PIK3CA mutations in HER2-positive breast cancer: an ongoing conundrum

The routine use of therapeutic agents that specifically target the human epidermal growth factor receptor-2 (HER2) has dramatically improved outcomes for patients with HER2-positive breast cancer. Data from contemporary trials indicate that the median survival for patients with metastatic HER2-positive disease is close to 5 years, and that long-term distant recurrence rates after adjuvant therapy are low [1–3]. As the number of HER2-targeted therapies has increased, it has become clear that not every patient needs to receive every available drug, and that a ‘one size fits all’ approach will lead to suboptimal outcomes.

It is thus important that studies are carried out to identify biomarkers that determine the long-term prognosis of HER2-positive breast cancers and/or predict their responses to specific therapies. Such biomarkers would allow tailoring treatment to those patients most likely to benefit and reducing overtreatment for patients who are destined to do well with less therapy. In addition, it would potentially identify patients whose response to existing therapies is poor and for whom novel treatments should be developed. Unfortunately, despite having data and tissue from large randomized adjuvant studies of trastuzumab for over 10 years, and metastatic studies for even longer, strong, validated predictors of outcome have largely remained elusive.

In this issue of Annals of Oncology, Loibl et al. [4] present results of a meta-analysis in which they specifically explore whether activating mutations in the PIK3CA gene of HER2-positive breast cancers are associated with reduced sensitivity to neoadjuvant therapy. The potential role of the PIK3CA gene as a mediator of tumor resistance to HER2-targeted therapies is well described [5, 6]. PIK3CA encodes the p110α subunit of the lipid kinase phosphoinositide 3-kinase (PI3K). When the HER2 receptor tyrosine kinase is active (as in HER2-positive breast cancers), PI3K is stimulated to phosphorylate phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3) at the plasma membrane. The canonical consequence of this is activation of the AKT kinase and the propagation of a network of intracellular signals mediating cell propagation. The AKT kinase and the propagation of a network of intracellular signals mediating cell proliferation, survival, metabolism, and growth [7].

Recent preclinical studies provide clues as to why the p110α subunit of PI3K may be particularly important for HER2-positive breast cancers. These studies suggest that HER2
signaling is mediated almost entirely through p110α, rather than one of the other three catalytic subunits of PI3K [8, 9]. For example, mice with both copies of the PIK3CA gene deleted are completely resistant to HER2 transgene-mediated tumor formation [9], and mice bearing both HER2 and a mutant PIK3CA transgenes develop mammary tumors faster than those bearing only an HER2 transgene [10]. It is thus very plausible that mutations in PIK3CA that constitutively activate p110α, such as the relatively common ‘hotspot’ mutations in exons 9 and 20, could confer resistance to therapeutic HER2-blockade, because inhibiting the HER2 kinase may not be sufficient to suppress downstream PI3K signaling. Such mutations are found in ~20% of HER2-positive breast cancers, and preclinically, they render tumors resistant to trastuzumab both in vitro and in vivo [6].

In the present study, Loibl et al. combine individual patient data from five neoadjuvant trials. In total, their analysis includes almost 1000 patients. Patients in each of the five trials received systemic chemotherapy, either with a taxane alone or with a taxane–anthracycline regimen. Each study also administered concurrent anti-HER2 therapy—trastuzumab, lapatinib, or their combination, varying between studies (Table 1). Using a robust definition of pathological complete response (no residual invasive or non-invasive disease in either breast or axillary nodes), the authors show that the presence of a PIK3CA mutation is associated with a significantly lower rate of pCR (wild-type pCR 29.6% versus mutant pCR 16.2%, P < 0.001).

The data in this analysis are not new, but are rather a compilation of previously presented data from the five individual trials [12, 14] (Table 1). Although a trend toward lower pCR rates in PIK3CA-mutant tumors was seen in each individual trial, the difference failed to reach statistical significance in the majority of them. The combining of individual patient data increases statistical power and confirms the validity of the association between PIK3CA mutations and lower rates of pCR.

The more novel finding in this work is that the association between PIK3CA mutations and lower rates of pCR was much stronger in hormone receptor (HR)-positive HER2-positive cancers (wild-type pCR 24.2% versus mutant pCR 7.6%, P < 0.001) than in HR-negative tumors (wild-type pCR 36.4% versus mutant pCR 27.2%, P = 0.125) and this interaction between HR and PIK3CA mutations was statistically significant (Pinteraction = 0.036). Previous analyses hindered by smaller sample sizes did not clearly demonstrate this effect. In addition, the investigators also confirm previous data highlighting that although the rate of pCR is lower in PIK3CA-mutant tumors regardless of the anti-HER2 therapy used, the difference is numerically greatest for patients receiving dual blockade with trastuzumab and lapatinib [12].

