Supplementary information

Supplementary Table 1. Dose-Limiting Toxicity Criteria.

Supplementary Table 2. Detailed adverse events by study arm.

Supplementary Table 1. Dose-Limiting Toxicity Criteria; CTCAE: NCI Common Toxicity Criteria for Adverse Events version 4.0.

Toxicity	DLT criteria
Blood and lymphatic system disorders	Anemia CTCAE Grade 3 for > 14 consecutive days
	Anemia CTCAE Grade 4
	Febrile neutropenia CTCAE Grade ≥ 3
	Neutropenia CTCAE Grade 3 for > 7 consecutive days
	Neutropenia CTCAE Grade 4
	Thrombocytopenia CTCAE Grade 3 for > 7 consecutive days and/or with signs of clinically significant bleeding
	Thrombocytopenia CTCAE Grade 4
Cardiac disorders	Cardiac toxicity CTCAE Grade ≥ 3 or cardiac event that is symptomatic or requires medical intervention
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin CTCAE Grade 3 (confirmed with a repeat Troponin within 24 hrs)
	ECG QTc interval prolonged CTCAE Grade ≥ 3
Vascular disorders/ Hypertension	Persistent hypertension CTCAE Grade ≥ 3 requiring more than one drug or more intensive therapy than previously
General disorders and administration site conditions	Fatigue CTCAE Grade 3 for > 7 consecutive days
Skin and subcutaneous tissue disorders [a]: Rash and/or photosensitivity	Rash or photosensitivity CTCAE Grade 3 for >7 consecutive days despite skin toxicity treatment, or any second or third occurrence of CTCAE Grade 3 rash regardless of duration
	Rash or photosensitivity CTCAE Grade 4
Metabolism and nutrition disorders: Hyperglycemia [b]	Hyperglycemia Grade 3(fasting plasma glucose 250 – 500mg/dL) (confirmed with a repeat fasting plasma glucose test within 48 hours) that does not resolve to grade 0 within 14 consecutive days (after initiation of oral anti-diabetic treatment)
	Hyperglycemia Grade 4
	Hyperglycemia leading to diabetic keto-acidosis, hospitalization for IV insulin infusion, or non-ketotic coma
GI disorders [a]	Diarrhea CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-diarrhea therapy
	Nausea/vomiting CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-emetic therapy
	Pancreatitis CTCAE Grade ≥ 3
Eye disorder	CTCAE Grade ≥ 3
Blood chemistries [c]	Blood bilirubin [d] CTCAE Grade 2 for > 7 consecutive days
	Blood bilirubin [d] CTCAE Grade ≥ 3
	AST or ALT CTCAE Grade ≥ 3 in conjunction with blood bilirubin [d] CTCAE Grade ≥ 2 of any duration
	AST or ALT CTCAE Grade 3 for > 7 consecutive days
	AST or ALT CTCAE Grade 4
	Serum alkaline phosphatase CTCAE Grade 4
	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 for > 7 consecutive days
	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 4

	Serum creatinine CTCAE Grade 2 for > 7 consecutive days
	Serum creatinine CTCAE Grade ≥ 3
Other hematologic and non-hematologic toxicities	Any other clinically significant CTCAE ≥ Grade 3 toxicity
	Any intolerable CTCAE Grade 2 toxicity
	Apart from the criteria listed above, if a lower grade AE leads to a dose interruption of more than 7 consecutive days of BYL719, this AE will be considered as DLT

[a] Patients will receive prophylactic treatment for rash with an antihistamine beginning on cycle 1 day 1. Patients will not initially receive prophylactic treatment for nausea/vomiting during Cycle 1. However, prophylactic treatment may be initiated in all patients at the dose level where these toxicities have been observed and in all further patients if at least 1 patient has experienced nausea/vomiting CTCAE Grade ≥ 3 or if at least 2 patients experienced skin toxicity or nausea/vomiting CTCAE Grade ≥ 2 (see Section 11.2 and Table 10-2 for further details). Anti-emetics may be applied for treatment if the patient has experienced nausea/vomiting CTCAE Grade ≥ 1, at the discretion of the physician.

[b] Hyperglycemia occurring during corticosteroids administration will be only be considered DLT if not resolved within 5 days after the end of corticosteroid treatment.

[c] For any hepatic toxicity CTCAE Grade 4, or CTCAE Grade 3 that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan should be performed to assess if it is related to disease progression.

[d] Refers to total bilirubin.

Supplementary Table 2. Detailed adverse events by study arm.

