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Pan-phosphatidylinositol 3-kinase inhibition with buparlisib in patients with relapsed or refractory non-Hodgkin lymphoma

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ABSTRACT

Activation of the phosphatidylinositol 3-kinase/mechanistic target of rapamycin pathway plays a role in the pathogenesis of non-Hodgkin lymphoma. This multicenter, open-label phase 2 study evaluated buparlisib (BKM120), a pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or refractory non-Hodgkin lymphoma. Three separate cohorts of patients (with diffuse large B-cell lymphoma, mantle cell lymphoma, or follicular lymphoma) received buparlisib 100 mg once daily until progression, intolerance, or withdrawal of consent. The primary endpoint was overall response rate based on a 6-month best overall response by cohort; secondary endpoints included progression-free survival, duration of response, overall survival, safety, and tolerability. Overall, 72 patients (26 with diffuse large B-cell lymphoma, 22 with mantle cell lymphoma, and 24 with follicular lymphoma) were treated. The overall response rates were 11.5%, 22.7%, and 25.0% in patients with diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma, respectively; two patients (one each with diffuse large B-cell lymphoma and mantle cell lymphoma) achieved a complete response. The most frequently reported (>20%) adverse events of any grade in the population in which safety was studied were hyperglycemia, fatigue, and nausea (36.1% each), depression (29.2%), diarrhea (27.8%), and anxiety (25.0%). The most common grade 3/4 adverse events included hyperglycemia (11.1%) and neutropenia (5.6%). Buparlisib showed activity in relapsed or refractory non-Hodgkin lymphoma, with disease stabilization and sustained tumor burden reduction in some patients, and acceptable toxicity. Development of mechanism-based combination regimens with buparlisib is warranted. (This study was funded by Novartis Pharmaceuticals Corporation and registered with *ClinicalTrials.gov* number, NCT01693614).

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Introduction

Non-Hodgkin lymphoma (NHL) accounts for 4% of all cancers¹ and resulted in an estimated 199,700 deaths worldwide in 2012.² NHL subtypes include diffuse large B-cell lymphoma (DLBCL; 22-36% of cases of NHL), mantle cell lymphoma (MCL; 1%-14% of cases of NHL), and follicular lymphoma (FL; 8%-32% of cases

of NHL).^{3,5} Response to treatment is heterogeneous due to the varying biology of each NHL subtype; disease course can be indolent or aggressive.^{6,7} The 5-year survival rate from 2006 to 2012 was 62% for patients with DLBCL, 56% for those with MCL, and 88% for those with FL.⁵ Combining rituximab, a monoclonal antibody targeting the CD20 antigen on B cells, with standard chemotherapy has improved NHL treatment outcomes.⁸ Despite high response rates to rituximab-based regimens, many patients become resistant to treatment or relapse after initially achieving a response.⁸

Phosphatidylinositol 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR) signaling regulates many cellular activities, including proliferation, survival, angiogenesis, and glucose metabolism.⁹ Due to its effects on B-cell signaling, dysregulation of PI3K signaling is associated with cancer development and may play a key role in the pathogenesis of NHL.¹⁰⁻¹⁴ Class I PI3K, the most common forms implicated in cancer, are heterodimers with regulatory (p85) and catalytic (p110) subunits.¹⁵ There are four class I isoform catalytic subunits, p110 α , p110 β , p110 γ , and p110 δ (encoded by *PIK3CA*, *PIK3CB*, *PIK3CG*, and *PIK3CD*, respectively),¹⁵ with varying levels of expression; p110 α and p110 β are ubiquitous, whereas p110 γ and p110 δ are mainly expressed in hematopoietic cells.^{15,16} Preclinical evidence indicates that B-cell malignancies frequently overexpress *PIK3CD*.^{17,18} The PI3K δ inhibitor idelalisib showed antitumor activity in patients with relapsed or refractory indolent NHL,^{19,20} and was subsequently approved in 2014 for the treatment of patients with relapsed FL and chronic lymphocytic leukemia (in the latter case in combination with rituximab).^{21,22}

Differential PI3K isoform expression levels have also been associated with different disease stages in NHL.²³ For example, in MCL, *PIK3CA* expression increased upon progression and was implicated as an escape mechanism for PI3K δ inhibition.^{14,23} Other members of the PI3K pathway, including the phosphatase and tensin homolog (PTEN; a negative regulator of PI3K activity) and mTOR (a downstream effector), also play a role in NHL.^{14,24} Thus, treating patients with a targeted drug that can inhibit all four isoforms of PI3K may help to block escape pathways, prolong responses, and improve outcomes compared to those achieved with treatment with an inhibitor specific for a single isoform, particularly in patients with relapsed or refractory disease.^{25,26} Buparlisib, a potent, oral pan-PI3K inhibitor, showed antitumor activity in lymphoma cell lines, induced apoptosis in DLBCL²⁷ and reduced myc-dependent proliferation in MCL,²⁸ showed preclinical activity in hematologic malignancies,^{28,29} and had clinical efficacy in solid tumors, including breast cancer.³⁰⁻³³ In this open-label phase 2 study, we evaluated the efficacy and safety of buparlisib in patients with relapsed or refractory DLBCL, MCL, or FL.

