Sponsor

Novartis

Generic Drug Name

LJM716, alpelisib

Trial Indication(s)

ESCC

Protocol Number

LJM76X2103

Protocol Title

A Phase Ib/II, open-label study of LJM716 in combination with BYL719 (alpelisib) compared to taxane or irinotecan in patients with previously treated esophageal squamous cell carcinoma (ESCC).

Clinical Trial Phase

Ib/II

Phase of Drug Development

Ib/II

Study Start/End Dates

26-Jul-2013 to 03-Jun-2016

Reason for Termination (If applicable)

The study had been terminated early due to limited anti-tumor activity observed in Phase Ib part of the study prior to determination of MTD/RP2D.

Study Design/Methodology

This was an open-label multicenter Phase Ib/II study. The Phase Ib part of the study was dose escalation part to determine the maximum tolerated dose (MTD) and/or identify the recommended Phase II dose (RP2D) for the combination of LJM716 and alpelisib in patients with ESCC. The Phase II part was open-label randomized study to

evaluate the anti-tumor activity of LJM716 and alpelisib combination treatment versus physician's choice of second-line therapy (paclitaxel, docetaxel, irinotecan) in previously treated ESCC patients.

Centers

Cliniques Universitaires Saint-Luc (Belgium); Gustave Roussy, Centre Georges François Leclerc, Institut de Cancérologie de l'Ouest (France); Princess Margaret Cancer Centre, BC Cancer Agency - Vancouver Cancer Centre (Canada); Department of Clinical Oncology, Prince of Wales Hospital (HongKong); Hospital Vall D'Hebron, Hospital Universitario 12 De Octubre, HOSPITAL Universitario Marques De Valdecilla (Spain); University of Chicago Medical Center, Karmanos Cancer Institute, University of Texas/MD Anderson Cancer Center, H. Lee Moffitt Cancer Center & Research Institute, Sidney Kimmel Comprehensive Cancer Center/Johns Hopkins Med, University of California at Los Angeles (USA); The Christie Hospital, Beatson West of Scotland Cancer Centre (Great Britain); Seoul National University Hospital, Asan Medical Center (Korea); National Cancer Centre (Singapore); National Taiwan University Hospital, National Cheng Kung University Hospital (Taiwan).

Publication

Not applicable

Objectives:

Primary Objectives

Phase Ib

- To estimate the maximum tolerated dose (MTD(s)) and/or identify the recommended Phase II dose (RP2D) of LJM716 in combination with alpelisib in ESCC patients.

Phase II

- To compare the antitumor activity of LJM716 in combination with alpelisib vs physician's choice of chemotherapy (paclitaxel, docetaxel, or irinotecan).

Secondary Objectives

- To characterize the safety and tolerability of LJM716-alpelisib combination.
- To further assess the anti-tumor activity of LJM716-alpelisib combination.
- To characterize the pharmacokinetic (PK) profiles of LJM716 and alpelisib when used in combination.

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

LJM716 in combination with alpelisib was investigated. LJM716 was provided a powder for solution for infusion as a lyophilized cake. Alpelisib was supplied as tablets of dosage strengths of 10, 50, and 200 mg.

The batch and formulation numbers of LJM716 and alpelisib are provided in the Table below

LJM716 and alpelisib formulation and batch numbers

Study drug and strength	Formulation control number	Batch number
Alpelisib 200 mg	6003037.006	X012 0113/ 13-7463CH
Alpelisib 200 mg	6003037.009	X150 0413/ 15-0577CH
Alpelisib 200 mg	6003036.003	X231 0112/ 13-0833CH
Alpelisib 50 mg	6003036.003	X230 0112/ 13-0833CH
Alpelisib 50 mg	6003036.009	X146 0413/ 15-0577CH
Alpelisib 50 mg	6003036.009	X146 0413/ 15-0782CH
Alpelisib 50 mg	6003036.003	X230 1112/ 13-7463CH
LJM716 150 mg	7008236.002	U012 1112/ 14-3983CH
LJM716 150 mg	7008236.002	Y046 0413/ 13-4250CH
LJM716 150 mg	7008236.002	Y048 0613/ 13-7463CH
LJM716 150 mg	7008236.002	Y048 0613/ 13-7463CH

Statistical Methods

MTD: The primary variable was the incidence of DLTs in first 28 days starting from Cycle 1 Day 1. Estimation of the MTD of the combination treatment was based upon the estimation of the probability of DLT rate in Cycle 1 for patients in the DDS. A 5-parameter BLRM for combination treatment was fitted on the DLT data accumulated throughout the dose escalation to model the dose-toxicity relationship of alpelisib and when given in combination with LJM716. The DLTs by worst grade based on the common terminology criteria for AEs (CTCAE) version 4.0 and type of AE were summarized based on DDS, by primary system organ class and preferred term (PT) for each dose cohort. Summary of posterior distribution of DLT rates was also provided. The final recommended MTD/RP2D was based on considerations of the

recommendation from the BLRM, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all different dose combinations tested.

Efficacy: Preliminary anti-tumor activity was assessed using Investigator read computed tomography /magnetic resonance imaging assessments evaluated under RECIST 1.1. All data including best overall response (BOR), progression free survival (PFS) and duration of response (DOR) were listed and summarized.

Pharmacokinetics: PK parameters were determined for all patient included in PK analysis set by a non-compartmental method using Phoenix WinNonlin.

Safety: The assessment of safety was based on the type and frequency of AEs and the number of laboratory values that fall outside of pre-determined ranges. Other safety data included electrocardiogram, vital signs, and specific safety event categories. Specific safety events studied were related to alpelisib, which included hyperglycemia, hypersensitivity, rash, nausea, vomiting, diarrhea, and pneumonitis.

