Neoadjuvant Therapy for Breast Cancer

Dimitrios Zardavas[1,2] and Martine Piccart[1,2]

[1]Breast International Group Headquarters (BIG-aisbl), Brussels 1000, Belgium; email: martine.piccart@bordet.be, dimitrios.zardavas@bigagainstbc.org

[2]Institut Jules Bordet, Université Libre de Bruxelles, Brussels 1000, Belgium

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Abstract

Neoadjuvant treatment of breast cancer refers to the use of different treatment modalities prior to surgical excision of the tumor. It has been accepted as a treatment option for patients with nonmetastatic disease, because it renders inoperable tumors operable and increases the rates of breast-conserving surgery, while achieving similar long-term clinical outcomes as adjuvant treatment. The neoadjuvant setting is being increasingly perceived as a research platform, where the biologic effects of traditional anticancer agents can be delineated, prognostic and predictive biomarkers can be identified, and the development of targeted agents can be expedited. Surrogate endpoints that can predict long-term clinical outcome and are evaluable early on, such as the pathologic complete response, offer valuable opportunities for rapid assessment of anticancer agents. Additionally, efforts for molecular profiling of the post-neoadjuvant residual disease hold the potential to lead to personalized therapy for breast cancer patients with early-stage high-risk disease.

INTRODUCTION

NAT: neoadjuvant therapy

BC: breast cancer

NCT: neoadjuvant chemotherapy

NHT: neoadjuvant hormonotherapy

HER2: human epidermal growth factor receptor 2

BCS: breast-conserving surgery

pCR: pathologic complete response

NSABP: National Surgical Adjuvant Breast and Bowel Project

DFS: disease-free survival

OS: overall survival

RFS: recurrence-free survival

FEC: fluorouracil, epirubicin, and cyclophosphamide

HR: hazard ratio

PFS: progression-free survival

RR: risk ratio

Neoadjuvant therapy (NAT) for cancer is defined as any anticancer treatment provided before the main treatment (the main treatment usually being surgery), thus constituting an induction therapy (1). In the setting of primary breast cancer (BC), types of NAT commonly applied are (*a*) neoadjuvant chemotherapy (NCT), (*b*) neoadjuvant hormonotherapy (NHT), and (*c*) neoadjuvant human epidermal growth factor receptor 2 (HER2) blockade. Several molecularly targeted agents are undergoing clinical assessment in the neoadjuvant setting of BC. The first recognized benefit of NAT was its ability to render inoperable tumors operable or to downstage locally advanced BC, thus increasing the rates of breast-conserving surgery (BCS) in women who would otherwise need mastectomy (2–4). Another advantage of NAT is that it enables the in vivo assessment of antitumor activity of both standard therapies and investigational agents, thus promising to boost the personalization of cancer treatment and accelerate the successful clinical development of targeted compounds (5).

The suggestion that pathologic complete response (pCR), as well as other biomarkers, can act as surrogate endpoints predicting long-term clinical outcome of BC patients undergoing NAT has been rigorously investigated, as we discuss below. In particular, the availability of cancer tissue at baseline, on treatment, and post treatment enables valuable research to elucidate mechanisms by which cancer cells adapt to the selective pressure of NAT, thus delineating mechanisms of resistance and/or sensitivity to the agents used. Another advantage of the NAT is its ability, when administered systemically, to attack micro-metastatic disease. In the present review, we provide a thorough overview of NAT in BC as it has evolved to the present day (**Figure 1**), highlighting the opportunities for successful clinical development of new targeted agents.

NEOADJUVANT CHEMOTHERAPY

Anthracycline-based NCT has been compared to the same regimens administered in the adjuvant setting in randomized clinical trials. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 study randomized 1,523 women to receive four cycles of doxorubicin/cyclophosphamide (AC) chemotherapy either pre- ($n = 747$) or postoperatively ($n = 759$). NCT resulted in 12% more lumpectomies performed in the neoadjuvant arm as compared to the adjuvant one (6). Additionally, there was no difference between the neoadjuvant and adjuvant arms in terms of disease-free survival (DFS), distant DFS, and overall survival (OS) ($p = 0.99$, 0.73, and 0.83 respectively) (7). There was a numerically higher rate of ipsilateral breast tumor recurrence in the neoadjuvant arm (7.9% versus 5.8%, $p = 0.23$), albeit not significant, whereas pCR was associated with improved clinical outcome [recurrence-free survival (RFS) 85.7%, $p < 0.0001$].

Similar findings were generated by the European Organization for Research and Treatment of Cancer (EORTC) trial 10902. In the EORTC trial, 698 patients with BC were randomized to receive four cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy administered either pre- ($n = 350$) or postoperatively ($n = 348$) (8). With a median follow-up of four years, no difference was observed between the two arms in terms of OS [hazard ratio (HR) 1.16; 95% CI 0.83–1.63, $p = 0.38$], progression-free survival (PFS) (HR 1.15; 95% CI 0.89–1.48, $p = 0.27$) and time to locoregional recurrence (HR 1.13; 95% CI 0.70–1.81, $p = 0.61$).

The equivalence of NCT to adjuvant chemotherapy was corroborated by a meta-analysis of nine randomized trials pooling 3,946 patients, although no taxane-based regimens were assessed among these studies (9). No significant difference was observed between neoadjuvant and adjuvant treatment in terms of death [risk ratio (RR) 1.00; 95% CI 0.90–1.12], disease progression (RR 0.99; 95% CI 0.91–1.07), and distant disease recurrence (RR 0.94; 95% CI 0.83–1.06). However, NCT

