Sponsor

Novartis

Generic Drug Name

None

Trial Indication(s)

Advanced solid tumors

Protocol Number

CLJM716X1101

Protocol Title

A phase I study of LJM716 in Japanese patients with advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

19-Sep-2013 to 06-Mar-2015

Reason for Termination (If applicable)

At the beginning of the study, the dose expansion part was planned to further characterize the safety, tolerability and Pharmacokinetics (PK)/Pharmacodynamics(PD) of LJM716 as a single agent and to make a preliminary assessment of the anti-tumor activity in the Esophageal squamous cell carcinoma (ESCC) patients. After that, Novartis obtained preclinical data to show the anti-tumor effect of the combination therapy of BYL719 and LJM716 on lung squamous cell carcinoma (SCC). Since the development plan of LJM716 is focusing on combination therapy rather than single agent therapy, it was decided not to further make any assessments of LJM716 as a single agent or in combination therapy in the dose expansion part of this study and to further explore the combination therapy in another study. This decision was not based on any safety-related matters.

Study Design/Methodology

Phase I, open-label, dose-escalation study to establish the maximum tolerated dose (MTD) or recommended dose for expansion (RDE) of LJM716 as single agent in Japanese patients that have advanced solid tumors.

Centers

2 centers in Japan

Publication

None

Objectives:

The primary objective was to estimate the MTD and/or RDE of LJM716 as a single agent when administered intravenous (IV) to Japanese patients with advanced solid tumors.

The secondary objectives were:

- To characterize the safety and tolerability of LJM716.
- To characterize PK of LJM716.
- To assess the preliminary anti-tumor activity of LJM716.
- To assess any emergence of anti-LJM716 antibodies.

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

LJM716 was given by IV infusion over 2 hours once weekly (QW), on Days 1, 8, 15 and 22 of each cycle, based on the patient's weight at the beginning of each cycle (adjustment in actual dose was not required if weight change was less than 10% from the last dose determination). The duration of LJM716 infusion could be extended beyond 2 hours to maintain the rate of infusion at or below 20 mg/min.

Statistical Methods

Dose escalation guided by a BLRM had shown to be superior in targeting the MTD than classical algorithmic designs such as the 3 + 3 approach and, when implemented with the escalation with overdose control (EWOC) principle, was shown to reduce the risk to patients on-study in comparison to other Bayesian designs].

Unless otherwise noted, the other safety and efficacy analyses were conducted by dose cohort. For continuous variables, descriptive statistics (n, Mean, standard deviation [SD], Median, Min, Max) were used. For discrete variables, the number and percentage of patients or events were presented. All data were listed appropriately.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male or female patients age 18 years or older
- Patients with the following indications:

  i) (Dose escalation part only): Human epidermal growth factor receptor (HER) 2 overexpressing locally advanced/ metastatic breast cancer or gastric cancer for which no effective treatment option exists:

  - For breast cancer: documented 3+ by immunohistochemistry, or amplification by in situ hybridization
  - For gastric cancer (including gastro-esophageal [GE] junction tumors): documented 3+ by immunohistochemistry, or 2+ by immunohistochemistry and amplification by in situ hybridization

  OR, ii) (Dose escalation part only): Recurrent or metastatic Squamous cell carcinoma of head and neck [SCCHN] regardless of HER2 status for which no effective treatment option exists

  OR, iii) Recurrent or metastatic ESCC regardless of HER2 status for which no effective treatment option exists

- ECOG Performance Status of 0-2
- During dose expansion part of the study, patients must have at least one measurable lesion as defined by RECIST v1.1 criteria.

Exclusion Criteria:

- Patients with untreated and/or symptomatic metastatic central nervous system (CNS) disease.
- Patients received prior specific anti-HER3 antibody treatment, including bi-specific antibodies with HER3 as one of the targets
- Prior anaphylactic or other severe infusion reaction to human immunoglobulin or antibody formulations. Prior hypersensitivity to any ingredients of LJM716 including crude materials (LJM716 is manufactured in a CHO-K1PD host cell line).
- Any of the protocol defined abnormal clinical laboratory results at the screening

Participant Flow Table

Patient disposition by treatment (Full Analysis Set [FAS])

	10 mg/kg QW LJM716 N = 3 n (%)	20 mg/kg QW LJM716 N = 3 n (%)	40 mg/kg QW LJM716 N = 6 n (%)	All patients N = 12 n (%)
Patient treated				
Treatment discontinued	3 (100)	3 (100)	6 (100)	12 (100)
Primary reason for EOT				
Progressive disease	3 (100)	3 (100)	6 (100)	12 (100)

Baseline Characteristics

Demographics by treatment (FAS)

