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Idelalisib for the treatment of non-Hodgkin lymphoma

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Abstract

Introduction—B-cell Non-Hodgkin lymphomas (B-NHLs) include a number of disease subtypes, each defined by the tempo of disease progression and the identity of the cancerous cell. Idelalisib is a potent, selective inhibitor of the delta isoform of phosphatidylinositol-3-kinase (PI3K), a lipid kinase whose over-activity in B-NHL drives disease progression. Idelalisib has demonstrated activity in indolent B-NHL (iB-NHL) and is approved for use as monotherapy in patients with follicular lymphoma and small lymphocytic lymphoma and in combination with rituximab in patients with chronic lymphocytic leukemia.

Areas Covered—Herein we review the development and pharmacology of idelalisib, its safety and efficacy in clinical studies of iB-NHL, and its potential for inclusion in future applications in iB-NHL and in combination with other therapies.

Expert Opinion—Idelalisib adds to the growing arsenal of iB-NHL pharmacotherapeutics and to the progression of the field toward precision agents with good efficacy and reduced toxicities. Nevertheless, idelalisib carries important risks that require careful patient counseling and monitoring. The appropriate sequencing of idelalisib with other proven treatment options in addition to its potential for combination with established or novel drugs will be borne out in ongoing and planned investigations.

Keywords

Idelalisib; B-cell; Lymphoma; Indolent

1. Introduction

B-cell malignancies, including non-Hodgkin lymphomas and leukemias, are one of the leading causes of cancer death [1]. The molecular and histologic classification schema of B-cell malignancies can be complex and continue to evolve [2]; functionally, the diseases are divided into “aggressive” and “indolent” according to their natural history. Indolent B-NHLs

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(iB-NHL), including chronic lymphocytic leukemia (CLL) and a minority of mantle cell lymphoma (MCL) [3], tend to follow a slow but relentlessly progressive course that ultimately, short of allogeneic transplantation, proves incurable. As all iB-NHL therapies confer a potential risk for toxicity, the paradigm for treating these diseases balances these risks with goals of symptom palliation, avoidance of disease-related complications including organ dysfunction, and prolongation of survival. Observation alone is typically recommended for asymptomatic patients with low-volume iB-NHL since therapy at that stage has no proven benefit on overall survival (OS) [4]. However, treatment is ultimately warranted in the vast majority of cases.

While occasionally localized and potentially manageable with irradiation or surgery, iB-NHLs are usually diagnosed in the advanced stage and require systemic therapy, the intensity of which is dictated by disease burden and patient fitness. Anti-CD20 immunotherapy, most commonly rituximab, with or without several rounds of cytotoxic chemotherapy such as bendamustine or anthracycline- or fludarabine-based combination regimens, is often employed in the first-line treatment setting for follicular lymphoma (FL) and CLL / small lymphocytic lymphoma (SLL); chlorambucil combined with one of the newer, monoclonal anti-CD20 antibodies obinutuzumab or ofatumumab is considered standard of care first-line therapy for CLL in patients who are older or less fit [5, 6].

Treatment of iB-NHL in the relapsed setting is guided by the success of earlier the regimen(s), the disease histology, and, of course, patient fitness. Historically, the duration of remission achieved with iB-NHL therapy roughly correlated with the intensity of the regimen and inversely with the number of prior treatments. This principle arose from treatment algorithms that employed multi-agent regimens with distinct components but overlapping pharmacology, resulting in additive toxicities and drug resistance. The development and implementation in recent years of novel, small molecule therapeutics have upended this paradigm. Idelalisib (formerly known as GS-1101 and CAL-101) is the agent in this class most recently approved by United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for certain relapsed iB-NHL. It adds to a growing collection of such agents with more precisely defined mechanisms of action and lower, less cumulative, toxicities.

