The Role of Neoadjuvant Trials in Drug Development for Solid Tumors

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Abstract

The relatively low success rate of phase II oncology trials in predicting success of novel drugs in phase III trials and in gaining regulatory approval may be due to reliance on the endpoint of response rate defined by the Response Evaluation Criteria in Solid Tumors (RECIST). The neoadjuvant treatment paradigm allows the anti-tumor activity of a novel therapy to be determined on a pathological basis at the time of surgery instead of by RECIST, which was not developed to guide clinical decision making or correlate with long-term outcomes. Indeed, the US Food and Drug Administration (FDA) endorsed pathological complete response (pCR) as a surrogate for overall survival in early-stage breast cancer and granted accelerated approval to pertuzumab based on this endpoint. We propose that pathological response is a biologically rational method of determining treatment effect that may be more likely to predict overall survival. We discuss some advantages of the neoadjuvant trial design, review the use of neoadjuvant therapy as standards of care, and consider the neoadjuvant platform as a method for drug development.
Introduction

The primary objective of phase II trials in oncology has been to determine whether a novel drug has sufficient antitumor activity to warrant further investigation in phase III trials. Because of the cost and number of patients required, the failure of a phase III trial has detrimental financial and human ramifications. Most observers have concluded that phase II studies in oncology have had a poor track record in predicting success in phase III trials as well as eventual regulatory approval (1). By one estimate, only 57% of oncology drugs taken from phase II to phase III obtain US Food and Drug Administration (FDA) approval, a proportion notably lower than for non-oncology drugs (2). The likelihood that a positive phase II trial of combination therapy will result in a subsequent trial that improves the standard of care within 5 years has been reported to be only 0.038 (3).

This low predictive value of phase II trials may be due to reliance on the endpoint of response rate (RR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) (2). RECIST was based on work done decades ago to standardize tumor responses in the absence of modern cross-sectional imaging techniques (4,5). Criteria for partial responses were based on the precision with which oncologists could differentiate solid spheres of different sizes under a layer of foam rubber (4), not based on clinical outcomes. There was never any claim that the partial response criteria correlated with clinically meaningful outcomes. In fact, the original WHO response criteria (5) and later RECIST (6) stressed that “it is not intended that these RECIST guidelines play a role in…decision making, except if determined appropriate by the
treatment oncologist” (6). Therefore, it is not surprising that RR has not been a reliable endpoint for phase II trials (7–9).

It seems reasonable to speculate that pathological complete response (pCR) might correlate more strongly with overall survival (OS) than response rates defined by RECIST. pCR is a biologically rational reflection of a therapy’s ability to eradicate metastatic disease and may therefore serve as a surrogate for OS. Since the number of tumor cells in undetectable micrometastases is many logs lower than the cell number in clinically evident tumors, even pathological responses less than complete eradication of the detectable tumor might correlate with improved overall survival. The strategy of neoadjuvant therapy (treatment prior to complete surgical resection) permits investigators to assess tumor response on a pathological basis. In this setting, it may be possible to assess treatment benefit in a more meaningful way than in traditional phase II trials using RECIST. In this review, we will consider the use of neoadjuvant trials as a way to identify treatments perhaps more likely to improve overall survival and as a strategy for drug development.

**Correlation of Pathological Response and Overall Survival**

Different measurements of pathological response after neoadjuvant therapy have been demonstrated to correlate with overall survival across various solid tumors (Table 1). The most extensive experience using neoadjuvant therapy is in breast cancer. A strong association between pCR and survival has been demonstrated in many multi-institutional, randomized neoadjuvant trials of chemotherapy in early-stage breast cancer (10–15). However, the definition of pCR varied across these neoadjuvant breast...
cancer studies and the relationship between pCR and long-term benefit was not always clear. To address these challenges, the FDA performed a pooled analysis of nearly 13,000 patients enrolled in neoadjuvant breast cancer trials (16). The eradication of invasive cancer in both the resected breast tissue and regional lymph nodes was found to correlate more strongly with improved long-term outcomes than was tumor eradication in the breast alone. In addition, the pooled analysis found individual patients who attain a pCR had a 64% reduction in the risk of death compared with patients who did not. At the individual trial level, there was only a weak association between increases in the proportion of patients achieving a pCR and the ability of treatment to improve OS. However, the heterogeneous patient populations, the low overall rates of pCR, and the lack of targeted therapy in the trials included in the analysis can explain this finding (17). Although the FDA ultimately concluded that pCR meets the surrogate endpoint criteria of being “reasonably likely to predict clinical benefit” (18), future pooled analyses of targeted therapy trials in biomarker defined breast cancer subtypes could help more firmly establish pCR as a surrogate endpoint for long-term outcomes (19).

