

A Review of PI3K Inhibitors in B-Cell Malignancies

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Abstract

The phosphoinositide 3-kinase (PI3K) pathway plays a primary role in cellular proliferation and metabolism. Inhibition of the PI3K pathway is an emerging area of drug development and cancer research. Idelalisib, copanlisib, and duvelisib are currently the only U.S. Food & Drug Administration–approved PI3K inhibitors available for use in hematologic malignancies. These PI3K inhibitors differ in their recommended indications, selectivity of PI3K isoforms, dosing, and potential toxicities. Several ongoing studies are aiming to expand the use of such drugs and identify unique combination regimens. This article discusses the current data supporting their place in therapy for B-cell malignancies, management of adverse events, and the clinical implications for advanced practitioners for the commercially available PI3K inhibitors.

Activation of the phosphoinositide 3-kinase (PI3K) pathway has become an area of interest in cancer pathophysiology and drug development. The PI3K pathway plays a primary role in cell signaling and cellular responses such as proliferation and metabolism, and overexpression of PI3K isoforms may be associated with the development of resistance to traditional chemotherapy (Krause, Hassenruck, & Hallek, 2018; Goncalves, Hopkins, & Cantley, 2018). The PI3K pathway is located downstream of B-cell receptors (BCR), and its activation likely plays a role in B-cell survival and proliferation (Mensah, Blaize, & Bry-

an, 2018). Currently, there are three PI3K inhibitors approved by the U.S. Food & Drug Administration (FDA) for use in hematologic malignancies: idelalisib (Zydelig), copanlisib (Aliqopa), and duvelisib (Copiktra; Bayer HealthCare Pharmaceuticals Inc., 2017; Gilead Sciences Inc., 2018; Verastem, Inc., 2018). Here we review their mechanisms of action, evidence supporting approval, places in therapy, and recommendations for adverse event (AE) management.

IDELALISIB

Idelalisib is an oral, highly selective PI3K δ inhibitor (Gilead Sciences Inc., 2018). Inhibition of the PI3K signaling pathway, which is active in

many B-cell leukemias, results in apoptosis of tumor cells. Idelalisib also inhibits several signaling pathways, including BCR, CXCR4, and CXCR5. It is indicated for the treatment of relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab (Rituxan) in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities. It is also approved for patients with relapsed small lymphocytic lymphoma (SLL) and for relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies. Use of idelalisib is limited, as it is not indicated or recommended for first-line treatment of CLL/SLL nor for the treatment of FL in combination with bendamustine and/or rituximab.

Chronic Lymphocytic Leukemia

Idelalisib was initially approved in Study 116 (NCT01539512), a multicenter, randomized, double-blind, placebo-controlled, phase III study comparing rituximab plus either idelalisib or placebo in patients with relapsed CLL who required treatment and were unable to tolerate standard chemoimmunotherapy due to coexisting medical conditions (Cumulative Illness Rating Scale [CIRS] > 6), reduced renal function (creatinine clearance < 60 mL/min), or grade \geq 3 neutropenia or thrombocytopenia from previous therapies (Furman et al., 2014). Prior therapy must have included either an anti-CD20 therapy or at least two prior cytotoxic regimens.

A total of 220 patients were randomized 1:1 to idelalisib at 150 mg orally twice daily or placebo, both combined with rituximab 375 mg/m² IV followed by 500 mg/m² IV every 2 weeks for 4 doses and then every 4 weeks for 3 doses (total of 8 infusions). Patients were stratified by presence of del(17p) or other *TP53* mutations, and lack of immunoglobulin heavy chain variable (*IgHV*) mutation. In the case of disease progression, patients in the placebo group were permitted to cross over and receive idelalisib, while those treated with idelalisib at 150 mg twice daily were allowed to dose escalate to 300 mg orally twice daily (Furman et al., 2014).

A significant improvement in the primary endpoint of median progression-free survival (PFS) was seen in the idelalisib combination arm (not reached vs. 5.5 months in the placebo arm, haz-

ard ratio [HR], 0.15; $p < .001$; Furman et al., 2014). Overall response rate (ORR) and overall survival (OS) at 12 months were also significantly improved (81% vs. 13%, odds ratio, 29.29; $p < .001$ and 92% vs. 80%, HR, 0.28; $p = .02$, respectively).

