Integrated safety analysis of umbralisib, a dual PI3Kδ/CK1ε inhibitor, in relapsed/refractory lymphoid malignancies

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Abstract:
Phosphoinositide 3-kinase-delta (PI3Kδ) inhibitors are active in lymphoid malignancies, though associated toxicities can limit their use. Umbralisib is a dual inhibitor of PI3Kδ and casein kinase-1ε (CK1ε). This study analyzed integrated comprehensive toxicity data from 4 open-label, phase 1 and 2 studies that included 371 adult patients (median age, 67 years) with relapsed/refractory non-Hodgkin lymphoma (follicular lymphoma [n = 147]; marginal zone lymphoma [n = 82]; diffuse large B-cell lymphoma/mantle cell lymphoma [n = 74]; chronic lymphocytic leukemia [n = 43]; and other [n = 25]) who were treated with recommended phase 2 dose of umbralisib 800 mg or higher once daily. At data cutoff, median duration of umbralisib treatment was 5.9 months (range, 0.1-75.1), and 107 patients (28.8%) received umbralisib for (greater than or equal to) 12 months. Any-grade treatment-emergent adverse events (TEAEs) occurred in 366/371 patients (98.7%), with the most frequent being diarrhea (52.3%), nausea (41.5%), and fatigue (31.8%). Grade (greater than or equal to) 3 TEAEs occurred in 189/371 of patients (50.9%), including neutropenia (11.3%), diarrhea (7.3%), and increased aminotransferases (5.7%). Treatment-emergent serious AEs occurred in 95/371 patients (25.6%). AEs of special interest were limited and included pneumonia (29/371 [7.8%]), noninfectious colitis (9/371 [2.4%]), and pneumonitis (4/371 [1.1%]). AEs led to discontinuation of umbralisib in 51 patients (13.7%). Four patients (1.1%) died due to AEs, none of which were deemed related to umbralisib. No cumulative toxicities were reported. The favorable long-term tolerability profile and low rates of immune-mediated toxicities support the potential use of umbralisib for the benefit of a broad population of patients with lymphoid malignancies.

Conflict of interest: COI declared - see note

COI notes: M.S.D. has received grants from AbbVie, Ascentage Pharma, AstraZeneca, Genentech, MEI Pharma, Novartis, Pharmaceuticals, Surface Oncology, TG Therapeutics, and Verastem; and personal fees from AbbVie, Adaptive Biotechnologies, Ascentage Pharma, AstraZeneca, BeiGene, Celgene, Eli Lilly, Genentech, Gilead Sciences, Janssen, MEI Pharma, Merck, Novartis, Pharmaceuticals, Research to Practice, Syros Pharmaceuticals, TG Therapeutics, Verastem, and Zentalis. O.A.O. is an employee of and has an equity interest in TG Therapeutics. W.J. has received grant from TG therapeutics. F.S. has received personal fees from Astex Pharmaceuticals and ADC Therapeutics. T.S.F. has received research grants from TG Therapeutics, Millennium, Novartis, Kyowa, Portola, and Curis; and personal fees from BeiGene, Genentech, Adaptive Biotechnologies, AbbVie, Verastem, Kite, MorphoSys, AstraZeneca, Pharmacyscics, Sanofi, Seattle Genetics, Celgene, and Bristol-Myers Squibb. P.L.Z. has received personal fees from Verastem, Celltrion, Gilead, Janssen-Cilag, Bristol Myers Squibb, Servier, Sandoz, MSD, Immune Design, Celgene, Portola, Roche, EUSA Pharma, Kyowa Kirin, and Sanofi. M.R.P. has received institutional
research funding for conduct of this trial from TG Therapeutics and other support from Janssen, EMD Serono, Pfizer, Pharmacynamics, Bayer, and Genentech. N.G. has received research grants from Bristol Myers Squibb, TG Therapeutics, Pharmacynamics, Genentech, and Gilead; and personal fees from Bristol Myers Squibb, TG Therapeutics, Seattle Genetics, Janssen, Pharmacynamics, AbbVie, Gilead, AstraZeneca, Karyopharm, Genmab, Incyte, and Epizyme. B.D.C. has received institutional grants from TG Therapeutics, AbbVie, AstraZeneca, Roche-Genentech, Seattle Genetics, Bristol Myers Squibb, Trillium, and Epizyme; and personal fees from TG Therapeutics, AbbVie, BeïGene, MorphoSys, Karyopharm, and SymBio. E.D. has received research grants from TG Therapeutics and ADC Therapeutics, and personal fees from AstraZeneca. D.M.B. has received institutional grants from AbbVie, ArQule, Ascentage, AstraZeneca, BeïGene, DTRM, Genentech, Juno/Celgene/BMS, LOXO, MEI Pharma, Novaris, Pharmacynamics, and TG Therapeutics; and personal fees from AbbVie, Genentech, Pharmacynamics, Pfizer, TG Therapeutics, Verastem; and non-financial support from Pfizer and Teva. J.A.R. has received institutional grants from Sarah Cannon Research Institute, Eli Lilly, Tesaro, TG Therapeutics, Genentech, Celgene, Merck, Bristol Myers Squibb, Boston Biomedical Inc., AstraZeneca, Novocure, Calithera Biosciences, Novartis, Guardant Health, Acerta Pharma, Rhizen Pharmaceuticals, Takeda Pharmaceuticals, Onconova Therapeutics, Sanofi, Citi Biopharma, Eisai, and Janssen. J.N.A. has received grants from TG Therapeutics, Janssen, Celgene, and Genentech; and personal fees from AbbVie, Pharmacynamics, Janssen, AstraZeneca/Acerta, BeïGene, Genentech, Sunesis, and Ascentage Pharma. P.F.C. has received personal fees from TG Therapeutics. E.L.-M. has received other support from Roche, Janssen, Amgen, Takeda, Novartis, AbbVie, Gilead, and Astellas. J.M.B. has received personal fees from Bristol Myers Squibb, Roche, AbbVie, Seattle Genetics, Tempus Labs, Gilead, Bayer, AstraZeneca, Verastem, MorphoSys, Adaptive Biotechnologies, Epizyme, and Kura. L.A.L. has received personal fees from Kiteharma, TG Therapeutics, Celgene/BMS, BeïGene, PCCY/Janssen, AbbVie, AstraZeneca, Seattle Genetics, ADC Therapeutics, Epizyme, and Karyopharm. C.Y.C. has received grants from Roche, Celgene, and AbbVie; and personal fees from TG Therapeutics, Roche, Janssen, MSD, Gilead, Ascentage Pharma, Acerta, and Loxo Oncology; and nonfinancial support from Roche. G.F. has received personal fees from Celgene, Pharmacynamics, Gilead, and Amgen. J.C.C. has received personal fees from Kite/Gilead, Novartis, MorphoSys, Bayer, Epizyme, AstraZeneca, Genentech, Karyopharm, and Celgene/Juno. J.M.P. has received other support from Gilead, AstraZeneca, BeïGene, and Loxo Oncology. J.P.S. has received personal fees from AstraZeneca, Acerta, AbbVie, Pharmacynamics, Janssen, TG Therapeutics, MEI Pharmaceuticals, Verastem, and Genentech. Y.H. is an employee of and has an equity interest in TG Therapeutics. H.P.M is an employee of and has an equity interest in TG Therapeutics. P.S. is an employee of and has an equity interest in TG Therapeutics. M.S.W. is an employee of and has an equity interest in TG Therapeutics. I.W.F. has received institutional grants from AbbVie, AstraZeneca, BeïGene, Gilead Sciences, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Pharmacynamics, Roche, Seattle Genetics, Takeda, TG Therapeutics, Unum Therapeutics, and Verastem, Acerta Pharmaceuticals, Agios, ArQule, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Curis, F. Hoffmann-La Roche Ltd, Forma Therapeutics, Forty Seven, Genentech, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Karyopharm Therapeutics, Loxo, Merck, Novartis, Pfizer, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Teva, Trillium Therapeutics, and Triphase Research & Development Corp; and other institutional support from AbbVie, AstraZeneca, BeïGene, Curio Science, Great Point Partners, Iksa Therapeutics, Gilead Sciences, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Nurix Therapeutics, Pharmacynamics, Roche, Seattle Genetics, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, and Yingli Pharmaceuticals. The remaining authors declare no competing financial interests.

