More on treatment de-escalation, biomarkers of response in human epidermal growth factor receptor 2 (HER2)-positive breast cancer: long-term outcomes and translational research findings of the PREDIX HER2 trial

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Unquestionably, the successive generations anti-human epidermal growth factor receptor 2 (HER2) therapies have made human epidermal growth factor receptor 2-positive (HER2$^+$) breast cancer (BC)—a condition until recently associated with a dismal prognosis (1)—one of the most curable types of cancer, even when diagnosed in more advanced stages (2-4).

Because of the high rates of complete responses attained by modern anti-HER2 therapies and the availability of 'rescue' treatments for poor/incomplete responders (5), neoadjuvant therapy (NAT) is now considered optimal for tumors larger than 2 cm and/or with lymph node involvement. Consequently, pathological complete response (pCR) gradually became the 'epicenter' of treatment decisions in HER2$^+$ BC (6)—the ultimate goal for patients undergoing NAT, and a powerful prognostic tool after this treatment—where it also guides decisions on further adjuvant treatment (5) and, especially for patients with high-risk residual disease (7), future research directions (8).

Considering the exquisite efficacy of novel HER2-targeted therapies—with pCR rates now achieving 2/3 of the cases (4)—a leading research question has been treatment de-escalation. Among the strategies under investigation, the removal of any non-taxane component (anthracyclines ± cyclophosphamide, carboplatin) (9-12) or even of chemotherapy altogether (10,11) from the schedule and/or a reduction in the number of chemotherapy cycles (9-12) are considered promising. However, due to the recent successes of antibody-drug conjugates (ADCs) in HER2$^+$ BC (3,5,13), these agents deserve special attention as potential substitutes for chemotherapy in NAT schedules.

This is precisely the primary question addressed by PREDIX HER2, a phase II, prospective, randomized clinical trial in which 202 patients with HER2+ BC were allocated 1:1 to receive either 'standard' docetaxel/trastuzumab/pertuzumab or the first-generation ADC trastuzumab emtansine (TDM1). In terms of the primary results, no differences in pCR (primary outcome) were observed; however, as also seen in the KRISTINE trial (14), a slightly higher number of on-treatment disease progression events were reported in the TDM1 arm—leading to some early switches to chemotherapy and dual-blockade as per study protocol (15).

In this update of the study published in the *Clinical Cancer Research* by Matikas *et al.* (16), the authors report on the results of the secondary endpoints event-free survival (EFS), relapse-free survival (RFS) and overall survival (OS). With 5.21 years of median follow-up, no differences between the study arms were seen (5-year EFS, RFS and OS of 89.6% *vs.* 88.6%, 91.6% *vs.* 94.7% and 96.7% *vs.* 97.7%, respectively). These results—the most mature to

date comparing an ADC to chemotherapy plus HER2-blockade in this setting—are in line with those of a similar study (14), and the reported outcomes are within the expected for the best available treatments in this setting (2-4)—hence providing further support for treatment de-escalation strategies with ADCs. However, because of the small size of the study, of the fact that patients received further (anthracycline-based) adjuvant chemotherapy in both arms (making the entire experimental regimen not truly 'chemotherapy-free'), that the standard arm did not contain a second/third cytotoxic agent (anthracycline ± cyclophosphamide or carboplatin) as per current standard practice (making the primary outcome of pCR trickier to interpret), these results should be considered neither definitive nor practice-changing—but instead hypothesis generating and a useful guidance for future research. Whether future research with ADCs as potential substitutes for chemotherapy should still focus on TDM1 or move on to new-generation ADCs—which have shown impressive results in the metastatic setting (13)—is a matter of debate; in support of a continued role for TDM1, one should highlight its favorable tolerability profile and safety track for use in a curative setting (3,5,17)—aspects that are currently less clear with, for instance, trastuzumab-deruxtecan (13,18).