2. Targeted therapies for iB-NHL

The new-age of treatments for iB-NHL began with rituximab, a chimeric monoclonal antibody of CD20, a surface phosphoprotein expressed on all B-cells. Rituximab has been on the market for nearly 20 years and serves as a backbone for myriad treatment regimens in iB-NHL. Ofatumumab and obinutuzumab are fully humanized anti-CD20 antibodies designed, in comparison to rituximab, to cause less infusion reactions and induce, respectively, superior complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. In practice, these newer antibodies appear to have comparable tolerability and modestly improved efficacy compared with rituximab in certain applications, including CLL [7]; they are currently not approved for other iB-NHL.

Lenalidomide, an immunomodulator with, additionally, direct anti-tumor and anti-angiogenic properties, is active in various iB-NHLs alone and in combination with rituximab [8-10] and approved for relapsed/refractory MCL [11]. The proteasome inhibitor (PI) bortezomib has demonstrated activity in FL in combination with rituximab and bendamustine [12, 13], alone and in combination with rituximab in lymphoplasmacytic lymphoma / Waldenstrom's macroglobulinemia LPL/WM [14, 15], and is FDA approved for use in relapsed MCL. Investigations of other PIs including carfilzomib and ixazomib are underway to identify active agents in the class with less neurotoxicity and improved ease of administration [16, 17].

The B-cell receptor (BCR) signaling axis is fundamental to B-cell lymphomagenesis, and consequently offers several therapeutic targets, among them the delta-isoform of phosphatidylinositol-3-kinase (PI3K) that is inhibited by idelalisib. The inhibition of Bruton tyrosine kinase (BTK), another enzyme in the BCR pathway essential to normal B cell development [18], by ibrutinib as a single-agent results in remarkable benefit to patients with CLL, MCL, and WM/LPL; ibrutinib gained FDA approval for these diseases in the relapsed setting in the last 2 years. Ibrutinib has shown some activity in other subtypes of iB-NHL [19], where its investigation is ongoing. Spleen tyrosine kinase (Syk), situated proximally to BTK and PI3K in the BCR pathway, represents another promising target [20].

3. Development of idelalisib

PI3Ks are a family of intracellular enzymes with diverse roles and tissue expression profiles. The PI3K pathway is known to contribute to cell survival in many cancers, including B-NHL [21], and to modulate several cell cycle processes including metabolism, apoptosis, proliferation, differentiation, homing, and retention [22]. The PI3K p110 subunit constitutes the catalytic domain of class I PI3Ks and exists as 4 isoforms, each encoded on separate genes. The p110-delta isoform is primarily expressed in cells of hematopoietic origin and constitutes a key component of the BCR pathway [23, 24]; the p110-alpha and -beta isoforms are expressed more generally and knock-out mice for both are embryonic lethal. The tissue-specificity of the p110-delta isoform suggested its “drugability:” knock-out mice survive but show B-cell deficits including B-lymphopenia and decreased antibody production [25]. Lannutti *et al.* [26], using an *in vitro* kinome-wide screen, found that idelalisib inhibits the p110δ isoform of PI3K with a 40- to 300-fold greater specificity compared to other PI3K class I enzymes.

4. Drug Chemistry

Idelalisib is a phenylquinazolin with the chemical name 5-fluoro-3-phenyl-2-[(S)-1-(9H-purin-6-ylamino)-propyl]-3H-quinazolin-4-one. Idelalisib has a molecular formula of $C_{22}H_{18}FN_7O$ and a molecular weight of 415.42 g/mol (Drug Summary Box). It has a pH-dependent aqueous solubility ranging from <0.1 mg/mL at pH 5-7 to over 1 mg/mL at pH 2 under ambient conditions [27]. Idelalisib tablets are orally administered and contain either 100 mg or 150 mg of idelalisib.