Preprint server: No;

Author contributions and disclosures: M.S.D., O.A.O, M.R.P., R.A., R.P., J.E., H.P.M., P.S., and M.S.W. designed protocol; O.A.O, W.J., P.L.Z, M.R.P., N.G., B.D.C, E.D., J.A.R., J.N.A., T.F, P.F.C., E.L., J.M.B., R.A., R.P., L.A.L., C.Y.C, G.F., J.E., J.C.C., J.M.P., P.S., and I.W.F., acquired data; M.S.D., O.A.O, M.R.P., J.A.R, R.A., R.P., G.F., J.M.P, H.P.M., and P.S. supervised the study; M.S.D., O.A.O, M.R.P, N.G., R.A., R.P., Y.H., H.P.M., P.S., and M.S.W. performed statistical analyses and/or provided input on the analysis and data interpretation; and all authors had access to the study data, critically reviewed or edited the manuscript, and approved the final version of the manuscript for submission.

Non-author contributions and disclosures: Yes; Luminology Scientific Communications (Linda M. Ritter, PhD, Scientific Director; Marina P. Gehring, PhD, Medical Writer; Suryanshi Nayyar, PharmD, Medical Fellow) for editorial assistance in the preparation of the manuscript (funded by TG Therapeutics, Inc). This study was supported by research funding from TG Therapeutics, Inc.

Agreement to Share Publication-Related Data and Data Sharing Statement: Please contact Denton Freeman (denton.freeman@tgtxinc.com) to access protocols and any data that are not publicly accessible.

Clinical trial registration information (if any): NCT01767766
https://clinicaltrials.gov/ct2/show/NCT01767766 NCT03207256
https://clinicaltrials.gov/ct2/show/NCT03207256 NCT03364231
https://clinicaltrials.gov/ct2/show/NCT03364231 NCT02793583
https://www.clinicaltrials.gov/ct2/show/NCT02793583
Integrated safety analysis of umbralisib, a dual PI3Kδ/CK1ε inhibitor, in relapsed/refractory lymphoid malignancies

Short title: INTEGRATED SAFETY ANALYSIS OF UMBRALISIB

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Presented in poster form at the 23rd European Hematology Association Congress, Stockholm, Sweden, 14-17 June 2018.
Key Points

- Umbralisib is a unique PI3Kδ/CK1ε inhibitor with a tolerable safety profile in relapsed/refractory lymphoid malignancies.
- Low rates of immune-mediated toxicities were observed with umbralisib.

**Primary Scientific Category:** Clinical Trials and Observations

**Secondary Scientific Category:** Lymphoid Neoplasia

**Subject Areas:** NEOPLASIA/Lymphomas and Other Lymphoproliferative: Signaling Therapies

NEOPLASIA/Newer Agents

**Key words:** non-Hodgkin lymphoma, umbralisib, PI3K inhibitors, immune-mediated toxicities
Abstract

Phosphoinositide 3-kinase-delta (PI3Kδ) inhibitors are active in lymphoid malignancies, though associated toxicities can limit their use. Umbralisib is a dual inhibitor of PI3Kδ and casein kinase-1ε (CK1ε). This study analyzed integrated comprehensive toxicity data from 4 open-label, phase 1 and 2 studies that included 371 adult patients (median age, 67 years) with relapsed/refractory non-Hodgkin lymphoma (follicular lymphoma [n = 147]; marginal zone lymphoma [n = 82]; diffuse large B-cell lymphoma/mantle cell lymphoma [n = 74]; chronic lymphocytic leukemia [n = 43]; and other [n = 25]) who were treated with recommended phase 2 dose of umbralisib 800 mg or higher once daily. At data cutoff, median duration of umbralisib treatment was 5.9 months (range, 0.1-75.1), and 107 patients (28.8%) received umbralisib for ≥12 months. Any-grade treatment-emergent adverse events (TEAEs) occurred in 366/371 patients (98.7%), with the most frequent being diarrhea (52.3%), nausea (41.5%), and fatigue (31.8%). Grade ≥3 TEAEs occurred in 189/371 of patients (50.9%), including neutropenia (11.3%), diarrhea (7.3%), and increased aminotransferases (5.7%). Treatment-emergent serious AEs occurred in 95/371 patients (25.6%). AEs of special interest were limited and included pneumonia (29/371 [7.8%]), noninfectious colitis (9/371 [2.4%]), and pneumonitis (4/371 [1.1%]). AEs led to discontinuation of umbralisib in 51 patients (13.7%). Four patients (1.1%) died due to AEs, none of which were deemed related to umbralisib. No cumulative toxicities were reported. The favorable long-term tolerability profile and low rates of immune-mediated toxicities support the potential use of umbralisib for the benefit of a broad population of patients with lymphoid malignancies.
Introduction

The phosphatidylinositol 3-kinase (PI3K) family of kinases is at the center of many signaling pathways, including the B-cell receptor (BCR) pathway. Dysregulated PI3K signaling drives abnormal cellular programming that characterizes several B-cell malignancies. The Class I PI3K comprises 4 distinct isoforms (α, β, δ, and γ) that control diverse and important cellular functions, with the δ and γ isoforms having a more restricted pattern of expression to cells of hematopoietic origin. PI3Kδ is highly expressed in leukocytes and plays an essential role in normal B-cell development, survival, and function, whereas PI3Kγ functions as a molecular switch between immune stimulation and suppression, and, when inhibited, increases inflammation. In patients with B-cell malignancies, PI3Kδ signaling is often constitutively active, making inhibition of this isoform an attractive target for non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) treatment.

The first 3 PI3K inhibitors, idelalisib, duvelisib, and copanlisib, have all demonstrated efficacy across indolent NHL subtypes, with overall response rates ranging from 43.7% to 57%. Idelalisib and duvelisib are also active in CLL, with overall response rates ranging from 56% to 85.5%. Use of these PI3K inhibitors is limited by high discontinuation rates due to a host of toxicities, particularly immune-mediated adverse events (AEs). Idelalisib and duvelisib carry black box warnings for infections (21%-48%), diarrhea or colitis (14%-20%), and pneumonitis (4% to 5%). Idelalisib also carries a black box warning for hepatotoxicity (16%-18%) and intestinal perforation (0.5%), whereas serious cutaneous reactions have been reported in about 5% of patients treated with duvelisib. Copanlisib has been associated with grade 3/4 hyperglycemia (41%), grade 3 hypertension (26%), grade 3/4 neutropenia (24%), serious and/or fatal infections (19%), noninfectious pneumonitis (5%), and grade 3/4 cutaneous reactions (2.8%/0.6%). These findings have been underscored in the pivotal clinical trials of idelalisib, duvelisib, and copanlisib, in which investigators reported grade ≥3 treatment-emergent AEs (TEAEs) in...
54% to 88% of patients, high TEAE-related discontinuation rates (up to 52%), and treatment-related deaths (3.9%-8.8%) despite short median follow-up times in most studies (6-32 months). Although the mechanistic basis for the toxicities observed with these PI3K inhibitors is not fully understood, simultaneous inhibition of PI3Kδ and PI3Kγ may contribute to hematologic and immune-mediated toxicities. Variations in the PI3K-isoform inhibition profile of each agent may explain, in part, the differences observed in incidence and severity of toxicities. It has been suggested that some toxicities may be isoform specific and not a class effect.

Umbralisib is a novel, oral, and selective dual inhibitor of PI3Kδ and casein kinase-1ε (CK1ε). Compared to other approved PI3K inhibitors, umbralisib has a unique chemical structure. Preclinical analysis has demonstrated potent PI3Kδ isoform inhibition at clinically achievable concentrations. Umbralisib exhibits more than 1500-fold greater selectivity (Kd) for PI3Kδ over the α and β isoforms and ≈225 times greater selectivity over the γ isoform. Furthermore, umbralisib uniquely inhibits CK1ε. This enzyme plays an important role in protein translation of oncogenes such as MYC, BCL2, and CCND1 (cyclin D1).

