Idelalisib for treatment of B-cell malignancies

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Purpose. The pharmacology, pharmacokinetics, clinical efficacy, safety and tolerability, dosing and administration, and place in therapy of idelalisib, a targeted therapy for certain types of non-Hodgkin’s lymphoma (NHL), are reviewed.

Summary. Historically, conventional cancer chemotherapy agents were recommended for the management of progressive lymphomas requiring systemic treatment; in recent years, however, emerging targeted therapies have altered the landscape of lymphoma treatment. Idelalisib, a novel oral phosphatidylinositol 3-kinase (PI3K) inhibitor, disrupts downstream signaling pathways involved in cancer cell growth and survival. Inhibition of PI3K has been demonstrated to produce durable treatment responses and improved survival outcomes in clinical trials involving patients with indolent forms of NHL. Idelalisib is indicated for use in combination with rituximab for treatment of relapsed chronic lymphocytic leukemia (CLL) and as monotherapy for relapsed small lymphocytic leukemia and follicular lymphoma after the failure of at least two systemic treatments. The recommended dosage of idelalisib is 150 mg orally twice daily; the medication can be taken without regard to mealtimes. The most common adverse effects of idelalisib include diarrhea, nausea, fatigue, cough, and pyrexia. Severe hepatotoxicity and gastrointestinal toxicities, including colitis and intestinal perforation, have also been reported in association with idelalisib use. Ongoing clinical studies are exploring the potential for expanded use of idelalisib in the management of other B-cell malignancies.

Conclusion. Idelalisib is a well-tolerated and effective treatment for patients with relapsed or refractory CLL or indolent NHL, providing a novel targeted therapeutic option for the management of these hematologic malignancies.

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Non-Hodgkin’s lymphoma (NHL) is the seventh most commonly diagnosed cancer in adults, accounting for 4% of new cancer cases and 3% of cancer-related deaths each year. In 2015, it was estimated that NHL would account for approximately 71,850 new cancer diagnoses and 19,790 deaths that year. B-cell neoplasms constitute up to 90% of NHL cases and range from indolent to aggressive lymphomas. Among the various indolent B-cell malignancies are chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and follicular lymphoma (FL). Idelalisib (Zydelig, Gilead Sciences, Inc.), formerly known as CAL-101 and GS-1101, a novel oral therapy that targets and inhibits phosphatidylinositol 3-kinase (PI3K), is indicated for the treatment of refractory cases of CLL, SLL, and FL. While CLL is the most common form of adult leukemia, CLL and SLL share common disease characteristics and are often referred to together and treated similarly. Collectively, CLL and SLL account for approximately 7% of cases of NHL. Both result in progressive accumulation of leukemic cells and prolymphocytes, but CLL is associated with relatively more peripheral blood involvement while SLL is relatively more localized to lymph nodes.
The median age at diagnosis of CLL or SLL is 72 years, which may affect treatment options in these patients due to the correlation of older age with poor performance status. First-line therapy in patients with good performance status is commonly a combination of rituximab and a regimen containing a purine analog, such as fludarabine. However, frail patients and those with significant comorbidities may not be able to tolerate these regimens but may instead receive a mustard analog-based regimen or single-agent treatment with rituximab.

Accounting for up to 25% of NHL cases, FL is the most common form of indolent lymphoma. A translocation of chromosomes 14 and 18 triggers overexpression of the B-cell CLL/lymphoma 2 gene, an oncogene that impairs cellular apoptotic mechanisms. This chromosomal abnormality has been linked to 90% of cases of FL and contributes to longstanding survival of lymphoma cells. On diagnosis, patients with early-stage disease are usually asymptomatic, with a low tumor burden, and do not typically receive systemic therapy; instead they will likely undergo active surveillance, as chemotherapy and radiation therapy have not been shown to yield significant survival benefits in early-stage disease. The majority of individuals with FL, however, are symptomatic at the time of diagnosis, with bulky late-stage disease, and require systemic chemotherapy.

