ARTICLE

Lapatinib-Related Rash and Breast Cancer Outcome in the ALTTO Phase III Randomized Trial


Affiliations of authors: Department of Medicine, Breast European Adjuvant Study Team (BrEAST) Data Centre, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium (AS, EdA, MP, HAAJr); Frontier Science (Scotland) Ltd, Grampian View, Kincraig, Kingussie, UK (DAt, IB, CC); Novartis Pharmaceuticals Corporation, East Hanover, NJ (YH); Alliance Statistics and Data Center, Mayo Clinic, Section of Biostatistics, Scottsdale, AZ (ACD); Sunnybrook Odette Cancer Centre, the University of Toronto and the NCIC Clinical Trials Group, Toronto, Ontario, Canada (KIP); The Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD (ACW); Sana Klinikum Offenbach, Offenbach, Germany (CJ); National Institute of Oncology, Budapest, Hungary (IL); Helios Klinikum Berlin-Buch, Berlin, Germany (MU); Royal Marsden Hospital NHS Trust, Sutton/Surrey, UK (IS); Patricia Ritchie Centre for Cancer Care and Research, The University of Sydney, Mater Hospital, North Sydney, Australia (FB); Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China (BX); Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru (HG); Mayo Clinic, Jacksonville, FL (EAP)

Correspondence to: Hatem A. Azim Jr., MD, PhD, Department of Medicine, BrEAST Data Centre, Institut Jules Bordet, Boulevard de Waterloo, 121, 1000 Brussels, BE (e-mail: hatemazim@icloud.com)

Abstract

Background: Previously we have shown that early development of rash is associated with a higher chance of achieving pathological complete response to neoadjuvant lapatinib. In the current analysis, we investigate its impact on survival in the ALTTO phase III adjuvant trial.

Methods: In ALTTO, patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer were randomly assigned to adjuvant trastuzumab, lapatinib, their sequence, or their combination for a total duration of one year. We evaluated whether the development of early lapatinib-related rash (ie, within 6 weeks) is associated with disease-free (DFS) and overall survival (OS). Landmark analysis at eight weeks and time-dependent analysis were tested in a multivariable model stratifying on trial’s stratification factors. All statistical tests were two-sided.

Results: Out of 6098 lapatinib-treated patients, 3973 (65.2%) were included in the landmark analysis, of whom 1389 (35.0%) had developed early rash. After median follow-up of 4.5 years, the development of early rash was associated with a trend of improved DFS (multivariable: hazard ratio [HR] = 0.87, 95% confidence interval [CI] = 0.73 to 1.03, P = .10) and statistically significantly improved OS (multivariable: HR = 0.63, 95% CI = 0.48 to 0.82, P < .001) compared with subjects without early rash. Compared with patients randomly assigned to trastuzumab (n = 2051), patients who were randomly assigned to trastuzumab/lapatinib combination and developed early rash (n = 692) had superior DFS (multivariable: HR = 0.72, 95% CI = 0.55 to 0.92, P = .01) and OS (multivariable: HR = 0.59, 95% CI = 0.39 to 0.90, P = .01). Time-dependent analysis suggests that the occurrence of rash is predictive of lapatinib benefit, both when given in combination or sequential to trastuzumab.

Conclusions: Our results indicate that early development of rash identifies patients who derive superior benefit from lapatinib-based therapy.

Received: October 16, 2015; Revised: December 15, 2015; Accepted: February 9, 2016

© The Author 2016. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
Lapatinib is a tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptors epidermal growth factor receptor (EGFR) (HER1) and human epidermal grown factor receptor 2 (HER2) (1–3). It is considered one of the key agents in managing metastatic HER2-positive breast cancer, particularly after failure of trastuzumab. Its combination with different agents in the metastatic setting has been shown to improve response rates and progression-free and, in some cases, overall survival (4–9).

Skin rash is an adverse event (AE) that has been linked with not only lapatinib (10–13) but also other EGFR TKIs (14,15). This AE seems to affect a considerable portion of patients; however, it is generally manageable and only in few instances results in treatment discontinuation (16). Current data indicate that patients developing skin rash secondary to other EGFR TKIs, eg, erlotinib or gefitinib, have better response rate and progression-free survival in lung, pancreas, and head and neck cancers (17–20).

