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Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

Alpelisib

Trial Indication(s)

Dose escalation: Advanced solid tumors; Dose expansion: locally advanced/metastatic, chemotherapy naïve, HER2-negative breast cancer and recurrent or metastatic head-and-neck squamous cell carcinoma

Protocol Number

CBYL719Z2101

Protocol Title

A phase Ib, open label, dose finding study of BYL719 in combination with paclitaxel in advanced solid tumors followed by two expansion phases in locally advanced/metastatic chemotherapy naive HER2-breast cancer patients and recurrent or metastatic head-and-neck squamous cell carcinoma patients pre-treated with platinum based therapy

Clinical Trial Phase

Ib

Phase of Drug Development

I

Study Start/End Dates

05-Mar-2014 to 19-Aug-2016

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was a multi-center, open-label Phase Ib dose finding study of alpelisib in combination with paclitaxel in patients with advanced solid tumors. The MTD/RP2D of oral daily dosing of alpelisib in combination with weekly paclitaxel was recommended based on dose-limiting toxicities using a Bayesian logistic regression model. A minimum of 9 patients were planned for enrollment in the dose escalation phase. The initial dose level of alpelisib was 300 mg daily and paclitaxel was administered weekly at the dose of 80 mg/m².

Due to the lack of data confirming a pharmacodynamic effect and clinical activity of alpelisib at determined MTD for the combination, challenges associated with regimen tolerability and the overall changing treatment landscape, Novartis decided to not continue with the expansion phase of the study. The study was terminated with completion of the dose escalation part.

Centers

5 centers in 4 countries: France (1), Italy (1), Spain (1), USA (2).

Objectives:

Primary objective in dose escalation phase was

- to determine the MTD and/or RP2D of QD alpelisib in combination with weekly paclitaxel.

Secondary objectives in dose escalation phase were

- to assess safety and tolerability of the combination,
- to characterize pharmacokinetics of alpelisib and paclitaxel when given in combination,

- to investigate potential drug-drug interaction between alpelisib and paclitaxel.

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

Alpelisib tablets were supplied to the Investigators at dose strengths of 50 mg and 200 mg. Paclitaxel was supplied as the commercially available product including generic formulation.

Statistical Methods

Available data were analyzed after each cohort of patients completed Cycle 1 for decisions on the dose for the next cohort and/or for determining the MTD/RP2D. The Full Analysis Set (FAS) was comprised of all patients who received at least one dose of study treatment (alpelisib and/or paclitaxel). The Safety Set included all patients who received at least one dose of study treatment (alpelisib and/or paclitaxel), and had at least one valid post-baseline safety assessment. Patients were classified according to dose level received, where dose level received was defined as the dose level assigned if it was received at least once, or the first dose level received when starting therapy if the assigned dose level was never received. The dose-determining set (DDS) consisted of all patients from the safety set who, during Cycle 1, either met the minimum exposure criterion and had sufficient safety evaluations, or had experienced a DLT during Cycle 1. A cycle was defined as 28 days of dosing. The pharmacokinetic analysis set consisted of all patients in the full analysis set who received at least one dose of study treatment (alpelisib and/or paclitaxel) and had at least one evaluable concentration measurement.

The primary analysis method for MTD determination was an adaptive Bayesian logistic regression model guided by the EWOC principle. An adaptive 5-parameter BLRM with EWOC principle guided the dose-escalation of each combination. The escalation with EWOC principle only recommends doses for which the risk of overdosing (true DLT rate exceeding 0.35) is less than 25% for the next dose level. The BLRM was fitted on the Cycle 1 DLT data accumulated throughout dose escalation to model the dose-toxicity relationship of alpelisib when given in combination with weekly paclitaxel.

The assessment of safety was based mainly on the type and frequency of AEs. Data were summarized, notable values were flagged, and any other information collected was listed as appropriate. Adverse events were coded using MedDRA version 19.0 terminology. CTCAE version 4.03 grading was used.

PK parameters were calculated for alpelisib and paclitaxel for all PK-evaluable patients using non-compartmental methods. Only primary PK parameters such as Cmax, Tmax, AUC0-24, AUCinf (only paclitaxel) were reported. PK parameters of paclitaxel metabolites and alpelisib metabolite BZG791 were determined but have not listed or summarized.

