

Umbralisib, a Dual PI3K δ /CK1 ϵ Inhibitor in Patients With Relapsed or Refractory Indolent Lymphoma

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PURPOSE Phosphatidylinositol-3-kinase (PI3K) inhibitors have shown activity in relapsed or refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). PI3K inhibitors have been hampered by poor long-term tolerability and toxicity, which interfere with continuous use. Umbralisib, a dual inhibitor of PI3K δ /casein kinase-1 ϵ , exhibits improved selectivity for PI3K δ compared with other PI3K inhibitors. This phase IIb trial was designed to evaluate the efficacy and safety of umbralisib in patients with R/R iNHL.

PATIENTS AND METHODS In this multicohort, open-label, phase IIb study, 208 patients with R/R marginal zone, follicular, or small lymphocytic lymphoma (MZL, FL, or SLL) unresponsive to prior treatments (≥ 1 MZL; ≥ 2 FL/SLL), including ≥ 1 anti-CD20–based therapy, were administered umbralisib 800 mg orally once daily until disease progression, unacceptable toxicity, or study withdrawal. Primary end point is overall response rate; secondary end points include time to response, duration of response, progression-free survival, and safety.

RESULTS The median follow-up is 27.7 months (efficacy) and 21.4 months (safety). The overall response rate was 47.1%, and tumor reduction occurred in 86.4% of patients. The median time to response was 2.7–4.6 months. The median duration of response was not reached for MZL, 11.1 months for FL, and 18.3 months for SLL. Median progression-free survival was not reached for MZL, 10.6 months for FL, and 20.9 months for SLL. At least one grade ≥ 3 treatment-emergent adverse event (TEAE) was reported in 53.4% of patients. TEAEs led to umbralisib discontinuation in 32 patients (15.4%). A total of 31 patients (14.9%) discontinued because of a treatment-related adverse event. Grade ≥ 3 TEAEs reported in $\geq 10\%$ of patients: neutropenia (11.5%) and diarrhea (10.1%). Increased ALT/AST (grade ≥ 3) occurred in 6.7%/7.2% of patients.

CONCLUSION Umbralisib achieved meaningful clinical activity in heavily pretreated patients with iNHL. The safety profile was manageable, with a relatively low incidence of immune-mediated toxicities and adverse event–related discontinuations.

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INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of mature B-cell neoplasms.¹⁻³ In the United States, NHL is the seventh most commonly diagnosed cancer and the most prevalent hematologic malignancy, with an estimated 77,240 new cases and 19,940 associated deaths in 2020.^{4,5} These lymphomas are generally classified as either indolent NHL (iNHL) or aggressive. Common iNHL subtypes include marginal zone, follicular, and small lymphocytic lymphoma (MZL, FL, and SLL).^{1,3} Management is usually tailored according to clinical presentation and patient characteristics. Although anti-CD20 therapy alone or

in combination is standard in untreated patients, little consensus exists for patients with relapsed disease.⁶⁻⁹ Several treatment options available for subsequent relapses include chemotherapy and targeted agents with or without anti-CD20–directed immunotherapy. However, successive relapses are associated with declining response rates, shorter remission times, and increased cumulative toxicity risk.¹⁰⁻¹³

The phosphatidylinositol-3-kinase (PI3K) inhibitor drug class has emerged for treatment of relapsed B-cell malignancies. A dysregulated PI3K signaling pathway may drive abnormal cellular programming that characterizes malignant B cells. In particular, the

ASSOCIATED CONTENT

See accompanying article on page 1671

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Convenient, safe, and effective new drugs can afford unprecedented opportunities to manage indolent lymphomas as a chronic disease, without the need for reliance on chemotherapy. Umbralisib is a unique, potent, oral, once-daily, dual inhibitor of phosphatidylinositol-3-kinase δ -isoform and casein kinase-1 ϵ , which has demonstrated efficacy and safety as a single agent and in combination, and may offer a novel nonchemotherapy treatment option for patients with relapsed or refractory disease.

Knowledge Generated

UNITY-NHL is a multicenter trial investigating umbralisib monotherapy in patients with relapsed or refractory marginal zone, follicular, and small lymphocytic lymphomas. These data reveal that umbralisib is associated with a manageable toxicity profile, leading to low rates of drug discontinuation and clinically meaningful efficacy in a heavily treated population.

Relevance

Available targeted treatment options for patients with relapsed or refractory disease are limited and associated with treatment-limiting toxicities. These data demonstrate that umbralisib may provide a novel targeted treatment option for previously treated patients with indolent lymphomas.

