PIK3CA amplification and PIK3CA mutation were validated as biomarkers for sensitivity to the single-agent phosphoinositide 3-kinase (PI3K) inhibitor, GDC-0941, in breast cancer models. A novel expression profile was developed to identify other breast cancers sensitive to PI3K inhibitors. These expression studies highlighted feedback networks connecting TORC1, PI3K, and mitogen-activated protein kinase (MAPK) pathways, and underscored the potential for combination therapies. Clin Cancer Res; 16(14): 3523-5. ©2010 AACR.

In this issue of Clinical Cancer Research, O'Brien et al. (1) assess the efficacy of a pan phosphoinositide 3-kinase (PI3K) inhibitor, GDC-0941, against a wide spectrum of breast cancer cell-line models. In their studies, they validate previously identified biomarkers of sensitivity. They also reveal PI3K-dependent gene expression patterns that may identify additional subsets of sensitive cancers, and may also provide insight into the feedbacks induced by PI3K inhibition, which may ultimately limit their effectiveness.

Using a large panel of breast cancer cell lines, this study confirms that cancers with HER2 amplification and/or PIK3CA mutations, but not those with PTEN deficiency, may be particularly sensitive to PI3K pathway inhibitors. These results support findings by Rosen and colleagues (2), who showed that breast cancers with PIK3CA mutation or HER2 amplification were sensitive to single-agent AKT inhibitors. Similarly, other studies have shown that cancers with PIK3CA mutations are sensitive to single-agent PI3K inhibitors and dual PI3K-mammalian target of rapamycin (mTOR) inhibitors (3, 4). Although there is more ambivalent evidence that cancers with PTEN loss will be highly sensitive to single-agent PI3K inhibitors, studies with cancer cell lines and genetically engineered mouse models have suggested that loss of p110β leads to decreased PI3K-AKT signaling and impedes cancer cell growth and tumorigenesis in such cancers (5, 6). In this study, the authors identify a subset of PTEN-deficient cancer cell lines as sensitive. These results suggest that additional biomarkers may be needed to isolate the sensitive subset. Importantly, however, O'Brien and colleagues identify several cell lines that are sensitive to PI3K inhibition, yet carry neither HER2 amplification nor PIK3CA mutation, highlighting the need for additional markers to identify patients who will best respond to PI3K-targeted therapies. The authors define a novel gene set, expanding beyond HER2 amplification and PIK3CA mutation, which is regulated by PI3K activation and is differentially expressed in sensitive and resistant cells.

Many laboratory studies define sensitivity to a specific drug according to its ability to decrease growth in vitro. Indeed, several studies, including the one by O'Brien and colleagues, use IC50 values as the primary mode to define sensitivity. This measure provides a quick and robust read-out that facilitates comparisons across a large panel of cancer models. Although such assays identify the cell lines whose growth is impacted by the drug, it remains less clear if such data will faithfully predict which cancers will respond to PI3K inhibitors (or other targeted therapies) in a clinical setting. For example, these data may identify cancer cell lines that grow more slowly in response to drug. However, in the clinic, this finding may still amount to disease progression, not tumor shrinkage. Of note, recent studies correlate significant responsiveness to PI3K inhibitors in vivo with the induction of cell death (7, 8). Thus, future efforts to discover clinically useful biomarkers may benefit from implementation of more stringent laboratory criteria for "sensitivity." Thus, O'Brien and colleagues subsequently analyze a subset of cell lines identified as sensitive, by determining the effects of PI3K inhibition on cell cycle arrest, expression of key regulators of the G1 to S transition, induction of apoptosis, and tumor shrinkage in vivo. Of note, despite similar in vitro IC50 values among the PIK3CA-mutant and HER2-amplified cell lines, they did not all show similar in vivo sensitivity. For example, one of the "sensitive" models showed substantial tumor growth in vivo. Indeed, it would be interesting to learn if this cancer cell line had failed to undergo apoptosis in response to PI3K inhibition. Thus, even among sensitive genotypes, we may need additional understanding and biomarkers to identify those cancers that will undergo tumor shrinkage in response to single-agent PI3K inhibitors in the clinic (Fig. 1).

