Review

Are we HER-ting for innovation in neoadjuvant breast cancer trial design?

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Abstract

Through the use of surrogate markers of efficacy, neoadjuvant studies may facilitate the implementation of new treatments into clinical practice. However, disease-free survival is the current standard outcome endpoint for registration of a novel treatment. The coupling of smaller neoadjuvant 'proof of principle' studies with larger adjuvant registration trials offers the promise of speeding up the time to market of new therapies. Clever new designs, such as the 'biological window' and 'learn on the way', can provide valuable insight regarding mechanisms of action and resistance of these novel drugs by identifying patients who are most likely to respond to a novel therapy early in the drug development process. Using the ongoing neoadjuvant trials with HER2 (human epidermal growth factor receptor 2)-directed therapy as a paradigm, this article discusses recent innovations in study design and the challenges of conducting translational research in the neoadjuvant setting.

Introduction

Neoadjuvant chemotherapy is the standard of care for patients with locally advanced and inflammatory breast cancer (IBC) [1], with the goal of improving operability and eradicating micrometastatic disease. In primary operable breast cancer, neoadjuvant chemotherapy increases the rate of breast conservation [2] and achieves similar overall survival (OS) as adjuvant chemotherapy [3] without compromising local control provided that careful multidisciplinary coordination is planned from the outset [4]. Currently, the same regimens used for adjuvant treatment are recommended for neoadjuvant therapy [5]. The initiation of chemotherapy prior to surgery allows for the identification of two distinct prognostic groups: patients able to attain a pathologic complete response (pCR) with a favourable long-term outcome and those with residual disease at surgery who are at a high risk of relapse [6]. Unfortunately, there is no additional therapy that has been shown to improve survival for patients failing to achieve a pCR to an anthracycline-taxane regimen [7] and this group of chemoresistant patients is desperately in need of novel therapeutic options.

There are many unresolved clinical questions regarding the use of neoadjuvant chemotherapy and additional locoregional treatment [5,6]. Well-designed neoadjuvant studies can quickly generate important preliminary data on the efficacy of novel therapies based on short-term endpoints such as pCR. They also offer an excellent opportunity to study the impact of systemic therapies on breast cancer biology, to explore surrogate markers of response (such as functional imaging), and to select promising biomarkers for future validation studies. The traditional model of conducting initial trials in metastatic breast cancer patients with refractory disease following standard therapy has been disappointing, as it demands a lot of effort and requires a long time before the drug reaches adjuvant registration. In addition, many new agents thought to be successful at controlling minimal residual disease have failed to demonstrate the efficacy for patients with advanced disease. As a result, a new pathway to accelerate the clinical development of emerging therapies is sorely needed.

ATAC = Arimidex, Tamoxifen, Alone or in Combination; CTC = circulating tumour cell; DFS = disease-free survival; GEP = gene expression profiling; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IBC = inflammatory breast cancer; neoALTTO = Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation; NOAH = NeOAdjuvant Herceptin; OS = overall survival; pCR = pathologic complete response.

The identification of the central role of the human epidermal growth factor receptor 2 (HER2) protein in the pathogenesis of HER2-overexpressing breast cancer is one of the greatest successes of modern oncology. Over the last 10 years, trastuzumab, a monoclonal antibody against the HER2 protein, has been approved for the treatment of HER2$^+$ breast cancer, and a variety of exciting novel anti-HER2-directed therapies that are entering clinical testing have been developed. As such, HER2$^+$ breast cancer represents the ideal paradigm for a discussion of targeted neoadjuvant breast cancer therapy. The purpose of this article is to review ongoing neoadjuvant randomised clinical trials in HER2$^+$ breast cancer evaluating novel HER2-directed agents, with an emphasis on recent innovations in trial design, platforms for the evaluation of surrogate endpoints and translational research, and the challenges in conducting neoadjuvant research.

