Efficacy and Safety of Capivasertib (AZD5363), a Potent, Oral Pan-AKT Inhibitor, in Patients with Relapsed or Refractory B-cell Non–Hodgkin Lymphoma (CAPITAL)

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ABSTRACT

Purpose: An unmet treatment need remains for relapsed/refractory (R/R) non–Hodgkin lymphoma (NHL), including the follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL) subtypes. The PI3K/AKT/mTOR pathway is dysregulated and associated with poor prognosis in NHL. The AKT inhibitor capivasertib has preclinical activity in hematologic malignancy models.

Patients and Methods: NCT05008055 was a modular, open-label, multicenter phase II study that examined oral capivasertib monotherapy in patients with R/R B-cell NHL who had received ≥2 prior lines of therapy. Patients had R/R FL (cohort 1A), MZL (cohort 1B), or MCL (cohort 1C). Capivasertib 480 mg twice daily was administered orally 4 days on/3 days off. The primary objective was to determine the objective response rate (ORR) by blinded independent central review.

Results: Thirty patients were enrolled (of 272 planned). The ORR for patients with R/R FL, MZL, and MCL were 18.8% (three of 16), 33.3% (one of three), and 30% (three of 10), respectively; 62.5% (10 of 16) of patients with R/R FL had stable disease. Baseline tumor PTEN expression was deficient/undetectable in the two patients who had a complete response and three of five patients who had a partial response. The most common capivasertib-related adverse events (AE) were diarrhea (63.3%), nausea (20%), vomiting (13.3%), and hyperglycemia (10%). Capivasertib-related grade ≥3 AE or serious AE were observed in nine and three patients, respectively.

Conclusions: The study was terminated early with a small sample size, limiting interpretation, although antitumor activity was limited. Future studies of capivasertib in hematologic malignancies would likely require biomarker-directed patient selection and/or combination therapy.

Introduction

Non–Hodgkin lymphoma (NHL) is the eighth most common cancer in the United States, representing an estimated 4% of all new cancer cases in 2024 (1). Although treatment options for some of the most common subtypes of NHL, including follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL), have increased in recent years (2–5), an unmet need for well-tolerated, effective treatment remains.

AKT kinases mediate signaling in the PI3K/AKT/mTOR pathway downstream of activated tyrosine kinases and PI3K (6, 7). PI3K/AKT/mTOR pathway dysregulation is frequent in cancer, and mutations in upstream regulators of AKT, such as PI3K lipid kinases and the tumor suppressors phosphatase and tensin homolog deleted from chromosome 10 (PTEN) and liver kinase B1, result in

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Translational Relevance

New well-tolerated, effective therapeutic options for patients with non–Hodgkin lymphoma (NHL) are needed. Capivasertib is a potent, selective inhibitor of all three isoforms of AKT, activation of which is associated with poor prognosis of NHL. We investigated capivasertib monotherapy (480 mg 4 days on/3 days off) in patients with relapsed/refractory follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma. Patients were not selected based on tumor biomarker expression and were heavily pretreated (2–5 lines of prior therapy). The observed efficacy of capivasertib monotherapy was not sufficient to warrant expansion of the trial, which was terminated early. The side effect profile of capivasertib was as expected based on previous trials, with diarrhea, nausea, vomiting, and hyperglycemia being the most common events. Myelosuppression was uncommon, and there was no evidence of immune-mediated adverse events. Future studies of capivasertib in relapsed/refractory NHL should focus on biomarker-selected patient populations and/or combination regimens.

AKT activation, which drives tumor growth and survival (6, 8). The three isoforms of AKT are directly activated in various types of solid tumors and hematologic malignancies (6, 7, 9–11). AKT activation is associated with resistance to established anticancer therapy, more advanced disease, and a poorer prognosis (8, 11–13).

The PI3K/AKT/mTOR pathway has been shown to be constitutively active in NHL (9), and inhibition of the pathway has an antiproliferative effect and causes apoptosis in multiple lymphoma types *in vitro* (14–16). AKT phosphorylation occurs due to PI3K/AKT/mTOR pathway activation in various types of NHL (9, 17) and it is associated with a poorer prognosis in diffuse large B-cell lymphoma (DLBCL; refs. 9, 17); the aggressive blastoid subtype of MCL may require constitutive AKT activation to survive (9, 18), and FL, for which PI3K inhibitors are effective (19), is sensitive to AKT inhibitors in xenograft models (9).

AKT inhibitors bind to the adenosine triphosphate active site of AKT, exerting cytotoxic and antiproliferative effects on human cancer cells, with a reduction in tumor cell proliferation and tumorigenesis (10, 20–23). Furthermore, AKT inhibition can promote tumor cell apoptosis through the activation of forkhead box O3 protein (FOXO3), formerly known as FOXO3a or FKHR-L1 (24, 25). Capivasertib is a potent, selective inhibitor of all three isoforms of AKT (9, 10). PTEN loss/inactivating mutations have been reported to correlate with sensitivity to capivasertib in preclinical models (26). Early phase I studies in solid tumors have described inhibition of FOXO3 nuclear translocation following capivasertib treatment (27). Capivasertib has demonstrated significant clinical benefit in patients with solid tumors, most notably in combination with fulvestrant in a phase III trial in patients with breast cancer harboring AKT pathway alterations (11). Data from this trial led to its approval in the United States for patients with hormone receptor–positive, HER 2–negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations (28).

