

OncLive[®]

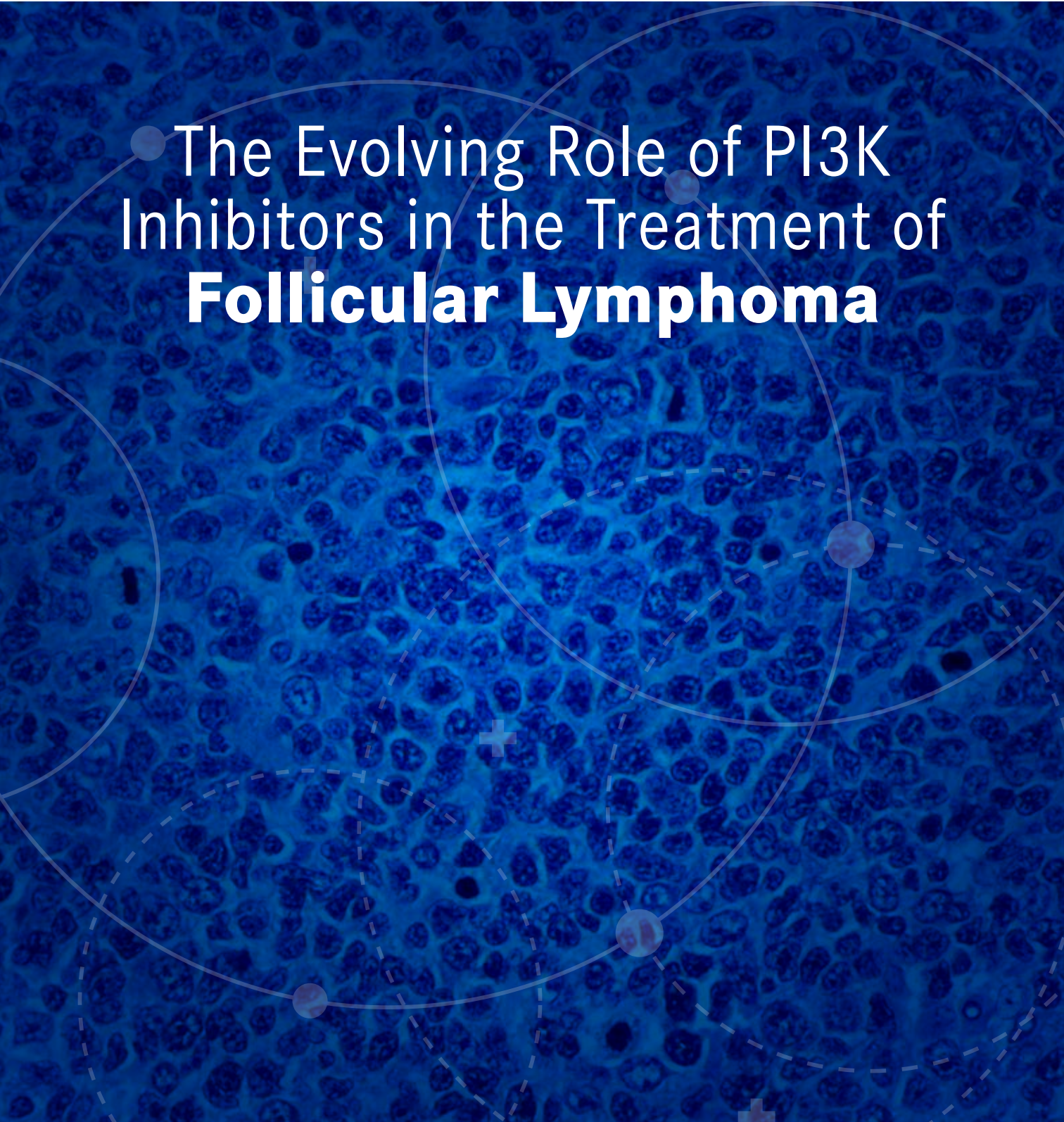
FOLLICULAR LYMPHOMA

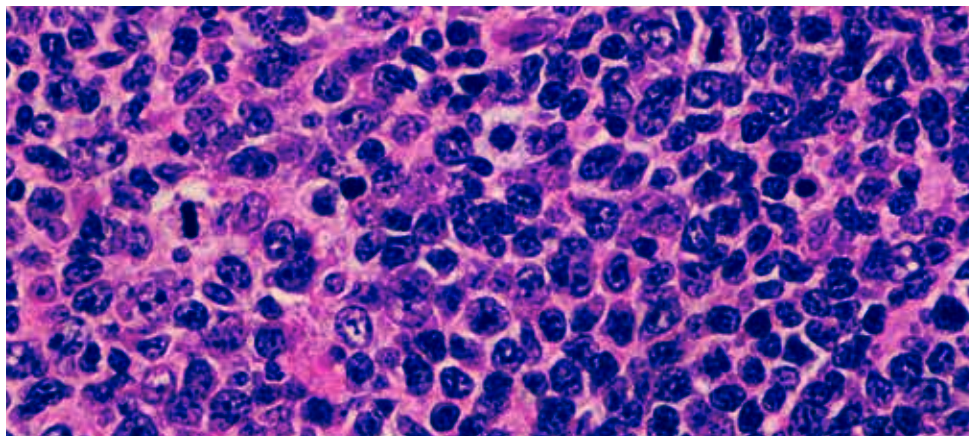
JUNE 18, 2021

VIRTUAL WORKSHOP

SCIENTIFIC **INTERCHANGE & WORKSHOP**

● The Evolving Role of PI3K
Inhibitors in the Treatment of
Follicular Lymphoma

A microscopic image of follicular lymphoma cells, showing a dense population of cells with characteristic follicular architecture. The image is overlaid with several geometric shapes: a large solid blue circle, a smaller solid blue circle, and a dashed white circle. A white plus sign is positioned near the center of the dashed circle. The overall background is a deep blue color.