δ -isoform (PI3K δ), with expression restricted to cells of hematopoietic origin, is highly expressed in leukocytes and plays an essential role in B-cell development, survival, and function.¹⁴⁻¹⁶ Several PI3K inhibitors have shown efficacy as monotherapy in the treatment of relapsed or refractory (R/R) iNHL,^{11,17,18} with overall response rates (ORRs) ranging from 43.7% to 57%.^{11,17,18} Despite the activity of existing PI3K inhibitors, high discontinuation rates because of toxicities limit their use.^{11,17,18} Common serious adverse events (SAEs) include infections, hyperglycemia, transaminitis, diarrhea and/or colitis, and other immune-mediated toxicities (eg, pneumonitis).^{17,19-22} Although the mechanistic basis for the toxicities observed with first-generation PI3K inhibitors is not fully understood, the differential PI3K-isoform inhibition profiles of each agent²³ and other specific pharmacologic properties have been implicated.^{24,25} For example, hyperglycemia is associated with PI3K α inhibition,²⁶ whereas hematologic and immune-mediated toxicities are attributed to PI3K δ/γ inhibition.²⁵

Umbralisib is a novel dual inhibitor of PI3K δ and casein kinase-1 ϵ (CK1 ϵ), with no known clinically relevant drug-drug interactions.^{24,27-29} Compared with other approved PI3K inhibitors, umbralisib has a unique chemical structure, and preclinical analysis demonstrated potent PI3K δ isoform inhibition at clinically achievable concentrations. Umbralisib exhibits more than 1,500-fold greater selectivity (Kd) for PI3K δ over the α - and β -isoforms and approximately 225-times greater selectivity over the γ -isoform.²⁴ PI3K γ functions as a molecular switch between immune stimulation and suppression and, when inhibited, increases inflammation.³⁰ In preclinical models, the loss of PI3K δ alone was not sufficient to result in autoimmunity.^{31,32} However, combined loss of PI3K γ and PI3K δ in T cells results in severe autoimmunity and inflammation,³³ suggesting that the lack of PI3K γ inhibition by umbralisib may be advantageous.

Additionally, umbralisib is unique in that it inhibits CK1 ϵ .^{29,34} This enzyme plays a pivotal role in protein translation of oncogenes (ie, *MYC*, *BCL2*, and *CCND1*) and has been shown to regulate elements of the β -catenin/wingless-type MMTV integration site (WNT) signaling pathway, which may influence the immunomodulatory effects of T cells.^{29,34,35} Therefore, improved isoform selectivity by umbralisib plus inhibition of CK1 ϵ may account for some of the reduced immune-mediated toxicities observed.^{34,36}

In a phase I dose escalation study, umbralisib showed activity in patients with a number of R/R hematologic malignancies, and 800 mg umbralisib (orally once daily) was identified as the recommended phase II dose.²⁴ This phase IIb registration trial was designed to evaluate the efficacy and safety of daily, single-agent umbralisib 800 mg in patients with R/R iNHL.

PATIENTS AND METHODS

Trial Oversight

UNITY-NHL was conducted in accordance with applicable regulatory requirements, and the Protocol (online only) was approved by each study site's independent ethics committee or institutional review board. Research was conducted in accordance with updated Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. UNITY-NHL was designed and sponsored by TG Therapeutics (New York, NY). All patients provided written informed consent. All study investigators vouch for the accuracy and completeness of reported data and analyses and confirm the trial's adherence to the protocol (Data Supplement, online only).

Data were collected, and trial procedures were overseen by trial investigators. Data were verified by the sponsors, analyzed by sponsor statisticians, and interpreted by

TABLE 1. Summary of Demographics and Baseline Characteristics (Umbralisib Intent-to-Treat Population)