Summary – Conclusions

Due to limited anti-tumor activity of the LJM716-alpelisib combination in Phase Ib, the study was terminated early and consequently the Phase II portion of the study was not conducted. Therefore, results of the Phase Ib portion are only provided. All the 48 patients treated in Phase Ib portion had discontinued study treatment at the time of the data base closure.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Written informed consent obtained prior to any screening procedures.
- Patients aged ≥ 18 years (male or female) with histologically confirmed ESCC.
- No more than one prior chemotherapy regimen for recurrent or metastatic ESCC (for Phase II only).
- Progression during or after platinum-based therapy for recurrent or metastatic ESCC, or recurrence within 6 months of platinum-based chemotherapy or chemoradiotherapy for localized disease.
- Measurable disease as determined by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. Lesions in previously irradiated areas were not to be considered measurable unless they have progressed since the radiotherapy (for Phase II only).
- World Health Organization (WHO)/Eastern cooperative oncology group (ECOG) Performance Status (PS) ≤ 2.

- Recovery from all AEs of previous anti-cancer therapies, including surgery and radiotherapy, to baseline or to common terminology criteria for adverse events (CTCAE) grade ≤ 1, except for alopecia.
- Negative serum pregnancy (β human chorionic gonadotropin) test in all pre-menopausal women and women < 12 months after the onset of menopause.

Exclusion criteria:

- Patients who received prior PI3K inhibitor or anti-HER3 antibody treatment, including bi-specific antibodies with HER3 as one of the targets (patients with prior exposure to pertuzumab or EGFR-targeted agents are eligible)
- Patients who did not have an archival or fresh tumor sample (or sections of it) available or readily obtainable.
- Patients with central nervous system metastatic involvement.
- Patients who received prior systemic anti-cancer treatment, such as cyclical chemotherapy or biological therapy within a period of time that is shorter than the cycle length used for that treatment (e.g. 6 weeks for nitrosourea, mitomycin-C) prior to starting study treatment.
- Patients who had received definitive radiotherapy ≤ 4 weeks prior to starting study drug, who have not recovered from side effects of such therapy and/or from whom ≥ 30% of the bone marrow was irradiated.
- Patients who had undergone major surgery ≤ 2 weeks prior to starting study treatment or who had not recovered from side effects of such procedure.
- Patients with any of the following laboratory values at Screening/Baseline:
  - Absolute neutrophil count < 1500/mm^3 [1.5 × 10^9/L]
  - Platelets < 100,000/mm^3 [100 × 10^9/L]
  - Hemoglobin < 9.0 g/dL
  - Serum creatinine > 1.5 × upper limit of normal (ULN) or calculated or directly measured CrCl (creatinine clearance) < 50% lower limit of normal
  - Serum total bilirubin > 1.5 × ULN
- AST/serum glutamate oxaloacetic transaminase or ALT/serum glutamic pyruvic transaminase > 2.5 × ULN
  - Fasting serum glucose > 140 mg/dL / 7.8 mmol/L
- Clinically significant cardiac disease or impaired cardiac function, such as any of the following:

  - Congestive heart failure requiring treatment (New York Heart Association grade ≥ 2), left ventricular ejection fraction < 50% as determined by multi-gated acquisition scan or echocardiogram, or uncontrolled arterial hypertension defined by blood pressure > 140/100 mm Hg at rest (average of 3 consecutive readings)
  - History or current evidence of clinically significant cardiac arrhythmias, atrial fibrillation and/or conduction abnormality, e.g. congenital long QT syndrome, high- grade/complete atrio-ventricular (AV)-blockage
  - Acute coronary syndrome (including myocardial infarction, unstable angina, coronary artery bypass graft, coronary angioplasty, or stenting) < 3 months prior to screening
  - QT interval adjusted according to Fredericia (QTcF) > 480 msec on Screening or C1D1 electrocardiogram (ECG)
- Patients who are currently receiving medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes (TdP) and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug treatment.
- Patients with diabetes mellitus requiring insulin treatment and/or with clinical signs or with fasting serum glucose ≥ 140 mg/dL / 7.8 mmol/L, or history of documented steroid-induced diabetes mellitus.
- Patients with diarrhea CTCAE grade ≥ 2.
- Any other condition, in the Investigator's judgment, preclude patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g. infection/inflammation, intestinal obstruction, unable to take oral medication, social/psychological complications.
- Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral alpelisib (e.g. total gastrectomy, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) or patients unable to take oral medication.
- History of another malignancy within two years, except cured basal cell carcinoma of the skin or excised carcinoma in situ of the cervix.
- History of squamous cell carcinoma of the head and neck (Phase II only).
- Known positive serology for human immunodeficiency virus.
- Patients with known hypersensitivity to any of the study drugs or their excipients
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 90 days after study drug discontinuation. Highly effective contraception methods include:

  - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male sterilization (at least six months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
  - Combination of any two of the following (a+b or a+c, or b+c):
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
    - Placement of an intrauterine device or intrauterine system
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- In case of use of oral contraception women had to be stable on the same pill for a minimum of 3 months before taking study treatment.
- Post-menopausal women were allowed to participate in this study. Women were considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman was confirmed by follow up hormone level assessment is she considered not of child bearing potential.
- Sexually active males, unless they use a condom during intercourse while taking study treatment and for 90 days after stopping study treatment and should not father a child in this period. A condom was required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Participant Flow Table

At total of 48 patients were enrolled in Phase Ib part of the study. Four different combination of doses of LJM716 and alpelisib have been explored:

- LJM716 10 mg/kg qw plus alpelisib 300 mg/day (n=14)
- LJM716 20 mg/kg qw plus alpelisib 300 mg/day (n=15)
- LJM716 30 mg/kg qw plus alpelisib 250 mg/day (n=11)
- LJM716 30 mg/kg qw plus alpelisib 300 mg/day (n=8)

All patients have discontinued study treatment at the time of the data base closure. The primary reason for discontinuation of the study treatment was disease progression (28 patients; 58.3%). Eight patients (16.7%) discontinued the study treatment due to AEs. Death was the reason for study treatment discontinuation in two patients (4.2%).