In breast cancer, we have previously investigated the association between the development of skin rash secondary to lapatinib and pathological complete response (pCR) in the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) trial (21), which compared trastuzumab, lapatinib, and their combination, all given with paclitaxel. We found that patients who developed early rash (ie, within 6 weeks of lapatinib initiation) have a higher chance of achieving pCR independent of other confounding factors (22).

To date, it is not fully elucidated why TKIs cause rash and why this side effect is associated with improved clinical outcome. EGFR signal transduction is known to be important in normal skin growth and homoeostasis, especially the epidermis component, which expresses EGFR on the keratinocytes (23,24). Thus, it is plausible that skin manifestations in response to TKIs that inhibit EGFR (like lapatinib) may be a surrogate of the therapeutic EGFR inhibitory effect on tumors. However, validation of this concept particularly in association with long-term outcome is yet to be confirmed in breast cancer.

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial is the largest adjuvant study to date in HER2-positive breast cancer, and its primary aim was to investigate the role of lapatinib in the adjuvant setting. The primary analysis indicated a statistically nonsignificant 16% reduction in disease-free survival (DFS) hazard rate with the combination of lapatinib and trastuzumab compared with trastuzumab (555 DFS events; hazard ratio [HR] = 0.84, 97.5% confidence interval [CI] = 0.70 to 1.02, P = .048) (25). In the current analysis, we hypothesized that patients who developed early lapatinib-related rash would derive superior benefit from lapatinib-based therapy.

### Methods

#### Study Patients

The Breast International Group and North Central Cancer Treatment Group/Alliance—BIG26/NO63D/EGF106708 (ALTTO) trial is an international, intergroup, open-label, phase III randomized trial. The detailed description of the trial, regimens, and key eligibility criteria are provided in the original report (25). In brief, patients were randomly assigned to one of four treatments as follows: intravenous (iv) trastuzumab, oral lapatinib (750 mg/day during chemotherapy and 1500 mg/day afterwards), a sequence of the two agents starting with 12 weekly doses of iv trastuzumab followed by a six-week “wash-out” and then 34 weeks of lapatinib at 1500 mg/day, and the combination of the two agents starting lapatinib at 750 mg/day during chemotherapy (reduced from an initial dose of 1000 mg/day based on safety data) with an escalation to 1000 mg/day after chemotherapy completion. Eligible patients had to have a histologically confirmed, completely excised invasive nonmetastatic centrally confirmed HER2-positive breast cancer and either node-positive disease or node-negative disease with pathological tumor size of 1 cm or greater.

ALTTO is registered at ClinicalTrials.gov number NCT00490139. Informed consent was obtained from all patients at study entry. The study was approved by the ethics committee of all participating sites. This substudy was approved by the ALTTO Executive Committee and was not preplanned as a part of the main analysis of the ALTTO trial. GlaxoSmithKline (GSK) funded the ALTTO trial; however, they were not involved in the design or conduction of this substudy.

### Rash Assessment

Skin rash was defined as per the Medical Dictionary for Regulatory Activities (MedDRA). The following reported AE preferred terms were included: ‘acne,’ ‘actinic keratosis,’ ‘dermatitis,’ ‘dermatitis aceneiform,’ ‘eczema,’ ‘erythema,’ ‘exfoliative rash,’ ‘rash,’ ‘rash generalized,’ ‘rash macular,’ ‘rash maculopapular,’ ‘rash papular,’ ‘rash pruritic,’ and ‘rash pustular’. These were the same terms used in the previously reported analysis investigating the association between lapatinib-related rash and pCR in the NeoALTTO trial (22). Grading of all AEs was made using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. According to the ALTTO protocol, patients with poorly tolerated skin AEs were managed as deemed appropriate by the investigator, including temporary lapatinib interruption but no longer than 14 days. For grade 4 rash manifested as toxic epidermal necrolysis (ie, Stevens-Johnson’s Syndrome, etc.), lapatinib was permanently discontinued.

