Sponsor

Novartis

Generic Drug Name

LJM716

Trial Indication(s)

Squamous cell carcinoma of head and neck (SCCHN), esophageal squamous cell carcinoma (ESCC), HER2 overexpressing metastatic breast or gastric cancer

Protocol Number

CLJM716X2101

Protocol Title

A Phase I open-label dose escalation study of LJM716 administered intravenously in adult patients with squamous cell carcinoma of head and neck, or human epidermal growth factor receptor 2 (HER2) overexpressing metastatic breast cancer or gastric cancer.

Clinical Trial Phase

I

Phase of Drug Development

I

Study Start/End Dates

26-Jul-2012 to 13-Mar-2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase I, open-label, multicenter dose-escalation study to estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) and preferred dosing schedule of LJM716 in adult patients with SCCHN, or ESCC, or HER2 overexpressing metastatic breast cancer (MBC) or gastric cancer (GC). The study consisted of a dose escalation part and a dose expansion part. During the dose escalation part at least 15 patients were to be treated in successive cohorts. The first cohort started with 3 mg/kg LJM716 once weekly by iv infusion and subsequently, higher dose levels was explored following the recommendations of an adaptive Bayesian logistic regression model (BLRM) guided by

overdose control criteria (EWOC). After the estimation of MTD/RDE the dose expansion part was started. During dose expansion, at least 30 additional patients were to be treated at MTD/RDE to further characterize the safety and tolerability of LJM716, and to make a preliminary assessment of the anti-tumor activity. Each treatment cycle was of 28 days duration.

Centers

This study was conducted at four centers in USA, one center in Canada, one center in Spain, one center in Taiwan and one center in South Korea.

Publication

None

Objectives:

***Primary objective*:** The primary objective of this study was to estimate the MTD and/or RDE and preferred dosing schedule of LJM716 as a single agent when administered iv to adult patients with SCCHN, or ESCC, or HER2 overexpressing metastatic breast cancer or gastric cancer.

***Secondary objectives*:** The secondary objectives of this study were:

- To characterize the safety and tolerability of LJM716
- To characterize the pharmacokinetic (PK) of LJM716
- To assess the pharmacodynamics (PD) response to LJM716 in tumor tissue (for patients with paired biopsy)
- To assess the PK/PD relationship of LJM716
- To assess the preliminary anti-tumor activity of LJM716
- To assess the emergence of anti-LJM716 antibodies

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

LJM716, starting dose of 3 mg/kg once weekly administered as i.v. infusion over two hours and subsequently, higher dose levels was explored following the recommendations of an adaptive Bayesian logistic regression model (BLRM) guided by overdose control criteria (EWOC).

Statistical Methods

The statistical analysis of this study was performed by Novartis personnel. SAS® version9.3 was used in all analyses other than Bayesian analyses. All data captured in the clinical database and derived values of each patient were listed, by treatment and patient unique identifier.

Categorical data were summarized using frequencies and percentages. Quantitative data were summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

The analysis sets used for defining the study data were:

Full Analysis Set (FAS)

The full analysis set (FAS) included all patients who received at least one dose (partial or complete) of LJM716. Patients were classified into a treatment group according to their planned dose regimen.

Safety Set (SS)

The safety set included all patients who received at least one dose (partial or complete) of LJM716, and had at least one valid post-baseline safety assessment. The statement that a patient had no adverse events (AEs) (on the AE case report form) constitutes a valid safety assessment.

Patients were classified to a treatment group according to the dose regimen received, where dose regimen received is defined as:

1. The dose regimen assigned if it was received at least once, or

2. The first dose regimen received when starting therapy with study treatment if the assigned dose regimen was never received.

Dose-Determining Set (DDS)

The dose-determining set (DDS) consisted of all patients from the safety set who either met the following minimum exposure criterion and had minimum safety evaluation, or experienced a dose-limiting toxicity (DLT) during the 1st cycle. Patients with following conditions in cycle 1 were considered to be met minimum exposure criteria:

- Once weekly dosing: three of the four planned doses of LJM716
- Once every 2 weeks dosing: two doses of LJM716
- Once every 4 weeks dosing: one dose of LJM716

For completion of minimum safety evaluations a patient was observed for at least 1 cycle (28 days following the dose on cycle 1 day 1) and was considered to have sufficient safety data by both the Sponsor and Investigators to conclude that a DLT did not occur in cycle 1.

The primary analysis method was an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle. Incidence of DLT in the first cycle was the primary variable. The dose-determining set was used, DLTs were listed and incidence was summarized by treatment group.

Assessment of preliminary efficacy was based on best overall tumor response as defined by the RECIST criteria: progressive disease (PD), stable disease (SD), partial response (PR) and complete response (CR).

All data including best overall response (BOR), duration of response (DOR) and progression free survival (PFS) was listed. Summaries of DOR, ORR and PFS were provided only for patients treated at the MTD/RDE meeting the inclusion/exclusion criterion of the dose-expansion part.

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 (Common Toxicity Criteria [CTC] version 4.03 grading limits or normal ranges as appropriate). Other safety data included electrocardiogram, vital signs etc.