Capivasertib monotherapy has demonstrated activity in lymphoma cell lines representative of MCL and DLBCL *in vitro* (29). Constitutively active PI3K–AKT signaling contributes to MCL pathogenesis, which has been confirmed using PTEN knockout or kinase-dead MCL cell lines that retain sensitivity to capivasertib (30). On the basis of these promising preclinical data and the association between AKT abnormalities and prognosis, we designed a modular, open-label, multicenter phase II study (NCT05008055) to examine the efficacy and safety of capivasertib monotherapy administered orally to patients with relapsed/refractory (R/R) B-cell NHL.

Patients and Methods

Study design

This was a modular, phase II, open-label, multicenter study to assess the efficacy and safety of capivasertib monotherapy in patients with R/R B-cell NHL. The study comprised a screening period of 28 days, a treatment period, and a follow-up period. During the treatment period, patients received treatment in 28-day cycles. The follow-up period comprised an end-of-treatment visit conducted within 7 days after treatment discontinuation, a posttreatment follow-up visit conducted 30 days after the last dose of study treatment, and a long-term follow-up (LTFU) period. During the LTFU period, subsequent antilymphoma therapy, drug-related serious adverse events (SAE), concomitant medication, and survival were assessed every 12 weeks.

This study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. Applicable International Conference on Harmonization Good Clinical Practice guidelines, laws, and regulations were followed. The protocol was approved by institutional review boards at each participating center. All patients provided written informed consent.

Patients

Patients had to be ≥18 years of age with a life expectancy >6 months and an Eastern Cooperative Oncology Group performance status ≤2. Patients were required to have bi-dimensionally measurable disease on cross-sectional imaging by CT or MRI with at least one nodal lesion >1.5 cm in the long axis or one extranodal lesion >1 cm in the long axis.

All patients had to have R/R disease, defined as relapsed, progressed, or refractory disease after failing to achieve at least a partial response (PR) after ≥2 prior lines of therapy (including an anti-CD20 mAb or an alkylating agent for patients with FL or ≥1 anti-CD20 mAb regimen for patients with MZL). Patients in cohort 1A were required to have a histologically confirmed diagnosis of R/R FL grade 1, 2, or 3A. Patients in cohort 1B were required to have a histologically confirmed diagnosis of MZL, including splenic, nodal, and extranodal subtypes, and patients in cohort 1C were required to have histologically confirmed MCL with documentation of monoclonal B cells that had a chromosome translocation t(11;14)(q13;q32) and/or overexpressed cyclin D1. All diagnoses were made by the investigator or a local pathologist. All patients were required to provide informed consent.

Patients were excluded from the study if they met exclusion criteria including but not limited to prior malignancy, cardiac conditions such as uncontrolled hypertension or a history of arrhythmia, inadequate bone marrow reserve or organ function, active infection, or prior treatment with any chemotherapy, immunotherapy, immunosuppressant medication, or anticancer agents within 2 weeks of the first dose of the study (see Supplementary Materials for full eligibility criteria).

Treatment

Capivasertib was administered orally at the maximum tolerated dosage of 480 mg twice daily, 4 days on and 3 days off until progression, as defined in the phase I dose-escalation study (27), unless there was evidence of unacceptable toxicity or if the patient/investigator requested that the treatment be stopped.

Temporary suspension of capivasertib treatment was permitted in case of substantial acute toxicity. A maximum of two dose reductions was allowed for each patient, from 480 mg twice daily to 400 mg twice daily and from 400 mg twice daily to 320 mg twice daily, 4 days on/3 days off. Dose re-escalations were not permitted.

Objectives

The primary objective of this study was to determine the efficacy of capivasertib in patients with R/R B-cell NHL based on objective response rate [ORR; proportion of patients achieving either a complete response (CR) or a PR as the best response for an individual patient following enrollment but before any subsequent antilymphoma therapy, up to and including Lugano progression] according to blinded independent central review (BICR).

Secondary objectives were to assess the efficacy of capivasertib based on the duration of response (DoR; time from the date of the first documented response until the date of documented progression or death due to any cause in the absence of disease progression), progression-free survival (PFS; time from the date of first dose until documented disease progression according to the Lugano 2014 classification for NHL as assessed by BICR or death due to any cause), overall survival (OS; time from the date of first dose until the date of death due to any cause), health-related quality of life using the European Organization for Research and Treatment of Cancer QLQ-C30, safety and tolerability, and the pharmacokinetics (PK) of capivasertib.

Exploratory objectives include evaluation of biomarkers that may correlate with response or resistance to capivasertib, including but not limited to PTEN loss.

