SUPPLEMENTARY APPENDIX

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

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Supplementary methods:

Patients:

Concomitant use of moderate and strong cytochrome P4503A inhibitors and inducers was not allowed. Additional exclusion criteria were grade ≥3 anxiety, active or documented history of major depressive episode, bipolar disorder, obsessive-compulsive disorder, schizophrenia, suicidal attempt or ideation, homicidal ideation, or severe personality disorders. Patients who had moderate to severe depression (Patient Health Questionnaire-9 [PHQ-9] score ≥12), moderate to severe anxiety (General Anxiety Disorder-7 mood questionnaire [GAD-7] score ≥15), or potential for suicidal thoughts or ideations (positive response to question 9 in the PHQ-9) were also excluded.

Objectives:

PFS was defined as the time from treatment start to the date of first documented progressive disease (PD) or death from any cause per local investigator assessment. DOR was defined as the time from first achieving CR or PR, among the responders, to the first documented PD or death due to lymphoma. OS was defined as the time from treatment start to death from any cause.

In addition, the disease control rate, defined as the proportion of patients with best overall response of CR or PR or stable disease, and the time-to-response (TTR), defined as the time from the date of start of treatment to the date of first documented response, were also calculated for each cohort. Exploratory objectives included identifying molecular profiles relevant to PI3K signaling (e.g., mutation, loss, and/or amplification of *PI3K*, *PTEN*, and *KRAS*).

Schedule of assessments (Described in the Online Supplementary methods):

Fasting plasma glucose, ECOG performance status, and electrocardiogram were assessed on Day 1 of each cycle and at the end of treatment. Cardiac imaging (i.e., multigated acquisition scan or echocardiogram) and coagulation studies were performed at screening and as clinically indicated. Tumor assessment was performed according to IWG criteria[1,2] every 8 weeks until disease progression or until 6 months after the last patient in the cohort had started the study treatment, whichever came first. In

addition, lipid profile, HbA1c and C-peptide were evaluated every 8 weeks, beginning on Day 1, Cycle 1, and at the end of treatment. Tumor evaluation was performed using computed tomography scans, or magnetic resonance imaging scans if computed tomography was not available. In the DLBCL cohort, chemistry specific to tumor lysis syndrome was performed on Days 2-4 of Cycle 1.

Bone marrow biopsy was performed only to confirm disease status in patients with radiographic CR. Archival tumor samples (blocks or slides) were collected at screening. Optional fresh tumor samples from biopsy or resection were taken at screening, Day 1 of Cycle 3, and at the end of treatment. The activation status of molecules involved in PI3K signaling (i.e., PI3K, AKT, KRAS, PTEN) was assessed in available tumor samples. *PI3KCA* and *PTEN* mutation analysis were evaluated by Sanger sequencing in 41 and 42 tumor samples, respectively. *PTEN* loss of expression was evaluated by immunohistochemistry using a rabbit monoclonal antibody (#9559; Cell Signaling Technology, Danvers, MA) in 50 tumor samples. Patient-reported questionnaires (PHQ-9[3] and GAD-7[4] patient self-rating mood scales) were completed at the beginning of each cycle and at the end of treatment. Safety was evaluated continuously throughout the study period using the Common Terminology for Adverse Events (CTCAE), version 4.03.

Statistical analyses:

The sample size of ≥22 patients in each cohort was determined so that a true ORR of 35% could be detected with a probability of ≥80% (e.g., power of 83.7% for 22 patients); maximum enrollment was capped at 28 patients. A significant result would require ≥6 responses (for 22-23 patients) or ≥7 responses (for 24-28 patients, in case of over-enrollment); for example, a minimal observed ORR of 27.3%, corresponding to 6 responses, would be required for a cohort of 22 patients. Enrollment of ≥22 patients in a cohort would result in different rejection criteria and power; for example, if n = 24, an observed ORR of 29.2% would have a power of 78.9%, and if n = 26, an observed ORR of 26.9% would have a power of 85.8%.