The safety set was used for summaries and listings of all safety data with the exception of DLT for which the DDS was used. Safety analyses were performed per treatment received. The FAS was used for safety listings.

PK concentration data was listed and summarized. In addition to descriptive statistics, graphical presentation of arithmetic mean (±standard deviation) and geometric mean serum concentrations for LJM716 at each scheduled timepoint was provided for each dose. PK parameters were determined for all patients using non-compartmental method using Phoenix WNL.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male or female patients age 18 years or older
- Patients with HER2+ breast cancer, or HER2+ gastric cancer, or squamous cell carcinoma of head and neck, or esophageal squamous cell carcinoma
- During dose expansion part of the study, baseline tumor tissue must be obtained by biopsy
- During dose expansion part of the study, patients must have measurable disease as defined by response evaluation criteria in solid tumors (RECIST) v1.1

Exclusion criteria

- Patients who received prior anti-human epidermal growth factor receptor 3 (anti-HER3) antibody treatment
- Patients with impaired cardiac function
- Patient with brain metastases that have not been adequately treated.
- Patients with malignant disease other than that being treated in this study
- Pregnant or nursing (lactating) women
- Patients with prior anaphylactic or other severe infusion reaction to human immunoglobulin or antibody formulations.
- Patients with laboratory abnormalities as specified in the protocol
- Other protocol defined inclusion/exclusion criteria may apply

Participant Flow

Patient disposition, by treatment group (Full analysis set)

	LJM716 qw 3 mg/kg N=1 n (%)	LJM716 qw 10 mg/kg N=5 n (%)	LJM716 qw 20 mg/kg N=6 n (%)	RDE LJM716 qw 40 mg/kg N=36 n (%)	LJM716 q2w 20 mg/kg N=6 n (%)	All patients N=54 n (%)
Patients treated						
Treatment discontinued	1 (100)	5 (100)	6 (100)	36 (100)	6 (100)	54 (100)
Primary reason for end of treatment						
Death	0	0	0	1 (2.8)	0	1 (1.9)
Physician decision	0	0	0	3 (8.3)	0	3 (5.6)
Progressive disease	1 (100)	5 (100)	6 (100)	27 (75.0)	6 (100)	45 (83.3)
Patient/ guardian decision	0	0	0	5 (13.9)	0	5 (9.3)

QW= once weekly; Q2W= once every 2 weeks; MTD= maximum tolerated dose; RDE= recommended dose for expansion

Baseline Characteristics

Demographic summary by treatment group (Full analysis set)

Demographics variable	LJM716 QW 3 mg/kg N=1	LJM716 QW 10 mg/kg N=5	LJM716 QW 20 mg/kg N=6	LJM716 QW 40 mg/kg N=36	LJM716 Q2W 20 mg/kg N=6	All patients N=54
Age (years)						
n	1	5	6	36	6	54
Mean	57.0	57.4	55.7	59.5	57.7	58.6
SD		8.23	8.80	10.41	10.93	9.85
Median	57.0	55.0	56.5	60.5	54.5	58.0
Minimum – Maximum	57 - 57	48 – 66	43 - 69	36 - 77	49 - 78	36 - 78
Age category (years) – n (%)						
<65	1 (100)	3 (60.0)	5 (83.3)	24 (66.7)	5 (83.3)	38 (70.4)
≥65	0	2 (40.0)	1 (16.7)	12 (33.3)	1 (16.7)	16 (29.6)
Sex – n (%)						
Female	0	2 (40.0)	2 (33.3)	11 (30.6)	2 (33.3)	17 (31.5)
Male	1 (100)	3 (60.0)	4 (66.7)	25 (69.4)	4 (66.7)	37 (68.5)
Race – n (%)						
Asian	0	0	0	17 (47.2)	0	17 (31.5)

	LJM716 QW 3 mg/kg	LJM716 QW 10 mg/kg	LJM716 QW 20 mg/kg	LJM716 QW 40 mg/kg	LJM716 Q2W 20 mg/kg	All patients
Demographics variable	**N=1**	**N=5**	**N=6**	**N=36**	**N=6**	**N=54**
Black	0	0	0	1 (2.8)	0	1 (1.9)
Caucasian	1 (100)	5 (100)	6 (100)	18 (50.0)	5 (83.3)	35 (64.8)
Other	0	0	0	0	1 (16.7)	1 (1.9)
Ethnicity – n (%)						
East Asian	0	0	0	16 (44.4)	0	16 (29.6)
Hispanic or Latino	0	0	2 (33.3)	2 (5.6)	3 (50.0)	7 (13.0)
Not reported	1 (100)	0	1 (16.7)	2 (5.6)	0	4 (7.4)
Other	0	4 (80.0)	2 (33.3)	13 (36.1)	2 (33.3)	21 (38.9)
Russian	0	0	0	0	1 (16.7)	1 (1.9)
Unknown	0	1 (20.0)	1 (16.7)	3 (8.3)	0	5 (9.3)
Height (cm)						
N	1	5	6	36	6	54
Mean	177.8	167.2	174.8	165.7	168.6	167.4
SD		3.60	6.24	9.42	8.53	8.97
Median	177.8	167.6	172.5	166.1	168.0	167.6
Minimum – Maximum	178 - 178	161- 170	168 - 185	149 - 184	158 - 179	149 - 185
Weight (Kg)*						
N	1	5	6	36	6	54
Mean	100.2	67.6	82.9	61.7	74.5	66.7
SD		13.34	21.77	15.50	21.49	18.30
Median	100.2	70.6	82.1	61.6	71.7	63.9
Minimum	100	54	54	35	45	35
Maximum	100	87	115	111	109	115
Baseline ECOG performance status						
0	0	1 (20.0)	1 (16.7)	7 (19.4)	2 (33.3)	11 (20.4)
1	1 (100)	4 (80.0)	5 (83.3)	26 (72.2)	4 (66.7)	40 (74.1)
2	0	0	0	3 (8.3)	0	3 (5.6)