Patient disposition by treatment group - Phase Ib (Full analysis set)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14 n (%)	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15 n (%)	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11 n (%)	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8 n (%)	All patients N=48 n (%)
Patients treated					
Treatment discontinued	14 (100)	15 (100)	11 (100)	8 (100)	48 (100)
Primary reason for end of treatment					
Adverse event	1 (7.1)	4 (26.7)	2 (18.2)	1 (12.5)	8 (16.7)
Death	0	2 (13.3)	0	0	2 (4.2)
Physician decision	2 (14.3)	1 (6.7)	0	2 (25.0)	5 (10.4)
Progressive disease	8 (57.1)	7 (46.7)	8 (72.7)	5 (62.5)	28 (58.3)
Subject/guardian decision	2 (14.3)	1 (6.7)	1 (9.1)	0	4 (8.3)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14 n (%)	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15 n (%)	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11 n (%)	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8 n (%)	All patients N=48 n (%)
Technical problems	1 (7.1)	0	0	0	1 (2.1)

Baseline Characteristics

The median age of all the patients treated in the study was 60.5 years (range: 32 years to 74 years). Majority of the patients were male (40 patients; 83.3%). Thirty-five patients (72.9%) were of Asian origin. Almost all the patients (95.8%) had ECOG PS of either 0 or 1 (19 patients; 39.6% and 27 patients; 56.3%, respectively). Two patients (4.2%) had an ECOG PS of 2.

Demographics and baseline characteristics by treatment group – Phase Ib (Full analysis set)

Demographics variable	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8	All patients N=48
Age (Years)					
n	14	15	11	8	48
Mean	61.6	55.5	61.5	61.8	59.7
SD	8.12	11.41	6.47	6.88	9.00
Median	61.5	54.0	64.0	61.5	60.5
Minimum	43	32	48	54	32

Demographics variable	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8	All patients N=48
Maximum	73	73	69	74	74
Age category (Years) -n (%)					
< 65	8 (57.1)	12 (80.0)	6 (54.5)	4 (50.0)	30 (62.5)
≥ 65	6 (42.9)	3 (20.0)	5 (45.5)	4 (50.0)	18 (37.5)
Sex -n (%)					
Male	10 (71.4)	15 (100)	9 (81.8)	6 (75.0)	40 (83.3)
Female	4 (28.6)	0	2 (18.2)	2 (25.0)	8 (16.7)
Predominant Race -n (%)					
Asian	8 (57.1)	12 (80.0)	9 (81.8)	6 (75.0)	35 (72.9)
Caucasian	6 (42.9)	3 (20.0)	2 (18.2)	2 (25.0)	13 (27.1)
Ethnicity -n (%)					
East Asian	7 (50.0)	10 (66.7)	8 (72.7)	6 (75.0)	31 (64.6)
Hispanic or Latino	2 (14.3)	2 (13.3)	0	0	4 (8.3)
Mixed Ethnicity	1 (7.1)	0	0	0	1 (2.1)
Not Reported	1 (7.1)	0	0	0	1 (2.1)
Other	1 (7.1)	1 (6.7)	0	1 (12.5)	3 (6.3)
Southeast Asian	1 (7.1)	2 (13.3)	1 (9.1)	0	4 (8.3)
Unknown	1 (7.1)	0	1 (9.1)	1 (12.5)	3 (6.3)
West Asian	0	0	1 (9.1)	0	1 (2.1)
Weight (kg)					

Demographics variable	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8	All patients N=48
n	14	15	11	8	48
Mean	57.4	59.9	61.7	62.4	60.0
SD	13.40	14.38	7.07	10.18	11.88
Median	54.6	55.0	60.9	66.5	59.0
Minimum	41	45	52	41	41
Maximum	89	101	75	72	101
WHO/ECOG performance status -n (%)					
0	6 (42.9)	5 (33.3)	5 (45.5)	3 (37.5)	19 (39.6)
1	8 (57.1)	9 (60.0)	6 (54.5)	4 (50.0)	27 (56.3)
2	0	1 (6.7)	0	1 (12.5)	2 (4.2)

Abbreviations: ECOG, eastern cooperative oncology group; WHO, world health organization.

Summary of Efficacy

Primary Outcome Results(s)

Please see safety section for Dose Limiting Toxicities (DLTs).

Secondary Outcome Result(s)

Summary of best overall response by treatment group as per Investigator (Full analysis set)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14 n (%)	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15 n (%)	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11 n (%)	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8 n (%)	All patients N=48 n (%)
Best overall response					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	4 (26.7)	1 (9.1)	1 (12.5)	6 (12.5)
Stable disease (SD)	4 (28.6)	2 (13.3)	3 (27.3)	1 (12.5)	10 (20.8)
Unconfirmed CR/PR	1 (7.1)	0	0	0	1 (2.1)
Progressive disease (PD)	6 (42.9)	7 (46.7)	6 (54.5)	4 (50.0)	23 (47.9)
Unconfirmed CR/PR	0	0	1 (9.1)	1 (12.5)	2 (4.2)
Unknown	4 (28.6)	2 (13.3)	1 (9.1)	2 (25.0)	9 (18.8)
Unconfirmed CR/PR	1 (7.1)	0	0	0	1 (2.1)
Overall response rate (ORR) (CR or PR)	0	4 (26.7)	1 (9.1)	1 (12.5)	6 (12.5)
95% CI	(0-23.2)	(7.8-55.1)	(0.2-41.3)	(0.3-52.7)	(4.7-25.2)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14 n (%)	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15 n (%)	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11 n (%)	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8 n (%)	All patients N=48 n (%)
Disease control rate (DCR) (CR or PR or SD)	4 (28.6)	6 (40.0)	4 (36.4)	2 (25.0)	16 (33.3)
95% CI	(8.4-58.1)	(16.3-67.7)	(10.9-69.2)	(3.2-65.1)	(20.4-48.4)