Assessments

Tumors were assessed using CT every 8 weeks until week 24, then every 12 weeks until week 60, and then every 12 weeks for MCL and every 24 weeks for FL and MZL PET or CT, or at any other time as clinically indicated. In addition, whole-body PET scans were performed every 8 weeks until week 24 and thereafter to confirm a CR or as clinically indicated. Response analyses were performed according to the Lugano 2014 classification for NHL and assessed by BICR using the response-evaluable analysis set (defined as all patients treated with study treatment with measurable disease at baseline). Investigator-assessed ORR was also reported. DoR was assessed based on all patients in the response-evaluable analysis set with a response, regardless of whether the patient withdrew from therapy. Assessment of PFS included all dosed patients, regardless of whether the patient withdrew from therapy, received another antilymphoma therapy, or clinically progressed before progression according to the Lugano 2014 classification for NHL. Assessment of OS included all patients, regardless of whether they withdrew from therapy or received another antilymphoma therapy.

All safety analyses used the safety analysis set (all patients who received any study treatment). Adverse events (AE) were coded using Medical Dictionary for Regulatory Activities version 26.0 and graded according to the Common Terminology Criteria for Adverse Events version 5.0. The following events of scientific and medical interest specific to understanding the safety profile of capivasertib were deemed AE of special interest (AESI): hyperglycemia, noninfectious diarrhea, infective pneumonia, rash, stomatitis, QT prolongation, and hematologic effects.

Furthermore, as part of exploratory biomarker analysis, tumor samples collected from patients at study start/baseline were centrally assessed for PTEN (Roche, SP218) and FOXO3a/1 (Cell Signaling Technology, D19A7) protein expression by IHC. PTEN protein loss/deficiency was defined as ≤10% tumor cells having absent or weak cytoplasmic PTEN staining (31, 32).

PK analyses used the PK analysis set (all patients who received at least one dose of capivasertib and for whom there was at least one reportable PK concentration). Blood samples for assessment of plasma PK were taken at 1, 2, and 4 hours after dose on cycle 1, day 1 and 0 to 90 minutes before dose on cycle 1, days 8, 15, and 22. PK was assessed as the plasma concentration of capivasertib before the dose (C_{trough}) and after the dose. Plasma PK parameters derived from a population PK model, as permitted by the data, were also assessed. Plasma concentration over time was measured, and the data were analyzed by population PK methods using nonlinear mixed-effects modeling. The influence of intrinsic (e.g., ethnicity, gender, and age) and extrinsic (e.g., concomitant medication) factors was evaluated.

Statistical analysis

Analysis of the primary efficacy endpoint of ORR was planned to be based on a sample size of 272 patients (94 patients in each of cohorts 1A and 1B and 84 in cohort 1C). This would have provided 80% power for an exact binomial test with a two-sided significance level of 0.05 to detect a difference between the null hypothesis proportion of 40% and the alternative hypothesis proportion of 55% in cohorts 1A and 1B and a difference between the null hypothesis proportion of 25% and the alternative hypothesis proportion of 40% in cohort 1C. However, the trial was closed early because efficacy was not sufficient to warrant expansion, meaning that planned interim efficacy analyses were not conducted.

Binomial exact 95% confidence intervals (CI) were calculated for ORR. Best overall response was summarized as the number of patients and percentage for each category [CR, PR, stable disease (SD), progressive disease (PD), and not evaluable]. No formal statistical analysis was carried out.

PK data were summarized using descriptive statistics.

Results

Patients

A total of 42 patients were screened, and 30 patients (16 with R/R FL, four with R/R MZL, and 10 with R/R MCL) were treated (**Fig. 1**). Baseline patient and disease characteristics are shown in **Table 1** (representativeness of study participants is described in Supplementary Table S1). Most patients were White (20 of 30, 66.7%) and had Ann Arbor stage III or IV disease at study entry (29 of 30, 96.7%), and all had received at least two prior lines of therapy.

At the data cutoff of August 22, 2023, 25 of 30 (83.3%) patients had discontinued treatment, mainly because of disease progression (n = 17/25, 68%; **Fig. 1**). In addition, four patients discontinued because of AE; two withdrew consent, and one each discontinued at the investigator's and patient's decision.

Efficacy

The median duration of follow-up in cohorts 1A, 1B, and 1C was 11.3 (1.4–19.1), 2 (1–11.5), and 2.5 (1.6–14.9) months, respectively.