After first-line therapy in CLL, SLL, and FL, treatment of relapsed or refractory disease depends largely on patient response and subsequent performance status. The advent of targeted therapies offers unique treatment options in lymphoid neoplasms. This review will discuss idelalisib’s pharmacology, pharmacokinetics, clinical efficacy, safety, dosing parameters, and place in therapy.

**Pharmacology**

Proliferation and survival of B-cell malignancies are highly dependent on extracellular signaling in the tumor microenvironment. PI3K is a protein kinase involved in the B-cell receptor (BCR) signaling cascade, influencing key downstream receptors that affect cellular development and regulation. PI3K may also be activated through BCR-independent pathways such as cytokine and receptor tyrosine kinases. Activation of PI3K results in the phosphorylation of several secondary messenger molecules and subsequent downstream activation of protein kinase B (AKT) and mechanistic target of rapamycin (mTOR). AKT and mTOR are responsible for inactivation of multiple apoptotic mechanisms while also increasing tumor cell survival through nuclear factor-kB stimulation. The proteins p110α, p110β, p110γ, and p110δ (PI3Kδ) are various isoforms of PI3K, with the latter driving activity in B lymphocytes. PI3K inhibition has been a point of interest in cancer research as an attractive target for antitumor therapy.

Idelalisib is a selective small-molecule inhibitor of PI3Kδ and the first Food and Drug Administration (FDA)–approved PI3K inhibitor in its class, having demonstrated efficacy in the management of multiple B-cell malignancies. By effectively blocking PI3Kδ and subsequent downstream activation of the PI3K-AKT signaling pathway, idelalisib reduces survival mechanisms involved in hematologic cancers.

**Pharmacokinetics**

The time to maximum plasma concentration (t_{max}) is 1.5 hours after a single oral dose of idelalisib taken on an empty stomach. Absorption is slowed when idelalisib is administered with a high-fat, high-calorie meal, resulting in a 1.4-fold increase in the area under the concentration–time curve (AUC). This increase is considered insignificant, and it is recommended that idelalisib be administered without regard to mealtimes. In dose-comparison studies, idelalisib was found to be greater than 84% protein bound, with a volume of distribution of 23 L at steady state. Once-daily administration of a 300-mg dose of idelalisib did not sustain adequate plasma drug concentrations, which were achieved with twice-daily, 150-mg dosing (mean ± S.D. concentration, 153 ± 83 ng/mL with the 300-mg dose versus 451 ± 267 ng/mL with the 150-mg dose). Furthermore, administration of doses above 150 mg twice daily did not produce proportional dose-dependent increases in the maximum plasma concentration (C_{max}) or AUC. Steady state is achieved within eight days of treatment initiation.
Idelalisib is hepatically metabolized by cytochrome P-450 (CYP) isozyme 3A4/5, aldehyde oxidase, and glucuronidation of uridine diphosphate glucuronosyltransferase enzyme 1A4 (UGT1A4). The primary metabolite, GS-563117, was identified to be inactive against PI3Kδ in vitro. The terminal half-life of idelalisib is 8.2 hours, and excretion is primarily in the feces (78%) and urine (14%).

Pharmacokinetic studies of idelalisib have been conducted in patients with renal or hepatic impairment. Patients with severe renal impairment, defined as a creatinine clearance (Cl crea) of 15–29 mL/min, did not have clinically relevant changes in Cmax or AUC values relative to healthy volunteers. Idelalisib exposure was unchanged in patients with severe renal impairment. No studies have been performed in patients with a Cl crea of <15 mL/min or in patients requiring dialysis. Patients with moderate or severe hepatic impairment, as defined by Child–Pugh classification, did not have clinically relevant Cmax changes relative to healthy matched volunteers; the mean AUC, however, was found to be increased by 60%, but that did not result in differences in idelalisib’s safety or tolerability.