5. Pharmacokinetics and pharmacodynamics of idelalisib

Idelalisib is an oral, selective, small-molecule that potently inhibits the adenosine triphosphate (ATP) catalytic domain of PI3K p110- δ , abrogating downstream signaling through Akt and mTOR and inhibiting B-cell functions including chemotaxis, adhesion, and viability [28]. Idelalisib is metabolized primarily to its oxidized, inactive metabolite GS-562117 (62% after 24 hours) via aldehyde oxidase and CYP3A with excretion of both drug and metabolite primarily in the feces (78%) in subjects with normal renal and hepatic function [29, 30]. Peak plasma concentration of idelalisib occurs approximately 1.5 hours after ingestion with a terminal half-life is 8.2 hours [27]; compared to the fasting state, co-administration of a high-fat meal increases idelalisib exposure 1.4-fold. Idelalisib exposure shows non-linear pharmacokinetics and exposure increases in a less than dose-proportional rate over the dose range of 50 mg to 350 mg twice daily [31]; steady state is achieved by day 8. Higher trough concentrations are achieved with twice daily compared with daily dosing. Age, gender, race, and weight have no effect on idelalisib exposure.

Idelalisib clearance is minimally reduced in patients with reduced renal function [32] and no dose adjustment is necessary for patients with creatinine clearance > 15 mL/min. The area under the curve (AUC) of idelalisib is increased to 1.7-fold in patients with transaminases or bilirubin above normal, and while no initial dose adjustment is recommended for patients with mild to moderate liver impairment, careful monitoring should be conducted [33]. Patients with transaminase elevation greater than 2.5-fold above the upper limit of normal (ULN) or bilirubin 1.5-fold above ULN have not been included in safety studies of idelalisib to date. Idelalisib is a strong CYP3A inhibitor and it is significantly metabolized by CYP3A: the AUC of idelalisib is reduced by 75% when co-administered with a strong CYP3A inducer and is increased 1.8-fold when co-administered with a strong CYP3A inhibitor [34]. Idelalisib does not affect QT/QTc at doses up to 400 mg (2.7-fold maximum recommended dose) [35]. Following 8 and 28 days of dosing, constitutive phosphorylation of Akt in cells from subjects with CLL was reduced to the background level of healthy subjects [36]. Plasma concentrations of CLL-related chemokines have additionally been shown to decrease on idelalisib therapy [36].

6. Clinical efficacy of idelalisib

6.1 Phase 1 trials

Study 101-02, the first to report data on the clinical activity of idelalisib, was a phase I sequential dose-escalation study investigating the safety, pharmacokinetics, pharmacodynamics, and activity of idelalisib in previously treated patients with hematologic malignancies, including patients with CLL ($n=18$), NHL ($n=29$), and acute myeloid leukemia ($n=10$) [37]. Subsequently, single-agent idelalisib was studied in B-NHL in several disease-specific phase I trials, including in relapsed/refractory MCL [38], relapsed iB-NHL [31], and relapsed/refractory CLL [36]. Idelalisib dosing ranged from 50 daily up to 350 mg twice daily. A maximum tolerated dose was not identified. Doses greater than 150 mg twice daily showed minimal increase in drug exposure establishing the optimal 150 mg twice daily dosing schedule.

In the study by Flinn *et al.*, 64 patients with relapsed iB-NHL (38 patients had FL, 11 patients had SLL, 6 patients had MZL, and 9 patients had WM/LPL) that had received a median of 4 prior therapies were treated [31]. Of 54 evaluable patients, 46 (85%) had reductions in lymph node area (with an ORR of 30 of 64 (47%), with evidence of dose-dependency. Twelve (19%) patients discontinued therapy due to adverse events (AEs). Median time to response (TTR) was 1.3 months (range 0.6 – 14 months) and the median duration of response (DOR) was 18.4 months (range 0.03 to 37 months). The parallel phase I study in MCL showed 32 of 39 (82%) patients with some response in lymph node size; the ORR was 16 of 40 patients (40%) with a median DOR of 2.7 months [38]. In the phase I CLL study, 54 patients with relapsed/refractory disease were treated, of whom 38 (70%) were treatment-refractory and 13 (24%) harbored high-risk genetic lesions of del17p and/or *TP53* mutations [36]. Forty-four (82%) patients achieved a lymph node response, and concurrent asymptomatic increases in absolute lymphocyte count were frequently observed, consistent with treatment-induced lymphocytosis described for BCR-inhibitors disrupting adhesion between tumor lymphoma cells and stroma and resulting in lymphocyte efflux into peripheral blood [22, 39]. The ORR was 39 of 54 (72%) according response criteria updated to account for treatment-related lymphocytosis [40], with median TTR of 1.0 month and median DOR of 16.2 months.

