The Neoadjuvant Model Is Still the Future for Drug Development in Breast Cancer

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Abstract

The many improvements in breast cancer therapy in recent years have so lowered rates of recurrence that it is now difficult or impossible to conduct adequately powered adjuvant clinical trials. Given the many new drugs and potential synergistic combinations, the neoadjuvant approach has been used to test benefit of drug combinations in clinical trials of primary breast cancer. A recent FDA-led meta-analysis showed that pathologic complete response (pCR) predicts disease-free survival (DFS) within patients who have specific breast cancer subtypes. This meta-analysis motivated the FDA’s draft guidance for using pCR as a surrogate endpoint in accelerated drug approval. Using pCR as a registration endpoint was challenged at ASCO 2014 Annual Meeting with the presentation of ALTTO, an adjuvant trial in HER2-positive breast cancer that showed a nonsignificant reduction in DFS hazard rate for adding lapatinib, a HER-family tyrosine kinase inhibitor, to trastuzumab and chemotherapy. This conclusion seemed to be inconsistent with the results of NeoALTTO, a neoadjuvant trial that found a statistical improvement in pCR rate for the identical lapatinib-containing regimen. We address differences in the two trials that may account for discordant conclusions. However, we use the FDA meta-analysis to show that there is no discordance at all between the observed pCR difference in NeoALTTO and the observed HR in ALTTO. This underscores the importance of appropriately modeling the two endpoints when designing clinical trials. The I-SPY 2/3 neoadjuvant trials exemplify this approach. Clin Cancer Res; 21(13); 2911–5. ©2015 AACR.

Introduction

Over the last 2 decades, there has been an explosion in the development of new drugs for cancer based on mechanistic preclinical research. However, relatively few have successfully improved clinical outcomes and ultimately reached the market. The traditional process of determining which drugs will ultimately benefit patients is long and expensive, with recent reports estimating a cost of over 2 billion dollars and time horizon of 10 to 15 years to get a promising drug to market (1). The greatest opportunity for curing cancer occurs when it is has not metastasized (2, 3). Despite the obvious advantage of focusing phase II and III trials in early disease, clinical drug development has traditionally begun in the metastatic setting. Metastatic benefit does not always predict adjuvant benefit and so there are false positives. Similarly, lack of benefit in metastatic disease may miss a benefit in primary disease and so there are almost certainly false negatives that we do not know about because they failed to pass the metastatic hurdle. The neoadjuvant platform provides what is likely to be a more informative mechanism of adjuvant benefit. A prototype demonstrating the greater impact of effective drugs when given early is imatinib (Gleevec) in CML (4). The introduction of imatinib led to a dramatic improvement in survival rates when patients were treated in the accelerated phase but not for those treated in blast crisis. Adjuvant therapies offer increased cure rates in numerous disease settings, with effective agents targeting micrometastatic, minimal residual disease.
Her2
bene
in the breast and lymph nodes, a pathologic complete response
indication of the treatment’s effect by making the posttreatment
the other hand, the neoadjuvant approach provides a very clear
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the patient’s tumor recurs. The number of events, and not the
little information accrues about the treatment’s effect until and if
the adjuvant approach is ill suited for evaluating its bene
There were several differences between the two trials, apart from
the timing of surgery. First, to state the obvious, they were different
trials. Even if two trials have exactly the same design and are
conducted in exactly the same populations, their results can be
markedly different. Second, the populations had different risks,
with 4-year DFS in NeoALTTO about 75% versus 87% in ALTTO. Risk
by itself is not usually a predictor of therapeutic bene
ALTTO also had a greater proportion of node
negative patients, although nodal status is not predictive of the
benefits of anti-HER2 therapy. However, ALTTO also had a greater
proportion of hormone-receptor positive tumors, and these are
less sensitive to anti-HER2 therapy. Third, the order of chemother-
apy was different in the two trials, although this probably had little
effect. Finally, pCR was assessed in NeoALTTO before the
anthracycline-based chemotherapy component of the regimen.
Anthracyclines are well known to be effective in HER2-positive
disease and this might have served to exaggerate the effects of
lapatinib, although the opposite could also have been true.
The ALTTO investigators recognized that the trial was under-
powered and they quite appropriately wanted to present whatever
information was available to patients as soon as reasonable,
despite the lower power. The planned number of DFS events in
the two arms in question was 850. The design was modified when
the overall event rate was lower than expected, with an announce-
ment of results planned at median follow-up of 4.5 years even if
there were fewer than 850 events at that time. The analysis
announced at ASCO 2014 had only 555 events. With an additional
295 events, the observed HR of 0.84 or even slightly higher would
have been statistically significant; although the additional events
would likely have changed the HR, the direction is not clear.

