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Regular Article

LYMPHOID NEOPLASIA

Phase 2 study of the safety and efficacy of umbralisib in patients with CLL who are intolerant to BTK or PI3Kδ inhibitor therapy

Anthony R. Mato,[1] Nilanjan Ghosh,[2] Stephen J. Schuster,[1] Nicole Lamanna,[3] John M. Pagel,[4] Ian W. Flinn,[5] Jacqueline C. Barrientos,[6] Kanti R. Rai,[6] James A. Reeves,[7] Bruce D. Cheson,[8] Paul M. Barr,[9] Suman Kambhampati,[10] Frederick Lansigan,[11] Jeffrey J. Pu,[12] Alan P. Skarbnik,[13] Lindsey Roeker,[14] Gustavo A. Fonseca,[15] Andrea Sitlinger,[16] Issam S. Hamadeh,[17] Colleen Dorsey,[14] Nicole LaRatta,[1] Hanna Weissbrot,[1] Eline T. Luning Prak,[1] Patricia Tsao,[1] Dana Paskalis,[18] Peter Sportelli,[18] Hari P. Miskin,[18] Michael S. Weiss,[18] Jakub Svoboda,[1] and Danielle M. Brander[16]

[1]University of Pennsylvania Cancer Center, Philadelphia, PA; [2]Atrium Health, Charlotte, NC; [3]New York-Presbyterian Columbia University Medical Center, New York, NY; [4]Swedish Cancer Institute, Seattle, WA; [5]Tennessee Oncology/Sarah Cannon Research Institute, Nashville, TN; [6]Northwell Health/CLL Research and Treatment Program, New Hyde Park, NY; [7]Florida Cancer Specialists/Sarah Cannon Research Institute, Fort Myers, FL; [8]Georgetown University Hospital Lombardi Comprehensive Cancer Center, Washington, DC; [9]Wilmot Cancer Institute, University of Rochester, Rochester, NY; [10]Sarah Cannon Research Institute at Research Medical Center, Kansas City, KS; [11]Dartmouth-Hitchcock Medical Center, Lebanon, NH; [12]Upstate Cancer Center, Syracuse, NY; [13]John Theurer Cancer Center, Hackensack, NJ; [14]Memorial Sloan Kettering Cancer Center, New York, NY; [15]Florida Cancer Specialists/Sarah Cannon Research Institute, St. Petersburg, FL; [16]Duke University Medical Center, Durham, NC; [17]Levine Cancer Institute, Gainesville, FL; and [18]TG Therapeutics, Inc., New York, NY

KEY POINTS

- **Umbralisib is safe and effective in this BTKi- and PI3Ki-intolerant CLL population.**

Intolerance is the most common reason for kinase inhibitor (KI) discontinuation in chronic lymphocytic leukemia (CLL). Umbralisib, a novel highly selective phosphatidylinositol 3-kinase δ (PI3Kδ)/CK1ε inhibitor, is active and well tolerated in CLL patients. In this phase 2 trial (NCT02742090), umbralisib was initiated at 800 mg/d in CLL patients requiring therapy, who were intolerant to prior BTK inhibitor (BTKi) or PI3K inhibitor (PI3Ki) therapy, until progression or toxicity. Primary end point was progression-free survival (PFS). Secondary end points included time to treatment failure and safety. DNA was genotyped for CYP3A4, CYP3A5, and CYP2D6 polymorphisms. Fifty-one patients were enrolled (44 BTKi intolerant and 7 PI3Kδi intolerant); median age was 70 years (range, 48-96), with a median of 2 prior lines of therapy (range, 1-7), 24% had del17p and/or *TP53* mutation, and 65% had unmutated *IGHV*. Most common adverse events (AEs) leading to prior KI discontinuation were rash (27%), arthralgia (18%), and atrial fibrillation (16%). Median PFS was 23.5 months (95% CI, 13.1–not estimable), with 58% of patients on umbralisib for a longer duration than prior KI. Most common (≥5%) grade ≥3 AEs on umbralisib (all causality) were neutropenia (18%), leukocytosis (14%), thrombocytopenia (12%), pneumonia (12%), and diarrhea (8%). Six patients (12%) discontinued umbralisib because of an AE. Eight patients (16%) had dose reductions and were successfully rechallenged. These are the first prospective data to confirm that switching from a BTKi or alternate PI3Ki to umbralisib in this BTKi- and PI3Ki–intolerant CLL population can result in durable well-tolerated responses. (*Blood*. 2021;137(20):2817-2826)

Introduction

The approvals of kinase inhibitors (KIs) in the United States, including ibrutinib, idelalisib, duvelisib, and acalabrutinib, with or without anti-CD20 antibodies, as well as the BCL2 inhibitor venetoclax, with or without anti-CD20 antibodies, have revolutionized the management of patients with chronic lymphocytic leukemia (CLL) in the frontline (ibrutinib with or without obinutuzumab, acalabrutinib with or without obinutuzumab, venetoclax + obinutuzumab) and relapsed/refractory (r/r) (ibrutinib, idelalisib + rituximab, duvelisib, acalabrutinib, venetoclax with or without rituximab) settings. In randomized clinical studies, these agents have consistently demonstrated favorable response rates, progression-free survival (PFS) advantages and now, in 5 studies, overall survival (OS) benefits.[1-14] Yet data from clinical trials also demonstrate that many CLL patients treated with KIs experience unique adverse events (AEs) and often discontinue KIs because of AEs, despite responsive disease.[4,10,15-18] In clinical practice, AEs, rather than CLL progression or Richter's transformation, are the most common reasons for discontinuation of ibrutinib and idelalisib; 50% to 63% of all discontinuations are due to AEs, with overall discontinuation rates between 41% and 47%.[19-21] Therefore, KI-intolerant CLL patients represent a sizable population in need of alternate treatment approaches.