Furthermore, in line with previous studies (19), the achievement of a pCR in the PREDIX HER2 trial also predicted excellent outcomes (RFS of 98.9%), while patients with residual disease had an event rate greater than 10%; the special interest in this information in the context of this trial is the fact that the prognostic value of pCR also applied to the TDM1 arm—thus providing further support for the reliability of a pCR induced by a non-chemotherapy treatment, as also observed the KRISTINE trial (14).

Because of the key role of pCR in guiding treatment decisions, there has been a renewed interest in the early identification of treatment-resistant tumors—i.e., of patients who will most likely fail to achieve a pCR. These patients (currently representing ±30–40% of the cases), as previously mentioned, have a worse prognosis, and will also require the use of lengthy, costly, and potentially more toxic 'rescue' adjuvant therapies (5); if early identified, they could (theoretically) be offered alternative approaches that might put them back on track to achieve a pCR. Furthermore, as the treatment de-escalation strategies evolve and popularize, the early identification of potential treatment failures has become an issue of utmost importance that should probably be incorporated into the design of these studies.

In this sense, in this same publication, Matikas *et al.* report on the results of an exploratory objective of the PREDIX trial of investigating the role of conventionally and digitally assessed tumor infiltrating lymphocytes (TILs), of baseline and post cycle two (C2) PET/CT contrast uptake, and the combined analysis of these biomarkers on pCR rates and long-term outcomes.

Historically, tissue biomarkers have been the focus of research on pCR and long-term outcomes prediction, with variable, but mainly unsatisfactory results (20). One of the problems of many of these studies is the fact that a single baseline (pretreatment) evaluation completely misses tumor evolution under the pressure of treatment; to remedy this, studies with on treatment re-biopsies have been proposed—but the results have also been limited in terms of supporting clinical practice (21).

A completely different, yet no less interesting approach, is to employ novel radiological tests that incorporate cell metabolism assessments—such as positron emission tomography (PET)—as potential biomarkers of response. Although radiological shrinkage of tumors has long been known to correlate with pCR (22,23) and even with long-term outcomes (24), these correlations have been largely imperfect (21,25-27). PET-based imaging, conversely, might be able to circumvent the problem of pure anatomical assessments that has plagued conventional radiology by also addressing tumor dynamics through the measurement of changes in cell metabolism (28). The rational for the use of PET as a predictor of pCR has been supported by numerous studies (29-36); in one of them, PET was also shown potentially superior to magnetic resonance in predicting pCR (36) and, in a previous randomized clinical trial, was successfully employed as a 'stopping rule' after two cycles of chemotherapy-free dual-blockade—allowing patients to be immediately switched to chemotherapy-based dual-blockade in case of non-response (with the caveat that only 37.9% of the PET early responders from the non-chemotherapy arm eventually achieved a pCR) (34).

Activation of the immune system, as measured by the expression of TILs and/or immune-related gene expression (iGES) signatures, has been intensely investigated as a potential biomarker in the neoadjuvant setting. While the expression of TILs in HER2+ BC has consistently correlated with poor prognostic features such as estrogen receptor (ER)-negativity (37-39) and high histological grade (39), it has at the same time correlated with higher pCR rates (37,38,40-42) and, in some (38,41) but not all studies (35,39), with improved cancer outcomes. However, in some studies, TILs

were shown potentially inferior to some iGES in predicting pCR in both HER2$^+$ (37,42) and triple negative breast cancer (TNBC) (43). Furthermore, as with Ki-67 (44), TILs measurements are tricky to standardize (38,45-47); hence the special interest in digital assessments—in addition to its potential cost-saving and wider applicability in places where restricted access to specialist pathologists is the rule. Finally, due to the limitations of TILs in predicting either pCR or long-term outcomes, more robust models of immune activation measurement have been proposed but have had limited applicability in clinical practice so far (40,48).

In PREDIX HER2, core biopsies were obtained at baseline and after C2. This analysis focused on the role of TILs as assessed by conventional (by a certified pathologist blinded for clinicopathologic and genomic characteristics and according to current recommendations) (38) and digital (i.e., automated, using a previously developed software) readings. Part (n=112) of the patients were also submitted to a PET/CT imaging at baseline and after cycles 2 and 6—always before the study biopsies. The analyses of PET/CT responses were based on maximal standardized uptake values (SUVmax) at baseline and after C2.