EDITORIAL & PRODUCTION

Senior Vice President
Jeff Prescott, PharmD

Associate Director, Content Services
Angelia Szwed, MS

Clinical Project Manager
Lauren Burawski, MA

Project Manager
Blair Langston

Associate Editor
Jillian Pastor-Mohr

Copy Chief
Jennifer Potash

Copy Supervisors
Rachelle Laliberte
Paul Silverman

Senior Copy Editor
Kelly King

Medical & Scientific Quality Review Editor
Stacey Abels, PhD

Copy Editors
Cheney Baltz
Georgina Carson
Kirsty Mackay
Ron Panarotti

Creative Director, Publishing
Melissa Feinen

Senior Graphic Designer
Kellie Ehrmann

SALES & MARKETING

Vice President, Sales, MJH Life Sciences™
Robert Goldsmith

Vice President & Executive Producer, MJH Productions
David Lepping

Executive Vice President, Oncology Professional Relations
Donna Short, MA

Director, Sales
Albert Tierney

Senior National Accounts Manager
Phil Conover

National Accounts Manager
Morgan Michon

National Accounts Associates
Shane Marchesani
Mary Lenyo

OPERATIONS & FINANCE

Circulation Director
Jon Severn

Vice President, Finance
Leah Babitz, CPA

Controller
Katherine Wycoff

CORPORATE

Chairman & Founder
Mike Hennessy Sr

Vice Chairman
Jack Lepping

President & CEO
Michael Hennessy Jr

Chief Financial Officer
Neil Glasser, CPA/CFE

Executive Vice President, Global Medical Affairs & Corporate Development
Joe Petroziello

Senior Vice President, Content
Silas Inman

Senior Vice President Operations
Michael Ball

Vice President, Human Resources and Administration
Shari Lundenberg

Vice President, Mergers & Acquisitions
Chris Hennessy

Executive Creative Director, Creative Services
Jeff Brown



KEY TAKEAWAYS

- ▶ Overactive phosphoinositide 3-kinase (PI3K) expression in cancer and immune dysregulation has reinvigorated research and development efforts to further develop therapeutic drugs targeting PI3K inhibitors.
- ▶ Although progress has been hindered by issues such as poor drug tolerance and drug resistance, several PI3K inhibitors have now received FDA regulatory approval (idelalisib, copanlisib, duvelisib, and umbralisib).
- ▶ Different toxicity profiles may factor into treatment selection of PI3K inhibitors, particularly in patients with comorbidities. Hepatic toxicity and immune-related colitis are the most clinically concerning with idelalisib and duvelisib; hyperglycemia and hypertension, with copanlisib. Based on early clinical evidence, zandelisib may potentially have the best toxicity profile and lowest incidence of grade 3 and higher adverse events among the PI3K inhibitors.
- ▶ The route of administration is a key difference among PI3K inhibitors.
- ▶ The potential role of chimeric antigen receptor T-cell therapy to treat patients with relapsed/refractory follicular lymphoma remains to be seen. Additional long-term follow-up data are needed in this patient population.

The Evolving Role of PI3K Inhibitors in the Treatment of Follicular Lymphoma

THE INTRODUCTION OF PHOSPHOINOSITIDE 3-KINASE (PI3K) INHIBITORS, tazemetostat, an EZH2 inhibitor, and chimeric antigen receptor (CAR) T-cell therapy, has presented new options for the management of relapsed/refractory (R/R) follicular lymphoma (FL), including for patients with high-risk features. However, therapy selection and sequencing are still unmet needs in the treatment of R/R FL. A panel of experts who specialize in the management of FL participated in a recent OncLive® Scientific Interchange and Workshop moderated by **Brad Kahl, MD**, discussed ways to estimate disease risk, treatment strategies in the front line and R/R settings, recent data on efficacy and toxicity of PI3K inhibitor-based regimens, and CAR T-cell therapy.

BACKGROUND

FL is the second most common type of non-Hodgkin lymphoma (NHL) in the United States and Western Europe, accounting for about 35% of NHLs, and has a median age of diagnosis of 65 years.¹ Most patients present with asymptomatic lymphadenopathy (less than 20% present with B symptoms), although histologic transformation to diffuse large B-cell lymphoma (DLBCL) occurs in 10% to 70% of patients at some point, with a risk of 2% per year.¹

The Ann Arbor Staging System is commonly used for anatomic staging of NHLs and stratifies patients as having localized disease (stage I), multiple sites of disease on the same side of the diaphragm (stage II), lymphatic disease on both sides of the diaphragm (stage III), and disseminated extranodal disease (stage IV).²

FL is also graded pathologically using World Health Organization criteria, which classifies samples from biopsies based on number of centroblasts per high-power field to assess potential aggressiveness of the tumor.¹ Grades 1, 2, and 3 FL correspond to 0 to 5, 6 to 15, and more than 15 centroblasts per high-power field, respectively, and grade 3 disease is subdivided based on the presence of centrocytes (3a) or pure sheets of centroblasts (3b).¹ Although the majority of patients have advanced stage at diagnosis,¹ patients only require immediate treatment if they have symptomatic nodal or extranodal disease, compromised end-organ function, B symptoms, or cytopenias.¹

ESTIMATING DISEASE RISK IN FOLLICULAR LYMPHOMA

The Follicular Lymphoma International Prognostic Index (FLIPI) uses age, disease stage, number of nodal areas involved, serum lactate dehydrogenase, and hemoglobin to categorize patients into low-, intermediate-, and high-risk groups.¹ Analysis of the outcome data from the National LymphoCare Study showed that, compared with the low-risk group, the overall survival

(OS) was significantly inferior for the intermediate- and high-risk groups, with unadjusted HRs of 2.37 and 6.17, respectively.³ Additionally, the FLIPI appeared to be useful for predicting outcomes of interest (OS, progression-free survival [PFS], and time to next treatment) across all treatment strategies, including rituximab-based regimens.³ The FLIPI2 was later introduced as a modified version of the FLIPI and includes age, bone marrow involvement, hemoglobin, greatest diameter of the largest involved node, and serum beta-2 microglobulin in its model, but the utility of the FLIPI2 relative to the FLIPI is unclear.¹ The Groupe d'Etude des Lymphomes Folliculaires criteria is another model that uses tumor burden and clinical findings for risk stratification.¹ However, duration of response to frontline therapy is likely an important predictor of outcomes not accounted for in these models, as an analysis from the National LymphoCare database showed that patients with progression of disease within 24 months (POD24) after first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy had worse OS than those who progressed more than 24 months after treatment (HR, 1.89; 95% CI, 1.18-3.03, $P=.008$).⁴

STAKEHOLDER INSIGHTS

Overall, outcomes of FL have improved over the past 30 to 40 years, likely due to the development of better treatment options. Risk tools are often used in FL to predict prognosis but are limited in that they are unable to precisely identify patients who should receive aggressive treatment at diagnosis. POD24 is associated with poor prognosis and is probably the strongest tool to re-stratify risk after the first relapse, and stakeholders recommended that these patients undergo biopsy to rule out histologic transformation.

