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Commentary

Biomarkers That Predict an Unclear Benefit From Adjuvant Trastuzumab, Pertuzumab and Pembrolizumab When Those Same Drugs Were Given Neoadjuvantly

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Conflict of Interest
Dr. Sorscher briefly worked at Invitae, Corporation but is no longer affiliated with Invitae. The author declare that they have no competing interests.

BIOMARKERS THAT PREDICT AN UNCLEAR BENEFIT FROM ADJUVANT TRASTUZUMAB, PERTUZUMAB AND PEMBROLIZUMAB WHEN THOSE SAME DRUGS WERE GIVEN NEOADJUVANTLY

The standard of care (SOC) regimens for many patients with early-stage HER2-positive breast cancer (HER2+ BC) includes both neoadjuvant and adjuvant trastuzumab or neoadjuvant and adjuvant trastuzumab plus pertuzumab and for patients with high-risk early-stage triple negative BC (TNBC), the SOC strategy includes both neoadjuvant and adjuvant pembrolizumab [1]. However, if there is a pathological complete response (pCR) from the neoadjuvant therapy (NAT), it is unclear whether the adjuvant phase of these regimens adds benefit or "clinical utility" compared to giving the NAT alone.

Ideally, studies randomizing patients after NAT who have pCRs and post-operative undetected circulating tumor DNA (ctDNA) (an emerging marker that correlates with pCR) with each of these neoadjuvant therapies to either resuming the drug(s) as adjuvant therapy vs. no adjuvant therapy would determine with the most certainty whether the adjuvant therapy phase with each drug improves outcome. However, such studies are problematic given the outstanding results seen with the current recommended standard therapies and taken together, there may already be adequate evidence that the adjuvant phase adds minimal benefit in mitigating recurrence risk. Although the toxicities of these drugs are modest, patients would understandably elect to forego adjuvant therapy if its benefit is unproven or apparently minimal.

ADJUVANT TRASTUZUMAB OR TRASTUZUMAB PLUS PERTUZUMAB AFTER NEOADJUVANT TRASTUZUMAB OR TRASTUZUMAB PLUS PERTUZUMAB

pCR from neoadjuvant systemic therapy for early-stage invasive BC has long been identified as an accurate predictor of disease-free survival (DFS) regardless of subtype [2]. With neoadjuvant

chemotherapy and trastuzumab for patients with HER2+ BC, followed by surgery and then by adjuvant trastuzumab, the DFS for patients whose tumors demonstrate a pCR is roughly 90%–100% [3,4]. From a study that included only patients with clinically larger, and/or apparent lymph node positive HER2+ BC, the 5-year DFS was 85% for those who received pertuzumab and trastuzumab, compared to 76% whose tumors did not show a pCR [5].

Recently, several studies have demonstrated that undetectable ctDNA during NAT or after surgery correlates extremely well with pCR. For example, from I-SPY 2, Magbanua et al. [6] reported that pCR was only 13% for those with detectable ctDNA 3 weeks from the start of therapy compared to 48% with undetectable ctDNA 3 weeks from the start of therapy.

Post-op undetectable ctDNA is also highly predictive of DFS. For example, Butler et al. [7] reported that those patients who had pCRs had experienced rapid declines in ctDNA during NAT and for the single patient in their report who had no pCR, ctDNA rose during NAT. McDonald et al. [8] reported that "after completion of NAT, ctDNA concentrations were lower in patients who achieved pCR compared to patients with residual disease."

From a meta-analysis, that included 11 studies, Papakonstantinou et al. [9] concluded that "detection of ctDNA both at baseline and after completion of NAT, significantly associated to worse recurrence-free survival." Lin et al. [10] reported that for patients with all BC subtypes, ctDNA positivity after NAT was an independent risk factor that predicted recurrence. Also, from BRE12-158, undetectable ctDNA together with undetectable circulating tumor cells (CTCs), predicted an 89% likelihood of distant DFS at 24 months compared to 52% likelihood if the post-operative ctDNA and CTCs were positive [11].

Taken together, the reported very high DFSs rates associated with pCR and/or undetectable ctDNA after NAT suggest that adjuvant therapy might add little benefit for patients with those biomarker results. On the other hand, patients in the studies described received adjuvant anti-HER2 therapy and it is possible that this contributed to the very high DFSs reported.