Parameter or Statistic	MZL (N = 69)	FL (N = 117)	SLL (N = 22)	Entire Population (N = 208)
Age, median (range), years	67 (34-88)	65 (29-87)	65 (49-86)	66 (29-88)
Sex, n (%)				
Male	33 (47.8)	72 (61.5)	13 (59.1)	118 (56.7)
Race, n (%)				
White	57 (82.6)	94 (80.3)	19 (86.4)	170 (81.7)
Black or African American	5 (7.2)	5 (4.3)	1 (4.5)	11 (5.3)
Asian	2 (2.9)	2 (1.7)	0 (0.0)	4 (1.9)
Others	5 (7.2)	16 (13.7)	2 (9.1)	23 (11.1)
ECOG performance status, n (%)				
0	38 (55.1)	65 (55.6)	14 (63.6)	117 (56.3)
1	29 (42.0)	48 (41.0)	8 (36.4)	85 (40.9)
2	2 (2.9)	4 (3.4)	0 (0.0)	6 (2.9)
Stage of disease at screening, n (%)				
I	4 (5.8)	14 (12.0)	1 (4.5)	19 (9.1)
II	7 (10.1)	17 (14.5)	1 (4.5)	25 (12.0)
III	12 (17.4)	36 (30.8)	6 (27.3)	54 (26.0)
IV	44 (63.8)	49 (41.9)	13 (59.1)	106 (51.0)
Unknown	2 (2.9)	1 (0.9)	1 (4.5)	4 (1.9)
Prior anti-CD20 R/R status, n (%)				
Relapsed	52 (75.4)	70 (59.8)	11 (50.0)	133 (63.9)
Refractory	15 (21.7)	37 (31.6)	7 (31.8)	59 (28.4)
Not applicable	2 (2.9)	10 (8.5)	4 (18.2)	16 (7.7)
No. of lines of prior systemic therapies				
Median (min-max)	2.0 (1-6)	3.0 (1-10)	2.0 (1-4)	2.0 (1-10)
1, n (%)	34 (49.3)	16 (13.7)	4 (18.2)	54 (26.0)
2, n (%)	17 (24.6)	33 (28.2)	8 (36.4)	58 (27.9)
3, n (%)	8 (11.6)	25 (21.4)	7 (31.8)	40 (19.2)
> 3, n (%)	10 (14.5)	43 (36.8)	3 (13.6)	56 (26.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; max, maximum; min, minimum; MZL, marginal zone lymphoma; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma.

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Trial Design and Patient Eligibility

UNITY-NHL was a phase IIb, open-label, multicohort analysis conducted at 120 sites in nine countries (Australia, Israel, Italy, Poland, Slovakia, South Korea, Spain, United Kingdom, and United States). Patients with R/R NHL were enrolled into one of the five cohorts: MZL, FL, SLL, mantle cell lymphoma, or diffuse large B-cell lymphoma. Study procedures and efficacy and safety results for MZL, FL, and SLL cohorts of the umbralisib monotherapy arm are reported here.

Eligible patients were ≥ 18 years of age and had histologically confirmed diagnosis of B-cell iNHL, subtyped based on WHO 2008 classification criteria (MZL splenic, nodal, or extranodal; FL grade 1, 2, or 3a; or SLL).¹ All patients had an Eastern Cooperative Oncology Group performance status score ≤ 2 . Patients with MZL were required to have had ≥ 1 prior lines of therapy, including ≥ 1 CD20-directed regimens, with failure to achieve at least partial response (PR) or with progressive disease after the most recent systemic regimen. Patients with FL or SLL were required to have relapsed or refractory disease after ≥ 2 prior lines of systemic therapy, including an anti-CD20 monoclonal antibody and an alkylating agent. All patients were required to have evidence of ≥ 1 of the following: bulky disease (> 5 cm), high lactate dehydrogenase, B symptoms, threatened organ function, splenomegaly,

TABLE 2. Summary of Prior Systemic Therapies (Intent-to-Treat Population)

Selected Systemic Therapy	MZL (N = 69)	FL (N = 117)	SLL (N = 22)
Most common systemic therapies by preferred name ($\geq 20\%$ of patients, overall)			
Rituximab	69 (100.0)	117 (100.0)	22 (100.0)
Cyclophosphamide	37 (53.6)	89 (76.1)	10 (45.5)
Vincristine	31 (44.9)	73 (62.4)	8 (36.4)
Prednisone	21 (30.4)	62 (53.0)	7 (31.8)
Bendamustine	22 (31.9)	66 (56.4)	13 (59.1)
Doxorubicin	15 (21.7)	60 (51.3)	3 (13.6)
Prior radiation therapy	6 (8.7)	11 (9.4)	0 (0.0)
Selected prior anticancer systemic therapies			
Anti-CD20 therapies	69 (100.0)	117 (100.0)	22 (100.0)
Anti-CD20 monotherapy only	15 (21.7)	0 (0.0)	2 (9.1)
Anti-CD20–based chemo-immunotherapy	52 (75.4)	117 (100.0)	20 (90.9)
Lenalidomide (mono or combo)	4 (5.8)	18 (15.4)	0 (0.0)
Lenalidomide plus anti-CD20 antibody	3 (4.3)	14 (12.0)	0 (0.0)
BTK inhibitor	2 (2.9)	10 (8.5)	5 (22.7)
Alkylating agent	48 (69.6)	117 (100.0)	20 (90.9)

Abbreviations: BTK, bruton tyrosine kinase; FL, follicular lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma.

cytopenias because of lymphoma, or effusions. Prophylaxis for *Pneumocystis jirovecii* pneumonia and antiviral therapy were mandated within 7 days before random assignment, which could later be discontinued at investigator discretion. Key exclusion criteria included prior anticancer therapy or any investigational drug within 21 days of day 1 of cycle 1 and prior hematologic stem-cell transplant, either autologous (within 6 months of study entry) or allogeneic (at any time). Study site information and additional inclusion or exclusion criteria are described online in the Data Supplement.