Supplementary Tables

Supplemental Table 1. Dose reduction and/or interruption by cohort

	DLBCL (n = 26)	MCL (n = 22)	FL (n = 24)	All patients (N = 72)
Baseline characteristics				
Number of patients with dose reductions, n (%)	7 (26.9)	7 (31.8)	8 (33.3)	22 (30.6)
Percent number of days received full dose, median (range)*	100 (14.3-100)	100 (6.6-100)	97.4 (4.2-100)	99.1 (4.2-100)
Patients requiring dose reduction, n (%)				
0	19 (73.1)	15 (68.2)	16 (66.7)	50 (69.4)
1	4 (15.4)	2 (9.1)	6 (25.0)	12 (16.7)
2	3 (11.5)	5 (22.7)	1 (4.2)	9 (12.5)
≥3	0	0	1 (4.2)	1 (1.4)
Reasons for dose reduction, n (%)				
Adverse event	7 (26.9)	7 (31.8)	8 (33.3)	22 (30.6)
Dosing error	0	0	1 (4.2)	1 (1.4)
Patients requiring dose interruption, n (%)				
0	15 (57.7)	12 (54.5)	9 (37.5)	36 (50.0)
1	6 (23.1)	3 (13.6)	11 (45.8)	20 (27.8)
2	4 (15.4)	3 (13.6)	3 (12.5)	10 (13.9)
≥3	1 (3.8)	4 (18.2)	1 (4.2)	6 (8.3)
Reasons for dose interruption, n (%)				
Adverse event	11 (42.3)	9 (40.9)	12 (50.0)	32 (44.4)
Scheduling conflict	0	2 (9.1)	3 (12.5)	5 (6.9)
Dosing error	0	1 (4.5)	3 (12.5)	4 (5.6)

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma.

*Denominator is the number of potential days dosed; full dose is 100 mg of buparlisib.

Supplemental Table 2. PI3K pathway activation status by cohort at screening

PI3K pathway aberration, n (%)	DLBCL (n = 26)	MCL (n = 22)	FL (n = 24)
***PI3KCA* mutation**			
Wild-type	17 (65.4)	11 (50.0)	13 (54.2)
Mutant	0	0	0
Unknown	2 (7.7)	0	5 (20.8)
Missing*	7 (26.9)	11 (50.0)	6 (25.0)
***PTEN* mutations**			
Wild-type	18 (69.2)	11 (50.0)	13 (54.2)
Mutant	0	0	0
Unknown	1 (3.8)	0	4 (16.7)
Missing*	7 (26.9)	11 (50.0)	7 (29.2)
***PTEN* loss of expression†**			
Yes	0	0	0
No	19 (73.1)	11 (50.0)	20 (83.3)
Unknown	1 (3.8)	1 (4.5)	0
Missing*	6 (23.1)	10 (45.5)	4 (16.7)

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma.

*Missing category includes patients without tumor available to identify activation status.

†*PTEN* negative: <10% protein expression by immunohistochemistry.