BOR is based on investigator's assessment of disease status using RECIST 1.1

CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met

The 95% CI is calculated using the Clopper-Pearson interval

Summary of primary PK parameters for LJM716 by day and treatment group at Cycle 1 Day 1 and Cycle 3 Day 1 (Pharmacokinetic analysis set)

		Cycle 1 Day 1		Cycle 3 Day 1	
Treatment group	**Statistics**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**
LJM716 10 mg/kg qw + BYL719 300 mg/day (N=14)	n	10	13	4	7
	Mean (SD)	18569 (5373)	196 (43)	49069 (12677)	356 (125)
	CV% mean	28.9	21.9	25.8	35.1
	Geo-mean	17850	192	47975	337
	CV% Geo-mean	30.8	20.8	24.2	37.4
	Median	17920	194	44802	362
	[Min; Max]	[10318; 28431]	[143; 308]	[39141; 67530]	[203; 523]
LJM716 20 mg/kg qw + BYL719 300 mg/day	n	11	13	4	5
	Mean (SD)	32679 (7010)	364 (91.2)	71939 (29197)	660 (203)

		Cycle 1 Day 1		Cycle 3 Day 1	
Treatment group	**Statistics**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**
(N=15)	CV% mean	21.5	25.1	40.6	30.7
	Geo-mean	32051	354	67509	634
	CV% Geo-mean	20.5	25.0	43.1	32.5
	Median	31877	353	67543	720
	[Min; Max]	[23750; 48025]	[249; 525]	[47025; 105644]	[440; 930]
LJM716 30 mg/kg qw + BYL719 250 mg/day (N=11)	n	9	10	3	5
	Mean (SD)	56503 (8979)	597 (87)	131967 (20983)	1106 (189)
	CV% mean	15.9	14.6	15.9	17.1
	Geo-mean	55867	592	130809	1093
	CV% Geo-mean	16.1	14.7	16.6	17.4
	Median	55877	596	136406	1050
	[Min; Max]	[43507; 69176]	[492; 738]	[109119; 150375]	[871; 1310]
LJM716 30 mg/kg qw + BYL719 300 mg/day (N=8)	n	6	8	1	3
	Mean (SD)	51053 (5663)	561 (85.2)	172205 (-)	1143 (150)
	CV% mean	11.1	15.2	-	13.2
	Geo-mean	50777	556	172205	1136
	CV% Geo-mean	11.6	15.2	-	13.8
	Median	51168	569	172205	1220
	[Min; Max]	[41365; 58010]	[433; 720]	[172205; 172205]	[970; 1240]

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 by day and treatment group at Cycle 1 Day 1 and Cycle 3 Day 3 (Pharmacokinetic analysis set)

		Cycle 1 Day 1				Cycle 3 Day 1			
Treatment group	**Statistics**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUCinf (hr*ng/ml)**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUCinf (hr*ng/ml)**
LJM716 10 mg/kg qw + BYL719 300 mg/day (N=14)	n	12	14	14	6	4	5	5	2
	Mean (SD)	21860 (12022)	1873 (1119)	-	31082 (8890)	21344 (13343)	1579 (1051)	-	13515 (10898)
	CV% mean	55.0	59.8	-	28.6	62.5	66.6	-	80.6
	Geo-mean	18549	1553	-	29957	16990	1261	-	11103
	CV% Geo-mean	69.7	74.1	-	31.0	108.6	96.9	-	114.7
	Median	19074	1755	4	32340	21728	1500	4	13515
	[Min; Max]	[6124; 38690]	[524; 4170]	[1.97; 7.95]	[20874; 40061]	[4824; 37095]	[368; 3130]	[1.98; 23.9]	[5809; 21221]
LJM716 20 mg/kg qw + BYL719 300 mg/day (N=15)	n	11	13	13	5	4	5	5	1
	Mean (SD)	23121 (10830)	2147 (1046)	-	28498 (12438)	21819 (8394)	1444 (1001)	-	32305 (-)
	CV% mean	46.8	48.7	-	43.6	38.5	69.3	-	-
	Geo-mean	20416	1855	-	25609	20263	1131	-	32305
	CV% Geo-mean	60.7	67.5	-	61.8	50.6	99.3	-	-
	Median	25574	2110	4	29136	23529	1560	4.17	32305
	[Min; Max]	[7035; 39645]	[509; 3570]	[1.9; 8.68]	[9818; 44417]	[10117; 30098]	[464; 2820]	[1.85; 23.8]	[32305; 32305]