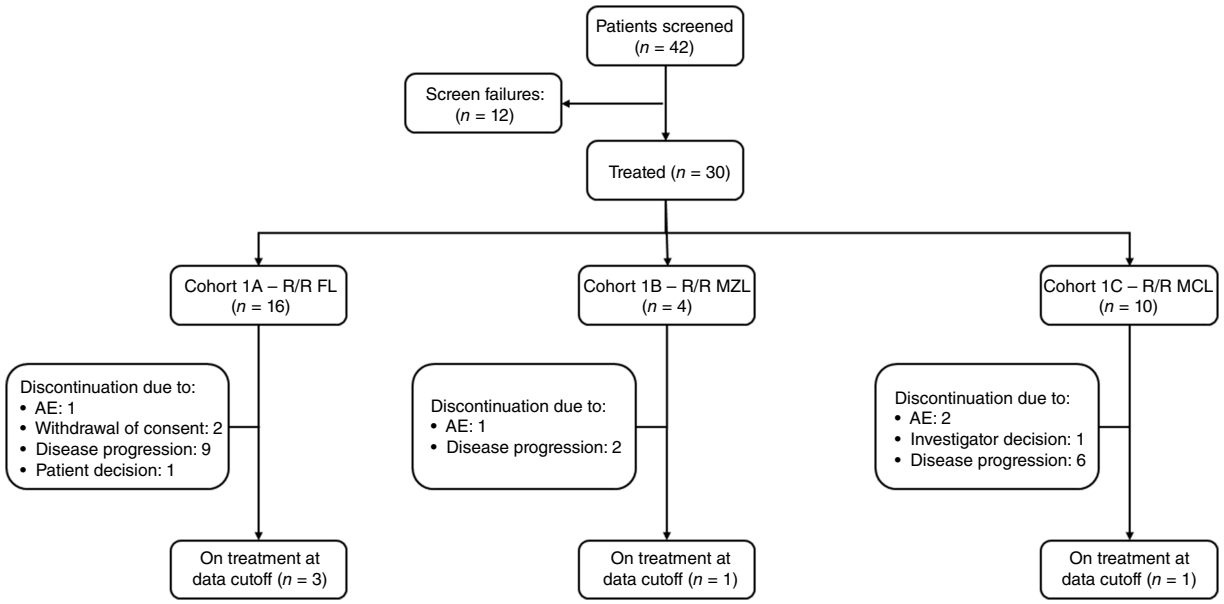

Figure 1.
CAPITAL study design and patient disposition.

In cohort 1A, three patients with R/R FL achieved an objective response of PR as assessed by BICR, for an ORR of 18.8% (95% CI, 4%–45.6%; **Table 2**). SD was reported as the BOR for 10 (62.5%) patients. As assessed by the investigator, six patients (37.5%) achieved an objective response (all partial responses), seven patients (43.8%) had stable disease, one patient had progressive disease, and two patients were not evaluable, resulting in an objective response rate of 37.5% (95% CI, 15.2%–64.6%). By BICR, the median time to response was 3.6 [95% CI, 1.6–not calculable (NC)] months, and the median DoR was 1.9 (95% CI, 1.7–NC) months. The median PFS was 5.4 (95% CI, 3.4–NC) months, with a PFS rate at 6 months of 33.8% (95% CI, 6.1%–65.7%). The median OS was NC.

In cohort 1B, one of three patients (33.3%) with MZL who were evaluable for response achieved an objective response of CR by both BICR and investigator assessment (**Table 2**). This response lasted >6 months. By BICR, the median PFS was NC, whereas the PFS rate at 6 months was 50.0% (95% CI, 0.6%–91%), and the median OS was NC.

In cohort 1C, the ORR was 30%, with one (10%) patient having a CR and two (20%) patients having a PR. As assessed by the investigator, all three patients had a CR (**Table 2**). By BICR, the median PFS was 1.9 (95% CI, 0.9–NC) months; PFS rate at 6 months and median OS were NC.

Overall, seven of 29 (24.1%) patients evaluable for response had an objective response to capivasertib therapy based on BICR, the median time to response was 2 (1.6–3.6) months, and the median DoR was 1.9 (1.7–NC) months (**Table 2**; **Fig. 2**). Whether there were any differences in time to response or DoR by disease type could not be assessed because of the low number of responses observed ($n = 7$).

Baseline tumor PTEN and FOXO3a/1 protein expression data were available for 11 patients (investigator assessment: CR, $n = 2$; PR, $n = 5$; and SD, $n = 4$; no patient with baseline tumor PTEN and FOXO3a/1 protein expression data had a best response of PD) who received capivasertib monotherapy. Of the two patients who had a CR, the patient with R/R MZL had cytoplasmic PTEN deficiency (≤10% tumor cells) and elevated FOXO3a/1 expression (80% cytoplasmic; **Fig. 3**), whereas the patient with R/R MCL had undetectable tumor cytoplasmic PTEN and FOXO3a/1 expression. Tumor FOXO3a/1 expression was undetectable in the five patients with a PR; tumor PTEN expression was undetectable in three of these patients and positive (>10%) in the other two patients. In the four patients with SD, tumor FOXO3a/1 expression was undetectable in three and approximately 50% in the remaining patient; tumor PTEN expression was positive (>10%) in all four patients (Supplementary Figs. S1 and S2).

Safety

The median capivasertib treatment duration was 2.3 (0.1–12.8) months for the overall patient population but was longer in cohort 1A [3.5 (0.8–12.8) months] than in cohorts 1B [0.9 (0.6–11.5) months] and 1C [1.6 (0.1–7.4) months]. The median number of cycles of treatment received was three (1–14) and was again greater in cohort 1A [4 (1–14) months] than in cohorts 1B [1 (1–12)] and 1C [2 (1–8)]. However, 21 of 30 (70%) patients missed at least one dose of capivasertib [11 of 16 (68.7%) in cohort 1A, three of four (75%) in cohort 1B, and seven of 10 (70%) in cohort 1C], 12 [40%; cohort 1A, seven of 16 (43.8%); cohort 1B, two of four (50%); and cohort 1C, three of 10 (30%)] patients had a dose interruption of a median of four (2–4) days in duration, and six [20%; cohort 1A, two of 16 (12.5%); cohort 1B, two of four (50%); and cohort 1C, three of 10 (30%)] patients had dose reductions due to AE [diarrhea (one each in cohorts 1B and 1C) and rash (one each in cohorts 1A and 1C) in two (6.7%) patients each, decreased neutrophil count (cohort 1C), and thrombocytopenia (cohort 1A)]. A dose reduction due to patient decision was observed in cohort 1B. Three (10%) patients experienced an AE that led to

Table 1. Baseline patient and disease characteristics (safety analysis set).

