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ARTICLE

The PI3Kδ inhibitor zandelisib on intermittent dosing in relapsed/refractory follicular lymphoma: Results from a global phase 2 study

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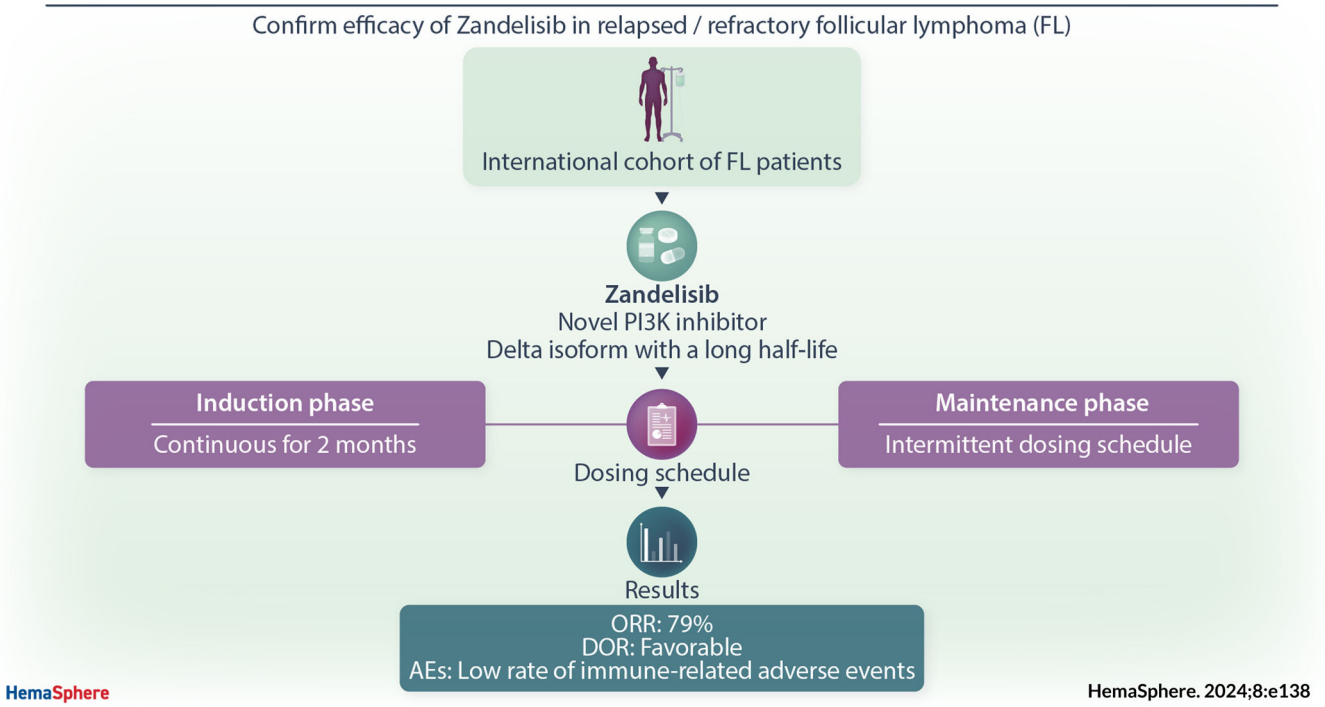
Graphical Abstract



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The PI3Kδ inhibitor zandelisib on intermittent dosing in relapsed/refractory follicular lymphoma: Results from a global phase 2 study

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Abstract

In this global phase 2 study in patients with relapsed/refractory follicular lymphoma (FL), zandelisib was administered on intermittent dosing to mitigate immune-related adverse events and infections that have been reported with oral PI3Kδ inhibitors administered daily continuously. Eligible patients with measurable disease and progression after at least two prior therapies were administered zandelisib until disease progression or intolerability. The primary efficacy endpoint was objective response rate (ORR) and the key secondary efficacy endpoint was duration of response (DOR). We report on 121 patients with FL administered zandelisib on intermittent dosing after 8 weeks of daily dosing for tumor debulking. The median number of prior therapies was 3 (range, 2–8) and 45% of patients had refractory disease. The ORR was 73% (95% confidence interval [CI], 63.9–80.4), the complete response (CR) rate was 38% (95% CI, 29.3–47.3), and the median DOR was 16.4 months (95% CI, 9.5–not reached). With a median follow-up of 14.3 months (range, 1–30.5), the median progression-free survival was 11.6 months (95% CI, 8.3–not reached). Twenty-one patients (17%) discontinued therapy due to an adverse event. Grade 3–4 class-related toxicities included 6% diarrhea, 5% lung infections, 3% colitis (confirmed by biopsy or imaging), 3% rash, 2% AST elevation, and 1% non-infectious pneumonitis. Zandelisib achieved a high rate of durable responses in heavily pretreated patients with relapsed/refractory FL. The intermittent dosing resulted in a relatively low incidence of severe class-related toxicities, which supports the evaluation of zandelisib as a single agent and in combination with indolent B-cell malignancies.

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INTRODUCTION

Class I phosphoinositide 3-kinases (PI3Ks) regulate a range of cellular activities, including metabolism, proliferation, and migration. PI3K signaling is one of the most frequent aberrantly activated pathways in cancer, and some PI3K family members are also involved in inflammation and autoimmunity.[1] The PI3Ks consist of a regulatory subunit in complex with a catalytic subunit (p110α, β, γ, or δ), with the δ isoform preferentially expressed in hematopoietic cells, where it plays a key role in lymphocyte development and function.[2,3]

Dysregulation of the PI3Kδ pathway may drive abnormal cellular function in malignant B cells and inhibition of this pathway is a validated therapeutic approach for patients with B-cell malignancies. Several PI3K inhibitors with various isoform specificity, all targeting the δ isoform to some extent, have achieved clinically meaningful response rates and, in controlled studies, have improved PFS compared to standard of care in patients with chronic lymphocytic leukemia (CLL) and indolent B-cell lymphoma.[4–9] Continuous PI3Kδ inhibition can cause T regulatory cell (Treg) dysregulation leading to autoimmune-like toxicities and chronic lymphocyte suppression associated with infections, with toxicities seen sometime late and often long-lasting.[10,11] These safety concerns resulted in underutilization, and in some cases, market withdrawal of various oral PI3Kδ inhibitors.

Zandelisib is an orally bioavailable PI3Kδ inhibitor with favorable pharmacologic properties, including high potency, specificity to the δ isoform at clinically relevant concentrations, plasma concentration half-life of ~28 h, preferential distribution to lymphoid tissue, and prolonged on-target residence time.[12] This pharmacological profile permits noncontinuous administration for lymphocyte repopulation with the objective of improving tolerability without compromising efficacy.