		Cycle 1 Day 1				Cycle 3 Day 1			
Treatment group	**Statistics**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUCinf (hr*ng/ml)**	**AUClast (hr*ng/ml)**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUCinf (hr*ng/ml)**
LJM716 30 mg/kg qw + BYL719 250 mg/day (N=11)	n	9	11	11	5	3	5	5	2
	Mean (SD)	19944 (9389)	1478 (645)	-	19192 (7395)	23164 (6419)	1582 (610)	-	23910 (8299)
	CV% mean	47.1	43.7	-	38.5	27.7	38.5	-	34.7
	Geo-mean	18325	1359	-	18219	22503	1468	-	23179
	CV% Geo-mean	44.2	45.3	-	36.1	31.1	49.0	-	36.6
	Median	17657	1320	4	18473	25355	1620	2	23910
	[Min; Max]	[11342; 40079]	[697; 2770]	[2; 7]	[12791; 31544]	[15937; 28200]	[680; 2400]	[0.5; 7.4]	[18042; 29778]
LJM716 30 mg/kg qw + BYL719 300 mg/day (N=8)	n	5	6	6	3	1	3	3	1
	Mean (SD)	26814 (4462)	2208 (493)	-	28165 (3122)	24275 (-)	1873 (1081)	-	24961 (-)
	CV% mean	16.6	22.3	-	11.1	-	57.7	-	
	Geo-mean	26542	2161	-	28047	24275	1694	-	24961
	CV% Geo-mean	15.7	23.4	-	11.3	-	57.1	-	
	Median	25842	2205	4	28469	24275	1310	4.15	24961
	[Min; Max]	[23328; 34281]	[1480; 2970]	[1.92; 7.98]	[24901; 31123]	[24275; 24275]	[1190; 3120]	[2; 7.93]	[24961; 24961]

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 Results

Dose limiting toxicities (DLTs) occurring during the first cycle by preferred term and treatment group (Dose determining set)

Preferred term	LJM716 10 mg/kg qw + BYL719 300 mg/day N=10 n (%)	LJM716 20 mg/kg qw + BYL719 300 mg/day N=10 n (%)	LJM716 30 mg/kg qw + BYL719 250 mg/day N=9 n (%)	LJM716 30 mg/kg qw + BYL719 300 mg/day N=6 n (%)	All patients N=35 n (%)
Patients with at least one event	3 (30.0)	3 (30.0)	2 (22.2)	2 (33.3)	10 (28.6)
Decreased appetite	0	1 (10.0)	0	0	1 (2.9)
Fatigue	1 (10.0)	0	0	0	1 (2.9)
Hyperbilirubinaemia	0	1 (10.0)	0	0	1 (2.9)
Hyperglycaemia	2 (20.0)	1 (10.0)	2 (22.2)	1 (16.7)	6 (17.1)
Vomiting	0	0	0	1 (16.7)	1 (2.9)

Numbers (n) represent counts of patients.
MedDRA version 19.0

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

Primary system organ class	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8	All patients N=48

	All grades n (%)	All grades n (%)	All grades n (%)	All grades n (%)	All grades n (%)
Total	**14 (100)**	**15 (100)**	**11 (100)**	**8 (100)**	**48 (100)**
Gastrointestinal disorders	14 (100)	14 (93.3)	10 (90.9)	8 (100)	46 (95.8)
Metabolism and nutrition disorders	14 (100)	11 (73.3)	8 (72.7)	6 (75.0)	39 (81.3)
General disorders and administration site conditions	10 (71.4)	12 (80.0)	7 (63.6)	5 (62.5)	34 (70.8)
Respiratory, thoracic and mediastinal disorders	9 (64.3)	9 (60.0)	4 (36.4)	7 (87.5)	29 (60.4)
Investigations	9 (64.3)	9 (60.0)	5 (45.5)	5 (62.5)	28 (58.3)
Infections and infestations	9 (64.3)	6 (40.0)	3 (27.3)	5 (62.5)	23 (47.9)
Skin and subcutaneous tissue disorders	9 (64.3)	3 (20.0)	4 (36.4)	5 (62.5)	21 (43.8)
Nervous system disorders	3 (21.4)	5 (33.3)	4 (36.4)	3 (37.5)	15 (31.3)
Musculoskeletal and connective tissue disorders	3 (21.4)	5 (33.3)	5 (45.5)	0	13 (27.1)
Blood and lymphatic system disorders	5 (35.7)	0	2 (18.2)	3 (37.5)	10 (20.8)
Cardiac disorders	3 (21.4)	2 (13.3)	1 (9.1)	2 (25.0)	8 (16.7)
Psychiatric disorders	1 (7.1)	2 (13.3)	2 (18.2)	2 (25.0)	7 (14.6)
Renal and urinary disorders	1 (7.1)	1 (6.7)	1 (9.1)	3 (37.5)	6 (12.5)
Vascular disorders	2 (14.3)	2 (13.3)	1 (9.1)	0	5 (10.4)
Eye disorders	1 (7.1)	1 (6.7)	1 (9.1)	0	3 (6.3)
Injury, poisoning and procedural complications	2 (14.3)	1 (6.7)	0	0	3 (6.3)

Primary system organ class	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14 All grades n (%)	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15 All grades n (%)	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11 All grades n (%)	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8 All grades n (%)	All patients N=48 All grades n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (7.1)	0	0	1 (12.5)	2 (4.2)
Congenital, familial and genetic disorders	0	0	1 (9.1)	0	1 (2.1)
Ear and labyrinth disorders	1 (7.1)	0	0	0	1 (2.1)
Endocrine disorders	1 (7.1)	0	0	0	1 (2.1)
Hepatobiliary disorders	0	1 (6.7)	0	0	1 (2.1)
Immune system disorders	1 (7.1)	0	0	0	1 (2.1)

Primary SOC's are sorted in descending frequency, as reported in the all patients, all grades column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
Only AEs occurring during treatment or within 30 days of the last study medication are reported

Adverse events (all grades and grades 3/4) (overall incidence greater than 5% patients), regardless of study drug relationship, by preferred term and treatment group (Safety set)