Summary of Efficacy

Primary Outcome Result(s)

Dose Limiting toxicities

Dose limiting toxicities occurring during the first cycle, by primary system organ class, preferred term and treatment (Dose determining set)

Primary system organ class Preferred term	LJM716 QW 3 mg/kg N=1 n (%)	LJM716 QW 10 mg/kg N=5 n (%)	LJM716 QW 20 mg/kg N=6 n (%)	LJM716 QW 40 mg/kg N=34 n (%)	LJM716 Q2W 20 mg/kg N=5 n (%)	All patients N=51 n (%)
Any primary system organ class						
Total	0	0	0	1 (2.9)	0	1 (2.0)
Gastrointestinal disorders						
Total	0	0	0	1 (2.9)	0	1 (2.0)
Diarrhoea	0	0	0	1 (2.9)	0	1 (2.0)
Metabolism and nutrition disorders						
Total	0	0	0	1 (2.9)	0	1 (2.0)
Hypokalemia	0	0	0	1 (2.9)	0	1 (2.0)

- DLTs are as identified by the investigator on the end of Cycle 1 eCRF.
- Primary system organ classes are presented by descending frequency;
Preferred terms are sorted within primary system organ class in
Descending frequency, as reported in the specified column
- A subject with multiple occurrences of an DLTs under one treatment is counted only once in the AE category
For that treatment.
- A subject with multiple DLTs within a primary system organ class is counted only once in the total row.

Secondary Outcome Result(s)

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

All Disease Types

	qw 3 mg/kg N=1 n (%)	qw 10 mg/kg N=5 n (%)	qw 20 mg/kg N=6 n (%)	MTD/RDE qw 40 mg/kg N=36 n (%)	q2w 20 mg/kg N=6 n (%)	All patients N=54 n (%)
Best overall response - n(%)						
Complete response (CR)	0	0	0	0	0	0
Partial response (PR)	0	0	0	0	0	0
Stable disease (SD)	0	2 (40.0)	3 (50.0)	10 (27.8)	2 (33.3)	17 (31.5)
Unconfirmed CR/PR	0	0	0	1 (2.8)	0	1 (1.9)
Progressive disease (PD)	1 (100.0)	3 (60.0)	3 (50.0)	21 (58.3)	4 (66.7)	32 (59.3)
Unknown	0	0	0	5 (13.9)	0	5 (9.3)

Best overall response 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

Summary of best overall response as per investigator by disease indication in patients (Full analysis set)

	qw 3mg/kg N=1 n (%)	qw 10mg/kg N=5 n (%)	qw 20mg/kg N=6 n (%)	MTD/RDE qw 40 mg/kg N=36 n (%)	q2w 20mg/kg N=6 n (%)	All patients N=54 n (%)
Breast cancer		1	2	5	2	10
Best overall response - n(%)						
Complete response (CR)		0	0	0	0	0
Partial response (PR)		0	0	0	0	0
Stable disease (SD)		0	1 (50.0)	1 (20.0)	0	2 (20.0)
Progressive disease (PD)		1 (100.0)	1 (50.0)	4 (80.0)	2 (100.0)	8 (80.0)
Unknown		0	0	0	0	0
Gastric cancer			1	7		8
Best overall response - n(%)						
Complete response (CR)			0	0		0
Partial response (PR)			0	0		0
Stable disease (SD)			1 (100.0)	1 (14.3)		2 (25.0)
Unconfirmed CR/PR			0	1 (14.3)		1 (12.5)
Progressive disease (PD)			0	5 (71.4)		5 (62.5)
Unknown			0	1 (14.3)		1 (12.5)

	qw 3mg/kg N=1 n (%)	qw 10mg/kg N=5 n (%)	qw 20mg/kg N=6 n (%)	MTD/RDE qw 40 mg/kg N=36 n (%)	q2w 20mg/kg N=6 n (%)	All patients N=54 n (%)
Esophageal cancer			1	12	2	15
Best overall response - n(%)						
Complete response (CR)			0	0	0	0
Partial response (PR)			0	0	0	0
Stable disease (SD)			1 (100.0)	5 (41.7)	1 (50.0)	7 (46.7)
Progressive disease (PD)			0	6 (50.0)	1 (50.0)	7 (46.7)
Unknown			0	1 (8.3)	0	1 (6.7)
Head and neck cancer	1	4	2	12	2	21
Best overall response - n(%)						
Complete response (CR)	0	0	0	0	0	0
Partial response (PR)	0	0	0	0	0	0
Stable disease (SD)	0	2 (50.0)	0	3 (25.0)	1 (50.0)	6 (28.6)
Progressive disease (PD)	1 (100.0)	2 (50.0)	2 (100.0)	6 (50.0)	1 (50.0)	12 (57.1)
Unknown	0	0	0	3 (25.0)	0	3 (14.3)

Best overall response 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

Duration of response

Analysis was not performed because none of the patients treated had complete response or partial response.