A single ascending dose study evaluating zandelisib in healthy volunteers established that 60 mg daily achieves trough plasma concentrations exceeding the IC_{90} for PI3Kδ inhibition in the basophil activation test.[13] A phase 1b dose escalation study in patients with relapsed/refractory follicular lymph (FL) and CLL evaluated zandelisib once daily continuously at 60, 120, and 180 mg, with the dose escalation terminated before reaching the maximum tolerated dose. It established 60 mg as the recommended dose for future development based on a favorable efficacy and safety profile and plasma concentrations above levels needed for PI3Kδ inhibition.[14]

A subsequent stage of the study evaluated zandelisib on intermittent dosing intended to allow Treg repopulation during treatment breaks to mitigate immune-related toxicities.[15] The intermittent dosing was started after an initial 8 weeks of daily dosing for tumor debulking and consisted of daily administration on 7 consecutive days to achieve sustained plasma concentrations above the IC_{90} for PI3Kδ inhibition followed by 21 days without treatment, 1 week for zandelisib plasma clearance, and 2 weeks for Treg repopulation.[16] Compared to the continuous daily dosing, zandelisib on intermittent dosing was associated with a lower incidence of severe diarrhea (5% vs. 21%) and pneumonia (2% vs. 16%).[17] In 43 patients with FL, the ORR was 78% and the median DOR was not reached in the intermittent dosing group versus an ORR of 76% and a median DOR of 21.9 months in the continuous dosing group. The present study was conducted to further characterize the efficacy and safety of zandelisib in patients with relapsed/refractory FL in a global trial (Clinicaltrials.gov identifier NCT03768505; registration date: December 4, 2018).

MATERIALS AND METHODS

Eligibility

Patients ≥18 years old (or 20 years in some countries) with histologically confirmed diagnosis of FL Grade 1, 2, or 3a were eligible if they had had measurable disease, lymphoma progression after ≥2 prior lines of standard systemic therapy, which must have included an anti-CD20 antibody and chemotherapy given concurrently or sequentially and no prior PI3Kδ inhibitor. Refractory disease was defined as no response or response lasting less than 6 months to last therapy. Other key eligibility criteria included ECOG performance status of 0 or 1, adequate hematologic (neutrophil count $\geq 1 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L), hepatic, and renal function, and no history of pneumonitis.

Study design

Initially, the study was designed as a randomized 2-arm trial in patients with R/R FL to evaluate zandelisib 60 mg administered daily continuously (CS arm) or daily continuously for 8 weeks followed by intermittent dosing (IS arm), with treatments administered in a 28-day cycle in both arms. Patients in both arms were administered one capsule a day, with those randomized to the IS arm receiving a placebo capsule on Days 8 to 28 of each cycle. Patients with disease progression had the option to unmask their treatment arm and be switched to daily dosing if they had been randomized to the IS arm.

Because maturing data from the phase 1b study showed that intermittent dosing resulted in better tolerability than continuous daily dosing without loss of efficacy, the CS arm was closed to enrollment, ongoing patients in the CS arm were switched to zandelisib on intermittent dosing, and all new patients were enrolled in the IS arm only.

Zandelisib was continued until disease progression or intolerability. Toxicity was managed with dose interruption, corticosteroids, if indicated, and restarting therapy by intermittent dosing in both treatment arms upon resolution of the adverse event. Pneumocystis jirovecii pneumonia (PJP) prophylaxis was optional initially, then made mandatory after two cases occurred in the study, which happened in 2022 after completion of patient accrual. Cytomegalovirus polymerase chain reaction levels were monitored every cycle in the first six cycles and then every three cycles, and antiviral therapy initiated if levels increased. Administration of hematopoietic growth factors and immunoglobulin replacement was not mandated and left at the discretion of the investigators.

Imaging with computed tomography (CT) or positron-emission tomography (PET)/CT scans was performed at baseline, every 2 months for the first 6 months, every 3 months until the end of 2 years of therapy, and then every 6 months. PET scans were obtained at screening, after 4 and 12 months of therapy, and at any time to confirm a complete response (CR). Disease assessment was by an Independent Review Committee (IRC) and by investigators using the Lugano Classification Criteria, modified to require a CT scan to confirm a partial response (PR), that is, PR by PET alone was not recognized.[18] An immune correlative study to evaluate T-cell subsets, chemokines, and cytokines over time was conducted in a subset of patients and was reported elsewhere.[19] A cohort enrolling patients with relapsed/refractory marginal zone lymphoma was terminated prematurely by the Sponsor MEI Pharma for business reasons, with 32 of 64 planned patients enrolled, which is not reported here.

The study was conducted mainly during the COVID-19 pandemic, which required modifications to the study plan to allow remote

telehealth study visits, home delivery of study drug, alternative location for laboratory tests, and remote monitoring. When available, COVID-19 vaccination was recommended but not mandated. COVID-19 infections were treated according to investigator decision. These changes were incorporated in protocol amendments, which were approved by regulatory authorities and Independent Review Boards/Ethics Committees.

Endpoints

The primary efficacy endpoint was ORR, defined as the proportion of patients achieving a best response of CR or PR by IRC. Key secondary efficacy endpoint was DOR (defined as the time from documentation of a response to treatment to first documentation of tumor progression or death because of any cause, whichever comes first). Additional secondary endpoints included PFS (defined as the time from study entry to first documentation of tumor progression or death because of any cause, whichever comes first), all assessed by IRC, ORR assessed by investigators, and overall survival (OS, defined as the time from study entry to death form any cause). Exploratory endpoints were time to treatment failure (TTF, defined as time from the first dose of zandelisib to treatment failure including any treatment discontinuation due to disease progression, toxicity, or death), time to first response (defined as the interval from first dose to first documentation of CR or PR) and the rate and duration of recapture of response measured in patients randomized to the IS arm who had achieved an objective response on ID and had disease progression and then received zandelisib daily. Safety endpoints included incidence and severity of adverse events (AEs), serious AEs, adverse event of special interest (AESIs) for PI3Kδ inhibitors, laboratory assessments, and deaths. Description and grading of AEs were reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0.

Statistical plan and analysis

Initially, the study was designed to enroll 150 patients with FL randomized 1-to-1 to the CS or IS arm. After closing the CS arm, the study protocol was revised to enroll 120 patients with FL in the IS arm, with the first 91 patients treated in this arm defining the primary efficacy population for regulatory reporting. The sample size of 91 patients was calculated to have at least 90% power to exclude the null hypothesis of an ORR of 48% at a one-sided α of 0.025 against the alternative hypothesis that ORR is ≥65%. The primary analysis in FL was defined in the protocol to occur approximately 14 months after completing enrollment of the primary efficacy population. For analysis, the IS FL group consisted of all FL patients randomized to or allocated to the IS arm and who received at least one dose of zandelisib. The CS group consisted of all patients who were randomized to the CS arm, including those who were switched to intermittent dosing after closing enrollment in the CS arm.

