



Clinical Trial Results Website

**Sponsor**

Novartis

**Generic Drug Name**

LJM716

**Trial Indication(s)**

HER2 overexpressing metastatic breast cancer or gastric cancer

**Protocol Number**

CLJM716X2102

**Protocol Title**

A multicenter, open-label, dose escalation, Phase I study of LJM716 administered intravenously in combination with trastuzumab in patients with HER2 overexpressing metastatic breast cancer or gastric cancer

**Clinical Trial Phase**

Phase 1

**Phase of Drug Development**

Phase 1

**Study Start/End Dates**

Study initiation date: 21-Sep-2012 (first patient first visit)

Early termination date: Not applicable



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Study completion date: 31-Mar-2016 (data cut-off date)

**Reason for Termination (If applicable)**

Not Applicable

**Study Design/Methodology**

This was a multicenter, open-label, dose escalation, phase I study to estimate the maximum tolerated dose (MTD) or a lower recommended dose for expansion (RDE) to use for further testing in patients with HER2 overexpressing metastatic or locally advanced breast or gastric cancer (MBC and MGC). The study consists of a dose escalation part and a dose expansion part.

**Centers**

This study was conducted at three centers in the United States, and one center each in Belgium, France, Italy, Netherlands, South Korea, Spain, Taiwan, and United Kingdom. A single patient at the center in France gave informed consent but was not included in any analysis set.

**Objectives:**

**Primary objective**

To estimate the maximum tolerated dose (MTD) or lower recommended dose for expansion (RDE) and preferred dosing schedule of LJM716 when administered in combination with trastuzumab in patients with HER2-overexpressing metastatic or locally advanced breast or gastric cancer (MBC and MGC).

**Secondary objectives**

- To characterize the safety and tolerability of LJM716, including both acute and chronic toxicities, when administered in combination with trastuzumab



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- To characterize the pharmacokinetics (PK) of LJM716 and trastuzumab when administered in combination
- To assess the pharmacodynamics (PD) response to LJM716 in tumor tissue (for patients with paired biopsies) when administered in combination with trastuzumab
- To assess the PK/PD relationship of LJM716 when administered in combination with trastuzumab
- To assess the preliminary anti-tumor activity of LJM716 in combination with trastuzumab
- To assess the emergence of anti-LJM716 antibodies

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

LJM716 was provided as 150 mg powder for solution for iv infusion. LJM716 was administered once weekly by iv infusion over two hours. The starting dose for dose escalation was 3 mg/kg once weekly.

Trastuzumab was supplied as a lyophilized sterile powder in vials for parenteral administration. Trastuzumab was administered once weekly (loading dose 4 mg/kg iv on Day 1 of Cycle 1, followed by 2 mg/kg iv weekly from Week 2 onwards).

#### **Statistical Methods**

**Patient populations:** The *full analysis set (FAS)* included all patients who received at least one dose of LJM716 and was used for most analyses. The *Safety set* included all patients who received at least one dose of LJM716 or trastuzumab and had at least one post-baseline safety assessment. The *Dose-determining set (DDS)* consisted of all patients from the safety set who received three of the four planned doses of LJM716 and three of the four planned doses of trastuzumab in Cycle 1, or who experienced a DLT

during the first cycle. The *PK analysis set* consisted of all patients who had at least one blood sample providing evaluable drug concentration data.

**Primary analysis:** A BLRM employing the escalation with overdose control (EWOC) principle was used during the dose escalation part for selecting doses and estimating the MTD or RDE. The MTD was defined as the highest dosage not expected to cause DLTs in the first treatment cycle in more than 33% of patients of the DDS. The RDE was defined as the dose with the



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highest posterior probability of DLT in the target interval [16% to 33%] among the doses fulfilling the overdose criteria, namely that there was a less than 25% chance that the true rate of DLTs fell in the excessive toxicity interval.

**Secondary analyses:** For the ORR and DCR, 95% confidence intervals (CIs) were calculated using the Clopper-Pearson interval, and a waterfall plot was provided presenting the best percentage change from Baseline in diameter of target lesions for each patient. PFS and associated 95% CIs were calculated using Kaplan-Meier techniques. PK parameters for LJM716 were determined using non-compartmental methods. All other variables were analyzed descriptively.

