NOVARTIS

Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

Alpelisib

Trial Indication(s)

Advanced solid malignancies

Protocol Number

CBYL719X1101

Protocol Title

A phase I study of BYL719, in adult patients with advanced solid malignancies

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

22-Sep-2011 (first patient first visit) to 25-Nov-2015 (last patient last visit)

Reason for Termination

Not applicable

Study Design/Methodology

This study was a first-in-Japanese trial of BYL719 and was designed as an open label, multi-center phase I dose escalation study.

The study consisted of a dose escalation part in patients with advanced solid tumors who had progressed despite standard therapy or for whom no standard therapy existed and an expansion part initiated at the MTD level in the molecularly screened patients whose tumor had genetic alteration of the PIK3CA gene in addition to the same patient characteristics as in the dose escalation part.

In the dose escalation part, the patients received BYL719 at 5 dose levels (90 mg/d, 180 mg/d, 270 mg/d, 350 mg/d, and 400 mg/d). BYL719 was administered orally as a single agent and a cycle was defined as 28 days. The dose escalation was guided by a Bayesian logistic regression model (BLRM) which is a well-established method to estimate the MTD/recommended dose for expansion in cancer patients.

Once MTD (or RP2D) had been defined, an expansion part was to be initiated at the MTD level or an appropriate lower dose based upon data from this study and Western studies in the molecularly screened patients whose advanced solid tumor showed *PIK3CA* alteration, to further characterize the safety, preliminary efficacy, as well as PK and PD profile of BYL719 in Japanese patients. Preliminary information about the food effect on the PK profile of BYL719 would also be obtained in the expansion part.

Centers

4 centers in Japan.

Objectives:

Primary objective

- To determine the MTD (and/or RP2D) of BYL719 as single agent in patients with advanced solid malignancies.

Secondary objectives

- To assess the overall safety and tolerability of BYL719.
- To characterize the full pharmacokinetic profile of BYL719 after single (Cycle 1 Day 1) and multiple administrations (Cycle 1 Day 8 and Cycle 2 Day 1) of BYL719.
- To assess the preliminary efficacy of BYL719.

Test Product (s), Dose(s), and Mode(s) of Administration

The test product, BYL719 tablet was given orally to all patients. (see 'Study Design/Methodology' for dose levels)

Statistical Methods

A 2-parameter BLRM guided by the escalation with overdose control (EWOC) principle was used to determine the MTD in the dose escalation part.

Doses were rescaled as d/d* based on the reference dose d* = 290. Then, the 2-parameter logistic model for these probabilities was of the form

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*)$$

where $\text{logit}(\pi(d))= \log(\pi_{(d)}/(1-\pi_{(d)}))$, and $\alpha, \beta>0$. As a consequence α was equal to the odds of the probability of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity was zero.

All data including BOR, ORR, DCR, and PFS were summarized. PFS at dose escalation part and expansion part was presented descriptively using a Kaplan-Meier curve for the MTD/RP2D only.

Only overall tumor assessments reported by investigator and performed before the start of any further anti -neoplastic therapies (i.e., any additional secondary anti-neoplastic therapy or surgery) were considered in the assessment of best overall response.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary that consisted of the system organ class (SOC) and preferred term (PT). AEs were graded according to the common toxicology criteria for adverse e vents (CTCAE) V4.03. CTCAE grade 5 (death) was not used in this study.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Patients with histologically-confirmed, advanced unresectable solid tumors.
- Availability of a representative formalin fixed paraffin embedded tumor tissue sample or fresh tumor sample.
- At least one measurable or non-measurable lesion.
- Age ≥ 18 years.
- Eastern Cooperative Oncology Group(ECOG) Performance Status ≤ 2.
- Patient with the following baseline laboratory values were allowed: serum total bilirubin level ≤ 1.5 × upper limit of normal (ULN), aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) levels ≤ 2.5 × ULN or ≤ 5.0 × ULN (if liver metastases was present), serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min, hemoglobin >9 g/dL, platelet count ≥ 100 × 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, calcium within normal limits, potassium within normal limits, magnesium ≥ the lower limit of normal, fasting glucose <140 mg/dL/7.8 mmol/L.

Key Exclusion Criteria:

- Brain metastasis unless treated and free of signs/symptoms attributable to brain metastasis in the absence of corticosteroid therapy and anti-epileptic therapy.
- Prior treatment with PI3K inhibitor.
- Patient with peripheral neuropathy NCI-CTC grade ≥ 2.
- Patient with diarrhea NCI-CTC grade ≥ 2.