Methods

Patients

Adult patients (aged ≥ 18 years) were eligible if they had histologically confirmed DLBCL, MCL, or FL that had relapsed or was refractory to one or more prior therapies. Patients were required to have one or more measurable nodal lesions (≥ 2 cm according to International Working Group criteria);^{34,35} if no such nodal lesion was present at baseline, one or more measurable

extra-nodal lesions were required. Additional inclusion criteria included an Eastern Cooperative Oncology Group performance status of ≤ 2 , adequate bone marrow and organ function, and fasting plasma glucose ≤ 120 mg/dL. Patients with DLBCL were either ineligible for autologous or allogeneic stem cell transplantation or had previously received a transplant.

Patients previously treated with PI3K inhibitors, or those with evidence of graft-versus-host disease, active or past central nervous system disease, poorly controlled diabetes mellitus (glycated hemoglobin $>8\%$), active cardiac disease, a history of myocardial infarction within 6 months, or documented congestive heart failure or cardiomyopathy were excluded (additional information is available in the *Online Supplementary Methods*). Patients were excluded if they had received anticancer therapy within 4 weeks (6 weeks for nitrosourea, monoclonal antibodies, or mitomycin-C) prior to starting the study.

Objectives

The primary objective was to determine the overall response rate, defined as the proportion of patients with a best overall response of complete or partial response, according to International Working Group criteria,^{34,35} in three different histological subgroups of NHL (i.e., DLBCL, MCL, and FL). The primary objective was assessed locally, per investigator, independently for each cohort, and was based on a 6-month best overall response. Secondary objectives were to assess progression-free survival, duration of response, overall survival, and safety and tolerability in the three histological subgroups (additional information is available in the *Online Supplementary Methods*).

Study design

This was a multicenter, open-label, single-arm, phase II study in patients with relapsed or refractory NHL (NCT01693614).

Patients with previously treated DLBCL, MCL, or FL received buparlisib 100 mg daily continuously in 28-day cycles until disease progression, death, or intolerable toxicity. Treatment interruptions due to toxicity lasting ≥ 28 days required permanent study drug discontinuation. Up to two dose reductions (to 80 mg or 60 mg daily) were allowed; patients needing additional reductions discontinued the study.

Patients provided written informed consent prior to entering the study. The study protocol and informed consent form were reviewed and approved by the independent ethics committee or institutional review board for each center. The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles of the Declaration of Helsinki.

Schedule of assessments

The assessment schedule is described in the *Online Supplementary Methods*.

Statistical analyses

The intent-to-treat population included all patients who received one or more dose of study treatment; the safety set included all patients who received one or more dose of study treatment and had one or more post-baseline safety assessments. The analysis for each cohort (i.e., DLBCL, MCL, and FL) was based on an exact binomial test comparing the overall response rate to a reference level of 10% in the intent-to-treat population, with a significance level of 5% (two-sided). An exact 95% Clopper-Pearson confidence interval (CI) for the overall response rate was calculated. Time-to-event endpoints (i.e., progression-free survival, duration of response, and overall survival)

were described using Kaplan–Meier curves with associated summary statistics. For progression-free survival and duration of response, patients not known to have progressed or who died by the data cut-off date were censored at the time of last tumor assessment or before any further anticancer therapy had been given. For overall survival, patients not known to have died at the data cut-off were censored at the date of their last contact (additional information is available in the *Online Supplementary Methods*).

Table 1. Baseline characteristics and patient disposition of the patients.