These results are consistent with our understanding of HER2 biology. We might expect that HER2-positive tumors with constitutive activation of PI3K show relative resistance to HER2-targeted therapies, chiefly due to the potential failure of anti-HER2 therapy to mitigate downstream signaling. Furthermore, constitutive activation of PI3K can lead to down-regulation of upstream HER2 and HER3 kinase activity through feedback inhibition, which could in itself render tumors less sensitive to anti-HER2 therapies [10, 21]. On deeper examination, however, there are a number of questions that remain unresolved.

First, we cannot determine from these data whether PIK3CA mutations are specifically associated with a worse response to chemotherapy, anti-HER2 therapy, or both, because all patients studied received concomitant chemotherapy.

Secondly, it is not obvious as to why the impact of a PIK3CA mutation on pCR rates should be greater in HR-positive tumors. Indeed, if the effect of a PIK3CA mutation was independent of HR-status, one would expect the absolute difference in pCR rates between mutant and wild-type tumors to be lower in HR-positive tumors, given that they have a lower pCR rate overall. Given that the opposite was seen, it suggests that the biological impact of a HER2-positive cancer’s PIK3CA mutation differs by HR status. Notably, HER2-positive tumors that are also HR-positive are much more likely to show a ‘luminal’ pattern of gene expression [22]. Given that PIK3CA mutations are associated with lower proliferation rates in HR-positive (presumably luminal) tumors more generally, the same might be true of luminal (as opposed to non-luminal) HER2-positive tumors. This in turn might be associated with a lower rate of pCR. An alternative mechanism for the greater impact of PIK3CA mutations on pCR rates in HR-positive cancers is that in these cancers, cross-talk between a mutation-activated PI3K pathway and the HR pathway leads to therapeutic resistance. This cross-talk is not relevant in HR-negative tumors, potentially explaining the lesser impact of PIK3CA mutations in these cancers.

Thirdly, one might expect that a significant reduction in pCR rates for PIK3CA-mutant tumors would be associated with an inferior clinical outcome, especially since an association between attainment of pCR after neoadjuvant anti-HER2 therapy and disease-free survival (DFS) has been established [23]. In the analysis presented by Loibl et al., however, the inferior pCR rate seen in PIK3CA-mutant tumors is not accompanied by a measurable change in DFS (HR for PIK3CA mutant versus wild-type was 1.07, P = 0.691). In some respects, this discrepancy resembles that observed when HR status (as opposed to PIK3CA status) is used as the biomarker. HER2-positive, HR-positive cancers have a markedly lower pCR rate to neoadjuvant HER2-targeted therapy when compared with HER2-positive, HR-negative tumors and yet their DFS rates are no worse [24]. In that instance, at least a part of the discrepancy between pCR and DFS might be explained by the use of adjuvant endocrine therapy, an effective treatment given only for HR-positive tumors, the effect of which is not measured in preoperative chemotherapy-based studies. In the present analysis, however, there is no PI3K-specific therapy given to PIK3CA-mutant tumors after surgery, so the same logic does not apply. Rather, it is possible that PIK3CA-mutant, early-stage HER2-positive tumors have an inherently more indolent biology and lower risk of recurrence, such that a failure to respond to neoadjuvant therapy does not translate into an inferior DFS [25].

A fourth point of confusion arises when the neoadjuvant data are contrasted with studies examining HER2-positive, PIK3CA-mutated breast cancer in other contexts (summarized in Table 1). In the setting of metastatic disease, for example, PIK3CA mutations have a negative prognostic impact in patients receiving anti-HER2 therapy, but have no bearing on the magnitude of response to that therapy—essentially the opposite of what is seen in the neoadjuvant context [19]. Furthermore, analyses of two randomized adjuvant trials comparing chemotherapy versus chemotherapy plus trastuzumab...
Table 1. Summary of the published and/or presented data detailing the impact of activating mutations in PIK3CA in HER2-positive breast cancers