Clinical efficacy

Treatment of CLL. The use of idelalisib in relapsed or refractory CLL was first investigated as part of a Phase I dose-escalation study to determine the optimal dosage, safety, efficacy, pharmacodynamics, and pharmacokinetics of single-agent idelalisib. Fifty-four patients were enrolled and assigned to various idelalisib dosing schedules, including 50–350 mg twice daily and 300 mg daily. The overall response rate (ORR), as assessed per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) modified criteria, was 72%, and 81% of patients had a greater than 50% reduction in lymph node size. Twenty-five 1 month (range, 0.9–12.9 months), the median progression-free survival (PFS) was 15.8 months, and the median duration of response (DOR) was 16.2 months (range not reported). Based on dose–response assessments, an oral idelalisib dosage of 150 mg twice daily was designated for use in future studies.

Idelalisib has been evaluated in combination with rituximab or bendamustine (or both) in relapsed or refractory CLL. In a Phase I study, 52 patients were given idelalisib 150 mg orally twice daily with rituximab (375 mg/m² i.v. weekly for eight doses), bendamustine (70 or 90 mg/m² i.v. on days 1 and 2 every four weeks for six doses), or both rituximab and bendamustine (four every weeks for six doses). The ORR was 81%, with a median time to response of 1.9 months (range, 1.5–8.3 months) and a median treatment duration of 18 months (range, 1–33 months) at data cutoff. At two years, PFS was 62% and overall survival (OS) was 85%. These observed durable responses led to Phase III studies to further evaluate the efficacy of idelalisib in combination regimens.

An international, multicenter, Phase III randomized, double-blind, placebo-controlled study evaluated idelalisib in combination with rituximab for relapsed CLL. Patients were eligible for study participation if their disease had progressed within 24 months of prior therapy and they were unable to receive additional cytotoxic chemotherapy due to persistent myelosuppression; reduced kidney function, defined as a Cl crea of <60 mL/min; or comorbidities, defined as a Cumulative Illness Rating Scale (CIRS) score of more than 6 on the 56-point scale. All patients received treatment with rituximab (375 mg/m² i.v. for one dose, 500 mg/m² i.v. every two weeks for four doses, and then 500 mg/m² i.v. every four weeks for three doses) and were randomly assigned to receive either idelalisib 150 mg orally twice daily or twice-daily oral placebo use. The primary endpoint was PFS. Secondary endpoints included OS; ORR, including complete response (CR) and partial response (PR); and lymph node response, defined as a decrease in lymphadenopathy of at least 50%.

The study included 220 patients with a median age of 71 years (range, 47–92 years), 58% of whom had high-risk disease (Rai stage 3 or 4); the median CIRS score was 8 (range, 1–18), and the patients had been exposed to a median of 3 prior agents (range, 1–12) for CLL treatment. Half of the patients (n = 110) received idelalisib 150 mg orally twice daily in combination with rituximab, while the other half received a matching placebo.

Interim data analysis was completed at 24 weeks (after 50% of anticipated events had occurred) and revealed a significant (p < 0.001) increase in the rate of PFS in the idelalisib group (93%) relative to the placebo group (46%). The median PFS was not reached in the idelalisib group, while the placebo group had a median PFS of 5.5 months (hazard ratio [HR], 0.15; 95% confidence interval [CI], 0.08–0.28; p < 0.001). OS was 92% in the idelalisib group versus 80% in the placebo group at 12 months (HR, 0.28; 95% CI, 0.09–0.86; p = 0.02). Median OS was not reached, and none of the patients achieved a CR. However, PRs were seen in 81% of patients in the idelalisib group and 13% in the placebo group (odds ratio [OR], 29.92; p < 0.001). Lymph node response was also higher in the idelalisib group (93%) than in the placebo group (4%) (p < 0.001). Based on these results, the authors terminated the study early due to the efficacy of idelalisib. Results of a post hoc subgroup analysis of outcomes in patients with poor prognostic factors such as the 17p deletion, mutations of the tumor suppressor gene TP53, and unmutated IGHV gene status also favored the idelalisib group.