All approved KIs (ibrutinib, acalabrutinib, duvelisib, and idelalisib) undergo extensive metabolism in the liver, mediated primarily

by CYP3A4 and CYP3A5.[22,23] It has been demonstrated that CYP2D6 also contributes to the metabolism of ibrutinib.[24] The genes coding for CYP3A4, CYP3A5, and CYP2D6 are highly polymorphic secondary to the presence of single nucleotide polymorphisms, and several variant alleles that alter enzymatic function have been identified (http://www.pharmvar.org). To our knowledge, there is a paucity of data linking the incidence of KI-related side effects to polymorphisms in *CYP3A4*, *CYP3A5*, and *CYP2D6*. Therefore, a hypothesis of intolerance may be secondary to undermetabolism of KIs, leading to increased drug exposure and off-target effects.

Umbralisib (TGR 1202) is a once-daily dual phosphatidylinositol 3-kinase δ (PI3Kδ)/CK1ε inhibitor with a unique chemical structure, improved selectivity for the δ isoform, and a favorable toxicity profile.[25] Umbralisib is unique in that it is not metabolized through the CYP metabolic pathway and, therefore, is an ideal agent to study in this patient population. An integrated safety analysis of 347 patients with lymphoid malignancies treated with umbralisib in the r/r setting demonstrated that the overall discontinuation rate due to AEs was <10%.[26]

The AE profiles associated with inhibitors of BTK or PI3K are distinct, with 2 large retrospective series demonstrating limited overlap in the AE profiles leading to discontinuation of ibrutinib or idelalisib.[19,20] Most importantly, "class switching" to an alternate KI (eg, BTK inhibitor [BTKi] to PI3K inhibitor [PI3Ki] or the opposite) in the setting of intolerance appeared to be an effective strategy to maintain response in these series.[20,21] For patients with prior intolerance to PI3Ki, greater specificity for the δ isoform and targeted inhibition of CK1ε,[27] which have been demonstrated to have a supportive effect on regulatory T cells,[28] may also allow for greater tolerance and/or ongoing response.[29] To prospectively test the strategy of switching to an alternate KI in the setting of intolerance, we conducted a phase 2 multicenter single-arm trial of umbralisib monotherapy in CLL patients who were intolerant to prior KI therapy and warranted further CLL-directed therapy (NCT02742090).

Methods

TGR-1202-201 is a phase 2 multicenter study conducted at 14 centers across the United States (clinicaltrials.gov: NCT02742090). This study was approved by the Institutional Review Board at each participating site, all patients provided informed consent, and the study was conducted according to Declaration of Helsinki and International Council for Harmonisation – Good Clinical Practice (ICH-GCP) guidances. Data cutoff for this report was 3 September 2019. Patients with CLL warranting therapy per the treating investigator's discretion were eligible for treatment with umbralisib if they were previously treated with a BTKi and/or PI3Kδi and discontinued treatment as a result of protocol-defined KI intolerance. This was based on guidance from the International Workshop on Chronic Lymphocytic Leukemia, which allows for more flexibility in treatment decision making in r/r settings, particularly when patients are sequencing between novel agents and it may be in the best interest of a patient not to require formal progression prior to starting a new line of therapy. Fluorescence in situ hybridization, IGHV mutational status, and a next-generation sequencing panel were performed centrally for all enrolled patients (Table 1).

Table 1. Patient baseline characteristics

Characteristic	Value
Evaluable for safety, n	51
Evaluable for PFS, n*	50
Measurable disease at study entry, n	36
Age, median (range), y	70 (48-96)
Time from CLL diagnosis to enrollment, median (range), mo	93 (11-285)
Males/females, n	28/23
ECOG PS score 0/1/2, n	23/24/4
Creatinine, median (range), mg/dL	0.94 (0.5-1.63)
Unmutated *IGHV*, %	65
Bulky disease	21 (41)
del(17p) and *TP53* mutated	5 (10)
del(17p) without *TP53* mutation	2 (4)
TP53 mutated without del(17p)	5 (10)
del(11q)	9 (18)
Evaluable for next-generation sequencing, n	46
Genetic mutations at baseline	
ATM	11 (24)
BTK	1 (2)
NOTCH1	4 (9)
PLCG2	2 (4)
SF3B1	7 (15)
TP53	10 (22)
Prior therapies, median (range)	2 (1-7)
Prior BTKi	44 (86)
Prior PI3Ki	7 (14)
Time on prior KI, median (range), mo	9 (0.7-38)
Time from discontinuation of prior KI to enrollment, median (range), mo	3 (1-12)
Required treatment within 6 mo of prior KI	39 (76)

Unless otherwise noted, data are n (%).

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

*One patient with confirmed Richter's transformation at enrollment (not eligible); excluded from PFS analysis.