Rates of serious AEs were comparable between groups (40% vs. 35%). The most frequently reported serious AEs in both groups were pneumonia, pyrexia, and febrile neutropenia. The most common AEs of any grade in the idelalisib group were pyrexia (29%), fatigue (24%), nausea (24%), and chills (22%). Common laboratory abnormalities of any grade included neutropenia (55%), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation (35%), anemia (25%), and thrombocytopenia (17%). Grade \geq 3 AEs reported in the idelalisib arm included diarrhea (4%), pyrexia (3%), fatigue (3%), chills (2%), dyspnea (2%), and rash (2%; Furman et al., 2014).

Small Lymphocytic Lymphoma and Follicular Lymphoma

Idelalisib's approval for use in relapsed SLL and FL is based on a single-group, open-label, phase II study conducted in patients with indolent non-Hodgkin lymphoma (iNHL) who were refractory to or had a relapse within 6 months following rituximab and alkylating agent-containing chemotherapy (Gilead Sciences Inc., 2018; Gopal et al., 2014). Idelalisib was administered at a dose of 150 mg orally twice daily until disease progression, unacceptable toxicities, or patient death. A total of 125 patients were included in the trial: FL ($n = 72$), SLL ($n = 28$), marginal-zone lymphoma (MZL; $n = 15$), and lymphoplasmacytic lymphoma (LL) with or without Waldenström's macroglobulinemia (WM; $n = 10$; Gilead Sciences Inc., 2018; Gopal et al., 2014).

The primary endpoint of ORR was 57% in all patients, with 6% of patients obtaining a complete response (CR; Gopal et al., 2014). The ORR in the 72 patients with FL was 54% (95% confidence interval [CI] = 42%–66%), with 8% of patients achieving a CR and 46% achieving a partial response (PR). For the 26 patients with SLL, an ORR of 58% was reported (95% CI = 37%–77%), with all responses being PRs. The overall median time to response was 1.9 months, median duration of response was 12.5 months, and median PFS was 11 months.

The most common AEs of all grades included diarrhea (43%), fatigue (30%), nausea (30%), cough (29%), and pyrexia (28%). Frequently reported laboratory abnormalities of any grade included decreased neutrophils (56%), increased ALT (47%), increased AST (35%), decreased hemoglobin (28%), decreased platelets (26%), increased alkaline phosphatase (22%), and increased bilirubin (10%). Any \geq grade 3 reported events included diarrhea (13%), pneumonia (7%), dyspnea (3%), nausea (2%), fatigue (2%), pyrexia (2%), abdominal pain (2%), vomiting (2%), rash (2%), asthenia (2%), decreased appetite (1%), and headache (1%; Gilead Sciences Inc., 2018; Gopal et al., 2014).

Idelalisib is generally well tolerated, but is associated with notable severe AEs. Nearly one third of patients in clinical trials experienced grade 3 or 4 neutropenia (Gilead Sciences Inc., 2018). Idelalisib has boxed warnings for serious and/or fatal diarrhea or colitis, intestinal perforation, hepatotoxicity, infections, and pneumonitis. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have also been reported. It is contraindicated in patients with a history of serious allergic reactions, including anaphylaxis and TEN. Warnings and precautions include monitoring patients for severe cutaneous reactions, anaphylaxis, neutropenia, and embryo-fetal toxicity (Gilead Sciences Inc., 2018).

Ongoing Trials

Idelalisib is a National Comprehensive Cancer Network (NCCN)-recommended treatment option given with or without rituximab for patients with relapsed/refractory CLL/SLL with or without del(17p)/*TP53* mutation (NCCN, 2019b). The use of bendamustine with rituximab with or without idelalisib is an alternative option for patients with relapsed/refractory CLL/SLL without del(17p)/*TP53* mutation based on interim analysis from a phase III trial showing superior efficacy of the three-drug combination in terms of median PFS (NCCN, 2019b; Zelenetz et al., 2017). Idelalisib is also included as a third-line or greater treatment option for patients with grade 1 to 2 FL (NCCN, 2019a).

Idelalisib has been studied in combination with standard therapies, such as bendamustine with rituximab and obinutuzumab (Gazyva),

and demonstrated an increased rate of death and serious AEs in patients treated for front-line CLL (NCT01980888) and early-line iNHL (NCT01980875; ClinicalTrials.gov, 2019).

Several ongoing trials to expand idelalisib's use are actively recruiting patients for alternative indications and combination regimens. Idelalisib is being studied in combination with rituximab and venetoclax in a phase I clinical trial in patients with relapsed/refractory CLL (RIVE-CLL, NCT03639324) and in combination with an experimental CD19-antibody in a phase II study in patients with relapsed/refractory disease after treatment with a Bruton's tyrosine kinase inhibitor (NCT02639910). Idelalisib is also being evaluated in combination with immunotherapy in patients with relapsed/refractory CLL or other low-grade B-cell NHLs in a phase II trial evaluating the addition of pembrolizumab (NCT02332980). Investigation is ongoing in the maintenance setting postallogeic hematopoietic stem cell transplant in a phase I trial evaluating safety in patients who had a transplant for a B-cell malignancy (ClinicalTrials.gov, 2019).