Although lenalidomide with rituximab is commonly considered for second-line treatment in patients without POD24, stem cell transplantation or clinical trial enrollment may be considered for medically fit patients with POD24.

PI3K INHIBITORS ON THE MARKET

Landscape

Class I PI3K inhibitors signal downstream of tyrosine kinases, G protein-coupled receptors, and GTPases, to regulate a variety of cellular activities, including metabolism, proliferation, and migration.^{5,6} PI3K signaling is one of the most frequently abnormally activated pathways in cancer.⁷

PI3K δ expression in all leukocyte types has afforded it with roles in immunity and hematological malignancies.⁸ PI3K δ inhibition interferes with the response of malignant B cells to a range of cytokines, chemokines, costimulatory molecules, and adhesion receptors, which support leukemic cell activities. PI3K δ inhibition also offers a direct negative impact on leukemia-supporting stromal cells and counteraction of microenvironment-derived proliferation and survival signaling pathways, particularly in chronic lymphocytic leukaemia⁹ and FL.¹⁰ PI3K δ inhibition also reduces the activity of cancer-promoting myeloid-derived suppressor cells¹¹ and cancer-associated macrophages,¹² which also decreases the capacity of the latter cells to yield reactive oxygen species that lead to the death of natural killer cells.¹³

FL has a strong dependence on microenvironmental signals provided by proliferating B cells and an array of supportive cells, including several types of follicular T cell: T follicular helper cells with robust pro survival activity through the CD40L-IL-4 axis, immunosuppressive T follicular regulatory cells, follicular reticular cells, tumor-associated macrophages, and follicular dendritic cells presenting

antigen presentation. PI3K δ inhibition disrupts this tumor-promoting FL microenvironmental cross talk. The overall effect of PI3K δ inhibition is a less supportive and less tolerogenic immune microenvironment.¹⁰

Efficacy

Because the δ isoform of PI3K plays a key role in development and function of B cells and PI3K δ signaling pathways often have elevated activity in B-cell cancers, PI3K inhibitors targeting the δ isoform have been identified as a promising target for treatment of indolent NHL.¹⁴

Idelalisib (Zydelig) is an oral PI3K δ inhibitor indicated for patients with relapsed FL who have received 2 or more prior systemic therapies.¹⁵ The results of a single-group, open-label, phase 2 study (NCT01282424) of 125 patients with indolent NHL, including 72 patients with FL, showed that the overall response rate (ORR) to idelalisib was 57% (95% CI, 48%-66%), although only 6% had a complete response (CR), and the median PFS and OS were 11.0 and 20.3 months, respectively.¹⁴ Adverse events (AEs) led to discontinuation of idelalisib in 25 patients, and the most common grade 3 or higher AEs included neutropenia (27%), elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (13%), diarrhea (13%), pneumonia (7%), and dyspnea (3%).¹⁴

Duvelisib (Copiktra) is an oral PI3K inhibitor with activity predominantly against the δ and γ isoforms and is indicated for adult patients with FL who have relapsed or are refractory to at least 2 prior systemic therapies.¹⁶ The open-label global phase 2 DYNAMO study (NCT01882803) showed an ORR of 47% (95% CI, 38%-56%), with 2 CRs in 129 patients with relapsed indolent NHL (including 83 patients with FL).¹⁷ The median PFS and OS were 9.5 months (95% CI, 8.1-11.8 months) and 28.9 months (95% CI, 21.4 months -

not estimable), respectively.¹⁷ Forty patients (31%) discontinued duvelisib because of treatment-emergent AEs, with neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%) as the most frequent grade 3 or higher events.¹⁷ In addition, colitis was reported in 10 patients (7.8%), pneumonitis occurred in 6 patients (4.7%), and serious opportunistic infections were reported in 3 patients (1 case each of bronchopulmonary aspergillosis, cytomegalovirus pneumonia, and *Pneumocystis jiroveci* pneumonia).¹⁷

Copanlisib (Aliqopa) is an intravenously administered PI3K inhibitor with activity predominantly against the α and δ isoforms and is indicated for treatment of adult patients with relapsed FL previously treated with at least 2 prior systemic therapies.¹⁸ A single-arm phase 2 study (NCT01660451) of 142 patients with indolent B-cell lymphoma showed that in the subgroup of 104 patients with FL, the objective response rate was 59%, with a CR rate (CRR) of 14%.¹⁹ Median PFS was 11.2 months, and the median OS had not yet been reached.¹⁹ The most common grade 3 or 4 AEs were hyperglycemia (grade 3, 34%; grade 4, 7%), hypertension (grade 3, 24%; grade 4; 0%), decreased neutrophil count (grade 3, 8%; grade 4, 16%), lung infection (grade 3, 13%; grade 4; 2%), and 3 nonfatal opportunistic infections (2 *P jiroveci* and 1 bronchopulmonary aspergillosis infections) were reported.¹⁹ Of the 6 grade 5 events that occurred during treatment or within 35 days of permanent treatment discontinuation, 3 were considered treatment related (lung infection, respiratory failure, and cerebral thromboembolic event).¹⁹

Umbralisib is an oral drug that inhibited PI3K δ and CK1 ϵ in biochemical and cell-based assays.²⁰ The accelerated approval for R/R FL that has been treated by at least 3 lines of systemic therapy²⁰ was based on the ORR of 45.3% (95% CI, 36.1%-