Characteristic	R/R FL (cohort 1A) (*N* = 16)	R/R MZL (cohort 1B) (*N* = 4)	R/R MCL (cohort 1C) (*N* = 10)	Total (*N* = 30)
Median age, years (range)	53.5 (40–80)	65 (63–74)	81 (58–87)	64 (40–87)
Male/female, *n* (%)	9 (56.3)/7 (43.8)	2 (50)/2 (50)	6 (60)/4 (40)	17 (56.7)/13 (43.3)
Race, *n* (%)				
Asian	5 (31.3)	1 (25)	0	6 (20)
White	10 (62.5)	3 (75)	7 (70)	20 (66.7)
Other	0	0	1 (10)	1 (3.3)
Not reported	1 (6.3)	0	2 (20)	3 (10)
Ethnicity				
Hispanic/Latino	3 (18.8)	0	1 (10)	4 (13.3)
Not Hispanic/Latino	12 (75)	4 (100)	5 (50)	21 (70)
Missing	1 (6.3)	0	4 (40)	5 (16.7)
ECOG performance status, *n* (%)				
0	11 (68.8)	1 (25)	4 (40)	16 (53.3)
1	5 (31.3)	2 (50)	5 (50)	12 (40)
2	0	1 (25)	1 (10)	2 (6.7)
Median number of prior lines of therapy, *n* (range)	3 (2–5)	2.5 (2–5)	2.5 (2–5)	3 (2–5)
Prior CAR-T therapy, (%)	0	0	2 (20)	2 (6.7)
Prior PI3K inhibitor therapy, *n* (%)	5 (31.3)	1 (25)	1 (10)	7 (23.3)
Prior autologous HSCT, *n* (%)	1 (6.3)	0	3 (30)	4 (13.3)
Prior allogeneic HSCT	0	0	1 (10)	1 (3.3)
Ann Arbor stage at study entry, *n* (%)				
II	0	0	1 (10)	1 (3.3)
III	3 (18.8)	0	2 (20)	5 (16.7)
IV	13 (81.3)	4 (100)	7 (70)	24 (80)
BM involvement, *n* (%)				
Yes	10 (62.5)	2 (50)	2 (20)	14 (46.7)
No	5 (31.3)	2 (50)	8 (80)	15 (50)
Missing	1 (6.3)	0	0	1 (3.3)
Disease status at study entry, *n* (%)			—	—
Relapsed after last line of therapy	11 (68.8)	2 (50)		
Relapsed <6 months after last treatment	6 (37.5)	0		
Refractory	5 (31.3)	2 (50)		
R/R FL				
Histologic grade, *n* (%)		—	—	—
Grade 1	4 (25)			
Grade 2	7 (43.8)			
Grade 3A	5 (31.3)			
FLIPI score, *n* (%)		—	—	—
High (≥3)	8 (50)			
Intermediate (2)	7 (43.8)			
Low (0–1)	1 (6.3)			
FLIPI-2 score, *n* (%)		—	—	—
High (3–5)	7 (43.8)			
Intermediate (1–2)	5 (31.3)			
Low (0)	4 (25)			
High tumor burden, *n* (%)	8 (50)	—	—	—
POD24, *n* (%)	5 (31.3)	—	—	—
R/R MZL				
MZL subtype, *n* (%)	—		—	—
Nodal		0		
Extranodal/MALT		2 (50)		
Splenic		2 (50)		
R/R MCL				
Simplified MIPI, *n* (%)	—	—		—
High			4 (40)	
Intermediate/low			2 (20)	
Missing			4 (40)	

Abbreviations: BM, bone marrow; CAR-T, chimeric antigen receptor T cell; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; HSCT, hematopoietic stem cell transplant; MALT, mucosa-associated lymphoid tissue; MIPI, Mantle Cell Lymphoma International Prognostic Index; POD24, progression of disease within 2 years.

Table 2. ORR by BICR.