	LJM716 10 mg/kg qw + BYL719 300 mg/day	LJM716 20 mg/kg qw + BYL719 300 mg/day	LJM716 30 mg/kg qw + BYL719 250 mg/day	LJM716 30 mg/kg qw + BYL719 300 mg/day	All patients

	N=14		N=15		N=11		N=8		N=48	
	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
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**13 (92.9)**	**14 (100)**	**10 (66.7)**	**15 (100)**	**5 (45.5)**	**11 (100)**	**6 (75.0)**	**8 (100)**	**34 (70.8)**	**48 (100)**
Diarrhoea	3 (21.4)	12 (85.7)	1 (6.7)	12 (80.0)	2 (18.2)	10 (90.9)	0	8 (100)	6 (12.5)	42 (87.5)
Decreased appetite	1 (7.1)	11 (78.6)	2 (13.3)	8 (53.3)	0	6 (54.5)	1 (12.5)	6 (75.0)	4 (8.3)	31 (64.6)
Hyperglycaemia	4 (28.6)	8 (57.1)	3 (20.0)	6 (40.0)	3 (27.3)	5 (45.5)	4 (50.0)	5 (62.5)	14 (29.2)	24 (50.0)
Weight decreased	0	7 (50.0)	1 (6.7)	8 (53.3)	0	5 (45.5)	0	3 (37.5)	1 (2.1)	23 (47.9)
Fatigue	3 (21.4)	6 (42.9)	1 (6.7)	5 (33.3)	1 (9.1)	6 (54.5)	3 (37.5)	4 (50.0)	8 (16.7)	21 (43.8)
Stomatitis	0	6 (42.9)	0	6 (40.0)	0	5 (45.5)	0	3 (37.5)	0	20 (41.7)
Cough	1 (7.1)	5 (35.7)	1 (6.7)	3 (20.0)	0	2 (18.2)	0	6 (75.0)	2 (4.2)	16 (33.3)
Nausea	0	4 (28.6)	0	3 (20.0)	1 (9.1)	3 (27.3)	0	4 (50.0)	1 (2.1)	14 (29.2)
Pyrexia	0	5 (35.7)	0	5 (33.3)	0	1 (9.1)	0	2 (25.0)	0	13 (27.1)
Vomiting	2 (14.3)	5 (35.7)	0	3 (20.0)	1 (9.1)	3 (27.3)	1 (12.5)	2 (25.0)	4 (8.3)	13 (27.1)
Dyspnoea	3 (21.4)	5 (35.7)	0	3 (20.0)	0	1 (9.1)	0	2 (25.0)	3 (6.3)	11 (22.9)
Anaemia	1 (7.1)	4 (28.6)	0	0	0	2 (18.2)	0	2 (25.0)	1 (2.1)	8 (16.7)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14		LJM716 20 mg/kg qw + BYL719 300 mg/day N=15		LJM716 30 mg/kg qw + BYL719 250 mg/day N=11		LJM716 30 mg/kg qw + BYL719 300 mg/day N=8		All patients N=48	
Preferred term	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Dysphagia	1 (7.1)	2 (14.3)	1 (6.7)	1 (6.7)	1 (9.1)	1 (9.1)	3 (37.5)	4 (50.0)	6 (12.5)	8 (16.7)
Hypokalaemia	1 (7.1)	3 (21.4)	0	2 (13.3)	0	1 (9.1)	1 (12.5)	2 (25.0)	2 (4.2)	8 (16.7)
Hypophosphataemia	0	2 (14.3)	0	0	1 (9.1)	2 (18.2)	3 (37.5)	4 (50.0)	4 (8.3)	8 (16.7)
Hypomagnesaemia	1 (7.1)	2 (14.3)	0	2 (13.3)	0	1 (9.1)	0	2 (25.0)	1 (2.1)	7 (14.6)
Non-cardiac chest pain	0	2 (14.3)	0	4 (26.7)	0	0	0	1 (12.5)	0	7 (14.6)
Asthenia	0	2 (14.3)	0	4 (26.7)	0	0	0	0	0	6 (12.5)
Constipation	0	1 (7.1)	0	4 (26.7)	0	0	0	1 (12.5)	0	6 (12.5)
Dehydration	0	1 (7.1)	1 (6.7)	2 (13.3)	0	2 (18.2)	1 (12.5)	1 (12.5)	2 (4.2)	6 (12.5)
Dry skin	0	1 (7.1)	0	1 (6.7)	0	2 (18.2)	0	2 (25.0)	0	6 (12.5)
Rhinorrhoea	0	0	0	3 (20.0)	0	0	0	3 (37.5)	0	6 (12.5)
Hypoalbuminaemia	0	1 (7.1)	0	2 (13.3)	0	0	1 (12.5)	2 (25.0)	1 (2.1)	5 (10.4)
Productive cough	0	1 (7.1)	0	0	0	0	0	4 (50.0)	0	5 (10.4)
Rash	0	3 (21.4)	0	0	0	1 (9.1)	0	1 (12.5)	0	5 (10.4)
Aspartate aminotransferase increased	1 (7.1)	1 (7.1)	0	2 (13.3)	0	0	0	1 (12.5)	1 (2.1)	4 (8.3)
Back pain	0	1 (7.1)	1 (6.7)	2 (13.3)	1 (9.1)	1 (9.1)	0	0	2 (4.2)	4 (8.3)
Blood creatinine increased	0	2 (14.3)	0	1 (6.7)	0	0	0	1 (12.5)	0	4 (8.3)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14		LJM716 20 mg/kg qw + BYL719 300 mg/day N=15		LJM716 30 mg/kg qw + BYL719 250 mg/day N=11		LJM716 30 mg/kg qw + BYL719 300 mg/day N=8		All patients N=48	
Preferred term	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)
Dysgeusia	0	1 (7.1)	0	1 (6.7)	0	2 (18.2)	0	0	0	4 (8.3)
Hypercalcaemia	0	1 (7.1)	0	0	0	1 (9.1)	1 (12.5)	2 (25.0)	1 (2.1)	4 (8.3)
Hypocalcaemia	1 (7.1)	1 (7.1)	0	1 (6.7)	0	1 (9.1)	1 (12.5)	1 (12.5)	2 (4.2)	4 (8.3)
Malaise	0	3 (21.4)	0	1 (6.7)	0	0	0	0	0	4 (8.3)
Musculoskeletal pain	1 (7.1)	1 (7.1)	0	1 (6.7)	0	2 (18.2)	0	0	1 (2.1)	4 (8.3)
Oedema peripheral	0	1 (7.1)	0	1 (6.7)	0	1 (9.1)	0	1 (12.5)	0	4 (8.3)
Oral candidiasis	0	2 (14.3)	0	0	0	0	0	2 (25.0)	0	4 (8.3)
Abdominal pain	0	1 (7.1)	0	0	1 (9.1)	1 (9.1)	0	1 (12.5)	1 (2.1)	3 (6.3)
Abdominal pain upper	0	2 (14.3)	0	0	0	0	0	1 (12.5)	0	3 (6.3)
Amylase increased	0	0	0	1 (6.7)	0	1 (9.1)	0	1 (12.5)	0	3 (6.3)
Bronchitis	0	1 (7.1)	0	1 (6.7)	0	1 (9.1)	0	0	0	3 (6.3)
Chills	0	1 (7.1)	0	1 (6.7)	0	1 (9.1)	0	0	0	3 (6.3)
Depression	0	1 (7.1)	0	0	0	1 (9.1)	0	1 (12.5)	0	3 (6.3)
Dysphonia	0	0	0	1 (6.7)	0	1 (9.1)	0	1 (12.5)	0	3 (6.3)
Gastrooesophageal reflux disease	0	0	0	1 (6.7)	0	0	0	2 (25.0)	0	3 (6.3)
Hypotension	0	2 (14.3)	1 (6.7)	1 (6.7)	0	0	0	0	1 (2.1)	3 (6.3)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14		LJM716 20 mg/kg qw + BYL719 300 mg/day N=15		LJM716 30 mg/kg qw + BYL719 250 mg/day N=11		LJM716 30 mg/kg qw + BYL719 300 mg/day N=8		All patients N=48	
Preferred term	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Pneumonia aspiration	0	0	1 (6.7)	1 (6.7)	1 (9.1)	1 (9.1)	1 (12.5)	1 (12.5)	3 (6.3)	3 (6.3)
Pruritus	0	2 (14.3)	0	0	0	1 (9.1)	0	0	0	3 (6.3)

