Idelalisib (Zydelig®)

National Drug Monograph
March 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Idelalisib is a novel, selective, small-molecule inhibitor of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ). This isoform is highly expressed in lymphoid cells and is involved in the malignant phenotype of CLL. By activating AKT and mTOR, it ultimately affects cell metabolism, migration, growth and survival.
Indication(s) Under Review in this document (may include off label)	Idelalisib is a kinase inhibitor that received FDA-approval for the treatment of patients with: • Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities. • Relapsed follicular B-cell non-hodgkins lymphoma (FL) in patients who have received at least 2 prior therapies • Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least 2 prior systemic therapies. Accelerated approval was granted for FL and SLL based upon the endpoint of overall response rate. Improvement in survival or disease-related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.
Dosage Form(s) Under Review	Tablets: 100 mg, 150 mg
REMS	☒ REMS ☐ No REMS ☐ Postmarketing Requirements REMS includes a Communication Plan and REMS Assessments to FDA regarding Boxed Warnings
Pregnancy Rating	Category D

Executive Summary

Efficacy	• CLL: Idelalisib plus rituximab provided a progression-free survival (PFS) and overall survival (OS) benefit in heavily pretreated patients, compared to those receiving rituximab alone. • NHL: Monotherapy with idelalisib provided an improvement in overall response rate (ORR). • NHL: Benefit in improvement of disease-related symptoms or overall survival has not yet been shown. Accelerated approval was granted for NHL; FDA awaits results from confirmatory trials.
Safety	• Boxed warnings include the risk of fatal and serious toxicities noted, such as hepatotoxicity, severe diarrhea, colitis, pneumonitis and intestinal perforation. • Patients should be monitored for the following: LFT's, complete blood counts, respiratory symptoms, abdominal pain and/or the incidence/severity of diarrhea. • Potential for drug interactions should be evaluated prior to initiating therapy.
Other Considerations	**Outcome in clinically significant area**: CLL: PFS at 24 wks: NR vs. 5.5 mos FL, SLL: ORR 57% (6% CR)

	Effect Size	CLL: PFS HR 0.15(0.08-0.28) p<0.001 FL, SLL: 95% CI, 48-66
	Potential Harms	CLL: ≥ Gr 3 neutropenia (34%), thrombocytopenia (10%) FL, SLL: ≥ Gr 3 neutropenia (27%), diarrhea (13%), ↑ ALT (13%)
	Net Clinical Benefit	CLL: Moderate FL, SLL: Negative

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Potential Impact

Projected place in therapy:

- Idelalisib + rituximab provide a treatment option to those patients who might not be appropriate candidates for other therapies in the relapsed/refractory CLL setting.
- The combination is one of the few select options that has shown efficacy in high risk patients, such as those with del (17p).
- NCCN guidelines list the idelalisib ± rituximab combination as a category 2A recommendation for relapsed/refractory CLL.
- Accelerated FDA-approval in patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) or relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies
- NCCN guidelines list idelalisib as a category 2A recommendation for patients with Follicular NHL (grade 1, 2) as a second-line or subsequent option.
- Boxed warnings may limit the use of idelalisib to select populations

Patient convenience:

- Idelalisib is an oral formulation, which can be a patient convenience, but the drug is dosed twice daily, which is often not convenient.
- Rituximab is administered as an IV infusion, which does not add to the convenience-factor of this treatment regimen for CLL.

Background

Purpose for review

Recent FDA approval.

Issues to be determined:
Does idelalisib offer advantages to currently available alternatives?
What safety issues need to be considered for idelalisib therapy?

Other therapeutic options

Key: BMS bone marrow suppression; N/V nausea/vomiting, PNA pneumonia, PFS progression-free survival; LAD lymphadenopathy; ORR overall response rate

Formulary Alternatives for relapsed/refractory (r/r) CLL	Other Considerations (formulation, initial PFS, r/r PFS, toxicities)
Fludarabine cyclophosphamide, rituximab (FCR)	Injectable; initial PFS 52 months
Fludarabine, rituximab (FR)	Initial PFS 42 mos Toxicities: BMS, infection, N/V, hair loss
Ibrutinib	Oral; r/r PFS 75% @ 26 months; effective in del (17p) Toxicities: diarrhea, bleed risk, pna, fatigue
Chlorambucil, rituximab	Oral; injectable; initial PFS 16 months Toxicities: neutropenia, infections
Pentostatin, cyclophosphamide, rituximab (PCR)	Injectable; initial PFS 33 months Toxicities: BMS, infections