Progression free survival

Progression free survival (PFS), for patients in the MTD/RDE arm (Full analysis set)

Disease type : Breast cancer		MTD/RDE patients (N= 5) n (%)
Number of PFS events	Death	0 (0.0)
	PD	5 (100.0)
	Total	5 (100.0)
Number censored		0 (0.0)
Kaplan-Meier estimates (%) PFS rate [95% CI] at:	6 months	20.00 [0.00-55.06]
25th percentile for PFS [95% CI]		1.22 [1.05-1.64]
Median PFS [95% CI]		1.28 [1.05-8.94]
75th percentile for PFS [95% CI]		1.64 [1.22-8.94]
CI= confidential interval		

Progression free survival (PFS), for patients in the MTD/RDE arm (Full analysis set)

Disease type : Esophageal cancer		MTD/RDE patients (N= 12) n (%)
Number of PFS events	Death	2 (16.7)
	PD	7 (58.3)
	Total	9 (75.0)
Number censored		3 (25.0)
Kaplan-Meier estimates (%) PFS rate [95% CI] at:	6 months	N.E. [N.E.-N.E.]
25th percentile for PFS [95% CI]		1.48 [1.05-1.64]
Median PFS [95% CI]		1.64 [1.64-3.48]
75th percentile for PFS [95% CI]		3.48 [1.64-N.E.]
CI= confidential interval; N.E.= not estimable		

Progression free survival (PFS), for patients in the MTD/RDE arm (Full analysis set)

Disease type : Gastric cancer		MTD/RDE patients (N= 7) n (%)
Number of PFS events	Death	1 (14.3)
	PD	6 (85.7)
	Total	7 (100.0)
Number censored		0 (0.0)
Kaplan-Meier estimates (%) PFS rate [95% CI] at:	6 months	0.00 [0.00-0.00]
25th percentile for PFS [95% CI]		0.99 [0.95-1.81]
Median PFS [95% CI]		1.68 [0.99-2.20]
75th percentile for PFS [95% CI]		2.20 [1.64-2.66]
CI= confidential interval		

Progression free survival (PFS), for patients in the MTD/RDE arm (Full analysis set)

Disease type : Head and neck cancer		MTD/RDE patients (N= 12) n (%)
Number of PFS events	Death	0 (0.0)
	PD	7 (58.3)
	Total	7 (58.3)
Number censored		5 (41.7)
Kaplan-Meier estimates (%) PFS rate [95% CI] at:	6 months	N.E. [N.E.-N.E.]
25th percentile for PFS [95% CI]		1.64 [0.72-1.81]

Median PFS [95% CI]	1.68 [1.64-3.02]
75th percentile for PFS [95% CI]	3.02 [1.64-N.E.]
CI= confidential interval; N.E.= not estimable	

Progression free survival (PFS), for patients in the MTD/RDE arm (Full analysis set)

Disease type : All disease types		MTD/RDE patients (N= 36) n (%)
Number of PFS events	Death	3 (8.3)
	PD	25 (69.4)
	Total	28 (77.8)
Number censored		8 (22.2)
Kaplan-Meier estimates (%) PFS rate [95% CI] at:	6 months	14.60 [1.74-27.47]
25th percentile for PFS [95% CI]		1.28 [1.05-1.64]
Median PFS [95% CI]		1.64 [1.64-1.81]
75th percentile for PFS [95% CI]		2.69 [1.68-8.94]
CI= confidential interval; N.E.= not estimable		

Summary of Pharmacokinetics

Summary of Primary PK parameters for LJM716 in serum by treatment group (FAS) Cycle 1 Dose 1

Treatment group	**Statistics**	**AUClast (hr*ug/mL)**	**Cmax (ug/mL)**	**Tmax (hr)**	**Tlast (hr)**
qw 3 mg/kg (N=1)	n	1	1	1	1
	Mean (SD)	6158 (-)	65.2 (-)		
	CV% mean				
	Geo-mean	6158	65.2		
	CV% Geo-mean				
	Median	6158	65.2	2.18	168
	[Min; Max]	[6158; 6158]	[65.2; 65.2]	[2.18; 2.18]	[168; 168]
qw 10mg/kg (N=5)	n	5	5	5	5
	Mean (SD)	21302 (3731)	204 (23.6)		
	CV% mean	17.5	11.6		
	Geo-mean	21010	203		
	CV% Geo-mean	19.3	11.2		
	Median	21537	201	4	170