	10 mg/kg QW LJM716 N = 3	20 mg/kg QW LJM716 N = 3	40 mg/kg QW LJM716 N = 6	All patients N = 12
Age* (years)				
N	3	3	6	12
Mean	65.3	61.0	52.0	57.6
SD	7.23	7.00	15.23	12.67
Median	69.0	58.0	51.5	58.0
Minimum	57	56	33	33
Maximum	70	69	75	75
Age category (years) - n (%)				
< 65	1 (33.3)	2 (66.7)	5 (83.3)	8 (66.7)
≥ 65	2 (66.7)	1 (33.3)	1 (16.7)	4 (33.3)
Sex - n (%)				
Female	2 (66.7)	1 (33.3)	3 (50.0)	6 (50.0)
Male	1 (33.3)	2 (66.7)	3 (50.0)	6 (50.0)
Weight* (kg)				

	10 mg/kg QW LJM716 N = 3	20 mg/kg QW LJM716 N = 3	40 mg/kg QW LJM716 N = 6	All patients N = 12
N	3	3	6	12
Mean	57.93	57.77	52.33	55.09
SD	12.952	7.650	4.901	7.769
Median	64.70	57.80	52.45	52.75
Minimum	43.0	50.1	45.1	43.0
Maximum	66.1	65.4	60.4	66.1
Height* (cm)				
N	3	3	6	12
Mean	158.70	161.17	164.08	162.01
SD	9.358	7.072	7.292	7.397
Median	163.80	164.10	160.95	162.55
Minimum	147.9	153.1	156.1	147.9
Maximum	164.4	166.3	173.5	173.5
WHO/ECOG performance status* - n (%)				
0	1 (33.3)	1 (33.3)	5 (83.3)	7 (58.3)
1	2 (66.7)	2 (66.7)	0	4 (33.3)
2	0	0	1 (16.7)	1 (8.3)

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Summary of best overall response as per investigator at maximum tolerated dose/recommended dose at dose escalation part (FAS)

	40 mg/kg QW LJM716 N = 6 n (%)

	40 mg/kg QW LJM716 N = 6 n (%)
BOR	
CR	0 (0.0)
PR	0 (0.0)
Stable disease	2 (33.3)
Unconfirmed CR/PR	1 (16.7)
Progressive disease	4 (66.7)
Unconfirmed CR/PR	0 (0.0)
Unknown	0 (0.0)
Unconfirmed CR/PR	0 (0.0)
ORR (CR or PR)	0 (0.0)
95% confidence interval	(0.0 - 45.9)

Summary of primary pharmacokinetic parameters for LJM716 by treatment group (Pharmacokinetic analysis set) - Cycle 1 –

Treatment	Statistics	AUClast (h*µg/mL)	Cmin (µg/mL)	Cmax (µg/mL)	Tmax (h)	Tlast (h)
10 mg/kg QW LJM716 (N = 3)	n	3	3	3	3	3
	Mean (SD)	18700 (7100)	65.8 (27.3)	195 (53.9)	N/A	N/A
	CV% mean	38.0	41.4	27.7	N/A	N/A
	Geo-mean	17700	61.8	189	N/A	N/A
	CV% Geo-mean	43.8	46.4	30.4	N/A	N/A
	Median	19700	65.2	206	4.38	167.83
	[Min; Max]	[11200; 25300]	[38.8; 93.3]	[136; 242]	[2.83; 9.57]	[166.47; 169.12]
20 mg/kg QW LJM716 (N = 3)	n	3	3	3	3	3
	Mean (SD)	33700 (5120)	137 (27.8)	362 (53.4)	N/A	N/A
	CV% mean	15.2	20.3	14.7	N/A	N/A
	Geo-mean	33400	135	359	N/A	N/A
	CV% Geo-	14.9	19.6	14.6	N/A	N/A

Treatment	Statistics	AUClast (h*µg/mL)	Cmin (µg/mL)	Cmax (µg/mL)	Tmax (h)	Tlast (h)
	mean					
	Median	32000	123	351	4.63	166.62
	[Min; Max]	[29600; 39400]	[119; 169]	[315; 420]	[2.07; 9.65]	[166.60; 168.28]
40 mg/kg QW LJM716 (N = 6)	n	6	6	6	6	6
	Mean (SD)	59000 (21500)	243 (100)	628 (136)	N/A	N/A
	CV% mean	36.5	41.2	21.6	N/A	N/A
	Geo-mean	55900	226	617	N/A	N/A
	CV% Geo-mean	37.0	42.6	21.4	N/A	N/A
	Median	55000	220	611	3.75	167.13
	[Min; Max]	[40000; 92000]	[154; 393]	[483; 840]	[2.02; 9.65]	[165.65; 168.00]

Summary of primary pharmacokinetic parameters for LJM716 by treatment group (Pharmacokinetic analysis set) - Cycle 3 –