**Discussion**

The current debate about the relevance of neoadjuvant end-
points in drug development is based on the conclusion, or rather,
the assumption, that the results of ALTTO were not consistent
with the results of NeoALTTO. Some of the arguments stem from
how statistical significance, or lack thereof, is interpreted. Statis-
tical significance does not imply truth and lack of statistical
significance does not imply falsity. In this case, reliance on a
yes/no interpretation of statistical significance leads to the wrong
conclusion. NeoALTTO was considered “statistically significantly
positive” for pCR, whereas ALTTO was reported to be “statistically
significantly negative” for DFS. The ALTTO and NeoALTTO results

**ALLTO and NeoALTTO Trials in Context**

It is within this context that the findings of the ALTTO trial were
presented at the American Society of Clinical Oncology 2014
Annual Meeting in Chicago (11). ALTTO showed that the addi-
tion of lapatinib to trastuzumab and standard adjuvant chemo-
therapy was associated with a nonsignificant reduction in DFS in
HER2-positive tumors. The HR was 0.84 (97.5% CI, 0.70–1.02)
on the basis of about 2,100 patients in each of the two groups. The
two-sided P value of 0.048 was not significant because the
investigators had added another comparison, the noninferiority
of trastuzumab followed by lapatinib versus trastuzumab, both
for a total of one year. These results were contrasted with
NeoALTTO, a neoadjuvant trial on HER2-positive tumors at
higher risk than those in ALTTO. NeoALTTO was reported in
2012 and showed a statistically significant improvement in the
rate of pCR (12).

The lack of a statistically significant improvement in DFS in
ALTTO despite the significant improvement in pCR in NeoALTTO
raised concerns about the validity of using pCR determined in the
neoadjuvant setting to predict DFS outcomes when the same
therapies are used in the more typical postsurgery adjuvant
setting. This presents an important opportunity to analyze the
reported results and to determine whether indeed we should back
away from pursuing pCR as an efficient and effective way of
predicting a therapy’s long-term bene

Despite the obvious potential advantages of early treatment,
the adjuvant approach is ill suited for evaluating its benefits. Very
little information accrues about the treatment’s effect until and if
the patient’s tumor recurs. The number of events, and not the
number of patients, determines the power of a clinical trial. On
the other hand, the neoadjuvant approach provides a very clear
indication of the treatment’s effect by making the posttreatment
tumor available at surgery. The eradication of all invasive disease
in the breast and lymph nodes, a pathologic complete response
(pCR), has been shown in many randomized trials of chemother-
apy and targeted therapies to confer a recurrence-free survival
benefit (5–8). The FDA meta-analysis quantifies the benefit that
experiencing a pCR confers by receptor subtype in women
with high-risk primary breast cancer (9). Importantly, the predictive
benefit of pCR is even greater when evaluated within subtypes
than when all subtypes are combined (7).

The ability of the neoadjuvant setting to predict survival ben-
efits to adjuvant therapy has already been demonstrated within
the context of Her2 þ breast cancer. In the NOAH trial, trastuzu-
imb, when added to standard anthracycline-based neoadjuvant
therapy, significantly improved pCR rates and subsequently
improved EFS [HR, 0.59; 95% confidence intervals (CI), 0.38–
0.90; P = 0.031; ref. 10]. This subsequently translated to a bene
of trastuzumab in the adjuvant setting that was demonstrated in
the combined NSABP B-31/NCCTG 9831 trial analysis, with an
absolute improvement in disease-free survival (DFS) of 12% (HR,
0.48; P < 0.0001; ref. 3), establishing a new standard of care for
Her2 þ nonmetastatic breast cancer.

