Dual Blockade with AFatinib and Trastuzumab as NEoadjuvant Treatment for Patients with Locally Advanced or Operable Breast Cancer Receiving Taxane-Anthracycline Containing Chemotherapy—DAFNE (GBG-70)

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Abstract

Purpose: Dual anti-HER2 blockade with trastuzumab/pertuzumab or trastuzumab/lapatinib in combination with anthracycline/taxane-based chemotherapy can reach pathologic complete response (pCR) rates of up to 60% in HER2-positive breast cancer. The DAFNE (Dual blockade with AFatinib and trastuzumab as NEoadjuvant treatment) phase II study (NCT015591477) investigated a dual blockade with the irreversible pan-HER inhibitor afatinib and trastuzumab in this setting.

Experimental Design: Participants with untreated, centrally HER2-positive breast cancer were treated for 6 weeks with afatinib (20 mg/d) and trastuzumab (8 mg/kg/3 weeks) alone; followed by 12-week treatment with paclitaxel (80 mg/m2/1 week), trastuzumab, and afatinib, followed by 12 weeks with epirubicin (90 mg/m2/3 weeks), cyclophosphamide (600 mg/m2/3 weeks), and trastuzumab before surgery.

Primary objective was pCR rate, defined as ypT0/is ypN0. We expected a pCR rate of 70%; 65 patients were needed to exclude a rate of \( \leq 55\% \).

Results: pCR rate was 49.2\% [90\% confidence interval (CI), 38.5–60.1\%] in 65 treated patients. Patients with hormone receptor–positive (\( N = 46 \)) or hormone receptor–negative (\( N = 19 \)) or hormone receptor–positive (\( N = 46 \)) tumors showed pCR rates of 63.2\% and 43.5\%, respectively (\( P = 0.153 \)). Patients with (\( N = 9 \)) or without (\( N = 56 \)) lymphocyte predominant breast cancer (LPBC) showed pCR rates of 100\% and 41.1\%, respectively (\( P < 0.001 \)). pCR rate was not different in patients with or without PIK3CA tumor mutations (\( P = 0.363 \)).

Clinical responses were seen in 96.3\% of 54 evaluable patients, and breast conserving surgery was possible in 59.4\% of 62 assessable patients. Most frequent nonhematologic grade 3–4 toxicities were diarrhea (7.7\%), increased creatinine (4.6\%), and infection (4.6\%). One patient developed symptomatic congestive heart failure.

Conclusions: Neoadjuvant treatment with afatinib, trastuzumab, and chemotherapy showed acceptable tolerability, and a pCR rate comparable with that of other anti-HER2 doublets but below challenging expectations. Clin Cancer Res; 21(13): 2924–31. ©2015 AACR.

Introduction

Outcome of patients with HER2-positive breast cancer has changed with the introduction of HER2-targeted systemic treatment. Prognosis of patients with HER2-positive tumors changed from unfavorable (1) to favorable (2) after trastuzumab was recommended as adjuvant treatment (3–5) as well as in combination with first-line chemotherapy (6), and even beyond progression (7). The HER2 receptor appears to be such a dominant target that also inhibition of dimerization of the HER2 and HER3 receptor with pertuzumab (8) or HER2-targeted cytotoxic drug delivery (9) improved survival in metastatic breast cancer.

When trastuzumab was given simultaneously to neoadjuvant chemotherapy, frequency of pathologic complete response (pCR) was substantially increased in such an extent that pCR benefits correlated with survival benefits (10). In fact, this was the only study in which such a strong correlation between pCR and long-term outcome was found in a global meta-analysis (11).
even higher pCR rates were reported with the introduction of dual HER2-blockade explicitly in HER2-positive/hormone receptor (HR)–negative disease. Trastuzumab and lapatinib (12) or trastuzumab and pertuzumab (13) given for 12 weeks in combination with a taxane reached a comparable pCR rate as longer sequential anthracycline–taxane-based chemotherapies with trastuzumab alone (14, 15). When trastuzumab and pertuzumab or lapatinib were given together with anthracycline–taxane or taxane–carboplatin-containing chemotherapies, pCR rates more than 60% were reached (16, 17). So far, dual blockade given simultaneously with an anthracycline did not increase cardiac toxicity; however, long-term observational data have not been reported yet.