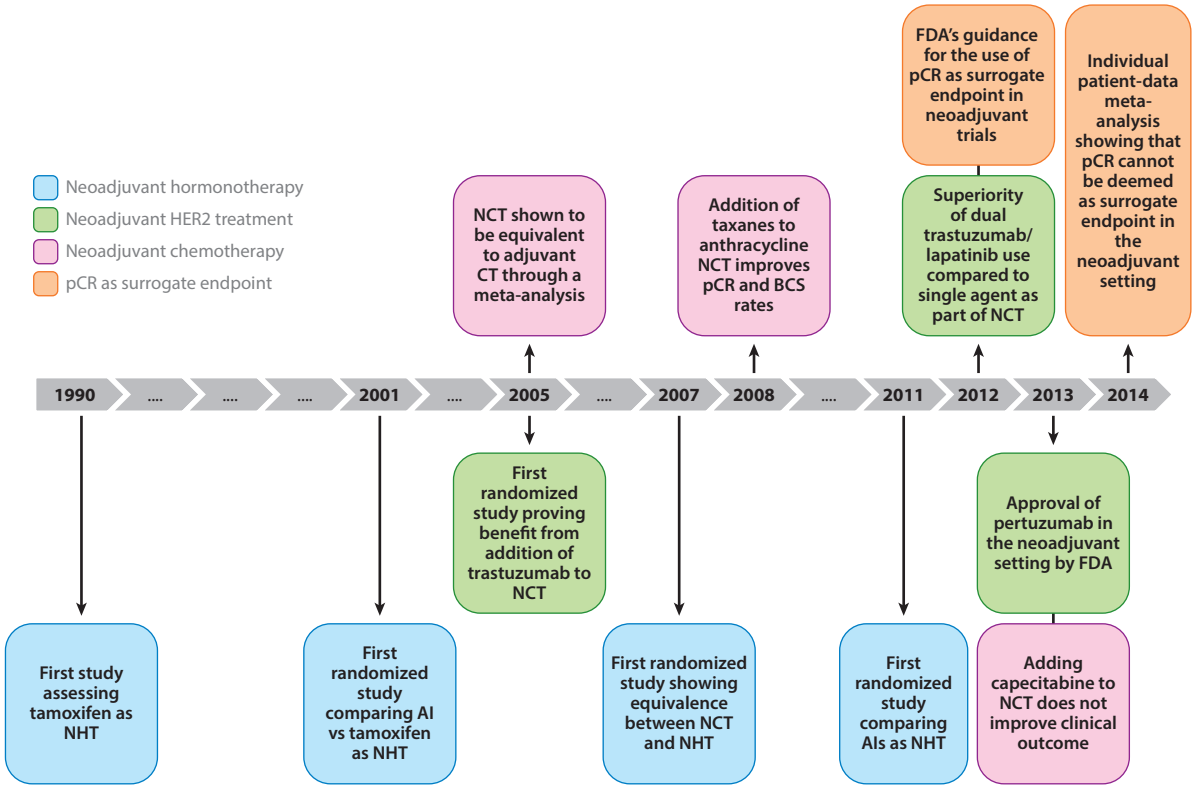

Figure 1

Milestones in the development of neoadjuvant treatment of breast cancer. Abbreviations: AI, aromatase inhibitor; BCS, breast-conserving surgery; CT, chemotherapy; FDA, US Food and Drug Administration; NCT, neoadjuvant chemotherapy; NHT, neoadjuvant hormonotherapy; pCR, pathologic complete response.

was associated with increased risk of locoregional disease recurrence as compared to adjuvant chemotherapy (RR 1.22; 95% CI 1.04–1.43), a finding that could be explained by the use of radiotherapy with no surgical tumor excision in women achieving complete clinical response to NCT in some of the trials (9).

Another important step in the development of NCT was the assessment of benefit derived from adding taxanes to anthracycline-based regimens in this setting. The NSABP B-27 trial randomized 2,411 patients to three treatment arms. Arm 1 received four preoperative cycles of doxorubicin/cyclophosphamide (AC) followed by surgery (n = 784); arm 2 received AC followed by four cycles of docetaxel and then surgery (n = 783); and arm 3 received AC followed by surgery with docetaxel administered in the adjuvant setting (n = 777) (10). There was no difference between the three arms in terms of DFS (arm 2 versus arm 1: HR 0.92; 95% CI 0.78–1.08, p = 0.29; arm 3 versus arm 1: HR 0.92; 95% CI 0.78–1.08, p = 0.29) and OS (p = 0.76). However, the addition of docetaxel in the neoadjuvant setting in arm 2 was associated with a higher clinical (91% versus 86%, $p < 0.001$) and pCR rate (26% versus 13%, $p < 0.001$) in comparison to the other two arms. Conversely, the Aberdeen trial, which randomized 162 patients with large or locally advanced BC to receive four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CVAP) NCT, followed by either four additional cycles of CVAP or four cycles

of docetaxel treatment, showed that the taxane-containing NCT improved clinical outcome of patients (11). The docetaxel-containing arm was associated with higher clinical response rate (66% versus 94%, p = 0.001) and higher pCR rate (15% versus 31%, p = 0.06), as well as with improved clinical outcome (five-year DFS 72% versus 90%, p = 0.04; and five-year OS 78% versus 93%, p = 0.04). This trial was included in a literature-based meta-analysis that pooled seven randomized trials (n = 2,455) assessing the addition of taxanes to anthracycline-based NCT for primary BC (12). Taxane-containing NCT regimens were correlated with increased rate of BCS (RR 1.11; 95% CI 1.02–1.21, p = 0.012) and numerically improved pCR rates, although the improvement was not statistically significant (RR 1.22; 95% CI 0.95–1.55, p = 0.11). However, among 2,375 evaluable cases, no difference was noted with regard to DFS (RR 0.91; 95% CI 0.80–1.02, p = 0.12), and no OS analysis was performed due to scarcity of available information (12).

OR rate: objective response rate

AI: aromatase inhibitor

ER: estrogen receptor

Efforts to incorporate other chemotherapeutic agents in anthracycline/taxane-based NCT have not met success till now. In particular, randomized clinical trials comparing NCT with or without capecitabine for BC have been conducted (13–17). A meta-analysis of five randomized trials involving 3,257 patients with non-metastatic BC showed no benefit with the addition of capecitabine in terms of pCR in breast (RR 1.10, 95% CI 0.87–1.40, p = 0.43), pCR in breast tumor and nodes (RR 0.99, 95% CI0.83–1.18, p = 0.90), objective response (OR) rate (RR 1.00, 95% CI 0.94–1.07, p = 0.93), or BCS (RR 0.98, 95% CI 0.93–1.04, p = 0.49) (18).