54.8%) seen in the FL subgroup in the UNITY-NHL trial (NCT02793583), a multicenter, open-label, registration directed phase 2 trial of patients with previously treated NHL.²¹ The CRR was 5.1%, and the median PFS was 10.6 months (95% CI, 7.2-13.7 months).²¹ The most common grade 3 or higher AEs were neutropenia (11.5%), diarrhea (10.1%), and elevated AST or ALT (7.2%), and rates of pneumonitis (all grades, 1.4%; grade \geq 3, 1.0%) and colitis (all grades, 1.4%; grade 3 or higher, 0.5%) were relatively low.²¹ The study authors noted that the relatively low incidence of immune-mediated toxicities with umbralisib in a previously reported cohort with R/R marginal zone lymphoma (MZL) may have been attributed to the better selectivity for the PI3K δ isoform and inhibition of CK1 ϵ .²¹

Zandelisib (ME-401) is a potent, selective oral PI3K δ inhibitor currently in development that has been studied using intermittent-schedule dosing, with a goal to reduce the incidence of immune-mediated AEs associated with PI3K δ inhibitors.²² Data from a phase 1b study (NCT02914938) of 57 patients with R/R B-cell malignancies, including 35 patients with FL, showed that zandelisib as monotherapy (n = 21) or with rituximab (n = 36) was well tolerated, with grade 3 or higher AEs of special interest including diarrhea (n = 2; 3.5%), colitis (n = 2; 3.5%), rash (n = 1; 2%), elevated ALT (n = 1; 2%), and pneumonitis (n = 1; 2%).²² The ORR was 83% in patients with FL (76% with monotherapy and 88% with combination therapy), with median duration of response and PFS not reached at a median follow-up of 9.7 months.²²

STAKEHOLDER INSIGHTS

Efficacy data appear similar across the PI3K inhibitors, but the toxicity profile is a key factor that has limited the widespread

use. Therefore, awareness of the risks for opportunistic infections and severe AEs is critical when using PI3K inhibitors. Although copanlisib appears to have a lower risk for colitis and pneumonitis, it can lead to significant hyperglycemia and hypertension, and the infusion schedule (3 consecutive weeks followed by 1 week off repeated indefinitely) can become burdensome for patients. Umbralisib appeared to have a more tolerable safety profile than the other PI3K inhibitors, and although the median follow-up for zandelisib is relatively short, the duration of response appears to be slightly better than with other PI3K inhibitors on the market.

TREATMENT RECOMMENDATIONS

According to the National Comprehensive Cancer Network (NCCN) guidelines, preferred regimens for medically fit patients in the first- and second-line settings include bendamustine plus obinutuzumab or rituximab; rituximab or obinutuzumab combined with CHOP or cyclophosphamide, vincristine, and prednisone (CVP); and lenalidomide plus rituximab, with the selection of therapy based on age, comorbidities, and future treatment possibilities.²³ Options for third-line therapy include PI3K inhibitors, tazemetostat (EZH2 inhibitor), and axicabtagene ciloleucel (anti-CD19 CAR T-cell therapy). Umbralisib is an option for fourth-line therapy in medically fit patients or third-line treatment of elderly or infirm patients.²³

STAKEHOLDER INSIGHTS

In the frontline setting, stakeholders reported choosing rituximab for patients with low tumor burden, rituximab with bendamustine for patients with high tumor burden, and R-CHOP

for patients in whom histologic transformation is a concern. In the second-line setting, multiple stakeholders said that they tend to use lenalidomide and rituximab if histologic transformation has not occurred, even in patients with POD24, and R-CHOP in patients with histologic transformation. The stakeholders said that they generally consider a PI3K inhibitor in the third or fourth line, although the “big question” for 1 stakeholder is the choice between a PI3K inhibitor or tazemetostat, which tends to have a better safety profile.

RECENT TRIALS OF PI3K INHIBITOR-BASED REGIMENS *Copanlisib With Rituximab*

The single-agent efficacy of copanlisib in patients with heavily pretreated indolent NHL led researchers to evaluate whether copanlisib plus rituximab could improve outcomes for patients who are rituximab sensitive or unable to receive chemotherapy.²⁴ The phase 3 CHRONOS-3 trial (NCT02367040) randomized patients (2:1) with relapsed indolent NHL to receive copanlisib or placebo in addition to rituximab.²⁴ The centrally assessed ORR was 81% in the copanlisib group and 48% in the placebo group, with CRRs of 34% and 15% in the copanlisib and placebo groups, respectively.²⁴ The median PFS was also longer in the copanlisib group than in the placebo group (21.5 months vs 13.8 months; HR, 0.52 [95% CI, 0.39-0.69]; $P < .0001$).²⁴ However, treatment-related AEs appeared to be more frequent in the copanlisib group, as 95% of patients reported an AE of any grade compared with 65% of the placebo group.²⁴ Furthermore, 103 (34%) of 307 patients in the copanlisib group had serious treatment-emergent AEs, with hyperglycemia (7%), pneumonitis (5%), and pneumonia (3%) being most commonly reported.¹⁵ In the

placebo group, events were reported in 11 (8%) of 146 patients, with the most common being pneumonia (3%) and febrile neutropenia (1%).¹⁵

STAKEHOLDER INSIGHTS

Although the combination of copanlisib and rituximab yields an improvement in clinical outcomes over rituximab alone, the once-weekly frequency of copanlisib infusions may be burdensome for patients with relapsed FL who have other options for therapy in the second-line setting.

