PERSPECTIVE ARTICLE

Lessons learned from experience of phosphatidylinositol 3-kinase inhibitors in chronic lymphocytic leukemia and lymphoma

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Abstract

The development of phosphoinositide 3-kinase (PI3K) pathway inhibitors for the treatment of lymphoma and chronic lymphocytic leukemia (CLL) has been a journey characterized by significant promise and important challenges.[1,2] Starting as a very rational targeted approach for B- and T-cell lymphoproliferative disorders, the development of PI3K inhibitors faced regulatory setbacks due to class-specific adverse events and complex interpretation of the survival outcomes.[3] The recently published CHRONOS-4 clinical trial,[4] a randomized placebo-controlled study comparing copanlisib in combination with bendamustine plus rituximab and placebo with bendamustine plus rituximab demonstrated that adding copanlisib to the standard-of-care bendamustine plus rituximab did not improve survival and increased toxicity. In this article, we examine the scientific rationale, clinical experience, regulatory hurdles, and future developments of PI3K inhibitors. We analyze the complexity of balancing PI3K therapeutic potential and safety.

Introduction

Phosphoinositide 3-kinase (PI3K) is a validated target in B- and T-cell lymphomas and chronic lymphocytic leukemia (CLL) with broad activity in different lymphoma subtypes.[5] Multiple studies exploring PI3Kδ inhibition with idelalisib, the PI3Kδ/γ inhibitor duvelisib, and the pan-PI3K inhibitor copanlisib showed impressive and durable responses in B-cell indolent non-Hodgkin lymphoma (NHL) and CLL, leading to rapid approval by the U.S. Food and Drug Administration (FDA) beginning in 2014[6-10] (Table 1).

Methods

We conducted a comprehensive review of the literature on PI3K inhibitor studies in CLL and lymphomas to analyze the approval process, the following setbacks, and the potential highlighted by this class of agents. We conducted our search through PubMed and the Cochrane Library for studies published between January 1, 2020 and December 31, 2024, using the search terms: "PI3K inhibitors", "idelalisib", "duvelisib", "copanlisib", "umbralisib", "zandelisib", "parsaclisib", "CLL" and "lymphoma". We also reviewed conference abstracts from the American Society of Hematology, European Hematology Association, International Conference on Malignant Lymphoma and American Society of Clinical Oncology meetings, FDA communications, and company press releases from 2010 onward. Studies included in this manuscript were clinical trials and relevant prospective and retrospective series reporting safety data and clinical efficacy of the use of PI3K inhibitors in CLL or lymphoma; we excluded studies that were pre-clinical, purely focused on solid tumors or focused on other hematologic disorders.

Significant toxicity in a targeted approach

The FDA approvals of the above PI3K inhibitors for therapeutic use in indolent NHL and CLL were based on their ability to prolong progression-free survival (PFS).[6,8-11] Nonetheless,

emerging evidence from subsequent trials demonstrated that inhibition of PI3K (especially δ) in regulatory T cells (Treg), which are highly dependent on this signal for their function, leads to important immune-related toxicities. This mechanism, besides inducing the dysregulation of Treg, also promotes the activation of Th17 cells.[12-15]

Phase II trials of idelalisib,[9,10,16,17] duvelisib,[6,18] copanlisib,[8] and umbralisib[19,20] reported high rates of drug discontinuation secondary to adverse events (15-31%) and dose reductions (11-34%), with severe adverse events (grade ≥3) in 87% of patients. Immune-related toxicities, including hepatitis, colitis and pneumonitis, were the most critical side effects detected in these trials, and in some cases led to severe consequences including fatal hepatotoxicity, intestinal perforation, and respiratory failure.[21] Neutropenia and severe infections were also commonly observed with PI3K inhibitors. These adverse events were associated with inhibition of the δ isoform. Other adverse events observed particularly with PI3Kα inhibition (e.g., hyperglycemia, hypertension) were predictable, transient, and hence were relatively easy to manage and did not lead to significant issues.