Similar results have been reported for the addition of gemcitabine to NCT for BC. Neo-tAnGo was an open-label, 2 × 2 factorial phase 3 trial that randomized 831 women with high-risk early BC to receive one of four treatment regimens: (*a*) epirubicin and cyclophosphamide, then paclitaxel (n = 207); (*b*) paclitaxel, then epirubicin and cyclophosphamide (n = 208); (*c*) epirubicin and cyclophosphamide, then paclitaxel and gemcitabine (n = 208); or (*d*) paclitaxel and gemcitabine, then epirubicin and cyclophosphamide (n = 208) (19). The study failed to show any increase in pCR with the addition of gemcitabine to anthracycline/taxane-based NCT: 70 (17%, 95% CI 14–21) of 404 patients in the epirubicin and cyclophosphamide then paclitaxel group achieved pCR compared with 71 (17%, 95% CI 14–21) of 408 patients who received additional gemcitabine (p = 0.98). The aforementioned results indicate that anthracycline/taxane-based NCT should be perceived as the standard of care in the neoadjuvant setting of BC.

NEOADJUVANT HORMONOTHERAPY

NHT with an aromatase inhibitor (AI) is increasingly used to treat postmenopausal women with estrogen receptor (ER)–positive, HER2-negative primary BC. Historically, the first evidence supporting the use of NHT was generated through studies and/or retrospective analyses conducted among cohorts of elderly women with locoregional BC receiving tamoxifen as primary treatment (20–24). These studies showed that primary tamoxifen treatment could not substitute for surgical removal of the tumor, but promising clinical response rates were reported, with some cases of complete responses (33.6%) that were associated with high five-year OS rates (92%) (22).

Subsequent randomized clinical trials compared tamoxifen versus AIs as NHT for primary BC (25–28). Eiermann et al. (25) randomized 337 postmenopausal women with ER- and/or progesterone receptor (PgR)–positive newly diagnosed BC to receive either letrozole or tamoxifen for four months. The study met its primary endpoint, with letrozole resulting in a significant increase in the OR rate (55% versus 36%, p < 0.001 for letrozole and tamoxifen respectively), as well as its secondary endpoints: ultrasound response (35% versus 25%, p = 0.042), mammographic response (34% versus 16%, p < 0.001), and BCS rate (45% versus 35%, p = 0.022).

The Immediate Preoperative Anastrozole, Tamoxifen, or Combined With Tamoxifen (IMPACT) trial randomized postmenopausal women with ER-positive operable or locally

advanced potentially operable BC to receive tamoxifen (n = 108), anastrozole (n = 113), or a combination of tamoxifen and anastrozole (n = 109) for three months (26). Patients in the three treatment arms achieved a clinical OR at a rate of 37%, 36%, and 39%, respectively, and an ultrasound response at a rate of 24%, 20%, and 28%, respectively (no significant difference). The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial randomized patients with operable or potentially operable hormone receptor–positive BC to receive anastrozole (n = 228) or tamoxifen (n = 223) with or without chemotherapy for 12 weeks before primary surgery (27). Similarly to IMPACT, the PROACT study showed a numerically higher, albeit not statistically significantly higher, rate of clinical OR (50% versus 46.2%) and ultrasound response (39.5% versus 35.4%) for anastrozole and tamoxifen, respectively.

ACOSOG: American College of Surgeons Oncology Group

STAGE is the only randomized study that compared AIs to tamoxifen as NHT among premenopausal women with BC (28). In this phase III study, 197 women with ER-positive, HER2-negative operable BC were randomly assigned to anastrozole (n = 98) or tamoxifen (n = 99), both combined with goserelin to achieve ovarian ablation for 24 weeks prior to surgery. Treatment with anastrozole resulted in a statistically significant increase in the rate of both clinical OR (70.4% versus 50.5%) and ultrasound- (58.2% versus 42.4%) and MRI- or CT-assessed responses (64.3% versus 37.4%).

A meta-analysis conducted among the aforementioned studies showed that AIs are superior to tamoxifen when used as NHT, since they were associated with improved clinical OR rates (RR 1.29; 95% CI 1.14–1.47, $p < 0.001$), ultrasound response rates (RR 1.29; 95% CI 1.10–1.51, $p = 0.002$), and BCS rate (RR 1.36; 95% CI 1.16–1.59, $p < 0.001$) (29).

The American College of Surgeons Oncology Group (ACOSOG) Z1031 trial explored potential differences in terms of antitumor activity between different AIs when given as NHT for hormone receptor–positive BC (30). This phase II trial randomized 377 postmenopausal women with ER-positive stage II–III BC to receive neoadjuvant exemestane (n = 124), letrozole (n = 127), or anastrozole (n = 123) for four months. Treatment with letrozole resulted in numerically higher, albeit not statistically significantly higher, clinical OR rate (74.8%), as compared with exemestane (62.9%) and anastrozole (69.1%).

NEOADJUVANT HER2 BLOCKADE TREATMENT

ERBB2 gene amplification and/or protein overexpression are observed in ~20% of BC cases and are associated with an aggressive clinical course of the disease (31). Trastuzumab is a monoclonal antibody (mAb) targeting HER2, with established activity in both the metastatic and adjuvant settings for patients with HER2-positive BC (32–35). In the neoadjuvant setting, initially a large number of single-arm phase II trials were conducted assessing trastuzumab in conjunction with different chemotherapy backbones (36–42). The main conclusion from these trials was that trastuzumab plus NCT showed promising antitumor activity, with reported pCR rates ranging between 12% and 76%, thus meriting further investigation within randomized studies (43).

Buzdar et al. (44) conducted the first randomized trial of NCT with or without trastuzumab, where patients with HER2-positive operable BC were randomized to receive four cycles of paclitaxel followed by four cycles of FEC NCT with or without simultaneous administration of trastuzumab for 24 weeks. The addition of trastuzumab led to a significant increase in the reported pCR rate (pCR 26% versus 65.2%, $p = 0.016$), thus leading to premature closure of the trial (n = 42). Of note, no case of clinical congestive heart failure was observed, despite the concurrent administration of trastuzumab with anthracyclines.

