HHS Public Access

Author manuscript

Ann Surg Oncol. Author manuscript; available in PMC 2015 June 29.

Published in final edited form as:

Ann Surg Oncol. 2015 May ; 22(5): 1408–1415. doi:10.1245/s10434-015-4405-7.

Landscape of Neoadjuvant Therapy for Breast Cancer

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Abstract

Neoadjuvant chemotherapy provides clinical outcomes equivalent to those achieved when the same regimen is provided in the adjuvant setting. The therapeutic response to neoadjuvant treatment may include a reduction in tumor burden that alleviates the morbidity associated with locoregional therapy. Important prognostic information can be gained based on the response to treatment and knowing the quantity and biology of the residual disease. The evaluation of investigational agents in the neoadjuvant setting is of particular value for accelerating drug development. This review highlights landmark trials and contemporary perspectives on neoadjuvant chemotherapy and hormonal therapy, treatment response as a prognostic biomarker, use of the neoadjuvant paradigm for new drug development, and clinical advances in neoadjuvant therapy by molecular subtype of breast cancer.

ADJUVANT SYSTEMIC THERAPY OVERVIEW

Systemic chemotherapy and endocrine- and human epidermal growth factor receptor 2 (HER2)-directed therapies represent major advances in the treatment of breast cancer. When prescribed with the intent to control or eliminate microscopic metastatic disease in patients with early stage (I—III) breast cancer, these “adjuvant” therapies have provided substantial contributions to the continued decline in mortality due to breast cancer observed over the past several decades.[1]

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) polychemotherapy overview established that systemic polychemotherapy delivered after surgery (adjuvant setting) reduces the annual odds of disease recurrence, breast cancer mortality, and all-cause mortality by 24, 15, and 14.9 %, respectively.[2,3] A recent update, which included the use of taxanes, demonstrated that, overall, polychemotherapy reduced the risk of breast cancer

DISCLOSURES The authors have no relevant financial disclosures.

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mortality by about 36 %. This corresponds with a reduction in the 10-year risk of death from breast cancer by one-third.[3] Currently, the most commonly utilized polychemotherapeutic agents worldwide are anthracycline- and taxane-containing regimens.

Adjuvant endocrine therapy is the mainstay of treatment for patients with estrogen receptor-positive (ER+) breast cancer. Tamoxifen, a selective ER modulator with partial agonist and antagonist activity, remains a standard treatment for both premenopausal and postmenopausal treatment of breast cancer. The EBCTCG overview demonstrated that 5 years of adjuvant tamoxifen reduced breast cancer mortality by approximately one-third during the first 15 years following definitive locoregional treatment—independent of PR status, age, nodal status, and use of chemotherapy.[4]

The third-generation aromatase inhibitors anastrozole, exemestane, and letrozole have been established to be of value for postmenopausal women with breast cancer, and there is increasing evidence for their use in the premenopausal treatment of invasive breast cancer along with ovarian function suppression.[5,6] For ER+ postmenopausal breast cancer, an American Society of Clinical Oncology Practice Guideline has recommended the use of aromatase inhibitors at some point during adjuvant endocrine therapy either as the initial therapy or following tamoxifen therapy.[7] The recommendation was based in part on a meta-analysis comparing tamoxifen and aromatase inhibitors that demonstrated an absolute 2.9 % decrease in breast cancer recurrence at 5 years.[8]

During the past decade, HER2-directed therapies represent a major advance in the systemic treatment and clinical outcomes of patients with early-stage HER2+ breast cancer. The joint analysis of the NSABP-B31 and NCCTG N9831 trials revealed a median follow-up of 3.9 years and that women receiving trastuzumab with polychemotherapy had significantly improved disease-free survival (DFS) [hazard ratio (HR) 0.52, $p < 0.001$] and overall survival (OS) (HR 0.61, $p < 0.001$) compared with women receiving polychemotherapy alone.[9] One year of adjuvant trastuzumab is the current standard care for patients with HER2+ breast cancer. Although the addition of lapatinib (either alone or in combination with trastuzumab) did not improve DFS or OS in the adjuvant setting,[10] accrual for other Phase III clinical trials (pertuzumab and neratinib) is ongoing or completed, and results are eagerly awaited.