- Patient with acute or chronic pancreatitis.
- Impaired cardiac function or clinically significant cardiac disease incl unstable angina pectoris ≤ 3 months prior to starting study drug and Acute Myocardial Infarction (AMI) ≤ 3 months prior to starting study drug.
- Patients with clinically manifest diabetes mellitus (treated and/or clinical signs or with fasting glucose ≥ 140 mg/dL/7.8 mmol/L), history of gestational diabetes mellitus or documented steroid-induced diabetes mellitus.
- Women who are pregnant or breast feeding.
- Patients of childbearing potential who were unwilling to take appropriate precautions (from Screening through follow-up) to avoid fathering a child or becoming pregnant.

Participant Flow Table

Patient disposition (Full analysis set)

Dose escalation part						Expansion part 350 mg		
	90 mg N=3	180 mg N=4	270 mg N=5	350 mg N=6	400 mg N=7	350 mg N=8	All N=14	All Patients N=33
Disposition Reason	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients treated								
Treatment discontinued	**3 (100)**	**4 (100)**	**5 (100)**	**6 (100)**	**7 (100)**	**8 (100)**	**14 (100)**	**33 (100)**
Primary reason for end of treatment								
Adverse event	0	0	2 (40.0)	2 (33.3)	3 (42.9)	2 (25.0)	4 (28.6)	9 (27.3)
Death	0	0	0	0	1 (14.3)	0	0	1 (3.0)
Lack of efficacy	3 (100)	2 (50.0)	3 (60.0)	4 (66.7)	3 (42.9)	6 (75.0)	10 (71.4)	21 (63.6)
Patient/Guardian decision	0	2 (50.0)	0	0	0	0	0	2 (6.1)
End of post-treatment evaluation								

Disposition Reason	Dose escalation part 90 mg N=3 n (%)	180 mg N=4 n (%)	270 mg N=5 n (%)	350 mg N=6 n (%)	400 mg N=7 n (%)	Expansion part 350 mg N=8 n (%)	350 mg All N=14 n (%)	All Patients N=33 n (%)
Patients no longer being followed for post-treatment evaluation	3 (100)	4 (100)	5 (100)	6 (100)	7 (100)	8 (100)	14 (100)	33 (100)
Primary reason for end of post-treatment evaluation								
Completed	2 (66.7)	4 (100)	5 (100)	5 (83.3)	6 (85.7)	8 (100)	13 (92.9)	30 (90.9)
Death	1 (33.3)	0	0	1 (16.7)	1 (14.3)	0	1 (7.1)	3 (9.1)

Baseline Characteristics

Demographic summary by treatment group (Full analysis set)

Demographic variable	Dose escalation part 90 mg N=3	180 mg N=4	270 mg N=5	350 mg N=6	400 mg N=7	Expansion part 350 mg N=8	350 mg All N=14	All Patients N=33
Age (Years)								
n	3	4	5	6	7	8	14	33
Mean	49.0	57.5	59.2	57.3	47.7	52.8	54.7	53.7
SD	13.75	13.28	16.48	5.43	17.91	13.07	10.43	13.55
Median	52.0	60.5	63.0	55.5	48.0	54.5	55.5	55.0
Minimum	34	39	40	52	24	31	31	24
Maximum	61	70	76	67	72	72	72	76
Age category (years) -n (%)								