One important safety warning issued by the FDA was related to the observation that PI3K inhibitors in combination with rituximab and/or bendamustine, despite promising efficacy in terms of PFS, were not associated with an improvement in overall survival (OS), and in some cases even had a negative impact secondary to non-lymphoma-related causes.[10,11,16,17,20]

Table 1. Summary of the efficacy of each PI3K inhibitor in different histological subtypes.

Compound	ORR (CR), %			
	FL	MZL	SLL	CLL*
Idelalisib	56 (14)	-	-	84 (10)
Copanlisib	59 (20)	78 (13)	-	-
Duvelisib	42 (1)	39 (6)	68 (0)	74 (0.6)
Umbralisib	45 (15)	49 (16)	50 (5)	-
Parsaclisib	71 (21)	78 (33)	-	33 (0)

*Data refer to pretreated patients only and not to those treated frontline. PI3K: phosphoinositide 3-kinase; FL: follicular lymphoma; MZL: marginal zone lymphoma; SLL: small lymphocytic lymphoma; CLL: chronic lymphocytic leukemia; ORR: overall response rate; CR: complete remission rate.

A broad brush by the Food and Drug Administration

After issuing the initial safety warnings, the FDA tried to regulate clinical trials with PI3K inhibitors, including providing advice on timing the administration and scheduling of these drugs,[22] which in part had already been implemented in the newest trials. In Spring 2022, when the FDA was due to evaluate the New Drug Application for umbralisib plus ublituximab (U2)[20] for CLL, it also scheduled an Oncologic Drugs Advisory Committee (ODAC) meeting to evaluate the entire PI3K inhibitor class. In April 2022, Nicholas Richardson and FDA colleagues published an editorial[3] in *The Lancet Oncology* right before the ODAC meeting, analyzing the long-term survival data and toxicity that led to the emergency meeting. The UNITY registration trial for U2, which enrolled both previously untreated and previously treated patients, had a numerically higher (but not statistically significantly higher) number of deaths on the U2 arm compared to the control arm, which received obinutuzumab plus chlorambucil.[20] These deaths, however, were primarily due to coronavirus disease 2019 (COVID-19) during the height of the pandemic. All patients who had received obinutuzumab plus chlorambucil finished therapy prior to the COVID-19 pandemic, while the patients who received U2 continued on both the PI3K inhibitor and continuous anti-CD20 antibody throughout the pandemic, making it difficult to distinguish the impact of the PI3K inhibitor *versus* that of the anti-CD20 antibody. Nonetheless, these findings led to the withdrawal of both the New Drug Application and umbralisib from the market for NHL.[3]

Following the ODAC meeting, the FDA established a mandate that any study seeking FDA approval of a PI3K inhibitor must be a randomized trial and have OS as the primary endpoint. This requirement made it difficult, if not impossible, to design a clinical trial in the setting of indolent diseases such as indolent NHL and CLL, for which life expectancy with current treatment and the natural course of disease are very long. The new FDA regulations halted the development of some auspicious drugs, such as zandelisib,[23] an unequivocally promising compound with a good side-effect profile. In the phase I trial of zandelisib plus zanubrutinib for relapsed or refractory follicular or mantle cell lymphoma, the rate of drug-related diarrhea was 2% compared to ≥10% seen with the other PI3K inhibitors.[23] The long half-life of zandelisib allowed intermittent dosing, which helped to reduce immune-related toxicity; <10% of patients had to discontinue zandelisib due to toxicity *versus* the 40% to 50% discontinuation rate observed (in real-world reports) with previous-generation PI3K inhibitors.[24,25] This study was discontinued prematurely because of the FDA requirement that all future PI3K inhibitor approvals in hematologic diseases be supported by randomized trial data.[23] The company had planned a randomized clinical trial in follicular lymphoma but abandoned it when the FDA introduced the requirement of prolonged observation for OS data. Moreover, within a many-year follow-up period, OS might not be a reliable estimate of therapy impact, given the long natural history of the disease and the subsequent treatments, including crossover to investigational drugs.[1,26]