The NOAH (NeOAdjuvant Herceptin) study randomized 235 women with HER2-positive locally advanced or inflammatory BC to receive doxorubicin/paclitaxel/cyclophosphamide,

methotrexate and fluorouracil (CMF) chemotherapy with or without simultaneous administration of trastuzumab for 30 weeks (45). The study met its primary endpoint, with the addition of trastuzumab to NCT leading to a significant increase in three-year event-free survival (three-year EFS 71% with trastuzumab versus 56% without; HR 0.59, 95% CI 0.38–0.90, p = 0.013), as well as its secondary endpoint of pCR rate (total pCR 38% versus 19%, p = 0.001; pCR in breast 43% versus 22%, p = 0.0007). In terms of cardiac safety, two cases of symptomatic cardiac failure were reported, despite concurrent trastuzumab/anthracycline administration.

EFS: event-free survival

A French study randomly assigned 120 patients with stage II and III HER2-positive BC, ineligible for BCS, to receive four cycles of epirubicin/cyclophosphamide, followed by four cycles of docetaxel with or without trastuzumab concurrently with the docetaxel NCT, resulting in increased pCR rates (pCR 26% with trastuzumab versus 19% without) (46). Finally, ABCSG-24, a study by the Austrian Breast and Colorectal Cancer Study Group, randomized 93 patients with HER2-positive BC to receive six cycles of epirubicin-docetaxel or epirubicin-docetaxel-capecitabine NCT with or without trastuzumab, and the addition of trastuzumab led to an increase, albeit not statistically significant, of the pCR rate (pCR 38.6% versus 26.5%, p = 0.212) (47).

The issue of potential benefit conferred by concurrent administration of trastuzumab and anthracyclines in the neoadjuvant setting was recently addressed by the ACOSOG Z1041 study (48). This was a phase 3 trial that randomized 282 women with operable HER2-positive BC to receive four cycles of FEC followed by 12 weeks of paclitaxel/trastuzumab treatment (sequential arm) or 12 weeks of paclitaxel followed by four cycles of FEC combined with trastuzumab for the whole duration (concurrent arm). In the sequential arm, the pCR rate in the breast reached 56.5% (95% CI 47.8–64.9), whereas in the concurrent arm it was 54.2% (95% CI 45.7–62.6). In terms of toxicity, higher rates of neutropenia (31.7% versus 25.3%) and fatigue (4.3% versus 8.5%) and lower rates of left ventricular ejection fraction drop by week 24 (7.1% versus 4.6%) were noted in the concurrent as compared to the sequential arm.

NEOADJUVANT DUAL HER2 BLOCKADE

Despite the significant antitumor activity of trastuzumab combined with cytotoxic chemotherapy in cases of HER2-positive BC, resistance remains an issue, so further therapeutic options are needed. One promising approach is the dual HER2 blockade, where different HER2 targeting agents with complementary mechanisms of action are combined (49). Trastuzumab constitutes the backbone of dual HER2 blockade strategies, with an abundance of preclinical evidence showing more potent HER2 inhibition when trastuzumab is combined with either lapatinib, a small-molecule reversible epidermal growth factor receptor (EGFR)/HER2 tyrosine kinase inhibitor (TKI) (50, 51), or pertuzumab, a humanized anti-HER2 mAb blocking the dimerization of HER2 with other HER family receptors (52). In the metastatic setting of HER2-positive BC, the trastuzumab plus lapatinib and trastuzumab plus pertuzumab dual HER2 blockade regimens have demonstrated significant antitumor activity (53, 54). These dual anti-HER2 regimens have also been assessed in the neoadjuvant setting of HER2-positive BC (**Figure 2**). The clinical trials Neo-ALTTO, CHER-LOB, TBCRC006, and NSABP-B41 have assessed trastuzumab plus lapatinib (55–58), while NeoSphere and TRYPHAENA have studied trastuzumab plus pertuzumab (59, 60). Important findings from these trials can be summarized as follows:

1. Dual HER2 blockade results in higher rates of pCR.
2. Dual HER2 blockade can be safely combined with cytotoxic chemotherapy. The TRYPHAENA and CHER-LOB studies provided evidence for safe coadministration of trastuzumab plus pertuzumab with anthracycline-based chemotherapy.