Non-formulary Alternative (if applicable) for relapsed/refractory CLL	Other Considerations (formulation, initial PFS, r/r PFS, toxicities)
Bendamustine, rituximab (BR)	Injectable; initial PFS 34 months; r/r PFS 24 months Toxicities: BMS, HS rxn
Chlorambucil, ofatumumab	Oral; injectable; initial PFS 23 months Toxicities: neutropenia, infection, pyrexia
Alemtuzumab	Injectable; accessible via special distribution program; ORR 38%; less effective with bulky LAD; effective in del (17p)
Chlorambucil, obinutuzumab	Oral; injectable; initial PFS 27 months Toxicities: neutropenia, infusion-related reactions, thrombocytopenia, infection
Formulary Alternatives for relapsed/refractory follicular B-cell NHL (FL)	**Other Considerations**
Rituximab, cyclophosphamide, vincristine, prednisone (R-CVP)	Injectable; ORR 80% Toxicities: N/V, peripheral neuropathy
Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP)	Injectable; ORR 85% Toxicities: BMS, alopecia, N/V
Non-Formulary Alternatives for relapsed/refractory follicular B-cell NHL (FL)	**Other Considerations**
Bendamustine, rituximab (BR)	Injectable; ORR 90% Toxicities: BMS

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2015) using the search terms idelalisib and Zydelig. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Idelalisib in Chronic Lymphocytic Leukemia (CLL)

Trial	Inclusion criteria	Interventions	Results
Furman 2014 MC, R, DB, PC, P3 N=220 patients 90 centers in US and Europe	CLL that progressed within 24 months of last treatment and unable to receive cytotoxic agents due to one of the following: Severe neutropenia or thrombo-cytopenia from cumulative marrow suppression of prior therapy; est'm CrCl < 60 ml/min; CIRS > 6 (unrelated to CLL) Prior tx included a CD20 ab-based regimen or at least 2 prior cytotoxic regimens.	Idelalisib + rituximab (R) vs. placebo + R Rituximab 375 mg/m2 x 1, then 500 mg/m2 IV every 2 wks x 4, then every 4 wks x 3 doses Idelalisib 150 mg PO BID Stratification by presence of: 17p deletion, TP53 mutations, Lack of mutated IGHV Disease assessment every 8 wks x 6 mos, then every 12 wks after	Idelalisib + rituximab (R) vs. placebo + R Results at 24 weeks Primary endpoint: PFS PFS: 93 vs. 46% Median PFS: NR vs. 5.5 mos; HR 0.15 [0.08-0.28]; p< 0.001 ORR: 81 vs. 13%; (all PR) OR 29.92; p<0.001 OS at 12 mos: 92 vs. 80%; HR 0.28; p=0.02 Treatment effect favored I+R in all prespecified subgroups SAE: 40 vs. 35%

Key: MC multi-center, R randomized, DB double-blind, PC placebo-controlled; P3 phase 3, CIRS Cumulative Illness Rating Scale, IGHV immunoglobulin heavy-chain variable region, TP53 tumor-suppressor p53; SG single-group; OL open-label, P2 phase 2, FL follicular lymphoma; SLL small lymphocytic lymphoma; LPL lymphoplasmacytic lymphoma, WM Waldenstrom's macroglobulinemia; PD progressive disease; ORR overall response rate; IRC Independent Review Committee; DOR duration of response; PFS progression-free survival; OS overall survival; SAE severe adverse events

Chronic Lymphocytic Leukemia (CLL)