Prognostic factors such as tumor size and lymph node status have traditionally been used to identify candidates for adjuvant chemotherapy. However, genomically unique subsets have now been identified that account for some of the heterogeneity in prognosis and chemotherapy responsiveness.[11,12] The commonly accepted molecular subsets include luminal A (ER+/PR+/HER2−, low proliferation); luminal B (ER+, low PR, HER2−, elevated proliferation); HER2+ (ER+ and ER− comprise unique HER2 subsets); and basal-like [commonly ER−/PR−/HER2−, triple-negative breast cancer (TNBC)]. Molecular profiling of ER+ breast cancer in particular can identify low-risk patients whose disease should be treated with endocrine therapy alone as well as a subset of high-risk patients (mainly with luminal B cancers) who would benefit from adjuvant chemotherapy.[13] In contrast, nearly all TNBC and HER2+ subsets are considered at “high risk. ” Much of the research in this area has focused on identifying patients considered resistant to standard

chemotherapy and who should be considered for novel treatments in addition to standard chemotherapy.

BENEFITS OF NEOADJUVANT CHEMOTHERAPY

Landmark Trials Defining the Benefits of Neoadjuvant Chemotherapy

Given the association of adjuvant systemic therapy with improved survival, investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) sought to test the hypothesis that earlier administration of systemic chemotherapy, in the neoadjuvant or presurgical setting, could further improve clinical outcomes by early elimination of microscopic metastatic disease. The NSABP B-18 trial randomized 1,523 patients with early-stage breast cancer to receive four cycles of neoadjuvant doxorubicin and cyclophosphamide (AC) followed by surgery or surgery followed by four cycles of adjuvant AC.[14] The surgical plan was confirmed prior to randomization, and those patients undergoing breast-conservation surgery underwent whole-breast radiation therapy.

Ultimately, the locoregional relapse and DFS and OS rates were identical in the two groups.[15] However, a larger proportion of patients undergoing neoadjuvant therapy underwent breast-conservation therapy (BCT) than those who underwent adjuvant chemotherapy (68 and 60 %; $p = 0.001$). Patients randomized to the neoadjuvant arm were additionally more likely to have negative axillary lymph nodes at the time of surgery when compared to the adjuvant arm. The European Organization for Research and Treatment of Cancer 10902 trial and other studies have demonstrated similar results.[16,17] From these definitive trials, the benefit of neoadjuvant therapy was initially thought to be mainly related to downstaging the disease to facilitate BCT and the potential to decrease morbidity associated with axillary surgery.

An interesting observation from a subgroup analysis of the NSABP B-18 and B27 trials was the difference in DFS between women randomized to the adjuvant and neoadjuvant groups according to age. Specifically, there were trends in favor of preoperative chemotherapy for DFS and OS in women less than 50 years of age (HR 0.85, $p = 0.09$ for DFS; HR 0.81, $p = 0.06$ for OS).[15] This is consistent with findings from the EBCTCG overview that demonstrated a more pronounced benefit from adjuvant chemotherapy for younger patients[2] and the International Breast Cancer Study Group data suggesting that premenopausal women with ER− disease may benefit from earlier initiation of adjuvant chemotherapy.[18]

The NSABP B-27 trial randomized 2411 women to (1) four cycles of neoadjuvant AC followed by surgery, (2) four cycles of neoadjuvant AC followed by four cycles of neoadjuvant docetaxel and surgery, and (3) four cycles of neoadjuvant AC followed by surgery and then four cycles of adjuvant docetaxel.[19] Although the addition of docetaxel improved the pathological complete response (pCR) rate—defined as the absence of invasive cancer in the breast—these findings did not translate into improved DFS and OS outcomes. Importantly, in a subset analysis, among patients experiencing a partial response to AC the DFS was better for those receiving neoadjuvant therapy than those given adjuvant docetaxel. Based on these results, if neoadjuvant chemotherapy (NAC) is pursued outside a

clinical trial, clinical outcomes may be optimal if all planned treatment is administered preoperatively.

Contemporary Perspectives on Neoadjuvant Therapy

Historically, systemic therapy has been administered in the adjuvant setting (after definitive breast surgery) with treatment decisions guided by the pathologic stage and tumor grade. With advances in the molecular classification of breast cancer, however, tumor biology is now a driving force in the development of systemic treatment recommendations. Thus, at the time of diagnosis, clinical and radiographic locoregional staging and molecular subtype can frequently provide sufficient information to formulate systemic therapy plans in the absence of surgical staging. Coupled with mature data supporting equivalent DFS and OS clinical outcomes, it has resulted in a paradigm shift in breast cancer treatment, with increased utilization of NAC. It also stimulated the formation of an international consensus expert panel to provide recommendations on the use of neoadjuvant therapy. In short, the panel suggests that NAC should be considered in any individual for whom adjuvant chemotherapy is indicated.[20]