Umbralisib has a pharmacokinetic profile with a half-life that allows for once-daily dosing, with no known clinically relevant drug-drug interactions. As of January 2021, more than 2000 patients with hematologic malignancies have been treated with umbralisib monotherapy or in combination with other agents. As previously reported, umbralisib has demonstrated efficacy across various lymphoma subtypes. Fowler et al recently reported that with a median follow-up of 27.7 months, patients with relapsed or refractory (R/R) marginal zone lymphoma (MZL), follicular lymphoma (FL), or small lymphocytic lymphoma (SLL) achieved an overall response rate of 47.1% after treatment with umbralisib monotherapy. Tumor reduction was observed in 86.4%. Furthermore, Gribben et al reported that umbralisib in combination with ublituximab (U2) significantly improved progression-free survival compared with standard-of-care chemoimmunotherapy in patients with treatment-naive or R/R CLL.
In order to better describe the safety profile of umbralisib, we performed an integrated safety analysis of pooled data obtained from the 4 phase 1 and phase 2 monotherapy clinical trials with the longest follow-up.

Methods

Trial oversight

Trial protocols were approved by the institutional review board or ethics committee at each participating site, and the study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent. All trials were sponsored by TG Therapeutics. Site investigators collected the data for trials in which they were involved. All study investigators vouch for the accuracy and completeness of reported data and confirm the trial’s adherence to the protocol (available in Supplemental Materials). All authors had access to the integrated data and take responsibility for the completeness and accuracy of the analyses.

Study design and participants

Study data were obtained from a pooled analysis of adult patients (≥18 years of age) from 4 open-label, phase 1 and 2 clinical trials. All patients in the safety population were required to have been treated with ≥1 dose of umbralisib monotherapy (≥800 mg daily), with treatment administered until disease progression, unacceptable toxicity, or study withdrawal. The pivotal UNITY-NHL trial (UTX-TGR-205; NCT02793583) is being conducted in the United States, Australia, Israel, Italy, Poland, Slovakia, South Korea, Spain, and the United Kingdom, whereas the other trials were, or are, being conducted only in
the United States. A list of participating study sites and details of the studies are provided in the Supplemental Appendix (Table S1). The 4 studies include:

1. TGR-1202-101 (NCT01767766) was a phase 1 dose-escalation trial evaluating the safety and efficacy of umbralisib in patients with R/R, histologically confirmed, hematologic malignancies (B-cell NHL, CLL, peripheral T-cell lymphoma, and Hodgkin lymphoma). A 3 + 3 design was used to determine the maximum tolerated dose of oral umbralisib taken once daily during all cycles (1 cycle = 28 days), with doses ranging from 50 mg to 1800 mg daily (only patients treated with ≥800 mg from this study were included in the analysis).

2. Patients who completed TGR-1202-101 study were allowed to continue umbralisib in UTX-TGR-501 (NCT03207256), an ongoing phase 2, long-term, open-label extension trial evaluating the safety and efficacy of umbralisib 800 mg or 1200 mg daily in patients with B-cell NHL or CLL.

3. TGR-1202-202 (NCT03364231) is an ongoing phase 2 clinical trial evaluating the efficacy and safety of umbralisib in patients with R/R MZL or Waldenström macroglobulinemia.

4. UNITY-NHL (UTX-TGR-205) is an ongoing phase 2b multicohort trial evaluating the efficacy and safety of umbralisib in patients with previously treated R/R indolent NHL (FL, SLL, and MZL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL).

Umbralisib 800 mg was administered orally daily with food in 28-day cycles. Concomitant granulocyte colony–stimulating factor support was allowed, except in the TGR-1202-101 study, in which initiation or escalation of cytokine therapy was disallowed during the first month of study treatment for dose limiting toxicity-evaluable patients. Patients were required to start prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) and antiviral therapy within 7 days prior to cycle 1/day 1, with the exception of the TGR-1202-101 and UTX-TGR-501 studies, in which prophylaxis was at investigator discretion.
Key eligibility criteria were similar for all 4 trials. Patients were required to have a diagnosis of R/R NHL or CLL and to have received ≥1 or ≥2 prior treatment regimens. In these trials, refractory was defined as progression during therapy or within 6 months of completing immediate prior therapy. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) status score of ≤2. Key exclusion criteria included major surgery, chemotherapy, or immunotherapy within the past 21 days; evidence of hepatitis B or C virus or known HIV infection; prior autologous hematologic stem cell transplant within 3 months (TGR-1202-101 and UTX-TGR-501) or 6 months (TGR-1202-202 and UTX-TGR-205) of study entry; or prior allogeneic hematologic stem cell transplant within 12 months (TGR-1202-101 and UTX-TGR-501) or any allogeneic hematologic stem cell transplant (TGR-1202-202 and UTX-TGR-205). Full inclusion and exclusion criteria can be found in the Supplemental Materials (Protocols).

Safety assessments

Safety was assessed based on duration of exposure (months) to drug, number of treatment cycles, and dose modifications. Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Each AE was mapped to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®), version 22.1. MedDRA terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Laboratory parameters in each study included, at a minimum, hemoglobin; hematocrit; platelet, white blood cell, absolute neutrophil, and lymphocyte counts; and serum chemistry parameters (sodium, magnesium, potassium, calcium, aspartate aminotransferase [AST], alanine aminotransferase [ALT], serum creatinine, total bilirubin [TBL], and alkaline phosphatase). A serious adverse event was defined as any untoward medical occurrence that resulted in death, was immediately life threatening, required at least
a 24-hour inpatient hospitalization or prolongation of existing hospitalization, and/or resulted in persistent or significant disability/incapacity.

**Statistical analysis**

All analyses were based on the umbralisib safety population (all patients who received ≥1 dose ≥800 mg of single-agent umbralisib). The last nonmissing measurement prior to the first study drug administration was considered the baseline. Data were summarized using descriptive statistics, and results were reported both overall and by disease type, as appropriate. Due to the heterogeneity of assessment schedules across studies, no pooled analyses were performed for vital signs, physical examinations, or electrocardiograms. All analyses were conducted using SAS Version 9.4.

**Data sharing statement**

Please contact Denton Freeman (denton.freeman@tgtxinc.com) to access protocols and any data that are not publicly accessible.

**Results**

As of September 1, 2019, data from 371 patients were available for analysis (FL, n = 147, MZL, n = 82; DLBCL/MCL, n = 74; CLL/SLL, n = 43; other tumor types, n = 25) (Table 1). The median age was 67 years (range, 22-95); 56.3% were male, 82.7% were white, and 96.0% had an ECOG performance status of 0 or 1. Fifty-four patients (14.6%) had received prior Bruton tyrosine kinase (BTK) inhibitor therapy, and 44 patients (11.9%) had received prior lenalidomide (alone or in combination). Overall, the median number of prior systemic therapies was 2 (range, 1-14) and the median time to progression from most recent
therapy was 2.1 months (range, 0.3-447.4). Additionally, 145 of 371 patients (39.1%) were refractory to their most recent line of prior treatment.

Patients received umbralisib for a median duration of 5.9 months (range, 0.1-75.1), with 92 of 371 patients (24.8%) receiving treatment for 12 to <24 months and 15 of 371 patients (4.0%) receiving treatment for ≥24 months (Table 2). The incidence of TEAEs overall and by NHL subtype are summarized in Table 3. The most common TEAEs (of any grade) were diarrhea (52.3%), nausea (41.5%), and fatigue (31.8%). The incidence of TEAEs was similar among patients with ≤3 months, 3 to 6 months, 6 to 12 months, or 1 to 2 years of exposure. (Additional information available online; Table S2.) The most common key TEAEs for patients treated with umbralisib for greater than 1 year (n = 107) were diarrhea (60.7%), neutropenia (17.8%), AST increase (16.8%), and ALT increase (15.0%). Treatment-emergent AEs with median onset time of ≤1 month included constipation (median onset, 1.0 month; median duration, 1.1 months) and diarrhea (median onset, 1.0 month; median duration, 0.6 months); with median onset ≤2 months, TEAEs included infectious colitis (median onset, 1.4 months; median duration, 0.4 months) and transaminase elevation (median onset, 1.9 months; median duration, 1.1 months). Adverse reactions with median onset time of ≥3 months included noninfectious colitis (median onset, 6.0 months; median duration, 0.7 months) and pneumonia (median onset, 3.7 months; median duration, 0.5 months) (Table 4). Toxicities of interest over time are shown in Figure 1. The prevalence of increased AST/ALT peaked by month 3 of umbralisib administration and occurred only rarely after month 6.