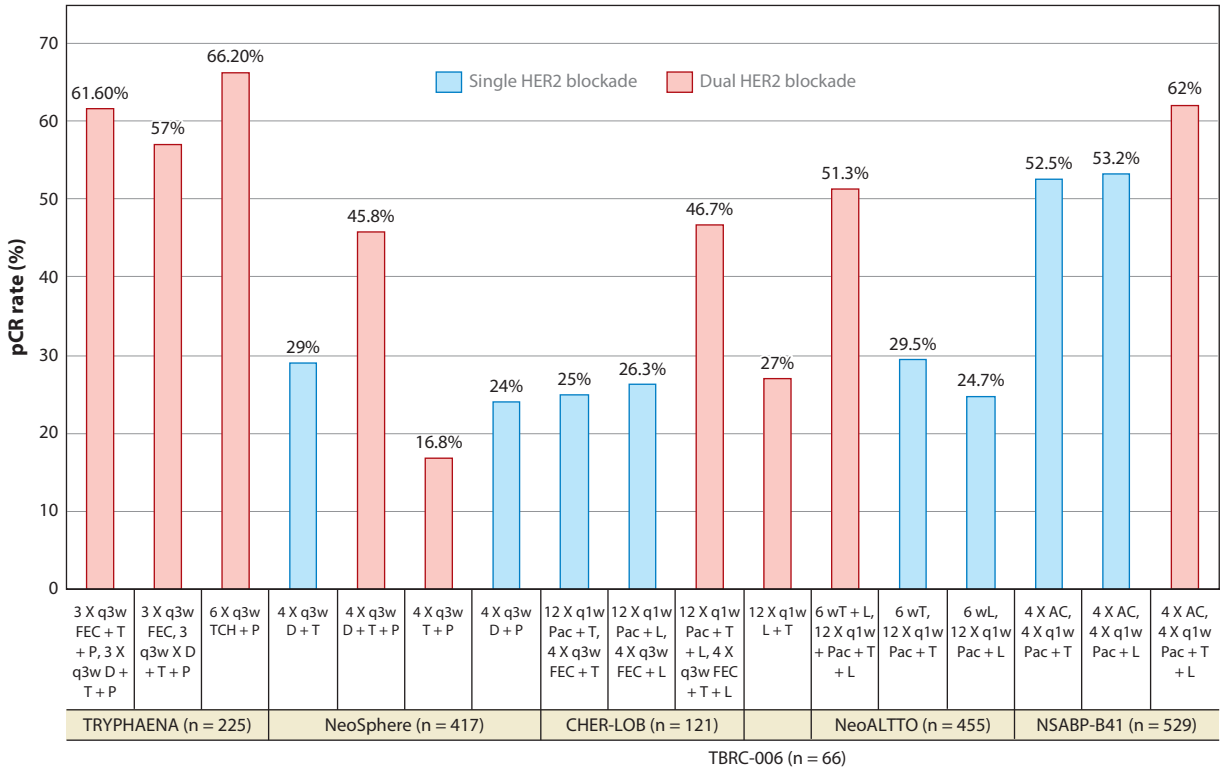

Figure 2

Studies of neoadjuvant dual HER2 blockade and pCR rates. Abbreviations: AC, doxorubicin and cyclophosphamide; D, docetaxel; FEC, fluorouracil, epirubicin, and cyclophosphamide; L, lapatinib; Pac, paclitaxel; pCR, pathologic complete response; P, pertuzumab; T, trastuzumab; TCH, carboplatin, docetaxel, and trastuzumab.

3. Higher pCR rates with dual HER2 blockade can be achieved in the subset of HER2-positive BC patients who are hormone receptor negative.
4. A subset of HER2-positive BC patients achieve pCR with dual HER2 blockade without the addition of cytotoxic chemotherapy. This indicates that a subpopulation of patients could be spared chemotherapy-induced side effects.
5. Longer courses of dual HER2 blockade result potentially in higher pCR rates, a finding that reflects the biologic importance of the HER2 signaling axis in this BC subtype.
6. Trastuzumab, pertuzumab, and lapatinib appear to be equally effective in the neoadjuvant setting when combined with cytotoxic chemotherapy as single HER2-blocking agents. However, none of these trials was designed to address this specific issue.

OTHER MOLECULARLY TARGETED AGENTS IN THE NEOADJUVANT SETTING

Bevacizumab is a mAb targeting vascular endothelial growth factor A (VEGF-A), a major proangiogenic factor. This agent has been assessed in metastatic BC, resulting in prolongation of PFS and RR but not OS (61–63). Preclinical evidence suggests that fewer angiogenic inducers and pathways are activated in early-stage disease than in advanced stages, providing the biologic

rationale for assessing bevacizumab in early-stage BC (64). Bevacizumab has been assessed in a number of phase II neoadjuvant trials, in combination with several cytotoxic chemotherapeutic regimens as well as with trastuzumab and endocrine therapy (65–69). Potent antitumor activity was noted, as well as manageable toxicities, so clinical development advanced further.

PI3K/AKT/mTOR: PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin

Recently, two large randomized phase III trials were reported, assessing bevacizumab in the neoadjuvant setting for HER2-negative BC. Bear et al. (70) randomly assigned 1,206 BC patients to receive neoadjuvant treatment consisting of docetaxel, docetaxel plus capecitabine, or docetaxel plus gemcitabine for four cycles, followed by four cycles of doxorubicin plus cyclophosphamide. Patients were randomly assigned to receive or not bevacizumab for the first six cycles of chemotherapy. The addition of bevacizumab significantly increased the pCR rates (28.2% versus 34.5%, $p = 0.02$), with a more pronounced beneficial effect on pCR in the hormone receptor–positive subgroup of patients (15.1% versus 23.2%, $p = 0.007$) as compared to the hormone receptor–negative subgroup (47.1% versus 51.5%, $p = 0.34$). Regarding toxicity, the addition of bevacizumab resulted in increased rates of hypertension, left ventricular systolic dysfunction, hand-foot syndrome, and mucositis. Von Minckwitz et al. (71) randomly assigned 1,948 patients with HER2-negative BC to receive neoadjuvant epirubicin and cyclophosphamide followed by docetaxel, with or without concomitant bevacizumab. The addition of bevacizumab resulted in a significant increase in the rates of pCR (odds ratio with addition of bevacizumab, 1.29; 95% CI 1.02–1.65, $p = 0.04$). Contrary to the results of the previous study, the beneficial effects of bevacizumab on pCR were seen in the hormone receptor–negative subgroup (27.9% versus 39.3%, $p = 0.003$), whereas there was no benefit observed in the hormone receptor–positive patients (7.8% versus 7.7%, $p = 1.00$). Regarding the toxicity profile, the addition of bevacizumab resulted in a higher incidence of grade 3 or 4 adverse events (febrile neutropenia, mucositis, hand-foot syndrome, infection, and hypertension), with no impact on surgical complications. Bevacizumab is currently undergoing rigorous clinical investigation in a plethora of clinical trials in the neoadjuvant setting, enrolling BC patients of all subtypes (**Table 1**).

The PI3K/AKT/mTOR signaling pathway represents a key signal transduction system, commonly deregulated in the setting of BC, and several blocking agents are under clinical development (72). There is substantial evidence associating PI3K pathway activation with mediation of resistance to both endocrine therapy and HER2 blockade in BC (73, 74). The most advanced class of PI3K blocking agents is that of rapalogs, with everolimus having received US Food and Drug Administration (FDA) approval in the setting of hormone-refractory metastatic BC (38). Preliminary results of antitumor activity in the neoadjuvant setting were generated by the RAD2222 clinical trial, which randomized 270 postmenopausal women with hormone receptor–positive BC to receive four months of neoadjuvant letrozole combined with everolimus or placebo (75). The everolimus-containing arm resulted in a significantly higher overall response rate by clinical palpation (68.1% versus 59.1%, $p = 0.062$), and in significantly increased antiproliferative response as assessed by Ki67 reduction to natural logarithm <1 at day 15 (57% versus 30%, $p < 0.01$). Currently, there are ongoing neoadjuvant clinical trials in all three major subtypes of BC (luminal, triple negative, and HER2 positive) (**Table 2**).