#### **Study Population: Key Inclusion/Exclusion Criteria**

- **Inclusion criteria**

Patients eligible for inclusion in this study had to meet all of the following criteria:

1. Age  $\geq$  18 years
2. Patients with histologically or cytologically confirmed diagnosis of breast cancer, or patients with documented cytologically or histologically confirmed gastric adenocarcinoma or gastroesophageal junction adenocarcinoma. Patients must have had metastatic or locally advanced-unresectable disease.
3. Documented HER2 positivity by local assessment, as follows:  
For breast cancer: 3+ by immunohistochemistry or amplification by in situ hybridization  
For gastric cancer: 3+ by immunohistochemistry or 2+ by immunohistochemistry with amplification by in situ hybridization.
4. Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq$  2.
5. Patients must have recovered from the adverse effects of any prior surgery, radiotherapy, or other antineoplastic therapy. Alopecia and Common Terminology Criteria for Adverse Events (CTCAE) grade 1 peripheral neuropathy were acceptable.
6. Willingness and ability to comply with all study procedures.
7. Written informed consent obtained prior to any screening procedures.
8. At least one prior trastuzumab-containing regimen.



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9. Patients with breast cancer must have received a minimum of one and a maximum of three prior anti-HER2-based regimens, with documented progression on the most recent regimen, which must have contained trastuzumab, ado-trastuzumab emtansine or lapatinib (if recurrence occurred during trastuzumab-containing adjuvant therapy, or  $\leq 12$  months after completion of adjuvant trastuzumab containing therapy, the patient was eligible. In this case, the adjuvant therapy was considered as one line of treatment for advanced disease).
10. Patients with gastric cancer must have received a minimum of one and a maximum of two prior anti-HER2-based regimens, with documented progression on the most recent regimen, which must have contained trastuzumab or ado-trastuzumab emtansine.

During the dose expansion part of the study:

11. Baseline tumor tissue must have been obtained by biopsy according to the institution's own guidelines and requirements for such procedure. Fine needle aspirate was not acceptable.
12. Patients must have had measurable disease as defined by RECIST v1.1 (at least one lesion  $\geq 10$  mm in at least one dimension when assessed by computer tomography (CT) or magnetic resonance imaging (MRI), or a cutaneous lesion with clearly defined margins that measures  $\geq 10$  mm in at least one dimension).

- **Exclusion criteria**

Patients eligible for this study must not have met **any** of the following criteria:

1. Patient with untreated and/or symptomatic metastatic central nervous system disease. However, patients with central nervous system metastases who underwent surgery or radiotherapy, whose disease was stable and who had been on a stable dose (10 mg or lower) of corticosteroids for at least 4 weeks prior to the first scheduled day of dosing were eligible.
2. Patients with a history of primary malignancy other than that being treated in this study, which currently required active clinical intervention.
3. Patients who did not have an archival tumor sample (or sections of it) available or readily obtainable.
4. Patients who received prior specific anti-HER3 antibody treatment, including bi-specific antibodies with HER3 as one of the targets (patients with prior exposure to pertuzumab were eligible).



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5. Prior to the first dose of study treatment, patients who had received systemic antineoplastic therapy or any investigational therapy within 4 weeks or within 5 half-lives of the therapy prior to starting study treatment, whichever was shorter, or for cyclical therapy, within one cycle length (e.g. 6 weeks for nitrosourea, mitomycin-C).
6. Patients who had major surgery within 28 days before study treatment or had not recovered fully from the adverse effects of any major or minor surgical procedures before study treatment.
7. Patients who received radiotherapy within 2 weeks prior to the first dose of study treatment except localized radiation therapy for symptomatic bone metastasis.
8. Patients who had active autoimmune disease requiring immunosuppressive therapy with the exception of low dose prednisone.
9. Patients who had a prior anaphylactic or other severe infusion reaction to human immunoglobulin or antibody formulations.
10. Any of the following clinical laboratory results during screening (i.e., within 21 days before the first dose of study treatment):
  - Absolute neutrophil count (ANC)  $<1,500/\text{mm}^3$  ( $1.5 \times 10^9/\text{L}$ )
  - Platelet count  $<90,000/\text{mm}^3$  ( $90 \times 10^9/\text{L}$ )
  - Bilirubin  $>1.5 \times$  upper limit of normal (ULN)
  - Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT)  $>2.5 \times$  ULN or  $>5.0 \times$  ULN if liver metastases were present
  - Serum creatinine  $>1.5 \times$  ULN or creatinine clearance  $<45$  mL/min (calculated via Cockcroft-Gault formula or 24 hour urine collection)
11. Serious medical or psychiatric illness or any condition that in the assessment of the Investigator rendered the patient not suitable for participation in this clinical study
12. History of an active infection (viral, bacterial, or fungal) requiring systemic therapy within 10 days before study treatment.
13. Known history of human immunodeficiency virus or active infection with hepatitis C virus or hepatitis B virus (testing for human immunodeficiency virus and viral hepatitis was not mandatory)
14. Patients with impaired cardiac function



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15. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test ( $>5$  mIU/mL). Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing and for at least 90 days after study treatment discontinuation or as specified in the local prescription guidelines for trastuzumab



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## **Participant Flow Table**