Although the prevalence of diarrhea was high during the first month of administration of umbralisib (101 of 371 [=27%]), the vast majority of events were grade 1 (82 of 101). Thirty patients (8.1%) received steroids for the management of AEs that were potentially immune mediated, including diarrhea or colitis (4%), hepatic dysfunction (2%), rash (2%), and pneumonitis (0.5%).
Grade ≥3 TEAEs occurred in 189 of 371 patients (50.9%). (Table 5) The most common grade ≥3 TEAEs included neutropenia (11.3%), diarrhea (7.3%), and ALT or AST increase (5.7%). Adverse events of special interest (of any grade) included pneumonia (7.8%), noninfectious colitis (2.4%), and pneumonitis (1.1%). No opportunistic infections (eg, PJP pneumonia or cytomegalovirus reactivation) were reported.

Any-grade TEAEs deemed by the investigators to be related to umbralisib occurred in 84.6% of patients. (Table 5) The most common TEAEs of any severity related to umbralisib were diarrhea (165 of 371 [44.5%]), nausea (121 of 371 [32.6%]), and fatigue (78 of 371 [21.0%]). (Additional information available online; Table S3.)

Serious TEAEs were reported in 95 of 371 patients (25.6%) and included pneumonia (11 of 371 [3.0%]) and diarrhea (9 of 371 [2.4%]). Serious TEAEs deemed related to umbralisib occurred in 44 of 371 patients (11.9%) and included pneumonia (7 of 371 [1.9%]), diarrhea (7 of 371 [1.9%]), and sepsis (4 of 371 [1.1%]). (Additional information available online; Table S4.)

Any-grade TEAEs were reported in 320 of 325 patients (98.5%) who had received prior anti-CD20–based chemoimmunotherapy, 44 of 44 patients (100.0%) who had received prior lenalidomide, and 53 of 54 patients (98.1%) who had received a prior BTK inhibitor. Grade ≥3 TEAEs occurred in 168 of 325 patients (51.7%) who had received prior anti-CD20–based chemoimmunotherapy, 20 of 44 patients (45.5%) who had received prior lenalidomide, and 21 of 54 patients (38.9%) who had received a prior BTK inhibitor.

Serious TEAEs were reported in 84 of 325 patients (25.8%) who had received prior anti-CD20–based chemoimmunotherapy, 8 of 44 patients (18.2%) who had received prior lenalidomide, and 9 of 54 patients (16.7%) who had received a prior BTK inhibitor. (Additional information available online; Table S5.)
Adverse events that led to dose interruptions, reductions, and discontinuation occurred in 162 of 371 (43.7%), 49 of 371 (13.2%), and 55 of 371 (14.8%) patients, respectively. Overall, umbralisib treatment was discontinued by 280 patients (75.5%) (Figure 2). The most common reason for discontinuation was progressive disease (186 of 371 [50.1%]), followed by AEs (51 of 371 [13.7%]). The most common TEAEs leading to umbralisib discontinuation were diarrhea (14 of 371 [3.8%]) and ALT or AST increase (10 of 371 [2.7%]); all were considered related to umbralisib except for 1 event of diarrhea that was attributed by the investigator to infection. (Additional information available online; Table S6.) Death due to AEs was reported in 4 of 371 patients (1.1%), none of which were deemed related to umbralisib. Specific causes of death included pleural effusion, septic shock, myocardial infarction, and Legionella pneumophila pneumonia. An additional 22 of 371 patients (5.9%) died due to progressive disease, and 3 of 371 patients (0.8%) had other or unknown causes of death.

The most common laboratory abnormalities in patients on umbralisib treatment (reported by ≥20% of patients overall and ≥5% of patients with grade ≥3) were leukopenia (143 of 369 [38.8%], grade 3: 19 of 369 [5.1%]); neutropenia (135 of 368 [36.7%], grade 3: 33 of 368 [9.0%]); anemia (decreased hemoglobin) (112 of 369 [30.4%], grade 3: 20 of 369 [5.4%]); increased AST (111 of 369 [30.1%], grade 3: 22 of 369 [6.0%]); increased ALT (107 of 369 [29.0%], grade 3: 21 of 369 [5.7%]), and lymphopenia (89 of 369 [24.1%], grade 3: 37 of 369 [10.0%]). End-of-study grade 3 and 4 abnormalities were reported for anemia (4.0% and none), lymphopenia (13.7% and 3.1%), neutropenia (3.6% and 3.6%), leukopenia (5.3% and 0.4%), ALT (2.7% and none), and AST (1.8% and none), respectively. ALT or AST ≥3× upper limit of normal (ULN) was reported in 46 of 371 patients (12.4%), and concurrent ALT or AST ≥3× ULN and total bilirubin >2× ULN were reported in 2 patients (1 with MZL and 1 with DLBCL). (Additional information available online; Table S7.) No clinically meaningful differences were observed in hematologic or serum chemistry parameters from baseline to study end or in analyses by subgroups.
sex, age, race, geographic region, or prior lines of therapy (data not shown). (Additional information available online; Tables S8 and S9.)

Discussion

This integrated safety analysis of 371 patients with relapsed or refractory lymphoid malignancies demonstrates that single-agent umbralisib is associated with a favorable tolerability profile, including low rates of serious immune-mediated toxicities. The most common TEAEs attributed to umbralisib (diarrhea, nausea, and fatigue) were reported at similar rates, regardless of duration of exposure. With a median duration of exposure of 5.9 months and approximately 29% of patients on treatment for ≥12 months, our data suggest a favorable long-term safety profile, with no cumulative toxicity over time. Importantly, despite the relatively favorable safety profile we observed with umbralisib, it also appears to provide similar efficacy as other PI3K inhibitors.11-13,25,29

About one-third of patients treated with umbralisib experienced a grade ≥3 TEAE attributed to umbralisib at some point in their course of treatment. The most common of these were neutropenia (8.9%), diarrhea (6.7%), and increased aminotransferase levels (5.4%). These rates are substantially lower than reported for other PI3K inhibitors in similar patient populations. For example, in pivotal studies, 8% to 27% of patients treated with idelalisib experienced grade ≥3 neutropenia, diarrhea, or aminotransferase elevations,11 and the overall incidence of grade ≥3 TEAEs in patients treated with idelalisib, duvelisib, or copanlisib in pivotal studies was 54%, 88%, and 53%, respectively.11-13

In our analysis, 13.7% of patients discontinued treatment due to AEs, which appears to be favorable in light of the 20.0%, 25%, and 52.0% discontinuation rates due to AEs in clinical trials of idelalisib, copanlisib, and duvelisib, respectively.11,12,17 Furthermore, in a large retrospective analysis, 94% (58 of
of patients treated with idelalisib discontinued therapy at a median of 6 months, suggesting that
discontinuation rates with these drugs may be even higher in the real-world setting.\textsuperscript{32} Toxicities from
these PI3K inhibitors have also been associated with death in 3.9% to 8.8% of patients.\textsuperscript{11,13} In our
analysis, deaths due to TEAEs were limited to 4 patients (1.1%), with none deemed by the investigator to
be related to umbralisib.