### Statistical Analysis

In the current analysis, we investigated the impact of lapatinib-related early rash (ie, within 6 weeks of lapatinib initiation) on patient’s outcome. This cutoff was based on our previous study in which rash within six weeks appeared to identify patients who derive superior benefit of neoadjuvant lapatinib (22). The a priori hypothesis was that lapatinib-treated patients who develop early rash have superior long-term outcome. We evaluated the association between the development of rash and classic clinicopathological factors and investigated the median time to developing rash. Cross-tabulation of clinic-pathological characteristics factors by rash status of the patients in the lapatinib-containing arms was performed using Chi square test.

In order to remove guarantee-time bias, we performed landmark analysis to investigate the prognostic value of rash among patients enrolled in the lapatinib-containing arms (26). All patients who ceased follow-up because of an event or other reasons before the landmark time (8 weeks) were excluded from the analysis (CONSORT diagram) (Figure 1). The selection of landmark at eight weeks was made before the data analysis and was based on the six-week cutoff of early rash, plus two more weeks to allow for the window between random assignment and treatment initiation. This analysis did not include the trastuzumab—lapatinib sequential arm as lapatinib was started at
week 18 in this arm. Patients were grouped according to the
time of developing rash (ie, “early” rash and others, where
“others” include patients who developed rash after more than 6
weeks of lapatinib initiation or patients who did not develop
rash). Two survival endpoints were investigated; DFS and OS,
which were defined as originally reported in the main ALTTO
analysis (25). We also compared the outcome of patients who
developed early rash or not in the trastuzumab/lapatinib combi-
nation to those treated with trastuzumab alone.

We finally performed time-dependent analysis and interac-
tion tests to evaluate whether rash is predictive of lapatinib
benefit. For the trastuzumab/lapatinib combination vs trastuzu-
mab-alone group, we used a model assuming that early-onset
rash (<6 weeks) may have a different effect from not-early rash
(>6 weeks) or no rash. The trastuzumab—lapatinib sequential
vs trastuzumab alone was modeled in a way that the effect of
treatment is also time dependent as patients are assumed to
start lapatinib at 18 weeks post–random assignment. For this
reason, rash could not be analyzed as early/nonearly in the se-
quential arm but as any rash developing during treatment.

All survival analyses were performed using Cox proportional
hazards, stratifying on the trial’s stratification factors, which
are: timing of chemotherapy (concurrent vs sequential), central
hormone receptor status (positive vs negative), and lymph node
status (not assessed [neoadjuvant chemotherapy], node-nega-
tive, 1-3, or >4 positive nodes). Analyses were stratified on the
additional covariates rather than including them as propor-
tional terms in the regression model; hence, proportionality as-
sumptions were not required.

All statistical analyses were performed using SAS9.3. A P
value of less than .05 was considered statistically significant,
and all statistical tests were two-sided.

**Results**

**Association Between Rash and Clinicopathological
Characteristics**

All patients who were enrolled to the ALTTO trial and had avail-
sable safety data were included in the current analysis (n = 8270).
Six thousand ninety-eight patients were randomly assigned to a
lapatinib-containing arm and received at least one dose of lapa-
tinib (CONSORT diagram) (Figure 1), of whom 2006 patients
(32.9%) developed early rash while 1025 (16.8%) and 3067 (50.3%)
developed rash after six weeks or did not develop rash,
respectively.

Table 1 reports the patients’ characteristics according to the
development of rash. Similar to our previous observation in the
NeoALTTO trial, early rash was more common in younger pa-
tients (age ≤ 50 vs >50 years: 54.4% vs 45.6%, P < .001).
Otherwise, no statistically significant association with any

---

**Figure 1.** ALTTO rash substudy CONSORT diagram. *Out of 6194 patients randomly assigned to lapatinib-containing arms with safety data, 96 patients did not actually receive any dose of lapatinib, resulting in 6098 eligible for the current analysis.
clinopathological parameter was observed (Table 1). Table 2 summarizes the onset of rash in relation to starting lapatinib in the different treatment arms. Considering all patients who received lapatinib and developed rash at any time (n = 3031), the median time to developing rash was 27 days (interquartile range [IQR] = 10 to 63 days).

