setting have also shown improvement in outcomes in the adjuvant setting (such as with trastuzumab), there can be exceptions as seen in the case of bevacizumab. In the large neoadjuvant trial,
<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Study arms</th>
<th>Identifier</th>
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<tr>
<td>PI3K/Akt/mTOR</td>
<td>BKM120 (buparlisib)</td>
<td>Pan-PI3K Inhibitor</td>
<td>Trastuzumab + BKM120 + paclitaxel, versus Trastuzumab + placebo + paclitaxel</td>
<td>NCT01816594 (NeoPHOEBE)</td>
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<td>GDC0032</td>
<td>Beta-sparing PI3K Inhibitor</td>
<td>GDC0032 and endocrine therapy</td>
<td>In planning</td>
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<td>Rad001 (everolimus)</td>
<td>mTOR (TORC1) Inhibitor</td>
<td>Rad001 + paclitaxel + cisplatin, versus paclitaxel + cisplatin</td>
<td>NCT00930930</td>
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<td>Ras/MAPK</td>
<td>Selumetinib</td>
<td>MEK1/2 Inhibitor</td>
<td>Selumetinib and chemotherapy</td>
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<td>AMPK</td>
<td>Metformin</td>
<td>Activation of the LKB1-AMPK pathway</td>
<td>Metformin + letrozole, versus letrozole</td>
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<td>EGFR</td>
<td>Cetuximab</td>
<td>Chimeric monoclonal antibody against EGFR</td>
<td>Ixabepilone + cetuximab versus ixabepilone</td>
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<td>Panitumumab</td>
<td>Fully human monoclonal antibody against EGFR</td>
<td>Panitumumab and chemotherapy</td>
<td>In planning</td>
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<td>HER2</td>
<td>Afatinib</td>
<td>EGFR and HER2 dual inhibitor</td>
<td>Paclitaxel + trastuzumab, versus paclitaxel + afatinib, paclitaxel + trastuzumab and afatinib, then AC</td>
<td>NCT01594177</td>
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<td>Neratinib</td>
<td>EGFR and HER2 dual inhibitor</td>
<td>Paclitaxel + trastuzumab, versus paclitaxel + neratinib, versus paclitaxel + trastuzumab + neratinib, then AC</td>
<td>NCT01008150 (NSABP FB-7)</td>
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<td>T-DM1</td>
<td>Trastuzumab-based antibody drug conjugate against HER2</td>
<td>T-DM1 + endocrine therapy, versus T-DM1, versus trastuzumab + endocrine therapy</td>
<td>NCT01745965 (ADAPT)</td>
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<td>Trastuzumab-based antibody drug conjugate against HER2</td>
<td>T-DM1 and pertuzumab</td>
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<td>HER3</td>
<td>MM-121</td>
<td>Fully human monoclonal antibody against HER3</td>
<td>MM-121 + paclitaxel, versus paclitaxel Followed by AC</td>
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</tr>
<tr>
<td>c-MET</td>
<td>Onartuzumab (MetMab)</td>
<td>Fully human monoclonal antibody against c-MET</td>
<td>Onartuzumab and chemotherapy</td>
<td>In Planning</td>
</tr>
<tr>
<td>JAK/Stat</td>
<td>Ruxolitinib</td>
<td>JAK-1/2 Inhibitor</td>
<td>Ruxolitinib and chemotherapy</td>
<td>In Planning</td>
</tr>
<tr>
<td>FGF</td>
<td>BIBF1120</td>
<td>Multikinase Inhibitor (FGF, VEGF, PDGF)</td>
<td>BIBF1120 + paclitaxel, versus paclitaxel</td>
<td>NCT01335464</td>
</tr>
<tr>
<td>DNA Repair</td>
<td>Veliparib (ABT-888)</td>
<td>PARP 1 and 2 Inhibitor</td>
<td>Veliparib + paclitaxel + carboplatin, versus paclitaxel + carboplatin</td>
<td>NCT01818063</td>
</tr>
</tbody>
</table>

(Continued on the following page)
GeparQuinto, path CR improvement with bevacizumab was restricted to the TNBC subgroup whereas in the other neoadjuvant trial, NASPB B 40, the path CR improvement restricted to the HR$^+$ subgroup (49, 50). Furthermore, the adjuvant phase III trial BEATRICE did not show any improvement in survival with bevacizumab in early-stage TNBC—an important caveat for this field (51). While the exact reason for the observed discrepancy is unclear, potential hypotheses include differences in study design, lack of patient selection based on biomarkers, differences in chemotherapy regimen, and the possibility that bevacizumab as monoangiogenic therapy results in an initial response followed by the rapid development of resistance due to activation of compensatory angiogenic pathways and thus potentially several antiangiogenic pathways need to be inhibited together to derive a meaningful clinical benefit.