	Dose escalation part					Expansion part	350 mg	
	90 mg	180 mg	270 mg	350 mg	400 mg	350 mg	All	All Patients
Demographic variable	**N=3**	**N=4**	**N=5**	**N=6**	**N=7**	**N=8**	**N=14**	**N=33**
< 65	3 (100)	3 (75.0)	3 (60.0)	5 (83.3)	5 (71.4)	7 (87.5)	12 (85.7)	26 (78.8)
≥ 65	0	1 (25.0)	2 (40.0)	1 (16.7)	2 (28.6)	1 (12.5)	2 (14.3)	7 (21.2)
Sex -n (%)								
Female	1 (33.3)	1 (25.0)	4 (80.0)	2 (33.3)	2 (28.6)	7 (87.5)	9 (64.3)	17 (51.5)
Male	2 (66.7)	3 (75.0)	1 (20.0)	4 (66.7)	5 (71.4)	1 (12.5)	5 (35.7)	16 (48.5)
Childbearing status -n (%)								
Able to bear children	0	0	1 (20.0)	0	1 (14.3)	1 (12.5)	1 (7.1)	3 (9.1)
Post-menopausal	0	0	3 (60.0)	0	1 (14.3)	6 (75.0)	6 (42.9)	10 (30.3)
Sterile - of childbearing age	1 (33.3)	1 (25.0)	0	2 (33.3)	0	0	2 (14.3)	4 (12.1)
Weight category (kg) -n (%)								
< 55	0	2 (50.0)	4 (80.0)	2 (33.3)	1 (14.3)	4 (50.0)	6 (42.9)	13 (39.4)
55 -<75	1 (33.3)	2 (50.0)	1 (20.0)	4 (66.7)	5 (71.4)	4 (50.0)	8 (57.1)	17 (51.5)
≥ 75	2 (66.7)	0	0	0	1 (14.3)	0	0	3 (9.1)
Body surface area (m^2)								
n	3	4	5	6	7	8	14	33
Mean	1.88	1.65	1.55	1.63	1.74	1.54	1.58	1.64
SD	0.099	0.135	0.208	0.118	0.183	0.202	0.172	0.191
Median	1.92	1.64	1.49	1.62	1.77	1.52	1.57	1.66
Minimum	1.8	1.5	1.4	1.5	1.4	1.2	1.2	1.2
Maximum	1.9	1.8	1.9	1.8	2.0	1.9	1.9	2.0
ECOG performance status -n (%)								
0	2 (66.7)	4 (100)	2 (40.0)	4 (66.7)	4 (57.1)	6 (75.0)	10 (71.4)	22 (66.7)
1	1 (33.3)	0	3 (60.0)	2 (33.3)	3 (42.9)	1 (12.5)	3 (21.4)	10 (30.3)
2	0	0	0	0	0	1 (12.5)	1 (7.1)	1 (3.0)

Primary Outcome Result

Refer to Safety Results section for primary outcome result.

Secondary Outcome Result

Best overall response (Full analysis set)

	Dose escalation part				Expansion part	350 mg	
90 mg	**180 mg**	**270 mg**	**350 mg**	**400 mg**	**350 mg**	**All**	**All Patients**
N=3	**N=4**	**N=5**	**N=6**	**N=7**	**N=8**	**N=14**	**N=33**
n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Best overall response							
Complete response (CR)	0	0	0	0	0	0	0	0
Partial response (PR)	0	0	0	1 (16.7)	0	0	1 (7.1)	1 (3.0)
Stable disease (SD)	2 (66.7)	2 (50.0)	2 (40.0)	4 (66.7)	2 (28.6)	6 (75.0)	10 (71.4)	18 (54.5)
Progressive disease (PD)	1 (33.3)	1 (25.0)	3 (60.0)	1 (16.7)	3 (42.9)	1 (12.5)	2 (14.3)	10 (30.3)
Unknown	0	1 (25.0)	0	0	2 (28.6)	1 (12.5)	1 (7.1)	4 (12.1)
Overall response rate (ORR)								
(CR or PR)	0	0	0	1 (16.7)	0	0	1 (7.1)	1 (3.0)
95% CI	(0.0 - 70.8)	(0.0 - 60.2)	(0.0 - 52.2)	(0.4 - 64.1)	(0.0 - 41.0)	(0.0 - 36.9)	(0.2 - 33.9)	(0.1 - 15.8)
Disease control rate (DCR)								
(CR or PR or SD)	2 (66.7)	2 (50.0)	2 (40.0)	5 (83.3)	2 (28.6)	6 (75.0)	11 (78.6)	19 (57.6)
95% CI	(9.4 - 99.2)	(6.8 - 93.2)	(5.3 - 85.3)	(35.9 - 99.6)	(3.7 - 71.0)	(34.9 - 96.8)	(49.2 - 95.3)	(39.2 - 74.5)

Summary of primary PK parameters of BYL719 at dose escalation part (Full analysis set)

Treatment	Statistics	AUC0-24 (hr*ng/mL)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 1						
90 mg (N=3)	n	3	3	3	3	3
	Mean (SD)	7290 (1510)	7280 (1510)	7650 (1680)	1180 (185)	N/A
	CV% mean	20.7	20.7	22.0	15.7	N/A