	DLBCL (n = 26)	MCL (n = 22)	FL (n = 24)	All patients (N = 72)
Baseline characteristics				
Median age, years (range)	64 (28-81)	69 (47-79)	61 (41-85)	65 (28-85)
Male, n (%)	18 (69.2)	18 (81.8)	13 (54.2)	49 (68.1)
Stage at last assessment prior to study entry, n (%)				
I/II	10 (38.5)	1 (4.5)	7 (29.2)	18 (25.0)
III/IV	16 (61.5)	20 (90.9)	17 (70.8)	53 (73.6)
Missing	0	1 (4.5)	0	1 (1.4)
Bulky disease	5 (19.2)	1 (4.5)	4 (16.7)	10 (13.9)
Elevated LDH	11 (42.3)	6 (27.3)	9 (37.5)	26 (36.1)
Prior bone marrow involvement	6 (23.1)	13 (59.1)	15 (62.5)	34 (47.2)
Median number of prior regimens (range)	3 (1-12)	2 (1-6)	2 (1-9)	2 (1-12)
Prior therapies, n (%)				
Alkylating agent	26 (100)	22 (100)	22 (91.7)	70 (97.2)
Rituximab*	25 (96.2)	20 (90.9)	23 (95.8)	68 (94.4)
Anthracycline	26 (100)	19 (86.4)	15 (62.5)	60 (83.3)
Bendamustine	3 (11.5)	6 (27.3)	12 (50.0)	21 (29.2)
Purines	1 (3.8)	2 (9.1)	1 (4.2)	4 (5.6)
Radiotherapy	9 (34.6)	3 (13.6)	6 (25.0)	18 (25.0)
Autologous SCT	6 (23.1)	7 (31.8)	4 (16.7)	17 (23.6)
Best response at last treatment, n (%)				
Complete response	4 (15.4)	7 (31.8)	10 (41.7)	21 (29.2)
Partial response	7 (26.9)	6 (27.3)	3 (12.5)	16 (22.2)
Stable disease	2 (7.7)	3 (13.6)	5 (20.8)	10 (13.9)
Progressive disease	10 (38.5)	4 (18.2)	4 (16.7)	18 (25.0)
Other†	3 (11.5)	2 (9.1)	2 (8.3)	7 (9.7)
WHO/ECOG performance status, n (%)				
0	9 (34.6)	10 (45.5)	17 (70.8)	36 (50.0)
1	14 (53.8)	12 (54.5)	6 (25.0)	32 (44.4)
2	3 (11.5)	0	1 (4.2)	4 (5.6)
Patients' disposition*				
Treatment disposition, n (%)				
Treatment ongoing	2 (7.7)	5 (22.7)	2 (8.3)	9 (12.5)
End of treatment	24 (92.3)	17 (77.3)	22 (91.7)	63 (87.5)
Primary reason for treatment cessation, n (%)				
Disease progression	11 (42.3)	5 (22.7)	7 (29.2)	23 (31.9)
Adverse events	6 (23.1)	9 (40.9)	4 (16.7)	19 (26.4)
Protocol deviation	5 (19.2)	2 (9.1)	0	7 (9.7)
Physician's decision	1 (3.8)	1 (4.5)	4 (16.7)	6 (8.3)
Patient withdrew consent	0	0	5 (20.8)	5 (6.9)
Patient/guardian decision	0	0	2 (8.3)	2 (2.8)
Death	1 (3.8)	0	0	1 (1.4)

Autologous SCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; FL: follicular lymphoma; LDH: lactate dehydrogenase; MCL: mantle cell lymphoma; WHO: World Health Organization. *In the FL cohort, one patient who did not receive rituximab and two patients who did receive rituximab also received prior investigational anti-CD20 therapy. †Other includes unconfirmed complete response (n=1, DLBCL; n=0, MCL and FL), unknown (n=2, DLBCL; n=1, MCL and FL), and not applicable (n=0, DLBCL; n=1, MCL and FL). ‡The date of data cut-off was February 25, 2015.

Results

Patients

Between February 28, 2013, and June 15, 2014, 72 patients were enrolled in the trial, including 26 with DLBCL, 22 with MCL, and 24 with FL (Table 1). Their median age was 65 years (range, 28-85) and 68.1% were male. Most patients (73.6%) had stage III/IV disease at initial diagnosis, and 36.1% of patients had elevated lactate dehydrogenase levels. All patients had received prior antineoplastic therapy, and 17 patients (23.6%) had undergone a prior autologous stem cell transplantation (6 with DLBCL, 7 with MCL, and 4 with FL). The median number of prior antineoplastic regimens was three (range, 1-12) for patients with DLBCL, two (range, 1-6) for patients with MCL, and two (range, 1-9) for patients with FL. The most frequently received prior antineoplastic therapy was an alkylating agent (n=70; 97.2%), followed by rituximab (n=68; 94.4%), anthracycline (n=60; 83.3%), and bendamustine (n=21; 29.2%). At last treatment, a best response of complete or partial response was achieved by 11 patients with DLBCL (42.3%; 15.4% complete responses and 26.9% partial responses), 13 with MCL (59.1%; 31.8% complete responses and 27.3% partial responses), and 13 with FL (54.2%; 41.7% complete responses and 12.5% partial responses): ten (38.5%), four (18.2%), and four (16.7%) patients, respectively, had refractory disease.

The most common reasons for discontinuing prior therapy were completion of the prescribed regimen (n=36; 50.0%), disease progression (n=24; 33.3%), and adverse events (n=5; 6.9%); other reasons were listed as “unknown” or “other”. The date of data cut-off was February 25, 2015 for all analyses, except for the analysis of best overall response, which occurred separately in each cohort when all patients within the cohort had received 6 months of treatment.

Table 2. Best overall response.

	DLBCL (n = 26)	MCL (n = 22)	FL (n = 24)
Best overall response at 6 months,* n (%) [95% CI]			
Complete response	1 (3.8)	1 (4.5)	0
Partial response	2 (7.7)	4 (18.2)	6 (25.0)
Stable disease	5 (19.2)	13 (59.1)	15 (62.5)
Progressive disease	12 (46.2)	2 (9.1)	1 (4.2)
Unknown†	6 (23.1)	2 (9.1)	2 (8.3)
Overall response rate‡	3 (11.5) [§] [2.5, 30.2]	5 (22.7) [7.8, 45.4]	6 (25.0) [9.8, 46.7]
Disease control rate	8 (30.8) [14.3, 51.8]	18 (81.8) [59.7, 94.8]	21 (87.5) [67.6, 97.3]