Zandelisib in Patients With POD24

Because of the association of POD24 with poor survival, some researchers have suggested that patients with POD24 may benefit from use of novel therapies at relapse.²⁵ Results of a phase 1b escalation/expansion trial (NCT02914938) of intermittent-schedule dosing of zandelisib (with or without rituximab) showed that the ORRs were 81.8% and 93.3% among patients with (n = 18) and without POD24 (n = 14), respectively, and the median duration of response was not reached at a median follow-up of 16.9 months.²⁵ Additionally, the intermittent-schedule dosing was well tolerated overall, with 3 patients (8%) discontinuing therapy due to an AE of any cause.²⁵ Grade 3 AEs of special interest included diarrhea in 2 cases (5.4%), colitis in 2 cases (5.4%), rash in 3 cases (8.1%), ALT elevation in 3 cases (8.1%), and AST elevation in 1 case (2.7%); no cases of pulmonary infection were reported.²⁵ Future studies include a global phase 2 study of zandelisib monotherapy in patients with FL or MZL after failure of 2 prior therapies (NCT03768505) and a phase 3 study of zandelisib with rituximab in patients with FL or MZL after failure on immunochemotherapy that plans to start enrollment in 2021.²⁵

STAKEHOLDER INSIGHTS

Zandelisib appeared to have good efficacy and tolerability in patients with POD24, although results from larger trials will be important to assess the efficacy relative to other PI3K inhibitors. Additionally, it is unclear whether the observed differences in efficacy among PI3K inhibitors is due to variations in pharmacokinetics or pharmacodynamics among the agents or differences in patient selection and trial size in the clinical studies.

Zandelisib With Zanubrutinib

Based on preclinical experiments showing a synergistic effect of PI3K and Bruton tyrosine kinase (BTK) inhibition in cell lines of mantle cell lymphoma,²⁶ researchers aimed to investigate whether combining the oral BTK inhibitor zanubrutinib with zandelisib would be an effective treatment regimen. A multi cohort phase 1b study (NCT02914938) of patients with R/R B-cell malignancies was conducted to identify the optimal dose and schedule for further evaluation in expansion cohorts.²⁷ The dosing of zandelisib 60 mg once per day for 2 cycles followed by intermittent-schedule dosing for the first 7 days of a 28-day cycle with zanubrutinib 80 mg twice per day (cohort 10C) was considered to be well tolerated, with 2 of 13 patients experiencing dose-limiting toxicities of grade 3 AST/ALT elevation in cycle 2 (1 of these patients was able to resume both drugs and the other patient discontinued treatment).²⁷ One patient had grade 3 laboratory tumor lysis syndrome, neutropenia, and thrombocytopenia, and 2 patients had neutropenia.²⁷ Additionally, a response rate of 100% was observed among 16 patients with indolent NHL and mantle cell lymphoma, including 2 CRs and 6 partial responses

among the 8 patients with FL.²⁷ The dosing schedule in cohort 10C is currently being evaluated in expansion cohorts of patients with R/R FL and mantle cell lymphoma.²⁷

STAKEHOLDER INSIGHTS

Despite the results observed in the phase 1b study, the stakeholders were cautiously optimistic as the combination did not yet show a clear benefit over monotherapy and added toxicity is expected. One stakeholder added that concurrent dosing would have to provide a substantial benefit over sequential dosing to warrant any additional toxicity associated with the combination.

STRATEGIES FOR IMPROVING TOLERABILITY OF PI3K INHIBITORS—STAKEHOLDER INSIGHTS

The stakeholders said that dose reductions or holidays often enable patients to stay on PI3K inhibitors, and most of the patients in their respective practices who have been on PI3K inhibitors long term are on a reduced or maintenance dose. However, 1 stakeholder said that he usually does not try to re-treat patients with PI3K inhibitors who have drug-related colitis or pneumonitis. In the stakeholders' experiences, diarrhea that occurs after 6 to 9 months of treatment is often a red flag for colitis and should be monitored closely, potentially with a referral for colonoscopy to determine the best strategy for management.

CAR T-CELL THERAPY

Tisagenlecleucel, a CAR T-cell therapy that targets CD19-expressing B cells, has shown durable responses in patients with R/R DLBCL²⁸ and pediatric and young adult patients with R/R B-cell lymphoblastic leukemia.²⁹ Because most patients with FL have a relapsed and remitting pattern of disease and have worse

outcomes after each subsequent line of therapy, researchers have aimed to investigate whether tisagenlecleucel can provide a durable treatment option.³⁰ The phase 2 ELARA trial (NCT03568461) showed that in the 94 patients evaluable for efficacy at the September 28, 2020, cutoff, the CRR was 66% and the ORR was 86.2%.³⁰ The probability of a response duration of at least 6 months was 79%.³⁰ Of the patients evaluable for safety (n = 97), 76.3% had grade 3 or higher AEs, with neutropenia being the most common (27.8%).³⁰ Tisagenlecleucel-related cytokine release syndrome (CRS) was reported in 48.5% of patients, although all of these events were grade 1 or 2.³⁰ Neurologic AEs were reported in 9.3% of patients (grade 3 or higher reported in 1%), with a median time to resolution of 2 days.³⁰ There were 3 deaths attributed to study indication.³⁰ The authors concluded that tisagenlecleucel was effective in patients with heavily pretreated R/R FL, including those in high-risk groups, and has a generally favorable safety profile.³⁰

Axicabtagene ciloleucel is another CD19-targeted CAR T-cell therapy approved for treatment of R/R large B-cell lymphoma after 2 or more lines of systemic therapy³¹ and is currently being studied in patients with relapsed or refractory indolent NHL in the phase 2, multicenter, single-arm ZUMA-5 trial (NCT03105336).³² In an analysis of participants stratified by POD24 status presented at the 2021 American Society of Clinical Oncology Annual Meeting, the ORR and CRR were 94% and 78%, respectively, in patients with FL and POD24 (the ORR and CRR were 97% and 90%, respectively, in patients without POD24).³² Responses were ongoing in 52% of patients with POD24 and 70% of patients without POD24 after median follow-ups of 17.1 months and 17.5 months, respectively.³² Grade 3 or higher AEs occurred in

84% and 88% of patients with and without POD24, respectively.³² Grade 3 or higher CRS occurred in 9% of patients with POD24 and 2% of those without POD24, and 17% of patients in POD24 and nonPOD24 groups had grade 3 or higher neurologic events.³² Three grade 5 AEs were reported in patients with POD24, including 1 case of multisystem organ failure in the context of CRS.³²

STAKEHOLDER INSIGHTS

Tisagenlecleucel and axicabtagene ciloleucel led to high ORR and CRR in patients with FL, even in heavily pretreated patients and patients with POD24. However, duration of follow-up is too short to establish whether these patients have truly durable responses or cure, and 1 stakeholder said that more relapses would likely be observed with longer follow-up. One stakeholder said that 5 years of follow-up data would likely be necessary to assess performance of CAR T-cell therapy, and he would consider it particularly promising if more than 25% of patients were in remission at 5 years. One stakeholder noted that the relatively low proportion of patients who received bridging therapy prior to CAR T-cell treatment may suggest that some of the patients had transformed disease. One stakeholder implied that he did not have much faith that PI3K inhibitors would perform well in transformed FL and therefore would likely opt for CAR T-cell therapy in this situation.