COPANLISIB

Unlike idelalisib, copanlisib is an intravenous, highly selective pan-class I PI3K inhibitor, targeting all four class I isoforms, α , β , γ and δ , with the highest affinity for α and δ (Patnaik et al., 2016). The expression of α and β isoforms on all cell types coupled with γ and δ isoforms in hematopoietic tissue cells contributes to the efficacy and toxicity observed with copanlisib (Mensah et al., 2018). In addition to PI3K signaling, copanlisib exerts its effects through apoptosis and BCR-independent inhibition of NF- κ B signaling (Paul et al., 2017). Copanlisib is administered as a 60-mg, 1-hour IV infusion on days 1, 8, and 15 of a 28-day cycle (Bayer HealthCare Pharmaceuticals Inc., 2017). It received FDA approval for the treatment of FL based on the phase II trial, CHRONOS-1, evaluating its efficacy in patients with relapsed/refractory iNHL.

Follicular Lymphoma

The CHRONOS-1 trial (NCT01660451) included 142 patients, of which 104 had a diagnosis of relapsed FL following at least two prior treatments, including rituximab and an alkylating agent (Dreyling et al., 2017). Most commonly, patients had received prior

chemotherapy in combination with an anti-CD20 monoclonal antibody. Patients were treated with copanlisib until disease progression or unacceptable toxicity, with a primary endpoint of ORR. The ORR for copanlisib was 59% (95% CI = 49%–68%), with 14% of patients achieving CRs and 44% of patients with PRs. In addition, the average duration of response was around 12.2 months, with a median time to response of 1.7 months (Dreyling et al., 2017).

Copanlisib is thought to be better tolerated than idelalisib due to differences in the pharmacokinetic properties of weekly IV infusions compared to daily oral administration, but it is not without its own notable AE profile (Patnaik et al., 2016). The CHRONOS-1 trial reported treatment-related AEs in 99% of patients receiving copanlisib, with 53% experiencing grade 3 AEs and 27% experiencing grade 4 AEs. The most common AEs of all grades were short-term hyperglycemia (50%), hypertension (30%), diarrhea (34%), neutropenia (30%), fatigue (30%), and fever (25%). Grade ≥ 3 AEs included hyperglycemia (41%), hypertension (24%), neutropenia (24%), lung infection (16%), and thrombocytopenia (7%; Dreyling et al., 2017).

Ongoing Trials

Current NCCN Guidelines recommend copanlisib as a third-line and subsequent therapy in FL (NCCN, 2019a). It is also being studied in patients with rituximab-refractory iNHL (CHRONOS-2, NCT02369016), in combination with rituximab in iNHL (CHRONOS-3, NCT02367040), and in combination with chemoimmunotherapy (CHRONOS-4, NCT02626455; ClinicalTrials.gov, 2019). Copanlisib has also shown promise as a treatment option in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients, specifically those of ABC subtype (ORR of 37.5% for ABC subtype vs. 13.6% for GCB subtype; Lenz et al., 2017). Ongoing trials are investigating its use alone or in combination for alternative indications including aggressive NHL, peripheral T-cell lymphoma, primary central nervous system lymphoma, and solid tumors such as head and neck, colon, and non-small cell lung cancer (ClinicalTrials.gov, 2019).

DUVELISIB

Duvelisib is an oral δ and γ PI3K inhibitor. Duvelisib is structurally similar to the δ isoform inhibitor,

idelalisib, but its dual isoform blockade inhibits cell signaling more efficiently (Vangapandu, Jain, & Gandhi, 2017). Duvelisib is dosed continuously at 25 mg orally twice daily without regard to food and is approved for use in relapsed/refractory CLL and SLL after two failed therapies. It also has accelerated approval for use in FL after two prior therapies due to the ORR seen in clinical trials (Verastem, Inc., 2018).