Prognostic Value of Early Rash in Lapatinib-Containing Treatment Arms

We evaluated the association between the development of early rash and DFS and OS using a landmark analysis at eight weeks. Out of 6098 lapatinib-treated patients, 3973 (65.2%) patients were included in the landmark analysis, of whom 1389 (35.0%) had developed early rash. At a median follow up of 4.5 years (min = 0.16 years, max = 6.31 years), we found that patients who were randomly assigned to either lapatinib alone or trastuzumab/lapatinib combination arm and developed early rash had better DFS (multivariable HR = 0.87, 95% CI = 0.55 to 0.92, P = .01) and OS (multivariable HR = 0.59, 95% CI = 0.39 to 0.90, P = .01) (Figure 2). By contrast, patients who were randomly assigned to the trastuzumab/lapatinib combination arm but did not develop early rash (n = 1319) had similar outcome to patients randomly assigned to the trastuzumab arm in terms of DFS (multivariable HR = 0.93, 95% CI = 0.77 to 1.12, P = .46) and OS (multivariable HR = 0.92, 95% CI = 0.69 to 1.22, P = .55) (Figure 2).

Time-Dependent Analysis and Predictive Value of Rash

Unlike lapatinib, trastuzumab with or without chemotherapy is less known to be associated with skin rash. Yet, up to 20% of patients randomly assigned to the trastuzumab-alone arm (n = 2051, DFS events = 292, OS events = 130), patients who were randomly assigned to the trastuzumab/lapatinib combination arm and developed early rash (n = 692) had better DFS (multivariable HR = 0.72, 95% CI = 0.55 to 0.92, P = .01) and OS (multivariable HR = 0.73, 95% CI = 0.59 to 0.77 to 1.12, P = .55) (Figure 2).
benefit of the trastuzumab—lapatinib sequence arm in terms of DFS (HR = 0.75, 95% CI = 0.59 to 0.96, Pinteraction = .05) and OS (HR = 0.55, 95% CI = 0.37 to 0.81, Pinteraction = .02). In addition, the results suggested that the occurrence of early rash was predictive of lapatinib benefit when given in combination with trastuzumab both for DFS (HR = 0.73, 95% CI = 0.54 to 0.98, Pinteraction = .10) and OS (HR = 0.55, 95% CI = 0.34 to 0.89, Pinteraction = .07) (Table 4).

Discussion

In the present study, we sought to determine whether early lapatinib-related rash could identify patients who derive maximum benefit of primary lapatinib-based therapy. This is the second analysis from a randomized controlled trial that confirms the association between early lapatinib-related rash and benefit of lapatinib. The first was in the neoadjuvant setting, and benefit was defined as higher chance of achieving pCR (22). In the current study, we show for the first time clear benefit in terms of OS.

As observed in the neoadjuvant setting, our study confirmed that early rash is more common in younger patients (age ≤ 50 years). The reason for this phenomenon is not clear. As the EGFR is important for normal epidermis growth and is expressed on the proliferating skin (27), it is possible that lapatinib effect on keratinocytes is age dependent. It is also possible that pharmacokinetic/pharmacodynamics changes during aging have an effect on the development of rash. Of note, studies of the effects of age on the pharmacokinetics of lapatinib have not been performed to date.

Previously, Fontanella et al. analyzed data from the GeparQuinto neoadjuvant trial, which investigated the role of neoadjuvant lapatinib but did not observe any association between the development of rash and outcome (28). There were several differences between both trials; NeoALTTO and GeparQuinto could explain this observation, most importantly the definition of rash, which was defined in the GeparQuinto as rash “any time” during the study (29). In the NeoALTTO trial, we did not find a statistically significant association between the development of rash at any time and pCR, yet only those