The favorable safety profile of umbralisib is particularly relevant for patients with indolent NHL, many of
whom have a chronic history that often requires ongoing treatment for prolonged periods.\textsuperscript{33} For these
patients, an important goal of treatment is to achieve durable disease control and reduce future relapse
risk.\textsuperscript{34} As with other promising new therapies in this space such as bispecific antibodies and next
generation Bruton Tyrosine Kinase inhibitors\textsuperscript{35-37}, minimizing toxicity risk—which would lead to a low
rate of treatment discontinuations—will allow safe use in the long-term. We observed no difference in
the rate of AEs based on prior therapy. Although not a comparative study, our analysis suggests that
umbralisib may have a more favorable safety profile than other PI3K inhibitors, especially as it relates to
hepatic toxicity, colitis, and immune-mediated AEs. Additionally, fatal and/or serious pneumonitis is
known to occur in ≈4% and ≈5% of patients receiving idelalisib or duvelisib, respectively.\textsuperscript{18,19} Of the 4
cases (1.1%) of pneumonitis reported with umbralisib, all had confounding factors: 1 patient was
attributed to progression of disease; 1 patient had a chronic history of bronchitis, asthma, and previous
pneumonia; 1 patient had pleural effusion noted 6 months prior to first dose of umbralisib, with cultures
suggesting infection; and 1 patient had pneumonia 1 week prior to the diagnosis of pneumonitis. Serious
AEs of diarrhea or colitis occurred in 14% to 20% of patients receiving idelalisib and 18% of patients
receiving duvelisib.\textsuperscript{18,19} Although colitis was observed infrequently in patients treated with umbralisib
(noninfectious, 2.4%; infectious, <1%), a causal association between umbralisib and colitis cannot be
excluded.
Our pooled safety analysis is consistent with other ongoing studies of umbralisib. For example, a phase 2, multicenter trial demonstrated a favorable safety profile in patients with CLL (N = 51) intolerant to prior BTK inhibitor or PI3K inhibitor therapy. In that study, umbralisib was well tolerated, with only 6 (12%) patients discontinuing due to an AE. No fatal AEs occurred, and only 1 patient discontinued due to a recurrent AE, which the patient also had experienced with a prior kinase inhibitor. At a median follow-up of 23 months, 32% of patients remained on study. At the cutoff date, 58% of patients had been on umbralisib for a longer duration than their prior kinase inhibitor.

As noted, immune-mediated toxicities occur frequently in patients treated with idelalisib, duvelisib, or copanlisib. It has been suggested that these toxicities may be linked to a decrease in the percentage of regulatory T (Treg) cells relative to effector T cells. One hypothesis regarding the potentially lower rates of immune-mediated toxicities observed with umbralisib is that idelalisib and duvelisib simultaneously inhibit both PI3Kδ and -γ isoforms, whereas umbralisib selectively inhibits PI3Kδ, with little to no PI3Kγ inhibition. PI3Kγ functions as a molecular switch between immune stimulation and suppression, and when inhibited, increases inflammation. In preclinical models, the loss of PI3Kδ alone was less likely to result in severe autoimmunity. However, combined loss of PI3Kδ and PI3Kγ in T cells resulted in severe autoimmunity and inflammation, suggesting that the lack of PI3Kγ inhibition by umbralisib may be advantageous. An additional hypothesis relates to the selective dual inhibition of both PI3Kδ and CK1ε by umbralisib. These unique features may contribute to the lower incidence of immune-mediated toxicities, as the inhibition of CK1ε, which is known to regulate β-catenin and thus WNT signaling in part, may have an influence on regulatory T-cell numbers and function. Future studies will elucidate the relative contribution of each of these proposed mechanisms of action.

One important implication of our data demonstrating the favorable safety profile of umbralisib is that it suggests that umbralisib is an agent that may combine well with other novel agents approved and in development for B-cell malignancies. Indeed, umbralisib is currently being explored in combination with
16 other commonly used therapies,\textsuperscript{25,45-49} and the safety profile of umbralisib combination regimens is generally consistent with the known safety profile of each individual drug, with some patients receiving daily umbralisib for up to 5 years.\textsuperscript{45,50} Additional studies evaluating umbralisib in combination with other therapies in patients with R/R lymphoid malignancies are ongoing (ClinicalTrials.gov identifiers: NCT03801525; NCT04016805; NCT03671590). Moreover, the feasibility of utilizing umbralisib in combination with ublituximab (an anti-CD20 antibody) in treatment-naïve patients with CLL was recently demonstrated, which is particularly notable because prior PI3K inhibitors showed prohibitive toxicities in the frontline setting in CLL.\textsuperscript{30}

A limitation of this integrated analysis is that these data were generated from 4 open-label, nonrandomized, phase 1 and 2 trials with unique study designs and eligibility criteria. However, a benefit of this strategy is that pooled, long-term data increase the potential for identifying less-common events. While a significant number of patients have had greater than 6 months of follow-up, the extended time to onset for immune-mediated adverse events with PI3K inhibitors may preclude full assessment of these adverse events in the present analysis. Another significant limitation is that our study does not directly compare umbralisib with other PI3K inhibitors. Such prospective, randomized clinical trial data would be needed to definitively confirm differences among these drugs, though it is uncertain whether such trials will ever be run. As such, despite its limitations, our study represents a robust dataset to help inform the choice of PI3K inhibitor used in clinical practice.

In summary, this integrated safety analysis demonstrates that continuous treatment with umbralisib is generally well tolerated in patients with B-cell malignancies, with low discontinuation rates and without significant treatment-limiting toxicities.

\textbf{Acknowledgments}
The authors thank the patients, their families, and caregivers who participated in this study; the investigators and coordinators at the clinical sites; those who contributed to the design, implementation, and data analyses; and Luminous Scientific Communications (Marina P. Gehring, PhD, Medical Writer; Suryanshi Nayyar, PharmD, Medical Fellow) for editorial assistance in the preparation of the manuscript (funded by TG Therapeutics, Inc). Mathew S. Davids is a Scholar in Clinical Research from the Leukemia & Lymphoma Society. Owen A. O'Connor is an American Cancer Society Research Professor. Danielle M. Brander is a NCCN Guidelines panel member.

This study was supported by research funding from TG Therapeutics, Inc.

**Authorship**

Contribution: M.S.D., O.A.O, M.R.P., R.A., R.P., J.E., H.P.M., P.S., and M.S.W. designed protocol; O.A.O, W.J., P.L.Z, M.R.P., N.G., B.D.C, E.D., J.A.R., J.N.A., T.F, P.F.C., E.L, J.M.B., R.A., R.P., L.A.L., C.Y.C, G.F., J.E., J.C.C., J.M.P., P.S., and I.W.F., acquired data; M.S.D., O.A.O, M.R.P, J.A.R, R.A., R.P., G.F., J.M.P, H.P.M., and P.S. supervised the study; M.S.D., O.A.O, M.R.P, N.G., R.A., R.P., Y.H., H.P.M., P.S., and M.S.W. performed statistical analyses and/or provided input on the analysis and data interpretation; and all authors had access to the study data, critically reviewed or edited the manuscript, and approved the final version of the manuscript for submission.