During the 28-day screening period, patients were required to undergo a fluorodeoxyglucose positron emission tomography (PET) with contrast-enhanced computed tomography (CT) scan of chest, abdomen, and pelvis (and neck, if clinically warranted). Treatment consisted of umbralisib 800 mg once daily with food on a 28-day cycle until disease progression, unacceptable toxicity, or study withdrawal. Umbralisib (TG Therapeutics) was supplied as 200 mg tablets. All patients were evaluated for response by CT, PET-CT, or magnetic resonance imaging at the end of cycle 3 and within 14 days before day 1 of cycles 6, 9, and 12. After cycle 12, response assessments occurred every 6 cycles or as clinically indicated. Patients with fluorodeoxyglucose-avid disease at screening were required to undergo PET-CT to confirm complete response (CR).

End Points

The primary end point was ORR, defined as the percentage of patients achieving CR or PR. Response criteria were based on the Lugano classification.³⁷ Complete remission was defined as complete disappearance of all evidence of

disease and disease-related symptoms; PR was defined as regression of measurable disease ($\geq 50\%$ decrease in the sum of the products of the diameters [SPD] of the index lesions coupled with no increase in size of other lymph nodes, liver, or spleen) and no new disease sites. Secondary end points included duration of response (DOR, defined as the time from documentation of a response to treatment to first documentation of tumor progression or death because of any cause, whichever comes first), progression-free survival (PFS, defined as the time from study entry to first documentation of tumor progression or death because of any cause, whichever comes first), and CR rate. Time to response (TTR, interval from enrollment to first documentation of CR or PR) was included as a post hoc analysis. Outcomes were assessed by an independent review committee (IRC); this analysis was considered primary. Investigator assessments for study end points were recorded.

Safety assessments included evaluation of adverse events (AEs), SAEs, and laboratory assessments. AE descriptions and grading scales were reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Diagnosis of colitis was based on investigator discretion. A summary of scheduled efficacy and safety assessments is provided online (Data Supplement).

Statistical Analysis

With a minimum of 60 patients with MZL enrolled, using a one-sided test having a 2.5% false-positive error rate to assess the null hypothesis that the IRC-reviewed ORR is 25%, the trial would have 90% power against the

TABLE 3. Summary of Overall Response (Intent-to-Treat Population)

Parameter	MZL (N = 69)	FL (N = 117)	SLL (N = 22)
	IRC ^a	IRC ^a	IRC ^a
ORR (CR + PR)			
n (%)	34 (49.3)	53 (45.3)	11 (50.0)
95% CI	37.0 to 61.6	36.1 to 54.8	28.2 to 71.8
CR			
n (%)	11 (15.9)	6 (5.1)	1 (4.5)
95% CI	8.2 to 26.7	1.9 to 10.8	0.1–22.8
PR			
n (%)	23 (33.3)	47 (40.2)	10 (45.5)
95% CI	22.4 to 45.7	31.2 to 49.6	24.4 to 67.8
Stable disease			
n (%)	23 (33.3)	40 (34.2)	8 (36.4)
95% CI	22.4 to 45.7	25.7 to 43.5	17.2 to 59.3
DCR (CR + PR + stable disease)			
n (%)	57 (82.6)	93 (79.5)	19 (86.4)
95% CI	71.6 to 90.7	71.0 to 86.4	65.1 to 97.1
Progressive disease			
n (%)	7 (10.1)	22 (18.8)	0 (0.0)
95% CI	4.2 to 19.8	12.2 to 27.1	0.0 to 15.4
Not evaluable			
n (%)	5 (7.2)	2 (1.7)	3 (13.6)
95% CI	2.4 to 16.1	0.2 to 6.0	2.9 to 34.9

NOTE. 95% CI was exact using the Clopper-Pearson method based on the binomial distribution. Data cutoff: July 13, 2020.

Abbreviations: CR, complete response; DCR, disease control rate; FL, follicular lymphoma; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PR, partial response; SLL, small lymphocytic lymphoma.

^aIRC assessment was the primary analysis for ORR.

alternative hypothesis that the ORR is 45%. With a minimum of 100 patients with FL, using a one-sided test having a 2.5% false-positive error rate to assess the null hypothesis that the IRC-reviewed ORR is 35%, the trial would have 90% power against the alternative hypothesis that the ORR is 51.5%. With a minimum of 25 patients with SLL and two-sided confidence intervals of the ORR derived using the Clopper-Pearson exact method, the 95% CI would be 34.9 to 75.6 for 14 responses. Futility was assessed at pre-specified timepoints, and the study was permitted to continue to full enrollment.