Treatment Response Provides Prognostic Information

A substantial benefit of administering chemotherapy in the neoadjuvant setting is the prognostic information obtained by pathological assessment of the tumor bed and lymph nodes after surgery. pCR was strongly associated with clinical outcomes in the NSABP B-18 and B-27 trials. In B18, those who achieved a pCR in the breast had improved DFS and OS (HR 0.47, $p = 0.0001$ and HR 0.32, $p = 0.0001$, respectively). The investigators therefore concluded that pCR after NAC was a relevant prognostic marker. Although similar findings have been demonstrated in several subsequent trials, a uniform definition of pCR has been lacking across studies.

One of the major themes emerging from NAC trials is that the pCR rates vary widely by molecular subtype. Notably, tumors exhibiting high proliferation (Luminal B, HER2+, TNBC) not only have higher rates of pCR (compared to Luminal A) but the pCR rates in these subsets appear to be most closely associated with DFS and OS.[21] The US Food and Drug Administration (FDA)-led meta-analysis of neoadjuvant studies (CTNeoBC) affirmed that the strongest association between pCR and long-term clinical outcome occurred in patients with aggressive breast cancer subtypes.[22] These data confirmed that the optimal definition of pCR includes ypT0/is ypN0 or ypT0 ypN0 as the presence or absence of ductal carcinoma in situ did not affect long-term clinical outcomes.

The residual cancer burden (RCB) provides a method for categorizing the extent of residual disease and prognosis after NAC.[23] RCB stratifies those not achieving a pCR into cohorts (RCB I—III) based on the amount of residual disease. The RCB calculation factors included the tumor bed size, percent cancer cellularity, percent in situ disease, the total number of positive axillary lymph nodes, and the diameter of the largest nodal metastasis. The benefit of utilizing RCB over the binary outcome of pCR or no pCR is the identification of patients with minimal residual disease (RCB-I) for whom prognosis and clinical outcomes are projected to be the same as for patients who achieve a pCR (RCB-0).

Another prognostic staging system, the CPS + EG, utilizes pretreatment clinical stage (C), post-treatment pathological stage (PS), ER status (E), and grade (G). It has been validated in multiple data sets.[24] Based on the scoring system, patient outcomes can be categorized into seven groups (scores 0–6) with different 5-year distant metastasis-free and disease-specific survival rates. The benefit of the CPS + EG system is the value of incorporating important independent risk factors associated with clinical outcomes beyond the post-treatment pathologic stage alone, thus allowing more precise assessment of the prognosis.

Although the RCB and CPS + EG systems are each clearly prognostic, additional markers to assess the response to chemotherapy (e.g., proliferation or imaging) may be necessary to determine chemotherapy responsiveness. One such marker, Ki67, is a proliferation marker that is an independent prognostic biomarker commonly measured in systemically untreated early-stage breast cancer. There are emerging data that post-treatment Ki67 (obtained at surgery after NAC or endocrine therapy) provides important prognostic information for patients with residual breast cancer.[25,26] Specifically, von Minckwitz et al. demonstrated that patients with Ki67 > 35 % after NAC exhibited significantly worse outcomes than those with levels ≤ 35 %.[25] Ki-67 has also been demonstrated to be an important marker of endocrine response. Despite these observations, routine clinical use of Ki67 in community practice continues to be limited by the lack the standardization of the test between pathology laboratories and among pathologists within the same laboratory.

Despite the fact that these biomarkers provide crucial prognostic information and can identify patients at high risk for systemic relapse, there have been no clinical advances beyond standard postsurgical treatment to help mitigate their risk. Clinical trial opportunities and novel treatment approaches are desperately needed to improve clinical outcomes for the majority of women who do not achieve a pCR.

Value of the Neoadjuvant Setting to Accelerate New Drug Development

The neoadjuvant setting provides a rich environment in which to evaluate investigational therapies. Whether it is a short course of preoperative therapy (“window of opportunity” trial) or standard systemic therapy compared with a novel agent or regimen, neoadjuvant clinical trials provide investigators with the advantage of testing a research hypothesis with an intact primary tumor and the ability to obtain serial blood and tumor samples to assess tumor response and/or to develop biomarkers predictive of the response to treatment. The neoadjuvant setting is also ripe for the development of imaging modalities to monitor, and ultimately predict, tumor response.[27–30]

Another appealing aspect of NAC is the ability to accelerate drug development given the shorter time required to obtain response phenotypes (weeks to months) when compared with survival phenotypes determined in the adjuvant setting (5–10 years). These findings led the FDA to publish a “guidance to industry” on the use of pCR as an endpoint to support accelerated approval of investigational drugs.[31] This guidance, updated in 2014, recommended that approval in the neoadjuvant setting would be contingent upon the demonstration of an improvement in DFS by future studies.