Preferred terms are sorted in descending frequency, as reported in the all patients, all grades column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
Only AEs occurring during treatment or within 30 days of the last study medication are reported

Serious Adverse Events and Deaths

Serious adverse events (all grades and grades 3 /4), regardless of study drug relationship, by preferred term and treatment group (Safety set)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14		LJM716 20 mg/kg qw + BYL719 300 mg/day N=15		LJM716 30 mg/kg qw + BYL719 250 mg/day N=11		LJM716 30 mg/kg qw + BYL719 300 mg/day N=8		All patients N=48	
	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**

Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	12 (85.7)	13 (92.9)	5 (33.3)	9 (60.0)	4 (36.4)	4 (36.4)	5 (62.5)	6 (75.0)	26 (54.2)	32 (66.7)
Dysphagia	1 (7.1)	1 (7.1)	1 (6.7)	1 (6.7)	1 (9.1)	1 (9.1)	1 (12.5)	1 (12.5)	4 (8.3)	4 (8.3)
Hyperglycaemia	2 (14.3)	2 (14.3)	0	0	0	0	1 (12.5)	1 (12.5)	3 (6.3)	3 (6.3)
Pneumonia aspiration	0	0	1 (6.7)	1 (6.7)	1 (9.1)	1 (9.1)	1 (12.5)	1 (12.5)	3 (6.3)	3 (6.3)
Dehydration	0	0	1 (6.7)	1 (6.7)	0	0	1 (12.5)	1 (12.5)	2 (4.2)	2 (4.2)
Dyspnoea	1 (7.1)	1 (7.1)	0	1 (6.7)	0	0	0	0	1 (2.1)	2 (4.2)
Oesophageal fistula	0	1 (7.1)	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	2 (4.2)
Oesophagobronchial fistula	1 (7.1)	1 (7.1)	0	0	0	0	1 (12.5)	1 (12.5)	2 (4.2)	2 (4.2)
Pneumonia	1 (7.1)	1 (7.1)	0	1 (6.7)	0	0	0	0	1 (2.1)	2 (4.2)
Vomiting	1 (7.1)	1 (7.1)	0	0	0	0	1 (12.5)	1 (12.5)	2 (4.2)	2 (4.2)
Acute kidney injury	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Acute respiratory distress syndrome	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Acute respiratory failure	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Aorto-oesophageal fistula	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Arrhythmia	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Arthritis bacterial	0	0	0	0	0	0	0	1 (12.5)	0	1 (2.1)
Asthenia	0	0	0	1 (6.7)	0	0	0	0	0	1 (2.1)
Back pain	0	0	0	0	1 (9.1)	1 (9.1)	0	0	1 (2.1)	1 (2.1)
Bacteraemia	0	0	0	1 (6.7)	0	0	0	0	0	1 (2.1)
Brain injury	0	0	1 (6.7)	1 (6.7)	0	0	0	0	1 (2.1)	1 (2.1)
Bronchitis	0	0	0	1 (6.7)	0	0	0	0	0	1 (2.1)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14		LJM716 20 mg/kg qw + BYL719 300 mg/day N=15		LJM716 30 mg/kg qw + BYL719 250 mg/day N=11		LJM716 30 mg/kg qw + BYL719 300 mg/day N=8		All patients N=48	
Preferred term	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)
Coma	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Completed suicide	0	0	1 (6.7)	1 (6.7)	0	0	0	0	1 (2.1)	1 (2.1)
Cystitis	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Decreased appetite	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Diarrhoea	0	1 (7.1)	0	0	0	0	0	0	0	1 (2.1)
Gastric ulcer	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Haemoptysis	0	0	1 (6.7)	1 (6.7)	0	0	0	0	1 (2.1)	1 (2.1)
Hypercalcaemia	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Hypophagia	0	1 (7.1)	0	0	0	0	0	0	0	1 (2.1)
Interstitial lung disease	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Lung infection	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Musculoskeletal pain	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Oesophageal achalasia	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Oesophageal perforation	0	0	0	0	1 (9.1)	1 (9.1)	0	0	1 (2.1)	1 (2.1)
Pericardial effusion	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Pleural fistula	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Pneumomediastinum	0	1 (7.1)	0	0	0	0	0	0	0	1 (2.1)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14		LJM716 20 mg/kg qw + BYL719 300 mg/day N=15		LJM716 30 mg/kg qw + BYL719 250 mg/day N=11		LJM716 30 mg/kg qw + BYL719 300 mg/day N=8		All patients N=48	