In neoadjuvant bladder cancer trials, pathological response less than complete responses have been associated with improved overall survival (20). In an analysis of 147 patients by Splinter et al., patients with muscle-invasive bladder cancer (MIBC) whose disease was downstaged to no muscle invasion (<pT2) after neoadjuvant chemotherapy experienced a 75% survival at 5-years compared to 20% survival for those whose tumors that still showed muscle-invasion (≥pT2 residual disease) (21). The equivalency of pCR and <pT2 in predicting overall survival after neoadjuvant chemotherapy for bladder cancer was confirmed in a prospective trial (22) and a
retrospective analysis (23). The development of the pathological response criteria for bladder cancer highlights the importance of considering the disease biology when defining the endpoint. Neoadjuvant phase II trials in MIBC are a model for rational drug development and can utilize <pT2 as a surrogate endpoint (24).

In other solid tumors, where eradication or significant down-staging of disease after neoadjuvant therapy is a rare event, investigators have used histopathologic methods to categorize response and correlate them with outcome. In stage IB-IIIA non small cell lung cancer (NSCLC), the median rate of pCR from 15 trials of neoadjuvant chemotherapy was only 4% (range 0-16%) (25). Pataer et al. (26) developed a technique for assessing response to neoadjuvant chemotherapy based on mean percentage of residual viable tumor cells taken from sampled tissue. In a comprehensive tissue analysis of 192 patients with resected stage I-IV NSCLCs given neoadjuvant chemotherapy, a cutoff of ≤ 10% viable tumor was associated with improvement in overall survival (HR 2.39, p=0.05 if >10% viable tumor) on multivariate analysis (26,27). These methods of evaluating pathological response (26) were applied prospectively in a trial of 50 patients with stage IB-IIIA NSCLC given neoadjuvant chemotherapy and bevacizumab (28). Of the 22% of patients with ≤10% viable tumor, 100% were alive at 3 years compared with only 49% of those who had >10% residual tumor (p=0.01); this remained significant after adjustment for stage (p=0.02). Although validation in larger studies across NSCLC histologies is needed, Hellman et al. proposed that ≤10% residual tumor in resected lung and lymph node tissue should be regarded as a surrogate of overall survival in patients with resectable NSCLCs given neoadjuvant chemotherapy (25).
These experiences, and others not discussed here (29–31), indicate that neoadjuvant treatment can lead to improved overall survival depending on how response is defined. While some trials used pCR as the endpoint, pathological responses less than complete may be associated with improved survival in certain tumor types.

**Neoadjuvant Therapy as Standard of Care**

Neoadjuvant administration of systemic therapy has the following potential benefits to patients: a) tumor cytotreduction leading to improved surgical outcome or, in some cases, less radical surgery; b) sooner treatment of systemic metastases without the possible barrier of postoperative complications; c) ability to determine, in a short period of time, if the tumor is sensitive to the systemic therapy. Indeed, neoadjuvant therapy is used as a standard of care for some tumors in carefully selected patients (29,32–34).

**Breast cancer**

In early-stage breast cancer, multiple studies have shown that neoadjuvant therapy improves overall survival and may also reduce the extent of local surgery required (10,35–37). The multidisciplinary approach required and the current controversies have been reviewed recently (32). Neoadjuvant therapy appears to be more beneficial in aggressive subtypes such as triple-negative and HER2-positive tumors that are more chemosensitive and have higher pCR rates (15,38).

**Bladder cancer**
Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy is a standard of care for muscle-invasive bladder cancer (MIBC). Randomized neoadjuvant trials using MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) (20) or CMV (cisplatin, methotrexate, and vinblastine) (39) prior to radical cystectomy have both been shown to improve survival compared to cystectomy alone. Patients receiving neoadjuvant MVAC had superior disease specific survival (HR=1.66, 95% CI, 1.22-2.45, p=0.002) and a trend toward superior overall survival (HR=1.33, 95% CI, 1.00-1.76) compared with patients who were managed with surgery alone, with an overall survival of 57% and 43% at 5 years, respectively (p=0.06). The neoadjuvant CMV trial reported that neoadjuvant CMV was associated with a 16% relative improvement in survival (p=0.037) and a 23% relative improvement in metastasis-free survival (p=0.0001) at 10 years. Given that gemcitabine and cisplatin (GC) is better tolerated and achieves similar survival rates to MVAC in the metastatic disease setting (40), it is frequently used as a substitute for MVAC in the neoadjuvant setting and has similar pathological response rates (41). In a meta-analysis of over 3,000 patients with MIBC, there was a 5-year overall survival benefit seen with neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy versus radical cystectomy alone (HR=0.86, 95% CI, 0.77-0.95, p=0.003) (33).