Search strategy

Ongoing clinical trials were identified using the ClinicalTrials.gov database on 22 May 2008 [8]. With the search terms 'neoadjuvant breast cancer' and 'HER2 positive', 29 studies were recognised; with the terms 'preoperative' and 'HER2 positive', no additional studies were identified. The selection was limited to neoadjuvant randomised clinical trials that include HER2$^+$ breast cancer. Trials investigating trastuzumab as the only HER2 agent were excluded from the review as we wished to focus on the neoadjuvant trials introducing novel therapies for early breast cancer. With this strategy, nine studies were identified and these are listed in Table 1 and Figure 1. Information regarding clinical trial design was largely collected from the ClinicalTrials.gov library; additional data (where available) were retrieved from the ClinicalTrials.gov (PDQ®) database of the National Cancer Institute (Bethesda, MD, USA) and through personal communication with the principal investigators of individual studies.

Prior randomised neoadjuvant studies in HER2$^+$ disease

Even in the absence of targeted therapy against the HER2 signalling axis, HER2$^+$ breast cancer demonstrates a higher rate of pCR to traditional neoadjuvant chemotherapy [9]. A retrospective single-series study suggests that patients with HER2$^+$ disease who experience a pCR to neoadjuvant chemotherapy (without anti-HER2 therapies) may experience a better disease-free survival (DFS) with long-term follow-up [10]. Three randomised studies in the neoadjuvant setting have evaluated the additional of trastuzumab to standard therapy (Table 2). After 42 of a planned 165 patients had been accrued, the M. D. Anderson study was initially stopped because the pCR rate with trastuzumab added to paclitaxel followed by 5-fluoruracil-epirubicin-cyclophosphamide (P→FEC) chemotherapy was 65% versus 25% with chemotherapy alone [11,12]. The larger NeOAdjuvant Herceptin (NOAH) trial reported similar findings with trastuzumab added to doxorubicin-paclitaxel followed by paclitaxel followed by cyclophosphamide-methotrexate-5-fluoruracil (AP→P→CMF) chemotherapy [13]. Interestingly, both of these studies administered anthracycline chemotherapy concurrently with trastuzumab and did not report a high rate of observed cardiac toxicity. However, the 16% rate of clinical grade 3/4 congestive heart failure observed in the pivotal first-line metastatic trial with concurrent trastuzumab and doxorubicin-cyclophosphamide (AC) would suggest that this approach should not be employed outside of a clinical trial setting [14]. More recently, the GeparQuattro study evaluating epirubicin, cyclophosphamide, and docetaxel with or without capecitabine and/or trastuzumab before surgery reported a similar doubling in the observed pCR rate with the addition of trastuzumab as seen in the NOAH study [15], using a more conventional schedule of initiating trastuzumab after the completion of anthracycline therapy.

Designs of the ongoing randomised neoadjuvant studies in HER2$^+$ disease

The majority of ongoing HER2-targeted trials are investigating the efficacy of lapatinib in the neoadjuvant setting for HER2$^+$ breast cancer (Table 1) [16-24]. Most of these studies use pCR as a primary endpoint. pCR has been proven to correlate with survival endpoints (DFS and OS) in neoadjuvant chemotherapeutic trials [25,26] but its precise definition is still debated. Whereas early trials regarded pCR as the absence of tumour on pathologic slides in breast and axillary lymph nodes, some of the later trials defined pCR as the absence of tumour in breast only without considering nodal evaluation in the operative specimen. In addition, definitions of pCR in neoadjuvant trials do not consistently account for the presence of minimal residual cellularity and residual *in situ* carcinoma. Recently, it was shown that the extent of residual breast cancer burden, calculated as a continuous index based on primary tumour measurements (size and cellularity) and lymph node metastases (number and size), correlates with survival outcomes [27]. Therefore, it is clear that a unified definition of pathologic response for neoadjuvant trials is required, much like the recent consensus statement regarding standard efficacy endpoints (STEEP) for adjuvant trials in early-stage disease [28]. Unfortunately, the definitions of response endpoints in the ongoing neoadjuvant trials with novel anti-HER2 agents are inconsistent (Table 1). It should be noted that there is even less evidence regarding the correlation between the extent of residual breast cancer burden following neoadjuvant targeted therapy (with or without chemotherapy) and survival [12,29].