Best objective response	R/R FL (cohort 1A)> (*N* = 16) *n* (%; 95% CI[a])	R/R MZL (cohort 1B) (*N* = 3) *n* (%; 95% CI[a])	R/R MCL (cohort 1C)> (*N* = 10) *n* (%; 95% CI[a])	Total (*N* = 29) *n* (%; 95% CI)
Overall response, *n* (%; 95% CI)				
CR	0 (0–20.6)	1 (33.3; 0.8–90.6)	1 (10; 0.3–44.5)	2 (6.9)
PR	3 (18.8; 4–45.6)	0 (0–70.8)	2 (20; 2.5–55.6)	5 (17.2)
SD	10 (62.5; 35.4–84.8)	0 (0–70.8)	0 (0–30.8)	10 (34.5)
PD	0 (0–20.6)	1 (33.3; 0.8–90.6)	2 (20; 2.5–55.6)	3 (10.3)
NE	3 (18.8; 4–45.6)	1 (33.3; 0.8–90.6)	5 (50; 18.7–81.3)	9 (31)
ORR (CR + PR), *n* (%; 95% CI)	3 (18.8; 4–45.6)	1 (33.3; 0.8–90.6)	3 (30; 6.7–65.2)	7 (24.1)
Median time to response, months (95% CI)	3.6 (1.6–NC)	1.7 (NC–NC)	2 (1.7–NC)	2 (1.6–3.6)
Median DoR, months (95% CI)	1.9 (1.7–NC)	NC (NC–NC)	1.9 (NC–NC)	1.9 (1.7–NC)
Patients remaining in response at (%)[b]	(*n* = 3)	(*n* = 1)	(*n* = 3)	(*n* = 7)
3 months	NC	100	NC	25
6 months	NC	100	NC	25
12 months	NC	NC	NC	NC

Abbreviation: NE, not evaluable.
[a]CI from exact binomial properties. Lugano 2014 classification for NHL as assessed by BICR.
[b]Calculated using the Kaplan–Meier technique.

discontinuation of treatment (grade 2 hemoptysis in cohort 1A and grade 3 erythema multiforme and grade 3 QT prolongation in one patient each in cohort 1C).

Overall, 29 of 30 (96.7%) patients experienced at least one AE (**Table 3**), with 25 (83.3%) patients having events considered possibly related to study treatment by the investigator. The most frequently reported AE were gastrointestinal events, with diarrhea [*n* = 21 (70%) patients; related to capivasertib in 19 (63.3%) patients] and nausea [*n* = 9 (30%) patients; related to capivasertib in six (20%) patients] being the most common (**Table 3**). Most diarrhea events occurred only on days on which capivasertib was dosed [18 (60%) patients]. None of the diarrhea events led to discontinuation, although the treatment dose was reduced and interrupted for two (6.7%) and three (10%) patients, respectively.

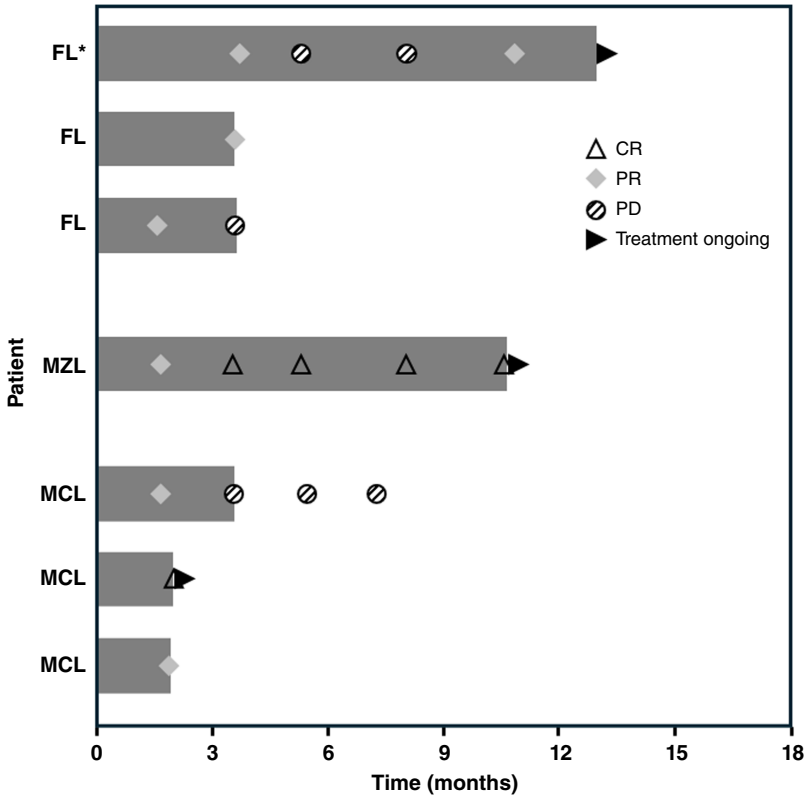

Figure 2.
Swimmer plots showing DOR for patients whose disease responded to capivasertib therapy (response evaluable analysis set). *Based on investigator assessment, this patient with R/R FL had a PR at all scheduled tumor assessments up to 48 weeks. Capivasertib treatment was therefore continued. However, by BICR, tumor response at 8 weeks was classified as SD and at 24 and 36 weeks as PD, as shown.

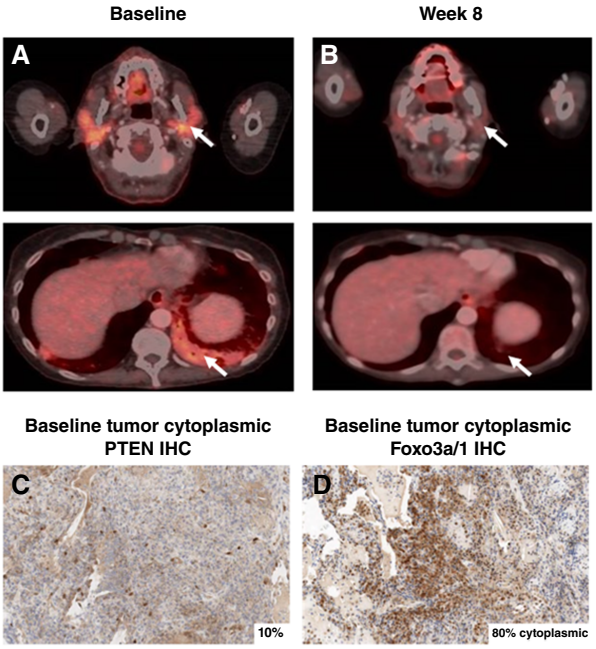

Figure 3.