Response rates were estimated with 95% confidence interval (CI) by the Clopper–Pearson method based on the binomial distribution. Secondary endpoints (DOR, PFS, TTF) were summarized using the Kaplan–Meier method. Median duration of follow-up, and 95% CI, was summarized by the reverse Kaplan–Meier method. Safety analyses were summarized descriptively. Continuous data were summarized using descriptive statistics, and frequencies and percentages were used to summarize categorical data. Other than for certain partial dates, missing data were not imputed and were treated as missing. All analyses were performed using SAS Version 9.4 or higher.

Trial oversight

The study, named TIDAL, was conducted in accordance with applicable regulatory requirements and the updated Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. A multinational 5-member Data Safety Monitoring Board provided independent oversight of the study. The protocol was approved by each study site's independent ethics committee or institutional review board, and all patients provided written informed consent before enrolling into the study. The study was designed and sponsored by MEI Pharma and cofunded by MEI Pharma, Inc. and Kyowa Kirin Co., Ltd. Data were collected and trial procedures were overseen by trial investigators. Data were verified by the sponsor, analyzed by sponsor statisticians, and interpreted by academic authors and sponsor representatives. The manuscript was prepared by the authors, and all authors had final responsibility for content and the decision to submit for publication.

RESULTS

Between June 2019 and August 2021, 166 patients with FL consented to participate in the study, 29 (17%) did not meet eligibility criteria and 137 received zandelisib, 121 randomized or allocated to the IS arm, and 16 randomized to the CS arm. The study was conducted in over 50 clinical sites globally (Supporting Information S1: Table S1). At the data cutoff of June 2, 2022, 43 of 121 patients (36%) in the IS arm were being administered zandelisib and 78 patients had discontinued therapy, with the primary reason reported as disease progression in 40%, AEs in 17%, withdrawal of consent in 3%, and other reasons in 3% (Figure 1).

Demographics and disease characteristics

For the 121 patients in the FL IS arm, the median age was 64 years (range, 31–87), 61% were male, and 75% were white. Patient enrollment was 64% in Europe, 20% in North America, and 16% in the East Asia-Pacific region. Baseline characteristics are presented in Table 1. The median number of prior therapies was 3 (range, 2–8) and 53% of patients had received at least three prior therapies. Prior systemic therapies included chemoimmunotherapy in 98% of patients, intensive therapy with stem cell transplant in 23%, and lenalidomide-based regimens in 17% (Supporting Information S1: Table S2). Disease was refractory to the last therapy in 45% of patients and 56% of patients had disease progression within 24 months of initiating first-line chemoimmunotherapy (POD24). There were no notable differences in demographics and disease characteristics between the IS and CS arms.

Efficacy

In 91 subjects comprising the protocol-defined FL IS primary efficacy population, the study met its predefined efficacy endpoint with an IRC-assessed ORR of 74% (95% CI, 63.3–82.3, $p < 0.001$). In the total FL IS group, 88 of 121 patients (73%, 95% CI, 63.9–80.4) achieved an objective response, including 46 complete responses (38%, 95% CI, 29.3–47.3) and 42 partial responses (35%, 95% CI, 26.3–43.9) (Table 2). Responses occurred early, with 87.5% of all responses first observed after 8 weeks of daily dosing.

In patient subsets with poor prognostic factors in the FL IS group, the ORR was 69% in patients with disease refractory to the last therapy and 62.5% in patients with ≥3 prior therapies (Supporting

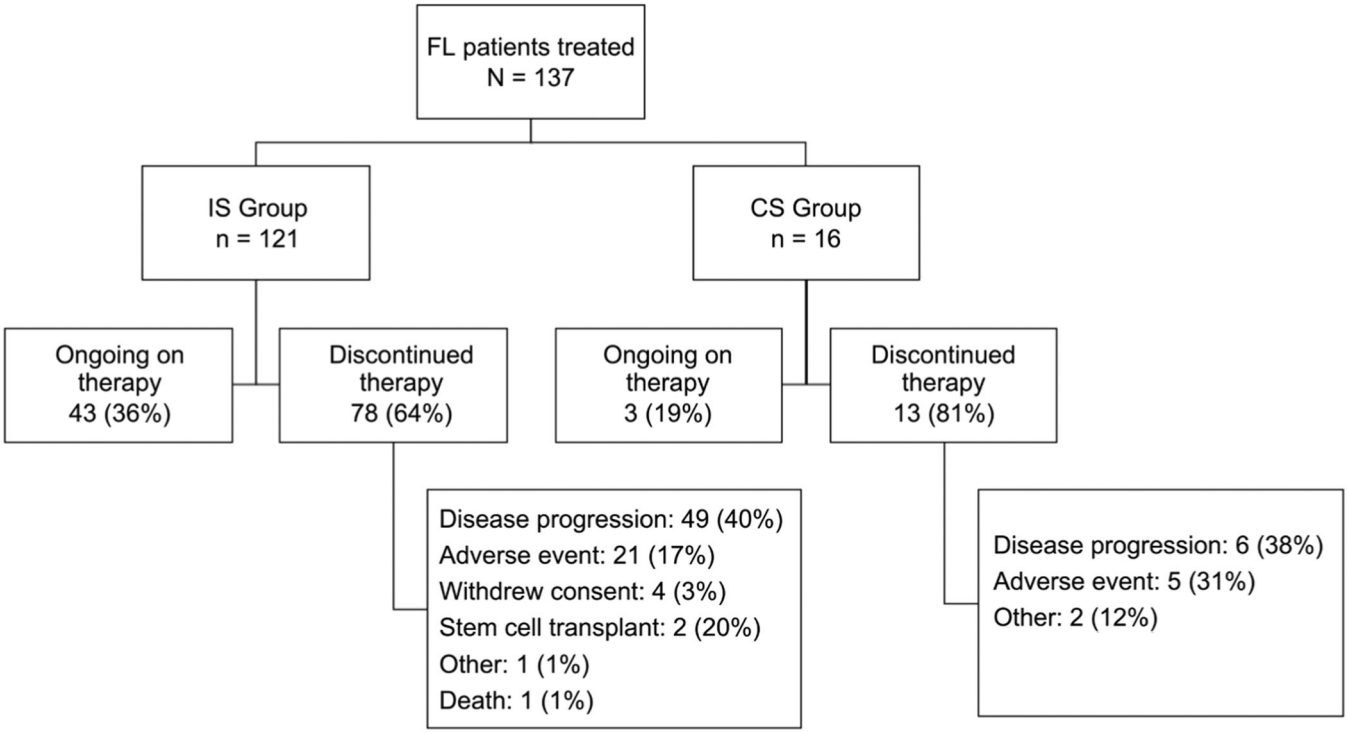

FIGURE 1 Patient flow and disposition.