Intolerance was standardized across all sites and defined in the protocol as unacceptable AEs attributable to KI therapy, where in the opinion of the investigator, treatment was discontinued, despite optimal supportive care, as a result of ≥1 of the following: ≥2 Common Terminology Criteria for Adverse Events grade ≥2 nonhematological toxicities, ≥1 grade ≥3 nonhematological toxicity, ≥1 grade 3 neutropenia with infection or fever, or any grade 4 hematological toxicities. Toxicities had to be persistent to the point that the investigator chose to discontinue therapy

because of the toxicity and not disease progression. All toxicities were required to resolve to grade ≤1 prior to umbralisib dosing. Patients could not have disease progression for ≥14 days following prior KI discontinuation to ensure that the primary reason for discontinuation was intolerance; additionally, prior KI had to have been discontinued within 12 months of initiating umbralisib. Patients were not excluded if they received additional lines of therapy between prior KI discontinuation and study enrollment.

Additional eligibility criteria included Eastern Cooperative Oncology Group Performance Status ≤2 and adequate bone marrow and organ function (absolute neutrophil count $\geq 1 \times 10^6$ per microliter, platelet count $\geq 3 \times 10^7$ per microliter, total bilirubin ≤1.5 times the upper limit of normal [ULN], alanine aminotransferase [ALT] and aspartate aminotransferase ≤2.5 times the ULN if no liver involvement or ≤5 times the ULN if known liver involvement, and creatinine clearance > 30 mL/min).

Genotyping

DNA was extracted from buccal swabs using the GenElute Mammalian DNA extraction kit (Sigma-Aldrich). A custom TaqMan PCR array plate (Applied Biosystems, Foster City, CA) containing lyophilized TaqMan SNP Genotyping Assays was used to genotype for CYP3A5*3, CYP3A5*6, CYP3A5*7, CYP3A4*1B, CYP3A4*22, CYP2D6*2, CYP2D6*3, CYP2D6*4, CYP2D6*6, CYP2D6*10, CYP2D6*17, CYP2D6*29, and CYP2D6*41.

CYP2D6 copy number assay

Copy number variations in the CYP2D6 gene were estimated by the TaqMan Copy Number Assay (Life Technologies, Foster City, CA). RNase-P served as the internal control, and primers targeting exon 9, intron 2, and intron 6 were selected for copy number analysis.

Phenotype derivation

The updated activity score method set forth by the Clinical Pharmacogenetics Implementation Consortium was used to derive CYP2D6 metabolizer phenotypes after accounting for CYP2D6 copy number variations.[30] CYP3A4 and CYP3A5 phenotypes were inferred based on the presence of loss-of-function (CYP3A4*22, CYP3A5*3, and CYP3A5*7) or gain-of-function (CYP3A4*1B) variants.

Umbralisib was self-administered orally, starting at 800 mg daily, on a continuous schedule until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, or death.

The primary study objective was to determine the PFS of umbralisib in patients who were intolerant to prior BTKi's and/or PI3Kδi's. PFS was defined as the interval from cycle 1, day 1 to the first documentation of definitive disease progression or death from any cause. Indications for therapy, response criteria, and disease progression were defined by the International Workshop on Chronic Lymphocytic Leukemia criteria.[31] Secondary end points were characterization of the genotype and metabolizer phenotype frequencies (for *CYP3A4*, *CYP3A5*, and *CYP2D6*), as well as evaluation of the safety profile, time to treatment failure, overall response rate (ORR), and duration of response in this KI-intolerant patient population.

The study aimed to enroll 50 patients to provide 82% power to detect a median PFS ≥12 months (vs 8-month median PFS representing the null hypothesis) using a 1-sided 1-sample log-rank test with a 5% type 1 error. Survival outcomes were estimated using the Kaplan-Meier method. The median survival time and probability of survival were estimated using 95% confidence intervals. All other analyses were descriptive. All statistical analyses were performed using SAS version 9.2.

Results

Baseline patient characteristics

A total of 51 patients were enrolled in the study between October 2016 and June 2018 and evaluable for safety. Fifty patients were evaluable for efficacy analyses; one patient with confirmed Richter's transformation at enrollment was not evaluable for efficacy. The median age at study entry was 70 years (range, 48-96), and median number of prior therapies was 2 (range, 1-7). Measurable lymphadenopathy and/or splenomegaly was not required for inclusion; 36 patients (71%) had measurable disease in lymph nodes and/or spleen on computed tomography imaging at the time of study entry. At enrollment, 24% of patients had deletion of chromosome 17p [del(17p)] and/or *TP53* mutation, 18% had deletion of chromosome 11q, and 65% had unmutated *IGHV*. Centralized genetic mutational testing used an Illumina TruSeq Custom Amplicon panel for polymerase chain reaction amplification and next-generation sequencing with the Illumina MiSeq System; genes were denoted as "mutated" when variant allele frequency within the sample was >15%. Mutational testing for ATM, BTK, NOTCH1, PLCG2, SF3B1, and TP53 was obtained in 46 of 51 patients. Mutations in BTK were identified in 2% (1/46) of patients, and mutations in PLCγ2 were identified in 4% (2/46) of patients. Baseline characteristics are described in Table 1.

Genotype data were available for 50 of 51 patients (98%; DNA collected from 1 patient was not sufficient for genotyping). The most prevalent variant alleles for *CYP3A4* and *CYP3A5* were *CYP3A4*1B* (6%) and *CYP3A5*3* (87%), respectively. With regard to *CYP2D6*, the most common variants observed in this study were *CYP2D6*2* (23%) and *CYP2D6*4* (29%). The genotype-inferred metabolizer phenotypes for each gene (*CYP3A4*, *CYP3A5*, and *CYP2D6*) are summarized in Table 2.