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Duvelisib was studied in the treatment of relapsed/refractory CLL/SLL in the phase III DUO trial, which randomized patients to duvelisib or ofatumumab (Arzerra), an anti-CD20 monoclonal antibody (NCT02004522; Flinn et al., 2018). A total of 319 patients were randomized 1:1 to receive duvelisib at 25 mg twice daily or ofatumumab per the relapsed CLL dosing in the package insert (Novartis Corporation, 2016). Patients were allowed to take duvelisib for 18 cycles, or until disease progression or unacceptable toxicity. The study met its primary endpoint of significantly improving median PFS of 13.3 months with duvelisib vs. 9.9 months with ofatumumab (HR, 0.52; 95% CI = 0.39–0.70; $p < .0001$), including patients with high-risk chromosome 17p13.1 deletions and/or *TP53* mutations (HR, 0.40; 95% CI = 0.24–0.67; $p = .0002$; Flinn et al., 2018).

Follicular Lymphoma

Duvelisib was studied for the treatment of patients with iNHL refractory to rituximab and either chemotherapy or radioimmunotherapy in the phase II DYNAMO trial (NCT01882803; Flinn et al., 2016). The primary endpoint of ORR was 43% in the FL subgroup, with a median PFS of 8.3 months. A 17% continued response rate was seen at 12 months. This study granted duvelisib accelerated approval for the treatment of FL.

Duvelisib is generally well-tolerated, but not without the risk of potentially severe side effects. In the DUO trial, the most common AEs were diarrhea (51%), pyrexia (29%), nausea (23%), and cough (21%; Flinn et al., 2018). In the DYNAMO trial, the most common grade ≥ 3 AEs were transient cytopenias (neutropenia [28%], anemia [12%], and thrombocytopenia [13%]) and diarrhea

(15%; Flinn et al., 2016). Boxed warnings include infections, diarrhea, colitis, cutaneous reactions, and pneumonitis without suspected infection (Verastem, Inc., 2018). Other toxicities noted in studies include lymphocytosis, hepatotoxicity, *Pneumocystis jirovecii* pneumonia (PJP), and cytomegalovirus (CMV) reactivation, most of which were grade ≤ 2 (Flinn et al., 2016, 2018).

Ongoing Trials

Several ongoing studies seek to expand the use of duvelisib. A phase I study aims to evaluate the long-term safety of duvelisib (NCT02711852; ClinicalTrials.gov, 2019). An additional study focusing on the maximum tolerated dose of duvelisib in combination with either romidepsin or bortezomib in relapsed/refractory T-cell lymphomas is also underway (NCT02783625). A phase Ib/II study in untreated, young CLL patients examines the use of duvelisib in combination with fludarabine, cyclophosphamide, and rituximab (FCR; NCT02158091; ClinicalTrials.gov, 2019). Duvelisib is being evaluated in combination with venetoclax (Venclexta) for relapsed or refractory CLL/SLL and in peripheral T-cell lymphoma (NCT03534323, NCT03372057; ClinicalTrials.gov, 2019). In summary, duvelisib is a preferred NCCN-recommended option for relapsed/refractory CLL/SLL and third-line therapy in FL, and many ongoing studies are evaluating its benefit in other indications.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

While idelalisib, copanlisib, and duvelisib all target the PI3K pathway via different isoforms, it is important to note the differences in approved indications and AE profiles among the three agents (Table 1). Idelalisib and duvelisib are available for oral administration, while copanlisib is administered intravenously. All three drugs are major CYP3A substrates and patients should be thoroughly evaluated for potential drug-drug and drug-food interactions (Bayer HealthCare Pharmaceuticals Inc., 2017; Gilead Sciences, Inc., 2018; Verastem, Inc., 2018).

PI3K inhibitors are generally well tolerated with appropriate AE management. Each agent's side-effect profile is related to the isoforms it in-

hibits. PI3K α and β isoforms are found in a variety of tissues throughout the body (Coutre et al., 2015; Greenwell, Ip, & Cohen, 2017). PI3K α isoforms have a critical role in insulin signaling. The δ isoform is preferentially expressed on leukocytes, while the γ isoform is implicated in the cardiovascular system, T-cell development, and T-cell signaling. Unexpected AEs were identified during drug development and should be considered when starting a patient on PI3K inhibitor therapy (Greenwell et al., 2017). It is important to maintain dose intensity, and any AEs should be detected early to avoid dose reductions and delays in therapy.

Diarrhea and Colitis

Diarrhea is a common side effect that may lead to dose reduction and/or PI3K inhibitor discontinuation (Coutre et al., 2015; Flinn et al., 2018; Greenwell et al., 2017). Diarrhea can occur at any time, even several months after the patient has started therapy. For patients receiving idelalisib or duvelisib, the median time to onset of diarrhea or colitis of any grade was 1.9 months and 2.2 months, respectively. Severe diarrhea events (grade 3/4) were more likely to occur later at 7.1 months for idelalisib and 4.9 months for duvelisib (Coutre et al., 2015; Flinn et al., 2018). Two types of diarrhea have been observed with idelalisib therapy: mild-moderate diarrhea and watery, nonbloody diarrhea. Mild-moderate diarrhea typically occurred within 8 weeks of therapy and responded to antimotility agents, while watery, nonbloody diarrhea was often unresponsive to antimotility therapy and thought to be immune mediated (Coutre et al., 2015; Greenwell et al., 2017).