Treatment	Statistics	AUClast (h*µg/mL)	Cmin (µg/mL)	Cmax (µg/mL)	Tmax (h)	Tlast (h)
10 mg/kg QW LJM716 (N = 3)	n	2	2	2	2	2
	Mean (SD)	48900 (19200)	233 (67.2)	442 (245)	N/A	N/A
	CV% mean	39.3	28.9	55.6	N/A	N/A
	Geo-mean	46900	228	406	N/A	N/A
	CV% Geo-mean	42.1	29.9	64.2	N/A	N/A
	Median	48900	233	442	9.52	167.53
	[Min; Max]	[35300; 62400]	[185; 280]	[268; 615]	[9.5; 9.53]	[167.20; 167.87]
40 mg/kg QW LJM716 (N = 6)	n	1	1	1	1	1
	Mean (SD)	243000 (-)	1210 (-)	2130 (-)	N/A	N/A
	CV% mean				N/A	N/A
	Geo-mean	243000	1210	2130	N/A	N/A
	CV% Geo-mean				N/A	N/A

Treatment	Statistics	AUClast (h*µg/mL)	Cmin (µg/mL)	Cmax (µg/mL)	Tmax (h)	Tlast (h)
	Median	243000	1210	2130	4.73	168.42
	[Min; Max]	[243000; 243000]	[1210; 1210]	[2130; 2130]	[4.73; 4.73]	[168.42; 168.42]

Summary of Safety

Safety Results

Determination of MTD/RDE

RD	The RD was declared at a dose of 40 mg/kg QW
MTD	Not determined

Dose-limiting toxicities occurring during the first cycle by primary system organ class, preferred term, maximum grade and treatment (DDS)

No DLT was observed during the first cycle of the study treatment.

A DLT was reported in 1 patient (40 mg/kg group) who experienced grade 3 pneumonia aspiration during Cycle 2.

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

Primary system organ class Preferred term	10 mg/kg QW LJM716 N = 3 n (%)	20 mg/kg QW LJM716 N = 3 n (%)	40 mg/kg QW LJM716 N = 6 n (%)	All patients N = 12 n (%)
- Any primary system organ class				
- Total	3 (100)	3 (100)	6 (100)	12 (100)
GASTROINTESTINAL DISORDERS				
- Total	3 (100)	3 (100)	4 (66.7)	10 (83.3)
DIARRHOEA	2 (66.7)	1 (33.3)	3 (50.0)	6 (50.0)
STOMATITIS	3 (100)	1 (33.3)	1 (16.7)	5 (41.7)
NAUSEA	1 (33.3)	1 (33.3)	1 (16.7)	3 (25.0)
DYSPHAGIA	0	1 (33.3)	1 (16.7)	2 (16.7)
VOMITING	1 (33.3)	1 (33.3)	0	2 (16.7)

Primary system organ class Preferred term	10 mg/kg QW LJM716 N = 3 n (%)	20 mg/kg QW LJM716 N = 3 n (%)	40 mg/kg QW LJM716 N = 6 n (%)	All patients N = 12 n (%)
ABDOMINAL DISTENSION	0	1 (33.3)	0	1 (8.3)
ABDOMINAL PAIN	0	0	1 (16.7)	1 (8.3)
ABDOMINAL PAIN UPPER	1 (33.3)	0	0	1 (8.3)
CHEILITIS	0	0	1 (16.7)	1 (8.3)
CONSTIPATION	0	0	1 (16.7)	1 (8.3)
HAEMORRHOIDAL HAEMORRHAGE	0	0	1 (16.7)	1 (8.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
- Total	2 (66.7)	3 (100)	5 (83.3)	10 (83.3)
FATIGUE	1 (33.3)	1 (33.3)	2 (33.3)	4 (33.3)
OEDEMA PERIPHERAL	1 (33.3)	2 (66.7)	1 (16.7)	4 (33.3)
PYREXIA	0	1 (33.3)	3 (50.0)	4 (33.3)
FACE OEDEMA	0	1 (33.3)	0	1 (8.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
- Total	2 (66.7)	1 (33.3)	3 (50.0)	6 (50.0)
COUGH	2 (66.7)	0	1 (16.7)	3 (25.0)
DYSPNOEA	0	1 (33.3)	1 (16.7)	2 (16.7)
DYSPHONIA	0	0	1 (16.7)	1 (8.3)
PNEUMONIA ASPIRATION	0	0	1 (16.7)	1 (8.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
- Total	2 (66.7)	1 (33.3)	3 (50.0)	6 (50.0)
PRURITUS	1 (33.3)	1 (33.3)	1 (16.7)	3 (25.0)
RASH	1 (33.3)	0	1 (16.7)	2 (16.7)
DRY SKIN	0	0	1 (16.7)	1 (8.3)
NAIL DISORDER	0	0	1 (16.7)	1 (8.3)
SKIN EROSION	0	0	1 (16.7)	1 (8.3)
INFECTIONS AND INFESTATIONS				
- Total	2 (66.7)	1 (33.3)	2 (33.3)	5 (41.7)
NASOPHARYNGITIS	0	1 (33.3)	2 (33.3)	3 (25.0)