The relatively low rates of CRS and neurologic toxicity in the FL population were also promising, although the stakeholders pointed out that the uptake for FL is likely to be limited because many patients are treated in the community setting (in which CAR T-cell therapy would require

a referral) and most patients with FL have good overall survival with other therapies.

FUTURE DIRECTIONS AND KEY TAKEAWAYS—STAKEHOLDER INSIGHTS

Although the treatment strategies for FL in the first- and second-line settings are similar among stakeholders, selection of treatment in the third-line setting is less straightforward. Although CAR T-cell therapy is preferred by some stakeholders from an outcomes perspective, factors such as insurance coverage, presence of a caregiver, and proximity to the cancer center influence the feasibility of providing this treatment for many patients. Because of these multiple logistical issues, use of CAR T-cell therapy will likely be limited unless long-term data show major improvements in PFS and OS. PI3K inhibitors or tazemetostat are likely to be the mainstay of third-line treatment for most patients and can lead to good responses if toxicities are managed appropriately. One of the stakeholders said that although it is not straightforward, he is inclined to select a PI3K inhibitor in the third-line setting for older, frailer patients who want a more conservative approach, whereas he would be more inclined to try CAR T-cell therapy in motivated younger, fitter patients. ■

REFERENCES

1. Freedman A, Jacobsen E. Follicular lymphoma: 2020 update on diagnosis and management. *Am J Hematol.* 2020;95(3):316-327. doi:10.1002/ajh.25696
2. Armitage JO. Staging non-Hodgkin lymphoma. *CA Cancer J Clin.* 2005;55(6):368-376. doi:10.3322/canjclin.55.6.368
3. Nooka AK, Nabhan C, Zhou X, et al. Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices. *Ann*

Oncol. 2013;24(2):441-448.

doi:10.1093/annonc/mds429

4. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol.* 2015;33(23):2516-2522. Published correction appears in *J Clin Oncol.* 2016;34(12):1430. doi:10.1200/JCO.2014.59.7534
5. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. *Cell.* 2017;170(4):605-635. doi:10.1016/j.cell.2017.07.029
6. Bilanges B, Posor Y, Vanhaesebroeck B. PI3K isoforms in cell signalling and vesicle trafficking. *Nat Rev Mol Cell Biol.* 2019;20(9):515-534. doi:10.1038/s41580-019-0129-z
7. Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB. Exploiting the PI3K/AKT pathway for cancer drug discovery. *Nat Rev Drug Discov.* 2005;4(12):988-1004. doi:10.1038/nrd1902
8. Vanhaesebroeck B, Perry MWD, Brown JR, André F, Okkenhaug K. PI3K inhibitors are finally coming of age. *Nat Rev Drug Discov.* 2021. doi:10.1038/s41573-021-00209-1
9. Aydin E, Faehling S, Saleh M, Llaó Cid L, Seiffert M, Roessner PM. Phosphoinositide 3-kinase signaling in the tumor microenvironment: what do we need to consider when treating chronic lymphocytic leukemia with PI3K inhibitors? *Front Immunol.* 2021;11:595818. doi:10.3389/fimmu.2020.595818
10. Serrat N, Guerrero-Hernández M, Matas-Céspedes A, et al. PI3K δ inhibition reshapes follicular lymphoma-immune microenvironment cross talk and unleashes the activity of venetoclax. *Blood Adv.* 2020;4(17):4217-4231. doi:10.1182/bloodadvances.2020001584
11. Ali K, Soond DR, Pineiro R, et al. Inactivation of PI(3)K p110 δ breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature.* 2014;510(7505):407-411. doi:10.1038/nature13444
12. Goulielmaki E, Bermudez-Brito M, Andreou M, Tzenaki N, Tzardi M, de Bree E, Tselentierou E, Makrigiannakis A, Papakonstanti EA. Pharmacological inactivation of the PI3K p110 δ prevents breast tumour progression by targeting cancer cells and macrophages. *Cell*