Naturally, the FDA's main concern is ensuring patients' safety. There is a critical need to understand why a PFS advantage has not translated into an OS advantage for some patients, and whether there are any late toxicities associated with PI3K inhibitors. This questionable OS disadvantage should also be examined in the context of the selection of patients

for trials. When evaluating OS of heavily pretreated patients – who are often participants in early-phase trials – several confounders and competing risks must be considered. Also, OS in these trials must be interpreted with caution as the trials were not powered to sustain this endpoint analysis, and the OS differences were not significant. The FDA's one-size-fits-all approach toward the entire class of PI3K inhibitors has severely affected research and development of a highly active drug mechanism.

The CHRONOS-4 trial experience

The CHRONOS-4 study,[4] a large, phase III randomized placebo-controlled study in indolent NHL, was designed with PFS as the primary endpoint and OS among the secondary endpoints prior to the FDA's post-marketing OS requirement. Copanlisib was administered in combination with bendamustine-rituximab (BR) and compared to placebo plus BR. A total of 534 patients with relapsed indolent NHL were randomized 1:1 to copanlisib plus chemioimmunotherapy or placebo plus chemoimmunotherapy. No significant difference in median PFS was observed between the copanlisib-BR and placebo-BR arms. Similarly, no significant differences were demonstrated in the secondary endpoints, including OS, overall response rate (ORR), and duration of response.[4] Interestingly, in the placebo-BR arm of the CHRONOS-4 trial, the PFS of patients treated with BR was significantly higher than in previous studies; unfortunately, the copanlisib-BR arm did not show further benefit. This outcome may have been influenced by shorter treatment durations and higher discontinuation rates due to adverse events in the copanlisib-BR arm. In the experimental arm, 83% of patients underwent dose modifications, including dose delays, reductions or interruptions, compared to 67% in the standard arm (placebo-BR). One-third of patients had to reduce the copanlisib dose, and a further 11% needed a reduction of PI3K inhibitor. Dose modifications of the BR schedule (interruptions or modifications) occurred in half of patients receiving copanlisib, leading to a shorter treatment exposure in the experimental arm.[27]

Serious treatment-emergent adverse events, including infections, hyperglycemia, diarrhea and hypertension, were more common in the copanlisib-BR arm, further compromising its tolerability.

Lessons learned

Isoform specificity

The PI3K pathway is important for cell metabolism, growth, and survival. It includes four isoforms: alpha (α), beta (β), gamma (γ), and delta (δ), each with unique roles in different cell types and different lymphoproliferative disorders (Tables 1 and 2).[28] Targeting each of these isoforms results in different side-effect profiles as well as different anti-lymphoma activity.

The δ isoform, expressed in hematopoietic stem cells, is important for B-cell development and function and its inhibition likely achieves the most relevant anti-lymphoma effect, albeit also with a key off-target toxicity affecting Treg.[29] The γ isoform instead might be more important to target in T-cell lymphoma.[30]

The activity of single-agent PI3K inhibitors, while excellent in low-grade B-cell malignancies, is not as high in other lymphoproliferative disorders. In diffuse large B-cell lymphoma, for example, where the potential efficacy of these agents seemed to be supported by genetic profiling studies,[31] PI3K inhibitors have demonstrated limited activity.[32,33] Similarly, in mantle cell lymphoma, an upregulation of various pathways (mostly PI3Kα) seems to limit the success of a single-target approach against PI3Kδ.[34]

Toxicity prevention and the importance of early signals

Many early trials of first-generation PI3K inhibitors lacked proper monitoring and dose adjustments to mitigate some of the adverse events. Aggressive monitoring and treatment of early neutropenia was not included in most trials. Many trials, even recent ones, failed to enforce appropriate prophylaxis for *Pneumocystis jirovecii* pneumonia, even after this infection had occurred in the dose-finding phases and been described in several reports.[6,10,35,36]

The convergence of the COVID-19 pandemic also presented a significant obstacle in the development of PI3K inhibitors.