Afatinib (BIBW 2992) is an irreversible pan-HER family receptor blocker, and is bioavailable after oral administration (18). Three phase II trials had been previously conducted in patients with metastatic breast cancer (19–21). Four of 35 patients showed a partial response (PR) and 15 stable metastatic breast cancers with afatinib monotherapy after failure of prior trastuzumab treatment. Mean duration of response was 153 days (19). Five of 28 patients included into a combination trial with afatinib and letrozole in estrogen receptor (ER)–positive, hormone-refractory, mostly HER2-negative patients had stabilization of disease for more than four cycles (20). A phase I study revealed a maximum tolerated dose of 20 mg afatinib when given in combination with weekly trastuzumab with diarrhea being the leading toxicity in 31% of patients (22).

The Dual blockade with Afatinib and trastuzumab as NEoadjuvant treatment (DAFNE) study investigated how far a dual blockade with trastuzumab and afatinib can lead to an even more complete blockade of the HER2 pathway, and therefore higher pCR rate.

**Patients and Methods**

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by each local Institutional Review Board. Patients were required to give written informed consent for study participation and biomaterial collection. The trial registration number at Clinicaltrials.gov is NCT01594177.

The DAFNE (Dual blockade with Afatinib and trastuzumab as NEoadjuvant treatment) study is a neoadjuvant proof-of-concept study in primary HER2-positive breast cancer patients investigating the use of the pan-HER inhibitor afatinib in addition to trastuzumab and chemotherapy. The study had an integrated window-of-opportunity phase testing the dual blockade with trastuzumab and afatinib and an obligatory biopsy after the 6-week window before starting chemotherapy. Only centrally HER2-positive breast cancer patients were included. As part of the translational program, measurements of hormone receptor status, Ki67, and stromal tumor-infiltrating lymphocytes (sTIL) were integrated into the central pathology before randomization and the PIK3CA genotype was determined. The DAFNE study provides further support for the predictive value of sTLIs and PIK3CA mutation in HER2-positive primary breast cancer.

**Translational Relevance**

The DAFNE (Dual blockade with Afatinib and trastuzumab as NEoadjuvant treatment) study is a neoadjuvant proof-of-concept study in primary HER2-positive breast cancer patients investigating the use of the pan-HER inhibitor afatinib in addition to trastuzumab and chemotherapy. The study had an integrated window-of-opportunity phase testing the dual blockade with trastuzumab and afatinib and an obligatory biopsy after the 6-week window before starting chemotherapy. Only centrally HER2-positive breast cancer patients were included. As part of the translational program, measurements of hormone receptor status, Ki67, and stromal tumor-infiltrating lymphocytes (sTIL) were integrated into the central pathology before randomization and the PIK3CA genotype was determined. The DAFNE study provides further support for the predictive value of sTLIs and PIK3CA mutation in HER2-positive primary breast cancer.

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**Patients**

Eligible patients had previously untreated, unilateral, nonmetastatic, histologically confirmed invasive breast cancer overexpressing or amplified HER2, that is, centrally confirmed immunohistochemistry score 3+ or in situ hybridization ratio >2.0. Tumors either ≥2 cm based on clinical or ultrasound assessment or diagnosed as inflammatory breast cancer were eligible. In patients with multifocal or multicentric breast cancer, the largest lesion was measured. Patients were required to have a Karnofsky performance status ≥80%; adequate hematologic, hepatic, renal, and pulmonary function. Left ventricular ejection fraction had to be >55% and known or suspected congestive heart failure (NYHA > I) or coronary heart disease, angina pectoris requiring antianginal medication, previous history of myocardial infarction, evidence of transmural infarction on ECG, uncontrolled or poorly controlled arterial hypertension (i.e., BP > 160/90 mm Hg under treatment with two antihypertensive drugs), rhythm abnormalities requiring permanent treatment, or clinically significant valvular heart disease were exclusion criteria. Other exclusion criteria were chronic inflammatory bowel disease, preexisting motor or sensory neuropathy of a severity grade ≥2 by NCI criteria, currently active infection, definite contraindications for the use of corticosteroids except inhalative corticoids, known hypersensitivity reaction to one of the investigational compounds or incorporated substances used in this protocol, concurrent treatment with chronic corticosteroids unless initiated >6 months before study entry and at low dose (<10 mg methylprednisolone or equivalent, sex hormones, or other experimental drugs or any other anticanter therapy, pregnancy or lactation, and male gender).