Treatment group	Statistics	AUClast (hr*ug/mL)	Cmax (ug/mL)	Tmax (hr)	Tlast (hr)
	[Min; Max]	[15247; 25167]	[179; 243]	[2.13; 4.53]	[166; 171]
qw 20mg/kg (N=6)	n	6	6	6	6
	Mean (SD)	32791 (9635)	369 (131)		
	CV% mean	29.4	35.6		
	Geo-mean	31547	348		
	CV% Geo-mean	31.9	39.1		
	Median	32641	386	3.88	167
	[Min; Max]	[19598; 45750]	[204; 568]	[2.08; 5.33]	[146; 169]
qw 40mg/kg (N=6)	n	6	6	6	6
	Mean (SD)	74637 (7182)	839 (143)		
	CV% mean	9.6	17.0		
	Geo-mean	74331	829		
	CV% Geo-mean	10.1	17.4		
	Median	76978	855	4.34	167
	[Min; Max]	[62072; 81019]	[676; 991]	[2.42; 8.42]	[166; 191]
q2w 20mg/kg (N=6)	n	6	6	6	6
	Mean (SD)	52659 (23302)	408 (137)		
	CV% mean	44.3	33.7		
	Geo-mean	48415	388		
	CV% Geo-mean	47.8	36.8		
	Median	46041	424	3.25	334
	[Min; Max]	[25562; 85454]	[246; 575]	[2.08; 4.03]	[261; 336]
qw 40mg/kg(EX) (N=30)	n	30	30	30	30
	Mean (SD)	73360 (18819)	706 (129)		
	CV% mean	25.7	18.3		
	Geo-mean	66675	695		
	CV% Geo-mean	71.4	18.5		
	Median	76370	717	3.79	166
	[Min; Max]	[2550; 99984]	[524; 959]	[2.05; 7.5]	[7.22; 171]

AUClast= area under the curve from time zero to the last measurable concentration sampling time; Cmax= maximum concentration of drug; Tmax= Time to peak drug concentration; Tlast= Last measureable concentration sampling time; CV= Coefficient of variation; Geo-mean=geometric mean; SD=standard deviation; Min=minimum; Max=maximum; EX=expansion

Summary of Primary PK parameters for LJM716 in serum by treatment group (FAS) Cycle 3 Dose 1

Treatment group	Statistics	AUClast (hr*ug/mL)	Cmax (ug/mL)	Tmax (hr)	Tlast (hr)	Effective HalfLife (hr)
qw 10mg/kg (N=5)	N	2	2	2	2	2
	Mean (SD)	44137 (3946)	383 (36.8)			221 (44.9)
	CV% mean	8.9	9.6			20.3
	Geo-mean	44048	382			219
	CV% Geo-mean	9.0	9.6			20.7
	Median	44137	383	3.13	167	221
	[Min; Max]	[41347; 46927]	[357; 409]	[2.13; 4.13]	[166; 168]	[190; 253]
qw 20mg/kg (N=6)	N	2	2	2	2	2
	Mean (SD)	64164 (27576)	581 (300)			226 (35)
	CV% mean	43.0	51.6			15.4
	Geo-mean	61129	541			225
	CV% Geo-mean	46.7	58.3			15.6
	Median	64164	581	4.04	168	226
	[Min; Max]	[44665; 83663]	[369; 793]	[4; 4.07]	[166; 169]	[202; 251]
qw 40mg/kg (N=6)	n	1	1	1	1	1
	Mean (SD)	213493 (-)	1550 (-)			339 (-)
	CV% mean					
	Geo-mean	213493	1550			339
	CV% Geo-mean					
	Median	213493	1550	4.5	166	339
	[Min; Max]	[213493; 213493]	[1550; 1550]	[4.5; 4.5]	[166; 166]	[339; 339]
q2w 20mg/kg (N=6)	n	2	2	2	2	2
	Mean (SD)	123001 (115286)	632 (480)			337 (132)
	CV% mean	93.7	76.0			39.3
	Geo-mean	92108	532			324
	CV% Geo-mean	160.3	102.9			42.1
	Median	123001	632	5.09	337	337
	[Min; Max]	[41482; 204521]	[292; 971]	[4.1; 6.08]	[337; 337]	[243; 431]

Treatment group	Statistics	AUClast (hr*ug/mL)	Cmax (ug/mL)	Tmax (hr)	Tlast (hr)	Effective HalfLife (hr)
qw 40mg/kg(EX) (N=30)	n	5	5	5	5	5
	Mean (SD)	185044 (41190)	1398 (379)			225 (37.7)
	CV% mean	22.3	27.1			16.7
	Geo-mean	181445	1360			223
	CV% Geo-mean	22.4	26.2			16.7
	Median	181817	1300	2.08	165	225
	[Min; Max]	[133142; 247687]	[998; 2010]	[2.03; 3.93]	[165; 189]	[181; 279]

PK parameters such as volume (V) and body clearance (CL) were not evaluable based on current concentration-time curves due to the high percentage (>20%) of extrapolation in the regression.