Still, is it likely that the adjuvant therapy phase does not add benefit. For example, the total duration of adjuvant therapy has been studied. Although a number of studies suggest that optimal benefit is related to one year of peri-operative trastuzumab, recently investigators reported from the PERSEPHONE trial that 6 months of adjuvant trastuzumab is non-inferior to 12 months [12]. Thus, it remains unclear whether the adjuvant trastuzumab affects DFS, compared to no adjuvant trastuzumab particularly for those with a pCR and post-op undetectable ctDNA after neoadjuvant trastuzumab.

Similarly, the optimal total duration of pertuzumab is unclear. The APHINITY trial confirmed that 6 months of adjuvant pertuzumab is superior to no adjuvant pertuzumab in patients who received no neoadjuvant pertuzumab and the relative reduction in recurrence risk was roughly the same as the relative reduction reported in those who received neoadjuvant pertuzumab but no adjuvant pertuzumab in the NeoSphere study [5,13-15]. Yet, per the National Comprehensive Cancer Network (NCCN) and UptoDate guidelines, one year of perioperative pertuzumab is considered SOC [1,16].

Proving whether adjuvant trastuzumab adds benefit after neoadjuvant trastuzumab or adjuvant pertuzumab adds benefit after neoadjuvant pertuzumab in patients who have a pCR

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and undetectable ctDNA in a randomized, prospective study would be a formidable task for a variety of reasons.

First, the DFS rate is so high for this group, that it would likely require a study that includes a very large number of patients to show a statistically significant benefit in DFS with compared to without adjuvant therapy. Also, neoadjuvant trastuzumab or trastuzumab plus pertuzumab followed by adjuvant trastuzumab or trastuzumab plus pertuzumab have been SOC for many years and proven to result in very high DFSs. Therefore, patients are not likely inclined to enroll on studies where they might be randomized to not receive a phase of a therapy (the adjuvant phase) that is SOC. Finally, adjuvant trastuzumab or trastuzumab plus pertuzumab typically adds only modest toxicity to treatment with only NAT.

In order for the guidelines to be changed one would need evidence that trastuzumab and pertuzumab are not clinically useful after neoadjuvant for patients who have a pCR. Clinical utility has been variously described, but generally might be proven to not exist when the harms of the therapy outweigh the benefits. Hayes described and referred to a "minimally clinical important difference (MCID)" as a result that might be considered tantamount to an intervention that lacks clinical benefit [17].

There are several examples of settings in which a randomized controlled prospective trial was not deemed necessary because if there is a benefit to, for example, SOC therapy, it is assumed to be so likely minimal that a randomized study was not deemed necessary. For example, on KATHERINE, no patients were included who had a pCR to chemotherapy and trastuzumab, with or without pertuzumab, because studies had suggested that the DFS was so favorable with the standard therapy, adjuvant trastuzumab, that the investigators decided to instead focus on a randomized study that included only those who did not have a pCR and randomized them to ado-trastuzumab vs. trastuzumab [18].

Tolaney et al. [19] approached a similar dilemma of whether a randomized study is needed to establish clinical utility by conducting a non-randomized trial. For years, the SOC has been 2 or 3 chemotherapy drugs (neoadjuvant or adjuvant therapy) plus one-year total peri-operative trastuzumab. The investigators were interested in whether a "biomarker" (pathologic stage 1 disease) predicted an outcome so favorable with paclitaxel alone plus one year of trastuzumab that additional chemotherapy would be expected to improve on results only minimally compared with paclitaxel and trastuzumab alone. In 2019, the authors reported that the 7-year DFS was 93%. The NCCN adopted this regimen as SOC for stage I disease, without proof from a randomized study of this regimen being statistically non-inferior compared to those regimens containing 2 chemotherapy drugs.