Interim analyses: available data were analyzed after each cohort completed Cycle 1 for decision making on the dose for the next cohort and/or for determining the MTD/RP2D. As a result of the decision not to continue with development of alpelisib in combination with paclitaxel, no interim analyses were performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male or female patients ≥ 18 years
- Patient had signed the Informed Consent Form prior to any screening procedures being performed and is able to comply with protocol requirement
- Patient had at least one measurable or non-measurable lesion as per RECIST 1.1
- Patient had tumor tissue available for the analysis of PI3K signaling. One tumor block (preferred) or a minimum of 15 unstained slides is recommended
- Patient had adequate bone marrow and organ function as defined by the following laboratory values:
  - Absolute Neutrophil Count ≥ 1.5×10^9/L
  - Platelets ≥ 100×10^9/L
  - Hemoglobin ≥ 9.0 g/dL
  - International Normalized Ratio ≤ 1.5
  - Serum creatinine ≤ 1.5× Upper limit of normal (ULN)
  - Total serum bilirubin ≤ 1.5× ULN
  - Alanine aminotransferase and aspartate aminotransferase ≤ 2.5× ULN (or 5× ULN if liver metastases are present)
  - Fasting plasma glucose ≤ 120 mg/dL or ≤ 6.7 mmol/L

- Patient was able to swallow and retain oral medication

Specific additional Inclusion criteria for the dose escalation part:

- Patient had a histologically-confirmed, advanced unresectable solid tumors who have progressed on standard therapy (or not been able to tolerate) within three months before screening/baseline visit or for whom no standard anticancer therapy exists.
- Patient had an ECOG performance status ≤ 2

Exclusion criteria

- Patient had received previous treatment with a PI3K or AKT inhibitor.
- Patient had a known hypersensitivity to paclitaxel or other products containing Cremophor
- Patient had a contraindication to use the standard pre-treatment for paclitaxel
- Patient had peripheral sensory neuropathy with functional impairment (CTC grade 2 neuropathy or higher, regardless of causality)
- Patient had diabetes mellitus requiring insulin treatment and/or with clinical signs
- Patient had any other condition that would, in the Investigator's judgment, preclude patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures
- Patient was currently receiving treatment with drugs known to be moderate or strong inhibitors or inducers of isoenzymes CYP3A or CYP2C8. The patient must have discontinued strong and moderate inducers of both enzymes for at least one week and must have discontinued strong and moderate inhibitors before the start of treatment.
- Patient who was currently receiving treatment with agents that are metabolized solely by CYP3A and/or have a narrow therapeutic window

Participant Flow Table

Disposition Reason	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=9 n (%)	BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=4 n (%)	BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=6 n (%)	All patients N=19 n (%)
Patient enrolled				
Treated	9 (100)	4 (100)	6 (100)	19 (100)
Patients treated				
End of treatment	9 (100)	4 (100)	6 (100)	19 (100)
Primary reason for end of treatment				
Adverse event	1 (11.1)	1 (25.0)	0	2 (10.5)
Physician decision	2 (22.2)	0	0	2 (10.5)
Progressive disease	5 (55.6)	3 (75.0)	4 (66.7)	12 (63.2)
Subject/guardian decision	1 (11.1)	0	2 (33.3)	3 (15.8)
Post Treatment follow-up after End of Treatment				
Not applicable*	8 (88.9)	4 (100)	6 (100)	18 (94.7)
Patients no longer being followed for post treatment follow-up	1 (11.1)	0	0	1 (5.3)
Primary reason for discontinuation of post treatment follow-up				
New therapy for study indication	1 (11.1)	0	0	1 (5.3)

*Patients who withdrew consent from the study, died, or decided not to go to post treatment follow-up at the end of treatment evaluation.
Percentage is based on N.

Baseline Characteristics

Demographic Variable	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=9	BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=4	BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=6	All patients N=19
Age -n (%)				