Information S1: Table S2). A boxplot of ORR for 13 baseline characteristics is available in Supporting Information S1: Figure S1. The investigator-assessed ORR was 72%, comparable to IRC assessment. The waterfall plot depicting changes in tumor volume from baseline shows that 109 of 112 patients (93%) with ≥1 post-baseline disease assessment experienced reduction of their disease by investigator assessment (Figure 2). Of the 16 patients randomized to the CS arm, 12 (75%, 95% CI, 47.6–92.7) achieved an IRC-assessed objective response. In the IS arm, 6 of 16 patients (37.5%) had a confirmed recapture of response after switch to daily dosing following disease progression on intermittent dosing.

With a median follow-up of 11.3 months (95% CI, 6.9–11.3) in responders in the FL IS group, the median DOR was estimated to be 16.4 months (95% CI, 9.5–not evaluable) (Figure 3). Of the 88 responders, 26 (30%) had subsequent disease progression, four (5%) died in remission (2 due to COVID-19 infection and two due to pulmonary infection), and 58 (66%) were censored, including 37 (42%) who were still on therapy at the data cutoff date, 13 (15%) who had disease progression by investigator assessment and were switched to daily dosing, five (6%) who had discontinued from the study, and three (3%) who received other lymphoma therapy. Thirteen of 21 patients who discontinued zandelisib due to an adverse event have achieved an objective response before discontinuation, and for 9 patients who were followed after discontinuation, the median duration of response after treatment discontinuation was 7.7 months (range, 0.7–11.0). The median DOR in the CS arm was 6.5 months (95% CI, 2.2–not evaluable). Of the 12 responders in the CS arm, eight (67%) had disease progression, two (17%) died in remission due to toxicity, and two (17%) were still on therapy at the data cutoff date. The DOR plots by patient subsets are available online (Supporting Information S1: Figure S2).

With a median follow-up of 11.0 months for the total FL IS group, the IRC-assessed median PFS was 11.6 months (95% CI, 8.3–not evaluable), with 38 patients (31%) remaining on therapy (Figure 3). The median TTF was 11.3 months (95% CI, 8.8–11.9). At a median follow-up of 16.9 months (95% CI, 14.9–18.9) the median OS was not reached, and the estimated OS was 77% (95% CI, 66–84) (Supporting Information S1: Figure S3). Overall, 24 patients (20%) in the IS group have died, 10 due to disease progression, 11 due to an adverse event, including seven related to COVID-19, and three where the reason was not available due to loss of follow-up (Supporting Information S1: Table S4).

Safety

The median duration of treatment in the FL IS group was 10.1 months (range, 0.1–30 months). Adverse events, regardless of relationship to zandelisib, led to treatment interruption in 59 patients (49%) and treatment discontinuation in 21 (17%). The most common adverse events leading to treatment discontinuation were diarrhea (3%) and colitis (2%), COVID-19 (2%), and cutaneous reactions (2%), detailed in Supporting Information S1: Table S5. Treatment discontinuation due to AEs deemed by the investigator to be related to zandelisib occurred in 16 patients (13%).

The most frequent adverse events (all grades, grade 3–4) were diarrhea (37%, 6%), nausea (22%, 0%), pyrexia (19%, 2%), fatigue (19%, 0%), and abdominal pain (16%, 1%) (Figure 4). A list of adverse events reported in ≥ 5% of patients can be found online (Supporting Information S1: Table S6). Grade 3–4 adverse events of special interest for PI3Kδ inhibitors were diarrhea (6%), colitis (3%), pneumonia (4%), stomatitis (3%), cutaneous reactions (3%), ALT elevation (2%), noninfectious pneumonitis (1%), and PJP infection (1%). Grade 3 diarrhea or colitis occurred early, with 7 of 11 cases reported in the first three cycles of therapy during daily administration of zandelisib (Supporting Information S1: Figure S4). The median time to resolution of grade 3 diarrhea/colitis was 12 days (range,

TABLE 1 Baseline characteristics in the follicular lymphoma population.

Parameter	IS (*N* = 121)	CS (*N* = 16)
Age		
Median (range), years	64 (31, 87)	63 (39, 80)
Number (%) with age ≥65 years	59 (48.8)	7 (43.8)
Sex, *n* (%)		
Male	74 (61.2)	13 (81.3)
Race, *n* (%)		
White	92 (76.0)	11 (68.8)
Black	1 (0.8)	0
Asian	15 (12.4)	3 (18.8)
Other	13 (10.7)	2 (12.5)
Region, *n* (%)		
North America	24 (19.8)	1 (6.3)
Europe	77 (63.6)	9 (56.3)
South Asia-Pacific	20 (16.5)	6 (37.5)
Stage at diagnosis, *n* (%)		
I–II	25 (20.7)	2 (12.5)
III–IV	94 (77.7)	14 (87.6)
Missing	2 (1.7)	0
Stage at study entry, *n* (%)		
I–II	22 (18.2)	1 (6.3)
III–IV	99 (81.8)	15 (93.7)
Grade at study entry, *n* (%)		
1	22 (18.2)	4 (25.0)
2	66 (54.5)	6 (37.5)
3a	32 (26.4)	6 (37.5)
Missing	1 (0.8)	0
Prior systemic cancer therapies, *n* (%)		
2	57 (47.1)	5 (31.3)
>2	64 (52.9)	11 (68.8)
Number of prior cancer therapies, median (range)	3 (2, 8)	3 (2, 4)
Patients with disease refractory to last therapy, *n* (%)	54 (44.6)	10 (62.5)
Patients with largest tumor diameter, *n* (%)		
≥5 cm	42 (34.7)	6 (37.5)
≥7 cm	19 (15.7)	3 (18.8)
Patients with disease progression <24 months from start of initial chemoimmunotherapy		
Yes	68 (56.2)	10 (62.5)
Patients with baseline ECOG performance status, *n* (%)		
0	79 (65.3)	11 (68.8)
1	40 (33.1)	5 (31.3)
>1	2 (1.7)	0
Patients with duration from last therapy to enrollment *n* (%)		
≤6 months	48 (39.7)	9 (56.3)

Abbreviations: CS, continuous schedule dosing group; IS, Intermittent schedule dosing group.

TABLE 2 Objective response rates as assessed by the Independent Review Committee.

Parameter	IS (*N* = 121)	IS PEP (*N* = 91)	CS (*N* = 16)
ORR (CR + PR)			
n (%)	88 (72.7)	67 (73.6)	12 (75.0)
95% CI	63.9–80.4	63.3–82.3	47.6–92.7
CR			
n (%)	46 (38.0)	34 (37.4)	6 (37.5)
95% CI	29.3–47.3	27.4–48.1	15.2–64.6
PR			
n (%)	42 (34.7)	33 (36.3)	6 (37.5)
95% CI	26.3–43.9	26.4–47.0	15.2–64.6
Stable disease			
n (%)	15 (12.4)	11 (12.1)	2 (12.5)
95% CI	7.1–19.6	6.2–20.6	1.6–38.3
Progressive disease			
n (%)	6 (5.0)	6 (6.6)	0
95% CI	1.8–10.4	2.5–13.8	
Not evaluable/not available			
n (%)	12 (9.9)	7 (7.7)	2 (12.5)
95% CI	5.2–16.7	3.1–15.2	1.6–38.3

Abbreviations: CS, continuous schedule dosing group; IS, intermittent schedule dosing group; IS PEP, intermittent schedule dosing group primary efficacy population.