Preferred term	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Pneumothorax	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Respiratory failure	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Respiratory Syncytial Virus infection	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Respiratory tract infection	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Sepsis	0	0	1 (6.7)	1 (6.7)	0	0	0	0	1 (2.1)	1 (2.1)
Septic shock	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Small intestinal obstruction	0	0	0	0	1 (9.1)	1 (9.1)	0	0	1 (2.1)	1 (2.1)
Stomatitis	0	1 (7.1)	0	0	0	0	0	0	0	1 (2.1)
Subcutaneous emphysema	0	1 (7.1)	0	0	0	0	0	0	0	1 (2.1)
Supraventricular tachycardia	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (2.1)	1 (2.1)
Tracheo-oesophageal fistula	0	0	0	0	1 (9.1)	1 (9.1)	0	0	1 (2.1)	1 (2.1)
Tumour necrosis	1 (7.1)	1 (7.1)	0	0	0	0	0	0	1 (2.1)	1 (2.1)
Urinary tract obstruction	0	0	1 (6.7)	1 (6.7)	0	0	0	0	1 (2.1)	1 (2.1)

	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14		LJM716 20 mg/kg qw + BYL719 300 mg/day N=15		LJM716 30 mg/kg qw + BYL719 250 mg/day N=11		LJM716 30 mg/kg qw + BYL719 300 mg/day N=8		All patients N=48	
Preferred term	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Weight decreased	0	0	0	0	0	0	0	1 (12.5)	0	1 (2.1)

Preferred terms are sorted in descending frequency, as reported in the all patients, all grades column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple AEs within a primary SOC is counted only once in the total row.

Only AEs occurring during treatment or within 30 days of the last study medication are reported

On-treatment deaths by preferred term (Safety set)

Primary cause of death Preferred term	**LJM716 10 mg/kg qw + BYL719 300 mg/day N=14 n (%)**	**LJM716 20 mg/kg qw + BYL719 300 mg/day N=15 n (%)**	**LJM716 30 mg/kg qw + BYL719 250 mg/day N=11 n (%)**	**LJM716 30 mg/kg qw + BYL719 300 mg/day N=8 n (%)**	**All patients N=48 n (%)**
Total	5 (35.7)	3 (20.0)	1 (9.1)	0	9 (18.8)
Other	5 (35.7)	3 (20.0)	1 (9.1)	0	9 (18.8)
OTHER					
Disease progression	2 (14.3)	1 (6.7)	0	0	3 (6.3)
Respiratory failure	2 (14.3)	0	0	0	2 (4.2)

Primary cause of death Preferred term	LJM716 10 mg/kg qw + BYL719 300 mg/day N=14 n (%)	LJM716 20 mg/kg qw + BYL719 300 mg/day N=15 n (%)	LJM716 30 mg/kg qw + BYL719 250 mg/day N=11 n (%)	LJM716 30 mg/kg qw + BYL719 300 mg/day N=8 n (%)	All patients N=48 n (%)
Completed suicide	0	1 (6.7)	0	0	1 (2.1)
Oesophageal carcinoma	1 (7.1)	0	0	0	1 (2.1)
Pleural effusion	0	0	1 (9.1)	0	1 (2.1)
Pneumonia	0	1 (6.7)	0	0	1 (2.1)

Preferred terms are sorted in descending frequency, as reported in the all patients, all grades column.
Deaths occurring up to 30 days after end of treatment are included.

Other Relevant Findings

Not applicable

Conclusion:

- The MTD/RP2D of LJM716 in combination with alpelisib has not been determined since the study had been terminated early due to limited anti-tumor activity observed in Phase Ib part of the study prior to determination of MTD/RP2D.
- The ORR (95% CI) for all patients combined was 12.5% (4.7%, 25.2%) and DCR (95% CI) was 33.3% (20.4%, 48.4%). Median PFS (95% CI) combined for all patients was 2.10 months (1.31, 3.06).
- Administration of LJM716 in combination with alpelisib did not suggest any effect on the PK of either drugs.
- The combination of LJM716 and alpelisib was acceptable, and the observed safety profile was consistent with prior experience with both LJM716 and alpelisib as single agents.

Date of Clinical Trial Report

21-Apr-2017