Table 2. Approved and experimental PI3K inhibitors.

Characteristic	Idelalisib	Copanlisib	Duvelisib	Umbralisib	Parsaclisib	Zandelisib
Isoform	PI3Kδ	PI3Kα + PI3Kδ (pan)	PI3Kγ + PI3Kδ	PI3Kδ + CK1ε	PI3Kδ	PI3Kδ
IC_{50} PI3Kα	820	0.5	1,602	>9,000	>20,000	5,022
IC_{50} PI3Kβ	565	3.7	85	>1,000	>20,000	208
IC_{50} PI3Kγ	89	6.4	27	>1,000	>10,000	2,137
IC_{50} PI3Kδ	2.5	0.7	2.5	22.23	1.1	5
Route of administration	Oral	Intravenous	Oral	Oral	Oral	Oral

PI3K: phosphoinositide 3-kinase; IC_{50}: half-maximal inhibitory concentration (expressed as nM).

Continuous treatment with PI3K inhibitors, which suppress B-cell function, was particularly concerning during the pandemic due to an increased risk of infections and compromised immune response.[1] The pandemic coincided with the full enrollment of several ongoing PI3K studies, potentially skewing data and complicating the interpretation of trial results. Furthermore, PI3K inhibitors were often studied together with other immunosuppressive therapies, including anti-CD20 antibodies, which are known to strongly suppress responses to COVID-19 infection and vaccination.[37]

Importance of the dose

Initial PI3K inhibitors were characterized by a lower binding affinity for the planned targets (δ or γ isoforms), creating two significant problems: (i) the maximum tolerated dose (MTD) did not cover the specific target (δ isoform) sufficiently to fully appreciate the activity of the drug; and (ii) targeting the δ isoform generated most of the described immunological side effects at the MTD. The mechanism of this toxicity is mostly related to the dysregulation of Treg and the activation of Th17 cells.[1,12,16]

From the beginning, it quickly became evident that targeting the MTD was not the best way to find the right dose for idelalisib and umbralisib.[9,21,36] Instead, the aim should have been to find an optimal biological dose, i.e., a dose that would still be effective but allow Treg to recover from dysregulation and avoid off-target toxicity. The eventual realization that intermittent dosing could be the solution to identifying the optimal biological dose emerged with a significant delay, during the development of zandelisib and parsaclisib.[24,35,38] Unfortunately, the first trial developed with this goal was launched 6 years after the approval of the first PI3K inhibitor.[39] iOnctura has developed roginolisib,[40] a novel first-in-class allosteric inhibitor of PI3Kδ. In phase I studies, predominantly in solid tumors but also including a small cohort of patients with lymphoma, the dose escalation was stopped at an optimal biological dose, based on δ inhibition. With this arrangement, roginolisib has so far shown very limited toxicity and limited drug discontinuation due to adverse events. A phase I study in uveal melanoma[41] showed no evidence of autoimmune toxicity and the Dana-Farber Cancer Institute has opened a CLL-specific study.[42]

Importance of the schedule

Optimal dosing strategies proved crucial in achieving a balance between efficacy and tolerability. A more refined development approach has been adopted for recent agents such as parsaclisib and zandelisib in B-cell lymphoma, employing an initial higher dose induction phase followed by dose reduction to manage side effects more effectively. Learning from the experience of earlier trials, later protocols highlighted the importance of adjusting dosing and schedule to minimize toxicity while maintaining clinical benefit. This lesson was particularly relevant when using PI3K inhibitors in combination.[38,39]

Parsaclisib is a highly selective next-generation inhibitor of PI3Kδ, with a selectivity for PI3Kδ exceeding 19,000-fold that for the other PI3K class I isoforms. In a phase I-II trial,[35] parsaclisib was tested in patients with relapsed or refractory B-cell lymphoma, both as a single agent, and in combinations. An intermittent dosing schedule of daily followed by weekly dosing was also assessed following an initial protocol amendment. Serious adverse events included diarrhea or colitis, fever, hypotension, and sepsis.[35]