Intolerance to prior KI

Prior to study entry, 44 patients (86%) discontinued a BTKi (ibrutinib, n = 42; acalabrutinib, n = 2) and 7 patients (14%) discontinued a PI3Ki (all idelalisib) because of intolerance. Of the 7 PI3Ki-intolerant patients, 4 also had prior ibrutinib exposure (2 with ibrutinib intolerance); however, the reason for study enrollment was idelalisib intolerance. All enrolled patients met the protocol-specified definition of intolerance to a prior KI (Table 3). The 51 patients had experienced a total of 73 AEs leading to discontinuation of the prior KI (median of 1 AE per patient; range, 1-3). Among patients who discontinued a prior BTKi, the 5 most common AEs leading to discontinuation were rash (14 events), arthralgia (9 events), atrial fibrillation (8 events), bleeding (4 events), and fatigue (4 events). Among the 7 patients who discontinued a prior PI3Ki, the 2 most common AEs leading to discontinuation were colitis (3 events) and pneumonitis (2 events). The median time on prior KI therapy before discontinuation due to intolerance was 9 months (range, 0.7-38 months). The median time from discontinuation of prior KI to study enrollment was 3 months (range, 1-12 months). Seventy-six percent

Table 2. Frequencies of *CYP3A4*, *CYP3A5*, and *CYP2D6* genotypes and inferred phenotypes

Genotypes	Frequency, n	Inferred phenotype	Phenotype frequency, n (%)
CYP3A4			
*1/*22	3	IM	3 (6)
*1/*1	41	NM	41 (82)
*1/*1B	6	RM	6 (12)
CYP3A5			
*3/*3	38	PM	40 (80)
*3/*7	2		
*1/*3	9	IM	9 (18)
*1/*1	1	NM	1 (2)
CYP2D6			
*3/*4	1	PM	8 (16)
*4*4	6		
*5/*5	1		
*4/*10	1		
*4/*41	1	IM	14 (28)
*1/*4	6		
*2/*4	6		
(*1/*4)x3*	2	IM-NM	2 (4)
*1/*10	3	NM	24 (48)
*1/*29	1		
*1/*41	3		
*1/*1	5		
*1/*2	8		
*2/*2	4		
(*1/*41)x4*	1	RM	2 (4)
(*1/*2)x4*	1		

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer.

*Denotes number of *CYP2D6* alleles (copy number variation).

(39/51) of enrolled patients required CLL-directed therapy within 6 months of discontinuation of prior KI.

Safety profile of umbralisib

All AEs occurring in ≥10% of patients on umbralisib are described in Table 4 (all grade, all causality). Four patients (8%) had recurrence of an AE that led to prior KI intolerance (bruising and diarrhea, diarrhea, rash, nausea and fatigue; all had prior ibrutinib). In 3 of these instances, the recurrent AE was of lesser severity and did not require umbralisib dose modification or discontinuation. In 1 patient, umbralisib was discontinued because of recurrence of a grade 3 drug-associated rash that had previously led to ibrutinib discontinuation. No prior idelalisib-treated patients (n = 7) had a recurrence of idelalisib-associated AEs while on umbralisib.

All AEs of special interest during umbralisib treatment (colitis, pneumonitis, and transaminitis), regardless of causality, are included in Table 5. The median duration of grade 3 diarrhea was 4 days (range, 1-54 days). No grade 4 diarrhea was observed. Of note, only 1 case of colitis was reported on study in a patient with del(17p)$^+$ CLL after 6 weeks on treatment. This episode of colitis resolved following a 2-week treatment interruption, and the patient remains on a reduced dose of umbralisib (600 mg daily) in complete remission (25 months on therapy). Eight patients (16%) had dose reductions due to an AE (ALT elevation, arthralgia, arthritis, headache, mucosal inflammation, cytopenias, and diarrhea), allowing them to continue umbralisib therapy. Six patients (12%) discontinued umbralisib because of an AE

Table 3. AEs leading to discontinuation of prior KI

Intolerant AE on prior tyrosine KI	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	All grades (n)
Rash	6	8		14
Arthralgia	3	5	1	9
Atrial fibrillation	5	2	1	8
Bleeding	1	3		4
Fatigue	2	2		4
Anorexia/weight loss	3			3
Colitis	1	2		3
Congestive heart failure	1	1	1	3
Pneumonitis	2	1		3
Bruising	2			2
Diarrhea	1	1		2
Hypertension	2			2
Nausea	2			2
Cough	1			1
Dizziness	1			1
Edema	1			1
Gastrointestinal toxicity	1			1
Hyperuricemia		1		1
Infection		1		1
Malaise	1			1
Mental status change	1			1
Myalgia	1			1
Pericardial effusion			1	1
Respiratory failure			1	1
Tendonitis			1	1
Brain abscess		1		1
Transaminitis	1			1
TOTAL	39	28	6	73

Table 4. All-causality AEs occurring in >10% of all treated patients (N = 51)

AE	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%
Diarrhea	17	33	11	22	4	8	0	0
Nausea	20	39	7	14	0	0	0	0
Fatigue	4	8	9	18	0	0	0	0
Insomnia	11	22	2	4	0	0	0	0
Thrombocytopenia	4	8	3	6	4	8	2	4
Headache	9	18	3	6	0	0	0	0
Neutropenia	1	2	2	4	2	4	7	14
Dizziness	8	16	2	4	0	0	0	0
Peripheral edema	8	16	1	2	0	0	0	0
Cough	6	12	2	4	0	0	0	0
Rash	7	14	1	2	0	0	0	0
Rash, maculopapular	8	16	0	0	0	0	0	0
Anemia	1	2	4	8	2	4	0	
Arthralgia	5	10	2	4	0	0	0	0
Contusion	7	14	0	0	0	0	0	0
Decreased appetite	5	10	2	4	0	0	0	0
Leukocytosis	0	0	0	0	7	14	0	0
Myalgia	5	10	2	4	0	0	0	0
Pneumonia	0	0	1	2	6	12	0	0
Pyrexia	4	8	2	4	1	2	0	0
Upper respiratory tract infection	4	8	3	6	0	0	0	0
Vomiting	5	10	2	4	0	0	0	0
AST/ALT increase	2	4	2	4	3	6	0	0

AST, aspartate aminotransferase.