Diarrhea should be evaluated promptly for other etiologies (infection, dietary factors, and medications), followed by stool workup and laboratory testing with colonoscopy for atypical or refractory cases (Coutre et al., 2015). Patients with grade 1/2 diarrhea may continue on PI3K inhibitor therapy with dietary optimization, loperamide, and close monitoring. Patients with unresolved grade 2 or grade ≥ 3 diarrhea should have PI3K inhibitor therapy held, and if negative for infection, should begin on a trial of budesonide at 9 mg orally once daily or prednisone at 1 mg/kg daily until symptoms resolve to \leq grade 1. If the

Table 1. Summary of the FDA Approved PI3K Inhibitors

	Idelalisib	Copanlisib	Duvelisib
Approved indication(s)	<ul style="list-style-type: none"> Relapsed CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities Relapsed SLL in patients who have received at least 2 prior systemic therapies Relapsed FL in patients who have received at least 2 prior systemic therapies 	Relapsed FL in patients who have received at least 2 prior therapies	<ul style="list-style-type: none"> Relapsed or refractory CLL or SLL in patients after at least 2 prior therapies Relapsed or refractory FL in patients after at least 2 prior therapies
Isoform inhibited	δ	α, β, δ, γ	δ, γ
Dosing and administration	150 mg po bid (± food); continue until disease progression or unacceptable toxicity	60-mg IV infusion on days 1, 8 and 15 of a 28-day cycle; continue until disease progression or unacceptable toxicity	25 mg po bid (± food); continue until disease progression or unacceptable toxicity
Adjustments	<ul style="list-style-type: none"> Renal: no dose adjustment provided Hepatic: no dose adjustment for patients with ALT, AST, or bilirubin > ULN; however, limited safety and efficacy data available with baseline AST or ALT >2.5 × ULN or bilirubin >1.5 × ULN 	<ul style="list-style-type: none"> Renal: no dose adjustment provided Hepatic: no dose adjustment provided 	<ul style="list-style-type: none"> Renal: no dose adjustment provided Hepatic: no dose adjustment provided
Drug-drug interactions	<ul style="list-style-type: none"> Strong CYP3A inhibitors: additional monitoring required Strong CYP3A inducers: avoid coadministration CYP3A substrates: avoid coadministration of sensitive CYP3A substrates 	<ul style="list-style-type: none"> Strong CYP3A inhibitors: reduce dose to 45 mg Strong CYP3A inducers: avoid coadministration 	<ul style="list-style-type: none"> Strong CYP3A inhibitors: reduce dose to 15 mg bid Strong CYP3A inducers: avoid coadministration CYP3A substrates: reduce dose of sensitive CYP3A substrates and monitor
Most common adverse events ^a	Pyrexia, fatigue, cough, chills, nausea, diarrhea, neutropenia, thrombocytopenia, anemia, AST/ALT elevation, increased alkaline phosphatase, rash	Hyperglycemia, hypertension, pyrexia, fatigue, nausea, diarrhea, neutropenia, thrombocytopenia, AST/ALT elevation, lung infection	Pyrexia, fatigue, neutropenia, nausea, diarrhea, anemia, lung infection, cough, rash, musculoskeletal pain

Note. CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; FL = follicular lymphoma; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CYP = cytochrome P450; ULN = upper limit of normal. Information from Bayer HealthCare Pharmaceuticals Inc., 2017; Gilead Sciences Inc., 2018; Verastem, Inc., 2018. ^aReported frequency > 20%.

patient is to resume PI3K therapy, lower doses can be considered with or without concomitant budesonide (Gilead Sciences, Inc., 2018; Greenwell et al., 2017; Verastem, Inc., 2018). There are no specific recommendations for the management of diarrhea or colitis from copanlisib; however, the package insert recommends holding therapy for grade 3 toxicities and dose reducing once toxicity has resolved (Bayer HealthCare Pharmaceuticals Inc., 2017).