CLINICAL ADVANCES IN NEOADJUVANT CHEMOTHERAPY AI\D HER2-DIRECTED THERAPY

HER2-Negative Breast Cancer

Several neoadjuvant clinical trials (GeparQuattro[32] and, NSABP B-40[33]) have evaluated the benefit of combining additional chemotherapy and a standard anthracycline- or taxane-based chemotherapy regimen. Results demonstrated no improvement in pCR rates with the addition of either capecitabine or gemcitabine.

In contrast, NSABP B-40,[33] GeparQuinto,[34] and CALGB 40603[35] demonstrated that the addition of bevacizumab to standard anthracycline- and taxane-based chemotherapy regimens resulted in a statistically significant improvement in pCR rates in the breast. Only GeparQuinto, however, maintained significant findings when evaluating the benefit of bevacizumab on pCR rates in the breast and axilla combined. Multiple studies (BEATRICE,[36] BETH,[37] ECOG 5103[38]) have confirmed a lack of DFS or OS benefit for the addition of bevacizumab to the adjuvant treatment of either HER2− or HER2+ breast cancer.

HER2+ Breast Cancer

In the NOAH trial, patients were randomized to receive neoadjuvant anthracycline- and taxane-based chemotherapy with or without trastuzumab.[39] The addition of trastuzumab to chemotherapy resulted in an increase in pCR rates in the breast and axilla (38 and 19 %, respectively; $p = 0.001$). At a median follow-up of 5.4 years, the DFS for those receiving trastuzumab was also improved (HR 0.64, $p = 0.016$).[40]

The administration of adjuvant trastuzumab after AC and concurrent with taxane-based chemotherapy was established as superior to sequential trastuzumab after completion of all chemotherapy in the N9831 clinical trial.[9] Subsequently, ACOSOG 21041 investigators sought to compare breast pCR rates between patients with locally advanced breast cancer randomized to neoadjuvant anthracycline-based chemotherapy alone followed by paclitaxel with trastuzumab versus neoadjuvant administration of trastuzumab concurrent with paclitaxel and anthracycline-based chemotherapy.[41] The lack of a difference in pCR rates between groups [56.5 and 54.2 %, respectively; adjusted odds ratio 0.90, 95 % confidence interval 0.55–1.49)] suggests that concurrent administration of trastuzumab with the anthracycline portion of the NAC is not needed. This study highlights the fact that an important clinical question can be answered quickly and with a limited number of patients (total $n = 235$) compared with the time and number of patients ($n = 3505$) required by the N9831 trial to answer a similar question regarding the most effective timing for initiation of trastuzumab.

Additional neoadjuvant clinical trials have explored the role of dual HER2 targeting in the neoadjuvant and adjuvant settings. In the NeoALLTO[42] and CHER-LOB[43] trials, the addition of lapatinib, a reversible tyrosine kinase inhibitor of epidermal growth factor receptor and HER2, to trastuzumab in combination with standard chemotherapy resulted in statistically significant increases in pCR rates in the breast and axilla. Given these findings,

there was great interest in the results of the ALLTO trial regarding the effect of adjuvant lapatinib on DFS and OS. The results from the trial demonstrated a trend toward improvement in DFS and OS, but the results were not statistically significant (DFS 0.84, p = 0.048).[10]

In the NeoSphere trial, the addition of pertuzumab, a monoclonal antibody directed against the dimerization domain of HER2, to trastuzumab with or without docetaxel was evaluated.[44] Dual targeting of HER2, with the addition of pertuzumab to trastuzumab and docetaxel, resulted in a significant increase in pCR rates in the intent-to-treat analysis (45.8 and 29.0 %, respectively; p = 0.0141). These findings led the FDA to grant accelerated approval of pertuzumab in the neoadjuvant treatment of HER2+ breast cancer. The findings were further supported by the high pCR rates observed in TRYPHAENA[45] and consistent with improved response rates and progression-free survival observed in CLEOPATRA[46] when pertuzumab was added to trastuzumab and docetaxel in the metastatic setting. Taken together, these trials have generated significant interest in results of the pending APHINITY trial, which will establish the role, if any, for pertuzumab in the adjuvant treatment of HER2+ breast cancer.