(pneumonitis in 2 cases; pancreatitis, pneumonia, dermatitis, and rash in 1 case each). No fatal AE was observed.

Outcomes on umbralisib and patient disposition

Figure 1 describes the disposition for all enrolled patients. With a median follow-up of 23 months (range, 14.7-34.6 months), 16 (32%) patients remain on study (Figure 1). The most common reason for discontinuation was disease progression, which occurred in 17 patients (Figure 1). The median PFS was estimated to be 23.5 months (95% confidence interval, 13.1–not estimable (Figure 2A). The estimated percentage of progression-free patients at 12 and 24 months was 72% and 46%, respectively. Importantly, at the cutoff date, 58% of patients had been on umbralisib for a longer duration than their prior KI (59% of prior BTK patients and 43% of prior PI3K patients). The median OS has not been reached (Figure 2B) at a median follow-up of 23 months (range, 14.7-34.6). Three deaths have been reported, all due to disease progression. Two deaths due to progression were reported within 3 months after discontinuing umbralisib; 1 was an ineligible patient found to have Richter's transformation within 4 weeks of treatment initiation and, in retrospect, likely had transformation at the time of enrollment. One patient died a year after subsequent treatment with venetoclax-based therapy.

The ORR to umbralisib among 48 evaluable patients was 44% (19/48 partial remission, 2/48 complete remissions). Thirty-four of 36 (94.4%) patients with measurable disease experienced any decrease in nodal size (supplemental Figure 1, available on the *Blood* Web site). Two patients did not have evaluable disease and were enrolled out of investigator concern for progression if they were to come off ibrutinib without an alternate therapy, based on prior history.

Table 5. AEs (all causality) of special interest across all treated patients (N = 51)

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	N	%	n	%	n	%
Colitis	0	0	1	2	0	0	0	0
Pneumonitis	1	2	1	2	0	0	0	0
Transaminitis	2	4	2	4	1	2	0	0

Discussion

We present the first trial demonstrating that patients intolerant to ibrutinib, acalabrutinib, or idelalisib can be managed safely and effectively utilizing a next-generation PI3Kδ-specific inhibitor. In this population defined by prior BTKi or PI3Ki intolerance requiring discontinuation, only 6 patients (12%) discontinued umbralisib as the result of an AE, and responses were durable (estimated median PFS, 23.5 months). Although the ORR is 44%, it is notable that additional patients with stable disease (many with low disease burden as a result of prior KI) likely derived clinical benefit with stable disease as best measured response. Although these data confirm observations from retrospective series that demonstrate minimal overlap in AE profiles for patients transitioning from a BTKi to a PI3Ki,[20,21] we also demonstrate that a small number of patients who discontinued idelalisib did not have recurrence of AEs leading to idelalisib discontinuation on umbralisib. Additionally, of the 4 (8%) patients who experienced recurrence of an AE that previously led to KI discontinuation, only 1 required drug discontinuation. At the time of data cutoff, 58% of patients had received umbralisib for a longer duration than their prior KI treatment. In this patient population hypothesized to be at high risk for AEs, umbralisib was well tolerated.

The genetic underpinnings of KI-related side effects are incompletely understood. To address this knowledge gap, we characterized the frequencies of various genotypes and metabolizer phenotypes for genes involved in the metabolism of these drugs. The *CYP3A5* poor metabolizer phenotype was prevalent in our patient population. We hypothesize that individuals with this genotype are exposed to higher plasma levels of ibrutinib, acalabrutinib, or idelalisib. Interestingly, the observed frequency of the *CYP2D6* poor metabolizer phenotype detected herein (16%), specifically the *CYP2D6*4* loss-of-function variant (https://cpicpgx.org/guidelines), was higher than expected (5-10%). This finding may suggest an association between CYP2D6 polymorphisms and the incidence of ibrutinib-related side effects. Larger studies are warranted to corroborate this association and uncover other genetic determinants of KI-related side effects.

Patients with CLL experience improved disease control and OS with targeted agents, including BTKi's and PI3K isoform inhibitors.[1-12] These successes have led to rapid approvals of KIs as monotherapy or in combinations for r/r (ibrutinib, idelalisib with or without rituximab, duvelisib, acalabrutinib) and previously untreated (ibrutinib with or without obinutuzumab, acalabrutinib with or without obinutuzumab) patients. Despite favorable efficacy, toxicity is the most common reason for KI discontinuation; it leads ~25% of patients initiating KIs outside of clinical trials to stop therapy.[19-21]