Zandelisib is a highly selective potent inhibitor of PI3Kδ that binds to this target 37-fold more tightly and for 138-times longer than old-school idelalisib. The planned schedule for zandelisib was daily administration for cycles 1 and 2 (28 days per cycle) at a continuous dose of 60 mg, also considered an "induction phase". From cycle 3, the drug was administered at 60 mg for the first 7 days of the cycle, with no administration between days 8 and 28. This intermittent dosing allowed Treg to recover and was effective at reducing immune-related toxic effects. An early-phase study[43] of zandelisib (with or without rituximab) that enrolled patients with relapsed or refractory follicular lymphoma showed an ORR of 87%, and the incidence of grade severe adverse events was low (neutropenia, 16%; transaminitis, 8%; diarrhea, 5%; colitis, 5%).[43]

Copanlisib, a potent pan-PI3K inhibitor with selectively greater activity against the α and δ isoforms, is the perfect example of intermittent-dosing administration; because of its intravenous formulation, there were great expectations for lower toxicity and an improved safety profile. In the CHRONOS-3 trial,[11] a large, phase III placebo-controlled study of copanlisib plus rituximab *versus* placebo plus rituximab in patients with indolent NHL who were ineligible or unwilling to receive chemotherapy, the PFS in the copanlisib-rituximab arm was superior to that in the placebo-rituximab arm, without improvement in OS.[11]

Combination strategies

Preclinical data had suggested a synergistic potential of PI3K inhibitors with other treatments, including chemotherapy (e.g., BR with idelalisib), although clinical results were variable.[16,44] The registration trial for BR-idelalisib in the setting of relapsed CLL showed both PFS and OS benefits with the addition of idelalisib, albeit with significant infectious toxicity, including cytomegalovirus reactivation.[16] Of note, combinations of PI3K inhibitors have been challenging not only because of the enhanced toxicity, but also because of the likelihood that the chemotherapy, by reducing lymphocyte counts, may also reduce the immune-mediated antitumor benefits of the PI3K inhibitor.[45]

In the CHRONOS-4 trial, pharmacokinetic analyses suggested that lower copanlisib exposure in the combination regimen, likely due to dose modifications, may have limited the potential clinical benefit. The combination with chemotherapy could also have decreased any antilymphoma effects by disrupting immune-mediated antitumor responses.[12,45] This finding contrasts with those of earlier studies in which high-

er copanlisib doses demonstrated a clear efficacy-toxicity relationship, highlighting the challenges of combining PI3K inhibitors with chemotherapy.[4] The failure of the copanlisib-BR combination to demonstrate clinical benefit prompted the termination of the CHRONOS-4 trial and a re-evaluation of the role of copanlisib in combination therapies for indolent NHL. However, the combination with histone de-acetylase inhibitors may tell a totally different story. Administering duvelisib (a PI3Kγ/δ inhibitor marketed by Secura Bio) with romidepsin[30] (a histone deacetylase inhibitor) in peripheral T-cell lymphoma reduced PI3K inhibitor-related toxicity, possibly due to the reported protection that histone deacetylase inhibition may afford to Treg. The combination of duvelisib and romidepsin resulted in a reduction of grade 3 or 4 hepatotoxicity: 14% *versus* 40% in a previous study with duvelisib monotherapy by the same center. In this case, the duvelisib antilymphoma effect seemed to be maintained, as the response rates were similar with monotherapy or the combination. The duvelisib-romidepsin combination also allowed patients to reach a higher MTD with duvelisib: the MTD was 25 mg twice a week for the single-agent study and 75 mg in combination with romidepsin,[30] further demonstrating the increased tolerability of the combination. Studies of similar combinations, such as tenalisib and romidepsin, are ongoing and thus far are showing a similar profile.[46]

The importance of publishing negative studies

Finally, especially in this context of evolving side-effect profiles, it is essential to publish negative studies in a timely manner to ensure progress and patients' safety. In 2016, an early warning by the FDA was issued when Gilead closed six early-line trials with idelalisib in combination with rituximab and/or chemoimmunotherapy in indolent NHL and CLL, because the combined mortality rate of three early-line trials was higher in the idelalisib-containing arms (7.4%) compared to the control arms (3.5%).[3] Most deaths were related to bacterial infections; however, infection prophylaxis and monitoring were not mandatory in these trials. Unfortunately, these trial outcomes have never been published.