Correlation between LJM716 serum concentrations or PK parameters and change from baseline in pHER3 levels in the tumor

Correlation between LJM716 PK exposure and pharmacodynamics (PD) marker responses were not examined due to the scarcity of PD data from low dose cohorts.

Post treatment change from baseline in phosphorylated HER3 (pHER3) levels in the tumor

Summary of tumor biomarkers by treatment (Full Analysis Set)
Biomarker group: pHER3

	MTD/RDE QW 40mg/kg (N=36)	All patients (N=54)
Normalized signal at Baseline		
n (%)	30 (83.3)	30 (55.6)
Below LLOQ (%)[1]	7 (19.4)	7 (13.0)
Mean	159.3	159.3
SD (CV%)	230.1 (144.5)	230.1 (144.5)
Median	59.0	59.0
Min, Max	10.4, 818.3	10.4, 818.3
Normalized signal at C3D1		
n (%)	5 (13.9)	5 (9.3)
Below LLOQ (%)[1]	3 (8.3)	3 (5.6)
Mean	46.1	46.1
SD (CV%)	62.9 (136.4)	62.9 (136.4)
Median	10.4	10.4

Min, Max	10.4, 155.5	10.4, 155.5
Absolute Change from baseline		
n (%)	4 (11.1)	4 (7.4)
Below LLOQ (%)[1]	2 (5.6)	2 (3.7)
Mean	-39.2	-39.2
SD (CV%)	116.1 (-296.5)	116.1 (-296.5)
Median	-32.1	-32.1
Min, Max	-187.3, 94.9	-187.3, 94.9
% Change from baseline		
n (%)	4 (11.1)	4 (7.4)
Below LLOQ (%)[1]	2 (5.6)	2 (3.7)
Mean	-17.3	-17.3
SD (CV%)	116.3 (-673.1)	116.3 (-673.1)
Median	-72.0	-72.0
Min, Max	-81.8, 156.6	-81.8, 156.6

[1] Values below the lower limit of quantitation (LLOQ) are imputed as (0.5* signal LLOQ)/concentration.
When both baseline and post baseline values are below LLOQ, change and fold-change from baseline are not imputed and reported as missing.
% are based on 'n'.
[2] SD=standard deviation; CV= Coefficient of variation; Min=minimum; Max=maximum;

Incidence of antibodies against LJM716

No assessed patients showed evidence of anti-LJM716 antibody.

Summary of Safety

Safety Results

Adverse Events by System Organ Class

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

Primary system organ class Preferred term	LJM716 qw 3 mg/kg N=1 n (%)	LJM716 qw 10 mg/kg N=5 n (%)	LJM716 qw 20 mg/kg N=6 n (%)	RDE LJM716 qw 40 mg/kg N=36 n (%)	LJM716 q2w 20 mg/kg N=6 n (%)	All patients N=54 n (%)
Any primary system organ class	1 (100)	5 (100)	6 (100)	36 (100)	6 (100)	54 (100)
Gastrointestinal disorders	1 (100)	3 (60.0)	6 (100)	33 (91.7)	5 (83.3)	48 (88.9)
General disorders and administration site conditions	0	5 (100)	5 (83.3)	33 (91.7)	3 (50.0)	46 (85.2)
Metabolism and nutrition disorders	1 (100)	5 (100)	5 (83.3)	24 (66.7)	3 (50.0)	38 (70.4)
Respiratory, thoracic and mediastinal disorders	0	3 (60.0)	1 (16.7)	24 (66.7)	4 (66.7)	32 (59.3)
Musculoskeletal and connective tissue disorders	1 (100)	2 (40.0)	2 (33.3)	20 (55.6)	4 (66.7)	29 (53.7)
Skin and subcutaneous tissue disorders	0	4 (80.0)	3 (50.0)	14 (38.9)	2 (33.3)	23 (42.6)

Primary system organ class Preferred term	LJM716 qw 3 mg/kg	LJM716 qw 10 mg/kg	LJM716 qw 20 mg/kg	RDE LJM716 qw 40 mg/kg	LJM716 q2w 20 mg/kg	All patients
	N=1	N=5	N=6	N=36	N=6	N=54
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigations	1 (100)	3 (60.0)	3 (50.0)	15 (41.7)	0	22 (40.7)
Infections and infestations	0	2 (40.0)	1 (16.7)	15 (41.7)	3 (50.0)	21 (38.9)
Nervous system disorders	0	4 (80.0)	3 (50.0)	13 (36.1)	1 (16.7)	21 (38.9)
Injury, poisoning and procedural complications	0	0	3 (50.0)	15 (41.7)	2 (33.3)	20 (37.0)
Blood and lymphatic system disorders	0	1 (20.0)	3 (50.0)	10 (27.8)	0	14 (25.9)
Psychiatric disorders	0	1 (20.0)	0	2 (5.6)	1 (16.7)	4 (7.4)
Renal and urinary disorders	0	1 (20.0)	0	3 (8.3)	0	4 (7.4)
Cardiac disorders	0	0	2 (33.3)	0	1 (16.7)	3 (5.6)
Ear and labyrinth disorders	0	0	0	2 (5.6)	0	2 (3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (16.7)	1 (2.8)	0	2 (3.7)

Primary system organ classes are presented by descending frequency; preferred terms are sorted within primary System organ class in descending frequency, as reported in the 'All patients' column
- A patient with multiple occurrences of an AE is counted only once for that AE.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Includes all AEs on study and up to 30 days after last dose.