- Death Dis.* 2018;9(6):678. doi:10.1038/s41419-018-0717-4
13. Akhiani AA, Hallner A, Kiffin R, Aydin E, Werlenius O, Aurelius J, Martner A, Thorén FB, Hellstrand K. Idelalisib rescues natural killer cells from monocyte-induced immunosuppression by inhibiting NOX2-derived reactive oxygen species. *Cancer Immunol Res.* 2020;8(12):1532-1541. doi:10.1158/2326-6066.CIR-20-0055
 14. Gopal AK, Kahl BS, de Vos S, et al. PI3K6 inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med.* 2014;370(11):1008-1018. doi:10.1056/NEJMoa1314583
 15. Zydelig. Prescribing information. Gilead Sciences Inc; 2014. Accessed July 11, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf
 16. Copiktra. Prescribing information. Verastem Inc; 2018. Accessed July 11, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf
 17. Flinn IW, Miller CB, Ardeshta KM, et al. DYNAMO: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. *J Clin Oncol.* 2019;37(11):912-922. Published correction appears in *J Clin Oncol.* 2019;37(11):912-922. doi:10.1200/JCO.18.00915
 18. Aliqopa. Prescribing information. Bayer HealthCare Pharmaceuticals Inc; 2017. Accessed July 11, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf
 19. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol.* 2017;35(35):3898-3905. Published correction appears in *J Clin Oncol.* 2018;36(5):521. doi:10.1200/JCO.2017.75.4648
 20. Ukoniq. Prescribing information. TG Therapeutics Inc; 2021. Accessed July 11, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213176s000lbl.pdf
 21. Zinzani PL, Samaniego F, Jurczak W, et al. Umbralisib, the once daily dual inhibitor of PI3K6 and casein kinase-1 ϵ demonstrates clinical activity in patients with relapsed or refractory indolent non-Hodgkin lymphoma: results from the phase 2 global Unity-NHL trial. Poster presented at: 62nd American Society of Hematology Annual Meeting and Exposition; December 7, 2020; virtual. Accessed July 12, 2021. Abstract 2934. <https://ash.confex.com/ash/2020/webprogram/Paper134851.html>
 22. Zelenez AD, Reddy N, Jagadeesh D, et al. Tolerability and durable responses of the PI3K6 inhibitor ME-401 administered on an intermittent schedule in relapsed/refractory(R/R) follicular lymphoma (FL) and other B-cell malignancies. *J Clin Oncol.* 2020;38(suppl 15):8016-8016. doi:10.1200/JCO.2020.38.15_suppl.8016
 23. NCCN. Clinical Practice Guidelines in Oncology. B-cell lymphomas, version 4.2021. Accessed July 10, 2021. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
 24. Matasar MJ, Capra M, Özcan M, et al. Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2021;22(5):678-689. Published correction appears in *Lancet Oncol.* 2021;22(6):e239. doi:10.1016/S1470-2045(21)00145-5
 25. Pagel JM, Reddy N, Jagadeesh D, et al. Efficacy and safety of the PI3K6 inhibitor zandelisib (ME-401) on an intermittent schedule (IS) in patients with relapsed/refractory follicular lymphoma (FL) with progression of disease within 24 months of first-line chemoimmunotherapy (POD24). *J Clin Oncol.* 2021;39(suppl 15):7550-7550. doi:10.1200/JCO.2021.39.15_suppl.7550
 26. de Rooij MF, Kuil A, Kater AP, Kersten MJ, Pals ST, Spaargaren M. Ibrutinib and idelalisib synergistically target BCR-controlled adhesion in MCL and CLL: a rationale for combination therapy. *Blood.* 2015;125(14):2306-2309. doi:10.1182/blood-2014-12-619163
 27. Soumerai JD, Jagadeesh D, Salman HS, et al. Initial results of the combination of PI3K6 inhibitor zandelisib (ME-401) and the BTK inhibitor zanubrutinib in patients (pts) with relapsed or refractory (R/R) B-cell malignancies. *J Clin Oncol.* 2021;39(suppl 15):7553-7553. doi:10.1200/JCO.2021.39.15_suppl.7553
 28. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med.* 2019;380(1):45-56. doi:10.1056/NEJMoa1804980
 29. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448. doi:10.1056/NEJMoa1709866
 30. Schuster SJ, Dickinson M, Dreyling M, et al. Efficacy and safety of tisagenlecleucel in adult patients with relapsed/refractory follicular lymphoma: primary analysis of the phase 2 ELARA trial. Abstract presented at: 2021 American Society of Clinical Oncology Annual Meeting; June 4-8, 2021; virtual. Accessed July 12, 2021. <https://meetinglibrary.asco.org/record/196296/abstract>
 31. FDA approves axicabtagene ciloleucel for large B-cell lymphoma. FDA. Updated October 25, 2017. Accessed July 12, 2021. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-large-b-cell-lymphoma>
 32. Jacobson CA, Chavez JC, Sehgal A, et al. Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24 months from initiation of first anti-CD20-containing chemoimmunotherapy (POD24). Abstract presented at: 2021 American Society of Clinical Oncology Annual Meeting. June 4-8, 2021; virtual. Accessed July 12, 2021. <https://meetinglibrary.asco.org/record/197216/abstract>



Brad S. Kahl, MD
Professor, Department of
Medicine, Oncology Division
Washington University School
of Medicine
St Louis, MO



John P. Leonard, MD
Senior Associate Dean for
Innovation and Initiatives
Weill Cornell Medicine
New York, NY

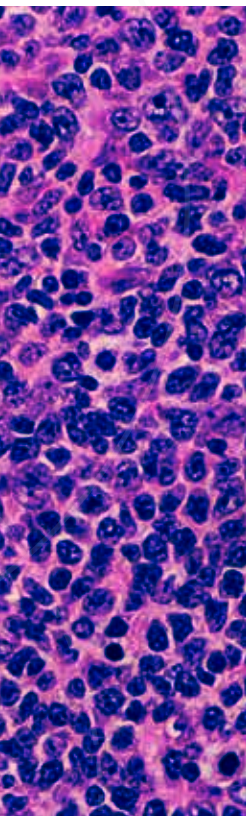
INTRODUCTION

Editors from OncLive® spoke with Brad S. Kahl, MD, and John P. Leonard, MD. These oncologists, who specialize in the treatment of hematologic malignancies and lymphoma, provided insight on the current management of follicular lymphoma and the emerging treatment landscape of PI3K inhibitors. Excerpts from their interviews* appear next.

*Interview transcripts are edited for clarity.

➤ TO SEE THE FULL VIDEO INTERVIEW, VISIT [ONCLIVE.COM](https://www.onclive.com).

Expert Perspectives in the Role of PI3K Inhibitors in the Treatment of Follicular Lymphoma



As it currently stands, what PI3K inhibitors are approved to treat patients with follicular lymphoma, and in what settings are these agents being incorporated in clinical practice?

KAHL: We have 3 PI3K inhibitors that are now available for use in recurrent follicular lymphoma. Idelalisib was the first one that was approved, then came copanlisib, duvelisib, and, more recently, umbralisib. Copanlisib is given intravenously; the other 3 are given orally. As a general rule, they are not used until third line and beyond. They all have similar efficacy profiles, with response rates in the 50% to 60% range and response durations within 10 to 12 months.