**Treatment plan**

Patients received afatinib at a daily dose of 20 mg for 17 weeks except during the first 2 weeks where afatinib 20 mg was given only every other day to reduce the risk of diarrhea and skin toxicities (23). Trastuzumab was started together with afatinib at one loading dose of 8 mg/kg and was continued at a dose of 6 mg/kg every 3 weeks for 10 cycles until surgery. Thereafter, additional cycles were given for a total duration of 1 year. Chemotherapy started after 6 weeks of afatinib with 12 weekly courses of paclitaxel 80 mg/m² followed by four 3-week cycles of epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² (EC) followed by surgery. As no cardiac safety data for afatinib in combination with anthracyclines were available, afatinib was stopped 2 weeks before the start of EC, but trastuzumab continued (for up to 1 year). Primary prophylaxis with lopramide 2 mg twice daily was obligatory during the first 4 weeks of afatinib/trastuzumab and the first 2 weeks of afatinib/trastuzumab/paclitaxel. Thereafter, prophylaxis with lopramide could be stopped if no diarrhea grade >1 had occurred (Fig. 1).

The protocol provided guidelines for dose reductions or delays in case of severe (grade 3–4) toxicities. Once study treatment was discontinued due to toxicities, it was not allowed to be resumed. No dose reduction of trastuzumab was allowed.

After surgery, patients received radiotherapy according to German national guidelines. All patients with hormone-sensitive tumors received adjuvant endocrine treatment with tamoxifen or an aromatase inhibitor according to national guidelines.

**Endpoints**

The primary endpoint was pCR, defined as absence of invasive breast cancer in breast and axillary lymph nodes (ypT0/is ypN0)
in all surgically excised specimen (24). Secondary analyses used other pCR definitions (ypT0 ypN0, ypT0 ypN0/+ , ypT0/is ypN0, ypTany ypN0, and regression grades according to Sinn and colleagues (25) for better comparison with the literature. Histopathologic reports were centrally reviewed by a qualified breast pathologist (K. Engels). Other secondary endpoints included toxicity and compliance, the correlation of skin toxicity and diarrhea with pCR, clinical response by physical examination and imaging tests after 6 weeks and at surgery, breast and axillary conservation rate, and comparison of the presence of lymphocyte predominant breast cancer (LPBC) as well as PIK3CA mutations with pCR. Examination of biomarkers on the collected biopsies has not been conducted so far.

Clinical response rates of the breast tumor were determined after 6 weeks of the two anti-HER2 agents alone and before surgery by imaging tests. Sonography was the preferred examination; however, if sonography appeared not to provide valid results or was not performed; other imaging tests were considered with the following priority: MRI, mammography, palpation for all categories except CR, which had to be confirmed in all available imaging tests. A clinical PR was defined as a reduction in the product of the two largest perpendicular diameters of the tumor size before start of chemotherapy and at surgery by 50% or more. If the reduction in size was less than 50% and no increase in size of >25% was present, response was documented as "no change." In case of an increase in size of >25% or a detection of a new breast lesion, progressive disease was stated. The same imaging method should be considered for the measurement before and after treatment.

Breast conservation requested tumor-free margins, and was stated if tumorectomy, segmentectomy, or quadrantectomy was the final surgical procedure. No breast conservation was achieved in case of total or partial mastectomies with or without reconstruction procedures as final procedure. Axillary conservation was defined as no axillary lymph node dissection deemed necessary after sentinel node biopsy. For safety evaluation of the preoperative therapy, toxicities were graded according to National Cancer Institute-Common Toxicity Criteria v. 2.0 NCI-CTC.

Tumor sections from core biopsies containing ≥60% stromal or intratumoral lymphocytes were considered as LPBC (26). PIK3CA mutations were centrally evaluated on core biopsies with a tumor cell content of ≥20% using classical Sanger sequencing of exon 9 and 20 (27).

Statistical analysis
The statistical analyses were run using SAS version 9.2 (SAS Institute Inc.). Participants who received at least one dose of study drug were included in the efficacy and toxicity analysis and the highest grade of toxicity was reported.