### **Patient disposition by treatment group (Full Analysis Set)**

	<b>LJM716 qw 3mg/kg N=2 n (%)</b>	<b>LJM716 qw 10mg/kg N=5 n (%)</b>	<b>LJM716 qw 20mg/kg N=4 n (%)</b>	<b>MTD/RDE LJM716 qw 40 mg/kg N=53 n (%)</b>	<b>All patients N=64 n (%)</b>
<b>Patients treated</b>					
Treatment discontinued	2 (100)	5 (100)	4 (100)	53 (100)	64 (100)
<b>Primary reason for end of treatment</b>					
Death	0	0	0	1 (1.9)	1 (1.6)
Physician Decision	0	0	0	3 (5.7)	3 (4.7)
Progressive Disease	2 (100)	3 (60.0)	4 (100)	46 (86.8)	55 (85.9)
Patient/Guardian Decision	0	2 (40.0)	0	3 (5.7)	5 (7.8)

## **Baseline Characteristics**



**Demographics and Baseline characteristics by treatment group (Full analysis set)**

Variable	LJM716 qw 3 mg/kg N=2	LJM716 qw 10 mg/kg N=5	LJM716 qw 20 mg/kg N=4	RDE LJM716 qw 40 mg/kg N=53	All patients N=64
<b>Age (years)</b>					
Mean (STD)	60.5 (2.12)	50.8 (7.95)	44.3 (9.54)	56.2 (11.80)	55.1 (11.58)
Median (range)	60.5 (59-62)	53.0 (39-59)	44.0 (36-53)	57.0 (32-82)	56.0 (32-82)
< 65 years – n (%)	2 (100)	5 (100)	4 (100)	43 (81.1)	54 (84.4)
≥ 65 years – n (%)	0	0	0	10 (18.9)	10 (15.6)
<b>Sex – n (%)</b>					
Female	2 (100)	5 (100)	3 (75.0)	30 (56.6)	40 (62.5)
Male	0	0	1 (25.0)	23 (43.4)	24 (37.5)
<b>Race – n (%)</b>					
Caucasian	2 (100)	4 (80.0)	2 (50.0)	31 (58.5)	39 (60.9)
Asian	0	1 (20.0)	1 (25.0)	20 (37.7)	22 (34.4)
Black	0	0	0	2 (3.8)	2 (3.1)
Other	0	0	1 (25.0)	0	1 (1.6)
<b>Ethnicity – n (%)</b>					
East Asian	0	1 (20.0)	1 (25.0)	17 (32.1)	19 (29.7)
Hispanic/Latino	0	1 (20.0)	0	4 (7.5)	5 (7.8)
Other	1 (50.0)	1 (20.0)	3 (75.5)	26 (49.1)	31 (48.4)
Not reported	1 (50.0)	2 (40.0)	0	6 (11.3)	9 (14.1)
<b>Height (cm)</b>					
Mean (STD)	164.0 (2.88)	165.1 (8.72)	168.1 (10.41)	167.0 (10.60)	166.8 (10.17)
Median (range)	164.0 (162-166)	168.6 (150-171)	164.8 (160-183)	167.0 (147-193)	167.0 (147-193)
<b>Weight (kg)</b>					

Variable	LJM716 qw 3 mg/kg N=2	LJM716 qw 10 mg/kg N=5	LJM716 qw 20 mg/kg N=4	RDE LJM716 qw 40 mg/kg N=53	All patients N=64
Mean (STD)	67.2 (1.83)	66.3 (11.89)	67.5 (9.22)	65.6 (13.25)	65.8 (12.58)
Median (range)	67.2 (66-68)	67.4 (47-79)	70.2 (55-75)	65.0 (39-109)	66.0 (39-109)
<b>ECOG performance status (WHO) – n (%)</b>					
0	1 (50.0)	3 (60.0)	2 (50.0)	34 (64.2)	40 (62.5)
1	1 (50.0)	2 (40.0)	1 (25.0)	18 (34.0)	22 (34.4)
2	0	0	1 (25.0)	1 (1.9)	2 (3.1)