CI: confidence interval; CR, complete response; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; *Data cut-off for best overall response had a 6-month primary analysis cut-off that corresponded to June 19, 2014, for the DLBCL cohort, February 25, 2015, for the MCL cohort, and August 7, 2014, for the FL cohort. †Reasons for unknown best overall response: no valid post-baseline assessment (n=7; 4 DLBCL, 2 FL, 1 MCL), all post-baseline assessments were not evaluable for response (n=2, 1 DLBCL, 1 MCL), stable disease too early (n=1, DLBCL). ‡Defined as complete response or partial response. §Of 26 patients with DLBCL, 16 patients had a clinical response (i.e., complete response, partial response or stable disease) to the last therapy prior to study entry; the overall response rate for these patients was 6.3% (1 patient achieved a partial response). ||Defined as stable disease or complete response or partial response.

Efficacy

Overall response rate

The overall response rates in the DLBCL, MCL, and FL cohorts were 11.5% (95% CI: 2.5-30.2), 22.7% (95% CI: 7.8-45.4), and 25.0% (95% CI: 9.8-46.7), respectively (Table 2). The primary endpoint was not met, since none of the cohorts reached the minimum number of responses to establish a 35% response rate required for statistical significance at the 5% level, based on the lower limits of the 95% CI (i.e., the 95% CI lower bound was <10% for all three cohorts). As shown in waterfall plots of the best overall response during buparlisib treatment, evaluable patients in all three cohorts had a reduction in investigator-assessed tumor size (Figure 1A-C). The disease control rates in the DLBCL, MCL, and FL cohorts were 30.8% (95% CI: 14.3-51.8), 81.8% (95% CI: 59.7-94.8), and 87.5% (95% CI: 67.6-97.3), respectively.

Time to response and duration of response

For the patients in the DLBCL cohort who responded, the median time to response was 2.1 months (range, 1.8-3.5) and the median duration of response was 2.2 months (95% CI: 1.2-not estimable). Of the three patients who responded, two relapsed. In the MCL cohort, the median time to response was 1.8 months (range, 0.9-9.4), while the median duration of response was not reached; of the five patients who responded, one patient subsequently relapsed. In the FL cohort, the median time to response and duration of response were 3.5 months (range, 1.6-5.9) and 11.0 months (95% CI: 3.9-not estimable), respectively; of the six patients who responded, two relapsed.

Progression-free survival

The median progression-free survival of patients with DLBCL, MCL, and FL was 1.8 months (95% CI: 1.5-4.0), 11.3 months (95% CI: 3.8-not estimable), and 9.8 months (95% CI: 3.8-not estimable), respectively (Figure 2A). The estimated 6-month progression-free survival rate was 12.6% (95% CI: 2.3-32.0) in the DLBCL cohort, 68.6% (95% CI: 39.8-85.7) in the MCL cohort, and 60.7% (95% CI: 31.7-80.6) in the FL cohort. The median follow-up time for progression-free survival was 1.7, 4.7, and 3.7 months for the DLBCL, MCL, and FL cohorts, respectively.

Overall survival

With a median follow-up time of 4.6 months, the median overall survival for the DLBCL cohort was 5.2 months (95% CI: 3.1-not estimable) (Figure 2B). For the MCL and FL cohorts the median follow-up time for overall survival was 8.2 months and 12.1 months, respectively, and the median overall survival was not reached for either cohort.

Safety

The median duration of exposure to buparlisib in the DLBCL, MCL, and FL cohorts was 7.5 weeks (range, 1.7-76.0), 20.6 weeks (range, 1.7-54.1), and 16.3 weeks (range, 3.3-81.3), respectively. As of the data cut-off, 47 patients (65.0%; 50.0%, 68.2%, and 79.2% in the DLBCL, MCL, and FL cohorts, respectively) had received buparlisib for ≥ 8 weeks and 21 patients (29.2%; 7.7%, 45.5%, and 37.5%, in the DLBCL, MCL, and FL cohorts, respectively) had received the drug for ≥ 24 weeks. Treatment was ongoing as of February 25, 2015, the data cut-off date, in nine patients (12.5%), including two with DLBCL, five