Treatment	Statistics	AUC0-24 (hr*ng/mL)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	Geo-mean	7180	7170	7520	1170	N/A
	CV% Geo-mean	22.0	22.0	23.2	15.2	N/A
	Median	7600	7590	7900	1070	2.00
	[Min; Max]	[5650; 8620]	[5650; 8620]	[5860; 9190]	[1070; 1390]	[1.50; 3.00]
180 mg (N=4)	n	4	4	4	4	4
	Mean (SD)	16800 (3520)	16700 (3530)	17600 (4020)	2000 (749)	N/A
	CV% mean	21.0	21.1	22.8	37.5	N/A
	Geo-mean	16500	16500	17300	1900	N/A
	CV% Geo-mean	19.8	19.8	21.4	37.5	N/A
	Median	15500	15500	16300	1820	2.46
	[Min; Max]	[14000; 21900]	[14000; 21900]	[14500; 23500]	[1370; 2990]	[1.50; 3.00]
270 mg (N=5)	n	4	5	4	5	5
	Mean (SD)	25200 (7340)	26300 (6850)	26200 (7780)	2790 (620)	N/A
	CV% mean	29.1	26.0	29.6	22.3	N/A
	Geo-mean	24300	25500	25300	2730	N/A
	CV% Geo-mean	31.8	29.5	32.5	23.1	N/A
	Median	25300	25800	26400	2660	2.02
	[Min; Max]	[16100; 34000]	[16000; 34000]	[16500; 35600]	[2000; 3530]	[2.00; 23.3]
350 mg (N=6)	n	6	6	6	6	6
	Mean (SD)	28600 (10200)	28600 (10200)	30400 (10600)	3800 (1830)	N/A
	CV% mean	35.7	35.7	35.0	48.1	N/A
	Geo-mean	27100	27100	28800	3460	N/A
	CV% Geo-mean	38.1	38.1	37.0	50.2	N/A
	Median	27600	27600	29200	3490	1.77
	[Min; Max]	[18000; 40300]	[17900; 40300]	[19600; 43300]	[2000; 6810]	[1.00; 3.00]
400 mg (N=7)	n	7	7	7	7	7
	Mean (SD)	41300 (17800)	41200 (17800)	43800 (19800)	4750 (1740)	N/A

Treatment	Statistics	AUC0-24 (hr*ng/mL)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	CV% mean	43.2	43.1	45.1	36.6	N/A
	Geo-mean	38400	38300	40600	4440	N/A
	CV% Geo-mean	42.8	42.7	42.9	44.1	N/A
	Median	40700	40700	42300	4850	2.00
	[Min; Max]	[21500; 76600]	[21500; 76500]	[23300; 84300]	[2070; 7050]	[1.50; 3.00]
Cycle 1 Day 8						
90 mg (N=3)	n	3	3		3	3
	Mean (SD)	7850 (1180)	7850 (1180)		1290 (30.0)	N/A
	CV% mean	15.0	15.0		2.3	N/A
	Geo-mean	7790	7780		1290	N/A
	CV% Geo-mean	15.9	15.8		2.3	N/A
	Median	8410	8400		1290	2.00
	[Min; Max]	[6500; 8640]	[6490; 8640]		[1260; 1320]	[1.00; 3.00]
180 mg (N=4)	n	3	3		3	3
	Mean (SD)	19700 (4280)	19700 (4280)		2540 (1060)	N/A
	CV% mean	21.7	21.7		41.6	N/A
	Geo-mean	19400	19400		2400	N/A
	CV% Geo-mean	20.9	20.9		43.9	N/A
	Median	17600	17600		2350	3.00
	[Min; Max]	[16900; 24600]	[16800; 24600]		[1590; 3680]	[1.50; 4.03]
270 mg (N=5)	n	3	4		4	4
	Mean (SD)	32400 (9830)	27700 (12300)		2920 (1390)	N/A
	CV% mean	30.3	44.2		47.5	N/A
	Geo-mean	31300	25500		2560	N/A
	CV% Geo-mean	32.7	51.4		72.1	N/A
	Median	32900	27600		3260	3.55