### **Summary of Efficacy**

#### **Primary Outcome Result(s)**

#### **Determination of MTD and/or RDE**

#### **Dose limiting toxicities (DLTs) –Dose Escalation (dose Determining Set)**

None

#### **Dose limiting toxicities (DLTs) –Dose Expansion during the first 28 days (Dose Determining Set)**

	LJM716 N=47	qw	40	mg/kg
Diarrhea	2			
Fatigue	1			

## Secondary Outcome Result(s)

### Summary of best overall response by treatment group, as evaluated by Investigator, overall (Full analysis set)

	LJM716 qw 3 mg/kg N=2	LJM716 qw 10 mg/kg N=5	LJM716 qw 20 mg/kg N=4	RDE LJM716 qw 40 mg/kg N=53	All patients N=64
<b>Best overall response – n (%)</b>					
Complete response (CR)	0	1 (20.0)	0	0	1 (1.6)
Partial response (PR)	1 (50.0)	0	0	3 (5.7)	4 (6.3)
Stable disease (SD)	1 (50.0)	2 (40.0)	0	21 (39.6)	24 (37.5)
Progressive disease	0	2 (40.0)	4 (100.0)	27 (50.9)	33 (51.6)
Unknown	0	0	0	2 (3.8)	2 (3.1)
<b>Overall response rate (ORR, CR or PR)</b>					
n (%)	1 (50.0)	1 (20.0)	0	3 (5.7)	5 (7.8)
95% CI	1.3, 98.7	0.5, 71.6	-	1.2, 15.7	2.6, 17.3
<b>Disease control rate (DCR, CR or PR or SD)</b>					
n (%)	2 (100.0)	3 (60.0)	0	24 (45.3)	29 (45.3)
95% CI	(15.8, 100.0)	(14.7, 94.7)	-	(31.6, 59.6)	(32.8, 58.3)

Best overall response is based on Investigator's assessment of disease status using *RECIST 1.1*

CR and PR had to be confirmed by repeated assessments performed  $\geq 4$  weeks after the criteria for response were first met

The 95% CI was calculated using the *Clopper-Pearson interval*

**Summary of best overall response by treatment group as evaluated by Investigator, breast cancer (Full analysis set)**

	LJM716 qw 3 mg/kg N=2	LJM716 qw 10 mg/kg N=5	LJM716 qw 20 mg/kg N=3	RDE LJM716 qw 40 mg/kg N=27	All BC patients N=37
<b>Best overall response – n (%)</b>					
Complete response (CR)	0	1 (20.0)	0	0	1 (2.7)
Partial response (PR)	1 (50.0)	0	0	0	1 (2.7)
Stable disease (SD)	1 (50.0)	2 (40.0)	0	13 (48.1)	16 (43.2)
Progressive disease	0	2 (40.0)	3 (100.0)	13 (48.1)	18 (48.6)
Unknown	0	0	0	1 (3.7)	1 (2.7)
<b>Overall response rate (ORR, CR or PR)</b>					
n (%)	1 (50.0)	1 (20.0)	0	3 (5.7)	5 (7.8)
95% CI	1.3, 98.7	0.5, 71.6	0.0, 70.8	0.0, 12.8	0.7, 18.2
<b>Disease control rate (DCR, CR or PR or SD)</b>					
n (%)	2 (100.0)	3 (60.0)	0	13 (48.1)	18 (48.6)
95% CI	(15.8, 100.0)	(14.7, 94.7)	(0.0, 70.8)	(28.7, 68.1)	(31.9, 65.6)

Best overall response was based on Investigator's assessment of disease status using *RECIST 1.1*

CR and PR had to be confirmed by repeated assessments performed  $\geq 4$  weeks after the criteria for response were first met. The 95% CI was calculated using the *Clopper-Pearson interval*

BC = breast cancer

**Summary of best overall response by treatment group as evaluated by Investigator, gastric cancer (Full analysis set)**

	LJM716 qw 20 mg/kg <sup>a</sup> N=1	RDE LJM716 qw 40 mg/kg <sup>1</sup> N=26	All GC patients N=27
<b>Best overall response – n (%)</b>			
Complete response (CR)	0	0	0
Partial response (PR)	0	3 (11.5)	3 (11.1)
Stable disease (SD)	0	8 (30.8)	8 (29.6)
Progressive disease	1 (100)	14 (53.8)	15 (55.6)
Unknown	0	1 (3.8)	1 (3.7)
<b>Overall response rate (ORR, CR or PR)</b>			
n (%)	0	3 (11.5)	3 (11.1)
95% CI	-	2.4-30.2	2.4-29.2
<b>Disease control rate (DCR, CR or PR or SD)</b>			
n (%)	0	11 (42.3)	11 (40.7)
95% CI	-	(23.4, 63.1)	(22.4, 61.2)

**Anti-LJM716 antibody formation by treatment group (Full analysis set)**

None

**AUClast and Cmax for LJM716 when combined with trastuzumab, by day and treatment group (Pharmacokinetic analysis set)**