At the present time, pCR is not robust enough to replace survival as an endpoint for the registration of novel therapies. Even though pCR appears to identify a subgroup with a favourable prognosis [6,25,30], therapies that improve the rate of pCR do not necessarily translate into long-term differences in survival, as demonstrated by the addition of taxane therapy in the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-27 trial [6]. However, the evaluation of pCR in neoadjuvant studies can provide a

Table 1

Ongoing randomised neoadjuvant studies targeting HER2 with new agents

ClinicalTrials.gov identifier	Sponsor and participating groups	Investigational drugs	Phase	Estimated enrolment	Status	Start/Completion	Primary endpoint	Translational research	Patient eligibility (all HER2+)
NCT00486668 [16]	NSABP GSK	Lapatinib Trastuzumab	III	522	Recruiting	July 2007 to July 2014[a]	- pCR (breast only)	GEP	$ER^{+/-}$ $PR^{+/-}$
NCT00499681 [17]	Vanderbilt-Ingram Cancer Center (Nashville, TN, USA) NCI	Lapatinib Letrozole	II	36	Recruiting	July 2007 to July 2010	- Change in percentage of $Ki67^+$ tumour cells - pCR	Biomarkers[b] Imaging	ER^+ and/or PR^+
NCT00450892 [18]	EORTC	Lapatinib Trastuzumab	I-II	114	Recruiting	Feb. 2007 to Dec. 2009	- pCR[c] - Safety and tolerability - RR - Phdinam.	GEP Phdinam.	$ER^{+/-}$ $PR^{+/-}$ Inflammatory BC included
NCT00567554 GeparQuinto [19]	GBG AGO Ovarian Cancer Study Group	Lapatinib Trastuzumab	III	2,547 (all patients)	Recruiting	Oct. 2007 to Dec. 2015	- pCR	Biomarkers CTCs Imaging Phgen.	$ER^{+/-}$ $PR^{+/-}$ Inflammatory BC included
NCT00674414 [20]	Fédération Nationale des Centres de Lutte Contre le Cancer (Paris, France)	Everolimus Trastuzumab	II	120	Recruiting	Apr. 2008 to Apr. 2014	- RR (clinical and echographic)	Phgen. Phdinam. Proteomics Biomarkers	$ER^{+/-}$ $PR^{+/-}$
NCT00545688 [21]	Hoffmann-La Roche (Grenzach-Wyhlen, Germany)	Pertuzumab Trastuzumab	II	400	Recruiting	Dec. 2007 to Oct. 2014	- pCR	NR	$ER^{+/-}$ $PR^{+/-}$ Inflammatory BC included
NCT00524303 [22]	GSK	Trastuzumab Lapatinib	II	99	Recruiting	Sept. 2007 to July 2013	- Pathologic RR	Biomarkers	$ER^{+/-}$ $PR^{+/-}$ Inflammatory BC included
NCT0053358 [23]	GSK BIG Grupo Espaniol de Estudio Tratamiento y Otras Estrategias Experi-mentales en Tumores Solidos (Madrid, Spain)	Trastuzumab Lapatinib	III	450	Recruiting	Sept. 2007 to Sept. 2019	- pCR (breast only)	Biomarkers Imaging CTCs	
NCT00548184 [24]	Baylor Breast Cancer Center (Houston, TX, USA) GSK	Lapatinib Trastuzumab	II	64	Not yet recruiting	Jan. 2008 to Jan. 2012	Biomarkers	Biomarkers	$ER^{+/-}$ $PR^{+/-}$

[a]Including the follow-up period; [b]translational research described as biomarkers in which no additional information about the techniques was given; [c]only for phase II part. AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; BC, breast cancer; BIG, Breast International Group (Brussels, Belgium); CTCs, circulating tumour cells; EORTC, European Organisation for Research and Treatment of Cancer; ER, oestrogen receptor; GBG, German Breast Group (Neu-Isenburg, Germany); GEP, gene expression profiling; GSK, GlaxoSmithKline (Uxbridge, Middlesex, UK); HER2, human epidermal growth factor receptor 2; NCI, National Cancer Institute (Bethesda, MD, USA); NSABP, National Surgical Adjuvant Breast and Bowel Project; NR, not reported; pCR, pathologic complete response; Phdinam., pharmacodynamics; Phgen., pharmacogenetics; PR, progesterone receptor; RR, response rate.