Treatment	Statistics	AUC0-24 (hr*ng/mL)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	[Min; Max]	[22300; 41900]	[13900; 41900]		[1000; 4140]	[3.00; 8.00]
350 mg (N=6)	n	4	4		4	4
	Mean (SD)	33400 (8070)	33400 (8040)		3870 (1410)	N/A
	CV% mean	24.2	24.1		36.4	N/A
	Geo-mean	32600	32600		3680	N/A
	CV% Geo-mean	24.9	24.9		38.9	N/A
	Median	33500	33400		3800	2.50
	[Min; Max]	[25600; 41000]	[25600; 41000]		[2570; 5330]	[1.50; 3.00]
400 mg (N=7)	n	7	7		7	7
	Mean (SD)	44600 (19800)	44500 (19700)		5050 (2060)	N/A
	CV% mean	44.3	44.3		40.8	N/A
	Geo-mean	40200	40100		4640	N/A
	CV% Geo-mean	56.6	56.5		49.7	N/A
	Median	49100	49000		4920	3.00
	[Min; Max]	[18300; 75300]	[18300; 75100]		[2130; 7340]	[2.00; 4.02]
Cycle 2 Day 1						
90 mg (N=3)	n	3	3		3	3
	Mean (SD)	9080 (2320)	9060 (2320)		1060 (172)	N/A
	CV% mean	25.6	25.6		16.3	N/A
	Geo-mean	8880	8860		1050	N/A
	CV% Geo-mean	25.9	25.9		15.9	N/A
	Median	8720	8690		999	3.00
	[Min; Max]	[6950; 11600]	[6950; 11500]		[921; 1250]	[1.50; 4.00]
180 mg (N=4)	n	3	3		3	3
	Mean (SD)	19600 (3650)	19600 (3640)		2200 (670)	N/A
	CV% mean	18.6	18.6		30.5	N/A
	Geo-mean	19400	19400		2130	N/A

Treatment	Statistics	AUC0-24 (hr*ng/mL)	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	CV% Geo-mean	20.0	19.9		29.2	N/A
	Median	21300	21300		1820	1.50
	[Min; Max]	[15400; 22100]	[15400; 22100]		[1800; 2970]	[0.500; 3.00]
270 mg (N=5)	n	2	2		2	2
	Mean (SD)	29100 (7380)	29100 (7420)		3120 (1730)	N/A
	CV% mean	25.4	25.5		55.6	N/A
	Geo-mean	28600	28600		2860	N/A
	CV% Geo-mean	26.1	26.2		64.2	N/A
	Median	29100	29100		3120	3.50
	[Min; Max]	[23900; 34300]	[23800; 34300]		[1890; 4340]	[3.00; 4.00]
350 mg (N=6)	n	4	4		4	4
	Mean (SD)	39600 (13400)	39500 (13400)		4800 (1740)	N/A
	CV% mean	34.0	33.9		36.4	N/A
	Geo-mean	37500	37400		4520	N/A
	CV% Geo-mean	41.6	41.5		43.7	N/A
	Median	43400	43300		5020	2.25
	[Min; Max]	[21300; 50200]	[21300; 49900]		[2530; 6620]	[1.50; 4.00]
400 mg (N=7)	n	1	1		1	1
	Mean (SD)	26500 (-)	26400 (-)		4390 (-)	N/A
	CV% mean					N/A
	Geo-mean	26500	26400		4390	N/A
	CV% Geo-mean					N/A
	Median	26500	26400		4390	2.00
	[Min; Max]	[26500; 26500]	[26400; 26400]		[4390; 4390]	[2.00; 2.00]

CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of statistical analysis of dose-normalized AUClast, AUC0-24 and Cmax by condition (Pharmacokinetics analysis set for expansion part)

					Food effect Comparison		
						90% CI	
PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUC0-24 ([hr*ng/mL]/[mg dose])	Fasted	5	72.10				
	Fed	5	113.00	Fed : Fasted	1.56	1.02	2.39
AUClast ([hr*ng/mL]/[mg dose]))	Fasted	6	67.80				
	Fed	6	105.00	Fed : Fasted	1.55	1.06	2.28
Cmax ([ng/mL]/[mg dose]))	Fasted	6	5.40				
	Fed	6	9.62	Fed : Fasted	1.78	1.13	2.79

n* = number of patients with non-missing values
All data are divided by the actual dose.

Safety Results

Primary outcome result : Determination MTD (and/or RP2D)

RP2D	350 mg/d in Japanese patients with advanced solid malignancie

DLTs occurring during the first cycle by primary system organ class and preferred term (Dose determining set)

Primary system organ class Preferred term	Dose escalation part 90 mg N=3 n (%)	 180 mg N=3 n (%)	 270 mg N=4 n (%)	 350 mg N=6 n (%)	 400 mg N=5 n (%)	Expansion part 350 mg N=0 n (%)	350 mg All N=6 n (%)	All patients N=21 n (%)
Any DLT	0	0	0	0	2 (40.0)	0	0	2 (9.5)
Infections and infestations								
Conjunctivitis	0	0	0	0	1 (20.0)	0	0	1 (4.8)
Skin and subcutaneous tissue disorders								
Total	0	0	0	0	2 (40.0)	0	0	2 (9.5)
Rash maculopapular	0	0	0	0	2 (40.0)	0	0	2 (9.5)