Table 2. Number of days from start of lapatinib to onset of rash*

<table>
<thead>
<tr>
<th>Onset of rash</th>
<th>Lapatinib (n = 2050)</th>
<th>Trastuzumab—lapatinib sequential (n = 1992)</th>
<th>Trastuzumab/lapatinib combination (n = 2056)</th>
<th>Total (n = 6098)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash any time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>1115</td>
<td>799</td>
<td>1117</td>
<td>3031</td>
</tr>
<tr>
<td>Median time to rash (Q1,Q3), d</td>
<td>29 (12, 64)</td>
<td>22 (9, 49)</td>
<td>29 (11, 68)</td>
<td>27 (10, 63)</td>
</tr>
<tr>
<td>Early rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>722</td>
<td>580</td>
<td>704</td>
<td>2006</td>
</tr>
<tr>
<td>Median time to early rash (Q1,Q3), d</td>
<td>15 (8, 28)</td>
<td>13 (7, 26)</td>
<td>14 (7, 26)</td>
<td>15 (7, 27)</td>
</tr>
<tr>
<td>Not early rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>393</td>
<td>219</td>
<td>413</td>
<td>1025</td>
</tr>
<tr>
<td>Median time to not early rash (Q1,Q3), d</td>
<td>87 (61, 165)</td>
<td>106 (61, 141)</td>
<td>89 (63, 169)</td>
<td>90 (62, 163)</td>
</tr>
</tbody>
</table>

*Q1 – first interquartile range; Q3 – third interquartile range.

Table 3. Prognostic value of early rash in all lapatinib-containing treatment arms*

<table>
<thead>
<tr>
<th>Type of rash</th>
<th>No.</th>
<th>Events No. (%)</th>
<th>Univariate HR (95% CI)</th>
<th>P†</th>
<th>Multivariable HR (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1268</td>
<td>238 (18.8)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T/L combination</td>
<td>1316</td>
<td>175 (13.3)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2584</td>
<td>413 (16.0)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Early rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>697</td>
<td>122 (17.5)</td>
<td>0.91 (0.73 to 1.13)</td>
<td>.40</td>
<td>0.95 (0.77 to 1.19)</td>
<td>.67</td>
</tr>
<tr>
<td>T/L combination</td>
<td>692</td>
<td>74 (10.7)</td>
<td>0.77 (0.59 to 1.01)</td>
<td>.06</td>
<td>0.74 (0.56 to 0.97)</td>
<td>.03</td>
</tr>
<tr>
<td>All</td>
<td>1389</td>
<td>196 (14.1)</td>
<td>0.86 (0.72 to 1.01)</td>
<td>.07</td>
<td>0.87 (0.73 to 1.03)</td>
<td>.10</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1268</td>
<td>124 (9.8)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T/L combination</td>
<td>1316</td>
<td>76 (5.8)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2584</td>
<td>200 (7.7)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Early rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>697</td>
<td>41 (5.9)</td>
<td>0.59 (0.42 to 0.85)</td>
<td>.004</td>
<td>0.61 (0.43 to 0.87)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>T/L combination</td>
<td>692</td>
<td>28 (4.0)</td>
<td>0.68 (0.44 to 1.04)</td>
<td>.08</td>
<td>0.64 (0.42 to 0.99)</td>
<td>.047</td>
</tr>
<tr>
<td>All</td>
<td>1389</td>
<td>69 (5.0)</td>
<td>0.62 (0.47 to 0.82)</td>
<td>&lt;.001</td>
<td>0.63 (0.48 to 0.82)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

* Landmark analysis was set to eight weeks post-random assignment. CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival; T/L combination = trastuzumab/lapatinib combination.
† P values were two-sided using Wald test from Cox model.
‡ Others (defined as patients who developed rash after 6 weeks from starting lapatinib or patients who did not develop rash) were used as comparator. All defined as lapatinib alone and trastuzumab/lapatinib combination.
patients who developed early rash had a higher chance of achieving a pCR (22). In the current study, we used the same definition of early rash and were able to show a statistically significant association with long-term outcome.

We did not observe a clear relationship between dose and development of rash. Previously, escalation of the dose of erlotinib until grade 2 rash is developed has been shown to be associated with improved survival in non–small cell lung cancer (30).
In our study, nearly 30% of patients developed early rash across the three lapatinib treatment arms despite that the dose varied from 1500 mg/day in the lapatinib-only and the sequential arms to 750 mg/day in the combination arm. Thus, based on our analysis, it does not appear that increasing the lapatinib dose to achieve rash is a strategy that is warranted with lapatinib.