Several phase I studies combined idelalisib with anti-CD20 antibodies [41] and conventional genotoxic chemotherapies including bendamustine, chlorambucil, and fludarabine, in relapsed or refractory CLL and no unexpected safety signals emerged [42, 43]. Conversely, combination of idelalisib with lenalidomide and rituximab for relapsed iB-NHL has shown prohibitive toxicity. Two groups reported early termination of clinical trials using this combination in a total of 15 patients, with toxicities including 1 death from hepatic failure, 1 death from pulmonary failure, and 4 instances of dose-limiting toxicities consistent with immune activation suggestive of cytokine release syndrome [44, 45].

6.2 Advanced phase trials

With promising results from phase I studies, a phase II multicenter, open-label study called Study 101-09 evaluated 125 patients with iB-NHL double-refractory to both rituximab and an alkylating agent [46-48]. Forty-one sites across the United States and Europe participated. Idelalisib was given at a dose of 150 mg twice daily, with dose reductions made for toxicity. The median age of subjects was 64, and the majority (N = 72) had a diagnosis of FL. Other diagnoses included SLL (N = 28), MZL (N = 15), and WM/LPL (N = 10). Patients were heavily treated previously, receiving a median of 4 prior regimens (range 2 – 12), representing a population with high-risk disease. Indeed, the median PFS from the last previous treatment regimen was only 4.6 months. Seventy patients (56%) met the primary endpoint of ORR: 58 with a partial response (PR) and 12 with a complete response (CR). The median TTR was 1.9 months which marked the first scheduled response assessment; the median time to complete response was 4.5 months. An additional 43 patients experienced stable disease (SD); overall, 90% of patients experienced some decrease in tumor size. Median DOR for responders was 13.9 months, and ranged from 11.8 months in patients with FL to 13.9 months in patients with SLL, to 18.4 months in patients with MZL and was not reached in patients with WM/LPL. Median PFS for all patients was 11.0 months,

significantly longer than the median PFS of 3.9 months for the previous regimen. The median OS for all patients was 30.8 months, with overall survival at 1 year estimated to be 80%.

These results served as the basis for the FDA granting accelerated approval to idelalisib for treating FL or SLL that is relapsed or refractory after at least 2 prior regimens [49]; the EMEA similarly has issued approval for the use of idelalisib as monotherapy in FL that is relapsed or refractory after at least 2 prior regimens. Several post-marketing requirements have been issued to verify clinical benefit and optimize safety, including results from two phase III studies ongoing and additional evaluations of long-term use and follow-up.

Follicular lymphoma is increasingly recognized for the heterogeneity of its natural history, with Casulo *et al.* recently describing a subset of patients that can be classified as high risk if disease progression occurs within 24 months of starting first-line therapy [50]. Accordingly, a subset analysis of Study 101-09 was performed on 37 patients that, retrospectively, met criteria for high-risk disease [51]. In this cohort the ORR was 57% and the median DOR for responders was 11.8 months, suggesting that the efficacy of idelalisib is maintained in this high-risk population.