Results from a Phase III randomized placebo-controlled study comparing idelalisib plus bendamustine and rituximab versus bendamustine and rituximab alone in relapsed or refractory CLL were presented at the 57th American Society of Hematology.
(ASH) Annual Meeting and Exposition. Patients included in this study had prior treatment containing an anti-CD20 antibody and a purine analog or bendamustine, unless refractory to bendamustine; progression of disease with 36 months of prior treatment; and good performance status. Patients were randomly assigned to receive 6 cycles of idelalisib 150 mg orally twice daily (or a matching placebo) in combination with bendamustine 70 mg/m² on days 1 and 2 of each cycle, rituximab 375 mg/m² on day 1 of the first cycle, and rituximab 500 mg/m² on day 1 of cycles 2–6. Idelalisib was continued until disease progression, death, intolerable toxicity, or withdrawal of consent. A total of 416 patients were enrolled, of whom 207 were randomly assigned to receive idelalisib in combination with bendamustine and rituximab and 209 received bendamustine and rituximab plus a placebo. The median PFS in the idelalisib group was 23 months, as compared with 11 months in the placebo group (HR, 0.33; 95% CI, 0.24–0.45; p = 2.8 × 10⁻¹⁴). Median OS was not reached for either group (HR, 0.55; 95% CI, 0.36–0.86; p = 0.008). The combination of idelalisib plus bendamustine and rituximab was found to be superior regardless of cytogenetic risk category.

**Treatment of indolent NHL.** The efficacy of idelalisib monotherapy for the treatment of patients with relapsed, indolent NHL refractory to rituximab and an alkylating agent was evaluated in an international, multicenter, single-group, open-label Phase II study. Patients were eligible for enrollment if they were refractory to at least two prior systemic treatments, including rituximab and an alkylating agent; exhibited evidence of progression within six months or less than a PR to therapy; and had radiographically measurable disease, defined as the presence of at least one lymph node with perpendicular dimensions of at least 2 × 1 cm. Patients meeting those criteria received idelalisib 150 mg orally twice daily. Of the 125 patients enrolled, 58% had FL (grade 1, 2, or 3a), 22% had SLL, 12% had marginal-zone lymphoma (MZL; splenic, nodal, or extranodal), and 8% had lymphoplasmacytic lymphoma with or without Waldenström’s macroglobulinemia. The primary endpoint was the ORR, and secondary endpoints included time to response, DOR, PFS, and OS.

A majority of the patients (89%) had advanced disease (stage III or IV) and patients were heavily pretreated, with a median of 4 therapies (range, 2–12). Patients received idelalisib for a median duration of 6.6 months (range, 0.6–23.9 months). Of the 122 patients with a measurable response from baseline, 110 (90%) had a reduction in the size of lymph nodes. The ORR was 57% (95% CI, 48–66%), with 6% of patients achieving a CR. Subgroup analyses showed that age, sex, the number of prior therapies, the duration of refractory disease after prior therapy, the presence of bulky disease or disease refractory to bendamustine, and disease subtype did not affect the rate of response. The median time to response was 1.9 months (range, 1.6–8.3 months), the median DOR was 12.5 months (range, 0.03–14.8 months), the median PFS was 11 months (range, 0.03–16.6 months), and the median OS was 20.3 months (range, 0.7–22.0 months) with an estimated one-year OS of 80%.