	Arm A Letrozole + Alpelisib Daily								Arm B Exemestane + Alpelisib Daily				Arm C Letrozole daily + Alpelisib 7d on, 7d off						Arm D Exemestane daily + Alpelisib 5d on, 2d off										All Arms (n=51)			
	250mg (n=3)				300mg (n=4)				300mg (n=7)				250mg (n=6)				300mg (n=6)				250mg (n=3)				300mg (n=6)				350mg (n=16)							
	All		G3		All		G3		All		G3		All		G3		All		G3		All		G3		All		G3		All		G3		All		G3	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
General																																				
Fatigue	3	100			4	100			7	100			2	33			3	50			1	33			5	83			8	50			33	65		
Fever	0	0			0	0			2	29			0	0			1	17			0	0			0	0			0	0			3	6		
Weight Loss	0	0			1	25			2	29			0	0			1	17			0	0			1	17			0	0			5	10		
Hypotension	0	0			0	0			0	0			0	0			1	17	1	17	0	0			0	0			0	0			1	2	1	2
Hot flashes	3	100			1	25			3	43			0	0			1	17			0	0			1	17			2	13			11	22		
Metabolic																																				
Hyperglycemia	2	67			3	75			4	57	1	14	6	100			4	67			2	67			5	83			14	87	4	25	40	78	5	10
Hypokalemia	0	0			1	25			0	0			0	0			1	17			0	0			0	0			0	0			2	4		
Hyperbilirubinemia	0	0			0	0			0	0			0	0			0	0			0	0			1	17	1	17	0	0			1	2	1	2
Hypomagnesemia	0	0			0	0			0	0			1	17			2	33			0	0			0	0			0	0			3	6		
GI																																				
Abdominal	1	33			3	75	1	25	1	14			0	0			2	33			0	0			1	17			2	12			10	20	1	2
Anorexia	2	67			4	100			4	57			2	33			3	50			0	0			4	67			8	50			27	53		
Diarrhea	1	33			3	75			3	43			1	17			4	67			1	33			1	17			14	87			28	55		
Dyspepsia	1	33			3	75			5	71			0	0			1	17			1	33			3	50			6	37			20	39		
GERD	0	0			0	0			0	0			1	17			1	17			0	0			2	33			3	19			7	14		
Mucositis	2	67			3	75			5	71			3	50			4	67			1	33			5	83			5	31			28	55		
Nausea/Vomiting	3	100			4	100			6	86			4	67			1	17			3	100			1	17			5	31			27	53		
Dermatologic																																				
Alopecia	2	67			1	25			1	14			2	33			0	0			1	33			2	33			6	37			15	29		
Dry skin	2	67			2	50			2	29			1	17			2	33			1	33			1	17			2	12			13	25		
Rash	2	67	1	33	3	75	2	50	4	57	4	57	3	50	2	33	2	33	2	33	0	0			2	33	2	33	6	37	4	25	22	43	17	33
Cardiac																																				

QTc prolongation	3	100		3	75	1	25	3	43		6	100		4	67		2	67		4	67		3	19		28	55	1	2
Respiratory																													
Dyspnea	1	33		0	0			1	14		1	17		2	33		0	0		2	33		2	12		9	18		
Rheumatologic																													
Arthralgia	2	67		3	75			1	14		1	17		1	17		0	0		0	0		3	19		11	22		
Joint ROM reduced	2	67		1	25			3	43		0	0		0	0		0	0		0	0		0	0		6	12		
Hematologic																													
Anemia	1	33		1	25			2	29		3	50		1	17		0	0		1	17		0	0		9	18		
Lymphopenia	0	0		1	25	1	25	0	0		1	17	1	17	0	0		0	0		0	0		1	6	1	6	3	6	3	6
Thrombocytopenia	0	0		0	0			2	29		0	0			0	0		0	0		1	17		0	0			3	6		
Leukopenia	1	33		0	0			3	43		1	17			1	17		0	0		0	0		1	6			7	14		
Neurologic																													
Dizziness	0	0		1	25			3	43		1	17			1	17		1	33		0	0		0	0			7	14		
Dysgeusia	1	33		0	0			1	14		0	0			0	0		1	33		2	33		5	31			10	20		
Investigational																													
ALP increased	0	0		2	50			1	14		1	17			2	33		0	0		2	33		4	25			12	24		
ALT increased	0	0		0	0			4	57		2	33			2	33		0	0		2	33		5	31			15	29		
AST increased	1	33		0	0			3	43		1	17			3	50		0	0		2	33		6	37			16	31		
Hypoalbuminemia	0	0		0	0			2	29		0	0			0	0		0	0		0	0		3	19			5	10		
Hypocalcemia	1	33		1	25			1	14		0	0			2	33		0	0		0	0		0	0			5	10		
Hypernatremia	0	0		0	0			1	14		0	0			0	0		0	0		0	0		3	19			4	8		
Hypoglycemia	0	0		0	0			0	0		0	0			0	0		0	0		0	0		0	0			0	0		
Lipase increased	2	67		1	25			3	43		2	33			2	33		0	0		3	50		6	37	2	12	19	37	2	4
Amylase increased	0	0		2	50			0	0		0	0			0	0		1	17		0	0		4	25			7	14		