Furthermore, among more heavily pretreated patients with two or three prior therapies, in whom disease was presumably a more common cause of death, the pooled mortality rate favored the idelalisib-containing arms (23.2% *vs*. 31.5% in control arms).[3] Two of the three trials individually showed an OS benefit for the idelalisib-containing arms, suggesting that patient selection is a critical component of the safe and optimal usage of these drugs.

New directions for PI3K inhibitors

Despite the challenges experienced in the early development of PI3K inhibitors, new molecules are emerging that offer potential pathways forward.

As described, duvelisib has shown promising results in peripheral T-cell lymphoma. A single-agent trial of duvelisib for patients with relapsed or refractory peripheral and cutaneous T-cell lymphoma demonstrated an ORR of approximately 50%, compared to a 30% ORR at best with existing FDA-approved agents. Responses were observed quickly, within the first 2 to 4 months of treatment. Transaminase elevation was the most relevant adverse event, and this was significantly decreased, as seen above, when combining the drug with romidepsin, making this a potential winning strategy in peripheral T-cell lymphoma.

Linperlisib,[47] another PI3Kδ inhibitor, is under development in China for relapsed or refractory follicular lymphoma and T-cell lymphoma. In follicular lymphoma, linperlisib demonstrated an impressive ORR (80%) in heavily pretreated patients, with a very limited side-effect profile in terms of autoimmune-related events, including diarrhea, interstitial lung disease, and transaminitis. Infectious pneumonia, however, was quite high (20% overall).[47] A phase II trial[48,49] of patients with relapsed or refractory peripheral T-cell lymphoma reported a 48% ORR (30% complete responses) with rapid responses. Grade 3 adverse events were neutropenia, pneumonia, anemia, thrombocytopenia, and upper respiratory tract infections. The company has announced the official activation of the phase III regulatory study in the USA, Europe and China.

These efforts highlight the ongoing interest in targeting the PI3K pathway, particularly as the understanding of the underlying biology and optimal dosing strategies continue to evolve. Improved dynamic assessment of side effects and more refined dosing strategies, as well as careful patient selection, are essential for the future success of PI3K inhibitors. The lessons learned from early clinical trials underline the need to balance drug efficacy with toxicity, in particular when combining PI3K inhibitors with other agents. These challenges may be successfully addressed with the next generation of PI3K inhibitors by strategically planning to use optimal biological dosing and scheduling and biomarker-based approaches. We believe that PI3K inhibitors should be evaluated based on their individual, specific properties rather than generally as a class, including by the FDA.

In conclusion, while the development of PI3K inhibitors has been full of challenges, including significant adverse effects and regulatory hurdles, the insights gained offer valuable lessons for the development of future therapies. By addressing the complexities of PI3K signaling, optimizing dosing strategies, and navigating regulatory landscapes, the next generation of PI3K inhibitors holds promise for improving outcomes in patients with B- and T-cell lymphomas.

Disclosures

PG reports consulting fees from ADC Therapeutics; serves on a data safety monitoring committee for Regeneron; and has participated in an advisory board for Ipsen Pharmaceuticals. PLZ reports consulting fees from EUSA Pharma, Merck, Sharp & Dohme, and Novartis; has participated in speakers' bureau for AstraZeneca, BeiGene, Bristol-Myers Squibb, Celltrion,

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Contributions

PLZ, JRB, and PG were involved in writing, reviewing and approving the manuscript.

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Data-sharing statement

The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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