Adverse events, regardless of study drug relationship, and by primary system organ class (Safety set)

Primary system organ class	Dose escalation part 90 mg N=3 n (%)	 180 mg N=4 n (%)	 270 mg N=5 n (%)	 350 mg N=6 n (%)	 400 mg N=7 n (%)	Expansion part 350 mg N=8 n (%)	350 mg All N=14 n (%)	All patients N=33 n (%)
-Total	3 (100)	4 (100)	5 (100)	6 (100)	7 (100)	8 (100)	14 (100)	33 (100)
Gastrointestinal disorders	2 (66.7)	3 (75.0)	5 (100)	6 (100)	6 (85.7)	6 (75.0)	12 (85.7)	28 (84.8)
Skin and subcutaneous tissue disorders	2 (66.7)	3 (75.0)	4 (80.0)	6 (100)	7 (100)	6 (75.0)	12 (85.7)	28 (84.8)
Metabolism and nutrition disorders	1 (33.3)	1 (25.0)	3 (60.0)	6 (100)	5 (71.4)	6 (75.0)	12 (85.7)	22 (66.7)
General disorders and administration site conditions	2 (66.7)	3 (75.0)	5 (100)	3 (50.0)	2 (28.6)	6 (75.0)	9 (64.3)	21 (63.6)

	Dose escalation part					Expansion part	350 mg	
	90 mg	180 mg	270 mg	350 mg	400 mg	350 mg	All	All patients
	N=3	N=4	N=5	N=6	N=7	N=8	N=14	N=33
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigations	1 (33.3)	2 (50.0)	4 (80.0)	5 (83.3)	5 (71.4)	3 (37.5)	8 (57.1)	20 (60.6)
Infections and infestations	2 (66.7)	3 (75.0)	2 (40.0)	3 (50.0)	5 (71.4)	3 (37.5)	6 (42.9)	18 (54.5)
Nervous system disorders	1 (33.3)	3 (75.0)	2 (40.0)	1 (16.7)	4 (57.1)	3 (37.5)	4 (28.6)	14 (42.4)
Psychiatric disorders	0	1 (25.0)	2 (40.0)	3 (50.0)	3 (42.9)	2 (25.0)	5 (35.7)	11 (33.3)
Blood and lymphatic system disorders	0	0	3 (60.0)	1 (16.7)	1 (14.3)	5 (62.5)	6 (42.9)	10 (30.3)
Respiratory, thoracic and mediastinal disorders	3 (100)	2 (50.0)	1 (20.0)	2 (33.3)	0	2 (25.0)	4 (28.6)	10 (30.3)
Musculoskeletal and connective tissue disorders	2 (66.7)	1 (25.0)	0	1 (16.7)	2 (28.6)	2 (25.0)	3 (21.4)	8 (24.2)
Eye disorders	0	1 (25.0)	1 (20.0)	0	3 (42.9)	1 (12.5)	1 (7.1)	6 (18.2)
Renal and urinary disorders	0	1 (25.0)	0	2 (33.3)	2 (28.6)	0	2 (14.3)	5 (15.2)
Endocrine disorders	0	0	0	0	2 (28.6)	1 (12.5)	1 (7.1)	3 (9.1)
Hepatobiliary disorders	0	1 (25.0)	0	0	1 (14.3)	1 (12.5)	1 (7.1)	3 (9.1)
Injury, poisoning and procedural complications	0	1 (25.0)	1 (20.0)	0	1 (14.3)	0	0	3 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (16.7)	0	2 (25.0)	3 (21.4)	3 (9.1)
Ear and labyrinth disorders	1 (33.3)	0	0	0	0	1 (12.5)	1 (7.1)	2 (6.1)
Vascular disorders	0	2 (50.0)	0	0	0	0	0	2 (6.1)

Adverse events (equal to or more than 15% incidence) and grade 3/4 adverse events (equal to or more than 5% incidence), regardless of study drug relationship, and by preferred term (Safety set)