Non-small cell lung cancer (NSCLC)

In patients with resectable NSCLCs, neoadjuvant chemotherapy can improve overall survival. In the 1990's, two small, randomized trials were terminated early on the basis of an interim analysis showing significant improvement in survival for neoadjuvant chemotherapy followed by surgery versus surgery alone (42,43). In a meta-analysis of
thirteen randomized controlled trials by Song et al. (34), patients with stage IB-III A NSCLC who received neoadjuvant chemotherapy had improved overall survival compared with patients who were managed with surgery alone (combined HR = 0.84; 95% CI, 0.77-0.92; p=0.0001). These results were similar to that of a prior meta-analysis, in which a combined HR of 0.82 (95% CI, 0.69-0.97) was obtained. A more recent phase III trial in patients with stage IB-III A NSLCC randomized patients to surgery alone or surgery plus neoadjuvant cisplatin and gemcitabine (44). The hazard ratio for overall survival was 0.63 (95% CI, 0.43 – 0.92, p=0.02) favoring the neoadjuvant chemotherapy arm. In addition, patients with stage IIB/IIIA disease had a survival benefit of 23.4% at 3 years.

**Other tumor types**

Randomized trials of neoadjuvant chemotherapy in other tumor types have demonstrated an improvement in overall survival when compared with surgery alone (29,30,45,46). Chemoradiotherapy is also routinely used in the neoadjuvant treatment of some solid tumors (47–49). These experiences further support the notion that pathological responses in the neoadjuvant setting can serve as a surrogate for overall survival.

**Neoadjuvant Therapy As a Platform for Drug Development**

In May 2012, the FDA published a draft guidance outlining the reasons for its acceptance of pathological complete response (pCR) as a surrogate in early-stage breast cancer and proposing a framework for its use in clinical trials (50). In September 2013, the FDA granted accelerated approval to pertuzumab for use in combination with
trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, early-stage breast cancer. The approval was based on the NeoSphere trial, which demonstrated an improvement in the pCR rate seen with pertuzumab and trastuzumab plus docetaxel compared with trastuzumab plus docetaxel (45.8% vs 29.0%; p=0.141) (51).

Although an improvement in pCR ultimately led to the accelerated approval of pertuzumab, the other factors that were crucial to the FDA decision reveal important, generalizable considerations for using neoadjuvant therapy as a platform for drug development (Figure 1). First, patients with HER2-positive breast cancer are at high risk for relapse with standard therapy (15). Second, the safety profile of pertuzumab alone and in combination with standard of care chemotherapy and trastuzumab had been reported in nearly 10,000 patients (17). Third, the FDA had conducted the aforementioned pooled analysis of neoadjuvant trials to establish the definition of pCR and to support the relationship between pCR and overall survival at the patient level (16). Lastly, the adjuvant APHINITY confirmatory trial was fully accrued and well underway at the time of accelerated approval, complying with the FDA requirement for a post-marketing clinical trial to verify meaningful clinical benefit (50).

The bar for the first approval of a drug based on pathological response was set high but has provided an impetus to pursue this pathway of expedited drug development in breast cancer and other solid tumors. Indeed, once a pathological response assessment has been validated as a surrogate in randomized clinical trials, it can be used as an endpoint in nonrandomized trials to screen drugs for anti-tumor activity based on historical controls. For example, two recent, single arm, phase II trials
in MIBC have evaluated dose dense MVAC (ddMVAC) in the neoadjuvant setting (52,53). Based on the pathological response rates seen in these trials, ddMVAC has been carried forward to randomized clinical trials in the neoadjuvant setting (NCT02177695 and NCT01812369).

Going Forward

Advances in molecularly targeted therapy and immunotherapy have led to an explosion of new drugs for cancer patients. Despite this progress, the field remains reliant on RECIST, an antiquated method of measuring responses never designed to correlate with clinically meaningful outcomes. We speculate that pathological responses as assessed in neoadjuvant trials might be expected to correlate stronger with overall survival. Indeed, pCR has already been endorsed by the FDA as a surrogate for overall survival in early-stage breast cancer (50). However, patient selection will remain important and the few patients who are thought to have a brief window of opportunity for curative surgery may not be appropriate for neoadjuvant treatment with experimental therapies. Conversely, if there already is a neoadjuvant therapy shown to improve OS, new drugs may have to be tested as add-ons to the standard therapy.