Efficacy and safety analyses included all patients with MZL, FL, or SLL who received ≥ 1 dose of single-agent umbralisib. The primary end point (ORR) was estimated with 95% CI by the Clopper-Pearson method based on the binomial distribution. Secondary end points (DOR, PFS, and TTR) were summarized using the Kaplan-Meier method. Safety analyses were summarized descriptively. Continuous (nonsurvival-related) data were summarized using descriptive statistics, and frequencies and percentages were used to summarize categorical data. Other than

for certain partial dates, missing data were not imputed and were treated as missing. All analyses were performed using SAS Version 9.4 or higher.

RESULTS

From May 2017 through September 2018, a total of 208 patients with relapsed iNHL were enrolled and treated (MZL [N = 69], FL [N = 117], and SLL [N = 22]). The intent-to-treat (ITT) cutoff date for these data was July 13, 2020. [Table 1](#) summarizes baseline demographics and clinical characteristics for each cohort. Overall, the median age was 66 years (range, 29–88); 56.7% were male, and 81.7% were White. Of the 208 patients, 51.0% had stage IV disease; 28.4% were refractory to their last anti-CD20–based therapy. The median number of prior treatments was 2 (range, 1–10), with 46.2% of patients having received ≥ 3 prior therapies. A summary of key prior systemic therapies is shown in [Table 2](#). All patients had received prior rituximab; the majority had received anti-CD20–based chemotherapy (75.4%, 100%, and 90.9% of patients with MZL, FL, and SLL, respectively). Some patients had

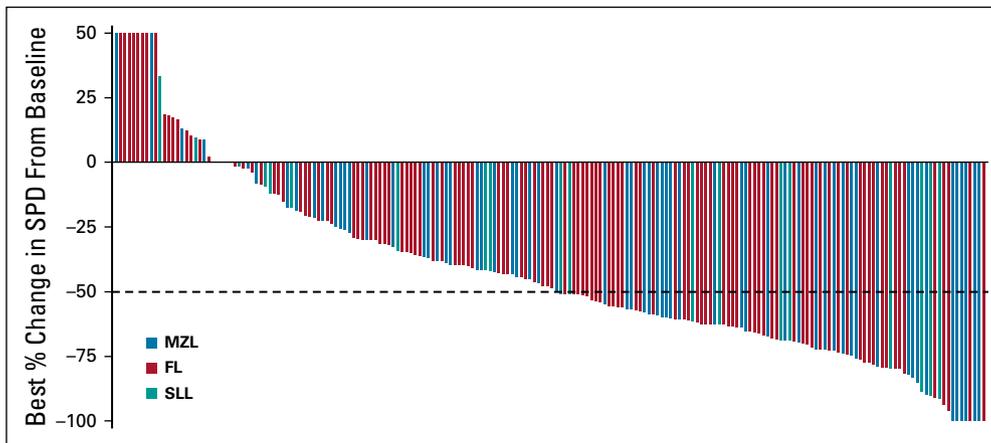


FIG 1. Response in index lesion size by independent review committee assessment (intent-to-treat population). The best percentage change in the sum of the product of the longest perpendicular dimensions (SPD) during umbralisib treatment, according to assessment by an independent review committee, is shown for patients with MZL, FL, or SLL. Data are shown only for those patients with at least one postbaseline radiographic assessment (N = 198). The majority of patients (86.4%) (with an available scan at data cutoff) showed a decrease in SPD (58 of 64 patients with MZL [90.6%], 96 of 115 patients with FL [83.5%], and 17 of 19 patients with SLL [89.5%]) as assessed by change from baseline. Data cutoff: July 24, 2020. FL, follicular lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; SPD, sum of products of perpendicular diameters.

received prior bruton tyrosine kinase inhibitor (2.9% MZL, 8.5% FL, and 22.7% SLL). Twelve patients in the FL cohort had undergone autologous stem cell transplant > 6 months before study entry. Additional baseline characteristics are available online (Data Supplement).

Efficacy

With a median follow-up of 27.7 months (MZL, 27.8 months [range, 22.4-36.1]; FL, 27.5 months [20.9-37.1]; SLL, 29.3 months [22.0-33.8]), the ORR was 47.1% for the ITT population, based on IRC assessment. For patients with MZL, FL, and SLL, respectively, ORRs were 49.3% (95% CI, 37.0 to 61.6), 45.3% (95% CI, 36.1 to 54.8), and 50.0% (95% CI, 28.2 to 71.8) (Table 3). IRC assessed ORR by subgroups available online (Data Supplement). ORR was consistent across the three subtypes of MZL. CR was seen in 11 (15.9%), 6 (5.1%), and 1 (4.5%) patient with MZL, FL, and SLL, respectively. PR and stable disease (SD) rates are shown in Table 3.