Figure 1

Title	Study design	Duration of neoadjuvant therapy
A study of AC followed by a combination of paclitaxel plus trastuzumab or lapatinib or both given before surgery to patients with operable HER2-positive invasive breast cancer [16]	R → AC → p + H; AC → p + L; AC → p + H + L	24 weeks (12 weeks + 12 weeks)
Letrozole and lapatinib in treating postmenopausal women with stage I, stage II, or stage III breast cancer that can be removed by surgery [17]	R → letro + L; letro + placebo	16 weeks
Docetaxel and lapatinib with or without combination chemotherapy or docetaxel and trastuzumab with combination chemotherapy in treating women with locally advanced, inflammatory, or resectable breast cancer [18]	R → FEC → T + L; FEC → T + H	18 weeks (9 weeks + 9 weeks)
A phase III trials program exploring the integration of bevacizumab, everolimus (RAD001), and lapatinib into current neoadjuvant chemotherapy regimens for primary breast cancer (GeparQuinto) [19]	* R → EC + H → TX + H; EC + L → TX + L	24 weeks (12 weeks + 12 weeks)
Trastuzumab with or without everolimus in treating women with breast cancer that can be removed by surgery [20]	R → H; H + everolimus	6 weeks
A study of pertuzumab in combination with herceptin in patients with HER2-positive breast cancer [21]	R → T + H; T + H + pertutzmab; H + pertutzmab; T + pertutzmab	NR
Lapatinib ± trastuzumab in addition to standard neoadjuvant breast cancer therapy [22]	NR	NR
neoALTTO (Neoadjuvant Lapatinib and/or trastuzumab treatment optimization) study [23]	R → H → p + H; L → p + L; H + L → p + H + L	18 weeks (6 weeks + 12 weeks)
A phase II trial of lapatinib and trastuzumab with or without endocrine therapy in locally advanced HER2-overexpressing breast cancer patients [24]	NR	NR

Trial design of ongoing randomised neoadjuvant studies targeting HER2 with new agents. *Only the randomization for HER2 positive patients is presented. AC, doxorubicin-cyclophosphamide; EC, epirubicin-cyclophosphamide; FEC, 5-fluoruracil-epirubicin-cyclophosphamide; H, trastuzumab; HER2, human epidermal growth factor receptor 2; L, lapatinib; letro, letrozole; NR, not reported; p, paclitaxel; R, randomisation, T, docetaxel; X, capecitabine.

critical early marker of efficacy, especially if a neoadjuvant study is coupled with a larger adjuvant registration trial using survival as its primary endpoint, such as in the case of the ongoing neoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) and the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trials. A similar model has been employed by the recently completed neo-tAnGo and tAnGo trials in nonselected

Table 2

Reported randomised phase III trials with neoadjuvant trastuzumab

Reference	Number of patients	Patient population	Design	HER2 assessment	pCR rate, percentage (95% CI)		
					No H	With H	*P* value
Buzdar *et al*., 2005 [11], 2007 [12]	42	65% T2 40% N0/ 57% N1	P → FEC vs. P + H → FEC + H	IHC 3+ or FISH+	26 (9-51)	65 (43-84)	NS
Gianni *et al*., 2007 [13]	228	60% T4 85% N+	AP → P → CMF vs. AP + H → P + H → CMF + H	IHC 3+ or FISH	23 (NR)	43 (NR)	0.002
Untch *et al*., 2008 [15]	453	NA	EC → D or EC → DX or EC → D → X vs. EC → D + H or EC → DX + H or EC → D + H → X + H	NA	20 (NR)	41 (NR)	<0.001

C, cyclophosphamide; CI, confidence interval; D, docetaxel; E, epirubicin; F, 5-fluoruracil; FISH, fluorescence *in situ* hybridization; H, trastuzumab; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; M, methotrexate; N, nodal status; NA, not applicable; NR, not reported; NS, not significant; P, paclitaxel; pCR, pathologic complete response; T, tumour size; X, capecitabine.

populations [31]. Adjuvant registration trials require an enormous financial and patient investment to detect small differences in long-term outcome. A well-designed neoadjuvant study can rapidly provide a 'go/no go' decision for an emerging therapy. Invaluable data for the appropriate selection of patients and the evaluation of endpoints for a subsequent adjuvant registration trial can be generated by a well-designed neoadjuvant pilot trial: this concept is currently being developed and explored by the Breast International Group (Brussels, Belgium).