Most Frequently Reported Adverse Events by Preferred Term n (%)

Adverse events, regardless of study drug relationship, by preferred term and treatment group (Safety set)

Preferred term	LJM716 qw 3 mg/kg N=1	LJM716 qw 10 mg/kg N=5	LJM716 qw 20 mg/kg N=6	RDE LJM716 qw 40 mg/kg N=36	LJM716 q2w 20 mg/kg N=6	All patients N=54
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (100)	5 (100)	6 (100)	36 (100)	6 (100)	54 (100)
Diarrhea	0	2 (40.0)	5 (83.3)	18 (50.0)	3 (50.0)	28 (51.9)
Decreased appetite	0	3 (60.0)	4 (66.7)	16 (44.4)	1 (16.7)	24 (44.4)
Pyrexia	0	2 (40.0)	2 (33.3)	18 (50.0)	0	22 (40.7)
Fatigue	0	2 (40.0)	2 (33.3)	14 (38.9)	1 (16.7)	19 (35.2)
Nausea	1 (100)	3 (60.0)	3 (50.0)	12 (33.3)	0	19 (35.2)
Infusion related reaction	0	0	3 (50.0)	13 (36.1)	1 (16.7)	17 (31.5)
Vomiting	1 (100)	1 (20.0)	2 (33.3)	10 (27.8)	2 (33.3)	16 (29.6)
Constipation	1 (100)	0	3 (50.0)	10 (27.8)	1 (16.7)	15 (27.8)
Dyspnea	0	1 (20.0)	1 (16.7)	10 (27.8)	3 (50.0)	15 (27.8)
Anemia	0	1 (20.0)	3 (50.0)	10 (27.8)	0	14 (25.9)
Hypomagnesaemia	0	3 (60.0)	3 (50.0)	7 (19.4)	1 (16.7)	14 (25.9)
Chills	0	0	2 (33.3)	11 (30.6)	0	13 (24.1)
Hypokalemia	1 (100)	2 (40.0)	0	9 (25.0)	1 (16.7)	13 (24.1)
Cough	0	1 (20.0)	1 (16.7)	8 (22.2)	1 (16.7)	11 (20.4)
Headache	0	2 (40.0)	1 (16.7)	7 (19.4)	0	10 (18.5)
Stomatitis	0	0	2 (33.3)	7 (19.4)	1 (16.7)	10

Preferred term	LJM716 qw 3 mg/kg N=1	LJM716 qw 10 mg/kg N=5	LJM716 qw 20 mg/kg N=6	RDE LJM716 qw 40 mg/kg N=36	LJM716 q2w 20 mg/kg N=6	All patients N=54
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
						(18.5)
Aspartate aminotransferase increased	0	2 (40.0)	1 (16.7)	6 (16.7)	0	9 (16.7)
Asthenia	0	0	2 (33.3)	5 (13.9)	2 (33.3)	9 (16.7)
Myalgia	0	0	1 (16.7)	7 (19.4)	1 (16.7)	9 (16.7)
Blood alkaline phosphatase increased	1 (100)	1 (20.0)	2 (33.3)	4 (11.1)	0	8 (14.8)
Hypophosphataemia	0	0	0	8 (22.2)	0	8 (14.8)
Pneumonia	0	0	0	8 (22.2)	0	8 (14.8)
Pruritus	0	1 (20.0)	1 (16.7)	5 (13.9)	1 (16.7)	8 (14.8)
Rash	0	0	1 (16.7)	6 (16.7)	1 (16.7)	8 (14.8)
Abdominal pain	0	0	0	6 (16.7)	1 (16.7)	7 (13.0)
Dehydration	0	1 (20.0)	2 (33.3)	4 (11.1)	0	7 (13.0)
Dry skin	0	1 (20.0)	2 (33.3)	4 (11.1)	0	7 (13.0)
Hypoalbuminaemia	0	0	3 (50.0)	4 (11.1)	0	7 (13.0)
Oedema peripheral	0	1 (20.0)	1 (16.7)	4 (11.1)	1 (16.7)	7 (13.0)
Weight decreased	0	1 (20.0)	2 (33.3)	4 (11.1)	0	7 (13.0)
Muscular weakness	0	1 (20.0)	1 (16.7)	2 (5.6)	2 (33.3)	6 (11.1)
Pleural effusion	0	1 (20.0)	0	4 (11.1)	1 (16.7)	6 (11.1)
Alanine aminotransferase increased	0	2 (40.0)	0	3 (8.3)	0	5 (9.3)
Back pain	0	1 (20.0)	0	3 (8.3)	1 (16.7)	5 (9.3)
Dizziness	0	0	1 (16.7)	3 (8.3)	1 (16.7)	5 (9.3)
Dysphagia	0	0	1 (16.7)	4 (11.1)	0	5 (9.3)
Hypocalcaemia	0	1 (20.0)	2 (33.3)	1 (2.8)	1 (16.7)	5 (9.3)
Hyponatraemia	0	0	2 (33.3)	3 (8.3)	0	5 (9.3)
Lipase increased	0	1 (20.0)	0	4 (11.1)	0	5 (9.3)
Neck pain	0	0	1 (16.7)	4 (11.1)	0	5 (9.3)
Productive cough	0	0	0	5 (13.9)	0	5 (9.3)
Hypercalcaemia	0	0	0	4 (11.1)	0	4 (7.4)
Hypotension	0	0	0	3 (8.3)	1 (16.7)	4 (7.4)
Musculoskeletal pain	0	0	0	4 (11.1)	0	4 (7.4)
Peripheral sensory neuropathy	0	1 (20.0)	0	3 (8.3)	0	4 (7.4)
Arthralgia	0	1 (20.0)	0	1 (2.8)	1 (16.7)	3 (5.6)
Blood bilirubin increased	0	0	0	3 (8.3)	0	3 (5.6)