The waterfall plot depicting changes in tumor volume (data for patients with ≥ 1 postbaseline radiographic assessment [n = 198]) shows that 58 of 64 (90.6%), 96 of 115 (83.5%), and 17 of 19 (89.5%) patients with MZL, FL, and SLL experienced reduction of their disease following umbralisib, respectively (Fig 1).

The median DOR was not reached for patients with MZL (95% CI, 10.3 to not estimable) and was 11.1 months (95% CI, 8.3 to 15.6) for patients with FL and 18.3 months (95% CI, 2.4 to not estimable) for patients with SLL (Fig 2). The median TTR (95% CI) for patients with MZL, FL, and SLL was 2.8 months (2.7 to 2.9), 4.6 months (3.0 to 5.6), and 2.7 months (2.4 to 2.8), respectively.

The median PFS was not reached for patients with MZL (95% CI, 12.1 to not estimable) and was 10.6 months (95% CI, 7.2 to 13.7) for patients with FL and 20.9 months (95% CI, 7.4 to 24.1) for patients with SLL (Fig 2). At 2 years, 50.5%, 18.1%, and 31.3% of patients with MZL, FL, and SLL remained progression free, respectively (Data Supplement).

Safety

Safety data were collected through January 1, 2020, corresponding to a median follow-up of 21.4 months (range, 14.6-30.8). The median duration of exposure for all patients was 8.4 months (range, 0.2-27.0). Patients with MZL, FL, and SLL had median durations of exposure of 9.8 months (range, 0.2-27.0), 7.6 months (range, 1.0-26.5), and 10.9 months (range, 0.7-25.1), respectively. At data cutoff, 60 patients (26, 27, and 7 with MZL, FL, and SLL, respectively) remained on treatment. Treatment-emergent AEs (TEAEs) occurring in $\geq 10\%$ of patients are listed in Table 4. Overall, 207 of 208 patients (99.5%) experienced TEAEs, of which 53.4% had ≥ 1 grade ≥ 3 event. The most frequent TEAEs (any grade; $\geq 20\%$ of patients) were diarrhea (59.1%), nausea (39.4%), fatigue (30.8%), vomiting (23.6%), and cough (20.7%). The majority of diarrhea events were grade 1 and typically manageable via dose holds; 46 patients (37%) received supportive care, which includes nine patients (7.3%) that received steroids.

The only grade ≥ 3 AEs that occurred in $\geq 10\%$ of patients were neutropenia (11.5%) and diarrhea (10.1%; all grade 3). Three patients experiencing grade 3 diarrhea had colonoscopies, none of which showed signs of colitis. Other