Primary system organ class Preferred term	10 mg/kg QW LJM716 N = 3 n (%)	20 mg/kg QW LJM716 N = 3 n (%)	40 mg/kg QW LJM716 N = 6 n (%)	All patients N = 12 n (%)
PARONYCHIA	2 (66.7)	0	1 (16.7)	3 (25.0)
CONJUNCTIVITIS	0	1 (33.3)	0	1 (8.3)
CYSTITIS	1 (33.3)	0	0	1 (8.3)
HERPES VIRUS INFECTION	1 (33.3)	0	0	1 (8.3)
INFLUENZA	1 (33.3)	0	0	1 (8.3)
VULVOVAGINAL MYCOTIC INFECTION	1 (33.3)	0	0	1 (8.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
- Total	0	1 (33.3)	3 (50.0)	4 (33.3)
ANAEMIA	0	1 (33.3)	2 (33.3)	3 (25.0)
NEUTROPENIA	0	0	1 (16.7)	1 (8.3)
METABOLISM AND NUTRITION DISORDERS				
- Total	1 (33.3)	2 (66.7)	1 (16.7)	4 (33.3)
DECREASED APPETITE	1 (33.3)	1 (33.3)	1 (16.7)	3 (25.0)
HYPONATRAEMIA	0	1 (33.3)	0	1 (8.3)
HYPOPHOSPHATAEMIA	0	0	1 (16.7)	1 (8.3)
NERVOUS SYSTEM DISORDERS				
- Total	1 (33.3)	1 (33.3)	2 (33.3)	4 (33.3)
HEADACHE	1 (33.3)	0	1 (16.7)	2 (16.7)
PERIPHERAL SENSORY NEUROPATHY	0	1 (33.3)	1 (16.7)	2 (16.7)
DIZZINESS	1 (33.3)	0	0	1 (8.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
- Total	0	1 (33.3)	2 (33.3)	3 (25.0)
ARTHRALGIA	0	0	1 (16.7)	1 (8.3)
MUSCLE SPASMS	0	1 (33.3)	0	1 (8.3)
MUSCULOSKELETAL PAIN	0	0	1 (16.7)	1 (8.3)
CARDIAC DISORDERS				
- Total	1 (33.3)	0	1 (16.7)	2 (16.7)
ATRIAL FIBRILLATION	0	0	1 (16.7)	1 (8.3)
HYPERTENSIVE HEART DISEASE	1 (33.3)	0	0	1 (8.3)

Primary system organ class Preferred term	10 mg/kg QW LJM716 N = 3 n (%)	20 mg/kg QW LJM716 N = 3 n (%)	40 mg/kg QW LJM716 N = 6 n (%)	All patients N = 12 n (%)
INVESTIGATIONS				
- Total	0	0	2 (33.3)	2 (16.7)
LYMPHOCYTE COUNT DECREASED	0	0	2 (33.3)	2 (16.7)
ELECTROCARDIOGRAM QT PROLONGED	0	0	1 (16.7)	1 (8.3)
WHITE BLOOD CELL COUNT DECREASED	0	0	1 (16.7)	1 (8.3)
EAR AND LABYRINTH DISORDERS				
- Total	0	1 (33.3)	0	1 (8.3)
VERTIGO	0	1 (33.3)	0	1 (8.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
- Total	1 (33.3)	0	0	1 (8.3)
CANCER PAIN	1 (33.3)	0	0	1 (8.3)
PSYCHIATRIC DISORDERS				
- Total	1 (33.3)	0	0	1 (8.3)
INSOMNIA	1 (33.3)	0	0	1 (8.3)

Deaths, serious adverse events and discontinuation due to AEs (Safety set)

	10 mg/kg QW LJM716 N = 3 n (%)	20 mg/kg QW LJM716 N = 3 n (%)	40 mg/kg QW LJM716 N = 6 n (%)	All patients N = 12 n (%)
Death				
Total	0	0	0	0
Due to study indication	0	0	0	0
Due to other causes	0	0	0	0
SAEs	0	1 (33.3)	1 (16.7)	2 (16.7)
Discontinued due to AE	0	0	0	0

Other Relevant Findings

None

Conclusion:

LJM716 was well tolerated with a manageable safety profile, and the RD of LJM716 was established at 40 mg/kg QW IV in Japanese patients – the same RD as determined in Western patients in a separate clinical trial.

Date of Clinical Trial Report

27-Oct-2015