SURROGATE ENDPOINTS IN THE NEOADJUVANT SETTING

The neoadjuvant setting provides an opportunity for rapid assessment of efficacy of anticancer drugs, with some short-term endpoints correlating with long-term clinical outcome of women receiving neoadjuvant treatment for BC. The FDA released a draft guidance in May 2012 that contained nonbinding recommendations regarding accelerated approval of new agents for patients with high-risk BC, on the basis of a surrogate endpoint that can predict long-term clinical

Table 1 Ongoing clinical trials assessing bevacizumab in the neoadjuvant setting

Trial (NCT identifier)	Phase	Subtype (n)	Treatment	Primary endpoint	Secondary endpoints
NCT00861705	II	HR+, HER2− BC (445)	Carboplatin +/− bevacizumab followed by AC	pCR	CRR, OR, RFS, RRR, TTFF, toxicity, postoperative complications
NCT00957125 (PROMIX)	II	HR+/−, HER2− (150)	Bevacizumab in combination with ET	OR characterized by radiological and functional imaging and biological tumor markers	DFS, safety
NCT01652560 (BIBC)	II	HR+/−, HER2− BC (50)	Bevacizumab plus NCT	ORR	OR
NCT01142778	II	HR+/−, HER2+ BC (156)	Trastuzumab in combination with docetaxel +/− bevacizumab	pCR	URR, rate of CS, DFS, OS, safety
NCT00723125	II	HR+/−, HER2− BC (60)	Bevacizumab in combination with carboplatin and Nab-paclitaxel	pCR	Safety, tolerability
NCT01321775	II	HR+/−, HER2+ (44)	Bevacizumab in combination with trastuzumab and paclitacel followed by postoperative CT	pCR	Tumor markers as potential predictive biomarkers
NCT01690325 (GALADON)	II	HR+/−, HER2+/− (94)	Bevacizumab in combination with docetaxel (plus trastuzumab for HER2+ BC)	pCR	NR
NCT00580333	II	TNBC (40)	Bevacizumab in combination with cisplatin	pCR	CRR, feasibility, toxicity, predictive biomarkers
NCT00408408	III	HR+/−, HER2− (1206)	6 Different NCT regimens +/− bevacizumab	pCR	cOR, cCR, cardiac events, surgical complications, toxicities, DFS

Abbreviations: AC, doxorubicin/cyclophosphamide; BC, breast cancer; cCR, clinical complete response; cORR, clinical objective response rate; CRR, clinical response rate; CS, conservative surgery; CT, chemotherapy; DFS, disease-free survival; ET, epirubicin/docetaxel; HER2, human epidermal receptor 2; HR, hormone receptor; NCT, neoadjuvant chemotherapy; NR, not reported; OR, objective response; OS, overall survival; pCR, pathologic complete response; RFS, recurrence-free survival; TNBC, triple-negative breast cancer; TTFF, time to first failure; URR, ultrasound response rate.

outcome (76). pCR was suggested to be such a surrogate endpoint, but the guidance emphasized that confirmatory trials should demonstrate a clinically meaningful and statistically significant improvement in either DFS or OS. This guidance was a result of accumulating evidence from numerous clinical trials that demonstrated a close association between pCR after NCT and favorable clinical outcome for patients with early-stage BC.

Nevertheless, some studies have failed to show that pCR predicts long-term clinical outcome. This discrepancy can be explained by methodologic limitations conferred by different definitions

Table 2 Ongoing neoadjuvant clinical trials with PI3K-blocking agents

Trial (NCT identifier)	Phase	Subtype (n)	Treatment	Primary endpoint	Secondary endpoints
NCT00930930	II	TNBC (145)	Cisplatin in combination with paclitaxel +/− everolimus	pCR	Rate of BCS, uCTR, toxicity, TR
NCT01816594 (NeoPHOEBE)	II	HR+/−, HER2+ BC (220)	Trastuzumab in combination with paclitaxel +/− BKM120	pCR	OCRR, rate of BCS, rate of patients with ypN0, safety
NCT01776008	II	*PIK3CA* mut, HR+, HER2− (87)	MK-2206 in combination with anastrozole +/− goserelin	pCR	CRR, RRR, toxicity
NCT01319539	II	HR+/−, HER2+/− BC (30)	MK-2206	Change in pAKT (Ser473) levels	PI3K/AKT expression, toxicity, BR to treatment

Abbreviations: BC, breast cancer; BCS, breast-conserving surgery; BR, biological response; CRR, clinical response rate; HER2, human epidermal receptor 2; HR, hormone receptor; OCRR, objective clinical response rate; pAKT, phosphorylated AKT; pCR, complete pathologic response; RRR, radiological response rate; TNBC, triple-negative breast cancer; TR, translational research; uCTR, clinical tumor response assessed by ultrasound; ypN0, node-negative disease at surgery.

of pCR used by different studies. To address this issue, the German Breast Group (GBG) and Arbeitgemeinschaft Gynaekologische Onkologie–Breast Group (AGO-B) conducted an individual patient-data meta-analysis among 6,377 patients with primary BC receiving NCT who participated in seven randomized clinical trials (77). Different definitions of pCR were compared, showing that patients achieving ypT0 ypN0 (no invasive and no in situ residuals in breast or nodes, $n = 955$) had improved DFS compared to patients with ypT0/is ypN0 [residual ductal carcinoma in situ (DCIS only), $n = 309$], ypT0/is ypN0/+ (no invasive residuals in breast but involved nodes, $n = 186$), ypT $\leq$ 1 mic ypN0/+ (only focal-invasive disease in the breast, $n = 478$) and no pCR ($n = 4{,}449$; $p < 0.001$). Using the clinicopathologic criteria recently recommended by the St Gallen panelists, the GBG/AGO-B study also examined the issue of the different predictive ability of pCR, defined as ypT0 ypN0, for clinical outcome among the different BC subtypes. pCR was associated with improved DFS among patients with luminal B/HER2-negative BC ($p = 0.005$), HER2-positive/nonluminal BC ($p < 0.001$), and triple-negative BC ($p < 0.001$), but not among patients with luminal A ($p = 0.39$) or luminal B/HER2-positive BC ($p = 0.45$). A retrospective single-institute analysis involving 2,302 patients treated with NCT compared the survival rates of those achieving pCR to those with pCR and residual DCIS (78). This analysis reported no negative impact of residual DCIS for patients experiencing complete eradication of the invasive component of BC in the breast and lymph nodes in terms of five-year DFS rates (87.1% in both groups), ten-year DFS rates (81.3% pCR versus 81.7% pCR+DCIS), five-year OS rates (91.9% versus 92.5%), ten-year OS rates (91.8% versus 92.5%), and five-year locoregional RFS rates (92.8% versus 90.9%).