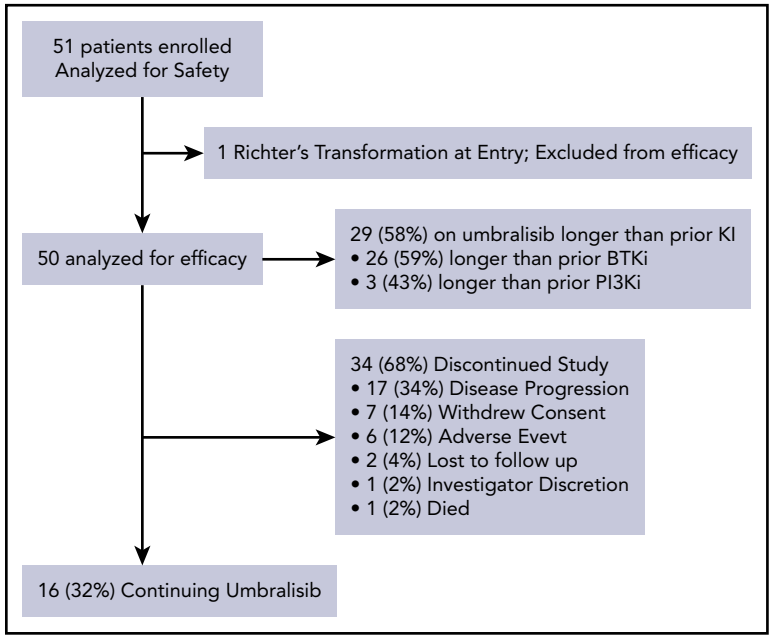
Toxicities from KIs and discontinuations of therapy are greater in certain populations, including older patients and those with comorbidities.[32] The Alliance 041212 trial randomized patients 65 years or older to receive ibrutinib regimens [ibrutinib or ibrutinib + rituximab (IR)] or bendamustine rituximab. At a median follow-up of 38 months, only 63% and 64% on the ibrutinib and IR arms, respectively, remained on ibrutinib. In contrast, the frontline Eastern Cooperative Oncology Group 1912 study examined IR vs fludarabine, cyclophosphamide, and rituximab for patients 70 years or younger. In this younger patient population, 79% of patients on the IR arm continued therapy with a median follow-up of 33.6 months.[5,8] Given that the median age at diagnosis of CLL is 71 years and many patients with CLL have comorbidities, toxicity is likely to remain the dominant reason for novel agent discontinuation and may become even more pronounced as KIs are increasingly used in clinical practice outside of clinical trial populations.

Although the original reports of CLL patients discontinuing ibrutinib portrayed a dismal prognosis,[15,16,33] follow-up studies demonstrate that patients with KI intolerance as a reason for discontinuation can have durable responses when transitioned to alternative targeted therapeutics.[20,21] However, there is no consensus on the optimal sequencing of treatment in patients discontinuing a first novel agent.

The use of venetoclax following relapse after KI therapy (idelalisib or ibrutinib) has been examined in a phase 2 clinical trial.[34,35] The investigator-determined ORR to venetoclax following relapse after idelalisib was 67%, with an estimated 12-month PFS of 79%, although patients with prior intolerance to idelalisib followed by progression (61%) and those with progression on idelalisib (36%) were analyzed together given the limited numbers (N = 36).[34] In a larger cohort of patients treated with venetoclax following ibrutinib failure (N = 91; 55% with progressive disease and 33% with intolerance to ibrutinib followed by disease progression), the investigator-assessed ORR was 65%, with median time to progression of 24.7 months.[35] Despite demonstrated efficacy in the post-KI setting, safe administration during the dose-escalation period requires hospitalization, tumor lysis syndrome can be significant if not managed appropriately, and disease control may not be immediate.[36] Further, PFS for patients on venetoclax after ibrutinib is closely tied to the depth of response, with those who do not achieve undetectable minimal residual disease status experiencing inferior PFS.[37] Traditional risk factors do not accurately predict the depth of response, making it difficult to predict who will achieve deep responses.[38,39] For selected patients, transition to an alternative KI, rather than venetoclax, may provide a safe and effective option. In a disease in which the goal is long-term disease control, an additional line of therapy prior to utilizing venetoclax may be of benefit, particularly because venetoclax remains active in patients who have failed >1 KI.[40]

Transitioning treatment within the BTKi class has proven a potentially effective strategy for some patients. Awan et al reported a small (N = 33) phase 2 trial of acalabrutinib (100 mg, twice

Figure 1. Patient disposition.



daily) for ibrutinib-intolerant patients.[41] The ORR was 81% and, at 19 months of follow-up, 23 of the patients remained on the drug, with only 3 discontinuations due to AEs. Additionally, for the 61 ibrutinib-related AEs associated with previous intolerance, 72% did not recur on acalabrutinib, and 13% recurred at a lower grade. In a larger series, Rogers et al reported outcomes of 60 ibrutinib-intolerant patients treated with acalabrutinib. In this cohort, 67% of patients remained on acalabrutinib, with a median follow-up of 19 months.[42] The most common reasons for discontinuation were CLL progression (13%) and acalabrutinib intolerance (10%).[42] In terms of the strategy of class-switching between BTKi's, there are recognized class effect toxicities for BTKi's for which transition within class may be a concern, including cardiac toxicities or bleeding risk.[43,44] In the frontline study of acalabrutinib for treatment-naive CLL, 64% of 99 treated patients experienced all-grade bleeding events.[45] In the phase 1 study of zanubrutinib, 2% experienced major hemorrhage, and 57% experienced bleeding (including contusion, hematuria, petechiae, purpura).[46] The role of other next-generation BTKi's will likely largely depend upon toxicity profile and remains unclear at this time. Several promising noncovalent BTKi's (eg, LOXO-305, ARQ531) have demonstrated safety and efficacy in ibrutinib-resistant disease with ibrutinib resistance–associated *BTK* C481S mutations.[47,48] However, follow-up on these agents is relatively short and how they will be sequenced into current management remains to be seen.