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

	Most common adverse events, n (%)							
	DLBCL (n = 26)		MCL (n = 22)		FL (n = 24)		All patients (N = 72)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any-cause adverse events (occurring in >5% of all patients)								
Fatigue	6 (23.1)	0	7 (31.8)	1 (4.5)	13 (54.2)	2 (8.3)	26 (36.1)	3 (4.2)
Hyperglycemia	10 (38.5)	6 (23.1)	10 (45.5)	1 (4.5)	6 (25.0)	1 (4.2)	26 (36.1)	8 (11.1)
Nausea	10 (38.5)	2 (7.7)	6 (27.3)	0	10 (41.7)	1 (4.2)	26 (36.1)	3 (4.2)
Depression	8 (30.8)	2 (7.7)	7 (31.8)	0	6 (25.0)	0	21 (29.2)	2 (2.8)
Diarrhea	5 (19.2)	0	6 (27.3)	0	9 (37.5)	0	20 (27.8)	0
Anxiety	6 (23.1)	2 (7.7)	7 (31.8)	1 (4.5)	5 (20.8)	0	18 (25.0)	3 (4.2)
Decreased appetite	2 (7.7)	0	6 (27.3)	1 (4.5)	6 (25.0)	0	14 (19.4)	1 (1.4)
Weight decreased	3 (11.5)	0	7 (31.8)	0	3 (12.5)	0	13 (18.1)	0
Asthenia	3 (11.5)	0	5 (22.7)	2 (9.1)	3 (12.5)	1 (4.2)	11 (15.3)	3 (4.2)
Constipation	3 (11.5)	0	5 (22.7)	0	3 (12.5)	0	11 (15.3)	0
Cough	2 (7.7)	0	4 (18.2)	0	4 (16.7)	0	10 (13.9)	0
Abdominal pain	4 (15.4)	0	3 (13.6)	0	1 (4.2)	1 (4.2)	8 (11.1)	1 (1.4)
Pruritus	2 (7.7)	0	3 (13.6)	0	3 (12.5)	0	8 (11.1)	0
Rash	2 (7.7)	0	3 (13.6)	1 (4.5)	3 (12.5)	0	8 (11.1)	1 (1.4)
Vomiting	5 (19.2)	0	0	0	3 (12.5)	0	8 (11.1)	0
Dyspepsia	2 (7.7)	0	1 (4.5)	0	4 (16.7)	1 (4.2)	7 (9.7)	1 (1.4)
Dyspnea	3 (11.5)	1 (3.8)	2 (9.1)	0	2 (8.3)	1 (4.2)	7 (9.7)	2 (2.8)
Tremor	1 (3.8)	0	4 (18.2)	1 (4.5)	2 (8.3)	0	7 (9.7)	1 (1.4)
Headache	0	0	1 (4.5)	0	5 (20.8)	1 (4.2)	6 (8.3)	1 (1.4)
Pyrexia	3 (11.5)	0	2 (9.1)	0	1 (4.2)	0	6 (8.3)	0
Urinary tract infection	2 (7.7)	2 (7.7)	1 (4.5)	0	3 (12.5)	0	6 (8.3)	2 (2.8)
Agitation	1 (3.8)	0	3 (13.6)	0	1 (4.2)	0	5 (6.9)	0
Anemia	1 (3.8)	1 (3.8)	2 (9.1)	1 (4.5)	2 (8.3)	0	5 (6.9)	2 (2.8)
Back pain	0	0	2 (9.1)	0	3 (12.5)	0	5 (6.9)	0
Confusional state	1 (3.8)	0	3 (13.6)	2 (9.1)	1 (4.2)	1 (4.2)	5 (6.9)	3 (4.2)