2–41 days). Grade 3–4 neutropenia was observed in 26% of patients; however, febrile neutropenia was uncommon, reported in 3 patients (2%). Other grade 3–4 laboratory abnormalities included anemia (7%), thrombocytopenia (6%), creatinine increased (2%), ALT increased (2%), and AST increased (1%).

Serious adverse events were reported in 46 patients (38%) in the FL IS group, with the most frequent events being COVID-19 infections (7%), pneumonia (4%), pyrexia (3%), and abdominal pain and colitis (2% each). In total, 17 patients (14%) had a COVID-19 infection, which was fatal in 7 (6%) and grade 3–4 in 6 (5%). Death due to AEs while on therapy occurred in seven patients, five from complications of COVID-19, one on Day 28 reported by the investigator as due to tumor lysis syndrome, although the patient had evidence of tumor progression in the retroperitoneal space with ureteral compression, and one due to recurrent pneumonia at Month 8.

DISCUSSION

In this study, zandelisib showed sustained antitumor activity in patients with FL whose disease had progressed after ≥2 prior lines of therapy including chemoimmunotherapy. Overall, 73% of patients achieved an objective response, including 38% with a complete response. Responses occurred rapidly, with 87.5% of all responses first observed after the initial two cycles of daily dosing. The rates of objective responses were favorable even in patients with poor prognostic factors such as relapse after at least three prior therapies (62.5%), disease refractory to last therapy (69%), and POD24 after initial chemoimmunotherapy (74%). A median duration of response of 16.4 months at this initial analysis, and a median PFS of 11.6 months represent a meaningful efficacy outcome in patients with relapsed/

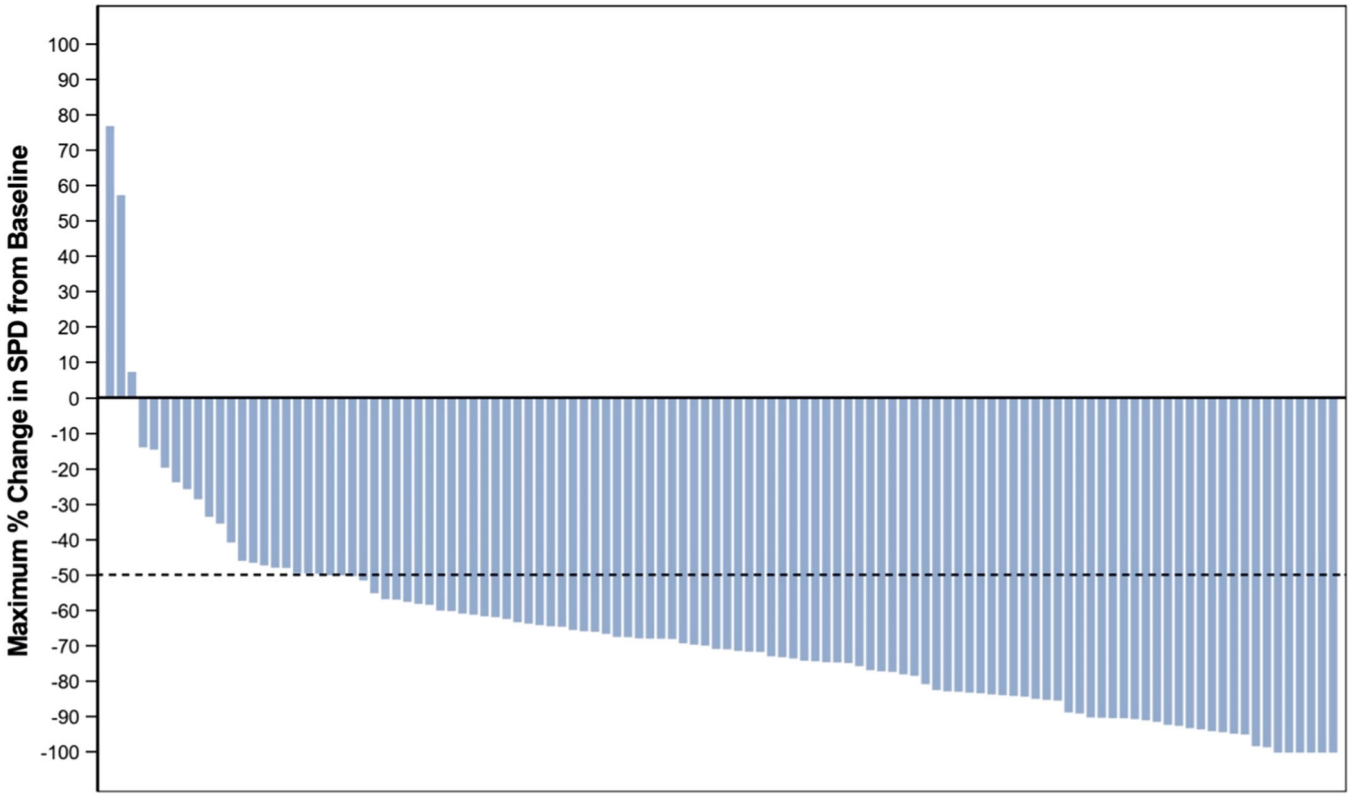

FIGURE 2 Change in tumor volume. Maximum change from baseline in the sum of perpendicular diameters in the follicular lymphoma Intermittent Schedule group.

refractory disease administered zandelisib for only 7 days in a 28-day cycle after an initial 8-week daily dosing induction. These findings are consistent with a previous report of zandelisib in indolent B-cell malignancies.[17]

Grade 3 diarrhea or colitis was reported in 9% of patients, and these cases occurred primarily during the first months of therapy when zandelisib was administered daily continuously, with a substantial reduction of risk in later cycles, when zandelisib was administered intermittently. Pulmonary events were uncommon, with pneumonia of any cause reported in five patients (5%), PJP infection in one patient who was not receiving prophylaxis, and noninfectious pneumonitis in one patient. Grade 3–4 ALT elevations were rare, occurring in two patients. Although the incidence of Grade 3–4 neutropenia was 26%, these events were transient and rarely associated with febrile neutropenia. Excluding three COVID-19 cases, treatment discontinuation due to adverse events occurred in 18 of 121 patients (15%), a rate similar or lower than 15% to 25% reported with other PI3Kδ inhibitors in global indolent lymphoma studies.[4,6,8,20] In total, 17 patients (14%) had a COVID-19 infection, which was fatal in seven (6%), comparable to other series in hematologic malignancies.[21,22] The COVID-19 pandemic has clearly affected study conduct, and infection occurring on study have negatively affected outcome, including patient withdrawals and deaths in responding patients. There was one death considered possibly related to zandelisib, which occurred at Month 8 in a patient with recurrent pneumonia. The other death reported as possibly related to zandelisib was due to tumor lysis syndrome, but was confounded by evidence of disease progression.