Treatment group	Cycle 1 Day 1 (first dose)	Cycle 3 Day 1 (expected steady state)
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Statistics	AUClast (µg*hr/mL)	Cmax (µg/mL)	AUClast (µg*hr/mL)	Cmax (µg/mL)
<b>qw 3 mg/kg (N=2), dose escalation part</b>				
N with data	1	2	1	1
Mean (STD)	7488	72.8 (7.14)	13658	131
CV% mean	-	9.8	-	-
Geo-mean	7488	72.6	13658	131
CV% geo-mean	-	9.9	-	-
Median (range)	7488	72.8 (67.7–	13658	131
<b>qw 10 mg/kg (N=5), dose escalation part</b>				
N with data	4	5	2	2
Mean (STD)	23083 (1780)	242 (11.8)	62454 (1967)	528 (36.8)
CV% mean	7.7	4.9	3.1	7.0
Geo-mean	23032	242	62439	527
CV% geo-mean	7.7	5.0	3.2	7.0
Median (range)	22982 (21451–24918)	246 (225-253)	63454 (61064-63845)	528 (502-554)
<b>qw 20 mg/kg (N=4), dose escalation part</b>				
N with data	4	4	0	0
Mean (STD)	38081 (4294)	406 (82.2)	-	-
CV% mean	11.3	20.2	-	-
Geo-mean	37894	399	-	-
CV% geo-mean	11.6	22.3	-	-
Median (range)	38599 (32472–	431 (292–470)	-	-
<b>qw 40 mg/kg (N=6), dose escalation part</b>				
N with data	4	6	3	3
Mean (STD)	96098 (20773)	1084 (178)	234889 (25931)	2000 (272)
CV% mean	21.6	16.4	11.0	13.6
Geo-mean	94307	1072	233963	1988
CV% geo-mean	23.1	16.6	10.8	13.4
Median (range)	98031 (69380–118949)	1055 (845–1320)	225841 (214694–264132)	1930 (1770–2300)

<b>qw 40 mg/kg (N=47), dose expansion part</b>				
N with data	0	47	0	22
Mean (SD)	-	795 (177)	-	1712 (553)
CV% mean	-	22.2	-	32.3
Geo-mean	-	777	-	1627
CV% geo-mean	-	22.1	-	34.7
Median (range)	-	749 (469–	-	1635 (583–3420)

## Summary of Safety

### Safety Results

Adverse events by primary system organ class (any grade: at least 5% of all patients; grade 3/4: all), regardless of study drug relationship

Primary system organ class	LJM716 qw 3 mg/kg N=2		LJM716 qw 10 mg/kg N=5		LJM716 qw 20 mg/kg N=4		RDE LJM716 qw 40 mg/kg N=53		All patients N=64	
	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any system organ class	2 (100)	1 (50.0)	5 (100)	3 (60.0)	4 (100)	1 (25.0)	53 (100)	25 (47.2)	64 (100)	30 (46.9)
Gastrointestinal disorders	2 (100)	1 (50.0)	5 (100)	1 (20.0)	4 (100)	0	52 (98.1)	10 (18.9)	63 (98.4)	12 (18.8)
General disorders and administration site disorders	1 (50.0)	0	3 (60.0)	0	3 (75.0)	0	33 (62.3)	6 (11.3)	40 (62.5)	6 (9.4)
Investigations	0	0	3 (60.0)	2 (40.0)	1 (25.0)	1 (25.0)	34 (64.2)	7 (13.2)	38 (59.4)	10 (15.6)
Metabolism and nutrition disorders	1 (50.0)	1 (50.0)	4 (80.0)	2 (40.0)	1 (25.0)	0	31 (58.5)	7 (13.2)	37 (57.8)	10 (15.6) <sup>9</sup> (14.1)
Skin and subcutaneous tissue disorders	1 (50.0)	0	2 (40.0)	0	2 (50.0)	0	23 (43.4)	0	28 (43.8)	0
Musculoskeletal and connective tissue disorders	1 (50.0)	0	3 (60.0)	0	1 (25.0)	0	17 (32.1)	2 (3.8)	22 (34.4)	2 (3.1)
Infections and infestations	1 (50.0)	1 (50.0)	1 (20.0)	0	1 (25.0)	0	16 (30.2)	2 (3.8)	19 (29.7)	3 (4.7)
Respiratory, thoracic and mediastinal disorders	1 (50.0)	0	2 (40.0)	1 (20.0)	1 (25.0)	0	15 (28.3)	1 (1.9)	19 (29.7)	2 (3.1)



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	LJM716 qw 3 mg/kg N=2		LJM716 qw 10 mg/kg N=5		LJM716 qw 20 mg/kg N=4		RDE LJM716 qw 40 mg/kg N=53		All patients N=64	
Primary system organ class	All n (%)	G 3/4 n (%)	All n (%)	G 3/4 n (%)	All n (%)	G 3/4 n (%)	All n (%)	G 3/4 n (%)	All n (%)	G 3/4 n (%)
Injury, poisoning, and procedural complications	0	0	1 (20.0)	1 (20.0)	0	0	14 (26.4)	0	15 (23.4)	1 (1.6)
Nervous system disorders	0	0	1 (20.0)	1 (20.0)	1 (25.0)	0	10 (18.9)	2 (3.8)	12 (18.8)	3 (4.7)
Psychiatric disorders	0	0	1 (20.0)	0	1 (25.0)	0	9 (17.0)	0	11 (17.2)	0
Blood and lymphatic system disorders	1 (50.0)	0	1 (20.0)	0	0	0	6 (11.3)	3 (5.7)	8 (12.5)	3 (4.7)
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	0	0	0	0	0	0	4 (7.5)	1 (1.9)	4 (6.3)	1 (1.6)
Cardiac disorders	0	0	2 (40.0)	0	0	0	2 (3.8)	0	4 (6.3)	0