We recognize several limitations of this study, including potential limitations related to the study population, design, and analyses. In particular, this study examined a pooled population of patients who were treated previously with BTK and/or PI3K. Reflecting the frequency of the proportionate use of these agents in clinical practice, the study population was predominantly exposed to BTK, limiting interpretability in the PI3K-intolerant population. Although guidelines were established to define KI intolerance, these rules were applied

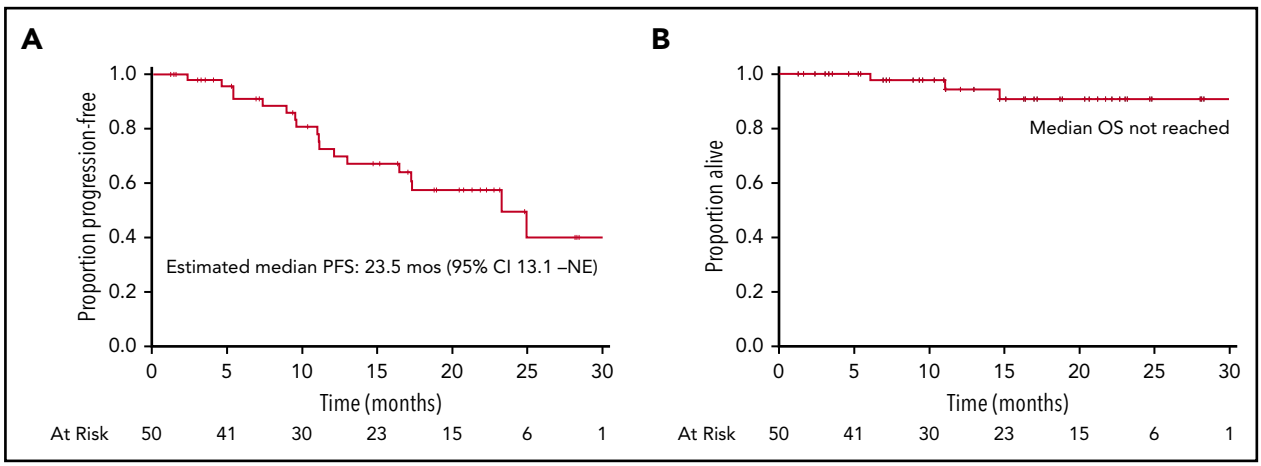


Figure 2. PFS and OS. Kaplan-Meier plots of PFS (A) and OS (B) for all patients evaluable for efficacy (n = 50). CI, confidence interval; NE, not estimable.

retrospectively and are subject to investigator discretion bias. Finally, interpretability of response rate is also limited given the inclusion of some patients without measurable disease.

Management of CLL/small lymphocytic lymphoma with the approved PI3Ki's has been limited by high rates of toxicity leading to discontinuation in the first year, despite promising initial response rates in high-risk patients. For example, recent data examining idelalisib and rituximab (vs acalabrutinib) in the r/r setting were notable for 86% grade 3-4 AEs and a 47% overall discontinuation rate as a result of AEs.[49] Similarly, the rate of grade 3-4 AEs was noted to be 87% in CLL patients treated with the PI3Ki duvelisib in the r/r setting.[4] Umbralisib has exhibited a favorable safety profile in r/r and previously untreated CLL, which continues with extended follow-up.[26] In this trial, umbralisib was safe and effective in a population entirely defined by prior intolerance to KIs. This provides a feasible sequencing strategy in the case of KI-intolerant patients, especially for those in whom switching within the BTKi class or to venetoclax is deemed unsafe or not feasible. Also, umbralisib may provide an additional line of treatment for those intolerant of their first KI prior to proceeding to venetoclax-based therapy if approved for CLL.

Given the noncurative nature of CLL therapy, adding effective lines of therapy to each patient's treatment sequence is likely to improve outcomes. These data may be particularly relevant because the combination of umbralisib and ublituximab is being studied in a randomized phase 3 study with potential indications in the frontline and r/r settings (NCT02612311).

Acknowledgment

This work was supported by TG Therapeutics, Inc.

Authorship

Contribution: A.R.M., N.G., S.J.S., N. Lamanna, J.M.P., I.W.F., J.C.B., K.R.R., J.A.R., B.D.C., P.M.B., S.K., F.L., J.J.P., A.P.S., L.R., G.A.F., A.S., C.D., N. LaRatta, H.W., J.S., and D.M.B. performed investigations and curated data; A.R.M., D.P., P.S., H.P.M., and M.S.W. wrote the manuscript; I.S.H., E.T.L.P., and P.T. provided resources; and D.P., P.S., and H.P.M. were in charge of project administration.

