Almost 20 years of cancer biology and genomic studies have identified phosphoinositide 3-kinase (PI3K) and the PI3K pathway as important players in tumor onset and maintenance. PI3K is therefore considered a well-validated target for cancer treatment, and hence the demand for inhibitors with drug-like properties was highly anticipated 5 years ago. At Novartis, after having considered different druggable targets (such as Akt or PDK1) in this pathway, our primary choice was to set up a structure-based medicinal chemistry PI3K program. NVP-BEZ235, a dual PI3K/mTOR inhibitor, was our first-generation molecule from this effort, with sufficient drug-like properties to promote it as a candidate for clinical use in the treatment of cancer. Since that time, we have made a great deal of progress in our understanding about the intricate mechanisms by which this pathway is regulated in different types of cancer with observable constitutive activation. The best example to illustrate this concept is the wealth of evidence regarding the importance of inhibition of key negative feedback loops that could significantly alter the therapeutic benefit of PI3K inhibitors. It is important to note that efforts are being made within the scientific community to better define patient stratification methods so as to maximize therapeutic responses to PI3K inhibitors. Along these lines, molecules with different mechanisms of action (e.g., pan-PI3K, dual PI3K/mTOR inhibitors, and isoform specific inhibitors, as well as inhibitors of Akt) are needed toward the goal of personalized medicine (i.e., each cancer being a separate disease and even within cancer type, subtypes with different addictions exist). It is becoming evident that PI3K inhibitors as single-agent entities might not hold up to their initial promise. Thus, it will be important to focus on robust translational research programs to best identify key combination partners for PI3K inhibitors. Future combination phase II trials will certainly be key to validate clinically what is currently being pursued in the laboratory.

Disclosure of Potential Conflicts of Interest

The author is a Novartis employee and shareholder.

Received October 1, 2011; accepted October 3, 2011; published November 9, 2011.
Molecular Cancer Therapeutics

PI3K Inhibitors for Cancer Treatment: Five Years of Preclinical and Clinical Research after BEZ235

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