Demographic Variable	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=9	BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=4	BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=6	All patients N=19
<65 Years	7 (77.8)	3 (75.0)	4 (66.7)	14 (73.7)
≥ 65 Years	2 (22.2)	1 (25.0)	2 (33.3)	5 (26.3)
Age (Years)				
n	9	4	6	19
Mean (SD)	53.6 (14.02)	59.3 (9.54)	61.2 (14.52)	57.2 (13.19)
Median (min-max)	56.0 (27.0 - 70.0)	58.0 (49.0 - 72.0)	62.5 (37.0 - 76.0)	57.0 (27.0 - 76.0)
Sex -n (%)				
Male	4 (44.4)	2 (50.0)	1 (16.7)	7 (36.8)
Female	5 (55.6)	2 (50.0)	5 (83.3)	12 (63.2)
Race -n (%)				
Caucasian	9 (100)	4 (100)	6 (100)	19 (100)
BSA(m^2)				
n	9	4	6	19
Mean (SD)	1.8 (0.30)	1.8 (0.16)	1.7 (0.20)	1.8 (0.24)
Median (min – max)	1.7 (1.4 - 2.3)	1.8 (1.6 - 1.9)	1.7 (1.4 - 1.9)	1.7 (1.4 - 2.3)
BMI (kg/m^2)				
n	9	4	6	19
Mean (SD)	23.4 (6.12)	26.1 (2.75)	24.3 (4.74)	24.2 (5.03)
Median (min – max)	20.6 (18.0 - 33.6)	25.9 (23.2 - 29.3)	25.1 (16.8 - 29.0)	23.2 (16.8 - 33.6)
ECOG performance status -n (%)				
0	6 (66.7)	2 (50.0)	2 (33.3)	10 (52.6)
1	3 (33.3)	2 (50.0)	4 (66.7)	9 (47.4)

Weight and height are taken from any vital signs evaluation performed on or before the first day of treatment.
Body surface area: BSA (m^2) = sqrt(wt(kg)×ht(cm)/3600)
Body Mass Index: BMI [kg/m2] = weight[kg] / (height[m]**2)
BMI and BSA are calculated based on raw data assessments.
ECOG: Eastern Cooperative Oncology Group

Summary of Efficacy

Primary Outcome Result(s)

Dose limiting toxicities during Cycle 1 by primary system organ class, preferred term and dose level (Dose-determining set)

Primary system organ class Preferred term	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=8 n (%)	BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=3 n (%)	BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=1 n (%)	All patients N=12 n (%)
Any primary system organ class				
Total	2 (25.0)	2 (66.7)	1 (100)	5 (41.7)
Blood and lymphatic system disorders				
Total	1 (12.5)	0	0	1 (8.3)
Leukopenia	1 (12.5)	0	0	1 (8.3)
Metabolism and nutrition disorders				
Total	1 (12.5)	2 (66.7)	1 (100)	4 (33.3)
Hyperglycaemia	1 (12.5)	2 (66.7)	1 (100)	4 (33.3)
Renal and urinary disorders				
Total	0	1 (33.3)	0	1 (8.3)
Acute kidney injury	0	1 (33.3)	0	1 (8.3)

A patient with multiple occurrences of DLTs under one treatment is counted only once in the AE category for that treatment. A patient with multiple DLTs within a primary system organ classes is counted only once in the total row.
Primary system organ classes are presented in alphabetical order; preferred terms are listed within system organ classes in order of descending frequency of AEs in the total column.
DLTs up to 28 days after the first dose of study treatment are included.
MedDRA Version 19.0 has been used for the reporting of adverse events.

Summary of posterior distribution of DLT rates at the time of MTD declaration (Dose Determining Set)

BYL719 dose (mg/day)	Posterior probabilities that Pr(DLT) is in interval					__Quantiles__		
	[0.0, 0.16)	[0.16, 0.35)	[0.35, 1.00]	Mean	SD	2.50%	50.00%	97.50%
50	0.368	0.570	0.062	0.201	0.087	0.067	0.188	0.400
100	0.233	0.670	0.096	0.229	0.088	0.089	0.218	0.425
150	0.129	0.706	0.165	0.261	0.091	0.111	0.254	0.462
200	0.065	0.645	0.290	0.299	0.099	0.130	0.292	0.512
250	0.037	0.513	0.450	0.342	0.112	0.147	0.336	0.577
300	0.025	0.378	0.597	0.389	0.128	0.161	0.383	0.652
350	0.018	0.275	0.708	0.439	0.146	0.174	0.434	0.731
400	0.014	0.207	0.779	0.490	0.164	0.183	0.490	0.802

Secondary Outcome Result(s)

Summary of primary PK parameters for paclitaxel at C1D1 (Pharmacokinetic analysis set)