Further insight into the predictive nature of pCR was gained by an international working group led by the FDA, known as Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). An individual patient data meta-analysis was performed among 11,955 patients involved in 12 randomized trials of neoadjuvant treatment of BC, with a median follow-up exceeding five years (79). pCR defined as either ypT0 ypN0 or ypT0/is ypN0 was more strongly associated with improved EFS and OS. In regard to EFS the following results were reported: HR 0.44, 95% CI

0.39–0.51 for ypT0 ypN0; and HR 0.48, 95% CI 0.43–0.54 for ypT0/is ypN0. In regard to OS the following results were reported: HR 0.36, 95% CI 0.30–0.44 for ypT0 ypN0; and HR 0.36, 95% CI 0.31–0.42 for ypT0/is ypN0) than ypT0/isypN0/+ (EFS HR 0.60, 95% CI 0.55–0.66; and OS HR 0.51, 95% CI 0.45–0.58). This study confirmed the association of pCR, defined as ypT0/is ypN0, with favorable clinical outcome among patients with aggressive types of BC, namely those with triple-negative BC (EFS HR 0.24, 95% CI 0.18–0.33; and OS HR 0.16, 95% CI 0.11–0.25) and those with HER2-positive, hormone receptor–negative BC who received trastuzumab (EFS HR 0.15, 95% CI 0.09–0.27; and OS HR 0.08, 95% CI 0.03–0.22). An important finding of this meta-analysis was the small association between increases in frequency of pCR and EFS (R^2 = 0.03, 95% CI 0.00–0.25) and OS (R^2 = 0.24, 95% CI 0.00–0.70), so that pCR could not be validated as a surrogate endpoint for improved EFS and OS (79).

In the setting of NHT, on-treatment levels of Ki67 have been identified as a potential prognostic biomarker. This has been exemplified by the association between high Ki67 expression levels after two weeks of NHT and worse relapse-free survival ($p = 0.004$) among women with hormone receptor–positive BC (80). In the previously mentioned RAD2222 study, higher reduction of Ki67 expression levels at day 15 was noted among women receiving letrozole plus everolimus than among those receiving letrozole plus placebo, with the former arm showing improved clinical response rates (75). The P24 trial randomized 337 postmenopausal women with hormone receptor–positive BC to receive letrozole or tamoxifen for four months in the neoadjuvant setting (25). Post-therapy pathology factors, including Ki67 levels, pathologic tumor size, nodal status, and ER status assessed by Allred score, were incorporated into a prognostic score called PEPI (Preoperative Endocrine Prognostic Index) (81). Low PEPI scores were associated with favorable clinical outcome in the P24 patients and within an independent cohort of patients treated in the IMPACT study (26). In particular, no recurrences were seen for patients with T1, N0 tumors and with a PEPI score of 0 (post-treatment tumor with Ki67 $\leq$ 2.7%, with maintained ER positivity). In the ACOSOG Z1031 trial, luminal A BC cases were found to have favorable PEPI scores more often than their luminal B counterparts (27.1% versus 10.7%; $p = 0.004$) (30). A prospective validation of the ability of PEPI score to predict favorable outcome for postmenopausal women receiving NHT will be attempted through the ALTERNATE (ACOSOG Z1103) trial, which will randomize more than 2,800 postmenopausal women with hormone receptor–positive BC to receive anastrozole, fulvestrant, or their combination as NHT (**http://www.clinicaltrials.gov/ct2/show/NCT01953588**).

NEOADJUVANT TRIALS AS A CLINICAL RESEARCH TOOL

Neoadjuvant trials in the setting of BC have been increasingly recognized as a promising platform for efficient clinical development of new anticancer agents (**Figure 3**) (82, 83). Taking into account a rapidly expanding arsenal of experimental targeted agents against BC, new trial designs are needed to expedite their successful clinical development (72). The in vivo assessment of investigational compounds coupled with the opportunity for serial tumor biopsies (pre-, mid-, and post-treatment) in the neoadjuvant setting render this platform a promising tool for the identification of putative predictive biomarkers (84). This has been recently exemplified by the identification of *GATA3* mutations in pre-treatment breast tumor tissue as predictors of sensitivity to NHT with AIs (85). Assessment of mid-treatment tumor tissue from patients receiving NHT has identified, as previously mentioned, high Ki67 levels as mediators of endocrine resistance (80). Decreased expression of DUSP4 (dual specificity protein phosphatase 4), a negative regulator of extracellular signal-regulated kinases (ERK), in post-treatment tumor tissue of triple-negative BC after NCT, has been recently identified as a mediator of resistance to NCT (86).