	Dose escalation part										Expansion part		350 mg			
	90 mg		180 mg		270 mg		350 mg		400 mg		350 mg		All		All patients	
	N=3		N=4		N=5		N=6		N=7		N=8		N=14		N=33	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Any AE	3 (100)	2 (66.7)	4 (100)	2 (50.0)	5 (100)	5 (100)	6 (100)	4 (66.7)	7 (100)	6 (85.7)	8 (100)	6 (75.0)	14 (100)	10 (71.4)	33 (100)	25 (75.8)
Diarrhoea	2 (66.7)	0	1 (25.0)	0	4 (80.0)	0	5 (83.3)	0	3 (42.9)	0	5 (62.5)	0	10 (71.4)	0	20 (60.6)	0
Hyperglycaemia	0	0	1 (25.0)	0	1 (20.0)	1 (20.0)	6 (100)	3 (50.0)	3 (42.9)	0	6 (75.0)	3 (37.5)	12 (85.7)	6 (42.9)	17 (51.5)	7 (21.2)
Rash maculo-papular	0	0	1 (25.0)	0	2 (40.0)	2 (40.0)	6 (100)	1 (16.7)	5 (71.4)	4 (57.1)	2 (25.0)	1 (12.5)	8 (57.1)	2 (14.3)	16 (48.5)	8 (24.2)
Decreased appetite	1 (33.3)	0	1 (25.0)	0	2 (40.0)	0	3 (50.0)	0	3 (42.9)	0	4 (50.0)	0	7 (50.0)	0	14 (42.4)	0
Pyrexia	0	0	2 (50.0)	0	4 (80.0)	1 (20.0)	2 (33.3)	0	2 (28.6)	0	3 (37.5)	0	5 (35.7)	0	13 (39.4)	1 (3.0)
Nausea	1 (33.3)	0	1 (25.0)	0	2 (40.0)	0	2 (33.3)	0	2 (28.6)	0	2 (25.0)	0	4 (28.6)	0	10 (30.3)	0
Insomnia	0	0	1 (25.0)	0	2 (40.0)	0	3 (50.0)	0	2 (28.6)	0	1 (12.5)	0	4 (28.6)	0	9 (27.3)	0
Rash	1 (33.3)	0	1 (25.0)	0	1 (20.0)	0	0	0	2 (28.6)	1 (14.3)	4 (50.0)	3 (37.5)	4 (28.6)	3 (21.4)	9 (27.3)	4 (12.1)
Pruritus	1 (33.3)	0	2 (50.0)	0	0	0	2 (33.3)	0	3 (42.9)	0	0	0	2 (14.3)	0	8 (24.2)	0
Anaemia	0	0	0	0	3 (60.0)	1 (20.0)	0	0	1 (14.3)	1 (14.3)	4 (50.0)	0	4 (28.6)	0	8 (24.2)	2 (6.1)
Stomatitis	0	0	0	0	2 (40.0)	0	2 (33.3)	0	2 (28.6)	0	2 (25.0)	0	4 (28.6)	0	8 (24.2)	0
Vomiting	1 (33.3)	0	1 (25.0)	0	0	0	3 (50.0)	0	1 (14.3)	0	1 (12.5)	0	4 (28.6)	0	7 (21.2)	0
Oedema peripheral	0	0	0	0	1 (20.0)	0	2 (33.3)	0	0	0	3 (37.5)	0	5 (35.7)	0	6 (18.2)	0
Blood creatinine increased	0	0	1 (25.0)	0	0	0	1 (16.7)	0	2 (28.6)	0	2 (25.0)	0	3 (21.4)	0	6 (18.2)	0
Dermatitis acneiform	2 (66.7)	0	0	0	1 (20.0)	0	1 (16.7)	0	2 (28.6)	0	0	0	1 (7.1)	0	6 (18.2)	0
Fatigue	0	0	1 (25.0)	0	0	0	1 (16.7)	0	1 (14.3)	0	2 (25.0)	0	3 (21.4)	0	5 (15.2)	0
Nasopharyngitis	0	0	1 (25.0)	0	0	0	1 (16.7)	0	2 (28.6)	0	1 (12.5)	0	2 (14.3)	0	5 (15.2)	0
Paronychia	0	0	1 (25.0)	0	0	0	2 (33.3)	0	1 (14.3)	0	1 (12.5)	0	3 (21.4)	0	5 (15.2)	0
Aspartate aminotransferase Increased	1 (33.3)	0	0	0	1 (20.0)	0	2 (33.3)	0	1 (14.3)	0	0	0	2 (14.3)	0	5 (15.2)	0
Blood insulin increased	1 (33.3)	0	1 (25.0)	0	0	0	1 (16.7)	0	2 (28.6)	0	0	0	1 (7.1)	0	5 (15.2)	0
Lipase increased	0	0	0	0	2 (40.0)	1 (20.0)	3 (50.0)	1 (16.7)	0	0	0	0	3 (21.4)	1 (7.1)	5 (15.2)	2 (6.1)
Weight decreased	0	0	1 (25.0)	0	0	0	2 (33.3)	0	1 (14.3)	1 (14.3)	1 (12.5)	0	3 (21.4)	0	5 (15.2)	1 (3.0)