<table>
<thead>
<tr>
<th>Disease setting</th>
<th>Trial</th>
<th>Treatment arms</th>
<th>Outcomes in PIK3CA mutant versus wild-type</th>
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</table>
T-H 16 weeks  
T-HL 16 weeks | No significant difference in pCR between mutant and wild-type (39% versus 47%) |
|                 | Neo ALTTO [12]a | L (6 weeks) → T-L (12 weeks)  
H (6 weeks) → T-H (12 weeks)  
HL (6 weeks) → T-HL (12 weeks) | Lower pCR in mutant (21.3%) versus wild-type (34.5%) (P = 0.03) |
|                 | CHER-LOB [13]a | TL (12 weeks) → FEC-L (12 weeks)  
TH (12 weeks) → FEC-H (12 weeks)  
THL (12 weeks) → FEC-HL (12 weeks) | No significant difference in pCR between mutant and wild-type (22.7% versus 33.3%) |
|                 | GeparQuattro [14]a | FEC-H (12 weeks) → D-H (12 weeks)  
FEC-H (12 weeks) → DX-H (12 weeks)  
FEC-H (12 weeks) → D-H (12 weeks) → XH (12 weeks) | No significant difference in pCR between mutant and wild-type (22.2% versus 35.4%)b |
|                 | GeparQuinto [14]a | EC-L (12 weeks) → D-L (12 weeks)  
EC-H (12 weeks) → D-H (12 weeks) | No significant difference in pCR between mutant and wild-type (20.5% versus 25.5%)b |
|                 | GeparSixto [14]a | T-M-HL (18 weeks)  
T-Mcb-HL (18 weeks) | Lower pCR in mutant (17.4%) versus wild-type (37.1%) (P = 0.01)b |
|                 | NeoSphere [15] | HP (12 weeks)  
D-H (12 weeks)  
D-P (12 weeks)  
D-HP (12 weeks)  
D-chb-H (18 weeks) | Lower pCR rate in PIK3CA-mutant tumors in all treatment groups (unpublished) |
|                 | TRYPHAENA [16] | FEC-HP (9 weeks) → D-HP (9 weeks)  
FEC (9 weeks) → D-HP (9 weeks)  
D-chb-HP (18 weeks) | No significant difference in pCR between mutant and wild-type (48.7% versus 64.3%) |
| Adjuvant        | NSABP-B31 [17] | AC (12 weeks) → T (12 weeks)  
AC (12 weeks) → T-H (12 weeks) → H (39 weeks) | No significant interaction between PIK3CA status and trastuzumab benefit  
No significant difference in DFS between mutant and wild-type |
|                 | FinHER [18] | D or V (9 weeks) → FEC (9 weeks)  
D-H or V-H (9 weeks) → FEC (9 weeks) | No significant interaction between PIK3CA status and trastuzumab benefit  
No significant difference in DDFS or OS between mutant and wild-type |
| Metastatic      | CLEOPATRA [19] | D-H → H  
D-HP → HP | No significant interaction between PIK3CA status and pertuzumab benefit  
Significantly worse prognosis in patients with PIK3CA-mutant tumors (control arm PFS 8.6 m versus 13.8 m; experimental arm PFS 12.5 m versus 21.8 m) |
|                 | EMILIA [20] | X-L  
T-DM1 | PFS and OS worse in PIK3CA-mutant tumors in XL arm (PFS 4.3 m versus 6.4 m; OS 17.3 versus 27.8 m) but not in T-DM1 arm (PFS 10.9 m versus 9.8 m, OS - NE) |

NB—the paper in this issue of *Annals of Oncology* [4] represents a combined analysis of Neo ALTTO, CHER-LOB, GeparQuattro, GeparQuinto, and GeparSixto. Definition of pCR was not identical in all neoadjuvant studies.

AC, Adriamycin and cyclophosphamide; CB, carboplatin; D, docetaxel; DFS, disease-free survival; DDFS, distant disease-free survival; EFS, event-free survival; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; L, lapatinib; NE, not estimable; M, non-pegylated liposomal doxorubicin; OS, overall survival; P, pertuzumab; T, paclitaxel; T-DM1, trastuzumab emtansine; V, vinorelbine; X, capecitabine.

Studies included in the present analysis by Loibl et al. [4].

Combined analysis of EFS in GeparQuattro, GeparQuinto, and GeparSixto showed no difference between patients with PIK3CA-mutant or wild-type tumors.
showed neither a prognostic nor a predictive association of PIK3CA mutations [17, 18].

Reconciling these data is not easy—why should HER2-positive tumor cells in an early-stage cancer be less responsive to neoadjuvant anti-HER2 therapy if they harbor a PIK3CA mutation, while those in a metastatic tumor, a PIK3CA mutation confers an inferior prognosis? Answers to these questions are partly confounded by the fact that studies often lack a ‘no HER2-therapy’ arm, rendering it difficult to assess the impact of PIK3CA mutations per se as predictors of response to therapy. It is notable, however, that a similar discrepancy between the biology of PIK3CA-mutant tumors in early versus advanced disease has been described for HR-positive, HER2-negative tumors [26].