Encouraging phase I data in CLL provided the foundation for Study 116, a phase III, multicenter, placebo-controlled study of rituximab with or without idelalisib for patients with CLL relapsed after at a minimum prior antiCD20 therapy or two lines of chemotherapy [52]. Ninety centers across the United States and Europe participated. All patients received 8 doses of rituximab and, after stratification for high risk genetic features including presence of deletion 17p, other *TP53* mutations, or lack of immunoglobulin heavy-chain variable region hypermutation, randomized to receive idelalisib at 150 mg or placebo twice daily. Patients with progression of disease in the placebo arm could transition to Study 117 and receive idelalisib. Patients were required to be unfit for cytotoxic chemotherapy based on pre-existing cytopenias, impaired renal function, or according to assessment of comorbidities. One-hundred and ten patients were enrolled into each arm of the trial. At 24 weeks, the primary endpoint of PFS was significantly greater in the idelalisib (93%) versus placebo (46%) group (hazard ratio, 0.15; 95% confidence interval, 0.08 to 0.28; $P < 0.001$), meeting predefined stopping criteria. Overall survival was also better in the idelalisib group (92% versus 80% at 12 months, $P = 0.02$). The ORR, all of which were PRs, was 81% in the idelalisib group. Idelalisib benefit was maintained across all subgroups evaluated, including those patients with high-risk genetic features. These data led to FDA approval of rituximab with idelalisib for patients with relapsed CLL in whom single agent rituximab would be an appropriate therapy due to comorbidities; the EMEA granted approval for the use of idelalisib with rituximab in patients with CLL who have received at least one prior therapy or as first line treatment in the presence of chromosome 17p deletion or other mutation in *TP53* in patients unsuitable for higher-intensity chemoimmunotherapy.

Combination of idelalisib with rituximab for older patients with CLL and naïve to prior therapy was examined in a single-arm phase II study reported by O'Brien *et al* [53]. Sixty-four patients (median age of 71, range 65 – 90) were treated and efficacy endpoints were impressive, with an ORR of 97% and a 3-year PFS of 83%. Early results of a 2:1

randomized, phase III study of ofatumumab with or without idelalisib for relapsed CLL recently were reported and met the primary endpoint of showing benefit in PFS, with a median of 16.3 months with combination therapy versus 8.0 months without [54].

6.3 Studies in WM/LPL

Though few in number, patients with WM/LPL treated with idelalisib have, to date, achieved impressive responses. Summarized by Coutre *et al.*, results are available for a total of 19 patients that have been treated on phase I and phase II studies [55]. Combined, the ORR was 13 of 19 (68%), with a median DOR of nearly 33 months in the phase I study and not yet reached in the phase II study.

6.4 Studies in aggressive B-NHL

Few investigations, to date, have evaluated idelalisib in aggressive B-NHL. In addition to the phase I study summarized above of idelalisib in MCL [38], a few combination studies have opened but lack mature results or were stopped due to unexpected toxicity. These include the phase I study of lenalidomide with idelalisib for relapsed MCL mentioned above [45], and a phase II study of idelalisib plus the Syk inhibitor GS-9973 in patients with various B-NHL including MCL and DLBCL was stopped early due to an unexpectedly high rate of pneumonitis [56].

6.5 Ongoing Trials

Several studies are active or planned evaluating idelalisib in B-cell malignancies. In iB-NHL, these include phase III studies of dose optimization (NCT02536300) and combination with rituximab (NCT01732913) and with rituximab and bendamustine (NCT01732926) [57, 58]. The dose optimization trial will randomize 240 patients with previously treated FL or SLL to receive idelalisib at either 150 mg twice daily or 100 mg twice daily, with the potential for dose-escalation in the latter group. In CLL, a phase III study comparing obinutuzumab plus chlorambucil with obinutuzumab plus idelalisib in patients with untreated disease (NCT01980875) opened in 2015, building off the promising phase II data of idelalisib plus rituximab [53]. Phase III studies of in CLL of bendamustine plus rituximab with or without idelalisib in the treatment-naïve and relapsed settings are underway [59, 60]. An additional phase II study in CLL is exploring a combination of 2 cycles of debulking bendamustine followed by obinutuzumab plus idelalisib (NCT02445131). To better define the promising results identified in WM/LPL, a phase II study of single agent idelalisib in 30 previously treated patients (NCT02439138) is recruiting participants. Combination studies currently ongoing include a phase II investigation of idelalisib with the novel BCL-2 inhibitor venetoclax for patients with CLL that has relapsed or is refractory to prior therapy with a BCR pathway inhibitor (NCT02141282). In addition, a phase 1b/II trial of idelalisib plus the anti-CD37 monoclonal antibody BI 836826 for previously treated CLL is planned (NCT02538614).