The results of post hoc safety and efficacy analyses of cohorts of patients with CLL and MZL were presented at the 57th ASH annual meeting. Single-agent idelalisib therapy was demonstrated to produce favorable outcomes in patients with relapsed or refractory disease. Phase III are currently being conducted to confirm those results. treatment of mantle cell lymphoma. Mantle cell lymphoma (MCL) is yet another subtype of NHL and accounts for approximately 6% of NHL cases annually. Given the efficacy of idelalisib in multiple B-cell malignancies, a Phase I dose-escalation study with an ongoing extension phase was conducted in patients with MCL who had measurable disease (at least one lesion measuring more than 2 cm) and were refractory to at least one prior regimen that included rituximab. Patients enrolled in the 48-week dose-escalation phase received idelalisib doses ranging from 50 to 350 mg twice daily for 28 days, a dose of 150 or 300 mg once daily for 28 days, or a 150-mg dose twice daily (21 days on and 7 days off). The primary efficacy endpoint was the ORR, and secondary endpoints were PFS and DOR.

The study included 40 patients with a median age of 69 years (range, 52–83 years) who were previously treated with rituximab-containing regimens (median, 4; range, 1–14); 32% of the patients had been treated with 6 or more regimens. The median duration of treatment was 3.5 months (range, 0.7–30 months); 40% of patients (95% CI, 24.9–56.7%) had a response to treatment, and 84.9% of patients had a decrease in lymph node size. While the maximum tolerated dose was not reached, patients receiving at least 300 mg of idelalisib daily (n = 16) had a higher ORR (69%) than patients (n = 24) receiving less than 150 mg twice daily (21%). The median time to response was 1.1 months (range, 0.9–9.4 months), with a median DOR of 2.7 months (95% CI, 1.0–8.1 months; range, 0.3–28.2 months). Overall, the median PFS was 3.7 months (95% CI, 2.7–8.2 months; range, 0.03–30.1 months), and one-year PFS was estimated to be 22.5%. However, receipt of fewer prior therapies correlated with improved PFS; patients who had received less than 6 therapies prior to enrollment (n = 27) had a median PFS of 8.2 months (range, 0.9–30.1 months), while those receiving 6 or more prior therapies (n = 13) had a median PFS of only 3.7 months (range, 0.03–14.8 months).

**Safety and tolerability**

The most common adverse effects observed in patients who received idelalisib monotherapy in clinical trials were diarrhea, nausea, fatigue, cough,
and pyrexia. Laboratory test abnormalities included alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations, neutropenia, anemia, and thrombocytopenia. When idelalisib was given in combination with rituximab, chills and infusion-related reactions were also commonly noted; however, similar rates of those adverse effects were seen in the placebo-plus-rituximab group. Tables 1 and 2 detail adverse drug reactions and laboratory test abnormalities noted in more than 10% of patients during clinical trials. Cases of anaphylaxis and severe cutaneous reactions, including toxic epidermal necrolysis, have been reported in association with idelalisib use. Labeling for idelalisib includes black-box warnings for hepatotoxicity, severe diarrhea or colitis, intestinal perforation, and pneumonitis.

**Hepatotoxicity.** Severe hepatotoxicity occurred in 14% of patients treated with idelalisib during clinical trials, including one reported fatality associated with acute liver failure. Additionally, 13% and 8% of patients experienced grade 3 or 4 increases in ALT and AST levels, respectively. Marked elevations in these hepatic enzymes typically occur within the first 12 weeks of treatment with idelalisib. It is recommended that clinicians monitor ALT and AST levels at baseline, every two weeks after initiation of idelalisib for the first three months, every month for the next three months, and every one to three months thereafter to help mitigate the risks of hepatotoxicity. If elevations in ALT or AST levels are greater than three times the upper limit of normal (ULN), monitoring should occur weekly until resolution (interruption of therapy is necessary if levels worsen to greater than five times the ULN); treatment may then be reinitiated at a reduced dose, as outlined in Table 3. However, during clinical trials of idela-

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**Table 1.** Comparative Adverse Effects of Idelalisib Combination Therapy and Monotherapy

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Idelalisib Plus Rituximab</th>
<th>Idelalisib Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or Higher</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (32)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (30)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 (28)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (24)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (22)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>12 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Night sweats</td>
<td>10 (19)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2.** Laboratory Abnormalities Reported With Idelalisib Combination Therapy and Monotherapy

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Idelalisib Plus Rituximab</th>
<th>Idelalisib Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or Higher</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>31 (57)</td>
<td>23 (43)</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>20 (37)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>16 (30)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>13 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>10 (19)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*AST = aspartate aminotransferase, ALT = alanine aminotransferase.
idelalisib, over one quarter of patients had a recurrence of transaminitis warranting discontinuation of therapy.