PET/CT scan images from the patient with R/R MZL who had a CR showing shrinkage of the tumor at 8 weeks after capivasertib (**B**) compared with baseline (**A**), as indicated by the white arrows. Representative baseline tumor PTEN (**C**) and FOXO3a/1 (**D**) expression by IHC staining.

Grade ≥3 AE were reported by 15 (50%) patients; these included diarrhea [three (10%) patients], rash [two (6.7%) patients], and thrombocytopenia [two (6.7%) patients]. Nine (30%) patients reported grade ≥3 AE possibly related to treatment, including diarrhea [three (10%) patients], rash [two (6.7%) patients], perirectal abscess, hyperglycemia, erythema multiforme, maculopapular rash, and QT prolongation (one patient each).

Five (16.7%) patients experienced at least one SAE. For three (10%) patients, these SAE were considered possibly related to study treatment by the investigator (grade 3 diarrhea, perirectal abscess and hyperglycemia, and erythema multiforme).

Overall, 26 (86.7%) patients experienced at least one AESI. The most frequently reported AESI were diarrhea [21 (70%) patients], rash [five (16.7%) patients], and neutropenia [three (10%) patients]. Diarrhea occurred in 15 (93.8%), two (50%), and four (40%) patients in cohorts 1A, 1B, and 1C, respectively. A total of 14 patients had grade ≥3 AESI [diarrhea (three patients, one in each cohort, related), rash (two patients, cohorts 1A and 1C, related), thrombocytopenia (two patients, cohorts 1A and 1C, not related), hyperglycemia (cohort 1C, related), maculopapular rash (cohort 1A, related), neutropenia (cohort 1A, related), erythema multiforme (cohort 1C, related), QT prolongation (cohort 1C, related), neutrophil count decreased (cohort 1C, not related), and COVID-19 pneumonia (cohort 1A, not related; one patient each)].

No deaths due to AE were reported.

PK

In all three cohorts, C_{max} was observed at 2 hours after dose on cycle 1, day 1 [cohort 1A ($n = 16$), geometric mean value 883.7 ng/mL; cohort 1B ($n = 4$), geometric mean value 962.9 ng/mL; and cohort 1C ($n = 9$), geometric mean value 976.1 ng/mL]. C_{trough} before dose on days 8, 15, and 22 was similar in the three cohorts (cohort 1A, 6.149, 5.844, and 7.974 ng/mL; cohort 1B, 8.477 ng/mL, 9.245 ng/mL, and NC; and cohort 1C, 14.31 ng/mL, 32.36 ng/mL, and NC, respectively).

Discussion

This modular, open-label, multicenter, phase II study was designed to determine the efficacy, safety, and PK profile of the novel pan-AKT inhibitor capivasertib in patients with common subtypes of R/R B-cell NHL. Capivasertib has demonstrated benefit in combination with fulvestrant and is approved in the United States for use in patients with hormone receptor–positive, HER 2–negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations (11, 28). However, the efficacy of capivasertib monotherapy in this trial in patients with unselected, heavily pretreated R/R FL, MZL, or MCL was not sufficient to warrant expansion of the trial despite promising preclinical data (33). The ORR was 24.1% (seven of 29 evaluable patients), and DoR was short at a median of 1.9 months. With these results and a rapidly evolving treatment landscape, it was decided to stop enrollment into the trial.

As a result of the early termination of the trial, the planned sample size for analysis of ORR was not met. Therefore, the efficacy results should be interpreted with caution, particularly considering the discrepancy in investigator and BICR assessment of response in the FL cohort, which seems to have been due to a difference in interpretation of PET assessments that resulted in a Deauville score of 4. In addition, tumor AKT activation was not a requirement for study entry, which may have reduced the efficacy of capivasertib in the study population. Retrospective analysis of baseline tumors (n = 11) suggested that, in the patient with R/R MZL who achieved a CR, loss of PTEN expression and elevated cytoplasmic FOXO3 were consistent with constitutive AKT signaling and may indicate potential sensitivity to the AKT inhibitor capivasertib (**Fig. 3**; Supplementary Figs. S1 and S2). In previous studies of capivasertib monotherapy in unselected populations with solid tumors, responses were seen only in patients with PI3K/AKT/mTOR mutations (27, 34); the response rate was higher in the expansion parts of these studies that included only patients with tumors harboring *PIK3CA* or *AKT1* mutations (27, 35). Similar results have been observed in other trials of single-agent AKT inhibitors in hematologic malignancies (36, 37). This suggests that future studies of AKT inhibition in R/R B-cell NHL should be driven by biomarkers.