Intermittent dosing appears to have reduced but not eliminated the risk of severe diarrhea/colitis and pulmonary infection. It is possible that beginning intermittent dosing from Cycle 1 would further reduce the incidence of grade 3 diarrhea/colitis as was observed in a study of zandelisib plus zanubrutinib in B-cell malignancies, where only one of 50 patients (2%) administered zandelisib at 60 mg on intermittent dosing beginning in Cycle 1 developed grade 3 diarrhea.[23] Improved tolerability with intermittent dosing enables the combination with other agents, such as rituximab in the phase 3 study of zandelisib plus rituximab versus chemoimmunotherapy in relapsed indolent B-cell lymphoma, also closed early with the termination of zandelisib development (NCT04745832).

Dosing schedules other than daily continuously were evaluated with other PI3K inhibitors, including idelalisib using a 3 weeks on/1 week off schedule, and parsaclisib using a 1 day on/6 days off schedule after initial 9 weeks of daily dosing, however, these approaches were not used in later studies.[5,20] The unique pharmacologic properties of zandelisib, primarily long half-life, significant distribution in lymphoid tissue, and prolonged target binding may be the reasons for continued tumor control during intermittent dosing.

Despite evidence of PI3Kδ inhibitors' antitumor activity in indolent B-cell lymphomas and chronic lymphocytic leukemia resulting in the marketing approval of several such compounds, this class of drug has recently faced significant regulatory challenges in the United States due to a possible detrimental effect on survival.[24] This led to the market withdrawal of several PI3Kδ inhibitors and raised the bar for approval of new drugs in this class, including the requirement for data from randomized trials and mature overall survival data.[24] This will be challenging for drugs in indolent orphan diseases and may deter development of new drugs aiming at this important target, including zandelisib.[25]

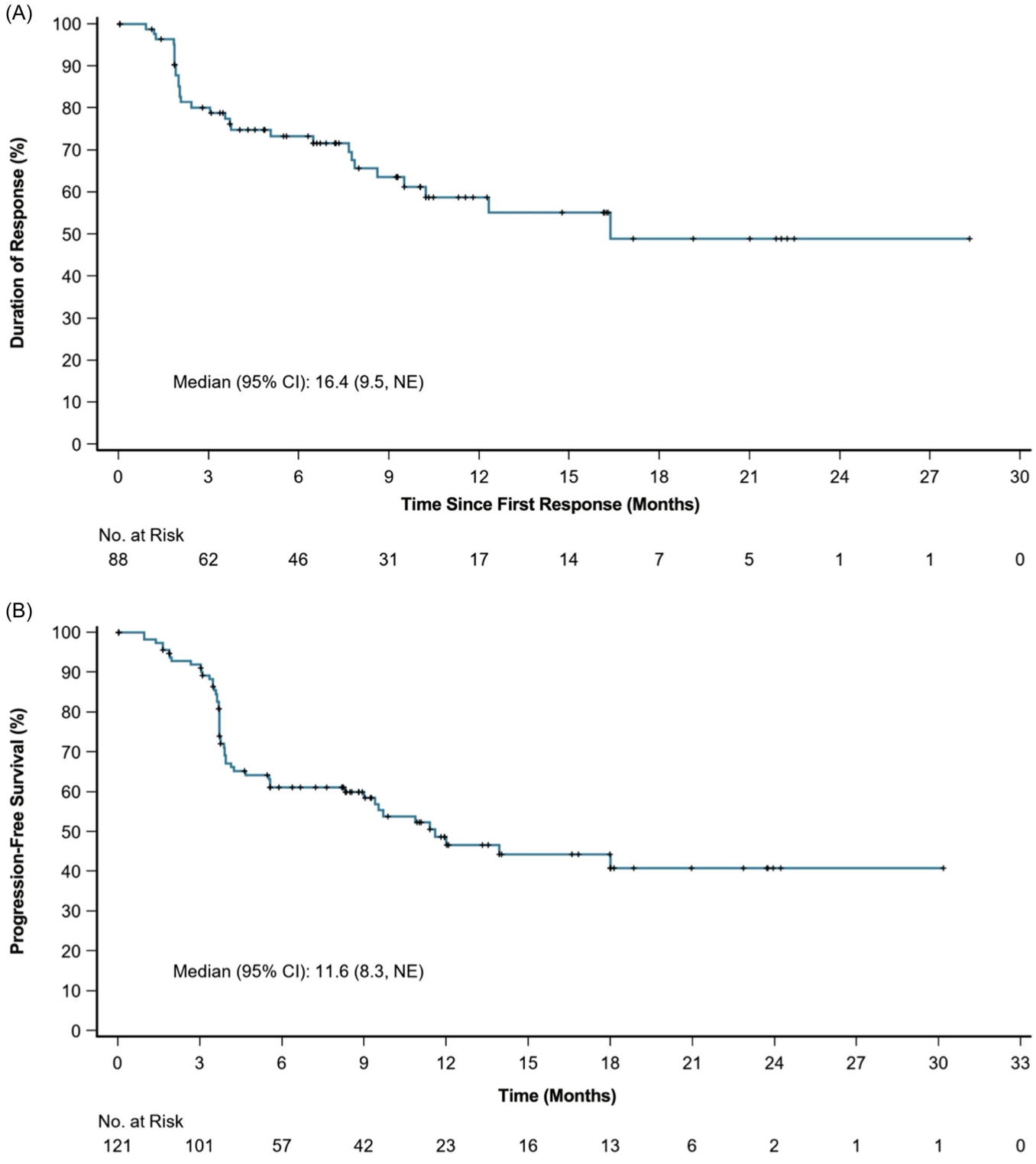

FIGURE 3 Duration of response (DOR) and progression-free survival (PFS). DOR (A) and PFS (B) in the follicular lymphoma Intermittent Schedule group. Tick marks indicate censored data.

In conclusion, in this uncontrolled trial, single-agent oral zandelisib resulted in a high rate of durable responses in patients with previously treated FL. The toxicity profile of the intermittent dosing may allow the development of more highly active combination regimens in indolent B-cell malignancies. While zandelisib clinical program was discontinued due to regulatory challenges, this study was instrumental in demonstrating that schedule optimization, in addition to dose optimization, early in drug development, can lead to a safer product without compromising efficacy.