**Gastrointestinal toxicity.** Diarrhea was the most frequently observed adverse effect among clinical trial participants, occurring in over 40% of patients, with severe (grade 3 or 4) diarrhea occurring in 13% of patients. The median time to the onset of diarrhea was 1.9 months (range, 0.0–29.8 months). Antimotility drugs such as loperamide are not useful in the management of idelalisib-induced diarrhea, which is best managed with dose interruptions; the median time to resolution of diarrhea can be up to 1 month (Table 4). Enteric budesonide or systemic corticosteroids may be considered for treatment of severe or unresolved diarrhea, as colitis and intestinal perforations have been reported. Patients with worsening abdominal pain, fever, chills, nausea, or vomiting should be instructed to discontinue therapy and be evaluated.

**Respiratory toxicity.** Cough, upper respiratory tract infections, and pneumonia have been observed in patients treated with idelalisib. Severe and fatal pneumonitis have also been reported with idelalisib use; the development of severe pneumonitis requires treatment with corticosteroids. Patients with worsening cough, shortness of breath, hypoxia, or interstitial infiltrates should be evaluated for pneumonitis. Idelalisib should be permanently discontinued in patients who develop pneumonitis if an alternative etiology cannot be established.

**Hematologic toxicities.** Neutropenia was the most common hematologic toxicity associated with idelalisib use during clinical development of the drug. When idelalisib was used in combination with rituximab during clinical trials, there was an increased frequency of grade 3 or 4 neutropenia (43%), as compared with a frequency of 27% with idelalisib monotherapy. Anemia and thrombocytopenia have also been observed with idelalisib use, and dose adjustments are required in patients with decreases in platelet counts to less than 25,000 cells/mm³. Of note, acute lymphocytosis will occur shortly after initiation of idelalisib in patients with CLL due to the mobilization and release of leukemic cells from lymph nodes; this will lead to a transient rise in the absolute lymphocyte count (ALC) that may persist for up to 12 months. While an increase of greater than 50% in the ALC may correlate with disease progression (assessed per IWCLL criteria), this phenomenon is consistent with treatment-induced lymphocytosis seen with the use of other agents affecting the BCR signaling pathway. Therefore, the IWCLL response criteria have been modified to account for nodal response with persistent lymphocytosis despite reductions in lymph nodes. Treatment should be continued in patients with hematologic toxicities if other disease markers are improving.

### Table 3. Recommended Monitoring and Idelalisib Dosage Modifications for Patients With Organ Impairment

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>CL₃ of ≥15 mL/min</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>CL₃ of &lt;15 mL/min</td>
<td>Use with caution</td>
</tr>
<tr>
<td><strong>Hepatic Impairment Before Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe impairment</td>
<td>No adjustment necessary; monitor closely for toxicity</td>
</tr>
<tr>
<td><strong>Hepatic Impairment During Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>ALT or AST concentration of 3–5 times ULN</td>
<td>Continue idelalisib and monitor ALT or AST concentration at least weekly until 1 times ULN or less</td>
</tr>
<tr>
<td>ALT or AST concentration of &gt;5–20 times ULN</td>
<td>Withhold idelalisib and monitor ALT or AST concentration at least weekly until 1 times ULN or less; then may resume idelalisib at 100 mg twice daily</td>
</tr>
<tr>
<td>ALT or AST concentration of &gt;20 times ULN</td>
<td>Discontinue idelalisib permanently</td>
</tr>
<tr>
<td>Bilirubin concentration of &gt;1.5–3 times ULN</td>
<td>Continue idelalisib and monitor bilirubin concentration at least weekly until 1 times ULN or less</td>
</tr>
<tr>
<td>Bilirubin concentration of &gt;3–10 times ULN</td>
<td>Withhold idelalisib and monitor bilirubin concentration at least weekly until 1 times ULN or less; then may resume idelalisib at 100 mg twice daily</td>
</tr>
<tr>
<td>Bilirubin concentration of &gt;10 times ULN</td>
<td>Discontinue idelalisib permanently</td>
</tr>
<tr>
<td>Recurrent hepatotoxicity</td>
<td>Discontinue idelalisib permanently</td>
</tr>
</tbody>
</table>

