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EDITORIALS



Idelalisib — A PI3K δ Inhibitor for B-Cell Cancers

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The phosphoinositide 3-kinase (PI3K) signal transduction pathway is highly active in tumors and drives many of the hallmarks of cancer. Efforts to develop PI3K inhibitors for oncology have been complicated by the existence of four distinct PI3K catalytic isoforms with partially overlapping functions. In addition, diverse resistance mechanisms and on-target toxic effects have been observed with many PI3K inhibitors.^{1,2}

In this issue of the *Journal*, two clinical teams report that idelalisib, a selective inhibitor of the delta isoform of PI3K, provides impressive efficacy and has an acceptable side-effect profile when used to treat patients with certain B-cell cancers.^{3,4} The emerging success of idelalisib illustrates the clinical translation of basic research studies of PI3K signaling in B cells.

Furman and colleagues³ report results from a phase 3 clinical trial in relapsed chronic lymphocytic leukemia (CLL). In this randomized, double-blind study, patients received anti-CD20 monoclonal antibody (rituximab) with either idelalisib or placebo. The patient population was heavily pretreated and considered not to be healthy enough to undergo additional chemotherapy, and many of the patients had undergone previous rituximab therapy. The overall response rate with the idelalisib combination was 81%, versus 13% in the control group. The median progression-free survival was 5.5 months with the control combination but was not reached with the idelalisib combination. On the basis of these results and acceptable safety, the study was halted at the time of the first data analysis.

Gopal et al.⁴ report results from a phase 2, uncontrolled trial of idelalisib monotherapy in patients with indolent non-Hodgkin's lymphoma. The overall response rate was 57%, with a median progression-free survival of 11 months, values sug-

gesting that the efficacy of idelalisib is similar or superior to those of other active treatment options in relapsed or refractory indolent non-Hodgkin's lymphoma. The toxic effects were acceptable and similar to those in the study by Furman et al., with common adverse events including diarrhea and aminotransferase elevations that were mostly reversible on dose discontinuation or reduction. Idelalisib plus rituximab was effective in patients with CLL who had high-risk genetic profiles, including chromosome 17p deletion (p53 loss), a finding that suggests that idelalisib should be tested earlier in the course of treatment for patients with CLL who have high-risk characteristics.

What is the biologic basis for the efficacy and side-effect profile of idelalisib? Along with ibrutinib, which targets Bruton's tyrosine kinase (BTK), idelalisib represents a new class of agents that target signal transduction downstream of the B-cell receptor (BCR) in malignant B cells.⁵ Low levels of BCR signaling occur continuously and are necessary for survival of normal mature B cells and some types of malignant B cells, including CLL cells. BCR signaling activates PI3K, a lipid kinase, to produce the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3), which recruits other proteins to the membrane (Fig. 1). BTK is a key PI3K effector in B cells; direct binding of this tyrosine kinase to PIP3 in the membrane drives calcium mobilization and downstream events, including cell division and survival.⁶ PI3K and BTK are also activated downstream of numerous other receptors on B cells, including CD40, cytokine receptors, and toll-like receptors. Strong genetic evidence supports the function of PI3K and BTK in B cells. Mutations that inactivate BTK or the p85 α regulatory subunit of PI3K cause similar immunodeficiencies in mice and humans, with few mature B cells and impaired

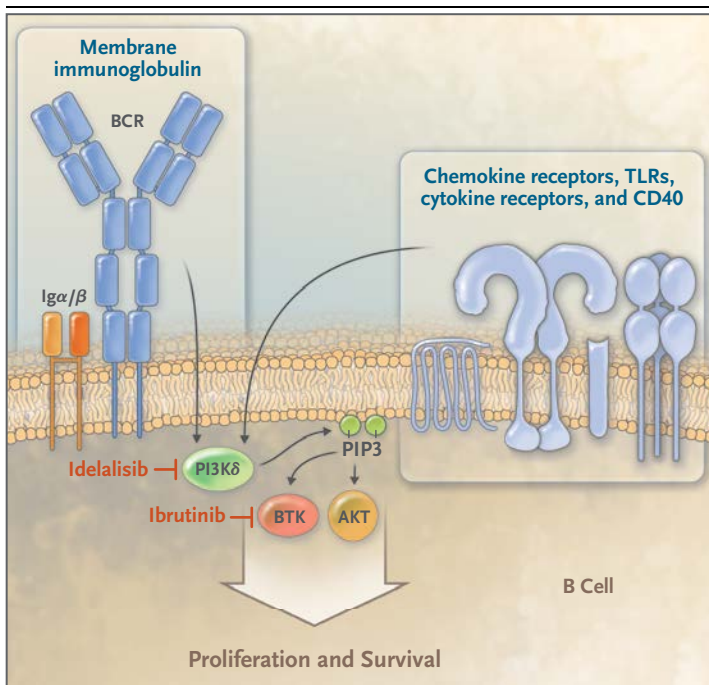


Figure 1. Mechanism of Action of Idelalisib and Ibrutinib.

B-cell receptor (BCR) signaling activates phosphoinositide 3-kinase (PI3K) to produce the second messenger, phosphatidylinositol 3,4,5-trisphosphate (PIP3), which activates Bruton's tyrosine kinase (BTK) and AKT, a prosurvival kinase that binds PIP3 and plays a key role in many solid tumors. Idelalisib, a selective inhibitor of the delta isoform of PI3K, targets signal transduction downstream of the BCR in malignant B cells, whereas ibrutinib targets BTK. PI3K and BTK are also activated downstream of numerous other receptors on B cells, including CD40, cytokine receptors, chemokine receptors, and toll-like receptors (TLRs). The BCR is composed of antibody heavy and light chains associated with two signaling chains, Igα and Igβ.

antibody production.⁷⁻⁹ Likewise, mice lacking PI3Kδ catalytic function show profound B-cell impairments.¹⁰ Thus, PI3Kδ and its downstream target BTK have unique functions in B cells that cannot be replaced by related kinases.

The efficacy of idelalisib and ibrutinib arises not only from direct inhibition of survival signaling but also from disruption of the localization of malignant B cells in a protective niche in lymph nodes⁵ (Fig. 1). Inhibitors of PI3K or BTK block chemokine receptor signaling, releasing tumor cells into the bloodstream, with transient lymphocytosis observed in most patients treated with idelalisib or ibrutinib. Combining idelalisib with rituximab appears to shorten the period of lymphocytosis and improve overall response rates.

As with most anticancer agents, idelalisib and

ibrutinib do not produce durable responses in all patients. Identifying and overcoming resistance mechanisms will be crucial for the most effective use of these agents. Since the two agents have acceptable side-effect profiles, it makes sense to test the combination of idelalisib and ibrutinib. This approach should suppress the emergence of rare clones with point mutations in the kinase domains of PI3Kδ or BTK. It will also be informative to monitor AKT activation as a possible resistance mechanism. AKT is a prosurvival kinase that binds PIP3 and plays a key role in many solid tumors (Fig. 1). Selective inhibitors of AKT are in development and might be tested in combination with PI3Kδ or BTK inhibitors. Although most clinical trials with PI3K inhibitors have focused on solid tumors with PI3K mutations or PTEN loss, it is likely that the first approval of a PI3K inhibitor will be in a disease in which neither PI3K nor PTEN is mutated but in which there is a cell-lineage-specific requirement for a specific PI3K isoform.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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