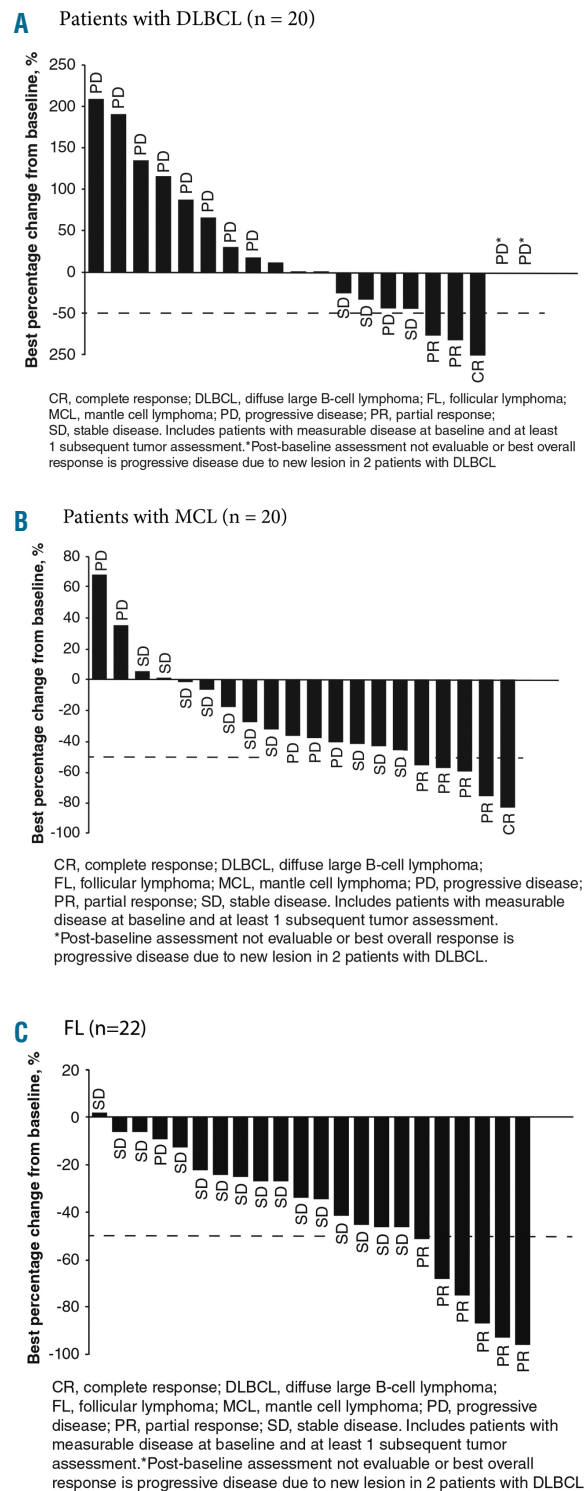


Figure 1. Best overall response with respect to best percentage change from baseline in investigator-assessed tumor size during buparlisib therapy for patients with measurable lesions divided by cohort The graphs include patients with measurable disease at baseline and ≥ 1 subsequent tumor assessments. The data cut-off was February 25, 2015, for all cohorts. (A) Patients with DLBCL (n=20), (B) patients with MCL (n=20), (C) patients with FL (n=22). Best overall response is indicated for each patient. Note that for two patients with DLBCL, the post-baseline assessment was not evaluable or best overall response was progressive disease due to a new lesion (asterisk). The dashed line shows the percentage change that represents the criterion for response, according to International Working Group criteria.^{34,35} CR: complete response; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; IWG: International Working Group; MCL: mantle cell lymphoma; PD: progressive disease; PR: partial response; SD, stable disease.

with MCL, and two with FL. The remaining 63 patients (87.5%) had discontinued treatment (Table 1). The most common primary reasons for treatment discontinuation were disease progression (n=23; 31.9%) and adverse events (n=19; 26.4%).

Of the 22 patients (30.6%; DLBCL, n=7; MCL, n=7; FL, n=8) who required a dose reduction, the majority required only one dose reduction (54.5%: DLBCL, 4/7; MCL, 2/7; FL, 6/8), while only one patient in the FL cohort required ≥3 dose reductions (Online Supplementary Table S1). Of the

patients requiring a dose reduction, all patients required a dose reduction due to adverse events (n=22: DLBCL, n=7; MCL, n=7; FL, n=8), and one patient in the FL cohort had an additional dose reduction due to a dosing error. The median percent of days with the full dose was 100% (range, 14.3-100%), 100% (range, 6.6-100%), and 97.4% (range, 4.2-100%) for patients in the DLBCL, MCL, and FL cohorts, respectively. Dose interruptions occurred in 36 patients (50.0%): 11 with DLBCL, 10 with MCL, and 15 with FL. Among patients whose dosing was interrupted,