Despite the complexity, we do offer some clinical suggestions based upon the data from Loibl et al., as well as other reports. Most importantly, we believe that there is currently no rationale for the routine testing of PIK3CA mutation status in HER2-positive breast cancers before administering neoadjuvant therapy. The presence of a mutation cannot yet dictate choice of therapy, and has no prognostic implications. Of course, this recommendation may change as our understanding of the underlying biology deepens. In addition, we advise caution when applying the current data to tumors treated with other HER2-directed neoadjuvant regimens. At present, the ‘gold-standard’ neoadjuvant regimen contains dual HER2-blockade with trastuzumab and pertuzumab, and the impact of PIK3CA mutations on response to this therapy has not been comprehensively explored.

Lastly, we believe that there remains a strong rationale for the development of novel targeted therapies to treat HER2-positive tumors harboring PIK3CA mutations. β-Sparing (or α-specific) PI3K inhibitors are the obvious choice, and early data suggest that the presence of a PIK3CA mutation in breast cancer might predict enhanced response to these agents [27, 28]. Furthermore, recent preclinical data provide a strong rationale for using CDK4/6 inhibitors in tumors that are HER2-amplified and/or mutant at PIK3CA [29, 30].

In summary, we congratulate Loibl et al. for successfully compiling the data from five different neoadjuvant trials in HER2-positive breast cancer to reach important conclusions. This study highlights the benefits of meta-analysis of individual patient data, and the results are thought-provoking. At present, however, when trying to comprehend the biology and behavior of PIK3CA-mutant HER2-positive breast cancer, we appear to still have more questions than answers.

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A tribute to biologics in advanced colorectal cancer treatment

Twelve years ago, a French trial on the sequential use of FOLFOX and FOLFIRI demonstrated for the first time the achievement of 20-month median survival time (MST) in advanced colorectal cancer [1]. Now, we celebrate approaching, and sometimes breaking, the 30-month barrier [2–4]. These results can certainly be due to a number of factors, including stage migration, better surgery and supportive care [5], but it is generally recognized that the new biologic drugs play the most important role in this improvement [6]. The paper by Yamazaki et al. [7] reports the best survival results obtained so far (31-month MST) on a mixed population of RAS wt and mutated patients using FOLFOX or FOLFIRI plus bevacizumab followed by the appropriate use of anti-EGFR agents in later lines of treatment. This confirms that bevacizumab is an excellent choice for first-line therapy, irrespective of the RAS status, and that all available biologics should be used for optimal outcome.

These excellent results are particularly relevant because of the quality of the study. Despite the fairly weak but justifiable primary end point (non-inferiority in progression-free survival), the internal validity of this trial is very strong. The external validity (generalizability) is maximal for patients eligible for the most efficacious regimens available today. In fact, the patients characteristics are slightly better than average, the median time on treatment is among the longest reported, the resection of metastases was carried out in 10% of patients, second-line treatment was given to 80% and anti-EGFR therapy was given to ~90% of RAS wt patients in the later course of the disease. All these figures reflect excellent trial conduct and overall patient management as well. One could argue that the relevance of these data is limited because these results were obtained on Japanese patients and because the dose of irinotecan used was slightly lower than that used in western countries (150 instead of the classical 180 mg/sqm). However, this concern is attenuated by the consistency of these results with those of several phase II trials reviewed by Yamazaki et al. [7] along with those recently reported in the randomized MAVERICC trial pursuing the same comparison of FOLFOX bevacizumab versus FOLFIRI-bevacizumab on western patients [8].

This paper does not change clinical practice but has a substantial impact on it in this disease concerning at least three aspects.

First, the confirmed efficacy of bevacizumab in first line. A common criticism of the potential benefit of bevacizumab is that a significant difference in overall survival was not observed in any of the randomized large trials of chemotherapy plus or minus bevacizumab, except for the registration trial that used a suboptimal irinotecan-containing regimen which is no longer used in practice [9]. This paper does not address that question, but its excellent efficacy results make it harder and harder not to recognize the very substantial contribution of the anti-VEGF agent to the overall improved outcome—especially if we compare these results with those of the similar sequential chemotherapy trial conducted in the pre-biologic era in France [1]. In that trial, the patient population, the duration of treatment, the reported toxicity and the percent of liver resection were similar to those of the present Japanese trial, although a slightly lower percent of second lines (68%) was given.

The significance of breaking the barrier of 30-month MST in this trial lies in the fact that this result has been achieved on a mixed population of RAS wt and RAS mut patients. Even the most toxic FOLFOXIRI bevacizumab combination did not reach this threshold on a similar population of patients [10]. Whenever the population is restricted to the RAS wt cohort, the MST is ~6 months longer compared with the mixed population and the threshold of 30 months is passed as a result of the additional efficacy of the anti-EGFR agents in this subset of patients [2–4].

Of course, these data do not help to clarify the debated question on the preference of anti-VEGF versus anti-EGFR in first