	Dose escalation part										Expansion part		350 mg			
	90 mg N=3		180 mg N=4		270 mg N=5		350 mg N=6		400 mg N=7		350 mg N=8		All N=14		All patients N=33	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Headache	0	0	0	0	1 (20.0)	0	0	0	2 (28.6)	0	2 (25.0)	0	2 (14.3)	0	5 (15.2)	0
Cough	1 (33.3)	0	0	0	0	0	2 (33.3)	0	0	0	2 (25.0)	0	4 (28.6)	0	5 (15.2)	0
Liver abscess	0	0	0	0	1 (20.0)	1 (20.0)	1 (16.7)	1 (16.7)	0	0	0	0	1 (7.1)	1 (7.1)	2 (6.1)	2 (6.1)
Lymphocyte count decreased	0	0	0	0	0	0	0	0	2 (28.6)	2 (28.6)	0	0	0	0	2 (6.1)	2 (6.1)
Dyspnoea	1 (33.3)	1 (33.3)	0	0	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (7.1)	1 (7.1)	2 (6.1)	2 (6.1)

Overall summary of frequencies of death, serious adverse events, and other significant adverse events by treatment group (Safety set)

	Dose escalation part					Expansion part	350 mg	
	90 mg N=3	180 mg N=4	270 mg N=5	350 mg N=6	400 mg N=7	350 mg N=8	All N=14	All patients N=33
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Deaths	1 (33.3)	0	0	1 (16.7)	1 (14.3)	0	1 (7.1)	3 (9.1)
SAEs	2 (66.7)	3 (75.0)	5 (100)	2 (33.3)	2 (28.6)	5 (62.5)	7 (50.0)	19 (57.6)
Suspected treatment-related	1 (33.3)	2 (50.0)	2 (40.0)	0	1 (14.3)	3 (37.5)	3 (21.4)	9 (27.3)
AEs leading to discontinuation	0	0	2 (40.0)	2 (33.3)	3 (42.9)	2 (25.0)	4 (28.6)	9 (27.3)
AEs requiring dose adjustment or interruption	1 (33.3)	2 (50.0)	4 (80.0)	4 (66.7)	6 (85.7)	7 (87.5)	11 (78.6)	24 (72.7)

Conclusion:

BYL719 as single agent showed an acceptable safety profile and encouraging preliminary efficacy in Japanese patients with advanced solid tumors.

Date of Clinical Trial Report

2 September 2016

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67359

Swissmedic Approval Date 24.03.2020

Novartis Study Code

CBYL719X1101

EudraCT Number

Not Applicable

Planned and Actual Number of Patients

Planned: 15

Actual: 33

Batch Numbers

Study drug and strength	Formulation control number	Batch number
BYL719 10 mg tablets	6003035.004	X189 0611
	6003035.004	X267 1111
	6003035.006	X130 0812
	6003035.006	X011 0133
BYL719 50 mg tablets	6003036.004	X190 0611
	6003036.004	X268 1111
	6003036.006	X131 0812
	6003036.006	X230 1112
BYL719 200 mg tablets	6003037.004	X191 0611
	6003037.004	X269 1111
	6003037.006	X132 0812
	6003037.006	X012 0113

Information on comparators drug dosage, route of administration, batch numbers

Not applicable

Publication(s)

- Ando Y, Iwasa S, Takahashi S, et al. Phase I study of alpelisib (BYL719), an α-specific PI3K inhibitor, in Japanese patients with advanced solid tumors. Cancer Sci. 2019;110(3):1021-1031.
- Tomomatsu J, Iwasa S, Saka H, et al. A phase 1 study of BYL719, an α-isoform selective PI3K inhibitor, in Japanese patients with advanced solid malignancies. Annals of Oncology. 2017;(suppl_5):v74-v108.
- Takahashi S, Ando Y, Saka H, et al. Phase I Study of Alpelisib (BYL719) in Japanese Patients (Pts) With Advanced Solid Tumors: Results in Pts Treated at the Recommended Phase II Dose (RP2D). AACR-NCI-EORTC Symposium on Molecular Targets and Cancer Therapeutics. 2015.

NOVARTIS

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