- The FDA approval of idelalisib in CLL was based on a phase 3 trial in relapsed disease by Furman, et al. that was stopped early at the interim analysis when benefit from the treatment arm was noted. Median exposure to idelalisib was 5 months.
- The study population (Furman 2014) included 78% of patients who were aged 65 years or older, 40% with moderate renal dysfunction (defined as CrCl < 60 ml/min), 35% had poor bone marrow function (grade 3 or higher anemia, thrombocytopenia or neutropenia) and 85% had a CIRS score > 6. The median CIRS score was 8 in each study group.
- Of note, CIRS scoring has not been validated in patients with hematologic malignancies, although its use has been studied in CLL patients. The assumption is that those with a higher CIRS score are less fit for standard chemo immunotherapy regimens. Therefore the fitness of the study population is unclear.
- Roughly 65% of the study population had advanced stage CLL (Rai stage 3 or 4) and a median time since CLL diagnosis of 9 years. More than 80% had unmutated IGHV and more than 40% had 17p deletion or TP53 mutations. Patients received a median of 3 previous therapies that included rituximab, cyclophosphamide, fludarabine, chlorambucil and bendamustine.
- The study was stopped at the first interim analysis, not at disease progression or unacceptable toxicity, as indicated in the labeling.
- Patients have the potential to remain on idelalisib therapy for extended periods. There were no complete responses observed; all responses were partial responses.
- Abstract data (Ghia, 2014) suggests improvement in Health-Related Quality of Life via Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) scale with idelalisib/ rituximab vs. placebo/ rituximab.
- NCCN guidelines give idelalisib ± rituximab a category 2A recommendation for patients with relapsed/refractory CLL regardless of age, del (17p) or del (11q) status.

Idelalisib in relapsed indolent non-hodgkin's lymphoma (NHL)

Trial	Inclusion criteria	Interventions	Results
Gopal 2014 SG, OL, P2 N=125 patients 72 w/FL; 28 w/SLL 15 w/marginal-zone NHL (MZL) 10 w/LPL/WM 41 sites in US and Europe	Dx B-cell indolent NHL without evidence transformation (FL, SLL, marginal-zone NHL, lymphoplasmacytic NHL with/without Waldenstrom's macroglobulinemia); Measurable disease; Received ≥ 2 prior therapies; refractory to rituximab and alkylating agent	Idelalisib 150 mg PO twice daily until PD Disease assessment every 2 weeks x 12 wks, every 4 wks from wk 12-24, every 6 wks From wk 24-48	Primary endpoint: ORR via IRC ORR 57% (CR 6%) FL 0.54 (0.42-0.66) SLL 0.61 (0.41-0.79) MZL 0.47 (0.21-0.73) LPL/WM 0.80 (0.44-0.98) Secondary endpoint: Median time to ORR 1.9 mos; Median DOR 12.5 mos; Median PFS 11 mos Median OS 20.3 mos OS @ 1 yr ~ 80% Median duration tx ~ 6.5 mos

Key: SG single-group, OL open-label, P2 phase 2, FL follicular lymphoma; SLL small lymphocytic lymphoma; LPL lymphoplasmacytic lymphoma, WM Waldenstrom's macroglobulinemia; PD progressive disease; ORR overall response rate; IRC Independent Review Committee; DOR duration of response; PFS progression-free survival; OS overall survival

Relapsed indolent NHL

- Study population included patients with median age 64 years; 64% male, 89% white. The majority (89%) had stage III or IV indolent NHL. Of those with follicular lymphoma (FL), 79% had intermediate risk or high risk International Prognostic Index (IPI) scores.
- Patients received a median of 4 prior regimens (range, 2-12) while 58% received 4 or more prior regimens. Most common prior regimens included: bendamustine/rituximab (48%), R-CHOP (45%), rituximab monotherapy (40%) and R-CVP (29%). High-dose chemotherapy and autologous stem-cell transplant was received by 11% of patients.
- FDA-approval is in patients who have received at least two prior systemic therapies; the NCCN guidelines list idelalisib as a category 2A recommendation for patients with Follicular NHL (grade 1, 2) as a second-line or subsequent option.
- To date, quality of life data in this population is not available.