**Translational Relevance**

The recent results of the ALTTO trial are consistent with the
predicted benefits from the neoALTTO trial, despite significant
differences in the patient populations of the two trials. These
results support the neoadjuvant setting as a suitable and
important setting for evaluating promising, new targeted
agents but highlight the essential requirement for rigorous
study design and statistical planning in confirmatory neoad-
juvant and adjuvant studies. Future efforts to confirm
improvements in pathologic complete response (pCR) should
focus on testing neoadjuvant therapies in trials in which event-
free survival (EFS) is an important endpoint and in which the
relationship between pCR and EFS is an important analysis.
This will definitively test the hypothesis that the neoadjuvant
strategy can significantly reduce the time, cost, and number of
patients to get new drugs approved and demonstrate that early
(pCR) and late (EFS) benefits of targeted therapy are highly
associated in specific biomarker-defined patient populations.

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show how using these terms, rather than considering the actual results, can lead to erroneous conclusions. In actuality, despite differences in the two trials that might be expected to lead to discordant results, the results of ALTTO are essentially perfectly predicted by NeoALTTO and the FDA meta-analysis (9).

This meta-analysis showed that the EFS HR for HER2-positive breast cancer patients achieving a pCR versus not pCR was 0.39 (95% CI, 0.31–0.50). (The FDA’s use of EFS was similar to ALTTO’s use of DFS except that ALTTO considered second primary cancers to be events. We will use DFS and EFS interchangeably.) An obvious and quite reasonable concern is that the HR in the meta-analysis may not apply for a particular experimental therapy. For example, adding lapatinib to trastuzumab might change some non-responders to having pCRs but might not prolong those patients’ EFS.

What HR would the FDA’s meta-analysis have predicted for ALTTO based on the pCR improvement in NeoALTTO? The primary endpoint in NeoALTTO was pCR in the breast, with the combination improving the rate by 22%; the improvement in pCR was 20% (49% for the combination vs. 29%) when pCR included both the breast and axilla. The "pCR" and "No pCR" curves, shown in Fig. 1, are smoothed versions of the EFS curves in the FDA’s meta-analysis of patients with HER2-positive tumors (18). The HR of 0.39, as indicated in the figure, is a 61% reduction in the hazard of recurrence. A 20% improvement in pCR would mean moving 1 in 5 patients from the “No pCR” curve to the “pCR” curve. Such a shift would obviously give rise to a reduction in EFS hazard for the combination that is smaller than 61%, although it would not be as small as one-fifth of this quantity. The resulting HR for the treatment comparison as shown in the figure is 0.83, almost exactly the observed value is 0.84 in ALTTO.

Taking this argument a step further, there are a total of five randomized trials that evaluated trastuzumab ± lapatinib in the neoadjuvant setting (including NeoALTTO), with a total of over 1,200 patients (Table 1). They are quite relevant in predicting ALTTO results. The combined overall pCR advantage of the combination of lapatinib, trastuzumab, and chemotherapy over trastuzumab/chemotherapy alone in these five trials was 13%. On the basis of the FDA meta-analysis, the EFS HR corresponding to a 13% pCR advantage in HER2-positive disease is 0.88. So using all the relevant neoadjuvant data, the results of ALTTO, with its HR of 0.84, are actually somewhat more positive than the FDA’s meta-analysis would predict. The difference between the expected 0.88 and the observed 0.84 is easily explained by random variability, but any surprise at the results of ALTTO should be because they were more, not less, positive than expected. In any case, the results of ALTTO support the relationship between pCR and EFS in the FDA’s meta-analysis whether using NeoALTTO alone or all five trials in Table 1.