Patients who developed early rash experienced skin toxicity after a median time of two weeks of initiating lapatinib and thus this could serve as an early marker of response to identify patients who are likely to derive meaningful benefit from this agent. This may have implications, especially in following patients in the metastatic setting where lapatinib plays an important role in the treatment armamentarium of metastatic HER2-positive breast cancer. In the adjuvant setting, the potential clinical application of our findings is rather limited at the time being as lapatinib is not currently approved in this setting. However, it is important to emphasize that patients who were randomly assigned to the dual combination and developed early rash had 41% reduction in the risk of death compared with patients randomly assigned to the current standard of care, trastuzumab. This finding is in line with our hypothesis and our previous findings in NeoALTTO, which underscores the robustness of this association. Hence, we believe that further testing of lapatinib in any setting should focus on those patients who develop rash although data in the metastatic setting are lacking. Our findings could be also of particular clinical relevance in countries in which resources are limited and in which other HER2-targeted agents are not routinely available.

This is an unplanned analysis of a prospectively conducted trial with subgroups of patients classified by an event measured after random assignment, thus we acknowledge the limitations and potential biases of such analysis. However, it is important to note that we evaluated a clear, literature-supported single hypothesis with predefined time cutoffs based on a previous evaluation of another randomized trial and opted to use landmark analysis in performing our statistical evaluation. The selection of landmark analysis at eight weeks was also preplanned before the data analysis. Thus, we believe this would very much limit the impact of any potential biases on the obtained results.

In conclusion, early rash is the first “biomarker” in the field of HER2-positive breast cancer to predict benefit to a HER2-targeted agent. The results of this study are consistent with our previous findings in the neoadjuvant setting, thus confirming that early development of skin rash can identify patients who would derive superior benefit of lapatinib.

Funding
The ALTTO trial was supported by GlaxoSmithKline (GSK) and the National Cancer Institute of the National Institutes of Health under Award Numbers U10CA180821 and U10CA180882 to the Alliance for Clinical Trials in Oncology, CA025224 to the legacy North Central Cancer Treatment Group (NCCTG), and CA077202 to the National Cancer Information Center (NCIC) Clinical Trials group. NCIC CTG participation was also supported by the Canadian Cancer Society Research Institute under Award Number 015469 and 021039.

Notes
This work was presented as a poster discussion in the 2015 San Antonio Breast Cancer Symposium.

The study funders had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

We thank the patients who participated in the ALTTO study; the Breast European Adjuvant Study Team Data Centre; the Breast Science Team; the Breast International Group Headquarters; the US National Cancer Institute (NCI), the North Central Cancer Treatment Group (NCCTG; Alliance); the ALTTO Executive and Steering Committee members; the Independent Data Monitoring Committee (IDMC) members; the Cardiac Advisory Board members; the three central pathology laboratories; GlaxoSmithKline; and the doctors, nurses, trial coordinators, and pathologists who participated in ALTTO.

Amir Sonnenblick is an European Society for Medical Oncology translational research fellow.

Hatem A. Azim Jr. served as a consultant and received honorarium from GSK and Novartis.

Evanandro de Azambuja has received honoraria from Novartis and travel grants from GSK.

Amylou C. Dueck has received grants from GSK during the conduct of the study.

Kathleen I. Pritchard reports personal fees from Sanofi-Aventis, grants and personal fees from AstraZeneca, personal fees from Pfizer, grants and personal fees from Roche, personal fees from Amgen, grants and personal fees from Novartis, personal fees from GlaxoSmithKline, personal fees from Boehringer Ingelheim, personal fees from Genomic Health, and grants and personal fees from Eisai outside the submitted work.

Antonio C. Wolff reports grants from NCI during the conduct of the study; and grants from Genentech and GSK outside the submitted work.

Christian Jakisch reports personal fees from Roche and GSK outside the submitted work.

Frances Boyle reports serving on advisory boards for GSK, Novartis, and Roche.

Edith A. Perez reports employment at Genentech, Inc., after completion of this study.

Martine Piccart reports personal fees from GSK, PharmaMar, Amgen, Astellas, AstraZeneca, Bayer, Eli Lilly, Invivis, MSD, Novartis, Pfizer, Roche-Gentech, Sanofi Aventis, Symphogen, Synthon, and Verastem during the conduct of the study.

All other authors have no conflict of interest to declare.

References