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PI3K signalling regulates several cellular activities, including growth and apoptosis.[1] Therefore, inhibition of PI3K presented an intriguing and novel therapeutic avenue to treat several haematological malignancies, such as chronic lymphocytic leukaemia, follicular lymphoma, and marginal zone lymphoma. Given the paucity of novel treatments for these malignancies in the relapsed and refractory settings, there was considerable interest when the first PI3K inhibitor, idelalisib, was approved in 2014.

Richard Pazdur, director of the US Food and Drug Administration's (FDA's) Oncology Center of Excellence (Silver Spring, MD, USA), stated in July, 2014, that idelalisib's approval "reflects the promise of the breakthrough therapy designation program and represents the FDA's commitment to working cooperatively with companies to expedite a drug's development, review and approval".[2] However, since then, growing scrutiny regarding the safety of these drugs led the US FDA to meet virtually on April 21, 2022, to discuss the appropriate approach for PI3K inhibitors. The FDA discussed PI3K inhibitors that are under development and whether randomised data should be mandated to judge the net balance of benefit in the intended population.[3]

In a Comment published in April, 2022, Nicholas Richardson and colleagues presented several considerations of the FDA in the development of future clinical trials, including dose exploration, avoidance of single-arm trials, and allowing for maturation of overall survival data before analysis.[4] We consider these proposed solutions and address several issues related to the development and approval of PI3K inhibitors.

First, single-arm trials are often insufficient to establish which drugs improve survival or quality of life. We have previously shown that surrogate endpoints, especially those used in single-arm trials (eg, response rate), have poor correlation with subsequent changes in survival.[5] All four approved PI3K inhibitors were studied with single-arm trials, including idelalisib (for chronic lymphocytic leukaemia and follicular lymphoma), copanlisib (for follicular lymphoma), duvelisib (for follicular lymphoma), and umbralisib (for follicular lymphoma). By contrast, the BTK inhibitor acalabrutinib was approved for patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma following two randomised controlled trials: ELEVATE-TN[6] and ASCEND.[7] ASCEND studied the efficacy of acalabrutinib in the relapsed or refractory setting for patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma and showed the feasibility of conducting randomised controlled trials in this disease setting. The FDA's absence of consistency in defining expectations for trial designs for cancer drugs has subsequently affected several PI3K inhibitors, such as zandelisib, which was studied in the phase 2 TIDAL study without a comparator group (NCT03768505).

Second, the FDA granted regular approval, after initial accelerated approval, for two PI3K inhibitors on the basis of surrogate endpoints.[4] Idelalisib received regular approval in 2014 for treatment of patients with relapsed chronic lymphocytic leukaemia in combination with rituximab, and duvelisib received regular approval in 2018 for relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic leukaemia after two or more therapies. Although these two approvals were based on the results of randomised controlled trials, both drug approvals came from the surrogate endpoint of progression-free survival, as overall survival data were considered immature. However, subsequent randomised controlled trials studying idelalisib in chronic lymphocytic leukaemia and final analysis of duvelisib versus ofatumumab showed little survival benefit and ultimately led to further scrutiny of both PI3K inhibitors. These differences in results emphasise the danger of using surrogate endpoints to measure efficacy. The FDA should standardise overall survival or quality-of-life outcomes as the benchmark for conversion from accelerated approval to regular approval.

Notably, Gilead Sciences (Foster City, CA, USA) halted six trials involving the study of idelalisib in treating relapsed chronic lymphocytic leukaemia, small lymphocytic lymphoma, and follicular lymphoma in March, 2016.[8] The FDA has only begun enacting corrective actions (eg, disavowing single arm studies) for the development and approval of PI3K inhibitors approximately 6 years later. Although the FDA's proposed changes could bring positive transformation to the development and approval processes for cancer drugs, the considerable delay of several years in the FDA's actions is too little, too late for many patients who died while being treated with the PI3K inhibitors. The saga of the PI3K inhibitors is still being written, but might ultimately prove to be a central defining story in the history of regulation of cancer drugs.

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