Insomnia	2 (7.7)	0	2 (9.1)	0	1 (4.2)	0	5 (6.9)	0
Muscle spasms	0	0	2 (9.1)	0	3 (12.5)	0	5 (6.9)	0
Thrombocytopenia	2 (7.7)	1 (3.8)	1 (4.5)	1 (4.5)	2 (8.3)	1 (4.2)	5 (6.9)	3 (4.2)
Vertigo	0	0	3 (13.6)	1 (4.5)	2 (8.3)	1 (4.2)	5 (6.9)	2 (2.8)
Dizziness	1 (3.8)	0	1 (4.5)	0	2 (8.3)	0	4 (5.6)	0
Dry skin	0	0	1 (4.5)	0	3 (12.5)	0	4 (5.6)	0
Hypokalemia	3 (11.5)	0	0	0	1 (4.2)	1 (4.2)	4 (5.6)	1 (1.4)
Neutropenia	2 (7.7)	2 (7.7)	1 (4.5)	1 (4.5)	1 (4.2)	1 (4.2)	4 (5.6)	4 (5.6)
Pain in extremity	1 (3.8)	0	2 (9.1)	1 (4.5)	1 (4.2)	0	4 (5.6)	1 (1.4)
Pleural effusion	0	0	2 (9.1)	0	2 (8.3)	1 (4.2)	4 (5.6)	1 (1.4)
Hematologic abnormalities								
Anemia	17 (65.4)	1 (3.8)	17 (77.3)	1 (4.5)	9 (37.5)	0	43 (59.7)	2 (2.8)
Thrombocytopenia	14 (53.8)	1 (3.8)	13 (59.1)	1 (4.5)	9 (37.5)	1 (4.2)	36 (50.0)	3 (4.2)
Lymphocytopenia	13 (50.0)	7 (26.9)	8 (36.4)	4 (18.2)	10 (41.7)	5 (20.8)	31 (43.1)	16 (22.2)
Leukopenia	13 (50.0)	3 (11.5)	5 (22.7)	3 (13.6)	4 (16.7)	0	22 (30.6)	6 (8.3)
Neutropenia	10 (38.5)	4 (15.4)	6 (27.3)	4 (18.2)	3 (12.5)	1 (4.2)	19 (26.4)	9 (12.5)
Lymphocytosis	4 (15.4)	1 (3.8)	8 (36.4)	2 (9.1)	5 (20.8)	0	17 (23.6)	3 (4.2)
Biochemical abnormalities (occurring in >10% of all patients)								
Hyperglycemia	17 (65.4)	6 (23.1)	15 (68.2)	4 (18.2)	19 (79.2)	5 (20.8)	51 (70.8)	15 (20.8)
Increased AST	11 (42.3)	0	12 (54.5)	1 (4.5)	8 (33.3)	0	31 (43.1)	1 (1.4)
Hypercholesterolemia	5 (19.2)	0	8 (36.4)	0	15 (62.5)	0	28 (38.9)	0
Hypertriglyceridemia	7 (26.9)	0	9 (40.9)	0	12 (50.0)	0	28 (38.9)	0
Increased AP	11 (42.3)	0	7 (31.8)	0	9 (37.5)	0	27 (37.5)	0
Increased GGT	14 (53.8)	3 (11.5)	6 (27.3)	2 (9.1)	3 (12.5)	1 (4.2)	23 (31.9)	6 (8.3)
Increased creatinine	9 (34.6)	0	6 (27.3)	0	4 (16.7)	0	19 (26.4)	0
Hyponatremia	10 (38.5)	0	3 (13.6)	1 (4.5)	6 (25.0)	2 (8.3)	19 (26.4)	3 (4.2)
Hypokalemia	11 (42.3)	1 (3.8)	4 (18.2)	0	3 (12.5)	1 (4.2)	18 (25.0)	2 (2.8)
Increased ALT	4 (15.4)	0	9 (40.9)	1 (4.5)	5 (20.8)	0	18 (25.0)	1 (1.4)
Hypophosphatemia	7 (26.9)	3 (11.5)	5 (22.7)	0	4 (16.7)	0	16 (22.2)	3 (4.2)
Hypoalbuminemia	6 (23.1)	0	4 (18.2)	0	4 (16.7)	0	14 (19.4)	0
Hyperkalemia	4 (15.4)	0	2 (9.1)	0	6 (25.0)	0	12 (16.7)	0
Uric acid	6 (23.1)	1 (3.8)	3 (13.6)	0	3 (12.5)	0	12 (16.7)	1 (1.4)
Hypernatremia	3 (11.5)	0	3 (13.6)	0	4 (16.7)	0	10 (13.9)	0
Hyperbilirubinemia	2 (7.7)	0	5 (22.7)	0	3 (12.5)	0	10 (13.9)	0

Increased lipase	1 (3.8)	0	5 (22.7)	0	3 (12.5)	0	9 (12.5)	0

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GGT, gamma-glutamyl transferase; MCL, mantle cell lymphoma.

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