*CL₃ = creatinine clearance, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

*Moderate-to-severe hepatic impairment defined as Child–Pugh class B or C.*
Dosing and dosage adjustments
The oral dosage of idelalisib recommended in the prescribing information is 150 mg twice daily. Doses should be administered within six hours of the usual dosing time, without regard to meals, and tablets should be taken whole. Idelalisib is currently available as 100- and 150-mg tablets. Idelalisib is labeled as a pregnancy category D agent due to findings indicating teratogenicity in animal studies, and use of the medication is not recommended during pregnancy. All females of reproductive potential should use effective contraception during treatment and for up to one month after the last dose of idelalisib.

Dosage adjustments are unnecessary for patients with a CLcr of ≥15 mL/min or baseline hepatic impairment. Recommendations on dosage modifications for organ impairment and treatment-related toxicities are provided in Tables 3 and 4, respectively. Idelalisib is a major substrate of CYP3A4 and undergoes minor metabolism through P-glycoprotein and UGT1A4. Idelalisib is also a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2C19, CYP2C8, and UGT1A1. The AUC is increased or decreased by up to 80% when idelalisib is coadministered with strong CYP3A inhibitors or inducers, respectively. Avoidance of interacting medications when possible is recommended.

Cost considerations
Costs may be a limiting factor for patients requiring treatment with idelalisib. The average wholesale price (AWP) of idelalisib 100- and 150-mg tablets is approximately $9,500 per bottle of 60 tablets; however, this does not account for the additional costs of rituximab infusions associated with the combination idelalisib-containing regimen for CLL described in FDA-approved labeling. Therefore, true comparative costs of idelalisib therapy and other approved or recommended regimens in the setting of relapsed or refractory disease (Table 5) are difficult to ascertain. To ensure patient access to the drug, the manufacturer of idelalisib offers a copayment assistance program for eligible patients that will help cover out-of-pocket costs up to 25% of the annual catalog price.

Place in therapy and future directions
CLL, SL, and FL are indolent diseases with the propensity to transform to more aggressive NHL. Initial management varies depending on disease staging, prognostic factors, and patient characteristics and can range from observation to chemoimmunotherapy. While favorable responses and outcomes can be achieved with fludarabine-based regimens, over one third of patients are refractory to treatment, with a median OS of 10 months. Subsequent therapeutic options are selected based on the duration of response and the presence of high-risk cytogenetics. Overall, rates of response to these therapies have ranged from 30% to 60%, with durable responses
Table 5. Cost Comparison of Recommended Agents for Relapsed or Refractory CLL, SLL, and FL

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>AWP ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib</td>
<td>150 mg orally twice daily for 30 days</td>
<td>9,495.36</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>240 mg orally daily for 30 days</td>
<td>11,002.60</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>70 mg/m² i.v. on days 1 and 2 of 28-day cycle</td>
<td>7,692.36</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg orally daily for 21 days of 28-day cycle</td>
<td>12,180.59</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Single dose of 375 mg/m² i.v.</td>
<td>6,024.47</td>
</tr>
</tbody>
</table>

*CLL = chronic lymphocytic leukemia, SLL = small lymphocytic lymphoma, FL = follicular lymphoma, AWP = average wholesale price.

References

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