Primary system organ classes are sorted in descending frequency, as reported in the all patients, all grades column

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

G = CTCAE grade



**Adverse events by preferred term (any grade: at least 5% of all patients; or grade 3/4: all), regardless of study drug relationship**

Preferred term	LJM716 qw 3 mg/kg N=2		LJM716 qw 10 mg/kg N=5		LJM716 qw 20 mg/kg N=4		RDE LJM716 qw 40 mg/kg N=53		All patients N=64	
	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	2 (100)	1 (50.0)	5 (100)	3 (60.0)	4 (100)	1 (25.0)	53 (100)	25 (47.2)	64 (100)	30 (46.9)
Diarrhoea	2 (100)	1 (50.0)	5 (100)	1 (20.0)	4 (100)	0	49 (92.5)	5 (9.4)	60 (93.8)	7 (10.9)
Weight decreased	0	0	2 (40.0)	1 (20.0)	0	0	21 (39.6)	0	23 (35.9)	1 (1.6)
Fatigue	1 (50.0)	0	3 (60.0)	0	2 (50.0)	0	16 (30.2)	3 (5.7)	22 (34.4)	3 (4.7)
Nausea	1 (50.0)	0	3 (60.0)	0	1 (25.0)	0	14 (26.4)	1 (1.9)	19 (29.7)	1 (1.6)
Hypokalaemia	1 (50.0)	1 (50.0)	3 (60.0)	2 (40.0)	1 (25.0)	0	13 (24.5)	3 (5.7)	18 (28.1)	6 (9.4)
Chills	0	0	1 (20.0)	0	0	0	16 (30.2)	0	17 (26.6)	0
Pyrexia	1 (50.0)	0	1 (20.0)	0	1 (25.0)	0	14 (26.4)	1 (1.9)	17 (26.6)	1 (1.6)
Decreased appetite	0	0	1 (20.0)	0	0	0	16 (30.2)	0	17 (26.6)	0
Infusion related reaction	0	0	1 (20.0)	0	0	0	13 (24.5)	0	14 (21.9)	0
Vomiting	1 (50.0)	1 (50.0)	1 (20.0)	0	0	0	12 (22.6)	0	14 (21.9)	1 (1.6)
Hypomagnesaemia	0	0	3 (60.0)	0	1 (25.0)	0	9 (17.0)	0	13 (20.3)	0
Abdominal pain	1 (50.0)	0	1 (20.0)	0	0	0	10 (18.9)	0	12 (18.8)	0
Insomnia	0	0	1 (20.0)	0	0	0	8 (15.1)	0	9 (14.1)	0
Rash	0	0	1 (20.0)	0	0	0	8 (15.1)	0	9 (14.1)	0
Stomatitis	0	0	0	0	0	0	9 (17.0)	0	9 (14.1)	0
Dyspepsia	0	0	2 (40.0)	0	0	0	6 (11.3)	0	8 (12.5)	0
Anaemia	1 (50.0)	0	0	0	0	0	6 (11.3)	3 (5.7)	7 (10.9)	3 (4.7)
Asthenia	0	0	0	0	0	0	7 (13.2)	1 (1.9)	7 (10.9)	1 (1.6)
Cough	1 (50.0)	0	0	0	0	0	6 (11.3)	0	7 (10.9)	0
Constipation	1 (50.0)	0	0	0	1 (25.0)	0	5 (9.4)	1 (1.9)	7 (10.9)	1 (1.6)
Dry skin	0	0	1 (20.0)	0	1 (25.0)	0	5 (9.4)	0	7 (10.9)	0
Headache	0	0	1 (20.0)	0	0	0	6 (11.3)	2 (3.8)	7 (10.9)	2 (3.1)
Lipase increased	0	0	1 (20.0)	1 (20.0)	0	0	6 (11.3)	3 (5.7)	7 (10.9)	4 (6.3)