The sample size calculation assumed that neoadjuvant anthracycline–taxane-based chemotherapy given simultaneously with trastuzumab results in a pCR rate of approximately 40%. If HER2 status is centrally reviewed, the pCR rate in this population will increase to 50% (28). The addition of a dual anti-HER2 blockade to chemotherapy should further increase the pCR by additional absolute 20% (12, 13). It was, therefore, assumed that the real pCR rate in this study will be 70%. To exclude a pCR rate of 55% or lower [i.e., the lower confidence interval (CI) of the observed pCR rate does not include 55%] 65 evaluable patients are required using a two-sided one group \( \chi^2 \) test with \( \alpha = 0.1 \) and \( 1 - \beta = 80\% \).

Results
Baseline characteristics
Between May 2012 and July 2013, 65 patients with centrally confirmed HER2-overexpressing tumors started treatment in 10 trial centers in Germany. Fourteen patients were not included in the study because positive HER2 status was not confirmed centrally (\( N = 9 \)) or due to other exclusion criteria (\( N = 5 \); Fig. 2). Baseline characteristics are summarized in Table 1. The median age was 50.0 (range, 29–73) years. The majority of patients had tumor stage T2 (76.6%), no nodal involvement (51.6%), tumor grade 3 (60%), and HRs were positive in tumors of 70.8% of patients.

Efficacy
pCR (ypT0/is ypN0) was reported in 32 of 65 patients that have started treatment (49.2%; 95% CI, 38.5–60.1%; Table 2). Twenty one (33.9%) patients had neither invasive nor noninvasive residuals in the removed breast and axillary specimens (ypT0 and ypN0). No invasive residuals in the breast (ypT0/is ypN0/+ ) were found in 36 (55.4%) patients. Pathologic tumor-free lymph
Afatinib and Trastuzumab with Neoadjuvant Chemotherapy (DAFNE)

Theory and rationale: DAFNE was designed to test the dual blockade of HER2 and PIK3CA in patients with HER2-positive breast cancer and wild-type or PIK3CA-mutated tumors, respectively. The primary endpoint was pathologic complete response (pCR) in the breast-conserving treatment (BCT) subgroup, as other patients were assigned to either the neoadjuvant chemotherapy (EC) or anti-HER2 treatment only. Five intervention arms were therefore compared: (A) dual blockade with afatinib, trastuzumab, paclitaxel, and EC; (B) afatinib and trastuzumab without EC; (C) EC alone; (D) paclitaxel with anti-HER2 treatment only; and (E) treatment as per investigator’s discretion.

Materials and methods: A total of 79 patients aged 18–75 years were screened. Inclusion criteria were locally advanced or inflammatory breast cancer, due to early onset of tumor progression during induction therapy, and no cardiac toxicity. Five patients (6.3%) were excluded due to early discontinuation. Median follow-up was 17.9 months. The primary endpoint was pCR rate of 55% or lower after a dual blockade with trastuzumab, afatinib, paclitaxel, and EC. To confirm the primary endpoint, an futility boundary and an efficacy boundary were set at p = 0.0492 and p = 0.0058, respectively. Secondary endpoints included efficacy and safety.

Results: Clinical objective response rate was 96.3%. Three (5.3%) and 21 (36.8%) of 57 evaluable patients already showed a pCR (P = 0.0053) and 23 (41.1%) of 56 patients without LPBC showed a pCR (P = 0.0053). All (100%) 9 patients with LPBC showed a pCR (P = 0.0053). No association of efficacy was observed in relation to the occurrence of skin toxicity (P = 0.269) or diarrhea (P = 0.841).

Toxicity
The most common grade 3–4 hematologic toxicities were neutropenia (53.8%) and leukopenia (32.3%), reported mainly during chemotherapy treatment. The incidences of grade 3–4 anemia and thrombocytopenia were low (4.6% or 0%, respectively). Most frequent grade 3–4 nonhematologic toxicities were diarrhea (7.7%), increased creatinine (4.6%), and infection (4.6%), occurring again mostly during chemotherapy treatment. Liver toxicity was frequent throughout all treatment phases, but never reached grades 3 or 4 (Table 3). A total of 22 serious adverse events occurred in 16 patients; 27.3% were gastrointestinal, 18.2% hematologic, 13.6% infections, and 9.1% related to the nervous system. One patient developed symptomatic congestive heart failure, 12 patients showed decreased or abnormal left ventricular ejection fraction throughout the treatment. Nine AEs of special interest were reported: N = 6 diarrheas grade 3, N = 1 rashes grade 3, and N = 2 renal failures grade 3. No hepatic injury or interstitial lung disease was reported.