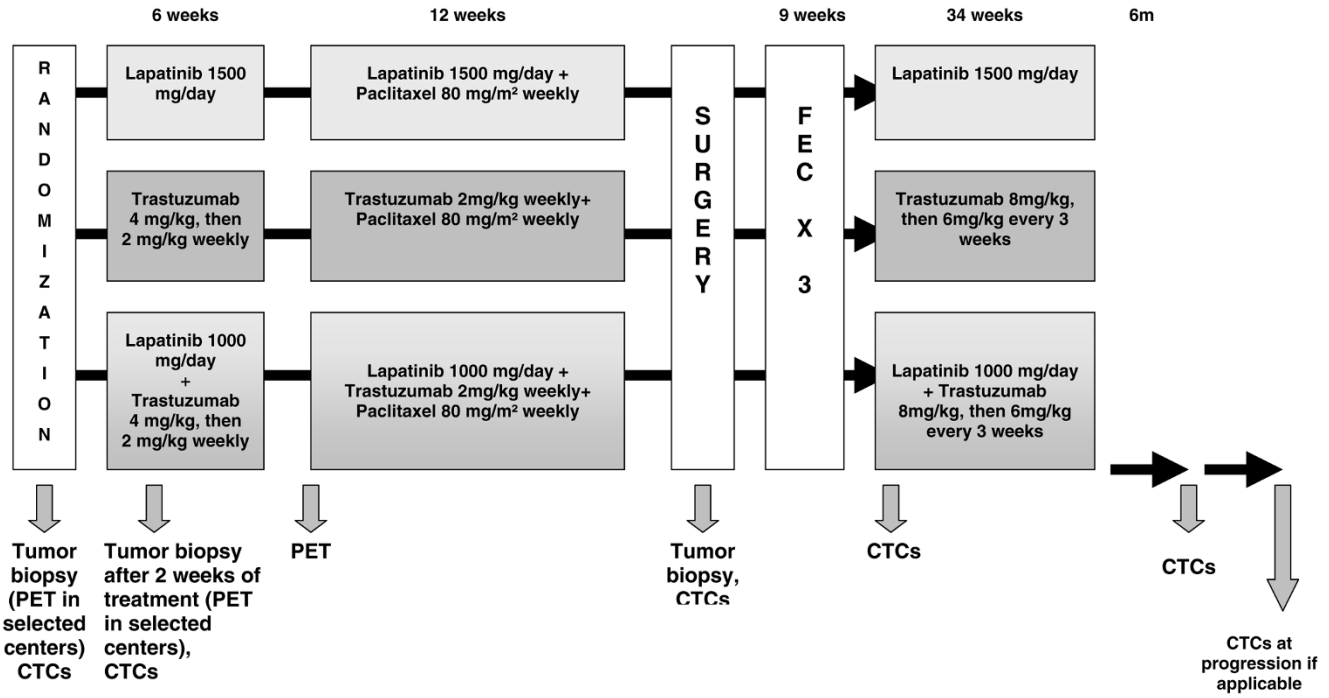
The proliferation marker Ki67 is another marker of interest to be used as a surrogate marker for efficacy, especially with endocrine therapy [17,32,33]. Declines in Ki67 after 2 weeks of neoadjuvant treatment showed no difference between tamoxifen and the combination of tamoxifen and anastrozole in the IMPACT (Immediate Preoperative 'Arimidex' [anastrozole], Tamoxifen, or Arimidex Combined with Tamoxifen) trial, while a significantly greater drop was found in the anastrazole-alone arm [33], mirroring the DFS results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial [34]. If these findings had been known before the launch of the ATAC trial, the combination arm likely would have been dropped from the study design from the outset, thereby saving considerable financial and patient resources.