ADJUVANT PEMBROLIZUMAB AFTER NEOADJUVANT PEMBROLIZUMAB

In KEYNOTE-522, patients with high-risk TNBC received either chemotherapy with neoadjuvant pembrolizumab followed by adjuvant pembrolizumab or no pembrolizumab before or after surgery [20]. The superior pCR (63% vs. 56%) and event-free survival at 36 months (84% vs. 76%) favored patients who received neoadjuvant together with adjuvant pembrolizumab compared to those who receive no pembrolizumab. Based on these results, the Food and Drug Administration approved and the NCCN endorsed pembrolizumab both

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before and after surgery, although it is unclear whether the adjuvant pembrolizumab affects the DFS [1].

The authors concluded that pembrolizumab before and after surgery should be considered SOC for these patients, but as in the settings described above, they raised the issue of whether the adjuvant pembrolizumab adds efficacy in patients, particularly for those with a pCR, since in that group the DFS was so very high-and similar to those who received neither neoadjuvant nor adjuvant pembrolizumab but nonetheless had a pCR. In fact, the 36-month DFS for those with a pCR was 92.6 vs. 94.5% in each group, respectively.

In other words, if neoadjuvant plus adjuvant pembrolizumab resulted in DFSs so similar to no pembrolizumab at all, for patients who have a pCR, it seems hard to imagine that the adjuvant phase adds more than a MCID in those who have received neoadjuvant pembrolizumab. Experts have similarly questioned the value of adjuvant pembrolizumab in those with pCRs after neoadjuvant pembrolizumab. Yara Abdou of the University of North Carolina said, "It is unclear whether pembrolizumab is necessary in the adjuvant setting, specifically in patients with pCR" [21]. In the UpToDate guidelines, Sikov et al. [22] wrote "we do not know the relative contributions of neoadjuvant vs. adjuvant administration".

In CREATE-X, patients with TNBC for patients whose tumors showed no pCR from neoadjuvant chemotherapy were randomized to receive either adjuvant capecitabine vs. no capecitabine. The authors wrote, "we excluded patients who had a pCR who were likely to be cured with standard chemotherapy regimens" [23]. The results showed that without a pCR, patients showed an improved DFS with adjuvant capecitabine compared to no capecitabine. Consequently, the NCCN has endorsed capecitabine, but only for those patients with tumors not demonstrating a pCR [15].

Thus, similar to the adjuvant trastuzumab and adjuvant trastuzumab and pertuzumab settings described above, it is not clear-in those who have a pCR-whether the adjuvant phase of pembrolizumab improves recurrence risk compared to no adjuvant pembrolizumab, but in all these cases, pCR is a very predictive biomarker of extremely favorable DFS.

In summary, the described studies confirm that pCR correlates with DFS and ctDNA correlates with pCR. The authors of KATHERINE and CREATE-X note that pCR predicts such a low likelihood of recurrence that they chose not to include patients with pCR on the experimental arms of those trials. Similarly, in the trials of HER2- patients [5,10,20], the DFS is so favorable for those with pCR or undetectable ctDNA that is seems unlikely that a randomized trial of adjuvant vs. no adjuvant therapy would demonstrate anything more than a minimal DFS benefit.

As a fellow, I was taught 2 key principles, the first being more therapy is likely better. The designs of the pivotal trials that resulted in more therapy becoming the standard without verifying that less might be equally effective is a reminder of that advice. "In designing a phase III trial, it is probably better to try the most you can safely give first. That way, if it doesn't work, at least you will know it wasn't because you didn't try to give more."

The only certain way to determine whether the adjuvant phases of trastuzumab, trastuzumab and pertuzumab, and pembrolizumab improve outcome in patients with pCRs and/or post-op undetectable ctDNA would be with prospective, randomized trials. However, given the high

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DFSs associated with pCR and/or post-operative undetectable ctDNA and given the anticipated hesitancy of patients to enroll on trials where patients would not receive the already proven, and highly effective SOC, and given the large number of patients needed to prove whether the adjuvant therapy phase adds benefits, it seems unlikely that these trials will be initiated.

Initiating non-randomized trials (as per Tolaney et al. [19]) in which all patients forgo the standard adjuvant therapy phase or discussing with patients the evidence that suggests that the adjuvant phase might only minimally affect the outcome might lead to patients understandably making an informed decision to decline adjuvant therapy in these settings, when the NAT is associated with a pCR and undetectable ctDNA.

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