Idelalisib and duvelisib carry some risk for pneumonitis, colitis, and transaminitis, so that risk has limited their use. There's also risk for opportunistic infections. With the [intravenous] product, copanlisib, those risks seem to be lessened, although it does have an administration schedule that is considered less patient-friendly because patients need to come into the clinic weekly—3 of every 4 weeks—for their infusion. There can be some risk of hyperglycemia and hypertension around the days of the infusion; that sometimes needs to be managed in an expedited fashion.

Umbralisib was approved a few months ago. When you look at the data for umbralisib, it suggests that there might be less risk of colitis and pneumonitis. Its chemical structure might be different enough to reduce that risk, so there's a chance that this could become a preferred PI3K inhibitor. It'll be nice to see some real-world evidence now that the agent is approved to see if it really does turn out to be a safer PI3K inhibitor than the others. There is potential that it could be.

Do these agents differ in terms of their mechanism of action? Does that have any bearing over choosing one rather than the other, or does that come down to oral versus intravenous? Does that come down to physician preference? How is that being navigated in the clinic?

LEONARD: Most of [the PI3K inhibitors] inhibit the delta isoform of PI3K, which results in part of their activity. However, there are some differences with copanlisib, which has different selectivity. Its effects, as far as toxicities, can relate more to issues around hypertension and blood glucose abnormalities.

The other 3 oral PI3K inhibitors, based on their selectivity, have less of those

glucose and blood pressure issues and more in the way of gastroenterologic toxicity [diarrhea, colitis, and liver enzyme abnormalities], as well as cytopenias.

KAHL: The key for any PI3K inhibitor to have efficacy is to target the delta isoform of PI3K. That's how they ultimately will kill the lymphoma cell...by inhibiting the delta isoform. Now they all have differing effects in the other isoforms.

For example, duvelisib hits the gamma isoform more; this has pros and cons. It increases the risk for pneumonitis, colitis, and the opportunistic infection because of what it does to T cells. At the same time, duvelisib is probably the best of the 4 agents for killing T cells, so I think it's a drug that could get approval in T-cell lymphomas at some point and be a useful addition to that hard-to-treat group of diseases.

Copanlisib hits the alpha isoform a little, which might contribute to the hyperglycemia. Umbralisib seems to hit gamma, alpha, and beta less, and that may be why it has a slightly better safety profile than the others. These subtle differences in how they hit the non delta isoforms could result in some clinically meaningful differences between the agents.

The efficacy seems to be similar, and safety is a little different, so in terms of choosing between these agents, does it come down to safety profile? Does it come down to, maybe, physician comfort? How do you select between these agents?

KAHL: How to select between the agents is a good question because the differences between them are relatively small. To give some examples: Let's say you had a patient who had insurance that made oral agents challenging to afford. Maybe copanlisib is a better choice for that patient with less out-of-pocket costs. Maybe you have a patient that isn't adherent with taking pills. Copanlisib could be a better choice for

that patient, too; they come to clinic for their treatment, go home, and then come back a week later to do it again.

Regarding the 3 available agents that are oral—idelalisib, duvelisib, umbralisib—I think people have been using idelalisib for a number of years and duvelisib for a few. There's familiarity and comfort there. There probably isn't much experience with [umbralisib]. As I said earlier, if it does turn out that umbralisib has somewhat of a better safety profile than the others, it would become the agent of choice. I'm anxious to get some experience with umbralisib so I can see how it performs for myself. I have a lot of experience with idelalisib and duvelisib, and I know what to expect with those.

LEONARD: Regarding the oral PI3K inhibitors, they've not been directly compared head-to-head. The common themes that come up as far as their [adverse] effect profiles include [gastrointestinal] toxicity [nausea, diarrhea, liver enzymes], and cytopenias in many cases. As you look across the studies, there might be very subtle differences in these frequencies of toxicity, but it's hard to say that there are dramatic or clear differences between these agents and their toxicity profiles. Some could come up with arguments as to why one might be preferred over the other, but with respect to their use, I think they're more similar than they are different. A physician's comfort—what they're familiar with—as well as reimbursement issues will define some of these choices.

Do you foresee these agents staying where they are, or do you see them moving into earlier treatment lines—maybe combination strategies or even newer-generation PI3K inhibitors that might have more utility in the first- or second-line settings?

KAHL: For the 4 existing PI3K inhibitors, as they're currently constructed, it's hard for me to envision any of



Brad S. Kahl, MD

“The key for any PI3K inhibitor to have efficacy is to target the delta isoform of PI3K. That's how they ultimately will kill the lymphoma cell...by inhibiting the delta isoform.”



John P. Leonard, MD

“There are other PI3K inhibitors in development. There are some groups that are looking at changing the dosing schedule to perhaps minimize the toxicity.”

them moving into earlier lines of therapy. Their activity and toxicity profiles aren't quite as good as some of the other available agents that we can use in earlier lines.

For these PI3K inhibitors to move into earlier lines, 1 of 2 things would have to happen: Either a new PI3K inhibitor would need to come along that has better efficacy and less toxicity or some terrific combination use of the drug could come along that would allow it to move into earlier lines of therapy. I don't see either of those 2 things happening imminently.

LEONARD: There are other PI3K inhibitors in development. There are some groups that are looking at changing the dosing schedule to perhaps minimize the toxicity. That would not only minimize toxicity but also perhaps improve efficacy based on the fact that patients won't have to stop the drug as much. Since we've had at least 1 PI3K inhibitor for some time, I don't think they're going to be used significantly as part of upfront therapy. These toxicities can be more challenging in the

data that we have as part of upfront therapy, so they're going to be primarily focused in relapsed and refractory patients. What would be useful is knowing if there are patient populations that can benefit more than others, and [the question is]: “What are the best combinations of these drugs beyond the empiric combination, largely giving it with an anti-CD20 antibody?”

Is there anything in terms of research efforts or ongoing trials with PI3K inhibitors that you'd like to highlight?

KAHL: There are several combination studies under way that people should keep their eyes open for—combinations with anti-CD20s and BTK inhibitors. Those are worth watching to see how those data unfold. There are new PI3K inhibitors in development and undergoing testing right now, even in pivotal trials. Based on emerging data, we could have a fifth PI3K inhibitor available a year from now. ■