Discussion
The DAFNE study did not reach its primary goal to exclude a pCR rate of 55% or lower after a dual blockade with trastuzumab...
and afatinib in combination with anthracycline-taxane-based chemotherapy. The result does formally not support a subsequent phase III trial comparing this combination with other dual blockade regimen, for example, trastuzumab plus pertuzumab or trastuzumab plus lapatinib given simultaneously to chemotherapy. Nevertheless confidence intervals are broad (38.5–60.1% for ypT0 ypN0 and 44.5–65.9% for ypT0 ypN0/+) and include reported pCR rates observed with other dual HER2-blockades (Table 4). The Tryphaena study reported a pCR rate (ypT0 is ypN0/) of 57.3% to 66.2% for pertuzumab/trastuzumab given completely or partly simultaneously to different chemotherapy backbone treatments (FEC followed by docetaxel or docetaxel/carboplatin). The NeoSphere study observed pCRs (ypT0 is ypN0/+) in 45.8% of the patients being treated with docetaxel, trastuzumab, and pertuzumab. The NeoALTTO study reported a pCR (ypT0 is ypN0/+) in 51.3% of the patients being treated for 18 weeks with trastuzumab and lapatinib, of which 12 were concomitant with weekly paclitaxel. However, these last two trials did not use an anthracycline as part of neoadjuvant treatment. Treatment effect in all these studies was strongly dependent

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Abbreviations: RG, regression grade 5 means no microscopic evidence of residual viable tumor cells (invasive or noninvasive) in all breast specimens and lymph nodes; grade 4, no residual tumor in breast specimens, but involved lymph nodes; grade 3, only residual noninvasive (in situ) tumor in breast tissue irrespective of lymph node status; grade 2, extensive tumor sclerosis with focal or multifocal evidence of only minimally invasive residual tumor (<0.5 cm), frequently extensive ductal carcinoma in situ; grade 1, increased tumor sclerosis with focal resorptive inflammation and/or marked cytopathic effects; and grade 0, no effect (adapted from Sinn et al.; ref. 25).
on HR status, pCR rates were 30% to 60% lower in patients with HR-positive tumors compared with patients with HR-negative tumors. Whereas in these three comparator trials only about 50% of patients had HR-positive tumors, this proportion in the DAFNE study was as high as 70.8%. Despite the small number of patients, the lower sensitivity of HR-positive tumors to chemo-targeted treatment was also observed in the DAFNE study, and might therefore explain the somewhat lower pCR rate. However, the results provide further support for the predictive value of LPBC and PIK3CA mutations in this treatment setting.

With the provision of loperamide as supportive treatment, afatinib appeared to be tolerated quite well, still almost one quarter of patients discontinued treatment with this tyrosine kinase inhibitor (TKI). However, skin toxicity and diarrhea appeared less in the DAFNE study compared with the lapatinib arms of NeoALTTO (grade 3 skin disorders 6.6%; grade 3 diarrhea 21.1%). Similar to the results of the DAFNE study no significant correlation was seen between the occurrence of such toxicities associated with lapatinib and pCR in the GeparQuinto study (29).
however, this is in opposite to a positive study observed in NeoALTTO (30).

The main weakness of the DAFNE study is the nonrandomized design and the relatively low sample size. Random selection of more resistant patients, for example, with HR-positive tumors and/or PIK3CA mutation could have significantly modified the overall results. As well the dose of afatinib with 20 mg/d might have been suboptimal, but the toxicity results of this study support that a higher dose in combination with trastuzumab and paclitaxel would not have been tolerable. A major strength of the study is the central confirmation of the receptor statuses, lymphocytic infiltrate, and PIK3CA status of all tumors, which prohibited the inclusion of patients with false HER2-positive disease.