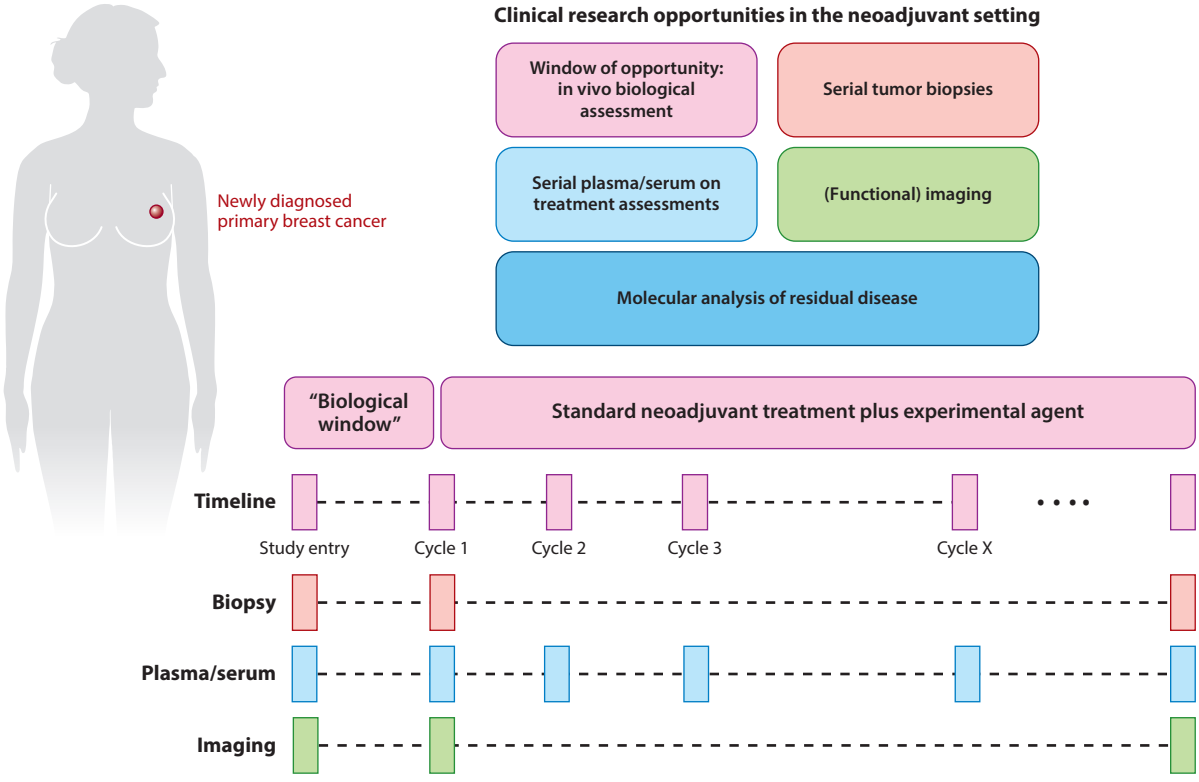

Figure 3

Neoadjuvant clinical trials as clinical research tool in breast cancer.

Another important research opportunity comes from post-neoadjuvant residual BC trials. Patients who undergo NCT and have residual disease upon its completion represent a high-risk population following standard treatment optionsand are suitable subjects for assessment of investigational therapeutic strategies. This approach will be assessed in the KATHERINE study (NCT01772472), which will enroll patients with HER2-positive residual BC after completion of NCT with trastuzumab and randomize them to receive either trastuzumab or a trastuzumab-mertansine conjugate (trastuzumab-DM1) in the adjuvant setting (**http://www.clinicaltrials.gov/ct2/show/NCT01772472**). Another study (NCT01074970) focusing on patients with residual triple-negative BC after completion of anthracycline- and/or taxane-based NCT will evaluate the efficacy of cisplatin with or without rucaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, with two-year DFS as the primary endpoint (**http://www.clinicaltrials.gov/ct2/show/NCT01074970**).

Window-of-opportunity trials represent an innovative study design, introduced recently in oncology, where patients receive an investigational compound for a window of time prior to administration of anticancer treatment. These studies can identify biologic effects of investigational compounds as assessed by either molecular analysis or functional imaging of the tumors. Such a randomized presurgical study assessed the biologic effects of metformin, administered for four weeks, on breast cancer proliferation (87). No statistically significant effect on Ki67 was shown; however, interesting differential effects according to metabolic characteristics of the patients were

documented. Another window study assessed the biologic effects of erlotinib, an anti-EGFR agent, administered for 6 to 14 days until the day before surgery among 41 patients with early-stage BC. Inhibition of tumor cell proliferation (Ki67) was observed in ER-positive, but not HER2-positive or triple-negative, BC patients, coupled with significant reduction of p-MAPK, p-AKT, p-S6, and S118 p-ERα. These observations suggest that EGFR inhibition could be assessed in conjunction with endocrine therapy in luminal BC (88).

The Neo-ALTTO clinical trial incorporated a biologic window in its design. Patients initially received trastuzumab, lapatinib, or their combination for a window of six weeks, before incorporation of standard NCT coupled with the HER2 blockade. Eighty-six patients had ^{18}F-FDG PET/CT (positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography) assessment at baseline and weeks 2 and 6 of anti-HER2 treatment (89). Interestingly, early metabolic responses were seen in the primary tumors already after two weeks of HER2 blockade. Overall, metabolic response was a predictor for pCR, since pCR rates were twice as high for ^{18}F-FDG PET/CT responders than nonresponders (week 2: 42% versus 21%, $p = 0.12$; week 6: 44% versus 19%, $p = 0.05$).

CONCLUSIONS

The neoadjuvant setting has been increasingly investigated and utilized as a therapeutic platform for patients with non-metastatic BC, in particular for inoperable tumors or cases where breast conservation is the treatment goal. Regarding NCT, high rates of pCR have been observed among patients with triple-negative BC and overall highly proliferative tumors. In the setting of HER2-positive BC, the addition of trastuzumab to NCT has led to increased rates of pCR, with dual HER2 blockade strategies under clinical assessment doubling these rates. In regard to hormone receptor–positive BC, NHT has been associated with high RRs, with neoadjuvant trials predicting the results of corresponding large adjuvant studies (90). It has already been suggested that due to its therapeutic potential as well as the associated research opportunities, neoadjuvant treatment could be recommended for all patients with early-stage BC (91). Different surrogate endpoints, such as pCR or mid-treatment Ki67 levels for NCT and NHT, respectively, can predict the long-term clinical outcome of patients with BC undergoing neoadjuvant treatment, thus promising to expedite the clinical development of new anticancer agents. Furthermore, it becomes increasingly apparent that the neoadjuvant platform offers unique research opportunities to delineate the biologic action of targeted compounds in vivo, identify predictive biomarkers of sensitivity and/or resistance, and finally identify patients at high risk of relapse, where investigational agents should be assessed. Taken together, these data indicate how the neoadjuvant setting changes BC management, offering a valuable platform to advance personalized cancer medicine.

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