Conflict-of-interest disclosure: M.S.D. has received grants from AbbVie, Ascentage Pharma, AstraZeneca, Genentech, MEI Pharma, Novartis, Pharmacymics, Surface Oncology, TG Therapeutics, and Verastem; and personal fees from AbbVie, Adaptive Biotechnologies, Ascentage Pharma, AstraZeneca, BeiGene, Celgene, Eli Lilly, Genentech, Gilead Sciences, Janssen, MEI Pharma, Merck, Novartis, Pharmacymics, Research to Practice, Syros Pharmaceuticals, TG Therapeutics, Verastem, and Zentalis. O.A.O. is an employee of and has an equity interest in TG Therapeutics. W.J. has received grant from TG therapeutics. F.S. has received personal fees from Astex Pharmaceuticals and ADC Therapeutics. T.S.F. has received research grants from TG Therapeutics, Millennium, Novartis, Kyowa, Portola, and Curis; and personal fees from BeiGene, Genentech, Adaptive Biotechnologies, AbbVie, Verastem, Kite, MorphoSys, AstraZeneca, Pharmacymics, Sanofi, Seattle Genetics, Celgene, and Bristol-Myers Squibb. P.L.Z. has received personal fees from Verastem, Celltrion, Gilead, Janssen-Cilag, Bristol Myers Squibb, Servier, Sandoz, MSD, Immune Design, Celgene, Portola, Roche, EUSA Pharma, Kyowa Kirin, and Sanofi. M.R.P. has received institutional research funding for conduct of this trial from TG Therapeutics and other support from Janssen, EMD Serono, Pfizer, Pharmacymics, Bayer, and Genentech. N.G. has received research grants from Bristol Myers Squibb, TG Therapeutics, Pharmacymics, Genentech, and Gilead; and personal fees from Bristol Myers Squibb, TG Therapeutics, Seattle Genetics, Janssen, Pharmacymics, AbbVie, Gilead, AstraZeneca, Karyopharm, Genmab, Incyte, and Epizyme. B.D.C. has received institutional grants from TG Therapeutics, AbbVie, AstraZeneca, Roche-Genentech, Seattle Genetics, Bristol Myers Squibb, Trillium, and Epizyme; and personal fees from TG Therapeutics, AbbVie, BeiGene, MorphoSys, Karyopharm, and Symbio. E.D. has received research grants from TG Therapeutics and ADC Therapeutics, and personal fees from AstraZeneca. D.M.B. has received institutional grants from AbbVie, ArQule, Ascentage, AstraZeneca, BeiGene, DTRM, Genentech, Juno/Celgene/BMS, LOXO, MEI Pharma,
Novaris, Pharmacyclics, and TG Therapeutics; and personal fees from AbbVie, Genentech, Pharmacyclics, Pfizer, TG Therapeutics, Verastem; and non-financial support from Pfizer and Teva. J.A.R. has received institutional grants from Sarah Cannon Research Institute, Eli Lilly, Tesaro, TG Therapeutics, Genentech, Celgene, Merck, Bristol Myers Squibb, Boston Biomedical inc., AstraZeneca, Novocure, Calithera Biosciences, Novartis, Guardant Health, Acerta Pharma, Rhizen Pharmaceuticals, Takeda Pharmaceuticals, Onconova Therapeutics, Sanofi, CTI Biopharma, Eisai, and Janssen. J.N.A. has received institutional grants from Sarah Cannon Research Institute, Eli Lilly, Tesaro, TG Therapeutics, Genentech, Celgene, Merck, Bristol Myers Squibb, Roche, AstraZeneca, Verastem, MorphoSys, Adaptive Biotechnologies, Epizyme, and Kura. L.A.L. has received institutional grants from Kite pharma, TG Therapeutics, Celgene/BMS, BeiGene, PCYC/Janssen, AbbVie, AstraZeneca, Seattle Genetics, ADC Therapeutics, Epizyme, and Karyopharm. C.Y.C. has received grants from Roche, Celgene, and AbbVie; and personal fees from Roche, Janssen, MSD, Gilead, Ascenta Pharma, Acerta, and Loxo Oncology; and nonfinancial support from Roche. G.F. has received institutional grants from Celgene, Pharmacyclics, Gilead, and Amgen. J.C.C. has received institutional grants from Kite/Gilead, Novartis, MorphoSys, Bayer, Epzyzme, AstraZeneca, Genentech, Karyopharm, and Celgene/Juno. J.M.P. has received other support from Gilead, AstraZeneca, BeiGene, and Loxo Oncology. J.P.S. has received personal fees from AstraZeneca, Acerta, AbbVie, Pharmacyclics, Janssen, TG Therapeutics, MEI Pharmaceuticals, Verastem, and Genentech. Y.H. is an employee of and has an equity interest in TG Therapeutics. H.P.M. is an employee of and has an equity interest in TG Therapeutics. P.S. is an employee of and has an equity interest in TG Therapeutics. M.S.W. is an employee of and has an equity interest in TG Therapeutics. I.W.F. has received institutional grants from AbbVie, AstraZeneca, BeiGene, Gilead Sciences, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Pharmacyclics, Roche, Seattle Genetics, Takeda, TG Therapeutics, Unum Therapeutics, and Verastem, Acerta Pharmaceuticals, Agios, ArQule, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Curis, F. Hoffmann-La Roche Ltd, Forma Therapeutics, Forty Seven, Genentech, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Karyopharm Therapeutics, Loxo, Merck, Novartis, Pfizer, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Teva, Trillium Therapeutics, and Triphase Research & Development Corp; and other institutional support from AbbVie, AstraZeneca, BeiGene, Curio Science, Great Point Partners, Iksuda Therapeutics, Gilead Sciences, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Nurix Therapeutics, Pharmacyclics, Roche, Seattle Genetics, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, and Yingli Pharmaceuticals. The remaining authors declare no competing financial interests.

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Table 1. Summary of demographics, baseline, and pretreatment disease characteristics (umbrelsilb safety population)

| Parameter/statistics | FL (N = 147) | MZL (N = 82) | DLBCL/MCL (N = 74) | CLL/SLL (N = 43) | Other (N = 25) | Total (N = 371) |
|----------------------|--------------|--------------|--------------------|------------------|---------------|----------------|
| Age, median y (range) | 65 (29-87)   | 68 (34-88)   | 72 (41-95)         | 64 (43-86)       | 62 (22-85)    | 67 (22-95)     |
| Female, n (%)        | 56 (38.1)    | 43 (52.4)    | 36 (48.6)          | 16 (37.2)        | 11 (44.0)     | 162 (43.7)     |
| Male, n (%)          | 91 (61.9)    | 39 (47.6)    | 38 (51.4)          | 27 (62.8)        | 14 (56.0)     | 209 (56.3)     |
| Race, n (%)          |              |              |                    |                  |               |                |
| White                | 120 (81.6)   | 67 (81.7)    | 68 (91.9)          | 35 (81.4)        | 17 (68.0)     | 307 (82.7)     |
| Non-White            | 13 (8.8)     | 10 (12.2)    | 4 (5.4)            | 7 (16.3)         | 6 (24.0)      | 40 (10.8)      |
| Unknown              | 1 (0.7)      | 0 (0)        | 0 (0)              | 0 (0)            | 2 (8.0)       | 3 (0.8)        |
| Not reported         | 13 (8.8)     | 5 (6.1)      | 2 (2.7)            | 1 (2.3)          | 0 (0)         | 21 (5.7)       |
| ECOG performance status, n (%) |            |              |                    |                  |               |                |
| 0                    | 80 (54.4)    | 42 (51.2)    | 29 (39.2)          | 22 (51.2)        | 4 (16.0)      | 177 (47.7)     |
| 1                    | 63 (42.9)    | 38 (46.3)    | 37 (50.0)          | 21 (48.8)        | 20 (80.0)     | 179 (48.2)     |
| 2                    | 4 (2.7)      | 2 (2.4)      | 8 (10.8)           | 0 (0)            | 1 (4.0)       | 15 (4.0)       |
| Time since initial diagnosis (mo) |              |              |                    |                  |               |                |
| Median (min, max)    | 69.6 (4.1, 374.9) | 70.7 (4.9, 340.7) | 43.4 (3.6, 446.5) | 63.8 (6.0, 184.3) | 65.2 (7.3, 193.3) | 63.8 (3.6, 446.5) |
| Stage of disease at screening or most recent, n (%)* |              |              |                    |                  |               |                |
| I                    | 14 (9.5)     | 5 (6.1)      | 2 (2.7)            | 1 (2.3)          | 0 (0)         | 22 (5.9)       |
| II                   | 18 (12.2)    | 7 (8.5)      | 4 (5.4)            | 1 (2.3)          | 0 (0)         | 30 (8.1)       |
| III                  | 43 (29.3)    | 13 (15.9)    | 18 (24.3)          | 6 (14.0)         | 0 (0)         | 80 (21.6)      |
| IV                   | 55 (37.4)    | 47 (57.3)    | 27 (36.5)          | 13 (30.2)        | 3 (12.0)      | 145 (39.1)     |
| Unknown              | 1 (0.7)      | 5 (6.1)      | 2 (2.7)            | 1 (2.3)          | 7 (28.0)      | 16 (4.3)       |
| Number of prior systemic therapies               |              |              |                    |                  |               |                |
| Median (min, max)    | 3 (1, 10)    | 2 (1, 7)     | 3 (1, 10)          | 2 (1, 8)         | 4 (1, 14)     | 2 (1, 14)      |
| Number of prior lines of therapy, n (%)           |              |              |                    |                  |               |                |
| <2                   | 21 (14.3)    | 38 (46.3)    | 14 (18.9)          | 11 (25.6)        | 3 (12.0)      | 87 (23.5)      |
| ≥2                   | 126 (85.7)   | 44 (53.7)    | 60 (81.1)          | 32 (74.4)        | 22 (88.0)     | 284 (76.5)     |
| Parameter/statistics                                      | FL (N = 147) | MZL (N = 82) | DLBCL/MCL (N = 74) | CLL/SLL (N = 43) | Other (N = 25) | Total (N = 371) |
|----------------------------------------------------------|--------------|--------------|--------------------|------------------|----------------|----------------|
| **Select prior systemic therapy, n (%)**                 |              |              |                    |                  |                |                |
| Anti-CD20 antibody                                       | 147 (100.0)  | 82 (100.0)   | 74 (100.0)         | 43 (100.0)       | 13 (52.0)      | 359 (96.8)     |
| Anti-CD20 monotherapy only                               | 3 (2.0)      | 18 (22.0)    | 0                  | 3 (7.0)          | 2 (8.0)        | 26 (7.0)       |
| Anti-CD20–based chemoimmunotherapy                       | 144 (98.0)   | 61 (74.4)    | 74 (100.0)         | 40 (93.0)        | 6 (24.0)       | 325 (87.6)     |
| Lenalidomide (monotherapy or in combination)            | 20 (13.6)    | 5 (6.1)      | 11 (14.9)          | 2 (4.7)          | 6 (24.0)       | 44 (11.9)      |
| Lenalidomide + anti-CD20 antibody                        | 16 (10.9)    | 4 (4.9)      | 8 (10.8)           | 1 (2.3)          | 0              | 29 (7.8)       |
| BTK inhibitor                                            | 12 (8.2)     | 5 (6.1)      | 22 (29.7)          | 6 (14.0)         | 9 (36.0)       | 54 (14.6)      |
| **Prior treatment relapsed/refractory status, n (%)**   |              |              |                    |                  |                |                |
| Relapsed                                                | 92 (62.6)    | 54 (65.9)    | 34 (45.9)          | 23 (53.5)        | 4 (16.0)       | 207 (55.8)     |
| Refractory†                                              | 55 (37.4)    | 20 (24.4)    | 40 (54.1)          | 19 (44.2)        | 11 (44.0)      | 145 (39.1)     |
| **Prior CD20 treatment relapsed/refractory status, n (%)** |              |              |                    |                  |                |                |
| Relapsed                                                | 80 (54.4)    | 52 (63.4)    | 29 (39.2)          | 11 (25.6)        | 0              | 172 (46.4)     |
| Refractory†                                              | 41 (27.9)    | 15 (18.3)    | 16 (21.6)          | 7 (16.3)         | 0              | 79 (21.3)      |
| Not applicable                                           | 10 (6.8)     | 2 (2.4)      | 8 (10.8)           | 4 (9.3)          | 0              | 24 (6.5)       |
| **Time since most recent progression, median (mo)**      | 2.0 (0.4, 235.8) | 1.8 (0.3, 176.1) | 1.7 (0.3, 447.4)  | 10.9 (0.6, 182.4) | 15.8 (0.3, 194.3) | 2.1 (0.3, 447.4) |