Second, neoadjuvant trials utilizing path CR as the primary outcome, while promising, are not intended for all patients or all subtypes of breast cancer. The risk:benefit ratio needs to be carefully evaluated. The FDA has emphasized that the neoadjuvant mechanism for drug approval is intended to treat populations with significant risk of relapse and would thus be best suited for TNBC, HER2$^+$ tumors, and possibly HR$^+$ tumors with high-risk features (i.e., grade 3 as opposed to grade 1 tumors). Third, path CR is by no means a "perfect" predictor by itself. For example, the Neo-ALTO did not show a statistically worse outcome in the lapatinib-alone arm, although the lapatinib-alone arm did appear to be worse in ALTTO (as per report from the independent data monitoring committee in 2010). Similarly, while pertuzumab has received accelerated approval in the neoadjuvant setting, results of the confirmatory trial in the adjuvant setting (APHINITY) will be needed to confirm the survival benefit with pertuzumab. Finally, while higher path CR is associated with improved survival, the exact magnitude of path CR that correlates with a specific amount of improvement in survival is not known. The FDA draft guidance does not specify the exact magnitude of improvement in path CR needed for drug approval and mentions the drugs will need to demonstrate a "large" improvement in magnitude of path CR. Thus the degree of path CR improvement needed must be individualized for each study agent and context.

**Summary**

Neoadjuvant trials provide a novel drug development model for potential rapid assessment of drug efficacy, identification of predictive biomarkers, discovery of mechanisms of resistance, and development of rational drug combinations that are synergistic and target compensatory pathways. A carefully planned, well-designed, randomized neoadjuvant trial can support accelerated approval on the basis of substantial improvement in the path CR and expedite the availability of an effective drug to a larger number of patients with breast cancer, as in the case with neoadjuvant pertuzumab. A number of neoadjuvant trials investigating novel drugs are ongoing, and multiple cooperative groups are currently in the process of launching a series of neoadjuvant trials as listed in Table 2. In the years to come, neoadjuvant trials testing novel therapies will help change the landscape of breast cancer therapeutics and lead to a potential paradigm shift in breast cancer management.

**Disclosure of Potential Conflicts of Interest**

J. Baselga is a consultant/advisory board member of Novartis. No potential conflicts of interest were disclosed by the other author.

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**Table 2. Ongoing randomized clinical trials testing novel anticancer therapies targeting the major oncogenic pathways in the neoadjuvant setting for localized breast cancer (Cont’d)**

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Study arms</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iniparib (SAR240550)</td>
<td>Induces DNA damage via gamma-H2AX (mechanism not fully understood)</td>
<td>Iniparib + paclitaxel (two different schedules), versus paclitaxel</td>
<td>NCT01204125 (NeoPARP)</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>Cross-links DNA to impair DNA repair</td>
<td>Carboplatin + thiotepa + cyclophosphamide, versus docetaxel + capecitabine, versus AC</td>
<td>NCT01057069 (neo-TN)</td>
</tr>
</tbody>
</table>

**Cell cycle**

| PD-0323991 (Palbociclib) | CDK 4/6 Inhibitor | Palbociclib and endocrine therapy | In planning |

**Apoptosis**

| LCL161 | Inhibitor of IAPs | LCL161 + paclitaxel, versus paclitaxel | NCT01617668 |

| All 3 arms stratified by homologous recombination defect (HRD) status. | All 3 arms stratified by homologous recombination defect (HRD) status. |

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Neoadjuvant Therapy as a Platform for Drug Development and Approval in Breast Cancer

Aditya Bardia and José Baselga


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