Autoimmune Hepatotoxicity

Severe autoimmune transaminitis has been reported with idelalisib and duvelisib, and to a lesser extent, copanlisib (Coutre et al., 2015; Dreyling et al., 2017; Flinn et al., 2018; Greenwell et al., 2017). With idelalisib, elevations in ALT/AST commonly occurred in the first 12 weeks, and were reversible with holding therapy. With duvelisib, median time to onset of ALT/AST elevation was 1.2 months, lasting about 2 weeks

(Coutre et al., 2015; Flinn et al., 2018). Concomitant hepatotoxic drugs should be discontinued. Patients with an ALT/AST $> 3 \times$ upper limit of normal (ULN) should have weekly monitoring until resolved. If > 3 to $5 \times$ ULN (grade 2), then therapy can be continued with labs monitored at least weekly until $\leq 1 \times$ ULN with idelalisib or $\leq 3 \times$ ULN for duvelisib. If > 5 to $20 \times$ ULN (grade 3), then therapy should be held and labs monitored at least weekly until $\leq 1 \times$ ULN with idelalisib or $\leq 3 \times$ ULN for duvelisib. At that time, treatment can resume at a lower dose. If ALT/AST $> 20 \times$ ULN, PI3K inhibitor therapy should be permanently discontinued (Coutre et al., 2015; Gilead Sciences, Inc., 2018; Greenwell et al., 2017; Verastem, Inc., 2018). There are no specific recommendations for the management of hepatotoxicity for copanlisib; however, the medication should be held for grade 3 toxicities and resumed at a lower dose (Bayer HealthCare Pharmaceuticals Inc., 2017). Most patients do not require treatment discontinuation as a result of hepatotoxicity.

Respiratory Symptoms and Pneumonitis

Patients who develop respiratory symptoms while on PI3K inhibitor therapy should be evaluated promptly due to concerns for autoimmune pneumonitis (Coutre et al., 2015; Greenwell et al., 2017). Fatal cases of pneumonitis have been reported in patients treated with idelalisib, duvelisib, and copanlisib. Patients should be evaluated for infectious causes including PJP. Patients with a mild, persistent cough, $< 5\%$ decrease in O_2 saturation, dyspnea with exertion, or interstitial infiltrates on imaging should discontinue PI3K inhibitor therapy. If the O_2 saturation decrease is $\geq 5\%$ or development of an oxygen requirement occurs, the patient should be admitted for a thorough evaluation including a high-resolution chest CT, potential bronchoscopy/bronchoalveolar lavage, and initiation of empiric prednisone at 1 mg/kg (Greenwell et al., 2017). Idelalisib should be permanently discontinued for patients with any severity of symptomatic pneumonitis or organizing pneumonia (Gilead Sciences, Inc., 2018). Treatment with copanlisib or duvelisib should only be permanently discontinued for grade ≥ 3 pneumonitis or grade 2 pneumonitis that does not resolve with steroid treatment (Bayer HealthCare Pharmaceuticals Inc., 2017; Verastem, Inc., 2018).

Rashes and Cutaneous Reactions

Cutaneous reactions, including severe reactions, have been reported with the PI3K inhibitors (Flinn et al., 2016; Greenwell et al., 2017). Toxic epidermal necrolysis and SJS have occurred with idelalisib and duvelisib therapy, and drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with duvelisib (Gilead Sciences, Inc., 2018; Verastem, Inc., 2018). Cutaneous reactions can present as exfoliative dermatitis, various rashes, pruritus, and other skin disorders. For grade 1/2 reactions, patients should be monitored closely and can be treated with supportive care, while grade ≥ 3 reactions should prompt holding PI3K inhibitor therapy and consulting dermatologic experts before determining if reinitiation of therapy is appropriate (Greenwell et al., 2017).

Opportunistic Infections

In clinical trials with the PI3K inhibitors, higher rates of opportunistic infections with PJP and CMV were reported (Cuneo et al., 2018; Dreyling et al., 2017; Greenwell et al., 2017). *Pneumocystis jirovecii* pneumonia prophylaxis is recommended for all patients receiving idelalisib and duvelisib, and for at-risk populations while receiving copanlisib. Monthly CMV monitoring is recommended for idelalisib and duvelisib. These agents should be discontinued in patients with symptomatic viremia and end-organ damage, and patients should begin appropriate antiviral treatment. For asymptomatic patients with increasing CMV levels, providers may consider holding PI3K inhibitor therapy and starting empiric antiviral therapy (Bayer HealthCare Pharmaceuticals Inc., 2017; Gilead Sciences, Inc., 2018; Verastem, Inc., 2018).