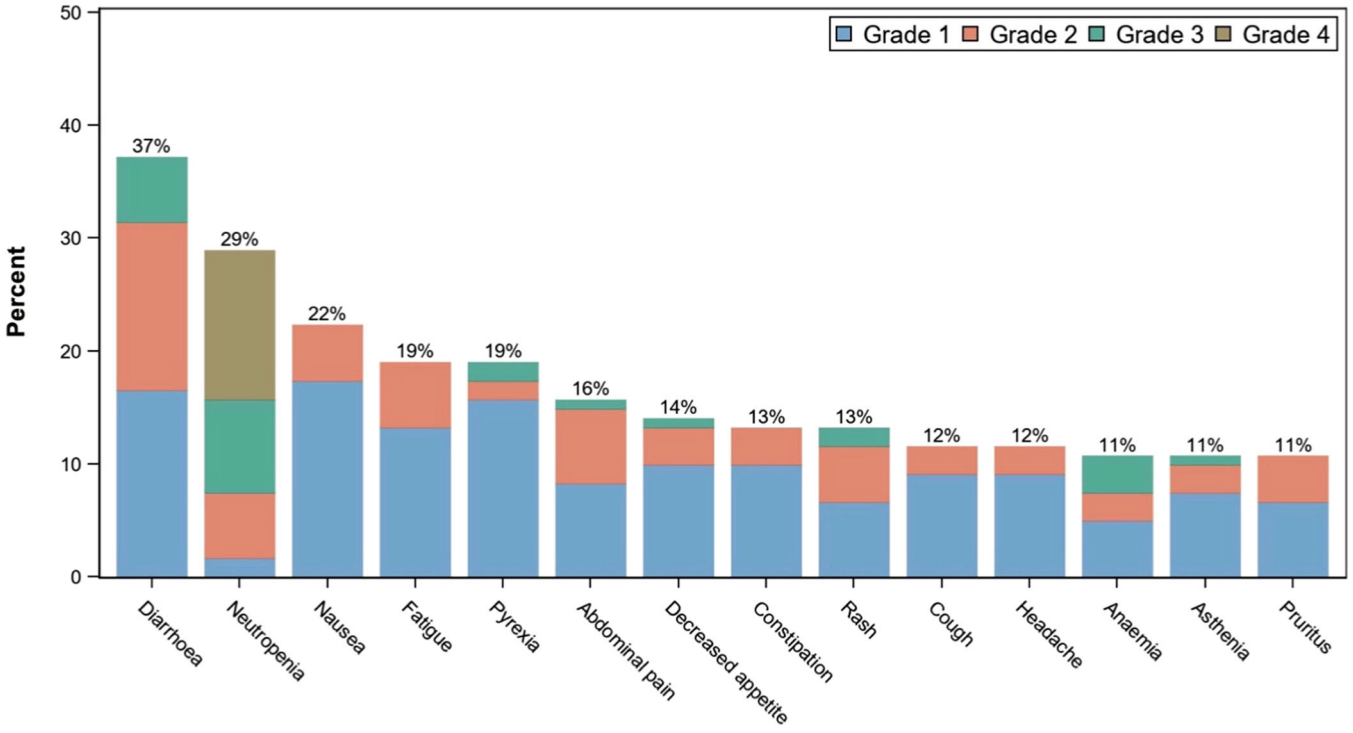

FIGURE 4 Treatment-emergent adverse events (AEs). Most common AEs (>10% of patients) in the follicular lymphoma Intermittent Schedule group.

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AUTHOR CONTRIBUTIONS

Richard G. Ghalie designed and supervised the trial, analyzed the data, and cowrote the paper. Andrew D. Zelenetz contributed to the study design, was the study chair and lead investigator, reviewed the data, and also reviewed and approved the article. Andrew D. Zelenetz, Wojciech Jurczak, Vincent Ribrag, Kim Linton, Graham P. Collins, Tycel J. Phillips, Nagendraprasad Sungala, Gerardo Musuraca, Oonagh Sheehy, Eric Van Den Neste, and Pier L. Zinzani contributed to patient management. Lu Miao performed statistical analyses of the data. All authors reviewed and approved the paper.

CONFLICT OF INTEREST STATEMENT

Andrew D. Zelenetz has received research support from MEI Pharma, Genentech/Roche, BieGene, Jansen, LOXO/Lily. He has been an advisor or consultant to MEI Pharma, BMS/Celgene/JUNO, Genentech/Roche, Gilead/Kite, BeiGene, Pharmacyclics, Jansen, Astra-Zeneca, and Novartis. Wojciech Jurczak has received research funding from MEI Pharma. Vincent Ribrag has received research funding from Astex and GSK; consulting fees from Servier, honoraria from Pharmar and Abbvie; travel support from AZD and GSK; and has participated on a data safety monitoring or advisory board for AZD, BMS, and Gilead. Kim Linton has received institutional research funding from Takeda, Roche, Genmab, and Abbvie; honoraria from Abbvie, Celgene, and Roche; has consulted for Abbvie, Roche, Genmab, Kite/Gilead, Beigene, BMS, and Celgene; participated on a speakers' bureau for Hartley Taylor, Abbvie, and BMS; provided expert testimony for NICE; and received travel support from Celgene. Graham P. Collins has received honoraria for speaker or advisory work from Roche, Takeda, Incyte, Kite, BMS, SecuraBio, Genmab, Sobi, and AstraZeneca; and research funding from Pfizer, BMS, Amgen, Beigene, and AstraZeneca. Javier López Jiménez has no conflicts of interest to disclose. Mark Bishton has consulted for Lilly, Incyte, Roche, and Beigene; and has received honoraria from Teva Pharma, Celltrion, and Roche. Bhagirathbhai Dholaria has received institutional research funding from Janssen, Angiocrine, Pfizer, Poseida, MEI Pharma, Orcabio, Wugen, Allovir, NCI, Atara, Gilead, Molecular Templates, BMS, AstraZeneca, Adicet, and Janssen; consulted or advised for Pluri Biotech, Boxer Capital, Ellipsis Pharma, Lumanity, Autolus, Acrotech, and ADC Therapeutics. Andrea Mengarelli has no conflicts-of-interest to declare. Tycel J. Phillips has received consulting fees as an advisor or advisory board participation for Abbvie, AstraZeneca, Bayer, Beigene, BMS, Eli Lily, Genentech, Genmab, Gilead, Kite, Incyte, Ipsen, Morphosys, Merck, Pharmacyclics, and Xencor; honoraria for lectures at the University of Michigan and Concert Network; and has held scientific committee leadership roles at Merck, Genentech, and Genmab. Nagendraprasad Sungala has no conflicts of interest to declare. GM had consulted for, received honoraria and travel support from Abbvie, Janssen, and Incyte; and participated on a data safety monitoring or advisory board for Abbvie, Janssen, Takeda, and LOXO. Oonagh Sheehy has no conflicts of interest to declare. Eric Van Den Neste has no conflicts of interest to declare. Mitsuhiko Odera is an employee of Kyowa Kirin Co. Lu Miao is an employee of MEI Pharma. Daniel P. Gold was an employee of MEI Pharma. Richard G. Ghalie is an employee of MEI Pharma. Pier L. Zinzani has been a consultant for Merck Sharp & Dohme, Eusa Pharma, Novartis. He has been on the Speakers Bureau of Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, AstraZenecam Takeda,

Susa Pharma, Kyowa Kirin, Novartis, Incyte, BeiGene. He has been on the advisory board of Secura Bio, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, AstraZeneca, Takeda, Roche, Eusa Pharma, Kuowa Kirin, ADC Therapeutics, Incyte, BeiGene.