Treatment	Statistics	AUCinf (ng*hr/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW	n	7	8	8	8
	Mean (SD)	4500 (1280)	4190 (1220)	2780 (970)	N/A
	CV% mean	28.4	29.1	34.8	N/A
	Geo-mean	4360	4060	2650	N/A
	CV% geo-mean	26.7	27.1	32.8	N/A
	Median	4400	3960	2530	1
	[Min; Max]	[3250; 6960]	[3030; 6720]	[1730; 4810]	[0.87; 1.17]
BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW	n	3	3	3	3
	Mean (SD)	4590 (2070)	4390 (1880)	3050 (1630)	N/A
	CV% mean	45	42.8	53.6	N/A

Treatment	Statistics	AUCinf (ng*hr/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
	Geo-mean	4320	4150	2770	N/A
	CV% geo-mean	43.4	41.4	56.4	N/A
	Median	3450	3450	2550	1
	[Min; Max]	[3350; 6980]	[3160; 6550]	[1720; 4870]	[0.45; 1.05]
BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW	n	5	5	5	5
	Mean (SD)	5110 (1080)	4810 (1010)	2740 (553)	N/A
	CV% mean	21.2	20.9	20.2	N/A
	Geo-mean	5000	4720	2700	N/A
	CV% geo-mean	24	23.7	19.5	N/A
	Median	5280	4960	2400	1
	[Min; Max]	[3370; 6290]	[3190; 5900]	[2330; 3560]	[0.5; 1.28]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of primary PK parameters for paclitaxel at C1D8 (Pharmacokinetic analysis set)

Treatment	Statistics	AUCinf (ng*hr/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW	n	8	9	9	9
	Mean (SD)	4460 (1020)	4310 (1050)	2870 (764)	N/A
	CV% mean	22.8	24.2	26.6	N/A
	Geo-mean	4370	4200	2790	N/A
	CV% geo-mean	22.8	24.9	26.3	N/A
	Median	4280	4050	2680	1
	[Min; Max]	[3320; 6030]	[3040; 5850]	[2080; 4060]	[0.5; 1.07]

Treatment	Statistics	AUCinf (ng*hr/mL)	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW	n	2	3	3	3
	Mean (SD)	5210 (2070)	4670 (1330)	2990 (497)	N/A
	CV% mean	39.8	28.5	16.6	N/A
	Geo-mean	5000	4560	2960	N/A
	CV% geo-mean	42.7	27.5	16.1	N/A
	Median	5210	4100	2760	0.8
	[Min; Max]	[3740; 6670]	[3730; 6200]	[2650; 3560]	[0.5; 1.17]
BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW	n	4	5	6	6
	Mean (SD)	4690 (1570)	4170 (1390)	1710 (1310)	N/A
	CV% mean	33.5	33.4	76.7	N/A
	Geo-mean	4470	3980	1250	N/A
	CV% geo-mean	37.8	36.2	114	N/A
	Median	4970	3780	1420	0.75
	[Min; Max]	[2810; 6000]	[2460; 5620]	[455; 3250]	[0; 2.67]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of primary PK parameters for alpelisib at C1D8 (Pharmacokinetic analysis set)

Treatment	Statistics	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW	n	9	9	9
	Mean (SD)	14500 (4400)	1580 (764)	N/A
	CV% mean	30.3	48.3	N/A
	Geo-mean	13800	1390	N/A
	CV% geo-mean	36.8	63.7	N/A
	Median	14000	1460	3.17
	[Min; Max]	[6410; 20200]	[374; 3200]	[1; 8.92]

Treatment	Statistics	AUC0-24 (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW	n	2	2	2
	Mean (SD)	27800 (2160)	3980 (1860)	N/A
	CV% mean	7.8	46.8	N/A
	Geo-mean	27700	3750	N/A
	CV% geo-mean	7.78	51.6	N/A
	Median	27800	3980	3.23
	[Min; Max]	[26200; 29300]	[2660; 5290]	[2.47; 4]
BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW	n	5	6	6
	Mean (SD)	42100 (21400)	3370 (1440)	N/A
	CV% mean	50.8	42.9	N/A
	Geo-mean	37100	3000	N/A
	CV% geo-mean	66.4	63.8	N/A
	Median	39200	3170	4.17
	[Min; Max]	[14500; 71100]	[990; 5040]	[3; 6]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of Safety

Safety Results

Treatment-emergent adverse events regardless of study treatment relationship, by primary system organ class, maximum CTC grade (Safety set)

	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=9			BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=4			BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=6			All patients N=19		
Primary system organ class	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades

	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	2 (22.2)	1 (11.1)	9 (100)	2 (50.0)	1 (25.0)	4 (100)	4 (66.7)	1 (16.7)	6 (100)	8 (42.1)	3 (15.8)	19 (100)
Gastrointestinal disorders	1 (11.1)	0	8 (88.9)	0	0	3 (75.0)	1 (16.7)	0	6 (100)	2 (10.5)	0	17 (89.5)
General disorders and administration site conditions	0	0	8 (88.9)	0	0	2 (50.0)	0	0	4 (66.7)	0	0	14 (73.7)
Metabolism and nutrition disorders	2 (22.2)	0	3 (33.3)	2 (50.0)	1 (25.0)	4 (100)	3 (50.0)	0	5 (83.3)	7 (36.8)	1 (5.3)	12 (63.2)
Nervous system disorders	0	0	7 (77.8)	0	0	3 (75.0)	0	0	2 (33.3)	0	0	12 (63.2)
Blood and lymphatic system disorders	1 (11.1)	1 (11.1)	6 (66.7)	1 (25.0)	0	2 (50.0)	2 (33.3)	0	3 (50.0)	4 (21.1)	1 (5.3)	11 (57.9)
Infections and infestations	0	0	6 (66.7)	1 (25.0)	0	3 (75.0)	0	0	2 (33.3)	1 (5.3)	0	11 (57.9)
Investigations	0	1 (11.1)	5 (55.6)	0	0	1 (25.0)	0	0	5 (83.3)	0	1 (5.3)	11 (57.9)
Respiratory, thoracic and mediastinal disorders	0	0	5 (55.6)	0	0	2 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	1 (5.3)	1 (5.3)	9 (47.4)
Skin and subcutaneous tissue disorders	0	0	6 (66.7)	0	0	1 (25.0)	0	0	2 (33.3)	0	0	9 (47.4)
Musculoskeletal and connective tissue disorders	0	0	3 (33.3)	0	0	2 (50.0)	0	0	3 (50.0)	0	0	8 (42.1)
Injury, poisoning and procedural complications	0	0	2 (22.2)	0	0	2 (50.0)	0	0	0	0	0	4 (21.1)
Renal and urinary disorders	0	0	0	1 (25.0)	0	2 (50.0)	0	0	2 (33.3)	1 (5.3)	0	4 (21.1)

Primary system organ class	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=9			BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=4			BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=6			All patients N=19		
	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Vascular disorders	0	0	2 (22.2)	0	0	1 (25.0)	0	0	1 (16.7)	0	0	4 (21.1)
Ear and labyrinth disorders	0	0	1 (11.1)	0	0	1 (25.0)	0	0	1 (16.7)	0	0	3 (15.8)
Eye disorders	0	0	2 (22.2)	0	0	1 (25.0)	0	0	0	0	0	3 (15.8)
Psychiatric disorders	0	0	1 (11.1)	0	0	0	0	0	1 (16.7)	0	0	2 (10.5)
Reproductive system and breast disorders	0	0	1 (11.1)	0	0	0	0	0	1 (16.7)	0	0	2 (10.5)
Cardiac disorders	0	0	0	0	0	0	0	0	1 (16.7)	0	0	1 (5.3)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity grade.
Primary system organ classes are sorted in descending frequency of all grades column in All patients.
MedDRA Version 19.0 has been used for the reporting of adverse events.

On-treatment deaths by preferred term (Safety set)

Primary reason for death Preferred term	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=9 n (%)	BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=4 n (%)	BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=6 n (%)	All patients N=19 n (%)
Total				
Small cell lung cancer	0	0	1 (16.7)	1 (5.3)
Other				
Total	0	0	1 (16.7)	1 (5.3)
Small cell lung cancer	0	0	1 (16.7)	1 (5.3)

Primary reason for death Preferred term	BYL719 150 mg QD + paclitaxel 80 mg/m^2 QW N=9 n (%)	BYL719 250 mg QD + paclitaxel 80 mg/m^2 QW N=4 n (%)	BYL719 300 mg QD + paclitaxel 80 mg/m^2 QW N=6 n (%)	All patients N=19 n (%)

Preferred terms are sorted in descending frequency reported in All patients group.
Deaths occurring up to 30 days after end of treatment are included.