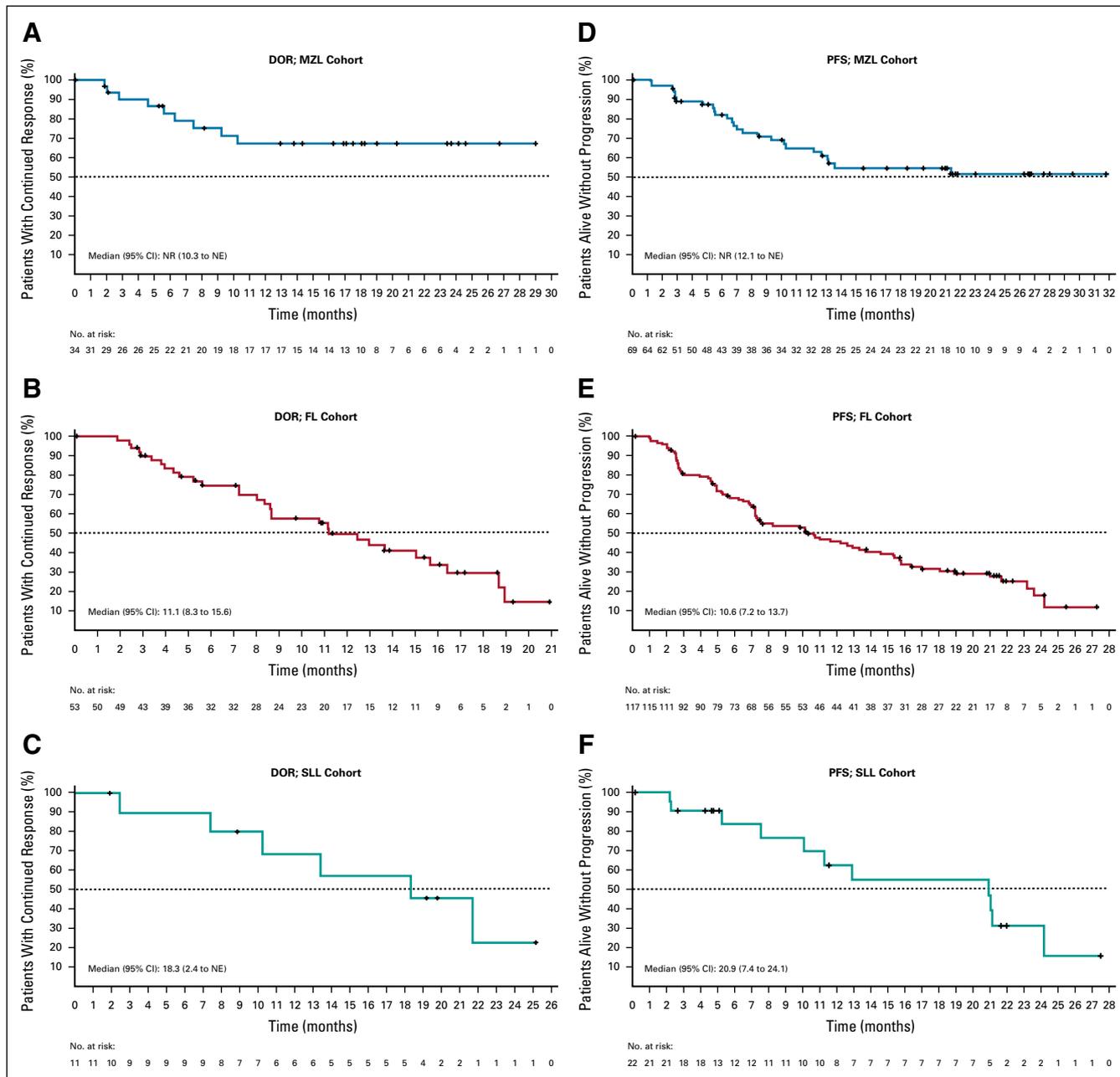


FIG 2. Kaplan-Meier curves for DOR and PFS by independent review committee assessment (ITT population). Kaplan-Meier curves are shown for the secondary end points of the DOR and PFS (respectively) among patients with MZL (A and D), FL (B and E), and SLL (C and F), who were treated with umbralisib (ITT population). The end points were assessed by an independent review committee. Data Cutoff: July 13, 2020. DOR, duration of response; FL, follicular lymphoma; ITT, intent-to-treat; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

grade 3 or 4 AEs of interest included opportunistic infections (7, 3.4%) and rash (4, 1.9%). Elevated levels of ALT and AST were observed in 20.2% (grade \geq 3 in 6.7%) and 18.8% (grade \geq 3 in 7.2%) of patients, respectively. Other AEs of interest included pneumonitis (1.4%; grade \geq 3 1.0%) and noninfectious colitis (1.9%; grade \geq 3 0.5%). Of the four patients experiencing noninfectious colitis, only one patient experienced overlapping diarrhea and received

a colonoscopy, which revealed normal gastrointestinal morphology. Colitis resolved in three of these four patients; they remained on umbralisib.

Overall, serious TEAEs were reported in 63 patients (30.3%), with grade \geq 3 serious TEAEs reported in 54 patients (26.0%). Serious TEAEs considered related to umbralisib were reported in 36 patients (17.3%). The most frequent serious TEAEs occurring in $>$ 1% of patients were

TABLE 4. TEAEs ($\geq 10\%$ Overall), System Organ Class, and Preferred Term (Intent-to-Treat Population)

System Organ Class ^a Preferred Term	Total (N = 208), n (%)	
	Any Grade	Grade ≥ 3
Any TEAE	207 (99.5)	111 (53.4)
Hematopoietic laboratory abnormalities		
Neutropenia	33 (15.9)	24 (11.5)
Any TEAE		
Diarrhea	123 (59.1)	21 (10.1)
Nausea	82 (39.4)	1 (0.5)
Fatigue	64 (30.8)	7 (3.4)
Vomiting	49 (23.6)	1 (0.5)
Cough	43 (20.7)	0 (0.0)
Decreased appetite	39 (18.8)	4 (1.9)
Dizziness	38 (18.3)	1 (0.5)
Headache	33 (15.9)	2 (1.0)
Upper respiratory tract infection	30 (14.4)	0 (0.0)
Insomnia	28 (13.5)	1 (0.5)
Edema peripheral	25 (12.0)	1 (0.5)
Pyrexia	24 (11.5)	0 (0.0)
Chemical laboratory abnormality		
ALT increased	42 (20.2)	14 (6.7)
AST increased	39 (18.8)	15 (7.2)
Blood creatinine increased	29 (13.9)	1 (0.5)

NOTE. Data cutoff: January 1, 2020.