Potential Off-Label Use

The following trials can be found in www.clinicaltrials.gov

- Study to Investigate Idelalisib in Combination With Chemotherapeutic Agents, Immunomodulatory Agents and Anti-CD20 Monoclonal Antibody (mAb) in Subjects With Relapsed or Refractory Indolent B-cell Non-Hodgkin's Lymphoma, Mantle Cell Lymphoma or Chronic Lymphocytic Leukemia
- A Randomized, Double-Blind and Placebo-Controlled Study of Idelalisib in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia (CLL)
- Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas
- A Study of Idelalisib (GS1101, CAL101) + Ofatumumab in Previously Untreated CLL/SLL
- Efficacy and Safety of Idelalisib in Combination With Obinutuzumab Compared to Chlorambucil in Combination With Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia
- Idelalisib monotherapy in relapsed/refractory CLL

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	**Fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, intestinal perforation** • Fatal and/or serious hepatotoxicity occurred in 14% of idelalisib-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and dose-reduce or discontinue as recommended. • Fatal and/or serious and severe diarrhea or colitis occurred in 14% of idelalisib-treated patients. Monitor for the development of severe diarrhea or colitis; Interrupt therapy, dose-reduce or discontinue as recommended. • Fatal and serious pneumonitis can occur. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue as recommended. • Fatal and serious intestinal perforation can occur in idelalisib-treated patients across clinical trials. Discontinue therapy for intestinal perforation.
Contraindications	• History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.
Warnings/Precautions	• Hepatotoxicity. Fatal and/or serious hepatotoxicity occurred in 14% of patients treated with idelalisib. ALT or AST elevations greater than 5x ULN have occurred and generally noted within the first 12 weeks of therapy. With dose-interruption, these elevated levels were reversible. Following resumption of idelalisib at a lower dose, 26% of patients had recurrent elevations of ALT and AST. Idelalisib should be discontinued for recurrent hepatotoxicity. Avoid concurrent use with other hepatotoxic agents. Monitor ALT and AST every 2 weeks for the first 3 month, then every 4 weeks for 3 months, then every 1 to 3 months thereafter. Monitor weekly if ALT or AST rises above 3x ULN, until resolved. Hold therapy if ALT or AST is greater than 5x ULN and monitor AST, ALT and total bilirubin weekly until resolved. • Severe diarrhea or colitis. Grade 3 or higher diarrhea or colitis has been reported in 14% of patients treated with idelalisib. Diarrhea can occur at any time and responds poorly to anti-motility agents. Avoid concurrent use with other drugs that can cause diarrhea. Diarrhea resolves between 1 week and 1 month, following interruption in therapy. Some cases may require use of corticosteroids. • Pneumonitis. Fatal and serious pneumonitis has been reported. Patients with pulmonary symptoms (cough, dyspnea, hypoxia) and interstitial infiltrates on radiologic exam or decline more than 5% in oxygen saturation should be evaluated for pneumonitis. If suspected, interrupt therapy until etiology

	determined. If caused by idelalisib, stop therapy and provide corticosteroids. • Intestinal Perforation. Fatal and serious intestinal perforation has occurred with idelalisib, some in combination with moderate to severe diarrhea. Instruct patients to promptly report any new or worsening abdominal pain, chills, fever, nausea or vomiting. Discontinue idelalisib permanently in patients with intestinal perforation. • Severe Cutaneous Reactions. One case of toxic epidermal necrolysis (TEN) occurred in a study with idelalisib, rituximab and bendamustine. Other severe or life-threatening cutaneous reactions have been reported. Monitor patients for development of severe cutaneous reactions and discontinue idelalisib when noted. • Anaphylaxis. Serious allergic reactions, including anaphylaxis, have been reported. Discontinue idelalisib permanently and institute supportive measures. • Neutropenia. Grade 3, 4 neutropenia has been reported in 31% of patients in clinical trials. Monitor blood counts at least every 2 weeks for the first 3 months of therapy, and at least weekly while neutrophil counts are less than 1.0 Gi/L (or 1.0 x 10^9/L = 1 x 10^3/microL = 1000/mm^3) • Embryo-fetal toxicity. Based upon findings in animals, fetal harm may result when idelalisib is administered to a pregnant woman. If used during pregnancy, or if pregnancy occurs during treatment, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential to avoid becoming pregnant while taking idelalisib. Use effective contraceptive methods during treatment and for at least one month after the last dose of idelalisib.