In these breast cancer models, O'Brien and colleagues highlight a feedback system in which PI3K inhibition...
leads to upregulation of ERBB3 and IRS proteins. This system may stimulate increased flux through downstream pathways, which may reinforce PI3K activation and also signal independently of PI3K. Similar feedback responses have also been described in which MAP/ERK kinase (MEK) or TORC1 inhibition increases PI3K/AKT activation (8–10). Further, Pandolfi and colleagues have described a PI3K-dependent feedback loop in which TORC1 inhibition leads to activation of MAPK signaling (11). These feedbacks will likely contribute to the limited success of single-PI3K pathway inhibitors. Indeed, several laboratories, including ours, have previously shown that combining PI3K and MEK inhibitors may effectively promote cell death and tumor regression in KRAS- and epidermal growth factor receptor (EGFR)-addicted cancers (8, 10, 12, 13).

These data presented by O’Brien and colleagues, illustrating feedback on ERBB3 and IRS proteins in response to PI3K inhibitors, nicely highlight that inhibition of this pathway will trigger cellular feedbacks that may ultimately limit their activity in the clinic. The authors observed decreased ERBB3 expression in PIK3CA mutant cell lines, and ERBB3 expression was increased in response to treatment with a PI3K inhibitor. Thus, these data correlated increased PI3K activity with decreased ERBB3 levels, and suggested that ERBB3 expression levels could be used as a biomarker for high activation of PI3K signaling, and perhaps, increased sensitivity to PI3K inhibitors. However, high basal expression of ERBB3 correlated with sensitivity to GDC-0941, when comparing the resistant and sensitive cancer cell lines (Supplementary Table S2), highlighting the complexity of some of these potential predictive markers.

Another interesting finding in this study is that PI3K inhibition led to loss of TORC1 signaling in sensitive cell lines, but failed to reduce TORC1 activation in resistant cancers. This finding suggests that TORC1 regulation may predict a cell’s level of addiction to PI3K signaling, but it remains unknown if the failure to downregulate TORC1 in resistant cells is central to their lack of responsiveness, and if such cancers would be more responsive to dual PI3K-mTOR inhibitors. Furthermore, it remains unknown whether all cancers in which PI3K regulates TORC1 signaling will invariably regress in response to single-agent PI3K inhibitors in vivo.

The authors note that all of the PTEN null lines identified in their panel as resistant have a basal-like phenotype and, therefore, are likely to exhibit an activated RAS-like transcriptional program that would shift dependence from PI3K to MEK/ERK signaling (9). Indeed, it has been shown that RAS mutations predict for resistance to single-agent PI3K inhibitors (3, 12, 13). Cell lines with KRAS mutations or significant activation of MEK/ERK signaling via another oncogenic driver may be more likely to be insensitive to single-agent PI3K inhibitors regardless of HER2 amplification, PTEN deletion, or PIK3CA mutational status. This finding further highlights the potential of combination therapies and the need for additional biomarkers that predict responsiveness to combined PI3K and MEK inhibition.

The report by O’Brien and colleagues identifies other potential biomarkers, in addition to HER2 amplification and PIK3CA mutation, that correlate with sensitivity in vivo. It will be interesting to determine if PI3K inhibitors induce substantial apoptosis in vitro and tumor regressions in vivo in these cancer models (without HER2 amplification or PIK3CA mutation). Of course, it will be crucial to assess biomarkers identified in laboratory studies in clinical samples from patients who respond to PI3K inhibitors. Neo-adjuvant trials in breast cancer patients can be leveraged to address these translational goals, because they correlate clinical efficacy and pathologic signs of response (e.g., changes in Ki67 levels and induction of caspase cleavage) with the presence of potential biomarkers.
Biomarkers derived from laboratory models and clinical specimens should further define cancers most likely to respond to PI3K inhibitors. Indeed, the use of additional stringent parameters to define “sensitivity” in laboratory models may yield more accurate predictions in the clinic. Additionally, it will be useful to consider biomarkers in addition to HER2 amplification and PIK3CA mutations, and to remain cognizant of feedback compensations, as we continue to further define those patients who will benefit most from single-agent PI3K pathway inhibitors, and those who will require different therapeutics approaches.

Disclosure of Potential Conflicts of Interest

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Alexa B. Turke and Jeffrey A. Engelman


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