Abbreviation: TEAE, treatment-emergent adverse event.

^aMedical Dictionary for Regulatory Activities (MedDRA).

diarrhea (3.4%), acute kidney injury (1.4%), anemia (1.4%), dehydration (1.4%), febrile neutropenia (1.4%), pneumonia (1.4%), sepsis (1.4%), and urinary tract infection (1.4%). One patient with SLL had a fatal myocardial infarction (unrelated to umbralisib); there were no other grade 5 AEs. TEAEs led to umbralisib discontinuation in 32 patients (15.4%); 31 of these (14.9%) discontinued because of a treatment-related AE. Twenty (20 of 32) patients continued to be followed for disease progression; nine of these patients went on to develop progressive disease, which occurred at an average of 7.2 months following umbralisib cessation. The most common grade ≥ 3 TEAEs leading to discontinuation of umbralisib (≥ 5 patients) were diarrhea (6, 2.9%) and ALT/AST increase (5, 2.4%). Additional information is available online (Data Supplement). TEAEs leading to dose reductions occurred in 24 (11.5%) patients; an umbralisib-related TEAE led to a dose reduction in 9.6% of patients.

DISCUSSION

Dysregulation of the PI3K pathway plays an important role in cancer biology.¹⁴⁻¹⁶ Although therapeutic targeting of the

pathway has produced clinical benefit for patients with iNHL, existing drugs in the class have limitations related to long-term tolerability.^{11,17,18} In this open-label, phase IIb study, oral once-daily umbralisib at a dose of 800 mg was effective in heavily pretreated patients with R/R iNHL. At a median follow-up of 27.7 months, primary study objective was met, with ORRs ranging from 45.3% to 50.0% for patients with MZL, FL, and SLL. The majority of patients (86.4%) experienced tumor size reduction with umbralisib. However, these results are similar to responses observed with first-generation PI3K inhibitors,^{11,17,18} making cross-trial comparisons limited. Notably, patients included in trials for some of the first-generation PI3K inhibitors were required to be double-refractory (to both rituximab and chemotherapy that included an alkylating agent).^{11,18}

Umbralisib was well-tolerated, exhibiting a safety profile similar across iNHL subtypes, which was consistent with previous phase I trials evaluating umbralisib alone or in combination therapy in patients with B-cell lymphomas.^{24,27,38} In UNITY-NHL, there was a low incidence of umbralisib-related discontinuations and no deaths because of TEAEs. These data contrast with pivotal trials of first-generation PI3K inhibitors, in which investigators reported high TEAE-related discontinuation rates (up to 52%) and treatment-related deaths (3.9%-8.8%) despite shorter median follow-up times in most studies (6, 9.7, and 32 months).^{11,17,18,39}

First-generation oral PI3K inhibitors are associated with fatal and/or serious immune-mediated toxicities, including diarrhea and/or colitis (idelalisib, 14% to 20% and duvelisib, 18%), pneumonitis (idelalisib, 4% and duvelisib, 5%), hepatotoxicity (idelalisib, 16% to 18% and duvelisib, 2% to 8%), and fatal and/or serious infections (idelalisib, 21% to 48% and duvelisib, 31%).^{21,22} The first-generation intravenous pan-PI3K inhibitor, copanlisib, is associated with fatal and/or SAEs, including hypertension 26%, hyperglycemia 41%, and infection 19%.²⁰ In UNITY-NHL, there was a relatively low incidence of infections and immune-mediated toxicities, including ALT/AST elevations. Although the precise mechanism for the toxicities observed with first-generation PI3K inhibitors is not yet known, attention has been focused on the individual agent's differential PI3K isoform inhibition profile²³ and its specific pharmacologic properties.^{24,25}

Given the long-term continuous dosing required for PI3K inhibitors in iNHL, identifying effective agents with safety profiles that minimize toxicity-related discontinuations is essential.¹⁹ Umbralisib is an effective and well-tolerated monotherapy treatment option for patients with R/R iNHL, serving as a platform for the development of novel combination regimens not enabled by currently available PI3K inhibitors. As of July 2020, more than 1,800 patients with B-cell malignancies have been treated with umbralisib, either alone or in combination with 16 other agents.^{24,27,38,40}

In UNITY-NHL, umbralisib showed meaningful clinical activity in patients with R/R iNHL consistent with that demonstrated by prior inhibitors of PI3K. However, the safety profile appears improved compared with first-

generation PI3K inhibitors, with manageable toxicities and a relatively low number of AE-related discontinuations. These results suggest that umbralisib has a favorable benefit-risk profile in this heavily pretreated population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Umbralisib, a Dual PI3K δ /CK1 ϵ Inhibitor in Patients With Relapsed or Refractory Indolent Lymphoma**

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