Safety Considerations

- Boxed warnings concerning the risk of hepatotoxicity, severe diarrhea/colitis, pneumonitis and intestinal perforation.
- Significant risk of neutropenia requires diligent monitoring of blood counts and monitoring for development of infection.
- Patient education, monitoring and reporting potential toxicities will be very important to use this therapy safely.
- Potential for drug interactions should be assessed when considering use of idelalisib.
- Idelalisib has been shown to cause lymphocytosis when given as a single agent. The combination of idelalisib and rituximab resulted in a shortened duration of lymphocytosis.
- The median duration of idelalisib exposure reported is 5 months, therefore long-term safety cannot be assessed.
- More patients in the idelalisib arm had dose interruptions due to adverse events or laboratory abnormalities (35.5 vs. 17.5%). A total of 16 (14.5%) vs. 0 patients, in the idelalisib vs. placebo arms, had a dose-reduction due to adverse event or lab abnormality.

Adverse Reactions

Common adverse reactions	Incidence $\geq$ 20%: diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, rash Incidence laboratory abnormalities $\geq$ 30%: neutropenia, hypertriglyceridemia, hyperglycemia, ALT elevations, AST elevations
Death/Serious adverse reactions	**CLL**: Serious adverse reactions reported in 49% of patients treated with idelalisib and rituximab. Most frequent reactions reported were pneumonia (17%), pyrexia (9%), sepsis (8%), febrile neutropenia (5%), diarrhea (5%). **NHL**: Serious adverse reactions were reported in 50% of patients treated with idelalisib. Most frequent reactions were pneumonia (15%), diarrhea (11%) and pyrexia (9%).
Discontinuations due to adverse reactions	**CLL**: Discontinuations occurred in 10% of patients; the most common reactions leading to discontinuation of therapy were hepatotoxicity and diarrhea/colitis. More patients in the idelalisib arm had dose interruptions due to adverse events or laboratory abnormalities (35.5 vs. 17.5%). A total of 16 (14.5%) vs. 0 patients, in the idelalisib vs. placebo arms patients had a dose-reduction due to adverse event or lab abnormality.

	NHL: Interruptions or discontinuations occurred in 50% of patients; most common reasons for interruption/discontinuation were diarrhea (11%), pneumonia (11%) and elevated transaminases (10%).

Drug Interactions

Drug-Drug Interactions

- Effects of other drugs on idelalisib: CYP3A4 inducers can reduce the AUC of idelalisib by 75% during coadministration. Avoid concomitant strong CYP3A4 inducers such as rifampin, phenytoin, St. John's wort or carbamazepine.
- Effects of other drugs on idelalisib: CYP3A4 inhibitors can increase the AUC of idelalisib 1.8 fold during coadministration. If concomitant strong CYP3A4 inhibitors are needed, monitor for signs of idelalisib toxicity and follow recommendations for dose modifications for adverse reactions.
- Effects of idelalisib on other drugs: idelalisib is a strong CYP3A4 inhibitor, which can increase the AUC of sensitive CYP3A substrates during coadministration. Avoid coadministration of idelalisib with CYP3A substrates.

Drug-food Interactions – none known

Drug-Lab Interactions – none known

Risk Evaluation

As of January, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	• Idelalisib: ibrutinib, IDArubicin, imatinib • Zydelig: Xtandi, Zytiga • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- NCCN guidelines list idelalisib ± rituximab as a category 2A recommendation for patients with relapsed/refractory CLL regardless of age, del (17p) or del (11q) status.
- NCCN guidelines list idelalisib as a category 2A recommendation as second-line or subsequent therapy for patients with follicular lymphoma.
- NICE anticipates a provisional document in October 2015.

Outcome in clinically significant area	CLL: PFS at 24 wks: NR vs. 5.5 mos FL, SLL: ORR 57% (6% CR)
Effect Size	CLL: PFS HR 0.15(0.08-0.28) p<0.001 FL, SLL: 95% CI, 48-66
Potential Harms	CLL: ≥ Gr 3 neutropenia (34%), thrombocytopenia (10%) FL, SLL: ≥ Gr 3 neutropenia (27%), diarrhea (13%), ↑ ALT (13%)
Net Clinical Benefit	CLL: Moderate FL, SLL: Negative

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

- Maximum starting dose is idelalisib 150 mg orally twice daily, taken with or without food.
- Tablets should be swallowed whole.
- Therapy should be continued until disease progression or unacceptable toxicity.
- Refer to the package insert for full dosing information, including dose modification for toxicities.