Triple Negative Breast Cancer

In the CALGB 40603 trial, the addition of neoadjuvant carboplatin to standard anthracycline- or taxane-based chemotherapy (weekly paclitaxel × 12 followed by four cycles of AC) was explored in patients with clinical stage II and III disease, ER and PR < 10 % expression, and HER2 negativity.[35] Rates of pCR in the breast and axilla were 41 % for standard chemotherapy and 54 % when carboplatin was added to the regimen (p = 0.0029). For patients participating in the GeparSixto trial, significant improvements in pCR rates in the breast and axilla were demonstrated when carboplatin was added to more complex neoadjuvant anthracycline- and taxane-based regimens in patients with TNBC (absolute increase of 20.8 %) but not those with HER2+ disease.[47] Crucial biomarker studies currently pending may help guide patient selection regarding the incorporation of carboplatin into standard systemic chemotherapy for TNBC. Optimal dosing and the schedule for carboplatin, which varied in these two trials, also remains to be determined. Despite these encouraging findings in a patient population in need of better therapeutic options, there are no published data to define the efficacy of adjuvant carboplatin and its impact on important DFS and OS clinical outcomes.

Use of Clinical Response to Tailor Chemotherapy

The benefit of transitioning patients not responding to initial NAC to a non-cross-resistant regimen has not been firmly established. In the GeparTrio trial, patients lacking clinical response to the first two cycles of neoadjuvant TAC (docetaxel, doxorubicin, cyclophosphamide) were randomized to four additional cycles of the same regimen or four cycles of NX (vinorelbine and capecitabine).[48] Although the switching strategy did not result in increased pCR or BCT rates, it did confer improved DFS and OS (HR 0.71, p < 0.001 and HR 0.79, p = 0.048, respectively). Subgroup analysis showed that switching regimens primarily benefited patients with ER+ tumors. Future studies evaluating the benefit

of switching therapies will need to specify treatments according to molecularly relevant subgroups.

NEOADJUVANT ENDOCRINE THERAPY

Clinical outcomes for patients with ER+ and/or PR+ (hormone receptor positive, or HR+) breast cancer is primarily mediated by tumor sensitivity to endocrine therapy. Given the success of NAC in downstaging disease in other biological subtypes of breast cancer, administration of endocrine therapy in the neoadjuvant setting has been explored. However, because endocrine therapy has a different mechanism of response (focused mainly on reducing the estrogen-induced effects on proliferation), pCR is rarely observed with endocrine therapy. Therefore, other measures of response (Ki-67) and clinical benefit have been explored. Clinical research evaluating the role of neoadjuvant administration of standard adjuvant endocrine therapies has primarily focused on postmenopausal women with locally advanced disease. More recently, novel agents to overcome de novo and acquired resistance to endocrine therapy have been evaluated in the neoadjuvant setting as well.

In the IMPACT trial, 330 postmenopausal patients with clinical stage II or III HR+ breast cancer were randomized to receive a 12-week intervention of (1) tamoxifen, (2) anastrozole, or (3) tamoxifen and anastrozole.[49] Following definitive locoregional treatment, all patients completed the adjuvant endocrine therapy according to their randomization assignments. Clinical and radiographic response rates to the neoadjuvant course were equivalent among groups, although a larger proportion of women were eligible for BCT in the anastrozole group than in the tamoxifen group (46 vs. 22 %, $p = 0.022$). Increased ER expression in tumors was associated with higher response rates. Other studies have demonstrated that aromatase inhibitors (AIs) are more effective than tamoxifen in terms of clinical and radiographic response and BCT feasibility rates.[50]

A cohort of patients ($n = 158$) from the IMPACT trial participated in a biomarker study analyzing primary breast tumor changes after a brief (2 weeks) course of neoadjuvant endocrine therapy. Those receiving anastrozole had more significant suppression of Ki67 (expressed as a percentage of the baseline level)[51] and lower post-treatment Ki67 levels[52] than those who were treated with tamoxifen or a combination of the drugs. The post-treatment Ki67 level was more strongly associated with recurrence-free survival (RFS) (log rank $p = 0.008$) than the pretreatment, baseline levels (log rank $p = 0.07$). These findings were consistent with results observed in the adjuvant Arimidex or tamoxifen alone or in combination trial. Further studies are needed to determine if change in Ki67 expression after a short course of neoadjuvant endocrine therapy is predictive of RFS and other clinical outcomes.