The eligibility criteria for the ongoing neoadjuvant anti-HER2 studies are similar. With the exception of the National Cancer Institute study [35] that includes only patients with hormone receptor-positive (HR^+) and $HER2^+$ breast cancer, all other studies include HR^+ and HR^- disease. Although HR^+ and HR^- $HER2^+$ breast cancer may exhibit different clinical behaviour [36], the joint inclusion of $HER2^+$ disease regardless of HR status in the evaluation of novel anti-HER2 therapy is justified, as trastuzumab has been shown to be effective regardless of the expression of hormonal receptors [37].

Perhaps more controversial is the joint inclusion of IBC together with locally advanced disease in the same study, as IBC represents a separate entity with distinct epidemiology, biology, and long-term outcome [38]. Although gene expression profiling (GEP) has identified the same five subtypes of IBC as originally described for noninflammatory breast cancer, differences in several key pathways and proteins do exist [39]. IBC should be evaluated in separate clinical trials or at least stratification should be planned at the time of randomisation.

In contrast to the classical design, in which an experimental therapy is compared with a standard therapy, examples of novel designs are available amongst the ongoing anti-HER2 neoadjuvant studies: the so-called 'biological window' design and 'learn on the way' design. The biological window design exposes the patients to a short period of therapy with the drug of interest alone to allow for the evaluation of biologic endpoints. This design can also provide valuable insight regarding drug pharmacodynamics and early evidence of drug activity and highlight potential mechanisms of resistance. As this phase of design is purely for research purposes and does not offer patients direct therapeutic benefit, there are ethical concerns that must be respected [40]. A short biological window period can be followed by a more classical design comparing standard neoadjuvant therapy with new combinations, including targeted therapy with curative intent, such as in the neoALTTO trial (Figure 2). In the future, these studies may lead to a reduction in overtreatment with chemotherapy, as they may identify patients with excellent response to targeted therapy alone that can be

Figure 2



neoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study design. CTCs, circulating tumour cells; FEC, 5-fluoruracil-epirubicin-cyclophosphamide; PET, positron emission tomography. Note: In the combined Lapatinib + Trastuzumab + Paclitaxel arm, there is a protocol amendment pending approval to reduce the Lapatinib dose to 750 mg/day because of concerns regarding excess diarrhea. Reprinted with permission from GlaxoSmithKline and SOLTI (Spanish Breast Cancer Cooperative Group).

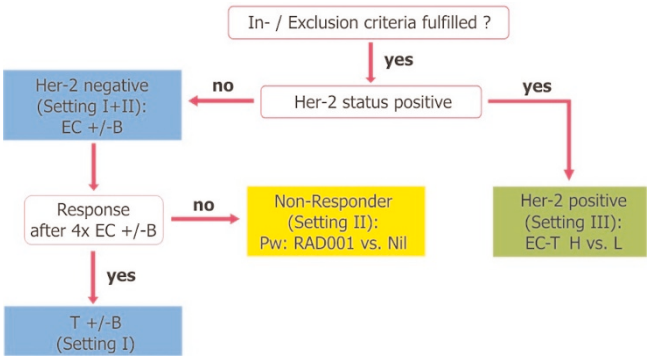
evaluated in a future chemotherapy-sparing study. Though feasible, such neoadjuvant studies require careful planning, enormous logistical support for material collection, and efficient screening systems to identify appropriate patients, all of which significantly increase the complexity and cost of conducting such research.

The 'learn on the way' design uses information gained from an initial treatment period to guide decisions regarding further therapy. A patient who does not demonstrate early clinical response at interim evaluation is unlikely to experience pCR with completion of standard neoadjuvant chemotherapy [41,42]. Thus, early-response evaluation can identify a subgroup of patients with poor long-term outcome, providing the opportunity to explore a switch to an alternative therapy to improve the likelihood of pCR. To date, studies evaluating neoadjuvant taxane [41] and capecitabine-vinca alkaloid [42] combinations in nonselected populations have failed to demonstrate a benefit for patients who do not respond to anthracycline-based therapy. The GeparQuinto study described in Figures 3-5 is an example of one such 'learn on the way' approach [7]. The 'learn on the way' design is an excellent opportunity to reduce overtreatment and validate surrogate markers of response. Unfortunately, in the GeparQuinto study, only the nonresponding HER2$^-$ cohort will undergo a second randomisation based upon early response, whereas in the HER2$^+$ cohort early response is not used to inform further decision-making. In the future, 'learn on the way' designs based upon biomarker endpoints rather than tumour shrinkage may be employed, although there are important challenges regarding the standardisation of cutoff values and interlaboratory reproducibility, along with the need for prompt assessment must be addressed using such a dynamic approach.

