Research Highlight

Targeting cancer with PI3K pathway inhibitors: who to aim at?

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Submitted Mar 04, 2012. Accepted for publication Mar 27, 2012.
DOI: 10.3978/j.issn.2218-676X.2012.03.06
Scan to your mobile device or view this article at: http://tcr.thepbpc.org/article/view/382/747

Breast and gynecological (ovarian, endometrial and cervical) cancers commonly harbor mutations activating the PI3K pathway, including *PIK3CA* mutation/amplification, *PTEN* loss or *HER2* amplification. Insight from the successful development of many targeted cancer therapeutics suggests that these tumor types with a high prevalence of mutations in the PI3K pathway would be ideal candidates for therapy with inhibitors of that pathway. This was indeed the case with imatinib to target Bcr-Abl positive CML patients and cKIT mutant GIST tumors; vemurafenib to target B-RAF^{V600E} melanoma; trastuzumab to target HER2 positive breast cancer; and crizotinib to target EML4-ALK positive lung tumors. Clinical trials of PI3K-pathway inhibitors are still underway across multiple advanced tumor types, with several studies selecting patients with breast or gynecological cancers. Early phase clinical development of PI3K pathway inhibitors will be accelerated not only by the identification of tumor types likely to respond, but also by the identification of robust biomarkers that are predictive of response.

Preclinical studies on PI3K and mTOR inhibitors indicate that mutations in *PIK3CA* may predict response and that MAPK pathway activation leads to resistance. Supporting these preclinical findings is the observation that patients with various tumor types exhibiting a *PIK3CA* mutation or loss of *PTEN* function benefited from the mTOR inhibitor everolimus, except when there was a concomitant BRAF/*KRAS* mutation (1). Specifically examining a patient population with breast or gynecological cancers, Janku and colleagues (2) investigated whether *PIK3CA* mutation status alone will be a valuable patient selection criterion for PI3K pathway inhibitors. Data was combined from 5 phase I or I/II clinical trials investigating the single agent PI3K inhibitor PX866 or the mTORC1 inhibitor Temsirolimus, or combination therapies Temsirolimus/Bevicuzimab/liposomal doxorubicin, Temsirolimus/Bevicuzimab or Sirolimus/Docetaxel. They found that 18% of patients had a *PIK3CA* mutation and that 30% of patients with this mutation (7/23 cases) respond to combination therapy that included a PI3K pathway inhibitor; compared to only 10% of *PIK3CA* wild type patients (7/70 cases). Thus, patients with a *PIK3CA* mutation had a better response rate to mTOR inhibition than patients without a mutation. However, interestingly, MAPK pathway activation did not appear to impact on this response, with 3/5 patients with both *PIK3CA* and *KRAS* mutations demonstrating partial response or stable disease. This could reflect differences in breast/gynecological versus other cancer types or that the combination of an mTOR inhibitor with a cytotoxic agent overcomes this resistance.

Whilst patient selectivity based on mutations in the exon 9 or 20 hotspots of *PIK3CA* alone significantly enriched the population of responders, there are several limitations of this study that need to be considered before it can be concluded that *PIK3CA* mutation status is a practical selection criterion for PI3K pathway inhibitors. The limitation of testing only a low number of *PIK3CA* mutant patients (23 patients) is compounded by the compilation of response data from 5 clinical trials using different PI3K pathway inhibitors in different drug combinations. Only one trial included a PI3K inhibitor and the remaining trials were mTORC1 inhibitors either as a single agent or in combination. No responders were found with single agent treatment (either PI3K or mTOR inhibitor) but

given that only 7 *PIK3CA* mutant patients received single agent treatment and the breakdown in patient numbers receiving either inhibitor was not given, no conclusions can be confidently drawn regarding how *PIK3CA* status impacts on response to these single agent treatments. All selected patients had failed standard therapy, and whether the combinational therapy included the previously failed therapeutics is not clear. So without the control arm for this study (*PIK3CA* mutant patients on the combination treatment less the mTOR inhibitor), it is difficult to draw sound conclusions. In addition, this study examines early phase clinical trial data that may be using non-efficacious doses, suggesting more responders may be observed once the optimal dosing strategy has been established.

One of the major difficulties facing the identification of predictive response biomarkers to PI3K pathway inhibitors is that there are so many ways to activate the pathway, and thus many potential biomarkers to evaluate. Moreover, multiple activating hits in the pathway are a common occurrence in gynecological cancers (3-6), suggesting that a single genetic lesion may be insufficient to fully activate the pathway. Given that not all *PIK3CA* mutant patients responded, and not all responders had *PIK3CA* mutations, the Janku study (2) would certainly have been strengthened by the assessment of changes in additional pathway members, including receptor tyrosine kinase status, *PTEN* loss, and AKT mutational status. However, even this may not solve the problem, since the function of these genes may be changed in multiple ways - for example, *PIK3CA* can be mutated or amplified and *PTEN* is subject to mutation, loss, or deregulation by post-translational mechanisms. Thus, to adequately characterize all the individual members of the pathway will require a large number of biomarkers to be assessed in every tumor. Rather, what is needed is a functional readout of the activity of the pathway.

Measuring PI3K pathway activity using one or several crucial activation readouts, such as phosphorylation of AKT, p70S6K or 4EBP1, could overcome the problem of looking for all potential genetic events that regulate signaling. However, preclinical and early clinical results using this approach have been varied, where some patients without high pAKT exhibit response to pathway inhibitors (7). It is likely that the non-linearity of the PI3K/AKT/mTOR pathway, with its complex regulatory feedback signaling, cross-talk to parallel pathways, and multitude of context dependant substrates (8), gives the analysis of just one or a few biomarkers little predictive power. Thus, as is the case for using mutational analysis in predicting response, multiple biomarkers will probably also be necessary for this 'activation readout' approach. The advent of cheaper high throughput protein expression arrays is likely to enable a more global analysis of pathway activity that can be used to assist in patient selection.

The clinical development of PI3K pathway inhibitors is currently a major focus in oncology. As for other targeted therapies, it will be crucial to identify those patients most likely to benefit from PI3K pathway inhibition. Disappointingly, we are not yet at the stage where we can confidently rely on biomarker-based patient selection into clinical trials of PI3K pathway inhibitors. The study by Janku and colleagues (2) suggests that *PIK3CA* mutation status in breast and gynecological cancer patients may be a promising strategy to enrich the population for responders. However, as we and others have observed (9), a number of confounding issues in the study make it difficult to determine if *PIK3CA* mutations are truly predictive of response to PI3K pathway inhibitors. Certainly, further studies will be important and evolving technologies enabling deeper and more systematic genotype and/or proteomic screening of patients entering trials should help identify patients most likely to benefit from treatment with PI3K pathway inhibitors. However, it will be important that future trials are more focused, specifically designed, and adequately powered in order to provide the level of evidence required to influence clinical practice.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2012.03.06). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kinross KM, Sheppard KE, Pearson RB, Phillips WA. Targeting cancer with PI3K pathway inhibitors: who to aim at? Transl Cancer Res 2012;1(2):119-121. DOI: 10.3978/j.issn.2218-676X.2012.03.06