Although afatinib (Giotrif) has been approved for patients with locally advanced or metastatic non–small cell lung cancer with activating EGFR mutation, a phase III randomized study (LUX-Neosphere) has been suboptimal, but the toxicity results of this study support that a higher dose in combination with trastuzumab and paclitaxel would not have been tolerable. A major strength of the study is the central confirmation of the receptor statuses, lymphocytic infiltrate, and PIK3CA status of all tumors, which prohibited the inclusion of patients with false HER2-positive disease.

In conclusion, the DAFNE trial did not meet its challenging primary endpoint to show a pCR rate of as high as 70% to suggest superiority of other currently available regimes using dual HER2 blockade in breast cancer.

Disclosure of Potential Conflicts of Interest

C. Hanusch is a consultant/advisory board member for Ingelheim Boehringer. S. Paepke is a consultant/advisory board member for PMF Medical Cologne, and Surgic Eye Munich. S. Kummel is a consultant/advisory board member for Celgene, EISAI, Novartis, and Roche AG. J. Huober receives reporting payments from speakers bureau honoraria from and is a consultant/advisory board member for GlaxoSmithKline and Roche. B. Gerber receives reporting payments from speakers bureau honoraria from AstraZeneca and EISAI. C. Denkert has ownership interest (including patents) in Sividon Diagnostics, Cologne. J.U. Blohmer is a consultant/advisory board member for Roche. G. von Minckwitz has ownership interest (including patents) in GBG Forschungs GmbH. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


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Table 4. Comparison of pCR rates in trials (>100 participants) investigating dual blockade of the HER2 receptor (32–35).

<table>
<thead>
<tr>
<th>Trial</th>
<th>DAFNE backbone</th>
<th>Neosaph (13)</th>
<th>Tryphena (16)</th>
<th>GeparSepto (32)</th>
<th>NeoALTTO (12)</th>
<th>NSABP B-41 (33)</th>
<th>CALGB 40601 (34)</th>
<th>GeparSixto (35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>P-EC</td>
<td>D</td>
<td>FEC-D/DCb</td>
<td>nP-EC</td>
<td>P</td>
<td>AC-P</td>
<td>P</td>
<td>MP + Cb</td>
</tr>
<tr>
<td>Duration (wks)</td>
<td>24 + 6</td>
<td>12</td>
<td>18</td>
<td>24 + 2</td>
<td>12 + 6</td>
<td>24</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Patients with two anti-HER2-directed agents</td>
<td>Haf</td>
<td>Hpt</td>
<td>Hpt</td>
<td>Hpt</td>
<td>HL</td>
<td>HL</td>
<td>HL</td>
<td>HL</td>
</tr>
<tr>
<td>N</td>
<td>65</td>
<td>107</td>
<td>223</td>
<td>395</td>
<td>145</td>
<td>171</td>
<td>117</td>
<td>273</td>
</tr>
<tr>
<td>pCR (ypT0/is ypNO), %</td>
<td>49.2</td>
<td>39.3</td>
<td>61.7</td>
<td>58</td>
<td>46.8</td>
<td>60.2</td>
<td>52</td>
<td>50.9</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; Af, afatinib; C, cyclophosphamide; Cb, carboplatin; D, docetaxel; E, epirubicin; F, 5-fluorouracil; H, trastuzumab; L, lapatinib; M, liposomal doxorubicin; nP, nab-Paclitaxel; P, paclitaxel; Pt, pertuzumab.

References


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Correction: Dual Blockade with AFatinib and Trastuzumab as NEoadjuvant Treatment for Patients with Locally Advanced or Operable Breast Cancer Receiving Taxane-Anthracycline Containing Chemotherapy—DAFNE (GBG-70)

In this article (Clin Cancer Res 2015;21:2924–31), which was published in the July 1, 2015, issue of Clinical Cancer Research (1), an incorrect clinicaltrials.gov trial registration number (NCT015591477) was printed in the abstract. The correct trial registration number is NCT01594177. The authors regret this error.

Reference

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Dual Blockade with AFatinib and Trastuzumab as NEoadjuvant Treatment for Patients with Locally Advanced or Operable Breast Cancer Receiving Taxane–Anthracycline Containing Chemotherapy — DAFNE (GBG-70)

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