Translational research

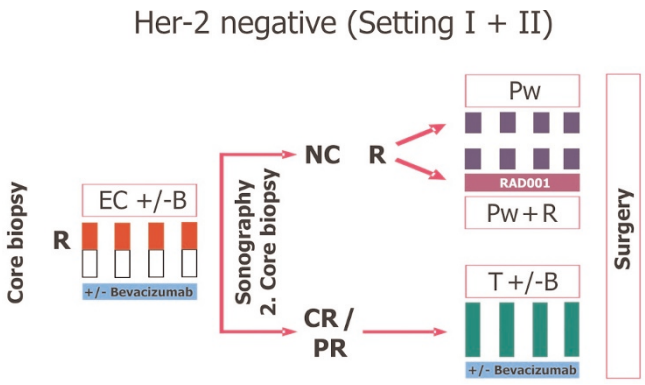
The neoadjuvant setting is an ideal platform to evaluate the predictive value of biomarkers using emerging technologies like GEP, proteomics, functional imaging, circulating tumour cells (CTCs), and the role of the host in the response to therapy (pharmacodynamic and pharmacogenetic substudies) (Table 1). Traditionally, translational research in breast cancer has been characterised by efforts to validate single predictive biomarkers using available tumour blocks from completed clinical trials, with largely disappointing results. With new techniques like GEP and biomarker models [43], several putative markers can be linked together to obtain a more powerful prognostic or predictive tool. The biological window design provides an especially valuable opportunity for the rapid evaluation of pharmacodynamic endpoints with biologic therapy.

Figure 3



Decision tree from GeparQuinto study. B, bevacizumab; EC, epirubicin-cyclophosphamide; H, trastuzumab; Her-2, human epidermal growth factor receptor 2; L, lapatinib; Pw, paclitaxel weekly; T, docetaxel. Reprinted with permission from GBG (German Breast Group).

Figure 4

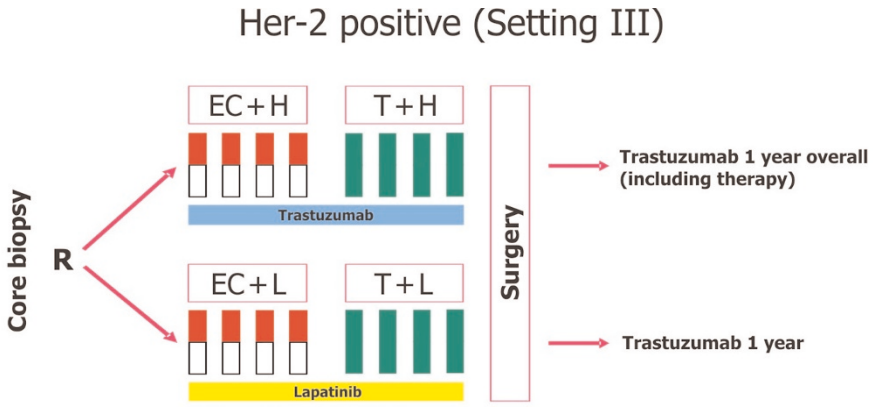


GeparQuinto study design for HER2-negative cohort. B, bevacizumab (15 mg/kg intravenously: day 1 q day 21 for eight cycles); C, cyclophosphamide (600 mg/m^2: day 1 q day 21 for four cycles); CR, complete response; E, epirubicin (90 mg/m^2: every 3 weeks for four cycles); Her-2, human epidermal growth factor receptor 2; NC, no change; PR, partial response; Pw, paclitaxel weekly (80 mg/m^2: weekly for 12 weeks total); Pw + R, paclitaxel weekly + RAD001 (5 mg daily); R, randomisation; T, docetaxel (100 mg/m^2: day 1 q day 21 for four cycles). Reprinted with permission from GBG (German Breast Group).