7. Safety and toxicity of idelalisib

7.1 Boxed Warnings

Though expression of the p110delta-isoform of PI3K is relatively specific to leukocytes [24, 26], multiple organ systems can show idelalisib-related toxicity. Treatment-emergent adverse events associated with idelalisib resulted in an FDA boxed warning for fatal and/or serious hepatotoxicity, diarrhea and colitis, intestinal perforation, and pneumonitis [27]. Mechanisms behind these toxicities are not well characterized.

Elevation in transaminases to > 5 times the ULN have been observed in 14% of patients using idelalisib; a single incident of fatal hepatotoxicity has been reported, as well [27]. Transaminase elevation typically occurs within the first 12 weeks of initiation of therapy, and is one of the most common reasons for dose modification or interruption. Every-other week monitoring of transaminases is indicated during this period, with gradual reduction in the frequency of monitoring thereafter. Transaminase elevations of > 5 to 20 times the ULN should result in treatment interruption, with resumption at a dose of 100 mg twice daily only upon normalization of values. Recurrent elevation in transaminases, reported in 26% of patients in whom a first episode occurs, or transaminase elevations in excess of 20 times the ULN, should result in permanent discontinuation. Avoidance of concurrent hepatotoxic medications with idelalisib is recommended.

Grade 3 idelalisib-associated diarrhea or colitis, defined as an increase of ≥ 7 bowel movements per day above baseline, has occurred in approximately 14% of patients [27]. Severe cases of idelalisib-related diarrhea are typically watery, not painful, not bloody, and insensitive to treatment with anti-motility agents or empiric antibiotics. According to the consensus recommendations of an expert panel convened to discuss idelalisib-related toxicities, idelalisib should be discontinued in the event of diarrhea that is either grade 3 or is grade 2 and unresolved after 24 – 48 hours of supportive care [61]. Additionally, patients should be treated with intravenous hydration as necessary and evaluated for underlying infection. Though not studied prospectively, corticosteroids appear to have a role in the management of serious episodes of idelalisib-related diarrhea. Oral, delayed-release budesonide, in addition to oral or intravenous corticosteroids are recommended in such circumstances. Upon resolution of diarrheal episodes that did not reach grade 4, or life-threatening, severity, idelalisib may be resumed at a dose reduction to 100 mg twice daily. Intestinal perforation has occurred in patients treated with idelalisib, including in the setting of severe diarrhea. Patients should therefore be counseled to report any new or worsening symptoms such as abdominal pain and nausea, and idelalisib should be permanently discontinued if bowel perforation occurs.

Pneumonitis has been reported in 24 of 760 (3%) of patients taking idelalisib and include 3 fatal complications. Pulmonary hypersensitivity related to idelalisib has been postulated as comparable to that observed in patients using mTOR inhibitors, and diagnosis should prompt cessation of therapy and consideration of corticosteroids.

7.2 Other Toxicities

In addition to the boxed warnings, serious complications associated with idelalisib use include severe cutaneous reactions, including a single reported case of toxic epidermal necrolysis, anaphylaxis, and cytopenias. Neutropenia and thrombocytopenia of grade 3 has been found in approximately 30% and 10% of patients using idelalisib, respectively [61]. Treatment interruption is only recommended in the event of grade 4 cytopenias, with careful resumption of therapy at 100 mg twice daily upon recovery. Lastly, idelalisib may cause embryo-fetal toxicity and pregnancy should be avoided during use of idelalisib.