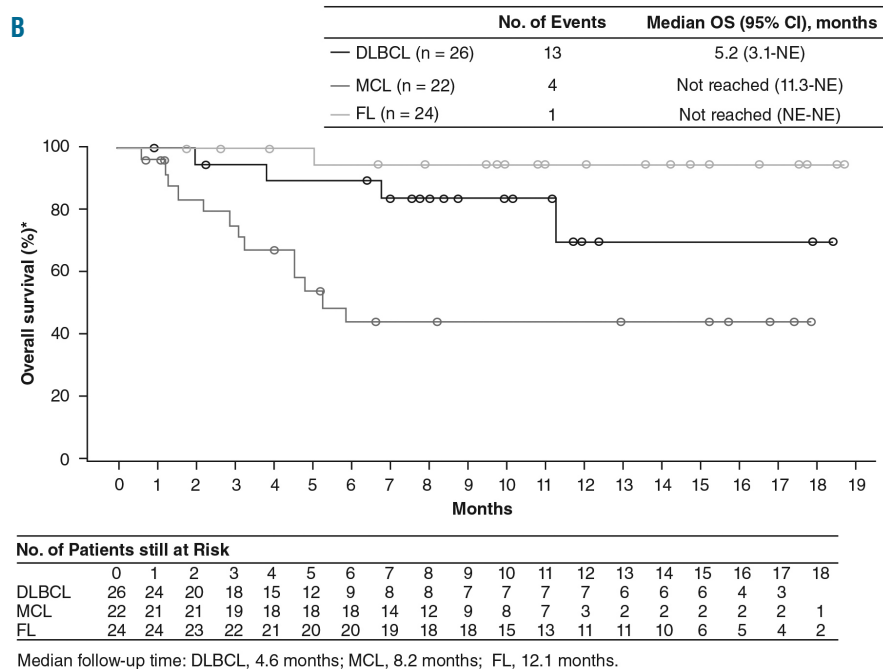
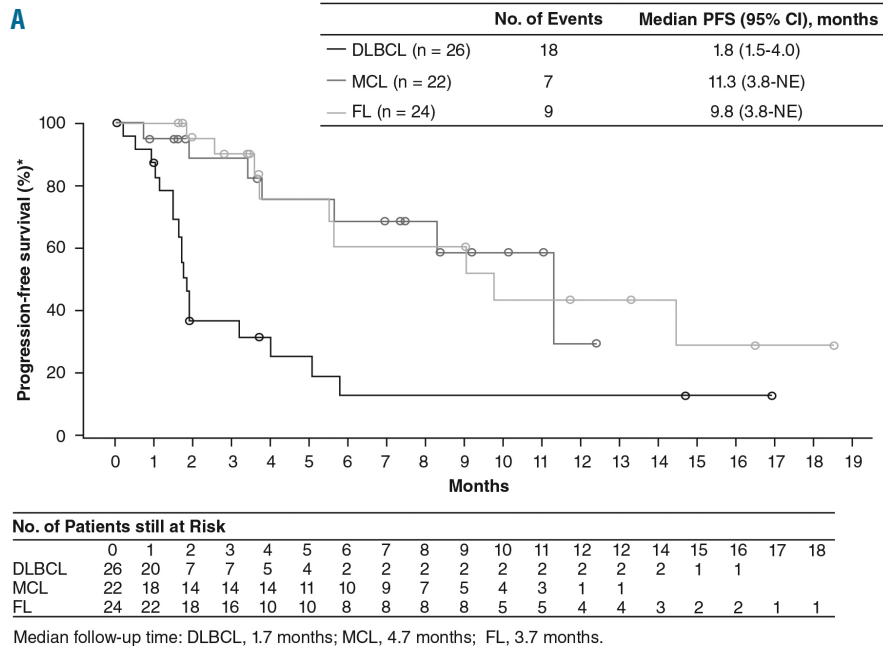


Figure 2. Kaplan-Meier curves for progression-free survival and overall survival. Kaplan-Meier curves for the secondary endpoints by cohort (DLBCL, MCL, and FL) are shown here together, but the curves are not meant to be compared between cohorts as the study was not designed to compare the three cohorts. (A) Progression-free survival curves; median follow-up time: DLBCL, 1.7 months; MCL, 4.7 months; FL, 3.7 months. (B) Overall survival curves; median follow-up time: DLBCL, 4.6 months; MCL, 8.2 months; FL, 12.1 months. CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

the reasons for the dose interruption included adverse events [n=32 (88.9%): DLBCL, n=11; MCL, n=9; FL, n=12], scheduling conflict [n=5 (13.9%): MCL, n=2; FL, n=3], and dosing error [n=4 (11.1%): MCL, n=1; FL, n=3]. The most common adverse events (occurring in >3 patients) that caused dose reduction or interruption were hyperglycemia (n=8), fatigue (n=6), and nausea (n=4).

Hyperglycemia, fatigue, and nausea (n=26; 36.1% each), depression (n=21; 29.2%), diarrhea (n=20; 27.8%), and anxiety (n=18; 25.0%) were the most frequently reported adverse events of any grade, regardless of their relationship with the study drug, occurring in >20% of patients (Table 3). The most frequently reported grade 3/4 adverse events, regardless of study drug relationship (occurring in ≥3 patients), were hyperglycemia (n=8; 11.1%), neutrope-

nia (n=4; 5.6%), fatigue, nausea, anxiety, asthenia, confusional state, and thrombocytopenia (each n=3; 4.2%). Mood disturbances (e.g., anxiety, agitation, confusional state, depression, stress, psychiatric decompensation) of any grade were reported in 29 patients (40.3%); 24 patients (33.3%) had grade 1/2 mood disorders, and five patients (6.9%) had grade 3/4 mood disorders. Laboratory hematologic and biochemical abnormalities of any grade were reported in 63 patients (87.5%) and 71 patients (98.6%), respectively (Table 3). Grade 3/4 hematologic and biochemical abnormalities occurring in more than 10% of patients were lymphocytopenia (n=16; 22.2%), hyperglycemia (n=15; 20.8%), and neutropenia (n=9; 12.5%) (Table 3). Grade 3/4 infections were reported in four patients with DLBCL, four patients with MCL, and

Table 3. Most frequently reported adverse events and laboratory abnormalities, regardless of relationship with the study drug.