DATA AVAILABILITY STATEMENT

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be shared with researchers who provide a methodologically sound proposal. Proposals should be directed to rghalie@meipharma.com; to gain access, data requestors will need to sign a data access agreement.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

REFERENCES

1. Perry MWD, Abdulai R, Mogemark M, et al. Evolution of PI3Kγ and δ inhibitors for inflammatory and autoimmune diseases. *J Med Chem*. 2019;62(10):4783-4814. doi:10.1021/acs.jmedchem.8b01298
2. Herman SEM, Johnson AJ. Molecular pathways: targeting phosphoinositide 3-kinase p110-delta in chronic lymphocytic leukemia. *Clin Cancer Res*. 2012;18(15):4013-4018. doi:10.1158/1078-0432.CCR-11-1402
3. Vanhaesebroeck B, Ali K, Bilancio A, Geering B, Foukas LC. Signalling by PI3K isoforms: insights from gene-targeted mice. *Trends Biochem Sci*. 2005;30(4):194-204. doi:10.1016/j.tibs.2005.02.008
4. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2017;35(35):3898-3905. doi:10.1200/JCO.2017.75.4648
5. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-hodgkin lymphoma. *J Clin Oncol*. 2019;37(11):912-922. doi:10.1200/JCO.18.00915
6. Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib, a dual PI3Kδ/CK1ε inhibitor in patients with relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2021;39(15):1609-1618. doi:10.1200/JCO.20.03433
7. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007. doi:10.1056/NEJMoa1315226
8. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018. doi:10.1056/NEJMoa1314583
9. Matasar MJ, Capra M, Özcan M, et al. Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2021;22(5):678-689. doi:10.1016/S1470-2045(21)00145-5
10. Abu-Eid R, Samara RN, Ozbun L, et al. Selective inhibition of regulatory T cells by targeting the PI3K-Akt pathway. *Cancer Immunol Res*. 2014;2(11):1080-1089. doi:10.1158/2326-6066.CIR-14-0095
11. Cuneo A, Barosi G, Danesi R, et al. Management of adverse events associated with idelalisib treatment in chronic lymphocytic leukemia and follicular lymphoma: a multidisciplinary position paper. *Hematol Oncol*. 2019;37(1):3-14. doi:10.1002/hon.2540
12. Moreno O, Wood J. Absorption, distribution, and binding profile of ME-401, a potent and selective oral small-molecule inhibitor of phosphatidylinositol 3-kinase δ (PI3Kδ) in animal and B-cell lymphoma models. *Target Oncol*. 2019;14(5):603-611. doi:10.1007/s11523-019-00668-y
13. Moreno O, Butler T, Zann V, Willson A, Leung P, Connor A. Safety, pharmacokinetics, and pharmacodynamics of ME-401, an oral, potent, and selective inhibitor of phosphatidylinositol 3-kinase P110δ, following single ascending dose administration to healthy volunteers. *Clin Ther*. 2018;40(11):1855-1867. doi:10.1016/j.clinthera.2018.09.006
14. Soumerai JD, Pagel JM, Jagadeesh D, et al. Initial results of a dose escalation study of a selective and structurally differentiated PI3Kδ inhibitor, ME-401, in relapsed/refractory (R/R) follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). *J Clin Oncol*. 2018;36(15_suppl):7519. doi:10.1200/JCO.2018.36.15_suppl.7519
15. Zelenetz AD, Soumerai JD, Jagadeesh D, et al. Preliminary safety and efficacy results with an intermittent schedule of the PI3kδ inhibitor ME-401 alone or in combination with rituximab for B-cell malignancies. *Blood*. 2018;132(Suppl 1):2893. doi:10.1182/blood-2018-99-115670
16. Mahnke K, Schönfeld K, Fondel S, et al. Depletion of $CD4^+CD25^+$ human regulatory T cells in vivo: kinetics of Treg depletion and alterations in immune functions in vivo and in vitro. *Int J Cancer*. 2007;120(12):2723-2733. doi:10.1002/ijc.22617
17. Pagel JM, Soumerai JD, Reddy N, et al. Zandelisib with continuous or intermittent dosing as monotherapy or in combination with rituximab in patients with relapsed or refractory B-cell malignancy: a multicentre, first-in-patient, dose-escalation and dose-expansion, phase 1b trial. *Lancet Oncol*. 2022;23(8):1021-1030. doi:10.1016/S1470-2045(22)00333-3
18. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3067. doi:10.1200/JCO.2013.54.8800
19. Kandathilparambil Sasi B, Martindale SP, Shupe SJ, et al. Mechanistic insights into immune related toxicities in subjects with relapsed/refractory follicular lymphoma treated with zandelisib. *Blood*. 2022;140(Suppl 1):3575-3576. doi:10.1182/blood-2022-159167
20. Lynch RC, Paneesha S, Avigdor A, et al. Phase 2 study evaluating the efficacy and safety of parsaclisib in patients with relapsed or refractory follicular lymphoma (CITADEL-203). *Blood*. 2020;136:36-37. doi:10.1182/blood-2020-134869
21. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. 2020;136(25):2881-2892. doi:10.1182/blood.2020008824
22. Wood WA, Neuberg DS, Thompson JC, et al. Outcomes of patients with hematologic malignancies and COVID-19: a report from the ASH Research Collaborative Data Hub. *Blood Adv*. 2020;4(23):5966-5975. doi:10.1182/bloodadvances.2020003170
23. Soumerai JD, Diefenbach CS, Samaniego F, et al. Safety and efficacy of the PI3Kδ inhibitor zandelisib in combination with the BTK inhibitor zanubrutinib in patients with relapsed/refractory (R/R) follicular lymphoma (FL) or mantle cell lymphoma (MCL). *Blood*. 2022;140(Suppl 1):189-191. doi:10.1182/blood-2022-157563
24. Richardson NC, Kasamon Y, Pazdur R, Gormley N. The saga of PI3K inhibitors in haematological malignancies: survival is the ultimate safety endpoint. *Lancet Oncol*. 2022;23(5):563-566. doi:10.1016/S1470-2045(22)00200-5
25. Brown JR, Danilov AV, LaCasce AS, Davids MS. PI3K inhibitors in haematological malignancies. *Lancet Oncol*. 2022;23(8):e364. doi:10.1016/S1470-2045(22)00300-X