Preferred term	LJM716 qw 3 mg/kg N=2		LJM716 qw 10 mg/kg N=5		LJM716 qw 20 mg/kg N=4		RDE LJM716 qw 40 mg/kg N=53		All patients N=64	
	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal pain upper	0	0	1 (20.0)	0	0	0	5 (9.4)	0	6 (9.4)	0
Back pain	0	0	0	0	0	0	6 (11.3)	0	6 (9.4)	0
Dyspnoea	0	0	0	0	0	0	6 (11.3)	1 (1.9)	6 (9.4)	1 (1.6)
AST increased	0	0	0	0	0	0	5 (9.4)	2 (3.8)	5 (7.8)	2 (3.1)
Amylase increased	0	0	0	0	0	0	5 (9.4)	1 (1.9)	5 (7.8)	1 (1.6)
Hyperglycaemia	0	0	0	0	0	0	5 (9.4)	0	5 (7.8)	0
Upper respiratory tract infection	0	0	0	0	0	0	5 (9.4)	0	5 (7.8)	0
Oropharyngeal pain	0	0	0	0	1 (25.0)	0	4 (7.5)	0	5 (7.8)	0
Anxiety	0	0	0	0	1 (25.0)	0	3 (5.7)	0	4 (6.3)	0
ALT increased	0	0	0	0	0	0	4 (7.5)	1 (1.9)	4 (6.3)	1 (1.6)
Dermatitis acneiform	0	0	0	0	1 (25.0)	0	3 (5.7)	0	4 (6.3)	0
Dysphagia	0	0	0	0	0	0	2 (3.8)	1 (1.9)	2 (3.1)	1 (1.6)
Pneumonia	0	0	0	0	0	0	2 (3.8)	1 (1.9)	2 (3.1)	1 (1.6)
Hypophosphataemia	0	0	0	0	0	0	2 (3.8)	2 (3.8)	2 (3.1)	2 (3.1)

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

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

G = CTCAE grade, ALT = alanine aminotransferase, AST = aspartate aminotransferase

**Adverse events, suspected to be study-drug related (any grade: at least 5% of all patients; or grade 3/4: all)**

Preferred term	LJM716 qw 3 mg/kg N=2		LJM716 qw 10 mg/kg N=5		LJM716 qw 20 mg/kg N=4		RDE LJM716 qw 40 mg/kg N=53		All patients N=64	
	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (50.0)	1 (50.0)	5 (100)	3 (60.0)	4 (100)	0	53 (100)	7 (13.2)	63 (98.4)	11 (17.2)
Diarrhoea	1 (50.0)	1 (50.0)	4 (80.0)	0	4 (100)	0	48 (90.6)	4 (7.5)	57 (89.1)	5 (7.8)
Chills	0	0	1 (20.0)	0	0	0	15 (28.3)	0	16 (25.0)	0
Weight decreased	0	0	2 (40.0)	1 (20.0)	0	0	12 (22.6)	0	14 (21.9)	1 (1.6)
Nausea	1 (50.0)	0	3 (60.0)	0	1 (25.0)	0	9 (17.0)	0	14 (21.9)	0
Fatigue	1 (50.0)	0	2 (40.0)	0	0	0	10 (18.9)	1 (1.9)	13 (20.3)	1 (1.6)
Pyrexia	0	0	1 (20.0)	0	1 (25.0)	0	11 (20.8)	1 (1.9)	13 (20.3)	1 (1.6)
Decreased appetite	0	0	1 (20.0)	0	0	0	10 (18.9)	0	11 (17.2)	0
Infusion related reaction	0	0	1 (20.0)	0	0	0	10 (18.9)	0	11 (17.2)	0
Hypokalaemia	0	0	3 (60.0)	2 (40.0)	0	0	7 (13.2)	2 (3.8)	10 (15.6)	4 (6.3)
Hypomagnesaemia	0	0	3 (60.0)	0	1 (25.0)	0	3 (5.7)	0	7 (10.9)	0
Rash	0	0	0	0	0	0	6 (11.3)	0	6 (9.4)	0
Stomatitis	0	0	0	0	0	0	6 (11.3)	0	6 (9.4)	0
Asthenia	0	0	0	0	0	0	5 (9.4)	0	5 (7.8)	0
Dry skin	0	0	1 (20.0)	0	1 (25.0)	0	3 (5.7)	0	5 (7.8)	0
Vomiting	1 (50.0)	0	0	0	0	0	4 (7.5)	0	5 (7.8)	0
Dyspepsia	0	0	2 (40.0)	0	0	0	2 (3.8)	0	4 (6.3)	0
Anaemia	1 (50.0)	0	0	0	0	0	2 (3.8)	0	3 (4.7)	0
ALT increased	0	0	0	0	0	0	2 (3.8)	1 (1.9)	2 (3.1)	1 (1.6)
AST increased	0	0	0	0	0	0	2 (3.8)	1 (1.9)	2 (3.1)	1 (1.6)
Lipase increased	0	0	1 (20.0)	1 (20.0)	0	0	0	0	1 (1.6)	1 (1.6)
Pulmonary embolism	0	0	1 (20.0)	1 (20.0)	0	0	0	0	1 (1.6)	1 (1.6)

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

Only AEs occurring during treatment or within 30 days of the last study medication are reported. G = CTCAE grade.