	Most common adverse events, n (%) All patients (n = 72)			Most common adverse events, n (%) All patients (n = 72)	
	All grades	Grade 3/4		All grades	Grade 3/4
Any-cause adverse events (occurring in >5% of all patients)					
Fatigue	26 (36.1)	3 (4.2)	Hypokalemia	4 (5.6)	1 (1.4)
Hyperglycemia	26 (36.1)	8 (11.1)	Neutropenia	4 (5.6)	4 (5.6)
Nausea	26 (36.1)	3 (4.2)	Pain in extremity	4 (5.6)	1 (1.4)
Depression	21 (29.2)	2 (2.8)	Pleural effusion	4 (5.6)	1 (1.4)
Diarrhea	20 (27.8)	0	Hematologic abnormalities		
Anxiety	18 (25.0)	3 (4.2)	Anemia	43 (59.7)	2 (2.8)
Decreased appetite	14 (19.4)	1 (1.4)	Thrombocytopenia	36 (50.0)	3 (4.2)
Weight decrease	13 (18.1)	0	Lymphocytopenia	31 (43.1)	16 (22.2)
Asthenia	11 (15.3)	3 (4.2)	Leukopenia	22 (30.6)	6 (8.3)
Constipation	11 (15.3)	0	Neutropenia	19 (26.4)	9 (12.5)
Cough	10 (13.9)	0	Lymphocytosis	17 (23.6)	3 (4.2)
Abdominal pain	8 (11.1)	1 (1.4)	Biochemical abnormalities (occurring in >10% of all patients)		
Pruritus	8 (11.1)	0	Hyperglycemia	51 (70.8)	15 (20.8)
Rash	8 (11.1)	1 (1.4)	Increased AST	31 (43.1)	1 (1.4)
Vomiting	8 (11.1)	0	Hypercholesterolemia	28 (38.9)	0
Dyspepsia	7 (9.7)	1 (1.4)	Hypertriglyceridemia	28 (38.9)	0
Dyspnea	7 (9.7)	2 (2.8)	Increased AP	27 (37.5)	0
Tremor	7 (9.7)	1 (1.4)	Increased GGT	23 (31.9)	6 (8.3)
Headache	6 (8.3)	1 (1.4)	Increased creatinine	19 (26.4)	0
Pyrexia	6 (8.3)	0	Hyponatremia	19 (26.4)	3 (4.2)
Urinary tract infection	6 (8.3)	2 (2.8)	Hypokalemia	18 (25.0)	2 (2.8)
Agitation	5 (6.9)	0	Increased ALT	18 (25.0)	1 (1.4)
Anemia	5 (6.9)	2 (2.8)	Hypophosphatemia	16 (22.2)	3 (4.2)
Back pain	5 (6.9)	0	Hypoalbuminemia	14 (19.4)	0
Confusional state	5 (6.9)	3 (4.2)	Hyperkalemia	12 (16.7)	0
Insomnia	5 (6.9)	0	Uric acid	12 (16.7)	1 (1.4)
Muscle spasms	5 (6.9)	0	Hypernatremia	10 (13.9)	0
Thrombocytopenia	5 (6.9)	3 (4.2)	Hyperbilirubinemia	10 (13.9)	0
Vertigo	5 (6.9)	2 (2.8)	Increased lipase	9 (12.5)	0
Dizziness	4 (5.6)	0	ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase.		
Dry skin	4 (5.6)	0			

one patient with FL. Of these, serious infections were reported in two patients with DLBCL (pneumonia and urinary tract infection), two patients with MCL (pneumonia and septic shock), and one patient with FL (lung infection). Treatment for patients who had infectious complications was at the discretion of the investigator.

Serious adverse events, regardless of a relationship with the study medication, of any grade and grade 3/4 were reported in 30 patients (41.7%: DLBCL, n=12; MCL, n=12; FL, n=6) and 26 patients (36.1%: DLBCL, n=10; MCL, n=12; FL, n=4), respectively. The most common serious adverse events were confusional state (n=3), pleural effusion (n=3), nausea (n=2), vomiting (n=2), dysphagia (n=2), and pneumonia (n=2). Serious adverse events suspected to be related to study medication were reported in 14 patients (19.4%: DLBCL, n=3; MCL, n=9; FL, n=2), and were all grade 3/4. Overall, 18 patients died, including eight on treatment (occurring \leq 30 days after study drug discontinuation): seven due to underlying DLBCL (n=6) and MCL (n=1), and one in the DLBCL cohort due to gastrointestinal hemorrhage suspected to be related to the study drug.

Exploratory analysis

Biomarkers were assessed using baseline archival tumor samples from 52 patients (72.2%) and fresh tumor samples from one patient (1.4%); all but one of the archival tumor samples were derived from the primary tumor. Of the patients with evaluable *PI3KCA* mutation status (19 with DLBCL, 11 with MCL, and 18 with FL) or *PTEN* mutation status (19 with DLBCL, 11 with MCL, and 17 with FL), none had mutations in *PI3KCA* or *PTEN* (Online Supplementary Table S2). Loss of *PTEN* expression was evaluable in 20, 12, and 20 patients with DLBCL, MCL, and FL, respectively; none of these patients met the criteria for loss of *PTEN* expression.