BTK, Bruton tyrosine kinase; max, maximum; min, minimum.

*Patients with NHL were staged by the Ann Arbor staging system; patients with CLL were staged by the Rai staging system.

†Refractory is defined as progression during or within 6 months of completing immediate prior therapy.
### Table 2. Extent of exposure to umbralisib

| Extent of exposure | FL (N = 147) | MZL (N = 82) | DLBCL/MCL (N = 74) | CLL/SLL (N = 43) | Other (N = 25) | Total (N = 371) |
|--------------------|--------------|--------------|--------------------|------------------|---------------|-----------------|
| **Duration (mo)**   |              |              |                    |                  |               |                 |
| Mean (SD)           | 9.8 (9.8)    | 10.3 (7.0)   | 4.7 (8.6)          | 14.7 (13.1)      | 3.9 (3.6)     | 9.1 (9.7)       |
| Median (min, max)   | 7.3 (0.1, 75.1) | 9.4 (0.2, 24.6) | 2.3 (0.1, 65.5)   | 12.5 (0.7, 55.2) | 2.3 (0.2, 14.0) | 5.9 (0.1, 75.1) |
| **Duration, n (%)** |              |              |                    |                  |               |                 |
| <3 mo               | 30 (20.4)    | 16 (19.5)    | 45 (60.8)          | 6 (14.0)         | 14 (56.0)     | 111 (29.9)      |
| 3 to <6 mo          | 32 (21.8)    | 16 (19.5)    | 15 (20.3)          | 6 (14.0)         | 7 (28.0)      | 76 (20.5)       |
| 6 to <12 mo         | 44 (29.9)    | 14 (17.1)    | 7 (9.5)            | 9 (20.9)         | 3 (12.0)      | 77 (20.8)       |
| 12 to <18 mo        | 23 (15.6)    | 19 (23.2)    | 4 (5.4)            | 9 (20.9)         | 1 (4.0)       | 56 (15.1)       |
| 18 to <24 mo        | 13 (8.8)     | 16 (19.5)    | 1 (1.4)            | 6 (14.0)         | 0             | 36 (9.7)        |
| ≥24 mo              | 5 (3.4)      | 1 (1.2)      | 2 (2.7)            | 7 (16.3)         | 0             | 15 (4.0)        |

Note: Duration of exposure (mo) = (date of last dose - date of first dose + 1)/30.4375. SD, standard deviation.
### Table 3. Summary of common TEAEs (≥10% total)

| System organ class/preferred term, n (%) | FL (N = 147) | MZL (N = 82) | DLBCL/MCL (N = 74) | CLL/SLL (N = 43) | Other (N = 25) | Total (N = 371) |
|----------------------------------------|--------------|--------------|-------------------|-----------------|--------------|----------------|
| Any TEAE                               | 144 (98.0)   | 82 (100.0)   | 72 (97.3)         | 43 (100.0)      | 25 (100.0)   | 366 (98.7)     |
| **Gastrointestinal disorders**          |              |              |                   |                 |              |                |
| Diarrhea                               | 83 (56.5)    | 50 (61.0)    | 27 (36.5)         | 24 (55.8)       | 10 (40.0)    | 194 (52.3)     |
| Nausea                                 | 62 (42.2)    | 28 (34.1)    | 33 (44.6)         | 23 (53.5)       | 8 (32.0)     | 154 (41.5)     |
| Vomiting                               | 35 (23.8)    | 16 (19.5)    | 19 (25.7)         | 15 (34.9)       | 1 (4.0)      | 86 (23.2)      |
| Constipation                           | 14 (9.5)     | 7 (8.5)      | 10 (13.5)         | 6 (14.0)        | 2 (8.0)      | 39 (10.5)      |
| Abdominal pain                         | 16 (10.9)    | 8 (9.8)      | 7 (9.5)           | 6 (14.0)        | 1 (4.0)      | 38 (10.2)      |
| **General disorders and administration site conditions** |              |              |                   |                 |              |                |
| Fatigue                                | 47 (32.0)    | 26 (31.7)    | 22 (29.7)         | 16 (37.2)       | 7 (28.0)     | 118 (31.8)     |
| Pyrexia                                | 14 (9.5)     | 10 (12.2)    | 10 (13.5)         | 8 (18.6)        | 5 (20.0)     | 47 (12.7)      |
| Edema peripheral                       | 14 (9.5)     | 13 (15.9)    | 7 (9.5)           | 3 (7.0)         | 2 (8.0)      | 39 (10.5)      |
| **Nervous system disorders**           |              |              |                   |                 |              |                |
| Dizziness                              | 27 (18.4)    | 13 (15.9)    | 9 (12.2)          | 12 (27.9)       | 4 (16.0)     | 65 (17.5)      |
| Headache                               | 21 (14.3)    | 19 (23.2)    | 8 (10.8)          | 8 (18.6)        | 4 (16.0)     | 60 (16.2)      |
| **Infections and infestations**        |              |              |                   |                 |              |                |
| Upper respiratory tract infection      | 21 (14.3)    | 11 (13.4)    | 5 (6.8)           | 8 (18.6)        | 1 (4.0)      | 46 (12.4)      |
| **Metabolism and nutrition disorders** |              |              |                   |                 |              |                |
| Decreased appetite                     | 25 (17.0)    | 18 (22.0)    | 9 (12.2)          | 7 (16.3)        | 6 (24.0)     | 65 (17.5)      |
| Hypokalemia                            | 18 (12.2)    | 7 (8.5)      | 8 (10.8)          | 2 (4.7)         | 4 (16.0)     | 39 (10.5)      |
| **Respiratory, thoracic, and mediastinal disorders** |              |              |                   |                 |              |                |
| Cough                                  | 25 (17.0)    | 18 (22.0)    | 7 (9.5)           | 13 (30.2)       | 9 (36.0)     | 72 (19.4)      |
| **Investigations**                     |              |              |                   |                 |              |                |
| ALT increased                          | 23 (15.6)    | 20 (24.4)    | 5 (6.8)           | 5 (11.6)        | 3 (12.0)     | 56 (15.1)      |
| AST increased                          | 18 (12.2)    | 23 (28.0)    | 6 (8.1)           | 5 (11.6)        | 3 (12.0)     | 55 (14.8)      |
| Blood creatinine increased             | 17 (11.6)    | 10 (12.2)    | 7 (9.5)           | 3 (7.0)         | 2 (8.0)      | 39 (10.5)      |
| **Blood and lymphatic system disorders** |              |              |                   |                 |              |                |
| Neutropenia                            | 19 (12.9)    | 11 (13.4)    | 8 (10.8)          | 12 (27.9)       | 3 (12.0)     | 53 (14.3)      |
| Anemia                                 | 13 (8.8)     | 7 (8.5)      | 10 (13.5)         | 7 (16.3)        | 4 (16.0)     | 41 (11.1)      |
| **Psychiatric disorders**              |              |              |                   |                 |              |                |
| Insomnia                               | 21 (14.3)    | 11 (13.4)    | 5 (6.8)           | 8 (18.6)        | 2 (8.0)      | 47 (12.7)      |
Note: TEAE sorting is done by decreasing frequency of system organ class and preferred term based on the total column.
### Table 4. Onset and duration of AEs