**Deaths, other serious adverse events, and adverse events leading to treatment discontinuation**

	LJM716 qw 3 mg/kg N=2 n (%)	LJM716 qw 10 mg/kg N=5 n (%)	LJM716 qw 20 mg/kg N=4 n (%)	RDE LJM716 qw 40 mg/kg N=53 n (%)	All patients N=64 n (%)
<b>On-treatment deaths<sup>1</sup></b>					
Total	0	0	0	4 (7.5)	4 (6.3)
Disease progression	0	0	0	3 (5.7)	3 (4.7)
General physical health deterioration	0	0	0	1 (1.9)	1 (1.6)
<b>SAEs</b>					
Total	1 (50.0)	1 (20.0)	1 (25.0)	16 (30.2)	19 (29.7)
Grade 3 or 4	1 (50.0)	1 (20.0)	0	13 (24.5)	15 (23.4)
Suspected as related to study drug	1 (50.0)	1 (20.0)	0	2 (3.8)	4 (6.3)
Grade 3 or 4	1 (50.0)	1 (20.0)	0	1 (1.9)	3 (4.7)
<b>AEs leading to discontinuation</b>					
Total	0	0	0	4 (7.5)	4 (6.3)
Grade 3 or 4	0	0	0	2 (3.8)	2 (3.1)

<sup>1</sup> Deaths occurring up to 30 days after the end of treatment are included.

**Serious adverse events in the RDE treatment group and overall (in more than 1 patient), by preferred term (Safety set)**

	RDE LJM716 qw 40 mg/kg N=53		All patients N=64	
Preferred Term	All n (%)	G 3/4 n (%)	All n (%)	G ¾ n (%)
Total	16 (30.2)	13 (24.5)	19 (29.7)	15 (23.4)
In more than 1 patient <sup>1</sup>				
Abdominal pain	1 (1.9)	0	2 (3.1)	0
Headache	2 (3.8)	2 (3.8)	2 (3.1)	2 (3.1)
Pneumonia	2 (3.8)	1 (1.9)	2 (3.1)	1 (1.6)

<sup>1</sup> Additional SAEs in 1 patient only include:

40 mg/kg treatment group: G4 dysphagia, G4 hypokalaemia, G4 tumour compression, G3 anemia, G3 ascites, G3 bile duct stenosis, G3 chest wall mass, G3 constipation, G3 dyspnoea, G3 gait disturbance, G3 lung infection, G3 nausea, G3 oesophageal stenosis, G3 gastrointestinal obstruction, G3 pleural effusion, G2 haematochezia, G2 infection, G2 melaena, G2 tumour haemorrhage, G1 chills.

Lower dose treatment groups: G3 diarrhoea, G3 gastrointestinal disorder, G3 lower respiratory tract infection, G2 procedural complications, G2 epilepsy, G3 pulmonary embolism, G2 radiation injury, G2 urinary retention

Only SAEs occurring up to 30 days after the end of treatment are included

G = CTCAE grade

**Conclusion:**

The following conclusions can be drawn from this Phase 1 dose escalation study of LJM716 in combination with trastuzumab in 64 patients with heavily pretreated, HER2 overexpressing metastatic breast or gastric cancer:

- The MTD/RDE of LJM716 for combination with trastuzumab was established at 40 mg/kg once weekly.
- The concentrations of LJM716 appeared to increase dose-proportionally in the tested dose range of 3 to 40 mg/kg. Assessment of C<sub>max</sub> and AUC<sub>last</sub> revealed no effect of trastuzumab on the PK of LJM716; the PK of trastuzumab was not assessed.
- Response and PFS data showed anti-tumor activity (ORR 7.8%, including one CR lasting more than 3 years and four PRs lasting between 4 and 9 months; DCR 45.3%; median PFS 1.8 months for breast cancer and 1.9 months for gastric cancer patients).
- The safety of LJM716 when combined with trastuzumab was found to be acceptable and treatment was generally well tolerated. No new or unexpected safety signals were detected. There were four on-treatment deaths, but none was suspected to be related to study drug. The few grade 3 or 4 AEs could be managed by providing appropriate oncology patient clinical care.
- There was no evidence of anti-LJM716 antibody formation and hence negative immunogenicity of LJM716.
- The PD response to LJM716 in tumor tissue and the PK/PD relationship were not assessed.

**Date of Clinical Trial Report**

Report date of Interim CSR (Primary): 24-May-2017

Report date of Final CSR: 15-Feb-2018