Discussion

Buparlisib elicited tumor reduction in patients with relapsed or refractory NHL; patients in all cohorts had reductions in tumor size, and the median progression-free survival was 1.8, 11.3, and 9.8 months in the DLBCL, MCL, and FL cohorts, respectively. The median overall survival, although not yet matured, was 5.2 months (95% CI: 3.1-not estimable) for the DLBCL cohort and was not reached for the MCL and FL cohorts.

The PI3K/mTOR pathway is frequently activated in NHL and plays an important role in the pathogenesis of this disease.¹⁴ However, mutations in key components of the PI3K pathway, such as *PIK3CA*, seem infrequent in this condition.^{10,36} Consistently, no *PIK3CA* or *PTEN* mutations were detected in the 42 tumor samples tested for mutations in this study. Despite previous reports of a reduction or loss of *PTEN* expression in approximately 21% of FL,³⁶ 37% of DLBCL,¹¹ and 15% of MCL samples,^{23,37} no *PTEN* loss was observed among the 50 tumors tested in this study, which may be explained by the stringent cut-off used for defining a loss of expression (< 10% expression by immunohistochemistry). Further investigation, including a broader evaluation of PI3K activation markers or multivariate analyses of baseline characteristics, would be needed to identify subpopulations of patients who might respond to buparlisib.

Preclinical models suggest that all PI3K isoforms (PI3K α , PI3K β , and PI3K δ) are expressed in leukocytes,³⁸ but that their relative levels of expression vary in NHL according to disease stage.²³ Specific PI3K isoform ratios are associated with relapse and have been implicated in resistance to PI3K δ inhibitors, but not PI3K α /PI3K δ inhibitors.²³

Previous studies on PI3K inhibitors that specifically target one or two PI3K isoforms have met with some success in indolent NHL (overall response rate of 65% with duvelisib),³⁹ in FL and in MCL (overall response rates of 45% and 40%, respectively, with idelalisib),^{40,41} but not in DLBCL (overall response rate of 0% with rigosertib).⁴² However, improved long-term outcomes (e.g., progression-free survival) with these agents have been limited in patients with relapsed or refractory disease; for example, the median progression-free survival of patients treated with idelalisib was 3.7 months among those with MCL and 7.6 to 11 months for patients with indolent NHL (the majority, 58% - 59%, with FL).^{20,40,41} Pan-PI3K inhibition results in similar or higher overall response rates (\leq 25% in DLBCL, 83% in MCL, and 20% - 50% in FL),⁴³⁻⁴⁵ with potentially longer progression-free survival. For example, in a study of the pan-PI3K inhibitor SAR245409, the overall response rate was 50% and the median progression-free survival was not reached after 8 months of follow-up in patients with relapsed or refractory FL.⁴⁵ In our study, patients with FL on treatment with buparlisib had an overall response rate of 25.0% and a median progression-free survival of 9.8 months. Thus, it appears that sustained inhibition of all PI3K isoforms has some effect on achieving response, but may have a more pronounced benefit on long-term outcomes for patients with FL and MCL. In general, PI3K inhibitors have a manageable safety profile in NHL,⁴⁶⁻⁴⁸ however, the European Medicines Agency has recently opened a review of idelalisib due to new safety concerns over serious adverse events (mostly infections) in ongoing clinical trials.

Buparlisib was generally well tolerated. Hyperglycemia, although frequently reported, is a known on-target effect of PI3K α inhibitors⁹ and, as in other buparlisib studies,³⁰ was manageable with standard antidiabetic therapy. Mood disorders have been previously reported in studies of buparlisib⁴⁹ owing, in part, to the ability of this drug to cross the blood-brain barrier.⁵⁰ For this reason, in this study, patients with active psychiatric disorders at screening were excluded, and the patients enrolled were prospectively followed with self-assessment questionnaires (i.e., GAD-7 and PHQ-9). As in previous studies, some patients with NHL experienced mood disorders that were not serious and were manageable with dose reduction/interruption or treatment with appropriate concomitant medication. In addition, patients developing any of these adverse events were referred for psychiatric consultation. Loss of appetite and weight (Online Supplementary Table S3) in patients may compromise quality of life, as reported in some previous studies.⁵¹

Most treatment-related adverse events with buparlisib were grade 1/2 and could be managed with dose reduction or interruption until resolution of toxicity. The rates of grade 3/4 elevations in alanine aminotransferase and aspartate aminotransferase, pneumonia, and diarrhea were lower with buparlisib than with a selective PI3K δ inhibitor in patients with relapsed or refractory NHL.²⁰

Although the overall response rate with buparlisib was not substantial, the observed progression-free survival in

this study warrants further evaluation of this agent in hematologic cancers. Combination of buparlisib with other treatments (i.e., targeted therapies, monoclonal anti-CD20 antibodies, checkpoint inhibitors, or standard chemotherapies) should be considered, particularly for patients with FL and MCL.

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