Post-treatment pathologic tumor size and nodal staging, as well as Ki67 and ER status, were independently associated with RFS and breast cancer-specific survival in the neoadjuvant letrozole and tamoxifen P024 trial[53] The preoperative endocrine prognostic index (PEPI) model was developed from this study by applying a weighted score to each of the variables. The PEPI model was subsequently validated and predicted RFS ($p = 0.002$) in the IMPACT

neoadjuvant hormonal therapy trial. Notably, the authors recorded no relapses in either study for the pathologic stage 1 or 0 group with a PEPI risk score of 0 during a combined median follow-up of 60.3 months (range 4.5–86.5 months). Based on these findings, the authors hypothesized that patients with a PEPI 0 score after neoadjuvant hormonal therapy are unlikely to benefit from adjuvant chemotherapy. The validation of a modified PEPI score of 0 (defined as T < 5 cm, N0, Ki67 < 2.7 %) is ongoing in the prospective ALTERNATE trial (NCT01953588), which will evaluate a 6-month course of neoadjuvant fulvestrant and anastrozole, alone or in combination, in postmenopausal women with stage II or III disease.

As AIs were associated with tumor response rates superior to those with tamoxifen in the neoadjuvant setting, the ACOSOG Z1031 trial was designed to answer the clinical question if there was a particular AI superior to other AIs. In this trial, postmenopausal women with clinical stage II or III breast cancer were randomized to receive one of the three FDA-approved AIs (letrozole, anastrozole, exemestane) for a 16-week course preoperatively.[54] An important conclusion from this trial was that these agents were associated with similar rates of conversion to BCT and reductions in Ki67 levels. The following response rates were observed: letrozole 74.8 %, anastrozole 69.1 %, axemestane 62.9 %. Response rates are comparable to trends observed in another study evaluating the effects of these three agents on circulating estradiol levels. Results indicated that the greatest suppression was observed in patients taking letrozole, and the least suppression was with exemestane.[55,56] Importantly, a prospective randomized, trial (MA.27) comparing anastrozole and exemestane demonstrated no difference in DFS or OS in the adjuvant setting.[57] The superiority of letrozole compared to the other AIs, in terms of long-term clinical outcomes, has not been established. Results from ongoing adjuvant trials (FACE, NCT00248170) arc eagerly awaited.

Neoadjuvant endocrine therapy may be considered for postmenopausal patients with ER+ clinical stage II and III breast cancer with high ER expression and luminal A characteristics, particularly those motivated to undergo BCT or for those who are at high risk for requiring primary surgical intervention. The AIs are preferred to tamoxifen, and a 4- to 6-month course is advised. For premenopausal women, neoadjuvant endocrine therapy remains largely investigational and is typically encouraged under the auspices of a clinical trial.

CONCLUSIONS

Neoadjuvant systemic therapy is a relevant therapeutic option for women with early-stage, operable breast cancer and for those with inoperable or inflammatory disease for which it was originally developed. Not only can it facilitate reduced morbidity associated with locoregional therapy or increased BCT rates, it holds promise for providing critical prognostic information based on the therapeutic response.

Important findings have been generated from neoadjuvant clinical trials, with the demonstration that in certain scenarios drug development could be accelerated by using chemotherapy response endpoints (pCR). There are emerging data, however, that pCR may not be the optimal endpoint for predicting long-term benefit for all classes of drugs (e.g., endocrine therapy) and molecular subtypes of breast cancer. Therefore, additional endpoints

(e.g., evaluation of Ki-67 in residual disease) must be studied prospectively to determine how best to study new drugs in the neoadjuvant setting.

ACKNOWLEDGMENT

The authors acknowledge the support provided in part by 1R01CA133049-01 (MPG), the Mayo Comprehensive Cancer Center Grant (CA15083; MPG), the Mayo Clinic Breast Cancer SPORE (CA 116201; MPG), and the Paul Calabresi Program in Clinical-Translational Research at the Mayo Clinic (CA 090628;TCH).

This educational review series, “Neoadjuvant Therapy in Breast Cancer” is supported by an educational grant from Genentech, Inc. The Society of Surgical Oncology offers CME/MOC for this educational review series. Visit moc.surgonc.org for additional information.

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