7.3 Cost

While small molecule inhibitors such as idelalisib are resulting in great advancements in managing iB-NHL, the potential for associated financial toxicity must be considered in appropriate context. While the price per cycle of idelalisib is itself typically prohibitive for patients without insurance or other financial assistance (approximately 9,500 USD for 60 tablets), the potential for prolonged treatment – itself an indication of success of therapy – adds an important, additional dimension to the cost-benefit equation. Shanafelt *et al.* modeled a hypothetical cohort of patients with CLL and reported that the incorporation of ibrutinib and idelalisib into the standard of care treatment paradigm increases the overall pharmaceutical cost of treating CLL by 38 to 70%; moving these agents to the front-line could increase drug costs by an entire order-of-magnitude further [62].

8. Conclusion

Idelalisib is an important addition to treatment options for patients with B-NHL and its use is approved as a single agent for patients with FL or SLL relapsed after 2 prior regimens and in combination with rituximab for patients with relapsed CLL for whom single agent rituximab would be an appropriate therapy. Idelalisib has shown impressive clinical activity, even in high-risk subtypes of iB-NHL, and is usually well tolerated. Several important treatment-emergent adverse events have been described, however, and in a minority of patients severe and potentially life-threatening toxicities occur. Consideration of these risks alongside the drug's efficacy guide current and future efforts to mitigate toxicities and optimize sequencing and combination of novel agents in B-NHL.

9. Expert Opinion

The treatment paradigm for B-NHL, especially iB-NHL, is rapidly evolving. Small molecule inhibitors directed at cell pathways essential to lymphomagenesis, including idelalisib, are now routinely used to manage these diseases. With these advances come important questions, including: 1) what strategies best monitor and mitigate idelalisib-associated toxicities, including financial; 2) how is idelalisib best combined and sequenced with other targeted and conventional treatments; 3) what does exposure to idelalisib change about the biology of iB-NHL and how does this affect disease behavior after idelalisib; and 4) how does the introduction of idelalisib and other targeted agents like it affect consideration for more intensive iB-NHL treatments including stem cell transplantation and chimeric antigen receptor T-cell (CAR) therapies.

The toxicities associated with idelalisib require that clinicians engage in careful counseling with patients. Unlike conventional, cyclically administered regimens, the continuous dosing of idelalisib does not lend itself to “built-in” clinical and laboratory assessments. Moreover, while patients may be comforted to learn that toxicities most common with conventional regimens including profound cytopenias, nausea, and alopecia are not as common with idelalisib, they must recognize that idelalisib-associated toxicities, though of a different nature, can be equally serious and even fatal. Additional research is needed to better understand the mechanisms underlying these off-target toxicities, whether they can be predicted by features of the disease or the patient's genetics, and how they can be minimized. Additionally, upfront discussion of the potential for financial toxicity is needed, and may benefit from inclusion of trained financial counselors and navigators [63].

Like antibiotics, targeted small molecule inhibitors such as idelalisib lend themselves to combinations that hit multiple oncogenic cellular pathways and do not result in additive toxicities. Ibrutinib and idelalisib synergistically modulate adhesion of MCL and CLL cells, supporting a rationale for combination therapy [64]. Preclinical data also support combination of idelalisib with the mTOR inhibitor temsirolimus [65], the BCL-2 inhibitor venetoclax [66], and Syk-inhibition [67]. In addition, though idelalisib plus rituximab has proven efficacy, it has been shown to have some antagonism with immune cell-mediated mechanisms of anti-CD20 antibodies [68]. Identification of biomarkers to guide selection of targeted agents and combinations promises substantial improvements in therapeutic efficacy and efficiency.

Both ibrutinib and idelalisib, as inhibitors of the BCR pathway, are FDA approved for specific applications in iB-NHL, including relapsed CLL. While not tested head-to-head, ibrutinib may be more commonly used first based on its earlier approval date, the apparent higher number of publications and trials with this agent, and the perceived favorable toxicity profile. One caveat to this trend is that the toxicities of the agents are not fully overlapping. Patients with an increased bleeding propensity including those who are therapeutically anticoagulated might face an increased risk of hemorrhage with ibrutinib and could instead benefit first from idelalisib. Furthermore, it is unknown whether resistance to one BCR pathway inhibitor will translate to resistance to others; there sequential use, therefore, is a reasonable strategy.