Treatment-emergent adverse events in more than 20% of patients overall regardless of relationship, by preferred term and maximum CTC grade (Safety set)

	BYL719 150 mg QD + paclitaxel 80 mg/m2 QW N=9			BYL719 250 mg QD + paclitaxel 80 mg/m2 QW N=4			BYL719 300 mg QD + paclitaxel 80 mg/m2 QW N=6			All patients N=19		
	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	2 (22.2)	1 (11.1)	9 (100)	2 (50.0)	1 (25.0)	4 (100)	4 (66.7)	1 (16.7)	6 (100)	8 (42.1)	3 (15.8)	19 (100)
Diarrhoea	1 (11.1)	0	6 (66.7)	0	0	3 (75.0)	1 (16.7)	0	5 (83.3)	2 (10.5)	0	14 (73.7)
Hyperglycaemia	1 (11.1)	0	2 (22.2)	2 (50.0)	1 (25.0)	4 (100)	2 (33.3)	0	5 (83.3)	5 (26.3)	1 (5.3)	11 (57.9)
Anaemia	1 (11.1)	0	6 (66.7)	0	0	1 (25.0)	1 (16.7)	0	1 (16.7)	2 (10.5)	0	8 (42.1)
Asthenia	0	0	5 (55.6)	0	0	1 (25.0)	0	0	2 (33.3)	0	0	8 (42.1)
Nausea	0	0	5 (55.6)	0	0	1 (25.0)	0	0	2 (33.3)	0	0	8 (42.1)
Fatigue	0	0	5 (55.6)	0	0	0	0	0	2 (33.3)	0	0	7 (36.8)
Lymphopenia	1 (11.1)	0	3 (33.3)	1 (25.0)	0	2 (50.0)	0	0	2 (33.3)	2 (10.5)	0	7 (36.8)
Neutropenia	0	1 (11.1)	4 (44.4)	0	0	1 (25.0)	1 (16.7)	0	2 (33.3)	1 (5.3)	1 (5.3)	7 (36.8)
Alopecia	0	0	5 (55.6)	0	0	0	0	0	1 (16.7)	0	0	6 (31.6)
Decreased appetite	0	0	1 (11.1)	0	0	2 (50.0)	0	0	3 (50.0)	0	0	6 (31.6)

	BYL719 150 mg QD + paclitaxel 80 mg/m2 QW N=9			BYL719 250 mg QD + paclitaxel 80 mg/m2 QW N=4			BYL719 300 mg QD + paclitaxel 80 mg/m2 QW N=6			All patients N=19		
	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Leukopenia	0	1 (11.1)	3 (33.3)	0	0	1 (25.0)	1 (16.7)	0	2 (33.3)	1 (5.3)	1 (5.3)	6 (31.6)
Weight decreased	0	0	1 (11.1)	0	0	1 (25.0)	0	0	4 (66.7)	0	0	6 (31.6)
Neuropathy peripheral	0	0	4 (44.4)	0	0	1 (25.0)	0	0	0	0	0	5 (26.3)
Oedema peripheral	0	0	4 (44.4)	0	0	0	0	0	1 (16.7)	0	0	5 (26.3)
Stomatitis	0	0	2 (22.2)	0	0	2 (50.0)	0	0	1 (16.7)	0	0	5 (26.3)
Vomiting	0	0	2 (22.2)	0	0	2 (50.0)	0	0	1 (16.7)	0	0	5 (26.3)
Hypokalaemia	1 (11.1)	0	1 (11.1)	0	0	2 (50.0)	0	0	1 (16.7)	1 (5.3)	0	4 (21.1)
Rash	0	0	3 (33.3)	0	0	1 (25.0)	0	0	0	0	0	4 (21.1)

A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity grade.
Preferred terms are sorted in descending frequency of all grades column in All patients.
MedDRA Version 19.0 has been used for the reporting of adverse events.

Other Relevant Findings

Not applicable.

Conclusion:

Despite the MTD of the alpelisib + paclitaxel combination has been confirmed at alpelisib 150 mg QD + paclitaxel 80 mg/m^2 QW, the overall tolerability of the regimen was challenging. In addition, there are no available data at alpelisib dose of 150 mg QD confirming potential pharmacodynamics activity (PI3K pathway inhibition) and/or clinical activity (as single agent alpelisib has shown anti-tumor activity in solid tumors from doses of 270 mg QD and higher). Other treatment opportunities are available for patients with head and neck squamous cell carcinoma or metastatic HER2-breast cancer. Therefore, the planned dose-expansion phase of the study has not been initiated. The study was closed with completion of the dose escalation phase.

Date of Clinical Trial Report

23-Jan-2017