Hypertension

Copanlisib's effect on PI3K δ has been associated with high rates of severe hypertension; blood pressure (BP) should be monitored pre- and postinfusion (Bayer HealthCare Pharmaceuticals Inc., 2017; Greenwell et al., 2017). A patient's BP should be controlled prior to initiating therapy and antihypertensive medications started with consideration for comorbidities. If a patient has a predose BP of $\geq 150/90$ mmHg, therapy should be held

until BP is < 150/90 mmHg for two consecutive measurements at least 15 minutes apart. If a patient experiences a postdose BP \geq 150/90 mmHg requiring antihypertensive treatment, then a dose reduction should be considered. If life-threatening consequences are present, then therapy should be discontinued. Providers may consider monitoring for proteinuria or other signs of end-organ damage, recommend home BP monitoring, and rule out other causes of hypertension. Patients should be educated on symptoms of hypertension such as dizziness and headache (Bayer HealthCare Pharmaceuticals Inc., 2017; Greenwell et al., 2017).

Hyperglycemia

Copanlisib is associated with the development of hyperglycemia, which generally peaks following infusion and resolves on its own in the majority of patients (Bayer HealthCare Pharmaceuticals Inc., 2017; Greenwell et al., 2017). Prior to therapy initiation, patients should be evaluated for diabetes or insulin resistance. Patients with diabetes should be well controlled before starting copanlisib. If predose fasting blood glucose levels are \geq 160 mg/dL or a random, nonfasting blood glucose level is \geq 200 mg/dL, copanlisib should be held until hyperglycemia resolves. If pre- or postdose blood sugar levels are \geq 500 mg/dL, then therapy should be dose reduced or discontinued. Patients should be educated on symptoms of hyperglycemia such as excess thirst, headaches, and frequent urination (Bayer HealthCare Pharmaceuticals Inc., 2017; Greenwell et al., 2017).

CONCLUSION

PI3K inhibitors play an important role in the management of several hematologic malignancies. Each of the FDA-approved agents, idelalisib, copanlisib, and duvelisib, have their own indications and AE profiles. Knowledge of their mechanism of action, dosing schedule, and potential AEs can assist in determining the best clinical course for the patient. As more PI3K inhibitors are approved and made commercially available, it is important to closely monitor for known AEs unique to each agent, along with those we have yet to discover. ●

Disclosure

The authors have no conflicts of interest to disclose.

References

- Bayer HealthCare Pharmaceuticals Inc. (2017). Aliqopa (copanlisib) package insert. Retrieved from http://labeling.bayerhealthcare.com/html/products/pi/Aliqopa_PI.pdf
- ClinicalTrials.gov. (2019). ClinicalTrials.gov. Retrieved from <https://clinicaltrials.gov/>
- Coutre, S. E., Barrientos, J. C., Brown, J. R., de Vos, S., Furman, R. R., Keating, M. J.,...Zelenetz A. D. (2015). Management of adverse events associated with idelalisib treatment: Expert panel opinion. *Leukemia & Lymphoma*, 56(10), 2779–2786. <https://doi.org/10.3109/10428194.2015.1022770>
- Cuneo, A., Barosi, G., Danesi, R., Fagioli, S., Ghia, P., Marzani, A.,...Zinzani, P. L. (2018). Management of adverse events associated with idelalisib treatment in chronic lymphocytic leukemia and follicular lymphoma: A multidisciplinary position paper. *Hematology Oncology*, 37(1), 1–12. <https://doi.org/10.1002/hon.2540>
- Dreyling, M., Santoro, A., Mollica, L., Leppä, S., Follows, G. A., Lenz, G.,...Zinzani, P. L. (2017). Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *Journal of Clinical Oncology*, 35(35), 3898–3905. <https://doi.org/10.1200/JCO.2017.75.4648>
- Flinn, I. W., Hillmen, P., Montillo, M., Nagy, Z., Illes, A., Etiene, G.,...Stilgenbauer, S. (2018). The phase 3 DUO trial: Duvelisib versus ofatumumab in relapsed and refractory CLL/SLL. *Blood*, 132(23), 2446–2455. <https://doi.org/10.1182/blood-2018-05-850461>
- Flinn, I. W., Miller, C. B., Ardesna, K. M., Tetreault, S., Assouline, S. E., Zinzani, P. L.,...Wagner-Johnston, N. D. (2016). Dynamo: A phase 2 study demonstrating the clinical activity of duvelisib in patients with relapsed refractory indolent non-hodgkin lymphoma [Abstract 1218]. *Blood (ASH Annual Meeting Abstracts)*, 128, 1218. Retrieved from <http://www.bloodjournal.org/content/128/22/1218?sso-checked=true>
- Flinn, I. W., O'Brien, S., Kahl, B., Patel, M., Oki, Y., Foss, F. F.,...Horwitz, S. (2018). Duvelisib, a novel oral dual inhibitor of PI3K- δ , γ , is clinically active in advanced hematologic malignancies. *Blood*, 131, 877–887. <https://doi.org/10.1182/blood-2017-05-786566>
- Furman, R. R., Sharman, J. P., Coutre, S. E., Cheson, B. D., Pagan, J. M., Hillmen, P.,...O'Brien, S. M. (2014). Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *New England Journal of Medicine*, 370(11), 997–1007. <https://doi.org/10.1056/NEJMoa1315226>
- Gilead Sciences, Inc. (2018). Zydelig (idelalisib) package insert. Retrieved from https://www.gilead.com/-/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf
- Goncalves, M. D., Hopkins, B. D., & Cantley, L. C. (2018). Phosphatidylinositol 3-kinase, growth disorders, and cancer. *New England Journal of Medicine*, 379, 2052–2062. <https://doi.org/10.1056/NEJMra1704560>
- Gopal, A. K., Kahl, B. S., de Vos, S., Wagner-Johnson, N. D., Schuster, S. J., Jurczak, W. J.,...Salles, G. A. (2014). PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma. *New England Journal of Medicine*, 370, 1008–1018. <https://doi.org/10.1056/NEJMra1704560>
- Greenwell, I. B., Ip, A., & Cohen, J. B. (2017). PI3K inhibitors: Understanding toxicity mechanisms and management. *Oncology Journal*, 31(11). Retrieved from <http://www.cancernetwork.com/oncology-journal/pi3k-inhibitors-understanding-toxicity-mechanisms-and-management>