Preferred term	LJM716 qw 3 mg/kg N=1	LJM716 qw 10 mg/kg N=5	LJM716 qw 20 mg/kg N=6	RDE LJM716 qw 40 mg/kg N=36	LJM716 q2w 20 mg/kg N=6	All patients N=54
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood creatinine increased	0	1 (20.0)	0	2 (5.6)	0	3 (5.6)
Bone pain	1 (100)	0	0	1 (2.8)	1 (16.7)	3 (5.6)
Disease progression	0	0	0	3 (8.3)	0	3 (5.6)
Hiccups	0	0	0	2 (5.6)	1 (16.7)	3 (5.6)
Hyperglycaemia	0	0	0	3 (8.3)	0	3 (5.6)
Hypophagia	0	0	0	3 (8.3)	0	3 (5.6)
Influenza like illness	0	1 (20.0)	1 (16.7)	1 (2.8)	0	3 (5.6)
Insomnia	0	1 (20.0)	0	1 (2.8)	1 (16.7)	3 (5.6)
Nasopharyngitis	0	1 (20.0)	1 (16.7)	0	1 (16.7)	3 (5.6)
Oral pain	0	0	0	2 (5.6)	1 (16.7)	3 (5.6)
Pain in extremity	0	0	1 (16.7)	2 (5.6)	0	3 (5.6)
Respiratory tract infection	0	0	0	2 (5.6)	1 (16.7)	3 (5.6)
Tremor	0	0	1 (16.7)	2 (5.6)	0	3 (5.6)

- Preferred terms are sorted in descending frequency, as reported in the All patient 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 adverse events is counted only once in the total row.
- Includes all AEs on study and up to 30 days after last dose.

Serious Adverse Events and Deaths

Deaths, other serious adverse events or related discontinuations – n (%) of subjects (Safety set)

	LJM716 QW 3 mg/kg N=1 n (%)	LJM716 QW 10 mg/kg N=5 n (%)	LJM716 QW 20 mg/kg N=6 n (%)	LJM716 QW 40 mg/kg N=36 n (%)	LJM716 Q2W 20 mg/kg N=6 n (%)	All patients N=54 n (%)
Death on study						
Total	0	0	0	9 (25.0)	1 (16.7)	10 (18.5)
Due to other causes	0	0	0	9 (25.0)	1 (16.7)	10 (18.5)
On treatment deaths	0	0	0	7 (19.4)	0	7 (12.9)
SAEs	0	2 (40.0)	3 (50.0)	24 (66.7)	3 (50.0)	32 (59.3)
Discontinued due to AE	0	0	0	0	0	0
Discontinued due to SAE	0	0	0	0	0	0

Other Relevant Findings

None

Conclusion:

- The RDE was established at 40 mg/kg dose once weekly. Two DLTs (hypokalemia and diarrhea) had occurred during the first cycle of treatment in one patient of the expansion phase.
- The exposure of LJM716 appeared to be dose-proportional in the tested dose range of 3 to 40 mg/kg. LJM716 had 2 to 3.5 fold accumulation at steady state after repeated dosing. The effective half-life of LJM716 is estimated to be in the range of 220 to 340 hrs.
- The safety and tolerability profile of LJM716 was found to be acceptable and it was generally well tolerated. No grade 3/4 infusion related reaction symptoms were observed. The adverse events and serious adverse events were generally not suspected to be related to the study drug and the few suspected SAEs or AEs could be well managed in patients receiving appropriate oncology patient clinical care.
- Seven on treatment deaths (during treatment with LJM716 or within 30 days after discontinuing) were reported during the study, which was noted in the RDE group. Three additional deaths were recorded in the database that occurred outside of the 30 day follow up window at 36, 38, and 128 days after the last dose of LJM716. None of the 10 deaths reported in the study were suspected to be related to study drug.

Date of Clinical Trial Report

12-Mar-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

13-Mar-2015

Date of Latest Update

Reason for Update