Moving forward, trials should be prospectively designed to test the neoadjuvant model. This strategy is being used in the development of neratinib. In contrast with lapatinib, this irreversible small-molecule inhibitor of the HER/ErbB family of receptor-tyrosine kinases provides a different mechanism of action and potentially greater potency than first-generation HER kinase inhibitors such as lapatinib. In preclinical studies, neratinib demonstrated in vitro activity against cancer cell lines of different phenotypes, including HER2-overexpressing as well as non-HER2-overexpressing cells. The potential efficacy of neratinib in the (neo)adjuvant setting was demonstrated in I-SPY 2, in which neratinib was evaluated in patients receiving standard adjuvant chemotherapy (paclitaxel qwk × 12, doxorubicin, and cyclophosphamide q2-3 wk × 4, T−AC; ref. 13). Patients with HER2-negative tumors were randomized to neratinib plus T−AC chemotherapy (i.e., N+T−AC vs. T−AC). Patients with HER2-positive tumors were randomized to the same experimental regimen (N+T−AC) versus trastuzumab +T−AC, allowing a direct comparison of neratinib with trastuzumab. Neratinib met the predictive probability criterion in the predefined HR^HER2 destroy signature (where HR stands for hormone receptor), “graduated,” and accrual ceased (115 N patients and 78 concurrently randomized controls). In the higher HR^HER2 signature, the probability of neratinib having a larger pCR rate than control was 95%. On the basis of these results, phase III testing of neratinib in I-SPY 3 is planned. I-SPY 3 has been designed specifically to test the hypothesis that drugs found in a phase II setting such as I-SPY 2 will show success by demonstrating a DFS improvement in a phase II trial in specific patient subsets previously identified in I-SPY 2. In I-SPY 3, both pCR and EFS are primary endpoints. The sample size is reestimated adaptively in I-SPY 3 based on the pCR results in the experimental and control arms, and on predictions of EFS effect with longer follow-up. The trial uses the modeling from the FDA meta-analysis, but because it is not clear that the meta-analysis applies in the setting of I-SPY 3 and with the treatment regimens in I-SPY 3, that model is updated based on the accumulating information about the relationship between pCR and EFS within those regimens.

The ALTTO results have caused some in the field to call for the abandoning of the neoadjuvant model for drug development in favor of a return to large conventional adjuvant clinical trials. However, as shown above, the statistical ALTTO/NeoALTTO relationship confirms the value of the neoadjuvant setting to identify active new agents that improve outcomes in early breast cancer. The results of ALTTO do not diminish the enthusiasm for

![Table 1. Neoadjuvant trials of lapatinib](image)

<table>
<thead>
<tr>
<th>Clinical trial (ref.)</th>
<th>Sample size</th>
<th>Improvement in pCR with addition of lapatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoALTTO (12)</td>
<td>277</td>
<td>20%</td>
</tr>
<tr>
<td>CALGB 40601 (18)</td>
<td>233</td>
<td>9%</td>
</tr>
<tr>
<td>CHELROB (19)</td>
<td>119</td>
<td>22%</td>
</tr>
<tr>
<td>NSABP B-41 (20)</td>
<td>529</td>
<td>11%</td>
</tr>
<tr>
<td>TRIO US B-07 (21)</td>
<td>92</td>
<td>5%</td>
</tr>
<tr>
<td>Total</td>
<td>1,250</td>
<td>13%</td>
</tr>
</tbody>
</table>

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**Figure 1.** Expected EFS curves for trastuzumab as well as for the combination of trastuzumab and lapatinib are shown based on the NeoALTTO results. Reprinted with permission from Berry (13).
testing promising new agents, but rather, provide further impetus to reduce the large size of adjuvant trials by focusing on agents with a higher impact and on patients with higher risk and having a particular biomarker signature.

The neoadjuvant approach presents the opportunity to speed drug development while simultaneously providing real-time benefits to patients who participate in such trials. Women who present with breast cancers that have a 30% or greater risk of developing metastatic disease in the first 5 years after diagnosis are usually advised to receive adjuvant chemotherapy. There is no reason, in the setting where that recommendation is clear, not to offer those patients systemic treatment before surgical resection. Surgical options are improved after neoadjuvant therapy for the vast majority of patients (16). Response to therapy provides prognostic and predictive information and informs decisions about adjuvant radiation treatments. For example, for some women with excellent response to systemic therapy, radiation can even be avoided after mastectomy (17).

The neoadjuvant approach, particularly in the context of carefully designed trials, maximizes information garnered and maximizes our ability to correlate early response with EFS outcomes.

However, the ascertainment of residual disease should be rigorous and standardized. The emerging rigorous standards for measuring pCR had not been developed at the start of the NeoALTTO trial. The primary endpoint of NeoALTTO was the breast only (not breast and axillary lymph nodes). The latter is the currently accepted standard and it is the basis of the FDA’s draft guidance for accelerated drug approval (13). Indeed, it is now critically important to standardize the procedures for pathologic assessment of residual disease across international clinical trial groups, specialty societies, and regulatory bodies, and this should increase the chance of accurate and reproducible results within and across trials.

In summary, pCR is a good predictor of EFS within breast cancer subtypes and should continue to be used as an opportunity to accelerate evaluation of promising agents. The results from ALTTO should not slow this acceleration. Instead, neoadjuvant endpoints maximize our ability to correlate early response with EFS.

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