- Krause, G., Hassenruck, F., & Hallek, M. (2018). Copanlisib for treatment of B-cell malignancies: The development of a PI3K inhibitor with considerable differences to idelalisib. *Drug Design, Development and Therapy*, *12*, 2577–2590. <https://doi.org/10.2147/DDDT.S142406>
- Lenz, G., Hawkes, E., Verhoef, G., Haioun, C., Thye, L. S., Heo, D. S.,...Salles, G. A. (2017). Phase II study of single-agent copanlisib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) [Abstract 7536]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, *35*(15). https://doi.org/10.1200/JCO.2017.35.15_suppl.7536
- Mensah, F. A., Blaize, J. P., & Bryan, L. J. (2018). Spotlight on copanlisib and its potential in the treatment of relapsed/refractory follicular lymphoma: Evidence to date. *OncoTargets and Therapy*, *11*, 4817–4827. <https://doi.org/10.2147/OTT.S142264>
- National Comprehensive Cancer Network. (2019a). NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. V4.2019. Retrieved from <https://www.nccn.org>
- National Comprehensive Cancer Network. (2019b). NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V5.2019. Retrieved from <https://www.nccn.org>
- Novartis Corporation. (2016). Arzerra (ofatumumab) package insert. Retrieved from <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf>
- Patnaik, A., Appleman, L. J., Tolcher, A. W., Papadopoulos, K. P., Beeram, M., Rasco, D. W.,...Ramanathan, R. K. (2016). First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. *Annals of Oncology*, *10*(27), 1928–40. <https://doi.org/10.1093/annonc/mdw282>
- Paul, J., Soujon, M., Wengner, A. M., Zitzmann-Kolbe, S., Sturz, A., Haike, K.,...Ningshu L. (2017). Simultaneous inhibition of PI3K δ and PI3K α induces ABC-DLBCL regression by blocking BCR-dependent and -independent activation of NF- κ B and AKT. *Cancer Cell*, *31*(1), 64–78. <https://doi.org/10.1016/j.ccell.2016.12.003>
- Vangapandu, H. V., Jain, N., & Gandhi, V. (2017). Duvelisib: A phosphoinositide-3 kinase delta/gamma inhibitor for chronic lymphocytic leukemia. *Expert Opinion on Investigational Drugs*, *26*(5), 625–632. <https://dx.doi.org/10.1080/2F13543784.2017.1312338>
- Verastem, Inc. (2018). Copiktra (duvelisib) package insert. Retrieved from https://www.accessdata.fda.gov/drug-satfda_docs/label/2018/211155s000lbl.pdf
- Zelenetz, A. D., Barrientos, J. C., Brown, J. R., Coiffier, B., Delgado, J., Egyed, M.,...Hillmen, P. (2017). Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed/refractory CLL- interim results of a phase 3 randomized, double-blind placebo-controlled trial. *Lancet Oncology*, *18*(3), 297–311. [https://doi.org/10.1016/S1470-2045\(16\)30671-4](https://doi.org/10.1016/S1470-2045(16)30671-4)