As key findings of the translational component of the study, patients with baseline TILs above the cut-point (≥10% *vs.* <10%) had higher pCR rates (51.4% *vs.* 28.1%, P=0.003), which also provided added value to clinical parameters and post C2 SUVmax in terms of predicting pCR [LR-$\Delta\chi^2$ =6.44, P=0.011; adjusted odds ratio (ORadj) =3.47, 95% confidence interval (CI): 1.28–9.43, P=0.014]. Baseline digitally-assessed tumor infiltrating lymphocytes (DTILs) were significantly correlated with TILs and also provided additional information to clinical parameters and post C2 SUVmax in terms of predicting pCR. However, there were no associations between the expression of TILs/DTILs and EFS. In terms of PET metabolic responses, decreases in uptake were observed in both arms, but the drop was greater in the THP arm (72.6% *vs.* 58.5%). Post C2 SUVmax was lower (P<0.001) and the relative decrease in SUV uptake was greater (80.2% *vs.* 58.4%, P<0.001) in patients who achieved a pCR. Furthermore, higher SUVmax after C2 indicated lower pCR rates (ORadj =0.65, 95% CI: 0.48–0.87, P=0.005), worse EFS [adjusted hazard ratio (HRadj) =1.27, 95% CI: 1.12–1.41, P<0.001] and provided information on EFS beyond pCR in multivariate analysis (HRadj =1.22, 95% CI: 1.09–1.37, P=0.007).

The finding that metabolic response and expression of TILs/DTILs provided added predictive and prognostic information—according to the authors, the main objective of this translational research study—is more difficult to interpret because they represent different realms of BC biology (effects of treatment in decreasing cell metabolism and immune mediation, respectively); additionally, if any single biomarker has individual prognostic/predictive value, it is intuitive to assume that any combination analysis of these markers might produce added value; in other words, had the authors focused on other biomarkers, similar results could have been produced. Furthermore, in small samples, as the complexity of the analyses growths, the results become more difficult to interpret because of the risk of statistical aberrations. Despite these limitations, the authors report impressive predictive power with this approach—with a pCR rate as low as 8.3% (for TILs) and 15.3% (for DTILs), in addition to significant effects on EFS, with the combination of lower baseline expression of TILs/DTILs and higher SUVmax after C2—findings that may deserve further investigation.

In summary, the translational research analyses of the PREDIX HER study provide meaningful insights into the holy grail research question of how to early identify treatment failures—i.e., the presence of residual disease on the surgical specimen. However, the problem with these elegant translational research studies is always the same: what to do with the information that patients with lower baseline expression of TILs/DTILs and higher SUVmax after C2 have a low probability of achieving a pCR? Any changes to clinical practice would certainly require validation by a prospective clinical trial in which, for instance, such patients were randomized to switch to an alternative treatment versus continue the same treatment—a strategy that, in the past, has largely failed (21,49). Furthermore, the exploratory nature of the analyses and the small number of patients included in the main study and, in particular, available for the translational research analyses (making the study considerably underpowered for this exploratory analysis), do not support the use of this information in clinical practice—which, however, does not diminish the value of the study in guiding future research on this subject. The author of this piece is particularly optimistic about the perspective of using imaging-led assessments of metabolic response, especially as more tumor biology-specific radiopharmaceuticals are developed—such as fluoroestradiol F 18 for ER-positive BC (50) and others in earlier stage of clinical development, including in HER2$^+$ BC (51). Such a strategy, in addition to providing a snapshot of the tumor biology, partially circumvents the barrier of tumor heterogeneity that has historically plagued biopsy-driven translational research studies. In this sense, PREDIX

HER2—one more trial to prospectively demonstrate the value of PET/CT in early identifying NAT failures in HER2$^+$ BC—should be considered a highly successful study that has potential implications for the design of future treatment de-escalation studies.

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