| Adverse event                              | Any grade (n) | Time to onset, mo Median (min, max) | Duration, mo Median (min, max) |
|--------------------------------------------|---------------|-------------------------------------|---------------------------------|
| **Blood and lymphatic system disorders**   |               |                                     |                                 |
| Anemia*                                    | 40            | 1.9 (0.0, 32.5)                     | 0.9 (0.0, 12.8)                 |
| Neutropenia (including febrile neutropenia)† | 53            | 1.9 (0.0, 16.6)                     | 0.5 (0.0, 11.7)                 |
| **Gastrointestinal disorders**             |               |                                     |                                 |
| Colitis (noninfectious)‡                   | 9             | 6.0 (2.8, 28.4)                     | 0.7 (0.2, 3.0)                  |
| Constipation                               | 39            | 1.0 (0.0, 37.7)                     | 1.1 (0.0, 54.2)                 |
| Diarrhea                                   | 194           | 1.0 (0.0, 22.8)                     | 0.6 (0.0, 53.7)                 |
| **Hepatobiliary disorders**                |               |                                     |                                 |
| Transaminase elevation§                    | 63            | 1.9 (0.0, 9.5)                      | 1.1 (0.0, 17.1)                 |
| **Infections and infestations**            |               |                                     |                                 |
| Colitis (infectious)‖                       | 3             | 1.4 (0.4, 1.6)                      | 0.4 (0.0, 0.9)                  |
| Pneumonia¶                                 | 29            | 3.7 (0.8, 25.2)                     | 0.5 (0.1, 18.0)                 |

Notes: Each occurrence of the same AE was counted as an independent AE. In case that 2 or more AEs overlapped or continued from one to another, they were combined as 1 AE in duration calculation. If the end date was missing (e.g., ongoing AE), it was imputed as the earliest of (safety data cutoff date, last treatment date + 30 days, end-of-study date, death date).

Grouped term for reactions with multiple preferred terms:

*Anemia, hemoglobin decreased.

Neutropenia, febrile neutropenia.

Colitis, colitis microscopic.

Alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hepatic enzyme increased.

*Clostridium difficile* colitis and enterocolitis viral.

Lower respiratory tract infection, pneumonia, pneumonia *Haemophilus*, pneumonia *Legionella*.  

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Table 5. Overview of TEAEs

|                       | FL (N = 147) | MZL (N = 82) | DLBCL/ MCL (N = 74) | CLL/SLL (N = 43) | Other (N = 25) | Total (N = 371) |
|-----------------------|--------------|--------------|---------------------|------------------|----------------|-----------------|
| Any TEAE, n (%)       | 144 (98.0)   | 82 (100.0)   | 72 (97.3)           | 43 (100.0)       | 25 (100.0)     | 366 (98.7)      |
| Related to umbralisib | 129 (87.8)   | 79 (96.3)    | 50 (67.6)           | 38 (88.4)        | 18 (72.0)      | 314 (84.6)      |
| Grade ≥3 TEAE, n (%)  | 71 (48.3)    | 47 (57.3)    | 38 (51.4)           | 26 (60.5)        | 7 (28.0)       | 189 (50.9)      |
| Related to umbralisib | 43 (29.3)    | 37 (45.1)    | 18 (24.3)           | 21 (48.8)        | 5 (20.0)       | 124 (33.4)      |
| TEAE outcome of death,* n (%) | 0 | 0 | 1 (1.4) | 2 (4.7) | 0 | 3 (0.8) |
| Serious TEAE, n (%)   | 34 (23.1)    | 27 (32.9)    | 17 (23.0)           | 13 (30.2)        | 4 (16.0)       | 95 (25.6)       |
| Related to umbralisib | 12 (8.2)     | 21 (25.6)    | 5 (6.8)             | 6 (14.0)         | 0              | 44 (11.9)       |
| Grade ≥3 serious TEAE, n (%) | 29 (19.7) | 24 (29.3) | 17 (23.0) | 10 (23.3) | 2 (8.0) | 82 (22.1) |
| Related to umbralisib | 12 (8.2)     | 19 (23.2)    | 5 (6.8)             | 5 (11.6)         | 0              | 41 (11.1)       |
| TEAE leading to umbralisib withdrawal, n (%) | 18 (12.2) | 18 (22.0) | 9 (12.2) | 7 (16.3) | 5 (20.0) | 57 (15.4) |
| Related to umbralisib | 16 (10.9)    | 15 (18.3)    | 6 (8.1)             | 6 (14.0)         | 3 (12.0)       | 46 (12.4)       |
| TEAE leading to dose reduction, n (%) | 18 (12.2) | 9 (11.0) | 4 (5.4) | 4 (9.3) | 4 (16.0) | 39 (10.5) |
| Related to umbralisib | 16 (10.9)    | 7 (8.5)      | 3 (4.1)             | 4 (9.3)          | 4 (16.0)       | 34 (9.2)        |
| TEAE leading to umbralisib interruption, n (%) | 67 (45.6) | 47 (57.3) | 25 (33.8) | 23 (53.5) | 6 (24.0) | 168 (45.3) |
| Related to umbralisib | 52 (35.4)    | 42 (51.2)    | 15 (20.3)           | 17 (39.5)        | 5 (20.0)       | 131 (35.3)      |

*No deaths were related to umbralisib.
†One additional death (pneumonia *Legionella*, in Study 1202-101) was recorded in the end-of-treatment summary case report form (CRF). AE outcome was not recorded as fatal in the AE CRF and is not included in this table.
FIGURE LEGENDS

Figure 1. Prevalence of select adverse events of clinical interest over time. Percentage of patients at risk for (A) ALT or AST elevation, (B) neutropenia, and (C) diarrhea by month and grade (1-4). N, number.
Figure 2. Patient disposition.
FIGURE 1

A. AST or ALT Elevation

B. Neutropenia

C. Diarrhea
FIGURE 2

Safety Population
N = 371

FL
N = 147
Discontinued
n=105
Reason
• Progressive disease: 74
• Adverse event: 18
• Investigator decision: 4
• Consent withdrawn: 3
• Other: 3
• Completed protocol-specified regimen: 1
• Lack of efficacy: 1
• Non-compliance with study: 1

MZL
N = 82
Discontinued
n=51
Reason
• Progressive disease: 23
• Adverse event: 18
• Investigator decision: 3
• Consent withdrawn: 5
• Other: 1

DLBCL/MCL
N = 74
Discontinued
n=69
Reason
• Progressive disease: 59
• Adverse event: 7
• Investigator decision: 3
• Consent withdrawn: 2
• Other: 3

CLL/SLL
N = 43
Discontinued
n=34
Reason
• Progressive disease: 19
• Adverse event: 3
• Investigator decision: 3
• Consent withdrawn: 3
• Other: 3
• Death: 3

Other
N = 25
Discontinued
n=21
Reason
• Progressive disease: 11
• Adverse event: 5
• Investigator decision: 1
• Consent withdrawn: 2
• Other: 2