The safety profile of oral capivasertib 480 mg twice daily monotherapy on a 4-day on/3-day off schedule was as expected (27, 34). Previous studies of capivasertib monotherapy have shown that diarrhea is the most common capivasertib-related AE (27, 34). Other AE related to capivasertib included nausea, vomiting, hyperglycemia, and rash, again in line with the results of previous studies of capivasertib monotherapy, although perhaps occurring at a lower incidence (27, 34). This could potentially be due to the relatively short duration of therapy (median three cycles), with diarrhea shown to occur on the day of capivasertib dosing. Diarrhea has also been observed with PI3K inhibitors, although the grade ≥3 AE associated with these agents are different from those of capivasertib observed in this study (38). The restriction of diarrhea predominantly to the day of capivasertib dosing suggests that the mechanism of the diarrhea associated with capivasertib is probably different from the immune-mediated colitis reported

Table 3. Summary of AE with capivasertib (safety analysis set).

	Patients, *n* (%)[a]			
	Cohort 1A (*n* = 16)	**Cohort 1B (*n* = 4)**	**Cohort 1C (*n* = 10)**	**Total (*n* = 30)**
Any AE	16 (100)	3 (75)	10 (100)	29 (96.7)
Any AE possibly related to treatment	14 (87.5)	3 (75)	8 (80)	25 (83.3)
Any grade ≥3 AE	7 (43.8)	1 (25)	7 (70)	15 (50)
Any grade ≥3 AE possibly related to treatment	3 (18.8)	1 (25)	5 (50)	9 (30)
Any AE resulting in death	0	0	0	0
Any SAE	2 (12.5)	0	3 (30)	5 (16.7)
Any SAE possibly related to treatment	0	0	3 (30)	3 (10)
Any AE leading to treatment discontinuation	1 (6.3)	0	2 (20)	3 (10)
Any AE leading to dose reduction	2 (12.5)	1 (25)	3 (30)	6 (20)
Any AE leading to treatment interruption	7 (43.8)	2 (50)	2 (20)	11 (36.7)
AE possibly related to treatment occurring in ≥5% of patients overall				
Diarrhea	14 (87.5)	2 (50)	3 (30)	19 (63.3)
Nausea	1 (6.3)	2 (50)	3 (30)	6 (20)
Vomiting	2 (12.5)	1 (25)	1 (10)	4 (13.3)
Fatigue	3 (18.8)	0	0	3 (10)
Hyperglycemia	1 (6.3)	0	2 (20)	3 (10)
Dizziness	1 (6.3)	0	1 (10)	2 (6.7)
Flatulence	1 (6.3)	0	1 (10)	2 (6.7)
Hyperuricemia	0	1 (25)	1 (10)	2 (6.7)
Muscle spasms	1 (6.3)	1 (25)	0	2 (6.7)
Rash	1 (6.3)	0	1 (10)	2 (6.7)
Rash maculo-papular	2 (12.5)	0	0	2 (6.7)

[a]Patients with multiple AE of the same type were counted only once. Includes AE and worsening of preexisting AE with an onset date after the first dose of study treatment and within 37 days after the last dose of study treatment or up to the day before to the start of subsequent therapy, whichever came first.

with PI3K inhibitors. Importantly, myelosuppression, observed with PI3K inhibitors (38), was uncommon with capivasertib monotherapy, and there was no evidence of immune-mediated AE. These data suggest that trials of capivasertib in combination with other PI3K/AKT/mTOR pathway inhibitors or other anticancer agents may be feasible, although the selection of combinations for study should be based on preclinical data indicating significant activity. This approach has been used successfully in breast cancer, in which capivasertib is approved in combination with fulvestrant (28), and many ongoing trials of AKT inhibitors in solid tumors and hematologic malignancies use combination regimens (39). The combination of capivasertib with Bruton tyrosine kinase (BTK) inhibitors, which are widely used to treat B-cell lymphomas, may warrant investigation because of the links between the AKT and BTK signaling pathways and the incidence of primary resistance to BTK inhibitors (40).

One AESI of electrocardiogram QT prolongation occurred in a patient in cohort 1C on day 1 after the first dose of capivasertib. This patient also had grade 2 QT interval corrected using Fridericia formula (QTcF) prolongation during the screening period, which resolved before starting capivasertib treatment. At this dose and based on previous studies, capivasertib would not be expected to cause QT prolongation (41). However, the investigator permanently discontinued study treatment on day 1 as a safety precaution based on the patient's age, risk factors (history of fibrillation), and worsening of baseline QT prolongation.

The observed plasma concentrations of capivasertib were comparable to those in other studies in adults (42–44), with C_{max} values ranging from 883.7 to 976.1 ng/mL and mean C_{trough} values ranging from 5.84 to 32.36 ng/mL.

The small sample size and early termination of this study limit the conclusions that can be drawn about the utility of capivasertib monotherapy in patients with R/R NHL. Achieving greater efficacy of capivasertib in indolent NHL may require biomarker-directed patient selection or use in combination with agents for which robust evidence of synergy emerges based on studies using preclinical models.

Data Availability

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. An AstraZeneca Vivli member page is also available outlining further details at https://vivli.org/ourmember/astrazeneca/.

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Note

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