Imaging modalities have not reliably been shown to predict the response to neoadjuvant therapy. This is, in part, because previous validation studies have been conducted in an incomplete and piecemeal manner. Given the rapidly expanding array of new imaging modalities, well-planned neoadjuvant studies with prospective integration of imaging endpoints are required to define and compare the role of molecular and functional imaging as early-response predictors. In contrast to traditional imaging modalities based upon anatomic evaluation of response, functional modalities such as magnetic resonance imaging [44-47], magnetic resonance spectroscopy [48], positron emission tomography [49,50], single photon emission computed tomography [51], ultrasound with enhancement [52], and optical imaging [53] have all shown the ability to predict early response and warrant prospective evaluation in phase III clinical trials. In particular, their ability to predict an early response using anti-HER2 therapy still needs to be demonstrated prospectively.

CTCs can be identified in the blood of 10% to 30% of patients with early breast cancer and their detection is associated with poor long-term DFS [54-56]. Currently, their prognostic and predictive value is also being investigated in neoadjuvant trials exploring the efficacy of novel anti-HER2 drugs (Table 1). Several methods of CTC detection have been described, although reverse transcription-polymerase

Figure 5



GeparQuinto study design for HER2-positive cohort. C, cyclophosphamide (600 mg/m^2: day 1 q day 21 for four cycles); E, epirubicin (90 mg/m^2: every 3 weeks for four cycles); H, trastuzumab (8 mg/kg: loading dose, 6 mg/kg: every 3 weeks); Her-2, human epidermal growth factor receptor 2; L, lapatinib (1,250 mg daily for 24 weeks: run-in phase cycles 1 and 5: 1,000 mg daily); R, randomisation; T, docetaxel (100 mg/m^2: every 3 weeks for four cycles). Reprinted with permission from GBG (German Breast Group).

chain reaction and immunomagnetic/fluorescent approaches are the most advanced [57,58].

Studies exploring the efficacy of novel anti-HER2 drugs not only are tumour-orientated but also will evaluate the role of the host with prospective pharmacogenetic and pharmacodynamic translational research studies. These studies will provide us with valuable knowledge regarding interindividual differences in drug metabolism and the efficacy of novel agents [59,60].

Translational research rarely leads directly to the registration of novel therapies, making it difficult to justify the high costs of adequately powered translational research to industrial trial sponsors [61]. However, innovative neoadjuvant translational research may identify patients likely to benefit from novel therapies that may ultimately reduce the number of participants needed for a subsequent registration study in the adjuvant setting as well as increase the probability of detecting a beneficial effect due to more accurate patient selection. As the examples of trastuzumab for breast cancer and gefitinib for lung cancer treatment illustrate, knowledge of the appropriate patient population for a novel targeted therapy can make the difference between a blockbuster drug and a drug that never makes it to market [62-66].

Conclusions

Ongoing neoadjuvant studies exploring the efficacy of novel anti-HER2 agents with innovative designs, like the 'biological window' and 'learn on the way', promise to deliver new knowledge of breast cancer biology and treatment. In the future, a greater collaborative effort between research groups is required to translate the new insights regarding the molecular heterogeneity of breast cancer into individualised therapies. Past failures have been marred by duplicative trial designs, poorly planned translational research, and overestimation of the benefit of experimental therapy in unselected populations. A new partnership between academic investigators, industry, patients, and policy-makers is needed, with a common understanding that properly conducted innovative neoadjuvant research can transform the dream of tailored therapy for breast cancer into reality.

Competing interests

FC has received unrestricted research grants from Hoffmann-La Roche (Grenzach-Wyhlen, Germany) and GlaxoSmithKline (Uxbridge, Middlesex, UK) and has participated in advisory boards for GlaxoSmithKline. MP has received honoraria from Hoffmann-La Roche, GlaxoSmithKline, AstraZeneca (London, UK), and Novartis (Basel, Switzerland). The other authors declare that they have no competing interests.

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