Patients and clinicians are, appropriately, increasingly de-prioritizing high-intensity therapies for relapsed iB-NHL including stem cell transplantation in favor of “stitching together” targeted therapies that bring substantially less upfront risk [69]. Importantly, however, targeted therapies including idelalisib are non-curative and likely to ultimately exhaust their efficacy in younger patients undergoing treatment for iB-NHL. For younger, fit patients with relapsed iB-NHL, these agents may best be used to “bridge” to consolidative stem cell transplantation and/or CART therapy. Timing of such consolidation poses challenges itself, for while deferring highly-toxic therapy is obviously desirable, allowing the development of BCR pathway resistance may confer still greater risk to patients [70].

Ongoing research will clarify many of the issues above in the coming years. For now, idelalisib provides an important, additional treatment option for patients with relapsed iB-NHL.

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Drug Summary Box

Drug name (generic)	Idelalisib
Phase (for indication under discussion)	Launched
Indication (specific to discussion)	Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia
Pharmacology description/mechanism of action	PI3 kinase delta inhibitor Protein kinase inhibitor CC chemokine ligand antagonist
Route of administration	Oral (tablet)
Chemical structure
Pivotal trial(s)	Gopal et al., Study 101-09 [46] and Furman et al., Study 116 [52]

Table 1

Summary of key clinical trials of idelalisib in indolent B-cell malignancies

Reference	Year Reported	Disease	Treatment	Study Type	Patients, <i>n</i>	Key results (anticipated)
Kahl et al. [38]	2014	R/R MCL	Idelalisib mg 50 → 350 mg PO BID	Phase 1	39	ORR 40%, mDOR 2.7 mo
Flinn et al. [31]	2014	Relapsed iB-NHL	Idelalisib mg 50 → 350 mg PO BID	Phase 1	64	ORR 47%, mDOR 18.4 mo
Brown et al. [36]	2014	R/R CLL	Idelalisib mg 50 → 350 mg PO BID	Phase 1	54	ORR 72%, mDOR 16.2 mo
Gopal et al. [46]	2014	Double-refractory iB-NHL	Idelalisib 150 mg PO BID	Phase 2	125	ORR 56%, mDOR 13.9 mo
Furman et al. [52]	2014	R/R CLL after at least 2 lines of therapy	Rituximab plus idelalisib 150 mg PO BID or placebo	Phase 3, randomized	220	PFS 93% versus 46% (HR 0.15, CI 0.08 – 0.28; P < 0.001)
NCT02536300	Active	Relapsed FL or SLL	Idelalisib 100 or 150 mg PO BID	Phase 3, randomized	TBD	(Dose optimization)
NCT01980875	Active	Untreated CLL	Obinutuzumab plus chlorambucil versus obinutuzumab plus idelalisib	Phase 3, randomized	TBD	(Optimal first line therapy for patients with CLL not candidates for fludarabine)

Bold = Pivotal study that led to approval by FDA, EMEA. ORR = Overall Response Rate. mDOR = Median duration of response. R/R = Relapsed or refractory. PFS = Progression free survival. HR = Hazard ratio. CI = 95% confidence interval.

Table 2

Summary of key toxicities associated with idelalisib

Toxicity	Frequency ^I	Management options
Elevation in transaminases > 5 times ULN	14%	Treatment interruption; dose reduction; treatment cessation
Grade 3 diarrhea or colitis	14%	Supportive care including intravenous hydration; treatment cessation; corticosteroids (oral and/or intravenous)
Pneumonitis	3%	Treatment cessation; corticosteroids
Cytopenias grade 3	Anemia = 2% Thrombocytopenia = 6- 10% Neutropenia = 31 – 34%	Treatment interruption; dose reduction

Bold = Constitutes a “black box warning.” ULN = Upper limit of normal.

^IReference Gilead Sciences Idelalisib Package Insert, 2014 and Coutre et al. [27, 61].