Special Populations (Adults)

	Comments
Elderly	• A total of 63% of patients in the clinical trials were age 65 and older. No major differences in effectiveness were noted. Differences were noted in the toxicity profiles as older patients had a higher incidence of discontinuation due to adverse reaction, serious adverse reaction and death compared to the younger population in both NHL and CLL trials.
Pregnancy	• Based upon animal data, idelalisib may cause fetal harm when administered to a pregnant woman. Idelalisib was teratogenic in animals. If drug is used during pregnancy, or if the patient becomes pregnant while taking drug, she should be apprised of the potential hazard to the fetus. Effective contraception should be used during therapy and for one month post-therapy with idelalisib.
Lactation	• No data identified. Drug is likely to be excreted in milk, therefore a decision should be made whether to discontinue nursing or discontinue the drug.
Renal Impairment	• No dose adjustment necessary for patients with creatinine clearance $\geq$ 15 ml/min.
Hepatic Impairment	• Patients with ALT, AST or bilirubin values greater than ULN experienced up to 1.7-fold increase in idelalisib AUC. Idelalisib has not been studied in populations with baseline ALT or AST values greater than 2.5x ULN or bilirubin values greater than 1.5x ULN. Those with LFT elevations should be monitored for drug toxicity.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- CLL is a condition characterized by an accumulation of mature, abnormally functioning lymphocytes. Non-functional lymphocytes that manifest primarily in the bone marrow and blood, are referred to as CLL. Disease found primarily in the lymph nodes is referred to as SLL.
- The median age at diagnosis of CLL is 67-72 years. The condition affects a higher population of males vs. females (1.7:1).
- There is no standard therapy for relapsed/refractory disease. Treatment will depend on the initial treatment regimen used, as well as the patient's response to initial therapy in terms of efficacy (quality and duration of response) and toxicity.
- Chemoimmunotherapy serves as a typical initial treatment plan, which will include chemotherapy and an anti-CD20 monoclonal antibody.
- Patients achieving an initial response that is comparable to the median PFS for that regimen are usually retreated with the same therapy at time of relapse; Patient with an initial response that is significantly less that the median PFS should be treated at relapse with a different combination of agents.
- Idelalisib and rituximab provide a treatment option to those patients who might not be appropriate candidates for other therapies in the relapsed/refractory CLL setting.
- The combination is one of the few select options that has shown efficacy in high risk patients, such as those with del (17p).
- NCCN guidelines list the idelalisib ± rituximab combination as a category 2A recommendation for relapsed/refractory CLL.

- Considerations include the risk for serious toxicities including hepatotoxicity, severe diarrhea, colitis, pneumonitis, intestinal perforation and neutropenia. The diarrhea is not responsive to anti-motility agents. Management involves dose-reduction and holding therapy. Idelalisib therapy can affect laboratory values in a high percentage of patients, which may increase the frequency and duration of monitoring.
- Although idelalisib is oral, the combination studied in CLL included IV rituximab therapy. Patients may have a difficult time adhering to the complete regimen.
- The median duration of idelalisib exposure reported in CLL is 5 months therefore long-term safety cannot be assessed. Patients have the potential to remain on idelalisib therapy for extended periods. There were no complete responses observed; all responses were partial responses.
- Of note, CIRS scoring has not been validated in patients with hematologic malignancies. The assumption is that those with a higher CIRS score are less fit for standard chemo immunotherapy regimens. Therefore the fitness of the study population is unclear.
- The study was stopped at the first interim analysis, not at disease progression or unacceptable toxicity, as indicated in the labeling.
- Accelerated FDA-approval was received for FL or SLL patients who have received at least two prior systemic therapies; the NCCN guidelines list idelalisib as a category 2A recommendation for patients with Follicular NHL (grade 1, 2) as a second-line or subsequent option.

References

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Ghia P, O'Brien S, Hillmen P, et al. Health-related Quality of Life (HRQL) Impact of Idelalisib in Patients with Relapsed Chronic Lymphocytic Leukemia: Phase 3 Results. American Society of Clinical Oncology 2014; Chicago, Illinois. Poster No.7099

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.