Another advantage of neoadjuvant trials is the availability of pre- and post-treatment tumor tissue for study. Investigation facilitated by the neoadjuvant paradigm has already contributed to our understanding of how tumor genomics and the immune microenvironment can serve as predictive biomarkers of response in solid tumors (Table 2). In patients who do not respond to treatment, the post-treatment tumor can provide critical information about mechanisms of treatment failure. Tumors can be
studied for intrinsic resistance or for the failure of the drug treatment to hit the intended molecular target. For immunotherapy treatments, studies of the tumor environment are likely to be very important. The ability to assess the activity of a drug \textit{in vivo} and to interrogate post treatment tissue will aide in the discovery of response and resistance mechanisms that can guide the next generation of clinical trials.

References


7. Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. J Clin Oncol. 2004;22(22):4442–5.


### Table 1. Examples of pathological response measurement that correlate with overall survival

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
<th>N</th>
<th>Pathological Response Definition</th>
<th>Hazard Ratio for Overall Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Pooled Analysis</td>
<td>2,761</td>
<td>pCR</td>
<td>HR 0.49 (0.33-0.71)</td>
<td>(16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,743</td>
<td>HER2+ pCR</td>
<td>HR 0.39 (0.31-0.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,157</td>
<td>HER2- pCR</td>
<td>HR 0.24 (0.18-0.33)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>AC</td>
<td>751</td>
<td>pCR</td>
<td>HR 0.32 P &lt; 0.001</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td>AC and AC-T</td>
<td>2,344</td>
<td>pCR</td>
<td>HR 0.36 P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Chemotherapy Trastuzumab</td>
<td>217</td>
<td>pCr</td>
<td>HR 4.9 (1.4 – 17.4) if no pCR P=0.12</td>
<td>(54)</td>
</tr>
<tr>
<td>Bladder</td>
<td>MVAC</td>
<td>147</td>
<td>&lt;pT2</td>
<td>HR Not Reported</td>
<td>(21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-year Landmark OS 75% vs 30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>GC</td>
<td>154</td>
<td>&lt;pT2</td>
<td>HR 6.7 (2.6-17.4) if &gt; pT2 P&lt;0.001</td>
<td>(23)</td>
</tr>
<tr>
<td>Lung</td>
<td>Docetaxel Cisplatin</td>
<td>75</td>
<td>pN0-N1</td>
<td>HR 0.22 (0.10 – 0.49) P = 0.0003</td>
<td>(55)</td>
</tr>
<tr>
<td>Lung</td>
<td>Variable Chemotherapy</td>
<td>192</td>
<td>&lt;10% viable tumor</td>
<td>HR 2.39 (0.99-5.78) if &gt;10% P=0.05</td>
<td>(26,27)</td>
</tr>
<tr>
<td>Esophageal and Esophagogastric</td>
<td>Variable chemotherapy</td>
<td>400</td>
<td>Tumor downstaging</td>
<td>HR 0.43 (0.31 – 0.59) P=&lt;0.001</td>
<td>(31)</td>
</tr>
</tbody>
</table>

AC= adriamycin and cyclophosphamide; T=paclitaxel; MVAC= methotrexate, vinblastine, adriamycin, and cisplatin; GC= gemcitabine and cisplatin; HR+/-=hormone receptor positive/negative; HER2+/-=human epidermal growth factor receptor 2 positive/negative; pCR=pathological complete response; <pT2=non muscle invasive bladder cancer; >pT2=muscle invasive bladder cancer; HR=hazard ratio; OS=overall survival.
**Table 2. Examples of predictive biomarker discovery facilitated by the neoadjuvant paradigm**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
<th>Predictive Biomarker</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Anti-HER2 agents</td>
<td>PIK3CA Mutations</td>
<td>(56)</td>
</tr>
<tr>
<td>Breast</td>
<td>Chemotherapy</td>
<td>BRCA1 Mutations</td>
<td>(57)</td>
</tr>
<tr>
<td>Breast</td>
<td>Anti-HER2 agents and chemotherapy</td>
<td>TILs</td>
<td>(58–61)</td>
</tr>
<tr>
<td>Bladder</td>
<td>Platinum based chemotherapy</td>
<td>DDR Deficiency</td>
<td>(62,63)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Platinum based chemotherapy</td>
<td>TILs</td>
<td>(64)</td>
</tr>
</tbody>
</table>

HER2 = Human epidermal growth factor receptor 2; PI3K = Phosphatidylinositol 3-kinase; TILs = tumor infiltrating lymphocytes; DDR = DNA damage repair
**Figure 1.** Considerations for designing neoadjuvant trials for drug development and approval
Figure 1:

- **Patient population**: High risk of recurrence
- **Investigational therapy**: Acceptable safety profile when combined with standard-of-care treatment
- **Definition of pathological endpoint**: Best association with OS
- **Confirmation of OS benefit**: Enroll confirmatory trial
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