Conflict-of-interest disclosure: A.R.M. has acted as a consultant or advisor for AbbVie, Adaptive Biotechnologies, AstraZeneca, Celgene, Genentech, Johnson & Johnson, Loxo Oncology, Pharmacyclics, Regeneron, Sunesis, TG Therapeutics (consulting and Data and Safety Monitoring Board), and Curio Biotech and has received research funding from AbbVie, Adaptive Biotechnologies, Acerta/AZ, DTRM Biopharma, Genentech, Johnson & Johnson, Loxo Oncology, Pharmacyclics, Regeneron, Sunesis, TG Therapeutics, Aprea Therapeutics, Aptose Biosciences, and Pfizer. N.G. has acted as a consultant or advisor for Celgene, Gilead Sciences, Janssen Pharmaceuticals, Pharmacyclics, Seattle Genetics, and TG Therapeutics; is a member of the speaker's bureau for AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Gilead Sciences, Janssen Pharmaceuticals, Pharmacyclics, and Seattle Genetics; and has received research funding from Celgene, Forty Seven Inc., Genentech, Pharmacyclics, and TG Therapeutics. S.J.S. has acted as a consultant or advisor for Allogene Therapeutics, AstraZeneca, BeiGene, Celgene, Genentech/Hoffman-La Roche, Loxo Oncology, Novartis, and Tessa Therapeutics; is a member of the speaker's bureau for DAVA Oncology; and has received research funding from Genentech/Hoffman-La Roche. N. Lamanna has acted as a consultant or advisor for AbbVie, AstraZeneca, BeiGene, Celgene, Genentech, Gilead Sciences, Janssen Pharmaceuticals, Juno, and Pharmacyclics and has received research funding from AbbVie, AstraZeneca, BeiGene, Genentech, Juno Therapeutics, MingSight Pharmaceuticals, Oncternal Therapeutics, TG Therapeutics, and Verastem Oncology. J.M.P. has received research funding from AstraZeneca, Gilead Sciences, and Pharmacyclics. J.A.R. has acted as a consultant or advisor for Bayer and is a member of the speaker's bureau for Celgene, Eisai, and Janssen Oncology. B.D.C. has acted as a consultant or advisor for AbbVie, Astellas Pharma, AstraZeneca, Bayer, Celgene, Epizyme, Gilead Sciences, Karyopharm Therapeutics, MorphoSys, Parexel, Pharmacyclics/Janssen Pharmaceuticals, Symbio, and TG Therapeutics; has received research funding from AbbVie, Acerta Pharma, Bristol Myers Squibb, Gilead Sciences, Roche/Genentech, Seattle Genetics, TG Therapeutics, and Trillium Therapeutics; and has had travel, accommodations, and expenses paid by Symbio. P.M.B. has acted as a consultant or advisor for AbbVie, Celgene, Genentech, Infinity Pharmaceuticals, Janssen Pharmaceuticals, Merck, MorphoSys, Novartis, Pharmacyclics, Seattle Genetics, and TG Therapeutics and has received research funding from Pharmacyclics. A.P.S. has acted as a consultant or advisor for AbbVie, AstraZeneca, Celgene, Genentech, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Pharmacyclics, and Seattle Genetics; is a member of the speaker's bureau for AbbVie, AstraZeneca, BeiGene, Celgene, Gilead Sciences, Genentech, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Kite, Pharmacyclics, Seattle Genetics, and Verastem Oncology; and has received research funding from AbbVie, Acerta, AstraZeneca, Bristol Myers Squibb, Janssen Pharmaceuticals, Pharmacyclics, TG Therapeutics, and Verastem Oncology. L.R. has received honoraria from Projects in Knowledge and the Vaniam Group; has stock and other ownership interests in Abbott Laboratories and AbbVie; and has received research funding from Aptose Biosciences. G.A.F. has received honoraria from, has acted as a consultant or advisor for, is a member of the speaker's bureau for, has received research funding from, and has had travel, accommodations, and expenses paid by Amgen and Celgene and has received research funding from TG Therapeutics. D.P., P.S., and H.P.M. are employees of and hold stock and other ownership interests in TG Therapeutics. M.S.W. holds a leadership position at and holds stock and other ownership interests in TG Therapeutics. J.S. has received honoraria from AstraZeneca, Bristol Myers Squibb, Imbrium Therapeutics, Kite, Kyowa, Pharmacyclics, and Seattle Genetics and has received research funding from Bristol Myers Squibb, Incyte, Pharmacyclics, Seattle Genetics, and TG Therapeutics. D.M.B. has acted as a consultant or advisor for AbbVie, ArQule, AstraZeneca, Genentech, Pharmacyclics, Pfizer, Teva, TG Therapeutics, and Verastem Oncology and has received research funding from AbbVie, ArQule, Ascentage Pharma, AstraZeneca, BeiGene, DTRM Biopharma, Genentech, Juno Therapeutics/Celgene/Bristol Myers Squibb, MEI Pharma, Pharmacyclics, TG Therapeutics, Tolero Pharmaceuticals, and Verastem Oncology. The remaining authors declare no competing financial interests.

ORCID profiles: 0000-0001-8724-1875A.R.M.P.M.B., 0000-0002-9733-401X; F.L., 0000-0001-6027-3359; J.J.P., 0000-0001-7498-3159; A.S., 0000-0002-2231-5527; E.T.L.P., 0000-0002-9478-9211.

Correspondence: Anthony R. Mato, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: matoa@mskcc.org.

Footnotes

Submitted 12 June 2020; accepted 9 November 2020; prepublished online on *Blood* First Edition 1 December 2020. DOI 10.1182/blood.2020007376.

Presented in abstract form at the American Society of Clinical Oncology 2018 Annual Meeting, Chicago, IL, 1 June 2018, the 23rd Annual Meeting of the European Hematology Association, Stockholm, Sweden, 16 June 2018, and the 15th International Conference on Malignant Lymphoma, Lugano, Switzerland, 20 June 2019.

Data sharing requests should be sent to Anthony R. Mato (matoa@mskcc.org).

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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